

Title: An Open Label, 1-Year Trial, Including a Double-Blind Placebo-Controlled Withdrawal Period, of Setmelanotide (RM-493), a Melanocortin 4 Receptor (MC4R) Agonist, in Early Onset POMC Deficiency Obesity Due to Bi-Allelic Loss-of-Function POMC or PCSK1 Genetic Mutation

NCT: NCT02896192

Date: July 24, 2018

CLINICAL STUDY PROTOCOL

Protocol RM-493-012

An Open Label, 1-Year Trial, including a Double-Blind Placebo-Controlled Withdrawal Period, of Setmelanotide (RM-493), a Melanocortin 4 Receptor (MC4R) Agonist, in Early Onset POMC Deficiency Obesity due to Bi-Allelic Loss-of-Function *POMC* or *PCSK1* Genetic Mutation

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.

EudraCT No.; 2016-002320-83

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Sponsor Signatory:



Document Version (Date):	08 JUN 2016	Version 1 (Original)
UK Specific Amendment	18 AUG 2016	Amendment 1 (UK Only)
GE Specific Amendment	08 SEP 2016	Amendment 2 (Germany Only)
FR Specific Amendment	14 SEP 2016	Amendment 3 (France Only)
Amendment	23 FEB 2017	Amendment 4 (All Countries/Sites)
FR Specific Amendment	26 APR 2017	Amendment 5 (France Only)
Amendment	22 MAY 2017	Amendment 6 (All Countries/Sites)
CAN Specific Amendment	11 JULY 2017	Amendment 7 (Canada Only)
GE Specific Amendment	07 AUG 2017	Amendment 8 (Germany Only)
Amendment	23 OCT 2017	Amendment 9 (US, Canada, Germany, UK Only)
FR Specific Amendment	08 NOV 2017	Amendment 10 (France Only)
Amendment	03 APR 2018	Amendment 11 (Global with exception of France)
CAN Specific Amendment	11 JUN 2018	Amendment 12 (Canada Only)
Amendment	24 JUL 2018	Amendment 13 (Global with exception of France)

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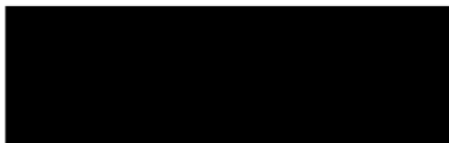
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An Open Label, 1-Year Trial, including a Double-Blind Placebo-Controlled Withdrawal Period, of Setmelanotide (RM-493), a Melanocortin 4 Receptor (MC4R) Agonist, in Early Onset POMC Deficiency Obesity due to Bi-Allelic Loss-of-Function *POMC* or *PCSK1* Genetic Mutation

REVIEWED/APPROVED BY:



Rhythm Pharmaceuticals, Inc.



Signature

24JUL2018

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/Ethics Committee. No changes will be made to the study protocol without the prior written approval of Rhythm and the Institutional Review Board/Ethics Committee, 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

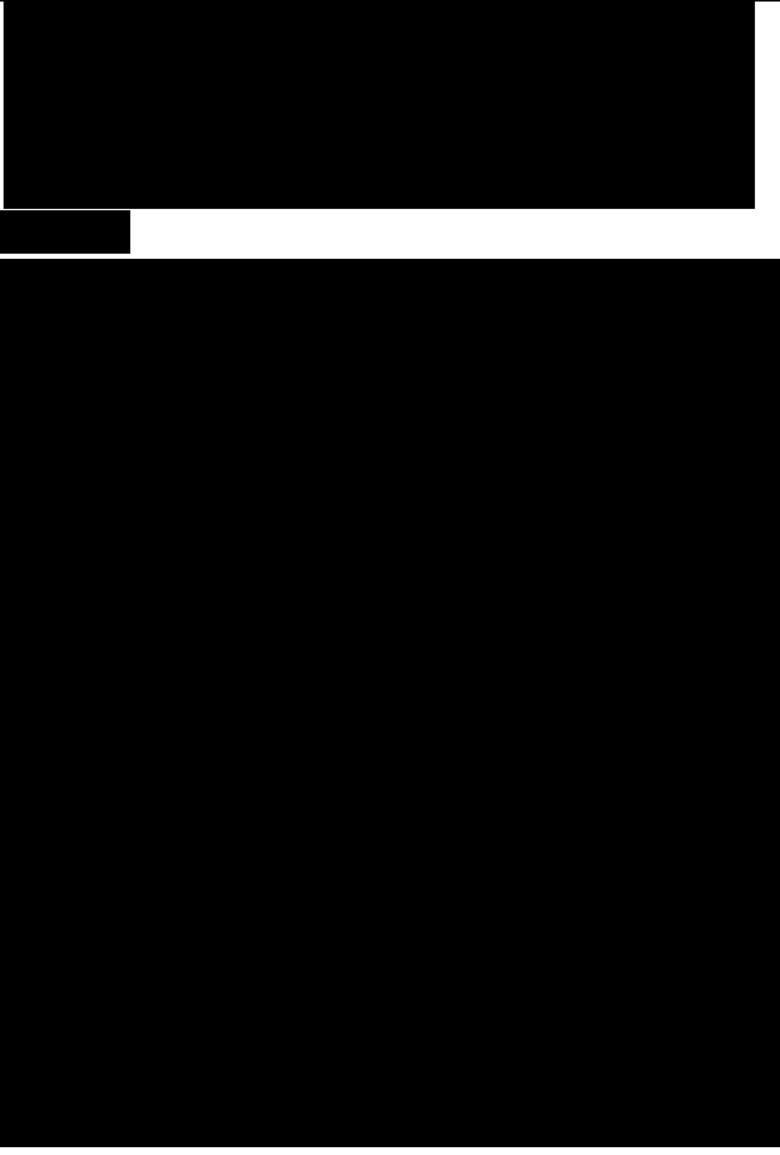
Investigator Signature

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-493-012
Protocol Title	An Open Label, 1-Year Trial, including a Double-Blind Placebo-Controlled Withdrawal Period, of Setmelanotide (RM-493), a Melanocortin 4 Receptor (MC4R) Agonist, in Early Onset POMC Deficiency Obesity due to Bi-Allelic Loss-of-Function <i>POMC</i> or <i>PCSK1</i> Genetic Mutations
Clinical Phase/Trial Type	Pivotal, ~1 year open label active treatment with a double-blind, placebo-controlled withdrawal period.
Treatment Indication	Treatment of POMC Deficiency Obesity
Objective(s)	<p><u>Primary</u></p> <ul style="list-style-type: none"> To demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change in patients with pro-opiomelanocortin (POMC) deficiency obesity due to rare bi-allelic or loss-of function mutations at the end of 1 year of treatment. <p><u>Secondary</u></p> <p>To assess the effect of setmelanotide, over one year, on:</p> <ul style="list-style-type: none"> Safety and tolerability of setmelanotide (including blood pressure [BP] and heart rate [HR]). Hunger for patients ≥ 12 years of age. Percent change in body fat mass. Glucose parameters: fasting glucose, glycated hemoglobin (HbA1c), oral glucose tolerate test (OGTT) with focus on parameters of insulin sensitivity. Waist circumference. During withdrawal from drug: reversal of weight and hunger reduction during the double-blind placebo-controlled withdrawal period. <div style="background-color: black; height: 40px; width: 100%; margin-top: 20px;"></div> <div style="background-color: black; height: 40px; width: 100%; margin-top: 20px;"></div>

	
Trial Design	<p>This is a pivotal study to assess long-term (~1 year) efficacy of setmelanotide in POMC deficiency obesity. The study will begin with an initial period of dose titration lasting between 2 and 12 weeks where the individual patient's therapeutic dose will be established by upwards dose titration in 2-week intervals. Thereafter, patients will continue on active treatment at their individually titrated optimal therapeutic dose for an additional 10 weeks, for a total combined dosing duration of 12 weeks at the individual patient's therapeutic dose [i.e., the last 2 weeks during dose titration plus 10 weeks open label treatment]. For patients who demonstrate at least 5 kg weight loss (or at least 5% weight loss if baseline body weight < 100 kg) at the end of the Open Label Treatment Period, they will continue onto the double-blind, variably-timed, placebo-controlled, withdrawal period lasting 8 weeks</p>

	<p>inclusive of a 4-week period of placebo treatment. The onset of the placebo period will be variable for each patient in order to mask the actual timing of the withdrawal period. Following the 8-week withdrawal period, patients will continue dosing at their therapeutic dose for ~32 weeks, resulting in a total of ~52 weeks dosing at their therapeutic dose.</p> <p>Where feasible, and for patients who agree to participate, there are optional sub-studies to evaluate [REDACTED]</p> <p>[REDACTED]</p>
Study Population	Male and female patients, 6 years of age and above, with a confirmed diagnosis of POMC Deficiency Obesity due to bi-allelic, loss-of-function <i>POMC</i> or proprotein convertase subtilisin/kexin type 1 (<i>PCSK1</i>) gene mutations.
Number of Patients & Study Centers	<p>It is currently anticipated that a total of ~10 patients will be enrolled in this study. The total number of patients required for registration is yet to be confirmed with applicable regulatory authorities, given that true prevalence of this ultra-rare disease is uncertain. Therefore, the total number of patients may be increased or decreased, in order to satisfy regulatory requirements for registration, depending upon the total number of affected patients identified.</p> <p>It is anticipated that ~ 10 centers located worldwide will participate in this study. In the event additional patients are to be enrolled, additional sites may be added, as necessary.</p>
Inclusion Criteria	<ol style="list-style-type: none"> 1. Bi-allelic, homozygous or compound heterozygous (a different gene mutation on each allele) genetic status for either the <i>POMC</i> or <i>PCSK1</i> genes, with the loss-of-function (LOF) variant for each allele conferring a severe obesity phenotype. 2. Age 6 years and above. 3. If adult age ≥ 18 years, obesity with body mass index (BMI) ≥ 30 kg/m²; if child or adolescent, obesity with BMI ≥ 95th percentile for age on growth chart assessment. 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 be able to understand and sign the written informed consent/assent, after being informed about the study.

	<ol style="list-style-type: none"> 5. Female participants of child-bearing potential must 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 FSH level in the post-menopausal lab range), or delayed pubertal development and failure to have achieved menarche, do not require contraception during the study. 6. Male participants with female partners of childbearing potential must agree to a double barrier method if they become sexually active during the study. Male patients must not donate sperm during and for 90 days following their participation in the study.
Exclusion Criteria	<ol style="list-style-type: none"> 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 weight loss or weight stabilization. Patients may be reconsidered approximately 1 month after cessation of such intensive regimens. 2. 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, or resulted in <10% weight loss compared to pre-operative baseline weight or 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 Rhythm prior to enrollment. 3. Diagnosis of schizophrenia, bipolar disorder, personality disorder or other Diagnostic and Statistical Manual of Mental Disorders (DSM-III) disorders that the investigator believes will interfere significantly with study compliance. 4. A Patient Health Questionnaire-9 (PHQ-9) score of ≥ 15. 5. Any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS). Any lifetime history of a suicide attempt, or any suicidal behavior in the last month. 6. Current, severe stable restrictive or obstructive lung disease as a consequence of extreme obesity, evidence of significant heart failure (NYHA Class 3 or greater), or oncologic disease, if these were severe enough to interfere with the study and/or would confound the results. Any

	<p>such patients should be discussed with the sponsor prior to inclusion.</p> <ol style="list-style-type: none"> 7. History of significant liver disease or liver injury, or current liver assessment for a cause of abnormal liver tests [as indicated by abnormal liver function tests, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, or serum bilirubin ($> 2.0 \times$ 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 will be exclusionary, but the presence of NAFLD would not be exclusionary. 8. History or presence of impaired renal function as indicated by clinically significant abnormal creatinine, blood urea nitrogen (BUN), or urinary constituents (e.g., albuminuria) or moderate to severe renal dysfunction as defined by the Cockcroft Gault equation < 30 mL/min (Appendix 11.10). 9. History or close family history (parents or siblings) of skin cancer or melanoma, or patient history of ocular-cutaneous albinism. 10. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions, determined as part of a screening comprehensive skin evaluation performed by a qualified dermatologist. Any concerning lesions identified during the screening period will be biopsied and results known to be benign prior to enrollment. If the pre-treatment biopsy results are of concern, the patient may need to be excluded from the study. 11. Volunteer 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. 15. Patients who have been placed in an institution through an official or court order, as well as those who are dependent on the sponsor, Investigator or study site.
Synopsis of Study Activities	<p>After an initial screening and confirmation of eligibility inclusive of an in depth retrospective medical history, patients will enter the Open Label Dose Titration Phase lasting between 2 and 12 weeks (depending upon the number of titration steps) where the individual patient's therapeutic dose</p>

will be established. Once the patient's therapeutic dose is determined, the patient will enter a 10-week Open Label Active Treatment Phase.

Following the dose titration and 10-week open label active treatment phases, patients who lose at least 5 kg (or 5% if < 100 kg at baseline) of weight from baseline, and who continue to show tolerability to setmelanotide, will continue into the 8-week Double-Blind Placebo Controlled Withdrawal phase. Patients who do not exhibit the required weight loss of at least 5 kg (5% if < 100 kg at baseline) will be withdrawn from the treatment, but should continue with the study assessments.

During this time, patients will be assigned to the 4-week sequence in which they receive placebo in a double-blinded sequence. The key objective of this phase is to implement the only double-blind, placebo-controlled period for this study that will inform patient's symptomatic hunger and weight change responses to stopping and then restarting active therapy with setmelanotide without awareness of the timing of the withdrawal.

Next, patients will resume with Open Label Active Treatment for an additional ~32 weeks, for a total of ~52 weeks of treatment at the individual patient's therapeutic dose (inclusive of the 4-week placebo withdrawal).

Study Procedures

The primary efficacy endpoint is the proportion of patients in the full analysis set (FAS) who meet the $\geq 10\%$ weight loss threshold (responders) after ~1 year of treatment, compared to the proportion from historical data (at most 5% responders in the null population). Therefore, frequent weight measurements will be obtained throughout the course of the trial. Supporting efficacy endpoints will include: Hunger assessed daily by a questionnaire using a Likert-type scale (ages 12 years and older) [REDACTED] as well as by 2 Global Hunger Questions for each patient over time, including during the Screening Period; body composition assessments including total body weight loss, [REDACTED] measured in kg as well as percent change from baseline; and waist circumference.

The safety and tolerability of setmelanotide QD SC injection will be assessed by the frequency and severity of adverse events (AEs) as well as changes in physical examinations, electrocardiograms (ECGs), vital signs (including resting BP and HR), laboratory evaluations, and injection site reactions.

	<p>Potential improvements in [REDACTED] glucose parameters as measured by fasting glucose, HbA1c and OGTT with focus on parameters of insulin sensitivity will be assessed over time.</p> <p>Several questionnaires will be utilized throughout the study to assess [REDACTED]</p> <p>[REDACTED]</p> <p>will be monitored over the entire course of the trial.</p>
Study Drug and Administration	<p>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 Rhythm.</p> <p>Setmelanotide drug product (RM-493-mPEG/DSPE formulation) is a sterile solution for injection. The product is manufactured at a concentration of 10.0 mg/mL.</p> <p>Placebo will be vehicle.</p> <p>Setmelanotide and placebo will be administered as subcutaneous (SC) injection once daily.</p> <p>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. Rhythm will provide extra placebo supplies for use during training.</p>
Statistical Considerations	<p>The objective of this study is to demonstrate statistically significant and clinically meaningful weight loss in patients with POMC deficiency obesity after 1 year of treatment.</p> <p>Given the rarity of this disorder, estimated power for expected weight change efficacy can be determined from the initial weight loss response observed in 2 patients evaluated in study RM-493-011 (the ongoing investigator-initiated, open-label, pilot study with setmelanotide in POMC deficiency obesity conducted in Berlin, Germany). Data from these first two POMC deficiency obesity patients were striking, with mean percent weight change = -10.0% (95% CI: -12.6%, -7.52%), for percent change from baseline after 9 weeks of treatment. As patients remain on treatment for 1 year, more weight loss is expected.</p>

The primary endpoint is proportion of patients in the FAS who demonstrate at least 10% weight at 1 year (10-14 months post baseline) compared to baseline. Patients with missing data after 10 months from baseline will be counted as not having 10% weight loss at 1 year. The primary research hypothesis is that this proportion is at least 5%. The null hypothesis is that this proportion is at most 5%. Since prior data on untreated POMC deficient patients suggests none will have 10% weight loss at 1 year without intervention, the 5% assumed null hypothesis value is conservative.

It is expected that treatment with RM-493 for 1 year is associated with a TRUE underlying probability of at least 10% weight loss at 1 year of at least 50%. That assumption yields at least 94% power to yield a statistically significant ($\alpha=0.05$ and 0.025 1-sided, due to discreteness of the binomial distribution) difference from the null hypothesis 5% value for $N=10$ FAS patients. If the TRUE probability of at least 10% weight loss at 1 year is 40%, then power is ~83%. The minimum OBSERVED proportion of $N=10$ patients with at least 10% weight loss at 1 year that would yield statistical significance ($\alpha=0.05$ and 0.025 1-sided, due to discreteness of the binomial distribution) is 0.3 (3 of 10).

As the sample size in this trial is limited due to rareness of POMC deficiency, one-sample summary statistics and individual patient listings will be provided to report and assess the data from the trial. Details will be in a separate Statistical Analysis Plan (SAP) document.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACTH	Adrenocorticotrophic hormone
ADA	Anti-drug antibody
AE	Adverse event
AgRP	Agouti-Related Peptide
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the curve
b-LPH	β-lipotropin
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
BIA	Bioelectrical impedance
BMI	Body mass index
BDNF	Brain-derived neurotrophic factor
BP	Blood pressure
BPM	Beats per minute
BUN	Blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CL	Total clearance
C _{max}	Peak observed concentration
C _{min}	Minimum observed concentration
CNS	Central nervous system
CO ₂	Carbon dioxide
CPK	Creatine phosphokinase
CRA	Clinical research associate
CRF	Case report form

Abbreviation	Definition
CSC	Clinical Safety Committee
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CVD	Cardiovascular disease
DHEA-S	Dehydroepiandrosterone sulfate
DXA	Dual-energy x-ray absorptiometry
DIO	Diet-induced obese
DSM-III	Diagnostic and Statistical Manual of Mental Disorders Version III
EC ₅₀	Half maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
Free T4	Free thyroxine
GC	Glucocorticoid
GCP	Good clinical practice
GGT	Gamma-glutamyltranspeptidase
GH	Growth hormone
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GnRH	Gonadotropin-releasing hormone
HbA1c	glycated hemoglobin
Hg	Mercury
HIV	Human immunodeficiency virus

Abbreviation	Definition
HR	Heart rate
IB	Investigator Brochure
ICH	International Conference for Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LepR	Leptin Receptor
LFT	Liver function tests
LH	Luteinizing hormone
MAD	Multiple ascending dose
MC	Melanocortins
MC1R	Melanocortin Receptor type 1
MC3R	Melanocortin Receptor type 3
MC4R	Melanocortin Receptor type 4
MedDRA	Medical Dictionary for Regulatory Activities
MHP	Mental health professional
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
NPY	Hypothalamic neuropeptide Y
OGTT	Oral glucose tolerance test

Abbreviation	Definition
PCSK1	Proprotein Convertase Subtilisin/Kexin Type 1
PD	Pharmacodynamic
PDO	POMC deficiency obesity
[REDACTED]	
[REDACTED]	
PT	Prothrombin time
PTT	Partial thromboplastin time
POMC	Pro-opiomelanocortin
PWS	Prader-Willi Syndrome
PYY	Peptide YY
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
[REDACTED]	
SMB	Safety Monitoring Board
SOA	Schedule of assessments
TEAE	Treatment emergent adverse event
[REDACTED]	
TSH	Thyroid stimulating hormone
US	United States
ULN	Upper limit of normal
UV	Ultraviolet
[REDACTED]	

Abbreviation	Definition
WMA	World Medical Association

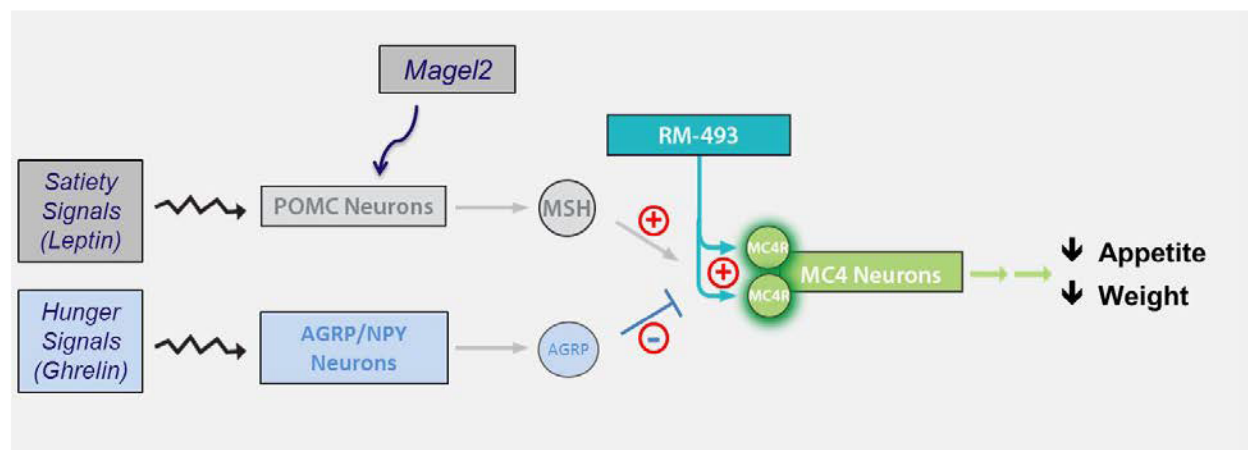
1. INTRODUCTION

1.1. Overview of Monogenic Early-Onset Obesity and the POMC – MC4R Pathway

Although human obesity is recognized as being influenced by both genetic and environmental factors, extreme morbid obesity with an onset in infancy or early childhood is often found to be more clearly caused by specific genetic factors. In fact, the identification of critical hypothalamic pathways that respond to both peripheral derived hormones (e.g., leptin) and to other neuropeptides and signaling molecules has subsequently led to the elucidation of many single gene disorders involving these same neuropeptide regulators ([van der Klaauw 2015](#)).

