STATISTICAL ANALYSIS PLAN

STUDY PART 1

408-C-1403

NCT02255422

A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Mitochondrial Myopathy

Analysis Plan Version/Date: Version 1.0 (Part 1)/03-12-2018

Approval and Signature Page

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Rationale for Version 2.0

The changes from Version 1.0 to Version 2.0 of the Statistical Analysis Plan were motivated by protocol amendments subsequent to the finalization of Version 1 of the SAP. Version 1 was finalized 29Apr2015 under protocol version 3 (October 13, 2014). The protocol was amended two times since Version 1 of the SAP (Protocol Version 4, 23Jun2015; Protocol Version 5, 29Oct2015). The current protocol allows for up to approximately 8 cohorts of patients in the dose-ranging portion of the study (Part 1). Additional modifications were made to provide clarity to the statistical methods used in the planned analysis.

The Version 2 of the SAP also specifies separate analysis plans for Part 1 and Part 2 of this study. Having separate analysis plans for each study part will allow for information learned in Part 1 to be applied to the analysis of Part 2.

Other notable modifications include:

- Number of patients increased with the addition of more cohorts in Part 1
- Clarify that separate analysis sets will be defined for each Part
- Reformatted to current template

1. INTRODUCTION

Study 408-C-1403 (the MOTOR study) is a 2-part, randomized, double blind, placebo-controlled, Phase 2 study designed to compare the efficacy and safety of RTA 408 to placebo in patients with mitochondrial myopathy. This document describes the statistical analysis methods and data presentations that Reata Pharmaceuticals, Inc. (Reata) will use to analyze data from the MOTOR study. Study related documents include the study protocol and case report form. A data safety monitoring board (DSMB) will be reviewing data on a regular basis to monitor the study for safety. The DSMB is managed by an independent unblinded statistical group, Statistics Collaborative, Inc. (SCI). A separate document contains details regarding the DSMB.

The database will be locked after each study part (*i.e.,* Part 1 and Part 2). This version of the SAP describes the analyses planned for Part 1 prior to database lock of Part 1. Unless otherwise specified, the analyses described in this document will be performed after database lock for Part 1 for inclusion in the discussion of Part 1 data in the final clinical study report (CSR). Any substantive changes made to the statistical analysis plan after database lock will be clearly documented and a justification will be given in the CSR.

This SAP is based on Version 5 of the study protocol dated October 29, 2015. If the protocol is subsequently amended, this SAP may be amended as well. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing. All analyses will be conducted using SAS version 9.2 or higher.

1.1 Study Objectives

In patients with mitochondrial myopathy, comparing those receiving RTA 408 versus those receiving placebo, the objectives of the MOTOR study are as follows:

1.1.1 Primary Objectives

The primary objectives of this study are:

- To evaluate the change in peak work during maximal exercise testing
- To evaluate the safety and tolerability of RTA 408

1.1.2 Secondary Objective

The secondary objective of this study is:

- To evaluate the change in 6-minute walk test (6MWT) distance

1.1.3 Exploratory Objectives

- To evaluate the change in peak oxygen utilization during maximal exercise testing
- To evaluate the change in peak blood lactate and pyruvate, peak heart rate, and rating of perceived exertion during submaximal exercise testing
- [redacted]

- [redacted]

1.2 Part 1 Study Design

Part 1 of this study will evaluate the efficacy, safety, PK, and PD of RTA 408 in the treatment of up to approximately 64 patients with mitochondrial myopathy.

The first part of the MOTOR study will be a randomized, placebo-controlled, double-blind, dose-escalation study to evaluate the safety of RTA 408 at 2.5 mg, 5 mg, 10 mg, 20 mg and higher dose levels (not to exceed 160 mg) in up to approximately 8 cohorts of patients with mitochondrial myopathy. A cohort consists of the next eight eligible patients randomized 1:3 to placebo (n=2) or the cohort specific dose of RTA 408 (n=6). Up to 8 cohorts will be enrolled in Part 1 to allow for adequate dose-ranging for selection of RTA 408 dose(s) to be used in Part 2.

Intra-patient dose-escalation will only be utilized in the first cohort to evaluate RTA 408 at the first two dose levels (2.5 mg and 5 mg). Patients enrolling in the first cohort will be randomized to RTA 408 2.5 mg or placebo. After the Week 2 visit, each patient in the first cohort will dose escalate to 5 mg (or remain on placebo) on Day 15 unless a dose-limiting toxicity (DLT) is reported in that patient. After the last patient in the first cohort completes their Week 4 visit (i.e., 2 weeks on 2.5 mg daily [or matching placebo] followed by 2 weeks on 5 mg daily [or matching placebo]), the data safety monitoring board (DSMB) and Sponsor will review all available safety information and make a decision regarding enrollment of the next cohort. Beginning with the second 8-patient cohort, once the eighth patient enrolled completes their Week 2 visit the DSMB will review all available safety information and recommend the dose of RTA 408 for the subsequent cohort. The DSMB dose recommendation for each cohort must not exceed 100% more than the highest dose of RTA 408 evaluated in this study, and the maximum permitted dose of RTA 408 is 160 mg. The dose-level for each new cohort will not exceed the DSMB recommended dose level, and it will be selected by the Sponsor based on review of available safety, efficacy, PK, and PD data. Prior to opening each cohort in Part 1 for enrollment, the Sponsor will evaluate all available data from doses studied in Part 1 to determine if enough information is available to select doses for Part 2 of the study. Once doses are selected for Part 2 by the Sponsor, no additional cohorts will be enrolled in Part 1.

1.2.1 Study Visits and Assessments

Detailed schedules of assessments for the MOTOR study are included in the study Protocol. Patients will self-administer study treatment once daily until they have completed 12 weeks (84 days) of study treatment, are discontinued from study treatment, or have withdrawn consent to participate in the study. A follow-up visit for safety will occur at Week 16 (4 weeks after last dose).

