CLINICAL STUDY PROTOCOL

Protocol RM-493-010

A Phase 2, Randomized, Double-Blind, Placebo-controlled Pilot Study to Assess the Effects of RM-493, a Melanocortin 4 Receptor (MC4R) Agonist, in Obese Subjects with Prader-Willi Syndrome (PWS) on Safety, Weight Reduction, and Food-Related Behaviors

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.

Study Sponsor: Rhythm Pharmaceuticals, Inc.
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Medical Monitor: [redacted]

Document Version (Date): [redacted]

CONFIDENTIALITY NOTE

APPROVAL SIGNATURE PAGE

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-controlled Pilot Study to Assess the Effects of RM-493, a Melanocortin 4 Receptor (MC4R) Agonist, in Obese Subjects with Prader-Willi Syndrome (PWS) on Safety, Weight Reduction, and Food-Related Behaviors

REVIEWED/APPROVED BY:

[redacted]

Signature

07Jan2016

Date

Rhythm Pharmaceuticals, Inc.

INVESTIGATOR STATEMENT [redacted]

I understand that all documentation provided to me by Rhythm Pharmaceuticals, Inc. 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, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board. No changes will be made to the study protocol without the prior written approval of Rhythm Pharmaceuticals, Inc. and the Institutional Review Board, except where necessary to eliminate an immediate hazard to the patient.

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

Investigator Name	Investigator Signature	Date

Investigational site or name of institution and location (printed)

CLINICAL STUDY SYNOPSIS

Sponsor	Rhythm Pharmaceuticals, Inc.
Investigational Drug Product	RM-493 (Melanocortin-4 Receptor Agonist)
Protocol Number	RM-493-010
Protocol Title	A Phase 2, Randomized, Double-Blind, Placebo-controlled Pilot Study to Assess the Effects of RM-493, a Melanocortin 4 Receptor (MC4R) Agonist, in Obese Subjects with Prader-Willi Syndrome (PWS) on Safety, Weight Reduction, and Food-Related Behaviors
Clinical Phase/Trial Type	Phase 2a/randomized, double-blind, placebo controlled, parallel-group, 4-week trea ment with a 2-week double-blind randomized withdrawal period
Treatment Indication	Obesity and other Signs and Symptoms of Prader-Willi Syndrome (BMI ≥27 kg/m)
Objective(s)	*Primary* After 4 weeks of double-blind study drug treatment: • To assess safety and tolerability of RM-493 • To assess the effect of RM-493 on weight loss • To assess the effect of RM-493 on hyperphagia-related behavior using the PWS Hyperphagia Questionnaire. *Secondary* • To evaluate changes in quality of life, other hyperphagia- and food-related behavior, and/or psychiatric status. • To evaluate the pharmacokinetics of RM-493 in Prader-Willi patients (substudy). • To assess the effect of RM-493 during a 2-week, double-blind, randomized withdrawal period. • To assess the percent change in body mass by DEXA in the active treatment group compared to the placebo group. • To assess the percent change in fat content by DEXA in the active treatment group compared to the placebo group. *Exploratory* [redacted]

	[redacted]
Trial Design	This will be a randomized, double-blind, placebo-controlled, parallel group study. It will consist of 4 sequential periods: (1) a 2-week single-blind placebo-controlled baseline period; (2) a 4-week, double blind, placebo-controlled, randomized parallel group period (primary analysis timepoint) where patients will be randomized 2:1:3 to placebo or one of two dose levels of RM-493; and (3) a 2-week, double-blind, randomized withdrawal period where half of each RM-493 group will remain on the same dose of active drug and the other half will receive placebo, and half of the placebo group will receive RM-493. In addition, there will be an optional 2-week open label extension period where every patient can participate and receive open label RM-493. In the first half of the study, approximately 20 subjects will be randomized to a placebo arm or one of 2 dosing arms with a 2:1:3 assortment between placebo, 0.5 mg of RM-493, and 1.5 mg RM-493. Subjects will initiate with 2 weeks of single-blind placebo lead-in phase (period 1) after which they will be randomized 2:1:3 to receive daily SC doses of RM-493 or placebo for 4 weeks. Based on the results of the interim analysis, in the second half of the study, for approximately 16 subjects, active doses will be increased to 1.5 mg of RM-493 and 2.5 mg of RM-493 with matching placebo. After completion of the primary 4-week, double-blind treatment (period 2), a double-blind, randomized placebo withdrawal (period 3) will initiate: patients within each of the RM-493 groups will be randomized 1:1 to either continue with the same dose or begin placebo treatment with the same dose volume (i.e., of those in the RM-493 active groups, half of each arm would receive placebo and half would continue on the same dose for an additional 2-weeks). The patients in the placebo group during the 4 week primary treatment period would also be randomized 1:1 to continue on placebo or to

	receive RM-493 at the corresponding dose/volume established during periods 1 and 2 during the randomized withdrawal phase (period 3). A follow-up open label extension phase of the trial (after the initial 4 weeks of study duration and the 2-weeks of randomized withdrawal) will be available for patients who completed the trial and wish to continue in the 2-week open label extension (period 4). The active doses to be studied in the trial are RM-493 1.5 mg and RM-493 0.5 mg QD (administered in the morning) by SC injection in the first half of the study, and 2.5 mg and 1.5 mg in the second half. Pre-dose RM-493 concentrations will be measured in all subjects on Day 42 and Day 70. In addition, a substudy of up to ~N=8 patients may participate in a pharmacokinetic substudy. Patients who participate in this substudy will have multiple blood samples collected over ~12 hours in the clinic (during the optional open-label, active dose 2-week extension period), and return th next day ~24 hours after dosing for one additional bl od sample collection.
Study Population	Obese males and females with confirmed diagnosis of PWS, due to chromosome 15 micro-deletion, maternal uniparental disomy, or imprinting defect, and a Body Mass Index (BMI) greater than or equal to 27 kg/m^2 who are able to have study medication administered by a health care professional or trained caretaker. Subjects with type 2 diabetes (HbA1c <7.5.0%) will be allowed to enter the study.
Number of Patients & Study Centers	Number of patients to be targeted: approximately 36 Study Center: Up to 8
Inclusion Criteria	1. PWS due to chromosome 15 micro-deletion, maternal uniparental disomy, or imprinting defect, confirmed by fluorescent in situ hybridization, chromosomal microarray, and/or methylation studies. Obese male or female volunteers weighing at least 50 kg with BMI ≥27 kg/m^2. 2. Age 16-65 years. 3. If a volunteer has diagnosis of type 2 diabetes, following criteria must be met: a. HbA1c <7.5% not being managed with insulin. Patients taking GLP-1 analogues (exenatide or liraglutide) must have been on stable dose for greater than 3 months. b. Fasting plasma glucose <140 mg/dL

c. No history of ketoacidosis or hyperosmolar coma

4. Vital signs must be within the following ranges and stable:
   a. Systolic blood pressure, 90-150 mm Hg
   b. Diastolic blood pressure, 50-90 mm Hg
   c. Pulse rate, 40-100 bpm
5. Stable body weight at home for ~2 months (self or guardian-reported loss/gain within ± 5%).
6. Blood pressure (≤150/90 mmHg); may include stable dose (≥ 30 days of use) of up to two anti-hypertensive medications that are intended to remain on a stable dose during the protocol.
7. Parent or guardian is able to communicate well with the investigator, to understand and comply with the requirements of the study, and be able to understand and sign the written informed consent. Due to the significant intellectual disability with PWS, assent is to be provided by the patient who cannot consent for himself or herself.
8. Results of screening clinical laboratory tests (CBC with differential and platelets and chemistry profile) must be within normal range or, if outside of the normal range, must be accepted by the investigator and sponsor as not clinically significant.
9. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months (and confirmed with a screening FSH level in the post-menopausal lab range), do not require contraception during the study. All other females of child-bearing potential must agree to use contraception as outlined in the protocol.
10. Males with female partners of childbearing potential must agree to a double barrier method if they become sexually active during the study and for 90 days following the study. Male subjects must not donate sperm for 90 days following their participation in the study.

Patients must be on a stable dose of any allowed chronic concomitant medications while participating in the study, as described in protocol. This is defined as no changes in medication for at least 60 days prior to Day 1 and no changes in dose for at least 30 days prior to Day 1; Note that stable concomitant usage (>3 months) of growth hormone, hormone replacement therapy, GLP-1 agents, statins, or other medications (excluding insulin, modafinil, anti-psychotics), and other medications commonly used in PWS patients are allowed (See Section 6.4.5 on Concomitant medications).

Exclusion Criteria	1. Recent use (within 3 month) of weight loss agents including herbal medication. 2. Diagnosis of schizophrenia, bipolar disorder, personality disorder or other DSM-III disorders which the investigator believes will interfere significantly with study compliance. 3. A PHQ-9 score of ≥15. 4. Any suicidal ideation of type 4 or 5 on the C-SSRS. 5. Clinically significant illness in the 8 weeks before screening. 6. History of clinically significant bleeding disorders. 7. Current, clinically significant liver, renal, pulmonary, cardiac, oncologic, or GI disease. 8. Diagnosis of type 1 diabetes mellitus or other active endocrine disorders (e.g., Cushing syndrome, or thyroid dysfunction except if on adequate thyroid or glucocorticoid replacement supplement). 9. Cardiovascular disease vent including history of CHF, coronary artery disease, MI, second degree or greater heart block or prolonged QT syndrome. 10. Blood pressure >150/90 mmHG. 11. Liver diseas or liver injury as indicated by abnormal liver function tests, SGOT (AST), alkaline phosphatase, or serum bilirubin (> 1.5 x ULN for any of these tests) or history of hepatic cirrhosis. 12. History or presence of impaired renal function as indicated by clinically significantly abnormal creatinine, BUN, or urinary constituents (e.g., albuminuria) or moderate to severe renal dysfunction as defined by the Cockroft Gault equation (< 50 mL/min). 13. History or close family history (parents or siblings) of melanoma. 14. Oculocutaneous albinism (occurs at ~1% in PWS). 15. Significant dermatologic findings as part of the Screening comprehensive skin evaluation performed by the dermatologist. Any concerning lesions identified during the screening period will be biopsied and results known to be benign prior to randomization. If the pre-treatment biopsy results are of concern, the patient will be excluded from the study. 16. Significant history of abuse of drugs or solvents in the year before screening or a positive Drugs of Abuse (DOA) test at screening. 17. History of alcohol abuse in the past year before screening or currently drinks in excess of 21 units per week (3 servings or units/day).

	18. Caffeine consumption exceeding 6 cups of caffeinated tea/coffee (or equivalent) per day. 19. Volunteer is, in the opinion of the Investigator, not suitable to participate in the study. 20. Participation in any clinical study with an investigational drug/device within 3 months prior to the first day of dosing. 21. Positive history for human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C tests or tuberculosis. 22. Serious adverse reaction or significant hypersensitivity to any drug. 23. Clinically significant blood loss or blood donation > 500 mL within 3 month. 24. Inadequate venous access. 25. History of low blood counts or recurring infections.
Synopsis of Study Activities	After an initial screening and confirmation of eligibility, volunteers will enter a two-week single-blind placebo run-in period. Those who are compliant in study drug administration and have demonstrated willingness to complete study procedures (weighing, questionnaire and diary completion) will be randomized to receive subcutaneous doses of RM 493 or placebo for 4 weeks of double-blind treatment (primary efficacy timepoint), followed by a 2-week double-blind randomized withdrawal period. Patients who comp ete will then be eligible for an optional open label exte sion treatment for 2 weeks. Overall, including the run-in the duration of study drug administration may be up to 10-weeks duration. Evaluations will occur at the following times indicated as Study Day numbers: Baseline (one visit between Day -30 and Day -1 in the screening period), at the onset of single blind treatment (Day 1), at the end of the single-blind placebo/onset of double blind treatment randomization (Day 15), after 2 weeks of randomized treatment (Day 28), primary evaluations at the end of double-blind study treatment (Day 42), secondary evaluations at the end of the randomized withdrawal period (Day 56), and at the end of the optional open label active drug extension (Day 70). At the visits, subjects will undergo safety and efficacy assessments (including but not limited to weight, vitals, 12-lead ECG, DEXA, [redacted] physical exam, food and behavior questionnaires/diaries and blood sampling for safety [redacted] evaluations.

	Participants will not be counseled on food intake or exercise, but will demonstrate an approximately stable diet at randomization by showing stable weight at home for the past two months (± 5%). All subjects also will be followed for approximately 1-3 months after last dose and undergo study termination procedures at the post-study follow up visit (Days 90-163), which may be at next scheduled routine clinic visit if within this timeframe.

