CLINICAL STUDY PROTOCOL

Protocol RM-493-015

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 Leptin Receptor (LEPR) Deficiency Obesity due to Bi-Allelic Loss-of-Function *LEPR* 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.

US IND No. 112,595

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CONFIDENTIALITY NOTE

APPROVAL SIGNATURE PAGE

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 Leptin Receptor (LEPR) Deficiency Obesity due to Bi-Allelic Loss-of-Function *LEPR* Genetic Mutation

REVIEWED/APPROVED BY:

[redacted] [redacted] 10Dec2018

Rhythm Pharmaceuticals, Inc. Date

INVESTIGATOR STATEMENT

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

This study will not commence without the prior written approval of a properly constituted Institutional Review Board/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-493-015
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 Leptin Receptor (LEPR) Deficiency Obesity due to Bi-Allelic Loss-of-Function *LEPR* 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 LEPR Deficiency Obesity
Objective(s)	<u>Primary</u> • To demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change in patients with LEPR deficiency obesity due to rare bi-allelic or loss-of function mutations at the end of 1 year of treatment. <u>Secondary</u> To assess the effect of setmelanotide, over one year, on: • Safety and tolerability of setmelanotide (including blood pressure [BP] and heart rate [HR]). • Hunger in patients ≥12 years old. • 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. 

	[redacted]
Trial Design	This is a pivotal study to assess long-term (~1 year) efficacy of setmelanotide in LEPR 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 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 of 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 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. Where feasible, and for patients who agree to participate, there [redacted]
Study Population	Male and female patients, 6 years of age and above, with a confirmed diagnosis of LEPR Deficiency Obesity due to bi-allelic, loss-of-function *LEPR* gene mutations.
Number of Patients & Study Centers	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 to satisfy regulatory requirements for registration, depending upon the total number of affected patients identified. It is anticipated that up to 10 centers located worldwide will participate in this study. If added patients are to be enrolled, additional sites may be added, as necessary.
Inclusion Criteria	1. Bi-allelic, homozygous or compound heterozygous (a different gene mutation on each allele) genetic status for either the *LEPR* 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/m^2; if child or adolescent, obesity with BMI ≥95th percentile for age on growth chart assessment. 4. Study participant and/or parent or guardian can communicate well with the investigator, to understand and comply with the requirements of the study, and can 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) or 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	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 due to 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 x 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. Previous history of significant hypersensitivity to exogenously injected peptides (e.g. urticaria, shortness of breath, or more severe responses including anaphylactoid reactions or anaphylaxis). 14. Inability to comply with QD injection regimen. 15. Patients who have been placed in an institution through and official or court order, as well as those who are dependent on the sponsor, Investigator, or study site.
Synopsis of Study Activities	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 and maximum allowable dose approved at the participating site) where the individual patient's therapeutic dose 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 of weight from baseline (or 5% if < 100 kg at 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 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 ≥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 numeric rating scale for patients 12 years or older and [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, fat loss, and [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. Potential improvements in [redacted] as well as glucose parameters as measured by fasting glucose, HbA1c and OGTT with focus on parameters of insulin sensitivity will be assessed over time. [redacted]. As required by Food and

	Drug Administration (FDA) for central nervous system (CNS)-active obesity medications, changes in [redacted] will be monitored over the entire course of the trial.
Study Drug and Administration	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 will be administered as subcutaneous (SC) injection once daily. 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.
Statistical Considerations	The objective of this study is to demonstrate statistically significant and clinically meaningful weight loss in patients with LEPR deficiency obesity after ~1 year of treatment. As patients remain on treatment for 1 year, more weight loss is expected. The primary endpoint is proportion of patients in the FAS who demonstrate at least 10% weight loss 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 LEPR 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 LEPR 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
[redacted]	
ADA	Anti-drug antibody
AE	Adverse event
AgRP	Agouti-Related Peptide
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
[redacted]	
b-LPH	β-lipotropin
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte
BIA	Bioelectrical impedance
BMI	Body mass index
[redacted]	
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
[redacted]	
CNS	Central nervous system
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRA	Clinical research associate
CRF	Case report form

Abbreviation	Definition
[redacted]	[redacted]
CSC	Clinical Safety Committee
[redacted]	
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
[redacted]	
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-glutamyl transpeptidase
GH	Growth hormone
GI	Gastrointestinal
[redacted]	
GnRH	Gonadotropin-releasing hormone
HbA1c	glycated hemoglobin
Hg	Mercury
HIV	Human immunodeficiency virus

Abbreviation	Definition
HR	Heart rate
[redacted]	
IB	Investigator Brochure
ICH	International Conference for Harmonization
IEC	Independent Ethics Committee
[redacted]	
INR	International normalized ratio
IRB	Institutional Review Board
[redacted]	[redacted]
LDH	Lactate dehydrogenase
LEPR	Leptin Receptor
LFT	Liver function tests
LH	Luteinizing hormone
MAD	Multiple ascending dose
MC	Melanocortin
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
[redacted]	[redacted]
PHQ-9	Patient Health Questionnaire 9
[redacted]	
POMC	Pro-opiomelanocortin
PT	Prothrombin Time
PTT	Partial thromboplastin time
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
SDS	Standard deviation score
[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

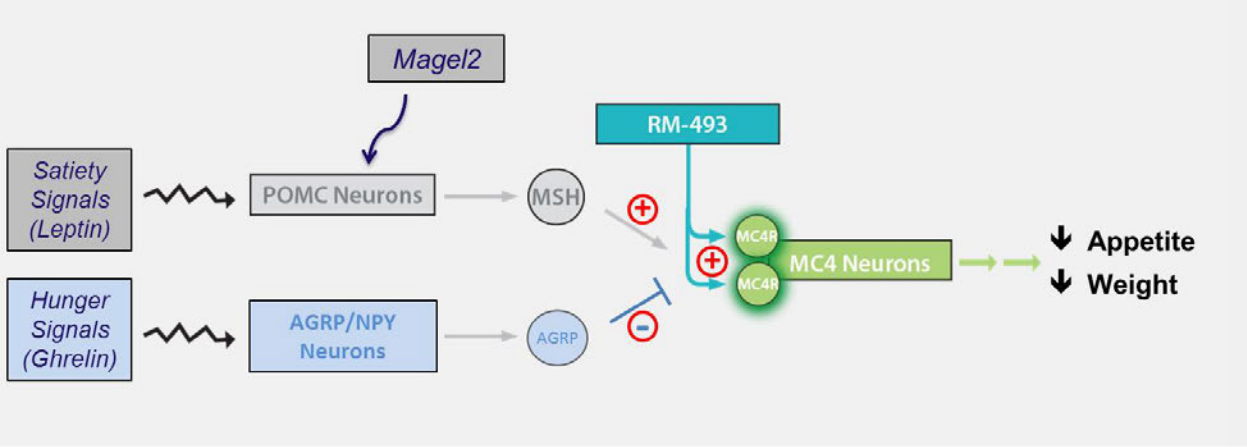
1. INTRODUCTION

1.1. Overview of Monogenic Early-Onset Extreme Obesity and the Importance of LEPR in 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 contributors. 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 express leptin receptors (LEPRs) on their cell surface, which can be activated by the anorexigenic, fat-derived hormone, leptin.

Figure 1: Schematic outline of hypothalamic food intake control

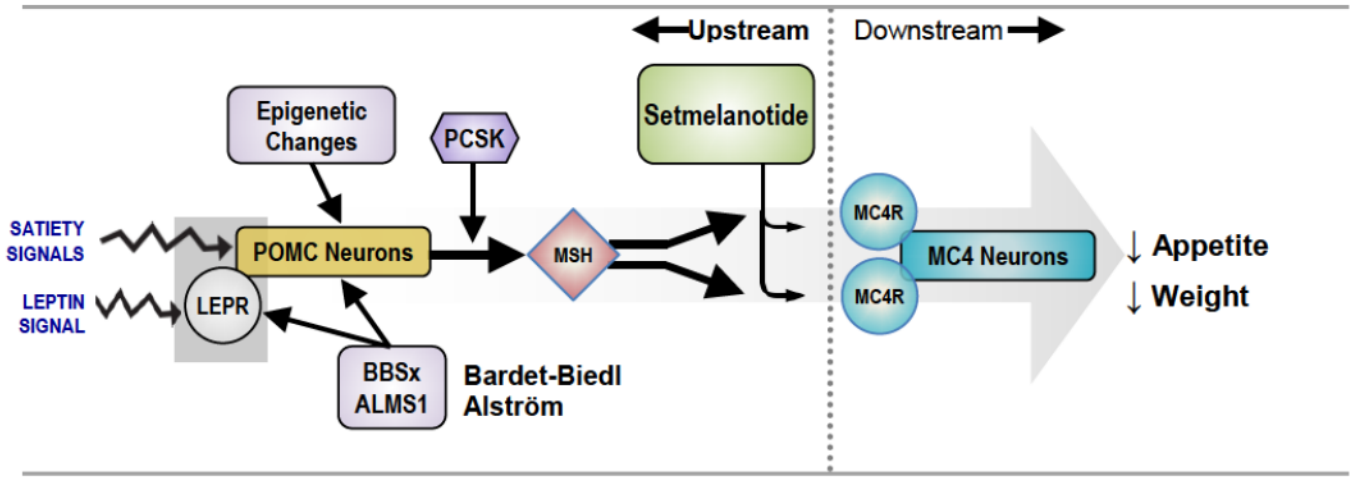


The importance of this pathway in hunger and weight reduction is supported by strong clinical genetic validation. Genetic defects for most of the steps in the LEPR-POMC-MC4R pathway (for simplicity referred to as the MC4 pathway hereafter) have resulted in the expected extreme obesity phenotype: for example, defects along the MC4 pathway have caused early onset, severe obesity and hyperphagia, and setmelanotide is hypothesized to be "replacement therapy" for these genetic defects that result in profound obesity and hyperphagia.

