SETMELANOTIDE

RM-493-014

Setmelanotide (RM-493) Phase 2 Treatment Trial in Patients with Rare Genetic Disorders of Obesity

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

[redacted]

EudraCT No. 2017-000387-14

Study Sponsor: Rhythm Pharmaceuticals, Inc.
222 Berkeley Street, Suite 1200
Boston, MA 02116, USA
[redacted]

Sponsor Signatory: [redacted]

Document Version (Date): Amendment 10, 20 February 2020

[redacted]

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APPROVAL SIGNATURE PAGE

Protocol Title:	Setmelanotide (RM-493) Phase 2 Treatment Trial in Patients with Rare Genetic Disorders of Obesity
Protocol Number:	RM-493-014
Document Version:	Amendment 10
Document Date:	20 February 2020

REVIEWED/APPROVED BY:

[redacted]

[redacted],	Signature	Date

Rhythm Pharmaceuticals, Inc.

INVESTIGATOR STATEMENT

Protocol Title:	Setmelanotide (RM-493) Phase 2 Treatment Trial in Patients with Rare Genetic Disorders of Obesity
Protocol Number:	RM-493-014
Document Version:	Amendment 10
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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)

1. SYNOPSIS

Name of Sponsor/Company:
Rhythm Pharmaceuticals, Inc.

Name of Investigational Product:
Setmelanotide (RM-493)

Name of Active Ingredient:
Setmelanotide (RM-493; a synthetic cyclic octapeptide and Melanocortin-4 [MC4] Receptor Agonist)

Title of Study:
Setmelanotide (RM-493) Phase 2 Treatment Trial in Patients with Rare Genetic Disorders of Obesity

Treatment Indication:
Treatment of obesity and hyperphagia in rare genetic disorders of obesity.

Study Center(s):
It is expected that approximately 50 – 75 global sites will participate in this study, with most sites located in North America, Europe and Middle East

Objectives:

Primary

To explore the impact of setmelanotide on obesity in patients with various specific rare genetic mutations.

Secondary

To assess the effects of setmelanotide on:

- Safety and tolerability
- Hunger
- Waist circumference

[redacted]

Trial Design:

This is a Phase 2 open-label, uncontrolled, proof-of-concept study assessing the effect of setmelanotide on patients with rare genetic disorders of obesity for which evidence supports a role of the leptin-melanocortin hypothalamic pathway (the "MC4 pathway"). This study is designed as a "basket study", using similar procedures to assess treatment effects on different genetic populations that share similar phenotypes of early onset, severe obesity and hyperphagia. The differing rare genetic causes of obesity that will be enrolled in this study are collectively referred to as different subgroups.

The study population will consist of male and female patients, 6 years of age and above, with rare genetic disorders of obesity caused by a mutation in the MC4 pathway.

Number of Patients (planned):

It is expected that approximately 150 patients will be included in this protocol across multiple subgroups. Since the subgroups in this study are all rare, it is expected that the size of each subgroup will range from 1 – 15 patients.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Patients with the following genotypes and/or clinical diagnosis:
    a. POMC/PCSK1/LEPR heterozygous
    b. POMC/PCSK1/LEPR compound heterozygous (two different mutations in gene) or homozygous deficiency obesity
    c. POMC/PCSK1/LEPR composite heterozygous (two or more mutations in two or more genes) deficiency obesity
    d. Smith-Magenis Syndrome (SMS)
    e. SH2B1 deficiency obesity
    f. Chromosomal rearrangement of the 16p11.2 locus causing obesity
    g. CPE compound heterozygous or homozygous deficiency obesity
    h. Leptin deficiency obesity with loss of response to metreleptin.
    i. SRC1 deficiency obesity
    j. MC4R deficiency obesity

    Note: The specific genotype for all patients must be reviewed by the Sponsor prior to study enrollment to confirm that the patient meets Inclusion Criterion #1. In addition, enrollment of patients in some subgroups may be prioritized by the Sponsor in order to ensure enrollment of patients with (1) well described, loss of function genetic mutations, (2) a variety of genetic variants, or (3) genetic variants likely to respond to setmelanotide.
2. Age 6 years and above.
3. Obese, defined as Body Mass Index (BMI) $\geq$ 30 kg/m^2 for patients $\geq$16 years of age or BMI $\geq$ 95th percentile for age and gender for patients 6 up to 16 years of age.
4. Study participant and/or parent or guardian is able to communicate well with the Investigator, to understand and comply with the requirements of the study, and is able to understand and sign the written informed consent/assent.
5. Female participants of child-bearing potential must be confirmed non-pregnant, and agree to use contraception as outlined in the protocol. Female participants of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation), post-menopausal for at least 12 months (and confirmed with a screening Follicle Stimulating Hormone [FSH] level in the post-menopausal lab range), 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 > 2% weight loss.
2. Use of any medication that is approved to treat obesity within three months of first dose of study drug (e.g., orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion).

   Note: Glucagon-like peptide-1 (GLP-1) receptor agonists may be used up to the dose approved for the treatment of diabetes mellitus (e.g., liraglutide up to a daily dose of 1.8 mg) as long as (1) is it not being prescribed for the treatment of obesity, (2) the dose has been stable for at least three months prior to enrollment, (3) the patient has not experienced weight loss during the previous three months, AND (4) the patient intends to keep the dose stable throughout the course of the study.
3. Gastric bypass surgery within the previous six months or any 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 the Sponsor prior to enrollment.
4. Diagnosis of schizophrenia, bipolar disorder, personality disorder, or other psychiatric disorder(s) that the Investigator believes will interfere significantly with study compliance. Neurocognitive disorders affecting ability to consent will not be disqualifying as long as an appropriate guardian able to give consent has been appointed.
5. A PHQ-9 score of ≥ 15 or any suicidal ideation of type 4 or 5 on the C-SSRS during Screening, any lifetime history of a suicide attempt, or any suicidal behavior in the last month.

   Note: Patients who are unable to complete the PHQ-9 or C-SSRS due to significant neurocognitive defects may be enrolled in the study, as long as in the opinion of the Primary Investigator there are no clinical signs or symptoms of suicidal behavior.
6. Current, clinically significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor to determine eligibility.
7. HbA1c >9.0% at Screening

8. History of significant liver disease or abnormal liver tests on Screening (i.e., > 1.5 x upper limit of normal [ULN] for alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase, or serum bilirubin).

   Note: Patients entering the study with SRC1 haploinsufficiency obesity must be evaluated during the Screening Period for hepatic fibrosis by appropriate imaging techniques (e.g., transient elastography or magnetic resonance elastography). Any patient with moderate or greater fibrosis (e.g., the equivalent of a METAVIR score ≥ 2) will be excluded from the study.

   Note: A patient with a diagnosis of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) may be allowed to enroll in the study, after consultation with the Sponsor. Other significant liver disease, such as cirrhosis, are exclusionary.

9. Glomerular filtration rate (GFR) <30 mL/min at Screening.
10. History or close family history (parents or siblings) of skin cancer or melanoma (not including non-invasive/infiltrative basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.
11. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive skin evaluation performed by a qualified dermatologist during Screening. 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.
12. Patient is, in the opinion of the Study Investigator, not suitable to participate in the study.
13. Participation in any clinical study with an investigational drug/device within 3 months prior to the first day of dosing.
14. Patients previously enrolled in a clinical study involving setmelanotide or any previous exposure to setmelanotide.
15. Significant hypersensitivity to any excipient in the study drug.
16. Inability to comply with QD injection regimen.
17. Females who are breastfeeding or nursing.

Investigational product, dosage and mode of administration:

Investigational product: Setmelanotide, 10 mg/mL in a sterile solution for injection

Dosage: Once daily dosing; for patients 6 up to 16 years of age, 1.0, 2.0, or 3.0 mg, and for patients ≥16 years of age, 2.0 or 3.0 mg

Mode of administration: Subcutaneous (SC) injection

Duration of treatment:

All patients receive study treatment for 16 weeks. Patients may elect to continue setmelanotide treatment by enrolling in an extension study (RM-493-022) immediately following the last dose in this study; if the extension study is not yet open at the current clinic site, patients may continue treatment in the current study for up to one year, resulting in treatment duration of up to 16 months.

Reference therapy, dosage and mode of administration:

NA

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint is the percent of patients in each subgroup showing at least a 5% loss of body weight over ~3 months. Supporting efficacy endpoints will include change from baseline in Daily and Global Hunger scores, [redacted] and waist circumference.

Safety:

The safety and tolerability of setmelanotide once daily (QD) subcutaneous (SC) injection will be assessed by the frequency and severity of adverse events (AEs) as well as changes in vital signs and laboratory evaluations.

[redacted]

As required by Food and Drug Administration (FDA) for central nervous system (CNS)-active obesity medications, [redacted]

Statistical considerations:

The objective of this study is to demonstrate clinically meaningful weight loss in patients with various rare genetic forms of obesity after a stable therapeutic dose period, which is expected to be ~3 months of treatment in most subjects. The primary endpoint is defined as the proportion of patients in each subgroup of rare genetic disorders of obesity (RGDO) who achieve at least 5% body weight reduction from baseline, at ~3 months of treatment with setmelanotide.

The study is exploratory in nature and the sample size of the study for each cohort is driven by clinical considerations. The total number of patients enrolled per subtype with specific genetic obesity mutations may be increased or decreased, depending upon the total number of affected patients identified.

These many rare genetic disorders are grouped together into one protocol for administrative reasons, and otherwise would have been studied in separate protocols. Hence, each rare genetic disorder will be treated as a separate population for any statistical analysis, and therefore no multiplicity adjustments will be planned in this early, proof-of-concept study.

Given the rarity of these disorders, estimated power for expected weight change efficacy will not be provided, but efficacy will be only summarized.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

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LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AgRP	Agouti-Related Peptide
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
ARC	Arcuate nucleus of the hypothalamus
AS	Alström syndrome
AST	Aspartate transaminase
AUC	Area under the curve
BBS	Bardet-Biedl syndrome
BIA	Bioelectrical impedance
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
BUN	Blood urea nitrogen
CCK	Cholecystokinin
[redacted]	[redacted]
CNS	Central nervous system
CO_2	Carbon dioxide
CPE	Carboxypeptidase E
CPK	Creatine phosphokinase
CRA	Clinical research associate
CRF	Case report form
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
CV	Cardiovascular
[redacted]	[redacted]
DIO	Diet-induced obese
EC	Ethics Committee
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
[redacted]	[redacted]
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
Free T4	Free thyroxine
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyltranspeptidase
GLP-1	Glucagon-like peptide-1
[redacted]	[redacted]
Hg	Mercury
HR	Heart rate
[redacted]	[redacted]
IB	Investigator Brochure
ICH	International Conference for Harmonisation
IEC	Independent Ethics Committee
IML	Intermediolateral column
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine device

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
[redacted]	
K_i	Inhibitory constant
LDH	Lactate dehydrogenase
LEPR	Leptin receptor
MC	Melanocortin
MC1R – MC5R	Melanocortin Receptor types 1-5
MDRD	Modification of Diet in Renal Disease
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
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	
POMC	Pro-opiomelanocortin
PT	Prothrombin time
PTT	Partial thromboplastin time
PVH	Paraventricular Hypothalamus
PWS	Prader-Willi Syndrome
PWS-FPD	Prader-Willi Syndrome – Food Problem Diary
PWS-SEQ	Prader-Willi Syndrome – Significant Event Questionnaire
PYY	Peptide YY
QD	Once daily (from the Latin: *quaque die*)
QW	Once weekly (from the Latin: *quaque* week)

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
RGDO	Rare Genetic Disorders of Obesity
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
[redacted]	[redacted]
SMS	Smith-Magenis Syndrome
SOA	Schedule of assessments
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
TSH	Thyroid Stimulating Hormone
US	United States
ULN	Upper limit of normal
UV	Ultraviolet
WMA	World Medical Association

4. SUMMARY

Setmelanotide (also known as RM-493) is a synthetic 8-amino acid cyclic peptide that functions as a potent melanocortin-4 receptor (MC4R) agonist. Three setmelanotide formulations have been used in nonclinical and clinical studies: setmelanotide in saline; setmelanotide in N-(Carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl- glycero-3-phosphoethanolamine sodium salt (setmelanotide/mPEG-DSPE); and setmelanotide-Once-Weekly (setmelanotide QW). Note that only the setmelanotide/mPEG-DSPE formulation and setmelanotide QW formulations are in use in clinical studies; the setmelanotide saline formulation is no longer employed.

