STATISTICAL ANALYSIS PLAN

Protocol RP103-MITO-002

A Long-Term Open-Label Extension Study of RP103-MITO-001 to Assess the Safety, Tolerability and Efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103) for Treatment of Children with Inherited Mitochondrial Disease

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse events
ADL	Activities of Daily Living
BSA	Body Surface Area
BMI	Body Mass Index
CRF	Case Report Form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
FARS	Friedreich Ataxia Rating Scale
FAS	Full Analysis Set
FDA	Food and Drug Administration
FRDA	Friedreich's Ataxia
GMFM	Gross Motor Function Measure
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
LHON	Leber's Hereditary Optic Neuropathy
MedDRA	Medical Dictionary for Regulatory Activities
NPMDS	Newcastle Pediatric Mitochondrial Disease Scale
NYHA	New York Heart Association
PT	Preferred Term
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization
6MWT	6-Minute Walk Test
8MW	8-Minute Walk
9-HPT	9-Hole Peg Test

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

Study RP103-MITO-002 was closed prematurely after decision by the Sponsor to end development of RP103 for mitochondrial disease. This statistical analysis plan (SAP) describes the safety analyses that will be performed for Study RP103-MITO-002, based on the study protocol dated 16DEC2014.

1.2. Study Objectives

The primary objective is to assess safety, tolerability and efficacy of long-term repeat dosing of RP103 in subjects with inherited mitochondrial disease.

The secondary objective is to assess the steady-state pharmacokinetics (PK) and pharmacodynamics (PD) of RP103 at steady state, in children with inherited mitochondrial disease.

2. STUDY DESIGN

2.1. Synopsis of Study Design

This is an open-label extension study of RP103-MITO-001 to assess the safety, tolerability, and efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103) for treatment of children with inherited mitochondrial disease.

Subjects who have completed all visits associated with Study RP103-MITO-001 will be offered enrollment in this extension study. If enrolled in RP103-MITO-002, subjects will return to the clinic quarterly (every 3 months) for detailed assessments.

Study visits will occur as follows:
Day 1 (Baseline): is the day of enrollment, and will occur simultaneously with the RP103-MITO-001 Study Exit Visit.
Quarterly Visits: will begin within 3 months (±7 days) of the RP103-MITO-002 Day 1 Visit and will continue quarterly (every 3 months).
Study Exit Visit: will take place upon study completion (i.e. marketing approval has been granted for RP103 and the subject is able to obtain in commercially), study termination, or upon individual subject termination.

The maximum treatment time in the study is estimated to be 24 months.

Upon RP103-MITO-002 study entry, subjects will continue on the last total daily dose of RP103 taken during the previous RP103-MITO-001 study. Subsequent RP103 dose adjustments are permitted (e.g. as the subject grows, or if deemed necessary by the Investigator for tolerability reasons).

The Sponsor's medical officer may be consulted for assistance making RP103 dose adjustment decisions at any time during the study. NOTE: For each subject, when calculating the number of

capsules to be taken every 12 hours (i.e. half of the prescribed total daily dose), if rounding is required to get a whole number of capsules to be taken, then rounding should be down and not up.

2.2. Randomization Methodology

As this is an open label study with a single test drug, no randomization methodology is employed.

2.3. Stopping Rules

Close monitoring of the subjects during the study is performed. Any decision to stop the clinical trial is immediately communicated to all Investigators and to the United States FDA and regulatory authorities of any other participating countries.

Individual subject dosing is stopped if:

- A subject exhibits a treatment-emergent adverse event of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher and not likely related to the underlying disease, and possibly, probably or definitely related to study drug.

A subject is discontinued if they exhibit an:

- Unexplained fever (> 38.5°C) for > 24 hours.

