Statistical Analysis Plan

Safety and tolerability of S 48168 (ARM 210) for the treatment of RYR1-related myopathies (RYR1-RM)

Sponsor Protocol No: [redacted]
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US IND No.: [redacted]

Compound Name: S 48168 (ARM210)

[redacted]
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Statistical Analysis Plan Signature Page

Compound Name: S 48168 (ARM210)

Protocol: [redacted]

Study Title: Safety and tolerability of S 48168 (ARM 210) for the treatment of RYR1-related myopathies (RYR1-RM)

Issue Date: 24 March 2020

Signature:_____ Date:_____

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1. INTRODUCTION

The following statistical analysis plan (SAP) provides the framework for the summarization of the data from this study. The SAP may change due to unforeseen circumstances. Any changes made from the planned analysis within protocol, after locking of the database will be documented in the clinical study report (CSR). The section referred to as Table Shells within this SAP describes the traceability of the tables, figures, and listings (TFLs) back to the data. Note that the header for this page will be the one used for the main body of the CSR.

Any additional exploratory analyses not addressed within this SAP and/or driven by the data, or requested by the SPONSOR, will be considered out of scope and must be described in the CSR.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary

Hypothesis: S 48168 (ARM210) treatment will have no safety concerns that limit further development and will be generally well tolerated in RYR1-RM patients.

Exploratory:

1. To determine PK of a 28-day administration of S 48168 (ARM210) in RYR1-RM affected individuals.

Hypothesis: There will be no clinically meaningful difference in S 48168 (ARM210) exposure at steady state in RYR1-RM affected individuals when compared to existing data established in healthy volunteers.

2. To explore if S 48168 (ARM210) treatment increases RyR1-calstabin1 binding in skeletal muscle of RYR1-RM affected individuals.

Hypothesis: S 48168 (ARM210) treatment will increase RyR1-calstabin1 binding, compared to baseline, as determined by co-immunoprecipitation of RyR1 and Calstabin 1 and decrease relative Fluo-4 signal compared to baseline.

3. To explore if S 48168 (ARM210) treatment improves muscle function, motor activity, and fatigue in RYR1-RM affected individuals.

Hypothesis: Treatment with S 48168 (ARM210) will increase grip and pinch strength, decrease the time to complete graded functional tests, increase the total MFM-32 % maximum score, and decrease the PROMIS-fatigue subscale score, when compared to baseline.

2.2 Endpoints

Primary:

Composite safety and tolerability profile

(Frequencies of the following: TEAEs ≥ grade 2 in severity (CTCAE version 5), all SAEs, and all AESIs).

Methods: Safety and tolerability of S 48168 (ARM210) will be determined by monitoring Adverse Events (AEs) over 28 days of treatment via patient interviews, patient diary reviews, physical examinations, echocardiograms, electrocardiograms (ECGs), vital signs, and laboratory safety tests. A reference dataset of AEs/SAEs obtained from a natural history study of RYR1-RM will also be available to assist in interpretation of safety events. The Columbia-Suicide Severity Rating Scale (C-SSRS) will also be administered pre- and post-intervention. The frequency and severity of clinically significant AEs will be compared between treatment and historical controls including a previously conducted natural history study at the NIH.

Exploratory:

1. To determine PK of a 28-day administration of S 48168 (ARM210) in RYR1-RM affected individuals.

Endpoints:

Day 1: AUC0 t, AUC0 inf, Cmax, Tmax, and t½

Day 28: AUCtau, Cmax, Tmax, Cmin, RAAUC, and RACmax

Secondary PK parameters will include: AUC0-24, AUC%extrap, Tmin, Kel, Tlag, and Day 13 Ctrough (associated with Day 14 pre-dose). Additional parameters may be calculated as appropriate.

Methods: Bloods for PK assessments will be drawn at baseline (Day 0, 24h PK), at the study mid-point (day 14 ± 2 days, trough PK), and at the final study visit (Day 28, 24h PK). Whole blood will be processed, and the plasma fraction stored for batch PK analyses.

2. To explore if S 48168 (ARM210) treatment increases RyR1-calstabin1 binding in skeletal muscle of RYR1-RM affected individuals.

Endpoint: Change from baseline in relative RyR1-calstabin1 binding (AU) and (pending sufficient tissue yield) change from baseline in relative Fluo-4 signal (AU).

Methods: Skeletal muscle tissue will be obtained from participants pre- and post-intervention by needle biopsy. This tissue will be assessed for RyR1-calstabin1

binding by co-immunoprecipitation followed by protein detection. The percentage of Calstabin1 binding to RyR1 pre-dose will be compared to the percentage obtained post-dose in each patient. Pending sufficient tissue yield, muscle membrane preparations may be assessed for changes in calcium permeability (Fluo-4 signal) using a thapsigargin assay.

3. To explore if S 48168 (ARM210) treatment improves muscle function, motor activity, and fatigue in RYR1-RM affected individuals.

Endpoints: Grip strength (kg), pinch strength (kg), time taken to complete each of the following (seconds): walk 10-meters, supine to stand, ascend 4 stairs, and descend 4 stairs, MFM-32 score for domains 1, 2, 3, and total (% of maximum score), PROMIS-fatigue subscale score (t-score).

Hypothesis: Treatment with S 48168 (ARM210) will increase grip and pinch strength, decrease the time take to complete graded functional tests, increase the total MFM-32 % maximum score, and decrease the PROMIS-fatigue subscale score, when compared to baseline.

Methods:

Grip and pinch strength: Participants will be seated comfortably with his/her elbow flexed to 90 degrees, with the forearm and wrist in neutral position. Participants will then be asked to squeeze the dynamometer and pinch the gauge. This process will be repeated three times with the best effort used for final analyses. A physical therapist will administer these study procedures.

Graded Functional Tests: Participants will complete a timed 10-meter walk test, supine to stand, ascend 4 stairs, descend 4 stairs, pre- and post- intervention. A physical therapist will administer these study procedures.

MFM-32: The MFM-32 scale, a validated measure of motor function, will be administered pre- and post-intervention by a physical therapist. The participant is asked to roll, sit, lift head from prone and supine position, get up from a lying position, prop on arms, kneel, crawl, stand and step.

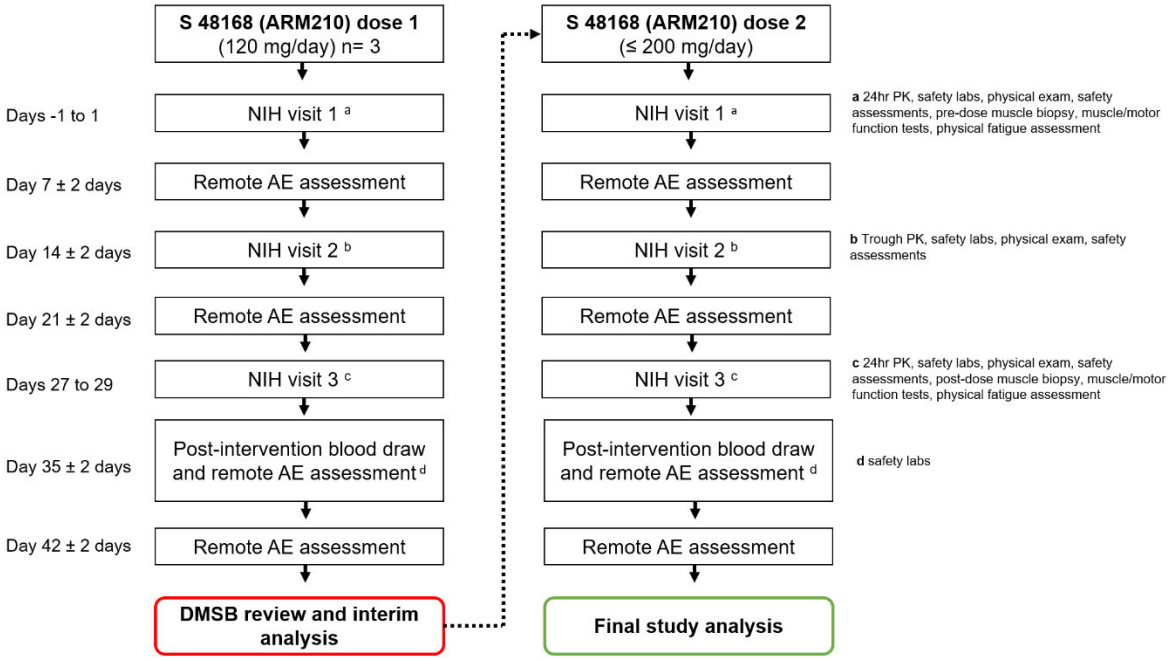
Fatigue Questionnaire: The validated PROMIS-fatigue subscale will be administered using the NIH toolbox app on an iPad. Participants will be asked to enter responses for fatigue-related quality of life questions pre- and post-intervention.