Setmelanotide is being evaluated for the treatment of severe early-onset genetic forms of obesity and associated co-morbidities, including subjects with pro-opiomelanocortin (POMC) deficiency obesity, leptin receptor (LEPR) deficiency obesity, Prader-Willi syndrome (PWS), Bardet-Biedl syndrome (BBS), Alström syndrome (AS), and other genetic forms of early-onset extreme obesity arising from defects demonstrated or hypothesized to impact the hypothalamic MC4R signaling pathway. Based on accruing genetic and clinical insights, other genetic forms of early-onset extreme obesity may also be evaluated in setmelanotide clinical studies. It is expected that setmelanotide would be indicated to treat the obesity and excess appetite or feeding behavior symptoms of these severe forms of genetic obesity.

Setmelanotide binds with high affinity (inhibitory constant [Ki] = 2.1 nM) to the human MC4R and is efficient in activating MC4R (half-maximal effective concentration [EC_{50}] = 0.27 nM). Setmelanotide was initially selected for clinical development based on its acceptable circulating half-life as a saline formulation administered as a continuous subcutaneous (SC) infusion (2.8 to 3.5 hours in non-human primates) and the ability to decrease body weight gain and suppress food intake in normal rats. Additional studies demonstrated the efficacy of setmelanotide in suppressing food intake and body weight gain in diet-induced obese (DIO) mice, rats, dogs, and monkeys. 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.

Setmelanotide has also been studied in relevant genetic models of obesity, including leptin-receptor deficient Zucker fa/fa rats (a rodent model of genetic obesity impacting the MC4R pathway) and Magel2-null mice (a mouse model for PWS). Treatment of Zucker fa/fa rats with setmelanotide resulted in reductions in both body weight and food intake relative to placebo control. Furthermore, treatment of Magel2-null mice with 0.1 mg/kg setmelanotide demonstrated a statistically significant decrease in cumulative food intake. These data demonstrate that setmelanotide is effective in rodent models of PWS and genetic obesity, supporting the potential efficacy and testing in both monogenic and syndromic obesity.

Significant safety margins are provided from a comprehensive set of toxicology studies, including repeat-dose and chronic toxicology studies in rats and monkeys, developmental and reproductive toxicology studies, and juvenile toxicology studies to support pediatric subject enrolment. These studies support the setmelanotide doses that have been used in clinical studies and that are anticipated in additional chronic studies in genetic obesity populations based on the no-observed-adverse-effect level (NOAEL) of various parameters evaluated in the toxicity studies.

Data obtained to date in the setmelanotide clinical program demonstrate robust weight reduction and hunger suppression in genetic obesity disorders impacting the leptin-melanocortin pathway upstream from the MC4 receptor, with proof-of-concept established for obesity associated with POMC deficiency, LEPR deficiency, BBS, and AS. Furthermore, setmelanotide has been generally well tolerated with a safety profile that supports continued development in rare genetic disorders of obesity.

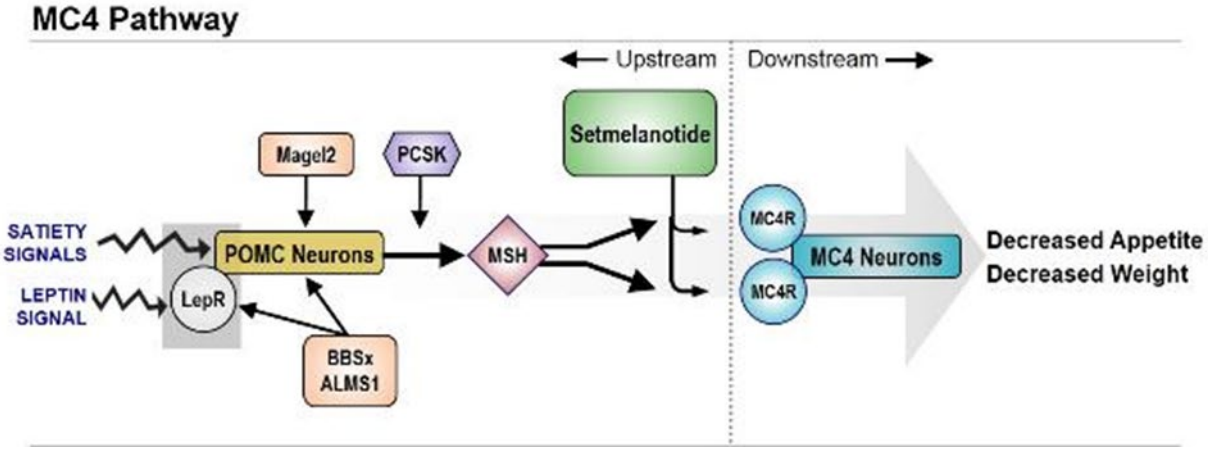
In summary, the unique mechanism of action of setmelanotide as an agonist of the MC4R enables a highly targeted approach to treat very severe obesity in patients with specific genetic defects in the MC4R signaling pathway. By restoring impaired signaling in this pathway, setmelanotide can serve as an indirect form of replacement therapy for these hypothalamic genetic deficiencies leading to extreme obesity, with the potential for dramatic improvements in body weight and appetite control.

5. INTRODUCTION

Rhythm is focusing the development of setmelanotide as a treatment for patients with rare genetic disorders of obesity (RGDO) due to specific genetic defects that impact the functioning of the MC4R pathway, a highly conserved hypothalamic pathway critical for regulation of appetite, energy expenditure, and body weight. The MC4R pathway is the key pathway regulating weight and hunger. Genetic defects in the MC4R pathway cause insatiable hunger, leading to severe and early-onset obesity

Figure 1 depicts a schematic of the MC4R pathway and includes specific "upstream" genes in which an inactivating mutation results in RGDO. Specifically, we are focusing on obesity arising from lack of activation of MC4Rs due to defects in "upstream" genes. By activating the MC4R (downstream portion of the pathway), setmelanotide is hypothesized to provide compelling and persistent efficacy. Setmelanotide, as a potent MC4R agonist, has demonstrated proof-of-concept in obesity resulting from POMC and LEPR deficiencies as well as obesity associated with BBS and AS, genetic syndromes that lead to cellular defects in LEPR signaling. Setmelanotide also has the potential to restore lost activity in the MC4R pathway in other "upstream" defects in genes such as *PCSK1* (responsible for POMC processing and thereby producing bioactive POMC peptides) and *Magel2* (postulated to contribute to some of the features of Prader-Willi syndrome [PWS]). In this way, setmelanotide may serve as a form of "personalized replacement" therapy to re-establish appetite and energy homeostasis regulation, and ultimately restore weight control in patients with specific genetic defects.

Figure 1: Schematic Diagram of the Hypothalamic MC4R Pathway Indicating Some of the Potential Molecular Defects in the MC4R Pathway, Upstream of the Receptor, a Focus of Rhythm Clinical Studies



5.1. Regulation of Appetite, Energy Expenditure, and Body Weight

In mammals, body weight regulation is a function of energy intake (in the form of caloric consumption) and energy expenditure (in the form of basal metabolism/physical exertion/thermogenesis). Persistent disturbances in this equation result in alterations in body weight

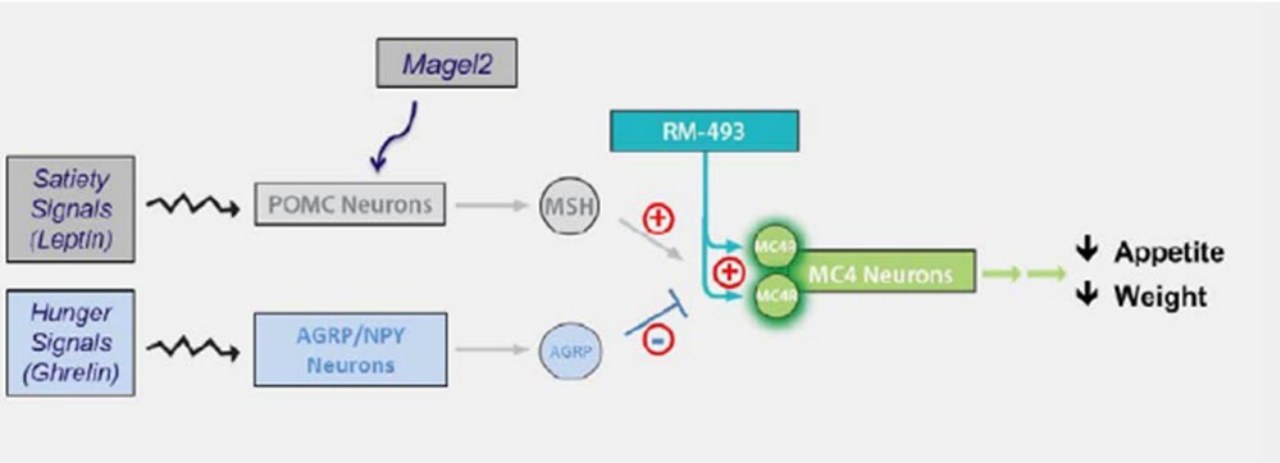
(weight gain if intake > expenditure, and weight loss if intake < expenditure). In principle, regulation of body weight is predicated on two key steps: 1) evaluation of current energy needs (sensory actions) and 2) subsequent generation of physiological responses (appropriate modulation of food intake and expenditure) to meet those needs (Gautron, 2015; Greenfield, 2009). The hypothalamus serves as a key sensory region that integrates information regarding energy state as communicated by several circulating humoral factors. Information about short-term energy needs (hunger vs satiety) is communicated by circulating factors such as cholecystokinin (CCK), ghrelin, and peptide YY (PYY); in contrast, longer-term energy state (adiposity) is conveyed by leptin and insulin. Upon receiving this information, neuronal pathways within the hypothalamus adjust their activity and modulate food intake and/or energy expenditure to achieve the acceptable energy state. One of the most critical neuronal pathways within the hypothalamus responsible for body weight regulation is the central melanocortin pathway.

5.2. The Central Melanocortin Pathway (Melanocortin4 Receptors Pathway)

The melanocortin pathway represents a fundamental component of centrally regulated energy balance.

Melanocortin actions are initiated in the arcuate nucleus of the hypothalamus (ARC) by two distinct and functionally opposing neuronal populations, POMC neurons that produce endogenous melanocortins (α-, β-melanocyte stimulating hormone [MSH]) and a neuronal population that produces agouti-related peptide (AgRP), an endogenous antagonist of melanocortins (Cone, 2005). Both these neuronal populations form the "upstream" part of the central melanocortin pathway (Figure 2). The primary role of both AgRP and POMC neurons is to evaluate energy demand by sensing humoral and neuronal inputs and to subsequently adjust its activity reflecting the current energy state. Once activated, both AgRP and POMC neurons release neurotransmitter/neuropeptides to engage "downstream" MC4R-expressing neurons to modulate food intake and energy expenditure to meet the energy demand (Krashes, 2016).

Figure 2: Schematic Outline of Hypothalamic Food Intake Control



The AgRP-producing neuronal population forms the anabolic arm of the melanocortin pathway: activated by caloric deficit (i.e., ghrelin) → release neuropeptide (i.e., AgRP) → inactivation (hyperpolarization) of downstream MC4R-expressing neurons → increase in energy intake, decrease in energy expenditure and weight gain (Liu, 2012; Yang, 2011; Aponte, 2011; Krashes, 2011). In contrast, POMC-expressing neurons form the catabolic arm: activated by caloric surplus (i.e., leptin [LEP]) → release of bioactive product of POMC processing (α-, β-MSH) → activation (depolarization) of downstream MC4R-expressing neurons → suppression of food consumption, increase in energy expenditure and weight loss (Atasoy, 2012; Zhan, 2013; Dodd, 2015). Consistent with catabolic actions of α- and β-MSH, inactivating mutations in *POMC* and *MC4R* results in early-onset extreme obesity defined by excessive hyperphagia and reduced energy expenditure (Yeo, 1998; Vaisse, 1998; Krude, 1998). Given the importance of this pathway in long-term body weight regulation, inactivating mutations in many critical components (LEP, LEPR, POMC, PCSK1, MC4R) of this pathway have been shown to cause RGDO characterized by intense feelings of hunger and marked hyperphagia.

