STATISTICAL ANALYSIS PLAN

STUDY PART 1

Study Title:	**A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia**
Name of Test Drug:	RTA 408 Capsules
Indication:	Friedreich's Ataxia
Sponsor:	Reata Pharmaceuticals, Inc.
Protocol No.:	RTA 408-C-1402
Protocol Version/Date	Version 7.0 (April 13, 2017)
Author Biostatistician:	[redacted]
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CONFIDENTIAL AND PROPRIETARY INFORMATION

SPONSOR APPROVAL

of the

Statistical Analysis Plan – Study Part 1

A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia

[redacted]

Date

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Date

[redacted]

Date

TABLE OF CONTENTS

1. INTRODUCTION 7
1.1 Study Objectives 7
1.1.1 Primary Objectives 7
1.1.2 Secondary Objective 7
1.1.3 Exploratory Objectives 7
1.2 Part 1 Study Design 8
1.2.1 Study Visits and Assessments 9
1.2.2 Data Safety Monitoring Board 9
1.2.3 Discontinuation of Treatment 9
1.2.4 Patient Termination 9
1.2.5 Randomization and Unblinding 10
1.3 Sample Size and Power 10
2. PLANNED ANALYSIS OF PART 1 11
2.1 Timing of Analysis 11
2.2 Interim Analysis 11
2.3 Endpoint Measures 11
2.3.1 Efficacy Endpoints 11
2.3.2 Safety Endpoints 11
2.3.3 Pharmacodynamic Endpoints 11
2.3.4 Pharmacokinetics Endpoints 12
2.4 Changes from Protocol-Specified Analysis 12
3. GENERAL CONSIDERATIONS FOR DATA ANALYSIS 13
3.1 Analysis Considerations 13
3.2 Analysis Sets 13
3.2.1 Randomized Analysis Set 13
3.2.2 Intent-to-treat Population (ITT) 13
3.2.3 Safety Population 13
3.2.4 Pharmacokinetic 13
3.3 Strata and Covariates 13
3.4 Examination of Patient Subsets 14
3.5 Multiple Comparisons 14
3.6 Missing Data 14
3.7 Visit Windows 14
3.7.1 Definition of Study Day 14

3.7.2 Definition of Study Baseline 14
3.7.3 Analysis Visits 14
3.7.4 Analysis Windows for Unscheduled Visits 15
3.7.5 Selection of Data in the Event of Multiple Records in a Visit 15
3.8 Rounding 15
4. BASELINE CHARACTERISTICS AND PATIENT DISPOSITION 16
4.1 Disposition of Patients 16
4.2 Demographics and Baseline Characteristics 16
4.3 Study Drug Administration 17
4.4 Inclusion and Exclusion Criteria 17
4.5 Medical History 17
4.6 Prior and Concomitant Medications 18
4.7 Protocol Deviations 18
5. EFFICACY ANALYSIS 19
5.1 Primary Efficacy 19
5.2 Secondary Efficacy 19
5.3 Exploratory Efficacy 20
5.3.2 Other Maximal Exercise Testing Measures (including Oxygen Utilization) 21
5.3.3 25-Foot Timed Walk Test (T25-FW) 22
5.3.4 Low-Contrast Letter Visual Acuity Test 22
5.3.5 9-Hole Peg Test (9-HPT) 22
5.3.6 Fatigue Severity Scale 23
5.3.7 SF-36 Health Survey Update 23
5.3.8 Full Neurological FARS Score 24
[redacted]
6. SAFETY ANALYSIS 25
6.1 Adverse Events 25
6.1.1 General Considerations for Analysis of Adverse Events 25
6.1.2 Adverse Event Dictionary 25
6.1.3 Treatment-Emergent Adverse Events 25
6.1.4 Adverse Event Severity 26
6.1.5 Relationship of Adverse Events to Study Drug 26
6.1.6 Serious Adverse Events 26
6.2 Clinical Laboratory Evaluations 27
6.2.1 General Considerations for Analyses of Laboratory Data 27

6.2.2 Summaries of Laboratory Results 27
6.2.3 Laboratory Abnormalities 27
6.2.4 Summaries of Laboratory Abnormalities 27
6.3 Vital Signs 28
6.4 Echocardiogram 28
6.5 Electrocardiogram 28
6.6 Physical Exam 29
6.7 Pregnancy 29
7. PHARMACODYNAMIC PARAMETERS 30
[redacted]
7.2 Platelet Samples 30
[redacted]
8. REFERENCES 31
9. APPENDICES 32

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 13Oct2014 under protocol version 3. The protocol was amended four times since Version 1 of the SAP (Protocol Version 4, 12May2015; Protocol Version 5, 29Sep2015; Protocol Version 6 23May2016; Protocol Version 7 13Apr2017). The current protocol allows for up to approximately 9 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
- Patients without pes cavus have been identified as a particular subgroup of interest based on emerging information.