Table 1: Schedule of Assessments

Assessment	V1: Screen[b]	V2: Day 1[c]	V3: Wk 1 Day 7±1[d]	V4: Wk 2 Day 14±3[e]	V5-6: Wk 4 Day 27±3	V5-6: Wk 4 Day 28[f]	V7: Wk 6 Day 42±3	V8: Wk 8 Day 56±3	V9: Wk 10 Day 70±3	V10-11: Wk 12[a] Day 83±3	V10-11: Wk 12[a] Day 84[f]	V12: Wk 16 Day 112±3
Informed consent	X											
Inclusion/Exclusion criteria assessment	X	X										
Demographics and baseline disease characteristics	X											
Prior and concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X	X										
Height	X											
Echocardiogram	X[g]									X		
Electrocardiogram	X[g]	X		X[h]		X		X			X	X
Vital sign measurements	X	X	X	X	X	X		X		X	X	X
Weight and BMI	X	X	X	X	X	X		X		X	X	X
Physical examination	X									X		X
Adverse event collection		X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry	X[i]	X	X	X		X		X			X	X
Hematology	X[i]	X	X	X		X		X			X	X
Urinalysis and microscopy	X[i]	X	X	X		X		X			X	X
BNP and NT-proBNP[j]	X	X	X	X		X		X			X	X
Hepatitis B and C and HIV[k]	X[i]											
Pregnancy test WOCBP[l]	X[i]	X		X		X		X			X	X
Randomization		X										
Study drug dispensation		X		X[m]		X		X				
Study drug return and pill count / diary[n]				X[o]		X		X			X	
Study drug administration[p]		<----------		----------		X		----------		----------	>	
Telephone contact							X		X			
Exercise regimen reporting	X	X			X					X		
Maximal exercise test[q]	X				X					X		
Submaximal exercise test[r]		X				X					X	
6-minute walk test	X	X				X		X			X	
Fatigue Severity Scale		X								X		
SF-36 Health Survey Update		X								X		
Muscle needle biopsy[s]		X									X	
PK analysis				X[t,u]		X[v]		X[t]			X[u,v]	
Blood biomarkers[w]		X[w]								X		

[a] These procedures should be performed for early termination.
[b] Screening procedures for each patient should occur over the course of a few days and must finish at least 1 day prior to randomization. Study Day -1 is the day prior to first dose of study drug.
[c] All Day 1 procedures should be performed prior to administration of first dose of study drug.
[d] Assessments for Visit 3 may be collected at a home health nurse visit (at appropriate locations and approved by Sponsor) or at the study center clinic.

[e] Assessments for Visit 4 must be collected at the study center if patients are enrolled in Part 1 of the study. If patients are enrolled in Part 2 of the study, Visit 4 assessments may be collected by a home health nurse.
[f] Visit 6 should be conducted within 18 hours to 48 hours of Visit 5, and Visit 11 should be conducted within 18 hours to 48 hours of Visit 10.
[g] For patients with echocardiograms and electrocardiograms collected within 30 days prior to the Screening Visit, the most recent echocardiogram and electrocardiogram can be used to assess cardiac function and patient eligibility.
[h] At Week 2, electrocardiogram is only required for patients in Part 1 of the study.
[i] A home health nurse visit may be used to collect all lab samples required at the Screening Visit.
[j] Patients must be allowed to rest for a minimum period of 1 hour following maximal or submaximal exercise testing before this blood sample is collected (at the same time as all of the central lab blood collection). This sample must be taken prior to the 6MWT. This sample should be taken with the patient in the same position (e.g., sitting or semi-recumbent) at all appropriate visits
[k] Blood samples will be collected to analyze for hepatitis B and C and HIV antibodies only in patients lacking evidence of a negative titer in the past year.
[l] Negative serum pregnancy test results are required at the Screening Visit before study enrollment, and negative urine pregnancy test results are required at all other times indicated for continued participation in the study.
[m] At Week 2, study drug dispensation is only required for patients in the first cohort of Part 1 of the study.
[n] A dosing diary check must be performed at study drug return and pill count.
[o] At Week 2, study drug return, pill count, and diary check are only required for patients in the first cohort of Part 1 of the study.
[p] Study drug should be administered in the presence of study staff in the clinic on Day 1 after all Day 1 assessments have been completed. Study drug should also be administered in the clinic on Days 14, 28 (Part 2 only), 56 (Cohort 1; Part 1 only) and 84 after the blood collection for predose PK analysis. All other doses can be administered at home. RTA 408 should be administered once daily through Day 84.
[q] On study days where multiple assessments are to be completed, the maximal exercise test will be the first functional assessment performed. Blood samples will be collected at rest, at the completion of the test, and at 5 and 10 minutes after the test. Maximal exercise testing should be repeated prior to randomization if the original Screening assessment was performed >30 days prior to Day 1.
[r] As part of the submaximal exercise test, blood samples will be collected at rest and at 10-minute intervals throughout the test.
[s] Muscle needle biopsy, which is optional, should be collected after all study visit assessments are performed, except on Day 1, in which muscle needle biopsy should be the second to last procedure performed, collected prior to study drug administration.
[t] For patients enrolled in the first cohort of Part 1 of the study, blood samples for PK analysis at Visit 4 and Visit 8 should be collected prior to study drug administration as well as 1, 2, 4, and 8 hours after study drug administration. A single blood sample for PK analysis at Visit 11 should be collected prior to study drug administration.
[u] For patients enrolled in the second and subsequent cohorts of Part 1 of the study, blood samples for PK analysis at Visit 4 should be collected prior to study drug administration as well as 1, 2, 4, and 8 hours after study drug administration. A single blood sample for PK analysis at Visit 11 should be collected prior to study drug administration.
[v] For patients enrolled in Part 2 of the study, blood samples for PK analysis at Visit 6 and Visit 11 should be collected prior to study drug administration.
[w] Blood collection for biomarkers will be optional. On Day 1, blood collection for blood biomarkers must occur prior to study drug administration.

Abbreviations: V=Visit; Wk=Week; 6MWT=6-minute walk test; BMI=body mass index; BNP= B-type natriuretic peptide; HIV=human immunodeficiency virus; NT-proBNP=N-terminal prohormone of B-type natriuretic peptide; PK=pharmacokinetic; WOCBP=women of childbearing potential

1.2.2 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be monitoring data from the study on a monthly basis throughout Part 1 to ensure the safety of the patients in the trial.

An independent statistical group, Statistics Collaborative, Inc., will prepare unblinded analyses for the DSMB and will not have a role in the statistical analysis plan (SAP) or day-to-day support of the study.

1.2.3 Discontinuation of Treatment

Discontinuation refers to a patient stopping administration of study drug. Reasons for study drug discontinuation may include the following:

- Occurrence of an adverse event or change in medical status that leads the investigator to be concerned about the patient's welfare
- Protocol violations
- Administrative reasons (e.g., inability to continue)
- Sponsor termination of the study
- Voluntary withdrawal
- Pregnancy during the study
- Investigator unblinding
- Other

Patients who are discontinued from study drug should still complete all study visits and undergo all scheduled study assessments, if possible.

1.2.4 Patient Termination

Termination refers to a patient stopping study drug and all study assessments and visits. Reasons for study termination include the following:

- Administrative reasons (e.g., inability to continue, lost to follow-up)
- Death
- Withdrawal of consent

Patients who terminate the study for any reason may not re-initiate study drug or study assessments at any time.

1.2.5 Randomization and Unblinding

The first cohort enrolled in Part 1 will be randomized 3:1 to RTA 408 2.5 mg or placebo. After the Week 2 visit, each patient in the first cohort will dose escalate to 5 mg (or remain on placebo) and remain on 5 mg through the remaining 10 weeks of treatment. Beginning with the second cohort enrolled in Part 1, patients will be randomized 3:1 to a specific dose of RTA 408 or placebo as recommended by the DSMB. Patients will remain at their randomized dose through the entire 12 weeks of treatment.

