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: NCT03746522

Date: August 14, 2018

CLINICAL STUDY PROTOCOL

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

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

[redacted]

Study Sponsor: Rhythm Pharmaceuticals, Inc.
500 Boylston Street, 11th Floor
Boston, MA 02116, USA
Telephone: 857.264.4282
Fax: 857.264.4299

Sponsor Signatory: [redacted]

Document Version (Date): 1.0 (August 14, 2018)

CONFIDENTIALITY NOTE

APPROVAL SIGNATURE PAGE

Protocol Title: 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

REVIEWED/APPROVED BY:

[redacted] [redacted] 14 Aug 2018

Rhythm Pharmaceuticals, Inc. Date

INVESTIGATOR STATEMENT

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

This study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB)/Ethics Committee (EC). No changes will be made to the study protocol without the prior written approval of Rhythm and the IRB/EC, except where necessary to eliminate an immediate hazard to the patient.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Investigator Name	Investigator Signature	Date

Investigational site or name of institution and location (printed)

CLINICAL STUDY SYNOPSIS

Sponsor	Rhythm Pharmaceuticals, Inc.

Investigational Drug Product

Setmelanotide (RM-493, Melanocortin-4 Receptor Agonist)

Protocol Number

RM-493-023

Protocol Title

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

Clinical Phase

Pivotal Phase 3

Treatment Indication

Treatment of obesity and hyperphagia in patients with BBS or AS

Investigator Study Sites

This study will be conducted at approximately 10 study sites located in the United States and Europe

Objective(s)

Primary

- To assess the effect of setmelanotide on the proportion of patients (≥12 years of age at baseline) treated with setmelanotide for approximately (~) 52 weeks who achieve a clinically meaningful reduction from baseline (ie, ≥10%) in body weight.

Key Secondary

- To assess the effect of setmelanotide on the proportion of all patients who achieve a ≥10% reduction from baseline in body weight after ~52 weeks of treatment with setmelanotide.
- To assess the effect of setmelanotide on mean percent change in body weight (in patients ≥12 years of age at baseline) compared with baseline after ~52 weeks of treatment with setmelanotide..
- To 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 with setmelanotide.
- To 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 with setmelanotide.

Other Secondary

- 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.
- To 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) at the Week 14 visit compared with placebo.
- To 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.

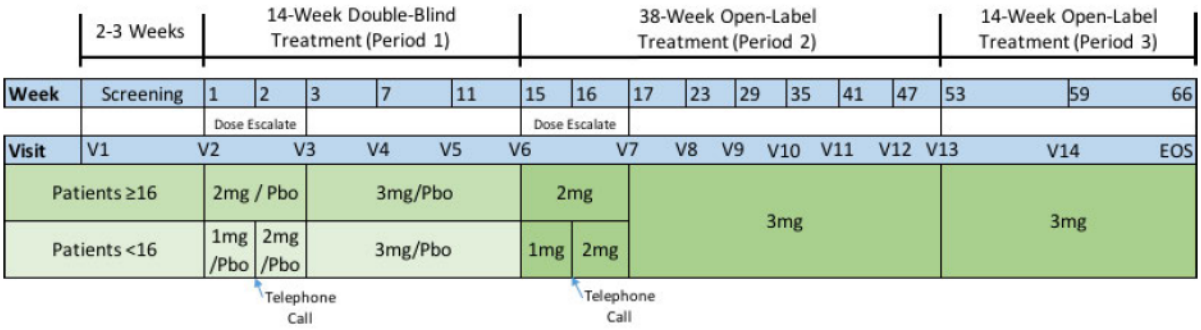
Methodology

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 Study Schematic below). 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 Period 2. To maintain the blind through Period 2, upward dose escalation to a fixed dose of 3 mg will be performed during the first 2 weeks of 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 of age) 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 1 mg setmelanotide 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 the schematic below.

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-titrated 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 Period 2. In Period 3, patients will be evaluated every 7 weeks.



Study assessments will be performed at the times specified in the Schedule of Assessments (SOA). Efficacy assessments will include: body weight; BMI; hunger; body composition, including [redacted]

As required in the United States (US) by the Food and Drug Administration (FDA), for clinical trials of central nervous system (CNS)-acting obesity medications, [redacted]

Primary and Secondary Endpoints

The primary endpoint is:

- The proportion of patients (≥12 years of age at baseline) who achieve a ≥10% reduction from baseline in body weight (ie, are 'responders') after ~52 weeks of treatment with setmelanotide.

The key secondary endpoints are:

- The proportion of all patients, regardless of age at baseline, who achieve a ≥10% reduction from baseline in body weight (ie, are 'responders') after ~52 weeks of treatment with setmelanotide.
- Mean percent change from baseline in body weight (in patients ≥12 years of age at baseline) after ~52 weeks of treatment with setmelanotide.
- 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 with setmelanotide.
- 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 with setmelanotide.

Other secondary endpoints are:

- Mean percent change from baseline in body weight (in patients ≥12 years of age at baseline) at the Week 14 visit compared with placebo.
- 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) at the Week 14 visit compared with placebo.
- 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.

Number of Patients

It is anticipated that approximately 30 patients (including at least 20 with BBS and at least 6 with AS) will be enrolled and randomized across approximately 10 centers worldwide.

Inclusion Criteria

A patient must meet all of the following criteria to be eligible for this study (refer to Section 4.1 of the protocol body for potential exceptions, given the ultra-rare nature of these diseases and the associated challenges with patient identification and recruitment).

1. BBS clinical diagnosis as per Beales, 1999 (with either 4 primary features or 3 primary and 2 secondary features from table below)

Bardet-Biedl Syndrome	
Primary Diagnostic Criteria	
• Rod cone dystrophy	• Learning disabilities
• Polydactyly	• Hypogonadism in males
• Obesity	• Renal anomalies
Secondary Diagnostic Criteria	
• Speech disorder/delay	• Mild spasticity (especially lower limbs)
• Strabismus/cataracts/astigmatism	• Diabetes mellitus
• Brachydactyly/syndactyly	• Dental crowding/hypodontia/small roots/high arched palate
• Developmental delay	• Left ventricular hypertrophy/congenital heart disease
• Polyuria/polydipsia (nephrogenic diabetes insipidus)	• Hepatic fibrosis
• Ataxia/poor coordination	
Source: Beales 1999	

or AS diagnosis as per Marshall, 2007 (using major and minor age adjusted criteria in the table below).

Alström Syndrome		
Diagnostic Criteria		**Minimum Required**
Major	**Minor**	
For patients 6 to ≤14 years of age		
• Mutation of *ALMS1* and/or family history of AS • Vision (nystagmus, photophobia, diminished acuity, if old enough for testing: cone dystrophy by ERG)	• Obesity and/or insulin resistance and/or T2DM • History of DCM/CHF • Hearing loss • Hepatic dysfunction • Renal failure • Advanced bone age	2 major criteria ***or*** 1 major and 3 minor criteria
For patients ≥15 years of age		
• Mutation of *ALMS1* and/or family history of AS • Vision (history of nystagmus in infancy/childhood, legal blindness, cone and rod dystrophy by ERG)	• Obesity and/or insulin resistance and/or T2DM • History of DCM/CHF • Hearing loss • Hepatic dysfunction • Renal failure • Short stature • Males: hypogonadism • Females: irregular menses and/or hyperandrogenism	2 major and 2 minor criteria ***or*** 1 major and 4 minor criteria
Source: Marshall 2007		
Abbreviations: CHF = congestive heart failure; DCM = dilated cardiomyopathy; ERG = electroretinography; T2DM = Type 2 diabetes mellitus		

- *Note*: at least 90% of patients with BBS and 100% of patients with AS must have genetically confirmed diagnosis at the time of enrollment
  - A genetically confirmed diagnosis of BBS is defined as a homozygous or compound heterozygous loss-of-function mutation in BBS genes; patients without a genetically confirmed BBS diagnosis must be reviewed with the Sponsor's medical monitor prior to enrollment.
  - A genetically confirmed diagnosis of AS is defined as a homozygous or compound heterozygous loss-of-function mutation in the *ALMS1* gene

  Once 10% of patients without a genetically confirmed BBS diagnosis have been enrolled in the study, sites will be notified that only genetically confirmed BBS patients may be enrolled.

2. ≥6 years of age.
3. Obese, defined as BMI ≥30 kg/m^2 for patients ≥16 years of age or weight >97th percentile for age and sex on growth chart assessment for patients 6 to 15 years of age.
4. Study participant and/or parent or guardian is able to communicate well with the Investigator, to understand and comply with the requirements of the study, and is able to understand and sign the written informed consent/assent.
5. Female participants of child-bearing potential must be confirmed non-pregnant and agree to use contraception as outlined in the protocol. Female participants of non-childbearing potential, defined as: surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation), post-menopausal for at least 12 months (and confirmed with a screening follicle stimulating hormone (FSH) level in the post-menopausal lab range), or failure to have progressed to Tanner Stage V and/or failure to have achieved menarche, do not require contraception during the study.
6. Male participants with female partners of childbearing potential must agree to use a double barrier method contraception if they become sexually active during the study or within 90 days following their participation in the study. Male patients must also not donate sperm during and for 90 days following their participation in the study.

Exclusion Criteria

A patient who meets any of the following criteria will be excluded from this study (refer to Section 4.1 of the protocol body for potential exceptions, given the ultra-rare nature of these diseases and the associated challenges with patient identification and recruitment)

1. Recent intensive (within 2 months) diet and/or exercise regimen with or without the use of weight loss agents (including herbal medications) that has resulted in >2% weight loss. These patients may be reconsidered approximately 1 month after cessation of such intensive regimens.
2. Current or prior (within prior 2 months) use of any medication, including those approved to treat obesity, that could impact the efficacy results of this study (eg, orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion, liraglutide). Patients on a stable dose and regimen (for at least 2 months) of medication to treat attention deficit hyperactivity disorder (ADHD) may be enrolled in the study as long as they agree to remain on the same dose and regimen during the study.
3. Prior gastric bypass surgery resulting in >10% weight loss durably maintained from the baseline pre-operative weight with no evidence of weight regain. Specifically, patients may be considered if surgery was not successful, resulted in <10% weight loss compared to pre-operative baseline weight, or there is clear evidence of weight regain after an initial response to bariatric surgery. All patients with a history of bariatric surgery must be discussed with, and receive approval from, the Sponsor prior to enrollment.
4. Diagnosis of schizophrenia, bipolar disorder, personality disorder or other Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V) disorders that the Investigator believes will interfere significantly with study compliance. Neurocognitive disorders affecting ability to consent will not be disqualifying as long as an appropriate guardian able to give consent has been appointed.
5. In patients with no significant neurocognitive deficits:
   - A Patient Health Questionnaire-9 (PHQ-9) score of ≥15 and/or
   - Any suicidal ideation of type 4 or 5 on the C-SSRS, any lifetime history of a suicide attempt, or any suicidal behavior in the last month.
6. Current, clinically significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor to determine eligibility.
7. History of significant liver disease or liver injury, or a current liver assessment due to abnormal liver tests (as indicated by abnormal liver function tests, alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase, or serum bilirubin >1.5× the upper limit of normal [ULN] for any of these tests) for an etiology other than non-alcoholic fatty liver disease (NAFLD). Thus, any underlying etiology besides NAFLD, including diagnosed non-alcoholic steatohepatitis (NASH), other causes of hepatitis, or history of hepatic cirrhosis is exclusionary, but the presence of NAFLD is not be exclusionary.
8. Moderate to severe renal dysfunction as defined by the Cockroft Gault equation <30 mL/min. .
9. History or close family history (parents or siblings) of skin cancer or melanoma (excluding non-invasive basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.
10. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of comprehensive skin evaluation performed by a qualified dermatologist during screening. Any concerning lesions identified during the screening period will be biopsied and results must be known to be benign prior to enrollment. If the pre-treatment biopsy results are of concern, the patient should be excluded from the study.
11. Patient is, in the opinion of the Study Investigator, not suitable to participate in the study.
12. Participation in any clinical study with an investigational drug/device within 3 months prior to the first day of dosing.
13. Significant hypersensitivity to study drug.
14. Inability to comply with the QD injection regimen.

Study Drug and Administration

All study drug (active and placebo) is for investigational use only and is to be used only within the context of this protocol. Active study drug, setmelanotide, and placebo will be supplied by the Sponsor.

Setmelanotide drug product (setmelanotide mPEG-DSPE formulation) is a sterile solution for injection. The product is manufactured at a concentration of 10.0 mg/mL.

Placebo is vehicle only and is identical in appearance to active treatment.

Setmelanotide and placebo will be administered as SC injection QD.

There will be extensive training of patients in drug administration including educational materials. Study-specific training materials will be provided to both the investigative staff and study participants and caregivers. Home nurses will be available, as needed, for additional training and to reinforce compliance. The Sponsor will provide extra placebo supplies for use during training.

Statistical Considerations

The primary statistical hypothesis is that the proportion of patients who are treated with setmelanotide for ~52 weeks who achieve ≥10% reduction from baseline in body weight is greater than a historical control rate of 10% in the ≥12 years old Full Analysis Set (≥12 yo FAS) (see definition in Section 8.2).

Data from the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS) were used to provide input for the sample size/power calculations. In particular, the natural history responder rate (percent of patients with weight loss ≥10% over a 1-year period) was assessed to determine the power estimates for the primary efficacy endpoint (see details in Section 8). The sample size is mainly driven by the primary hypothesis; although the rarity of the population is also taken into consideration.

Data from CRIBBS suggest that the proportion of subjects ≥12 years old who had ≥10% spontaneous weight reduction from the previous 1-year period is approximately 6.4%. The power calculations assume a null historical control value of 10% who show at least a 10% weight loss, which is expected to be a conservative estimation. It is also expected that treatment with setmelanotide for ~52 weeks is associated with a true underlying probability of at least 66% who demonstrate at least 10% weight loss after ~52 weeks.

A sample size of 7 patients provides ~95% power at 1-sided alpha of 0.05 and ~91% power at 1-sided alpha of 0.025, to yield a statistically significant difference compared to a historical control rate of 10%, based on a one-sample test, assuming a 66% response rate in patients who are treated with setmelanotide. The Sponsor has chosen 1-sided, alpha=0.05 as the scientific success criterion associated with the primary analysis.

Although these data suggest that powering the study for the primary endpoint will require a minimal number of patients (N<10), the size of the trial is also a function of the rarity of BBS and AS and a desire to better understand the effect of setmelanotide in these patient populations. Hence, approximately 30 patients (including 6 AS patients) are planned to be enrolled in the study. This number is suitable for a single pivotal trial to support the indications in BBS and AS and to provide robust information for both the between group analysis of the placebo-controlled, double-blinded period and the one-sample comparison to the historical control response rate after the planned 38 week open-label treatment period.

The primary analysis on the primary efficacy endpoint will be based on the ≥12 yo FAS. By nature of the study design, 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 (end of Period 2); hence, a linear model based extrapolation will be used to impute their measurements after ~52 weeks setmelanotide treatment for the primary analysis. In general, missing values unrelated to study treatment (eg, due to lost to follow-up or missed visit) will also be imputed with the linear model based extrapolation, but missing values due to treatment-related reasons (eg, lack of efficacy or AEs) will be imputed as treatment failures. A data snapshot will be taken for the primary analysis, and a supplemental supportive analysis will be performed on a locked database following study completion.

