Rhythm Pharmaceuticals, Inc.

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

Statistical Analysis Plan

Final Version 2.1
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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
Sponsor:	Rhythm Pharmaceuticals, Inc. 500 Boylston Street Boston, MA 02116, USA [redacted]
Protocol Number:	RM-493-010
Document Date/Version:	January 7, 2016, Amendment 5

[redacted]

Signature:_____

Date:_____

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatory:

[redacted]

Rhythm Pharmaceuticals, Inc.
500 Boylston Street
Boston, MA 02116, USA
[redacted]

Signature:__[redacted]

Date:_____22 Aug 2016_____[redacted]_____

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LIST OF ABBREVIATIONS

Abbreviation	Definition
°C	Degrees Celsius
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
BID	bis in die or twice a day
BUN	Blood urea nitrogen
CBC	Complete blood count
cm	Centimeter
CPK	Creatine Phosphokinase
CRO	Contract Research Organization
DEXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full Analysis Set
FRPQ	Food related problems questionnaire
GGT	Gamma-glutamyltranspeptidase
IA	Interim analysis
iSAP	Interim statistical analysis plan
kg	Kilogram
LDH	Lactate dehydrogenase
LFT	Liver function test
MAD	Multiple ascending dose
MC4R	Melanocortin 4 receptor
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
ORO	Observer reported outcome
PK	Pharmacokinetic
PP	Per Protocol
PWS	Prader-Willi Syndrome
QD	qua´que di´e or every day
QoL	Quality of life
SAE	Serious adverse event
SAF	Safety Set

SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
WBC	White blood count

1 INTRODUCTION

This document presents the statistical analysis plan (SAP) for Rhythm Pharmaceuticals, Inc. (Rhythm), Protocol No. 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.

It contains the details and methods to be used to perform the proposed efficacy and safety analyses, including planned summary tables and by-patient listings.

This SAP was based on [redacted]. The reader of this SAP is encouraged to also read the clinical protocol, and other relevant documents for details on the planned conduct of this study. Other than the schedule of study procedures which is provided in Appendix 1, operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

The objectives listed below (primary, secondary and exploratory) are found in the protocol.

Study RM-493-010 is a Phase 2 study designed to provide the basis for pivotal data in a Phase 3 study or studies to follow. The PWS population is very rare, and patients are difficult to identify and recruit. Therefore the number of participants studied will be small. In addition, there is no precedent for an approved effective treatment for the hyperphagia and obesity of PWS. As a consequence, endpoints have not been well studied, and key questions on tools, endpoints, populations, age-related effects, and other parameters remain to be answered. This study has been designed to explore these questions, and to provide a rationale for a more robust Phase 3 study design. As a result of the small number of patients and the lack of clarity on clinically important endpoints for PWS, this study includes numerous endpoints for which no multiplicity adjustment is planned. It will also include an interim analysis when approximately half the patients have been randomized, with the likelihood that study parameters may be altered and adjusted to reflect additional understanding of the effects of setmelanotide in this population. This approach is justified given the evolving understanding of PWS and any information and/or conclusions will be confirmed in a prospective, rigorous Phase 3 study or studies to follow.

2 STUDY OBJECTIVES

2.1 Primary Objectives

After 4 weeks of double-blind study drug treatment, the primary objectives of this study are to:

- 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

2.2 Secondary Objectives

The key secondary objectives are to:

- Evaluate the 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

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

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

(1) 2-week single-blind, placebo-controlled baseline period; and

(2) 4-week, double blind, placebo-controlled, randomized parallel group period (primary analysis time point) where patients will be randomized 2:1:3 to placebo or one of two dose levels of RM-493; and

(3) 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; and
(4) an optional 2-week open label extension period where every patient can participate and receive open label RM-493.

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.

Approximately 20 subjects will be randomized to a placebo arm or one of 2 dosing arms. 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 in a 2:1:3 allocation (Placebo/low dose/high dose).

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

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 (150 mcl) of RM-493 for 2 weeks.

The overall study duration will be approximately 12 months; individual patient participation will be approximately 5 months (from Screening period through OL follow-up period).

Study patients will receive study drug by SC injection 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). Patients and/or their caretakers 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).

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), and return the next day for one additional assessment for pharmacokinetics.

Two study diagrams are presented

Figure A: First Half of Study Schema of Dose Allocation (original protocol through Amendment 4)

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

3.2 Randomization Methodology

In the first half of the study, approximately 20 subjects will be randomized to a placebo arm or one of 2 dosing arms in a 2:1:3 allocation. 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 active or placebo.

All patients will be pre-randomized to their status/treatment group for the first 3 periods of the study at the initial randomization at the start of Period 1. Those who are compliant in study drug administration and have demonstrated willingness to complete study procedures (weighing, questionnaire and diary completion), will continue to receive subcutaneous doses of RM-493 or placebo per randomization to the Double-blind study, for 4 weeks of double- blind treatment (Period 2), followed by a 2-week double-blind randomized withdrawal period (Period 3), as specified in the initial randomization schedule. Everyone will receive active drug during the optional open label active drug extension (Period 4).

Period 1: 2-week single-blind, placebo-controlled baseline period
Period 2: 4-week double-blind, placebo-controlled randomized parallel group period
Period 3: 2-week double-blind randomized withdrawal period
Period 4: optional 2-week open label extension period
Post Study Follow-up: ~1-3 month follow-up after last dose

Figure C: Treatment groups by Period

Protocol Version	Treatment Group	Period 1 Trt	Period 2 Trt	Period 3 Trt	Period 4 Trt	Post Study Follow-up
Original through Amend ment 4	Placebo	PBO 50 uL	RM-493 0.5 mg	RM-493 0.5mg	RM-493 1.5 mg	
				PBO 50 uL		
		PBO 150 uL	PBO 150 uL	RM-493 1.5 mg		
				PBO 150 uL		
	RM-493 0.5 mg	PBO 50 uL	PBO 50 uL	RM-493 0.5 mg		
				PBO 50 uL		
	RM-493 1.5 mg	PBO 150 uL	RM-493 1.5 mg	RM-493 1.5 mg		
				PBO 150 uL		
Amend ment 5	Placebo	PBO 150 uL	RM-493 1.5 mg	RM-493 1.5mg	RM-493 2.5 mg	
				PBO 150 uL		
		PBO 250 uL	PBO 250 uL	RM-493 2.5 mg		
				PBO 250 uL		
	RM-493 1.5 mg	PBO 150 uL	PBO 150 uL	RM-493 1.5 mg		
				PBO 150 uL		
	RM-493 2.5 mg	PBO 250 uL	RM-493 2.5 mg	RM-493 2.5 mg		
				PBO 250 uL		

Patients will be assigned to one of the double-blind treatment arms in the order in which they are entered into the randomization system and according to a randomization schedule that is uploaded into eCOS. Patients who are randomized but not dosed will be replaced; in order to

maintain balance between treatment groups having a small sample size, replacements will have the same treatment as the original randomized patient being replaced, via a system (IWRS) randomization. Patients who discontinue from the study or study treatment prematurely after receiving at least one dose of the study drug will not be replaced.