This protocol will evaluate the effect of setmelanotide in one ultra-rare genetic disorder of obesity that is caused by mutations in the LEPR upstream of the MC4R (as shown in Figure 2, in the context

of other rare genetic disorders of obesity that are hypothesized to impact the MC4 pathway). Rhythm is studying these other rare disorders in separate protocols.

Figure 2: The role of LEPR in the setting of rare genetic disorders of obesity due to defects in the upstream part of the MC4 pathway.



1.1.1. POMC Deficiency Obesity

The prototype disease for rare genetic disorders of obesity due to defects in the MC4 pathway is POMC deficiency obesity (which is an indication where setmelanotide is being studied in a different pivotal protocol, Study RM-493-012). In this disease, neuropeptides synthesized and processed from the POMC gene are absent or deficient due to defects in two genes. Specifically, POMC deficiency 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, POMC deficiency obesity is caused by two monogenic disorders resulting in missing MSH neuropeptide synthesis and/or processing, with subsequent absence of signaling through the MC4 pathway.

This brief background on POMC deficiency obesity is provided to set the context for the Phase 2 proof of concept clinical results for POMC deficiency obesity (see below), which was an early predictor of results for setmelanotide treatment in LEPR deficiency obesity.

1.1.2. LEPR Deficiency Obesity

LEPR mutation carriers suffer from severe hyperphagia and obesity, similar in presentation to POMC deficiency obesity, caused by a similar pathogenesis, i.e. lack of activation of the MC4 pathway, which prevents control of weight and hyperphagia.

Leptin's role in obesity has been elucidated by characterization of severely obese people with homozygous mutations that impair the activity of leptin (including disruption of signaling at the LEPR) (Clement 1998). Patients deficient in the leptin protein itself now have access to recombinant

Metreleptin treatment, so the focus for this protocol will be on those patients with *LEPR* homozygous (or combined heterozygous) mutations. As for *POMC* and *PCSK1* gene deficiencies, the loss of activation through the key MC4 pathway is hypothesized to be restored by MC4R agonist activation by setmelanotide. LEPR deficiency may occur in approximately 1-5% of subjects with severe, early onset obesity associated with severe hyperphagia (Farooqi 2007) and so may be slightly more prevalent than POMC deficiency obesity. Affected subjects manifest intense hyperphagia, severe obesity, alterations in immune function, and delayed puberty, all in the absence of developmental delay (Clement 1998, Farooqi 2007).

As mentioned above, obesity and hyperphagia develop due to the missing activation of POMC neurons, which in turn leads to the occurrence of MSH deficiency and impaired regulation of satiety and energy expenditure. This occurs because POMC neurons are not activated based on the missing leptin signal. Patients with POMC and LEPR gene mutations exhibit a clinical 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.

1.2. Rationale and Justification for the Proposal to Treat LEPR deficient patients 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 (MCs) 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 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.

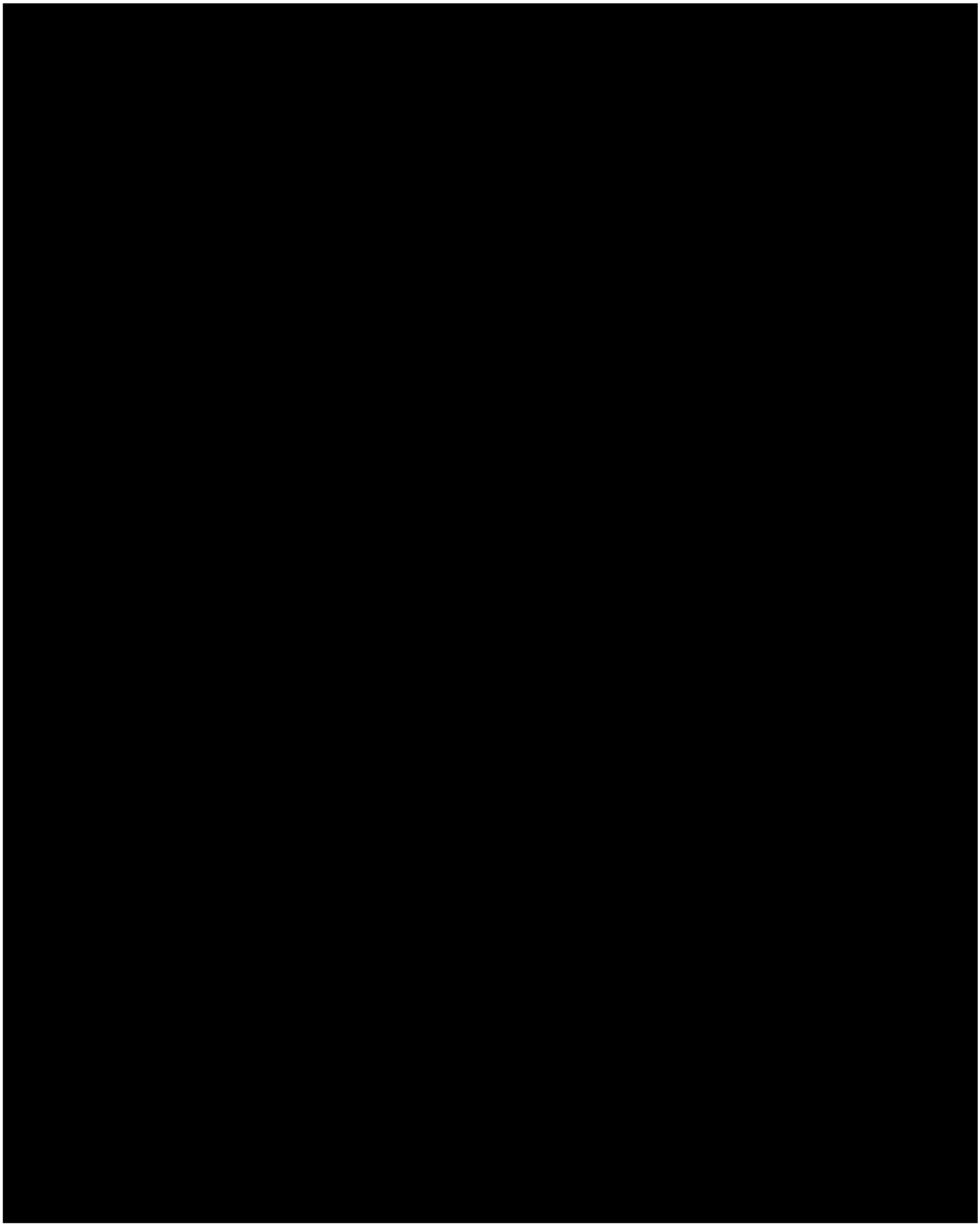
Obesity may also occur if the POMC neurons are not activated based on the missing leptin signal, due to a leptin receptor mutation. This may be due to a leptin deficiency (loss-of-function mutation in the *leptin* gene), where treatment with leptin has been demonstrated to result in significant weight loss [3]. However, patients with a mutation in the *LEPR* gene cannot benefit from treatment with metreleptin. Obesity persists in patients with LEPR deficiency because of the failure of the LEPR to activate POMC neurons, which in turn results in a lack of the production of MSH. For this reason, setmelanotide treatment is likely to lead to activation of the MC4R in these cases, and thereby to a reduction in hyperphagia and increased body weight. In both the POMC and LEPR deficient patient populations, under-expression of the POMC gene product due to these genetic defects results in a partial MSH deficiency, which can be overcome with setmelanotide treatment.

The use of setmelanotide for the treatment of LEPR deficiency obesity specifically, and as a proof of concept that setmelanotide can act as "replacement therapy" for defects in the broader MC4 pathway (such as POMC deficiency obesity), is supported by two sets of clinical data: results in two POMC gene deficiency patients and initial results in the three LEPR deficiency patients.

1.2.1. Initial Clinical Data in Two POMC Deficiency Obesity Patients

For POMC deficiency patients, the conclusion that setmelanotide can serve as replacement therapy for defects in the MC4 pathway is supported by clinical results in two POMC deficient patients, both with *POMC* gene mutations. The evidence is based on a 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, which aimed for weekly weight loss of ~2 kg/week, the primary endpoint was weight loss. Other key endpoints included hunger score (body composition, insulin and glucose parameters, metabolic and cardiovascular risk factors, energy expenditure, and general safety and tolerability.