5.3. The Melanocortin4 Receptors

The melanocortins regulate a wide range of physiological processes such as energy balance, steroidogenesis, sexual function, cardiovascular (CV) function, glucose homeostasis, emotional behavior, and secretion of several endocrine and exocrine factors (Marks, 2001; Foster, 2003; Wikberg, 2008; Tao, 2010). All these diverse functions are regulated via five melanocortin receptors, MC1-5Rs. The MC1R is the classical MSH receptor expressed in skin and hair follicles that regulates pigmentation. The MC2R is the classical adrenocorticotropic hormone (ACTH) receptor expressed in the adrenal cortex that regulates adrenal steroidogenesis and stress response. The MC3Rs are predominantly in the central nervous system (CNS) and their role is not well defined (Giradet, 2014). The MC5R is expressed widely and involved in regulating exocrine gland secretions (Chen, 1997). MC4R is predominantly located in the CNS; however, MC4R expression in also observed in gut. MC4R regulates many different physiological endpoints such as appetite, energy expenditure, glucose homeostasis, and CV functions (Krashes, 2016).

Over last 2-3 decades, a myriad of pharmacological studies in rodents and humans have suggested that MC4Rs are critical for regulation of appetite and overall body weight (Theile, 1998; Millington, 2001; Semjonous, 2009). This was corroborated by genetic findings that show the absence of MC4R signaling causes profound obesity and hyperphagia in both rodents and humans. While pharmacological studies (Theile, 1998; Millington, 2001; Semjonous, 2009) in rodents have implicated many different brain regions mediating appetite regulating effects, conditional knock-out mouse models suggest that the paraventricular hypothalamus (PVH) is the major site of action for MC4R-mediated appetite regulation (Balthasar, 2005; Shah, 2014; Garfield, 2015). It is believed that MC4R-regulated energy expenditure is mediated by cholinergic preganglionic sympathetic neurons in the intermediolateral column (IML) of the spinal cord (Berglund, 2014). In addition to energy balance, MC4R activation is also associated with increase in BP and HR via the autonomic nervous system. Collectively, these observations suggest that an MC4R agonist should be effective for treating genetic forms of obesity by producing persistent and robust weight loss.

5.4. Rare Genetic Disorders of Obesity (RGDO)

Human obesity is recognized as being influenced by both inherited and environmental factors, with few single genes demonstrated to carry major phenotypic effects on their own (Stunkard, 1986; Wardle, 2008). Although obesity is widespread and becomes more prevalent during adolescence and adulthood, many of the most severe forms of obesity begin early in infancy and childhood. Recent research has revealed numerous genetic mechanisms and specific mutations that lead to rare monogenic disorders characterized by RGDO (van der Klaauw, 2015; Martos-Moreno, 2014). Complementary experiments in genetic rodent models and RGDO patients have led to the identification of a critical set of genes in the MC4R pathway (van der Klaauw, 2015). The MC4R hypothalamic pathway was initially validated as an important genetic underpinning for some forms of obesity with the discovery that single genetic defects in MC4R result in early-onset and severe obesity (Vaisse, 1998; Yeo, 1998). Now, an expanding set of monogenic obesity defects (in addition to loss of function mutations in the MC4R itself) have been identified; these obesity mutations involve genes in this pathway that are either upstream of MC4R – specifically, POMC deficiency obesity, pro-hormone convertase 1 (PCSK1) and LEPR deficiency obesity – or genes that are downstream of MC4R (O'Rahilly, 1995; Ramachandrappa, 2011).

Human genetics studies have identified several diseases that are the result of genetic defects affecting the MC4R pathway, including:

- POMC deficiency obesity due to mutations in the POMC gene
- PCSK1 deficiency due to mutations in the PCSK1 gene, leading to a hormone processing defect that also causes POMC deficiency obesity
- LEPR deficiency obesity due to mutations in the LEPR gene

These MC4R pathway mutations can cause RGDO that progresses over time and can become life-threatening in severity.

Rhythm is developing setmelanotide for the treatment of severe early-onset genetic forms of obesity arising from defects demonstrated or hypothesized to occur upstream of the MC4R receptor and impact the hypothalamic MC4R signaling pathway. Based on accruing genetic and clinical insights, different genetic forms of early-onset extreme obesity may also be evaluated in setmelanotide clinical studies. It is expected that setmelanotide would be indicated to treat the obesity and excess appetite or feeding behavior symptoms of these severe forms of genetic obesity.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Study Objectives

The objective of this study is to assess the safety and efficacy of setmelanotide after ~3 months of treatment, with the hopes of establishing "Proof of Concept" within each subtype of patients that show significant weight loss. The significant weight loss may vary depending on disease state and will be described in more detail in the Statistical Analysis Plan (SAP).

Primary

To explore the impact of setmelanotide on obesity in patients with various specific rare genetic mutations.

Secondary

To assess the effects of setmelanotide on:

- Safety and tolerability
- Hunger
- Waist circumference

[redacted]

6.2. Study Endpoints

Primary Endpoint

The proportion of patients in each subgroup of RGDO who achieve at least 5% body weight reduction from baseline, at ~3 months treatment with setmelanotide.

Secondary Endpoints

- Safety and tolerability of setmelanotide injection, assessed by the frequency and severity of AEs, vital signs, and laboratory evaluations
- Change and percentage change from baseline in body weight
- Change from baseline in Daily and Global Hunger scores
- Change from baseline in waist circumference

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Design and Plan of the Study

This is a Phase 2, proof-of-concept study to assess initial safety and efficacy of setmelanotide within each identified subtype of rare genetic disorders of obesity.

Screening Period

Upon providing informed consent, patients will enter the Screening Period, during which they will be assessed for eligibility and complete all screening procedures as described in the Schedule of Events. Each patient's genetic information will be reviewed by the Sponsor to confirm the patient is eligible for the study. During the Screening Period, each patient will be instructed to complete a hunger questionnaire on a daily basis and will be required to have completed at least four days of the questionnaire prior to first dose.

Treatment Period

Eligible patients will return to the clinic within 8 – 2 weeks of completing the Screening Visit for the Baseline Visit (Visit 2) and first dose of setmelanotide.

Dose levels for all patients will escalate to a final dose of 3.0 mg/day during an initial dose-titration phase, but the starting dose will depend on patient age. Patients 6 up to 16 years old will initially be dosed at 1.0 mg/day for 2 weeks, beginning at the Baseline Visit on Study Day 1. Starting on Day 15, the dose will escalate to 2.0 mg/day and remain at that level for 2 weeks, until the patient returns to clinic for Visit 3 on Day 29. At Visit 3, the dose will be escalated to 3.0 mg/day; the patient will continue dosing at 3.0 mg/day for 12 weeks.

Patients ≥16 years old will initiate dosing at 2.0 mg/day at the Baseline Visit, and continue dosing at that level for 2 weeks. The dose will be escalated to 3.0 mg/day beginning on Study Day 15, and the patient will continue that dose for 14 weeks.

Study site staff will call all patients at their homes after the first 2 weeks of treatment to ensure the escalation occurred as planned and collect any AEs.

Patients will continue dosing at 3.0 mg/day, and return to the clinic every four weeks (Visits 3-5) to complete the assessments in Table 3. After 16 weeks in the study, patients will return to the clinic for Visit 6. At Visit 6, the patient will receive the last setmelanotide injection. Participation in the study will then conclude in one of the following two ways:

- Complete Visit 6 and enroll in a separate extension study, Rhythm Study RM-493-022. If RM-493-022 is not yet open at the clinic site, the patient will continue daily setmelanotide injections and other activities per the current study, as presented in the SOA (Table 3). The patient will return to the clinic for Bridging Visits every 12 weeks for up to one year, until the extension study opens at the site. Additional clinic visits may be scheduled at the discretion of the PI.

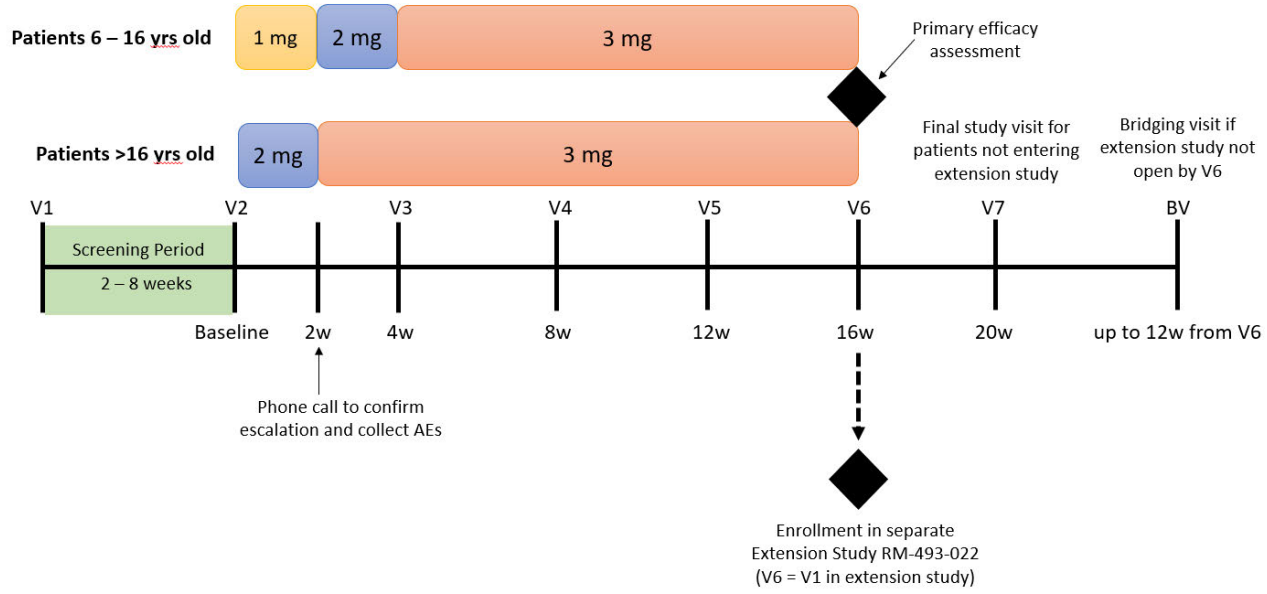
- Decide not to participate in the extension study and proceed to the final study visit (Visit 7) in 4 weeks.

Patients on study per a previous amendment should transition to dose escalation as outlined in this protocol:

- Patients who are in the dose titration phase and are not currently at a dose of 3.0 mg/day will be assessed by the Primary Investigator and the Sponsor, to determine if an increase in the dose to 3.0 mg/day is appropriate.
- Patients who have completed dose titration and are assigned to a dose of less than 3.0 mg/day will be assessed by the PI to determine if an increase in the dose to 3.0 mg/day is appropriate.
- Patients who are post 16 weeks may roll into the separate extension study (RM-493-022) directly or via Bridging Visits, or proceed to the final study Visit 7 and finish the study.

A flow chart summarizing Study RM-493-014 is presented in Figure 3.

Figure 3: Flow Chart for Study RM-493-014



7.2. Rationale for the Doses

All patients will escalate to 3.0 mg/day after 2 – 4 weeks on treatment, depending on age. Patients 6 up to 16 years old will start at a dose of 1.0 mg/day for 2 weeks, escalate to 2.0 mg/day for 2 weeks,

and then to 3.0 mg/day for 12 weeks. Patients ≥16 years old will start at a dose of 2.0 mg/day for 2 weeks and then escalate to 3.0 mg/day for the remaining 14 weeks of treatment. Previous setmelanotide studies have employed a similar dose escalation scheme to reach the maximum dose of 3.0 mg with no safety concerns.

7.3. Justification of the Study Design

Overall, data obtained to date in the setmelanotide clinical program demonstrate robust weight reduction and hunger suppression efficacy in specific genetic obesity disorders impacting the leptin-melanocortin pathway upstream from the MC4 receptor, with proof-of-concept established for obesity associated with POMC deficiency, LEPR deficiency, BBS, and AS. A detailed summary of the efficacy seen in these patients is provided in the IB (Section 5.4), which is updated on a regular basis. Furthermore, clinical safety data support this development focus in MC4R pathway genetic obesity disorders. These data are also summarized in the IB (Section 5.3)

It is expected that setmelanotide might be effective in treating other genetic obesity disorders that impact the leptin-melanocortin pathway and present phenotypically with obesity and hyperphagia. This study is designed to enroll multiple patient populations that share the phenotype of obesity and hyperphagia, and in which there is scientific evidence (either clinical or nonclinical) of a relationship to decreased functioning of the leptin-melanocortin pathway. The intention is to enroll a small number of patients suffering from each of these disorders, in order to evaluate the safety, tolerability, and efficacy in each population, and provide data to determine whether further clinical development is appropriate.

