Title : A Phase 3 Trial of Setmelanotide (RM-493), a Melanocortin-4 Receptor (MC4R) Agonist, in Bardet-Biedl Syndrome (BBS) and Alstrom Syndrome (AS) Patients with Moderate to Severe Obesity

NCT: NCT0374522

Date: October 29, 2020

STATISTICAL ANALYSIS PLAN

PROTOCOL RM-493-023

A Phase 3 trial of Setmelanotide (RM-493), a Melanocortin-4 Receptor (MC4R) Agonist, in Bardet-Biedl Syndrome (BBS) and Alström syndrome (AS) Patients with Moderate to Severe Obesity

Protocol Number:	RM-493-023
Protocol Version and Date:	Version 3.1: September 9, 2020 Version 3.0: 16 August 2020 Version 2.0: 04 February 2019 Version 1.1: 10 October 2018 Original: 14 August 2018
Name of Test Drug:	Setmelanotide (RM-493)
Phase:	Phase 3
Methodology:	Randomized, Double-Blind, Placebo-Controlled (Period 1), Open-Label (Periods 2 and 3)
Sponsor:	Rhythm Pharmaceuticals, Inc. 222 Berkeley Street, Suite 1200 Boston, MA 02116, USA Tel: (857) 264-4282 Fax: (857) 264-4299
Analysis Plan Date:	29 October 2020
Analysis Plan Version:	Version 3.0

APPROVAL SIGNATURE PAGE

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Sponsor:	Rhythm Pharmaceuticals, Inc. 222 Berkeley Street, Suite 1200 Boston, MA 02116, USA
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Document Date / Version:	29 October 2020 / Version 3.0

[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.

Sponsor Signatory:

[redacted]

Rhythm Pharmaceuticals, Inc.

Signature: [redacted]

Date: 10/29/2020

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[redacted]

TABLES INCLUDED IN THE TEXT

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
AG	Active Growth Analysis Set
AS	Alström Syndrome
ATB	Active Treatment Baseline
BBS	Bardet-Biedl Syndrome
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
BP	Blood Pressure
CI	Confidence Interval
CRF	Case Report Form
CRIBBS	Clinical Registry Investigating Bardet-Biedl Syndrome Database
CS	Completers Set
CSR	Clinical Study Report
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
DUS	Designated Use Set
ECG	Electrocardiogram
[redacted]	[redacted]
FAS	Full Analysis Set
[redacted]	[redacted]
HDL	High Density Lipoprotein
HR	Heart Rate
IQ	Intelligence Quotient
[redacted]	
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NDA	New Drug Application

Abbreviation	Definition
[redacted]	[redacted]
PCPB	Placebo-Controlled Period Baseline
PCS	~14 Week Placebo-Controlled Analysis Set
[redacted]	
PP	Per-Protocol
PP at EOP1	Per-Protocol Set at End of Period 1
PP at EOP2	Per-Protocol Set at End of Period 2
QD	Once-Daily
SA	Safety Analysis
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
[redacted]	
SH	Stable Height Analysis Set
SOA	Schedule of Assessments
[redacted]	
WHO	World Health Organization
[redacted]	[redacted]

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-493-023, A Phase 3 trial of Setmelanotide (RM-493), a Melanocortin-4 Receptor (MC4R) Agonist, in Bardet-Biedl Syndrome (BBS) and Alström syndrome (AS) Patients with Moderate to Severe Obesity. This SAP is based upon protocol version dated 26 August 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.

In addition, the SAP is intended to clarify many of the details of the more limited discussion in the statistical section of the protocol, therefore, the SAP will expand on and 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 Clinical Study Report for the study as appropriate. It should be noted that a cohort of the supplemental patients was added into the protocol in the midcourse of the study. However, the sponsor has specified that the patients categorized in the pivotal cohort include all the enrolled BBS/AS patients at the time of the planned sixth AS patient enrollment. Based on this definition, and up to the finalization of the SAP, it is concluded that a total of 38 patients (the first 32 BBS patients and 6 AS patients) will make up the pivotal cohort. The full list of pivotal cohort patients is provided in Appendix I. All analyses for CSR and Submission, including demographics, disposition, baseline characteristics, efficacy, and safety etc., will be performed and the conclusions will be drawn based on the data from the pivotal cohort of patients. The purpose of the supplemental cohort is to gain more treatment experience. Therefore, unless stated otherwise, all analyses in the SAP refer to pivotal cohort only.

1.2. Study Objectives

A brief note of initial clarification: as outlined in more detail in Sections 1.3.1 and 3.10.1, the nature of the study design includes a randomized, double blinded and placebo-controlled 14-week Period 1, followed directly by a ~38 weeks open label, active treatment Period 2, resulting in ~52 weeks on therapy. Patients then continue into another 14 weeks longer-term treatment. However, the primary analysis is planned after the last enrolling patient has finished Period 2 (i.e., at the end of ~52 weeks of overall therapy (placebo and/or active).

The approach to the primary analysis (i.e., main analysis for New Drug Application [NDA] filing or applications in other regulatory agencies as appropriate) is outlined in Section 4.3.1.

Taking into account that enrollment has been ongoing for some time, many patients will be well into their second year of treatment at the time the primary analysis is planned (as the last patient ends ~52 weeks of overall therapy on the study). Thus, it is anticipated only a small percentage of patients who are initially randomized into the placebo arm may have less than ~52 weeks of setmelanotide treatment by the timing of the primary analysis (end of Period 2)

for NDA or other regulatory filings.

1.2.1. Primary Objective

The primary objective of the study is to assess the effect of setmelanotide on the proportion of patients (≥ 12 years of age at baseline) treated for ~52 weeks who achieve a clinically meaningful reduction from baseline (i.e., ≥10%) in body weight.

1.2.2. Secondary Objectives

The key secondary objectives of the study are to:

- Assess the effect of setmelanotide on mean percent change from baseline in body weight (in patients ≥12 years of age at baseline) after ~52 weeks of treatment.
- Assess the effect of setmelanotide on the mean percent change from baseline in the weekly average of the daily hunger score (in patients ≥12 years of age at baseline) after ~52 weeks of treatment.
- Assess the effect of setmelanotide on the proportion of patients who achieve a ≥25% improvement in the weekly average of the daily hunger score (in patients ≥12 years of age at baseline) after ~52 weeks of treatment.

Other secondary objectives of the study are to:

- Assess the effect of setmelanotide on the mean percent change from baseline in body weight (in patients ≥12 years of age at baseline) at the Week 14 visit compared with placebo.
- Assess the effect of setmelanotide on the mean percent change from baseline in the weekly average of the daily hunger score (in patients ≥12 years of age at baseline) at the Week 14 visit compared with placebo.

1.2.3. [redacted]

[redacted]

1.3. Study Design

1.3.1. Synopsis of Study Design

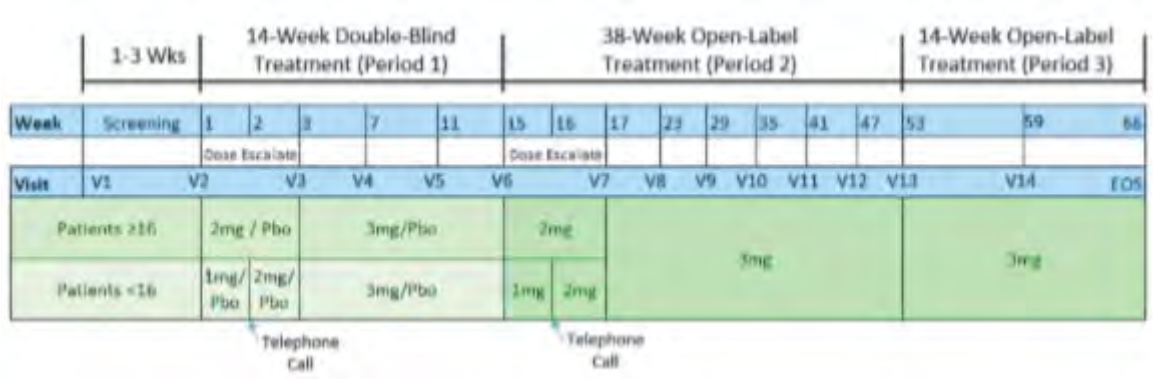
This is a pivotal study to confirm the long-term (approximately 1 year in most patients) efficacy and safety of setmelanotide treatment in patients who have BBS or AS.

The study will consist of 3 treatment periods (see Figure 1). After obtaining informed consent, potential patients will be screened to determine study eligibility. Eligible patients will enter a 14-week, randomized, double-blind, placebo-controlled treatment period (Period 1) that will be followed by a 38-week open-label treatment period (Period 2) in which all patients will receive setmelanotide. The primary analysis will be performed after the last patient enrolled has completed Period 2. To maintain the blind through Period 2, dose escalation to a fixed dose of 3 mg will be performed during the first 2 weeks in both the double-blind (Period 1) and 38-week open-label (Period 2) treatment periods. Following Period 2, patients will continue to receive open-label setmelanotide for 14 weeks (Period 3) after which they may be enrolled into a separate treatment extension study.

Patients will be randomized in a 1:1 ratio, stratified by age group (≥12 years or <12 years) and disease (BBS or AS), to receive either setmelanotide QD or placebo QD via SC injection for the first 14 weeks. Patients who are ≥16 years of age will start on setmelanotide 2 mg or matching placebo during the 2-week dose escalation and will increase to 3 mg or matching placebo at the beginning of Week 3. Patients who are <16 years of age will start on setmelanotide 1 mg or matching placebo during Week 1, will increase to 2 mg or matching placebo at the beginning of Week 2, and will increase to 3 mg or matching placebo at the beginning of Week 3. During the 14-week double-blind treatment period, patients will be evaluated at the beginning of Weeks 2 (telephone call only, patients <16 years old), 3, 7, 11, and 15 as depicted in Figure 1.