3. STUDY DESIGN

This is a Phase 1, single-site, open label, safety and tolerability, PK, and PD trial of S 48168 (ARM210) with the target of 8 individuals with *RYR1*-RM completing the study. Up to 14 participants with *RYR1*-RM will be dosed for 28 days at 120 mg or $\leq$ 200 mg daily of S 48168 (ARM210). This study will be conducted in the US at the

National Institutes of Health (NIH) in the Neurogenetics Branch of NINDS in collaboration with ARMGO Pharma Inc (the Sponsor), and Les Laboratoires Servier.

The overall design of the study is shown below



For each participant, the study duration will be approximately 2 months from enrollment to completion. Overall there will be three inpatient visits at the NIH CC, Bethesda, MD; one prior to the first dose, one mid-intervention, and one at the end of the dosing period. Study participants will be contacted by telephone/ secured email approximately 1 week after each visit for a follow-up regarding AEs and can describe daily any symptoms in a subject diary. Follow-ups will also serve to encourage study compliance. The dosing interval S 48168 [ARM210] will be 28 days. Biopsy samples obtained at NIH, during visit 1 (pre-treatment) and visit 3 (post-treatment) will be analyzed. Approximately 7 ± 2 days following cessation of S 48168 (ARM210), participants will be contacted by telephone/ secure email for a follow up regarding AEs and will have blood drawn locally, for follow up safety clinical laboratory tests, to be sent to NIH and analyzed by the NIH CC laboratory. A study investigator will contact participants by telephone to remind them of upcoming, scheduled local phlebotomy appointments. A final follow-up AE assessment will be conducted by telephone/ secure email 14±2 days following cessation of S48168 (ARM210).

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

Discontinued subjects may be replaced at the discretion of the Sponsor in consultation with the PI and DSMB. The pre-screening accrual ceiling will be up to 50 subjects with a target number of 8-20 completers.

The FIH study [redacted] that will be the historical control was divided into two parts; part 1 is a randomized placebo-controlled blinded single rising dose escalation study where 5 dose levels were tested ([redacted]), and part 2 is a four-panel rising multiple dose study ([redacted] for 14 days of dosing. PK data from the 240 mg dose level will be utilized for comparisons between healthy subjects and *RYR1*-RM patients. [redacted]

4. ANALYSIS POPULATIONS

4.1 Analysis Populations

Safety Population: All subjects who received at least one dose of the study drug will be included in the safety evaluations.

PK Population: All subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses.

Pharmacodynamic/Target Engagement: All subjects who complete the study will be included in the pharmacodynamics/target engagement analysis.

Muscle/Motor Function (Grade Functional Tests and MFM32): All subjects who complete the study will be included in the muscle/motor function assessments.

Quality of Life: All subjects who complete the study will be included in the quality of life assessments.

4.2 Preliminary Data and Interim Analysis

Interim PK analysis will be conducted by Nuvisan (contract vendor) as follows:

First dose group (120 mg/day): Full PK analysis (see Table 6:1 for PK parameters) once the first three participants have completed dosing for 28 days. This will allow verification that the observed PK results from these RYR1-RM affected individuals agree with PK results from previous studies in healthy volunteers and that the Cmax limit [redacted] was not exceeded. At this stage of drug development, a PK value that would not require a dose adjustment would be considered as similar. This would mean 50% lower or 200% higher than that of healthy volunteers. Based on PK results and safety data from the first dose group, the dose to be administered in subsequent

participants may be increased to ≤ 200 mg/day. This will be based on DSMB recommendations and investigator and sponsor's joint decision.

Second dose group (≤ 200 mg/day): PK analysis for Cmax once the first three participants have completed dosing for 28 days. This will allow verification that the Cmax limit [redacted] was not exceeded. If this is the case, then all remaining samples will be shipped to the contract laboratory for analysis at the end of the study, when full PK analysis beyond the Cmax measurement will occur for all of the samples obtained from this group.

5. TREATMENT DESCRIPTIONS

S 48168 (ARM210) requires an IND, and the FDA approved IND number is: [redacted]. The company manufacturing S 48168 (ARM210) is Laboratoires Servier. Study drug will be shipped by Laboratoires Servier directly to the NIH Pharmacy as therapeutic units. The study sponsor is ARMGO Pharma Inc.

S 48168 (ARM210) will be supplied as 20 mg gastro-resistant tablets ([redacted]).

([redacted])

Table 5.1 Description of Treatments

Treatment	Short Description (text, tables, figures, listings, SAS output)	Abbreviated Description (footnotes)
Sponsor Protocol: [redacted]		
A	Single oral 120 mg S 48168 (ARM210) QD for 28 days (patients)	Single oral 120 mg S 48168 (ARM210) (6 x 20 mg tablets) daily for 28 days (patients)
B	Single oral 200 mg S 48168 (ARM210) QD for 28 days (patients)	Single oral 200 mg S 48168 (ARM210) (10 x 20 mg tablets) daily for 28 days (patients)
Sponsor Protocol: [redacted]		
C	Single oral 120 mg S 48168 (ARM210) QD for 14 days (healthy subjects)	Single oral 120 mg S 48168 (ARM210) (3 x 40 mg tablets) daily for 14 days (healthy subjects)
D	Single oral 240 mg S 48168 (ARM210) QD for 14 days (healthy subjects)	Single oral 240 mg S 48168 (ARM210) (1 x 200 mg and 1 x 40 mg tablets) daily for 14 days (healthy subjects)

6. SAFETY

All case report form (CRF) data will be listed by subject and chronologically by assessment time points. This will include rechecks, unscheduled assessments, and early termination.

Applicable continuous variables will be summarized using n, arithmetic mean, SD, minimum, median, and maximum. Frequencies and percentages will be used to summarize categorical variables.

The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

6.1 Subject Discontinuation

Subjects will be summarized by number of subjects enrolled, completed, and discontinued the study with discontinuation reasons by treatment and study overall.

6.2 Demographics

Descriptive statistics will be calculated for continuous variables (age, weight, height, and body mass index) by treatment and study overall.

Frequency counts will be provided for categorical variables (race, ethnicity, and sex) for each treatment and study overall.

6.3 Adverse Events

All adverse events (AEs) reported during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 21.0.

All adverse events will be reviewed by the Medical Monitor and graded in accordance with CTCAE version 5 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm)

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, treatment, severity, relationship to study medication, and action; however, only treatment-emergent AEs (TEAEs) will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after study drug administration. Each TEAE will be attributed to a treatment based on the onset date and time of the AE.

An AE will also be considered treatment emergent if: onset date of an AE is missing; if onset time of an AE is missing and the onset date is the same as the treatment dosing date; and if both AE onset date and time are missing.

TEAEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT). Summary tables will include number of subjects reporting the AE and as percent of number of subjects dosed by treatment and study overall. The number of AEs will be tabulated in a similar manner. Tables which tabulate the number of TEAEs by severity and relationship to study treatment will also be included.