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
~	Approximately
ACTH	Adrenocorticotropic hormone
ADA	Anti-drug antibody
ADHD	Attention deficit hyperactivity disorder
AE(s)	Adverse event(s)
ALT	Alanine transaminase
AS	Alström Syndrome
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
BBS	Bardet Biedl syndrome
BIA	Bioelectrical impedance
BMI	Body mass index
BNDF	Brain-derived neurotrophic factor
BP	Blood pressure
BUN	Blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CGIC	Caregiver Global Impression of Change
CGIS	Caregiver Global Impression of Severity
C_{max}	Maximum observed concentration
CNS	Central nervous system
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRA	Clinical research associate
CRF	Case report form

Abbreviation	Definition
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
DIO	Diet-induced obese
DSM-III	Diagnostic and Statistical Manual of Mental Disorders Version III
[redacted]	[redacted]
EC_{50}	Half maximal effective concentration
[redacted]	[redacted]
eCRF	Electronic case report form
[redacted]	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
Free T4	Free thyroxine
GCP	Good clinical practice
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
HR	Heart rate
[redacted]	[redacted]
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation	Definition
IRB	Institutional Review Board
IUD	Intrauterine device
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
LEPR	Leptin Receptor
LFT	Liver function tests
LH	Luteinizing hormone
MAD	Multiple ascending dose
MC1R	Melanocortin receptor type 1
MC4R	Melanocortin receptor type 4
MedDRA	Medical Dictionary for Regulatory Activities
MSH	Melanocyte stimulating hormone
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NHLBI	National Heart, Lung, and Blood Institute
NOAEL	No observed adverse effects level
ObsRO	Observer Reported Outcome
[redacted]	[redacted]
OTC	Over the counter
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PI(s)	Principal Investigator(s)
[redacted]	[redacted]
POMC	Pro-opiomelanocortin

Abbreviation	Definition
PP	Per Protocol
PT	Prothrombin Time
PTT	Partial thromboplastin time
PVN	Paraventricular nucleus
PWS	Prader-Willi syndrome
PWS-FPD	Prader-Willi Syndrome Food Problem Diary
[redacted]	[redacted]
PYY	Peptide YY
QD	Once daily
SA	Safety analysis
SAE(s)	Serious adverse event(s)
SC	Subcutaneous
[redacted]	[redacted]
[redacted]	[redacted]
SOA	Schedule of assessments
[redacted]	[redacted]
T_{max}	Time to observed maximum concentration
TSH	Thyroid stimulating hormone
US	United States
ULN	Upper limit of normal
UV	Ultraviolet
[redacted]	[redacted]
WHO	World Health Organization
[redacted]	[redacted]
WMA	World Medical Association

1. INTRODUCTION

1.1. Purpose of Study

This pivotal, phase 3 study is designed to confirm the efficacy and safety of setmelanotide, a potent melanocortin receptor type 4 (MC4R) agonist, for the treatment of obesity and hyperphagia in patients with Bardet Biedl syndrome (BBS) or Alström syndrome (AS). The study's primary efficacy endpoint will evaluate the proportion of patients (≥12 years of age at baseline) who lose ≥10% of their baseline body weight following approximately (~) 52 weeks of treatment with setmelanotide compared to a historical control rate. The study will consist of 3 treatment periods. 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 Period 2. Following Period 2, patients will continue open-label treatment for 14 weeks (Period 3) after which they may be enrolled into a separate treatment extension study.

1.2. Overview of Bardet Biedl and Alström Syndromes

Primary cilia are evolutionarily conserved organelles whose dysfunction lead to human disorders now defined as ciliopathies. Human ciliopathies present pleiotropic and overlapping phenotypes that often include retinal degeneration, cystic renal anomalies and significant, early-onset obesity. Increasing evidence implicates an intriguing involvement of cilia in lipid/energy homeostasis, and support key roles of ciliary genes in the development and pathology of obesity and hyperphagia.

1.2.1. Bardet Biedl Syndrome

BBS, one of the ciliopathies, is a rare pleiotropic autosomal recessive disorder characterized by a syndromic phenotype with an overall prevalence of 1 in 125,000–160,000 in people of European descent (Forsythe 2013). The clinical presentation of BBS includes marked obesity and hyperphagia in addition to several other disease features that likely do not rise from hypothalamic impairment. These latter features include rod-cone dystrophy, postaxial polydactyly, cognitive impairment, hearing loss, speech deficit, hepatic fibrosis, genitourinary malformations, renal abnormalities, diabetes mellitus, hypertension, and congenital heart disease (Bardet 1995, Biedl 1995, Beales 1999, Forsythe 2013, Forsythe 2015).

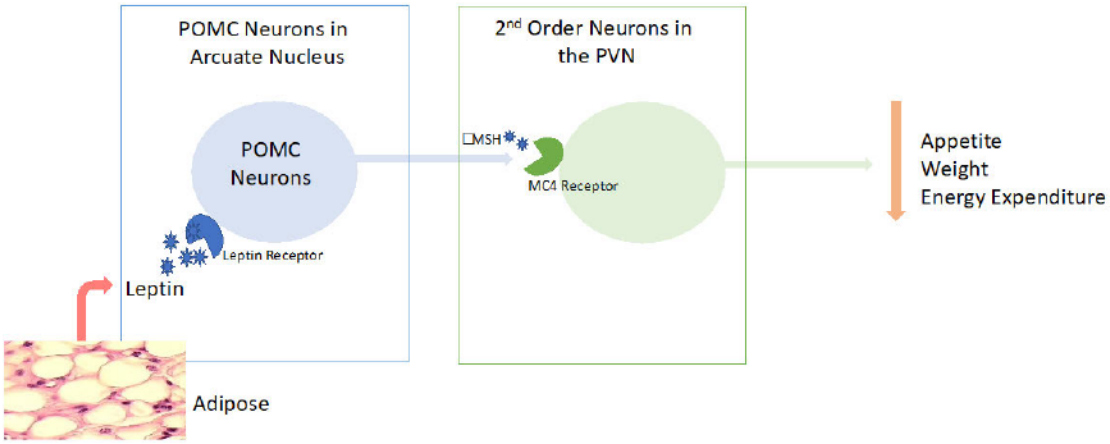
Of all these manifestations, obesity and hunger may be the most disturbing (Grace 2003). While birth weight in affected patients is usually normal, significant weight gain due to increased food intake and decreased energy expenditure (Forsythe 2015) begins in the first year and is a lifelong issue for most (72-92%) (Forsythe 2013). Relative to healthy subjects with comparable a comparable body mass index (BMI), patients with BBS tend to have higher adiposity (Grace 2003), significantly more abdominal visceral fat (Feuillan 2011), and less lean mass (Locke 2009). In one cohort from Newfoundland, a region where the prevalence of BBS is approximately 10 times more common than in the rest of the world, morbid obesity (BMI >40 kg/m^2) occurs in 25% of subjects (Moore 2005).

BBS is caused by mutations in as many as 21 different genes, all of which participate in cilia functioning (Supistin 2016), and is therefore considered a primary ciliopathy. Eight of the most conserved BBS proteins (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9 and BBS18) form a

core complex, known as the BBSome, that associates with the ciliary membrane and functions as a unit to sort and direct trafficking of receptors and other proteins to the ciliary membrane (Nachury 2007, Loktev 2008). The BBS3 protein appears critical for recruitment of the BBSome complex onto the ciliary membrane (Loktev 2008), while BBS6, BBS10 and BBS12 form a complex that facilitates assembly of the BBSome (Seo 2010). While the function of the remaining BBS proteins is less well characterized, the existence of these functional connections among the BBS proteins helps explain the phenotypic similarities among patients carrying mutations in such varied BBS genes (Guo 2011).

Extensive research suggests the obesity phenotype in BBS is caused by impaired transport of the leptin receptor to the ciliary membrane of pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus (Guo 2011). Under normal conditions, leptin, a hormone predominantly made by adipose cells, stimulates firing and gene expression in POMC neurons, promoting the secretion of alpha-melanocyte stimulating hormone (α-MSH). This stimulates the MC4R located in the second order neurons in the paraventricular nucleus (PVN) of the hypothalamus to decrease hunger and weight and increase energy expenditure (Figure 1). Impaired or absent leptin receptor signaling in POMC neurons would be expected to reduce MC4R stimulation in second order neurons, resulting in an increase in appetite, reduced metabolic rate, and increased weight.

Figure 1 Leptin – Melanocortin Pathway



There is no cure for BBS. Treatment generally focuses on the specific signs and symptoms in each individual. Management of obesity includes education, diet, exercise, and behavioral therapies beginning at an early age. Complications of obesity, such as abnormally high cholesterol and diabetes mellitus, are treated as they are in the general population (National Institutes of Health 2013).

1.2.2. Alström Syndrome

AS, like BBS, is a ciliopathy characterized by a syndromic phenotype that includes progressive cone-rod dystrophy leading to blindness, sensorineural hearing loss, congestive heart failure, and marked childhood obesity associated with hyperinsulinemia and type 2 diabetes mellitus (Girard 2011, DeVries 2014). However, it is caused by bi-allelic recessive mutations in a single gene,

ALMS1. While the exact function of *ALMS1* has not yet been elucidated, it is known to play a pivotal role in the function, formation, and maintenance of primary cilia (Knorz 2010). *ALMS1* has been shown to be involved in energy balance and satiety regulation (Alverez-Satta 2015). AS is considerably rarer than BBS, with ~ 950 cases estimated worldwide (Orphanet 2018).

While AS shares many of the same clinical features as BBS, the disorders can usually be distinguished clinically and confirmed through genetics. While the dominant phenotype in BBS is typically developmental defects, in AS it is metabolic function. Beginning in infancy, patients with AS have progressive multiorgan pathology that typically leads to truncal obesity, insulin resistance, hyperinsulinemia, hyperleptinemia, and hyperlipidemia by 5 years of age and progresses to type 2 diabetes mellitus (T2DM). The incidence of T2DM is one of distinguishing features between AS and BBS. In patients with AS the incidence of T2DM is ~50-75% compared with <25% in patients with BBS (Girard 2011).

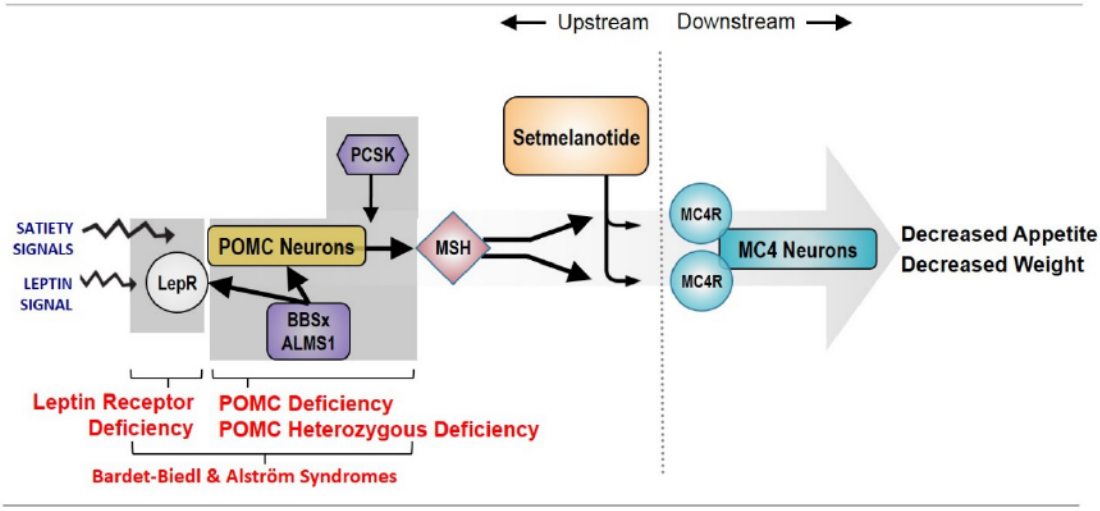
Obesity is observed almost universally in patients with AS; excessive weight gain typically begins within the first year of life. Hyperphagia and obsession with food are also common in patients with AS (Marshall 2007). As with BBS, there is no cure for AS.

1.3. Setmelanotide for the Treatment of Bardet Biedl and Alström Syndromes

Although large efforts to stabilize body weight with the help of physicians, psychologists, nutritionists, and special exercise programs are often made in these patients, invariably these programs are not successful, and affected patients continue to gain weight steadily. In older patients, short intervals of weight stability (but without weight-loss from their baseline condition of severe obesity) have been possible, but only with extraordinary efforts. This lack of response is not surprising, as the extreme hunger and food-seeking behaviors underpinning obesity associated with defects in the leptin-melanocortin pathway are not addressed by any of these efforts.

Setmelanotide is a MC4R agonist that retains the specificity and functionality of naturally occurring α-MSH, which is the natural ligand for the MC4R. Setmelanotide has the potential to restore lost activity in the MC4R pathway by bypassing the defects upstream of the MC4R and directly activating MC4R neurons in the hypothalamus below such defects (Figure 2). Thus, setmelanotide may serve as a "replacement" therapy to re-establish weight and appetite control in patients with disorders, such as BBS and AS, that are mediated by higher order defects.