Study Visits	Study participation will involve:
	
	• Screening: 1 visit (up to 30 days)
	• Treatment: 5 visits
	  ○ 4 "full" outpatien visits involving safety and efficacy assessments and lab sample collection
	  ○ 1 interim visit that may be conducted in clinic or via phone, however it is recommended that this visit be conducted in the clinic
	  ○ All subjects – pre-dose blood sample for PK collected on Days 42 and 70
	  ○ PK subset subjects only – one day (during the second week of the optional open-label active dose extension period) involving serial PK sample collection up to 12 hours with an additional sample ~24 hours post dose
	• Follow-Up: 1 visit (at next routine clinic visit if within 1-3 months after end of treatment)
	• Open label extension: 1 visit at the end of the optional open label active drug extension.
	
	Potential Total = as few as 5 or up to 8 clinic visits (duration up to 4 weeks of screening and up to 10 weeks of study drug administration, including 2 weeks of single-blind placebo run-in treatment) including screening and optional extension,
	
	See Schedule of Assessments for a detailed list of study procedures at each visit.

Study Drug and Administration	RM-493 drug product will be a sterile solution for injection. The product will be manufactured at a concentration of 10.0 mg/mL, filled with ≥0.5 mL/vial. Matching placebo will be vehicle. Both RM-493 and placebo are supplied as single-use vials, that must be stored under refrigerated conditions (2°C to 8°C), and may only be punctured *once* using aseptic technique. RM-493 and placebo will be administered as a subcutaneous (SC) injection using a ~0.5 mL insulin syringe. In the first half of the study, a total daily dose of 0.5 mg (50 microliters

	or 5 units in an insulin syringe) or 1.5 mg (150 microliters or 15 units in an insulin syringe) of RM-493, or equivalent volume of placebo, will be self-administered or administered by a caretaker once daily (in the morning) via SC injection during the treatment period. In the second half of the study, total daily dose of 1.5 mg (150 microliters or 15 units in an insulin syringe) or 2.5 mg (250 microliters or 25 units in an insulin syringe) of RM-493, or equivalent volume of placebo, will be self-administered or administered by a caretaker once daily (in the morning) via SC injection during the treatment period. Specific instructions regarding the volume to administer will begin during the initial single-blind phase (period) and continue through period 2 and 3 at the same dose/volume as established in the initial single-blind placebo run-in period. All subjects in the optional, open-label, active RM-493 treatment phase (period 4) will receive 2.5 mg (250 mcl) of RM-493. SC administration will be allowed in the abdomen, thighs, and buttocks. Caretakers and patients (as needed) will be given sp cific training in study drug administration, and will practice and show competence during the screening period before patients can enter the placebo-controlled run-in period. Since the volume of administration is different for the different doses of RM-493, placebo patients will be allocated to matching placebo at matching volumes to maintain the blinded nature of the study throughout all study periods except for the final open-label active period. All subjects in this final open-label, active treatment phase (period 4) will re eive 2.5 mg (250 mcl) of RM-493. The allocation schedule will be so constructed to account for this study design feature. Note also that every subject will receive single-blind placebo during the 2-week placebo run-in period. Also note that patients will receive kits for weekly dosing. At the end of the 4-week double-blind treatment period, half of the RM-493 active patients will be randomized to a placebo withdrawal in a double-blinded fashion, and receive kits for placebo or RM-493 to maintain the blind.
Evaluation Criteria	Body weight change from baseline (as a percentage of baseline total body weight (primary endpoint) and as kg of weight loss and percent change in body mass and fat content by DEXA (secondary endpoints)) over the 4-week double-blind dosing period will be evaluated to document RM-493's effect on obesity in PWS. In addition, the effect of the randomized withdrawal on weight will be explored. It is expected that subjects will be weight stable or experience a

minimal-modest level of weight gain during the 2 week placebo lead-in period. With initiation of double-blind 4-week RM-493/placebo treatment phase, body weight changes (reduction, lack of gain, or reduced rate of gain) will be assessed as the primary efficacy endpoint.

The safety and tolerability of RM-493 by SC injection will be assessed by comparing the frequency and severity of adverse events as well as changes in physical examinations, ECGs, [redacted] vital signs, laboratory evaluations and injection site reactions (see Appendix).

PWS Hyperphagia Questionnaire (Dykens, 2014) will be the primary hyperphagia-related behavior endpoint of the study, evaluated at both the end of the 4-week double-blind treatment phase, at the end of the 2-week randomized double-blind withdrawal phase and again at the end of the optional open label extension [redacted]

Other quality of life or behavioral measurements may also be evaluated including the Food Related Problem Questionnaire, (Russell, 2003), [redacted] and the Symptom and Global Assessments. Daily jo nal to quantify aberrant behavior and/or Rate of Eating measurement will also be used.

[redacted]

Assessment of basal metabolic rate (via VO_2 consumption) will also be measured.

Changes in symptom scores for loss of appetite will be assessed over the duration compared to placebo. All safety/tolerability and symptom scores will be compared across dose levels and with placebo lead-in phase of the study.

The plasma PK of RM-493 will be assessed in all subjects by a trough (pre-dose) concentration after 4 weeks of double-blind treatment (Day 42) and on Day 70. In a subset of subjects, PK will be assessed by a 24-hour profile after at least 1 week of open-label treatment (RM-493 2.5 mg QD only). From the 24-hour profile, noncompartmental methods

	will be used to determine PK parameters including C_{max}, T_{max}, AUC_{24hour}, volume of distribution (Vd), and total clearance (CL). Additionally, while no issues have been raised in previous studies with RM-493, [redacted] will be monitored. Guidance is provided for any worsening of [redacted] during the study. In addition, specific guidelines for dermatological events, liver function abnormalities, and penile erections are provided in the Appendix. At all times, this guidance is subject to the clinical judgment of the Investigator and study consultants (if applicable).
Power Statement	Prior data from the 4 week Phase 1b treatment arms of Study RM-493-002 (MAD study) yielded the following summary statistics for mean change from baseline after 4 weeks: Pooled SD for Placebo: SD=1.1, N=12 Pooled SD for RM-493: 2.3, N=18 Assuming SD=1 1 for placebo and SD=2.3 for RM-493, if the true mean difference in 1-month weight loss between treatments is 2.5 kg in this study (N=12 placebo and N=12 RM-493) th re would be 94% power to yield a statistically significant (alpha=0.05, 1-sided) difference between treatments (83% power if true difference is 2 kg). The minimum observed difference in mean weight loss after 4 weeks of treatment, between RM-493 and placebo that would be statistically significant is 1.3 kg.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ABPM	Ambulatory Blood Pressure Measurement
ACTH	Adrenocorticotropic Hormone
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the curve
BMI	Body mass index
BPM	Beats per minute
BUN	Blood urea nitrogen
C_{max}	Peak observed concentration
C_{min}	Minimum observed concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRF	Case report form
CSC	Clinical Safety Committee
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular disease
DEXA	Dual-energy x-ray absorptiometry
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
FSH	Follicle Stimulating Hormone
GCP	Good clinical practice
GGT	Gamma-glutamyltranspeptidase
Hg	Mercury
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IRB	Institutional Review Board

Abbreviation	Definition
LDH	Lactate dehydrogenase
MAD	Multiple ascending dose
MC1R	Melanocortin Receptor type 1
MC3R	Melanocortin Receptor type 3
MC4R	Melanocortin Receptor type 4
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No observed adverse effects level
PD	Pharmacodynamic
PK	Pharmacokinetic
POMC	Pro-opiomelanocortin
PWS	Prader-Willi Syndrome
[redacted]	
SAD	Single ascending dose
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SOA	Schedule of assessments
T_{max}	Time to observed maximum concentration
US	United States

1. INTRODUCTION

1.1. Obesity

Obesity, defined as a body mass index (BMI) ≥30 Kg/m^2, is associated with significant co-morbidities and mortality. The World Health Organization has stratified patients into different classes of obesity; Class I BMI 30.0-34.9 Kg/m^2, Class II BMI 35-39.9 Kg/m^2 and Class III ≥ 40 Kg/m^2. Obesity and overweight, defined as a BMI ≥25 Kg/m^2, are the primary causes of Type 2 diabetes mellitus, with up to 80% of type 2 diabetes estimated to be attributable to the combined effects of inactivity and obesity/overweight.[1] Obesity, in particular, is attributed as the cause of death in >300,000 persons in the United States (US) and in 2.8 million persons worldwide, making it the 5th leading global risk for death, and shortens life-span by ~7 years in women and 6 years in men. Notably, obesity is also a significant risk factor for cardiovascular disease (CVD), with obese persons being 2 to 3 × more likely to develop CVD than those who are of normal weight.[1] Overall, 20 to 30% of CVD mortality is estimated to be attributable to overweight.[1] Other significant health conditions associated with overweight and obesity include cancers, hypertension, dyslipidemia, sleep apnea, polycystic ovary syndrome, infertility, osteoarthritis, and cerebrovascular, gallbladder, and liver disease.[1,2, 3] Obesity is also associated with physical impairment, with the level of impairment increasing with the level of obesity, and psychological issues such as anxiety and depression.[4]

Obesity and diabetes are successfully treated by weight loss, with weight loss, in turn, associated with improvement in other obesity-related co-morbidities, including resolution of hypertension, hyperlipidemia, and sleep apnea.[5] In order to achieve weight loss goals, lifestyle and behavioral modifications (e.g., diet and exercise) are first recommended. Gastric bypass surgery is considered the only effective long-term therapy currently available, with an associated mean weight loss of 20 to 40 Kg (44 to 88 lbs) and a reduction in BMI of up to 24 Kg/m^2.[6, 7] However, bariatric surgery may be considered only for severely obese (Class III obesity) patients with a BMI ≥ 40 Kg/ m^2, or patients with a BMI ≥ 35 Kg/ m^2 (Class II obesity) with at least 1 severe co-morbidity, who meet strict eligibility criteria.[6]

Developing new, more effective therapies for obesity is challenging, as feeding represents a complex, physiologic function necessary for survival, with many redundant stimulatory pathways. Furthermore, as treatment for obesity is intended for longer-term or chronic administration, the safety of such treatment is paramount. Additionally, providing a non-surgical therapy for those with Class II or III obesity would provide a high unmet medical need.

1.2. Introduction to Prader-Willi

Prader-Willi syndrome (PWS) is a complex, multisystem genetic disorder characterized by multiple endocrine, neurological and behavioral abnormalities (Cassidy 2012). A defining feature of PWS is childhood-onset hyperphagia and obesity, with an insatiable appetite that persists through adulthood. PWS results from the lack of expression of several paternally inherited genes in a ~2 Mb region on chromosome 15 (15q11.2-13). Loss of the expressed sequences in PWS can occur by one of three genetic mechanisms: microdeletion of the paternal chromosome (~ 70% of cases), maternal uniparental disomy (~30% of cases), or an imprinting defect (1-3% of cases). The PWS imprinted region encodes several paternally-expressed polypeptides, long noncoding RNAs, numerous small nucleolar RNA (snoRNAs) and antisense

transcripts. The exact function of each of these genes is currently under investigation. No single gene mutation has been found that explain all of the PWS clinical features, but MAGEL2 gene (Schaaf et al., 2013) and SNORD116@ snoRNAs (Cassidy et al., 2012) appear to be dominant contributors to the PWS phenotype.

Symptoms associated with PWS are believed to result, in part, from a defect in hypothalamic function. PWS progresses from hypotonia, poor feeding and failure to thrive in infancy (Phase 1a) through recognizable nutritional phases, and onto the onset of hyperphagia and lack of satiety (Phase 3) sometime during mid-childhood (Miller et al 2011). Morbid obesity ensues without fail if the environment is not strictly controlled at all times, and PWS is recognized as the most common genetic cause of life-threatening obesity in children. Adolescents and adults with PWS typically exhibit insatiable appetite, hypoactivity, and food seeking behaviors. Often, there is a constant preoccupation with food accompanied by a physiological drive to eat so powerful that most individuals with PWS will go to great lengths to eat large quantities of food, even if it is spoiled, indigestible, or unpalatable to others.

The underlying pathophysiological basis of the PWS phenotype remains unclear. Current therapies for PWS show limited efficacy and are directed to various symptoms associated with the disease process. Growth hormone (GH) deficiency is present in almost all children, and many adults, with PWS, and GH replacement therapy is effective in increasing height, improving body composition, increasing bone mineral density and favorably impacting development and behavior. However, it does not affect hyperphagia. To date, no medication has proven effective in regulating appetite in PWS. Bariatric surgery is not accompanied by a decrease in appetite that occurs in typical individuals and is contraindicated in this population (Scheimann 2008). Other medications evaluated to date in PWS have proven ineffective (Zipf 1990, Tan 2004) or have been associated with unacceptable side effects (Motaghedi 2011).

Adult PWS patients require strict environmental control and constant supervision to prevent life-threatening overeating and extreme obesity. Without supervision, individuals with PWS will die prematurely as a result choking (especially during episodes of voracious eating), stomach rupture or tissue necrosis, or from complications caused by morbid obesity (Stevenson a, b). The need for continuous supervision in all settings greatly impacts quality of life and can be a significant burden to families. The inability to control food intake is often the biggest obstacle keeping those with PWS from living independently, participating in normal social events and working in unrestricted settings.