To maintain the study blind, all study drug kits will be packaged with blinded labels. Investigators will distribute the blinded study drug kits by kit number to patients as assigned by the IWRS. All patients, investigators, site personnel, and laboratories with direct involvement in the conduct of the study or their designees will be blinded to treatment assignments and

appropriate measures will be taken to ensure the blind is maintained to reduce potential bias. Some Sponsor personnel may have access to treatment assignments during dose escalation (Part 1).

1.3 Sample Size and Power

The sample size for Part 1 (i.e., 8 per cohort for 64 total patients in Part 1) is based on a dose-escalation scheme to evaluate initial safety and PD activity of RTA 408 in this patient population. The small number of patients at each dose in Part 1 is not expected to fully characterize safety, efficacy, or PD, but rather inform the DSMB and Sponsor of the appropriate doses to select for Part 2.

2. PLANNED ANALYSIS OF PART 1

This study consists of two distinct parts: a placebo-controlled, dose-ranging part (Part 1) followed by a second placebo-controlled part (Part 2) utilizing one dose selected from Part 1. Analyses planned for Study Part 2 will be described in a separate document.

2.1 Interim Analysis

A DSMB will be reviewing data on an ongoing basis from the study to ensure patient safety. The DSMB will not recommend stopping the study for efficacy. The DSMB charter describes the interim reviews of safety. No other formal interim analyses are planned for this study.

2.2 Timing of Analysis

The primary analysis of Part 1 will be performed after all patients enrolled in Part 1 have completed Part 1 and the Part 1 records are locked in the EDC system. Other analyses of Part 1 data may be performed prior to database lock in order to plan for Part 2 of this study.

2.3 Endpoint Measures

Unless otherwise specified, efficacy measures are obtained for all patients.

2.3.1 Efficacy Endpoints

The primary efficacy endpoint is change in peak work. Peak work will be derived by dividing the maximum work load (watts) at each visit by the patient's baseline weight (kg). Peak work will be rounded to the 0.0001 digit.

The secondary efficacy endpoint is the change in 6-minute walk test (6MWT) distance.

Exploratory endpoints for this trial include:

- To evaluate the change in peak oxygen utilization during maximal exercise testing
- To evaluate the change in peak blood lactate and pyruvate, peak heart rate, and rating of perceived exertion during submaximal exercise testing
- To evaluate the change in Fatigue Severity Scale score
- To evaluate the change in SF-36® Health Survey Update (SF-36) score
- Parameters assessed from blood lactate and serum pyruvate during submaximal exercise testing

2.3.2 Safety Endpoints

Safety parameters include results of echocardiogram, ECG, vital sign measurements, weight, BMI, physical examination, AEs, SAEs, concomitant medications, and laboratory tests (clinical chemistry, hematology, urinalysis, microscopy, and pregnancy tests [as indicated]).

[redacted]

[redacted]

2.4 Changes from Protocol-Specified Analysis

There are no planned changes to analyses from what is described in the protocol.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

3.1 Analysis Considerations

All individual data will be listed as recorded in the database. All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

Only patients in the appropriate analysis set will be included in summary statistics. For endpoints discussed in this SAP, all available data for each patient will be included in summaries.

Patients randomized to RTA 408 in cohort 1 will escalate from 2.5 mg to 5 mg at Week 2. These patients will be categorized as the 5-mg treatment group for data presentations. Patients enrolled in all other cohorts will remain on their randomized dose for all 12 weeks of treatment, and will be categorized according to their randomized treatment for data presentations. Patients randomized to placebo within each cohort will be pooled for data presentations into a single placebo treatment group.

All raw patient data will be converted to SDTM for submission to FDA, however, only the analysis data will be presented in individual-patient data listings.

Continuous data will be summarized by treatment using descriptive statistics (number, mean, standard deviation [SD], minimum, median, quartiles (Q1, Q3), and maximum). Categorical data will be summarized by treatment using frequency tables (number and percentage).

3.2 Analysis Sets

For Part 1 of the study, the following analysis sets will be defined.

3.2.1 Full Analysis Set

The full analysis set (FAS) includes all enrolled patients in Part 1, whether or not they received study drug. The FAS will be used to assess patient disposition and efficacy endpoints. Patients will be summarized according to the treatment to which they were randomized.

3.2.2 Safety Analysis Set

The safety analysis set includes all patients who received at least 1 dose of study drug. The safety analysis set will be used to assess safety endpoints. Patients who receive at least 1 dose of RTA 408 will be classified in the RTA 408 group at the highest dose level received.

3.2.3 Pharmacokinetic

The Pharmacokinetic analysis set will be a stand-alone analysis.

3.3 Strata and Covariates

Randomization in Part 1 of this study is not stratified. Since sample size per dose level will be small, no covariates will be considered for the primary analysis of Part 1.

3.4 Examination of Patient Subsets

Emerging data have identified patients with baseline blood lactate levels ≤ 2.0 mM at rest during the submaximal exercise test and patients with baseline resting heart rate ≤ 80 bpm during the submaximal exercise test as particular subgroups of interest. Analyses of submaximal exercise testing parameters data may be performed on these subgroups of interest.

3.5 Multiple Comparisons

No adjustments for multiplicity will be considered for analysis of Part 1 data.

3.6 Missing Data

Missing data will not be imputed for the primary analysis of safety, PK, PD, or exploratory efficacy endpoints. The planned statistical methods use all available data, therefore no imputation is planned for the primary analysis of the primary and secondary efficacy endpoints (i.e., peak work and 6MWD). Sensitivity analyses may be performed as appropriate to assess the impact of missing data.

3.7 Visit Windows

3.7.1 Definition of Study Day

Study day is the day relative to the first dose of study drug administration. Study day for events on or after the date of the first dose will be defined as the number of days from the date of the first dose of study drug, plus 1 day, so that the date of the first dose will be defined as Day 1.

For events before the date of the first dose, study day will be calculated as the difference in days between the date of the first dose and the date of interest. Thus, the day before the date of the first dose will be defined as Day -1.

3.7.2 Definition of Study Baseline

The average of Screening and Day 1 assessments will be used as baseline for 6MWT. For all other parameters, study baseline is defined as the last non-missing observation obtained prior to administration of the first dose on Study Day 1. Baseline will be defined as analysis visit 0.

3.7.3 Analysis Visits

The CRF nominal study visits will be used for all safety analyses. For efficacy analyses or when otherwise specified, summaries by visit will be done using analysis visits defined below.

Analysis Visit Number	Label	Protocol Visit Number	Target Study Day
0	Baseline	1, 2	≤1
4	Week 4	5, 6	28
8	Week 8	8	56
12	Week 12	10, 11	84

3.7.4 Analysis Windows for Unscheduled Visits

Unscheduled visits will be reflected in summarization of changes to worst post-baseline measures.