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.

3.3 Efficacy Endpoints and Safety Parameters

All primary and key secondary endpoints are analysed during Period 2, the 4-week double blind period of the study. Other secondary endpoints (for which data are available) are assessed during Period 3 (the randomized withdrawal) and Period 4 (open label active extension).

3.3.1 Primary Efficacy Endpoint

The primary efficacy endpoints are the:

- Body weight (kg): Percent change from baseline (Period 2)
- PWS Hyperphagia Questionnaire: Percent Change from baseline (Period 2) Overall Score

3.3.2 Secondary Efficacy Endpoints

3.3.2.1 Key secondary efficacy endpoint:

- Body weight (kg): Change from baseline (Period 2)
- PWS Hyperphagia Questionnaire: Percent Change/Change from baseline (Period 2)
    - Overall Score (Change from Baseline only – Period 2)
    - 3 domains
        - Hyperphagic Drive
        - Hyperphagic Behaviors
        - Hyperphagic Severity
    - Individual Questions
- DEXA (body fat): Percent Change/Change from Baseline (Period 2)
- DEXA (body mass): Percent Change/Change from Baseline (Period 2)

3.3.2.2 Additional Secondary endpoints are:

- Body weight (kg): Percent Change/Change from baseline (Period 3) (Period 4)

- Body weight (kg): Percent Change/Change from baseline (Period 2/3) for continuous active and continuous placebo treatments
- PWS Hyperphagia Questionnaire: Percent Change/Change from baseline (Period 3) (Period 4)
- DEXA (body fat): Percent Change/Change from Baseline (Period 4)
- DEXA (body mass): Percent Change/Change from Baseline (Period 4)

[redacted]

3.3.4 Safety Endpoints

Safety and tolerability of RM-493 will be assessed throughout the study.

Safety and tolerability endpoints include:

- AE review
- Injection Site Evaluation

[redacted]

- Clinical laboratory safety tests (subset) including:
  - Hematology: Hemoglobin, Hematocrit, WBC, Platelets
  - Chemistry: Bun, Creatinine, Potassium, ALT, AST, Total Bilirubin, Alkaline phosphatase, GGT, CPK, Glucose
- Vital signs

- ECG evaluations
- Physical examination, Comprehensive Skin Examination, and Height
- Concomitant medication

3.3.5 Pharmacokinetic Endpoints

Blood samples for measurement of plasma RM-493 will be collected from all patients on Day 1 pre-dose and within 5 minutes before study drug is administered on Day 42. Additionally, in a subset of patients participating in the optional PK substudy, (any day from Day 63 through Day 69), PK samples may be collected pre-dose and at selected time points for up to 24 hours post-dose. Samples will be assayed for RM-493 levels. PK analysis will be included in a separate PK analysis plan.

3.4 Analysis Populations

The following patient populations will be evaluated and used for presentation and analysis of the data.

Safety Set (SAF): All subjects who were randomized and received at least 1 dose of study medication and have at least one post-dose safety assessment (within Period 2) will comprise the SAF. Subjects will be classified into groups based on actual treatment received. The SAF will be used for all safety analyses.

Intent to Treat (ITT): All randomized subjects. If there is a greater than 15% difference from the FAS, efficacy tables for the ITT population will also be generated.

Full Analysis Set (FAS): All randomized subjects who have received at least 1 dose of randomized study medication with a baseline and at least 1 post-baseline efficacy observation within Period 2 will comprise the FAS. Subjects will be classified based on randomized treatment group, regardless of the actual treatment taken. The FAS will be used for analyses of all efficacy endpoints.

Per Protocol Set (PP): A subset of the FAS who completed the 4-week double blind treatment period (Period 2) with no major protocol violations. The list of deviations that will exclude data from the PP population will be finalized by the Sponsor and **documented prior to any unblinding of data** for analysis.

Major protocol violations may include, among others:

1. Violation of key inclusion/exclusion criteria, as reviewed by study clinician.
2. Violation of legal documents including, but may not be limited to informed consent and patient privacy.
3. Subjects who received the wrong treatment or incorrect dose.
4. Non-compliance on study withdrawal criteria:

a. Non-adherence to study drug regimen (must be at least 67% compliant with study medication) or protocol requirements.
b. Non-compliance with instructions or failure to return for follow-up.

Subjects will be classified based on randomized treatment group, regardless of the actual treatment taken.

The FAS Population is the primary population for the analysis of efficacy parameters. The PP subset is also used for the primary and key secondary endpoint analyses. The SAF is the primary population for the analysis of safety endpoints.

4 STATISTICAL METHODS

This SAP may not describe all analyses that will be performed for this study. Additional analyses may be requested by the Sponsor and performed to supplement the results outlined in this SAP. All post-hoc analyses that have not been identified in this plan but are included in the clinical study report (CSR) will be clearly identified in the text of the CSR.

4.1 Sample Size Justification

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:	SD=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 RM493), 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.

4.2 General Considerations

Data will be described and analyzed using the Statistical Analysis System (SAS), version 9.2 or higher on a Windows platform (SAS Institute Inc., Cary, NC). Adverse events and medical history will be coded using MedDRA Version 18.1. Prior and concomitant medications will be coded to provide Anatomical Therapeutic Chemical (ATC) levels 2 (therapeutic main groups) and 4 (chemical subgroups) using the December 2014 version of the World Health Organization (WHO) Drug Dictionary.

Individual patient data will be presented in by-patient data listings. Descriptive statistics (number of patients [n], mean, standard deviation [SD], median, minimum [Min] and maximum [Max]) will be presented for continuous data. For categorical data, the frequency and percentage of patients in each category will be presented; percentages will be based on the number of patients with non-missing observations.