The study is halted and FDA (or participating regulatory authority) will be consulted if:

- Two or more subjects develop the same CTCAE Grade 3 adverse event;
- One subject develops a CTCAE Grade 4 adverse event;
- One or more unexpected drug-related deaths.
- Onset of one or more drug-related cases of:
  - Heart failure (NYHA Class II or greater);
  - Respiratory failure (Type 1 or Type 2);
  - Acute liver failure (associated with an international normalized ratio (INR) of greater than 1.5, and any degree of mental alteration (encephalopathy) in a subject without preexisting cirrhosis);
  - Malignant hypertension (i.e., Diastolic blood pressure > 140 mmHg);
  - Nephrotic syndrome which includes protein in the urine (more than 3.5 grams per day) and one or more of the following clinically significant symptoms: low blood protein levels and/or high cholesterol levels and/or high triglyceride levels and/or edema.

2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in **Table 1**.

Table 1 Schedule of Assessments

PROCEDURE	Baseline Day 1	Quarterly Visits Every 3 months	Study Exit
Allowable Visit Window	*None*	*+/- 7 days*	*+/- 7 days*
Informed Consent	X		
Assess/Confirm Eligibility	X		
Enrollment	X		
Medical and Medication Histories	X		
Monitoring of Adverse Events	X	X	X
Adverse Events Checklist	X	X	X
Review of Concomitant Meds	X	X	X
Vital Signs[a] (including body temperature)	X	X	X
Height, Weight, Head Circumference[a]	X	X	X
BMI / BSA Calculations[a]	X	X	X
12-lead ECG[a]	X	X	X
Physical Examination[a]	X	X	X
Clinical Laboratory Tests[a,b]	X	X	X
Serum Pregnancy Test [a](if applicable)	X	X	X
Breath Samples for Hydrogen Sulfide[a]	X	X	X
PD Biomarker Sample Collection [b,c]	X	X	X
PK Sample Collection [c]	X	X	X
Record Seizure Activity[d]	X	X	X
Subject Diary Training/Dispense	X	X	
Subject Diary Collect/Review/Sign	X	X	X
RP103 Administration	X	X	X
Dispense and / or Collect RP103[e]	X	X	X
Administer age-specific NPMDS	X	X	X
Conduct two of the following assessments, already specified during participation in previous Study RP103-MITO-001:			
6-minute Walk Test ; Jama Dynamometer	X	X	X
Barry-Albright Dystonia Scale	X	X	X
Friedreich Ataxia Rating Scale	X	X	X
Modified Lansky Play Performance Scale	X	X	X
Gross Motor Function Measure	X	X	X
Vision/Eye Examination	X	X	X

Schedule of Events Footnotes

[a] RP103-MITO-001 Study Exit is to take place on the same day as RP103-MITO-002 Day 1 (Baseline). Data collected from the RP103-MITO-001 study (i.e. medical history, ongoing adverse events, concomitant

medications, Study Exit vital signs) may be carried forward to the extension study clinical database. Data recording and entry instructions will be supplied via the electronic CRF instructions.

[b] Clinical Laboratory Tests and PD Biomarkers are specified in Protocol Table 2; Samples for Clinical Laboratory Tests and PD Biomarkers should be collected at the same time as PK blood samples.

[c] PK blood samples will be collected within 30 minutes before or after the RP103 morning dose.

[d] Seizure activity may be recorded by patients/caregivers using a paper seizure diary handed out by the site, or the form provided on www.seizuretracker.com website. If patients use the web-based form, it must be printed out and used as source documentation for any associated CRF data entry.

[e] RP103 from the previous Study RP103-MITO-001 must be taken for the morning dose and associated PK blood draws on the day of Study Exit. Then, RP103 for Study RP103-MITO-002 is to be dispensed for the evening dose (RP103-MITO-002 Day 1) and to be taken every 12 hours for the remainder of participation in Study RP103-MITO-002.

2.5. Safety Variables

The safety profile of RP103 will be investigated through analysis of the following safety assessments: clinical laboratory tests, vital signs, physical examination, 12-lead ECG, urinalysis, serum pregnancy, concomitant medications, and subject incidence of treatment-emergent adverse events.

3. SUBJECT POPULATIONS

3.1. Population Definitions

The following analysis population will be used.

3.1.1. Safety Analysis Set (SAF)

The safety analysis set (SAF) is defined as all subjects who received at least one dose of study drug (RP103).

The SAF is the primary population for the analysis of safety endpoints.