After the initial 14-week double-blind treatment period (Period 1), all patients will immediately transition to receive open-label setmelanotide QD via SC injection for 38 weeks (Period 2). To preserve the blind, all patients will be re-escalated to the 3 mg clinical dose. Thus, beginning at Week 15, patients who are ≥16 years of age will receive open-label setmelanotide 2 mg for 2 weeks, followed by a dose increase to 3 mg beginning at Week 17, and patients who are <16 years of age will receive open-label setmelanotide 1 mg during Week 15, 2 mg during Week 16, and 3 mg beginning at Week 17. Patients will be evaluated at the beginning of Weeks 16 (telephone call only, patients <16 years old) and 17 and then every 6 weeks thereafter during this Period 2. In Period 3, patients will be evaluated every 7 weeks.

Figure 1 Study Design Schematic



1.3.2. Randomization Methodology

This study will be open label, except for a 14-week double-blind, placebo-controlled period.

Patients who qualify for the study will return to the site on Day 1 of the double-blind period. Prior to randomization, the Investigator will ensure that the patient continues to meet inclusion and exclusion criteria. Patients who continue to be eligible to participate in the study will be assigned a unique randomization number based on a randomization code that will be generated prior to the start of the study. The randomization number codes the patient's initial treatment assignment (for the double-blind period) to either setmelanotide or placebo. The randomization scheme will randomize patients in a 1:1 ratio, stratified by age group (≥12 years or <12 years) and disease (BBS or AS), to receive either setmelanotide or placebo during the first 14 weeks of the study. Randomization numbers will not be re-used once assigned. Please refer to the official randomization plan for greater details.

The Investigator, study site staff, clinical research organization staff providing site management, and Medical Monitor will not have access to the actual treatment assignment administered during the 14-week double-blind, placebo-controlled treatment period (Period 1) except in the case of an emergency until all randomized participants have completed both the 14-week double-blind, placebo-controlled period and the 38-week open-label portion of the study (Period 2).

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 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

Should the study be closed prematurely, all study materials must be returned to the Sponsor or designee.

Every attempt will be made to maintain the blind through the end of the 38-week, open-label treatment period (Period 2) (i.e., until the database snapshot prior to completing the primary analysis). 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. The Primary Investigator will be provided with access to a system to unblind their patients, but if possible, the decision to break the blind should first be discussed with the Medical Monitor. If the blind is broken, the reason, when, and how the blind was broken will be documented.

1.3.4. Study Procedures

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

Table 1 Schedule of Assessments: Screening through Week 53 Visit (End of Period 2)

	Screening Visit	Double-Blind Treatment (Period 1)					38-Week Open-Label Treatment (Period 2)								
		SET or PBO Escalation			SET or PBO		SET Escalation			SET					
Visit (V) Number	**V1**	**V2**		**V3**	**V4**	**V5**	**V6**		**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
Study Week	**-3***	**1**	**2**	**3**	**7**	**11**	**15**	**15**	**17**	**23**	**29**	**35**	**41**	**47**	**53**
Study Day	**(n/a)**	**1**	**8**	**15**	**43**	**71**	**99**	**106**	**113**	**155**	**197**	**239**	**281**	**323**	**365**
Informed consent/assent	X														
Inclusion/exclusion review	X	X													
Medical history review	X														
Genetic testing[1]	X														
Archive sample for storage[2]		X					X†								X†
Comprehensive skin exam[3]	X														
Fitzpatrick scale	X	X													
Pregnancy test[4]	X	X†		X†	X†	X†	X†		X†	X†	X†	X†	X†	X†	X†
Study drug administration/dispense[5]		X		X	X	X	X		X	X	X	X	X	X	X
[redacted]															
Daily hunger questionnaire[6]	X	◄ Daily† ►													
Global hunger assessment[9]	X			X†			X†		X†		X†				X†
[redacted]															
Telephone call			X					X							

	Screening Visit	Double-Blind Treatment (Period 1)					38-Week Open-Label Treatment (Period 2)								
		SET or PBO Escalation			SET or PBO		SET Escalation			SET					
Visit (V) Number	V1	V2		V3	V4	V5	V6		V7	V8	V9	V10	V11	V12	V13
Study Week	-3*	1	2	3	7	11	15	15	17	23	29	35	41	47	53
Study Day	(n/a)	1	8	15	43	71	99	106	113	155	197	239	281	323	365
[redacted]															
[redacted]															
Concomitant medications review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nutritional counselling and monitoring	X			X		X			X		X		X		X
[redacted]															

* 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.

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

1 A blood sample will be obtained at Screening to confirm a genetic diagnosis of AS or BBS. However, patients may be entered into the study based on clinical diagnosis of BBS (≤10% of BBS patients) or prior genetic diagnosis of BBS (≥90% of BBS patients) or AS (100% of AS patients) (refer to Section 4.2). The DNA will not be studied or "typed" for any other purpose, unless patients are re-consented.

2 Extra retain samples will consist of 2 serum and 2 plasma (K2EDTA) vacutainer tubes and two 5ml urine tubes.

3 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.

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

5 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. 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.

[redacted]

8 Daily hunger questionnaire scores will be recorded on a daily basis, prior to the patient's morning meal. If the patient is unable to assess their own hunger due to impaired cognitive function, a parent/caregiver assessment of hyperphagia (PWS-FPD) will be completed instead (see Appendix 11.5.2). During the Screening Period, the patient must complete the daily hunger questionnaire in the electronic diary at least four of the seven days prior to V2. Subjects who do not meet this requirement should not be randomized into the study. V2 may be rescheduled if needed to fulfill this requirement.

9 Global hunger questions (Appendix 11.5) will be administered in clinic as follows: Question 1 will be asked at Screening, and Questions 1 and 2 will then be asked as specified in the SOA once dosing has been initiated (Day 1). The Parent/Caregiver Global Hunger and the [redacted] should be used when the patient is unable to assess their own hunger.

[redacted]

Table 2 Schedule of Assessments: 14-Week Open-Label Treatment (Period 3) and Early Termination Visit

	14-Week Open-Label Treatment (Period 3)		
Visit Number (V)	**V14**	**V15 (EOS)**	**Early Termination Visit**
Study Week	**60**	**66**	
Study Day	**414**	**462**	
Archive sample for storage[1]		X†	
Comprehensive skin exam[2]		X	X
Fitzpatrick scale		X	X
Pregnancy test[3]	X†	X†	X†
Study drug administration/dispense[4]	X	X	
[redacted]			
Daily hunger questionnaire[7]	◄——— Daily† ———		X
Global hunger assessment[8]		X†	X†
[redacted]			
Concomitant medications review	X	X	X
Nutritional counselling and monitoring		X	

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

1 Extra retain samples will consist of 2 serum and 2 plasma (K2EDTA) vacutainer tubes and two 5ml urine tubes.

2 A comprehensive skin evaluation will be performed by a dermatologist.
3 All pregnancy tests will be serum; dosing may continue with results pending.
4 Patients/caretakers will draw up and self-administer/administer the drug once daily 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.

[redacted]

7 Daily hunger questionnaire scores will be recorded on a daily basis, prior to the patient's morning meal. If the patient is unable to assess their own hunger due to impaired cognitive function, a parent/caregiver assessment of hyperphagia [redacted] will be completed instead (see Appendix 11.5.2).
8 Global hunger Questions 1 and 2 (Appendix 11.5) will be asked. The Parent/Caregiver Global Hunger and the [redacted] should be used when the patient is unable to assess their own hunger.

[redacted]

1.3.5. Efficacy, [redacted] Parameters

A summary of these endpoints outlining the Analysis Set (population), age limitations, details of the pre-specified baseline, and other pertinent details is found in Table 3.

The primary efficacy endpoint is the proportion of patients (≥12 years of age) who achieve a ≥10% reduction from baseline in body weight after ~52 weeks of treatment in the Full Analysis Set (FAS) population.

The following 3 endpoints have been identified as key secondary efficacy endpoints.

- Mean percent change from baseline in body weight (in patients ≥12 years of age after ~52 weeks of treatment in the FAS population.
- Mean percent change from baseline in the weekly average of the daily hunger score (in patients ≥12 years of age) after ~52 weeks of treatment in the FAS population.
- The proportion of patients who achieve a ≥25% improvement in the weekly average of the daily hunger score (in patients ≥12 years of age) after ~52 weeks of treatment, in the FAS population.

Other secondary endpoints include:

- Mean percent change from baseline in body weight (in patients ≥12 years of age) at the Week 14 visit after treatment with setmelanotide as compared with placebo in the ~14 Week Placebo-controlled Analysis Set (PCS) population.
- Mean percent change from baseline in the weekly average of the daily hunger score (in patients ≥12 years of age) at the Week 14 visit after treatment with setmelanotide as compared with placebo in the PCS population.

[redacted]

[redacted]

2. ANALYSIS POPULATION

2.1. Population Definitions

The following analysis populations will be evaluated and used for presentation and analysis of the data. [redacted]

- Screening Analysis Set: All patients who signed the informed consent form.
- Safety Analysis (SA) Set: All patients who received at least 1 dose of study drug (placebo or setmelanotide). Analysis performed on the safety set will be based on patients according to treatment received.
- FAS: All patients (irrespective of age) who received at least 1 dose of setmelanotide and have baseline data.
- DUS: All patients in the FAS who demonstrate at least 5 kg weight loss (or at least 5% if baseline body weight is < 100 kg) over the first 14 weeks of active setmelanotide treatment, regardless of later disposition.