Figure 2 Schematic Diagram of the Hypothalamic MC4 Pathway Illustrating the Role of Setmelanotide Treatment to Replace Genetic Obesity Defects, including BBS and AS, that are Upstream of the MC4 Receptor



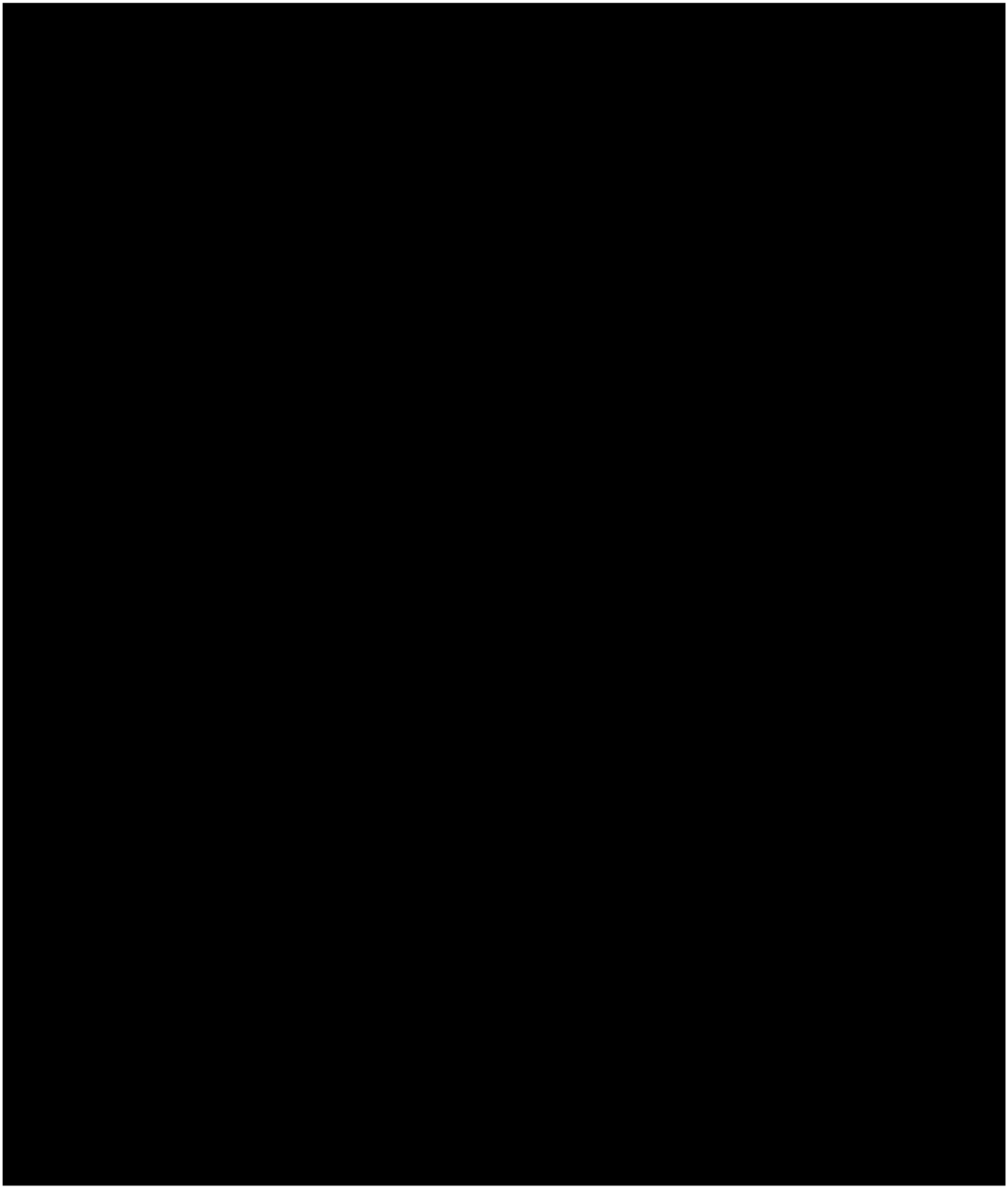
1.4. Setmelanotide Overview

[redacted]

The nonclinical and clinical data for setmelanotide are briefly described below; more detailed information is provided in the Investigator's Brochure (IB).

1.4.1. Nonclinical Overview

[redacted]



1.4.2. Clinical Overview

Setmelanotide has been evaluated in 12 clinical studies to date, 8 of which are completed and 4 of which are ongoing. [redacted]

Setmelanotide has been well tolerated in these studies with no major safety issues identified. The data from these studies continue to support the hypothesis that setmelanotide does not cause increases in heart rate (HR) or blood pressure (BP) as has been observed in previously studied MCR4 agonists.

1.4.2.1. Clinical Efficacy in Patients with BBS and AS, Two Forms of Ciliopathy Obesity

[redacted]

1.4.2.2. Clinical Safety

Overall, setmelanotide has been well tolerated and has shown a similar adverse event (AE) profile in both healthy obese subjects and in patients with a variety of rare genetic disorders associated with the MC4R pathway.

The following AEs have been reported at a higher incidence rate in setmelanotide-treated study participants compared to placebo: fatigue, diarrhea, nausea, vomiting, darkening of skin lesions, skin discoloration/hyperpigmentation, decreased appetite, penile erections, headache, back pain, and injection site pruritis.

1.4.3. Mechanism-Related Adverse Experiences of Interest

The most significant safety issue for MC4R agonist compounds in an obese patient population is the potential for mechanism-based increases in BP or HR, which were observed with another MC4R agonist (LY2112688, Eli Lilly and Company) at all doses tested in a clinical study in healthy volunteers.

Setmelanotide was developed with the specific goal to provide equal or greater efficacy as LY2112688 in animal models without producing the cardiovascular side effects observed with LY2112688. Nonclinical studies in obese monkeys showed that setmelanotide did not increase BP or HR, and clinical data suggest that there is little, if any, evidence to suggest that changes from baseline in BP or HR are greater in patients who received setmelanotide compared with those who received placebo, nor is there evidence of pharmacokinetic (PK)/PD relationship between exposure and changes in BP or HR (Gottesdiener 2015).

Other potential safety and/or tolerability issues reported from clinical and/or nonclinical studies with other MC4R agonists in the literature include nausea and vomiting, male penile erections, increases in female sexual arousal, and off-target activity at the closely related MC1R (which mediates melanin production in the skin, producing tanning).

2. STUDY OBJECTIVES

2.1. Primary Objective

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

2.2. Secondary Objectives

2.2.1. Key Secondary Objectives

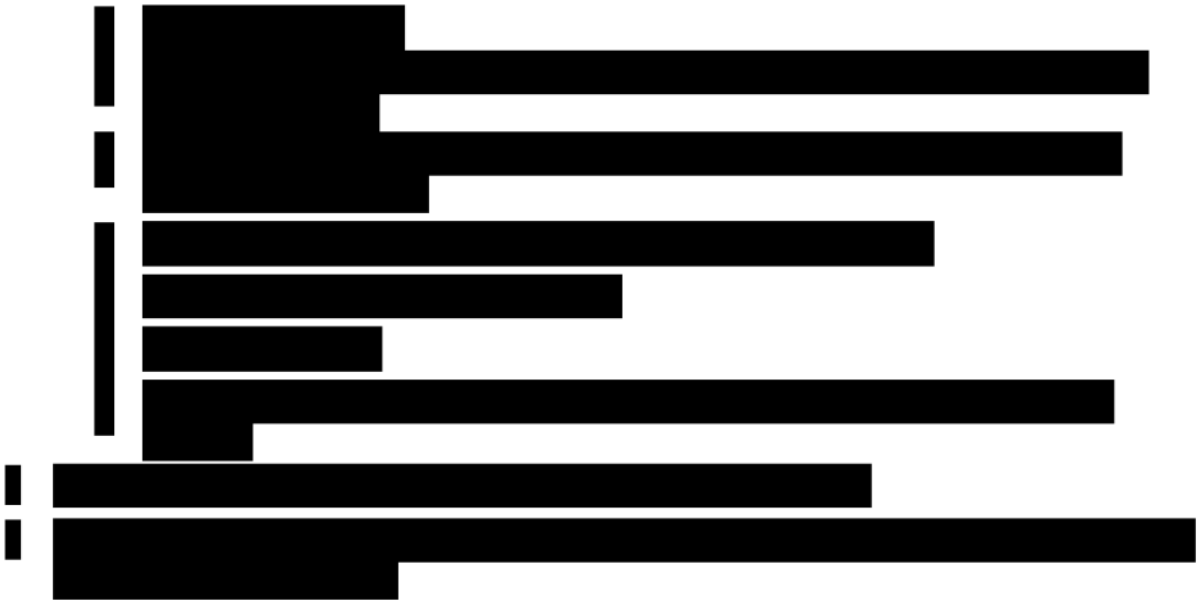
The key secondary objectives of this study are to:

- Assess the effect of setmelanotide on the proportion of all patients who achieve a ≥10% reduction from baseline in body weight after ~52 weeks of treatment with setmelanotide.
- Assess the effect of setmelanotide on mean percent change in body weight (in patients ≥12 years of age at baseline) compared with baseline after ~52 weeks of treatment with setmelanotide.
- 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 with setmelanotide.
- 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 with setmelanotide.

2.2.2. Other Secondary Objectives

Other secondary objectives of this 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 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) 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.



3. INVESTIGATIONAL PLAN

3.1. Overall Design and Plan of the Study

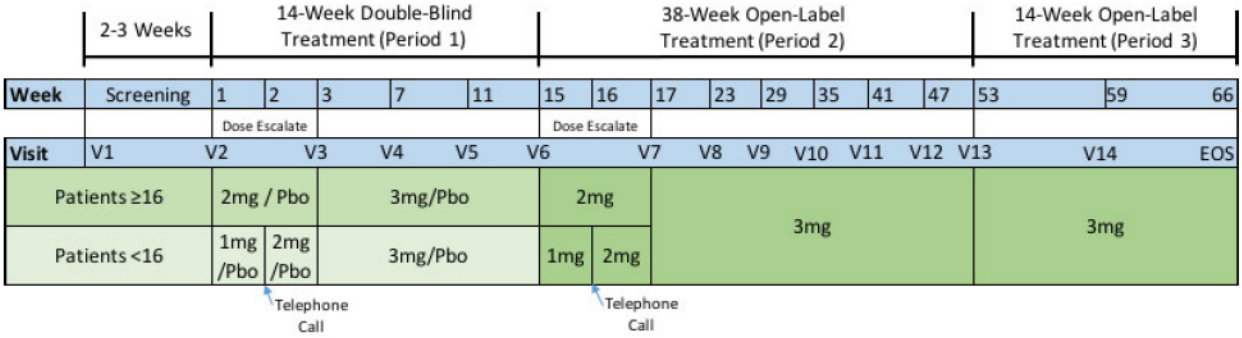
This is a pivotal study to confirm the long-term (approximately 1 year in most patients) efficacy and safety of setmelanotide treatment in patients who have BBS or AS.

The study will consist of 3 treatment periods (see Figure 3). 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 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 3.

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 3 Study Design Schematic



3.2. Dose Selection Rationale

[redacted]

Based on historical data indicating that most patients at least 16 years of age had minimal, if any, additional growth in height, a starting dose of 2.0 mg was selected for patients who are ≥16 years of age at enrollment with a planned dose escalation to a clinical dose of 3.0 mg after 2 weeks. To be more conservative in the younger patient population, where the smallest patient is expected to weight at least 29 kg, a starting dose of 1.0 mg was selected for patients <16 years of age at enrollment. Upward dose escalation in these patients will occur in 2 steps; at the end of Week 1, the dose will be increased to 2.0 mg and at the end of Week 2, the dose will be increased to 3.0 mg.

[redacted]

3.3. Study Endpoints

3.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint in this confirmative, Phase 3 study is:

- The proportion of patients (≥12 years of age at baseline) who achieve a ≥10% reduction from baseline in body weight (ie, are 'responders') after ~52 weeks of treatment with setmelanotide.

3.3.2. Secondary Endpoints

3.3.2.1. Key Secondary Endpoints

The following 4 endpoints have been identified as key secondary efficacy endpoints.

- The proportion of all patients, regardless of age at baseline, who achieve a ≥10% reduction from baseline in body weight (ie, are 'responders') after ~52 weeks of treatment with setmelanotide.
- Mean percent change from baseline in body weight (in patients ≥12 years of age at baseline) after ~52 weeks of treatment with setmelanotide.
- 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 with setmelanotide.
- 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 with setmelanotide.

3.3.2.2. Other Secondary Endpoints

Other secondary endpoints include:

- Mean percent change from baseline in body weight (in patients ≥12 years of age at baseline) at the Week 14 visit compared with placebo.
- 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) at the Week 14 visit compared with placebo.
- 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.

3.3.3. [redacted]

[redacted]

3.4. Justification of the Study Design

Setmelanotide is being evaluated as a potential treatment for rare, genetically defined obese populations. [redacted]

Both BBS and AS patients are included in the patient population of this study. While there is significant overlap in the clinical features of these syndromes, there are also some well known differences. However, despite any differences, the mechanism that drives the propensity for the obesity/hyperphagia phenotype is likely the same between the 2 syndromes, abnormal primary ciliary development and impaired leptin receptor signaling arising from BBSome dysfunction in

hypothalamic neurons caused by *BBS* or *ALM1* mutations. Because setmelanotide's mechanism of action in the MC4R pathway is downstream from the leptin receptor, it has the potential to be effective in both diseases.

Confirmation of efficacy will be based on weight loss response after ~52 weeks (1 year) of setmelanotide treatment compared to a historical weight loss rate taken from a large well characterized registry of BSS patients. The 1-year treatment duration was chosen to allow sufficient time for potential weight loss and to ensure that early weight loss is sustained. However, the study will also include a 14-week double-blind, placebo-controlled period in which 50% of patients will receive matching placebo and 50% will receive setmelanotide. Results from this placebo-controlled period will provide an insight into the immediate effect of setmelanotide compared with placebo on early weight loss and the unrelenting hunger/hyperphagia that is characteristic in these diseases. In particular, the effect of setmelanotide on hunger scores should be rapid and the evaluation strengthened by this initial placebo portion of the study. A full year double-blind, placebo-controlled period was not considered because the projected weight loss responder rate of the untreated population is well understood from the CRIBBS registry. Importantly, patient retention would be especially challenging in a full year placebo-controlled trial.

The rationale for using patients ≥12 years of age at baseline for the primary efficacy analysis is provided in Section 8.5.1.

3.5. Study Termination

This study may be prematurely terminated, if in the opinion of the Investigator (at a participating site) or the Sponsor (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 the Sponsor.

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

- Determination of unexpected, significant, or unacceptable risk to patients.
- Failure to enter patients at an acceptable rate.
- 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.

4. STUDY POPULATION

4.1. Number of Patients

It is anticipated that approximately 30 patients (at least 20 with BBS and at least 6 with AS) will be enrolled and randomized across approximately 10 centers worldwide. Given the rare incidence of these diseases, if additional patients are identified, they may be enrolled as available to gain additional experience.

The specific inclusion and exclusion criteria for enrolling patients in this study are presented in the sections below. As these diseases are ultra-rare, identification of patients is extremely difficult. Therefore, any criteria not fulfilled by a patient with a confirmed BBS or AS diagnosis will be reviewed with the Sponsor. Assuming no severe health concerns, a joint determination will be made regarding the acceptability of enrolling patients not fulfilling all criteria on a case by case basis. Any exceptions to the inclusion and exclusion criteria will be documented in writing and approved by the Sponsor prior to dosing the patient.

4.2. Inclusion Criteria

1. BBS clinical diagnosis as per Beales, 1999 (with either 4 primary features or 3 primary and 2 secondary features from table below)

Bardet-Biedl Syndrome	
Primary Diagnostic Criteria	
• Rod cone dystrophy	• Learning disabilities
• Polydactyly	• Hypogonadism in males
• Obesity	• Renal anomalies
Secondary Diagnostic Criteria	
• Speech disorder/delay	• Mild spasticity (especially lower limbs)
• Strabismus/cataracts/astigmatism	• Diabetes mellitus
• Brachydactyly/syndactyly	• Dental crowding/hypodontia/small roots/high arched palate
• Developmental delay	• Left ventricular hypertrophy/congenital heart disease
• Polyuria/polydipsia (nephrogenic diabetes insipidus)	• Hepatic fibrosis
• Ataxia/poor coordination	
Source: Beales 1999	

Or AS diagnosis as per Marshall, 2007 (using major and minor age adjusted criteria in the table below).