Serious adverse events (SAEs), if present, will also be listed. Applicable narratives will be included in the CSR.

Frequencies of TEAEs ≥ grade 2 in severity (CTCAE version 5), all SAEs, and all AE of Special Interest (AESI) will be tabulated by SOC/TE.

The frequency and severity of clinically significant AEs will be compared descriptively between treatment and historical controls including a previously conducted natural history study at the NIH.

7. PHARMACOKINETIC ANALYSIS (EXPLORATORY)

7.1 Measurements and Collection Schedule

All concentration data will be included in the calculation of the individual PK parameters, the individual concentration-time plots (based on actual sample times), and in the mean concentration-time plots (based on nominal sample times). However, if there are any significant deviations from nominal sample times, some concentration data may be excluded from mean concentration-time plots and/or additional concentration-time plots of the mean data may be provided. All deviations and excluded data will be provided and discussed in the CSR.

7.2 Bioanalytical Method

Plasma sample analysis for S 48168 (ARM210) will be performed by Nuvisan Pharma Services (Germany) using validated procedures and methods.

7.3 Investigational Product and PK Analyte Information

S 48168 (ARM210) can be described as follows. S 48168 (ARM210) in the hemifumarate salt formulation has an empirical formula $C_{18}H_{18}NO_3S \cdot C_2H_2O_2$ and a molecular weight of 387.42 g/mol. The free base has a molecular weight of 329.42 g/mol.

7.4 Pharmacokinetic Concentrations

Serial blood samples for the determination of plasma S 48168 (ARM210) will be collected at predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose on Days 1 and 28. A predose sample will also be collected on Day 14.

7.5 Noncompartmental Pharmacokinetic Analysis and Parameter Calculation

7.5.1 Plasma Pharmacokinetic Parameters

The appropriate noncompartmental PK parameters will be calculated from the plasma S 48168 (ARM210) concentration-time data using Phoenix® WinNonlin® Version 7.0 or higher sample times will be used in the calculations of the PK parameters. The calculation of the actual time for S 48168 (ARM210) will be in respect to the start of dose administration time of S 48168 (ARM210) on every PK day. All PK parameters included in the protocol are listed in Table 6.1 below, and are defined as appropriate for study design.

Table 6.1. Noncompartmental Pharmacokinetic Parameters to be Calculated (Day 1)

Parameter	Definition	Method of Determination
AUC0-24	Area under the concentration-time curve from time 0 to the 24 hours postdose	Calculated using the Linear Trapezoidal with Linear Interpolation Method. If a value could not be obtained at 24 hours the parameter will be set to missing
AUC0-t	Area under the concentration-time curve from time 0 to the time of the last observed/measured non-zero concentration	Calculated using the Linear Trapezoidal with Linear Interpolation Method
AUC0-inf	Area under the concentration-time curve from time 0 extrapolated to infinity	AUC0-inf = AUC0-t + (Clast/kel) where Clast is the last observed/measured concentration
AUC%extrap	Percent of AUC0-inf extrapolated	Calculated as (1 - AUC0-t/AUC0-inf)*100
Cmax	The maximum observed concentration	Taken directly from bioanalytical data
Tmax	The time to reach Cmax	Taken from clinical database as the difference in the time of administration and the time of the blood draw which is associated with the Cmax.
Kel	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve.	The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma concentrations).
t½:	Apparent first-order terminal elimination half-life	Calculated as 0.693/Kel

Parameter	Definition	Method of Determination
Tlag	Lag time – the time delay between drug administration and the onset of absorption; where onset of absorption	Calculated as the time point prior to the first observed/measured non-zero plasma concentration

Table 6.2. Noncompartmental Pharmacokinetic Parameters to be Calculated (Day 28)

Parameter	Definition	Method of Determination
AUC0-tau	The area under the concentration versus time curve from the start of drug infusion over the final dosing interval (tau)	Calculated using the linear trapezoidal method with linear interpolation. Tau is equal to 24 hours.
Cmax,ss	The maximum observed concentration at steady state	Taken directly from bioanalytical data
Tmax,ss	The time of the maximum observed concentration at steady state	Taken directly from bioanalytical data. Tmax,ss is the first time point if Cmax,ss occurs at 2 time points
Cmin	Minimum observed concentration at the end of the dosing interval	Taken directly from bioanalytical data
Tmin	Time to reach Cmin	Taken directly from bioanalytical data. Tmin is the first time point if Cmin occurs at 2 time points
RA(AUC)	Accumulation ratio for AUC (steady state versus single dose)	Calculated as AUCtau Day 28/AUC0-24 Day 1
RA(Cmax)	Accumulation ratio for Cmax (steady state versus single dose)	Calculated as Cmax Day 28/Cmax Day 1.
Ctrough_D13	Day 13 Ctrough	Taken directly from bioanalytical data. Day 13 Ctrough is the predose of Day 14

Pharmacokinetic parameters will not be calculated for subjects with less than 2 consecutive postdose time points with quantifiable concentrations. Subjects for whom there are insufficient data to calculate the PK parameters will be included in the concentration tables only and excluded from the descriptive statistics.

Concentrations will be presented in the report at the same precision as received from the bioanalytical laboratory. Concentrations below the lower limit of quantification (LLOQ) will be assigned a value of zero if they occur between time zero (predose) and the first measurable plasma concentration after the first dose and missing thereafter, and will be treated as such for the purpose of calculating PK parameters and summary statistics.

The Kel will be determined using linear regressions composed of least 3 data points. The Kel will not be assigned if 1) the terminal elimination phase is not apparent, 2) if Tmax is one of the 3 last data points, or 3) if the R^2 value is less than 0.8. In cases where the Kel interval is not assigned, the values of t½, AUC0-inf and AUC%extrap are considered not calculable and will not be reported. Wherever the resulting t½ is

more than half as long as the sampling interval, the Kel values and associated parameters (t½, AUC0-inf and AUC%extrap) may not be presented as judged appropriate and in accordance with Celerion SOPs.

7.6 Data Summarization and Presentation

All S 48168 (ARM210) PK concentration and PK parameter descriptive statistics will be generated using WinNonlin® Version 7.0 or higher and/or SAS Version 9.4.

Summary statistics, including sample size (n), arithmetic mean (mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), median, minimum, and maximum will be calculated for all nominal concentration time points. The plasma concentrations of S 48168 (ARM210) will be calculated by nominal time. Excluded subjects due to major protocol deviations will be included in the concentration table listing, but will be excluded from the summary statistics and noted as such in the tables. All BLQ values will be presented as "BLQ" in the concentration table listing and footnoted accordingly.

The level of precision for each statistic will be presented as follows: mean, median, minimum, maximum, SEM, and SD in same precision as in bioanalytical data, n will be presented as an integer, and CV% will be presented to 1 decimal place.

Summary statistics (n, mean, SD, CV%, SEM, median, minimum, and maximum, geometric means, and geometric CV%) will be calculated for plasma S 48168 (ARM210) PK parameters. Excluded subjects will be included in the PK parameter table listing, but will be excluded from the summary statistics and noted as such in the tables. PK parameters will be tabulated by dose level and listed by subject and parameter.

Mean and individual concentration-time profiles will be presented on linear and semi-log scales. Linear mean plots will be presented with and without SD.

7.7 Statistical Analysis of PK Parameters

All data will be summarized and compared descriptively with no formal statistical analysis performed in this study.

8. PHARMACODYNAMICS/TARGET ENGAGEMENT AND MOTOR FUNCTIONS

8.1 Pharmacodynamic/Target Engagement (Exploratory):

All participants will undergo two needle muscle biopsies during the study in order to determine S 48168 (ARM210) PD in the RYR1-RM population. Biopsy 1 will take place pre-dose during study visit 1 (Day -1/Day 1, pre-treatment). Biopsy 2 will take place during study visit 3 (Day 27/28, post-treatment). Baseline (pre-treatment) and

post-treatment biopsies will be assayed for RyR1-Calstabin1 interaction as % RyR1-Calstabin1 binding of normal control muscle. % RyR1-Calstabin1 binding will be listed by subject with summary statistics calculated to compare between pre- and post-treatment biopsy results.