1. INTRODUCTION

Study 408-C-1402 (the MOXIE 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 Friedreich's ataxia. This document describes the statistical analysis methods and data presentations that Reata Pharmaceuticals, Inc. (Reata) will use to analyze data from the MOXIE study. [redacted] is MOXIE's blinded study statistical group responsible for conducting the analyses described in this document. Within each study part, [redacted] will remain blinded to study treatment assignments until after the database is locked. 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, [redacted] 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 7 of the study protocol dated April 13, 2017. 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 Friedreich's ataxia, comparing those receiving RTA 408 versus those receiving placebo, the objectives of the MOXIE 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 the modified Friedreich's ataxia rating scale (FARS) score

1.1.3 Exploratory Objectives

- To evaluate the change in peak oxygen utilization during maximal exercise testing
- To evaluate the change in performance on a timed 25-foot walk test
- To evaluate the change in performance on a low-contrast letter visual acuity test
- To evaluate the change in performance on a 9-hole peg test (9-HPT)
- To evaluate the change in Fatigue Severity Scale score

- To evaluate the change in SF-36® Health Survey Update (SF-36) score
- To evaluate the change in the full FARS score
- [redacted]
- To evaluate the change in pharmacodynamic (PD) markers of activity in platelet, [redacted] samples [redacted]
- To characterize the pharmacokinetics of RTA 408 and potential metabolites after oral administration of RTA 408 Capsules

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 72 patients with Friedreich's ataxia.

The first part of the MOXIE 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 300 mg) in up to approximately 9 cohorts of patients with Friedreich's ataxia. 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 9 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 300 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 MOXIE 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).

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, [redacted], 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
- Other

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. 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.

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 72 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.

2. PLANNED ANALYSIS OF PART 1

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

2.1 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.

2.2 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.

2.3 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).

The secondary efficacy endpoint is the change in modified FARS (mFARS) score. The mFARS consists of only the neurological portion of the full FARS neurological assessment (i.e., the full FARS minus the peripheral nervous system). Additional details regarding the derivation of the modified FARS score can be found in Section 5.2.

Exploratory endpoints for this trial include:

- Parameters (other than peak work) collected during maximal exercise testing
- 25-Foot Timed Walk Test (T25-FW)
- Low-Contrast visual acuity test at different contrast levels (100%, 2.5%, 1.25%)
- 9-Hole Peg Test (9-HPT)
- Fatigue Severity Scale
- SF-36 Health Survey Update (PCS, MCS, Utility Index Score)
- Full Neurological FARS Score
- [redacted]

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]).

2.3.3 Pharmacodynamic Endpoints

A number of PD markers will be assessed in this study. Frataxin levels will be assessed using [redacted] platelet samples at Sponsor approved sites, [redacted].

[redacted] platelet data may not be available for analysis at the time of database lock. Should this be the case, [redacted] platelet data will be summarized in separate reports.

[redacted]

Available pharmacodynamic endpoints will be summarized in a similar manner as clinical laboratory data in Section 6.2 if data are collected from a sufficient number of patients. All PD endpoints will be listed.

2.3.4 Pharmacokinetics Endpoints

Pharmacokinetics will be summarized and reported in a stand-alone PK report performed by either Reata or a vendor other than [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.

Individual patient data will be presented in data listings. The listings will include all available data for all patients. Unless otherwise noted, all data will be listed.

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 Randomized Analysis Set

The Randomized Analysis Set will include all patients who are randomized for the study. The randomized analysis set will be used to assess patient disposition. Patients will be summarized according to the treatment to which they were randomized.

3.2.2 Intent-to-treat Population (ITT)

The intent-to-treat (ITT) population includes all enrolled patients in Part 1, whether or not they received study drug. Patients randomized to 2.5 mg in Part 1, Cohort 1, dose escalate to 5 mg at Week 2. All patients receiving active dose in Cohort 1 will be summarized as the 5 mg dose. All other patients remain on their randomized treatment throughout the study (i.e., no intra-patient dose-escalation) and will be categorized by their randomized treatment group.

3.2.3 Safety Population

The safety population includes all patients who received at least 1 dose of study drug. Patients who receive at least 1 dose of RTA 408 will be classified in the RTA 408 group at the highest dose level received.

3.2.4 Pharmacokinetic

The Pharmacokinetic analysis set will be defined in a separate analysis plan as it 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 pes cavus as a particular subgroup of interest. Some safety and efficacy analyses may be performed on subjects with pes cavus.

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 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 mFARS). If more than 10% of Week 12 assessments are missing, a sensitivity analysis of the primary and secondary endpoints will be performed with missing data imputed using Jump to Reference (J2R) multiple imputation (Ratitch B, 2013).

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 FARS, modified FARS, maximal exercise test parameters, 25FWT, and 9HPT. 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. When specified, summarizes by visit will be done using analysis visits defined below.