Alström Syndrome		
Diagnostic Criteria		**Minimum Required**
Major	**Minor**	
For patients 6 to ≤14 years of age		
• Mutation of *ALMS1* and/or family history of AS • Vision (nystagmus, photophobia, diminished acuity, if old enough for testing: cone dystrophy by ERG)	• Obesity and/or insulin resistance and/or T2DM • History of DCM/CHF • Hearing loss • Hepatic dysfunction • Renal failure • Advanced bone age	2 major criteria ***or*** 1 major and 3 minor criteria
For patients ≥15 years of age		
• Mutation of *ALMS1* and/or family history of AS • Vision (history of nystagmus in infancy/childhood, legal blindness, cone and rod dystrophy by ERG)	• Obesity and/or insulin resistance and/or T2DM • History of DCM/CHF • Hearing loss • Hepatic dysfunction • Renal failure • Short stature • Males: hypogonadism • Females: irregular menses and/or hyperandrogenism	2 major and 2 minor criteria ***or*** 1 major and 4 minor criteria
Source: Marshall 2007		

Abbreviations: CHF = congestive heart failure; DCM = dilated cardiomyopathy; ERG = electroretinography; T2DM = Type 2 diabetes mellitus

- *Note*: at least 90% of patients with BBS and 100% of patients with AS must have genetically confirmed diagnosis at the time of enrollment
  - A genetically confirmed diagnosis of BBS is defined as a homozygous or compound heterozygous loss-of-function mutation in BBS genes; patients without a genetically confirmed BBS diagnosis must be reviewed with the Sponsor's medical monitor prior to enrollment.
  - A genetically confirmed diagnosis of AS is defined as a homozygous or compound heterozygous loss-of-function mutation in the *ALMS1* gene.

  Once 10% of patients without a confirmed BBS diagnosis have been enrolled in the study, sites will be notified that only genetically confirmed BBS patients may be enrolled.

2. ≥6 years of age.
3. Obese, defined as BMI ≥30 kg/m^2 for patients ≥16 years of age or weight >97th percentile for age and sex on growth chart assessment for patients 6 to 15 years of age.
4. Study participant and/or parent or guardian is able to communicate well with the Investigator, to understand and comply with the requirements of the study, and is able to understand and sign the written informed consent/assent.
5. Female participants of child-bearing potential must be confirmed non-pregnant and agree to use contraception as outlined in the protocol. Female participants of non-childbearing potential, defined as: surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation), post-menopausal for at least 12 months (and confirmed with a screening follicle stimulating hormone (FSH) level in the post-menopausal lab range), or

failure to have progressed to Tanner Stage V and/or failure to have achieved menarche, do not require contraception during the study.

6. Male participants with female partners of childbearing potential must agree to use a double barrier method contraception if they become sexually active during the study or within 90 days following their participation in the study. Male patients must also not donate sperm during and for 90 days following their participation in the study.

4.3. Exclusion Criteria

1. Recent intensive (within 2 months) diet and/or exercise regimen with or without the use of weight loss agents (including herbal medications) that has resulted in >2% weight loss. These patients may be reconsidered approximately 1 month after cessation of such intensive regimens.
2. Current or prior (within prior 2 months) use of any medication, including those approved to treat obesity, that could impact the efficacy results of this study (eg, orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion, liraglutide). Patients on a stable dose and regimen (for at least 2 months) of medication to treat attention deficit hyperactivity disorder (ADHD) may be enrolled in the study as long as they agree to remain on the same dose and regimen during the study.
3. Prior gastric bypass surgery resulting in >10% weight loss durably maintained from the baseline pre-operative weight with no evidence of weight regain. Specifically, patients may be considered if surgery was not successful, resulted in <10% weight loss compared to pre-operative baseline weight, or there is clear evidence of weight regain after an initial response to bariatric surgery. All patients with a history of bariatric surgery must be discussed with, and receive approval from, the Sponsor prior to enrollment.
4. Diagnosis of schizophrenia, bipolar disorder, personality disorder or other Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V) disorders that the Investigator believes will interfere significantly with study compliance. Neurocognitive disorders affecting ability to consent will not be disqualifying as long as an appropriate guardian able to give consent has been appointed.
5. In patients with no significant neurocognitive deficits:
   - A PHQ-9 score of ≥15 and/or
   - Any suicidal ideation of type 4 or 5 on the C-SSRS, any lifetime history of a suicide attempt, or any suicidal behavior in the last month.
6. Current, clinically significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor to determine eligibility.
7. History of significant liver disease or liver injury, or a current liver assessment due to abnormal liver tests (as indicated by abnormal liver function tests, alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase, or serum bilirubin >1.5× the upper limit of normal [ULN] for any of these tests) for an etiology other than non-alcoholic fatty liver disease (NAFLD). Thus, any underlying etiology besides NAFLD,

including diagnosed non-alcoholic steatohepatitis (NASH), other causes of hepatitis, or history of hepatic cirrhosis is exclusionary, but the presence of NAFLD is not be exclusionary.

8. Moderate to severe renal dysfunction defined as <30 mL/min (Appendix 11.6).
9. History or close family history (parents or siblings) of skin cancer or melanoma (excluding non-invasive basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.
10. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of comprehensive skin evaluation performed by a qualified dermatologist during screening. Any concerning lesions identified during the screening period will be biopsied and results must be known to be benign prior to enrollment. If the pre-treatment biopsy results are of concern, the patient should be excluded from the study.
11. Patient is, in the opinion of the Study Investigator, not suitable to participate in the study.
12. Participation in any clinical study with an investigational drug/device within 3 months prior to the first day of dosing.
13. Significant hypersensitivity to study drug.
14. Inability to comply with QD injection regimen.

4.4. Patient Identification and Registration

The Investigator and the Investigator's study staff will identify potential patients for the study. Patients who are candidates for enrollment into the study will be evaluated for eligibility by the Investigator to ensure that the inclusion and exclusion criteria have been satisfied and that the patient is eligible for participation in this clinical study.

All patients screened for the study will be assigned a unique screening number representing a combination of the site number and a sequential 3-digit number. Screening numbers will be assigned sequentially starting at 001 (ie, the first patient screened at site 10 would be assigned screening number 10001).

4.5. Withdrawal of Patients

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 Schedule of Assessments (SOA) in Section 6, even if they are no longer receiving study drug.

In case of discontinuation, all AEs should be followed as described in 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.

4.6. Duration of Patient Participation

Individual patient participation in this study is expected to last for approximately 69 weeks (~3 week screening period plus 66 weeks of treatment across Periods 1 through 3).

The end of the trial will be defined as the last patient's last visit.

5. STUDY TREATMENTS

5.1. Study Drugs

All study drugs are for investigational use only and are to be used only within the context of this protocol. All investigational study drugs (setmelanotide and placebo) will be supplied by the Sponsor.

Setmelanotide is the investigational test drug being evaluated in this clinical study. Setmelanotide is an 8 amino acid, cyclic peptide that is highly selective and potent agonist at the human MC4R.

Setmelanotide drug product (setmelanotide mPEG-DSPE formulation) is a sterile solution for injection. The product is manufactured at a concentration of 10.0 mg/mL.

The reference therapy for the double-blind period of this study is a placebo vehicle.

Setmelanotide and placebo are clear, colorless to slightly opalescent solutions essentially free of visible particulates, and are suitable for a double-blind study.

5.2. Study Drug Administration and Dose Escalation

5.2.1. Administration

Study patients will receive study drug by SC injection QD (administered in the morning).

There will be extensive training of patients in drug administration including educational materials. Study specific training materials will be provided to both the investigative staff and study participants and caregivers. The Sponsor will provide extra placebo supplies for use during training.

The goal is for the patient or their caretaker to successfully self-administer the study drug at home. Given the rarity of BBS and AS, arrangements may be made for those who are not able to successfully self-administer the study drug to have assistance by a visiting home health care practitioner.

Patients and/or their caretakers (including home health practitioners) will be responsible for all procedures associated with study drug administration, ie, drawing up and self-administering the study drug QD (including during the practice sessions).

To ensure patients or their caregivers can successfully self-administer study drug, a training session(s) in the clinic with placebo (or saline) will occur during screening before entering the randomized, double-blind study period. This training/practice can occur as many times as necessary throughout the study to assure proper technique. The training/practice does not pertain to the home health practitioners.

Patients will be required to fast overnight for all clinic visits. Water will be allowed throughout the fasting period.

5.2.2. Study Drug Dose Escalation and Adjustments

Dose escalation will occur during the first 2 weeks of both the double-blind placebo-controlled and the open-label study periods (see Table 1). The reason for repeating the dose escalation

procedure at the start of the open-label period is to maintain the blind of the study and not reveal which group originally started with placebo/active treatment.

Doses should not be adjusted after the dose escalation phase has been completed unless discussed and approved by the Sponsor.

Table 1 Dose Escalation Schedule

Study Week	Patients ≥16 years of age (Dose in mg)	Patients <16 years of age Dose (mg)
1	2.0 or placebo	1.0 or placebo
2	2.0 or placebo	2.0 or placebo
3-14	3.0 or placebo	3.0 or placebo
15	2.0	1.0
16	2.0	2.0
17-78	3.0	3.0

5.3. Method of Assigning Patients to Treatment

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.

5.4. Blinding, Packaging, and Labeling

5.4.1. Blinding and Breaking the Blind

This study will be open label, with the exception of a 14-week double-blind, placebo-controlled period.

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. Every attempt will be made to maintain the blind through the end of the 38-week, open-label treatment period (Period 2) (ie, until the database snapshot prior to completing the primary statistical 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 request to break the blind should be discussed with the Medical Monitor and the Sponsor, whenever possible. If the blind is broken, the reason, when and how the blind was broken will be documented.

5.4.2. Packaging and Labeling

All study drugs, including placebo or saline for practice, will be supplied by the Sponsor; placebo/saline for practice SC administration will not be blinded.

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

To ensure that the patient and site are blinded with respect to each patient's randomized treatment assignment, placebo and setmelanotide are identical in appearance and are supplied in identical packaging. Each vial will contain a code that identifies the contents as either placebo setmelanotide. At each site visit during the double-blind period, an unblinded study pharmacist will select the correct study drug based on the patient's randomized treatment assignment and will provide the blinded study medication to the patient or the patient's caregiver.

Following completion of the double-blind period, the study pharmacist will provide open-label (ie, unblinded) vials of setmelanotide to the patient or the patient's caregiver.

5.5. Preparation, Handling, and Storage

All study drug must be kept in a secure, limited-access storage area at a temperature between 2°C to 8°C. Both setmelanotide and placebo are stable at room temperature for a short period that will allow patients to transport study drug home; ice packs and cooler bags will be provided for patients and caretakers who will travel long distances from the clinic. Patients will be encouraged to proceed directly home after clinic visits in which study drug is dispensed to minimize the amount of time the study drug is exposed to elevated temperatures.

A separate pharmacy manual with specific instructions will be provided to the investigative site.

5.6. Assessment of Treatment Compliance

To evaluate the efficacy, [redacted] of the study drug, it is critical that patients receive study drug as directed. All used study drug will also be collected to assess compliance with the protocol.

Patients and/or caretakers will be required to maintain a study drug diary to monitor compliance. In addition, the time of dosing will be recorded in the patient diary. This information will be recorded directly into an electronic data capture device. Home nurses will be available, as needed, for additional training and to reinforce compliance.

If a patient does not receive the entire dose of study drug, the amount administered will be recorded. In addition, the reason(s) is to be recorded in source documents and the eCRF.

Additionally, at all clinic visits, a blood sample will be collected prior to dosing in clinic to measure trough concentrations of setmelanotide in plasma.

5.7. Study Drug Accountability

Accountability for the study drug at the study site is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or another appropriate individual. Drug accountability records indicating the delivery date to the site, inventory at the site, use by each patient, return of all used study drug to the study center, and return to the Sponsor (or disposal of the drug, if approved by the Sponsor) will

be maintained by the clinical site. These records will adequately document that the patients were provided the medication (setmelanotide or placebo) and doses as specified in the randomization code and protocol and should reconcile all study drug received from the Sponsor. Reasons for departure from the expected dispensing regimen must also be recorded. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. The Sponsor or its designee will review drug accountability at the site during monitoring visits.

All unused and used study drug will be returned by patients, and retained at the site until inventoried by the monitor. All unused, used or expired study drug will be returned to the Sponsor or if authorized, disposed of at the study site and documented.

5.8. Prior and Concomitant Treatment

5.8.1. Permitted Medication

Female patients may use hormonal contraception as well as hormone replacement therapy.

Unless concomitant medications are likely to present a strong potential safety concern, the general goal of this protocol is to allow as many as possible patients with these ultra-rare conditions to participate in the study. Therefore, patients are allowed chronic concomitant medications (eg, as described below) while participating in the study:

- Growth hormone
- Contraceptives (see Section 6.2.1 for requirements for contraception)
- Hormone replacement therapy (eg, estrogen, progestins, androgens)
- Anti-hypertensives
- Statins and other lipid-lowering therapies
- Thyroxine or other thyroid supplements
- Other medications commonly used in obese patients including: endocrine therapies (eg, estrogens, bisphosphonates, hydrocortisone, vitamin and calcium supplements, diabetic therapies including insulin); and other medications (eg, carnitol, Coenzyme Q10, vitamins, anti-constipation medications, anti-allergic medications).
- Apart from low threshold drugs (eg, anticonvulsants, digoxin, warfarin sodium), other medications may be permitted if on a stable dose (for at least 1-2 months) upon consultation with the Sponsor.

There is little evidence that setmelanotide will result in drug interactions at present, but data are limited. Patients and caretakers should be carefully questioned about medication use to ensure that potential patients are carefully warned of possible side effects from drug interactions that could occur with the specific list of medications that an individual patient will be receiving.

Patients will be reminded at each visit that if it becomes necessary for a patient to take any other medication during the study, from Screening until the Final Study Visit, they must inform the study staff immediately, and the specific medication(s) and indication(s) must be discussed with the Investigator. All concomitant medications taken during the study must be recorded in the source documents and on the eCRF.

5.8.2. Prohibited Medication and Substances

Medications, including those approved to treat obesity, that could impact the efficacy results of this study are prohibited (eg, orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion, liraglutide).

Stimulant (and non-stimulant, if decreased appetite/weight loss is listed side effect) medication (eg, to treat attention deficit hyperactivity disorder [ADHD]) cannot be started during the study. Patients who have been on a stable dose and regimen for at least 2 months prior to study entry may continue to receive the same dose and regimen during the study.

Anorectic agents or drugs with anorexia as a non-rare side effect are prohibited for the duration of the study.

5.8.3. Concomitant Procedures

Concomitant procedures conducted during the study, including those used to treat adverse events, are to be reported on the eCRF.

6. STUDY ASSESSMENTS

6.1. Overview of Schedule of Assessments

The SOA for treatment Periods 1 and 2 is depicted in Table 2 and the SOA for the treatment Period 3 and the early termination visit (if needed) is depicted in Table 3.

Although the study procedures and assessments required per protocol are classified as "No or Minimal Risk" (apart from DXA which is classified as "Minor Increase over Minimal Risk") per the 2008 Guidance Document "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population", considerations for reducing pain in distress in participants younger than 18 years of age are included in Appendix 11.7.

Upon providing informed consent, patients will enter the Screening Period. During the Screening Period, patients will be assessed for eligibility and instructed to complete a hunger questionnaire (Appendix 11.5) daily to enhance the understanding of hunger associated with BBS and AS, prior to treatment with study medication. During Screening, a detailed medical history will be obtained, including medical chart review (Appendix 11.3), to collect information pertaining to the natural history of BBS and AS.

