

STATISTICAL ANALYSIS PLAN

A Phase 1, Double-blind, Placebo-controlled, Randomized, Two-Part, Ascending Dose-escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Rejuveinix (RJX) in Healthy Participants

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Protocol No. RPI003

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation or Specialist Term | Explanation |
|---------------------------------|---|
| AE | adverse event |
| BMI | body mass index |
| CRA | clinical research associate |
| CRF | case report form |
| CSR | clinical study report |
| CV | coefficient of variation |
| DMP | data management plan |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| HR | heart rate |
| ΔHR | change from baseline heart rate |
| ΔΔHR | placebo corrected change from baseline heart rate |
| hsCRP | high-sensitivity C-reactive protein |
| ICAM-1 | intercellular adhesion molecule 1 |
| ICF | informed consent form |
| IL-6 | interleukin 6 |
| ITT | intent to treat |
| Kg | kilogram |
| IV | intravenous |
| MAD | multiple ascending dose |
| MedDRA | medical dictionary for regulatory activities |
| mg | milligram |
| mL | milliliter |
| n | number |
| PK | pharmacokinetics |
| PD | pharmacodynamic |
| pH | negative of the base 10 logarithm of the molar concentration, measured in units of moles per liter, of hydrogen ions. |

| Abbreviation or Specialist Term | Explanation |
|---------------------------------|---|
| PR (interval) | the period, measured in milliseconds, that extends from the beginning of the P wave (the onset of atrial depolarization) until the beginning of the QRS complex (the onset of ventricular depolarization) |
| Δ PR | change from baseline PR |
| $\Delta\Delta$ PR | placebo corrected change from baseline PR |
| PT | preferred term |
| QRS (duration) | time interval from onset to end of the QRS complex, a reflection of left ventricular depolarization in the heart's electrical cycle as measured by electrocardiogram; |
| Δ QRS | change from baseline QRS |
| $\Delta\Delta$ QRS | placebo corrected change from baseline QRS |
| QT | interval between Q and T wave in the heart's electrical cycle |
| QTc | corrected QT |
| QTcF | Fridericia-corrected QT |
| Δ QTcF | Change from baseline QTcF |
| $\Delta\Delta$ QTcF | Placebo corrected change from baseline QTcF |
| RJX | rejuveinix |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SOC | system organ class |
| SRC | safety review committee |
| TBC | to be confirmed |
| TEAE | treatment-emergent adverse event |
| VCAM-1 | vascular cell adhesion molecule 1 |

2 INTRODUCTION

This statistical analysis plan (SAP) is consistent with the statistical methods section of the final study protocol (Version 2.0, dated 14 Sep 2018) and includes additional detail of the safety summaries and the pharmacodynamics analysis to be included in the clinical study report (CSR). The details of the dose proportionality analysis of PK parameters are included in this document and this analysis will be done at ICON.

A separate plan describing the QT/QTC analyses will be prepared by ERT and a separate plan describing the bioanalytical and pharmacokinetic (PK) analysis will be prepared by AltaSciences.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

- To assess the safety and tolerability of escalating doses of RDX administered as single and multiple intravenous (IV) infusions in healthy volunteers

3.2 Secondary Objectives

- To assess the PK profile of cyanocobalamin, ascorbic acid, thiamine, magnesium, and niacinamide after escalating doses of RDX when administered as single and multiple IV infusions in healthy volunteers
- To assess the PD of escalating doses of RDX when administered as single and multiple IV infusions in healthy volunteers
- To assess the effect on electrocardiogram (ECG) parameters, including concentration-QTc analysis, of RDX administered as single and multiple IV infusions in healthy volunteers
- To establish the optimal clinical dose to be investigated in patients with critical limb ischemia

3.3 Exploratory Objective

- To assess the effect of RDX on intercellular adhesion molecule 1, vascular cell adhesion molecule 1, high-sensitivity C-reactive protein (hsCRP), interleukin 6, and other exploratory biomarkers when administered as single and multiple IV infusions in healthy volunteers

3.4 Primary Endpoints

The safety and tolerability of RDX will be assessed by changes from baseline for the following endpoints:

- adverse events (AEs)
- ECG parameters
- neurological assessments (pyramidal functions, limb strength, cerebellar functions, sensory functions)
- vital signs (body temperature, respiratory rate, heart rate, and sitting systolic and diastolic blood pressure)
- clinical safety laboratory samples (hematology, biochemistry, urinalysis)
- concomitant medications