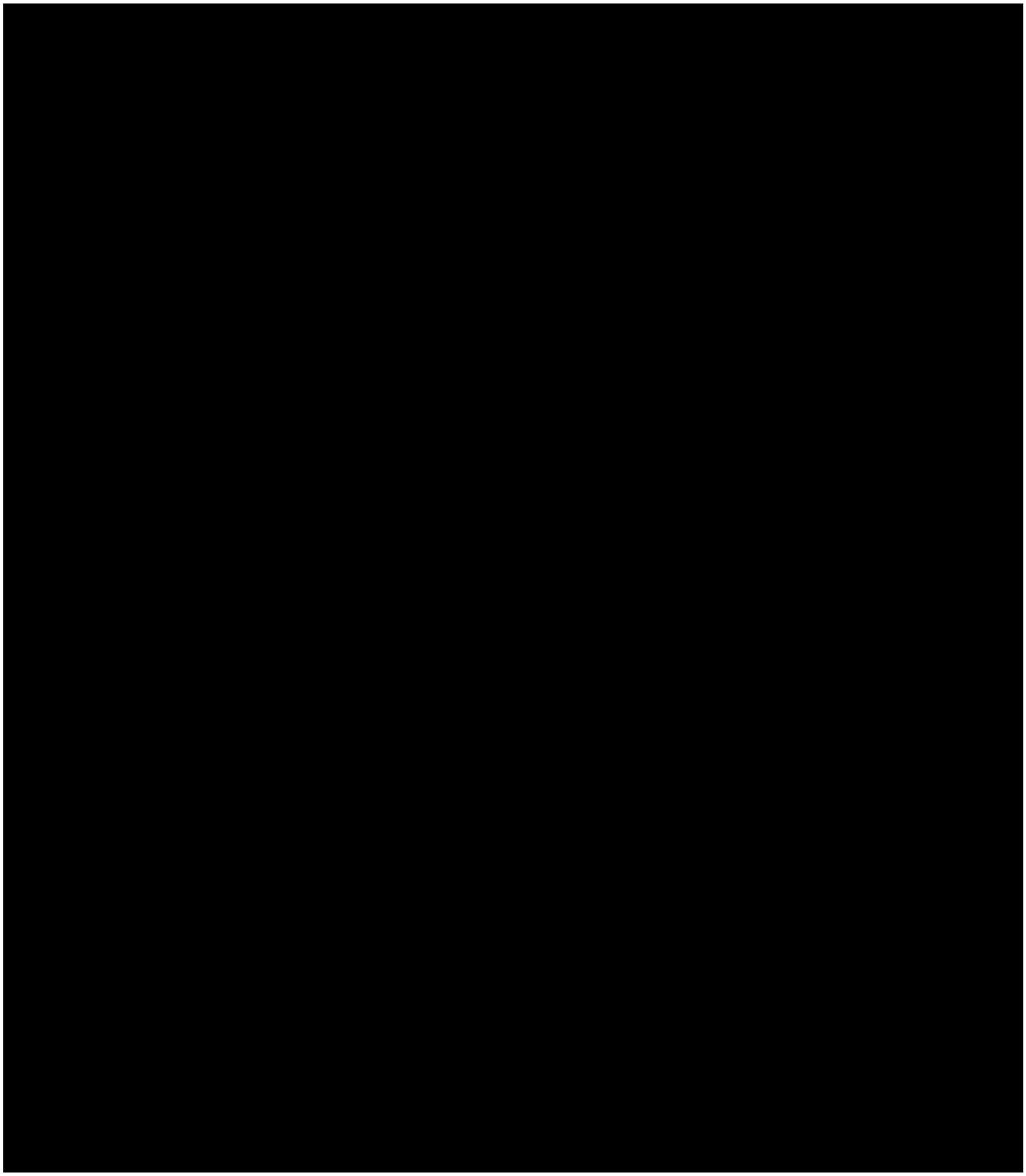
Because the study was designed as the first replacement of melanocortin activation in a POMC deficiency patient, a low starting dosage of setmelanotide 0.25 mg subcutaneous (SC), once daily was employed, with slow dose escalation (the dose was steadily increased every 1-2 weeks until the mean weight loss was approximately 2 kg per week).



[redacted]

1.2.2. Initial Clinical Data in Three LEPR Deficiency Obesity Patients

[redacted]



1.2.3. Clinical Safety in POMC and LEPR Deficiency

POMC and LEPR deficiency obesity patients receiving open-label setmelanotide in RM-493-011 have reported intermittent mild adverse events and have tolerated and maintained long-term setmelanotide injections. Mild pain and induration at injection sites were reported primarily early in treatment, and have been less frequent with injection site rotation over time. Skin and prior skin nevi darkened over time, with hair change from red to brown also noted. Fatigue, dry mouth, and feelings of emptiness or sadness with waning of hunger were intermittently reported by individual patients.

Initial dosing and dose escalation of setmelanotide did not demonstrate BP or HR increases as monitored during full day clinic visits at each titration step. Thereafter, systolic and diastolic BP and HR demonstrated clinically meaningful reductions over time in association with weight reduction (Kühnen, 2016).

One patient experienced an SAE of influenza immunization reaction during the study, which required overnight observation in hospital due to decreased BP and allergic symptoms. This patient had experienced a similar severe influenza immunization reaction in the past, prior to starting setmelanotide; therefore, this SAE was considered unrelated to study drug. There have been no discontinuations due to treatment emergent AEs.

1.2.4. Proof-of-Concept Summary

These Phase 2 clinical data demonstrate the compelling efficacy of setmelanotide in two adult patients with POMC deficiency obesity and the initial three patients with LEPR deficiency obesity. The effect of treatment was very substantial and obvious, even in the setting of an open-label trial. The effect of treatment was also clearly reversed upon withdrawal of the drug in the first POMC 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, small n setting (in two genetic disorders of obesity), because these patients had previously demonstrated long-term refractoriness to attempted weight loss or hunger amelioration in medical care provided by their Berlin, Paris or UK physicians for over 2 decades.

In summary, setmelanotide may provide for the restoration of more normal hunger / appetite with intact satiety responses and active regulation of energy expenditure, serving 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 in a variety of MSH-deficient syndromes, including LEPR deficient patients. These “precision medicine” therapeutic effects of setmelanotide are evident in appropriately identified patients with monogenic loss-of-function mutations in the *LEPR* gene; this trial will also be testing for similar therapeutic responses in additional LEPR deficiency obesity patients from other global and US clinical sites.

1.3. Setmelanotide Properties and Additional Clinical Experience

Setmelanotide is an 8-amino acid, cyclic peptide that binds with high affinity (inhibitory constant [Ki] = 2.1 nM) to the human MC4R and is efficient in activating MC4R (50% effective concentration [EC_{50}] = 0.27 nM).

1.3.1. Nonclinical Experience

The setmelanotide peptide was initially selected for clinical development based on its acceptable circulating half-life (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 *fa/fa* 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.

[redacted] Finally, chronic toxicology, reproductive, and juvenile toxicology studies using the RM-493-mPEG/DSPE formulation have all completed their in-life portions, with no new toxicological findings reported, and reports are being prepared.

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. Many 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 placebo 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] $\geq 30 m^2$) volunteers, of whom ~40 received a single setmelanotide dose and ~160 received repeated doses for 3, 14, 28 or 90 days. In addition, setmelanotide has been studied in ~40 patients with rare genetic disorders of obesity (including POMC deficiency obesity, LEPR deficiency obesity and Prader-Willi syndrome), with a very small number of patients having completed more than one-year of treatment.

Setmelanotide has been evaluated in 6 completed clinical studies and 3 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.

Adverse event (AE) that have been numerically greater with setmelanotide treatment as compared to placebo (whether rated as "drug-related" or not by investigators) may include: fatigue, diarrhea, nausea, vomiting, darkening of skin lesions, skin discoloration/ hyperpigmentation, decreased appetite, penile erections, headache, back pain, and injection site pruritus.

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

LEPR 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 50 cases currently described in the literature, with most cases diagnosed as children. Therefore, we anticipate patient identification to be challenging and are targeting enrolling at least 10 individuals (pediatric, adolescents and/or adults), mostly from among already identified patients, to assess the safety and efficacy of setmelanotide in patients with LEPR deficiency obesity. Given the rarity and unmet need of LEPR deficiency and the initial compelling results in the first LEPR patients and the two POMC deficiency obesity patients treated, a conventional placebo controlled trial is not likely to be feasible. Due to the ultra-rare prevalence of LEPR deficiency obesity, if additional patients are identified beyond the target enrollment of 10, they may be enrolled.

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 LEPR deficiency 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 to confirm any drug effects.

2.1.1. Primary Objective:

- To demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change in patients with LEPR 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 old.
- 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.

[redacted]

[redacted]

[redacted]

2.2. Study Endpoints

The primary endpoint is the proportion of patients in the full analysis set (FAS) who meet the ≥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] in patients ≤16 years of age 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]

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 Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) for those ≥12 years of age. [redacted]

Body composition assessments including total body weight loss, fat loss, and [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 will be assessed. OGTT will not be performed for subjects with a diagnosis of Type 1 or Type 2 diabetes.