After the Screening Period in which confirmation of patient eligibility and ability for patients or their caretakers to successfully self-administer study drug is determined (or if arrangements for a visiting home health care practitioner are necessary), patients will be randomized to receive either setmelanotide or placebo and will enter the 14-week double-blind treatment period (Period 1). Following completion of the double-blind treatment period, all patients will receive setmelanotide in a 38-week open-label treatment period (Period 2) followed by a 14-week open-label treatment period (Period 3).

Any patient withdrawing from the study will complete the Early Termination Visit, if possible, and will be encouraged to complete all remaining study visits. For those patients not willing to complete study visits at the clinic, home health care practitioner visits or telephone follow-up may be acceptable to obtain minimum patient self-reported data (ie, weight, AEs, etc.).

Detailed descriptions of the [redacted] procedures to be conducted during this study are provided in the following sections.

Patients will be required to fast overnight on the day preceding all site visits, beginning with the initial Screening Visit. Patients will be allowed to take their usual medications with a sip of water on the morning of each clinic visit.

The Screening Period can occur within ~3 weeks of Day 1, and should be scheduled within this timeframe to allow test results to be received and continued eligibility of patients confirmed prior to the first dose on Day 1. Assessments may occur over multiple days during the Screening Period. To obtain sufficient baseline data on symptoms of hunger (collected daily), the screening period should be a minimum of 2 weeks.

To provide flexibility to the patient and study staff, the actual scheduling of clinic visits can occur within a flexible window of time (ideally ±3 days). However, as these patient populations are ultra-rare, all data collected, even if outside of visit windows, will be included in all analyses of endpoints.

Additionally, if the patient resides a considerable distance from the Investigative Site, arrangements may be made for a home health practitioner to conduct a visit at the patient's home or for the patient to be seen at their local physician's office, to obtain the applicable data/samples. These arrangements must be approved by the Sponsor in advance, to be sure that important data/samples can be properly collected, and any safety procedures robustly implemented.

However, patients must be seen at the Investigative Site at an absolute minimum at least once for Screening, and for visits for Weeks 1, 3, 15, 17, 29, 41, 53, and 66 or Early Termination visit.

Table 2 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	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[8]	X	◄ Daily† ►													
Global hunger assessment[9]	X			X†			X†		X†		X†				X†
[redacted]															

	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**
Injection site inspection[21]		X		X	X	X	X		X	X	X	X	X	X	X
[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	X	X	X	X	X	X

† 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). This sample may also be used for genotyping other obesity-related genes. 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 will be completed instead (see Appendix 11.5.2).

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).

[redacted]

[redacted]

21 Injection site evaluations and scoring (by the clinical staff) will include identification and measurement of areas of erythema, edema, and induration, as well as the presence of localized pain, tenderness, and itching. Additional evaluation data can be collected at any visit where there are injection site reactions even if not a timepoint for formal assessment.

[redacted]

[redacted]

Table 3 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	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 will be completed instead (see Appendix 11.5.2).

8 Global hunger Questions 1 and 2 (Appendix 11.5) will be asked.

[redacted]

6.2. Patient Requirements

6.2.1. Contraception

Setmelanotide has not been completely evaluated in nonclinical Developmental and Reproductive Toxicology Studies to date; therefore, the effects of setmelanotide on embryo-fetal development are unknown at this time. It is imperative all study patients adhere to the contraception requirements as outlined below.

Females must not be pregnant and must have a negative serum pregnancy test result at the Screening Visit and negative urine pregnancy test on Day 1, with results known prior to initiating dosing; pregnancy testing will be monitored during the study.

For female patients who are able to bear children, a highly reliable form of contraception must be used/practiced throughout the study and for 90 following the study. Highly reliable acceptable for of contraception include: hormonal (ie, oral, implantable, or injectable) and single-barrier method (ie, condom), or an Intrauterine Device (IUD) and single-barrier method (ie, condom) or vasectomized partner. True abstinence is acceptable only if it is the preferred and usual lifestyle of the patient.

Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) post-menopausal for at least 12 months (and confirmed with a screening FSH level in the post-menopausal range), or failure to have progressed to Tanner Stage V and/or failure to have achieved menarche, do not require contraception during the study. Younger female patients who are not sexually mature will be assessed for Tanner staging and advised accordingly.

It is not known if this treatment will affect spermatogenesis. Therefore, males with female partners of childbearing potential must agree to use contraception (eg, if they have not had a vasectomy then should either (a) abstain from reproductive sexual intercourse or (b) use a double barrier method (ie, condom and diaphragm and spermicide) if they become sexually active during the study and for 90 days following the study. Male patients must not donate sperm for 90 days following their participation in the study.

6.2.2. Protection from Sun

Skin hyperpigmentation, or tanning, was observed in the cynomolgus monkey toxicology studies and the human Phase 1/2 studies. These events were reversible upon cessation of study drug. However, it is still uncertain if exposure to sunlight might exacerbate the tanning effects of setmelanotide.

It is also important that patients do not participate in any activities that will intentionally cause their skin to tan (eg, visit ultraviolet (UV) tanning salons, use spray tanners, self-tanning lotions).

6.3. Informed Consent/Assent and Screening

6.3.1. Informed Consent/Assent

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

6.3.2. Screening

Prior to entering the double-blind treatment period, upon providing informed consent, patients will enter the Screening Period. During the Screening Period, patients will be assessed for eligibility and instructed to complete a hunger questionnaire daily to enhance the understanding of hunger symptoms associated with BBS and AS, prior to treatment with study drug. As both disorders are ultra-rare, obtaining daily hunger scores as well as a very detailed medical history (medical record review) during Screening, will allow for the collection of important patient specific data (see Appendix 11.3; eg, growth and weight curves, other associated hormonal or metabolic abnormalities, pediatric developmental milestones or disturbances, and possible orthopedic or respiratory complications due to weight gain) that will allow for a better understanding of these rare forms of obesity.

6.3.2.1. Genetic Testing

A blood sample will be obtained at Screening for genetic confirmation of BBS or AS. However, patients may be entered into the study based on clinical diagnosis of BBS after review with the Sponsor's medical monitor (≤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). This sample may also be used for genotyping other obesity-related genes. Any remaining sample will be stored for possible future testing of obesity-related genes that could impact efficacy responses. The DNA will not be studied or "typed" for any other purpose, unless patients are re-consented. Samples will be labeled with the patient identification number and initials.

6.3.2.2. Demographics and Medical History

A complete medical history along with demographic data will be obtained for all patients during the Screening Period. Data to be recorded in the source document and eCRF include the patient's gender, race, date of birth and concomitant medication use. Additionally, a detailed review of the patient's medical records will be performed to collect important retrospective data to better understand the natural history of BBS and AS per Appendix 11.3.

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

6.4. Efficacy Measurements

6.4.1. Weight

Weight (kg) will be recorded as shown in the SOA in Table 2 and Table 3. All measurements will be done in triplicate at each timepoint. Whenever possible, the same scale should be used throughout the study, including the Screening Visit, and should be calibrated on a regular basis. Weight should be measured at approximately the same time at each visit and after fasting for at least 8 hours. Patients should be in light clothing or underwear, with no shoes and have emptied their bladder.

[redacted]

6.4.5. Hunger/Hyperphagia Assessments

Hunger (or hyperphagia) will be assessed as shown in the SOA in Table 2 and Table 3.

6.4.5.1. Patient Assessments of Hunger

Patients who are ≥12 years old and able to assess their own hunger will answer two Global Hunger Questions and will complete a Daily Hunger Questionnaire.

Global Hunger Questions for Patients ≥12 Years of Age: [redacted]

Daily Hunger Questionnaire for Patients ≥12 Years of Age: [redacted]

[redacted]

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

The Global Hunger Questions and Daily Hunger Questionnaire are described in Appendix 11.5.1. These will be recorded directly into an electronic data capture device.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.8. Clinical Procedures and [redacted] Assessments

[redacted]

6.8.1. Concomitant Medication Review

A review of concomitant medications will be conducted during the Screening Period and at every study visit. Any medications taken by study patients will be recorded in source documents and on the appropriate eCRF.

6.8.2. [redacted], Comprehensive Skin Examination, and [redacted]

[redacted]

[redacted]

6.8.2.2. Comprehensive Skin Examinations

Comprehensive skin examinations will be performed by a Dermatologist.

The Investigator will identify a Dermatologist to serve as a consultant for the Investigative Site.

Each patient will receive a complete, comprehensive skin exam as part of Screening, prior to any setmelanotide treatment. Any atypical lesions should be considered for biopsy prior to study start. The dermatologist will continue to monitor each patient, performing comprehensive skin examinations according to the SOA in Table 2 and Table 3.

In the event a patient experiences changes to skin or skin lesions that are unresolved (or have not significantly improved or are close to resolution) at the end of study, the patient may be asked to return for additional follow up assessments to document progress towards resolution.

6.8.3. Fitzpatrick Scale

Each patient is to be categorized for skin type according to the Fitzpatrick scale (Fitzpatrick 1975) . The Fitzpatrick Scale is depicted in Appendix 11.2.

[redacted]

[redacted]

[redacted]

6.8.9. Diet and Nutritional Counseling

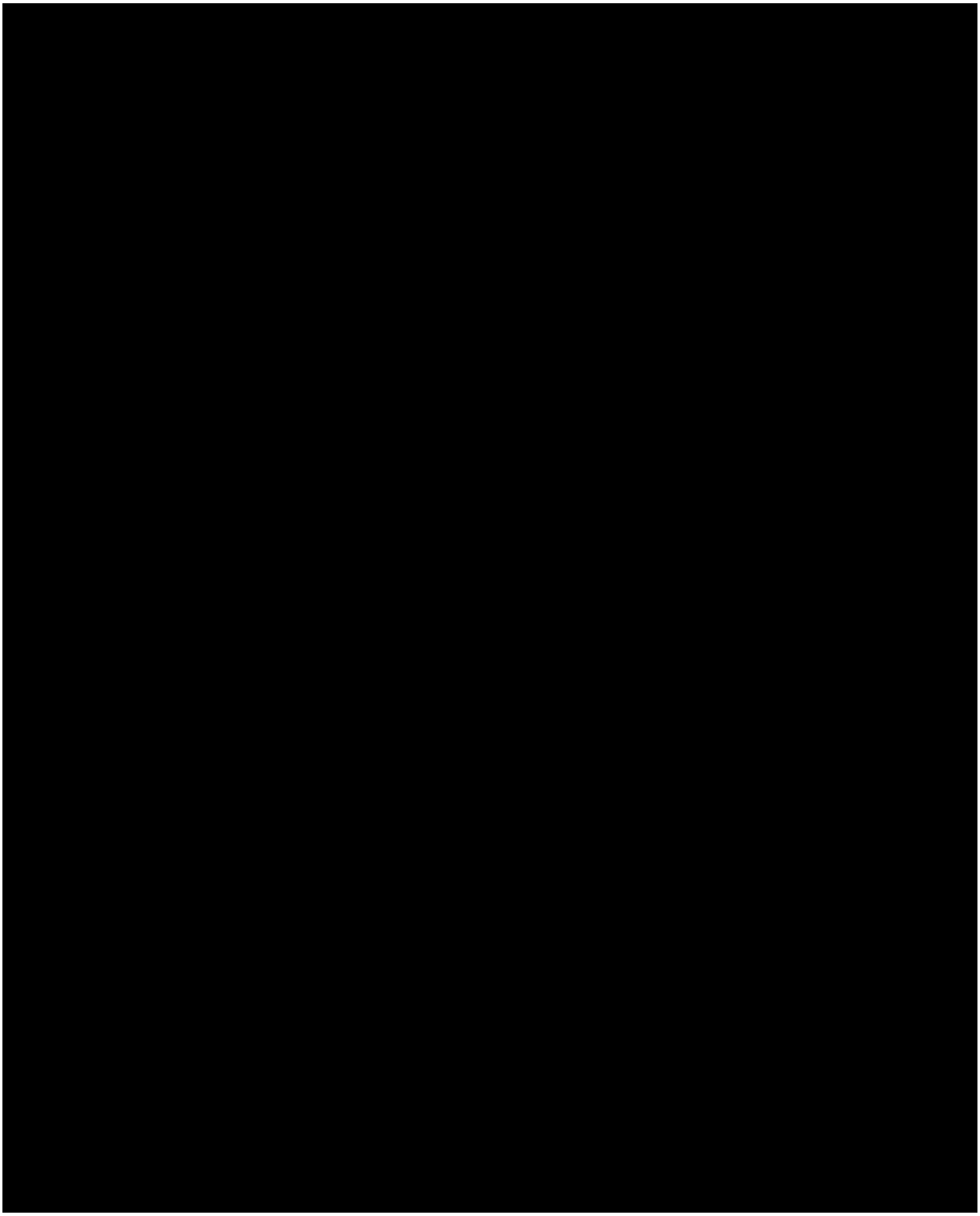
For adolescents and adult patients, no special dietary counseling will be part of this trial, but patients will be counseled to continue on their usual diet at home.

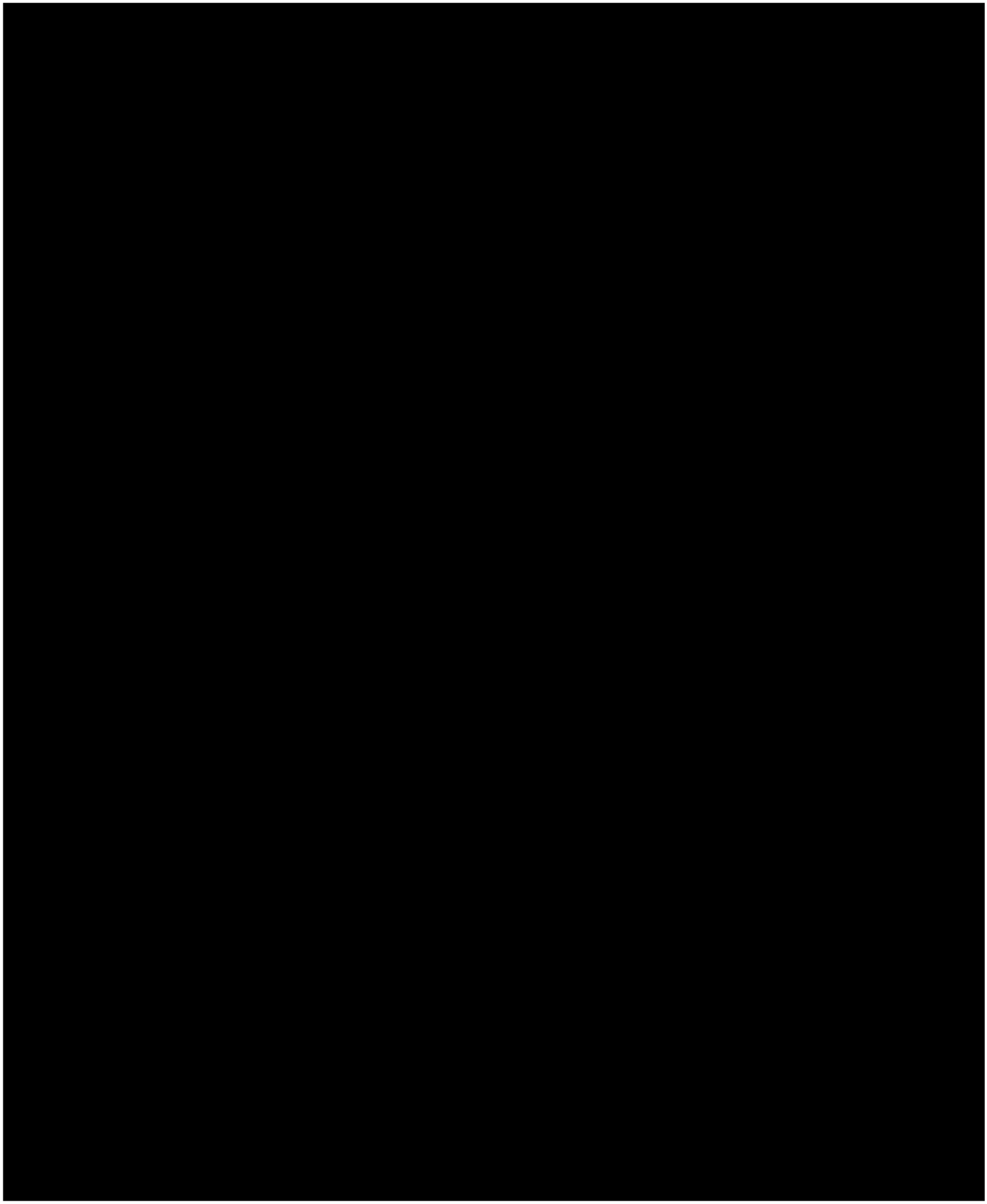
For pediatric patients, nutritional counseling and monitoring will be performed by an appropriate dietician or nutritionist (or equivalent) according to the SOA in Table 2 and Table 3, to ensure that pediatric patients have adequate nutritional/dietary intake to maintain proper growth and development. Additional laboratory assessments indicative of nutritional status may be monitored as appropriate (eg, albumin, vitamin D, total lymphocytes, and IGF1).