Analysis Visit	Label	Visit Number	Approximate Study Day
0	Baseline	0,1	≤1
4	Week 4	5	28
8	Week 8	7	56
12	Week 12	9	83
12	Week 12	10	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 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:

Visit Number	Analysis Visit	Study Day	Analysis Window
1	0	1	Study Day ≤1
5	4	28	21 ≤ Study Day ≤ 35
7	8	56	49 ≤ Study Day ≤ 63
9	12	83	76 ≤ Study Day ≤ 90
10	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. BASELINE CHARACTERISTICS AND PATIENT DISPOSITION

4.1 Disposition of Patients

A disposition summary will include:

- Number and percentage of patients randomized in each cohort
- Number and percentage of patients in the ITT
- Number and percentage of patients in the safety analysis set
- Number of patients dose escalated (Cohort 1 only)
- Number and percentage of patients completing treatment at each dose
- Number and percentage of patients discontinuing treatment at each dose
- Number and percentage of patients by reason for discontinuing treatment at each dose
- Number and percentage of patients completing study at each dose
- Number and percentage of patients terminating study at each dose
- Number and percentage of patients by reason for terminating study at each dose

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 the last dose of study drug, study completion status, and reason for termination (if applicable).

4.2 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

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

- Age at FA onset
- Duration of diagnosis

- Average number of hours exercised per week
- GAA1 repeat length
- GAA2 repeat length

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

- Ambulatory status
- Ambulatory assistive devices
- History of cardiomyopathy
- History of areflexia
- Presence of pes cavus
- Presence of extensor plantar reflex(Babinski reflex)
- Foot surgery
- History of sensory neuropathy
- History of swallowing difficulties
- Visual acuity less than 20/25
- History of scoliosis
- Prior scoliosis surgery

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

4.3 Study Drug Administration

Study drug compliance will be assessed using the number of pills dispensed and the number returned from each bottle. The number of doses taken is assumed to be the difference between the total dispensed and the total returned. The expected number of doses will be derived based on the interval between date dispensed and date returned. Percent compliance is derived as ((taken/expected)*100).

Number and percentage patients with >80% and ≤80% compliance will be summarized descriptively by treatment and visit. The percentages will be based on the number of patients in the safety analysis set. No treatment comparisons will be made.

A listing will be provided that displays study drug administration data including compliance.

4.4 Inclusion and Exclusion Criteria

A listing of inclusion or exclusion violations for randomized patients as well as a similar listing for screen failures will be provided.

4.5 Medical History

Medical history summary will be presented by treatment. Percentages will be based on the number of patients in the safety analysis set. Medical history will be sorted alphabetically and all data will be listed.

4.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary (December, 2012) for anatomical therapeutic chemical classification (ATC) and preferred drug name. A patient who used multiple medications will be counted only once for each ATC and preferred drug name. ATC and preferred drug name within each ATC will be sorted alphabetically. Coded concomitant medications will be summarized by treatment. Percentages will be based on the number of patients in the safety analysis set.

Prior medications are defined as those medications disclosed as being taken prior to Study Day 1 on the CRF. Concomitant medications are defined as any medications that was either not taken prior to Study Day 1 (according to the CRF), or was taken prior to Study Day 1 but was ongoing at time of the first dose administration.

4.7 Protocol Deviations

All protocol deviations will be captured on the CRF and reviewed by the Sponsor according to their SOPs. Major protocol deviations will be identified by the Sponsor based on blinded review of the data, and will be flagged in the listing.

5. EFFICACY ANALYSIS

Primary analysis of the efficacy data will be based on the ITT population, which will include all patients randomized in Part 1 of the study. Analyses will be performed for each RTA 408 dose level and also all RTA 408 patients pooled for comparison with all placebo patients pooled.

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, and will include an additional column to summarize the pooled RTA 408 patients.

5.1 Primary Efficacy

Peak work (w/kg) is calculated as the maximum workload (w) at each visit divided by baseline weight (kg) for each patient. A positive change from baseline suggests an improvement.

Peak work for patients treated with RTA 408 will be compared with placebo after 12 weeks of treatment using mixed models repeated measures (MMRM) analysis, with treatment group, time, and the interaction between treatment and time as fixed factors. Analysis visits 0, 4, and 12 will be used. An unstructured covariance matrix will be assumed. If convergence can't be achieved, a compound symmetry covariance matrix will be evaluated.

The difference between RTA 408 (each dose level and all doses pooled) and placebo in change from baseline of mean peak work will be estimated along with the 95% confidence interval at each protocol scheduled time point. A p-value to test the effect of RTA 408 on peak work will only be provided at Week 12.