1.2.1. Rationale for Use of an MC4R Agonist in Prader-Willi Syndrome

1.2.1.1. Hypothalamic deficiencies in Prader-Willi Syndrome

Prader-Willi syndrome phenotype includes, hyperphagia, hypogonadism, and hyperghrelinemia (Purtell, 2011). Developmental hypothalamic deficiencies in PWS can explain some of these traits and anatomic deficiencies include, a reduced number of oxytocin neurons (Swaab et al., 1995; Atasoy et al., 2012), abnormal GnRH, LHRH neurons and reduced GHRH and GH. In addition, adjusted plasma BDNF in PWS is lower than in Obese Controls (Han et al., 2010). Importantly, NPY, AGRP and POMC neuronal anatomy appear normal in the post-mortem PWS brain, while levels of the stomach derived orexigen ghrelin are high, potentially explaining food seeking behavior in PWS, through activation of hypothalamic NPY and AGRP pathways. The apparently normally expressed pro-orexigenic NPY and AGRP pathways in PWS patients can

potentially be controlled by activation of the MC4R, thus controlling appetite and improving metabolism in PWS patients (see next sections).

1.2.2. Justification for the proposal to treat Prader-Willi syndrome with an MC4R agonist:

Preclinical models have shown that Ghrelin upregulates hypothalamic NPY and AgRP expression (Martins, 2012). In the absence of NPY and AgRP, in NPY -/-; AgRP -/- (double KO) mice, ghrelin fails to elicit responses for appetite and metabolism (Chen et al., 2004), indicating that it is likely that the orexigenic action of ghrelin is mediated through these two neuropeptides. In turn, the orexigenic effects of NPY/AgRP can be fully overcome by anorexigenic MC4R agonists with a possible contribution from MC3R activation (Murhpy et al., 1998). In line with this finding ghrelin is without efficacy in MC3R -/-; MC4R -/- (double KO) mice (Chen et al., 2004). POMC neurons express the natural ligands, α- and β-MSH that can activate the downstream MC3R and MC4R, with the MC4R being the dominant driver of appetite and metabolism.

Recent rodent data indicates that POMC neurons in Magel2 KO mice are defective in that they fail to respond normally to the effects of the anorexigenic peptide leptin. As leptin levels are normal in PWS a deficiency in POMC neurons may explain how ghrelin's orexigenic effects, through NPY and AgRP remains unopposed by leptin's anorexigenic signals, mediated through the melanocortins. In line with this proposal, Magel2 KO mice are hypersensitive to the action of exogeneously administered MT-II, an MC3R/MC4R agonist (Mercer et al., 2013), which acts just downstream of POMC neurons. This finding provides a rational for testing an MC4R agonist in PWS patients. Brain-derived neurotrophic factor (BDNF) functions downstream of the leptin-melanocortin signaling pathway to control energy balance. MC4R agonism may therefore also modulate BDNF levels in PWS and this in turn control aspects of metabolism and appetite (Xu et al., 2003; Caruso et al., 2012). AgRP can also inhibit oxytocin neurons. While oxytocin neurons can promote appetite control, they are also critical in social behavior and are argued to be abnormally regulated in autism spectrum disorder. MC4R agonism may therefore also contribute to treatment of autism spectrum behaviors in PWS patients, by increasing MC4R agonist tone on remaining oxytocin neurons (Sabatier 2013).

In summary, MC4R agonism may overcome the orexigenic effects of NPY and AgRP. Given the proposed deficiency in POMC mediated leptin signaling in PWS, it is conceivable that MC4R agonism can be used to control appetite and possibly improve on behavioral symptoms of PWS patients, through the activation of a diverse set of downstream mediators. The synthetic MC4R agonist RM-493, a first in class cardio-vascularly safe and efficacious MC4R agonist is potent at activating the MC4R and has moderate MC3R agonist activity. RM-493 is therefore ideally positioned to evaluate potential clinical benefits of MC4R agonism, in the treatment of PWS patients.

1.3. RM-493

1.3.1. Background

The melanocortins (MCs) are a family of peptide hormones, including adrenocorticotropic hormone (ACTH), α-melanocyte-stimulating hormone (MSH), β-MSH, and γ-MSH that are derived from a common precursor, proopiomelanocortin (POMC). The MC system is involved in the regulation of energy homeostasis and body weight [8, 9, 10], as well as steroidogenesis,

sexual function, cardio vascular (CV) function, emotional behavior, and the secretion of several endocrine and exocrine factors. Given the various physiological functions that their activation can modulate, the MC receptors represent a therapeutic target for a variety of indications.

Melanocortin type 4 receptors (MC4R) are located in many of the brain regions known to be involved in feeding regulation and have been identified as the dominant MC receptor involved in body weight regulation.[8] When stimulated, the MC4R induces a dramatic reduction in food intake and body weight and increases insulin sensitivity.

MC4R receptors have also been hypothesized to play a role in other physiological processes. Preclinical models have demonstrated pro-erectogenic effects with some MC4R agonists, while erectogenic activity has been noted with some MC4R agonists in the clinic [11] but not with others [12, 13]. In addition, some MC4R receptor agonists may have mediated increased sympathomimetic tone, leading to increases in heart rate and blood pressure in both preclinical and clinical studies [14], but not with all agents [12, 13, 15]. Whether these additional physiological effects are truly mediated by MC4R agonism and how this is mediated with the complex receptor interactions of the MC4R receptor is unclear.

1.3.2. Preclinical Studies

[redacted]

RM-493 was initially selected for clinical development based on its ability to decrease body weight gain and suppress food intake in normal rats. Subsequent studies demonstrated the efficacy of RM-493 in suppressing food intake and body weight gain in diet-induced obese mice, rats, dogs, and Rhesus macaques, as well as in genetic models of obesity, including leptin-deficient ob/ob mice and obese Zucker rats. Furthermore, RM-493 is associated with reversal of insulin resistance and significant lowering of plasma triglycerides, cholesterol, and free fatty acids. Most of these preclinical studies were performed with continuous 24-hr subcutaneous (SC) infusions, due to the lack of suitable injectable formulations.

[redacted]

In a preclinical study of BIM-22493 (now RM-493) in diet induced obese rhesus macaques, animals treated for 8 weeks by continuous SC infusion demonstrated decreased food intake and weight loss during the first four weeks of drug administration [16]. In the last 4 weeks, food consumption increased to pre-treatment levels with continued weight loss, resulting in 13% total weight loss over the 8-week treatment period. Energy expenditure measured by doubly labeled water was increased at the end of the treatment period, however the contribution of spontaneous physical activity or change in metabolic rate is not known.

[redacted]

1.3.3. Overview of Clinical Studies

A brief summary of clinical data is provided below, which also includes a short summary of interim data from the ongoing Phase 2a study in obese patients. Except where noted, in all the studies below, RM-493 was administered by *24-hour continuous subcutaneous (SC) infusion* using an infusion pump. .

To date (October 7 2013), a total of ~59 subjects have been exposed to RM-493 in two Phase 1 studies, an additional ~12 subjects have been exposed in a third Phase 1 short term study to assess 24-hour energy expenditure (ongoing), and ~37 patients have been exposed in a Phase 2a study (ongoing). In the initial Phase 1 clinical studies, RM-493 has been administered at doses ranging from 0.0025 to 0.1 mg/kg/24 hours (0.12 – 9.12 mg mean total daily dose). Of these, a small number of patients have received RM-493 by SC injection (same formulation of RM-493 administered by infusion, not optimized for once daily SC injection). Of the total of >70 subjects in Phase 1 studies, all were healthy obese (BMI 30-40 kg/m^2) volunteers, of whom ~32 received a single RM-493 dose and ~39 received repeated doses for 3 to 28 days.

1.3.3.1. Phase 1 Clinical Studies

[redacted]

1.3.3.2. Phase 2a Clinical Study

Preliminary data is available from Study RM-493-003, a Phase 2a double-blind, placebo controlled randomized study of healthy obese patients. In this study, patients were randomized 1:1 to placebo or RM-493 1 mg/day (administered as continuous infusion over 24 hours using the OmniPod insulin pump). Patients were treated for 12 weeks, followed by a 12 week recovery period off treatment.

[redacted]

[redacted]

1.3.3.3. The Once Daily SC Injection Formulation of RM-493

The new once daily SC injection formulation of RM-493 (DSPE formulation) is lipid based. These lipids were selected to provide a less aqueous injectable solution which would prolong the absorption of RM-493 using well characterized or naturally occurring excipients. [redacted]

Formulation composition, as well as expected daily exposure of excipients at the anticipated clinical dose, is summarized in Table 1.

[redacted]

All formulation components have been used previously in approved injectable products in amounts similar to or greater than those in the new formulation.

[redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective:

After 4 weeks of double-blind study drug treatment:

- To assess safety and tolerability of RM-493.
- To assess the effect of RM-493 on weight loss.
- To assess the effect of RM-493 on hyperphagia-related behavior using the PWS Hyperphagia Questionnaire.

2.1.2. Secondary Objectives:

The secondary objectives are to assess:

- To evaluate changes in quality of life, other hyperphagia- and food-related behavior, and/or psychiatric status.
- To evaluate the pharmacokinetics of RM-493 in Prader-Will patients (substudy)
- To assess the effect RM-493 during a 2-week, double-blind, randomized withdrawal period.
- To assess the percent change in body mass by DEXA in the active treatment group compared to the placebo group.
- To assess the percent change in fat content by DEXA in the active treatment group compared to the placebo group.

[redacted]

2.2. Study Evaluations

Body weight change from baseline (as a percentage of baseline total body weight (primary endpoint) and as kg of weight loss and percent change in body mass and fat content by DEXA (secondary endpoints)) over the 4-week double-blind dosing period will be evaluated to document RM-493's effect on obesity in PWS. In addition, the effect of the randomized withdrawal on weight will be explored. It is expected that subjects will experience a minimal-modest level of weight gain during the 2 week placebo lead-in period. With initiation of double-blind 4-week RM-493/placebo treatment phase, body weight changes (reduction, lack of gain, or reduced rate of gain) will be assessed as the primary efficacy endpoint.

The safety and tolerability of RM-493 by SC injection will be assessed by comparing the frequency and severity of adverse events as well as changes in physical examinations, ECGs, [redacted] vital signs, laboratory evaluations and injection site reactions (see Appendix 11.1).

PWS Hyperphagia Questionnaire (Dykens, 2014) will be the primary hyperphagia-related behavior endpoint of the study, evaluated at both the end of the 4-week double-blind treatment phase, at the end of the 2-week randomized double-blind withdrawal phase, and again at the end of the open label extension. [redacted]

Other quality of life or behavioral measurements may also be evaluated including the Food Related Problem Questionnaire (Russell, 2003), [redacted] and Symptom and Global Assessments. Daily journal to quantify aberrant behavior, [redacted] and/or Rate of Eating measurement will also be used.

[redacted]

Assessment of basal metabolic rate (via VO2 consumption) will also be measured.

Changes in symptom scores for loss of appetite will be assessed over the duration compared to placebo. All safety/tolerability and symptom scores will be compared across dose levels and with placebo lead-in phase of the study.

The plasma PK of RM-493 will be assessed in all subjects by trough (pre-dose) concentrations measured after 4 weeks of double-blind treatment on Day 42 (both RM-493 doses) and at the end of the optional open-label extension on Day 70 (RM-493 2.5 mg QD only). In addition, a subject of subjects will provide a 24-hour profile after at least 1 week of optional, open-label treatment (RM-493 2.5 mg QD only). For the 24-hour profile, noncompartmental methods will be used to determine PK parameters including C_{max}, T_{max}, AUC_{24hour}, volume of distribution (Vd), and total clearance (CL).

Additionally, [redacted] will be monitored. Guidance is provided for [redacted] during the study. In addition, specific guidelines for dermatological events, liver function abnormalities, and penile erections are provided in the Appendix. At all times, this guidance is subject to the clinical judgment of the Investigator and study consultants (if applicable).

3. INVESTIGATIONAL PLAN

3.1. Overall Design and Plan of the Study

This will be a randomized, double-blind, placebo-controlled, parallel group study. It will consist of 4 sequential periods:

(1) a 2-week single-blind, placebo-controlled baseline period with approximately one third receiving a lower volume placebo run-in dose and approximately two-thirds receiving a higher volume placebo-run-in dose;
(2) a 4-week, double blind, placebo-controlled, randomized parallel group period (primary analysis timepoint) where patients will be randomized 2:1:3 to placebo or one of two dose levels of RM-493; and
(3) a 2-week, double-blind, randomized withdrawal period where half of each RM-493 group will remain on the same dose of active drug and the other half will receive placebo, and half of the placebo group will receive RM-493 at a corresponding dose/volume level.
(4) In addition, there will be an optional 2-week open label extension period (period 4) where every patient can participate and receive open label RM-493.

