

Excerpts from Clinical Study Report (CSR) Draft 2

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

Protocol Number: RPI003

Draft 2; 20 March 2020

Study Design Review (Italics indicates not excerpted from Draft 2 CSR)

The primary objective was to assess the safety and tolerability of escalating doses of RJX administered as single and multiple IV infusions in healthy participants. The secondary objectives of the study were to assess the following parameters after escalating doses of RJX administered as single and multiple IV infusions; to assess the RJX Pharmacokinetic (PK) profile of cyanocobalamin, ascorbic acid, thiamine, magnesium, and niacinamide; assess RJX Pharmacodynamics (PD); assess the effect of RJX on ECG parameters, including concentration-QTc analysis; and to assess dosing for an optimal safe and tolerable dose to be investigated in future patient studies.

Findings for the exploratory objectives (to assess the effect of RJX on laboratory parameters ICAM-1, VCAM-1, hsCRP, IL-6, and other exploratory biomarkers) are not presented in this report as they do not relate directly to safety and tolerability assessments. The raw data listings of the biomarker results will be reported in the final Clinical Study Report (CSR) and will undergo a separate analysis to be presented as an addendum in the final CSR.

Study Design

This was a double-blind, placebo-controlled, randomized study to assess the safety, tolerability, PK, and PD of RJX in healthy participants and conducted as a 2-part study.

Part 1

Part 1 was a single ascending dose escalation study in 52 participants, 6 cohorts in total. Cohorts 1 to 5 included 8 participants per cohort (6 RJX: 2 placebo) aged 18 to 50 years, inclusive. Cohort 6 investigated an older population of 12 participants (9 RJX: 3 placebo) aged 51 to 70 years, inclusive. The assignment to either RJX or placebo was blinded to the participants, investigators, and staff at the study site. Part 1 consisted of screening (Days -21 to -1), treatment, and follow-up periods. Participants who met eligibility criteria were admitted to the study site on Day -1, when continued eligibility was assessed. Participants commenced a standardized diet the day prior to dosing to control vitamin intake. Participants received a single dose of investigational product (IP) as an IV infusion on Day 1. Cohort 1 included the initial dosing of a sentinel group (1 RJX and 1 placebo). The remaining 6 participants in Cohort 1 (5 RJX: 1 placebo) were dosed when, in the opinion of the investigator, there were no significant safety concerns identified in the sentinel participants within the first 24 hours after administration of the dose (RJX or placebo).

Participants were confined to the study site from Day -1 to Day 2 (24 hours post-dose) and then returned to the study site on Day 5 for a final follow-up visit. Safety, PK, and PD samples were collected at selected timepoints throughout the study.

Part 2

Part 2 of the study was a multiple ascending dose (MAD) escalation study in 24 participants, 3 cohorts of 8 participants (6 RJX: 2 placebo). The MAD arm of the study commenced in parallel with Cohort 6 of Part 1 following completion and review of the safety findings for Cohorts 1 to 5 in Part 1. Participants were randomly assigned to receive 1 of 3 doses of RJX or placebo (6 RJX: 2 placebo) every day for 7 days. Part 2 consisted of screening (Day -21 to Day -1), treatment, and follow-up periods. Participants who met eligibility criteria were admitted to the study site on Day -1, when continued eligibility was assessed. Participants commenced a standardized diet the day prior to dosing to control vitamin intake. Participants were confined to the study site from Day -1 to Day 8 (24 hours post the final dose on Day 7) and then returned to the study site on Day 12 for a final follow-up visit. Safety, PK, and PD samples were collected at selected timepoints throughout the study.

Number of Participants Planned and Analyzed

- 52 participants in Part 1 and 24 participants in Part 2 were planned and analyzed.
- No participant discontinued early from the study or from dosing.

In Part 1 (SAD), IP (*investigational product – RJX*) was administered as a 100 mL IV infusion over 45 minutes (\pm 5 minutes) on a single occasion on Day 1 as follows:

Cohort 1: 0.024 mL/kg; Cohort 2: 0.076 mL/kg; Cohort 3: 0.240 mL/kg; Cohort 4: 0.500 mL/kg;
Cohort 5: 0.759 mL/kg with each Cohort RJX (n = 6)/placebo (n = 2);
Cohort 6: 0.500 mL/kg RJX (n = 9)/placebo (n = 3)

In Part 2 (MAD), IP was administered as a 100 mL IV infusion over 45 minutes (\pm 5 minutes), as in Part 1, every day for 7 days as follows:

Cohort 1: 0.240 mL/kg; Cohort 2: 0.500 mL/kg; Cohort 3: 0.759 mL/kg and
each Cohort RJX (n = 6)/placebo (n = 2)

Safety

Safety endpoints included AEs, physical and neurological examinations, clinical laboratory evaluations, vital sign measurements, safety 12-lead ECGs, and concomitant medications.