Unscheduled visits will not be used, unless they meet the criteria for a baseline observation (e.g. last observation prior to initial double-blind drug administration).

A by-patient listing will be provided which includes all derived efficacy data for which the derivation is not otherwise provided. The data as collected will be provided in the relevant by-patient listing of the raw data.

Unless specified otherwise, by-patient listings will be provided for all data as contained in the raw database.

Reporting of treatment groups in summary tables will be performed with placebo groups (high and low dose groups) combined. The primary focus for the treatment group analysis will be on Period 2 (the 4-week double blind period). Additional analyses will focus on specific intervals (Period 3; effect of randomized change in treatment from active to placebo, and placebo to active); Period 4 (the open label, 1.5 mg dose 2-week active extension), and Period 1 (the double-blind, placebo controlled run-in period).

The final study analysis will include summaries from pooled data using identical active doses (e.g., 0.5 mg, 1.5 mg, 2.5 mg) across the whole study, including data from before and after any interim analysis. As mentioned above, all placebo data will be pooled as well.

Supplemental exploratory analyses will be done for Period 1 (run-in) data to help in understanding of the variability of PWS subjects in a clinical trial; this data will complement the placebo data obtained later in the trial.

Lastly, if the data support that all active groups show similar efficacy, a pooled “active” vs placebo exploratory analysis will also be conducted.

The design of this study raises additional questions on data analysis, as patients may have alternating period of active and placebo treatment after beginning double-blind treatment in Period 2. Data may be summarized by periods and treatment sequences (e.g., within the “withdrawal” phase of Period 3 and/or the open label active extension of Period 4), by focus on patients who remain on the same treatment vs. those whose treatment changes (e.g., to evaluate the difference in hyperphagia in those who remain on an active dose in both Period 2 and 3, vs those that receive active in Period 2 but are withdrawn to placebo in Period 3). It is anticipated that some of these exploratory analyses will be informed by the interim analysis.

4.2.1 Derived Data

The following implementations will be made for derived data:

Table 1. Derived Variables

Variable	Derivation
General	
weight (kg)	weight (lb) × 0.454; regardless of unit, take average of weight values for any one timepoint; if only 1 value is present for a timepoint,,this value will be used in the analysis
height (cm)	height (in) × 2.54
body mass index (kg/m^2)	weight (kg) / [height (m)]^2
temperature (°C)	[temperature (°F) - 32] × 5/9
age (yr)	integer part of (date of informed consent – date of birth) / 365.25
Study Days and Periods	
relative day, prior to treatment with study drug	date of visit – date of study drug administration [Day 1 is the day immediately prior to treatment with first study drug in the placebo controlled run-in period.]
relative day, on or after day of study drug	date of visit – date of study drug administration + 1 [Day 1 is the day treatment with DB study drug was administered.]
relative time for efficacy endpoints	date and time of the evaluation – date and time of the end of the last injection of study drug
relative time for safety evaluations	date and time of the evaluation – date and time of the start of the first injection of study drug
Baseline	See Section 4.2.5
change from baseline	See Section 4.2.5

Abbreviations: C=Centigrade, F=Fahrenheit

4.2.2 Handling of Missing Data

. For a sensitivity analysis on the primary efficacy endpoints (Body Weight and PWS Hyperphagia Questionnaire), missing data from subjects who do not adhere to therapy will be imputed with the mean value from those subjects on the same arm that also did not adhere to therapy, but had the measurement for the primary endpoint.

Imputation will not be performed in the case of partial or missing dates. The relative study days, where determined, will be calculated for full dates only

Incomplete AE dates will be derived based on the following guidelines:

- The dates that are missing or incomplete are derived as follows:

  If the start date/time of an AE is partially or completely missing, the date/time will be compared as far as possible with the date/time of the start of administration of study drug. The AE will be assumed to be treatment-emergent if it cannot be definitively shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach).

The following general rules will be used:

- If the start time of an AE is missing but the start date is complete, an AE will only be excluded as being treatment-emergent if the start date is before the date of study drug administration or if the stop date/time is before study drug administration.

- If the start time and day are missing but the start month and year are complete, an AE will only be excluded as being treatment-emergent if the start month/year is before the month/year of study drug administration or if the stop date/time is before study drug administration.

- If the start day and month are missing but the start year is complete, an AE will only be excluded as being treatment-emergent if start year is before the year of study drug administration or if the stop date/time is before study drug administration.

- If the start date is completely missing, an AE will be considered treatment-emergent unless the stop date/time is before study drug administration.

4.2.3 Visit Windows

Visit windows will not be employed in the analysis, i.e., data will not be excluded from the analysis based on whether the data fell outside of visit windows.

4.2.4 Multiplicity

There will be no multiplicity adjustments in this Phase 2a pilot study.

4.2.5 Baseline Definition

Baseline will be determined separately for each efficacy endpoint and safety parameter. That is, a missing baseline for one endpoint/parameter does not mean that the baseline will be missing for the other endpoints/parameters. For endpoints with discrete visits, baseline will use the last observation prior to dosing.

The baseline for each of the analysis periods is specified below:

Period 1 Baseline = Screening/Day 1 (based on assessment)
Period 2 Baseline = Day 15
Period 3 Baseline = Day 42
Period 4 Baseline = Day 56

where Days 15, 42, and 56 refer to the baseline of the respective period and not the actual study day for any one patient.

Change from baseline is defined as:

Period 1 (Day 15 value – Day 1 value)
Period 2 (Day 42 value – Day 15 value)
Period 3 (Day 56 value – Day 42 value)
Period 4 (Day 70 value - Vay 56 value)

For patients with either a continuous active or a continuous placebo dosing over time, information may be summarized using the following intervals:

Period 2/3:	Day 15 through Day 56
Continuous low dose:	Day 15 through Day 56
Continuous high dose:	Day 15 through Day 70
Continuous placebo:	Day 1 through Day 56

4.3 Statistical Hypothesis

For the co-primary efficacy endpoint, the null hypothesis is that the mean percent change from baseline (Period 2) in Weight (kg) for patients taking RM-493 is the same as for those taking placebo. That is,

H_{p0}: $\mu_{pA} = \mu_{pP}$

H_{p1}: $\mu_{pA} \neq \mu_{pP}$

where μ_{pA} and μ_{pP} is the mean percent change in weight (kg) at Day 42 (Week 6), for patients on active treatment (RM-493 0.5 mg and placebo 50 uL) and (RM-493 1.5 mg and placebo150 uL), respectively.