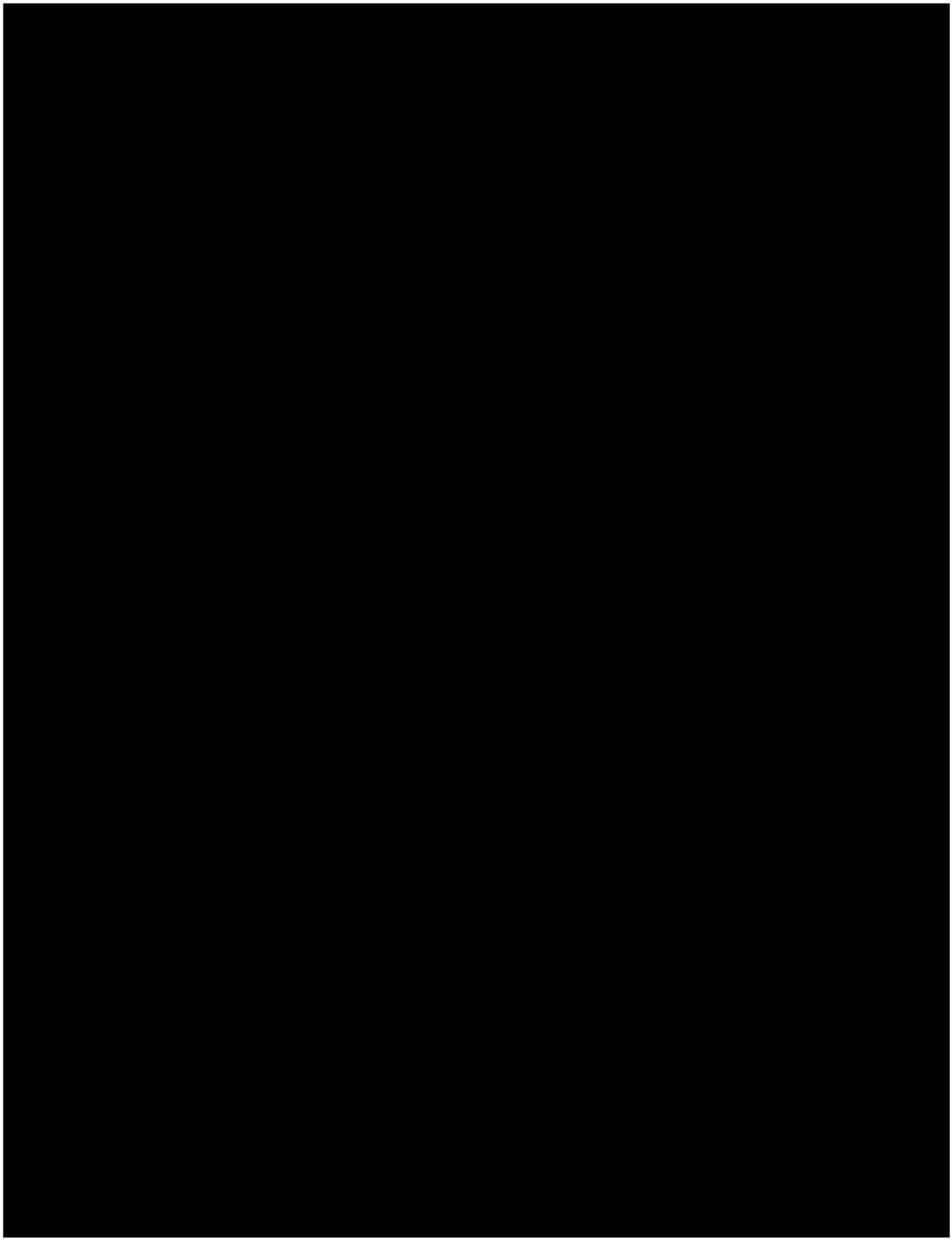
[redacted]

6.9. Order of Assessments

[redacted]







[redacted]

[redacted]

8.2. Analysis Populations

The following analysis populations will be used in the statistical analyses.

Screening Analysis Set: is defined as all subjects who signed the informed consent form.

Safety Analysis Set (SA): is defined as all patients who received at least 1 dose of study drug (placebo or setmelanotide). Analyses performed on the safety set will be based on patients according to the treatment received.

Full Analysis Set (FAS): is defined as all randomized patients (irrespective of age) who received at least 1 dose of study drug (placebo or setmelanotide) and have baseline data. Analyses performed on the FAS will be based on subjects as randomized.

In addition, a subset of the FAS is defined as follows:

- **≥12 years old Full Analysis Set (≥12 yo FAS):** is defined as patients in the FAS who are ≥12 years of age at baseline.

In addition to above, the following 2 analysis sets or subsets may be used for supportive/exploratory analyses (note that in the following 2 exploratory analysis sets, if a patient's height at the primary endpoint timepoint, ie, ~Week 53 visit, is not available, then the last available measurement of height will be used to define the analysis sets).

- **Stable Height Full Analysis Set:** is defined as patients in the FAS who grow ≤2 cm in height from baseline to the primary endpoint timepoint (ie, ~Week 53 visit for patients randomized to setmelanotide or ~Week 66 visit for patients randomized to placebo) or to the last available timepoint if it occurs prior to the primary endpoint.
- **Active Growth Full Analysis Set**: is defined as patients in the FAS who grow >2 cm in height from baseline to the primary endpoint timepoint (ie, ~Week 53 visit for patients randomized to setmelanotide or ~Week 66 visit for patients randomized to placebo) or to the last available timepoint if it occurs prior to the primary endpoint.

Per-Protocol Set (PP): all subjects in the FAS without any major protocol violations

8.3. Definition of Baseline

Baseline for statistical analyses of data from the double-blind period is defined as the last available measurement prior to the randomization (ie, Day 1), for patients randomized into either the setmelanotide or placebo group.

Baseline for statistical analyses following ~52 weeks setmelanotide treatment is defined as follows:

- For patients initially randomized into the setmelanotide group, baseline is defined as the last available measurement prior to the randomization (ie, Day 1)
- For patients initially randomized into the placebo group, baseline is defined as the last available measurement prior to the first dose of open-label setmelanotide treatment (ie, Week 14 or pre-dose Week 15)

8.4. Timing of Analyses

By nature of the study design, 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 (end of Period 2); hence, a linear model based extrapolation will be used to impute their measurements after ~52 weeks setmelanotide treatment for the primary analysis. In general, missing values unrelated to study treatment (eg, due to lost to follow-up or missed visit) will also be imputed with the linear model based extrapolation, but missing values due to treatment-related reasons (eg, lack of efficacy or AEs) will be imputed as treatment failures. A data snapshot will be taken for the primary analysis.

Once the study is complete (ie, the last patient has completed his/her last visit), the database will be locked and a supplemental supportive analysis will be provided.

No formal interim analysis is currently planned for this study.

8.5. Efficacy Analyses

8.5.1. Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of patients (≥12 years of age at baseline) who achieve a ≥10% reduction from baseline in body weight (ie, are 'responders') after ~52 weeks of treatment with setmelanotide. The statistical hypothesis for the primary efficacy endpoint is:

$$H0: p_t \leq 10\% \quad \text{vs} \quad H1: p_t > 10\%$$

where p_t is the response rate after ~52 weeks of setmelanotide treatment (ie, ~Week 53 for patients randomized to setmelanotide and ~Week 66 for patients randomized to placebo).

The subgroup of patients ≥12 years of age was selected for the primary analysis because this is the group of patients for whom the interpretation of weight loss is most straightforward. Normal weight gain that accompanies increases in patient height during childhood growth and development can confound interpretation of the efficacy of weight loss drugs (Kelly 2016).

[redacted]

The statistical hypothesis will be tested using an exact binomial test, at a 1-sided 0.05 significance level. The 1-sided 0.05 significant level was chosen based on the small sample size due to the rarity of the disease. A 2-sided 90% confidence interval (CI) will be calculated using the exact Clopper-Pearson method. The success criterion for the primary hypothesis requires the rejection of the null hypothesis at the 1-sided 0.05 significance level. The statistical criterion

corresponds to the 2-sided 90% CI for setmelanotide of the response rate excluding 10% (ie, lower bound of the CI >0.10).

The primary analysis on the primary efficacy endpoint will be based on the ≥12 yo FAS. Timing of the analysis and general missing data handling principles are described in Section 8.4. A sensitivity analysis based on data as observed (ie, no imputation on missing values) will be provided. Additional sensitivity analysis based on Per-Protocol Analysis Set will be explored as appropriate.

8.5.2. Secondary Efficacy Analyses

8.5.2.1. Key Secondary Efficacy Analyses

Due to the rarity of the disease indication and small sample size, formal multiplicity adjustment procedures will be not enforced. However, to assist the comprehensive assessment and interpretation of the setmelanotide efficacy, appropriate statistical testing will be performed on the key secondary efficacy endpoints according the following hierarchical order to control the overall type I error rate. The p-values and the corresponding confidence intervals will be provided.

- The proportion of all patients, regardless of age at baseline, who achieve a ≥10% reduction from baseline in body weight (ie, are 'responders') after ~52 weeks of treatment with setmelanotide.

  This is a similar endpoint to the primary endpoint but includes all patients, ie, regardless of age at baseline. The similar statistical method, analysis strategy and missing value handling approach that are described in Section 8.5.1 for the primary endpoint will be used. Additional supportive analyses on this endpoint based on Per-Protocol Analysis Set, the Stable Height FAS and the Active Growth FAS may be conducted as appropriate.

- Mean percent change from baseline in body weight (in patients ≥12 years of age at baseline) after ~52 weeks of treatment with setmelanotide.

  This is a continuous endpoint. [redacted] Therefore, the analysis on this endpoint will be based on a one-sample rank test, at a 1-sided 0.05 significance level, in the ≥12 yo FAS. The 2-sided 90% CI for the percent change from baseline in body weight will be provided. The similar analysis strategy and missing value handling approach that are described in Section 8.4 will be used while change from baseline will be imputed as 0 for treatment failures.

- 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 with setmelanotide.

  This binary endpoint will be analyzed using the similar statistical method, analysis strategy and missing value handling approach that are described in Section 8.5.1 for primary endpoint, based on the ≥12 yo FAS.

- 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 with setmelanotide.

  The continuous endpoint will be analyzed with a one-sample rank test, at a 1-sided 0.05 significance level, in the ≥12 yo FAS. The 2-sided 90% CI for the percent change from baseline will be provided. The similar analysis strategy and missing value handling approach that are described in Section 8.4 will be used while change from baseline will be imputed as 0 for treatment failures.

8.5.2.2. Other Secondary Efficacy Analyses

The analysis on these other secondary efficacy endpoints will be performed based on patients ≥12 years of age at baseline.

- Mean percent change from baseline in body weight (in patients ≥12 years of age at baseline) at the Week 14 visit compared with placebo.

  The analysis on this secondary endpoint will be a between group comparison, based on a two-sample rank test, at a 1-sided 0.05 significance level. The 2-sided 90% CI will be provided. The analysis will be based on ≥12 yo FAS. The similar analysis strategy and missing value handling approach that are described in Section 8.4 will be used while change from baseline will be imputed as 0 for treatment failures.

- 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) at the Week 14 visit compared with placebo.

  The between-group comparison on the proportion of patients who achieve a ≥25% improvement in the weekly average of the daily hunger score at the Week 14 visit will be conducted with a unconditional exact binomial test, at a 1-sided 0.05 significance level. The 2-sided 90% CI will be calculated using the exact Clopper-Pearson method for each group. The analysis will be based on the ≥12 yo FAS. The similar analysis strategy and missing value handling approach that are described in Section 8.5.1 will be used.

- 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.

  The between-group comparison, analysis strategy and missing value handling approach on this endpoint will be conducted with the same approach as the one used for the mean percent change from baseline in body weight at the Week 14 visit compared with placebo.

8.5.3. [redacted]

[redacted]

8.7. Multiplicity

No multiplicity adjustments are required, because this study has only 1 primary endpoint. This controls the overall alpha at 0.05, 1-sided.

There are multiple key secondary efficacy endpoints planned in the study (see Section 3.3.2.1). 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. Therefore, the Sponsor has pre-specified a step-down procedure (a hierarchical order of testing for the key secondary efficacy endpoints, see Section 8.5.2.1) to control Type-1 error, if needed for this purpose.

9. ADMINISTRATIVE REQUIREMENTS

9.1. Good Clinical Practice

The study will be conducted in accordance with the ICH for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and IB. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

9.2. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see Appendix 11.8). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

9.3. Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

9.4. Patient Confidentiality

In order to maintain patient privacy, all source documents/eCRFs, study drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the source documents/eCRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

9.5. Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by the Sponsor, and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol should not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The Sponsor or designee will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documents/eCRF.

9.6. Data Management

9.6.1. Data Handling

Data will be recorded at the site on source documents and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRA will verify data recorded in the eCRF system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the eCRF system. Electronic CRFs will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

9.6.2. Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

9.6.3. Data Entry

Data must be recorded using the eCRF system as the study is in progress. All study site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11). All passwords will be strictly confidential.

9.6.4. Medical Information Coding

For medical information the following thesauri will be used:

Medical Dictionary for Regulatory Activities (MedDRA) for adverse events

World Health Organization (WHO) Drug for concomitant medications

9.6.5. Data Validation

Validation checks programmed within the eCRF system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

Electronic CRFs must be reviewed and electronically signed by an Investigator who signed the protocol.

9.7. Direct Access to Source Data

Monitoring and auditing procedures developed or reviewed and approved by the Sponsor will be followed, to comply with GCP guidelines.