Additionally, unscheduled assessments will be used in the place of missing scheduled efficacy and safety assessments, if the unscheduled assessment was collected within ±7 days of the scheduled assessment. Study day will be calculated for each unscheduled assessment and compared to the protocol defined study day for each visit. In general, analysis windows for unscheduled visits will be defined as follows:

Analysis Visit	Target Study Day	Analysis Window
0	1	Study Day ≤1
1 (Safety Only)	7	2 ≤ Study Day ≤ 10
2 (Safety Only)	14	11 ≤ Study Day ≤ 20
4	28	21 ≤ Study Day ≤ 35
8	56	49 ≤ Study Day ≤ 63
12	84	77 ≤ Study Day ≤ 91

Records from unscheduled visits that do not fall within an analysis window will be listed, but will not be analyzed.

3.7.5 Selection of Data in the Event of Multiple Records in a Visit

If multiple assessments fall within the same analysis visit, the assessment closest to the target visit day specified in the protocol study procedures will be used. If two assessments are equidistant from a post-baseline target visit day, the earlier assessment will be used.

3.8 Rounding

The method of rounding for data presentation is provided in Appendix 2.

4. STUDY POPULATION

4.1 Disposition of Patients

Enrollment and disposition will be summarized. A patient will be defined as enrolled if they sign the informed consent form. A disposition summary will include the number and percentage of patients who:

- Enrolled in the study
- Are in the safety analysis set
- Are in the full analysis set
- Number of patients dose escalated (Cohort 1 only)
- Completed treatment through Week 12
- Prematurely discontinued from study treatment
- Completed the study
- Prematurely terminated from the study.

The disposition summary will also include the primary reason for discontinuation from study treatment or termination from the study.

Disposition summaries will be presented by randomized treatment. Percentages will be based on the number of randomized patients.

A listing of patient disposition will include the date of first dose of study drug, date of last dose of study drug, total weeks of treatment, study treatment completion status, study completion status, and reason(s) for study drug discontinuation and/or study termination.

4.2 Protocol Deviations

Where available, protocol deviations will be listed by deviation category (e.g., eligibility criteria, out of window visit, serious adverse event (SAE) reporting, study procedures, treatment procedures). All deviations, including major protocol deviations that could potentially affect the efficacy or safety conclusions of the study, will be identified prior to database lock. Protocol deviations will be listed in a data listing and summarized by deviation category.

4.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics summaries, for patients in the safety analysis set, will include:

- Age (years at study baseline)
- Sex
- Race
- Ethnicity
- Weight (kg)

- Height (cm)
- Baseline peak work
- Baseline resting heart rate during the submaximal exercise test
- Baseline serum creatine kinase (CK)

Due to the number of measures, baseline characteristics will be provided in a separate summary. Continuous statistics will be provided for:

- Age at mitochondrial myopathy onset
- Years since mitochondrial myopathy onset (at study baseline)

Frequency tables (number and percentage) will be provided for discrete measures:

- Clinical diagnosis
- Stroke-like episodes in the past year
- Ophthalmoplegia in the past year
- Polyneuropathy in the past year
- Seizures in the past year

Demographic and baseline characteristics will be summarized by randomized treatment group.

4.4 Medical History

Medical history will be mapped to preferred terms (PT) and system organ classes (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA®) Dictionary (version 14.1). Medical history items will be summarized by MedDRA SOC and PT and patient listing will be provided.

5. STUDY DRUG AND OTHER MEDICATIONS

5.1 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary (B2_DDE_HD_Sep2011-With PerfTerm) for anatomical therapeutic chemical classification (ATC) and preferred drug name.

A prior medication is any medication that is taken prior to the first dose of study drug. A concomitant medication is any medication taken at the time of first study treatment or a medication that was started after the start of study drug dosing. Specifically, concomitant medications are medications

- that are continued from screening and continued after the first study drug dosing, or
- that have start dates or stop dates within the treatment period.

A medication can be classified as both prior and concomitant if it was started prior to study treatment and continued during the treatment period.

Prior and concomitant medications will be summarized for each treatment group by WHO DD ATC class and preferred name. These summaries will present the number and percentage of patients using each medication. Patients may have more than one medication per ATC class and preferred name. At each level of patient summarization, a patient is counted once if he/she reported one or more medications at that level. Each summary will be ordered by descending order of incidence of ATC class and preferred name within each ATC class.

In addition, patients who take excluded medications sensitive substrates for cytochrome P450 2C8 or 3A4, moderate or strong inhibitors or inducers of cytochrome P450 3A4, or substrates for p-glycoprotein transporter (defined in the Protocol Section 9.2.1) during the study will be listed.

5.2 Duration of Study Treatment and Exposure to Study Drug

The duration of study drug exposure is defined as the number of days on treatment from the first dose of study drug until the last dose of study drug (last dose – first dose + 1). Study drug exposure will be summarized by descriptive statistics. Summaries will include the number of doses received (or dispensed), total dose (mg) received (or dispensed), average daily dose (mg), study drug compliance, and duration (days) of exposure during the study treatment period.

Total number of doses dispensed and total dose (mg) dispensed will be calculated from total number of kits (bottles) recorded on the Study Drug Dispensation eCRF. Total number of doses received will be calculated from information on the eCRF of Study Drug Return and Study Drug Dispensation, as the total number of doses dispensed – total number of doses returned. The total dose (mg) received can be calculated in similar way. The average daily dose (mg) will be calculated as total dose (mg) / (total number of days of exposure).

Study drug compliance (%) will be calculated as 100 × total number of doses received / total number of doses expected. Patients are expected to dose daily, therefore 84 doses expected at Week 12.

All study drug dispense and accountability data will be listed in patient listing.

6. EFFICACY ANALYSIS

Primary analysis of the efficacy data will be based on the full analysis set, which will include all patients enrolled in Part 1 of the study. Analyses will be performed for each RTA 408 dose level. Summary statistics for observed values, change from baseline, and percent change from baseline (including 95% CI and quartiles) will be presented by randomized treatment group.

6.1 Primary Efficacy Analysis

Peak work (w/kg) is calculated as the maximum workload (w) at each visit divided by baseline weight (kg) for each patient. Peak work should be rounded to the nearest 0.0001 digit. A mixed-model for repeated measures (MMRM) analysis will be used to analyze the primary efficacy variable. All scheduled peak work values collected through the Week 12 visit will contribute to the primary analysis. The primary efficacy variable, the change from baseline in peak work value, will be calculated for each post first dose time point through Week 12 visit (i.e., Weeks 4 and 12). Missing data for the Phase 2 portion will not be imputed for the primary analysis. The primary inference will be the test of LS mean at each time point. The primary endpoint is the mean change from baseline in peak work at Week 12.

Patients must complete the maximal exercise test for at least 4 minutes to be considered a valid test. Maximal exercise test trials which were 4 minutes or less in duration will not be used in the primary efficacy analysis.