Likewise, for the co-primary efficacy endpoint for the PWS, the null hypothesis is that the mean percent change from baseline (Period 2) in the Overall Score for the Dykens PWS assessment for patients taking RM-493 is the same as for those taking placebo. That is,

H_{s0}: $\mu_{sA} = \mu_{sP}$

H_{s1}: $\mu_{sA} \neq \mu_{sP}$

where μ_{sA} and μ_{sP} is the mean percent change in the PWS Overall score at Day 42 (Week 6), for patients on active treatment (RM-493 0.5 mg and placebo 50 uL) and (RM-493 1.5 mg and placebo150 uL), respectively.

4.4 Study Patients

Screen Failure: A patient screened for participation in the RM-493-010 study who does not meet all of the inclusion and/or who meets any of the exclusion criteria for enrolment will be deemed a screen failure and will not be randomized.

Patients may also be considered screen failures during the 14-day, single-blind, placebo run-in phase. 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 diary 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).

4.4.1 Disposition of Patients

Summary data will be presented by dose group and overall, based on the number of patients enrolled as well as defined by the analysis populations. Patient disposition will be tabulated and include the number screened and the number who participated in the placebo run-in period. Screen failure data during the placebo run-in period as well as screen failures prior to the placebo run-in period will also be summarized. The number of patients in the ITT Set, Safety Set, the Full Analysis Set, and the Per Protocol Set, and the number who withdrew prior to completing the study along with their primary reason for withdrawal, and the Period

in which they discontinued, will be presented. A breakdown of patients by site and treatment group, within the Safety Set will be provided.

A by-patient listing including the details of the study disposition will be provided for all patients (including screen failures that are prior to or during the single blind run-in period).

4.4.2 Summary of Populations and Protocol Deviations

A summary of the populations and associated defining criteria will be presented in a tabular format for selected populations (ITT, SAF, FAS, PP).

For the ITT population, the number of patients with a protocol violation (determined through joint clinical / statistical review prior to data base lock), as well as a summary of protocol deviation categories will be presented. Protocol deviation categories will be summarized by category and center.

The list of important protocol deviations related to study inclusion/exclusion criteria, patient management/assessment, or conduct of the study will be finalized by the Sponsor and documented prior to database lock or any unblinding of data. Specific criteria will be reviewed prior to database lock, and will include such criteria as contraindicated concomitant medications or incorrect dose group and other items as deemed appropriate by the Sponsor.

All important protocol deviations will be summarized and presented in a by-patient data listing.

4.4.3 Demographic and Disease Characteristics

Demographic data will include patient age, gender, race, and ethnicity. Baseline characteristics include weight, height, BMI, and waist circumference. Demographic and baseline characteristics will be tabulated for all patients in the SAF population by dose group and overall.

A by-patient listing will be presented for all patients in the SAF population.

4.4.4 Study Drug Administration

Study drug exposure will be presented for all patients in the SAF. Injection information will include total study drug exposure, individual administering dose, quantity of dose administered (full or partial), and reason for dose interruption or modification and will be tabulated by period 2 and 3.

Exposure data will be presented in a by-patient data listing for all patients in the SAF population.

4.4.5 Medical History

A by-patient listing of medical history data will be provided in a data listing.

4.4.6 Concomitant Medications

By-patient listings of all concomitant medications will be provided.

4.5 Efficacy Endpoints and Analyses

4.5.1 Primary Efficacy Endpoints

There will be 2 co-primary endpoints analysed.

Percent change from baseline in body weight, and percent change from baseline in the Overall score for the PWS Hyperphagia questionnaire over the 4-week double-blind dosing period (Period 2) will be assessed as co-primary efficacy endpoints.

The **Hyperphagia Questionnaire** is a 10-item instrument designed to measure food-related preoccupations and problems in PWS, as well as the severity of these concerns. Three factors identified from this questionnaire are:

- Hyperphagic Drive (e.g. how persistent in asking for food; how easy to direct away from food; items 1,3,6,9)
- Hyperphagic Behaviors (e.g. how fast or clever in obtaining food; how often steal food; items 2,4,5,8)
- Hyperphagic Severity (time spent talking about food; extent that food interferes with everyday functioning; items 7,10)

Items are rated by care providers on a 5-point scale (1=not a problem to 5=a severe and/or frequent problem). The questionnaire can be found in Appendix 2. 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 (maximum overall score of 50). Missing values will not be imputed. If a single item in a factor is missing for a patient, that factor will be missing.

These endpoints will be tabulated by dose group for the FAS and PP populations. There will be no adjustment for multiplicity.

4.5.1.1 Primary Analysis

The primary analysis involves comparison of percent change from baseline during Period 2 between the RM-493 active treatment groups and placebo. A mixed model repeated measures analysis of variance with fixed terms for treatment, time, treatment-by-time interaction and baseline covariate as well as a random effect for subjects will be used to assess the primary efficacy endpoint. 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 regimens. Of note, the 0.5 mg dose was included in the study as an anticipated no-effect or minimal effect dose for dose ranging.

Least square (LS) mean changes from baseline for each treatment group, and LS mean difference between each active RM-493 dose group and placebo, and the associated 95% confidence intervals for the difference will be provided, along with the reported p-values (one-sided). In addition change from baseline will be tested using a 2-sided statistical test at alpha=0.05.

Sample SAS code that can be used to implement the MMRM analysis is provided below:

```
proc mixed data=adef  method=reml;
  class subjid trtpn visitnum;
  model pcgresn = trtpn visitnum trtpn*visitnum base / solution ddfm=satterthwaite;
  repeated visitnum / type=un subject=subjid;
  lsmeans trtpn*avisitn  / cl alpha=0.05;
  lsmeans trtpn*avisitn / diff=control ('1' 'Day x') cl;  *[where '1' represents group=placebo];
run;
```

In an effort to examine the robustness of the results obtained from the analysis of the co-primary endpoints, sensitivity analyses will be performed. The sensitive analysis will be undertaken by imputing missing data from subjects who do not adhere to therapy with the mean value from those subjects on the same arm that also did not adhere to therapy, but had the measurement for the primary endpoint.

By-patient data listings will be provided.