  For any DUS analysis, the DUS subgroup includes:

  - Those patients initially randomized into the setmelanotide group in the double blinded, randomized, placebo-controlled period that achieved at least 5 kg weight loss (or at least 5% if baseline body weight is < 100 kg) from baseline at Week 15 visit.
  - Those patients who initially randomized in the placebo group in the double blinded, randomized, placebo-controlled period, and achieved at least 5 kg weight loss (or at least 5% if baseline body weight is < 100 kg) from week 15 (i.e., just prior to their first active dose of setmelanotide at week 15) through week 29 (i.e., after 14 weeks of active treatment with setmelanotide).
- PCS: All randomized patients who received at least 1 dose of placebo or setmelanotide and have baseline data. This population is specifically defined for the 14-week placebo-controlled, double-blind period (Period 1). Analysis performed on PCS will be based on subjects as randomized.
- Per-Protocol Set at End of Period 1 (PP at EOP1): All subjects in PCS without any major protocol violations that will result in exclusion of the subjects from the analysis.
- Per-Protocol Set at End of Period 2 (PP at EOP2): All subjects in FAS without any major protocol violations that will result in exclusion of the subjects from the analysis.
- Completers Set (CS): all subjects in the PP at EOP1 population who continue on active treatment or placebo to complete a full 14-week placebo-controlled double blinded period (Period 1)

The FAS population is the primary population for the analysis of efficacy endpoints. The DUS population may be used for sensitivity analyses of efficacy endpoints, as appropriate.

The SA Set is the primary population for the analysis of safety endpoints.

The following analysis sets may be used for supportive/exploratory analyses (note that in the following exploratory analysis sets, if a patient's height at the primary endpoint timepoint,

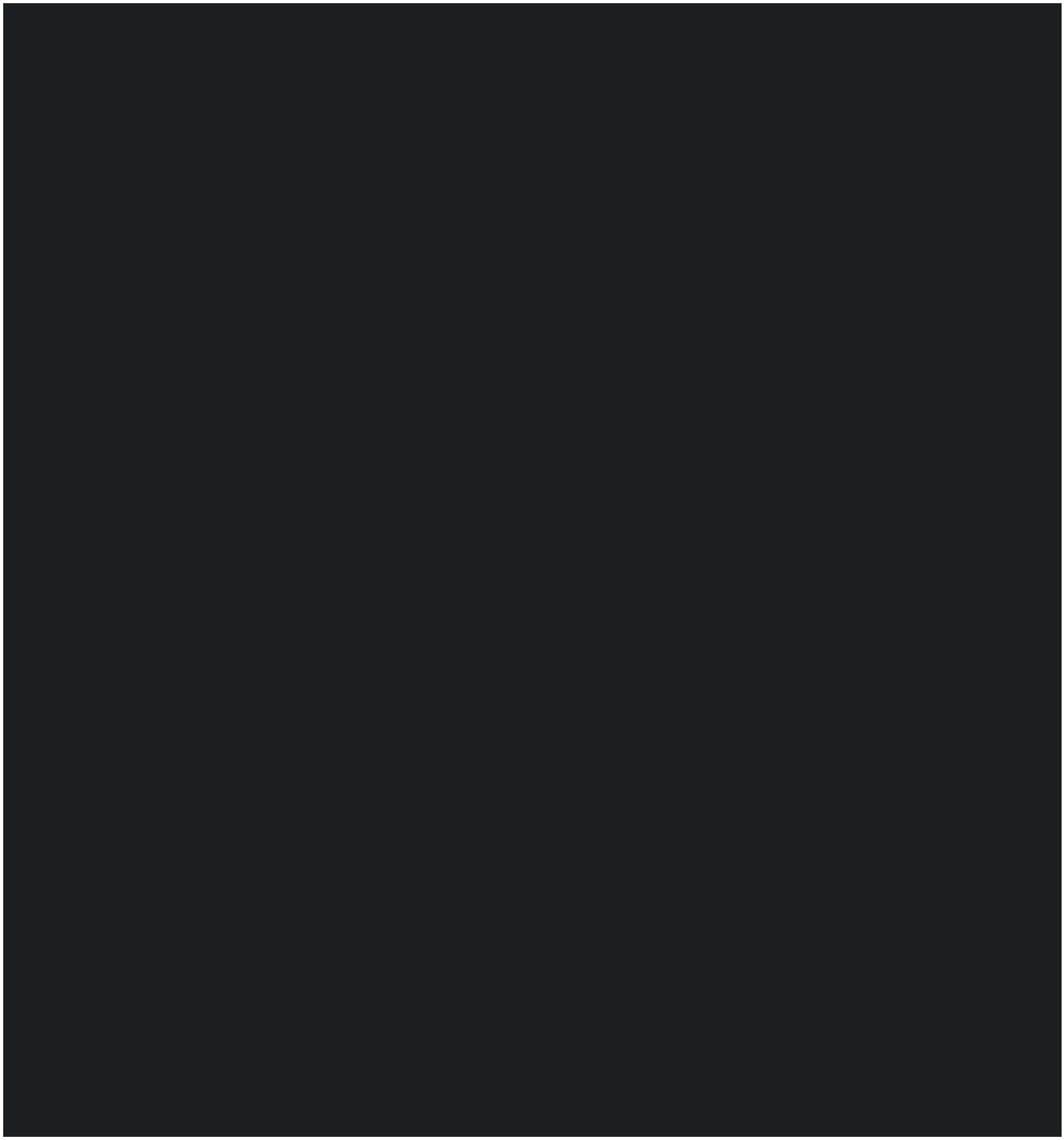
i.e., ~Week 53 visit, is not available, then the last available measurement of height will be used to define the analysis sets).

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 subject'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 the data monitoring group (or designee) as applicable; this file will include a description each 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. An analysis performed on the PP set may be provided only if the number of patients in the PP set is 20% less than that in FAS/PCS set.

All protocol violations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS



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 Harmonization 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 subjects within each category of the parameter will be presented. For continuous variables, the number of subjects (N), mean, 95% confidence interval of the mean, median, standard deviation (SD), minimum, and maximum values will be presented.

Formal statistical hypothesis testing will be performed on the primary efficacy endpoint with testing conducted at the 1-sided, 2.5% level of significance. Summary statistics will be presented, as well as confidence intervals (CIs), as described in the sections below. Trial success will be based on a 1-sided p-value <0.025.

3.3. Computing Environment

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

3.4. Baseline Definitions

To assess the dual nature of efficacy parameters, two efficacy baseline definitions will be used.

- Placebo-controlled period baseline (PCPB): is defined as the last available measurement prior to the first dose of setmelanotide or placebo. PCPB will be used for efficacy analysis based upon 14 weeks of treatment with either setmelanotide or placebo.
- Active treatment baseline (ATB): is defined as the last available measurement prior to the first dose of active setmelanotide. ATB will be used for efficacy analyses based upon ~52 weeks of treatment.

For safety, including key laboratory (e.g. hematology and chemistry) parameters, the last measurement prior to the first dose of setmelanotide or placebo will be used as the baseline.

3.5. Methods of Pooling Data

Data will be pooled across genetic obesity populations (BBS and AS). The primary analysis will be performed based on pooled pivotal patients. Separate tabulations for efficacy parameters may be provided for the two genetic obesity populations, but no formal tests for differences in efficacy between groups will be carried out. BBS is a polygenic disorder; many participants may have “private” mutations different from all others in the study, and disparities in response by genotype are to be anticipated even within the BBS cohort, making formation of subgroups for statistical testing likely impossible.

3.6. Adjustments for Covariates

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

3.7. Multiple Comparisons/Multiplicity

No multiplicity adjustments are required for the primary analysis as this study has only 1 primary endpoint. This controls the overall alpha at 0.025, 1-sided.

There are multiple key secondary efficacy endpoints planned in the study (see Section 1.3.5.1). However, based on the rarity of this disease, and the small number of patients to be enrolled in this study, the ability to use extremely rigorous statistical approaches to address multiplicity for these secondary endpoints is limited. Therefore, for publication, nominal-p-values will be used to interpret *each endpoint separately* in this small study. The Sponsor acknowledges that this approach may increase the probability of potential Type 1 error for the *set* of key secondary efficacy endpoints being analyzed. While this SAP does not envision multiplicity adjustments in this study, the Sponsor has pre-specified a step-down procedure (a hierarchical order of testing for the key secondary efficacy endpoints) to control Type-1 error, if needed for any purpose. The key secondary endpoints are presented according to the Sponsor-specified hierarchical order in Section 4.3.2.

3.8. Subgroups

3.8.1. Subgroup Analysis by Disease Type

Subgroup analysis by disease type (e.g., BBS and AS; clinically defined or genetically defined) on primary efficacy and key secondary efficacy endpoints will be summarized separately. Analysis on the secondary endpoints, i.e., mean percent change of weight and hunger score at ~14 week from baseline, will be conducted for each disease type. A 1-sided p-value and corresponding 95% 2-sided confidence interval will be provided. Please note that the study is not powered for individual subgroups, but powered based on the overall number of the pooled patients across disease types. Thus, the p-values for the subgroup analyses are exploratory and should be interpreted with caution and clinical judgement.

Please note that patients who enter the study based solely on clinical criteria (even if later they are confirmed by genetic testing) will define the "clinically-defined" subgroup. Therefore, appropriate efficacy analysis by disease type subgroups will be performed based on clinically defined subgroup criteria.