3.5 Secondary Endpoints

The following endpoints will be evaluated to determine the PK of RJX:

- concentrations and PK parameters of RJX components in plasma/serum; cyanocobalamin, ascorbic acid, thiamine, magnesium and niacinamide

The PD of RJX will be assessed by changes from baseline for the following endpoints:

- pH from venous blood
- pH for urine
- bicarbonate

To assess the effect of RJX on ECG parameters, the following endpoints will be evaluated:

- change from baseline in heart rate (HR), QTcF, PR, and QRS intervals (Δ HR, Δ QTcF, Δ PR and Δ QRS) and placebo-corrected Δ HR, Δ QTcF, Δ PR, and Δ QRS ($\Delta\Delta$ HR, $\Delta\Delta$ QTcF, $\Delta\Delta$ PR and $\Delta\Delta$ QRS)
- categorical outliers for HR, QTcF, PR, QRS
- frequency of treatment emergent changes of T-wave morphology and U-wave presence

3.6 Exploratory Endpoints

The PD of RJX will be assessed by changes from baseline for exploratory biomarkers, including: intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), high sensitivity C-reactive protein (hsCRP), and interleukin 6 (IL-6).

4 STUDY DESIGN

4.1 General

The study is designed as a double-blind, placebo-controlled, randomized study to assess the safety, tolerability, PK, and PD of RDX in healthy participants. This study will be conducted as a 2-part study.

4.1.1 Part 1

Part 1 is designed as single ascending dose (SAD) escalation study in 52 participants in 6 cohorts.

- Cohorts 1 to 5 will include 8 participants per cohort (6 RDX: 2 placebo) between 18 and 50 years of age, inclusive
- Cohort 6 will investigate an older population of 12 participants 51 to 70 years of age, inclusive (9 RDX: 3 placebo)

The assignment to either RDX or placebo will be blinded to the participants, investigators, and study site staff.

Part 1 will include screening, treatment, and follow-up periods. Screening will be between Days -21 and -1 to determine eligibility in the study. Participants who meet the eligibility criteria will be admitted to the study site on Day -1, when they will be assessed for continued eligibility.

Participants will commence a standardized diet the day prior to dosing to control vitamin intake.

Participants will receive a single dose of investigation product as an IV infusion on Day 1.

Cohort 1 will include the initial dosing of a sentinel group (1 RDX and 1 placebo). The remaining 6 participants in Cohort 1 (5 RDX: 1 placebo) will be dosed if, in the opinion of the investigator or delegate, there are no significant safety concerns identified in the sentinel participants within the first 24 hours after administration of the dose (RDX or placebo).

Participants will be confined to the study site from Day -1 to Day 2 (24 hours post dose) and then required to return to the study site on Day 5 for follow-up. Safety and PK assessments will be performed at selected timepoints throughout the study.

4.1.2 Part 2

Part 2 of the study is designed as a multiple ascending dose (MAD) escalation study in 24 participants as 3 cohorts of 8 participants (6 RDX: 2 placebo). The MAD arm will commence in parallel with Part 1, Cohort 6 following completion and review of the safety findings for Part 1, Cohorts 1 to 5.

Participants will be randomly assigned to receive 1 of 3 proposed doses of RDX or placebo (6 RDX: 2 placebo) daily for 7 days.

Part 2 will consist of screening, treatment, and follow-up periods. Screening will occur between Days -21 and -1 to determine eligibility in the study. Those participants who meet the eligibility criteria will be admitted to the study site on Day -1, when their continued eligibility will be assessed. Participants will commence a standardized diet the day prior to dosing to control vitamin intake.

Participants will be confined to the study site from Days -1 to 8 (24 hours post final dose on Day 7) and then return to the study site on Day 12 for follow-up. Safety and PK assessments will be performed at selected timepoints throughout the study.

4.1.3 Dose Escalation in Parts 1 and 2

Details about dose escalation are described in Section 6.3.2 of the study protocol.

4.2 Study Population

The study population will include 76 healthy male and female participants between 51 to 70 years of age (Part 1, Cohort 6) or 18 and 50 years of age (all other cohorts), inclusive, with a body mass index (BMI) of 18 to 35 kg/m², weight not exceeding 132 kg, negative serology and drug and alcohol testing, and clinical laboratory test results within normal reference range or judged to be not clinically significant.