Suppose it is assumed that the treatment variable ***trt*** has two levels (1=placebo, 2=active) and values for ***analysis visit*** are (0, 4, 12). The following SAS code serves as sample code to provide the estimated difference, confidence interval, and p-value.

```
Proc Mixed data=x order=data;
  Class patno trt week;
  model resp =  trt week trt*week /s;
  Repeated week / sub = patno type = un;
  lsmeans trt*week / diff cl;
  contrast "Active vs Pbo" trt -1 1  trt*week 0 -1 0 1 ;
  estimate "Active vs Pbo" trt -1 1  trt*week 0 -1 0 1 ;
Run;
```

The pairwise dose group comparisons with placebo will be estimated using a separate repeated measures model than the model that pools the RTA 408 dose levels. If it is assumed the treatment variable ***trt*** now has three levels (1=placebo, 2=low dose, 3=high dose), the contrast and estimate statements to obtain pairwise differences are:

```
  contrast "Low vs Pbo" trt -1 1 0 trt*week 0 -1 0 1 0 0;
  estimate "Low vs Pbo" trt -1 1 0 trt*week 0 -1 0 1 0 0;
  contrast "High vs Pbo" trt -1 0 1 trt*week 0 -1 0 0 0 1;
  estimate "High vs Pbo" trt -1 0 1 trt*week 0 -1 0 0 0 1;
```

This requires a separate execution of Proc Mixed where the active treatments are not pooled.

5.2 Secondary Efficacy

The secondary endpoint of this study is the modified FARS score. The Friedreich's Ataxia Rating Scale is a validated composite measure consisting of scores obtained from a standard neurological examination for Friedreich's ataxia patients. The FARS examination for the

MOXIE study is divided into 5 sections: Bulbar (section A), Upper Limb Coordination (section B), Lower Limb Coordination (section C), Peripheral Nervous System (section D), and Upright Stability (section E).

A higher FARS or mFARS score reflects greater Friedreich's ataxia disease severity thus, a negative change from baseline suggests an improvement.

Assessments in each section are added to get the section score. FARS is the total of sections A through E. Modified FARS is the total of sections A through C, and E (i.e., omit section D from the full FARS score). If the FARS assessment is performed but a measurement or section of the FARS is missing, values should be imputed using LOCF for just the missing measurement or section to avoid an artificial score decrease. If the FARS assessment is not performed the FARS result should remain null for the primary analysis, since missing data are not imputed.

The modified FARS score will be analyzed using repeated measures analysis of variance with the same 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.

5.3 Exploratory Efficacy

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

As with the primary and secondary endpoints, exploratory endpoints will be analyzed using pooled patients at 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.

5.3.2 **Other Maximal Exercise Testing Measures (including Oxygen Utilization)**

In addition to the primary efficacy endpoint of peak work, the following other parameters are also assessed during maximal exercise testing.

	At Rest (Prior to Test)	**At Maximal Work (End of Test)**
Heart rate (bpm)	X	X
VO_2[a] **(mL/kg/min)**	X	X
O_2 pulse[b] **(mL/beat)**	X	X
Systolic blood pressure (mmHg)	X	X
Diastolic blood pressure (mmHg)	X	X
Oxygen saturation (SpO_2) (%)	X	X
Forced vital capacity (FVC) (L)	X	
Forced expiration volume within one second (FEV1) (L)	X	
Maximum voluntary ventilation (MVV) (L/min)	X	
%Predicted FVC (%)	X	
VCO_2[a] **(mL/kg/min)**		X
Anaerobic threshold (L/min)		X
Time to reach maximal work (Min:Sec)		X
Maximum rating of perceived exertion (BORG; 0-20 scale)		X
Maximum minute ventilation (VE) BTPS (L/min)		X
Tidal Volume (L)		X
Maximum respiratory rate (breaths/min)		X
Breathing Reserve (%)		X

[a] Analysis of maximal VO2 and resting VO2 will be performed using adjustments for baseline weight:

- Maximal_VO2_adj=Maximal_VO2*1000/weight (kg);
- Resting_VO2_adj=Resting_VO2*1000/weight (kg);

[b] O_2 pulse will be calculated for analysis: O_2 pulse = (Maximal_VO2 (in units of mL/min)*1000)/Maximal_HR)

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 [heart rate, VO_2

(L/min) and VO_2 (ml/mg/min), diastolic blood pressure, systolic blood pressure, 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.

5.3.3 **25-Foot Timed Walk Test (T25-FW)**

The T25-FW is a quantitative mobility and leg function performance test based on time in seconds to complete a 25- foot walk. Only the completed walk from each visit will be used for analyses. Observed and reciprocal values (i.e., 1/time) will be analyzed at each visit. Changes in reciprocal values are calculated as:

- Change from baseline = 1/(Time to complete 25-foot walk test at Visit X) - 1/(Time to complete 25-foot walk test at Baseline)

Analysis of reciprocals has limited utility but is provided to show information on general trends only. Transforming changes from baseline on the reciprocal scale are not interpretable.