Thus, the hypothalamus serves as a key integrative region of the brain and includes both stimulatory and inhibitory pathways/regions that coordinately regulate appetite, caloric intake and energy expenditure. As depicted in Figure 1, the peripheral hormone ghrelin stimulates hypothalamic neuropeptide Y (NPY) and Agouti-Related Peptide (AgRP)-producing neurons, which each increase appetite and reduce metabolic rate. These two neuropeptides (NPY and AGRP) are “downstream” from peripheral ghrelin and provide powerful orexigenic (i.e., appetite-stimulating) signals that can each be countered by melanocortin agonists through activation of the melanocortin 4 receptor (MC4R). Under normal conditions, the natural ligands for the MC4R in the hypothalamus are derived from pro-opiomelanocortin (POMC) neurons. POMC neurons in-turn can be activated by the anorexigenic, fat-derived hormone, leptin and by other brain signals.

Figure 1: Schematic outline of hypothalamic food intake control

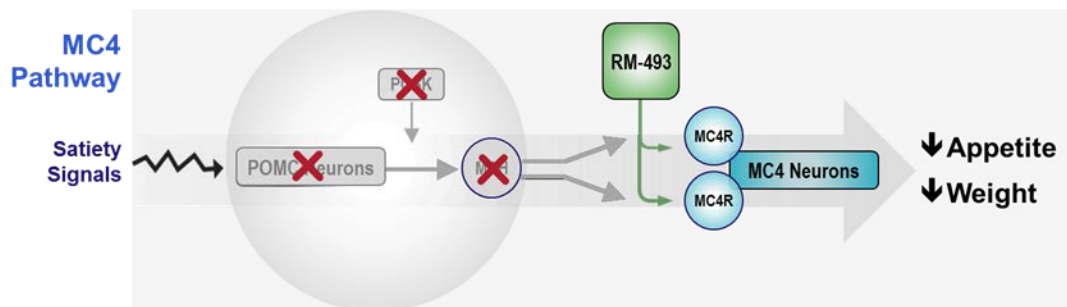


1.1.1. POMC Genetic Obesity

In patients with POMC deficiency obesity (selectively abbreviated as PDO in subsequent sections of this document), neuropeptides synthesized and processed from the POMC gene are absent or deficient due to defects in two genes. Specifically, PDO results from one of two different homozygous genetic defects, both upstream of MC4R: 1) loss of function mutations in the POMC gene itself or 2) mutations in the Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1) gene, which encodes the proprotein convertase subtilisin/kexin type 1 that processes POMC into derivative melanocyte stimulating hormone (MSH) neuropeptides that bind to

MC4R in target hypothalamic neurons ([Seidah 2012](#); [van der Klaauw 2015](#), [Coll 2004](#), [Ramachandrappa 2011](#)). Therefore, clinical PDO is caused by two monogenic disorders resulting in missing MSH neuropeptide synthesis and/or processing, with subsequent absence of signaling through the POMC – MC4R pathway, mediating central nervous system (CNS) control of appetite and weight regulation as depicted in Figure 2.

Figure 2: Reduction in satiety signaling from defects in POMC neurons



1.1.2. Loss of POMC Gene Function

POMC deficiency due to loss of the POMC gene is a rare autosomal recessive genetic disorder characterized by severe, early-onset obesity and profound hyperphagia as hallmark clinical features along with variable penetrance for traits of red hair, pale skin, adrenocorticotrophic hormone (ACTH) deficiency, and secondary cortisol deficiency ([Pagon 2013](#), [Jackson 1997](#), [Krude 1998](#)). Patients with such POMC gene mutations exhibit an onset very early in life, often beginning in infancy, with rapid weight gain that is associated with voracious, overactive appetite and pronounced hyperphagic feeding behaviors. Remarkable weight increases over many standard deviations from the normal weight growth curves are typical in these patients. The obesity and hyperphagia in these patients can be explained by the lack of MSH activation of MC4R in hypothalamic nuclei controlling energy homeostasis. Red hair and skin paleness can also develop due to the lack of MSH effect on the melanocortin 1 receptors (MC1R) within the skin, but this phenotypic feature is variable in part depending on ethnic background. The lack of ACTH production by the pituitary gland and activation of melanocortin 2 receptors (MC2R) in the adrenal glands may result in secondary adrenal deficiency. Patients are often diagnosed soon after birth due to adrenal insufficiency. If the diagnosis is missed in early infancy, patients can die from adrenal glucocorticoid insufficiency (many POMC deficiency patients have had siblings with unexplained early deaths). However, if patients are identified and begun on life-sustaining glucocorticoid (GC) replacement, or if patients have residual expression of ACTH from the pituitary, voracious infant feeding and weight gain is noted, and obesity develops rapidly during early infancy. The diagnosis of POMC deficiency is confirmed by the presence of biallelic variants in the POMC gene. Other endocrine abnormalities observed include central hypothyroidism due to thyroid stimulating hormone (TSH) deficiency, adult-onset growth hormone (GH) deficiency, and adolescent-onset hypogonadotropic hypogonadism due to lack of luteinizing hormone (LH) or follicle-stimulating hormone (FSH) ([Pagon 2013](#)). The primary hormone deficiencies are treated by appropriate replacement therapies (GC, levothyroxine, GH, gonadotropin-releasing hormone (GnRH)/sex steroids).

1.1.3. Loss of PCSK1 Gene Function

The clinical phenotype of PCSK1 genetic mutation patients is more complex than the presentations of POMC gene defect patients in some respects, but they share the prominent phenotype of early-onset obesity and severe hyperphagia ([Jackson 1997](#), [O’Rahilly 1995](#), [Jackson 2003](#)). The two initial patients described with PCSK1 enzyme deficiency are representative of the disease; both were compound heterozygotes for PCSK1 loss-of-function mutations and had severe early-onset obesity. Gastrointestinal symptomatology (primarily malabsorption and chronic diarrhea) are prominent early in life, resulting in somewhat less dramatic infant weight increases compared to POMC gene defect patients (Martin 2013). The first patient also had hypogonadotropic hypogonadism, postprandial hypoglycemia, and low cortisol, and was shown to have impaired POMC peptide and proinsulin processing ([Farooqi 2007](#)). The second patient also had small intestinal absorption dysfunction and abnormal gut hormone processing ([Martin 2013](#)). It is likely that the obesity and hyperphagia in these subjects is related to the impairment of POMC processing, which becomes more prominent as gut maturation progresses and gastrointestinal (GI) symptoms improve in early childhood; however, it is not possible to exclude the possibility that defects in the processing of a number of other hormones may also be abnormal, and could potentially contribute to the early-onset obesity phenotype ([Jackson 1997](#)). Similar to POMC-deficiency, patients are managed by appropriate hormone replacement therapy.

1.2. Rationale and Justification for the proposal to treat PDO with an MC4R agonist

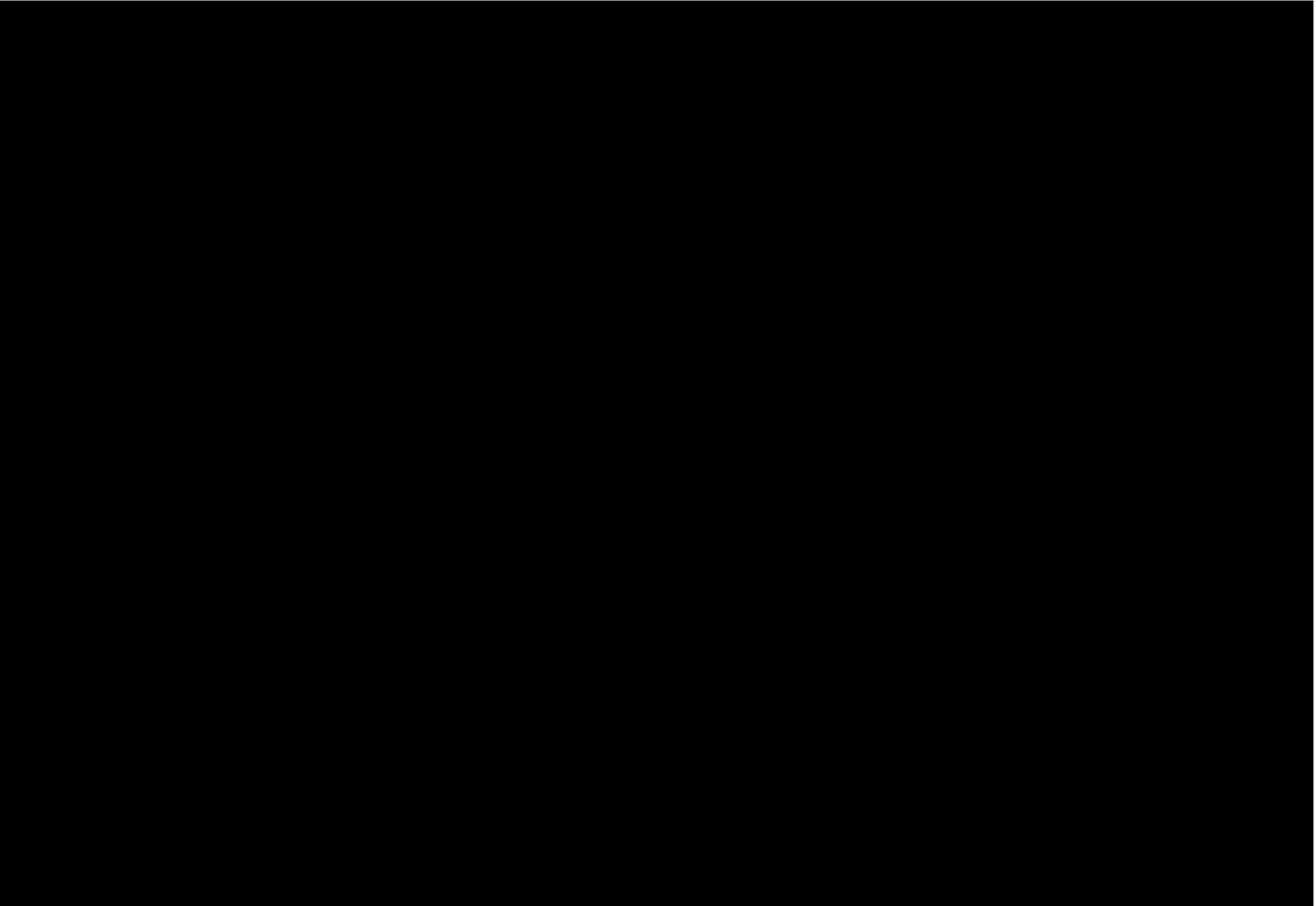
Setmelanotide is a MC4R agonist that retains the specificity and functionality of the naturally occurring POMC-derived neuropeptide, α -MSH, which is the natural ligand for MC4R.

The melanocortins (MC) are a family of peptide hormones (including ACTH, α -MSH, β -MSH, and γ -MSH) that are all derived from the common precursor, POMC. The MCs regulate energy homeostasis and body weight ([Wikberg 2008](#), [Foster 2003](#), [Marks 2001](#)). MC4Rs are expressed throughout the central nervous system and are involved in the regulation of behavior and metabolic processes associated with energy homeostasis (satiety, energy expenditure). MC4R has been identified as the dominant MC receptor involved in body weight regulation. Therefore, setmelanotide has the potential to restore lost activity in the POMC-MC4R pathway by bypassing the defects upstream of MC4R and directly activating MC4R neurons in the hypothalamus below such defects. Thus, setmelanotide may serve as another form of “replacement” therapy to re-establish weight and appetite control in patients with these monogenic disorders.

The use of setmelanotide for the treatment of PDO is supported by clinical studies in two POMC deficient patients. The evidence is based on a 90 day (13- week) investigator-initiated and sponsored Phase 2, non-randomized, open label pilot study with setmelanotide (Study RM-493-011) in up to 6 POMC deficiency patients. After efficacy-gated dose escalation, aiming for weekly weight loss of ~2 kg/week, the primary endpoint is weight loss with other key endpoints including hunger score (using the [REDACTED])

[REDACTED] body composition, insulin and glucose parameters, metabolic and cardiovascular risk factors, energy expenditure, and general safety and tolerability. Study RM-493-011 is a non-IND study being conducted in Berlin, Germany and has been approved by the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte; BfArM), with a EudraCT number of 2014-002392-28.

Because the study was designed as the first replacement of melanocortin activation in a POMC-deficient patient, a low starting dosage of setmelanotide 0.25 mg subcutaneous (SC), once daily was employed, with slow dose escalation (the dose was steadily increased every 1-2 weeks until the mean weight loss was approximately 2 kg per week). The first subject completed 13 weeks of setmelanotide therapy (main study), was off treatment for three weeks, and then was retreated for >26 weeks as part of the Extension Phase. Preliminary data on this patient are available through November 15, 2015.



These proof-of-concept clinical data demonstrate the compelling efficacy of setmelanotide in the two adult patients with PDO. The effect of treatment was clearly reversed upon withdrawal of the drug in the first patient, but re-initiation of therapy again demonstrated the beneficial effects of setmelanotide. Such dramatic weight and feeding behavior changes are quite convincing, even if observed in an open-label, n=2 setting, because these patients had previously demonstrated long-term refractoriness to attempted weight loss or hunger amelioration in medical care provided by their Berlin or Paris physicians for over 2 decades. While data are not available from PCSK1 deficient patients, the results from the POMC deficient patients present a medically plausible basis of effectiveness in PCSK1 patients due to similar defects in the POMC-MC4R pathway secondary to neuropeptide and hormonal processing impairment.

In summary, setmelanotide may provide for the restoration of more normal hunger / appetite with intact satiety responses and active regulation of energy expenditure, in essence as a form of

replacement therapy that ultimately can lead to markedly improved weight regulation with profound body weight and fat mass loss over time. These “precision medicine” therapeutic effects of setmelanotide are clearly evident in appropriately identified patients with monogenic loss-of-function mutations in the POMC gene; this trial will also be testing for similar therapeutic responses in additional POMC deficiency obesity patients from other global and US clinical sites. This study also seeks to evaluate the therapeutic effect of setmelanotide in similar early-onset, extreme obesity patients with mutations in the PCSK1 gene involved in POMC neuropeptide processing and possibly in monogenic obesity patients with mutations of genes involved in the upstream regulation of the POMC-MC4 hypothalamic pathway.

1.3. Setmelanotide Background and Clinical Experience

1.3.1. Pre-clinical experience

The setmelanotide peptide was initially selected for clinical development based on its acceptable circulating half-life as a saline formulation (2.8 - 3.5 hours in non-human primates) and the ability to decrease body weight gain and suppress food intake in normal rats. Subsequent studies demonstrated the efficacy of setmelanotide in suppressing food intake and body weight gain in diet-induced obese (DIO) mice, rats, dogs, and monkeys, as well as in genetic models of obesity, including leptin-deficient ob/ob mice and leptin receptor deficient obese Zucker rats. Later studies in obese monkeys showed that setmelanotide did not increase blood pressure (BP) or heart rate (HR), a potential concern observed with other MC4R agonist compounds.

To support clinical studies, the toxicological profile of setmelanotide formulations has been evaluated in repeated-dose continuous SC infusion toxicity studies up to 13 weeks in duration in rats and monkeys. The formulation used in almost all of these studies, including the pivotal 28-day and 13-week toxicology studies, was RM-493 in 0.9% sodium chloride for injection (RM-493-saline formulation), tested over a range of concentrations. An International Conference on Harmonisation (ICH)-compliant battery of *in vitro* and *in vivo* genetic toxicity studies that included a bacterial mutation assay, a chromosomal aberration assay in cultured human peripheral blood lymphocytes and a rat micronucleus study has been completed with this formulation. In addition, a 7-day repeat dose local tolerability bridging study was conducted with RM-493-mPEG/DSPE in rodents. Finally, chronic toxicology, reproductive, and juvenile toxicology studies using the RM-493-mPEG/DSPE formulation are all well-underway since early 2016.

1.3.2. Mechanism-Related Adverse Experiences of Interest

The most significant potential safety issue for MC4R agonist compounds is the concern about potential mechanism-based increases in HR and BP. An MC4R agonist, LY2112688 (Eli Lilly and Company), had been studied in the clinic and caused HR and BP increases at all doses (e.g., up to a mean 9.4 mm Hg increase in systolic blood pressure [SBP] at the highest dose). ([Greenfield 2009](#), [Kievit et al 2013](#)) While the increases were not an immediate safety concern for the healthy volunteers in the Lilly study, similar but chronic increases in an obese patient population would have been problematic.

Setmelanotide was developed in nonclinical studies to analyze and obviate these cardiovascular (CV) effects. A large number of nonclinical studies were performed to demonstrate that setmelanotide did not cause similar CV effects as LY2112688, while still delivering equal or greater efficacy in animal models. The underlying premise of the development program was that setmelanotide in humans would deliver efficacy on weight loss without unacceptable CV effects.

The clinical effects of setmelanotide were recently reviewed, and there was little, if any evidence of BP or HR change from baseline vs pbo in any study, nor evidence of a PK/PD relationship (Gottesdiener 2015).

Other potential safety and/or tolerability issues that have been reported from published literature for some MC4R agonists in clinical and animal studies have included nausea and vomiting, male penile erections, increases in female sexual arousal, and off-target activity at the closely related MC1R (which mediates melanin deposition in the skin, producing tanning). In addition to careful CV monitoring, the setmelanotide program was designed to include careful monitoring for these potential mechanism-based effects in the initial clinical studies.

1.3.3. Setmelanotide Clinical Safety and Tolerability Summary

Setmelanotide has been evaluated in Phase 1 and Phase 2 clinical studies in healthy obese volunteers. As of November 2015, approximately 200 healthy obese subjects exposed to setmelanotide at doses ranging from 0.0025 to 2.0 mg/kg/24 hours (0.12 – 9.12 mg total daily dose). Of these 200 subjects, the majority were healthy obese (body mass index [BMI] $\geq 30\text{-m}^2$) volunteers, of whom 40 received a single setmelanotide dose and 160 received repeated doses for 3, 14, 28 or 90 days.

Setmelanotide has been evaluated in 6 completed clinical studies and 2 ongoing clinical studies, and is generally well tolerated. The data from these studies continue to support the hypothesis that setmelanotide does not cause increases in HR and BP.

Notably different adverse event (AE) rates apparent in setmelanotide-treated subjects compared to placebo include: fatigue, diarrhea, nausea, vomiting, darkening of skin lesions, skin discoloration/hyperpigmentation, decreased appetite, penile erections, headache, back pain, and injection site pruritis.

Overall study discontinuations were rare, as were Serious Adverse Events (SAEs). There has been only one SAE that was considered possibly drug related (atypical chest pain in a patient administered setmelanotide; cardiac and pulmonary causes were carefully evaluated and excluded). Four other SAEs reported were considered not drug-related: 1) severe groin strain, 2) severe abdominal pain, (responded rapidly to treatment in the hospital), 3) biliary dyskinesia in a patient administered placebo, and 4) numbness in the arm following excessive alcohol consumption (which resolved in 2 days).

For a complete summary of all pre-clinical and clinical data, please refer to the current Setmelanotide Investigator's Brochure (IB).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

POMC deficiency obesity is an ultra-rare genetic condition characterized by severe early onset obesity and profound hyperphagia (characterized by patients as increased appetite and hunger with impaired satiety) with numerous comorbidities, and likely early mortality. To our knowledge through patient identification efforts, there have been less than 25 cases currently described in the literature, with all cases diagnosed as children and with only 3 reaching adulthood thus far. Therefore, we anticipate patient identification to be challenging and are targeting enrolling approximately 10 individuals (pediatric, adolescents and/or adults) in order to assess the safety and efficacy of setmelanotide in patients with PDO. Given the rarity and unmet need of PDO, and the initial compelling results in the first two patients treated, a conventional placebo controlled trial is not recommended. The objective of this study is twofold; first, to assess safety and efficacy of setmelanotide after 1 year of chronic treatment. Secondly, since there are so few patients with PDO available, and this study is an open label design, evidence of drug effect will be sought within each patient's course of treatment. Therefore, each patient will participate in a short, double-blind placebo-controlled withdrawal period that will allow patients to serve as their own control to assess any reversal effects on weight and hunger in order to confirm any drug effects. Due to the ultra-rare prevalence of POMC deficiency obesity, if additional patients are identified beyond the target enrollment of 10, they may be enrolled.

2.1.1. Primary Objective:

- To demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change in patients with POMC deficiency obesity due to rare bi-allelic or loss-of function mutations at the end of 1 year of treatment.

2.1.2. Secondary Objectives:

To assess the effect of setmelanotide, over one year, on:

- Safety and tolerability of setmelanotide (including BP and HR).
- Hunger for patients ≥ 12 years of age.
- Percent change in body fat mass.
- Glucose parameters: fasting glucose, glycated hemoglobin (HbA1c), oral glucose tolerance test (OGTT) with focus on parameters of insulin sensitivity.
- Waist circumference.
- During withdrawal from drug: reversal of weight and hunger reduction during the double-blind placebo-controlled withdrawal period.

2.1.3.



2.1.4. [REDACTED]

2.2. Study Endpoints

The primary endpoint is the proportion of patients in the full analysis set (FAS) who meet the $\geq 10\%$ weight loss threshold (responders) after ~ 1 year of treatment, compared to the proportion from historical data (at most 5% responders in the null population).

Supporting secondary, [REDACTED] endpoints include:

The safety and tolerability of setmelanotide QD SC injection will be assessed by the frequency and severity of AEs as well as changes in physical examinations, electrocardiograms (ECGs), vital signs (including resting BP and HR), laboratory evaluations, monitoring for changes in [REDACTED] and injection site reactions.

Hunger will be assessed daily throughout the study. Patients ≥ 12 years of age will self-report their hunger by responding to three questions asking about their hunger at its worst, hunger in the morning (prior to dosing), and hunger on average in the previous 24 hours using [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Two global hunger questions will also be administered to assess patients' perceptions of their current status and change from baseline at key timepoints, including the [REDACTED]

[REDACTED]

Body composition assessments including total body weight loss, [REDACTED] measured in kg as well as percent change from baseline at the end of 1 year of treatment.

Glucose parameters as measured by fasting glucose, HbA1c and OGTT with focus on parameters of insulin sensitivity over time. OGTT will not be performed for subjects with a diagnosis of Type 1 or Type 2 diabetes.

Waist circumference will be measured according to US National Heart Lung and Blood Institute criteria [2000 NHLBI] over time.