Waist circumference will be measured per 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 to assess the efficacy of stopping and restarting setmelanotide treatment.

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

[redacted]

[redacted]

[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. [redacted]

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]

Additionally, as required by the Food and Drug Administration (FDA) for all CNS-active obesity medications, [redacted] Guidance is provided for any worsening of depression or suicidality 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 Phase 3 study to assess long-term (1 year) efficacy of setmelanotide in LEPR deficiency obesity.

After providing informed consent, patients will enter the Screening Period. During the Screening Period, patients will be assessed for eligibility and instructed to complete a hunger questionnaire daily for a minimum of one week and ideally two weeks to establish a baseline and to enhance the understanding of hunger symptoms associated with LEPR deficiency obesity prior to treatment with setmelanotide. As LEPR deficiency 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 [redacted] 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.

After the Screening Period, there are four treatment phases to the study:

Open Label Dose Titration Phase (2 – 12 weeks)

In this phase of the study, a patient's individual therapeutic dose will be established. The starting dose is 1.0 mg for adult patients and 0.5 mg for adolescent and 0.25 mg for pediatric patients. Patients will return to the clinic every two weeks to assess their weight loss and hunger scores and dosing will increase every two weeks in 0.5 mg increments until a patient's individual therapeutic dose is established per the guidelines in Appendix 11.8.

As this is a global study, the maximum allowable dose differs across countries based on feedback from competent authorities. The US, UK and the Netherlands have approved a maximum dose of 3.0 mg, while Germany and France have approved a maximum dose of 2.5 mg. Therefore, the duration of the dose titration stage will range from 2 to 12 weeks, depending on the number of escalations required to define the therapeutic dose and the approved maximum dose in the country of the participating site.

Open Label Phase (10 weeks)

After establishing a patient's individual therapeutic dose, the patient will continue dosing for an additional 10 weeks, resulting in 12 total weeks of treatment at their therapeutic dose (including the last 2 weeks at the therapeutic dose in the dose titration phase). To continue treatment after 12 weeks of treatment at their therapeutic dose, patients must achieve a weight loss of 5 kg or greater from baseline if their baseline weight was greater than 100 kg or a weight loss of > 5% from baseline if their baseline weight was < 100 kg. Patients who do not achieved these weight loss criteria will be discontinued from treatment, but should continue with other study procedures through study end.

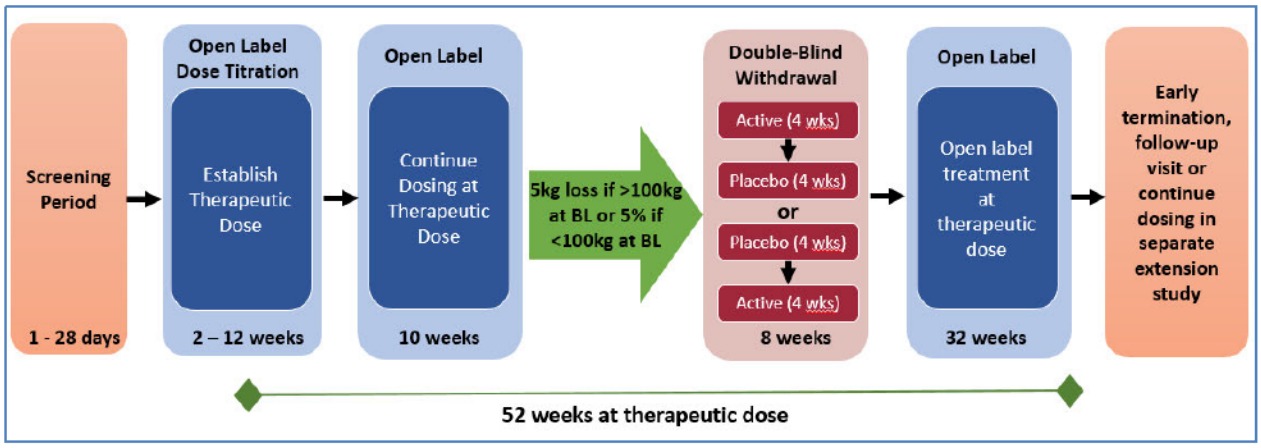
Placebo-Controlled, Double-Blinded Withdrawal Phase (8 weeks)

Patients that achieve a 5 kg or 5% weight loss after 12 weeks of treatment at their therapeutic dose will receive either placebo or active for four weeks and then cross-over to the opposite treatment for four weeks. The treatment assignment during the first four-week period will be double-blinded so that the sites and patients do not know if their first four-week block of treatment is placebo or active.

Open Label Treatment Phase (32 weeks)

After completing the placebo-controlled, double-blinded withdrawal phase, patients will continue dosing at their individual therapeutic dose for an additional 32 weeks. At the end of the 32 weeks, patients can enroll in a separate long-term extension study to continue receiving setmelanotide (Study RM-493-022) or they can complete treatment with a final visit approximately 30 days after their last dose.

Figure 7: Study Schema



It is anticipated that at least 10 patients will be enrolled in this study. However, due to the ultra-rare prevalence of this population, if more patients are identified during the conduct of the study, they may also be enrolled.

In addition, for patients at sites where feasible, and who agree to participate, [redacted]

3.2. Rationale for the Doses

A recent investigator-initiated trial (RM-493-011) of setmelanotide in this population of monogenic obesity patients used a similar dose titration scheme that demonstrated minimal initial weight loss at doses of 0.25 – 0.5 mg QD, yet meaningful and progressive weight loss with QD doses of 1.0 mg and above. In addition, there was no evidence of increased sensitivity or new safety issues arising in this sentinel patient trial at any dose of setmelanotide to date.

This range of doses is also supported by data in the general obese population: (1) doses assessed in the Multiple Ascending Dose (MAD) Phase 1b study, which consistently resulted in clinically important, statistically significant, therapeutic effects in healthy obese individuals; (2) doses that provide the PK profile of the once daily SC injectable formulation of setmelanotide to achieve a trough as close as possible to anticipated target of ~3-5 ng/mL.

However, because the number of monogenic POMC/LEPR 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 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 every 2-week basis up to a maximum total

daily dose of 3.0 mg or 2.5 mg depending on the maximum approved dose in the participating country.

Dosing in adolescent and pediatric patients will follow the same deliberate dose titration approach employed for adult subjects, except that the starting dose will be 0.5 mg per day for adolescent patients and 0.25 mg for pediatric patients as opposed to 1.0 mg, i.e. setmelanotide dose titration increases will be stepwise, rising by 0.5 mg at each 2-week titration step. For all pediatric patients, the maximum allowable dose will be 2.5 mg/day. The top dose for adolescent patients will be 2.5 or 3.0 mg depending on the maximum approved dose in the participating country.

During the dose titration phase, [redacted] the dose is incrementally increased to explore the exposure-response curves for safety and efficacy. 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 the dose titration stage for adolescents and adults is either 3.0 mg or 2.5 mg (depending on the maximum approved dose in the participating country) and 2.5 mg for all pediatric patients (aged 6 – 11 years old). Toxicology studies in rats and monkeys provide extremely large margins (>150-fold) to human clinical exposures at the 2.5 and 3.0 mg/day doses (in mg/m^2 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 10 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 to dose up to 2.5 or 3.0 mg to demonstrate robust efficacy on weight loss and hunger reduction. The top dose of 2.5 or 3.0 mg is supported by the excellent safety profile observed in POMC and LEPR patients after prolonged dosing at 1.5 and 2.0 mg.

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 and LEPR 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 LEPR 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 LEPR 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 *LEPR* 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 and Rhythm will notify the applicable competent authorities and ethics committees as per ICH E6 R2 and the EU Clinical Trials Directive (2001/20/EC).

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 LEPR 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 LEPR deficiency obesity.

4. STUDY POPULATION

4.1. Number of Patients

It is currently anticipated that at least 10 patients will be treated for ~1 year with setmelanotide. Given the ultra-rare incidence of the 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 *LEPR* 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 the *LEPR* gene, 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/m^2; 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 is 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.
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.

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 arising because 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 x 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. Previous history of significant hypersensitivity to exogenously injected peptides (e.g. urticaria, shortness of breath, or more severe responses including anaphylactoid reactions or anaphylaxis).
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 representing 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. Specific predefined events for discontinuation, as well as additional guidelines for safety monitoring, are included in Appendices 11.4 – 11.7.
- 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 is <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 are no longer receiving 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 (i.e. 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 support for patient and caregiver travel, will make available visiting home health care professionals, and any other necessary logistical support to ease the burden on the patient to facilitate compliance.

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 period that will allow patients to transport study drug home; ice packs and cooler bags will be provided for patients and caretakers who will travel long distances from the clinic. Patients will be encouraged to proceed directly home after clinic visits in which study drug is dispensed to minimize the amount of time the study drug is exposed to elevated temperatures.