Approximately 36 subjects will be randomized to a placebo arm or one of 2 dosing arms with a 2:1:3 assortment between placebo, lower dose of RM-493 and higher volume RM-493. In the first half of the study, dosing arms were 0.5 mg of RM-493 and 1.5 mg RM-493. Based on the results of the interim analysis, in the second half of the study, dosing arms will be 1.5 RM-493 and 2.5 RM-493. *Subjects will initiate with 2 weeks of single blind placebo lead-in phase, using a 0.5 mg (50 mcl), 1.5 mg (150 mcl), or 2.5 mg (250 mcl) dose volume corresponding to the eventual dose of active drug or placebo they will receive during periods 2 and 3,* after which they will be randomized 2:1:3 to receive daily lower volume or higher volume SC doses of placebo, or RM-493 for 4 weeks.

After completion of the primary 4 week, double-blind treatment (period 2), a double-blind randomized placebo withdrawal (period 3) will initiate: patients within each of the RM-493 groups (n ~ 6 for lower volume RM-493 and n ~ 18 for higher volume RM-493) will be randomized 1:1 to either continue with the same dose or begin placebo treatment with the same dose volume regardless of remaining on active RM-493 or switching to placebo as part of the randomization. The patients in the placebo group during the 4 week primary treatment period would also be randomized 1:1 to continue on placebo or to receive RM-493 at the corresponding dose/volume established during periods 1 and 2 during the randomized withdrawal phase (period 3).

A follow-up open label extension phase of the trial (after the initial 4 weeks of study duration and the 2-weeks of randomized withdrawal) will be available for patients who completed the trial and wish to continue in the 2-week open label extension. For this final treatment period, all subjects will receive 2.5 mg (250 mcl) of RM-493 for 2 weeks.

The active doses to be studied in the trial are RM-493 2.5 mg, 1.5 mg and 0.5mg QD (administered in the morning) RM-493 by SC injection.

A single blood sample for trough (pre-dose) RM-493 concentrations will be collected from all subjects on Day 42 and Day 70. In addition, a substudy of up to N=8 patients may participate in a pharmacokinetic substudy. Patients who participate in this substudy would be required to spend ~12 hours in the clinic (during second week of the optional open-label, active-dose 2-week

extension period) for serial blood sample collection, and to return the next day at about 24 hours after dosing for one additional blood sample collection.

[redacted]

3.3. First Half of Study Justification of the Study Design ([redacted]

To date, RM-493 has been studied in an ascending single-dose and a multiple dose study in healthy obese volunteers for up to 28 days and in a Phase 2a study for up to 12 weeks, with a second Phase 2a study just initiating. This study will have as a primary endpoint of weight loss over 4 weeks (where 1 kg/week weight loss has been noted in healthy obese volunteers in Phase 1b studies).

This study will incorporate a 2-week, single blind placebo controlled run-in, so that the baseline data from each individual patient can provide a within-subject control. As a result, the analysis of weight (and other key endpoints) will be based on change from baseline for each individual, then compared between the two active groups (2 doses of RM-493) and placebo after 1 month of treatment.

Since patients may be subject to strong bias (placebo responses) when trying a new therapy for a disease with few treatment options (PWS), the psychological endpoints (e.g., hyperphagia symptoms) will be assessed both at the end of 4 weeks of double blind treatment, but also supported by an analysis at the end of a randomized placebo controlled withdrawal phase (a study design frequently used in psychiatric studies). This will allow careful assessment of any changes that occur as randomized patients are withdrawn from study drug.

Lastly, in order to offer some therapy to all patients who participate, any patient who completes the main body of the study will have the option to participate in a 2-week open label active drug extension using a 1.5 mg dose of RM-493 that is expected to be most effective.

PWS patients often require a broad set of concomitant medications that differ from patient to patient (though some, like growth hormone are common). As a result, concomitant medications are allowed during the course of this trial if patients are on a medication for at least 60 days and

have been on a stable dose of that medication for at least 30 days (or for more than 3 months for contraceptives, hormone replacement therapy, GLP-1 agents, or statins), the medication does not have a small therapeutic index, and if each patient is carefully warned of potential side effects of drug interactions for their particular list of medications. Note that at present, there is no reason to suspect any risk of drug interactions (RM-493 itself is not metabolized in *in-vitro* experiments, and it is not an inhibitor of any tested CYPs [see IB]), but a full evaluation of the potential of RM-493 to cause drug interactions has not been completed (e.g., evaluation of effects on transporters).

3.4. Justification for Study Design changes and Doses after the Interim Analysis

A limited interim analysis of data from this study was completed after ~N=16 PWS patients completed the 4-week double blind period of the study. This analysis, which has not been shared with study participants, study investigators, or Rhythm study personnel involved in the conduct of the study, was primarily designed to assess futility and to allow planning of future studies.

These results do not support futility, but showed promising data for the two primary endpoints (percent weight loss and overall hyperphagia score). As expected, these interim results were not definitive based on the small numbers of patients in each treatment group. However, the limited analyses of the 4-week double blind period (primary efficacy period) and the data from the 2-week, double-blind, randomized withdrawal/crossover period supported that the 0.5 mg daily dose provided minimal efficacy (as expected, as this dose was included to define an ineffective dose). [redacted]

Therefore, an additional higher dose of 2.5 mg has been included in this protocol, allowing discontinuation of any additional patients treated at the 0.5 mg daily dose. Doses up to 10 mg have been given in single doses to general obese patients, and the limited toxicity was nausea (and in some cases vomiting (which generally are not symptoms reported in PWS patients, who are very resistant to nausea). Otherwise doses up to 2 mg have been administered for up to 12 weeks in healthy obese volunteers (as outlined in our Investigator Brochure). [redacted]. Based on the excellent safety profile observed in the first half of the study at doses up to 1.5 mg, the dose for the open label extension phase is being increased to 2.5mg, in order to provide additional experience at that dose in patients with PW.

In addition, unrelated to the interim analysis, Rhythm has been working on a new daily version of the hyperphagia observer-reported-outcomes questionnaire. The FDA guidance on development of these patient- and observer-reported outcomes strongly requests that this data be collected on a daily basis. As a result, Rhythm has worked with a PRO-speciality group to develop a potential [redacted] This

amendment will include a very simple questionnaire that has daily look-back period as an exploratory endpoint.

3.5. Study Termination

This study may be prematurely terminated, if in the opinion of the Investigator 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.
- Insufficient adherence to protocol requirements.
- Insufficient complete and/or evaluable data.
- Plans to modify, suspend or discontinue the development of the study drug.

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

3.6. Internal Safety Monitoring Committee

This study will be monitored by an internal safety monitoring committee, who will be responsible for careful safety evaluations of ongoing treatment in this pilot study. The safety monitoring committee will be comprised of the principal investigator(s) from the following sites [redacted]. If additional expertise is needed to review the data, the safety monitoring committee may also include (as ex officio members): (1) up to one other senior clinical specialist at Rhythm not directly associated with the study; (2) members of Rhythm's scientific advisory board with exceptional experience in early phase development: e.g., [redacted] and/or (3) the Dermatologists from each center. In addition, an unblinded non-Rhythm statistician, not otherwise involved in the conduct of the study, may provide support, data and analyses.

The safety monitoring committee will meet at least once monthly to review listings of blinded safety and tolerability data (AEs, laboratories, ECG, etc) in order to provide an overview of any potentially concerning safety issues in the trial. After approximately the first 8 patients completing the study, a more comprehensive review, including both blinded listings as well as mean total patient safety data (blinded) will be performed, along with a review of any outlier data (blinded). This will be repeated when approximately half the patients (N~18) are complete.

While it is not expected that the committee will review unblinded data, if necessary to make a safety determination, the committee can requ,est and review individual patient data, which can be unblinded if critical for safety evaluation. A record of all data unblinded, and all dissemination of the data, will be carefully tabulated, as will a record of all decisions made by the safety monitoring committee.

Separately, the safety committee can review, if desired, blinded PK analyses (i.e., PK information not identified with any identifying patient information). The safety monitoring committee can make minor adjustments in the schedule for study assessments and PK sampling (as long as the amount of blood draw remains the same), and may introduce minor adjustments

in the safety monitoring schedule if needed to address any minor potential safety or tolerability or logistical concerns (e.g., changing the timing of a procedure, such as physical examination or other similar procedure).

In addition, the safety monitoring committee will be responsible for any changes in dose or study procedures due to safety concerns; any such changes in dose will be documented in a protocol amendment after careful assessment in relation to in-depth review of safety and tolerability information (AEs, safety labs, vital signs, ECGs, injection site reactions, and other data. The IRB will be notified of, and approve the amendment for any dose adjustment, with the supporting rationale. Note that it is not anticipated to make any changes in dose during the study.

4. STUDY POPULATION

4.1. Number of Patients

It is anticipated that approximately 36 patients will be enrolled in this study. The study population will include obese males and females with confirmed diagnosis of PWS, due to chromosome 15 micro-deletion, maternal uniparental disomy, or imprinting defect, and a Body Mass Index (BMI) greater than or equal to 27 kg/m^2 who are able to have study medication administered by a health care professional or trained caretaker. Subjects with type 2 diabetes (HbA1c <7.5%) will be allowed to enter the study.

The specific inclusion and exclusion criteria for enrolling patients in this study are presented in Sections below, respectively.

4.2. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for the study:

1. PWS due to chromosome 15 micro-deletion, maternal uniparental disomy, or imprinting defect, confirmed by fluorescent in situ hybridization, chromosomal microarray, and/or methylation studies. Obese male or female volunteers weighing at least 50 kg with BMI ≥27 kg/m^2.
2. Age 16-65 years
3. If a volunteer has diagnosis of type 2 diabetes, following criteria must be met:
    a. HbA1c <7.5% not being managed with insulin. Patients taking GLP-1 analogues (exenatide or liraglutide) must have been on stable dose for at least 3 months.
    b. Fasting plasma glucose <140 mg/dL
    c. No history of ketoacidosis or hyperosmolar coma
4. Vital signs must be within the following ranges and stable.
    a. Systolic blood pressure, 90-150 mm Hg
    b. Diastolic blood pressure, 50-90 mm Hg
    c. Pulse rate, 40-100 bpm
5. Stable body weight at home for ~2 months (self or guardian-reported loss/gain within ± 5%).
6. Blood pressure (≤150/90 mmHg); may include stable dose (≥ 30 days of use) of up to two anti-hypertensive medications that are intended to remain on a stable dose during the protocol
7. Parent or guardian is able to communicate well with the investigator, to understand and comply with the requirements of the study, and be able to understand and sign the written informed consent. Due to the significant intellectual disability with PWS, assent is to be provided by the patient who cannot consent for himself or herself.
8. Results of screening clinical laboratory tests (CBC with differential and platelets and chemistry profile) must be within normal range or, if outside of the normal range, must be accepted by the investigator and sponsor as not clinically significant.

9. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months (and confirmed with a screening FSH level in the post-menopausal lab range), do not require contraception during the study. All other females of child-bearing potential must agree to use contraception as outlined in the protocol.
10. Males with female partners of childbearing potential must agree to a double barrier method if they become sexually active during the study and for 90 days following the study. Male subjects must not donate sperm for 90 days following their participation in the study.
11. Patients must be on a stable dose of any allowed chronic concomitant medications while participating in the study, as described in protocol. This is defined as no changes in medication for at least 60 days prior to Day 1 and no changes in dose for at least 30 days prior to Day 1.Note that stable concomitant usage (>3 months) of growth hormone, hormone replacement therapy, GLP-1 agents, statins or other medications (excluding insulin, modafinil, anti-psychotics), and other medications commonly used in PWS patients are allowed (See Section 6.4.5 on Concomitant Medications).

4.3. Exclusion Criteria

If any of the following exclusion criteria are met, the patient is not eligible for the study:

1. Recent use (within 3 month) of weight loss agents including herbal medication.
2. Diagnosis of schizophrenia, bipolar disorder, personality disorder or other DSM-III disorders which the investigator believes will interfere significantly with study compliance.
3. A PHQ-9 score of ≥15.
4. Any suicidal ideation of type 4 or 5 on the C-SSRS.
5. Clinically significant illness in the 8 weeks before screening.
6. History of clinically significant bleeding disorders.
7. Current, clinically significant liver, renal, pulmonary, cardiac, oncologic, or GI disease.
8. Diagnosis of type 1 diabetes mellitus or other active endocrine disorders (e.g., Cushing syndrome, or thyroid dysfunction except if on adequate thyroid or glucocorticoid replacement supplement).
9. Cardiovascular disease event including history of CHF, coronary artery disease, MI, second degree or greater heart block or prolonged QT syndrome.
10. Blood pressure >150/90 mmHg.
11. Liver disease or liver injury as indicated by abnormal liver function tests, SGOT (AST), alkaline phosphatase, or serum bilirubin (> 1.5 x ULN for any of these tests) or history of hepatic cirrhosis.
12. History or presence of impaired renal function as indicated by clinically significantly abnormal creatinine, BUN, or urinary constituents (e.g., albuminuria) or moderate to severe renal dysfunction as defined by the Cockroft Gault equation (< 50 mL/min).
13. History or close family history (parents or siblings) of melanoma.
14. Oculocutaneous albinism (occurs at ~1% in PWS).