7.4. Study Termination

This study may be prematurely terminated if, in the opinion of the Investigator (at a participating site) or Rhythm), 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.
- Termination of an individual population for a specific disorder of obesity if data from at least two, and possibly up to five, patients in that disorder fail to show substantial weight loss (e.g., no patients meet the threshold for continuation into extensions).

In addition, it is still unclear how many patients will be required to assess the safety and efficacy of setmelanotide in each of these rare conditions before it is appropriate to transition to pivotal trials. Therefore, this study (or enrollment of any individual population within the study) may be either temporarily held or terminated when Rhythm determines that there are sufficient patient data in Phase 2 to support initiation of pivotal efficacy and safety studies.

7.5. Data Safety Monitoring Board

As this is an open-label study, all data will be available to the Sponsor on a real-time basis. Primary Investigators will be responsible to review and evaluate safety data from their patients in a continuous manner. Cumulative safety data from the study will be reviewed by the Sponsor on an ongoing basis for any safety signals or tolerability concerns. Additionally, this study will be monitored by a Data Safety Monitoring Board, which will include outside advisors and will meet on a periodic basis to review the cumulative safety data from the trial and will make a recommendation to continue or modify the study, if needed.

8. STUDY POPULATION

8.1. Number of Patients

It is expected that approximately 150 patients will be included in this protocol across multiple subgroups. Since the subgroups in this study are all rare, it is expected that the size of each subgroup will range from 1 – 15 patients.

8.2. Inclusion Criteria

1. Patients with the following genotypes and/or clinical assessment:
   a. POMC/PCSK1/LEPR heterozygous
   b. POMC/PCSK1/LEPR compound heterozygous (two different mutations in gene) or homozygous deficiency obesity
   c. POMC/PCSK1/LEPR composite heterozygous (two or more mutations in two or more genes) deficiency obesity
   d. Smith-Magenis Syndrome (SMS)
   e. SH2B1 deficiency obesity
   f. Chromosomal rearrangement of the 16p11.2 locus causing obesity
   g. CPE compound heterozygous or homozygous deficiency obesity
   h. Leptin deficiency obesity with loss of response to metreleptin
   i. SRC1 deficiency obesity
   j. MC4R deficiency obesity

   Note: The specific genotype for all patients must be reviewed by the Sponsor prior to study enrollment to confirm that the patient meets Inclusion Criterion #1. In addition, enrollment of patients in some subgroups may be prioritized by the Sponsor in order to ensure enrollment of patients with (1) well described, loss-of-function genetic mutations, (2) a variety of genetic variants, or (3) genetic variants likely to respond to setmelanotide.
2. Age 6 years and above.
3. Obese, defined as Body Mass Index (BMI) $\geq$ 30 kg/m^2 for patients $\geq$16 years of age or BMI $\geq$ 95th percentile for age and gender for patients 6 up to 16 years of age.
4. Study participant and/or parent or guardian is able to communicate well with the Investigator, to understand and comply with the requirements of the study, and is able to understand and sign the written informed consent/assent.
5. Female participants of child-bearing potential must be confirmed non-pregnant, and agree to use contraception as outlined in the protocol. Female participants of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation), post-menopausal for at least 12 months (and confirmed with a screening Follicle-Stimulating Hormone [FSH] level in the post-menopausal lab range), 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.

8.3. Exclusion Criteria

1. Recent intensive (within 2 months) diet and/or exercise regimen with or without the use of weight loss agents including herbal medications that has resulted in > 2% weight loss.
2. Use of any medication that is approved to treat obesity within three months of first dose of study drug (e.g., orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion). **Note:** Glucagon-like peptide-1 (GLP-1) receptor agonists may be used up to the dose approved for the treatment of diabetes mellitus (e.g., liraglutide up to a daily dose of 1.8 mg) as long as (1) is it not being prescribed for the treatment of obesity, (2) the dose has been stable for at least three months prior to enrollment, (3) the patient has not experienced weight loss during the previous three months, AND (4) the patient intends to keep the dose stable throughout the course of the study.
3. Gastric bypass surgery within the previous six months or any 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 the Sponsor prior to enrollment.
4. Diagnosis of schizophrenia, bipolar disorder, personality disorder or other psychiatric disorder(s) that the Investigator believes will interfere significantly with study compliance. Neurocognitive disorders affecting ability to consent will not be disqualifying as long as an appropriate guardian able to give consent has been appointed.
5. A PHQ-9 score of ≥ 15 or any suicidal ideation of type 4 or 5 on the C-SSRS during Screening, any lifetime history of a suicide attempt, or any suicidal behavior in the last month. **Note:** Patients who are unable to complete the PHQ-9 or C-SSRS due to significant neurocognitive defects may be allowed to enroll in the study, as long as in the opinion of the Primary Investigator there are no clinical signs or symptoms of suicidal behavior.
6. Current, clinically significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor to determine eligibility.
7. HbA1c >9.0% at Screening
8. History of significant liver disease or abnormal liver tests on Screening (i.e. > 1.5 x upper limit of normal [ULN] for alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase, or serum bilirubin). **Note:** Patients entering the study with SRC1 haploinsufficiency obesity must be evaluated during the Screening Period for hepatic fibrosis

by appropriate imaging techniques (e.g., transient elastography or magnetic resonance elastography). Any patient with moderate or greater fibrosis (e.g., the equivalent of a METAVIR score ≥ 2) will be excluded from the study. **Note:** A patient with a diagnosis of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) may be allowed to enroll in the study, after consultation with the Sponsor. Other significant liver disease, such as cirrhosis, are exclusionary.

9. Glomerular filtration rate (GFR) <30 mL/min at Screening.
10. History or close family history (parents or siblings) of skin cancer or melanoma (not including non-invasive/infiltrative basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.
11. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive skin evaluation performed by a qualified dermatologist during Screening. 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.
12. Patient is, in the opinion of the Study Investigator, not suitable to participate in the study.
13. Participation in any clinical study with an investigational drug/device within 3 months prior to the first day of dosing.
14. Patients previously enrolled in a clinical study involving setmelanotide or any previous exposure to setmelanotide.
15. Significant hypersensitivity to any excipient in the study drug.
16. Inability to comply with QD injection regimen.
17. Females who are breastfeeding or nursing.

8.4. Patient Identification and Registration

All patients screened for the study will be assigned a unique screening number which will be a combination of study number (014), 3-digit site number, and a sequential 3-digit number; this screening number 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 014-010-001). Once a patient number has been assigned, it cannot be reused.

8.5. 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 treatment or study withdrawal. For specific predefined events, additional monitoring and guidance for the Investigator is provided in Appendix D and Appendix E.
- Non-adherence to study drug regimen or protocol requirements.
- Non-compliance with instructions or failure to return for follow-up.

8.6. Duration of Patient Participation

After completing the screening assessments within 8 – 2 weeks, all patients will participate in the study for a minimum of 16 additional weeks. After 16 weeks, the duration of patient participation will be as follows:

- +0 weeks for patients immediately enrolling into a separate extension study (Rhythm Protocol RM-493-022). Total duration: 16 weeks.

  +TBD weeks for patients completing Bridging Visits until the extension study is initiated at the site. The purpose of the Bridging Visits is to ensure continuous treatment for patients if initiation of the extension study is delayed at the site. The Bridging Visits can occur at a frequency of up to every 12 weeks (for a maximum of 1 year) and/or at the discretion of the Primary Investigator. Total duration: uncertain, but > 16 weeks, maximum of 16 months.
- +4 weeks for patients not entering the extension study and proceeding to the final study visit. Total duration: 20 weeks.

9. STUDY TREATMENTS

9.1. Study Drug

The setmelanotide injection solution is a clear to slightly opalescent and colorless to slightly colored solution, practically free of visible particles, prepared as a sterile solution for once-a-day administration by SC injection.

The drug product is formulated at a concentration of 10 mg/mL, and 1 mL of setmelanotide is filled in a 2 mL glass vial which is then packaged in a cardboard carton.

9.2. Study Drug Dose Levels

The dose levels are outlined in Table 2. The dose escalation at Study Day 15 (start of Week 3) will occur at the patient's home. The site will call the patient to confirm that the escalation has occurred and to record any AEs.

Table 2: Study Drug Dose Levels by Study Week and Patient Age

Study Week	For Patients 6 up to 16 Years Old (mg/day)	For Patients ≥ 16 Years Old (mg/day)
1 and 2	1.0	2.0
3 and 4	2.0	3.0
5 to 16	3.0	

Dose levels may deviate from this plan after consultation with the Sponsor, if necessary due to an AE, or other safety or tolerability concern. No dose greater than 3.0 mg per day will be administered during this study. Additionally, patients who are currently enrolled in this study at the time of this protocol amendment, and who are not currently at a dose of 3.0 mg per day, will be assessed by the Primary Investigator and the Sponsor to determine if an increase in the dose to 3.0 mg per day is appropriate.

9.3. Blinding

This study will be open-label, so there is no blinding.

9.4. Packaging and Labeling of Study Drug

All study drug will be labelled as per the local regulations and provided in a cardboard box that contains a single vial.

9.5. Handling and Storage of Study Drug

All study drug must be kept in a secure, limited-access storage area at a temperature between 2°C and 8°C. Setmelanotide is 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 to patients to transport the

drug to their home. Once home, the un-opened study drug must be stored in the patient's refrigerator. Opened study drug may be stored at room temperature for up to 30 days.

9.6. Assessment of Treatment Compliance and Study Drug Accountability

Accountability for the study drug at the study site is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the delivery date to the site, inventory at the site, use by each patient, return of all used study drug to the study center, and return to Rhythm (or disposal of the drug, if approved by Rhythm) will be maintained by the clinical site. Reasons for departure from the expected dispensing regimen must also be recorded. The Sponsor or its designee will review drug accountability at the site during monitoring visits.

Compliance to dosing will be monitored throughout the study by having the patient complete a daily dosing log that records daily dosing information, including the time of dosing, location of the injection, and the amount of drug dosed. If a patient is non-compliant with the dosing schedule, the Sponsor may implement steps to ensure compliance, e.g., sending a nurse to the patient's home for retraining or having a nurse administer the study drug.

9.7. Prior and Concomitant Treatment

Prohibited Medication and Substances

Unless concomitant medications are likely to present a strong potential safety concern, the general goal of this protocol is to allow as many patients with these ultra-rare conditions to participate in the study as possible.

Medications that are approved to treat obesity (e.g., orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion) are not allowed within three months of first dose of study drug (e.g., enrollment) and are prohibited during the course of the study.

GLP-1 receptor agonists may be used up to the dose approved for the treatment of diabetes mellitus (e.g., liraglutide up to a daily dose of 1.8 mg) as long as (1) it is not being prescribed for the treatment of obesity, (2) the dose has been stable for at least three months prior to enrollment, (3) the patient has not experienced weight loss during the previous three months, AND (4) the patient intends to keep the dose stable throughout the course of the study.

Other medications that may cause weight loss (e.g., stimulants) are allowed as long as the patient (1) has used a stable dose for at least three months prior to enrollment, (2) has not lost weight during the previous three months, and (3) intends to keep the dose of the medication stable through the course of the study.

All concomitant medications should be kept at a stable dose throughout the course of the study, unless a dose change is necessary to treat an AE.

10. SCHEDULE OF ASSESSMENTS

The Schedule of Assessments (SOA) is presented in Table 3.