3.8.2. Subgroup Analysis of Pediatric Subjects

Subgroup analysis on pediatric populations will be conducted. The subgroup analysis may be performed based on the following age (at informed consent) categories:

- Patients <12 years old (i.e., 6-11 years old)
- Patients <17 years old (i.e., 6-16 years old)

Analysis of the primary efficacy and key secondary efficacy endpoints may be repeated for these two subsets and presented separately. Between-treatment group analysis (setmelanotide vs placebo) within each age category on the secondary endpoints, i.e., mean percent change of weight and hunger score at ~14 week from baseline, may be conducted. [redacted] The number of the pediatric patients in the pivotal cohort may be small, so these subgroup analyses may combine pediatric patients from both pivotal and supplemental cohorts as necessary.

A 1-sided p-value and corresponding 95% 2-sided confidence interval will be provided. Please note that the study is powered based on the overall number of the pooled patients, thus the p-values for the subgroup analysis are exploratory and should be interpreted with caution and clinical judgement.

3.9. Withdrawals, Dropouts, Loss to Follow-up

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

- Non-adherence to study drug regimen or protocol requirements.
- Non-compliance with instructions or failure to return for follow-up.

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

Any patient that discontinues treatment prior to completing the study should be strongly encouraged to complete all remaining visits and procedures as outlined in the SOA, even if they are no longer receiving study drug.

In case of discontinuation, all AEs should be followed as described in Protocol Section 7.4; any skin AEs should continue to be followed, if at all feasible, for ~60-90 days to confirm near or complete resolution (as has been shown in previous studies).

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

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 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.

3.10.1. Analyses of Patients Who were Initially Randomized into Placebo Arm with Less than ~1 Year of Data at [redacted]

By nature of the study design (as introduced above in Section 1.2), a small percentage of patients who are randomized into the placebo arm may have less than ~52 weeks of setmelanotide treatment by the timing of the primary analysis (when the last patient enrolled has completed Period 2). Hence, the primary analysis will include a multiple imputation (MI) model (SAS PROC MI) that will be used to impute the measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximates 52 weeks of setmelanotide treatment. The final multiple imputed datasets will be analyzed using Rubin's rule (with SAS PROC MIANALYZE).

Due to the relatively small number of observation (i.e., number of patients) and large number of the visits (~15 protocol specified visits), there may not be enough observations to fit regression models in the multiple imputation. Therefore, protocol specified visits will be combined as appropriate, and the averaged values (across the combined visits) per the new derived Visit Categories (VC) will be used in the regression in the multiple imputation (SAS PROC MI). The multiple imputation model will contain the following new visit categories (VC) derived as follows:

- VC1=Average (V1, V2)
- VC2=Average of Scheduled Visits between VC1 and VC3
- VC3=Visit Occurring Closest to Day 98/14 Weeks within analysis window
- VC4=Average of Scheduled Visits between VC3 and VC5
- VC5=Visit Occurring Closest to Day 365/52 Weeks within analysis window
- VC6=Average of Scheduled Visits between VC5 and VC7
- VC7=Visit Occurring Closest to Day 462/66 Weeks within analysis window

Note, Early Termination visits will be treated as scheduled visits and may slot into any VC as fits criteria. Further, imputation of weight for 52 week analysis will focus on VC5 (for subjects initiated on active treatment) and VC7 (for subjects initiated on placebo) as these VCs are identified similarly, if not exactly, as the true timepoint would be identified, if it were not missing.

The above planned combination of the visits may be adjusted if the model cannot be fitted due to small sample size. Details will be defined in the ADRG.

Once VCs are identified, they will be time aligned by treatment arm before multiple imputation occurs.

That is, subjects initially randomized into the active treatment arm will have:

- VC1
- VC2
- VC3
- VC4
- VC5 (52 Weeks on Active Treatment)

While subjects initially randomized into the placebo arm will have:

- VC3
- VC4
- VC5
- VC6
- VC7 (52 Weeks on Active Treatment)

Monotone regression will then be used to impute the missing values, assuming proper missingness structure. The monotone regression method will impute 100 datasets. A seed of 2187 has been randomly generated and will be used.

Fully conditional specification (FCS) regression may be used in the case that monotone regression is deemed not appropriate.

Daily hunger scores will have weekly average hunger score calculated and these weekly averages mapped to Visit Categories with the same algorithm as above.

3.10.2. Approach on Missing Value Due to Other Reasons for ~52 Weeks Analysis

Every effort should be made to avoid missing values, but patients may have missing values due to other reasons such as lost to follow up, early dropout/discontinuation, missed visit, AEs etc. in addition to the administrative reason by the nature of the study design as described above. In these cases, the same principal and MI approach will be used for imputation of the missing value as outlined above. However, for the primary and key secondary analyses, these imputed values will then be replaced with the patient's baseline

value. This constitutes a treatment failure approach for these patients as the effective change and percent change from baseline will equate to 0. To assess the robustness of the analysis, a sensitivity analysis will also be conducted based on the imputed values themselves (no baseline replacement). For analyses outside of the primary and key secondary analyses, handling may differ based upon the analysis specified. Endpoints/analyses requiring imputations that are closely related to the primary or key secondary analyses will utilize the same handling as the primary and key secondary endpoints (baseline replacement). Other analyses utilizing imputation that are not closely related to the primary or key secondary analyses will utilize the values generated via multiple imputation and will not be replaced with baseline values. The specific handling for these analyses will also be outlined in the appropriate section below.

3.10.3. Approach on Missing Value in ~14-Week Placebo-Controlled, Double-Blinded Period (Period 1)

Patients may have missing values in Period 1 for many reasons such as drop out, early discontinuation, missed visits, or AEs etc. Missing values in this period will be imputed with a similar MI approach as 52 week analysis as defined in the primary imputation approach.

However, as this analysis revolves around 14 week timepoint, VC3 will be the focus of the imputation model. VC1, VC2, and VC3 will used in the multiple imputation model (SAS PROC MI) for 14 week timepoint with treatment group as a class factor. A sensitivity analysis may be conducted based on treatment failure approach on the missing value imputation for this period as appropriate.

3.11. Visit Windows

Every effort should be made to ensure that all visits occur according to the protocol SOA, including any dropouts. 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 is 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. Specific visit windows will be defined in a separate specification document. Windows around analysis time points will be outlined below. All available data will be listed for each subject.

3.11.1. Analysis Window for Primary Analysis (i.e., ~52-Week Treatment) at the End of Period 2

The primary analysis will occur after the last enrolled patient has completed Period 2. i.e., ~52 weeks of treatment. An +/- 2 months window will be used for the primary endpoint. If a patient has a missing measurement at ~52 weeks of setmelanotide treatment but does have another non-missing measurement within 10-14 months (40-56 weeks) of active setmelanotide treatment, the measurement closest to 52 weeks will be used. If a patient has two non-missing visits within this window that are equidistant from 52 weeks, the earlier visit will be used.

Given the fact that patients are staggered entering into the study and randomized into active treatment or placebo in the initial 14-week period, some patients will already have more than 1 year (i.e., 52 weeks) of active treatment at the time of the data cut for NDA submission (Primary Analysis). It is also likely that some other patients will have less than 1 year of active treatment.

The examples below help to illustrate the approach outlined above:

- Example 1: A patient who was initially randomized to setmelanotide arm in Period 1, but may have already had 15 months setmelanotide treatment and available data at the time of the primary analysis. The patient's primary endpoint will be defined as the closest one to 52-weeks of active treatment within the 10-14 months window.
- Example 2: A patient who was initially randomized to placebo in Period 1 but may have already been in the study for 15 months, having received 3 months of placebo then 12 months of active setmelanotide. The patient's primary endpoint will be defined as the closest one to 52-weeks of active treatment within the 10-14 month window.
- Example 3: A patient who was initially randomized to placebo in Period 1 but may have been in the study for only 10 months, having received 3 months placebo then 7 months of active setmelanotide. The patient's primary endpoint will be defined as the patients ~12 months active treatment measurement as generated via multiple imputation method described above, since the patients active setmelanotide treatment duration is less than 10 months.
- Example 4: A patient who was initially randomized to placebo in Period 1 but may have been in the study for 14 months, having received 3 months placebo then 11 months of active setmelanotide. The patient's primary endpoint will be defined as the closest done to 52-weeks of active treatment within the 10-14 months window.

There are two planned visits in Period 3 (14-week open-label treatment): Visit 14 (~Week 60) and Visit 15 (EOS, ~Week 66). The analyses and summaries on data collected in this period will not be a main priority of the primary analysis for NDA submission or analyses in other regulatory agencies. However, an additional supportive analysis may be provided on these data after the approximately last patient in pivotal cohort completes the last visit at the end of period 3.

The additional supportive analysis and summary at end of period 3 will be based on relative visits/days (i.e., staggered alignment) from the first dose of the setmelanotide, below examples illustrate the staggered alignment for analysis,

- V2 (Week 1) of patients initially randomized in setmelanotide group (planned first dose visit of setmelanotide) will align with V6 (Week 15) of patients initially randomized in placebo group (i.e, planned first dose visit of setmelanotide).
- V13 (Week 53) of patients initially randomized in setmelanotide group (~52 week visit on setmelanotide) will align with V15 (Week 66) of patients initially randomized in placebo group (i.e, ~52 weeks visit on setmelanotide).
- Other visits will be aligned in a similar fashion.

3.11.2. Analysis Window for 14 Week Analysis

A +/-1-month (4-week) window will be used for the analysis and summary of the 14-week endpoints.

3.12. Interim Analyses and Timing of Planned Analyses

No formal interim analysis is currently planned for this study. However, various data cuts may occur in support of regulatory submissions such as a New Drug Application. 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.