If there is sufficient remaining tissue, % Ca^{2+} leak from RyR1 will be determined and listed by subject and compared between pre- and post-treatment biopsies.

8.2 Motor Functions and Quality of Life (Exploratory):

Timed Functional Tests: Timed functional tests will be performed on Day -1 (pre-treatment) and Day 27 (post-treatment) and include10-meter walk test, supine to stand, ascend 4 stairs, and descend 4 stairs. The recorded time will be listed by subject and summarized descriptively for each test to compare between pre- and post-treatment biopsy results.

Grip/Pinch Strength: Day -1 versus Day 27 hand grip and pinch strength will be documented quantitatively using dynamometry. This will also be assessed at trial mid-point (Day 14). The results will be listed by subject and summarized descriptively to compare hand grip and pinch strength (kg) between pre- and post-treatment.

Motor Function Measure 32:

Day -1 versus Day 27 motor function will be documented quantitatively using the scoring of the MFM32 for the following: total score, domain 1 (standing and transfers), domain 2 (axial and proximal motor function), and domain 3 (distal motor function). The resulting scores will be listed by subject and summarized descriptively to compare between pre- and post-treatment.

Quality of Life Questionnaire: PROMIS-fatigue subscale questionnaires will be completed by participants during study visits 1 (Day -1), 2 (Day 14), and 3 (Day 27) with a raw score, theta, t-score, and standard error reported. All results will be listed by subject and summarized descriptively, as applicable, to compare between pre- and post-treatments.

8.3 Clinical Laboratory Tests (Serum Chemistry, Hematology, Urinalysis)

Serum chemistry, hematology and urinalysis tests will be performed at Screening and on Days 14, 27 and 35 (Follow-up).

Out-of-range values and corresponding recheck results will be listed.

For all numeric laboratory values, descriptive statistics will be presented for each laboratory test by assessment time point and treatment. Change from baseline will be summarized in a similar manner. Baseline is defined as the screening result closest

and prior to first dose which may include unscheduled or recheck results. Postdose unscheduled event and recheck results will not be included in summaries.

For each laboratory test, a shift table will be developed to compare the frequency of the results at baseline (above normal, normal, or below normal) with the respective postdose results.

8.4 Vital Signs

Blood pressure and pulse are assessed at Screening, predose on Day 1 and on Days 14 and 28. Respiratory rate, temperature and pulse oximetry are measured at Screening and on Days 14 and 28.

Summary statistics will be calculated for all vital sign parameters by timepoint and treatment. Change from baseline (Predose Day 1) for blood pressure and pulse will be summarized for post baseline by timepoint and treatment. Baseline is defined as the result closest and prior to first dose on Day1 which may include unscheduled or recheck results. Postdose unscheduled event and recheck results will not be included in summaries.

8.5 12-Lead Electrocardiogram

12-lead electrocardiogram (ECG) will be assessed at Screening and Days 14 and 28 for HR, RR, PR, QRS, QT and QTcF. All ECG parameters will be listed by subjects with QTcF>450 msec flagged. Summary statistics will be calculated for each parameter and presented by timepoint and treatment. Postdose unscheduled event and recheck results will not be included in summaries.

8.6 Concomitant Medications

All concomitant medications recorded during the study will be coded with the WHO Dictionary March 2018 B3 and listed.

8.7 Physical Examination

Full physical examinations will be performed at Screening and on Days 14 and 27. Symptom driven physical examination may be performed at other times, at the PI or designee's discretion. All data found in the CRF will be listed.

8.8 The Columbia-Suicide Severity Rating Scale (C-SSRS)

C-SSRS will be administered at Screening, Day 14 and Day 27. Results recorded on the CRF will be listed.

8.9 Pulmonary Function Test

Each participant will perform pulmonary function testing (PFTs) to assess vital capacity (VC) at screening. Results recorded on the CRF will be listed.

8.10 Medical and Surgical History

All medical and surgical history recorded during the study will be coded with the MedDRA 21.0 and listed.

9. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

The analyses described in this SAP are aligned with those analyses described in the protocol.

10. SUMMARY TABLES AND FIGURES

Summary tables and figures are numbered following the International Conference on Harmonization (ICH) structure but may be renumbered as appropriate during the compilation of the tables and figures for the CSR. Note that all summary tables and figures will be generated using SAS® Version 9.3 or higher, as appropriate.

10.1 In-text Summary Tables and Figures

The following is a list of table and figure titles that will be included in the text of the CSR. Tables and figures will be numbered appropriately during compilation of the CSR.

Section 10:

Table 10-1 Subject Disposition Summary

Section 11:

Table 11-1 Demographic Summary

Table 11-2 Summary of Plasma S 48168 (ARM210) Pharmacokinetics Following Single Dose of 120 mg, 200 mg, and 240 mg S 48168 (ARM210) (Treatments A, B, C, and D) (Day 1)

Table 11-3 Summary of Plasma S 48168 (ARM210) Pharmacokinetics Following Single Dose of 120 mg, 200 mg and 240 mg S 48168 (ARM210) (Treatments A, B, C, and D) (Days 14 and 28)

Figure 11-1 Arithmetic Mean Plasma S 48168 (ARM210) Concentration-Time Profiles of Following Single Dose Administration of 120 mg, 200 mg,

and 240 mg S 48168 (ARM210) on Day 1 (Treatments A, B, C, and D) (Linear Scale)

Figure 11-2 Arithmetic Mean Plasma S 48168 (ARM210) Concentration-Time Profiles of Following Single Dose of 120 mg and 200 mg S 48168 (ARM210) in Patients (Day 28) and 120 mg and 240 mg S 48168 (ARM210) in Healthy Subjects (Day 14) (Linear Scale)

Note to Programmer: For Figures 11-2 superimpose both the Days 14 (Healthy)and 28 (Patient). All figures are to be generated in color.

Section 12:

Table 12-1 Adverse Event Frequency by Treatment - Number of Subjects Reporting the Event (% of Subjects Dosed)

10.2 Section 14 Summary Tables and Figures

The following is a list of table and figure titles that will be included in Section 14 of the report. Table and figure titles may be renumbered as appropriate during the compilation of the report.

14.1 Demographic Data Summary Tables

Table 14.1.1 Summary of Disposition (Safety Population)
Table 14.1.2 Demographic Summary (Safety Population)

14.2 Pharmacokinetic/Pharmacodynamic Data Summary Tables and Figures

14.2.1 Plasma S 48168 (ARM210) Tables

Table 14.2.1.1 Plasma S 48168 (ARM210) Concentrations (<units>) Following Single Oral Administration of 120 mg S 48168 (ARM210) (6 x 20 mg Tablets) for 28 Days (Patients) (Treatment A) (Days 1-28) (Pharmacokinetic Population)

Table 14.2.1.2 Plasma S 48168 (ARM210) Concentrations (<units>) Following Single Oral 200 mg S 48168 (ARM210) (10 x 20 mg Tablets) for 28 Days (Patients) (Treatment B) (Days 1-28) (Pharmacokinetic Population)

Table 14.2.1.3 Plasma S 48168 (ARM210) Concentrations (<units>) Following Single Oral 120 mg S 48168 (ARM210) (3 x 40 mg Tablets) for 14 Days (Healthy Subjects) (Treatment C) (Days 1-14) (Pharmacokinetic Population)

Table 14.2.1.4 Plasma S 48168 (ARM210) Concentrations (<units>) Following Single Oral 240 mg S 48168 (ARM210) (1 x 200