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

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 10 weeks. Once the patient's therapeutic dose is determined, the same dose/volume will be administered throughout the remainder of the study.

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

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 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 patients and the 3 LEPR 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/LEPR 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 (per 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	0.25
3-4	1.5	1.0	0.5
5-6	2.0	1.5	1.0
7-8	2.5	2.0	1.5
9-10	3.0*	2.5	2.0
11-12	NA	3.0*	2.5

*Can only escalate to 3.0 mg if approved by the participating country's competent authority, otherwise the maximum allowable 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 to allow the patient the opportunity to respond.

Although LEPR deficient patients have not been treated long term with setmelanotide, there is limited long term data in the two POMC deficient patients. This data demonstrates that even when BMI's near normalization, dose reductions have prompted increases in hunger scores until the resumption of the individual patients initially determined therapeutic dose. However, as experience is limited, during the 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, except for 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 assignation.

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 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

To evaluate the safety, tolerability, [redacted] and pharmacodynamics 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 another appropriate individual. Drug accountability records indicating the delivery date to the site, inventory at the site, use by each patient, return of all used study drug to the study center, and return to 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 unused, used 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., carnitol, Coenzyme Q10, vitamins, anti-constipation medications, anti-allergic medications).
h. Apart from 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 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 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" (apart from DEXA which is classified as "Minor Increase over Minimal Risk") per the 2008 Guidance Document "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population", considerations for reducing pain in distress in participants younger than 18 years of age are included in Appendix 11.11.

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

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 (per 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 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. 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 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 to obtain minimum patient self-reported data (i.e.: weight, AEs, etc.).

Detailed descriptions of the safety, PD and [redacted] procedures to be conducted during this study are provided in the sections below. 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 (Appendix 11.12). 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. 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.

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, 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, 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**	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]
[redacted]		
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]
[redacted]		
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	
[redacted]		
Daily Hunger Questionnaire[20]	X	X[5]
Global Hunger Questions[33]	X	
[redacted]		
Body Composition[23]	X	
[redacted]		
Anti-RM-493 antibody samples	X	X[5, 26, 31]
Adverse Event assessment[25]	X	X
Concomitant meds review	X	X
Nutritional counseling and Monitoring[36]	X	
Telephone contact		X

Optional Sub-Studies

[redacted]		

Study Period	Screening**	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)**
[redacted]		

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]	X[4,5]
Physical examination[1]				X	
Height[1]				X	
Comprehensive skin exam[2]					
[redacted]					
Weight/waist circumference[11]	X[5]	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	X
Injection site inspection[14]	X	X	X	X	X
Vital signs[15]	X[5]	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]	
[redacted]					
Daily Hunger Questionnaire[20]	X[5]	X[5]	X[5]	X[5]	X[5]
Global Hunger Questions[33]				X[5]	X[5]
[redacted]					
Body Composition[23]				X	
[redacted]					
Anti-RM-493 antibody samples		X[5, 26]		X[5, 26]	
Adverse Event assessment[25]	X	X	X	X	X
Concomitant meds review	X	X	X	X	X
Nutritional counseling and Monitoring[36]		X	X		
Telephone contact	X	X	X	X	X

Optional Sub-Studies

[redacted]					
[redacted]					

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 (V) Visit Number / 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	
Comprehensive skin exam[2]				X		X	X
[redacted]							
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]	
[redacted]							
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
[redacted]							
Body Composition[23]						X	
[redacted]							
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
Nutritional counseling and Monitoring[36]	X	X	X	X	X	X	
Telephone contact	X	X	X	X	X	X	X

Optional Sub-Studies

[redacted]

Table 6-1: Schedule of Assessments Footnotes

1 A complete physical examination will be conducted at screening and at the end of study. Abbreviated physical exams will be conducted on intervening visits (V6 and V9). As part of the complete physical exams at screening and end of study, [redacted] Menarche and menstrual history will be obtained in all females. Adrenarche staging will be performed. Testicular volumes will be documented by the Prader methodology for males, and breast development will be documented for females. Height will be measured during the Screening Period only for those patients ≥18 years of age. Height will be measured per 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 can 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 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 10 weeks, in which patients will return to the clinic approximately every 2 weeks to establish the individual patient's therapeutic dose per 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 (except for 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.

10 [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 daily in the morning. On days with clinic visits, the patients/caretakers will administer the drug in the clinic in the presence of the clinical staff to assure proper technique. Patients/caretakers will return all used vials to the clinic when they visit (the number recorded) and both clinic administered study drug, as well as outpatient study drug administration will be recorded in a study diary.

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) per 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. ECGs will be collected electronically, in triplicate, at each timepoint, per instructions in Section 6.4.7. ECGs will be in a format where the electronic copy can be provided for central reading, if needed

18 Safety laboratories will include: CBC with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO_2, albumin, total protein, glucose, BUN, creatinine, uric acid, AST, ALT, GGT, CPK, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, calcium, phosphorus), urinalysis 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 hours minimum) are required at all timepoints where feasible. [redacted] and HbA1c will also be included.

19 [redacted]

[redacted]

20 Daily hunger questionnaire scores will be assessed by asking the patient to score their hunger [redacted] Daily hunger questionnaire scores will be recorded daily, prior to the patient's morning meal.

21 [redacted]

22 [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 per 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 per 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 monthly, 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 is established at the first dose level)

32 A blood sample will be obtained at Screening for genotyping for mechanisms considered to be possibly related to the safety or efficacy response to the study medication (e.g., other obesity related genes).

33 [redacted]

34 [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 IGF1).

37 Collect between 8 and 10 am

38 [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 10 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 France, the [redacted] are compulsory, and not optional.

† Test not conducted at this visit for patients 6 to 11 years.

** 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 completely evaluated in nonclinical Developmental and Reproductive Toxicology Studies to date; therefore, the effects of setmelanotide on embryo-fetal development are unknown at this time. It is imperative all study patients adhere to the contraception requirements as outlined below.

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

For females who are 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) when used together with a single-barrier method (i.e. condom), or an Intrauterine Device (IUD) when used together with a single-barrier method (i.e. condom) or vasectomized partner. True abstinence is acceptable only if it is the preferred and usual lifestyle of the patient.

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

It is not known if this treatment will affect spermatogenesis. Therefore, males with female partners of childbearing potential must agree to use contraception (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 and spermicide) if they become sexually active during the study and for 90 days following the study. Male patients must not donate sperm for 90 days following their participation in the study.

6.2.2. Protection from Sun

Skin hyperpigmentation, or tanning, was observed in the cynomolgus monkey toxicology studies, and the human Phase 1 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., BIA). 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 to collect important retrospective data to better understand the natural history of LEPR deficiency per Appendix 11.3.

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

6.4.3. 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 assessments. [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 per the SOA using a wall-mounted stadiometer. All measurements will be done in triplicate at each timepoint and recorded to the nearest 10^{th} of a decimal place. The stadiometer should be calibrated at the time of use or within the previous four hours.

[redacted]

[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 per 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.

ECG Procedures

All ECGs should be performed in triplicate per the Schedule of Assessments with the following guidelines:

- ECG technicians should be thoroughly trained in the administration of a 12-Lead ECG, the institution's specific protocols and procedures for ECG tests and the requirements of the study protocol.
- ECG equipment should be modern equipment with the capacity for digital signal processing to allow for central reading. The same make and model of ECG machine with the same style of leads should be used for all patients. Such equipment should be

recently serviced and calibrated. Machine calibration records and performance data should be maintained on file.

- Patients should be in a supine position and have rested for 10 minutes.
- ECGs at each protocol timepoint should be recorded in triplicate, with at least 1 minute between recordings.

Reading ECGs

Site monitoring:

Sites should read ECGs for study monitoring and CRFs per their usual procedures.

Central Reading:

Rhythm may elect, if needed for regulatory reasons, to collect ECGs for central reading. If so, the intention will be that a single Central reader will read all ECGs. Therefore, all ECGs must be available and stored electronically for this purpose. When sent for Central reading, the ECGs must be prepared to be read in a blinded fashion. Central readers of ECGs should be blinded to time, treatment and subject identifier.

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 per 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, CO_2, 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] and HbA1c:

[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 per the SOA. An overnight fast of at least 8 hours in 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.

[redacted]

[redacted]

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.

[redacted]

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 per the SOA.

Global Hunger Questions: Two global questions will be asked at certain study visits per the Schedule of Assessments. 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 [redacted]

[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 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 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 and IGF1).

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

[redacted]

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.

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 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.

[redacted]

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 (ECs) 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 per 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.

This study will also 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 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.

7.5.1. Depression or Suicidality

A patient should be referred to a MHP if he/she has:

- A [redacted].
- Any suicidal behavior.
- Any [redacted].

A referral to a MHP should also be made if in the opinion of the Investigator it is necessary for the safety of the patient. If a patient's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the patient, at the discretion of the MHP, should be continued in the trial.

8. STATISTICAL PROCEDURES

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

8.1. Sample Size Estimation and Primary Power Statement

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 LEPR 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.