To ensure improvements in weight and hunger are drug related in this ultra-rare patient population, a varying double-blind placebo withdrawal period will be implemented that will allow each patient to serve as their own control. Weight and hunger will be measured during this period in order to assess the efficacy of stopping and restarting setmelanotide treatment.

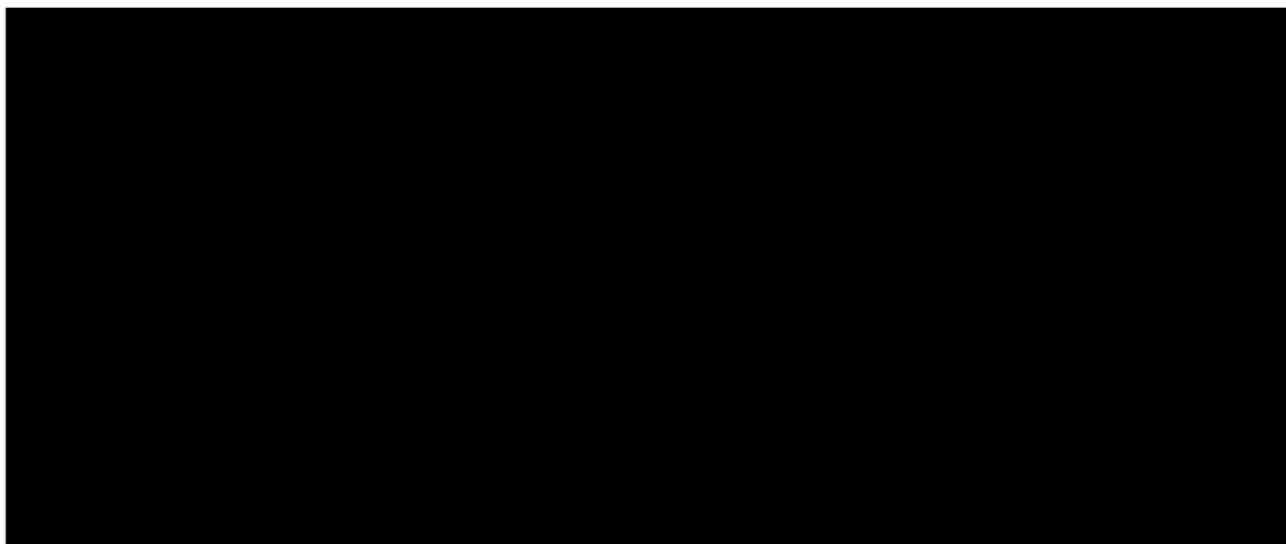
Potential improvements in [REDACTED] will be assessed over time.

[REDACTED]

Changes in growth and development in patients <18 years of age will be assessed with regular height, weight and BMI determinations (including Z score calculations) for eventual comparison to age- and gender-matched populations. In addition, annual [REDACTED] evaluations employing [REDACTED] over the course of the study.

Given the small number of patients expected to participate in the various sub-studies [REDACTED] it is not anticipated that any conclusions will be made about effects of setmelanotide on these parameter, however, trends over time will be explored.

[REDACTED]



[REDACTED] will be monitored. Guidance is provided for any worsening of [REDACTED] during the study. In addition, specific guidelines for dermatological events, liver function abnormalities, and penile erections are provided in the [Appendices](#). At all times, these guidances are subject to the clinical judgment of the Investigator and study consultants (if applicable).

3. INVESTIGATIONAL PLAN

3.1. Overall Design and Plan of the Study

This is a pivotal study to assess long-term (1 year) efficacy of setmelanotide in POMC deficiency obesity. As this is a global study, the maximum allowable dose differs across countries based on feedback from competent authorities. Currently, the US, Canada and UK have approved a maximum daily dose of 3.0 mg, while Germany and France have approved a maximum daily dose of 2.5 mg. The study will begin with an initial period of dose titration in 0.5 mg increments and lasting between 2 and 12 weeks depending on the number of escalations required to define the individual's therapeutic dose and the approved maximum dose in the country of the participating site. Thus, each subject will have his/her dose individualized (depending on the number of dosing increments administered) where the individual patient's therapeutic dose will be established (refer to Appendix 11.8) by upwards dose titration in 2 week intervals. Thereafter, patients will continue on active treatment at their individually titrated optimal therapeutic dose for an additional 10 weeks, for a total combined dosing duration of 12 weeks at the individual patient's therapeutic dose [i.e., the last 2 weeks during dose titration plus 10 weeks open label treatment]. For patients who demonstrate at least 5 kg weight loss (or at least 5% weight loss if baseline body weight < 100 kg) at the end of the Open Label Treatment Period, they will continue onto the double-blind, variably-timed, placebo-controlled, withdrawal period lasting 8 weeks inclusive of a 4-week period of placebo treatment. The onset of the placebo period will be variable for each patient in order to mask the actual timing of the withdrawal period. Following the withdrawal period, all patients will complete ~1 year of total therapeutic dosing. It is planned that the individual patient's therapeutic dose, established during the initial period of dose titration, will continue throughout the study.

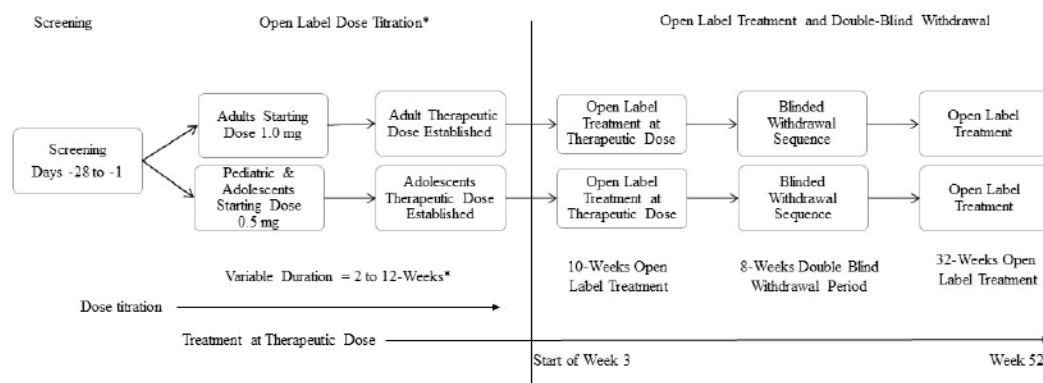
After completing ~1 year of total dosing, patients can enroll in a separate long-term extension study to continue receiving setmelanotide (Study RM-493-022) or they can complete ~1 year of treatment and have a final study visit approximately 30 days after their last dose.

It is anticipated that ~10 patients will be enrolled in this study. Due to the ultra-rare incidence of this population of patients, if more patients are identified during the conduct of the study, they may be enrolled.

In addition, for patients at sites where feasible, and who agree to participate, there are optional sub-studies to evaluate [REDACTED]

[REDACTED] It is anticipated that only a modest number of patients and sites will participate in each sub-study, and care should be taken not to overburden individual patients.

Thus, patients will progress sequentially through the study as depicted in Figure 3 below.

Figure 3: Study Schema

*The last two weeks of the Open Label Dose Titration Phase in which the therapeutic dose for an individual patient is established will be considered the first two weeks of Open Label Treatment. Subsequently patients will then receive an additional 10 weeks of active treatment in the Open Label Treatment for a total combined duration of 12 weeks, before transitioning into the Double Blind Withdrawal Phase.

Prior to entering dose titration, 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 on a daily basis in order to enhance the understanding of hunger symptoms associated with POMC deficiency obesity, prior to treatment with setmelanotide. As PDO is 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; e.g., 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 this rare monogenic form of obesity.

The dose titration phase will consist of an open-label active treatment phase initiating with a starting dose of setmelanotide titrated upwards every two weeks, over a maximum of 12 weeks according to Section 5.2.1 and Appendix 11.8. During the dose titration phase, careful assessments of safety and tolerability will occur. Once the patient's individual efficacious dose has been determined, and no further upwards dose titration is anticipated, patients will continue to dose daily for an additional 10 weeks of open label treatment, and that dose will continue for the rest of the study (except for the placebo withdrawal phase where double-blind supplies will be provided). For patients who have reached the maximum dose, but have not lost the target weight as described in Appendix 11.8, they will continue through the 10-week open label active treatment phase in order to allow the patient the opportunity to respond.

Following the dose titration and 10-week open label active treatment phases, only patients who lose at least 5 kg (or 5% if baseline < 100 kg) of weight from baseline, and who continue to show tolerability to setmelanotide, will continue in the remainder of the study. Patients who do not exhibit the required weight loss of at least 5 kg (5% if < 100 kg at baseline) will no longer receive active treatment. Note that all patients discontinued from the study (either those who

meet this “stopping rule”, or those discontinued for any other reason), will be asked to complete key clinic visits throughout the one-year study duration).

Next, patients will enter the double-blind placebo-controlled phase lasting a total of 8 weeks. Each patient will have a variably timed placebo withdrawal period with the sequence remaining double-blind for all patients and investigative staff. The key objective of the double blind withdrawal phase is to implement a varying sequence of active and placebo-controlled withdrawal period in a manner that will allow each patient to serve as their own control to inform hunger and weight change responses to stopping and restarting setmelanotide treatment.

Upon completion of the 8-week double-blind placebo withdrawal phase, patients will then resume open label active treatment at the established therapeutic setmelanotide dose for 32 additional weeks (52 weeks total, including the 4 weeks of placebo in the double-blind placebo-controlled withdrawal period).

3.2. Rationale for the Doses

[REDACTED]

However, because the number of monogenic POMC obesity patients exposed to MC4R agonists such as setmelanotide to date is very small, the dose of setmelanotide will be carefully titrated upwards for each patient on an individual basis in order to identify one’s safe and efficacious dose. The initial dose of setmelanotide to be administered to adults will be a daily dose of 1.0 mg QD by SC injection, with incremental increases of 0.5 mg on an every 2 week basis up to a maximum total daily dose of 3.0 mg. It is not expected that patients will necessarily will be titrated to doses as high as 3.0 mg (or 2.5 mg depending on the maximum approved dose in the participating country).

Dosing in pediatric patients age 6 through 11 years inclusive will follow the same deliberate dose titration approach employed for adult and adolescent subjects. Dosing will entail starting with 0.5 mg in pediatric subjects age 6 years to 11 years inclusive as is currently implemented for adolescent subjects age 12 years through age 17 years. Setmelanotide dose titration increases will be stepwise, rising by 0.5 mg at each 2-week titration step. Finally, we have set 2.5 mg/day to be the top dose to evaluate in pediatric subjects age 6 through age 11 years inclusive.

Thus, the starting dose for pediatric and adolescents will be 0.5 mg QD by SC injection, and will follow the same upwards dosing titration as for adults, with a maximum total daily dose of up to 2.5 mg for pediatrics and 2.5 or 3.0 mg for adolescents, depending on the maximum approved dose in the participating country.

During the dose titration phase and again during the ~32 week open label treatment phase,

Once a patient fulfills the dose titration weight loss and/or hunger score targets (Appendix 11.8), the individual patient's therapeutic dose will have been achieved, no further dose titration will occur, and patients will proceed into the 10-week Open Label Active Treatment Phase.

The highest potential dose allowed in dose titration is 3.0 mg or 2.5 mg depending on the maximum approved dose in the participating country. Toxicology studies in rats and monkeys provide extremely large margins (>150-fold) to human clinical exposures at the 3.0 mg/day dose (in mg/m² comparisons; greater margins were achieved on a mg/kg basis). Doses up to 10 mg have been given in single doses to general obese patients, and the limiting toxicity was nausea (and in some cases vomiting). Otherwise doses up to 2.0 mg/day have been administered for up to 12 weeks in healthy obese volunteers and doses of up to 2.5 mg/day administered for up to 12 weeks represents the highest dose studied in patients with Prader-Willi Syndrome with no new safety issues arising while this trial has been in progress (as outlined in the RM-493 Investigator Brochure). The most common adverse event was local injection site reactions (which can be easily monitored). While the experience to date from the two initial patients with POMC deficiency obesity suggests that the likely titrated dose (every 2 weeks) may be 1.5 mg/day, this protocol allows the chance for potential doses twice higher if needed to demonstrate robust efficacy on weight loss and hunger reduction. The 3.0 mg dose is close to previously administered doses of 2.5 mg as well, and is also supported by the excellent safety profile observed in the first POMC patients at doses up to 1.5 mg for longer than 6 months of active treatment.

3.3. Justification of the Study Design

Setmelanotide is being evaluated as a potential treatment for rare, genetically defined obese populations. An investigator-initiated Phase 2a proof of concept study in POMC deficient patients (RM-493-011) is currently ongoing and that study forms the basis for the current protocol, as noted in Section 1.2.

Percent change in body weight will be the primary endpoint for this registration protocol, with long-term efficacy to be evaluated after 1 year of study. There is no planned comparison to a randomized placebo group given the rarity of monogenic POMC deficiency obesity. To provide support in assessing setmelanotide treatment in this open-label single-arm trial design, individual patients will also be evaluated during a double-blind placebo-controlled withdrawal phase in which patients can serve as their own control to assess any reversal effects on weight and reported hunger scores. In addition, the history of un-remitting hunger and weight gain reported in these patients will be carefully documented (see Appendix 11.3) to substantiate that the weight loss anticipated in this study is drug-related.

The proposal for the double-blind placebo-controlled withdrawal period is based on: (1) the compelling response to setmelanotide demonstrated by the sentinel patients enrolled in the open-label investigator-initiated study; (2) change from baseline and/or short-term reversibility evaluations off treatment may establish the impact and reproducibility of active drug effects, especially in the POMC deficiency obesity patients, who are expected to have long, natural history evaluative data for marked weight gain prior to treatment available for comparisons; and

(3) placebo comparisons with so few POMC or PCSK1 genetic mutation patients existing, all of whom are expected to demonstrate a very high need for therapy, would not be feasible or probably ethically acceptable.

3.4. Study Termination

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

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

- Determination of unexpected, significant, or unacceptable risk to patients.
- Failure to enter patients at an acceptable rate. This is particularly important, as the number of patients hoped to enroll in this study represents a substantial portion of all already identified patients worldwide.
- Insufficient adherence to protocol requirements.
- Insufficient complete and/or evaluable data.
- Plans to modify, suspend or discontinue the development of the study drug.

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

In addition, it is still unclear how many patients will be required in a pivotal study to assess the safety and efficacy of setmelanotide in POMC deficiency patients, an ultra-rare condition. Therefore, this study may be terminated when Rhythm, in consultation with regulatory authorities, determines that there is sufficient patient data to support the potential application for registration of this drug for an indication in POMC deficiency obesity.

4. STUDY POPULATION

4.1. Number of Patients

It is currently anticipated that a total of ~10 enrolled patients will be treated for ~1 year with setmelanotide. Given the ultra-rare incidence of this disease, if additional patients are identified, they may be enrolled as available to gain additional experience. The study population will include obese males and females that are at least 6 years old with confirmed diagnosis of bi-allelic or loss-of-function POMC or PCSK1 loss of function gene mutation.

Given this study involves participants <18 years of age, measures should be taken to reduce pain and distress in this younger population. Considerations for the study staff are included in [Appendix 11.11](#).

The specific inclusion and exclusion criteria for enrolling patients in this study are presented in the section below. As these patients are ultra-rare, any criteria not fulfilled will be reviewed with Rhythm. 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 Rhythm prior to dosing the patient.

4.2. Inclusion Criteria:

1. Bi-allelic, homozygous or compound heterozygous (a different gene mutation on each allele) genetic status for either the POMC or PCSK1 genes, with the loss-of-function (LOF) variant for each allele conferring a severe obesity phenotype.
2. Age 6 years and above.
3. If adult age ≥ 18 years, obesity with BMI ≥ 30 kg/m²; if child or adolescent, obesity with BMI ≥ 95 th percentile for age on growth chart assessment.
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 be able to understand and sign the written informed consent/assent, after being informed about the study.
5. Female participants of child-bearing potential must 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 FSH level in the post-menopausal lab range), or have delayed pubertal development and failure to have achieved menarche, do not require contraception during the study. Male participants with female partners of childbearing potential must agree to a double barrier method if they become sexually active during the study. Male patients must 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 weight loss or weight stabilization. Patients may be reconsidered approximately 1 month after cessation of such intensive regimens.

2. 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, or resulted in <10% weight loss compared to pre-operative baseline weight or 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 Rhythm prior to enrollment.
3. Diagnosis of schizophrenia, bipolar disorder, personality disorder or other Diagnostic and Statistical Manual of Mental Disorders (DSM-III) disorders that the investigator believes will interfere significantly with study compliance.
4. A Patient Health Questionnaire-9 (PHQ-9) score of ≥ 15 .
5. Any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS). Any lifetime history of a suicide attempt, or any suicidal behavior in the last month.
6. Current, severe stable restrictive or obstructive lung disease as a consequence of extreme obesity, evidence of significant heart failure (NYHA Class 3 or greater), or oncologic disease, if these were severe enough to interfere with the study and/or would confound the results. Any such patients should be discussed with the sponsor prior to inclusion.
7. History of significant liver disease or liver injury, or current liver assessment for a cause of abnormal liver tests [as indicated by abnormal liver function tests, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, or serum bilirubin ($> 2.0 \times$ 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 will be exclusionary, but the presence of NAFLD would not be exclusionary.
8. History or presence of impaired renal function as indicated by clinically significant abnormal creatinine, blood urea nitrogen (BUN), or urinary constituents (e.g., albuminuria) or moderate to severe renal dysfunction as defined by the Cockcroft Gault equation < 30 mL/min (Appendix 11.10).
9. History or close family history (parents or siblings) of skin cancer or melanoma, or patient history of ocular-cutaneous albinism.
10. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions, determined as part of a screening comprehensive skin evaluation performed by a qualified dermatologist. Any concerning lesions identified during the screening period will be biopsied and results known to be benign prior to enrollment. If the pre-treatment biopsy results are of concern, the patient may need to be excluded from the study.
11. Volunteer 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.
15. Patients who have been placed in an institution through an official or court order, as well as those who are dependent on the sponsor, Investigator or study site.

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 which will be a combination of the site number and a sequential 3-digit number which will be used to identify patients throughout their participation in the study. Screening numbers will be assigned sequentially starting at 001 (i.e.; the first patient screened at site 10 would be assigned screening number 10001). Once a patient number has been assigned, it cannot be reused.

4.5. Withdrawal of Patients

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

- AEs, which justify ceasing treatment. For specific predefined events, additional monitoring and guidance for the Investigator is provided in Appendices 11.3 and 11.5.
- Non-adherence to study drug regimen or protocol requirements.
- Non-compliance with instructions or failure to return for follow-up.
- Failure to demonstrate 5 kg of weight loss (or 5% if baseline body weight < 100 kg) at the end of the 10-week open label treatment phase.

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

All patients who no longer receive active treatment prior to completing the ~1-year treatment period should be strongly encouraged to complete all remaining visits and procedures as outlined in the Schedule of Assessments in Section 6.

In case of withdrawal from the study (withdrawing consent), all adverse events should be followed as described in Section 7.4; any skin adverse experiences 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).

Rhythm will provide assistance for any 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 in order to facilitate compliance.

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 Rhythm.

Setmelanotide drug product (RM-493-mPEG/DSPE formulation) is a sterile solution for injection. The product is manufactured at a concentration of 10.0 mg/mL.

Placebo will be vehicle.

Setmelanotide and placebo are clear, colorless to slightly opalescent solutions essentially free of visible particulates, and are suitable for a double blind study. Setmelanotide and placebo will be administered as SC injection once daily.

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 time 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 in order 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.

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. Rhythm will provide extra placebo supplies for use during training.

5.2. Study Drug Dose and Administration

Study patients will receive study drug by SC injection once daily (administered in the morning). The dose titration phase will consist of a dose titration phase of up to 12 weeks. Once the patient's therapeutic dose is determined, the same dose/volume will be administered throughout the remainder of the study.

The ultimate goal is for the patient or their caretaker to successfully self-administer the study drug themselves at home. Given the rarity of PDO patients, 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 at all times, i.e., drawing up, and self-administering the study drug once daily (including during the practice periods).

In order to ensure patients or their caregivers can successfully self-administer study drug, a training period in the clinic with placebo (or saline) during screening will occur before entering into the open label dose titration phase. This training/practice period can occur as many times as necessary throughout the study to assure proper technique. The training/practice period 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.

5.2.1. Dose Titration and Adjustments

Experience in the first two POMC deficient patients enrolled in the investigator-initiated trial (RM-493-011), as noted above, has shown marked reductions in hunger and weight without revealing any new or unanticipated AEs to date. The efficacious dose in these patients has ranged from total daily doses of 1-2 mg of setmelanotide. However, due to the small number of POMC deficient patients exposed to setmelanotide to date, careful increases in dose titrations will be conducted.

The first dose of setmelanotide will be administered at the start of the Dose Titration Phase beginning with week 1. Patients will return to the clinic every 2 weeks to assess for efficacy and if individual patient doses are to be titrated upwards (according to Table 1 and Appendix 11.8). During the Dose Titration Phase, the patient's therapeutic dose will be identified. Doses should not be increased by more than 0.5 mg. Doses should not be adjusted after the dose titration phase has been completed unless discussed and approved by the Sponsor.

Table 1: Dose Titration Schedule

Dose Titration Week	Adult Dose (mg)	Adolescent Dose (mg)	Pediatric Dose (mg)
1-2	1.0	0.5	0.5
3-4	1.5	1.0	1.0
5-6	2.0	1.5	1.5
7-8	2.5	2.0	2.0
9-10	3.0*	2.5	2.5
11-12	NA	3.0*	NA

*Escalation to 3.0 mg only if approved by the participating country's competent authority, otherwise the maximum daily dose is 2.5 mg.

For patients who may have reached the maximum dose but have not lost the target weight as described in Appendix 11.8, patients will be allowed to continue into the 10 week open label active treatment phase in order to allow the patient the opportunity to respond.

Although long term treatment with setmelanotide is limited, long term experience in the first two sentinel POMC deficient patients has demonstrated that even when BMI's near normalization, that dose reductions have prompted increases in hunger scores, and the resumption of the individual patients' initially determined therapeutic dose. However, as experience is limited, during the Additional ~32 week Open Label Treatment Phase, if patients' body weight normalizes to an appropriate level (i.e. BMI <27 for adults or an age and gender value equivalent

to <95th percentile for pediatrics or adolescents), a dose reduction may be considered upon consultation with the sponsor.