14.2.2 Plasma S 48168 (ARM210) Figures

Figure 14.2.2.1 Mean (SD) Plasma S 48168 (ARM210) Concentration-Time Profiles of Following Single Dose Administration of 120 mg, 200 mg, and 240 mg S 48168 (ARM210) on Day 1 (Treatments A, B, C, and D) (Linear Scale) (Pharmacokinetic Population)

Figure 14.2.2.2 Mean Plasma S 48168 (ARM210) Concentration-Time Profiles of Following Single Dose Administration of 120 mg, 200 mg, and 240 mg S 48168 (ARM210) on Day 1 (Treatments A, B, C, and D) (Linear Scale)

Figure 14.2.2.3 Mean Plasma S 48168 (ARM210) Concentration-Time Profiles of Following Single Dose Administration of 120 mg, 200 mg, and 240 mg S 48168 (ARM210) on Day 1 (Treatments A, B, C, and D) (Semi-Log Scale)

Figure 14.2.2.4 Mean (SD) Plasma S 48168 (ARM210) Concentration-Time Profiles of Following Multiple Daily Doses 120 mg and 200 mg S 48168 (ARM210) in Patients (Day 28) and 120 mg and 240 mg S 48168 (ARM210) in Healthy Subjects (Day 14) (Linear Scale) (Pharmacokinetic Population)

Figure 14.2.2.5 Mean Plasma S 48168 (ARM210) Concentration-Time Profiles of Following Multiple Daily Doses 120 mg and 200 mg S 48168 (ARM210) in Patients (Day 28) and 120 mg and 240 mg S 48168 (ARM210) in Healthy Subjects (Day 14) (Linear Scale)

Figure 14.2.2.6 Mean Plasma S 48168 (ARM210) Concentration-Time Profiles of Following Multiple Daily Doses 120 mg and 200 mg S 48168 (ARM210) in Patients (Day 28) and 120 mg and 240 mg S 48168 (ARM210) in Healthy Subjects (Day 14) (Semi-Log Scale)

Note to Programmer: For Figures 14.2.2.4 through 14.2.2.6 superimpose both the Days 14 and 28 for All figures are to be generated in color.

14.2.3 Pharmacodynamic/Target Engagement Tables

Table 14.2.3.1 Mean % RyR1-Calstabin1 Binding

14.2.4 Motor Function and Quality of Life Tables

Table 14.2.4.1 Summary of Timed Functional Tests

Table 14.2.4.2 Summary of Motor Function Measure 32

Table 14.2.4.3 Summary of Quality of Life Questionnaire

14.3 Safety Data Summary Tables

14.3.1 Displays of Adverse Events

Table 14.3.1.1 Treatment-emergent Adverse Event Frequency by Treatment – Number of Subjects Reporting the Event (% of Subject Dosed) (Safety Population)

Table 14.3.1.2 Treatment-emergent Adverse Event Frequency by Treatment – Number of Adverse Events (% of Total Adverse Events) (Safety Population)

Table 14.3.1.3 Treatment-emergent Adverse Event Frequency by Treatment, Severity, and Relationship to Drug – Number of Adverse Events (Safety Population)

Table 14.3.1.4 Frequency of Treatment-emergent Adverse Event with Grade 2 or Greater Severity, are Serious, or Are of Special Interest by Treatment (Safety Population)

14.3.2 Listings of Deaths, other Serious and Significant Adverse Events

Table 14.3.2.1 Serious Adverse Events (Safety Population)
<if no serious adverse event occurred, a statement 'No serious adverse event is reported'>

14.3.3 Narratives of Deaths, other Serious and Certain other Significant Adverse Events

14.3.4 Abnormal Laboratory Value Listing (each patient)

Table 14.3.4.1 Out-of-Range Values and Recheck Results – Serum Chemistry (Safety Population)

Table 14.3.4.2 Out-of-Range Values and Recheck Results – Hematology (Safety Population)

Table 14.3.4.3 Out-of-Range Values and Recheck Results – Urinalysis (Safety Population)

14.3.5 Displays of Other Laboratory, Vital Signs, Electrocardiogram, Physical Examination, and Other Safety Data

Table 14.3.5.1 Clinical Laboratory Summary and Change from Baseline – Serum Chemistry (Safety Population)

Table 14.3.5.2 Clinical Laboratory Shift from Baseline – Serum Chemistry (Safety Population)

Table 14.3.5.3 Clinical Laboratory Summary and Change from Baseline – Hematology (Safety Population)

Table 14.3.5.4 Clinical Laboratory Shift from Baseline – Hematology (Safety Population)
Table 14.3.5.5 Clinical Laboratory Summary and Change from Baseline – Urinalysis (Safety Population)
Table 14.3.5.6 Clinical Laboratory Shift from Baseline – Urinalysis (Safety Population)
Table 14.3.5.7 Vital Sign Summary and Change from Baseline (Safety Population)
Table 14.3.5.8 12-Lead Electrocardiogram Summary (Safety Population)

14.4 Section 16 Data Listings

Data listings are numbered following the ICH structure but may be renumbered as appropriate during the compilation of the TFLs for the CSR. The following is a list of appendix numbers and titles that will be included as data listings:

16.1 Study Information

Appendix 16.1.9 Statistical Methods

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

16.2 Subject Data Listings

16.2.1 Subject Discontinuation

Appendix 16.2.1 Subject Discontinuation (Safety Population)

16.2.2 Protocol Deviations

Appendix 16.2.2 Protocol Deviations

16.2.3 Subjects Excluded from Pharmacokinetic Analysis

Appendix 16.2.3 Subjects Excluded from Pharmacokinetic Analysis

Note: Appendices 16.2.2 and 16.2.3 are generated in MS Word for inclusion in the study report.

16.2.4 Demographic Data

Appendix 16.2.4.1 Subject Information (Safety Population)
Appendix 16.2.4.2 Demographics (Safety Population)
Appendix 16.2.4.3 Physical Examination - Full (Safety Population)

Appendix 16.2.4.4 Physical Examination – Symptom Driven (Safety Population)
Appendix 16.2.4.5 Medical and Surgical History (Safety Population)
Appendix 16.2.4.6 Tobacco Use (Safety Population)
Appendix 16.2.4.7 CYP2C8 Genotyping (Safety Population)
Appendix 16.2.4.8 Echocardiogram (Safety Population)
Appendix 16.2.4.9 Pulmonary Function Test (Safety Population)

16.2.5 Compliance and/or Drug Concentration Data

Appendix 16.2.5.1 Inclusion/Exclusion Criteria not Met (Safety Population)
Appendix 16.2.5.2 Dose Administration Times (Safety Population)
Appendix 16.2.5.3 Pharmacokinetic Blood Sampling (Safety Population)
Appendix 16.2.5.4 Skeletal Muscle Needle Biopsy (Safety Population)
Appendix 16.2.5.5 Concomitant Medications (Safety Population)
Appendix 16.2.5.6 Subject Contact (Safety Population)
Appendix 16.2.5.7 Subject Diary (Safety Population)

16.2.6 Individual Pharmacokinetic/Pharmacodynamic Response Data

Appendix 16.2.6.1 Plasma S 48168 (ARM210) Concentrations Versus Time (Linear and Semi-Log Scale) for Subject #
Appendix 16.2.6.2 Percent (%) RyR1-Calstabin1 Binding (Pharmacodynamic Population)
Appendix 16.2.6.3 Motor Function Measure 32 (Safety Population)
Appendix 16.2.6.4 Graded Functional Testing (Safety Population)
Appendix 16.2.6.5 Grip and Pinch Strength (Safety Population)
Appendix 16.2.6.6 Fatigue Questionnaire (Safety Population)
Appendix 16.2.6.7 C-SSRS – Baseline – Suicidal Ideation (Safety Population)
Appendix 16.2.6.8 C-SSRS – Baseline – Intensity of Ideation (Safety Population)
Appendix 16.2.6.9 C-SSRS – Baseline – Suicidal Behavior (Safety Population)
Appendix 16.2.6.10 C-SSRS – Baseline – Actual Attempts (Safety Population)
Appendix 16.2.6.11 C-SSRS – Since Last Visit – Suicidal Ideation (Safety Population)
Appendix 16.2.6.12 C-SSRS – Since Last Visit – Intensity of Ideation (Safety Population)
Appendix 16.2.6.13 C-SSRS – Since Last Visit – Suicidal Behavior (Safety Population)