15. Significant dermatologic findings as part of the Screening comprehensive skin evaluation performed by the dermatologist. Any concerning lesions identified during the screening period will be biopsied and results known to be benign prior to randomization. If the pre-treatment biopsy results are of concern, the patient will be excluded from the study.
16. Significant history of abuse of drugs or solvents in the year before screening or a positive *Drugs of Abuse* (DOA) test at screening.
17. History of alcohol abuse in the past year before screening or currently drinks in excess of 21 units per week (3 servings or units/day).
18. Caffeine consumption exceeding 6 cups of caffeinated tea/coffee (or equivalent) per day.
19. Volunteer is, in the opinion of the Investigator, not suitable to participate in the study.
20. Participation in any clinical study with an investigational drug/device within 3 months prior to the first day of dosing.
21. Positive history for human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C tests or tuberculosis.
22. Serious adverse reaction or significant hypersensitivity to any drug.
23. Clinically significant blood loss or blood donation > 500 mL within 3 month.
24. Inadequate venous access.
25. History of low blood counts or recurring infections.

4.4. Patient Identification and Registration

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

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

4.5. Withdrawal of Patients

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

Adverse events which justify treatment or study withdrawal. For specific predefined events, additional monitoring and guidance for the Investigator is provided in Appendices 11.6 and 11.7.

Non-adherence to study drug regimen or protocol requirements.

Non-compliance with instructions or failure to return for follow-up.

If a patient is withdrawn or discontinued from the study, the primary reason for withdrawal from the study is to be recorded in the source documents/CRF.

All patients withdrawn prior to completing the treatment period should complete the remaining study procedures and visits as outlined for the Early Termination Visit procedures in the Schedule of Assessments in Section 6.

All adverse events must be followed until the post-study follow-up visit, but any skin adverse experiences should continue to be followed, if at all feasible, for ~60-90 days to confirm near, or complete resolution (as has been shown in previous studies).

5. STUDY TREATMENTS

5.1. Study Drugs

All study drugs are for investigational use only and are to be used only within the context of this study. All active investigational study drugs (RM-493 and placebo) will be supplied by Rhythm.

RM-493 drug product will be a sterile solution for injection. The product will be manufactured at a concentration of 10.0 mg/mL filled with ≥0.5 mL/vial. Placebo will be vehicle. RM-493 drug product and placebo are described in below. Both RM-493 and placebo are supplied as single-use vials and may only be punctured once under aseptic conditions.

RM-493 and placebo are clear, colorless to slightly opalescent solutions essentially free of visible particulates, and are suitable for a double blind study. RM-493 and placebo will be administered as subcutaneous injection using a ~0.5 mL insulin syringe. There will be extensive training of patients in drug administration (see below) including frequent supervision of drug administration, and educational training materials will be provided to the study staff and patients. Rhythm will provide extra placebo supplies for use during training.

All study drug must be kept in a secure, limited-access storage area at a temperature between 2°C to 8°C. RM-493 and placebo are stable at room temperature for a short time period that will allow patients to transport study drug home. Patients will be encouraged to proceed directly home after clinic visits in which study drug is dispensed in order to minimize the amount of time the study drug is exposed to elevated temperatures. Ice packs and cooler bags will be provided for subjects and caretakers who will travel long distances from clinic.

5.2. Study Drug Dose and Administration

The active doses studied in the first half of the trial were RM-493 1.5 mg and RM-493 0.5 mg QD. The active doses to be studied in the second half of the trial are RM-493 1.5 mg and RM-493 2.5 mg. Study patients will receive study drug by SC injection (administered in the morning) for up to 10 weeks (either RM-493 or placebo, if including the single-blind placebo run in, the 4 week double blind treatment period, the 2-week randomized withdrawal period, and the optional open label active drug extension). Specific instructions regarding the volume to administer will begin during the initial single-blind phase (period) and continue through period 2 and 3 at the same dose/volume as established in the initial single-blind placebo run-in period. All subjects in the optional, open-label, active RM-493 treatment phase (period 4) will receive 2.5 mg (250 mcl) of RM-493. Patients and/or their caretakers (including home health practitioners) will be responsible for all procedures for study drug administration at all times, i.e., drawing up, and self-administering the study drug once daily (including during the practice periods (see below)).

This study consists of 4 sequential periods: (1) a 2-week single-blind, placebo baseline period with approximately one third receiving a lower volume placebo run-in dose and approximately two thirds receiving a higher volume placebo-run-in dose; (2) a 4-week, double blind, placebo-controlled, randomized parallel group period (primary analysis timepoint) where patients will be randomized 2:1:3 to placebo or one of two dose levels of RM-493; and (3) a 2-week, double-blind, randomized withdrawal period where half of each RM-493 group will remain on the same dose of active drug and the other half will receive placebo, and half of the placebo group will receive RM-493 at a corresponding dose/volume level. In addition, there will be an optional 2-

week open label extension period (period 4) where every patient can participate and receive open label RM-493.

Approximately 36 subjects will be randomized to a placebo arm or one of 2 dosing arms with a 2:1:3 assortment between placebo, lower volume of RM-493, and higher volume of RM-493. *Subjects will initiate with 2 weeks of single blind placebo lead-in phase using either a lower or higher dose volume corresponding to the eventual dose of active drug or placebo they will receive during periods 2 and 3*, after which they will be randomized 2:1:3 to receive daily SC doses for 4 weeks of placebo, or 0.5 mg or 1.5 mg of RM-493 in the first half of the trial, or placebo, or 1.5 mg or 2.5 mg of RM-493 in the second half of the trial.

After completion of the primary 4-week, double-blind treatment (period 2), a double-blind, randomized placebo withdrawal (period 3) will initiate: patients within each of the RM-493 groups will be randomized 1:1 to either continue with the same dose or begin placebo treatment with the same dose volume, all using the same dose/volume regardless of remaining on active RM-493 or switching to placebo as part of the randomization. The patients in the placebo group during the 4 week primary treatment period would also be randomized 1:1 to continue on placebo or to receive RM-493 at the corresponding dose/volume established during periods 1 and 2 during the randomized withdrawal phase (period 3).

A follow-up open label extension phase of the trial (after the initial 4 weeks of study duration and the 2-weeks of randomized withdrawal) will be available for patients who completed the trial and wish to continue in the 2-week open label extension. For this final treatment period, all subjects will receive 2.5 mg (250 mcl) of RM-493 for 2 weeks.

Since the volume of administration is different for the different doses of RM-493, placebo patients will be allocated to matching placebo at matching volumes to maintain the blinded nature of the study throughout all study periods except for the final open-label active period. All subjects in this final open-label, active treatment phase (period 4) will receive 2.5 mg (250 mcl) of RM-493. The allocation schedule will be so constructed to account for this study design feature. A schema of dose allocation during the study is depicted in Figure 5.2.

The run-in period is designed with some flexibility but is planned to be initiated with a training period in the clinic with vehicle during screening before initiation into the single-blind placebo controlled run-in period. Note that every subject will receive single-blind placebo during the 2-week placebo run-in period. It is important during this single blind period that patients and their caregivers remain blinded to the knowledge that they are receiving placebo.

Patients will be required to fast (as much as possible in this population) for a minimum of 8 hours prior to the study drug administration on the day of 24-hour PK sampling for those in the PK substudy. Water will be allowed throughout the fasting period.

Study drug will be packaged in kits with approximately a weekly supply, and uniquely identified to allow blinded assignment by the study staff. Note that everyone will receive placebo during the run-in period, and everyone will receive active drug during the optional open label active drug extension.

A separate study drug administration guide will be provided to patients and staff.

Figure 5.2.1: First Half of Study Schema of Dose Allocation (original protocol through [redacted]

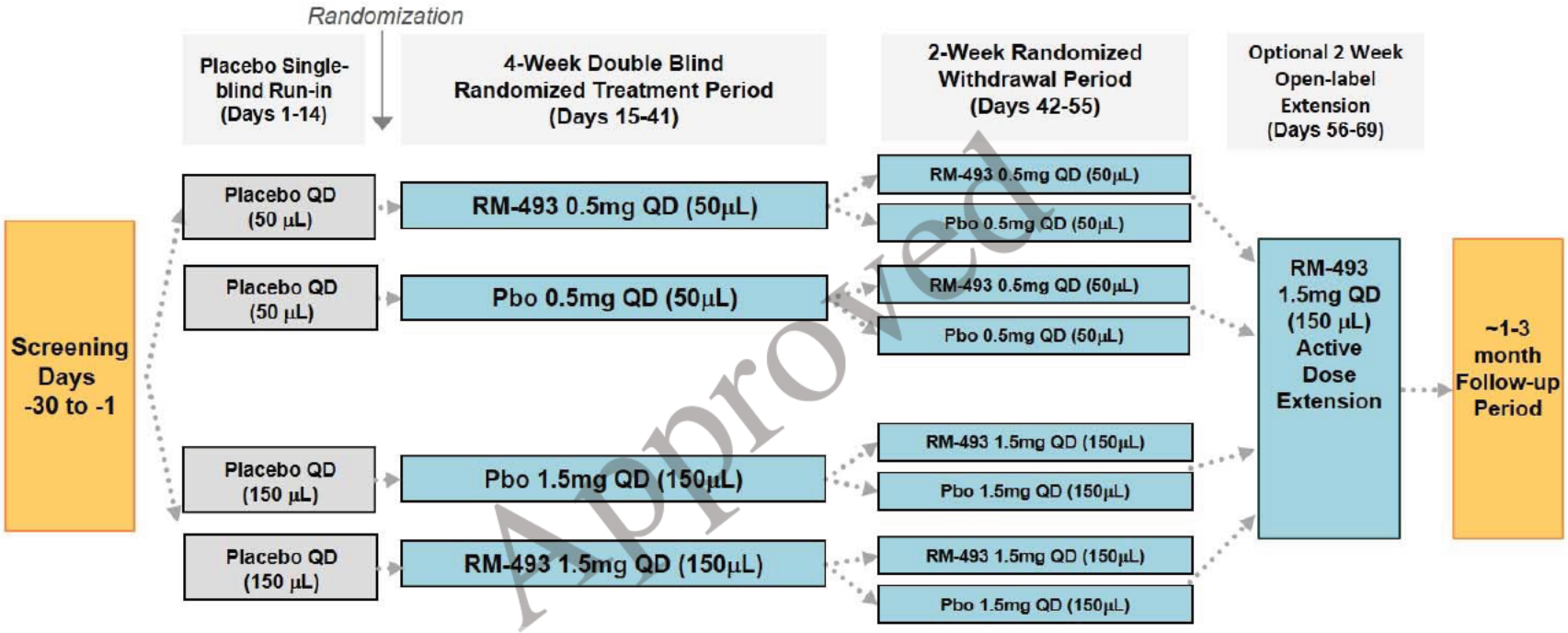
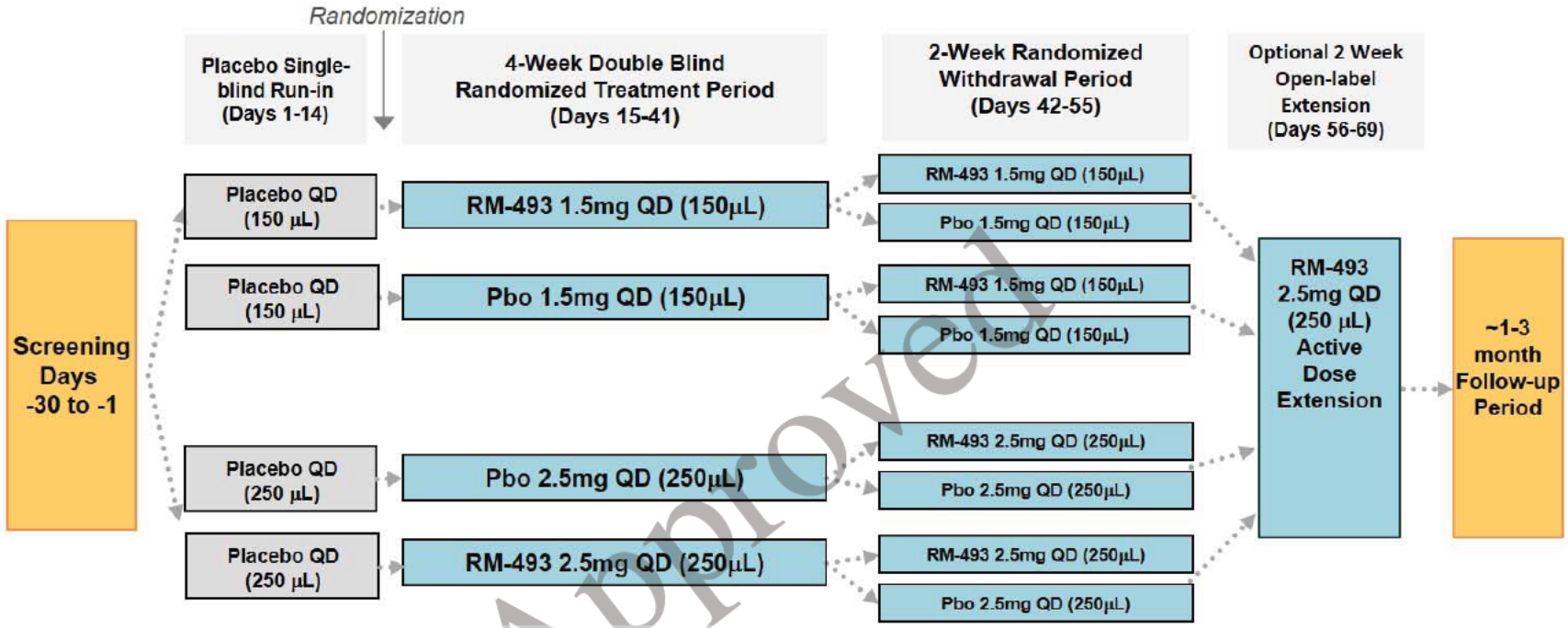