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) and will include on-site review of the source documents/CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, and fax).

All unused study drug and other study materials are to be returned to the Sponsor after the clinical phase of the study has been completed (see Section 5.7).

Regulatory authorities, the IRB/IEC, and/or the Sponsor's clinical quality assurance group or designee may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

9.8. Source Document/Case Report Form Completion

Source documents/CRFs will be completed for each study patient. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's source document/CRF. The source document/CRF should indicate the patient's participation in the study and should document the dates and details of study procedures, adverse events, and patient status.

The Investigator, or designated representative, should complete the source document/CRF as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the source document/CRF to endorse the recorded data.

The Sponsor will retain the originals of all CRFs. The Investigator will retain all completed source documents/CRFs.

9.9. Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least two years after the last marketing application approval or two years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

9.10. Liability Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

9.11. Publication of Study Findings and Use of Information

All information regarding setmelanotide supplied by the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study.

The information obtained from the clinical study will be used towards the development of setmelanotide and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

It is the intention of the Sponsor and the academic investigators to publish the results of this study in a peer-reviewed journal upon completion. For this purpose, a publication committee of the key investigators will likely be identified and initiated during this trial.

10. REFERENCES

Alverez-Satta M, Castro-Sanchez S, Valverde D. Alström syndrome: current perspectives. Appl Clin Genet. 2015;8:171-179. Review.

Bardet G. On congenital obesity syndrome with polydactyly and retinitis pigmentosa. Obes Res. 1995 Jul;3(4):387-99.

Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. J Med Genet. 1999 Jun;36(6):437-46.

Biedl A. A pair of siblings with Adiposa-genital dystrophy. Obes Res. 1995 Jul;3(4):404.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

DeVries TI, van Haelst MM. Ciliary disturbances in syndromal and non-syndromal obesity. J Pediatr Genet. 2014;3:79–88.

Feuillan P, Ng D, Han J, Sapp J, Wetsch K, Spaulding E, Zheng Y, Caruso R, Brooks B, Johnston J, Yanovski J, Beisecker L. Patients with Bardet-Biedl syndrome have hyperleptinemia suggestive of leptin resistance. J Clin Endocrinol Metab. 2011 Mar;96(3):E528-E535. Epub 5 Jan 2011.

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

Forsythe E, Beales PL. Bardet-Biedl syndrome. Eur J Hum Genet. 2013;21:8-13. Epub 20 June 2012. Review.

Forsythe E, Sparks K, Hoskins B, Bagkeris E, McGowan B, Carroll P, Huda M, Mujahid S, Peters C, Barrett T, Mohammed S, Beales P. Genetic predictors of cardiovascular morbidity in Bardet-Biedl syndrome. Clin Genet. 2015;87:343-349.

Girard D, Petrovsky N. Alström syndrome: insights into the pathogenesis of metabolic disorders. Nat Rev Endocrinol. 2011 Feb;7:77–88. Review.

Gottesdiener K, Connors H, Van der Ploeg L, Fiedorek F, Hylan M, Louis W, Lasseter K. Analysis of the synthetic peptide RM-493, a melanocortin-4 receptor (MC4R) agonist, on cardiovascular parameters in three Phase1b/2a studies. Poster - Obesity Society, 2015.

Grace C, Beales P, Summerbell C, Jebb SA, Wright A, Parker D, Kopelman P. Energy metabolism in Bardet-Biedl syndrome. Int J Obes Relat Metab Disord. 2003 Nov;27(11):1319-1324.

Guo DF, Rahmouni K. Molecular basis of the obesity associated with Bardet-Biedl syndrome. Trends Endocrinol Metab. 2011 Jul;22(7):286-293. Review.

Haitina T, Ringholm A, Kelly J, Mundy NI, Schiöth HB. High diversity in functional properties of melanocortin 1 receptor (MC1R) in divergent primate species is more strongly associated with phylogeny than coat color. Mol Biol Evol. 2007 Sep;24(9):2001-2008.

Kelly A, Fox C, Rudser K, Gross A, Ryder J. Pediatric obesity pharmacotherapy: current state of the field, review of the literature, and clinical trial considerations. Lancet. 2016 Jul;40(7):1043-1050.

Knorz V, Spalluto C, Lessard M, Purvis T, Adigun F, Collin G, Hanley N, Wilson D, Hearn T. Centriola association of ALMS1 and likely centrosomal functions of the ALMS motif-containing proteins C10orf90 and KIAA1731. Molecular Biol Cell. 2010;21:3617-3629.

Locke M, Tinsley C, Benson M, Blake D. TRIM32 is an E3 ubiquitin ligase for dysbindin. Hum Mol Genet. 2009;18(13):2344-2358.

Loktev A, Zhang Q, Beck J, Searby C, Scheetz T, Bazan J, Slusarski D, Sheffield V, Jackson P, Nachury M. A BBSome subunit links ciliogenesis, microtubule stability, and acetylation. Dev Cell. 2008 Dec 9;15:854-865.

Marshall J, Beck S, Maffei P, Naggert JK. Alström syndrome. Eur J Hum Genet. 2007 Dec;15(12):1193-1202. Epub 17 Oct 2007. Review.

Moore S, Green J, Fan Y, Bhogal A, Dicks E, Fernandez B, Stefanelll M, Murphy C, Cramer B, Dean J, Beales P, Katsanis N, Bassett A, Davidson W, Parfrey P. Clinical and genetic epidemiology of Bardet-Biedl syndrome in Newfoundland: a 22-year prospective, population-based, cohort study. Am J Med Genet. 2005 Feb;132A(4):352-360.

Nachury M, Loktev A, Zhang Q, Westlake C, Peränen J, Merdes A, Slusarski D, Scheller R, Bazan J, Sheffield V, Jackson P. A core complex of BBS proteins cooperates with the GTPase Rab8 to promote ciliary membrane biogenesis. Cell. 2007 Jun;129:1201-1213.

Nakayama K, Shotake T, Takeneka O, Ishida T. Variation of the melanocortin 1 receptor gene in the macaques. Am J Primatol. 2008;70(8):778-785.

NHLBI. The Practical Guide Identification, Evaluation, and Treatment of Overweight and Obese in Adults. NIH Publication No. 00-4084, October 2000.

National Institutes of Health [Internet]. Department of Health and Human Services (US); [reviewed 2013 Sep; cited 2018 Jun 05]. Genetics home reference. Your guide to understanding genetic conditions. Bardet-Biedl syndrome. Available from: https://ghr.nlm.nih.gov/condition/bardet-biedl-syndrome.

Orphanet [Internet]. French National Institute for Health and Medical Research (INSERM). 1997 - . Alström Syndrome; [cited 2018 Mar 01]. Available from: http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=1328&Disease_Disease_Search_diseaseGroup=Alstrom-syndrome&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group of diseases=Alstrom-syndrome&title=Alstrom-syndrome&search=Disease_Search_Simple.

Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009 Mar;20(3):629-37.

Seo S, Baye L, Schulz N, Beck J, Zhang Q, Slusarski D, Sheffield V. BBS6, BBS10, and BBS12 form a complex with CCT/TRiC family chaperonins and mediate BBSome assembly. PNAS. 2010 Jan;107(4):1488-1493.

Supistin, 2016 Suspistin E, Imyanitov E. Bardet-Biedl syndrome. Mol Syndromol. 2016;7:62-71. Epub 15 Apr 2016. Review.

11. APPENDICES

11.1. Injection Site Evaluations

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

Local Skin Tolerability Assessment

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

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

Initials: _____

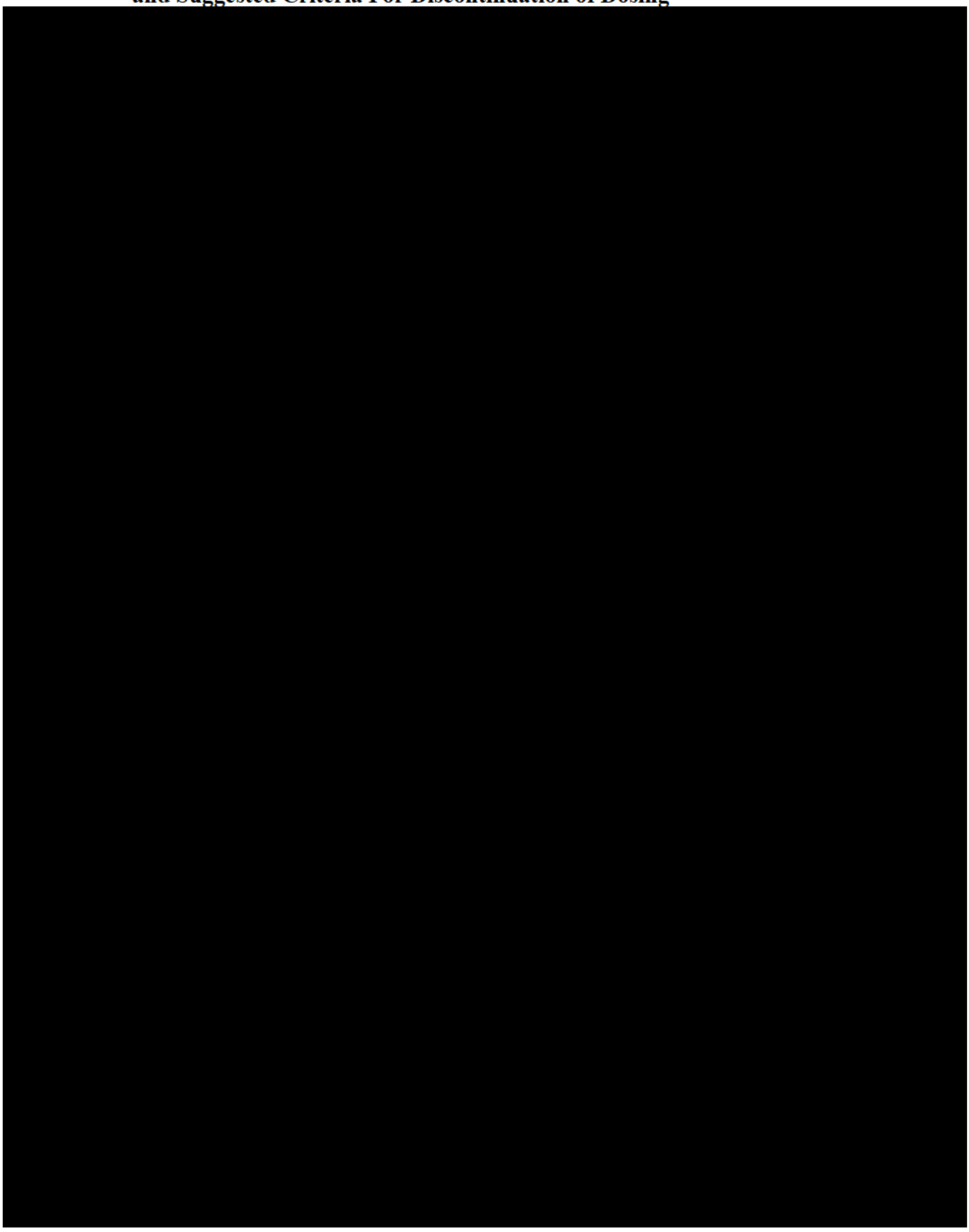
11.2. Fitzpatrick Classification Scale

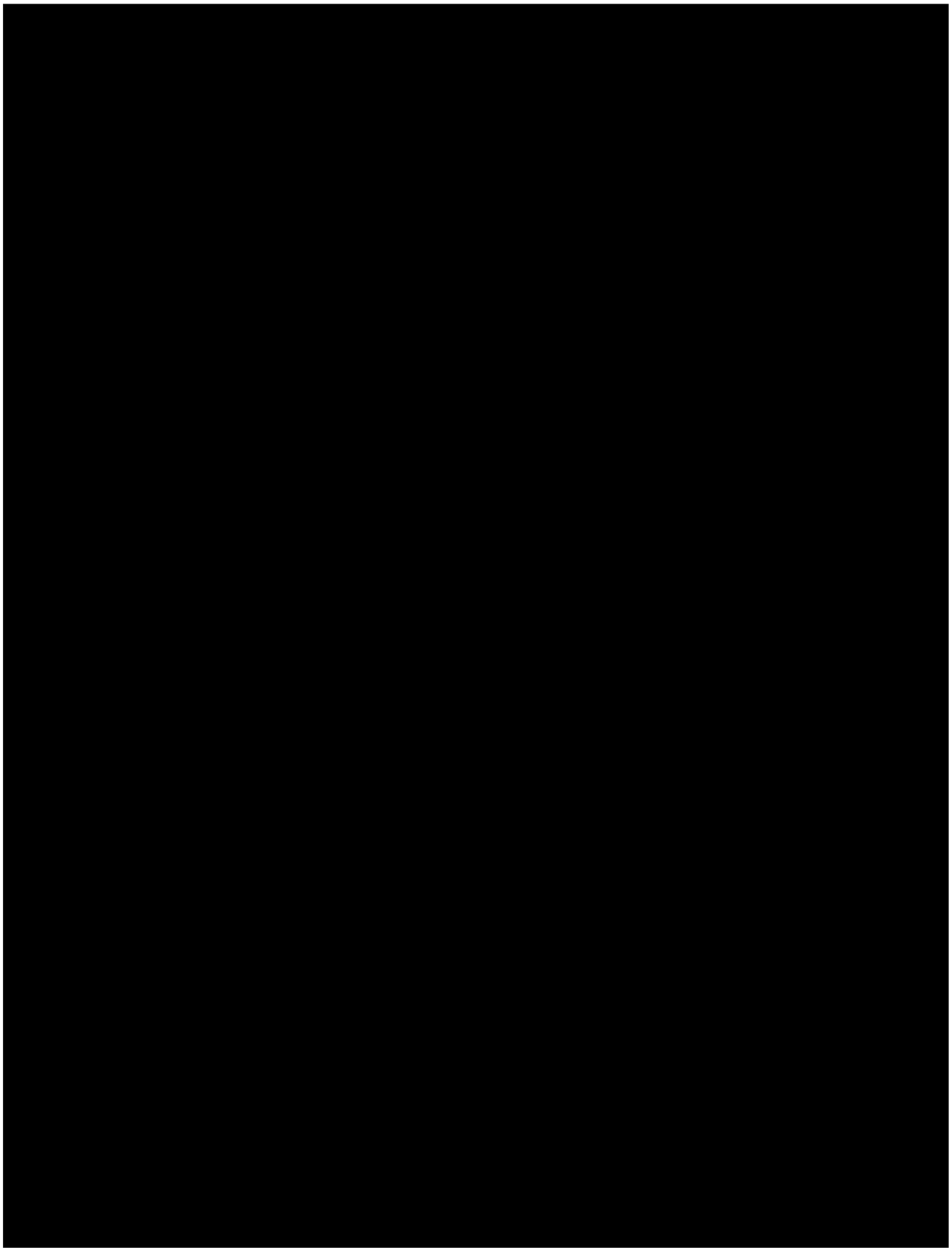
Skin Type	Skin Color	Characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel, or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, 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