Appendix 16.2.6.14 C-SSRS – Since Last Visit – Actual Attempts (Safety Population)

16.2.7 Adverse Events Listings

Appendix 16.2.7.1 Adverse Events (I of II) (Safety Population)
Appendix 16.2.7.2 Adverse Events (II of II) (Safety Population)
Appendix 16.2.7.3 Adverse Event Preferred Term Classification (Safety Population)

16.2.8 Listings of Individual Laboratory Measurements and Other Safety Observations

Appendix 16.2.8.1.1 Clinical Laboratory Report - Serum Chemistry (Safety Population)
Appendix 16.2.8.1.2 Clinical Laboratory Report - Hematology (Safety Population)
Appendix 16.2.8.1.3 Clinical Laboratory Report - Urinalysis (Safety Population)
Appendix 16.2.8.1.4 Clinical Laboratory Report - Urine Drug Screening (Safety Population)
Appendix 16.2.8.1.5 Serology (Safety Population)
Appendix 16.2.8.1.6 Pregnancy Test (Safety Population)
Appendix 16.2.8.1.7 Serum FSH (Safety Population)
Appendix 16.2.8.1.8 Urine Alcohol Test (Safety Population)
Appendix 16.2.8.2 Vital Signs (Safety Population)
Appendix 16.2.8.3 12-Lead Electrocardiogram (Safety Population)

11. TABLE AND FIGURE SHELLS

The following table shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the tables that will be presented and included in the final report. Unless otherwise noted, all tables will be presented in Times New Roman font size 8. These tables will be generated off of the Celerion ADaM data structure. ADaM datasets are created in accordance with CDISC guidance (ADaM Model 2.1 and ADaM implementation guide 1.1).

Safety table shells will be completed at a later date.

11.1 In-text Summary Tables Shells

In-text Tables 11-2 and 11-3 will be in the following format:

Table 11-2 Summary of Plasma S 48168 (ARM210) Pharmacokinetics Following Single Dose of 120 mg, 200 mg, and 240 mg S 48168 (ARM210) (Treatments A, B, C, and D) (Day 1)

Pharmacokinetic Parameters	Treatment <Y>	Treatment <X>
Param1 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param2 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param3 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param4 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Treatment <Y>: <Label for Second Treatment> Treatment <X>: <Label for First Treatment> AUCs and Cmax values are presented as geometric mean and geometric CV%. Tmax values are presented as median (min, max). Other parameters are presented as arithmetic mean (± SD). Source: Tables <XXXX> and <YYYY>		

Notes for Generating the Actual Table:

Treatments
Treatment A: Single oral 120 mg S 48168 (ARM210) QD for 28 days (patients)
Treatment B: Single oral 200 mg S 48168 (ARM210) QD for 28 days (patients)
Treatment C: Single oral 120 mg S 48168 (ARM210) QD for 14 days (healthy subjects)
Treatment D: Single oral 240 mg S 48168 (ARM210) QD for 14 days (healthy subjects)

Presentation of Data:

- The following PK parameters will be presented in the following order and with following units: Day 1: AUC0-t <unit>, AUC0-inf <unit>, AUC%extrap <unit>, Cmax <unit>, Tmax <unit>, Kel <unit>, t½ <unit>, and Tlag <unit>
  Day 28: AUC0-tau <unit>, Cmax,ss <unit>, Tmax,ss <unit>, Cmin <unit>, Tmin <unit>, RA(AUC) <unit>, RA(Cmax) <unit>, and Ctrough_D13 <unit>
- n will be presented as an integer (with no decimal);
- Summary statistics will be presented with same precision as defined in post-text shells
- Table 11-2 source table is Tables 14.2.1.5, 14.2.1.7, 14.2.1.9, and 14.2.1.11.
- Table 11-3 source table is Tables 14.2.1.6, 14.2.1.8, 14.2.1.10, and 14.2.1.12.

Celerion Note: Per study design needs, the following changes are made to this table relative to Celerion's standard shell. For Tables 11-2 and 11-3 there will be a column for each Treatment. Put the "Treatment" as well as the "Dose Level" administered. Also add the Day in brackets.

Program: /CAXXXXX/sas_prg/pksas/intext-pk-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_intext_pkparam.sas DDMMMYYYY HH:MM

11.2 Section 14 Summary Tables Shells

Safety table shells will be provided in later version.

Tables 14.2.1.1 through 14.2.1.4 will be in the following format.

Table 14.2.1.1 Plasma S 48168 (ARM210) Concentrations (<units>) Following Single Oral Administration of 120 mg S 48168 (ARM210) (6 x 20 mg Tablets) for 28 Days (Patients) (Treatment A) (Days 1-28) (Pharmacokinetic Population)

			Sampling Time (hr)								
Subject Number	Treatment Sequence	Study Period	Predose	XX	XX	XX	XX	XX	XX	XX	XX
X	XXXX	X	BLQ	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
X	XXXX	X	BLQ	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
X	XXXX	X	BLQ	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
X	XXXX	X	BLQ	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
X	XXXX	X	BLQ	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
X	XXXX	X	BLQ	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
n			XX	XX	XX	XX	XX	XX	XX	XX	XX
Mean			XXX.X	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X
SD			XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX
CV%			.	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SEM			XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX
Minimum			XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Median			XXX.X	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X
Maximum			XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of <XX> are treated as <0> before the first quantifiable concentration and as missing elsewhere.
. = Value missing or not reportable.

Notes for Generating the Actual Table:

Presentation of Data:

- Concentrations will be presented to same precision as in bio data.
- Summary statistics presentation with respect to the precision of the bio data: n = integer; Mean and Median +1; SD and SEM +2, Min and Max +0, CV% to 1 decimal

Programmer Note:

- Template to be used CPConc1.
- See Section 6.4 for PK sample collection times.
- Remove "Treatment Sequence" and "Study Period" columns from the table.
- Footnote for BLQ should be updated following multiple doses see Section 6.5 for details.

```
Program:  /CAXXXXX/sas_prg/pksas/pk-conc-tables.sas       DDMMMYYYY  HH:MM
Program:  /CAXXXXX/sas_prg/pksas/pk-conc-tables-sig.sas   DDMMMYYYY  HH:MM
Program:  /CAXXXXX/sas_prg/pksas/adam_conc.sas            DDMMMYYYY  HH:MM
```

Tables 14.2.1.5 through 14.2.1.12 will be in the following format.

Table 14.2.1.5 Plasma S 48168 (ARM210) Pharmacokinetic Parameters Following Single Oral Administration of 120 mg S 48168 (ARM210) (6 x 20 mg Tablets) for 28 Days (Patients) (Treatment A) (Day 1) (Pharmacokinetic Population)

			Parameters					
Subject Number	Treatment Sequence	Study Period	Param1 (units)	Param2 (units)	Param3 (units)	Param4 (units)	Param5 (units)	Param6 (units)
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
X	XXXX	X	XXXX	X.XX	XXX	XXXX	XX.X	X.XXXX
n			XX	XX	XX	XX	XX	XX
Mean			XXXX.X	X.XXX	XXXX.X	XXXX.X	XX.XX	X.XXXXX
SD			XX.XXXX	X.XXXX	XX.XXXX	XX.XXXX	XX.XXX	X.XXXXXX
CV%			XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SEM			XX.XXXX	X.XX	XX.XXXX	XX.XXXX	XX.XXX	X.XXXXXX
Minimum			XXXX	X.XXX	XXXX	XXXX	XX.X	X.XXXX
Median			XXXX.X	X.XX	XXXX.X	XXXX.X	XX.XX	X.XXXXX
Maximum			XXXX	X.XXX	XXXX	XXXX	XX.X	X.XXXX
Geom Mean			XXXX.X	XXXX.X	XXXX.X	XXXX.X	XXXX.X	XXXX.X
Geom CV%			XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

. = Value missing or not reportable.