Figure 5.2.2: Second Half of Study Schema of Dose Allocation (after Interim Analysis)



5.3. Method of Assigning Patients to Treatment

Patients who qualify for the study will return to the site on Day -1 (e.g., randomization will formally take place at the end of the placebo-controlled run-in period, after compliance during the run-in period is assessed). Prior to randomization, the Investigator will ensure that the patient continues to meet inclusion and exclusion criteria, and perform all pre-dose procedures. Once a patient is determined to be eligible for randomization by the Investigator, the Investigator or the Investigator's research staff will randomize the patient according to a centralized randomization process.

Note all patients will be pre-randomized to their status/treatment group for the randomized withdrawal part of the protocol at the initial randomization.

5.4. Blinding, Packaging, and Labeling

5.4.1. Blinding and Breaking the Blind

This is a randomized, double-blind, placebo-controlled study. Blinding and randomization will be accomplished so that all study-related staff remain blinded to patient assignation.

The Investigator, study site staff, clinical research organization staff providing site management, and Medical Monitor will not have access to the randomization scheme during the study except in the case of an emergency. Breaking the blind for a patient should be done only in the event of a medical emergency where the identity of study drug is necessary to appropriately treat the patient. The request to break the blind should be discussed with the Medical Monitor and Rhythm, whenever possible. If the blind is broken, the reason, when and how the blind was broken will be documented. Every attempt will be made to maintain the blind throughout the study.

5.4.2. Packaging and Labeling

Study drug is provided in single-use vials. The study drug is supplied in glass vials and is provided in kits according to the randomization schedule for patients enrolled in the study. All study drugs, including placebo for practice, will be supplied by Rhythm.

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

5.5. Duration of Patient Participation

The overall study duration will be approximately 12 months, as currently planned. Individual patient participation in the study (Screening Period, Run-in, Treatment Period, withdrawal period, open label optional extension and Follow-up Period) will be approximately 5 months.

Screening, inclusive of the placebo practice period, will occur within 30 days prior to entry into the single-blind placebo-run in period.

5.6. Assessment of Treatment Compliance

In order to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of the study drug, it is critical that patients receive study drug as directed. All used vials and syringes will be collected to assess compliance with the protocol.

All injections of study drug are to be self-administered by the study patient or a trained caretaker. Patients and/or caretakers will be required to maintain a study drug diary to monitor compliance. In addition, the time of dosing will be recorded in the patient diary.

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

5.7. Study Drug Accountability

Accountability for the study drug at the study site is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the delivery date to the site, inventory at the site, use by each patient, return of all vials to the study center, and return to Rhythm (or disposal of the drug, if approved by Rhythm) will be maintained by the clinical site. These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from Rhythm. Reasons for departure from the expected dispensing regimen must also be recorded. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. The Sponsor or its designee will review drug accountability at the site during monitoring visits.

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

5.8. Prior and Concomitant Treatment

5.8.1. Permitted Medication

Female patients may use hormonal contraception as well as hormone replacement therapy (provided they have been using the medication for 3 months prior to study enrollment).

Patients must be on a stable dose of any allowed chronic concomitant medications (e.g., as described below) while participating in the study. This is defined as no changes in medication for at least 60 days prior to Day 1 and no changes in dose for at least 30 days prior to Day 1; or for more than 3 months for contraceptives, hormone replacement therapy, GLP-1 agents, or statins.

a. Growth hormone
b. Contraceptives (must be on stable dose for ≥3 months);
c. Hormone replacement therapy (must be on a stable dose ≥3 months);
d. Antihypertensives (<3 medications on a stable dose for ≥ 30 days);
e. Statins (dose must be ≤ half the maximum dose; must be on a stable dose ≥3 months);
f. Thyroxin or other thyroid supplements (stable dose for ≥ 30 days).

g. Other medications commonly used in PWS patients including: endocrine therapies (e.g., estrogens, Fosamax, hydrocortisone, vitamin and calcium supplements, diabetic therapies except for insulin); psychiatric medications (e.g., SSRI's, Topamax, anti-depressants, anti-psychotics, anti-anxiety medications, modafinil); and other medications (e.g., carnitor, Coenzyme Q10, vitamins, anti-constipation medications, anti-allergic medications).

There is little evidence that RM-493 will result in drug interactions at present, but data is limited. Patients and caretakers should be carefully assessed to determine that potential patients are on a stable dose of medication (see above), specifically screened to determine if stable doses are expected during the course of the study, and carefully warned of possible side effects of drug interactions that could occur with the specific list of medications that an individual patient will be receiving.

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

5.8.2. Prohibited Medication and Substances

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

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

5.8.3. Concomitant Procedures

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

6. STUDY ASSESSMENTS

6.1. Overview of Schedule of Events

The Schedules of Assessments (SOA) to be conducted during the study are depicted in Table 6-1.

After an initial screening and confirmation of eligibility, volunteers will enter a two-week single-blind placebo run-in period (period 1). Those who are compliant in study drug administration and have demonstrated willingness to complete study procedures (weighing, questionnaire and dairy completion), will be randomized to receive subcutaneous doses of RM-493 or placebo for 4 weeks of double-blind treatment (primary efficacy timepoint) (period 2), followed by a 2-week double-blind randomized withdrawal period (period 3). Then patients who complete will be eligible for an optional open label extension treatment for 2 weeks (period 4). Overall, including the run-in, the duration of study drug administration may be up to 10-weeks.

Evaluations will occur at the following times indicated as Study Day numbers: Baseline (one visit between Day -30 and Day -1 in the screening period), at the onset of single blind treatment (Day 1), at the end of the single-blind placebo/onset of double blind treatment randomization (Day 15), after 2 weeks of randomized treatment (Day 28), primary evaluations at the end of double-blind study treatment (Day 42), secondary evaluations at the end of the randomized withdrawal period (Day 56), and at the end of the optional open label active drug extension (Day 70).

At the visits, the subjects will undergo safety and efficacy assessments (which may include, but are not limited to, weight, vitals, 12-lead ECG, DEXA, [redacted] physical exam, food and behavior questionnaires/diaries) and blood sampling for safety, [redacted] and pharmacokinetic evaluations. Evaluations at Day 28 may be conducted via phone, or in-clinic, per the SOA.

Participants will not be counseled on food intake or exercise, but will demonstrate an approximately stable diet at randomization by showing stable weight at home for the past two months (± 5%).

All subjects also will be followed for approximately 1-3 months after last dose and undergo study termination procedures at the post-study follow up visit (Days 90-163), which may be at next scheduled routine clinic visit if within this timeframe.

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

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

The Screening Period can occur within ~30 days of Day 1 (entry into the run-in), and should be scheduled within this timeframe to allow for test results to be received and continued eligibility of patients confirmed prior to Day 1.

In order to provide flexibility to the patient and study staff for the number of clinic visits, the actual scheduling of clinic visits can allow some flexibility in timing of visits (for example, +/- 2 days of scheduled visit dates). In addition, the protocol provides windows for key study visits (e.g., Day 15, 42, 56 and -2 or +4 for Day 70; see Schedule of Assessments) but this can be

considered approximate if needed for flexibility. It is also possible to allow flexibility for the inpatient 24-hr PK sampling (substudy), which can occur any day during the second week of the optional 2-week open label active extension. In addition, the screening and run in can be scheduled on the same day, as long as the lab results are back in time for the start of run-in phase; this allows patients who are not located near the clinic to have 2 visits within one trip. If combined, study procedures required to be performed in the Screening Visit and also required in the Baseline visit per the SOA should be performed in the Screening portion of the single visit and do not need to be repeated during the Baseline portion of the visit.. Study personnel will still need to record two separate visits in required study documentation, but both visits will have the same date. The Treatment Period interim visit can be conducted via phone or in the clinic at the discretion of the investigator (example, the investigator may wish to conduct in person if the patient is located near the clinic, or via phone if the patient lives a long distance from clinic). Finally, the Post-Study follow up visit should be scheduled approximately 1- 3 months after end of treatment, and can be at next scheduled routine clinic visit if within this timeframe.

Table 6-1: Schedule of Assessments

Study Period / Study Day / Procedure	Screening[4] Days -30 to -1	Onset Single-Blind Treatment Run-in[4] Days 1-14	Double Blind Treatment Days 15-41		End Double Blind/ Onset Withdrawal Period Days 42-55	End Withdrawal / Onset Optional Open Label Extension Days 56-69	End Open Label Extension	Post-Study Follow Up Days 90 to 163[24]
		Run-In[4] Day 1[6,]	Onset Treatment Period Day 15±2-	Treatment Period Interim Visit ~Day 28[4,6]	Treatment Period End, Onset Withdrawal Day 42±2	Onset Optional Expansion ~Day 56±2	Final Visit Day 70 -2 or +4	Follow up Visit
Informed consent	X							
Inclusion/Exclusion review	X	X[5]						
Medical history review	X	X[5]	X[15]					
Pregnancy test	X	X[5]	X[15, 26]		X	X		X
Physical examination[1]	X		X[15]		X			X
Height	X							
Comprehensive skin exam[2]	X							X
[redacted]								
Fitzpatrick scale[7]	X							
[redacted]								
Weight[redacted]	X	X[5]	X[15]	X[23]	X	X	X	X
DEXA			X[22]		X[22]		X	
Archive sample for storage[11]		X[5]			X		X	
Single-Blind placebo practice		X						
Randomization to treatment[3]			X[3]					
Study treatment administration[12]		X	X[6]	X[6,23]	X[6]	X	X	
Injection site inspection[13]		X	X	X[23]	X	X	X	X
Vital signs[14]	X	X[5]	X[15]	X[23]	X	X	X	X
ECG (12-lead)[16]	X				X[16]			X
Safety laboratory tests[17]	X		X[15]	X[23]	X		X	X
Questionnaires/Assessments[20]	X	X[5]	X[15]	X	X	X	X	X
PK blood sampling[18]		X[5]			X[18]	X[25]	X[18]	
Basal Metabolic Rate[21]		X[21]			X[21]		X	
Anti-RM-493 antibody samples		X[5]				X		X
Adverse Event assessment[19]	X	X[5]	X[15]	X	X	X	X	X
Concomitant meds review	X	X[5]	X[15]	X	X	X	X	X
Telephone contact[8]		X		X	X	X		X

Table 6-1: Schedule of Assessments (continued)

1 A complete physical examination will be conducted at Screening (or at the discretion of the site, at Day -1), and Day 90. Height will be measured during the Screening Period only.

2 A comprehensive skin evaluation will be performed by a dermatologist. Any concerning lesions identified during the screening period will be biopsied and results known to be benign prior to randomization. If the pre-treatment biopsy results are of concern, the patient will be excluded from the study.

3 Randomization to occur after all pre-dose procedures completed on Day 15.

4 The screening and run in can be scheduled on the same day, as long as the lab results are back in time for the start of run-in phase. Study procedures required to be performed in the Screening Visit and also required in the Baseline visit per the SOA should be performed in the Screening portion of the single visit and do not need to be repeated during the Baseline ortion of the visit.. Study personnel will still need to record two separate visits in required study documentation, but both visits will have the same date.

5 On Day 1, prior to the initial injection of run-in single blind study drug.

6 Clinic Visit Schedule: For Days 1-14 (run-in) patients will receive a telephone ontact approximately 1 week into the Run-In; During the double blind 4-week treatment period (Days 15 to 42), there will be an optional in clinic or telephone contact visit at ~2 weeks into the treatment period (~Day 28 ± 2 days). There will be a clinic visit at the nset of Withdrawal Period (~Day 42 ± 2 days); at the end of the 2-week randomized withdrawal period (~Day 56 ± 2 days), at the end of th optional open label period (~Day 70 - 2 days or +4 days) and at the poststudy visit (~1-3 months after last active dose).