5.3. Method of Assigning Patients to Treatment

Patients who qualify for the study will return to the site on Day 1 of the dose titration phase. Prior to initiating open label dose titration, the Investigator will ensure that the patient continues to meet inclusion and exclusion criteria, and perform all pre-dose procedures.

Once the pre-dose procedures are completed, the patient deemed eligible for the study, the first dose of setmelanotide will be administered in the presence of the Investigator or the Investigator's research staff.

Since this is an open label study, except for the double-blind withdrawal period, all patients will be assigned to active treatment except for during the double-blind withdrawal phase.

5.4. Blinding, Packaging, and Labeling

5.4.1. Blinding and Breaking the Blind

This study will be open label, with the exception of the 8-week double-blind, placebo controlled variably timed withdrawal period. Blinding will be accomplished so that all patients and study-related staff remain blinded to study drug and patient assignment.

The Investigator, study site staff, clinical research organization staff providing site management and Medical Monitor will not have access to the actual treatment sequence being administered during the 8-week double-blind placebo controlled phase, except in the case of an emergency. 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 Rhythm, whenever possible. If the blind is broken, the reason, when and how the blind was broken will be documented. Every attempt will be made to maintain the blind throughout the study.

5.4.2. Packaging and Labeling

All study drugs, including placebo for practice, will be supplied by Rhythm.

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

5.5. Duration of Patient Participation

Individual patient participation in this study (Screening period [2-4 weeks], open label dose titration period [12 weeks maximum duration], open label active treatment [10 weeks], double-blind placebo-controlled withdrawal period [8 weeks], and open label treatment [32 weeks]) will range between a minimum of approximately 54 weeks and a maximum of approximately 66 weeks, as currently planned.

Patients who have had a positive response to setmelanotide after 1 year of treatment will have the opportunity to enroll in a future, separate, extension protocol, in order to allow for continued treatment. This future extension protocol will be submitted and approved by applicable regulatory authorities prior to patients dosing beyond this protocol's study duration.

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

5.6. Assessment of Treatment Compliance

In order to evaluate the safety, tolerability, [REDACTED] of the study drug, it is critical that patients receive study drug as directed. All used study drug will 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.

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 CRF.

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 other 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 Rhythm (or disposal of the drug, if approved by Rhythm) will be maintained by the clinical site. These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from Rhythm. 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 used, unused or expired study drug will be returned to Rhythm 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 this ultra-rare condition to participate in the study. Therefore, patients are allowed chronic concomitant medications (e.g., as described below) while participating in the study:

- a. Growth hormone;
- b. Contraceptives;
- c. Hormone replacement therapy;
- d. Anti-hypertensives;
- e. Statins and other lipid-lowering therapies;
- f. Thyroxine or other thyroid supplements;

- g. Other medications commonly used in obese patients including: endocrine therapies (e.g., estrogens, Fosamax, hydrocortisone, vitamin and calcium supplements, diabetic therapies including insulin); and other medications (e.g., carnitor, Coenzyme Q10, vitamins, anti-constipation medications, anti-allergic medications).
- h. With the exception of low threshold drugs (i.e.: anticonvulsants, digoxin, Coumadin, etc.), other medications may be permitted if on a stable dose upon consultation with the Sponsor.

There is little evidence that setmelanotide will result in drug interactions at present, but data is limited. Patients and caretakers should be carefully assessed to determine that potential patients are specifically screened to determine if stable doses are expected during the course of the study, and carefully warned of possible side effects of 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 course of the study must be recorded in the source documents and on the CRF.

5.8.2. Prohibited Medication and Substances

Medications that could impact the efficacy assessments during the study are prohibited.

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 CRF.

6. STUDY ASSESSMENTS

6.1. Overview of Schedule of Assessments

The Schedule of Assessments (SOA) to be conducted during the study are depicted in [Tables 6-1A, 6-1B and 6-1C](#).

Although the study procedures and assessments required per protocol are classified as “No or Minimal Risk” (with the exception of DEXA which is classified as “Minor Increase over Minimal Risk”) according to the 2008 Guidance Document “Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population”, considerations for reducing pain in distress in participants younger than 18 years of age are included in [Appendix 11.11](#).

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 11.9) on a daily basis in order to enhance the understanding of hunger associated with PDO, prior to treatment with setmelanotide. During Screening, a detailed medical history will be obtained, including medical chart review (Appendix 11.3), in order to collect information pertaining to the natural history of PDO.

After the Screening Period in which confirmation of patient eligibility and ability for patients or their caretakers to successfully self-administer placebo is determined (or if arrangements for a visiting home health care practitioner are necessary), patients will enter the open-label dose titration phase. In this phase, the first dose of setmelanotide will be administered at the start of Dose Titration beginning at week 1. Patients will return to the clinic every 2 weeks for their doses to be titrated upwards (according to Section 5.2.1 and Appendix 11.8). During the dose titration phase, the patient’s optimal dose will be identified, and dose escalation will stop.

Once a patient’s therapeutic dose is determined, the patient will enter a 10-week open label active treatment phase.

Following the 10-week open label active treatment phase, patients will begin the 8-week double-blind placebo-controlled withdrawal period where patients will be assigned to the 4-week sequence in which they receive placebo in a double-blinded sequence. The key objective this phase is to implement the only double-blind, placebo-controlled period for this study that will inform patient’s symptomatic hunger and weight change responses to stopping and then restarting active therapy with setmelanotide without awareness of the timing of the withdrawal. Given this short, maximum 4-week interval, it is expected that all subjects will be able to tolerate and report on symptoms and weight changes during this double-blind, placebo-controlled phase. If patients are not able to tolerate the anticipated weight gain and return of symptoms of hunger, patients may be allowed to resume open label active treatment upon discussion and agreement from Rhythm. Any such agreement will be documented in writing and approved by Rhythm prior to resuming the patient on active treatment.

Thereafter patients will resume open label active treatment for an additional ~32 weeks, for a total of ~52 weeks of treatment at the individual patient’s therapeutic dose (inclusive of the 4-week placebo withdrawal).

Following the dose titration and 10-week open label active treatment phases, only patients who lose at least 5 kg of weight from baseline (or 5% if baseline weight < 100 kg), and who continue

to show tolerability to setmelanotide, will continue into the rest of the study. Patients who do not exhibit the required weight loss of at least 5 kg (or 5% if baseline weight < 100 kg) will be withdrawn from the study, and complete the Early Termination Visit.

For patients who complete the study but do not wish to enroll into the future long-term extension study (as noted in Section 5.5), patients will be required to return for a Final Visit ~30 days after the last dose of setmelanotide, for a final follow-up safety assessment. Any ongoing AEs reported at this visit should be monitored as outlined in Section 7.4. For patients who enroll in the future long-term extension protocol, this visit is not required. 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 in order to obtain minimum patient self-reported data (i.e.: weight, AEs, etc.).

Detailed descriptions of the safety, [REDACTED] procedures to be conducted during this study are provided in the following sections. The amount of blood volume to be drawn for these procedures is within the acceptable limits for each visit and over the duration of the study. However, blood draws may be challenging in this population of extremely obese patients due to poor access to their veins. In these instances, the PI should contact the Medical Monitor to prioritize sampling, with samples being collected for safety the highest priority.

Patients will be required to fast overnight on the day preceding all 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 ~ 4 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. All screening bloodwork should be collected between Study Day -28 and -14 in order to ensure the WHO maximum cumulative blood volumes are not exceeded over the course of the study. In order to obtain sufficient baseline data on symptoms of hunger (collected daily), the screening period should be a minimum of two weeks and up to four weeks.

In order to provide flexibility to the patient and study staff for the number of clinic visits, the actual scheduling of clinic visits can allow flexibility in timing of visits. During the Dose Titration phase, the goal will be for visits to occur within +/- 3 days. But as this patient population is ultra-rare, and 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 to the patient's home or for the patient to be seen at their local physician's office, in order 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, for any dose titration, start, middle and end of the double-blind placebo controlled withdrawal period, and at the 6 month, 9 month and end of 1 year of treatment (primary efficacy

endpoint), and Early Termination visits (i.e.; Visits V1, any V2, V3, V5, V6, V7, V8, V10, V11, and V13).

Table 6-1A: Schedule of Assessments: Screening and Dose Titration[#]

Study Period		Screening ^Δ	Open Label Dose Titration ⁶
Procedure	Visit Number (V)	V1	V2a ⁶
Start of Dose Titration Week (Dose Titration Study Day ± 3 days)		-4 to 0 (-28 to -1)	1 (1)
Informed consent/Assent		X	
Inclusion/Exclusion review		X	X ⁵
Medical history review		X	X ⁵
Genetic Testing ³²		X	
Pregnancy test		X	X ^{4, 5}
Physical examination ¹		X	
Height ¹		X	
Comprehensive skin exam ²		X	
Fitzpatrick scale		X	
Open label placebo practice		X	
Dose Titration Decision ²⁴			X ⁵
Weight/waist circumference ¹¹		X	X ⁵
Archive sample for storage ¹²		X	
Study treatment administration ¹³			X
Injection site inspection ¹⁴			X
Vital signs ¹⁵		X	X ^{5, 16}
ECG (12-lead) ¹⁷		X	X ^{5, 17}
Safety laboratory tests ¹⁸		X	X ⁵
OGTT ²⁸		X	
Daily Hunger Questionnaire ²⁰		X	X ⁵
Global Hunger Questions ³³		X	
Body Composition ²³		X	
Anti-RM-493 antibody samples		X	X ^{5, 26, 31}
Adverse Event assessment ²⁵		X	X
Concomitant meds review		X	X
Telephone contact			X
Nutritional Counseling and Monitoring ³⁶		X	

Table 6-1A (Cont.): Schedule of Assessments: Screening and Dose Titration[#]

Study Period	Screening	Open Label Dose Titration ⁶
Procedure Visit Number (V)	V1	V2a ⁶
Start of Dose Titration Week (Dose Titration Study Day \pm 3 days)	-4 to 0 (-28 to -1)	1 (1)
Optional Sub-Studies		

Table 6-1B: Schedule of Assessments: 10 Week Active Treatment and 8 Week Double-Blind Placebo Controlled Withdrawal

Study Period	Open Label			Double Blind	
	Active Treatment ⁷			Placebo-Controlled Withdrawal ⁷	
Procedure	Visit Number (V) Start of Week (Study Day)	V3 3 (15)	V4* 5 (29)	V5 9 (57)	V6 13 (85) V7 17 (113)
Pregnancy test		X ^{4,5}	X ^{4,5}	X ^{4,5}	X ^{4,5}
Physical examination ¹				X	
Height ¹				X	
Comprehensive skin exam ²					
Weight/waist circumference ¹¹		X ⁵	X ⁵	X ⁵	X ⁵
Archive sample for storage ¹²				X ⁵	
Therapeutic Dose Established		X			
Study treatment administration ¹³		X	X	X	X
Injection site inspection ¹⁴		X	X	X	X
Vital signs ¹⁵		X ⁵	X ⁵	X ⁵	X ⁵
ECG (12-lead) ¹⁷				X ⁵	
Safety laboratory tests ¹⁸			X ⁵	X ⁵	
OGTT ²⁸				X ⁵	
Daily Hunger Questionnaire ²⁰		X ⁵	X ⁵	X ⁵	X ⁵
Global Hunger Questions ³³				X ⁵	X ⁵
Body Composition ²³				X	
Anti-RM-493 antibody samples			X ^{5, 26}		X ^{5, 26}
Adverse Event assessment ²⁵		X	X	X	X
Concomitant meds review		X	X	X	X
Telephone contact		X	X	X	X
Nutritional Counseling and Monitoring ³⁶			X	X	

Optional Sub-Studies

Table 6-1C: Schedule of Assessments: Additional 32 Week Open Label Treatment

Study Period		Open Label						Early Termination / Final Visit ⁹
		Active Treatment ⁸						
Procedure	Visit Number (V) Start of Week (Study Day)	V8 21 (141)	V9 27 (183)	V10* 33 (225)	V11 39 (267)	V12* 45 (309)	V13 53 (365)	
Pregnancy test		X ^{4, 5}	X ^{4, 5}	X ^{4, 5}	X ^{4, 5}	X ^{4, 5}	X ^{4, 5}	X
Physical examination ¹			X				X	X
Height ¹			X		X		X	X
Comprehensive skin exam ²					X		X	X
Weight/waist circumference ¹¹		X ^{5, 35}	X ^{5, 35}	X ^{5, 35}	X ^{5, 35}	X ^{5, 35}	X ^{5, 35}	X
Archive sample for storage ¹²							X ⁵	
Study treatment administration ¹³		X	X	X	X	X	X	
Injection site inspection ¹⁴		X	X	X	X	X	X	
Vital signs ¹⁵		X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	X
ECG (12-lead) ¹⁷			X ⁵				X ⁵	
Safety laboratory tests ¹⁸			X ⁵		X ⁵		X ⁵	X
OGTT ²⁸							X ⁵	
Daily Hunger Questionnaire ²⁰		X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	X
Global Hunger Questions ³³		X ⁵	X ⁵				X ⁵	X
Body Composition ²³							X	
Anti-RM-493 antibody samples			X ^{5, 26}		X ^{5, 26}		X ^{5, 26}	X ^{5, 26}
Adverse Event assessment ²⁵		X	X	X	X	X	X	X
Concomitant meds review		X	X	X	X	X	X	X
Telephone contact		X	X	X	X	X	X	X
Nutritional Counseling and Monitoring ³⁶		X	X	X	X	X	X	

Optional Sub-Studies

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Table 6-1: Schedule of Assessments Footnotes

- 1 A complete physical examination will be conducted at screening and at the end of study. [REDACTED]
[REDACTED]
[REDACTED] Height will be measured during the Screening Period only for those patients ≥ 18 years of age. Height will be measured according to the [SOA](#) for those patients < 18 years of age. Height (cm) will be measured, without shoes, socks or hats according to the SOA using a wall-mounted stadiometer. All measurements will be done in triplicate at each timepoint and recorded to the nearest 10th of a decimal place. The stadiometer should be calibrated at the time of use or within the previous four hours.
- 2 A comprehensive skin evaluation will be performed by a dermatologist. Any concerning lesions identified during the screening period will be biopsied and results known to be benign prior to first dose of setmelanotide. If the pre-treatment biopsy results are of concern, the patient will be excluded from the study.
- 3 Optional sub-studies for Investigative Sites that are able to carefully perform these assessments and have patients willing and able to participate. In the event a site can perform multiple sub-studies, care needs to be taken in order to not overburden with multiple additional assessments/visits.
- 4 Urine pregnancy test may be performed in order to expedite availability of results prior to dosing on Dose Titration Day 1. All other pregnancy tests will be serum; dosing may continue with results pending.
- 5 Prior to study drug administration.
- 6 The Dose Titration phase will be a variable schedule lasting a minimum of 2 weeks and a maximum of 12 weeks, in which patients will return to the clinic approximately every 2 weeks in order to establish the individual patient's therapeutic dose according to Appendix 11.8. Given the variable number of dose titration steps in the Dose Titration Phase, each Dose Titration Visit Number (V) will remain V2 with an alphabetized suffix added to each titration visit (i.e.; first dose titration at start of Week 1 = V2a, second dose titration at start of Week 3 = V2b, etc.). This will allow for the Visits to be appropriately tracked. Additionally, each dose titration visit will have the same pre- and post-dose assessments as outlined in the [SOA](#) (with the exception of Anti-RM-493 antibodies and [REDACTED]).
- 7 Once the patient's individual therapeutic dose is established the patient will enter the Open Label Active Treatment phase for 10 additional weeks, for a combined total of 12 weeks of dosing at the therapeutic dose. During this time, the study calendar will be reset, starting when the therapeutic dose was initiated (i.e. the last 2 weeks of dose titration when the therapeutic dose was established). Therefore, the Open Label Active Treatment phase starts at the beginning of Week 3 (V3). Patients losing 5 kg of weight (or 5% if baseline weight < 100 kg) at the end of the Open Label Treatment phase will enter the Double-Blind Placebo Controlled Withdrawal phase lasting 8 weeks.
- 8 Upon completion of the Double-Blind Placebo Controlled Withdrawal phase, patients will resume Open Label Active Treatment for an additional ~32 weeks.
- 9 Early Termination: For those patients who withdraw consent or are withdrawn and not willing to complete the remaining study visits, the early termination visit assessments should be performed, when possible. Additionally, patients who withdraw and are not willing to return for the remaining clinic visits can be contacted via phone, if amenable, to collect self-reported patient data (i.e.: weight, hunger, AEs, etc.). Final Visit: For patients who complete the study but do not wish to enroll into the future long-term extension study (as noted in Section 5.5), patients will be required to return for a Final Visit ~30 days after the last dose of setmelanotide, for a final follow-up safety assessment. Any ongoing AEs reported at this visit should be monitored as outlined in Section 7.4. For patients who enroll into the long-term extension study, this visit is not required.

- [REDACTED]
- 11 Weight is to be measured at the clinic using the same scale after patients have emptied their bladder and while fasting. Patients are to wear light clothing or underwear, no shoes, and will be weighed at approximately the same time of day. Weight measurements are to be done in triplicate; waist circumference will be single measures.
 - 12 Extra retain samples will consist of 2 serum and 2 plasma (K2EDTA) vacutainer tubes.
 - 13 Study drug is administered by patients/caretakers beginning the morning of Day 1 and for the duration of dosing. Patients/caretakers will draw up and self-administer/administer the drug once on a daily basis in the morning. On days with clinic visits, the patients/caretakers will administer the drug in the clinic in the presence of the clinical staff to assure proper technique. Patients/caretakers will return all used vials to the clinic when they visit (the number recorded) and both clinic administered study drug, as well as outpatient study drug administration will be recorded in a study diary.
 - 14 Injection site evaluations and scoring (by the clinical staff) will include identification and measurement of areas of erythema, edema and induration, as well as the presence of localized pain, tenderness and itching. Additional evaluation data can be collected at any visit where there are injection site reactions even if not a timepoint for formal assessment.
 - 15 All BP and HR measurements are to be obtained in the sitting position following at least 5 minutes of rest. All measurements will be taken in triplicate, approximately 2 minutes apart. When possible, BP should be taken in the non-dominant arm throughout the study, using the same methodology (automated or manual) according to Appendix 11.7. Body temperature (°C) and respiration rate (breaths/minute) will be obtained in the sitting position following at least 5 minutes of rest.
 - 16 During Day 1 and for any dose titration, vitals will be collected prior to dosing and then approximately hourly post-dose for up to 8 hours.
 - 17 A single 12-lead ECG will be performed in the supine position following a period of at least 10 minutes of rest. On days in which dose titration occurs, measures will be obtained prior to dosing and approximately 8 hours post-dose
 - 18 Safety laboratories will include: CBC with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO₂, albumin, total protein, glucose, BUN, creatinine, uric acid, AST, ALT, GGT, CPK, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, calcium, phosphorus), urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination. Safety laboratories shall also include a coagulation profile (prothrombin time [PT] or international normalized ratio [INR], and partial thromboplastin time [PTT], also referred to as activated partial thromboplastin time [aPTT]). Fasting samples (8-hour minimum) are required at all timepoints where feasible. [REDACTED] and HbA1c will also be included.
- [REDACTED]
- 20 Daily hunger questionnaire scores will be assessed by asking the patient to score their hunger based on a [REDACTED] Daily hunger questionnaire scores will be recorded on a daily basis, prior to the patient's morning meal.
- [REDACTED]

- [REDACTED]
- 23 Body composition may be performed using an appropriate method available at sites (e.g. BIA, DXA, etc.) Refer to Section 6.3.3 regarding appropriate methodology for assessing this patient population.
- 24 Once all the pre-dose assessments have been performed, the decision to dose titrate according to Appendix 11.8 will be made. If the patient's therapeutic dose has been established, the patient will transition into the 10-week Open Label Active Treatment Phase, receive their therapeutic dose, and complete the V3 post-dose assessments as defined in the [SOA](#). If the patient's therapeutic dose has not been established according to Appendix 11.8, the patient will be administered study drug, complete the dose titration post-dose assessments as defined in the V2 [SOA](#), and return to the clinic in ~2 weeks for the next sequential Visit 2 (i.e.; V2b, V2c, etc.).
- 25 Adverse events will be recorded from the time a patient provides informed consent. AEs reported after dosing on Day 1 will be considered treatment-emergent AEs.
- 26 Any patients with positive anti-drug antibodies will be followed ~every 3 months until titers resolve or return to baseline.
- 27 Telephone contact by site on a monthly basis, or more frequently, if needed.
- 28 Following collection of pre-meal (time 0) blood samples, patients will be given a standard oral glucose tolerance test. The following blood samples will be obtained during each OGTT: Blood glucose and insulin at approximately 30, 60 90 and 120 minutes after meal start. OGTT will not be performed for subjects with a diagnosis of Type 1 or Type 2 diabetes.
- 29 ~8 hours post-dose on Day 1 only.
- 30 ~8 hours post-dose.
- 31 To be collected at Study Day 15 and Day 29 during the dose titration phase (i.e. V2b and V2c or V2b and V3, if the patient's therapeutic dose has been established at the first dose level).
- [REDACTED]

- 33 Global Hunger Questions (Appendix 11.9) 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.
- [REDACTED]

- 35 For pediatric patients, weight will be measured every 2-3 weeks between visits during the additional 32 week open label treatment phase, at the patient's home by a parent or caregiver.
- 36 For pediatric patients only, Nutritional Counseling and Monitoring will be performed by an appropriate dietician or nutritionist (or equivalent) to ensure that pediatric patients have adequate nutritional/dietary intake to maintain proper growth and development. Additional laboratory assessments indicative of nutritional status may be monitored, as appropriate (e.g. albumin, vitamin D, total lymphocytes and [REDACTED]).
- [REDACTED]

- # Once a patient's therapeutic dose has been established according to Appendix 11.8, no further dose titrations will occur, and patients will transition directly into the 10 week Open Label Active Treatment phase. Therefore, the Dose Titration phase will be a minimum of 2 weeks and a maximum of 12 weeks.
- * For patients that reside a considerable distance from the clinic, these visits are optional clinic visits, and may be performed by the patient's local physician or home health care professionals.
- + If the visit is performed by a home health care professional, assessment may be performed at the next schedule in clinic visit.
- ^ For patients enrolled in Germany and France, the Quantitative Skin Color Assessments and Serial Photographs are compulsory, and not optional.
- § For patients previously enrolled, the assessment should be performed at the patient's next scheduled visit.
- † Test not conducted at this visit for patients 6 to 11 years.
- Δ All screening bloodwork should be collected between Study Day -28 and -14 in order to ensure the WHO maximum cumulative blood volumes are not exceeded over the course of the study.