Table 3: Schedule of Assessments

Study Period/Procedure	**Screening**	**Study Treatment**						**EOS Visit**	**Bridging Visit(s) [31] + up to 12 weeks from V6 (up to one year from V6)**	**Treatment Discontinuation Visit**
Clinic Visit Number	**V1**	**V2**	**-**	**V3 [29]**	**V4**	**V5**	**V6 [30]**	**V7**		
Start of Week X	**-8 to -2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**		
Study Day (± 3 days)	-56 to -14	1	15	29	57	85	113	141		
Sponsor review of patient genetics/Genetic Testing [1]	X									
Informed consent/Assent [33]	X									
Inclusion/Exclusion review	X	X								
Medical history review	X									
Physical examination [2]	X	X		X	X	X	X	X	X	X
Comprehensive skin exam [3]	X						X			X
Fitzpatrick classification scale	X						X	X		X
Hepatic imaging [35]	X									
Weight [4]	X	X		X	X	X	X	X	X	X
Waist circumference [5]	X	X		X	X	X	X	X	X	X
Height [6]	X			X	X	X	X	X	X	X
[redacted]										
Vitals [8]	X	X		X	X	X	X	X	X	X
ECG (12-lead) [9]	X	X[36]		X			X		X	X
Pregnancy test [10]	X	X [32]		X	X[32]	X[32]	X[32]		X[32]	X[32]
Daily hunger questionnaires [11]	X	Daily [32]								X[32]
Global hunger assessment [12]		X[32]		X[32]	X[32]	X[32]	X[32]	X	X[32]	X[32]
[redacted]										

Table 3: Schedule of Assessments (Continued)

Study Period/Procedure	Screening	Study Treatment						EOS Visit	Bridging Visit(s) [31] + up to 12 weeks from V6 (up to one year from V6)	Treatment Discontinuation Visit
Clinic Visit Number	V1	V2	-	V3 [29]	V4	V5	V6 [30]	V7		
Start of Week X	-8 to -2	0	2	4	8	12	16	20		
Study Day (± 3 days)	56 to 14	1	15	29	57	85	113	141		
[redacted]										
Safety laboratory tests [19]	X	X		X[32]	X[32]	X[32]	X[32]	X	X[32]	X[32]
[redacted]										
Anti-drug antibody samples	X	X		X			X	X	X	X
[redacted]										
Injection site inspection [24]		X		X	X	X	X		X	X
Telephone call [25]			X							
Study drug administration [26]		Daily dosing							X	
Dispense/Return study drug [27]		X		X	X	X	X		X	
Adverse event assessment [28]	X	X	X	X	X	X	X	X	X	X

Table 3: Schedule of Assessments (Continued)

Study Period/Procedure	Screening	Study Treatment						EOS Visit	Bridging Visit(s) [31] + up to 12 weeks from V6 (up to one year from V6)	Treatment Discontinuation Visit
Clinic Visit Number	**V1**	**V2**	**-**	**V3 [29]**	**V4**	**V5**	**V6 [30]**	**V7**		
Start of Week X	**-8 to -2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**		
Study Day (± 3 days)	**56 to 14**	**1**	**15**	**29**	**57**	**85**	**113**	**141**		
Concomitant medications review	X	X	X	X	X	X	X	X	X	X
[redacted]										

V, Study Visit Number; EOS, End of Study; [redacted].

1. Prior to conducting any screening assessments, Sponsor will review and approve the specific genotype to ensure it meets the criteria for the patient populations included in the study (Section 11.1).
2. A complete physical examination will be conducted at Screening and at the EOS V7. At other timepoints, an abbreviated examination will be performed. The abbreviated examination should focus on heart, lungs, skin, neurologic exam, and any areas of previous abnormal findings, noting any changes from baseline. In addition, [redacted] for assessment of pubertal development will be conducted for those patients who have yet to reach [redacted] Whenever possible, the same trained health care professional will conduct the exam and [redacted] (Section 11.5).
3. A comprehensive skin evaluation will be performed by a dermatologist. The skin exam should include a full body skin exam (head-to-toe skin examination) from a trained and licensed 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. Additionally, any lesion or change in an existing lesion during the course of the study must be evaluated by the dermatologist and biopsied, if clinically indicated in the opinion of the dermatologist. Any biopsies must be evaluated by a trained dermatopathologist, and biopsy reports must be part of the study information for each patient (Section 11.6).
4. Weight (kg) is to be measured at the clinic using the same scale throughout the study, after patients have emptied their bladders and bowels and after fasting for at least 8 hours. Patients are to wear light clothing or underwear and no shoes, and will be weighed at approximately the same time of day. Weight measurements are to be done in triplicate (Section 11.8).
5. Waist circumference (cm) will be single measures (Section 11.9).
6. For patients ≥18 years of age, height needs to be measured at the screening visit only. Height (cm) will be measured, without shoes, socks, or hats, using a wall-mounted stadiometer. All measurements will be done in triplicate at each timepoint and recorded to the nearest 10th of a decimal place (Section 11.10).

[redacted]

8. All BP and HR measurements are to be obtained in the sitting position following at least 5 minutes of rest. All measurements will be taken in triplicate, approximately 2 minutes apart. When possible, BP should be taken in the non-dominant arm throughout the study, using the same

methodology (automated or manual). Body temperature (°C) and respiration rate (breaths/minute) will be obtained in the sitting position following at least 5 minutes of rest (Section 11.13).

9. A single 12-lead ECG will be performed in the supine position following a period of at least 10 minutes of rest (Section 11.14). At visit 2 the ECG will be performed before and 8 hours after dosing.
10. A urine pregnancy test may be performed to expedite availability of results prior to dosing on Day 1. All other pregnancy tests will be serum tests (Section 11.15); dosing may continue with results pending.

[redacted]

19. Safety laboratory tests 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), and urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination. Safety laboratories will also include a coagulation profile (PT or INR, and PTT also referred to as aPTT).

[redacted]

23. Blood samples will be collected prior to dose administration in the [redacted].
24. 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 in which there are injection site reactions, even if not a timepoint for formal assessment (Appendix A).
25. Site should call the patient to confirm the proper dose escalation has occurred, and to collect AEs.
26. Patients/caretakers will draw up and self-administer/administer the drug once daily in the morning beginning the morning of Day 1 and for the duration of dosing. On days with clinic visits, the patients/caretakers will administer the drug in the clinic in the presence of the clinical staff to assure proper technique.
27. Patients/caretakers will return all (the number recorded) used vials to the clinic when they visit, and both clinic-administered study drug as well as outpatient study drug administration will be recorded in a study diary.
28. 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.
29. Patients who are <16 years of age will receive first daily dose of 3.0 mg at V3, at clinic site.
30. Study endpoints are analyzed at V6. After completing V6, patient enters a separate extension study (Protocol RM-493-022), does not enter the extension study and returns for the final study Visit 7 in 4 weeks, or completes Bridging Visits for up to one year or until the extension study is initiated.
31. Bridging Visits only needed if separate extension study RM-493-022 is not initiated at site at the time of V6.
32. Collected prior to study drug administration.
33. Although the study procedures and assessments required per protocol are classified as "No or Minimal Risk" (with the exception of [redacted] which may be classified as "Minor Increase over Minimal Risk") according to 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 J.

[redacted]

35. Only applicable to SCR1 patients.
36. During visit 2 ECG will be collected prior to dosing and ~8 hours post-dose.

11. PATIENT ASSESSMENTS AND REQUIREMENTS

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, and perform blood draws (at the specified time point, if applicable). Adjustments may be made depending upon specific circumstances and in consultation with the Sponsor.

11.1. Sponsor Review of Patient Genetics and/or Genetic Testing

The genetic background of each patient must be reviewed by the Sponsor prior to study enrollment to confirm that the patient meets inclusion criteria. For patients that have not had a previous genetic sample taken, a blood sample will be obtained at Screening for genetic confirmation of a genetic disorder of obesity.

In addition, enrollment of patients in some subgroups may be prioritized by the Sponsor in order to ensure enrollment of patients with (1) well described, high-impact genetic mutations, (2) a variety of genetic variants, or (3) genetic variants likely to respond to setmelanotide.

11.2. 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.

11.3. Inclusion/Exclusion Review

Inclusion and exclusion criteria are to be reviewed per the SOA (Table 3) to ensure the patient is eligible for the study.

For Exclusion Criterion 9, GFR at Screening will be determined using the Modification of Diet in Renal Disease (MDRD) Equation in patients ≥18 years of age (Appendix H), and the Bedside Schwartz Equation in patients <18 years of age (Appendix I).

11.4. Demographics, Concomitant Medications and Medical History Review

Medical history and demographic data including the patient's gender, race, date of birth, and concomitant medication use will be obtained for all patients during the Screening Period (Appendix C).

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

11.5. Physical Examination

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.

Changes from baseline in any physical examination findings identified by the Investigator as clinically significant must be recorded as an AE on the appropriate electronic Case Report Form (eCRF).

Patients will also be assessed at baseline according to [redacted]; any patients who have not reached [redacted] will be assessed according to the SOA (Table 3).

11.6. Comprehensive Skin Exam

The Investigator will identify a trained and licensed dermatologist to serve as a consultant for the Investigative Site.

The dermatologist will perform comprehensive skin examinations, which should include a full body skin exam (head-to-toe skin examination). Each patient will receive this comprehensive, head-to-toe dermatology examination as part of Screening and prior to the end of the study. Any worrisome lesion should be biopsied prior to study start, and all biopsies must be evaluated by a trained dermatopathologist.

Additionally, any lesion or change in an existing lesion during the course of the study must be evaluated by the dermatologist and biopsied, if clinically indicated in the opinion of the dermatologist. All biopsies must be evaluated by a trained dermatopathologist.

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.

Biopsy reports must be part of the study information for each patient.

Protection from Sun

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 or self-tanning lotions, etc.).

11.7. Fitzpatrick Scale

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

11.8. Weight

Weight (kg) will be recorded as shown in the SOA (Table 3). All measurements will be done in triplicate at each timepoint. Whenever possible, the same scale should be used throughout the study, including the Screening Visit, and should be calibrated on a regular basis. Weight should be

measured at approximately the same time at each visit and after fasting for at least 8 hours. Patients should be in light clothing or underwear, with no shoes, and should have emptied their bladders and bowels.

11.9. 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 (Table 3). 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 bladders.

11.10. Height

Height (cm) will be measured, without shoes, using a wall-mounted stadiometer according to the SOA (Table 3). All measurements will be done in triplicate at each timepoint. Height will be used along with body weight to determine BMI.

11.12. Hepatic Fibrosis

Patients entering the study with SRC1 haploinsufficiency obesity must be evaluated during screening with an appropriate imaging test for hepatic fibrosis. Transient elastography and magnetic resonance elastography are both acceptable options for imaging. Other imaging modalities may be acceptable, with approval by the Sponsor. Patients will be excluded from the study if they are

determined by the Primary Investigator to have moderate or greater liver fibrosis (e.g., the equivalent of a METAVIR score ≥ 2).

11.13. Vital Signs

Vital signs will be obtained in the sitting position following at least 5 minutes of rest at the time points indicated in the SOA (Table 3).

Blood Pressure and Heart Rate

Blood pressure (BP; mmHg) and heart rate (HR; beats per minute [bpm]) evaluations will be performed using the same methodology throughout the study (manual or automated). For a detailed description of the standardized BP measurement to be utilized in this study, see Appendix F.

Special attention should be paid to ensure the appropriate cuff size in this patient population.

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.

11.14. ECG (12-lead)

Single 12-lead ECGs will be performed following a period of at least 10 minutes of rest in the supine position. ECGs will be collected according to the SOA (Table 3). During Visit 2 ECG will be collected prior to dosing and ~8 hours post-dose.

11.14.1. ECG Procedures

All ECGs should be performed according to the SOA (Table 3) 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.
- 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.

11.14.2. Reading ECGs

- Site Monitoring: Sites should read ECGs for study monitoring and eCRFs per their usual procedures.
- Central Reading: The Sponsor 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 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 patient identifier.

11.15. Pregnancy Test

Contraception

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

For females able to bear children, including pre-pubertal females if relevant, a highly reliable form of contraception must be used/practiced throughout the study and for 90 days following the study. Highly reliable acceptable forms of contraception include hormonal (i.e., oral, implantable, or injectable) AND single-barrier method (i.e., condom), or an Intrauterine Device (IUD) AND single-barrier method (i.e., condom) or 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, 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. Females who begin the study having failed to reach Tanner Stage 5 or achieve menarche, but do so during the study, will be counseled on pregnancy and contraception, and will immediately be treated as a female of child-bearing potential for the remainder of the study, with the required pregnancy tests at all visits.

It is not known if this treatment will affect spermatogenesis. Therefore, males with female partners of childbearing potential must agree to use contraception: (A) use a double barrier method [i.e., condom AND diaphragm with spermicide during intercourse]), (B) had a vasectomy, or (C) abstain from sexual intercourse. True abstinence is acceptable only if it is the preferred and usual lifestyle of the patient. Male patients must not donate sperm for 90 days following participation in the study.