4.3 Evaluations at Screening and Check-in

A detailed schedule of events is provided in Table 6 (for Part 1) and Table 7 (for Part 2) in Section 8.1 of the study protocol.

4.4 Randomization and Treatment Assignments

Participants will be randomly assigned to receive either RJX or placebo.

A computer-generated randomization schedule and kit list will be prepared prior to the start of the study. Investigational product will be prepared and dispensed in accordance with the randomization schedule and kit list. The master randomization schedule and kit list will be made of randomly permuted blocks of appropriate sizes, as determined by the unblinded study team member producing the schedules. The schedules will be generated through the Statistical Analysis System software, version 9.3.

After signing the informed consent form (ICF), each participant will be given a unique screening number according to the screening order. Then, prior to dosing, each participant will be allocated a randomization number according to their chronological order of inclusion in the study. This number will correspond to a treatment (RJX or placebo) as specified on the pre-determined randomization schedule.

Confirmation of the randomization number allocated will be documented in the drug accountability records and recorded in the eCRF. Both the screening and randomization numbers

will be used to identify the participant throughout the study period and on all study-related documentation.

If a participant is replaced, the replacement should take the same treatment assignment as the original participant to ensure that the treatment groups stay balanced.

4.4.1 Investigational Product Administration

Investigational product will be administered as follows:

Table 1: Investigational Products Administered – Part 1

| Investigational Product | Route of administration | Dose (mL/kg) | Dose frequency | Infusion Time |
|-------------------------|-------------------------|---|----------------------|--------------------------------------|
| RJX | Intravenous | Cohort 1: 0.024 Cohort 2: 0.076 Cohort 3: 0.240 Cohort 4: 0.5 Cohort 5: 0.759 Cohort 6: *RJX | Single dose on Day 1 | 100 mL over 45 minutes (± 5 minutes) |
| Placebo | Intravenous | NA | Single dose on Day 1 | 100 mL over 45 minutes (± 5 minutes) |

* Dose in elderly participants (Cohort 6) to be determined following review of safety and PK data from Cohorts 1 to 5

Table 2: Investigational Products Administered – Part 2

| Investigational Product | Route of administration | Starting Dose (mL/kg) | Dose frequency | Infusion Time |
|-------------------------|-------------------------|---|--|--------------------------------------|
| RJX | Intravenous | Cohort 1: 0.240 Cohort 2: 0.5 Cohort 3: 0.759 Cohort 4: TBC* Cohort 5: TBC* | Dosing every day for 7 days (Day 1 to Day 7) | 100 mL over 45 minutes (± 5 minutes) |
| Placebo | Intravenous | NA | Dosing every day for 7 days (Day 1) | 100 mL over 45 minutes (± 5 minutes) |

*To Be Confirmed. Following completion and review of the safety and PK findings for Cohorts 1-5 in Part 1, Part 2 will commence in parallel with Cohort 6 of Part 1. The starting dose for each Part 2 cohort will be determined following completion and review of the safety findings from Part 1 (Cohorts 1-5) and preceding Part 2 Cohorts but will not exceed 0.759 mL/kg.

Participants in each cohort will be dosed in staggered dosing. All doses will be administered as IV infusion by study unit staff.

Food restrictions in relation to dosing are described in more detail in Section 6.3.1 of the study protocol. The rate of administration of RJX as well as details about dose limiting toxicities and

maximum tolerated dose can be found in Sections 6.3.4 and 6.3.5 of the study protocol, respectively.

4.4.2 Concomitant Medications

Should any treatment/medication other than the investigational product be used, the investigator must note the use of the concomitant medication in the source documentation and the CRF. This record should include the drug name (generic name), total daily dose, route of administration, start and stop date of administration, and the indication.

Concomitant medications will be recorded from Day -1 throughout the study for both study parts.

4.4.3 Compliance

Investigational product will be administered via IV by study site staff.

Every attempt will be made to select participants who have the ability to understand and comply with instructions. Noncompliant participants may be discontinued from the study. The time and day of investigational product administration will be recorded. Drug accountability records will be maintained by the study site.

4.5 Evaluation of Treatment Safety

4.5.1 Adverse Events

An AE is defined as any untoward medical occurrence, in a clinical study participant administered a medicinal product, that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Assessment of AEs starts with signing informed consent.

It is the responsibility of the investigator to document all AEs that occur during the study. The AEs will be elicited by asking the participant a nonleading question, for example, "Have you experienced any new or changed symptoms since we last asked/since your last visit?" The AEs should be reported on the appropriate page of the eCRF.