6.2. Patient Requirements

6.2.1. Contraception

Setmelanotide has not been evaluated in any pre-clinical 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 females able to bear children, a highly reliable form of contraception must be used/practiced throughout the study and for 90 days following the study. Highly reliable acceptable forms of contraception include: hormonal (i.e., oral, implantable, or injectable) and single-barrier method (i.e., condom), or an Intrauterine Device (IUD) and single-barrier method (i.e., condom) or vasectomised 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 delayed pubertal development and failure to have achieved menarche, do not require contraception during the study.

It is not known if this treatment will affect spermatogenesis. Therefore, males with female partners of childbearing potential must agree to use contraception (e.g., if they have not had a vasectomy then should either (a) abstain from reproductive sexual intercourse or (b) use a double barrier method (i.e. condom and diaphragm with spermicide) during intercourse) 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 and Phase 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 (e.g.; visit ultraviolet (UV) tanning salons, use spray tanners, self-tanning lotions, etc.).

6.3. Efficacy Measurements

6.3.1. Weight

Weight (kg) will be recorded as shown in the [SOA](#), and generally will be assessed and recorded every two weeks during the earlier phases of the study. 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 when patients are fasting and at approximately the same time at each visit. Patients should be in light clothing or underwear, with no shoes and have emptied their bladder.

For pediatric patients, weight will be measured more frequently during the Additional 32 week Open Label Treatment Phase as shown in the SOA, at the patient's home. For these home measurements, the parent or caregiver should be instructed to follow the same procedures noted above.

6.3.2. Waist Circumference

Waist circumference (cm) will be measured according to the National Heart, Lung, and Blood Institute (NHLBI) criteria [[NHLBI 2000](#)] during the study as shown in the [SOA](#). All measurements will be single measures. Whenever possible, the same study staff member should perform the measurement for a given patient to minimize variability. Waist circumference should be measured when patients are fasting and at approximately the same time at each visit. Patients should be in light clothing and have emptied their bladder.

6.3.3. Body Composition

Participants will have body composition measurements performed using an appropriate methodology that is available at the site (e.g.: DXA scans, bioelectrical impedance (BIA), etc.) over the course of the study.

For DXA methodology, which uses low dose x-rays to non-invasively assess skeletal and soft tissue density, half-body scans may be performed for patients that extend beyond the scanning area. The risk associated with exposure to ionizing radiation is minimal and further minimized through the exclusion of pregnant women. If patients are severely obese and cannot be measured in the DXA scanner available due to practical limitations (size of DXA machine), then other methodologies should be considered (i.e., bioimpedance). If DXA is available but patients are too large to enter at Screening, DXA should be added at a time when patients may have lost enough weight to do adequate DXA measurements (as DXA may provide additional information above BIA, for example) in addition to the methodology used at Screening.

If body composition instruments are not available at a specific site, and arrangements cannot be made to obtain these measurements, the sponsor may waive the requirement for body composition measurements at that site.

6.4. Clinical Procedures and Safety Assessments

6.4.1. 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.

6.4.2. 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 CRF 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 in order to collect important retrospective data to better understand the natural history of PDO according to 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 or not any changes have occurred since the previous visit.

6.4.3. Physical Examination, Comprehensive Skin Examination, and Height

Physical Examinations

A complete physical examination will include review of peripheral lymph nodes, head, eyes (including conjunctiva), ears, nose, mouth and oropharynx, neck, heart, lungs, abdomen, musculoskeletal including back, extremities and neurologic. [REDACTED]

All physical examinations are to be conducted in adequate light.

Changes from baseline in any physical examination findings identified by the Investigator as clinically significant must be recorded as an AE on the appropriate CRF.

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 as outlined in the Schedule of Assessments.

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.

Height

Height (cm) will be measured, without shoes, socks or hats according to the SOA using a wall-mounted stadiometer. All measurements will be done in triplicate at each timepoint and recorded to the nearest 10th of a decimal place. The stadiometer should be calibrated at the time of use or within the previous four hours.

[REDACTED]

6.4.5. **Fitzpatrick Scale**

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

6.4.6. **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 CRF.

6.4.7. **Vital Signs**

Vital signs will be obtained in the sitting position following at least 5 minutes of rest each time they are measured according to the [SOA](#).

Blood pressure and heart rate

Blood pressure (BP; mmHg) and heart rate (HR; bpm) will be performed using the same methodology throughout the study (manual or automated) as outlined in Appendix 11.7. Special attention should be paid to ensure the appropriate cuff size in this patient population, as noted in the [Appendix](#).

Repeat measures and more frequent monitoring can be implemented for significant increases in BP or HR.

To allow for a trough blood pressure reading, the patient should be instructed not to take the study medication on study days when vital signs are to be measured in the clinic.

Body temperature and respiration rate

Body temperature (°C) and respiration rate (breaths/minute) will be obtained in the sitting position following at least 5 minutes of rest.

6.4.8. **12-Lead Electrocardiogram**

Single 12-lead electrocardiograms will be performed following a period of at least 10 minutes of rest in the supine position. On days when doses are titrated, ECGs will be obtained prior to dosing, and at ~8 hours post-dose.

6.4.9. **Clinical Laboratory Tests**

All screening bloodwork should be collected between Study Day -28 and -14 in order to ensure the WHO maximum cumulative blood volumes are not exceeded over the course of the study.

Clinical safety laboratory tests are to be performed by the local laboratory and patients are to be fasting for 8 hours. Labs are to be drawn prior to dosing.

All clinically significant laboratory abnormalities will be followed-up by repeat testing and further investigated according to the judgment of the Investigator.

Liver function test abnormalities will be evaluated in accordance with FDA Guidance ([2009](#)) as described in the Appendix 11.6.

Specific tests are described below.

6.4.9.1. Hematology, Clinical Chemistry and Urinalysis

Hematology and clinical chemistry samples will be collected in the fasted state.

Hematology:

Complete blood count with platelet count and standard indices will be obtained.

Chemistry:

Sodium, potassium, chloride, CO₂, albumin, total protein, glucose, blood urea nitrogen (BUN), creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (GGT), creatine phosphokinase (CPK), alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), calcium and phosphorus.

Coagulation profile:

Prothrombin time (PT) or international normalized ratio (INR), and partial thromboplastin time (PTT), also referred to as activated partial thromboplastin time (aPTT).

Urinalysis:

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

6.4.9.2. [REDACTED] HbA1c:

[REDACTED]
[REDACTED] Blood samples will need to be collected when the patient is in the fasted state.

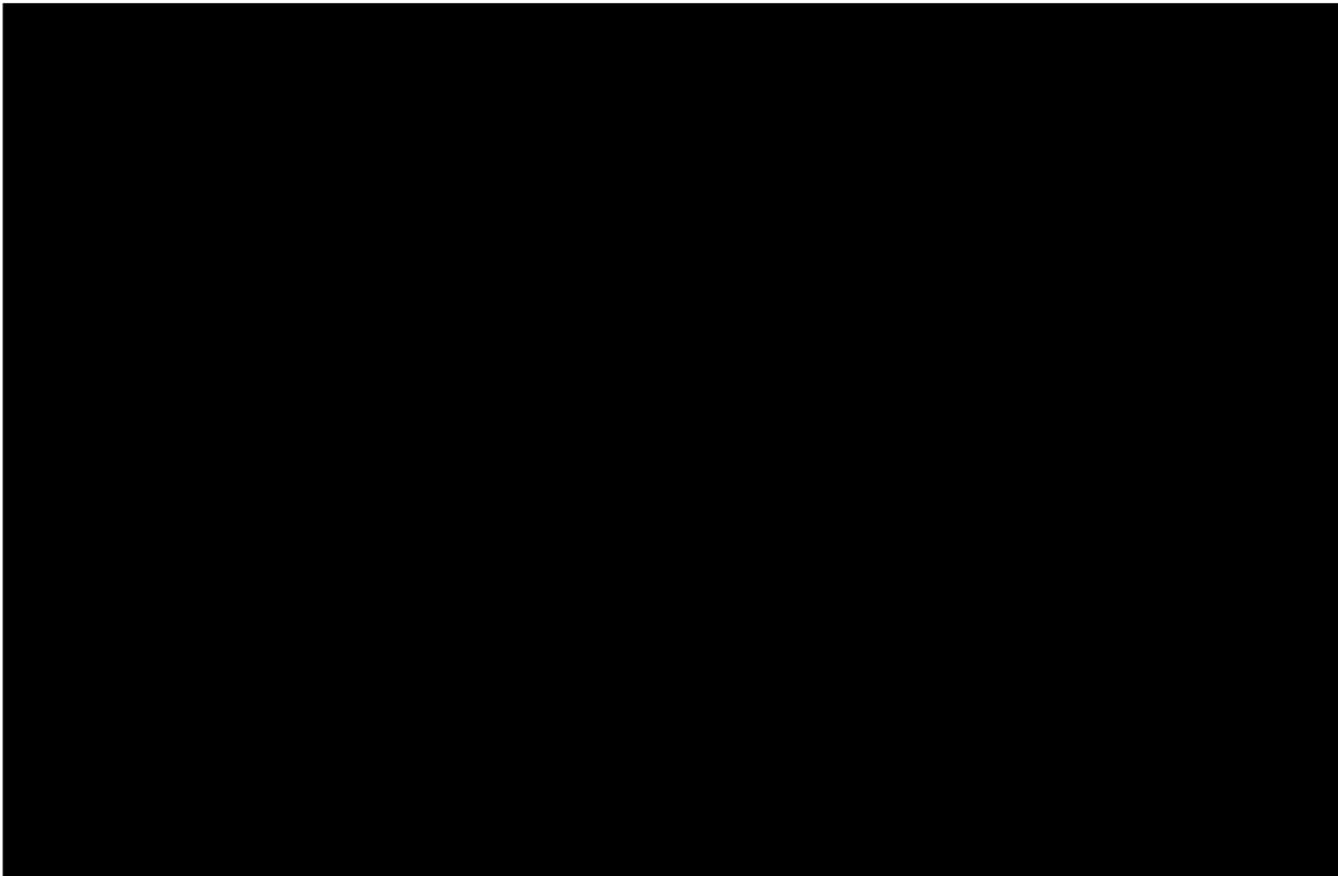
HbA1c levels will be measured as outlined in the [SOA](#).

6.4.10. Oral Glucose Tolerance Test (OGTT)

OGTT will be performed to evaluate study drug effects on post prandial glucose and insulin. A baseline OGTT will be performed and a follow-up OGTT will be conducted according to the SOA. An overnight fast of at least 8 hours duration is required prior to administration of the OGTT. Following collection of pre-meal (time 0) blood samples, patients will be given a standard OGTT meal. OGTT will not be performed for subjects with a diagnosis of Type 1 or Type 2 diabetes. The following blood samples will be obtained during each MTT:

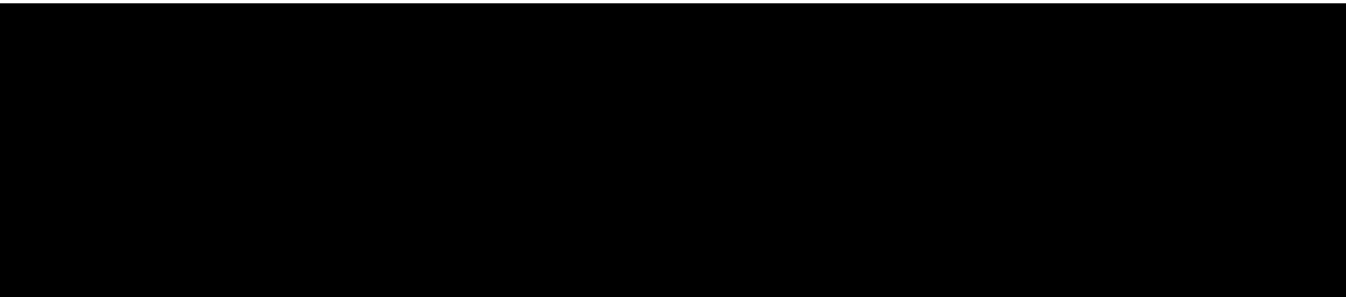
- Blood glucose: Time 0 (pre-meal) and approximately 30, 60, 90 and 120 minutes after meal start.
- Blood insulin: Time 0 (pre-meal) and approximately 30, 60, 90 and 120 minutes after meal start.

Homeostasis Model of Assessment – Insulin Resistance (HOMA-IR) will be calculated using the fasting glucose and insulin levels obtained as part of the MTT.



6.4.12.1. *Samples for Storage/Archive*

Extra retain samples will be used in the event that unscheduled diagnostic tests are required for safety reasons, or for additional [REDACTED] that are currently not defined but are directly related to the aims of this study. These samples will be retained until the study has been completed, and until the Sponsor has notified the study site in writing that the samples can be discarded.



6.4.13. *Injection Site Evaluation and Scoring*

Injection sites will be carefully inspected, evaluated and scored during the study period. The injection site evaluation will include identification and measurement of areas of erythema, edema and induration, as well as the presence of localized pain, tenderness and itching. A sample injection site evaluation form is included in Appendix 11.1.

In addition, unscheduled evaluations may also be recorded as warranted by clinical conditions.

6.4.14. Anti-RM-493 Antibody (ADA) Measurements

Blood samples for measurement of anti-RM-493 antibodies will be collected prior to dosing, and then at the time-points identified in the SOA. Any patient with a positive titer will be followed until resolution.

6.4.15. Patient Questionnaires

The patient questionnaires will be answered by the patient and/or caretaker after careful training.

Hunger Scores

Hunger will be assessed using a daily questionnaire as well as a set of two global questions according to the SOA.

Global Hunger Questions: Two global questions will be asked at certain study visits according to the SOA. For patients ≥ 12 years of age, the patient will answer the questions themselves. [REDACTED]

Daily Hunger Questionnaire: Hunger will be assessed daily in all patients.

For patients ≥ 12 years of age, a set of three questions will be asked using a numeric rating score from [REDACTED]

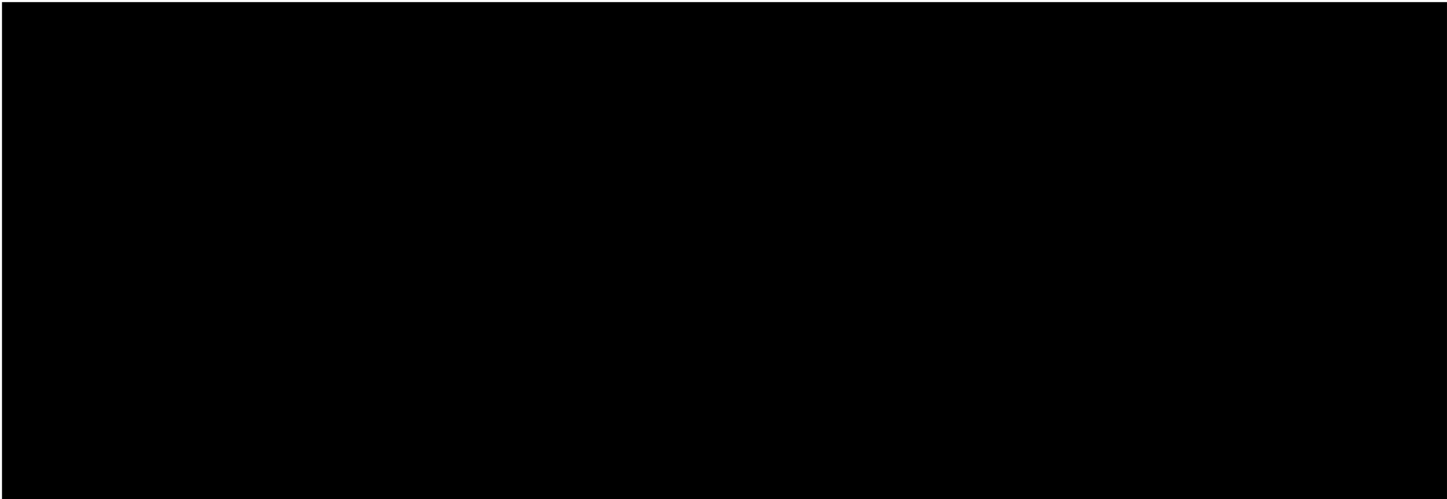
The daily hunger questionnaire will be completed daily, prior to dosing in the morning. Patients will record their hunger scores prior to the morning meal (fasted).

The Global Hunger Questions and Daily Hunger Questionnaire is located in Appendix 11.9.

[REDACTED]



[REDACTED]

[REDACTED]



6.4.16. 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, to ensure that pediatric patients have adequate nutritional/dietary intake to maintain proper growth and development. Additional laboratory assessments indicative of nutritional status may be monitored as appropriate (e.g. albumin, vitamin D, total lymphocytes  

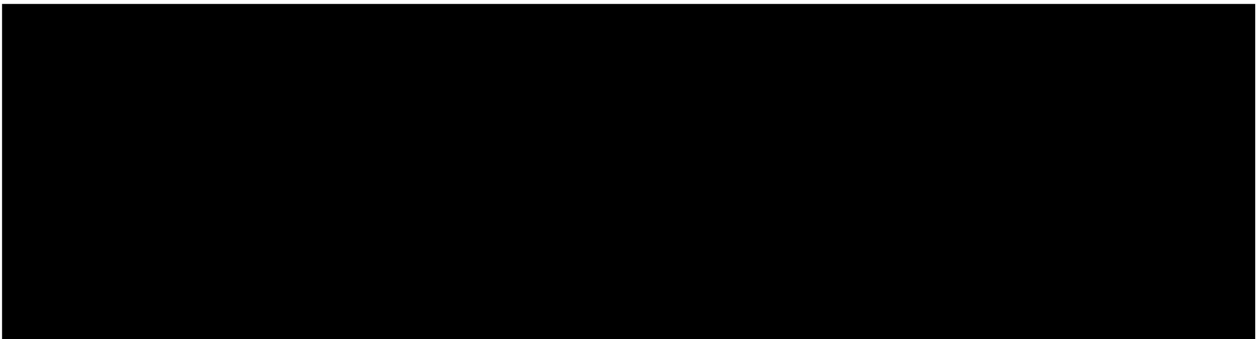
6.4.17. Adverse Events

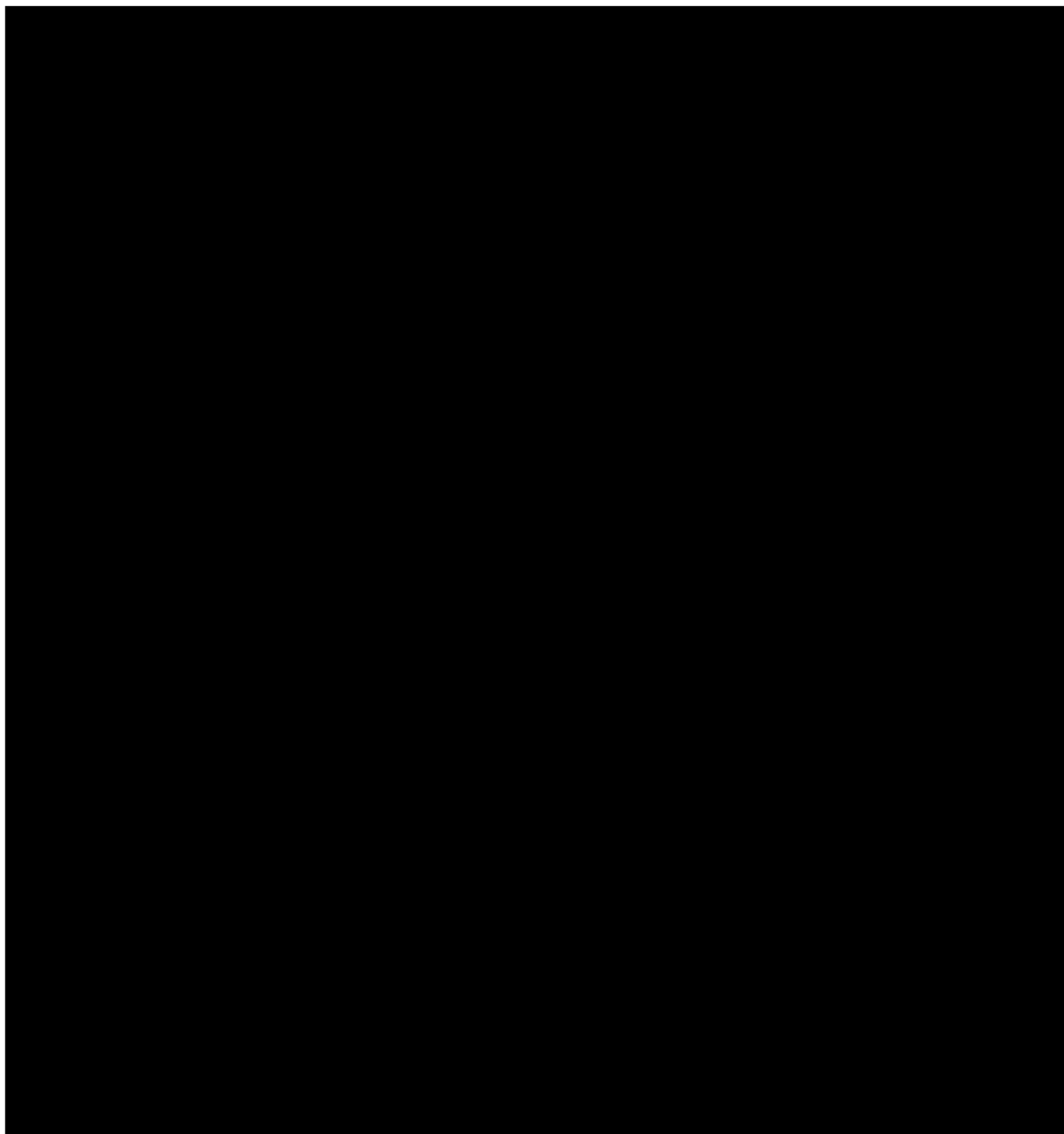
Each patient must be carefully monitored for the development of any AEs throughout the study from Screening through the Final Study Visit. This information should be obtained in the form of non-leading questions (e.g., “How are you feeling?”), and from signs and symptoms detected during each examination, from laboratory evaluation, observations of study personnel, and spontaneous reports from patients.