T25-FW will be summarized at baseline and each time point along with the change from baseline by treatment. Analysis visits 0, 4, 8, and 12 will be used. Longer walk times reflect more impairment in mobility thus, a negative change from baseline suggests an improvement.

5.3.4 **Low-Contrast Letter Visual Acuity Test**

Loss of low contrast visual acuity is a principal ophthalmologic manifestation of Friedreich's ataxia. Low-contrast letter visual acuity is collected at three different contrast levels (100%, 2.5%, or 1.25%). The aggregate score (100%+2.5%+1.25%) will be summarized at baseline and each time point along with the change from baseline by treatment. Only the measure for both eyes will be summarized. Analysis visits 0, 4, 8, and 12 will be used. Lower score indicates greater visual impairment thus, a positive change from baseline suggests an improvement.

5.3.5 **9-Hole Peg Test (9-HPT)**

The 9-HPT is a brief, standardized, quantitative test of upper extremity function. Both the dominant and non-dominant hands are tested twice. The scores for the dominant and non-dominant hand will be analyzed separately. The two trials for each hand are averaged. The average time for each hand will be summarized at baseline and each time point along with change from baseline by treatment. Observed and reciprocal values (i.e., 1/time) will be analyzed at each visit. Changes in reciprocal values are calculated as:

- Change from baseline = 1/(Time to complete 9-hole peg test at Visit X) - 1/(Time to complete 9-hole peg test at Baseline)

Analysis of reciprocals has limited utility but is provided to show information on general trends only. Transforming changes from baseline on the reciprocal scale are not interpretable.

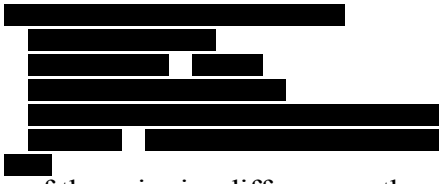
Analysis visits 0, 4, 8, and 12 will be used. Longer time reflects more impact on one's upper extremity function by the disease thus, a negative change from baseline suggests an improvement.

5.3.6 Fatigue Severity Scale

The Fatigue Severity Scale is a self-administered test designed to measure the severity of the fatigue symptoms based on 9 questions (Krupp, 1989). An individual score for each question ranges from 1 to 7 where 1 indicates strong disagreement and 7 indicates strong agreement. The average of the 9 questions for each patient is used for analysis at each visit. If an individual score is missing, the average of available scores will be used. This average score will be summarized at Baseline and Week 12 along with change from baseline by treatment. Larger scores reflect more impact of the disease thus, a negative change from baseline suggests an improvement.

Since there is only one scheduled post-baseline assessment, an analysis of covariance model with treatment group as a fixed factor 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. Analysis visits 0 and 12 will be used.

Suppose it is assumed that the treatment variable ***trt*** has two levels (1=placebo, 2=active). The following SAS code serves as sample code to provide the estimated difference, confidence interval, and p-value.



To obtain estimates of the pairwise differences, the code will need to be updated to account for additional levels of the treatment variable. The following contrast and estimate statements may be used to obtain pairwise differences.

This requires a separate execution of Proc Mixed where the active treatments are not pooled.

5.3.7 SF-36 Health Survey Update

The SF-36 is a multi-purpose, short-form health survey with 36 questions. It yields an eight-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group.

SF-36 breaks into 8 domains. Physical Functioning (items 3a-3j), Role-Physical (items 4a-4d), Role-Emotional (items 5a-5c), Social Functioning (items 6, 10), Bodily Pain (items 7, 8), Mental Health (items 9b, 9c, 9d, 9f, 9h), Vitality (items 9a, 9e, 9g, 9i) and General Health Perceptions

(items 1, 11a-11d). Change in Health (item 2) is an overall health status assessment that compares to one year ago. The score is converted to a 0 - 100 scale, with 0 indicating poor health and 100 indicating good health.

The overall composite score (SF-6D Utility Index Score), the MCS (mental component scale) and the PCS (physical component scale) as defined by the SF-36 manual will be summarized at baseline and analysis visit 12 along with the change from baseline by treatment. Lower scores reflect poor quality of life thus, a positive change from baseline suggests an improvement.

Since there is only one scheduled post-baseline assessment, an analysis of covariance model with treatment group as a fixed factor. 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. Analysis visits 0 and 12 will be used.

5.3.8 **Full Neurological FARS Score**

Scores will be summarized at Baseline and each time point along with change from baseline by treatment. Analysis visits 0, 4, and 12 will be used. Both the overall Neurological section score (sum of sections A through E) as well as the total score from each subsection will be summarized. Higher scores reflect greater Friedreich's ataxia disease severity thus, a negative change from baseline suggests an improvement.

[redacted]

6. SAFETY ANALYSIS

Safety data (including AEs, laboratory data, vital signs, electrocardiogram [ECG] data, echocardiogram data, and physical examinations) will be listed and summarized for patients in the safety analysis set. All safety data collected on or after the date of the first dose of study drug through completion of the study Part 1 will be summarized by treatment.