4.5.2 Secondary Efficacy Endpoints

4.5.2.1 Key secondary efficacy endpoints

Key secondary efficacy endpoints will be analysed for Period 2 for 3 treatment groups (see Table C, Period 2) for both the FAS and PP populations. Endpoints include:

- Change from baseline to end of Period 2 in body weight (kg), and
- Percent change/change from baseline in PWS Hyperphagia questionnaire for each of Overall Score (change from baseline only), 3 domains and individual scores (Period 2).
- Percent change/change from baseline in DEXA (Body Fat) and (Body Mass) for Period 2

Change from baseline in body weight over the 4-week double-blind dosing period will be assessed as a key secondary efficacy endpoint. Change in body weight during Period 2 will be tabulated by dose group.

Percent Change/Change from baseline in PWS Hyperphagia Questionnaire for each of Overall score (Change from baseline only), 3 domains and individual scores will be assessed as key secondary efficacy endpoints. Change and percent change in PWS during Period 2 will be tabulated by dose group.

Analyses for the key secondary endpoints will employ the similar methods used for the primary analyses (see Section 4.5.1.1).

4.5.2.2 Secondary endpoints

Additional secondary efficacy endpoints will be analysed for the FAS population only. Endpoints include:

- Body weight (kg): Percent Change/Change from baseline (Period 3) (Period 4)
- Body weight (kg): Percent Change/Change from baseline (Period 2/3) for continuous active and Placebo treatments
- PWS Hyperphagia Questionnaire: Percent Change/Change from baseline (Period 3) (Period 4)
- DEXA (body fat): Percent Change/Change from Baseline (Period 4)
- DEXA (body mass): Percent Change/Change from Baseline (Period 4)

The **Body weight (kg) percent change and change from baseline (Period 3) (Period 4)**, will be assessed for Period 3 and for Period 4.

The **Body weight (kg) percent change and change from baseline (Period 2/3)** for continuous active and Placebo treatments only (e.g. 4 treatment groups), will be assessed for Period 2 through Period 3.

The **PWS Hyperphagia Questionnaire percent change/change from baseline (Period 3) (Period 4)**, will be assessed for Period 3 and Period 4 with treatment groups corresponding to each period. Summaries will be generated for the Overall score, the 3 PWS domains, and individual questions.

The **DEXA (body fat) percent change/change from baseline (Period 4),** will be assessed from end of Period 2 (Day 42) to end of Period 4 (Day 70), with treatment groups corresponding to these periods.

The **DEXA (body fat) percent change/change from baseline (Period 4**) will be assessed from end of Period 2 (Day 42) to end of Period 4 (Day 70), with treatment groups corresponding to these periods.

A similar model to that used for the primary endpoint analysis will be used for analysis of all secondary endpoints.

By-patient data listings will be provided.

[redacted]

The **food related problem questionnaire Percent change/change from baseline (Period 2) (Period 3) (Period 4)** will be assessed for each of these time periods between baseline and end of Periods 2, 3, and 4 for the respective treatment groups found in those time periods.

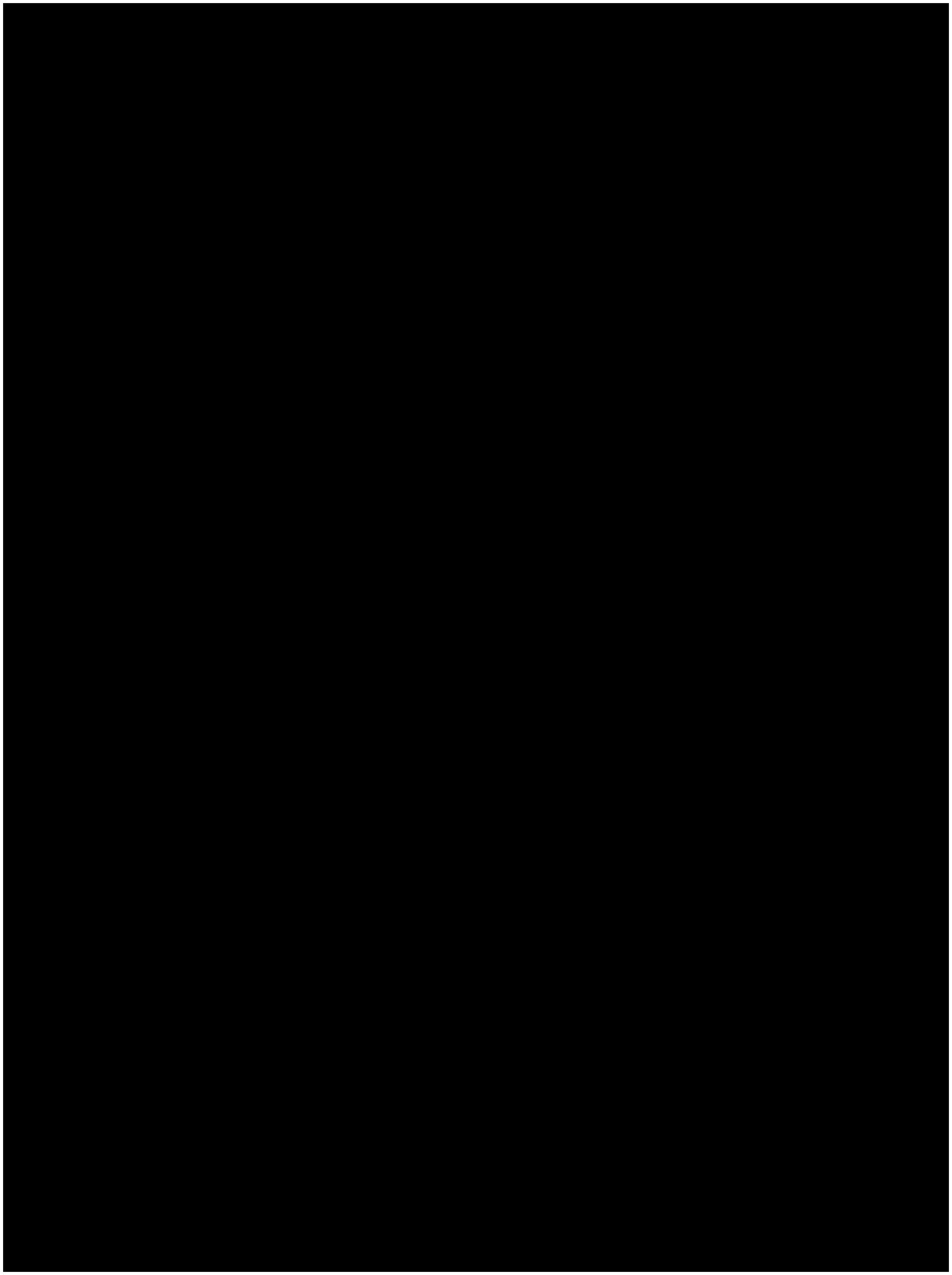
The Food-Related Problems Questionnaire is a tool specifically designed for patients with Prader-Willi Syndrome to rate preoccupation with food, impairment of satiety, difficulty with self-control and other food-related 'challenging' behavior. There are 16 questions on this 7-point Likert scale, with responses from 0 (never) to 6 (always), with a response of 7 (does not apply) included for 6 items on the scale. There are 3 open-ended questions. The maximum possible score is 96 for the total FRPQ, where a higher score indicates a 'worse' condition. See Appendix 3.