[redacted]

[redacted]

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

The Global Hunger Questions and Daily Hunger Questionnaire are described in Appendix G. The Global Hunger Questions will be completed during specified study visits at the clinic and the Daily Hunger Questionnaire will be recorded each day directly into an electronic data capture device (paper version can be used if needed).

[redacted]

[redacted]

[redacted]

[redacted]

11.18. Safety Laboratory Tests

Clinical safety laboratory tests will be performed by a central laboratory. Blood and urine samples are to be collected following an 8-hour fast and prior to dosing, according to the SOA (Table 3).

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

Specific tests are described below.

In certain situations, it may not be feasible to complete all blood draws scheduled for a specific visit (e.g., a younger patient, or difficulty with phlebotomy due to obesity). In this situation, the Investigator may use his/her discretion to determine which laboratory tests are completed. Laboratory tests should be prioritized in the following manner:

1. Safety labs; including hematology, chemistry, and coagulation profile.

[redacted]

3. All other laboratory measures, such as [redacted]

Any patient who does not complete all blood draws as described in the SOA on two visits should be discussed with the Sponsor.

Hematology, Clinical Chemistry, and Urinalysis

- Hematology

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

- Chemistry

Sodium, potassium, chloride, carbon dioxide (CO_2), albumin, total protein, glucose, blood urea nitrogen (BUN), creatinine, uric acid, AST, 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.

[redacted]

[redacted]

11.21. Anti-drug Antibody Samples

Blood samples for measurement of anti-drug antibodies (ADA) will be collected according to the SOA (Table 3). Any patient with a positive titer will be followed until resolution.

[redacted]

11.24. Injection Site Inspection

Injection sites will be carefully inspected, evaluated, and scored according to the SOA (Table 3). 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 A.

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

11.25. Telephone Call

The site will call a patient's home on Day 15 to assess AEs and ensure the patient escalated to the appropriate dose depending on age, as outlined in the SOA (Table 3).

11.26. Study Drug Administration

Study drug will be administered daily as outlined in the SOA (Table 3).

11.27. Dispensing/Return of Study Drug

Study drug will be dispensed as outlined in the SOA (Table 3) and Section 9.5. Any unused drug will be returned to the clinic site and the Sponsor as described in Section 9.6.

11.28. Adverse Event Assessment

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 (NCI CTCAE) grading system.

Complete details on AE monitoring are provided in Section 12.

11.29. Concomitant Medication(s) Review

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

12. ADVERSE EVENTS

Monitoring of AEs will be conducted throughout the study. AEs will be recorded in the CRFs from Screening through the Final Study Visit. AEs that occur after the start of study drug administration will be considered TEAEs. SAEs will be recorded through the Final Study Visit (EOS Visit 7, or Treatment Discontinuation). 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).

12.1. 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 AE (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 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.

12.2. 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 **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 the Sponsor or its designee.

- All SAE correspondence should be addressed to
- Email: RhythmSafety.SM@ppdi.com

[redacted]

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), Ethics Committees (EC), and all participating Investigators on an expedited basis. It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of all unexpected serious adverse drug reactions involving risk to human patients. An unexpected event is one that is not reported in the IB (see IB Section 6.1.3, Reference Safety Information).

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.

12.2.1. Assessment of Severity

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).

AEs 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, the temporal relationship is such that study drug would not have had any reasonable association with the observed event, or another reasonable explanation for the event (e.g., a pre-existing clinical condition or other concomitant treatment) is more likely.
- **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.

12.2.2. Adverse Events and Risks

Overall, setmelanotide has been generally well-tolerated in previous studies. Drug-Related TEAEs (for which the AE 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 Primary Investigators (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 IB for a comprehensive summary of the AEs reported to date.

12.2.3. 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 informed consent form 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, and which the Investigator considers to be related to study drug, must be reported to Rhythm or its designee.

12.2.4. 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 and periodic telephone calls made to the patients by the study staff. In the event a patient is withdrawn from treatment due to an AE, the patient should be encouraged to complete the final study/early termination visit in order to monitor the event to resolution and obtain additional protocol-defined safety assessments.

Depression or Suicidality

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

- A PHQ-9 score ≥ 10.
- Any suicidal behavior.
- Any suicidal ideation of type 4 or 5 on the C-SSRS.

A referral to an 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.

Any elevation in PHQ-9 or C-SSRS score should be evaluated to determine whether it meets the criteria for reporting as an AE.

13. DATA ANALYSIS/STATISTICAL PROCEDURES

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

13.1. Sample Size Estimation

The objective of this study is to demonstrate statistically significant and clinically meaningful weight loss in patients with various rare genetic forms of obesity after ~3 months of treatment. The primary endpoint is defined as the proportion of patients in each subgroup of RGDO who achieve at least 5% body weight reduction from baseline, at ~3 months treatment with setmelanotide. It is estimated that at least 5 patients with each rare genetic disorder of obesity will be recruited.

Given the rarity of this disorder, estimated power for expected weight change efficacy will not be provided, but efficacy will be only summarized.

13.2. Hypotheses

Setmelanotide leads to a clinically relevant reduction of percent body weight after ~3 months of treatment in each population of patients with rare genetic disorders of obesity (each population analyzed separately). No formal statistical hypothesis will be tested, given the exploratory nature of the study.

13.3. Definition of Population(s) for Analysis

This protocol includes a variety of very rare genetic obesity populations who are included in this protocol as a matter of administrative convenience (as each population is so rare, and this protocol anticipates very small numbers of patients in each population). Hence each population will be analyzed separately as ≥2 patients are enrolled and complete the ~3-month treatment period.

13.4. Statistical Methods

Statistical methods, populations, and approaches to missing data will be outlined in the SAP.

The primary endpoint is defined as the proportion of patients in each subgroup of RGDO who achieve at least 5% body weight reduction from baseline, at ~3 months of treatment with setmelanotide. Summary of the primary endpoints and the associated Clopper-Pearson confidence interval will be provided.

The comparison of post-treatment values versus baseline 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; weight change after 1 year of treatment in subjects who continue in the study past 3 months will also be analyzed without adjustment for multiplicity. In addition, no adjustment for multiplicity will be included for the many rare genetic obesity populations in this study as these different populations are included in this study only for administrative convenience. All the p-values and/or confidence intervals should be considered exploratory.

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, efforts will be made to keep all patients in the study, and 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 of setmelanotide will be summarized. Plasma concentrations may be compared to pharmacodynamic endpoints.

13.5. Timing of Analyses

It is planned that an analysis may be completed once ~2-3 patients in each genetic obesity population have completed ~3 months of treatment with setmelanotide, data have been cleaned and finalized, and the database is locked for assessments. Additional supplemental analyses will be conducted for patients who enter into long-term extensions.

13.6. Statistical Analysis Plan

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

14. ADMINISTRATIVE REQUIREMENTS

14.1. Good Clinical Practice

The study will be conducted in accordance with the International Council on Harmonisation (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.

14.2. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. 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.

14.3. 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 requirements.

14.4. 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.

14.5. 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 its 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.

14.6. Data Management

14.6.1. 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.

14.6.2. Computer Systems

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

14.6.3. Data Entry

Data must be recorded using the eCRF system while the study is in progress. All study site personnel must log into the system using their secure user names and passwords 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.

14.6.4. Medical Information Coding

For medical information the following thesauri will be used:

- MedDRA for AEs
- WHO Drug for concomitant medications

14.6.5. 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.

14.7. Direct Access to Source Data

Monitoring and auditing procedures developed or reviewed and approved by Rhythm will be followed, in order to comply with GCP guidelines.

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

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

All unused study drug and other study materials are to be returned to Rhythm after the clinical phase of the study has been completed (see Section 9.6).

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.

14.8. 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, AEs, 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.

14.9. 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.

14.10. 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.

14.11. Publication of Study Findings and Use of Information

All information regarding setmelanotide supplied by Rhythm to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Rhythm. It is understood that there is an obligation to provide Rhythm with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of setmelanotide and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

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

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16. APPENDICES

APPENDIX A. INJECTION SITE EVALUATIONS

Injection sites will be assessed using a form similar to that presented below at the time points outlined in the SOA (Table 3), and in the setting of any injection site reaction adverse experience.

Local Skin Tolerability Assessment

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

[a] If present, region will be measured, length and width as appropriate.

Initials: _____

APPENDIX B. FITZPATRICK CLASSIFICATION SCALE

Fitzpatrick Classification Scale

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

(Fitzpatrick, 1975)

[redacted]

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APPENDIX F. STANDARDIZATION OF BLOOD PRESSURE MEASUREMENT

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

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

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

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

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

f. Note the systolic pressure at the onset of at least two consecutive beats (Phase 1 Korotkoff sounds). Blood pressure levels should always be recorded in even numbers and read to the nearest 2 mm Hg mark on the manometer.
g. Record the diastolic pressure at the cessation of the Korotkoff sounds (Phase V). Listen for 10 to 20 mm Hg below the last sound heard to confirm disappearance, and then deflate the cuff rapidly and completely.

7. For automatic measurement:
   a. Take automatic measurements and record.
8. Record the patient's position and the arm used for the measurement.
9. Wait 2 minutes before repeating the pressure measurement in the same arm to permit the release of blood trapped in the arm veins.
10. Note that all three readings at each timepoint should be captured on the case report form, as well as the average.
11. 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>

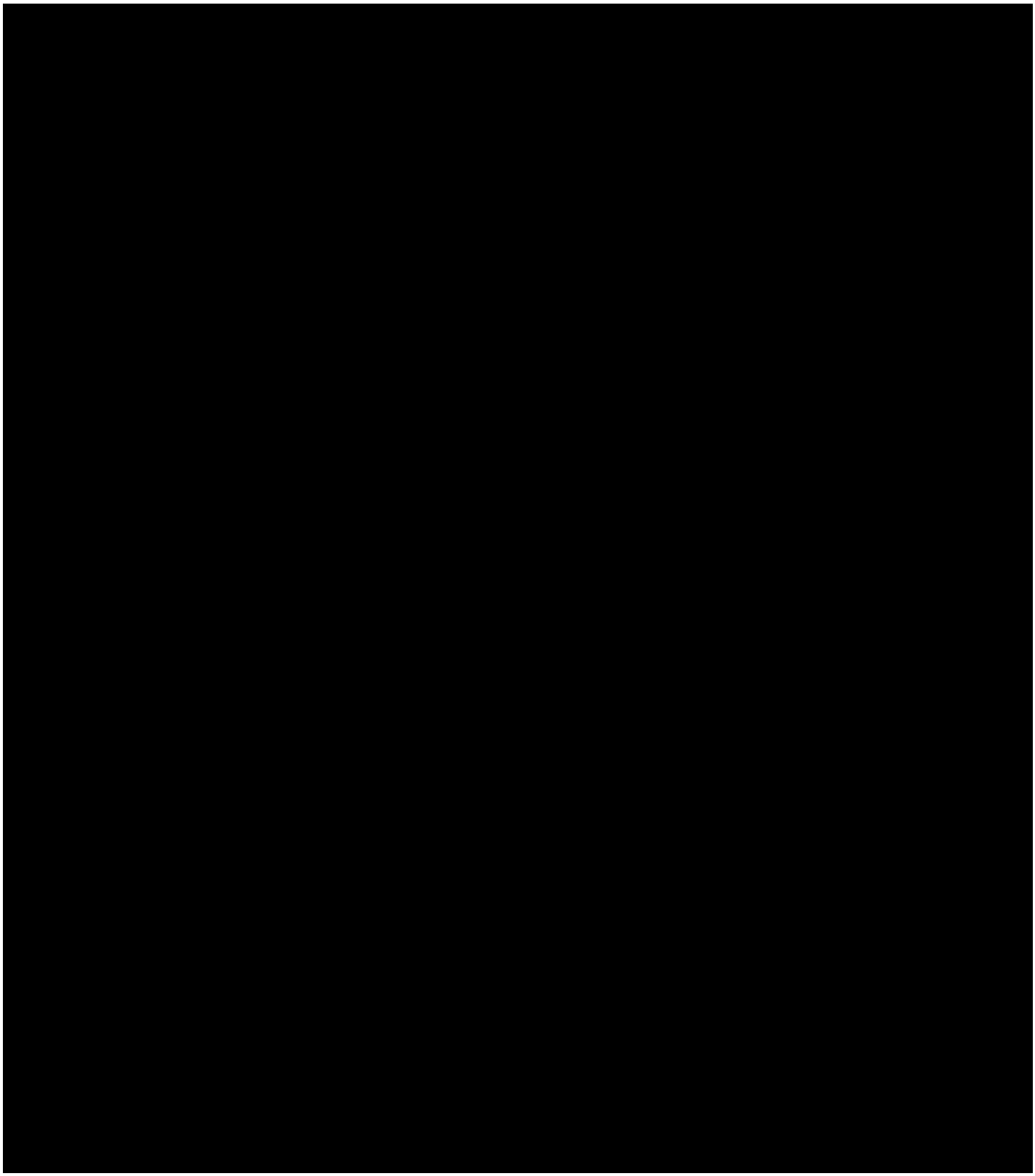
[MANUAL] In some subjects, particularly in patients with hypertension, the sounds heard over the brachial artery when the cuff pressure is high disappear as the pressure is reduced and then reappear at some lower level. This early, temporary disappearance of sound is called the auscultatory gap and occurs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