The following power table shows the power to detect various proportions who achieve 10% weight loss at 1 year for LEPR patients, assuming a null hypothesis value of 5% responders for alpha = 0.05, 1-sided:

True Underlying Proportion	Power to Reject Null Hypothesis and Conclude True Proportion is Higher
0.2	0.322
0.3	0.617
0.4	0.833
0.5	0.945
0.6	0.988
0.7	0.998
0.8	>0.999
0.9	>0.999

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 values versus baseline and of proportions to null hypothsis 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 (i.e. percent of patients who achieve at least 10% weight loss after 1 year of treatment versus the null hypothesis value of 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 LEPR deficiency patients who continue to tolerate setmelanotide after 1 year of treatment, and who show clinically important weight loss, will be continued in 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. Their data will also be summarized and pooled with data from patients who entered this pivotal 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 11.7). 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, 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 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*	☐	☐	☐	☐	
Edema*	☐	☐	☐	☐	
Induration*	☐	☐	☐	☐	
Itching	☐	☐	☐	☐	
Pain or Tenderness*	☐	☐	☐	☐	
Other: _____	☐	☐	☐	☐	

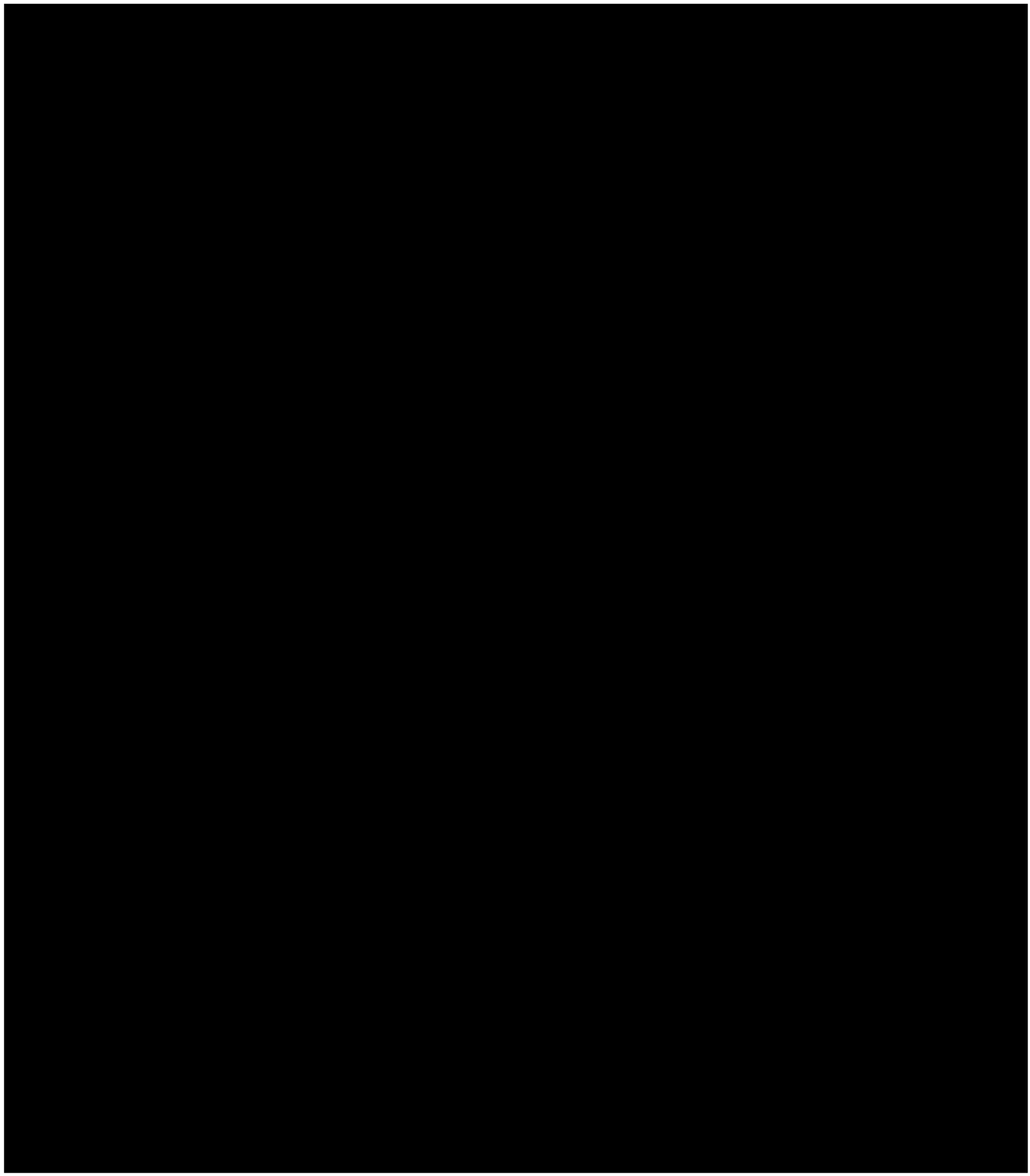
*If present, region will be measured, length and width as appropriate.

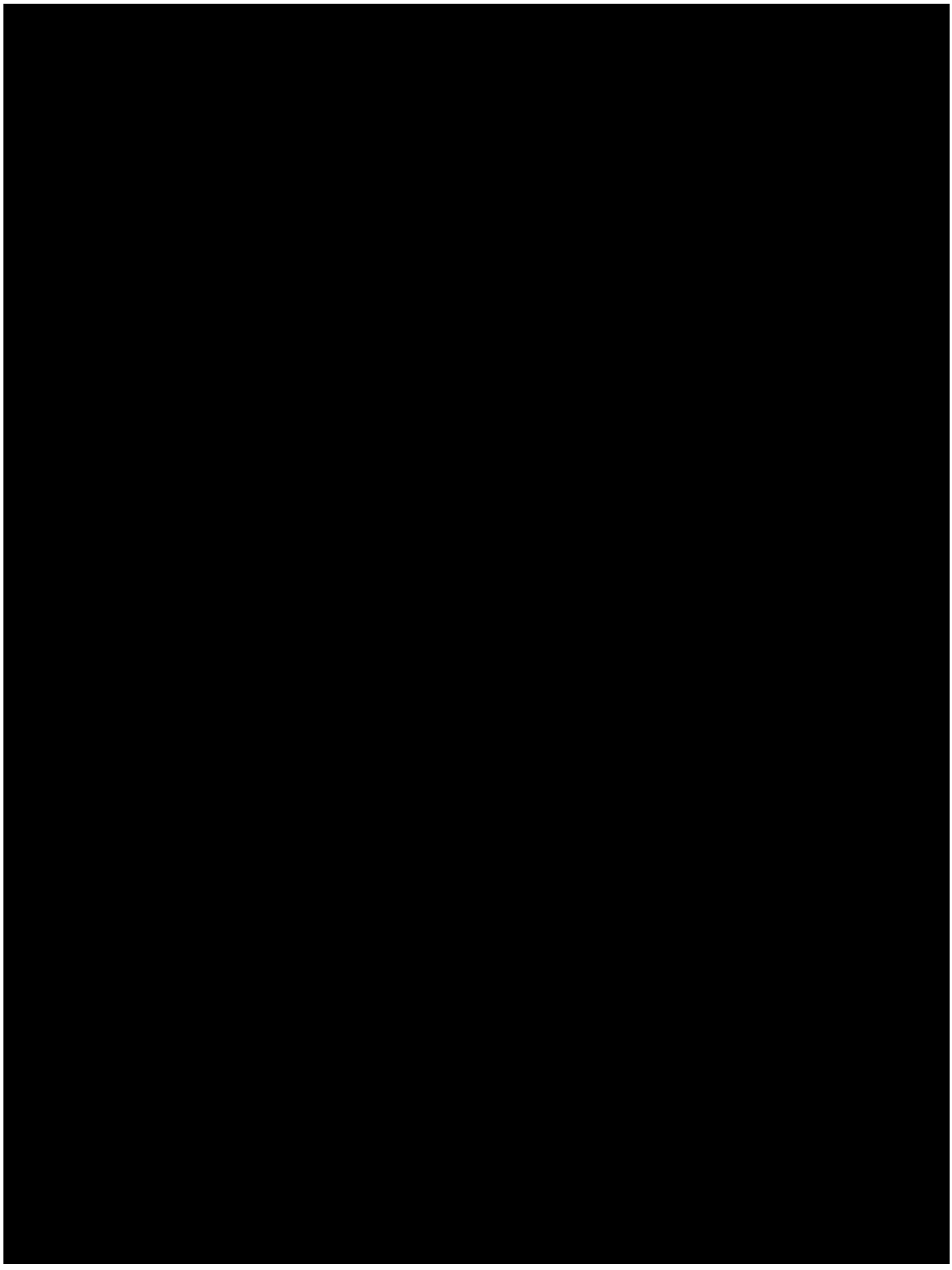
Initials: _____

11.2. Fitzpatrick Classification Scale

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

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





the Phase 1/2 studies demonstrates the changes in lesions reverse upon cessation of study drug, so if a lesion continues to darken or change after study treatment has been completed, careful consideration should be given for further dermatological evaluation or biopsy. If drug is discontinued, all patients with clinically indicated lesions are to be followed by the Dermatologist until progress towards resolution of the event (up to ~60-90 days after last dosing, if needed).