4.5.2 Clinical Laboratory Assessments

The laboratory safety tests to be analyzed are described in more detail in Section 7.1.7 of the study protocol.

4.5.3 Vital Signs

Daily vital signs (screening, check-in, and follow-up; also refer to Protocol Appendix 1, Tables 6 and 7**Error! Reference source not found.**) measurements will include body temperature, respiratory rate, heart rate, and systolic and diastolic blood pressure.

4.5.4 Safety Electrocardiograms

A safety 12-lead ECG will be performed after the patient has rested comfortably in the supine or semi-supine position for at least 5 minutes.

The following parameters will be assessed: heart rate, PR, QRS, QT, and QTcF (Fridericia's formula). The investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

In Part 1, a safety 12-lead ECG will be performed at every visit except follow-up. In Part 2, a safety 12-lead ECG will be performed at every visit except check-in (refer to Protocol Appendix 1, Tables 6 and 7**Error! Reference source not found.**).

4.5.5 Physical and Neurological Examinations

Full physical examinations will be performed at screening and follow-up by a physician or a clinically qualified delegate at the site. The physical examination will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system. Any findings made during the physical examination must be noted regardless of whether they are part of the patient's medical history. An abbreviated physical examination will be performed at check-in.

Daily neurological assessments per standard of care will include pyramidal functions, limb strength, cerebellar functions, and sensory functions.

4.5.6 Weight and Height

Body weight (in kg; wearing light clothes, no shoes) and height (in cm) will be measured. Height and weight measurements will be used to calculate body mass index (BMI).

4.5.7 Protocol Deviation Reporting

If any issue relating to the safety of study participant arises that requires a deviation from the protocol, the study unit through the investigator may immediately make such a deviation. The nature and reasons for the protocol deviations/violations will be recorded in the participant's eCRF. All protocol deviations/violations will be captured by the study unit. Failure to obtain samples due to clinical issues, such as problems with venous access, will not be considered protocol violations. Changes in dose levels or the implementation of additional cohorts as directed by the SRC will not be considered protocol deviations.

Procedural deviations found by the clinical research associate (CRA) during monitoring visits and data deviations captured on the case report form (CRF) and found through programming and examining the database will be listed by participant.

4.6 Pharmacodynamic Assessments

The PD of RJX will be assessed by changes from baseline in blood pH, blood bicarbonate urinary pH, and exploratory biomarkers.

4.6.1 Blood pH, Bicarbonate, and Biomarkers

Blood samples collected for the evaluation of pH, bicarbonate, and biomarkers including: ICAM-1, VCAM-1, hsCRP, and IL-6 will be collected for Part 1 cohort 6 and Part 2 as specified in Protocol Appendix 2.

The PD blood samples can be collected at the same time as the PK sample where timepoints coincide. The sample required for the PD assessment will be aliquoted into separate PD tubes. Additional details on the collection of PD blood samples are included in the Laboratory Procedures Manual.

4.6.2 Urinary pH

In Part 1 and Part 2, the pH of RJX will be evaluated in urine. The urine sample will be collected prior to infusion and at the first voluntary void post the end of infusion to evaluate urine pH and exploratory biomarkers. Additional details on the collection of PD urine samples are included in the Laboratory Procedures Manual.

5 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

No changes.

6 QUALITY CONTROL AND QUALITY ASSURANCE METHODS FOR DATA ANALYSIS

Case report forms will be monitored and collected by ICON. All monitored CRFs will be sent to the Data Management group at ICON and processed according to the ICON Study Specific Procedure SSP DM-39570002.01 Data Management Plan (DMP). The DMP describes CRF data processing, edit checks, data query management, medical dictionary coding, SAE reconciliation, data transfers, and data quality review through database lock or any necessary reopening of the database. After database lock, the data will be retrieved from the database using SAS® for Windows Version 9.4 or newer (SAS Institute, Inc., Cary, NC).

7 STATISTICAL METHODS

7.1 General

All statistical analyses will be performed using the statistical software SAS for Windows Version 9.4 or newer (SAS Institute, Inc., Cary, NC).

Continuous data will be summarized using descriptive statistics including number of participants, mean, median, standard deviation, standard error, 90% confidence interval, minimum, and maximum by treatment and timepoint, where appropriate.