Notes for Generating the Actual Table:

Presentation of Data:

- Template to be used CPPar1.
- PK Parameters will be presented in the following order and with following units: Day 1: AUC0-t <unit>, AUC0-inf <unit>, AUC%extrap <unit>, Cmax <unit>, Tmax <unit>, Kel <unit>, t½ <unit>, and Tlag <unit>. Day 28: AUC0-tau <unit>, Cmax,ss <unit>, Tmax,ss <unit>, Cmin <unit>, Tmin <unit>, RA(AUC) <unit>, RA(Cmax) <unit>, and Ctrough_D13 <unit>
- n will be presented as an integer (with no decimal);
- Parameter values for exposure based parameters (i.e. AUCs, Cmax) will be presented with, at maximum, the precision of the bio data, and, at minimum, 3 significant figures (to be determined by the PKist once bio data are received). Summary statistics for exposure parameters will be presented as: Mean, Median, and Geom Mean+1; SD and SEM +2, Min and Max +0.
- Values for time-based parameters (i.e. Tmax, t1/2) will be presented with 2 decimals. Summary statistics for time-based parameters will be presented as: Mean, Median, and Geom Mean +1; SD +2, Min and Max +0. Accumulation ratios will be presented like time-based parameters.
- Values for rate constants (i.e. Kel) will be presented with 3 significant figures. Summary statistics for Kel will be presented as: Mean, Median, and Geom Mean +1; SD and SEM +2, Min and Max +0.
- CV% and Geom CV% for all parameters will be presented with 1 decimal.
- Remove "Treatment Sequence" and "Study Period" columns from the table.

Program: /CAXXXXX/sas_prg/pksas/pk-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_pkparam.sas DDMMMYYYY HH:MM

Table 14.2.1.12 will be in the following format.

Table 14.2.1.13 Intervals (Hours) Used for Determination of Plasma S 48168 (ARM210) Kel Values (Pharmacokinetic Population)

Subject Number	Treatment Sequence	Treatment <X> Interval	Treatment <X> R2	Treatment <X> n	Treatment <Y> Interval	Treatment <Y> R2	Treatment <Y> n
X	XX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
X	XX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
X	XX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
X	XX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
X	XX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
X	XX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X

Treatment <X>: <Label for First Treatment>
Treatment <Y>: <Label for Second Treatment>
R2 = Coefficient of determination
n = Number of points used in Kel calculation
. = Kel value not reportable.

Notes for Generating the Actual Table:

Treatments

- Treatment A: Single oral 120 mg S 48168 (ARM210) QD for 28 days (patients)
- Treatment B: Single oral 200 mg S 48168 (ARM210) QD for 28 days (patients)
- Treatment C: Single oral 120 mg S 48168 (ARM210) QD for 14 days (healthy subjects)
- Treatment D: Single oral 240 mg S 48168 (ARM210) QD for 14 days (healthy subjects)

Presentation of Data:

- Interval start and stop times will be presented to 1 decimal or 3 sig figures min;
- R2 will be presented to 3 decimals;
- n will be presented as an integer (with no decimal)

Programmer Note:

- Use template CPKel1 for generation of table.

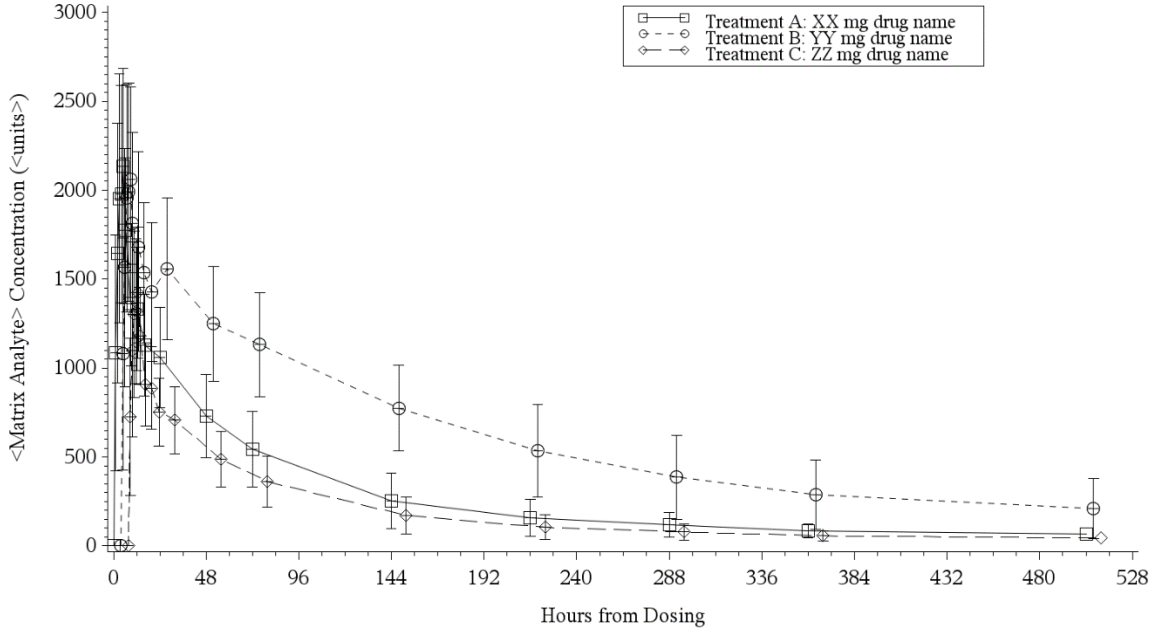
Program: /CAXXXXX/sas_prg/pksas/kel-tables-parallel.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_kel.sas DDMMMYYYY HH:MM

11.3 Figures Shells

Note: In-text figures 11-1, 11-2, and mean figures of 14.2.2 will be in the following format.

Figure 14.2.2.1

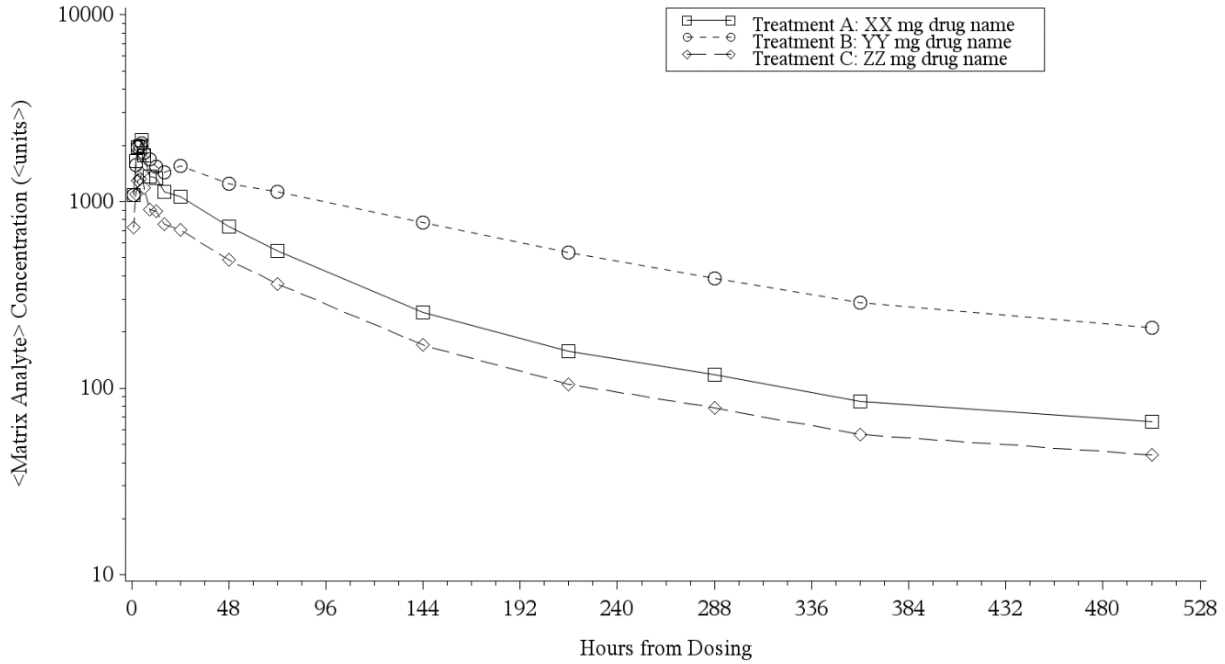
Mean (SD) <Matrix Analyte> Concentrations Versus Time
(Linear Scale)