7 The Fitzpatrick assessment will be performed.

8 Telephone contact weekly by site for any visit more than 1 week apart.

[redacted]

10 Weight is to be measured using the same scale after patients have emptied their bladder and while fasting. Patients are to wear scrubs or equivalent, no shoes, and will be weighed at approximately the same time of day. Weight measurements are to be done in [redacted]

11 Extra retain samples (2 red top and 2 purple top vacutainer) will be taken pre-dose prior to double-blind study drug, and at the end of the 4-week double blind treatment period before first dose of the withdrawal period.

12 Study drug is administered by patients/caretakers beginning the morning of Day 1 through to Day 70 (-2 days, +4 Days); e.g., the last day of Optional Extension). Patients/caretakers, including home health practitioners, will draw up and self-administer/administer the drug on a daily basis. Home health practitioners may draw up study drug into syringes for storage in refrigerator for up to 2-days in advance, if desired, for patient/caretaker self-administration. On days with clinic visits, the patients/caretaker will administer the drug at the clinic in the presence of

the clinical staff. Patients/caretakers will return all empty syringes and vials to the clinic when they visit (the number recorded) and both clinic administered study drug, as well as outpatient study drug administration will be recorded by the patient in a study diary.

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

14 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. On Day 1 and Day 14, patients will have vitals obtained pre-dose. When possible, BP should be taken in the same 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.

15 On Treatment Day 15, at the end of the single-blind placebo run-in but prior to beginning dosing in the 4 week double blind treatment period.

16 A single 12-lead ECG will be performed in the supine position following a period of at least 10 minutes of rest, at Screening, on Day 42 and at poststudy.

17 Safety laboratories to be collected at screening. Safety laboratories also to be collected on Day 15, 28 (if clinic visit occurs) 42, Day 70 and at Poststudy. CBC with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO2, albumin, total protein, glucose, BUN, creatinine, uric acid, AST, ALT, GGT, CPK, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, calcium, phosphorus), urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination. Fasting samples (8 hr minimum) are required at all timepoints where feasible in this population

18 A blood sample for PK will be drawn within 5 minutes before d sing on Day 42 and Day 70 (during the clinic visit) for each patient. These PK samples will be drawn with patients/caretakers being reminded there should be NO study drug administration at home; the drug will be administered in the clinic AFTER the PK sample is obtain d. For the PK sample, the actual collection (clock) time will be recorded, as well as the time of the previous day's study drug injection time as reported by the patient/caretaker. Exception: patients who participate in the PK substudy between Days 63 and 69 do not ne d to have PK repeated on Day 70 visit.

19 Adverse events will be recorded from the time a p tien provides informed consent. Adverse events reported after randomization will be considered as treatment-emergent adverse events.

20 Questionnaires and other assessments include the Dykens Hyperphagia, [redacted] Food-Related Problems Questionnaire, [redacted] and Symptom and Global Assessments.

21 Basal metabolic rate for baseline should be obtained ONCE during screening or during the 14 day double-blind placebo-controlled run-in, but must be completed before initiation of the first dose of the 4-week double blind treatment period. Post-dose basal metabolic rate should be assessed ONCE during the 4-week double blind treatment period, preferably on Day~ 42± 2 days and once during open label treatment period, preferably on day 70 (-2, +4 days).

22 Performed or collected on visits where starting (or changing) the study drug treatment. DEXA may be performed prior to or after treatment administration.

23 To be performed only if visit performed in clinic; an in-clinic visit is recommended.

24 Follow-up visit to be conducted 1- 3 months after completion of treatment

25 Starting on any day from Day 63 through 69 (the second week of the optional open-label, active-dose extension period), a substudy of patients will have a 24-hour PK profile obtained (as outlined in a separate PK manual). Blood samples will be collected at 0 (within 5 minutes

BEFORE dosing), 1, 2, 4, 6, 7, 8, 9, 10, 12, and 24 hours after dosing. The samples collected at 1 and 2 hours will be collected within 5 minutes of the scheduled time; the samples at 4 to 12 hours will be collected within 10 minutes of the scheduled time, and the 24-hour sample will be collected within 10 minutes BEFORE the next dose of study drug. For each PK sample, the actual collection (clock) time will be recorded.

26 On day 15, urine pregnancy test to be performed prior to dosing for the 4 week double blind treatment period; all other pregnancy testing time points will be obtained from serum.

6.2. Patient Requirements

6.2.1. Contraception

RM-493 has not been evaluated in any pre-clinical Developmental and Reproductive Toxicology Studies to date, therefore, the effects of RM-493 on embryo-fetal development are unknown at this time. It is imperative all study subjects adhere to the contraception requirements as outlined below.

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

For females able to bear children, a hormonal (i.e., oral, implantable, or injectable) and single-barrier method (i.e., sponge), or a double-barrier method of birth control (i.e., condom with spermicide) or abstinence must be used/ practiced throughout the study and for 90 days following the study.

Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months (and confirmed with a screening FSH level in the post-menopausal range), do not require contraception during the study.

It is not known if this treatment will affect spermatogenesis. Therefore, males with female partners of childbearing potential must agree o use contraception (e.g., if they ;have not had a vasectomy then should either (a) abstain from reproductive sexual intercourse or (b) use a condom and contraceptive foam during intercourse) if they become sexually active during the study and for 90 days following the study. Male subjects must not donate sperm for 90 days following their participation in the study

6.2.2. Protection from Sun

Skin hyperpigmentation, or ta ning, was observed in the cynomolgus monkey toxicology studies, and the human Phase 1/2 studies. These events were reversible upon cessation of study drug. However, it is still uncertain if exposure to sunlight might exacerbate the tanning effects of RM-493.

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

6.3. Efficacy Measurements

6.3.1. Weight

Weight (Kg) will be recorded as shown in the Schedule of Assessments (SOA), and generally will be assessed and recorded once weekly. All measurements will be done in triplicate at each timepoint. The same scale should be used throughout the study, including the Screening Visit, and should be calibrated on a regular basis. Weight should be measured when patients are fasting and at approximately the same time at each visit. Patients should be in underwear or scrubs (or equivalent), with no shoes and have emptied their bladder.

[redacted]

6.3.3. Body Composition DEXA

Participants will have three DEXA procedures to measure body compositions over the course of the study. DEXA uses low dose x-rays to non-invasively assess skeletal and soft tissue density. Half-body scans may be performed for subjects that extend beyond the scanning area. The risk associated with exposure to ionizing radiation is minimal and further minimized through the exclusion of pregnant women.

6.4. Clinical Procedures and Safety Assessments

6.4.1. Informed Consent

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

6.4.2. Demographics and Medical History

A complete medical history along with demographic data will be obtained for all patients during the Screening Period. Data to be recorded in the source document and CRF include the patient's gender, race, date of birth and concomitant medication use.

A recent medical history will be obtained on Day 1 prior to randomization to assess continued study eligibility and adherence to final inclusion/exclusion criteria. This recent medical history includes a review for changes from screening as well as a review of the patient's recent medication use and to assess whether or not any changes have occurred since the previous visit.

6.4.3. Physical Examination, Comprehensive Skin Examination, and Height

Physical Examinations

A complete physical examination will include review of peripheral lymph nodes, head, eyes (including conjunctiva), ears, nose, mouth and oropharynx, neck, heart, lungs, abdomen, musculoskeletal including back, extremities and neurologic, will be performed during the Screening Period (or at the discretion of the site, can be performed at Day -1), and at the Final Study Visit.

Abbreviated symptom-directed physical examinations (e.g., general, heart, lungs, abdomen, skin (not comprehensive), and extremities) will be performed during the Treatment Period, and follow up period as shown in the SOA.

All physical examinations are to be conducted in adequate light.

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

Comprehensive Skin Examinations

Comprehensive skin examinations will be performed by a Dermatologist. Comprehensive skin exams will be performed according to the SOA.

At screening, a specific focus of the comprehensive skin examination will be the identification of any skin lesions that appear to have dysplastic or malignant potential that could interfere with the interpretation of study outcomes regarding skin changes. In such cases, the patient will be excluded from the study. However, any lesions of concern can be biopsied and if confirmed to be benign prior to randomization, patients can be enrolled in the study.

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 Final Study Visit, the patient may be asked to return for additional follow up assessments to document progress towards resolution for ~60-90 days after last treatment.

[redacted]

Height

Height (cm) will be measured without shoes, during Screening using a wall-mounted stadiometer.

6.4.4. Fitzpatrick Scale

Each patient is to be categorized for skin type according to the Fitzpatrick scale [18] during the Screening Period. The Fitzpatrick Scale is depicted in Appendix 11.5.

6.4.5. Concomitant Medication Review

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

6.4.6. Vital Signs

Vital signs will be obtained in the sitting position following at least 5 minutes of rest each time they are measured, at the times outlined in the SOA.

Blood pressure and heart rate

Blood pressure (BP; mmHg) and heart rate (HR; bpm) are to be measured according to the SOA. At each timepoint, BP and HR measurements will be performed *in triplicate approximately 2*

minutes apart, using the same methodology throughout the study (manual or automated). Careful attention should be paid to using an appropriately sized BP cuff.

When possible, BP should be taken in the same arm throughout the entire study period.

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

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 according to the SOA.

6.4.7. 12-Lead Electrocardiogram

Single 12-lead electrocardiograms will be performed following a period of at least 10 minutes of rest in the supine position according to the SOA.

6.4.8. Clinical Laboratory Tests

Clinical safety laboratory tests are to be performed by the local laboratory as outlined in the Schedule of Assessments and patients are to be fasting for 8 hours. Labs are to be drawn prior to dosing.

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

Liver function test abnormalities will be evaluated in accordance with FDA Guidance (2009) as described in the Appendix 11.8.

Specific tests are described below.

6.4.8.1. Hematology Clinical Chemistry and Urinalysis

Hematology:

Complete blood count with platel t count and standard indices will be obtained.

Chemistry:

Sodium, potassium, chloride, CO_2, albumin, total protein, glucose, blood urea nitrogen (BUN), creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (GGT), creatine phosphokinase (CPK), alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), calcium and phosphorus.

Urinalysis:

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

6.4.8.2. Serum Samples for Storage

Extra retain samples will be taken pre-dose prior to double-blind study drug, and at the end of the 4-week double blind treatment period and will be used only in the event that unscheduled diagnostic tests are required for safety reasons, or for [redacted] that are currently not defined but are directly related to the aims of this study. These samples will be retained until the study

has been completed, and until the Sponsor has notified the study site in writing that the samples can be discarded.

6.4.9. Injection Site Evaluation and Scoring

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

Injection site evaluations and scoring will be conducted according to the SOA. In addition, unscheduled evaluations may also be recorded as warranted by clinical conditions.

6.4.10. Anti-RM-493 Antibody Measurements

Blood samples for measurement of anti-RM-493 antibodies will be drawn pre-dose, and thereafter according to the SOA.

6.4.11. Patient Questionnaires

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

PWS Hyperphagia Questionnaire (Dykens, 2014)

The PWS Hyperphagia Questionnaire is a tool for assessing hyperphagia-related behavior and will be a primary endpoint of the study, evaluated at both the end of the 4-week double-blind treatment phase, and again at the end of the 2-week randomized double-blind withdrawal phase.

Food Related Problems Questionnaire (Russell 2003)

The Food-Related Problems Questionnaire is a tool specifically designed for patients with Prader-Willi Syndrome to rate preoccupation with food, impairment of satiety, difficulty with self-control and other food-related 'challenging' behavior.

[redacted]

[redacted]

[redacted]

[redacted]

6.4.12. Diet and Behavior Training and Counseling

No special dietary counseling will be part of this trial, but patients will be counseled to continue on their usual diet at home. In addition, only patients who have been stable in weight (e.g., having had a stable weight at home of less than ±5%a change in weight over the last 2 months) will be included in the study.

Study participants should not initiate rigorous exercise routines while on study, but will be encouraged to do activities consistent with a healthy lifestyle (i.e.: walking).

6.4.13. Adverse Events

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

All AEs, including injection site reactions and potential systemic reactions will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grading system. Only injection site reactions considered clinically significant by the Investigator will be recorded as AEs.

Complete details on adverse event monitoring are provided in Section 7.1.

6.4.14. Order of Assessments

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

6.5. Pharmacokinetic Measurements

6.5.1. Sample Collection Schedule

Blood samples for PK analysis are to be drawn according to the SOA (Table 6-1). Plasma will be harvested from these samples and analyzed for RM-493 concentration. The site will be provided with separate instructions for sample processing and shipment.