6.1.1 Statistical Hypothesis

For the primary efficacy endpoint, the null hypothesis is the Week 12 mean ($[\mu_{OMAV}] - [\mu_{PBO}]$) change from baseline in peak work = 0 w/kg. The alternative hypothesis is the Week 12 mean ($[\mu_{OMAV}] - [\mu_{PBO}]$) change from baseline in peak work $\neq$ 0 w/kg.

A positive change from baseline suggests an improvement.

6.1.2 Statistical Model

The MMRM model will include change from baseline in peak work as the dependent variable, treatment group, protocol scheduled time point (analysis visit), and the interaction between treatment and time as fixed effects, patient as a random effect. Analysis visits 0, 4, and 12 will be used. Within-patient correlations will be modeled using an unstructured covariance structure. Time ordering is a repeated measure within patients. It is assumed that errors for different patients are independent with an unstructured covariance structure. The estimation method for the model will be restricted maximum likelihood (REML). The SAS pseudo-code is as follows:

```
proc Mixed data=efficacy method=reml;
  Class usubjid trt avisit;
  model resp=trt avisit trt*avisit /s;
  repeated avisit / subject=usubjid type=un rcorr;
  lsmeans trt*week / diff cl alpha=0.05;
run;
```

In the event the MMRM model with an unstructured covariance structure does not converge, the following covariance structures will be as substitution in the following order. Each subsequent covariance structure will be used only if all previous covariance structure(s) is (are) used and the model(s) did not converge.

1. Toeplitz covariance structure (assuming measurements from samples taken closer together in time are more highly correlated than those from samples taken farther apart).
2. First order of auto-regressive [AR(1)] covariance structure (assuming measurements from samples taken closer together in time are more highly correlated than those from samples taken farther apart).
3. Compound symmetry covariance structure (assuming equal correlation for measurements from a patient, regardless of how far apart in time when they were taken).

6.1.3 Reporting Results

The least squares (LS) mean, standard error (SE) of the LS mean, and two-sided 95% confidence interval (CI) of the LS mean and p-value will be reported at each time point for (1) each dose level of RTA 408 and (2) the difference between each dose and placebo. For part 1 of the study, statistical testing will be performed at every time point that peak work is measured. The difference between RTA 408 and placebo in change from baseline in peak work at Week 12 test is the primary endpoint. The mean change from baseline in peak work at all other time points will be considered exploratory, so tests at these time points will be performed with no adjustments for multiple comparisons.

A plot of the LS mean differences with 95% CIs of change from baseline in eGFR value over time will be presented for selected doses.

6.2 Secondary Efficacy

The secondary endpoint of this study is the modified change in 6-minute walk test (6MWT) distance score.

The baseline 6MWD result is the average of Screening and Day 1 6MWT values.

Pulse oximetry at resting and the end of the 6MWT will be summarized using summary statistics, at described in Section 3.1.

The change from baseline in 6MWT will be analyzed using the same MMRM model used for the primary efficacy endpoint. Analysis visits 0, 4, 8 and 12 will be used. The pairwise dose group comparisons with placebo will be estimated using the difference in adjusted means and 95% CI for the difference in changes from baseline to Week 12.

6.3 Exploratory Efficacy

Summary statistics and 95% confidence intervals for treatment differences in mean change from baseline, using the same MMRM model used for the primary and secondary endpoints, will be provided for all exploratory endpoints unless otherwise noted. P-values will be provided for descriptive purposes only.

For parameters having repeated measurements within an analysis visit during the maximal and submaximal exercise test, the MMRM code should incorporate the analysis visit and assessment time (during the exercise test) in the analysis:

```
Proc Mixed data=x order=data;
  Class patno trt week;
  model resp =  trt*time*week /s;
  Repeated time*week / sub = patno type = un;
```

```
lsmeans trt*time*week / diff cl alpha=0.05;
Run;
```

For blood lactate measurements during the submaximal exercise test, the repeated measures model will incorporate baseline resting blood lactate as a covariate:

```
Proc Mixed data=x order=data;
  Class patno trt week;
  model resp =  trt*time*week baseline_resting_lactate /s;
  Repeated time*week / sub = patno type = un;
  lsmeans trt*time*week / diff cl alpha=0.05;
  Run;
```

As with the primary and secondary endpoints, exploratory endpoints will be analyzed using individual doses of RTA 408 versus placebo pooled. A separate model that does not pool the RTA 408 doses will be used to obtain pairwise differences for each dose level versus pooled placebo.

For parameters having repeated measurements within an analysis visit during the maximal and submaximal exercise test, the change from resting (delta) for parameters measured at resting and a certain timepoint during the maximal or submaximal exercise test will be reported as:

- Delta = [Parameter at Y min] – [Parameter at resting]

In the maximal exercise test, laboratory measurements may be measured at resting, at the end of the maximal exercise test, 5 min after the end of the maximal exercise test, and 10 min after the end of the maximal exercise test.

In the submaximal exercise test, efficacy and laboratory measurements are recorded at resting, at 10 min, 20 min, and 30 min.

The change from baseline is defined for parameters measured at resting and a certain timepoint during the maximal of submaximal exercise test is defined as:

- Change from Baseline in Delta= [Parameter at Y (At Visit X) - Parameter at resting(At Visit X)] - [Parameter at Y min (At Baseline) - Parameter at resting(At Baseline)]

6.3.1 Other Maximal Exercise Testing Measures (including Oxygen Utilization)

Various parameters in addition to peak work are assessed during maximal exercise testing, as listed below in Table 2.

Table 2: Maximal Exercise Testing Measures

Parameter	At Rest (Prior to Test)	At Maximal Work (End of Test)
Expired Air Gas Volume (VeBTPS) (L/min)[a]	X	X
Cardiac Output (L/min)[a]	X	X
Heart Rate (bpm)[a]	X	X
Oxygen Saturation (SpO2) (%)	X	X
Diastolic Blood Pressure (mmHg)[a]	X	X
Systolic Blood Pressure (mmHg)[a]	X	X
Carbon Dioxide Production (VCO_2) (mL/kg/min)[a, b]	X	X
Oxygen Consumption (VO_2) (mL/kg/min)[a, b]	X	X
Arteriovenous Oxygen Difference (a-VO2diff) (mLO2/dlQ)[a]	X	X
Respiratory Exchange Ratio	X	X
Borg		X
Leg Effort Rating of Perceived Exertion		X
Exercise Duration (min)		X
Maximal work (W/kg)		X
Maximal workload (W)		X
O2 pulse (%)[c]		X

[a]Observed values and difference between resting and peak performance for these parameters will be summarized at baseline and at each timepoint.
[b] Analysis of VO_2 and VCO_2 will be performed using adjustments for weight at the visit week in which the maximal exercise test was performed, such that VO_2 and VCO_2 are in units of mL/kg/min
[c] O_2 pulse will be calculated for analysis: O_2 pulse = (Maximal_VO_2 (in units of mL/min)*1000)/Maximal_HR)

For parameters measured at resting and at the end of the maximal exercise test, the change from resting and the change from baseline should be calculated.