All AEs, including injection site reactions and potential systemic reactions will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grading system.

Complete details on AE monitoring are provided in Section 7.

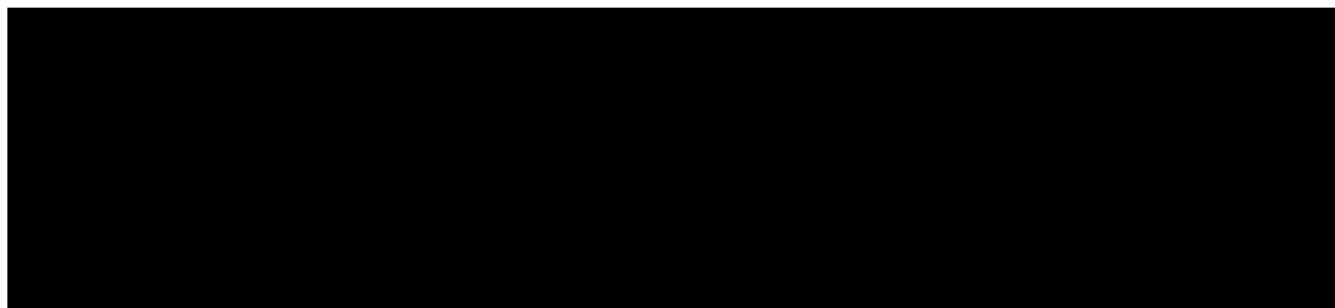
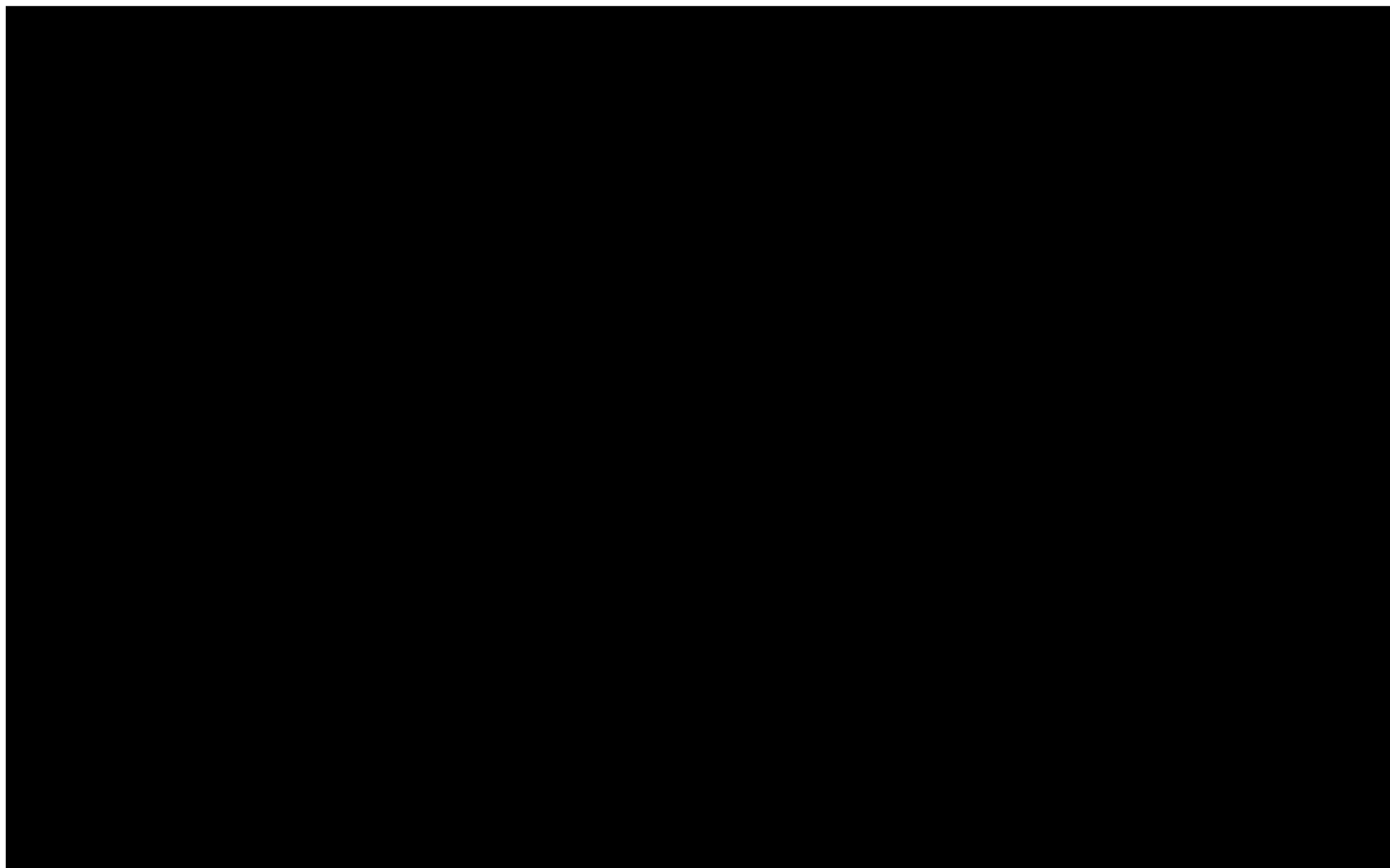
6.4.18. Optional Sub-Studies





6.4.19. Order of Assessments

When scheduled at the same time point, the order of procedures should be as follows: obtain vital signs, perform 12-lead ECG, followed by blood draws (at the specified time point, if applicable). Adjustments may be made depending upon specific circumstances.



Plasma will be harvested from each blood sample collected for PK analysis and the plasma will be frozen, shipped to a bioanalytical laboratory designated by the sponsor, and analyzed for RM-493 concentration.

7. ADVERSE EVENTS

Monitoring of adverse events will be conducted throughout the study. Adverse events will be recorded in the CRFs from Screening through the Final Study Visit. Adverse events that occur after the start of study drug administration will be considered treatment emergent adverse events (TEAEs). SAEs will be recorded through the Final Study Visit. All adverse events should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

7.1. Definitions, Documentation, and Reporting

An **adverse event (AE)** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

An AE or suspected adverse reaction is considered serious (**SAE**) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

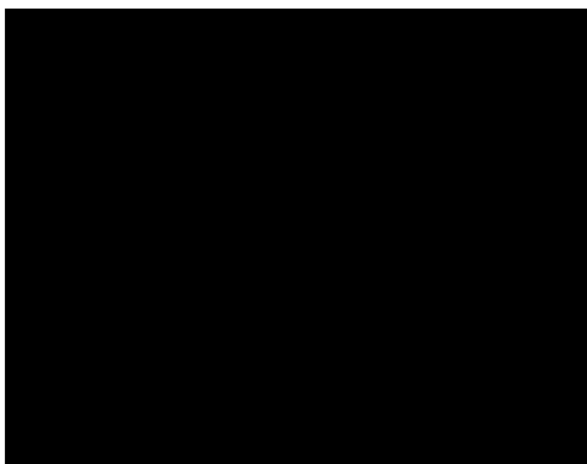
- Death.
- Life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- In-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

7.2. Procedures for AE and SAE Reporting

Each patient must be carefully monitored for the development of any AEs. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?") and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from patients.

All AEs (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate CRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

All SAEs that occur during the course of the study must be reported by the investigator to the Medical Monitor **within 24 hours** from the point in time when the investigator becomes aware of the SAE. All SAEs must be reported whether or not considered causally related to the study drug. SAE forms will be completed and the information collected will include patient number, a narrative description of the event and an assessment by the investigator as to the severity of the event and relatedness to study drug. Follow-up information on the SAE may be requested by Rhythm or its designee.



All SAE correspondence should be addressed to [REDACTED] for tracking and documentation purposes.

If there are serious, unexpected adverse drug reactions associated with the use of the study drug, Rhythm or designee will notify the appropriate regulatory agency(ies), Ethic Committees (EC) and all participating investigators on an expedited basis. It is the responsibility of the investigator to promptly notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) where required of the IRB/IEC of all unexpected serious adverse drug reactions involving risk to human patients. An unexpected event is one that is not reported in the IB.

For both serious and non-serious AEs, the Investigator must determine both the intensity of the event and the relationship of the event to study drug administration. Only those injection site reactions considered clinically significant by the Investigator will be recorded as AEs.

Intensity of all AEs including clinically significant treatment-emergent laboratory abnormalities, injection site reactions and potential systemic reactions will be graded according to the CTCAE Version 4.03. The CTCAE grade refers to the severity of the AE and ranges from Grade 1 (mild AE), Grade 2 (moderate AE), Grade 3 (severe AE) and Grade 4 (life-threatening or disabling AE) to Grade 5 (death related to AE).

Adverse events not listed by the CTCAE will be graded as follows:

Mild: discomfort noticed but no disruption of normal daily activity.

Moderate: discomfort sufficient to reduce or affect daily activity.

Severe: inability to work or perform normal daily activity.

Life threatening: represents an immediate threat to life.

Relationship to study drug administration will be determined by the investigator according to the following criteria.

None: No relationship between the event and the administration of study drug. The event is related to other etiologies, such as concomitant medications or patient's clinical state.

Unlikely: The current state of knowledge indicates that a relationship to study drug is unlikely or the temporal relationship is such that study drug would not have had any reasonable association with the observed event.

Possible: A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the patient's clinical state or other modes of therapy administered to the patient.

Probable: A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.

For the purpose of safety analyses, all AEs that are classified as possible or probable will be considered treatment-related events.

7.3. Adverse Events and Risks

Overall, setmelanotide has been generally well-tolerated in previous studies. Drug-Related TEAEs (for which the adverse event was assessed as possibly or probably related to study drug by the investigator) were reported. Because very few studies have been done using setmelanotide, there may be other unknown side effects. The PIs (or a covering clinician) will be available at all times to study participants in the event of a clinical emergency; both this availability and how to reach the investigators in an emergency will be clearly communicated orally and in writing to study participants. All study interventions will be provided free of cost.

Please refer to the current Investigator's Brochure for a comprehensive summary of the AEs reported to date.

7.3.1. Medical monitoring

The medical monitoring for the study may be delegated to a medical monitor supplied by the CRO managing the operational conduct of this study. The PI has overall responsibility for the integrity of the study and participant safety. This information, as well as any other unanticipated problems involving risks to patients or others, will also be reported to the FDA.

7.3.2. Safety Monitoring Board (SMB)

This study will be monitored by a safety monitoring committee, who will be responsible for careful safety evaluations of patients, while treatment continues in this study.

During the conduct of study, responsibilities of the SMB will be to review periodically the study data by performing a qualitative and quantitative safety assessment. In addition, the SMB should determine whether the basic study assumptions remain valid, and evaluate whether the overall integrity, scientific merit and conduct of the study are still acceptable. The SMB will make decisions regarding continuation or termination of the study or suggest changes in the design of the study or its procedures or both.

The SMB members will be comprised of both internal Rhythm employees (i.e. Rhythm's CMO) and persons independent of Rhythm. The SMB will meet quarterly throughout the duration of the trial.

7.4. Monitoring of Adverse Events and Period of Observation

AEs will be recorded on the CRFs starting from Screening up to and including the Final Study Visit. SAEs and deaths will be recorded on the CRFs starting from the time the ICF is signed and continuing through the Final Study Visit. All AEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Any SAE that occurs at any time after completion of the study, which the investigator considers to be related to study drug, must be reported to Rhythm or designee.

7.5. Guidelines for Additional Monitoring and Suspension of Dosing for a Patient

Patients will be monitored carefully during the treatment period during on site clinic visits as well as periodic telephone calls made to the patients by the study staff. In the event a patient is withdrawn from treatment due to an AE, the patient should be encouraged to complete the final study/early termination visit in order to monitor the event to resolution and obtain additional protocol defined safety assessments.

Specific guidelines for dermatological events, elevated liver function tests (LFTs), and penile erections are provided in the [Appendices](#). At all times, this guidance is subject to the clinical judgment of the Investigator and study consultants (if applicable).

The Investigator shall notify the Medical Monitor in the event any study participant fulfills any of the criteria defined in the appendices noted above, or undergoes additional monitoring for any of the events defined herein.



8. STATISTICAL PROCEDURES

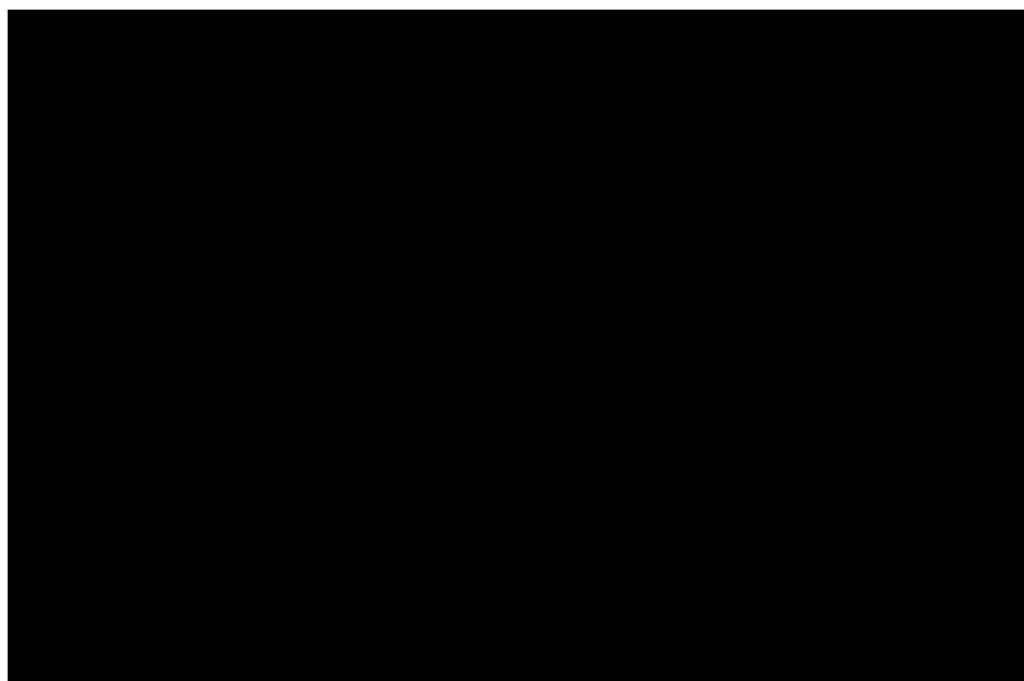
This section describes the plans for analysis. Details on the statistical plan will be provided in a complete Statistical Analysis Plan. Any additional analyses and specific conventions for analysis will be described in the Statistical Analysis Plan (SAP) and Clinical Study Report.

8.1. Sample Size Estimation

The primary endpoint is proportion of patients in the FAS who demonstrate at least 10% weight at ~1 year (10-14months post baseline) compared to baseline. Patients with missing data after 10 months from baseline will be counted as not having 10% weight loss at 1 year. The primary research hypothesis is that this proportion is at least 5%. The null hypothesis is that this proportion is at most 5%. Rationale for the 5% historical control value for this comparison is as follows.

The available data suggests that 0% of POMC deficiency patients would demonstrate at least 10% weight loss in a single year, even with extraordinary measures. The exception might be after bariatric surgery, as some patients have had very short-term improvements, though over time their overwhelming hunger leads to weight regain. In the absence of such measures in our clinical trial (exclusions from the trial), and the general contraindication of bariatric surgery in this population, it is defensible to consider that no (0%) patients would meet these criteria and the statistical comparison for this endpoint should be a comparison to a 0% proportion. Despite this strong rationale based on the natural history of these patients, since the data are limited and the number of patients in the trial is small, it is probably more appropriate to go beyond this very conservative estimate of 0% responders, to do our historical control comparisons assuming that a small proportion of the population (i.e. 5%, or a null of 0.05) *might* show a 10% weight loss in any given calendar year; hence we propose a categorical comparison to a 5% responder estimate in untreated historical patients.





Patient

Assuming POMC deficiency patients will be a total sample size of ~10 patients in the one year study, all power statements will assume $n=10$ patients in the study. The actual numbers for this ultra-rare disease may be larger or smaller.

It is expected that treatment with RM-493 for 1 year is associated with a TRUE underlying probability of at least 10% weight loss at 1 year of at least 50%. That assumption yields at least 94% power to yield a statistically significant ($\alpha=0.05$ and 0.025 1-sided, due to discreteness of the binomial distribution) difference from the null hypothesis 5% value for $N=10$ FAS patients. If the TRUE probability of at least 10% weight loss at 1 year is 40%, then power is ~83%. The minimum OBSERVED proportion of $N=10$ patients with at least 10% weight loss at 1 year that would yield statistical significance ($\alpha=0.05$ and 0.025 1-sided, due to discreteness of the binomial distribution) is 0.3 (3 of 10).

8.2. Statistical Methods

Statistical methods, populations and approaches to address multiplicity of secondary endpoints and missing data will be outlined in the SAP.

The primary analysis will be conducted based on a Full Analysis Set (FAS), which is defined as all subjects who received at least 1 dose of study medication and have a baseline measurement (regardless of whether at least one post-baseline efficacy assessment is observed). All available measurements (including data from patients who discontinue active treatment) will be included in the analysis. The comparison of post-treatment mean values versus baseline and of proportions to null hypothesis values will be carried out via 1-sided statistical test at an $\alpha=0.05$. No adjustment for multiplicity is needed for the single primary endpoint (proportion of patients with at least 10% weight loss at 1 year in comparison to baseline versus the null hypothesis value 0.05).

For the primary endpoint, and all other endpoints, the last value obtained prior to the first dose of active treatment will be considered the baseline value for statistical analyses.

As this patient population is extremely rare, all data collected even if outside of visit windows, will be included in all analyses of endpoints.

AEs will be coded by using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, and treatment group for the number and percent of AEs reported, the number of patients reporting each AE, and the number of patients with any AE.

A by-patient AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided.

Safety data including laboratory evaluations and vital signs assessments will be summarized by time of collection and by treatment group. In addition, change from baseline to any post-dose values will be summarized for vital signs and clinical laboratory results. Frequency of patients with abnormal safety laboratory results will be tabulated by treatment.

Plasma concentrations will be summarized. Plasma concentrations may be compared to PD endpoints.

8.3. Timing of Analyses

It is planned that an analysis may be completed once all planned patients have completed ~1 year of treatment, data has been cleaned and finalized, and the database is locked for assessments (including the double-blind placebo controlled withdrawal phase, the only part of the study which is not open label).

8.4. Long-Term Extensions and Pooling of Patients from other Studies

It is expected that patients who continue to tolerate setmelanotide after 1 year of treatment, and who show clinically important weight loss, will be continued on long-term extensions (to be fully outlined in a future extension protocol, as noted in Section 5.5), on a year by year basis. Additional analyses will summarize the long-term experience as appropriate.

It is also expected that some patients may not enter this study (for logistical reasons) but will be participating in an essentially identical protocol (Study RM-493-011) with a long-term extension phase. After assessing that study conduct and upon determining essentially identical treatment procedures to this study, these patients will also be carefully identified in the Clinical Study Report, and their data will also be summarized and pooled, based on treatment duration, with data from patients who entered this study in a supplemental analysis.

8.5. Statistical Analysis Plan

The full Statistical Analysis Plan for this study will provide more detailed statistical procedures prior to any planned analysis.

9. ADMINISTRATIVE REQUIREMENTS

9.1. Good Clinical Practice

The study will be conducted in accordance with the International Council on Harmonization (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 0). 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/CRFs, 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 Rhythm or its designee and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the source documents/CRFs 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 Rhythm, 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 Rhythm. 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. Rhythm 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 Rhythm, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documents/CRF.

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:

MedDRA for adverse events

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 Rhythm will be followed, in order to comply with GCP guidelines.

The study will be monitored by Rhythm 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 Rhythm after the clinical phase of the study has been completed (see Section 5.7).

Regulatory authorities, the IRB/IEC, and/or Rhythm'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.

Rhythm 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. Rhythm must be notified in writing if a custodial change occurs.

9.10. Liability Insurance

Rhythm 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 Rhythm 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 Rhythm. It is understood that there is an obligation to provide Rhythm 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 Rhythm 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 the course of this trial.