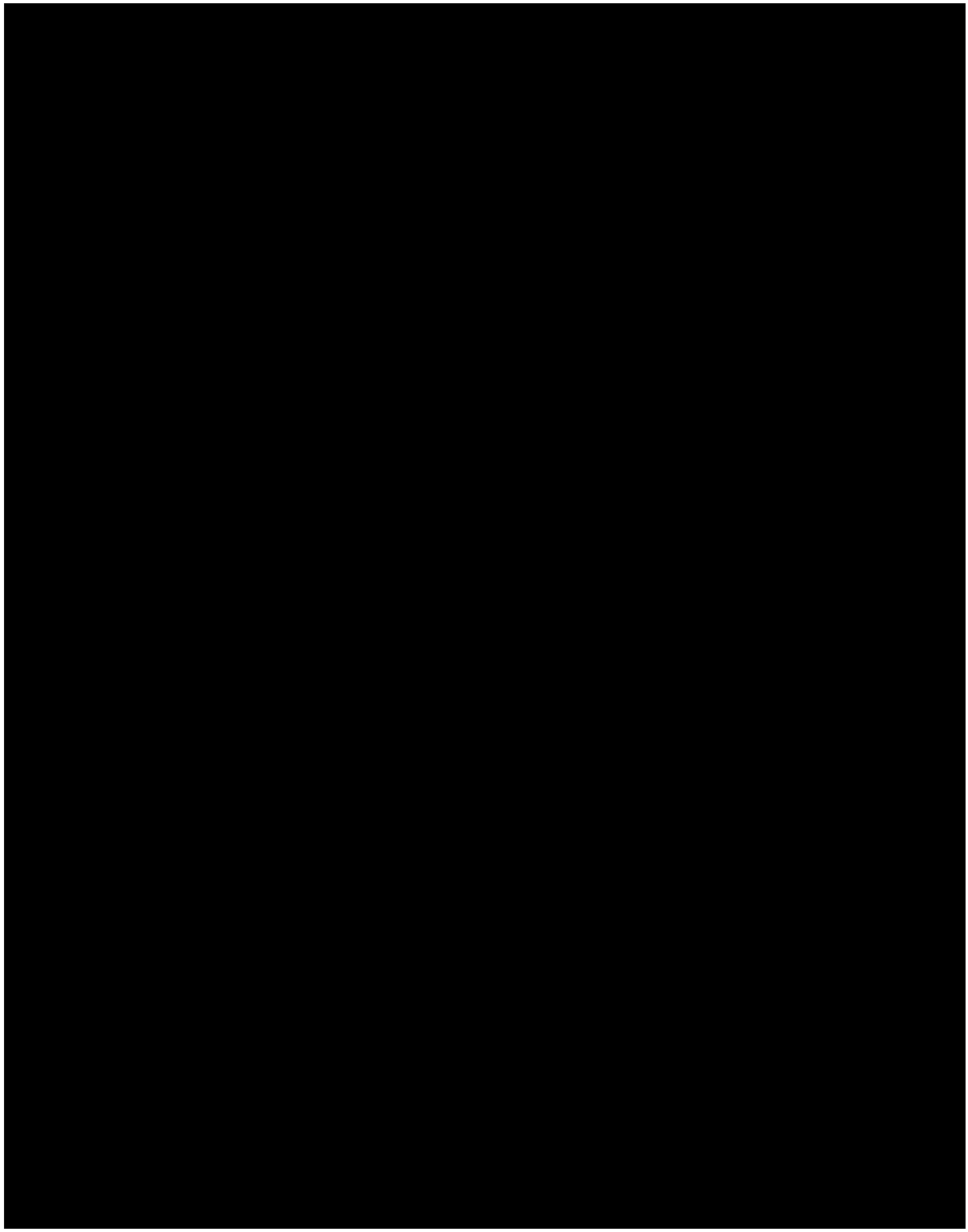
Along with the total item score, three (3) subscales will be presented for:

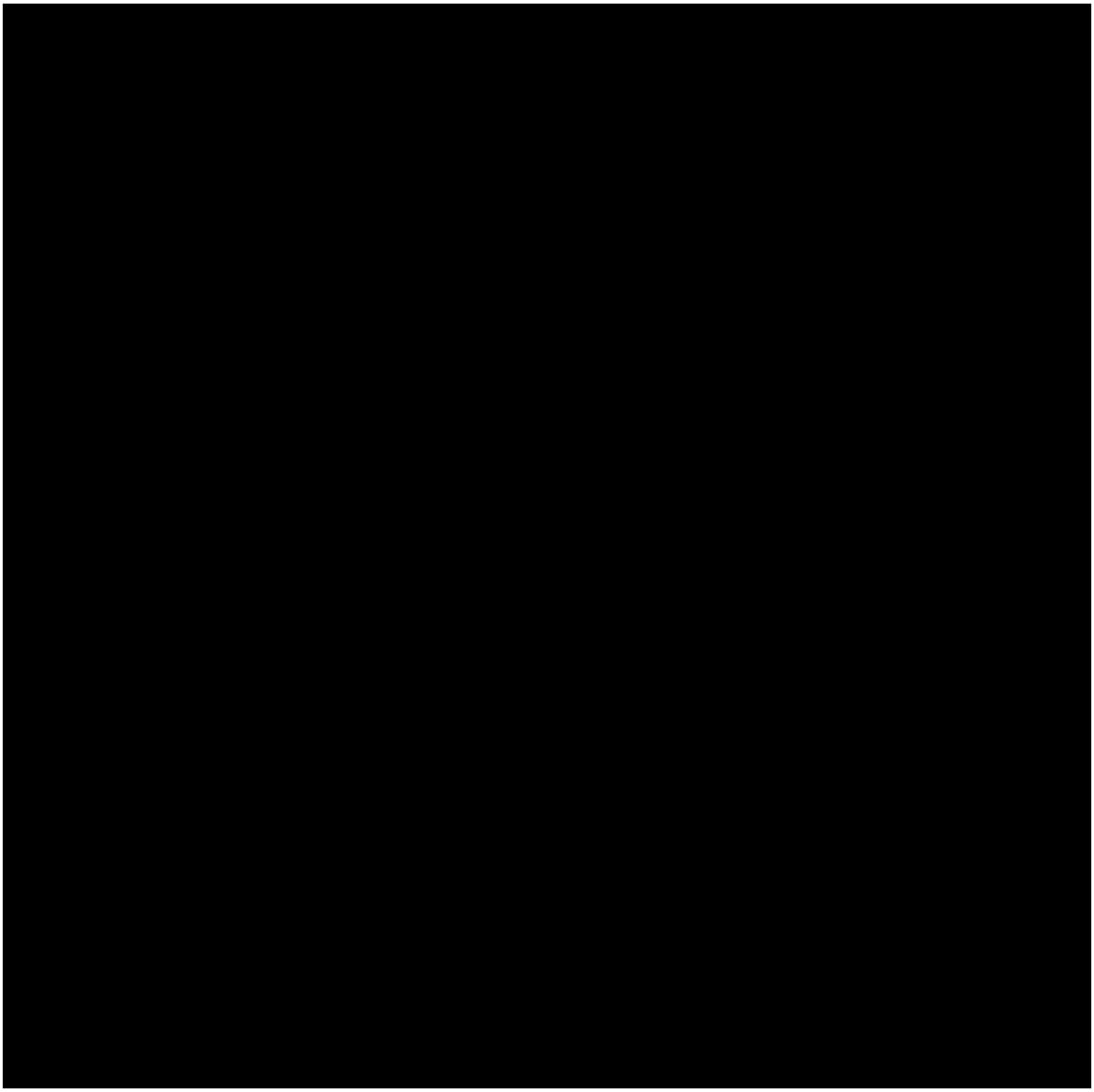
1. Preoccupation (items 1,5,15)
2. Impairment of satiety (items 8,9,13,14,16)
3. Composite negative behavior (2,4,8; 12,15; 3,7,14)

The individual item score and each subscale will be analyzed by each of the 3 periods, using descriptive statistics for visit and mean changes from baseline for each treatment group. If a single item in a factor is missing for a patient, that factor will be missing.

[redacted]







4.6 Subgroup Analyses

An additional subgroup DEXA analysis will be conducted for the first 8 subjects enrolled prior to [redacted] who received DEXA testing at Day 0 and Day 15, using the mean of these two values as baseline (with Day 15 data alone serving as the baseline for the analysis of the entire study population).

In addition, pre-specified subgroup analysis may be performed based on the following:

- Age (16-40; 41-64; >65 years; in addition, if patients between 12-16 are included in the trial, an additional age group analysis will be include for these patients to support inclusion of younger and pediatric patients into future studies.

- Gender
- BMI (greater vs less than the median BMI)
- Overall hyperphagia score (greater vs less than the median hyperphagia score)
- By growth hormone usage (yes or no)
- By institutionalized care situation (if permitted in the study; yes or no)

4.7 Correlation and [redacted]

An exploratory analysis may be done with correlations between pharmacokinetics and/or efficacy endpoints (weight loss, change in hyperphagia scores) and between different instruments will be explored.

4.8 Safety Analyses

4.8.1 Adverse Events (AEs)

Adverse events are to be recorded from signing the informed consent through the Final Study Visit (~ 2 weeks post treatment). All AEs (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded. An adverse event is considered to be treatment-emergent if the onset date/time is during or after administration of double-blind study drug or, in the event that onset time precedes double-blind study drug administration, the adverse event increases in severity during or after administration of double-blind study drug; in either case through 1-week after the last treatment dose.

Imputations will be used for determining treatment emergence for adverse events with partial dates (see Section 4.2.2); the unimputed partial dates will be included in the data listings.

A top line summary of AE incidence will be presented by treatment group. The number and percentage of patients with any treatment-emergent AE (TEAE), with any TEAE leading to study drug discontinuation, serious TEAE, and with any AE based on an injection site assessment will be summarized by dose group and period. In addition, the TEAE and SAE tables will be analysed by AE severity.

The following AE summaries will be produced by SOC and preferred term, by period:

- Incidence of TEAEs
- Incidence of TEAEs by severity
- Incidence of SAEs
- Incidence of SAEs by severity

A frequency of injection site reactions (Erythema, Edema, Induration, Itching, Pain or Tenderness, Other) will also be produced by each period, summarized by dose group.

All AEs will be provided in a by-patient listing which will include both the term reported on the CRF (verbatim term) and the preferred term and SOC to which it is coded. Relative start and stop days will be included along with the actual onset and resolution dates and times. AEs that are not considered treatment-emergent will be provided in a separate listing.

In addition, separate listings will be provided for the following, whether or not considered to be treatment-emergent (non treatment-emergent AEs will be flagged):

- Serious adverse events (SAEs)
- Adverse events leading to death or discontinuation of study drug (treatment-emergent)
- Adverse events of potential special interest: hypertension, tachycardia, penile erections, changes in female sexual arousal, skin and lesion pigmentation changes (tanning), thromboembolic events. All AEs will be designated AEs of special interest (yes/no and assigned to a category) by blinded review of the study team prior to locking the data base and any unblinding.

4.8.2 Clinical Laboratory Evaluations

Laboratory evaluations are performed at Screening, Days 1, 15, 28, 42, 70-163. A subset of lab parameters that have been collected will be summarized for Period 1 (Screening, Day 1, and Day 15) and Period 2 (Days 15, 28, 42):

- Hematology: Hemoglobin, Hematocrit, WBC, Platelets
- Chemistry: Bun, Creatinine, Potassium, ALT, AST, Total Bilirubin, Alkaline phosphatase, GGT, CPK, Glucose

Change from baseline (Day 15) to Day 28 and end of Period 2 (Day 42) (and during screening and Period 1) in selected Hematology and Chemistry laboratory parameters will be summarized by dose group for all patients in the SAF population. If a Day 15 assessment is missing, the last non-missing assessment prior to Day 15 should be used. By-patient data listings will be presented and in addition, a listing of all abnormal laboratory data values will be presented.