The change from resting (delta) for parameters measured at resting and at the end of the maximal exercise test is defined as:

- Delta = Parameter at maximal work - Parameter at resting

The change from baseline is defined for parameters measured at resting and at the end of the maximal exercise test is defined as:

- Change from baseline in Delta= [Parameter at maximal work(At Visit X) - Parameter at resting(At Visit X)] - [Parameter at maximal work(At Baseline) - Parameter at resting(At Baseline)]

Observed values and difference between resting and peak performance for these parameters will be summarized at baseline and at each timepoint. For all assessments, each parameter will be summarized at baseline and at each time point along with the change from baseline by treatment. For parameters measured at resting and at the end of the maximal exercise test [VeBTPS, cardiac output, heart rate, VO_2 (L/min) and VO_2 (ml/mg/min), VCO_2 (L/min) and VCO_2 (ml/mg/min), diastolic blood pressure, systolic blood pressure, a-VO_2diff, and SPO_2 (%)], the change from resting and the change from baseline should be calculated.

The change from resting (delta) for parameters measured at resting and at the end of the maximal exercise test is defined as:

- Delta = Parameter at maximal work - Parameter at resting

The change from baseline is defined for parameters measured at resting and at the end of the maximal exercise test is defined as:

- Change from baseline in Delta= [Parameter at maximal work(At Visit X) - Parameter at resting(At Visit X)] - [Parameter at maximal work(At Baseline) - Parameter at resting(At Baseline)]

Only summary statistics will be provided.

6.3.2 Maximal Exercise Testing Laboratory Parameters

The following serial laboratory parameters are assessed at resting, at peak work, 5 minutes after reaching peak work, and 10 minutes after reaching peak work. The MMRM analysis should incorporate the visit and time (during the exercise test) interaction for maximal exercise testing laboratory parameters, as described in Section 6.3.

Table 3: Laboratory Parameters Collected During Maximal Exercise Testing

Parameter	At Rest (Prior to Test)	At Maximal Work (End of Test)	5 min After End of Test	10 min After End of Test
Blood Glucose (mg/dL)	X	X	X	X
Blood Lactate (mM)	X	X	X	X
Blood Pyruvate (mM)	X	X	X	X
Blood Potassium (mM/L)	X	X	X	X

Observed values and difference between resting and 0, 5, or 10 minutes after peak performance for these parameters will be summarized at baseline and at each timepoint. For parameters measured at resting and 0, 5, or 10 minutes after the end of the maximal exercise test, the change from resting and the change from baseline should be calculated.

The change from resting (delta) for parameters measured at resting and 10 min after the end of the maximal exercise test is defined as:

- Delta = [Parameter at 0, 5, or 10 min after end of exercise testing] – [Parameter at resting]

The change from baseline is defined for parameters measured at resting and 0, 5, or 10 min after the end of the maximal exercise test is defined as:

- Change from Baseline in Delta= [Parameter at Y min after end of exercise testing(At Visit X) - Parameter at resting(At Visit X)] - [Parameter at Y min after end of exercise testing(At Baseline) - Parameter at resting(At Baseline)]

Summary statistics at resting, at the completion of the maximal exercise test, 5 minutes after exercise test, and 10 minutes after exercise test will be provided.

6.3.3 Submaximal Exercise Testing Parameters

The following parameters are assessed at resting, at 10 minutes, 20 minutes, and 30 minutes during the submaximal exercise test.

Table 4: Submaximal Exercise Testing Parameters

Parameter	At Rest (Prior to Test)	10 minutes	20 minutes	30 minutes (End of Test)
Borg		X	X	X
Leg Effort Rating of Perceived Exertion		X	X	X
Heart Rate (bpm)[a]	X	X	X	X
Carbon Dioxide Production (VCO_2) (mL/kg/min)[a,b]	X	X	X	X
Oxygen Comsumption (VO_2) (mL/kg/min)[a,b]	X	X	X	X
Expired Air Gas Volume (VeBTPS) (L/min)[a]	X			X
Cardiac Output (L/min)[a]	X			X
Arteriovenous Oxygen Difference (a-VO_{2diff}) (mLO2/dlQ)[a]	X			X
Respiratory Exchange Ratio[a]	X			X
Starting Workload (W)	X			
Exercise Duration (min)				X
Final Workload (W)				X

[a]Observed values and difference between resting and 30 minutes for these parameters will be summarized at baseline and at each timepoint. For parameters measured at resting and at the end of the submaximal exercise test (for patients who complete 30 minutes of the test), the change from resting and the change from baseline should be calculated.

[b] Analysis of VO_2 and VCO_2 will be performed using adjustments for weight at the visit week in which the submaximal exercise test was performed

The change from resting (delta) for parameters measured at resting and at the end of the submaximal exercise test is defined as:

- Delta = Parameter at 10, 20, or 30 min - Parameter at resting

The change from baseline is defined for parameters measured at resting and at the end of the submaximal exercise test is defined as:

- Change from baseline in Delta= [Parameter at Y min (At Visit X) - Parameter at resting(At Visit X)] - [Parameter at Y min (At Baseline) - Parameter at resting(At Baseline)]

Summary statistics at resting, at 10 minutes, 20 minutes, and 30 minutes will be provided.

The MMRM analysis should incorporate the visit and time (during the exercise test) interaction for change from baseline heart rate, as described in Section 6.3 .

The change from baseline resting heart rate is defined as:

- Change from baseline in Heart Rate= [Heart Rate at Y min (At Visit X) - Heart Rate at resting(At Visit X)] - [Heart Rate at Y min (At Baseline) - Heart Rate at resting(At Baseline)]

Analysis visits 0, 4, 8 and 12 will be used. The pairwise dose group comparisons with placebo will be estimated using the difference in adjusted means and 95% CI for the difference in changes from baseline to Week 12.

6.3.4 Submaximal Exercise Testing Laboratory Parameters

The following laboratory parameters are assessed at resting, at 10 minutes, 20 minutes, and 30 minutes during the submaximal exercise test.

Parameter	At Rest (Prior to Test)	10 minutes	20 minutes	30 minutes (End of Test)
Blood Glucose (mg/dL)[a]	X	X	X	X
Blood Lactate (mM)[a]	X	X	X	X
Blood Pyruvate (mM)[a]	X	X	X	X

[a]Observed values and difference between resting and 30 minutes for these parameters will be summarized at baseline and at each timepoint. For parameters measured at resting and at the end of the submaximal exercise test (for patients who complete 30 minutes of the test), the change from resting and the change from baseline should be calculated.