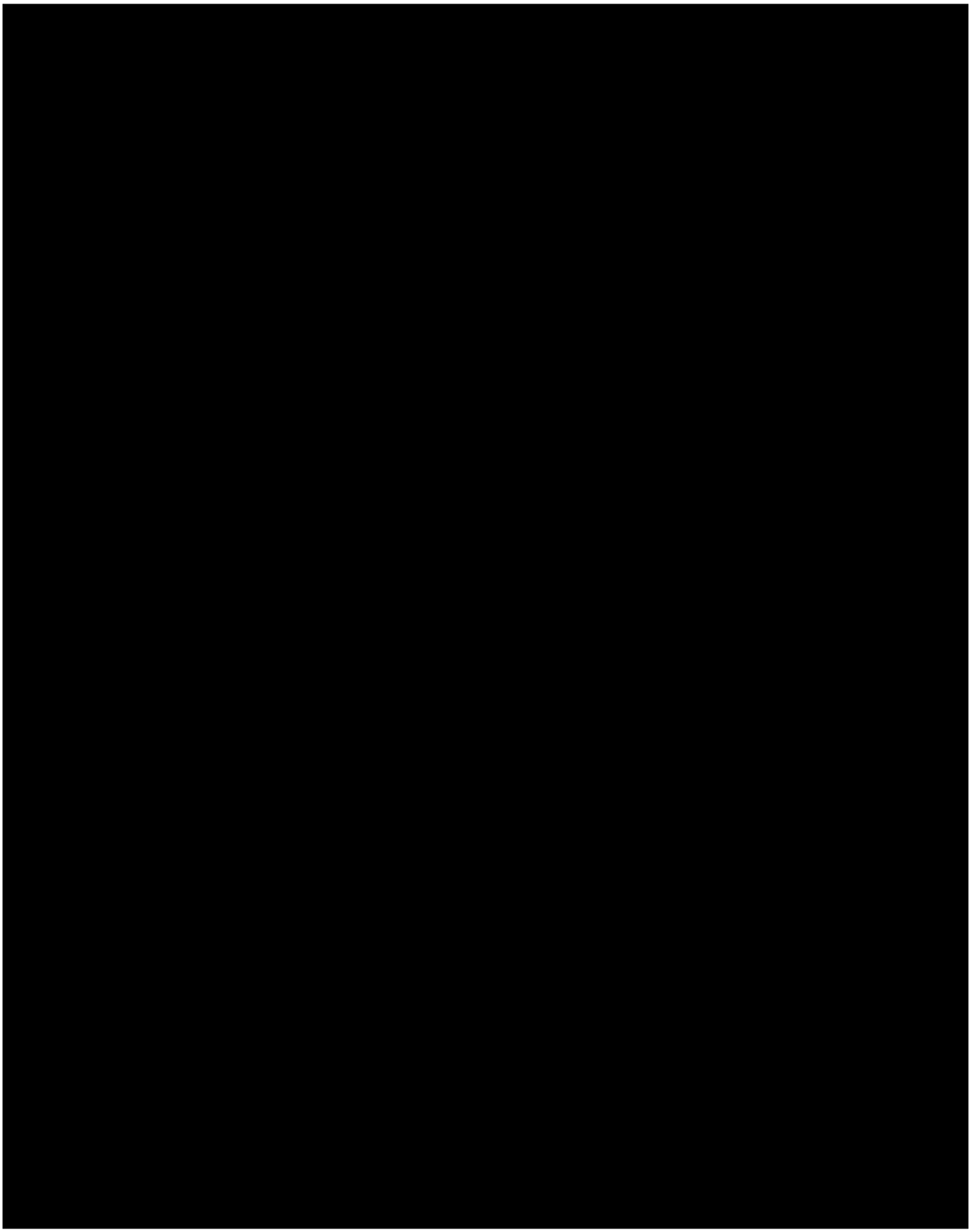
Fitzpatrick 1975

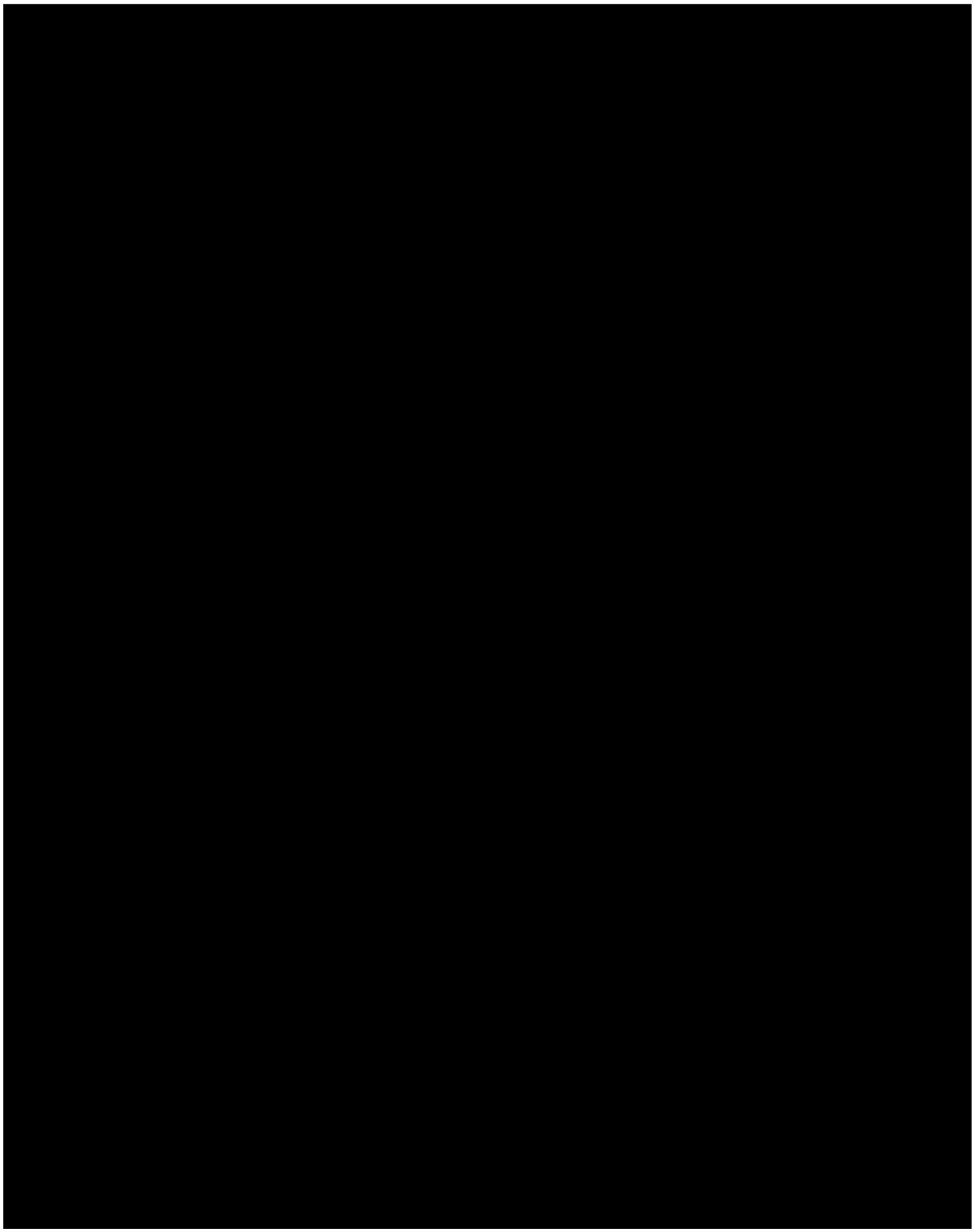
11.3. Past Medical History and Growth Curve Information

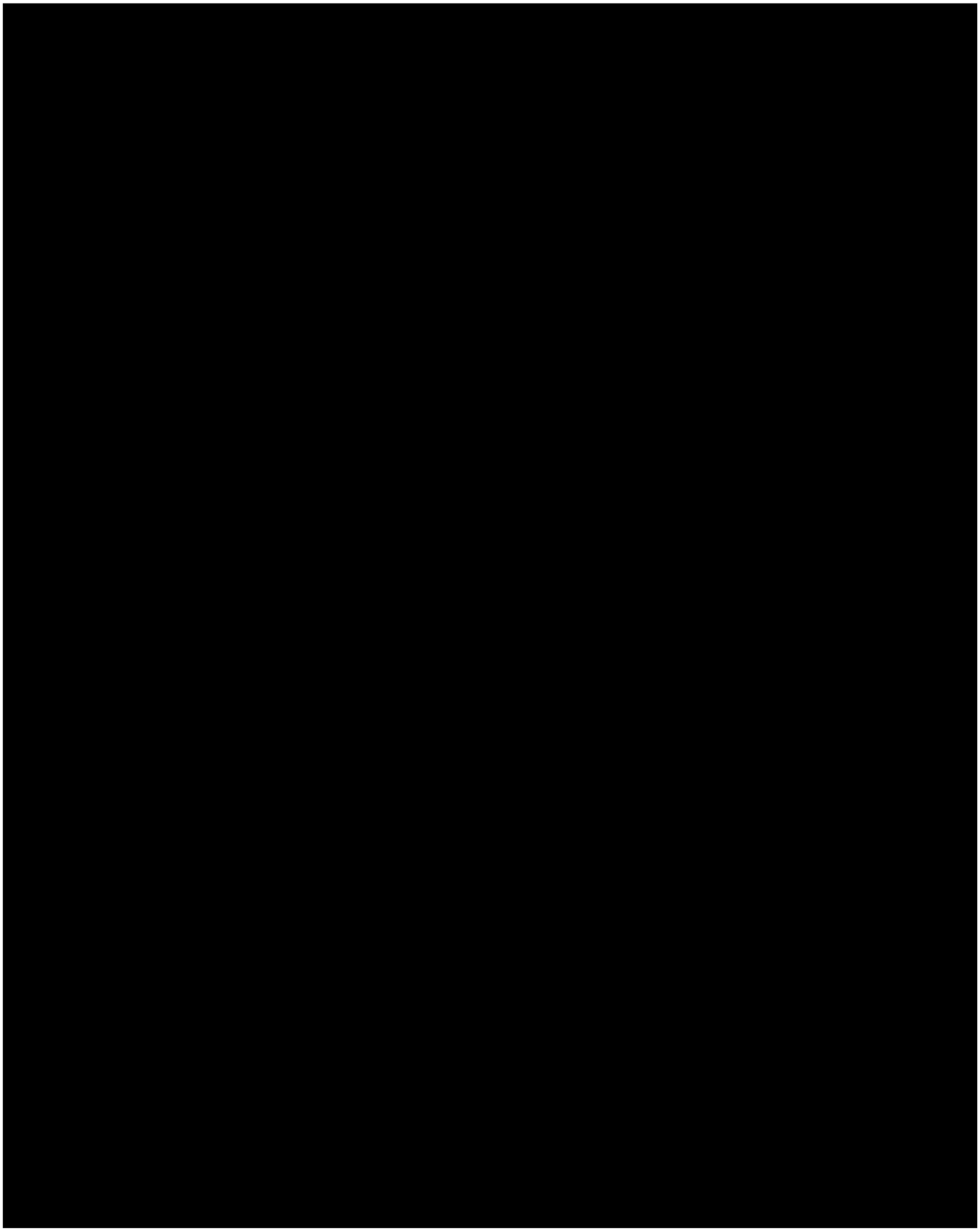
11.4. Guidance for Monitoring Potential Treatment-Related Dermatological Changes and Suggested Criteria For Discontinuation of Dosing











11.6. Creatinine Clearance Estimate

11.6.1. Cockcroft-Gault Equation

In patients, >16 years of age, the Cockcroft-Gault equation (Cockcroft 1976) should be used as follows:

Male Creatinine Clearance mL/min = 1.0 * ((140 - Age) / (Serum Creat)) * (Weight (kg) / 72)
Female Creatinine Clearance mL/min = 0.85 * ((140 - Age) / (Serum Creat)) * (Weight (kg) / 72)

Where: age is in years and serum creatinine is in mg/dL.

11.6.2. Schwartz Equation

In patients, ≤16 years of age, the creatinine-cystatin C equation (Schwartz 2009) should be used as follows:

$GFR=39.1[height/Scr]^{0.516}[1.8/cystatin\ C]^{0.294} \times [30/BUN]^{0.169}[1.099]^{male}[height/1.4]^{0.188}$

Where:

GFR= Glomerular filtration rate in cc/min/1.73m^2
Ht = Height in meters
Cystatin C = mg/L
BUN = mg/dL

11.7. Considerations for reducing pain and distress in the pediatric population

Although the study procedures and assessments required per protocol are classified as "No or Minimal Risk" (apart from DXA which is classified as "Minor Increase over Minimal Risk") per the 2008 Guidance Document "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population", considerations for reducing pain in distress in participants younger than 18 years of age are suggested below.

- The clinical trial may only be conducted if it subjects the person concerned to as little burden and other foreseeable risks as possible;
- Physical and emotional pain should be prevented as much as possible, and effectively treated when unavoidable.
- To minimize pain, distress, and fear, facilities should be appropriate to childcare, and the personnel should be trained to look after children and supervised by experienced health care professionals. Staff should be trained to communicate with both parents (or legal representative) and children. Generally, this would assume non-adult patients are being studied at experienced pediatric centers.
- For most procedures, the child should always be accompanied by a trial-related staff member who could provide reassurance. At the sign of distress and/or dissent the procedure should be stopped; a short pause to allow the child to feel in control, further explanation and an assessment of the situation may be needed to reassure the child, or to decide to abandon the procedure at the discretion of the Investigator.
- In all situations, investigations/interventions should be limited to the minimum required for obtaining valid data and performed using size-/age-appropriate material and devices, including limiting in advance the number of attempts for sampling.
- Study drug injections should only be performed by parents (or home health care professionals), unless the child is of suitable age and competency, and desires the ability to do so.
- Although almost all study procedures are classified as low risk (except for DXA which is classified as "minor increase over minimal risk"), risk should be continuously monitored and assessed by appropriate personnel.
- For assessments in which there is a psychological component measures should be taken to minimize distress. For example, Tanner Staging assessments could utilize a diagram for the child to point to and indicate what stage they currently are, vs. having to have an exam without clothes.

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

11.8. Declaration of Helsinki

World Medical Association Declaration of Helsinki:

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Patients

Adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, and the 41st WMA General Assembly, Hong Kong, September 1989, the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added); 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added); and 59th WMA General Assembly, Seoul, October 2008.

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human patients, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human patients to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human patients. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human patients, the well-being of the individual research patient must take precedence over all other interests.
7. The primary purpose of medical research involving human patients is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is patient to ethical standards that promote respect for all human patients and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human patients in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients.
12. Medical research involving human patients must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human patients must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for patients and provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study patients to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the Sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human patients must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research patients must always rest with the physician or other health care professional and never the research patients, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human patients must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first patient.
20. Physicians may not participate in a research study involving human patients unless they are confident that the risks involved have been adequately assessed and can be satisfactorily

managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human patients may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research patients.
22. Participation by competent individuals as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human patients, each potential patient must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential patient must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients as well as to the methods used to deliver the information. After ensuring that the potential patient has understood the information, the physician or another appropriately qualified individual must then seek the potential patient's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential patient is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research patient who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential patient, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research patient who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential patient's dissent should be respected.
29. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for

involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the patient or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human patients and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research patients.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be patient to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.