Data collected from all randomized participants will be presented in data listings. Both absolute values and change-from-baseline values for each participant will be given where applicable. All continuous data will be listed with the same precision as is presented in the database. Data listings will be sorted by part, treatment, participant identification, and timepoint.

Categorical data will be summarized by both participant and timepoint. Participant data will be summarized using the count of distinct participants who fall into the category and the percentage of the total number of participants. Timepoint data will be summarized using the count of the assessments that fall into the category and the percentage of the total number of assessments.

Percentages will be rounded up or down to the next integer percentage. Population counts (either number of participants or number of timepoints at the assessment) for each treatment group will be used as the denominator in the calculation of percentages unless otherwise specified.

7.2 Handling of Dropouts or Missing Data

All data from withdrawn participants will be included in all analyses up to the time of withdrawal regardless of the duration of treatment. There will be no imputation for missing data unless otherwise specified.

7.3 Multicenter Studies

This is a single-center study.

7.4 Examination of Subgroups

No subgroup analyses are planned.

7.5 Analysis Populations

Intent to Treat (ITT) Population: all randomized participants based on the randomized treatment, regardless of which treatment the participant actually received; used for all summaries of baseline and demographic data; all associated listings will be produced for the ITT population

Safety Analysis Population: participants who received at least 1 dose of the investigational product (RJX or placebo); used for all summaries of baseline, demographic data, safety data and PD data; all listings regarding safety data will be produced for the safety analysis population

PK Analysis Set: participants who received at least one dose of the investigational product and provided at least one quantifiable plasma concentration of cyanocobalamin, ascorbic acid, thiamine, magnesium or niacinamide.

PK Evaluable Analysis Set: participants who received at least one dose of the investigational product for whom at least one estimable PK parameter could be reliably estimated.

The following analysis population is also defined in the clinical study protocol:

- QT/QTc Analysis Set

This analysis population will not be defined in this SAP, since the QT/QTc analyses will be prepared by ERT.

7.6 Participant Accountability

Summaries of analysis populations and participant disposition will be presented by treatment and overall using ITT Population for each part separately and will contain the following information:

- Number and percent of participants who were randomized
- Number and percent of participants who were dosed and received treatment
- Number and percent of participants who received all doses planned (Part 2 only)
- Number and percent of participants who completed the study
- Number and percent of participants who discontinued early and reason for early discontinuation
- Number and percent of participants in each population

Participant enrollment and disposition, including reasons for early withdrawal from the study, will be summarized by treatment. Participant disposition will be presented in listings.

7.7 Protocol Deviation Reporting

Protocol deviations identified by the clinical research associate during monitoring visits and deviations captured on the CRF and identified through programming and examining the database will be listed by participant.

7.8 Participant Demographics and Baseline Characteristics

Summaries of baseline and demographic characteristics will be based on the ITT Population as well as Safety Analysis Set. Baseline and demographic data (including gender, age, race, ethnicity, weight, height, and BMI) will be summarized by treatment.

7.9 Dose Proportionality Analysis

The dose proportionality of the main PK parameters C_{max} , $AUC_{0\text{-last}}$ (SAD), AUC_{tau} (MAD), and $AUC_{0\text{-inf}}$ (SAD and MAD) will be investigated using the following power model:

$\log(\text{parameter}) = a + b * \log(\text{dose})$, where a is the intercept, b is the slope and dose is the actual dose in mL/kg.

Each log-transformed PK parameter for the RJX components cyanocobalamin, ascorbic acid, thiamine, magnesium and niacinamide will be fitted to a power model with fixed effect term for log-transformed dose and subjects as random effects. For each PK parameter, the slope and associated 90% CI will be presented. If the 90% CI for the slope of the regression line contains 1 then it can be concluded that the PK parameter is dose proportional.

Dose proportionality may be assessed within different dose ranges if deemed appropriate. All dose proportionality assessments will include data from at least three dose levels.

Scatterplots including regression line for all PK parameters of all analytes versus dose in mg will be generated.

7.10 Analysis of Safety Data

7.10.1 General

Safety parameters will be listed and summarized using standard descriptive statistics for values for each treatment at each timepoint as well as changes from baseline of each cohort separately.

7.10.2 Adverse Events

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data (Aes) will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and association with investigational product, as perceived by the investigator. Symptoms reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities (MedDRA).

The Aes will be grouped by MedDRA system organ class (SOC) and preferred term (PT) and summarized by actual treatment/dose level.

Treatment-emergent adverse events (TEAEs) are defined as Aes that commence on or after the time of start of first investigational product administration.