3.2. Protocol Deviations

The following protocol deviations will be recorded and summarized in the final report: 1) eligibility (inclusion/exclusion) violations, 2) study drug dosing violations, 3) excluded medication violations, 4) procedures performed outside the protocol-specified window, 5) procedures not done, 6) subject non-compliance and 7) other, to be specified by the Investigator. All protocol deviations will be presented in a by-subject data listing.

4. STATISTICAL METHODS

4.1. Sample Size Justification

The sample size will be up to 35 subjects (the number of subjects dosed in study RP103-MITO-001).

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

Tabulations will be produced for appropriate demographic, baseline, and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, standard deviation, minimum and maximum values will be presented. Additional statistics may be presented for certain endpoints as described in the sections below.

All output will be incorporated into Microsoft Excel or Word files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

4.2.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.2 or later), unless otherwise noted. Adverse Events will be coding using MedDRA version 17.0 or later. Concomitant medications will be coded using World Health Organization (WHO) Drug (June 2013).

4.2.3. Methods of Pooling Data

Not applicable to the present study.

4.2.4. Adjustments for Covariates

No formal statistical analysis that adjusts for possible covariate effects is planned.

4.2.5. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this exploratory study with a descriptive interpretation.

4.2.6. Withdrawals, Dropouts, Loss to Follow-up

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator may withdraw a subject from the study if, in the Investigator's opinion, it is not in their best interest to continue participation. Notification of early termination will immediately be made to the Sponsor's representative(s).

In case of early termination the subject must return to the clinical for a Study Exit visit within 4 weeks after last dosing (28 days +/- 7 days) and perform all assessments detailed in the Schedule of Events (**Table 1**). The reason for discontinuation will be recorded in source documentation and the eCRF.

Subjects may be withdrawn from the study for the following reasons:

- Adverse event(s);
- Pregnancy;
- Withdrawal of consent;

- Subject non-compliance;
- Investigator decision;
- Sponsor decision, i.e., cancellation of drug development;
- Request from regulatory agency (e.g. FDA), Institutional Review Board, or Ethics Committee.

4.2.7. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the CRF will be included in data listings that will accompany the clinical study report.

4.2.8. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the nominal visit as recorded in the database. In data listings, the relative day of all dates will be presented. Relative days will be calculated relative to the first dose of study drug. Day 1 will be the first day of study drug administration in the study, and the day prior to the first dose of study drug administration will be Day -1. There will be no Day 0.

4.2.9. Baseline Definitions

For all endpoints involving a baseline measure, baseline will be the value obtained at day 1.

4.3. Interim Analyses

No interim analyses are planned for this study.

4.4. Subject Disposition

Subject disposition will be tabulated, including the number of subjects enrolled and treated, the number of subjects that withdrew prior to completing the study and primary reasons for withdrawal, as well as the number of subjects in the Safety Analysis Set.

A by-subject listing of study completion information, including the reason for premature study withdrawal, if applicable, will be presented.

4.5. Demographic and Baseline Characteristics

Demographic, baseline characteristics, mitochondrial disease subtype, and medical history is summarized using descriptive statistics and presented for the SAF.

Age, height, weight, body mass index (BMI), and body surface area (BSA) will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum). The number and percentage of subjects by sex and racial/ethnic category will also be presented.

All collected demographic, baseline characteristic, and medical history data will be provided in data listings.

4.6. Safety Analyses

Safety analyses will be conducted using the Safety Analysis Set.

4.6.1. Study Drug Exposure

Descriptive statistics will be presented for total duration of exposure in days, computed as the last dose - first dose + 1. Duration of exposure will also be summarized in weeks by dividing the exposure in days by 7. Additionally, the number and percent of subjects completing dosing through duration categories (>= 1 day, >= 12 weeks, >= 24 weeks, etc.) will be presented. Dosing compliance will be assessed by tabulating the number of days in which a subject missed a dose up through date of study discontinuation. All dosing data will be presented in a data listing with a record for each dosing event as documented on the subject daily diaries and in-clinic administration records.