The CRF nominal study visits will be used for all safety analyses. Unscheduled visits will be reflected in summarization of changes to worst post-baseline measures where appropriate.

6.1 Adverse Events

AEs will be summarized by treatment as defined by the safety analysis set.

6.1.1 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.

6.1.2 Adverse Event Dictionary

AEs will be coded using MedDRA® (Medical Dictionary for Regulatory Activities) version 16.0 or higher. In MedDRA, each verbatim term is mapped to a preferred term and high level term (HLT), which is then mapped to a system organ class. Tables and listings will present data at the SOC and PT level.

6.1.3 Treatment-Emergent Adverse Events

6.1.3.1 Definition of Treatment-Emergent

Treatment-emergent adverse events are events that either:

- Date of onset on or after the date of the date of first dose and not more than 30 days after the date of the last dose of study drug, or
- Had no recorded date of onset with a stop date after the first dose of study drug, or
- Had no recorded date of onset or stop date

6.1.3.2 Incomplete Dates

If the date of onset is incomplete, then the month and year of onset (or year alone if month is not recorded) determines whether the event is treatment-emergent. The event is treatment-emergent if the month and year of onset (or year of onset) of the event is:

- The same as or after the month and year (or year) of the first dose of study drug, and
- The same as or before the month and year (or year) of the date of the last visit.

6.1.4 Adverse Event Severity

The investigator will grade the severity of the AEs as mild, moderate, or severe as defined in the study protocol.

6.1.5 Relationship of Adverse Events to Study Drug

Association or relatedness to the study medication will be graded by the investigator as either probably, possibly, unlikely, or unrelated according to criteria specified in the study protocol.

6.1.6 Serious Adverse Events

As defined in the protocol and captured on the CRF, an SAE is an adverse event that results in any of the following:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in a congenital anomaly or birth defect in an offspring of a patient taking study drug;
- Is an important medical event.

6.1.6.1 Summaries of Adverse Events

Treatment-emergent AEs will be summarized by treatment at onset of the AEs. For each treatment, SOC, and PT, the number and percentage of patients reporting an event will be calculated. In summary tables, SOC will be presented alphabetically and events within SOC will be presented by decreasing frequency count.

Summary tables (number and percentage of patients) of AEs (by SOC and PT) will be provided by treatment as follows:

- All treatment-emergent AEs
- All treatment-emergent related AEs (probably or possibly related)
- All treatment-emergent AEs by severity
- All treatment-emergent serious adverse events (including deaths)
- All treatment-emergent adverse events leading to discontinuation of study drug

Listings will be provided showing:

- All AEs
- Serious adverse events (including deaths)
- AEs leading to discontinuation of study drug

6.1.6.2 Additional Analysis of Adverse Events

No additional analysis of AEs is planned.

6.2 Clinical Laboratory Evaluations

Laboratory data will be summarized at baseline and at each time point by treatment. Only values obtained at scheduled assessment times will be included in by-visit summary statistics. When appropriate, change from baseline to worst post-baseline (including unscheduled visits) value will be summarized. Specific assessment times are given in the protocol.

Continuous laboratory data results which are less than the lower limit of quantification or above the upper limit of quantification will be imputed to the value of the lower or upper limit plus or minus one significant digit, respectively (e.g., if the result of a continuous laboratory test is < 20, a value of 19 will be assigned). A baseline value is defined as the last available measurement obtained prior to administration of the first dose. If multiple values for a given lab test exist for a particular day, the last one drawn will be used for summarization.

6.2.1 General Considerations for Analyses of Laboratory Data

Clinical laboratory results will be provided by a central lab. Clinical laboratory test results, including results from hematology, chemistry and urinalysis will be listed by patient.

6.2.2 Summaries of Laboratory Results

Selected laboratory evaluations and change from baseline will be summarized by treatment, laboratory category (hematology, chemistry), test, and study visit using continuous statistics. Laboratory tests to be summarized are provided in Appendix 1. Line graphs of change from baseline will be generated for selected laboratory tests, such as ALT, AST, GGT, Ferritin, and CK. Line graphs will include mean ± SE over time for change from baseline.

Due to the nature of urinalysis parameters, summaries of continuous statistics will not be provided.

6.2.3 Laboratory Abnormalities

Laboratory results are not captured on the CRF. All flags with respect to normal or abnormal results will be identified by the central lab and presented in the data listings.

6.2.4 Summaries of Laboratory Abnormalities

The number and percentage of patients with laboratory normality and abnormality categories (Normal, Low, High) as well as the treatment-emergent shift will be summarized by treatment, laboratory category (hematology, chemistry, and urinalysis), and laboratory test. Baseline, Last post-baseline, and shift to last post-baseline value will be presented. An initial set of parameters of specific interest (ALT, AST, GGT, Ferritin, and CK) will be summarized using shift tables, though additional parameters may be added in an ad hoc manner.