All TEAEs will be summarized by actual treatment/dose level. The number and percentage of participants experiencing Aes and the number of TEAEs will be tabulated. The following summaries will be presented:

- Overall summary of TEAEs
- All TEAES by SOC and PT
- All TEAEs by SOC, PT, and severity

- All TEAEs by SOC, PT, and relationship to investigational product
- SAEs by SOC and PT

Any SAEs, Aes with outcome of death, or Aes resulting in discontinuation of study or IP will be listed separately. A separate summary table of adverse events of interest will be tabulated for neurological and infusion related events.

7.10.3 Clinical Laboratory Assessments

Observed values and actual changes from baseline (defined as last value prior to first IMP administration) of continuous laboratory parameters (hematology and clinical chemistry) will be summarized descriptively, by actual treatment/dose level, and visit/timepoint. Categorical outcomes will be summarized by frequency tables. Shift tables representing categorical change of laboratory results from baseline to each post-baseline visit will be presented. Urinalysis results will be summarized at each timepoint by actual treatment/dose level at each timepoint using frequency tables. Pregnancy and infertility related data will be listed. Lab normal ranges will also be listed.

7.10.4 Vital Signs

Observed values and actual changes from baseline (defined as last value prior to first IMP administration) of vital signs will be summarized descriptively by actual treatment/dose level and visit/timepoint. Categorical outcomes will be summarized by frequency tables.

7.10.5 Safety Electrocardiograms

Observed values and actual changes from baseline (defined as last value prior to first IMP administration) of ECG parameters will be summarized descriptively by actual treatment/dose level and visit/timepoint. Safety 12-lead ECG interpretations (categorical outcomes) will be summarized by frequency tables.

7.10.6 Physical and Neurological Examinations

Physical examination data as well as neurological examination data will be listed only.

7.10.7 Concomitant Medications

Prior medications are those medications that were stopped prior to first dose of investigational product. Concomitant medications are medications taken at least once after investigational product. Medications stopped on the same day as investigational product will be considered prior medications.

Prior and concomitant medications will be listed. Concomitant medication summary tables will be grouped by PT and show the number and percentage of participants by PT for all participants overall. For the summaries of concomitant medications, participants who take the same medication (in terms of the PT) more than once will only be counted once for that medication.

7.11 Pharmacodynamic Analysis

Pharmacodynamic parameters like blood bicarbonate and pH, urinary pH, and relevant exploratory biomarkers (Part 1 cohort 6 and Part 2 only) will be summarized at each timepoint by actual treatment and each dose level by using descriptive statistics, unless results are categorical. Categorical outcomes will be summarized by frequency tables (see section 9.1). Data will be assessed for clinical safety and clinical significant changes from baseline and additional statistical analyses and interpretations may be added in an amendment.

7.12 Sample Size

The sample size for this study has been selected without performing a formal sample size calculation. The sample size was chosen empirically and is customary for Phase 1 studies evaluating safety and PK parameters; it is not based on statistical hypothesis testing.

7.13 Interim Analysis

The SRC will review the safety data and PK data (only safety data in Cohorts 1 and 2 in Part 1) prior to escalation to the next cohort for both parts of the study. The safety and PK findings of the Part 1 (SAD) Cohorts 1 to 5 will be reviewed by the SRC prior to commencing Part 2 (MAD).

7.14 General Conventions for Tables, Listings and Figures

For summary tables, unless otherwise specified, the number of decimal places provided in the SAS output will be based on the accuracy of the least accurate value in the raw data as follows:

| | |
|----------------------|---|
| n | integer |
| Arithmetic mean | 1 decimal place more than the least accurate number in the raw data |
| SD | 2 decimal place more than the least accurate number in the raw data |
| CV(%) | 2 decimal places |
| Geometric mean | 1 decimal place more than the least accurate number in the raw data |
| Median | 1 decimal place more than the least accurate number in the raw data |
| Minimum | same number of decimal places as raw data |
| Maximum | same number of decimal places as raw data |
| Confidence interval | same number of decimals as the associated statistic |
| Geometric mean ratio | 2 decimal places |