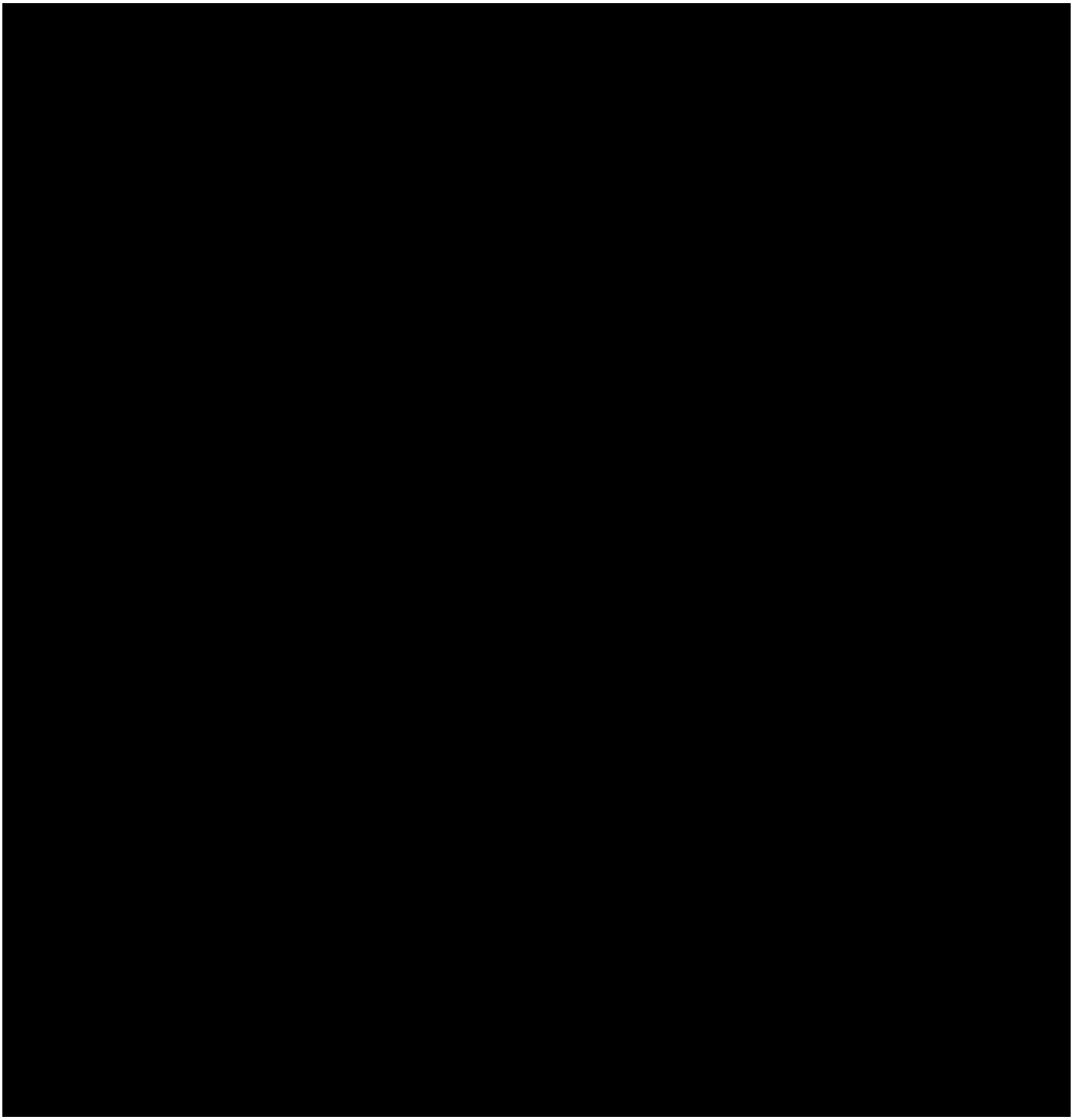
Effect of Arm Position

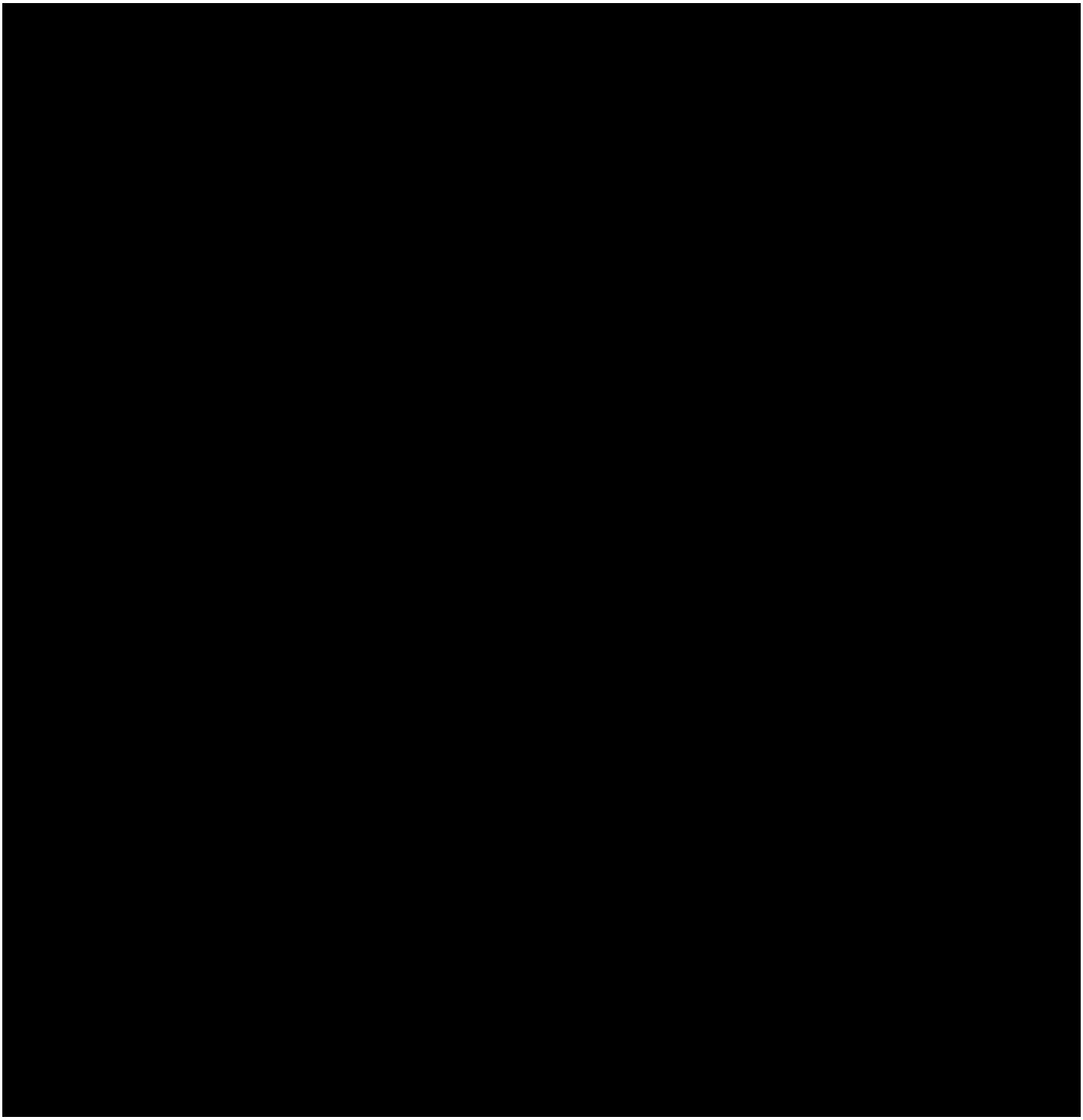
The pressure in the arm increases as the arm is lowered from the level of the (phlebostatic axis); conversely, raising the arm above this position lowers the pressure measurement. The effect is largely explained by hydrostatic pressure or by the effect of gravity on the column of blood. Therefore, when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