The timing of the planned analyses:

[redacted]

- [redacted]

4. STUDY ANALYSES

4.1. Subject Disposition

Subject disposition will be tabulated and include the number screened, the number randomized, the number treated in total, the number dosed with setmelanotide, the number dosed with placebo, the number in each subject population for analysis, and the number who withdrew prior to completing the study and reason(s) for withdrawal.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented. Subject disposition will include patients in the Screening Analysis Set.

4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized and presented by randomized treatment group and overall. Age at baseline as well as height, weight, and BMI at baseline and initiation of active treatment will be summarized using descriptive statistics (N, mean, 95% confidence interval of the mean, SD, median, minimum, and maximum). The number and percentage of subjects in each sex, ethnicity, race, and clinically- or genetically-defined genetic deficiency categories (BBS; all AS patients were required to be genetically identified to enter the trial) also will be presented. The percentage of cognitively impaired subjects will be provided. The Fitzpatrick Classifications Scale will also be summarized. No formal statistical comparisons will be performed. Subject demographics will include patients in the Safety Analysis Set. A separate demographics summary will be created for patients ≥12 years of age in the Full Analysis Set.

Medical history will be summarized in a table and presented in a by-patient listing.

4.3. Efficacy Analyses

In general, efficacy analyses will be conducted using the FAS population. Additional supportive analysis based on the DUS, CS, and/or PP Sets etc. may be provided as appropriate. Unless stated otherwise, all the analysis on hunger score data will be based on patients ≥12 years of age while only descriptive summary will be provided for patients <12 years of age (due to the different hunger score questionnaire tools). Descriptive statistics for endpoints analyzed at ~52 weeks will have their visits aligned by approximate relative day on setmelanotide (active treatment visit).

4.3.1. Primary Efficacy Analysis

The primary efficacy analysis on the primary efficacy endpoint will be conducted in patients ≥12 years of age (at informed consent) in the FAS population.

The primary efficacy endpoint is the proportion of patients (≥12 years of age) who achieve a ≥10% reduction in body weight from baseline after ~52 weeks of treatment. The null hypothesis (H0) to be tested is that the proportion of patients treated for ~52 weeks who achieve ≥10% reduction in body weight from baseline is less than or equal to a historical control rate of 10%. The alternative hypothesis (H1) is that the proportion is greater than a historical control rate of 10%:

H0: $p_t \leq 10\%$ vs H1: $p_t > 10\%$

where p_t is the response rate after ~52 weeks of treatment.

Please note that there are two different uses of "10%" above, which is explained here for clarity:

- The use of "10%" in the endpoint definition is the **response criteria** for an individual patient. If a patient achieves a ≥10% reduction from baseline in body weight, the patient will be categorized as a responder in this analysis. Otherwise, the patient will be categorized as a non-responder.
- The use of "10%" as the historical control **rate** is the historical reference/control response rate to be statistically compared to the observed response rate in patients treated with setmelanotide. The observed response **rate** of setmelanotide will be calculated with the number of responders (using the above 10% endpoint definition) divided by the number of total patients.

[redacted]

The primary endpoint will have binomial proportions calculated for each of the 100 imputed datasets. The outcomes from the 100 imputed datasets will be combined using Rubin's Rule to provide an overall estimate against the null hypothesis with corresponding confidence intervals and p-value (Little and Rubin, 2002). The 1-sided 0.025 significant level was chosen based on the small sample size due to the rarity of the disease. The success criterion for the primary hypothesis requires the rejection of the null hypothesis at the 1-sided 0.025 significance level. The statistical criterion corresponds to the 2-sided 95% CI for setmelanotide of the response rate excluding 10% (i.e., lower bound of the CI >0.10).

This analysis may be repeated on the following analysis sets: DUS, PP at EOP2, SH, AG, as appropriate.

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

Descriptive statistics for the change and percent change from baseline in body weight (kg) may be presented in the FAS population by active treatment visit.

4.3.2. Key Secondary Efficacy Analyses

Statistical testing will be performed on the key secondary efficacy endpoints according to the

following hierarchical order. Where applicable, the secondary endpoint will be compared against the null hypothesis for each of the 100 imputed datasets. The outcomes from the 100 imputed datasets will be combined using Rubin's Rule to provide a p-value and corresponding confidence interval as appropriate.

Body Weight Percent Change from Baseline in Patients ≥ 12 Years of Age:

Mean percent change from baseline in body weight for patients in the FAS population will be analyzed after ~52 weeks of treatment. Analyses will be based on a one-sample t-test for each of the 100 imputed datasets and assuming mean percent change from baseline in bodyweight of zero. The outcomes from the 100 imputed datasets will be combined using Rubin's Rule to provide a p-value and corresponding confidence intervals. This will be evaluated at a 1-sided, 0.025 significance level.

Sensitivity analysis based on the DUS population may be provided as needed.

Descriptive statistics for the change and percent change from baseline in body weight (kg) may be presented in the FAS population by active treatment visit.

Daily Hunger Score Percent Change from Baseline in Patients ≥ 12 Years of Age:

Mean percent change from baseline in the weekly average of the daily hunger scores for patients in FAS population will be analyzed after ~52 weeks of treatment. Analyses will be based on a one-sample t-test for each of the 100 imputed datasets with assumed mean percent change from baseline in weekly average of daily hunger scores of zero. The outcomes from the 100 imputed datasets will be combined using Rubin's Rule to provide a p-value and corresponding confidence intervals. This will be evaluated at a 1-sided, 0.025 significance level.

Prior to analysis, daily hunger scores for each of the 3 hunger assessments will be averaged separately 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. [redacted] Rhythm believes that the 1 out of 7 days approach will largely prevent missing data and best utilize the data points available. Unless specified otherwise, this will be applicable for all hunger score related analysis.

Sensitivity analysis based on the DUS population may be provided as needed.

Descriptive statistics for the change and percent change from baseline in weekly average of daily hunger scores may be presented based on FAS population by active treatment visit.

Daily Hunger Score Reduction (Threshold of 25%) in Patients ≥ 12 Years of Age:

The proportion of patients in the FAS population who achieve a ≥25% improvement from baseline in the weekly average of the daily hunger score after ~52 weeks of treatment will be analyzed similarly to the primary efficacy endpoint. Prior to analysis, daily hunger scores for each of the 3 hunger assessments will be averaged separately by week, as outlined above.

Descriptive statistics for the change and percent change from baseline in weekly average of daily hunger scores will be presented based on FAS population for analysis visits. Due to the

suitability of using the hunger score tool in younger patients, this will be conducted in patients >=12 years of age at baseline.

4.3.3. Other Secondary Efficacy Analyses of the 14-week, placebo-controlled period

These analyses will be performed on patients in the PCS population, (i.e., on data from the ~14-week, placebo-controlled, randomized, double-blinded period, or Period 1). Where applicable, the secondary endpoint will be compared against the null hypothesis for each of the 100 imputed datasets. The outcomes from the 100 imputed datasets will be combined using Rubin's Rule to provide a p-value and corresponding confidence interval as appropriate.

[redacted]

Body Weight Percent Change from Baseline at 14 Weeks:

The analysis on this secondary endpoint will be a between-group comparison to investigate if setmelanotide-treated patients (≥ 12 years old) exhibit a greater decrease in percent change in body weight from baseline at ~14 weeks of therapy, as compared to placebo-treated patients.

This analysis will be based on a two-sample t-test for each of the 100 imputed datasets. The outcomes from the 100 imputed datasets will be combined using Rubin's Rule to provide a p-value and corresponding confidence intervals. This will be evaluated at a 1-sided, 0.025 significance level.

Sensitivity analyses based on PP at EOP1 and CS may be provided.

Descriptive statistics for the change and percent change from baseline in body weight (kg) may be presented for the PCS population by visit by randomized treatment.

Daily Hunger Score Percent Change from Baseline at 14 Weeks

The analysis on this secondary endpoint will be a between group comparison to investigate if setmelanotide-treated patients exhibit a greater improvement from baseline at ~14 weeks of therapy in weekly average of daily hunger scores, as compared to placebo-treated patients. This analysis will be based on a two-sample t-test for each of the 100 imputed datasets. The outcomes from the 100 imputed datasets will be combined using Rubin's Rule to provide a p-value and corresponding confidence intervals. This will be evaluated at a 1 sided, 0.025 significance level.

Prior to analysis, daily hunger scores for each of the 3 hunger assessments will be averaged separately by week, as outlined above. Sensitivity analyses based on PP at EOP1 and CS may be provided.

Descriptive statistics for the change and percent change from baseline in weekly average of daily hunger scores may be presented based on the PCS population by visit by randomized treatment. Due to the suitability of using the hunger score tool in younger patients, this will be conducted in patients >=12 years of age at baseline.

4.3.4. Sensitivity Efficacy Analyses

Non-Replacement Analysis:

In order to look at the impact of missing weight data on the proportion of patients (≥12 years of age) who achieve a ≥10% reduction in body weight from baseline and percent change from baseline after ~52 weeks of treatment, a non-replacement analysis may be done. For the primary analysis and key secondary analyses, patients who have missing 52 week weight data due to nature of study design will utilize the MI imputed 52 week values (described in the above Section 3.10.1) but patients who have missing 52 week data for any other reason will be considered treatment failures (including change and percent change from baseline set to 0). For this sensitivity analysis to be performed on primary and key secondary endpoints, all patients who have missing 52 week data, regardless of the cause, will have their MI imputed 52 week values used and no values will be set to baseline. Similar to the primary and key secondary analyses, this sensitivity analysis will generate 100 imputed datasets as appropriate and the outcomes from the 100 imputed datasets will be combined using Rubin's Rule to provide a p-value and corresponding confidence intervals.