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:

a. Situate the individual in a quiet environment with the arm resting at heart level.
b. [MANUAL] For manual measurements, place the manometer at eye level, sufficiently close to read the calibration markings on the gauge or column.
c. 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.
d. [MANUAL] Locate the brachial artery along the inner upper arm by palpation.
e. 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.)
f. For manual measurements:
    i. 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.
    ii. Rapidly and steadily deflate the cuff. Then wait 15 to 30 seconds before re-inflating.
    iii. 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.
    iv. Rapidly and steadily inflate the cuff to the maximal inflation level as determined in Step f.
    v. Release the air in the cuff so that the pressure falls at a rate of 2 to 3 mm per second.
    vi. 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.
    vii. 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.

g. For automatic measurement:
    i. Take automatic measurements and record.
h. Record the patient's position and the arm used for the measurement.
i. Wait 2 minutes before repeating the pressure measurement in the same arm to permit the release of blood trapped in the arm veins.
j. Note that all three readings at each timepoint should be captured on the case report form, as well as the average.
k. 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

<u>The Auscultatory Gap</u>

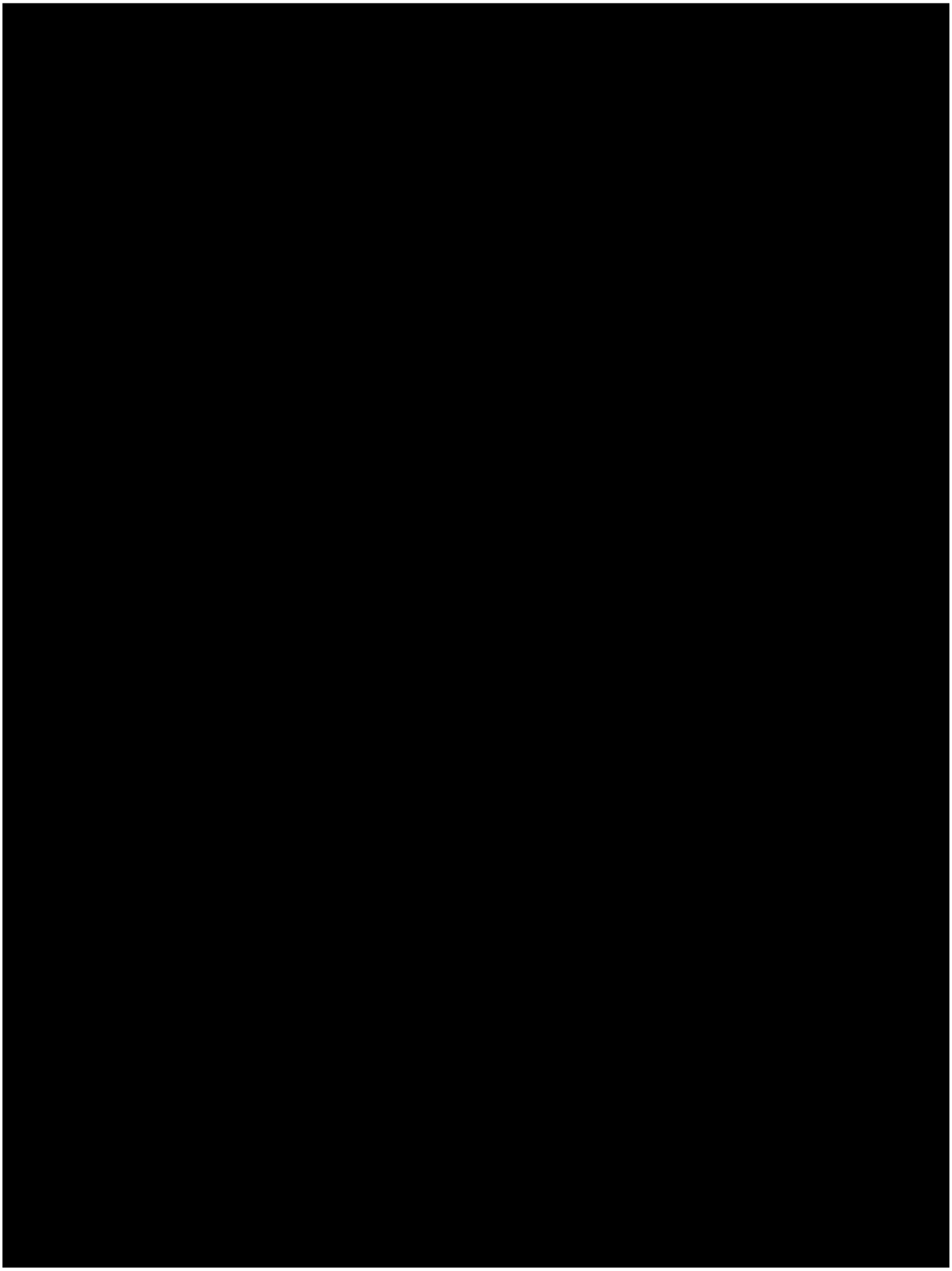
[MANUAL] In some subjects, particularly in patients with hypertension, the sounds heard over the brachial artery when the cuff pressure is high disappear as the pressure is reduced and then reappear at some lower level. This early, temporary disappearance of sound is called the auscultatory gap and occurs 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.