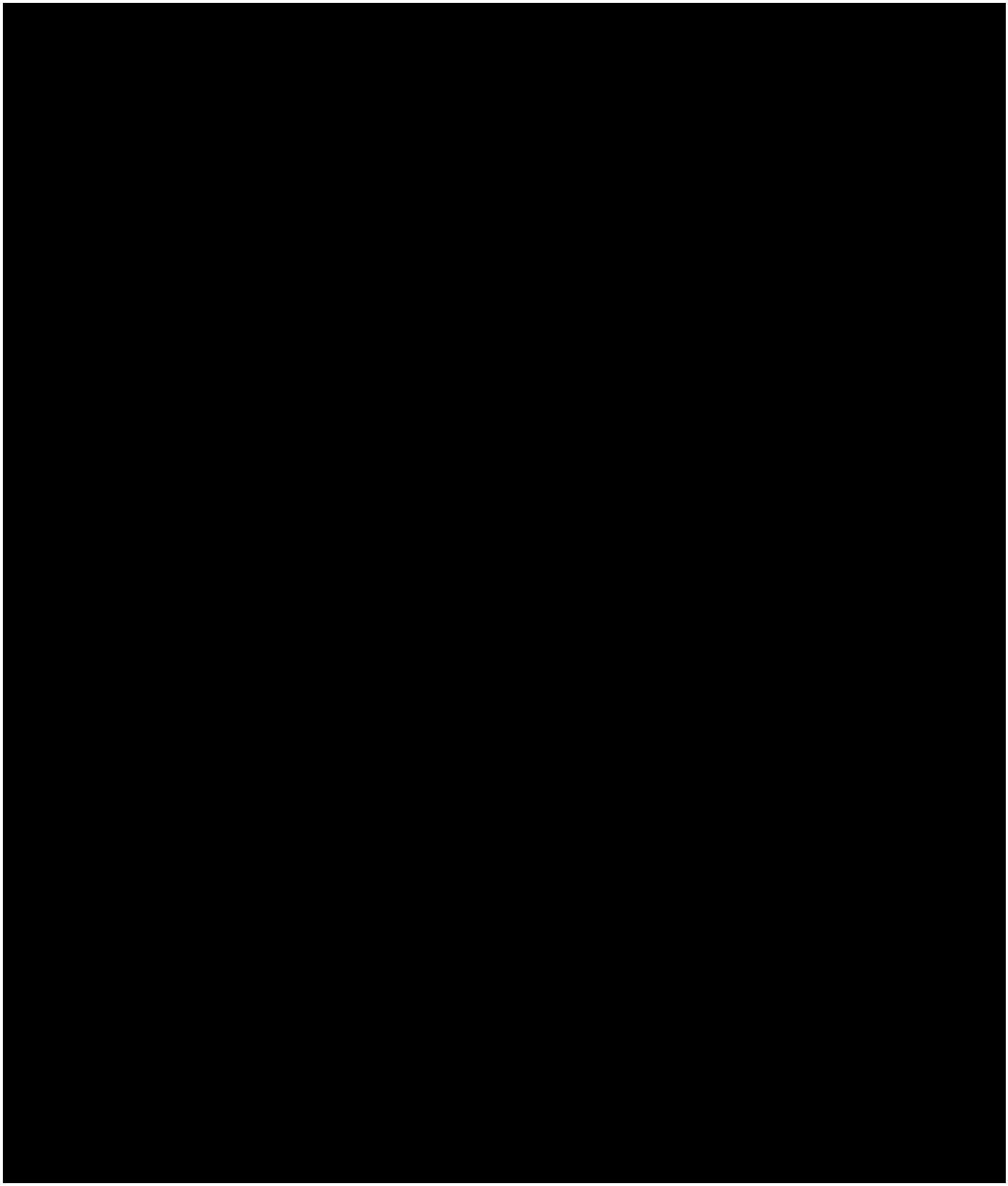
Large Arm Size

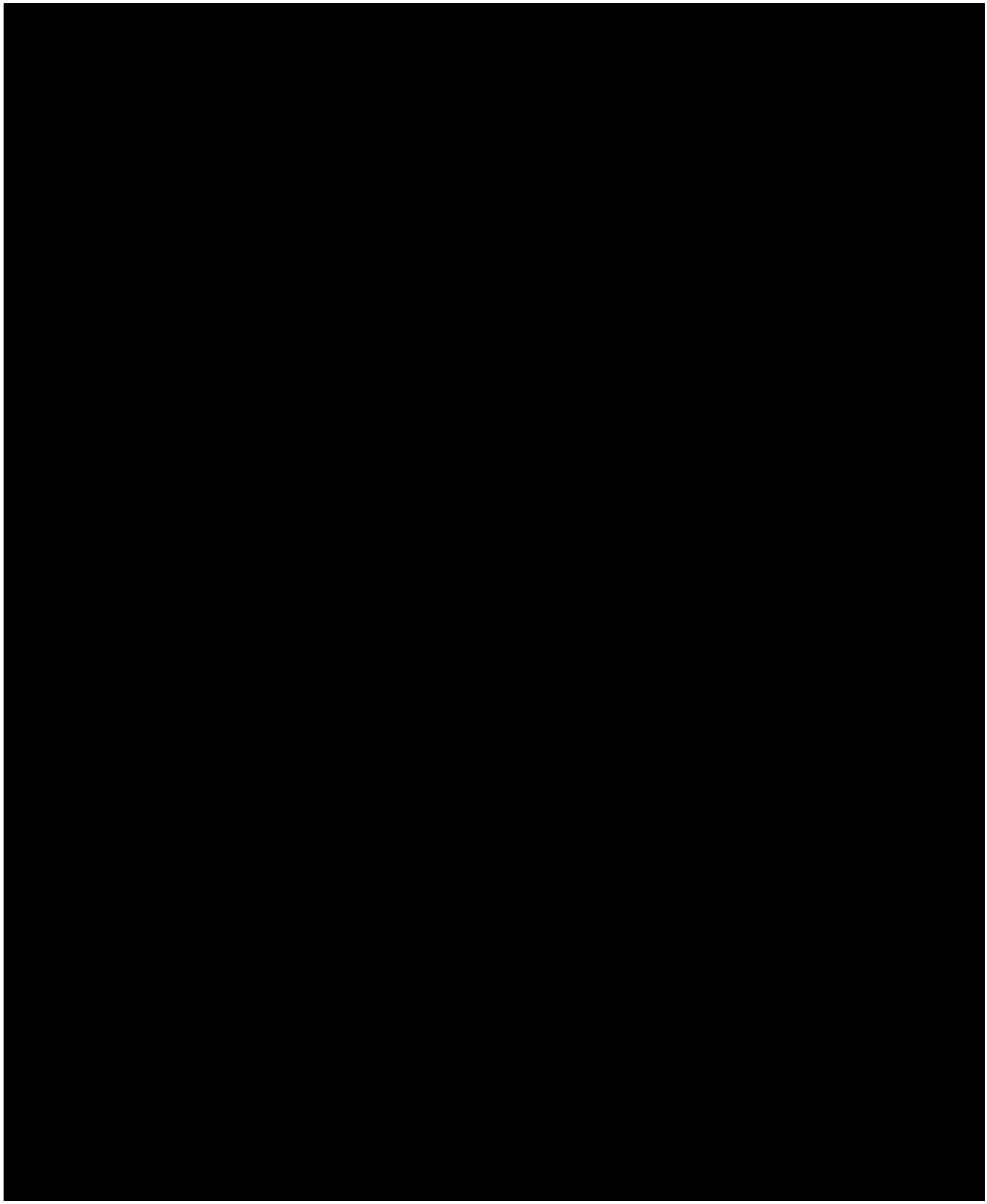
Falsely elevated indirect pressure measurements may be obtained in patients with increased arm girth if the standard-sized bladder and technique are used. This is caused by the use of bladders that are too small, with subsequent excessive loss of cuff pressure through the thick, compressible soft tissues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

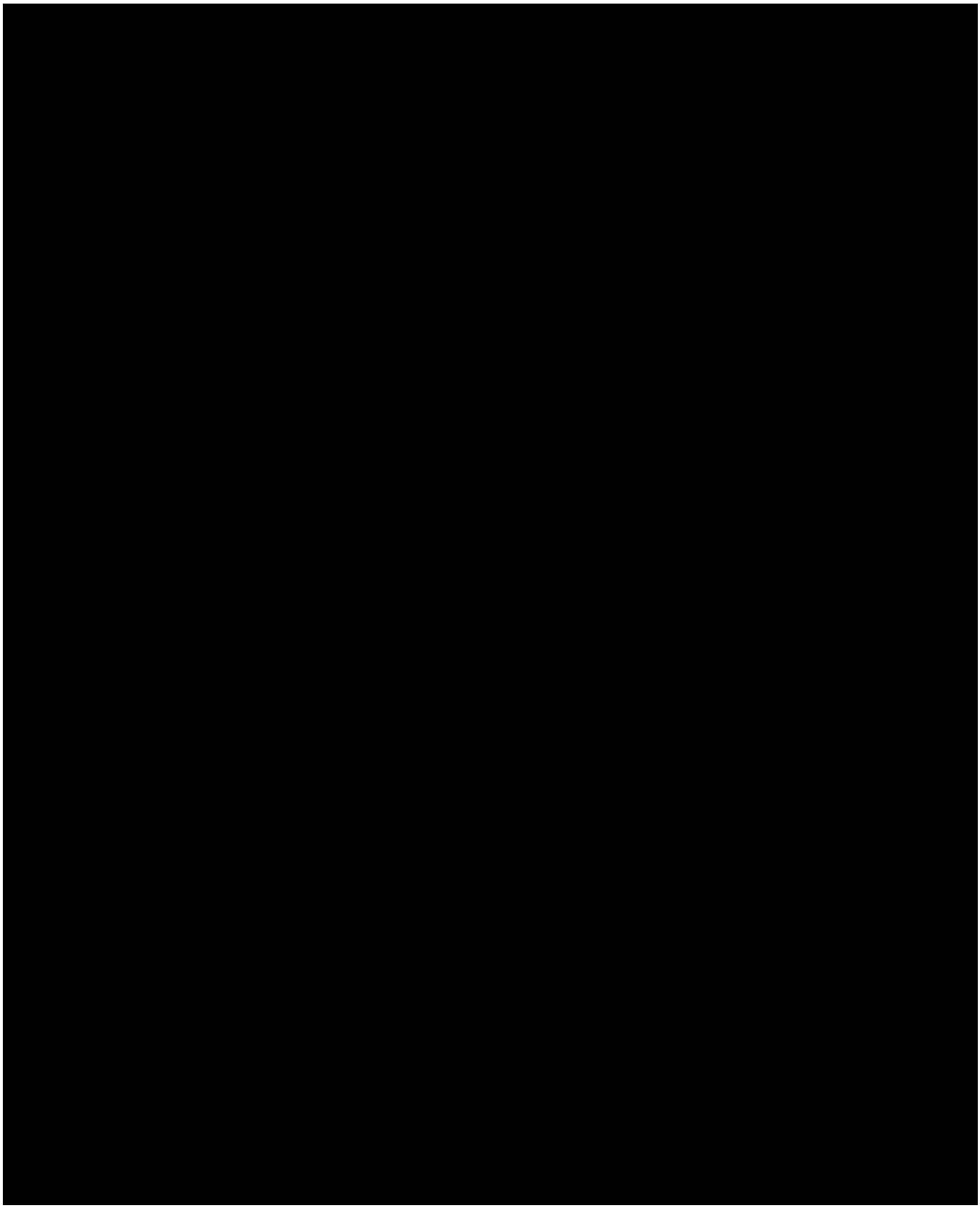












APPENDIX H. CREATININE CLEARANCE ESTIMATE

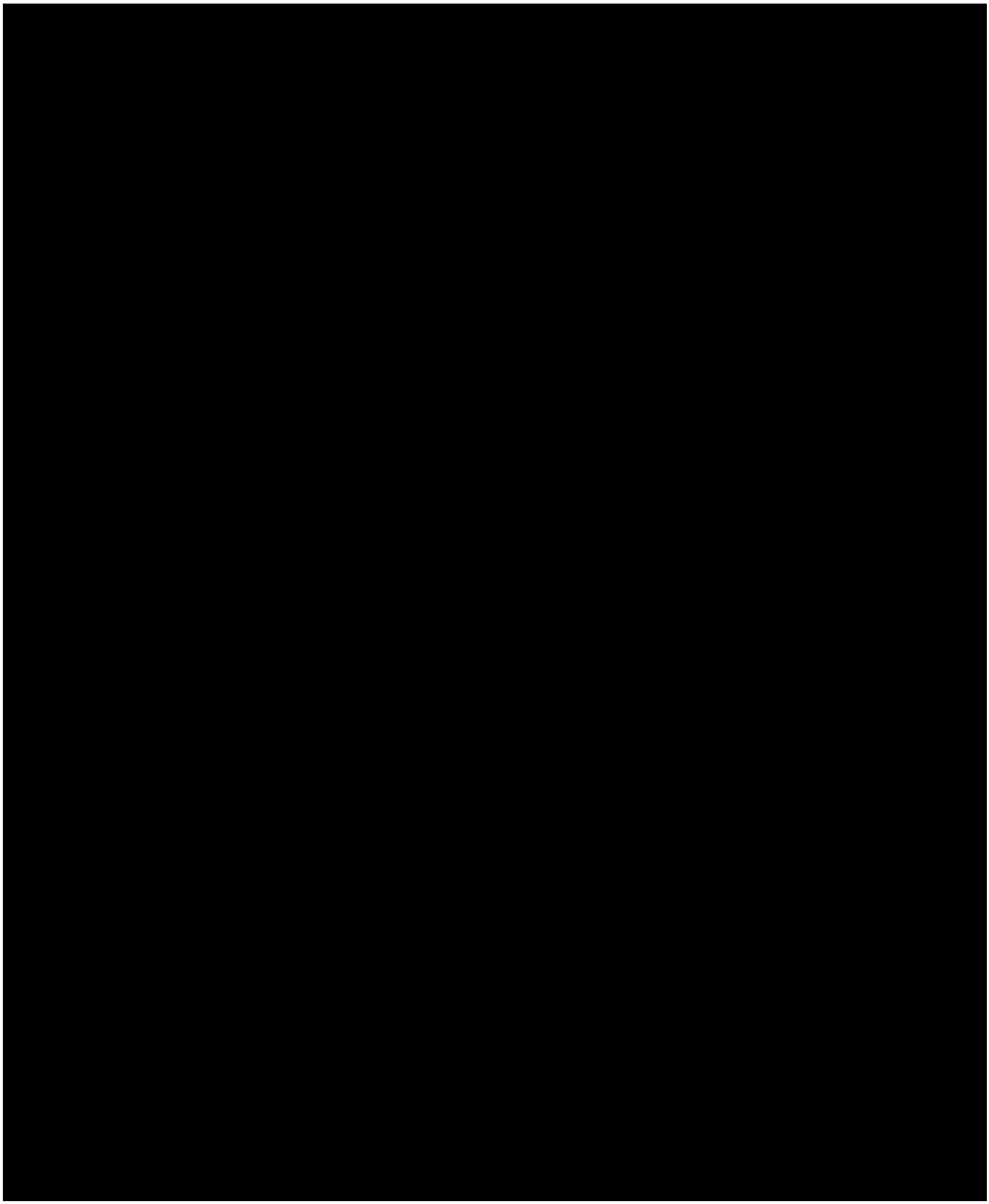
In patients ≥18 years of age, the Modification of Diet in Renal Disease Equation should be used as follows:

GFR = 175 x (creatinine in mg/dL)$^{-1.154}$ x (age in years)$^{-0.203}$ x (0.742 if female) x (1.210 if African American)

APPENDIX I. BEDSIDE SCHWARTZ EQUATION

In patients <18 years of age, the Bedside Schwartz Equation should be used as follows:

GFR (mL/min/1.73 m^2) = (0.41 × height in centimetres) / creatinine in mg/dL



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