Active Treatment-Completer's Analysis:

In order to look at the impact of missing weight data on the proportion of patients (≥12 years of age) who achieve a ≥10% reduction in body weight from baseline and percent change from baseline after ~52 weeks of treatment, a placebo-completer's analysis may be done. For the primary analysis and key secondary analyses, patients who have missing 52 week weight data due to nature of study design will utilize the MI imputed 52 week values (described in the

above Section 3.10.1) but patients who have missing 52 week data for any other reason will be considered treatment failures (including change and percent change from baseline set to 0). For this sensitivity analysis to be performed on primary and key secondary endpoints, the same data handling will apply, however, placebo-subjects who did not complete 52 weeks of setmelanotide treatment due to the administrative data cut will be excluded. Similar to the primary and key secondary analyses, this sensitivity analysis will generate 100 imputed datasets as appropriate and the outcomes from the 100 imputed datasets will be combined using Rubin's Rule to provide a p-value and corresponding confidence intervals.

Daily Hunger:

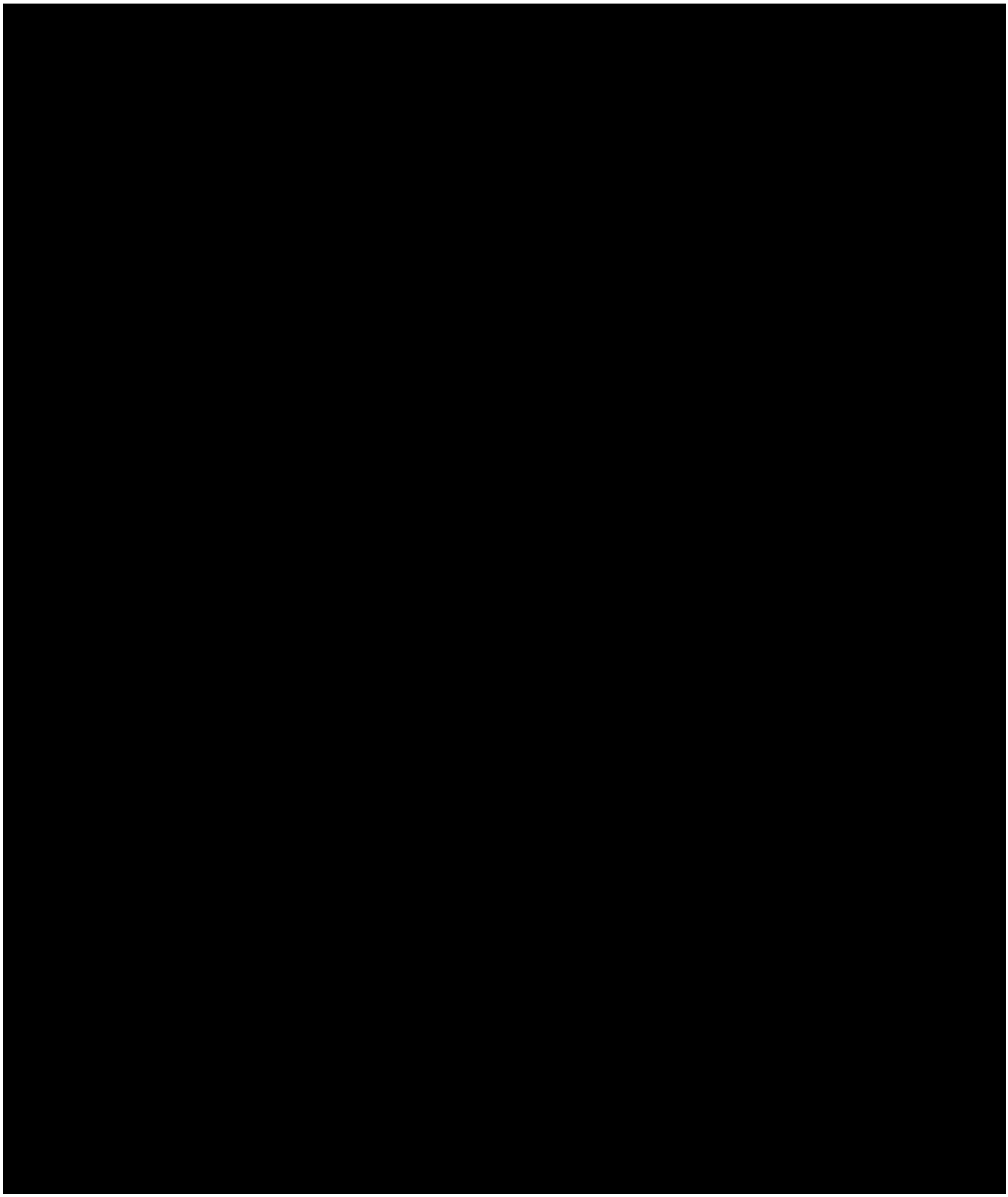
In order to look at the impact of missing hunger data, a sensitivity analysis may be done to examine if there are any differences in conclusions drawn by data availability; analysis for daily hunger scores will be repeated for patients with at least 3 of 7 days of data present. No imputations will be made for missing data.

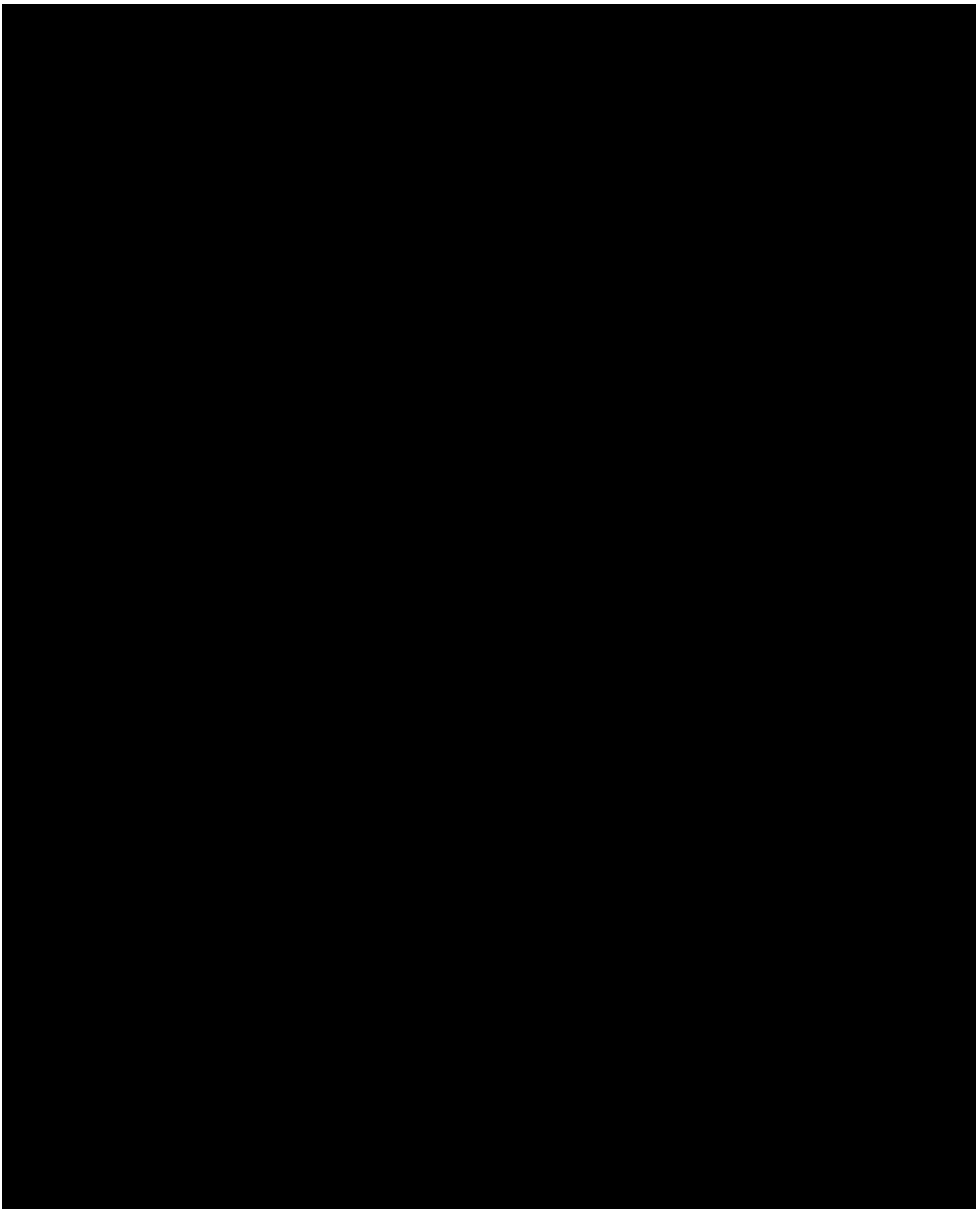
Treatment Failure Analysis:

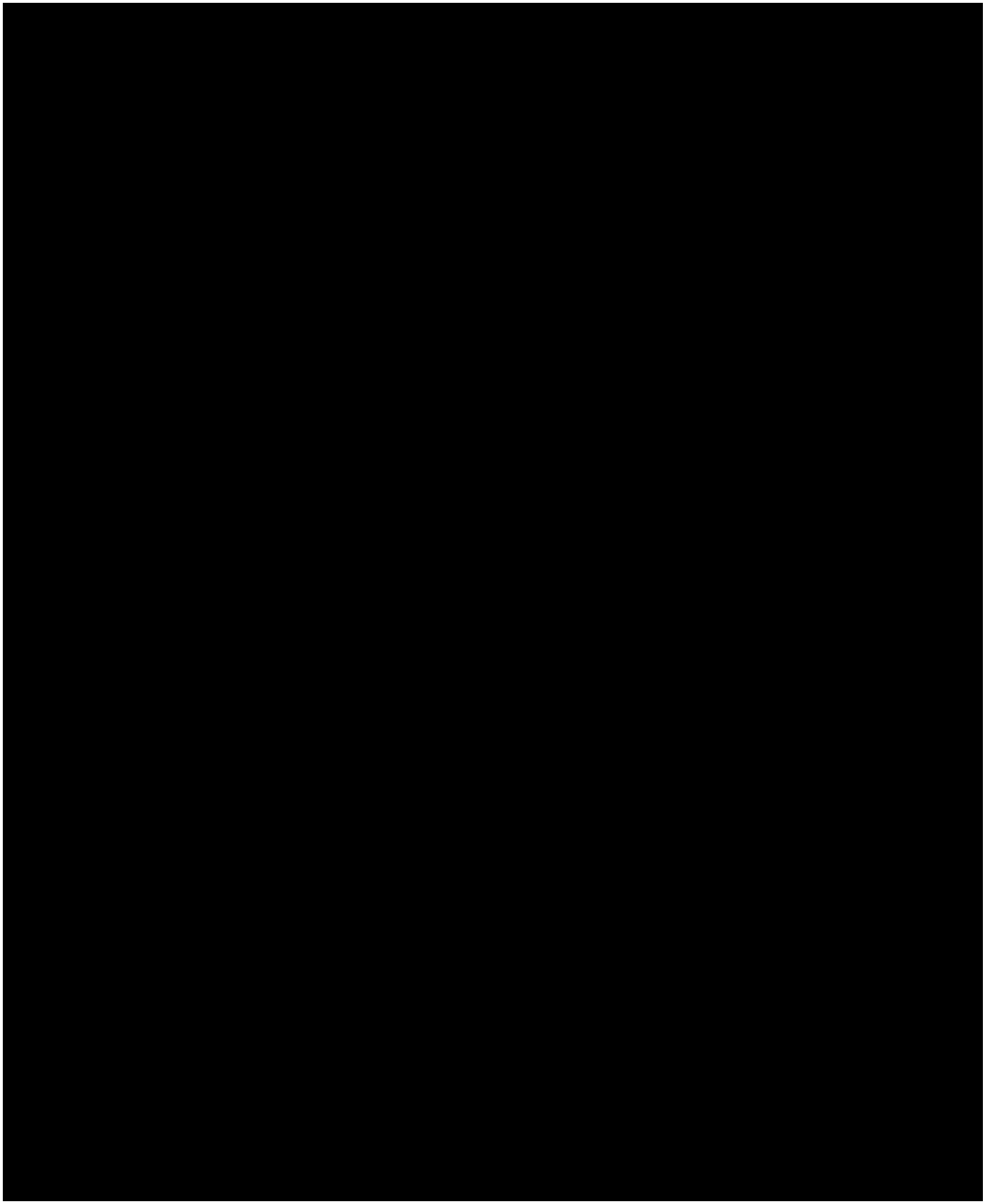
In order to look at the impact of missing data on the comparisons between setmelanotide-treated patients and placebo patients after ~14 weeks of treatment, a sensitivity failure analysis may be done. For the non-key, secondary endpoints, patients who have missing 14 week data will be considered treatment failures. Similar to the secondary analyses, this sensitivity analysis will be based on a two-sample t-test for each of the 100 imputed datasets. The outcomes from the 100 imputed datasets will be combined using Rubin's Rule to provide a p-value and corresponding confidence intervals.

4.4. [redacted]

[redacted]







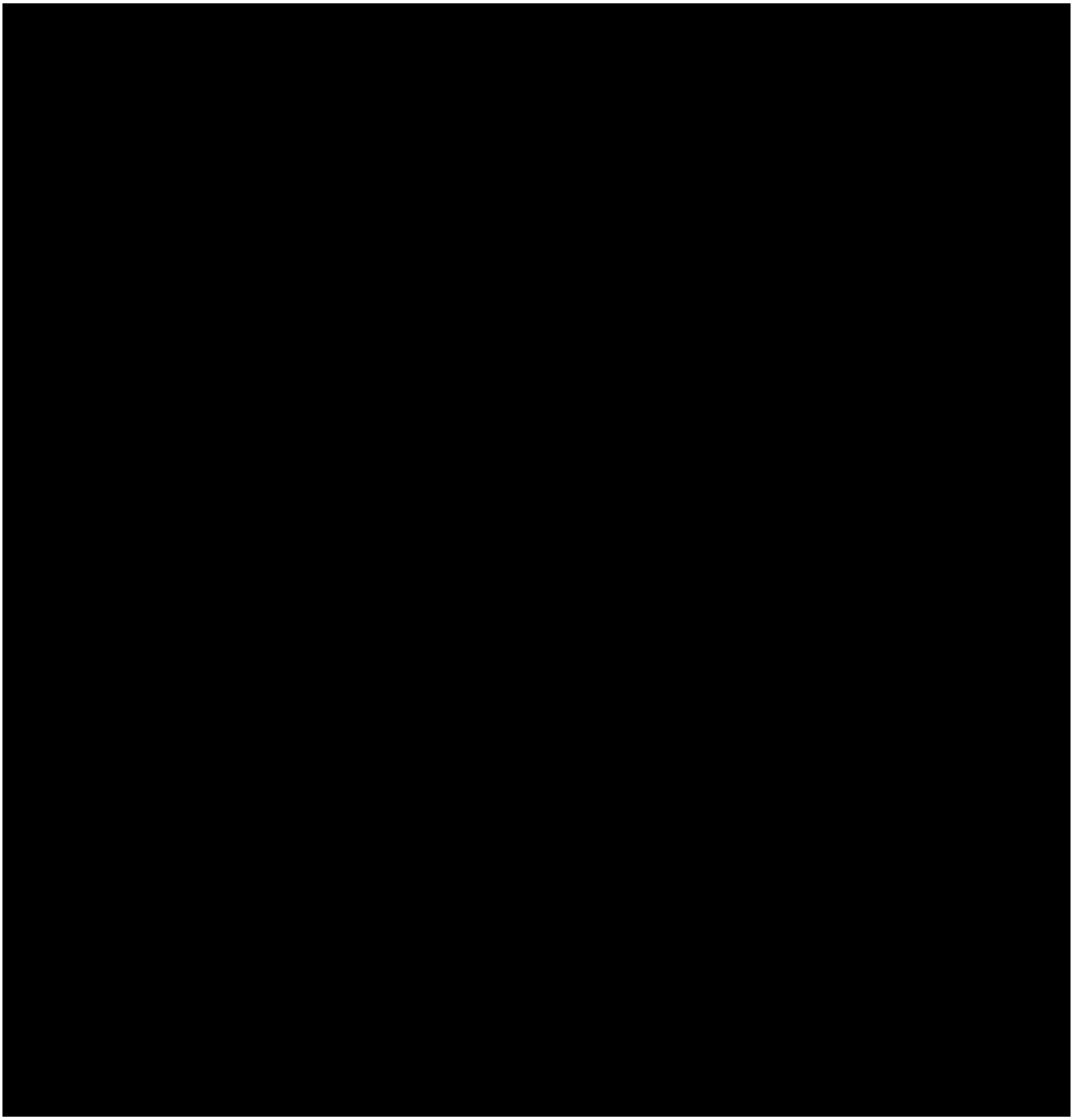


Table 3 Summary of Core Analysis Elements

Endpoints	Analysis Set [1] Primary (Sensitivity)	Main Patient Group	Baseline[2]	Subgroup Analysis
Primary				
Proportion of patients who achieve a ≥10% reduction from baseline in body weight after ~52 weeks of treatment	FAS (SH, AG, PP at EOP2)	≥12 years old	ATB	BBS, AS, <12 yo, <17 yo
Key Secondary (after ~52 weeks of treatment)				
Mean percent change from baseline in body weight	FAS (DUS)	≥12 years old	ATB	BBS, AS, <12 yo, <17 yo
Mean percent change from baseline in the weekly average of the daily hunger score	FAS (FAS: 3/7 daily responses, DUS)	≥12 years old	ATB	BBS, AS, <12 yo
Proportion of patients who achieve a ≥25% improvement in the weekly average of the daily hunger score	FAS (FAS: 3/7 daily responses)	≥12 years old	ATB	BBS, AS
Secondary (at the Week 14 visit)				
Mean percent change from baseline in body weight after treatment with setmelanotide as compared with placebo	PCS (PP at EOP1, CS)	≥12 years old	PCPB	BBS, AS, <12 yo, <17 yo
Mean percent change from baseline in the weekly average of the daily hunger score after treatment with setmelanotide as compared with placebo	PCS (PP at EOP1, CS, PCS: 3/7 daily responses)	≥12 years old	PCPB	BBS, AS, <12 yo

Endpoints	Analysis Set [1] Primary (Sensitivity)	Main Patient Group	Baseline[2]	Subgroup Analysis
[redacted]				