Adverse Events (AEs)

AEs Neurological: No neurological AEs of interest were reported....

AEs – Conclusions from Safety and Tolerability Evaluations

Conclusions from safety and tolerability evaluations were as follows:

- There were no SAEs, severe AEs, deaths, or AEs leading to discontinuation of IP or the study.

- Overall, TEAEs (treatment-emergent adverse events) were as follows:
 - In Part 1 (52 participants), there was a total of 13 AEs (10 participants).

This included 2 TEAEs (2 participants) in placebo, none of which were considered related. The rest were in Cohorts 1, 2, 4, 5, and 6 SAD dosing. Of these, 1 TEAE (1 participant) in each of Cohorts 1 and 2 was considered related, 2 TEAEs (2 participants) in each of Cohorts 4 and 5 were considered related, and no TEAEs in Cohorts 3 and 6 were considered related.
 - In Part 2 (24 participants), there was a total of 14 AEs (8 participants).

This included 4 TEAEs (1 participant) in placebo, 3 of which (1 participant) were considered related. The rest were in Cohorts 1, 2, and 3 MAD dosing. Of these, 3 TEAEs (2 participants) in Cohort 2 were considered related and no TEAEs in Cohorts 1 and 3 were considered related.
- The most frequently reported TEAE in either study part was headache, as follows:
 - In Part 1 (4 headache TEAEs, 4 participants overall):
 - In Part 2 (2 headache TEAEs, 2 participants overall):

AEs infusion related

- No infusion-related AEs of interest were reported for participants who received placebo, in Part 1 Cohorts 1 through 6, or in Part 2 in Cohorts 1 and 3.
- In Part 2 Cohort 2 (0.500 mL/kg, all RJX dosing), there were infusion-related TEAEs of interest that did not require treatment (*3 participants and 4 events*). The infusion-related AEs of interest did not require additional treatment.
- They were no SAEs and did not cause participants to discontinue the study or dosing. All of the infusion-related AEs recovered/resolved with no sequelae.

Clinical Laboratory Evaluations

- There were no clinically meaningful changes identified in observed laboratory values or changes from baseline when compared with placebo or evaluated by increasing dose level. Individual post-dose clinically significant laboratory values were considered unlikely related to placebo or RJX.
- Post-dose laboratory values that were TEAEs were reported for 2 participants in Part 2. Neither event required treatment or caused the participants to discontinue the study or dosing.

Vitals, Blood Pressure and Electrocardiograms

- Individual post-dose vital sign results that were considered TEAEs were either considered unlikely related to placebo (1 participant in Part 1, Cohort 3 [placebo], mild TEAE of hypotension on Day 1 that was 20 hours in duration) or considered possibly related to RJX (1 participant in Part 1, Cohort 1 [0.024 mL/kg RJX], mild TEAE of blood pressure systolic decreased on Day 1 that was 11 minutes in duration).

- There were no 12-lead safety ECG abnormal clinically significant findings and no notable changes compared with baseline.

Pharmacokinetics (PK)

- Concentrations and PK parameters of the RJX components were evaluated to determine the PK of RJX *and yielded no unusual or unexpected PK results.*

Pharmacodynamics (PD)

- *As the PD data is primarily targeting mechanism of action data, it is therefore not a primary requirement or primary outcome of this study for safety and tolerability. The PD data will be collated, interpreted and theoretically applied in a future report.*

Cardiodynamics

- RJX at the studied doses did not have a clinically relevant effect on cardiac conduction, i.e., the PR and QRS intervals.

Conclusions

- Safety and tolerability were well demonstrated through escalating doses at all levels of RJX in single and multiple IV infusions in healthy participants.
- No remarkable safety-related changes were observed with regard to clinical laboratory results after single and multiple doses of RJX.
- The product was well tolerated as evidenced by no SAEs nor any severe AEs observed as per FDA definitions.
- Based on safety and PK results, a safe and tolerable clinical dose range to be investigated in patients with CLI was established as 0.024 mL/kg RJX to 0.759 mL/kg RJX. Since the optimal dose was not achieved in this study for safety or tolerability, further research will be required to exceed the 0.749 mL/kg maximal dose evaluated in this study.

Disclosure:

The final Quality Assurance review and release of the complete clinical study report is currently in process. The final released report will be submitted to Reven's FDA - IND as soon as it is available; -at which time additional details may be provided upon request and with appropriate non-disclosure agreements in place.