Treatments B and C are shifted to the right for ease of reading
Program: /CAXXXXX/sas_prg/pksas/adam_meangraph.sas DDMMMYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/meangraph.sas DDMMMYYY HH:MM

Figure 14.2.2.2

Mean <Matrix Analyte> Concentrations Versus Time
(Semi-Log Scale)



Program: /CAXXXXX/sas_prg/pksas/adam_meangraph.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/meangraph.sas DDMMMYYYY HH:MM

Notes for Generating the Actual Mean Figure:

- Legend will
  - Treatment A: Single oral 120 mg S 48168 (ARM210) QD for 28 days (patients)
  - Treatment B: Single oral 200 mg S 48168 (ARM210) QD for 28 days (patients)
  - Treatment C: Single oral 120 mg S 48168 (ARM210) QD for 14 days (healthy subjects)
  - Treatment D: Single oral 240 mg S 48168 (ARM210) QD for 14 days (healthy subjects)
- Y axis label will be <Plasma S 48168 (ARM210) Concentration (<unit>)"
- X axis label will be "Time (Hours)"
- More than 1 treatment day so add the footnote: "x Treatment(s)" administration is shifted to the right for ease of reading.
- For footnote when there are more than 1 treatment add footnote to indicate if it is for healthy subjects or patients that are shifted.
- Please generate figures in color. Please use the same color and symbol for each treatment throughout.

12. LISTING SHELLS

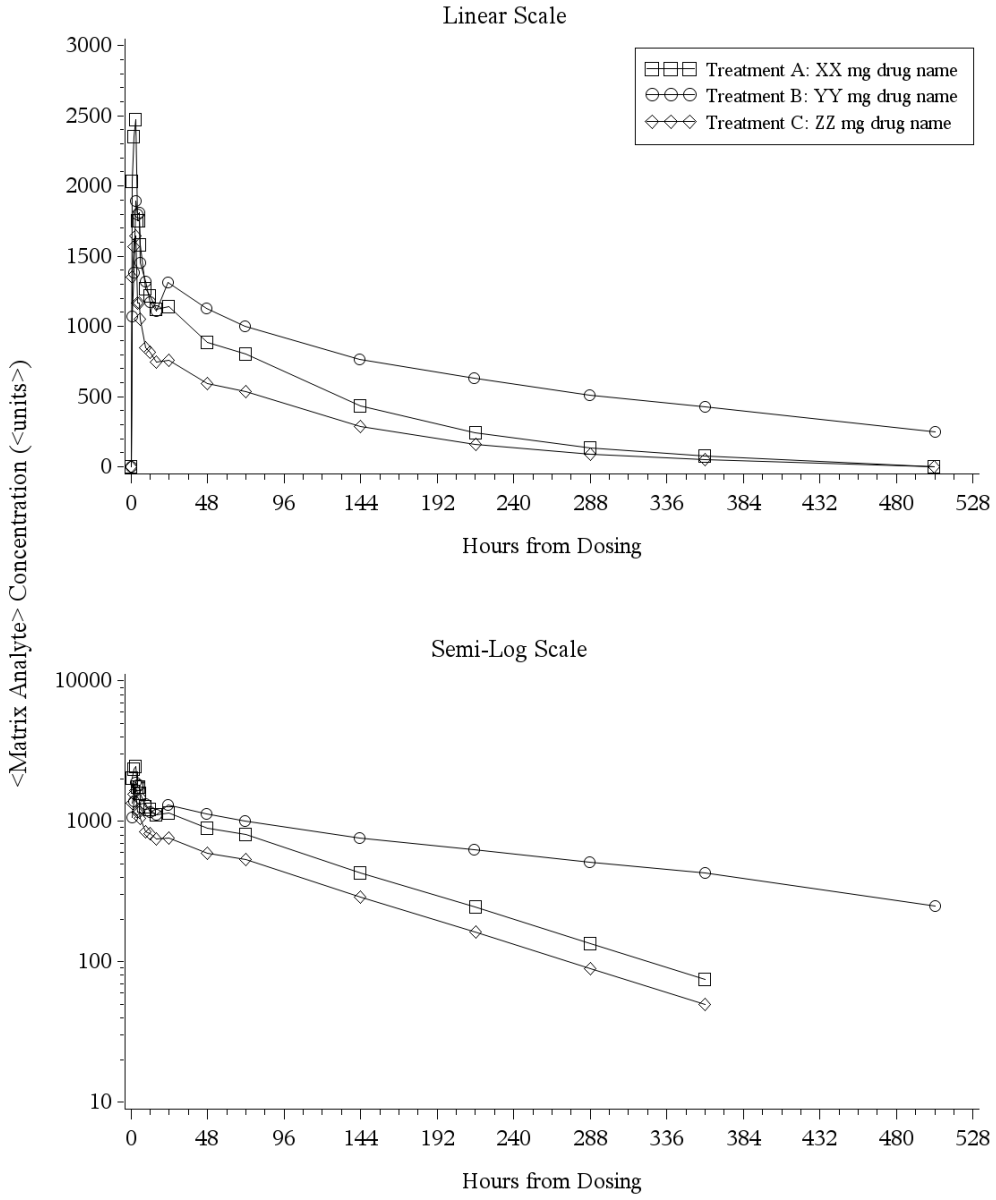
The following listing shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the listings that will be presented and included in the final report. These listings will be generated off of the Celerion SDTM datasets (SDTM Tabulation Model Model 1.4 mapped in accordance with SDTM Implementation Guide 3.2). All listings will be presented in Courier New size font 9.

CRF listing shells will be completed at a later date.

Figures in Appendix 16.2.6.1 will be in the following format:

Figure PFPConc5

Appendix 16.2.6.1
Individual <Matrix Analyte> Concentrations Versus Time
for Subject X



Program: /CAXXXXX/sas_prg/pksas/adam_indgraph.sas DDMMMYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/indgraph-all.sas DDMMMYYY HH:MM

Notes for Generating the Actual Individual Figure:

Treatments

- Treatment A: Single oral 120 mg S 48168 (ARM210) QD for 28 days (patients)
- Treatment B: Single oral 200 mg S 48168 (ARM210) QD for 28 days (patients)
- Treatment C: Single oral 120 mg S 48168 (ARM210) QD for 14 days (healthy subjects)
- Treatment D: Single oral 240 mg S 48168 (ARM210) QD for 14 days (healthy subjects)

- Y axis label will be <Matrix> <analyte> Concentration (unit)
- X axis label will be "Hours From Dosing"
- Reference line will not be included for the LOQ

PKist Note:

- Our standard is same scale for all subjects, but if one or 2 subjects are are driving the scale resulting in poor resolution for all other subjects, then it may be more appropriate to scale individual plots to each subject's data.
- Individual profiles will be generated with Days 1, 14, and/or 28 overlayed.
- Please generate figures in color. Please use the same color and symbol for individual treatments/cohorts throughout.

Program: /CAXXXXX/sas_prg/pksas/indgraph-all.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_indgraph.sas DDMMMYYYY HH:MM