6.2.4.1 Transaminases

To assess the potential for drug induced liver injury, the follow criteria will be summarized:

- Number of patients with ALT more than 3x, 5x, 10x or 20xULN
- Number of patients with AST more than 3x, 5x, 10x or 20xULN
- Number of patients with either ALT or AST more than 3x, 5x, 10x or 20xULN

- Number of patients with ALP >1.5xULN
- Number of patients with Total Bilirubin >2xULN
- Number of patients with AST or ALT >3xULN with an associated Total Bilirubin >1.5xULN
- Number of patients with AST or ALT >3xULN with an associated Total Bilirubin >2xULN

A summary table that includes frequencies and percentages of patients that meet any of the above criteria at the same visit will be provided. A listing of subjects with abnormal ALT, AST, or Total Bilirubin will also be provided.

6.3 Vital Signs

Vital signs assessments include systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg), oral body temperature (°C), heart rate (HR, bpm), respiration rate (RR, breaths/min), height (m), weight (kg), and BMI (m^2/kg).

Vital signs will be summarized at baseline and at each time point along with the change from baseline by treatment. Only values obtained at scheduled assessment times will be included in by-visit summary statistics. Specific assessment times are given in the protocol. All data will be listed.

6.4 Echocardiogram

Cardiac function [ejection fraction (%), left and right wall thickness (mm), septum thickness (mm) and LVMI (g/m^2)] measurements are captured on Echocardiogram will be summarized at baseline and each time point along with the change from baseline by treatment, only values obtained at scheduled assessment times will be included. Specific assessment times are given in the protocol.

6.5 Electrocardiogram

ECG results will include ventricular rate (bpm), PR interval (ms), QRS duration (ms), QT (ms), and QTc (ms).

ECG results will be summarized at baseline and at each time point by treatment. Only values obtained at scheduled assessment times will be included. Specific assessment times are given in the protocol.

The number and percentage of patients with investigator findings of normal, abnormal (not clinically significant) and abnormal (clinically significant) as well as the shift to abnormal (clinically significant) will be presented by treatment and protocol scheduled assessment times. In addition to by-visit frequencies, the most abnormal as well as the shift to most abnormal will be summarized.

All ECG data will be listed.

6.6 Physical Exam

Physical exam results will be summarized at baseline and at each time point by treatment. Only values obtained at scheduled assessment times will be included in by-visit summary statistics. Specific assessment times are given in the protocol.

The number and percentage of patients with investigator findings of normal, abnormal (not clinically significant) and abnormal (clinically significant) as well as the shift to abnormal (clinically significant) will be presented by treatment and protocol scheduled assessment times. In addition to by-visit frequencies, the most abnormal as well as the shift to most abnormal will be summarized.

All physical exam findings will be listed.

6.7 Pregnancy

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

7. PHARMACODYNAMIC PARAMETERS

Levels of frataxin and other mitochondrial enzymes will be summarized in a similar manner as clinical laboratory data in Section 6.2 using the Safety Analysis set.

[redacted]

7.2 Platelet Samples

If data are available for at least 10% of patients at Week 12, frataxin levels and changes from baseline from platelet samples will be listed and summarized by treatment.

[redacted]

8. 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.

9. APPENDICES

Appendix 1. List of Laboratory Tests

Appendix 2. Programming Specifications

Appendix 3. Tables, Listings, and Figures

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.

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
- Values that are between 0 and .5% should be displayed as "<0.5%"

Appendix 3. Tables, Listings, and Figures

	Table of Contents	
Table 14.1.1	Patient Disposition	Randomized
Table 14.1.2	Demographic and Baseline Characteristics	ITT
Table 14.1.3	Baseline Characteristics	ITT
Table 14.1.4	Medical History	ITT
Table 14.1.5	Prior Medications	ITT
Table 14.1.6	Concomitant Medications	ITT
Table 14.2.1	Study Drug Exposure by Visit	ITT
Table 14.2.2.1	Peak Work	ITT
Table 14.2.2.2	Peak Work	ITT Subjects without Pes Cavus
Table 14.2.2.3	Peak Work	ITT Subjects with Pes Cavus
Table 14.2.2.4	Peak Work (Multiple Imputation)	ITT
Table 14.2.3.1	Modified FARS	ITT
Table 14.2.3.2	Modified FARS	ITT Subjects without Pes Cavus
Table 14.2.3.3	Modified FARS	ITT Subjects with Pes Cavus
Table 14.2.3.4	Modified FARS (Multiple Imputation)	ITT
Table 14.2.4.1	Oxygen Utilization	ITT
Table 14.2.4.2	Spirometry	ITT
Table 14.2.4.3	Other Exercise Peak Performance Measures	ITT
Table 14.2.4.4	Peak Exercise Ventilatory Response	ITT
Table 14.2.5	25-Foot Timed Walk Test	ITT
Table 14.2.6	Low Contrast Letter Visual Acuity Test	ITT
Table 14.2.7	9-Hole Peg Test	ITT
Table 14.2.8	Fatigue Severity Scale	ITT
Table 14.2.9	SF-36 Questionnaire - Version 2.0	ITT
Table 14.2.10	Full FARS	ITT
[redacted]	[redacted]	[redacted]