All patients will have a blood sample collected for PK analysis before study drug is administered on Day 1 and within 5 minutes before study drug is administered on Day 42 and Day 70. The actual (clock) time each PK blood sample is collected will be recorded in the source documents and CRF. For the blood samples on Day 42 and Day 70, the actual time of the previous day's drug injection, as provided by the patient or caregiver, will also be recorded. Patients providing samples for the PK substudy (see next paragraph) do not need to provide a blood sample on Day 70.

Patients participating in the optional PK substudy (anticipated to be up to ~N=8) will have blood samples collected over 24 hours starting on any day from Day 63 through 69 (the second week of the optional, active-dose extension). Blood samples will be collected at 0 (within 5 minutes before dosing), 1, 2, 4, 6, 7, 8, 9, 10, 12, and 24 hours after dosing. The samples collected at 1 and 2 hours will be collected within 5 minutes of the scheduled time; the samples at 4 to 12 hours will be collected within 10 minutes of the scheduled time, and the 24-hour sample will be collected within 10 minutes BEFORE the next dose of study drug. For each PK sample, the actual collection (clock) time will be recorded.

7. ADVERSE EVENTS

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

7.1. Definitions, Documentation, and Reporting

An **adverse event (AE)** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event 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 adverse event or suspected adverse reaction is considered serious (**SAE**) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

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

7.2. Procedures for AE and SAE Reporting

Each patient must be carefully monitored for the development of any adverse events. 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 adverse events (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 page of the CRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an adverse event and must be recorded on the appropriate pages of the CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

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

[redacted]

Rhythm Pharmaceuticals, Inc.
855 Boylston Street, 11th Floor
Boston, MA 02116

[redacted]

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

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

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

Intensity of all AEs including clinically significant treatment-emergent laboratory abnormalities, injection site reactions and potential systemic reactions will be graded according to the CTCAE Version 4.0. The CTCAE grade refers to the severity of the AE and ranges from Grade 1 (mild AE), Grade 2 (moderate AE), Grade 3 (severe AE) and Grade 4 (life-threatening or disabling AE) to Grade 5 (death related to AE).

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

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

Moderate: discomfort sufficient to reduce or affect daily activity.

Severe: inability to work or perform normal daily activity.

Life threatening: represents an immediate threat to life.

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

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

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

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

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

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

7.3. Adverse Events and Risks

Overall, RM-493 has been generally well tolerated in previous studies. Drug-Related TEAEs (for which the adverse event was assessed as possibly or probably related to study drug by the investigator) were reported in 19 of 32 (59.3%) subjects who received RM-493 and 6 of 26 (23.1%) subjects who received placebo. Below we have listed other known side effects of RM-493. Because very few studies have been done using RM-493, there may be other unknown side effects. The PIs (or a covering clinician) will be available at all times to study participants in the event of a clinical emergency. Both this availability and how to reach the investigators in an emergency will be clearly communicated orally and in writing to study participants. All study interventions will be provided free of cost.

The following side effects were fairly common with RM-493 treatment and are usually mild:

- Decreased appetite
- Nausea
- Diarrhea
- Skin discoloration/darkening
- Penile erection in males/genital discomfort and sexual arousal in females
- Vertigo
- Dry mouth
- Headache

Side effects that are less common, but could require medical attention include:

- Vomiting
- Nightmares
- Nipple disorder (rare)
- Dermal cyst (rare)

Side effects that are rare but serious include

- Anorexia
- Significant genital discomfort in females (very rare)
- Depression or sad mood (very rare)

Side effects that have not been seen in clinical trials, but will be carefully assessed in the study (see below, Section 7.5 Guidelines for Additional Evaluations and Suspension of Dosing for a Patient):

- Prolonged erections in males (>4 hours)
- Significant increases in Liver Function tests
- Cancerous changes in skin lesions

7.3.1. Medical monitoring

The medical monitoring for the study will be done by a medical monitor supplied by Rhythm Pharmaceuticals. The PI has overall responsibility for the integrity of the study and participant safety. This information, as well as any other unanticipated problems involving risks to subjects or others, will also be reported to the IRB.

7.4. Monitoring of Adverse Events and Period of Observation

Adverse events will be recorded on the CRFs starting from Screening up to and including the Final Study Visit. Serious adverse events and deaths will be recorded on the CRFs starting on Day 1 and continuing through the Final Study Visit. All AEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

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

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

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

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

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

[redacted]

8. STATISTICAL PROCEDURES

The statistical analyses and data summaries will be provided by Cytel. This section describes the plans for analysis. Any additional analyses and specific conventions for analysis will be described in the Clinical Study Report.

8.1. Sample Size Estimation

Prior data from the 4 week Phase 1b treatment arms of Study RM493-002 (MAD study) yielded the following summary statistics for mean change from baseline after 4 weeks:

Pooled SD for Placebo: SD=1.1, N=12

Pooled SD for RM493: 2.3, N=18

Assuming SD=1.1 for placebo and SD=2.3 for RM-493, if the true mean difference in 1-month weight loss between treatments is 2.5 kg in this study (N=12 placebo and N=12 RM-493), there would be 94% power to yield a statistically significant (alpha=0.05, 1-sided) difference between treatments (83% power if true difference is 2 kg). The minimum observed difference in mean weight loss after 4 weeks of treatment, between RM493 and placebo that would be statistically significant is 1.3 kg.

8.2. Populations for Analysis

The Efficacy population for analysis will be the Full Analysis Set (FAS) which will consist of all patients with a baseline and at least one post-dose efficacy observation. The primary efficacy analysis excludes data observed after discontinuation. In addition, a Per Protocol population (e.g., completers of the 4-week double blind treatment period) will be conducted.

The Safety Population consists of patients who receive any of the study drug injection and have at least one post-dose safety assessment.

The Pharmacokinetic (PK) Evaluable Population is defined as all patients in the Safety Population who have evaluable plasma concentration-time profiles for RM-493 in the substudy.

8.3. Procedures for Handling Missing, Unused, and Spurious Data

No data will be imputed; all analyses and summaries will be based on observed data only, and no data will be excluded unless they are associated with a major protocol violation (which will be defined prior to data unblinding).

8.4. Interim Analysis

If recruitment is slow (e.g., >6 months), then an administrative interim analysis may be conducted with analysis of group mean data for key efficacy endpoints to assess overall futility. A limited interim analysis of data from this study was completed after ~N=16 PWS patients completed the 4-week double blind period of the study. This analysis, which has not been shared with study participants, study investigators, or Rhythm study personnel involved in the conduct of the study, was primarily designed to assess futility and to allow planning of future studies.

8.5. Statistical Methods

Analyses will be based on observed data only; no data will be imputed.

Continuous efficacy endpoints will be assessed via repeated measures, longitudinal mixed analysis of variance model which will include fixed effects terms for treatment, timepoint, treatment-by-timepoint interaction, and baseline covariate, and random effect for subjects. An unstructured covariance matrix will be used to model the expected different variances among the treatments. T-tests derived from the model will use Satterthwaite's degrees of freedom estimates. The assumption of normality will be assessed via the Shapiro-Wilk statistic as a diagnostic of closeness to normality, not as a conditional test associated with efficacy endpoint analyses. Other graphical assessments of residuals from the model fit may be examined. If a substantial departure from normality is observed, a transformation such as log (post/pre) or rank may be used to analyze the data as a sensitivity analysis; however, the analysis on the original scale of observation will be reported.

The comparison of each dose of RM-493 with placebo will be carried out via 1-sided statistical test at alpha=0.05, with no adjustment for multiplicity for comparisons with two dose regiments. This is justified by the pilot nature of this small study.

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.

The Hyperphagia Questionnaire is a 10 item instrument that was specifically designed to measure food-related preoccupations and problems in PWS, as well as the severity of these concerns. Items reflected parent and offspring reports of hyperphagic symptoms gleaned from ongoing research and clinic programs for persons with PWS and their families. The severity items were based on the definition of symptom-related impairment as operationalized by the American Psychiatric Association[40]. Previous factor analyses identified three robust factors: Hyperphagic Drive (e.g., how persistent in asking for food; how easy to direct away from food); Hyperphagic Behaviors (e.g., how fast or clever in obtaining food, how often steal food), and Hyperphagic Severity (time spent talking about food; extent that food interferes with everyday functioning). Items are rated by care providers on a 5-point scale (1 = not a problem to 5 = a severe and/or frequent problem) and are listed in Appendix 11.2 [41]. Raw scores for each factor will be used in data analyses, and the three domains will be summed for an overall summary index of hyperphagia.

Plasma RM-493 and RM-493 antibody concentrations will be summarized, and may be compared to PD endpoints.

Noncompartmental methods will be used to compute PK parameters for RM-493, and will be fully described in a separate PK analysis plan. The parameters computed from the 24-hour profile will include C_{max}, T_{max}, AUC_{24hour}, volume of distribution (Vd), and total clearance (CL);

parameters describing elimination may not be computed due to the limited number of blood samples collected to characterize the elimination profile.

9. ADMINISTRATIVE REQUIREMENTS

9.1. Good Clinical Practice

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

9.2. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see Appendix 11.9). The IRB 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 approval has been obtained. The protocol, Investigator Drug Brochure, 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 by the Investigator.

9.3. Patient Information and Informed Consent

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

9.4. Patient Confidentiality

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

9.5. Protocol Compliance

The investigator will conduct the study in compliance with the protocol provided by Rhythm, and given approval/favorable opinion by the IRB 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 approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB 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. Rhythm or designee will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

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

9.6. Data Management

9.6.1. Data Handling

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

9.6.2. Computer Systems

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

9.6.3. Data Entry

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

9.6.4. Medical Information Coding

For medical information the following thesauri will be used:

MedDRA for adverse events

WHO Drug for concomitant medications

9.6.5. Data Validation

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

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

9.7. Direct Access to Source Data

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

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

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

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

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

9.8. Source Document/Case Report Form Completion

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

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

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

Rhythm will retain the originals of all CRFs. The investigator will retain all completed source documents/CRFs.

9.9. Record Retention

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

9.10. Liability Insurance

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

9.11. Publication of Study Findings and Use of Information

All information regarding RM-493 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 RM-493 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

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

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11. APPENDICES

11.1. Injection Site Evaluations

Injection sites will be assessed using a form similar to the depiction below at the timepoints outlined in the SOA.

Local Skin Tolerability Assessment

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

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

Initials: _____

[redacted]

[redacted]

11.3. Food-Related Problem Questionnaire

Russell H, Oliver C The assessment of food-related problems in individuals with Prader-Willi syndrome. British Journal of Clinical Psychology 2003; 42, 379-92.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.7. Fitzpatrick Classification Scale

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

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

[redacted]

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

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

As previously mentioned, penile erections in males are effects associated with MC4R agonism, and have been seen in RM-493 Phase 1 studies. However occurrence of these events does not appear to correlate with dose and duration of dosing, as the number of events did not increase with dose or duration of dosing. These events have been intermittent usually lasting less than 20 minutes, painless, and resolved without intervention. If a patient reports a painless, non-erotic erection of more than one hour duration, patients will be instructed to urgently contact the Investigator, and based on Investigator judgment, study drug injection is to be immediately discontinued. If after study drug discontinuation the event does not resolve, further treatment may be provided as clinically indicated.

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

11.10. Evaluation of Abnormal Liver Function Tests (LFTs)

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

1. If ALT or AST>3 ULN, repeat in 48-72 hrs.
2. If repeat ALT or AST are still >3 ULN, repeat LFTs (including transaminase, alkaline phosphatase and bilirubin levels) every 48-72 hrs. In addition, the following should be performed:

    Obtain a detailed history of symptoms, prior and concurrent diseases, concomitant drug use (including OTC, herbal and dietary supplements), alcohol and recreational drug use and special diets

    Obtain history of exposure to environmental chemical agents

    Consider evaluation for acute viral hepatitis types A, B, C, D and E, autoimmune or alcoholic hepatitis, nonalcoholic steatohepatitis (NASH), biliary tract disease and ischemic liver injury

    Consider additional tests to evaluate hepatic function, as appropriate, such as INR.

    Consider hepatology consultation

Frequency of repeat testing can be reduced if LFT abnormalities stabilize or if the patient is asymptomatic and study drug is discontinued.

3. Discontinue study drug administration if:

    ALT or AST>8xULN on any single determination

    ALT or AST >5xULN for more than 2 weeks

    ALT or AST >3xULN with total bilirubin >2xULN or INR >1.5

    ALT or AST >3xULN with the appearance of fatigue, fever, rash, and/or eosinophilia (>5%) or nausea, vomiting, right upper quadrant pain or tenderness that is more frequent and/or more severe than patient's baseline DG symptoms

4. Follow-up to Resolution: All study patients with clinically significant treatment-emergent LFT abnormalities should be followed until values return to normal or baseline levels

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

11.11. Declaration of Helsinki

World Medical Association Declaration of Helsinki:

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Patients

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

A. INTRODUCTION

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

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

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

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

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

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

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

C ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

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

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