Laboratory values for Hematology or Chemistry tests that are normally numeric, but are presented with a character string (e.g.'<1') will take the numeric value without the symbol (e.g. '<1' would be '1') for use in the analysis tables. Listings will present the original data.

- Laboratory values will be tabulated (n %) with observed value and change from baseline over time and presented by dose group.

By-patient listings of all laboratory results will be provided. These listings will report the laboratory results in SI units. Laboratory values that are clinically significantly abnormal will be identified in the data listings.

Plots of change from baseline (or percent change from baseline, as appropriate) will be provided including all pre-baseline (screening and Period 1), Period 2 baseline (Day 15) and all post-dose values for placebo and active dose groups through Period 2.

4.8.3 Vital Signs

Vital signs measures for blood pressure (systolic and diastolic) and heart rate will be tabulated (n %) with observed value and change from baseline over time for Period 2 (Screening values and Days 15 (baseline), 28, and 42) and presented by dose group. The average of blood pressure and heart rate values for any one timepoint will be taken; if only 1 value is present for a timepoint, this value will be used in the analysis.

By-patient listings of vital signs results will be provided.

4.8.4 Physical Examinations

A by-patient listing of physical examination details will be provided; a summary table is not planned. Significant findings (new or worsening after baseline findings) from the physical examination are to be recorded as AEs.

4.8.5 ECG

ECG measurements are to be taken at screening, Day 42 and follow-up. A by-patient listing of ECG evaluations will be provided.

4.9 Pharmacokinetic Evaluation

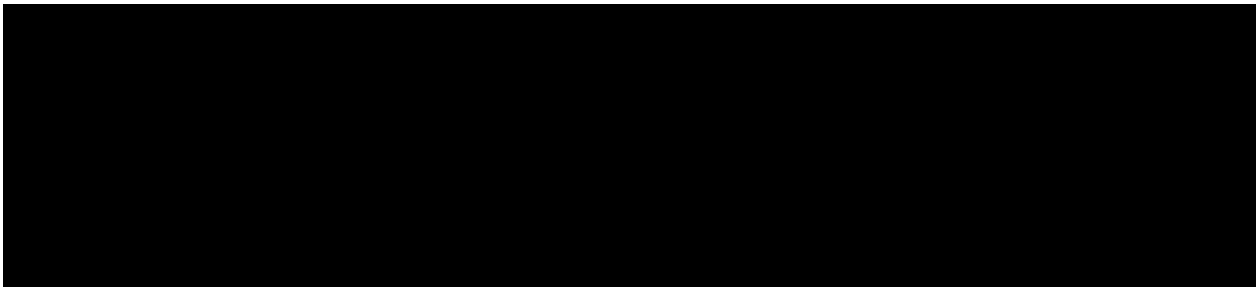
Plasma concentrations of RM-493 will be reported separately from these analyses.

4.10 Interim Analysis

See separate iSAP

4.11 Patient Profiles

No patient profiles will be provided.



5 REPORTING OUTPUT

All outputs will be produced using SAS version 9.2 or higher. The REPORT procedure will be used to produce all tables and listings whenever possible. All statistical appendices (supportive SAS output) will be output directly from the appropriate SAS procedure.

All table and listing outputs will stand on their own by being appropriately titled, footnoted and labelled such that the contents of their output are clear without reference to other study documents. All outputs will contain a footer indicating the name of the program used to produce the output and the date and time the output was generated; pages will be numbered 'x of y'. The block of information containing notes, footnotes, and listing/table/figure generation will be flush with the bottom margin.

Tables, listings, and figures will be numbered according to ICH Guidelines E3, Structure and Content of Clinical Study Reports.

All tables, listings, and statistical appendices will be produced to landscape orientation and will be incorporated into a Word document (margins 1.5" at the top and 1" at the left, right, and bottom) using Courier New 8 point font or higher.

All adverse event and concomitant medication listings will contain relative study days for the start and end dates of events being reported in addition to the actual dates and times of the events. Day 1 is the day study drug is administered. Day -1 is the day immediately preceding Day 1; there is no Day 0 in this study. Formulae for calculating the relative study days are provided in Table 1.

Unless indicated otherwise in the shells, listings of efficacy data will contain the relative time for the evaluation. The formula for calculating the relative time is provided in Table 1.

Listings will include all patients with data relevant to the particular listing and will be ordered by patient and visit within each treatment arm

Unless specified otherwise, percentages will be based on the number of non-missing observations (which will not always be the same as the number of patients in the treatment arm). The header will contain the number of patients in the treatment arm.

All percentages will be rounded and reported to a single decimal point (xx.x%) except for a percentage of 100% which will be reported as 100%. A value of 0% will be reported as a blank.

Analyses that include P values will report the P value to 3 decimal places with a leading zero (e.g., 0.023). P values <0.0005 will be reported as <0.001 not 0.000; p-values greater than 0.9995 will be reported as >0.999 not 1.000.

Unless it is not practical, mean and median values will be formatted to one more decimal place from the measured value. The standard deviation will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value. The number of decimal places in the measured value will not necessarily be reflected in the table and listing shells.

6 APPENDICES

Appendix 1: Schedule of Assessments

Study Period / **Study Day**	**Screening** **Days -30 to -1**	**Onset Single-Blind Treatment Run-in** **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]**
Procedure		**Run-In** **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		X[5]	X[15]	X	X	X	X	X

Appendix 1: Schedule of Assessments

Study Period **Study Day**	**Screening** **Days -30 to -1**	**Onset Single-Blind Treatment Run-in** **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]**
Procedure		**Run-In** **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**
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

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 consecutive days, as long as the lab results are back in time for the start of run-in phase.
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 contact 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 onset 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 the 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]

[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 triplicate, [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 14, 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 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 dosing 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 obtained. 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 need to have PK repeated on Day 70 visit.

19 Adverse events will be recorded from the time a patient 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, Food-Related Problems Questionnaire and [redacted].

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.