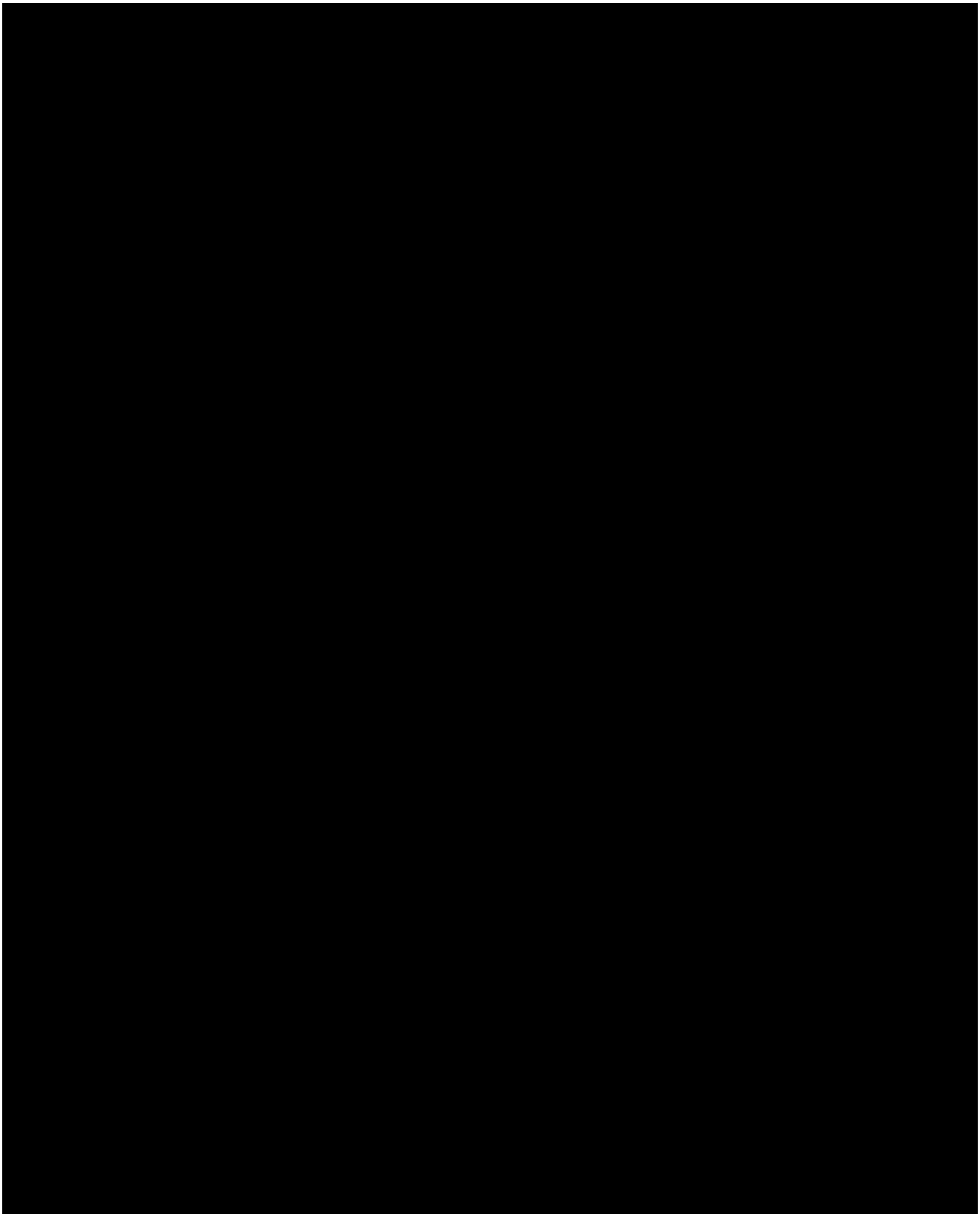
Endpoints	Analysis Set [1] Primary (Sensitivity)	Main Patient Group	Baseline[2]	Subgroup Analysis
[redacted]				

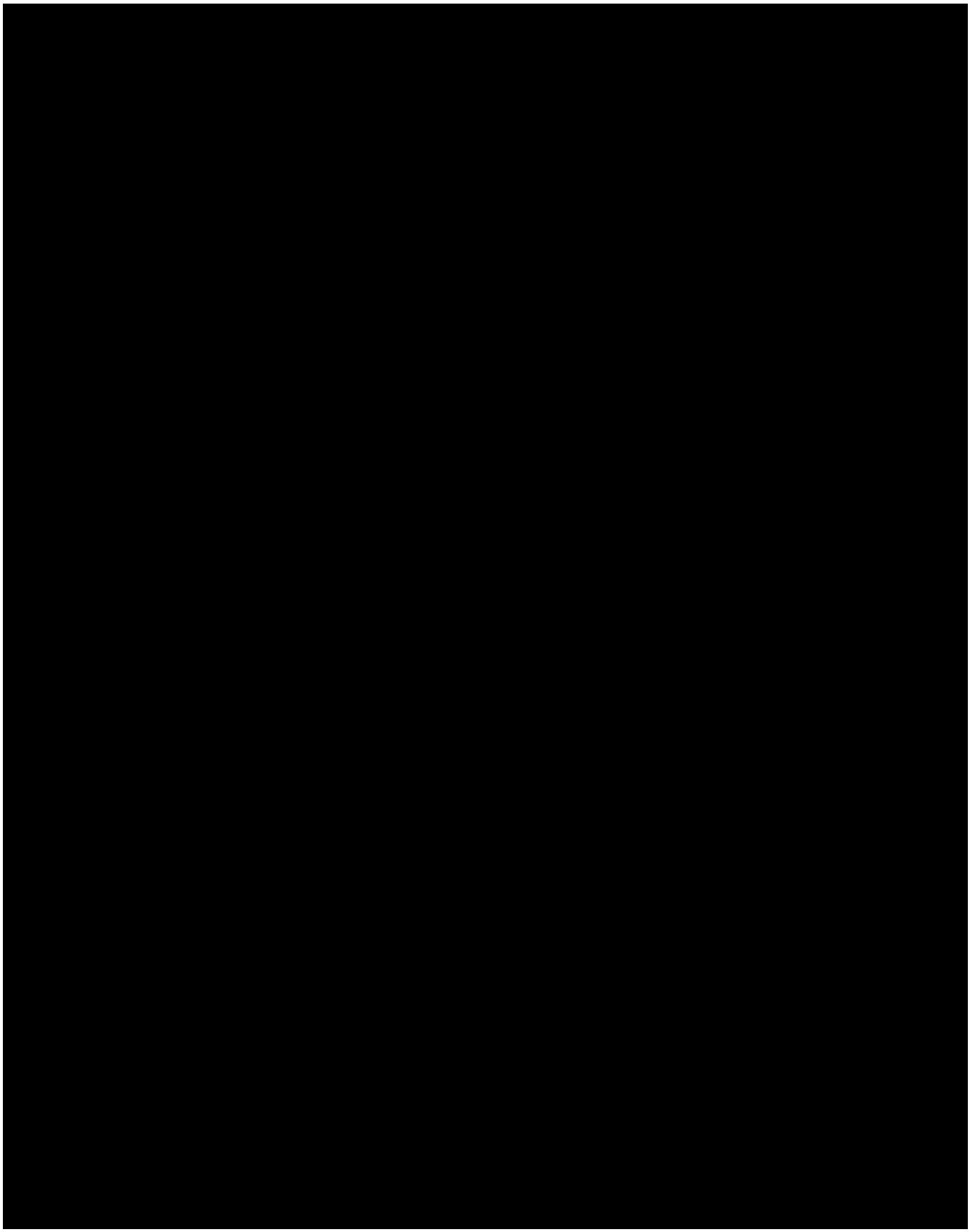
Endpoints	Analysis Set [1] Primary (Sensitivity)	Main Patient Group	Baseline[2]	Subgroup Analysis
[redacted]				

Notes:

(1): FAS = Full Analysis Set; DUS = Designated Use Set; PCS = ~14 Week Placebo-controlled Analysis Set; CS = Completers Set; SH = Stable Height Analysis Set; AG = Active Growth Analysis Set; PP at EOP1 = Per-Protocol Set at End of Period 1; PP at EOP2 = Per-Protocol Set at End of Period 2; (see definition in Section 2.1)

(2): PCPB = Placebo-controlled period baseline; ATB = Active treatment baseline (see definition in Section 3.4)





4.7. Early Analyses on the ~14 Week Placebo-Controlled, Double-Blinded, Randomized Period (Period 1)

The study has a ~14 week placebo-controlled, double-blinded and randomized period (Period 1). Analysis of Period 1 data at an early but appropriate time may be useful in planning additional clinical studies both in the same population as well as in other rare genetic disorders of obesity. Hence, Rhythm may consider the following approach to this data as it is expected every pivotal patient will have completed Period 1 by approximately the end of 1Q2020.

The data on the ~14 weeks placebo-controlled period will be cleaned and finalized. Then, once clean and finalized, in a blinded fashion, an analysis on the Period 1 secondary efficacy endpoints and specified safety analysis below may be conducted by a separate independent statistician group otherwise unrelated to the study (e.g., by a separate team at Rhythm's outside statistical designated vendor). The results of this analysis will not be released or shared with any Rhythm personnel, or anyone connected with the study, until the last pivotal patient enrolled has completed Period 2 (~52 weeks of treatment), at the time of the primary analysis.

If conducted, no change in the conduct of this study will be made and any conclusions will be used to plan and initiate additional clinical studies. In addition, all analyses will only include group-mean data results, with no information on any individual patient data.

Rhythm does not expect any bias to be introduced or any impact on the type 1 error since the group-mean data will not be available until the study is completed through the end of Period 2. Selected safety summaries will also be provided for this 14-week, placebo-controlled, double-blinded, randomized period (Period 1).

The below selected summaries may be provided for this analysis:

- Disposition and drug compliance to be summarized by group.
- Group mean efficacy to be analyzed for the two secondary endpoints as planned in Section 4.3.3 (Other Secondary Endpoint Section).
- [redacted]

5. [redacted]

- [redacted]
- [redacted]
- [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.

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