8 TABLES, FIGURES, AND LISTINGS

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| Section 14.1 | Demographic and Subject Characteristics Data Summaries |
| Table 14.1.1 | Summary of Subject Disposition (ITT Population) |
| Table 14.1.2 | Summary of Analysis Populations (ITT Population) |
| Table 14.1.3 | Demographic and Baseline Characteristics (ITT Population) |
| Table 14.1.4 | Demographic and Baseline Characteristics (Safety Analysis Population) |
| Section 14.2 | Pharmacodynamic/ Dose Proportionality Summaries |
| Table 14.2.1 | Summary of Blood Bicarbonate and pH (Safety Analysis Population) |
| Table 14.2.2 | Summary of Urine pH (Safety Analysis Population) |
| Table 14.2.3 | Summary of Exploratory Biomarkers (Part 1 Cohort 6 and Part 2 only) (Safety Analysis Population) |
| Table 14.2.4 | Dose Proportionality Analysis of RDX AUC and C_{max} (PK Evaluable Analysis Set) |
| Figure 14.2.1.1 | Scatterplot C_{max} versus dose in mg (PK Evaluable Analysis Set) |
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| Figure 14.2.1.3 | Scatterplot AUC_{last} versus dose in mg (PK Evaluable Analysis Set) |
| Section 14.3 | Safety Data Summaries |
| Section 14.3.1 | Displays of Adverse Events |
| Table 14.3.1.1 | Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Population) |
| Table 14.3.1.2 | Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Population) |
| Table 14.3.1.3 | Summary of Treatment-Emergent Adverse Events by Severity Grade (Safety Analysis Population) |

Table 14.3.1.4 Summary of Treatment-Emergent Adverse Events by Relationship to Investigational Product (Safety Analysis Population)

Table 14.3.1.5 Summary of Neurological Adverse Events of Interest by Relationship to Investigational Product (Safety Analysis Population)

Table 14.3.1.6 Summary of Infusion Related Adverse Events of Interest by Relationship to Investigational Product (Safety Analysis Population)

Section 14.3.2 **Listings of Deaths, Other Serious and Certain Significant Adverse Events**

Table 14.3.2.1 Listing of Adverse Events Leading to Death (Safety Analysis Population)

Table 14.3.2.2 Listing of Serious Adverse Events (Safety Analysis Population)

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Section 14.3.3 **Narratives of Deaths, Other Serious and Certain Significant Adverse Events**

Section 14.3.4 **Abnormal Laboratory Value Listing**

Table 14.3.4.1 Listing of Abnormal Laboratory Results (Safety Analysis Population)

Table 14.3.4.2 Observed and Change from Baseline for Clinical Laboratory Parameters (Safety Analysis Population)

Table 14.3.4.3 Hematology Laboratory Data Shift from Baseline to Post-Baseline Results by Part (Safety Analysis Population)

Table 14.3.4.4 Clinical Chemistry Laboratory Data Shift from Baseline to Post-Baseline Results by Part (Safety Analysis Population)

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Section 14.3.5 **Additional Safety Data Summaries**

Table 14.3.5.1 Summary of Vital Sign Results by Part, Category, Treatment and Test (Safety Analysis Population)

| | |
|----------------|---|
| Table 14.3.5.2 | Absolute and Change from Baseline Vital Signs by Part, Treatment and Test (Safety Analysis Population) |
| Table 14.3.5.3 | Observed and Change from Baseline for 12-Lead Electrocardiogram Parameters (Safety Analysis Population) |
| Table 14.3.5.4 | 12-Lead Safety ECG Interpretation (Safety Analysis Population) |
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|-----------------------|--|
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| Listing 16.1.7 | Randomization Allocation (ITT Population) |
| Section 16.2.1 | Discontinued Subjects |
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| Section 16.2.4 | Demographic Data |
| Listing 16.2.4.1 | Demographics and Baseline Characteristics (ITT Population) |
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Section 16.2.7 Adverse Event Listings

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Section 16.2.8 Individual Laboratory Measurements by Subject

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Listing 16.2.8.6 Serology Results (Safety Analysis Population)

Listing 16.2.8.7 Vital Signs (Safety Analysis Population)

Listing 16.2.8.8 12-Lead Electrocardiogram Results (Safety Analysis Population)

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Listing 16.2.8.10 Physical Examination Findings (Safety Analysis Population)

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Listing 16.2.8.12 Prior and Concomitant Medications (Safety Analysis Population)

Listing 16.2.8.13 Concomitant Procedures (Safety Analysis Population)

Listing 16.2.8.14 Pharmacodynamic Parameters (Safety Analysis Population)

Listing 16.2.8.15 Investigator Comments (Safety Analysis Population)