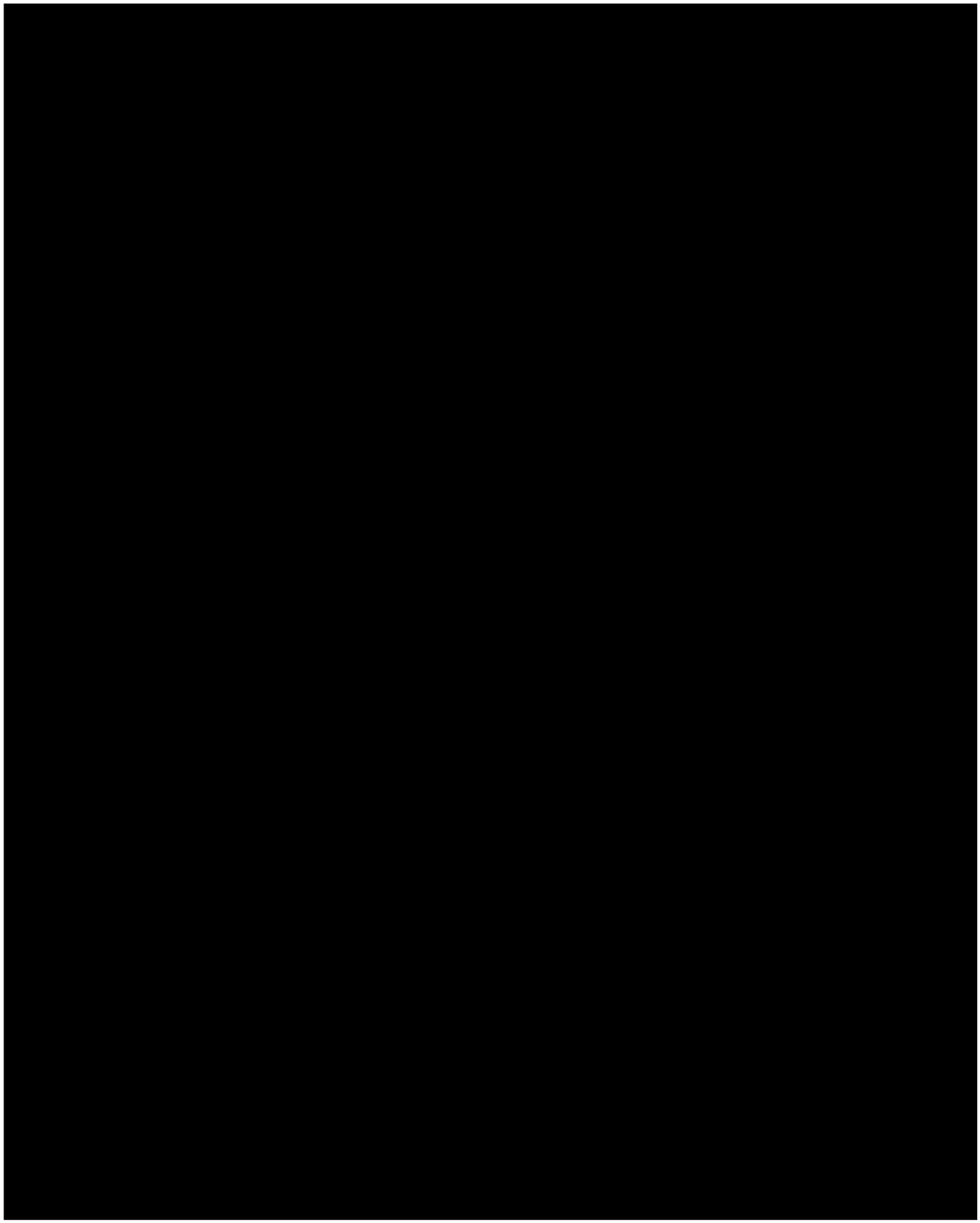
<u>Effect of Arm Position</u>

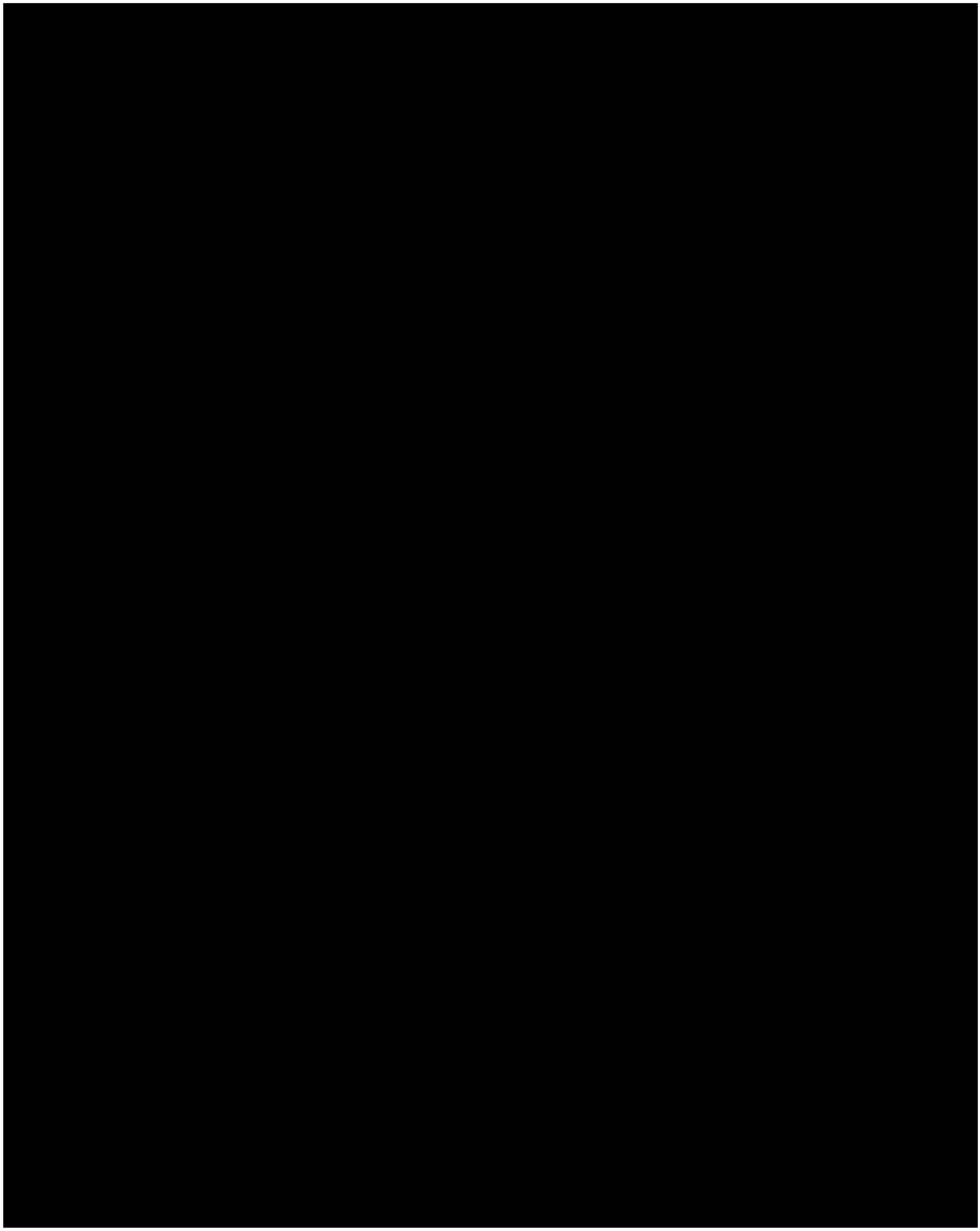
The pressure in the arm increases as the arm is lowered from the level of the (phlebostatic axis); conversely, raising the arm above this position lowers the pressure measurement. The effect is largely explained by hydrostatic pressure or by the effect of gravity on the column of blood. Therefore, when measuring indirect blood pressure, the patients 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.**

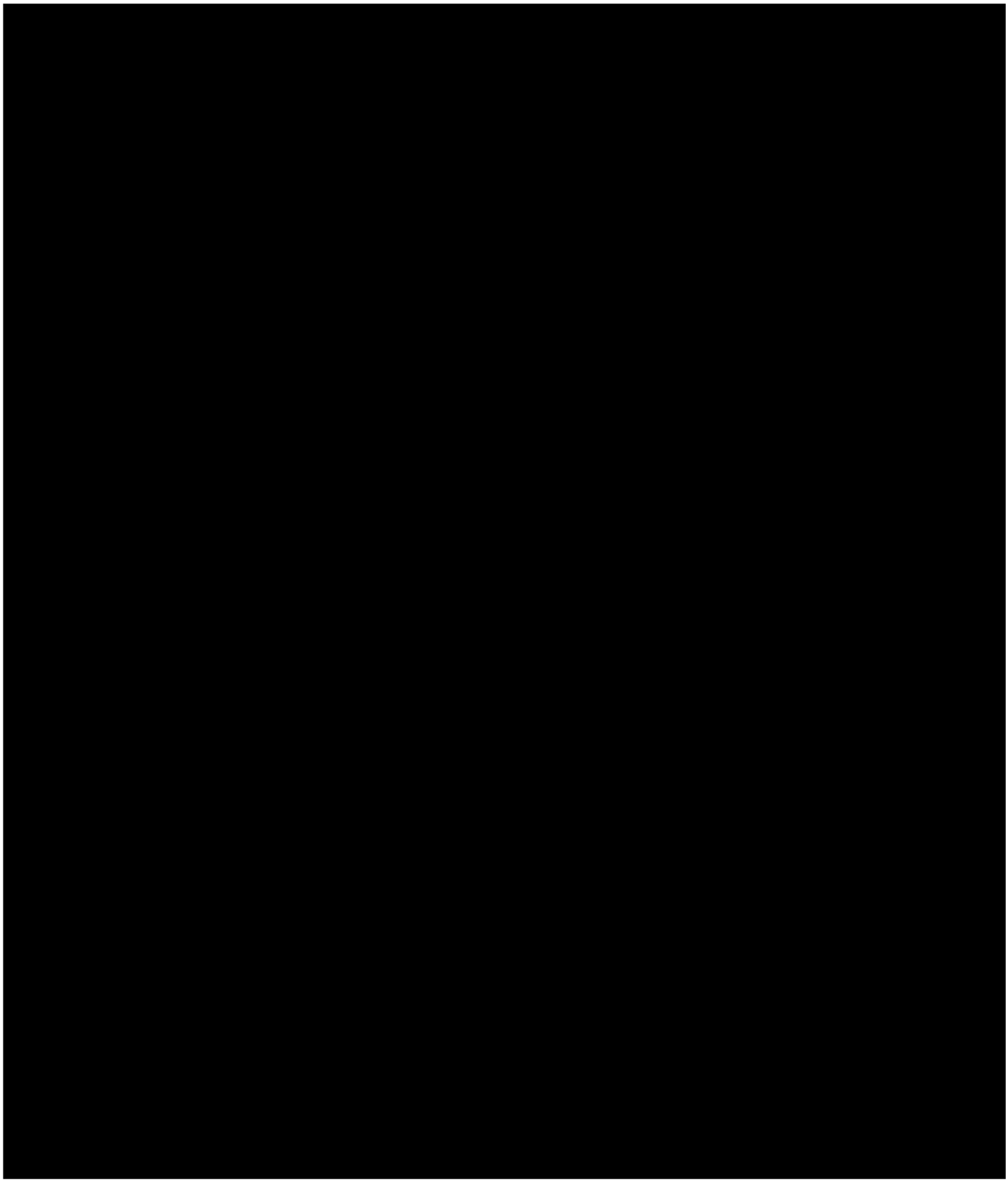
Large Arm Size

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 - Age) / (Serum Creat)) * (Weight (kg) / 72)

Female Creatinine Clearance mL/min = 0.85 * ((140 - Age) / (Serum Creat)) * (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" (apart from DEXA which is classified as "Minor Increase over Minimal Risk") per the 2008 Guidance Document "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population", considerations for reducing pain in distress in participants younger than 18 years of age are suggested below.

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

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

11.12. Blood Volumes for Study Tests

The blood volumes for study assessments are listed in Tables 1 and 2 below.

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																	
[redacted]																		
Archive sample	12										12							12
Safety Laboratory Tests	16	16	16	16	16	16	16		16		16			16		16		16
OGTT	35										35							35
[redacted]																		
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**

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
[redacted]																		
Archive sample	12										12							12
Safety Laboratory Tests	16	16	16	16	16	16	16		16		16			16		16		16
OGTT	35										35							35
[redacted]																		
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.