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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*	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Edema*	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Induration*	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pain or Tenderness*	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other: _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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

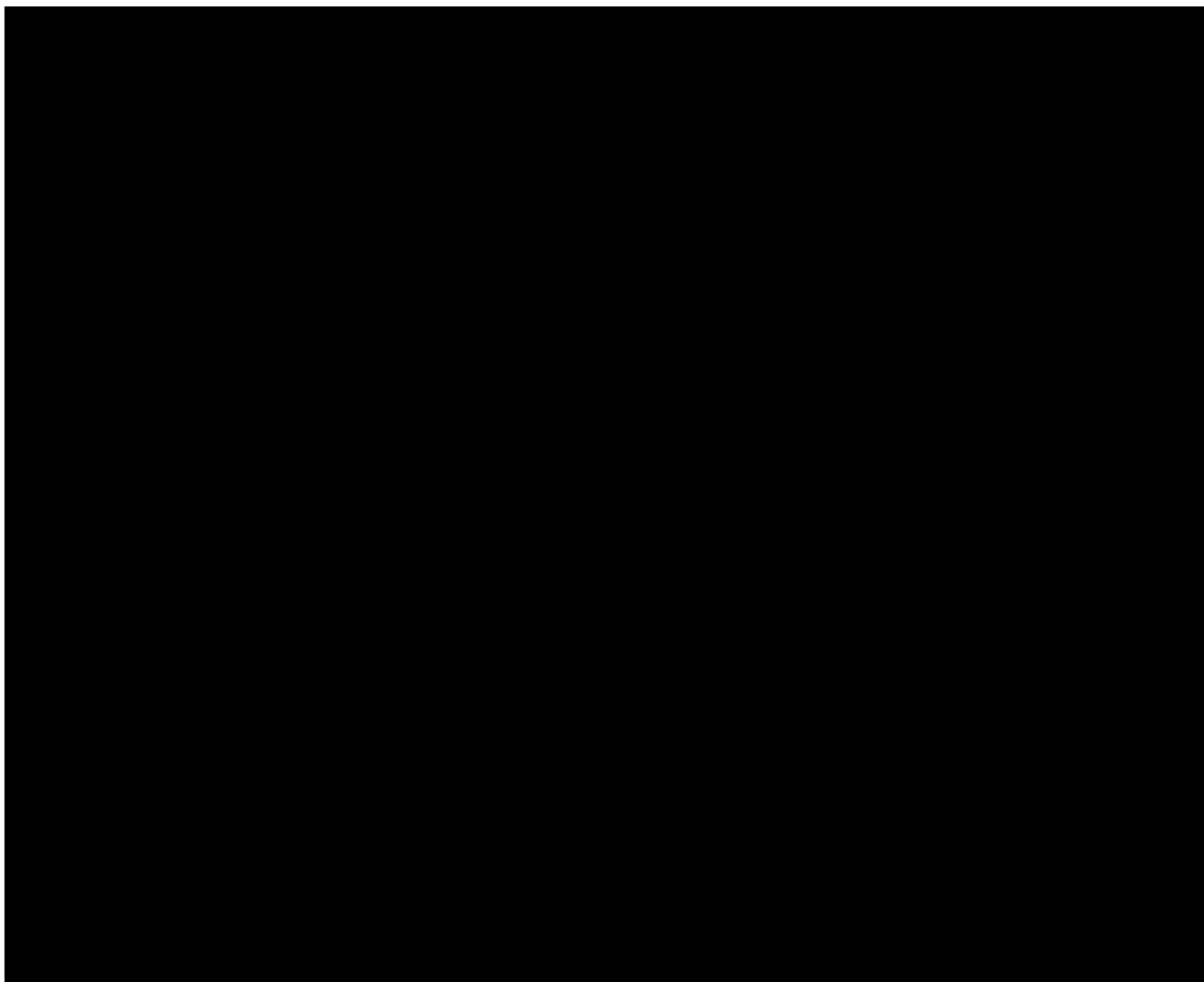
Initials: _____

11.2. Fitzpatrick Classification Scale

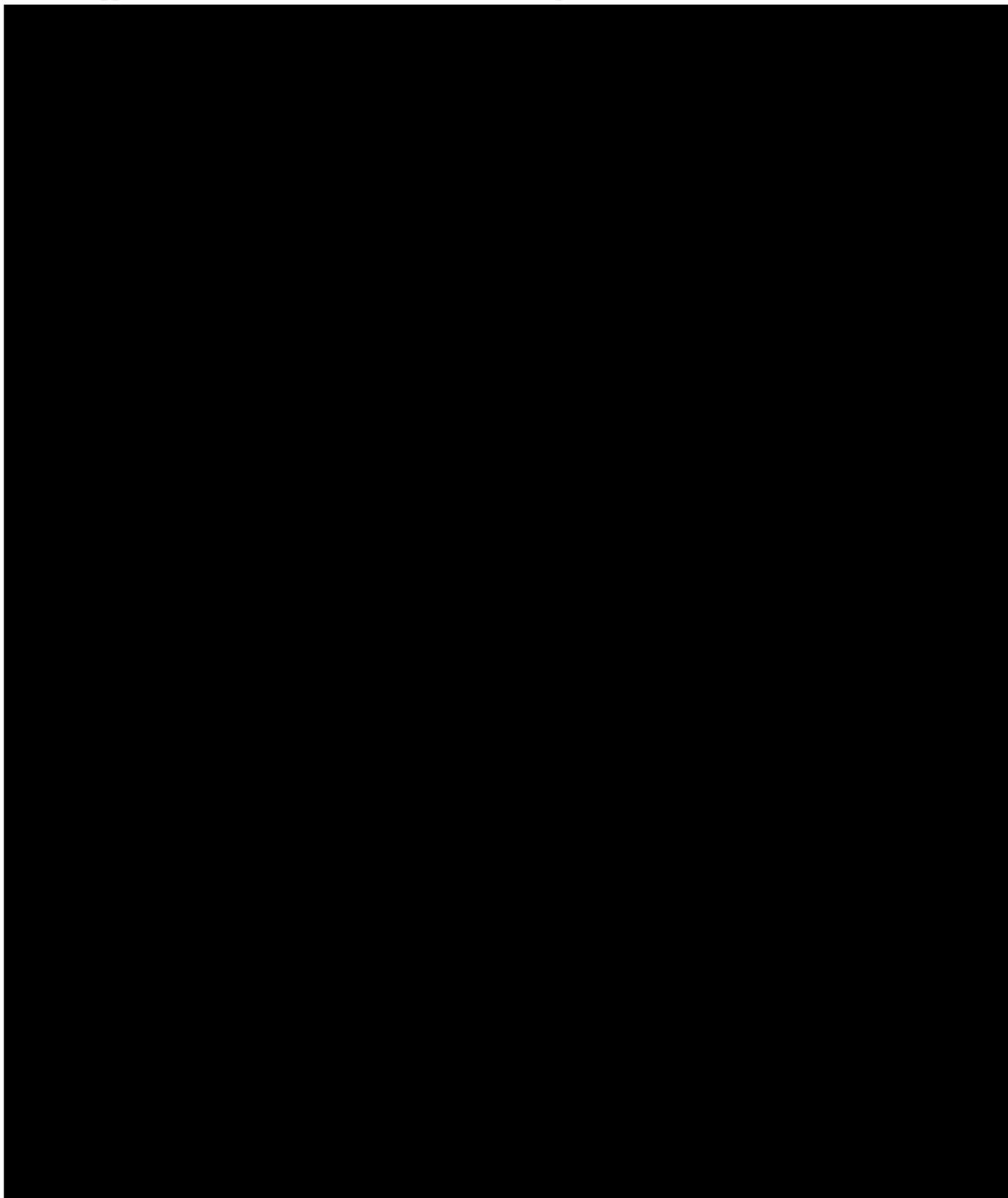
Skin Type	Skin Color	Characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel, or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn,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

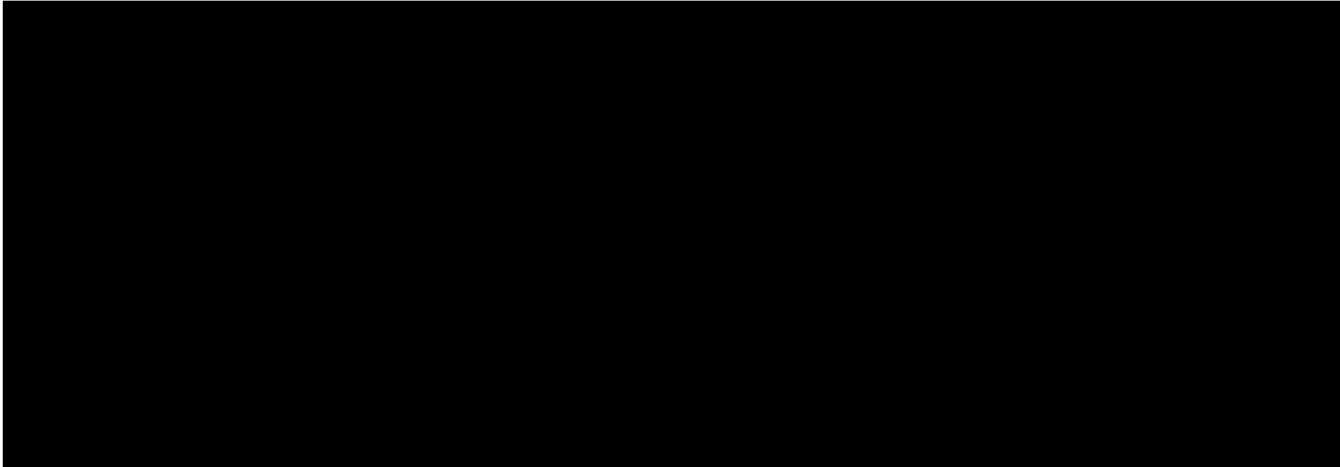
Fitzpatrick TB: Soleil et peau. J Med Esthet 1975;2:33034.

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





11.5. Guidance for Monitoring Potential Treatment-Related Penile Erections and Suggested Criteria for Discontinuation of Dosing

The Investigator will identify a Urologist to serve as a consultant for the Investigative Site in the event a patient reports a clinically significant erection. Male patients will be instructed to immediately report any non-erotic erections lasting for more than 30 minutes, or a painful erection of any duration, to the Investigator.

As previously mentioned, penile erections in males are effects associated with MC4R agonism, and have been seen in setmelanotide Phase 1 and 2 studies. However, occurrence of these events does not appear to correlate with dose and duration of dosing, as the number of events did not increase with dose or duration of dosing. These events have been intermittent usually lasting less than 20 minutes, painless, and resolved without intervention. Some patients have had a series of such erections over a multi-hour interval, with intermittent flaccidity. If a patient reports a painless, non-erotic continuous erection of more than one-hour duration, based on Investigator judgment, study drug injection is to be immediately discontinued. If after study drug discontinuation the event does not resolve, further treatment may be provided as clinically indicated.

Erections lasting more than four hours or painful erections of shorter duration are of serious concern, especially since the presence of pain may connote localized penile ischemia. No painful or prolonged erections have been reported in Phase 1 or 2 studies, however, in the event one is reported, study drug injection is to be stopped immediately and an examination of the patient performed by the Investigator. The Urology Consultant is to be notified immediately and is to provide emergent instructions regarding further evaluation and treatment.

11.6. Evaluation of Abnormal Liver Function Tests (LFTs)

While there has been no signal of elevated LFTs during the Phase 1/2 studies of RM-493, nor any signal identified in the toxicological studies, the following is guidance for evaluation of any LFT abnormalities identified during the course of this study

1. If ALT or AST > 3 ULN, repeat in 48-72 hrs.
 2. If repeat ALT or AST are still > 3 ULN, repeat LFTs (including transaminase, alkaline phosphatase and bilirubin levels) every 48-72 hrs. In addition, the following should be performed:
 - Obtain a detailed history of symptoms, prior and concurrent diseases, concomitant drug use (including OTC, herbal and dietary supplements), alcohol and recreational drug use and special diets
 - Obtain history of exposure to environmental chemical agents
 - Consider evaluation for acute viral hepatitis types A, B, C, D and E, autoimmune or alcoholic hepatitis, nonalcoholic steatohepatitis (NASH), biliary tract disease and ischemic liver injury
 - Consider additional tests to evaluate hepatic function, as appropriate, such as INR.
 - Consider hepatology consultation
- Frequency of repeat testing can be reduced if LFT abnormalities stabilize or if the patient is asymptomatic and study drug is discontinued.
3. Discontinue study drug administration if:
 - ALT or AST > 8xULN on any single determination
 - ALT or AST > 5xULN for more than 2 weeks
 - ALT or AST > 3xULN with total bilirubin > 2xULN or INR > 1.5
 - ALT or AST > 3xULN with the appearance of fatigue, fever, rash, and/or eosinophilia (> 5%) or nausea, vomiting, right upper quadrant pain or tenderness that is more frequent and/or more severe than patient's baseline DG symptoms
 4. Follow-up to Resolution: All study patients with clinically significant treatment-emergent LFT abnormalities should be followed until values return to normal or baseline levels

Adapted from: US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Silver Spring, MD. July 2009.

11.7. Standardization of Blood Pressure Measurement

For BP measurements, the patient will remain in the sitting position **for at least 5 minutes** before any BP readings are recorded. Systolic and diastolic blood pressures will be determined by averaging three (3) consecutive measurements obtained 2 minutes apart. None of the 3 consecutive readings can be >5 mm Hg from the calculated average of the 3 readings. If this occurs, obtain additional readings, 2 minutes apart, until 3 consecutive stable measurements are obtained. Record only the 3 stable readings, in addition to the mean, the initial time of the measurement and the arm used for the measurement in the case report forms (as outlined below).

The following instructions will be followed for both manual and automatic blood pressure measurements (with steps specific to manual identified by “[MANUAL]”).

Please pay special attention to selecting the appropriate cuff size for this patient population, as noted below.

The accuracy and reliability of blood pressure readings will increase by following these standardized steps:

1. Situate the individual in a quiet environment with the arm resting at heart level.
2. [MANUAL] For manual measurements, place the manometer at eye level, sufficiently close to read the calibration markings on the gauge or column.
3. Select the appropriately sized cuff. The proper cuff size should be used on the **non-dominant arm throughout the study**. Bladder width should be at least 40% of arm circumference; bladder should be at least 80% of arm circumference.
4. [MANUAL] Locate the brachial artery along the inner upper arm by palpation.
5. Wrap the cuff smoothly and snugly around the arm, centering the bladder over the brachial artery. The lower margin should be 2.5 cm above the antecubital space. (Do not rely on cuff marking; find the center by folding the bladder in half.)
6. For manual measurements:
 - a. Determine the level for maximal inflation by observing the pressure at which the radial pulse is no longer palpable as the cuff is rapidly inflated (palpated systolic) and by adding 30 mm Hg.
 - b. Rapidly and steadily deflate the cuff. Then wait 15 to 30 seconds before re-inflating.
 - c. For manual measurements, position the stethoscope over the palpated brachial artery below the cuff at the antecubital fossa. Ear pieces should point forward. The bell head of the stethoscope should be applied with light pressure, ensuring skin contact at all points. Heavy pressure may distort sounds.
 - d. Rapidly and steadily inflate the cuff to the maximal inflation level as determined in Step a.
 - e. Release the air in the cuff so that the pressure falls at a rate of 2 to 3 mm per second.
 - f. Note the systolic pressure at the onset of at least two consecutive beats (Phase 1 Korotkoff sounds). Blood pressure levels should always be recorded in even numbers and read to the nearest 2 mm Hg mark on the manometer.
 - g. Record the diastolic pressure at the cessation of the Korotkoff sounds (Phase V). Listen for 10 to 20 mm Hg below the last sound heard to confirm disappearance, and then deflate the cuff rapidly and completely.
7. For automatic measurement:
 - a. Take automatic measurements and record.

- b. Record the patient's position and the arm used for the measurement.
- c. Wait 2 minutes before repeating the pressure measurement in the same arm to permit the release of blood trapped in the arm veins.
- d. Note that all three readings at each timepoint should be captured on the case report form, as well as the average.
- e. For each patient, the method used for BP determinations (manual or automatic) should be used throughout the study. In addition, the same size cuff should be used throughout. Care should be taken to make all measurements in the same position (sitting) for all measurements.

Rounding Rules for Blood Pressure Measurements

Blood pressure readings will be recorded to the nearest **even** mm Hg. **Do not round off to the nearest 5 or 10 mm Hg BP reading.** Therefore, a 142/94 reading should not be reported as 140/95, but should be reported as 142/94.

When calculating the **means** (average) of the readings, the following rules should be used:

If the value is XX.1 to XX.4, it should be rounded down (example: A diastolic mean of 97.2 would be recorded as 97, as would a mean of 97.4).

If the value is XX.5 or greater it should be rounded up (example: A diastolic mean of 97.5 would be recorded as 98, as would a mean of 97.9).

The **mean** of the readings may be an odd number.

Special Pitfalls and Problems

The Auscultatory Gap

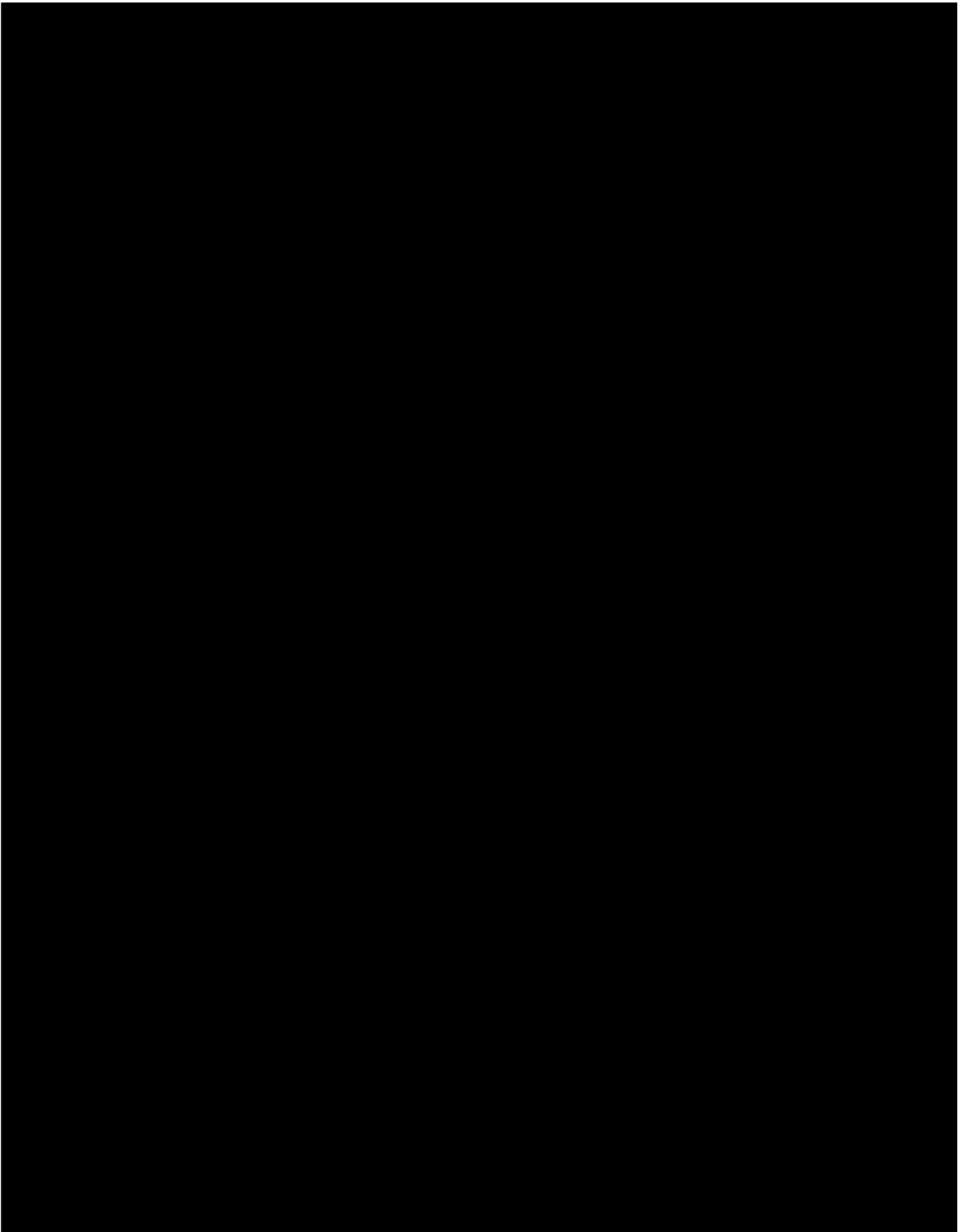
[MANUAL] In some subjects, particularly in patients with hypertension, the sounds heard over the brachial artery when the cuff pressure is high disappear as the pressure is reduced and then reappear at some lower level. This early, temporary disappearance of sound is called the auscultatory gap and occurs during the latter part of Phase I and Phase II. Because this gap may extend over a range as great as 40 mm Hg, one may seriously underestimate the systolic pressure or overestimate the diastolic pressure, unless its presence is excluded by first palpating for disappearance of the radial pulse as the cuff pressure is raised.