Table 14.3.1.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety
Table 14.3.1.1.2	Overall Summary of Treatment-Emergent Adverse Events	Safety without Pes Cavus
Table 14.3.1.1.3	Overall Summary of Treatment-Emergent Adverse Events	Safety with Pes Cavus
Table 14.3.1.2.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
Table 14.3.1.2.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety without Pes Cavus
Table 14.3.1.2.3	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety with Pes Cavus
Table 14.3.1.3	Treatment-Emergent Adverse Events Possibly or Probably Related to Study Drug	Safety
Table 14.3.1.4	Treatment-Emergent Adverse Events by Maximum Severity	Safety
Table 14.3.1.5	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety
Table 14.3.1.6	Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug	Safety
Table 14.3.2.1	Hematology Laboratory Results	Safety
Table 14.3.2.2	Shift in Hematology Laboratory Parameters	Safety
Table 14.3.2.3	Chemistry Laboratory Results	Safety
Table 14.3.2.4	Shift in Chemistry Laboratory Parameters	Safety
Table 14.3.2.6	Overall Summary of Liver Function Tests	Safety
Table 14.3.3	Vital Signs	Safety
Table 14.3.4	Echocardiogram Results	Safety
Table 14.3.5.1	12-Lead ECG Results	Safety
Table 14.3.5.2	12-Lead ECG Findings	Safety
Table 14.3.6	Physical Exam	Safety
[redacted]	[redacted]	[redacted]
Table 14.4.2	Frataxin Levels from Platelet Samples	Safety
[redacted]	[redacted]	[redacted]
Figure 14.2.2.1	Mean ± SE of Peak Work Over Time	ITT
Figure 14.2.2.2	Mean ± SE of Peak Work Over Time	ITT without pes cavus
Figure 14.2.2.3	Mean ± SE of Peak Work Over Time	ITT with pes cavus

Figure 14.2.3.1	Mean ± SE of Modified FARS Over Time	ITT
Figure 14.2.3.2	Mean ± SE of Modified FARS Over Time	ITT without pes cavus
Figure 14.2.3.3	Mean ± SE of Modified FARS Over Time	ITT with pes cavus
Figure 14.2.4.1	Mean ± SE Chemistry Laboratory Results	Safety
Listing 16.4.1	Patients Disposition	All Patients
Listing 16.4.2	Demographics and Baseline Characteristics	All Patients
Listing 16.4.3.1	Inclusion/Exclusion Criteria	All Randomized Patients
Listing 16.4.3.2	Listing of Screen Failures	Screen Failures
Listing 16.4.4	Protocol Deviations	All Patients
Listing 16.4.5	Pregnancy Test	All Patients
Listing 16.4.6	Medical History	All Patients
Listing 16.4.7	Prior and Concomitant Medications	All Patients
Listing 16.4.8	Study Drug Dosing Compliance	All Patients
Listing 16.4.9	Maximal Exercise	All Patients
Listing 16.4.10	Modified FARS	All Patients
Listing 16.4.11	Other Exercise Parameters	All Patients
Listing 16.4.12	25-Foot Timed Walk Test	All Patients
Listing 16.4.13	Low Contrast Letter Visual Acuity Test	All Patients
Listing 16.4.14	9-Hole Peg Test	All Patients
Listing 16.4.15	Fatigue Severity Scale	All Patients
Listing 16.4.16	SF-36 Questionnaire - Version 2.0	All Patients
Listing 16.4.17	Full FARS	All Patients
[redacted]	[redacted]	[redacted]
Listing 16.4.19.1	Adverse Events	All Patients
Listing 16.4.19.2	Serious Adverse Events	All Patients
Listing 16.4.19.3	Adverse Events Leading to Discontinuation of Treatment	All Patients
Listing 16.4.20.1	Lab - Hematology	All Patients

Listing 16.4.20.2	Lab - Chemistry	All Patients
Listing 16.4.20.3	Lab – Urinalysis	All Patients
Listing 16.4.21	Patients with Abnormal Liver Function Tests	All Patients
Listing 16.4.22	Vital Signs	All Patients
Listing 16.4.23	Echocardiogram	All Patients
Listing 16.4.24	12-Lead ECG Results	All Patients
Listing 16.4.25	Physical Exam	All Patients
[redacted]	[redacted]	[redacted]
Listing 16.4.27	Frataxin Levels from Platelet Samples	All Patients
[redacted]	[redacted]	[redacted]