4.6.2. Adverse Events

Adverse events will be coded using the MedDRA (version 17.0) coding system and displayed in tables and data listings using system organ class (SOC) and preferred term (PT).

Analyses of AEs will be performed for those events that are considered treatment-emergent, where a treatment-emergent adverse event (TEAE) is defined as any AE with onset after Day 1 of drug administration. TEAEs will also be summarized. If the start date of an AE is partially or completely missing, the date will be compared as far as possible with the date of the start of administration of study drug. If the start date/time of an AE is partially or completely missing, the date/time will be compared as far as possible with the date/time of the start of administration of study drug. The AE will be assumed to be treatment emergent if it cannot be definitely shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach). The following approach will be taken:

- If the start time of an AE is missing but the start date is complete, an AE will only be excluded as being treatment emergent if the start date is before the date of Day 1 study drug administration or if the stop date/time is before Day 1 study drug administration.
- If the start time and day are missing but the start month and year are complete, an AE will only be excluded as being treatment emergent if the start month/year is before the month/year of Day 1 study drug administration or if the stop date/time is before Day 1 study drug administration.
- If the start day and month are missing but the start year is complete, an AE will only be excluded as being treatment emergent if start year is before the year of Day 1 study drug administration or if the stop date/time is before Day 1 study drug administration.
- If the start date is completely missing, an AE will be considered treatment-emergent unless the stop date/time is before Day 1 study drug administration.

These imputations will be used for determining treatment emergence for adverse events; the un-imputed partial dates will be included in the data listings.

Adverse events are summarized by subject incidence rates; therefore, in any tabulation, a subject contributes only once to the count for a given SOC or preferred term.

The number and percentage of patients with any treatment-emergent AE (TEAE) and with any related TEAE, with any Grade >= 3 TEAE, with any serious TEAE, and with any TEAE leading

to withdrawal of study drug, and will be tabulated. In these tabulations, related is defined as any TEAE deemed possibly, probably or definitely related to study drug by the investigator.

Tabulations by SOC and PT will also be produced for all treatment-emergent AEs and for serious TEAEs, presented in alphabetical order by SOC and PT.

No formal hypothesis-testing analysis of adverse events incidence rates will be performed.

All adverse events occurring on study will be listed in subject data listings. By-subject listings also will be provided for the following: subject deaths; serious adverse events; and adverse events leading to treatment withdrawal or death.

4.6.3. Laboratory Data

Clinical laboratory values will be expressed using the International System of Units (SI) units.

The actual value and change from baseline to each on study evaluation will be summarized at all visits using descriptive statistics for each clinical laboratory parameter, including hematology, clinical chemistry and urinalysis.

All laboratory data including hematology, chemistry, urinalysis and serum pregnancy will be provided in data listings.

4.6.4. Vital Signs and Physical Examinations

The actual value and change from baseline to each on study evaluation will be summarized for vital signs. By-subject listings of vital sign measurements will be presented in data listings.

All abnormal physical examination findings will be presented in a data listing.

4.6.5. Neurological Examination

Individual subject changes will be summarized by shift tables. These tables will show the number of subjects who had values that shifted from normal, abnormal – not clinically significant, or abnormal – clinically significant at baseline to normal, abnormal – not clinically significant, or abnormal – clinically significant at the last observed value.

Abnormal neurological examination findings will be provided in a data listing.

4.6.6. Electrocardiogram

Individual subject changes will be summarized by shift tables. These tables will show the number of subjects who had values that shifted from normal, abnormal – not clinically significant, or abnormal – clinically significant at baseline to normal, abnormal – not clinically significant, or abnormal – clinically significant at each visit and the last observed value.

All ECG data for each subject will be provided in data listings.

4.6.7. Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary. The use of concomitant medications will be included in by-subject data listing.

5. CHANGES TO PLANNED ANALYSES

The study was closed prematurely and results will be summarized in an abbreviated clinical study report. Thus, certain analyses described in the protocol (all efficacy analyses, pharmacokinetic and pharmacodynamic analyses, analysis of seizure activity, summaries of AEs by severity, AEs by relationship to study drug, and AE method of collection) will not be performed.

6. [redacted]

[redacted]

[redacted]