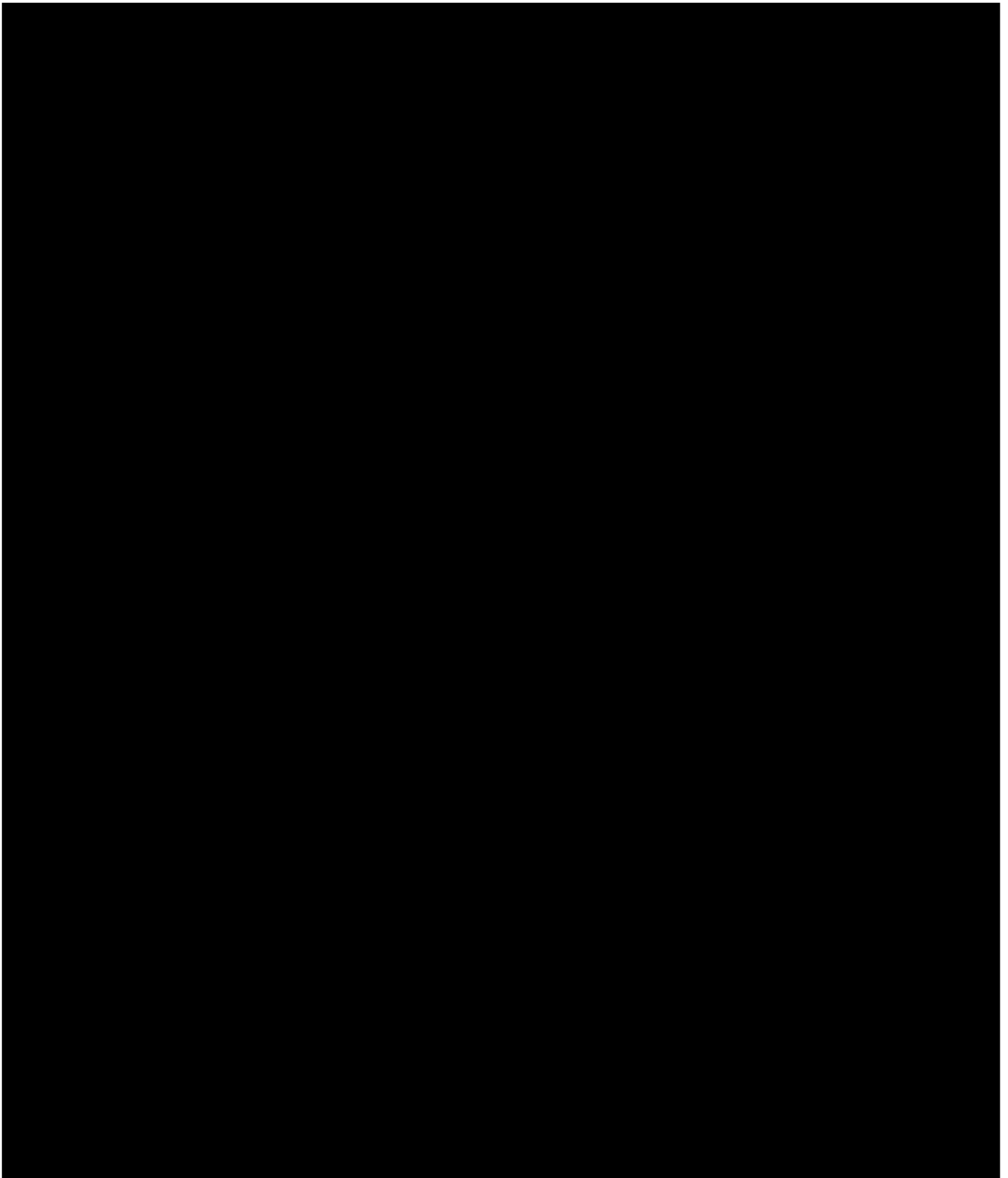
Effect of Arm Position

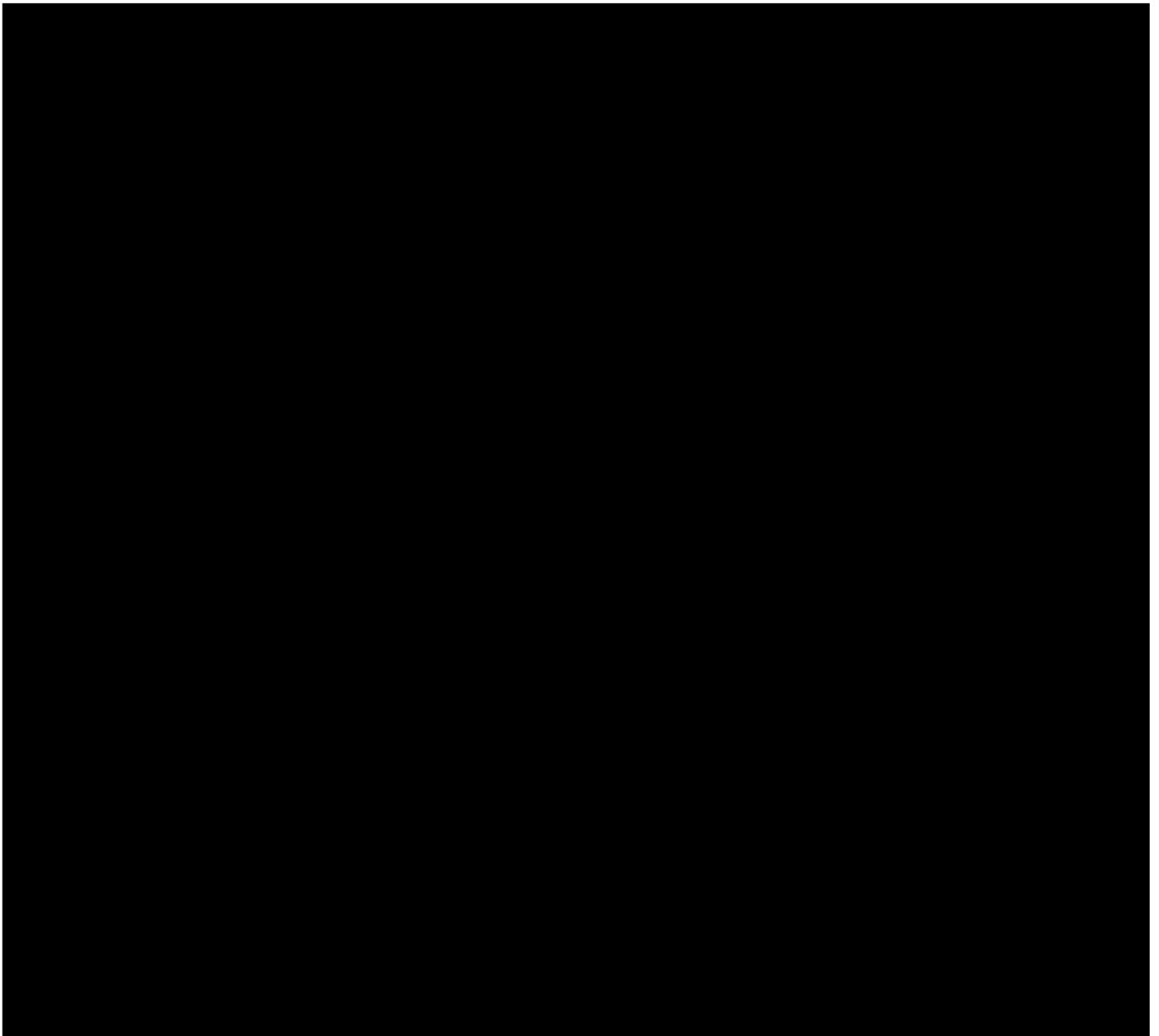
The pressure in the arm increases as the arm is lowered from the level of the (phlebostatic axis); conversely, raising the arm above this position lowers the pressure measurement. The effect is largely explained by hydrostatic pressure or by the effect of gravity on the column of blood. Therefore, when measuring indirect blood pressure, the patient's arm should be positioned so that the location of the stethoscope head (preferably the bell or its equivalent) is at the level of the heart. This location of the heart is arbitrarily taken to be at the junction of the fourth intercostal space and the lower left sternal border. **When the patient is seated, placing the arm on a nearby tabletop a little above waist level will result in a satisfactory position.**

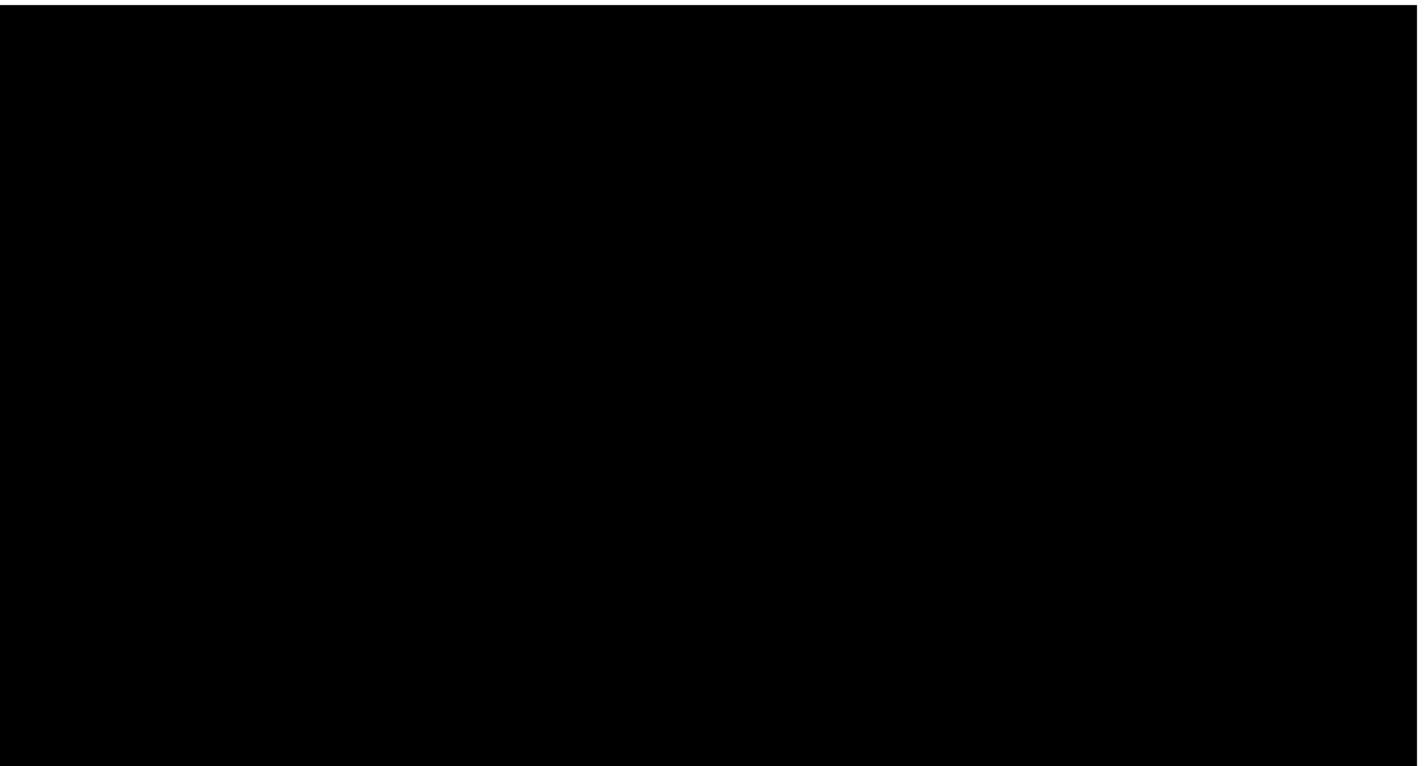
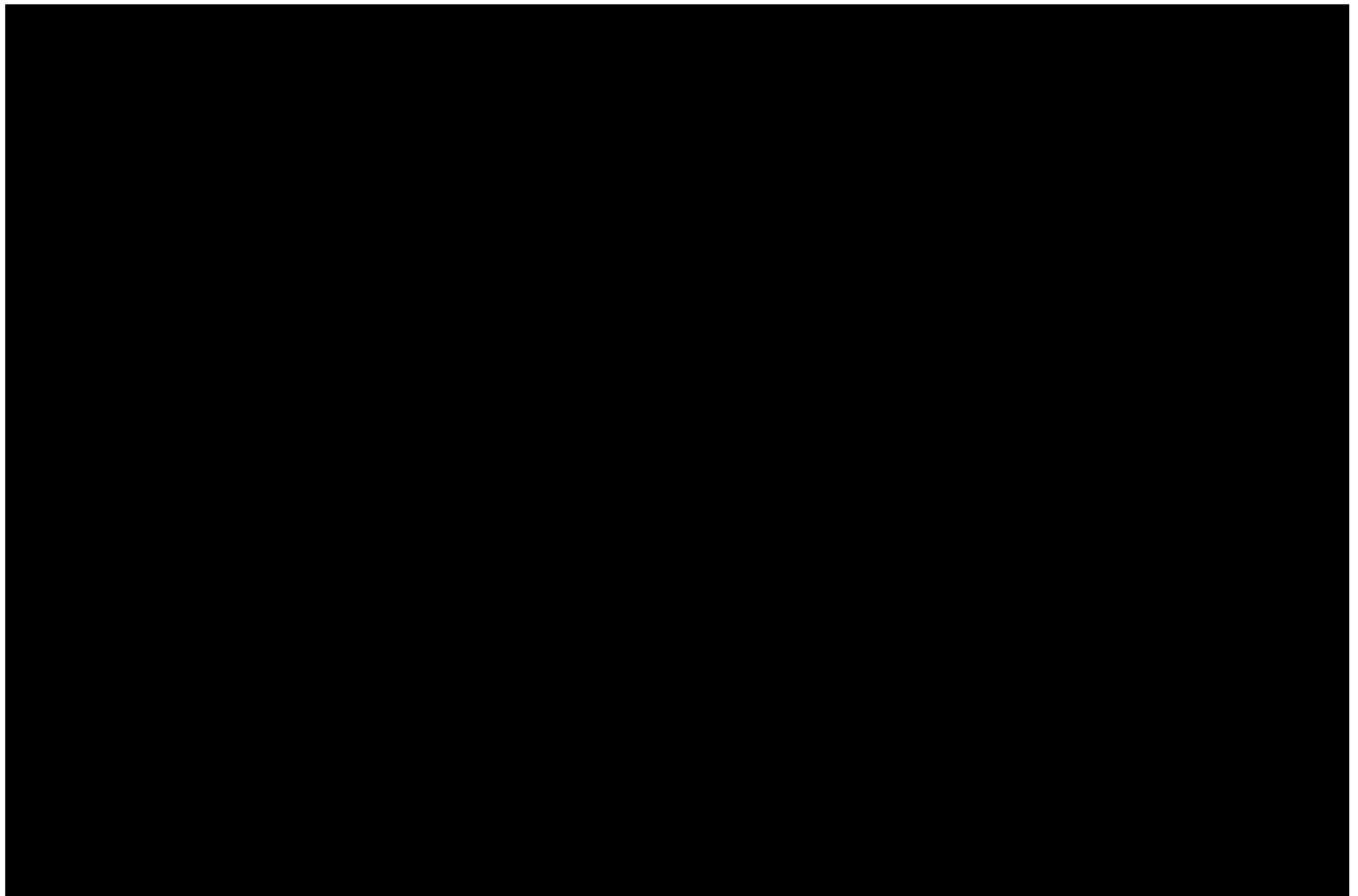
Large Arm Size

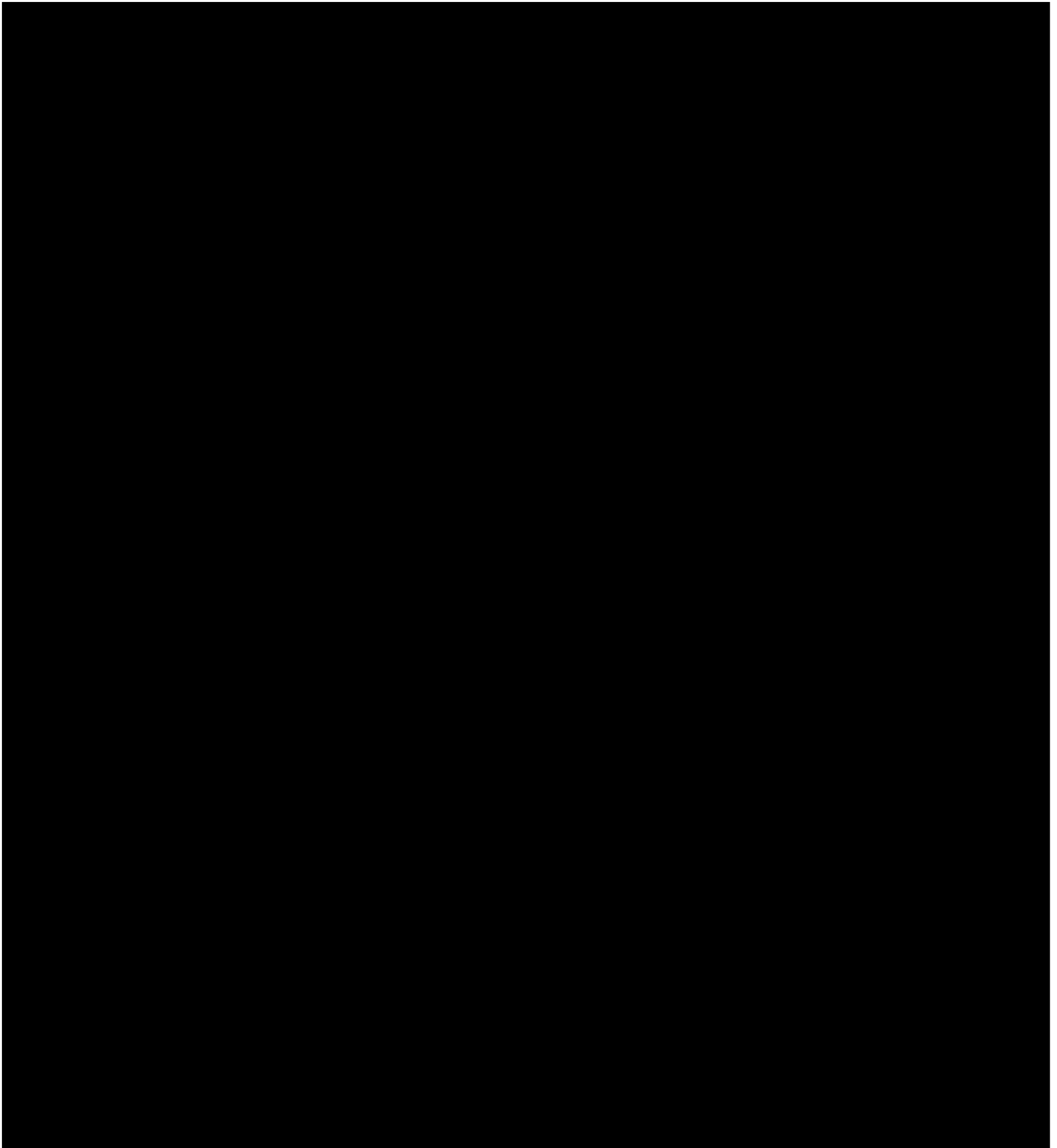
Falsely elevated indirect pressure measurements may be obtained in patients with increased arm girth if the standard-sized bladder and technique are used. This is caused by the use of bladders that are too small, with subsequent excessive loss of cuff pressure through the thick, compressible soft tissues of the large arms. This problem may be minimized by using a bladder width that is 40 to 50% of measured arm circumference. In individuals with moderately large arm size, a large adult cuff (32 to 42 cm wide) will usually be adequate, but a larger cuff (38-50 cm) should be available, if necessary.

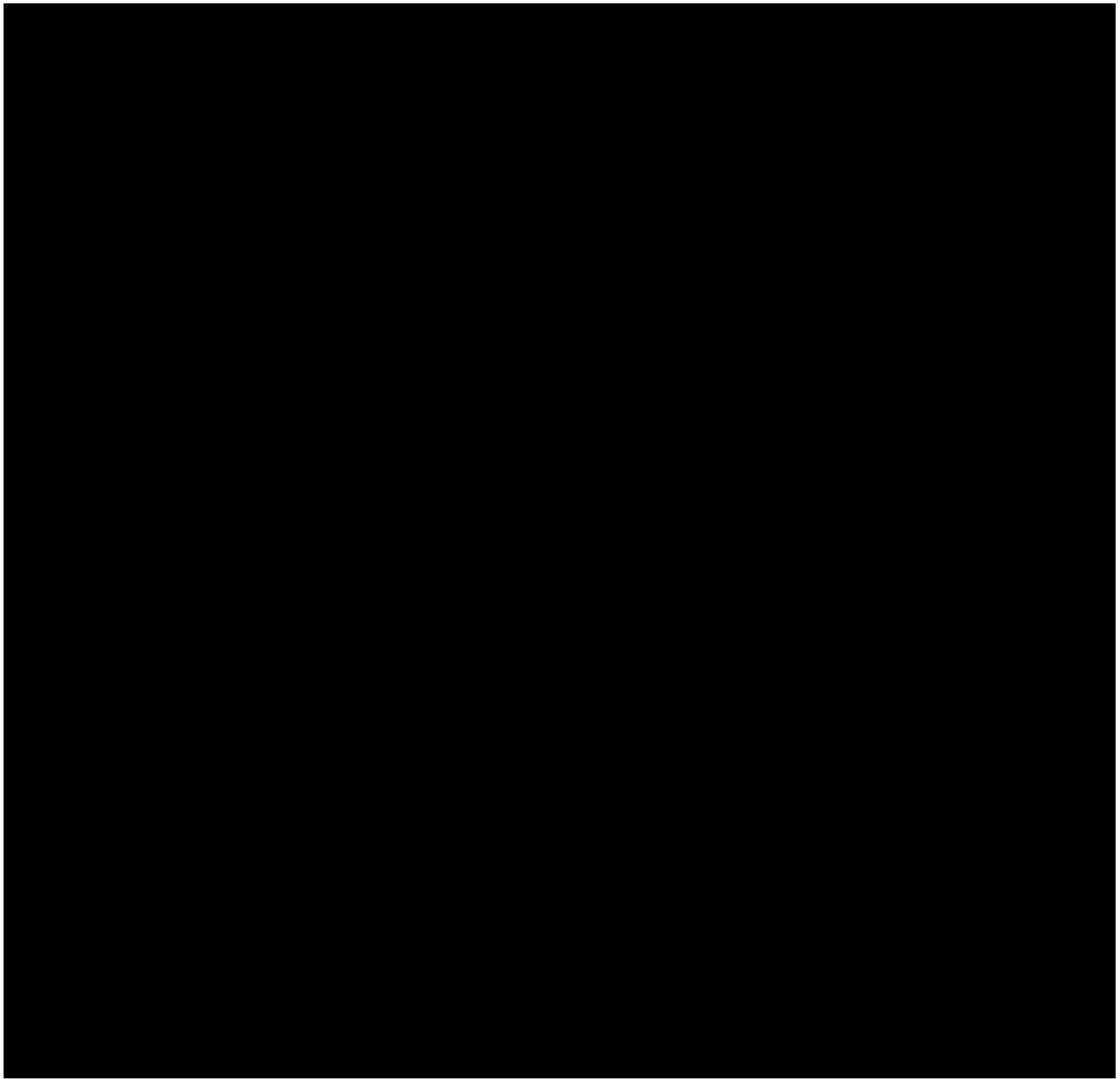












11.10. Creatinine Clearance Estimate by Cockcroft-Gault Equation

Male Creatinine Clearance mL/min = $1.0 * ((140 - \text{Age}) / (\text{SerumCreat})) * (\text{Weight (kg)} / 72)$

Female Creatinine Clearance mL/min = $0.85 * ((140 - \text{Age}) / (\text{SerumCreat})) * (\text{Weight (kg)} / 72)$

Age in years

Serum creatinine in mg/dL

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

11.11. 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” (with the exception of DEXA which is classified as “Minor Increase over Minimal Risk”) according to the 2008 Guidance Document “Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric 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.
- In order 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 definitely 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 (with the exception of DEXA 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. [REDACTED]

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 tox 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.

11.12. Blood Volumes for Study Tests

The blood volumes for study assessments are listed in Tables 1 and 2 below. These blood volumes are estimated from standard sized collection tubes, and may vary slightly, based on local lab policies and procedures.

Table 1: Blood Volumes for Study Tests - Participants Ages 6 to 11 years:

	Screen	Visit 2a	Visit 2b	Visit 2c	Visit 2d	Visit 2e	Visit 2f	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
Weeks	4	2	2	2	2	2	2	2	2	4	4	4	4	6	6	6	6	8
Blood volume in mL																		
Archive sample	12										12							12
Safety Laboratory Tests	16	16	16	16	16	16	16		16		16			16		16		16
OGTT	35										35							35
Anti-RM-493 Antibodies	5	5	5						5		5			5		5		5
Total per Visit (mL)	107	54	24	19	61	19	19	6	54	0	104	0	6	57	0	99	0	104

PK will be performed at either Visit 2d or Visit 3, not both visits.

Table 2: Blood Volumes for Study Tests - Participants ≥ 12 years:

	Screen	Visit 2a	Visit 2b	Visit 2c	Visit 2d	Visit 2e	Visit 2f	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
Blood volume in mL																		
Serum Pregnancy	4		4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Archive sample	12										12							12
Safety Laboratory Tests	16	16	16	16	16	16	16		16		16			16		16		16
OGTT	35										35							35
Anti-RM-493 Antibodies	5	5	5						5		5			5		5		5
Total per Visit (mL)	111	120	70	65	65	65	65	10	64	10	114	10	10	127	10	67	10	174

11.13. 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.