The change from resting (delta) for parameters measured at resting and at the end of the submaximal exercise test is defined as:

- Delta = Parameter at 10, 20, or 30 min - Parameter at resting

The change from baseline is defined for parameters measured at resting and at the end of the submaximal exercise test is defined as:

- Change from baseline in Delta= [Parameter at Y min (At Visit X) - Parameter at resting(At Visit X)] - [Parameter at Y min (At Baseline) - Parameter at resting(At Baseline)]

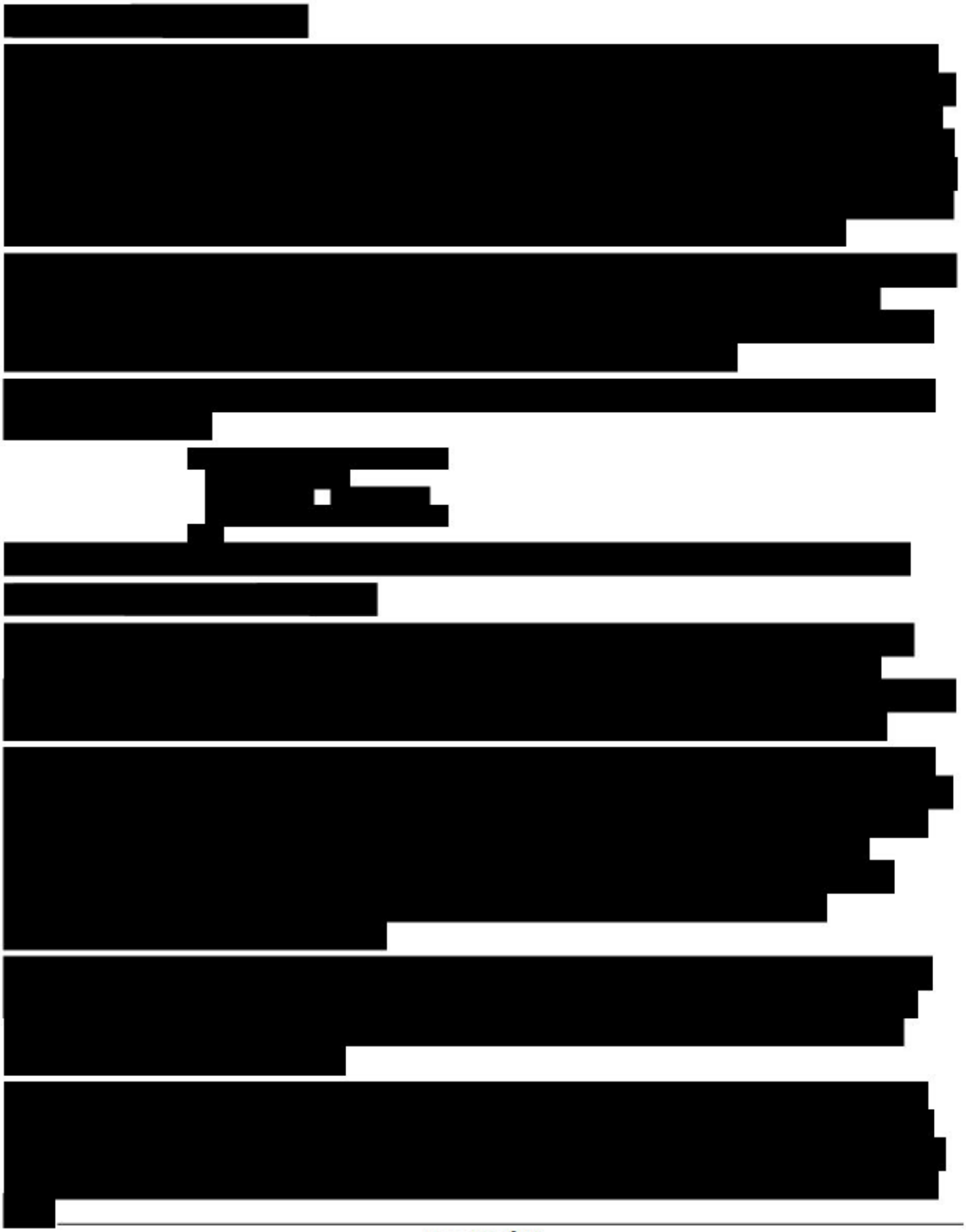
Summary statistics at resting, at 10 minutes, 20 minutes, and 30 minutes will be provided.

The MMRM analysis of change from baseline blood lactate should incorporate the visit and time (during the exercise test) interaction for submaximal exercise testing laboratory parameters, as described in Section 6.3 .

The change from resting blood lactate is defined as:

- Change from baseline in Blood Lactate= [Blood Lactate at Y min (At Visit X) - Blood Lactate at resting(At Visit X)] - [Blood Lactate at Y min (At Baseline) - Blood Lactate at resting(At Baseline)]

Analysis visits 0, 4, 8 and 12 will be used. The pairwise dose group comparisons with placebo will be estimated using the difference in adjusted means and 95% CI for the difference in changes from baseline to Week 12.



7. SAFETY ANALYSIS

Safety and tolerability are evaluated by AEs, SAEs, clinical laboratory test results, body weight, vital sign, 12-lead electrocardiogram [ECG], echocardiogram, and physical examination assessments. All analyses of the safety data will be performed using the safety analysis set. Descriptive statistics (described in Section 3) will be presented by treatment group assignment in the safety analysis set.

7.1 Adverse Events and Serious Adverse Events

All adverse event verbatim terms on eCRFs will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA®) Dictionary (version 14.0). All reported AEs, SAEs, and deaths will be listed in separate patient listings.

7.1.1 General Considerations for Analysis of Adverse Events

General considerations for AE summaries and calculations are:

- Multiple events by preferred term (PT) and system organ class (SOC) will be counted once only per patient for each treatment.
- For summaries by severity, only the most severe event will be counted per patient for each treatment.
- For summaries by relationship, only the most related event will be counted per patient for each treatment.
- An AE with a missing resolution date or incomplete date that is not identified as continuing will be assumed to be continuing and no duration will be calculated.
- AEs will be summarized by the highest dose received.
- Only treatment-emergent adverse events (TEAEs) will be included in summaries.

7.1.2 Treatment-Emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as any AEs, regardless of relationship to study drug, that have an onset or worsen in severity on or after the first dose of study drug. If it cannot be determined whether the AE is treatment-emergent due to a partial onset date, then it will be counted as a TEAE. Adverse events with incomplete start dates will be considered TEAEs, if:

- Onset time is missing but the onset date is on Study Day 1.
- Day and month are missing and the year is equal to or after the year of the first date of study drug dosing;
- Day is missing and the year is after the year of the first date of study drug dosing;
- Day is missing and the year is equal to the year of the first date of study drug dosing and the month is equal to or after the month of the first date of study drug dosing; or
- Year is missing.

7.1.3 Related Adverse Events

Related AEs are those with relationship to study drug reported as "possibly related", "probably related", or "definitely related". If severity (relationship) of an AE to study drug is not recorded, the severity (relationship) will be imputed as 'severe' ('definitely related').

7.1.4 Summary of Treatment-Emergent Adverse Events and Serious Adverse Events

All TEAE summary tables will include the number and percentages of patients reporting TEAEs. A summary of TEAEs by severity, seriousness, and relation to study drug will be tabulated. In addition, TEAEs will be summarized by MedDRA system organ class and preferred term. Patients can have more than one TEAE per system organ class and preferred term. These summaries will include the following:

- All TEAEs
- TEAEs by worst severity
- Related TEAEs
- TEAEs leading to study drug interruption (if any)
- TEAEs leading to study drug discontinuation (if any)
- All treatment-emergent SAEs
- Treatment-emergent SAEs by worst severity
- Related treatment-emergent SAEs.

At each level of patient summarization, a patient is counted once if he/she reported one or more TEAE at that level. If a patient reported the same TEAE on multiple occasions, the highest severity (severe > moderate > mild) or study drug relationship (related > probable > possible > unlikely > unrelated) recorded for the event will be summarized. Each summary will be ordered by descending order of incidence of system organ class and preferred term within each system organ class.

7.2 Clinical Laboratory Evaluations

Clinical laboratory results (including chemistry, hematology, urine pH, and urine specific gravity) from the central laboratory and change from baseline will be summarized using descriptive statistics at each scheduled time point. Post-baseline laboratory assessments missing or below LLD will not be imputed, unless otherwise specified in Section 3. Box plot graphs and line graphs may be generated for selected laboratory tests, such as ALT, AST, GGT, creatine kinase (CK), and ferritin. Line graphs will include mean ± SE over time for both the observed values and for the change from baseline values.

In addition, a summary table will be provided for number and percentage of patients meeting the following pre-specified threshold level at any time during the study.

Table 5: Pre-Specified Threshold Levels for Categorical Laboratory Summaries

Lab Parameter	Pre-Specified Level
Magnesium	< 1.3 mEq/L (0.65 mmol/L)
BNP	> 200 pg/mL
ALT, AST	> 3 × upper limit of normal (ULN)
ALT, AST	> 8 × ULN
ALT, AST	> 5 × ULN for more than 2 weeks
ALT, AST, TBL	> 3 × ULN and (TBL > 2 × ULN × ULN)

Urinalysis results (other than pH and specific gravity) will not be summarized.

All laboratory results (including pregnancy test results) will be listed. Laboratory results that are above or below normal limits will be flagged in the listings.

7.3 Vital Signs

Descriptive statistics for blood pressure, heart rate, respiratory rate, and temperature including baseline values and change from baseline values, will be summarized by time point. All vital signs parameters will be listed.

7.4 Body Weight

Descriptive statistics for body weight that are collected on the eCRF and change from baseline values will be will be summarized and listed by time point. Boxplot and line graphs of change from baseline over time for weight will be plotted.

7.5 Echocardiogram

Echocardiogram (ECHO) data, such as cardiac function [ejection fraction (%), left ventricular end-diastolic posterior wall thickness (PWTd), left ventricular end-diastolic septal thickness (LVSTd), left ventricular end-diastolic internal dimension (LVIDd), left ventricular end-systolic internal dimension (LVIDs), left atrial antero-posterior dimension, Right Ventricular Wall Thickness in diastole (RVWTd), left ventricle mass (index)] measurements are collected on the eCRF. Descriptive statistics for observed values and change from baseline will be presented for each ECHO assessment.

All ECHO parameters will be listed.

7.6 Electrocardiogram

Electrocardiogram (ECG) data, such as ventricular rate (bpm), PR interval (ms), QRS duration (ms), QT (ms), and QTc (ms) are collected on the eCRF. Descriptive statistics for observed values and change from baseline will be presented for each ECG assessment.

In addition, number and percentage of patients with any abnormal values (i.e., above a pre-specified threshold) will be summarized by time point and overall while on study drug. The pre-specified levels of ECG QTc thresholds are consistent with FDA guidance (See Table 6 below).

Table 6: Pre-Specified Threshold Levels for ECG Parameters

ECG Parameter	Pre-Specified Level
PR	>200 msec
QTcF	>450, >480 or >500 msec, >30 or >60 msec increase from baseline
Heart rate	<40, >100 beats/min

All ECG parameters will be listed. Any results that exceed the above levels (provided in the above table) will be flagged in the listing.

7.7 Physical Examination

Abnormal clinically significant findings will be reported as Medical History or Adverse Events depending on day of onset. Abnormal non-clinically significant findings from physical examinations will be listed.

7.8 Pregnancy

A listing will be provided serum and urine pregnancy results of all on-study pregnancies, if applicable.

[redacted]

[redacted]

10. REFERENCES

Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The Fatigue Severity Scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121-1123

Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharm Stat 2013;12:337-47.

11. APPENDICES

Appendix 1. **List of Laboratory Tests**

Appendix 2. **Programming Specifications**

Appendix 1. List of Laboratory Tests

Blood samples will be collected throughout the study for hematology, chemistry, and urinalysis for clinical laboratory evaluation.

Test panels will include the following:

Hematology	Chemistry	Urinalysis
Hematocrit	Blood urea nitrogen (BUN)	Specific gravity
Hemoglobin	Creatinine	Ketones
HbA1C	Total bilirubin	pH
Red blood cell (RBC) count	Alanine aminotransferase (ALT)	Protein
White blood cell (WBC) count	Aspartate aminotransferase (AST)	Blood
Neutrophils	Alkaline phosphatase (ALP)	Glucose
Bands (if detected)	Ferritin	Urobilinogen
Lymphocytes	Sodium	Bilirubin
Monocytes	Potassium	
Basophils (if detected)	Calcium	
Eosinophils (if detected)	Inorganic phosphorus	
Absolute platelet count	Magnesium	
Mean corpuscular hemoglobin (MCH)	Chloride	
Mean corpuscular volume (MCV)	Bicarbonate	
Mean corpuscular hemoglobin concentration (MCHC)	Uric acid	
Reticulocyte count	Cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	
	Creatine phosphokinase (CPK)	
	Lactate dehydrogenase (LDH)	
	High-density lipoprotein cholesterol (HDL-C)	
	Low-density lipoprotein cholesterol (LDL-C)	
	Very-low-density lipoprotein cholesterol (VLDL-C)	
	Gamma-glutamyl transpeptidase (GGT)	
	Estimated glomerular filtration rate (eGFR) using the MDRD-4 formula	

Appendix 2. Programming Specifications

Continuous data will be listed corresponding to the precision measured or calculated. Measures of central tendency will be presented using one additional decimal place than the precision of the data. Variability summaries will be presented using two additional significant digits relative to the precision of the underlying data. Quartiles, the minimum, and the maximum will be presented using the precision of the data. Rounding for derived values should be one additional decimal place to which the raw data were entered. For instance, if the raw data are rounded to the 0.001 decimal place, the derived values must be rounded to the 0.0001 decimal place.

All percentages are to be expressed as integers with one decimal place. The convention for rounding percentages is as follows:

- Values greater than or equal to x.x5% are rounded up
- Values between 0 and x.x5% are rounded down