Safety and pharmacokinetics of prosetin, a novel, brain penetrant MAP4K inhibitor in development for the treatment of ALS

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ProJenX

Introduction

ER stress—the series of pathways that are activated when cells accumulate misfolded proteins—is a common feature across ALS subtypes[1]. ALS motor neurons are more sensitive to ER stress-induced neurodegeneration than control motor neurons or other neuronal subtypes, which may explain their selective vulnerability to the disease[2].

We identified MAP4Ks as key regulators of ER stress-mediated neurodegeneration and found that MAP4K inhibitors protect human motor neurons in this context[3]. However, existing MAP4K inhibitors demonstrated poor CNS exposure and other unfavorable ADME properties, making them unsuitable drug candidates for ALS.

We optimized a series of MAP4K inhibitors for properties specific to the treatment of ALS, and selected prosetin, a highly potent, preferentially CNS penetrant, orally bioavailable MAP4K inhibitor, as a lead candidate[3].

We evaluated its safety and efficacy *in vivo* in two ALS mouse models and confirmed through nonclinical safety and toxicity studies that prosetin is well-tolerated at and above pharmacologically relevant doses.

Based on results from preclinical studies, we initiated PRO-101, a first-in-human study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of prosetin in healthy volunteers and people living with ALS.

PRO-101 (NCT05279755) is an ongoing three-part, randomized, double-blind, placebo-controlled Phase 1 clinical trial.

1. Ito, Y. *et al.* Involvement of CHOP, an ER-stress apoptotic mediator, in both human sporadic ALS and ALS model mice. *Neurobiol Dis* **36**, 470–476 (2009).
2. Thams, S. *et al.* A stem cell-based screening platform identifies compounds that desensitize motor neurons to endoplasmic reticulum stress. *Mol Ther* (2018) doi:10.1016/j.ymthe.2018.10.010.
3. Bos, P. H. *et al.* Development of MAP4 Kinase Inhibitors as Motor Neuron-Protecting Agents. *Cell Chem Biol* (2019) doi:10.1016/j.chembiol.2019.10.005.

Materials and Methods

PRO-101 Objectives

- PRO-101 was initiated to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of prosetin.
  - The primary objective of PRO-101 is to evaluate the safety and tolerability of single and multiple doses of prosetin as assessed by all adverse events, safety laboratory tests (clinical chemistry, hematology, and urinalysis), vital signs, physical examinations, neurological examinations, ophthalmic examinations, and ECGs.
  - The secondary objective of PRO-101 is to evaluate the pharmacokinetic profile of single and multiple doses of prosetin in plasma.
  - The exploratory objective of PRO-101 is to evaluate the pharmacodynamic profile of multiple doses of prosetin through biomarker analysis.

PRO-101 Participants

- PRO-101 is a three-part clinical trial designed to evaluate single ascending doses (Part 1a) and multiple ascending doses (Part 1b) in up to 56 healthy volunteers, and multiple doses in up to 16 people living with ALS (Part 1c).
  - Parts 1a and 1b enroll healthy adult males and females, 18-65 years of age
  - Part 1c will enroll male or female participants with ALS, ≥18 years of age

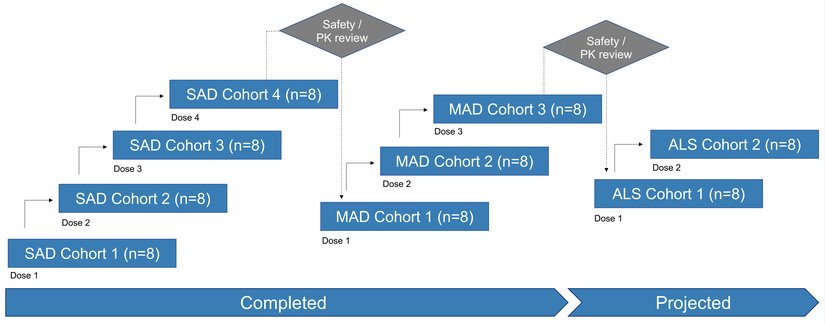
Study Interventions and Procedures

- Each dosing cohort includes 8 participants, who are randomized 6:2 to receive either prosetin or placebo.
- Prosetin is administered in oral solution form. The clinical formulation is manufactured following USP <795> standards under the direction of a compounding pharmacist at the Phase 1 clinical trial unit (Worldwide Clinical Trials, San Antonio, TX).
- In Part 1a, participants received a single dose of prosetin. In Part 1b, participants receive a once-daily dose of prosetin over 14 days.

Pharmacokinetic Analysis

- Plasma samples from each prosetin-treated subject are analyzed using a validated method and liquid chromatography-tandem mass spectrometry (LC-MS/MS). Control plasma samples from placebo subjects are analyzed only at the 12h timepoint.
- Pharmacokinetic parameters are calculated using noncompartmental methods, using an appropriate model for plasma data and oral administration. The evaluable pharmacokinetic population includes all subjects who have sufficient concentration-time data to estimate at least one of the planned pharmacokinetic parameters.

PRO-101 Trial Design and Status



Safety and tolerability of prosetin following single and multiple doses

To date, 48 participants have completed study PRO-101. Of these, 36 have been exposed to either single or multiple doses of prosetin. No participants have discontinued the trial prematurely. Demographic characteristics of participants are summarized below in Table 2.

Safety is evaluated by a Safety Review Committee consisting of the study investigator, medical monitor, and clinical pharmacologist. Safety assessments and interim results are summarized in Table 1.

Safety assessments are performed at pre-specified timepoints throughout the study. Participants are monitored for adverse events from the first dose through the end of the study.

Table 1. SAFETY ASSESSMENTS: INTERIM RESULTS

Adverse events	• No moderate or severe adverse events (AEs) reported • One mild AE (headache) deemed potentially prosetin-related in Cohort A2 • No prosetin-related AEs reported in other cohorts
Safety laboratory tests	• No clinically significant abnormalities reported
Vital signs	• No clinically significant abnormalities reported
Physical examination	• No abnormalities reported
Neurological examination	• No abnormalities reported
Ophthalmic examination	• No abnormalities reported
ECGs (12-lead)	• No clinically significant abnormalities reported

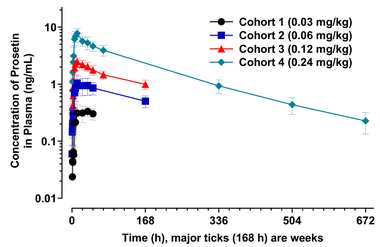
Table 2. INTERIM DEMOGRAPHICS OF PRO-101

Dose Level (mg/kg)	0.03 SD	0.06 SD	0.12 SD	0.24 SD	0.06 14 Days	0.10 14 Days	Total
Cohort	A1	A2	A3	A4	B1	B2	
Mean Age (Range)	46.9 (30-62)	39.5 (24-62)	38.1 (21-51)	33 (20-50)	40.1 (31-60)	42.3 (19-56)	40.0 (19-62)
Gender (M/F)	3M/5F	3M/5F	5M/3F	4M/4F	5M/3F	5M/3F	25M/23F
Race							
Black/African American	4	2	5	3	6	3	25
White	4	4	3	5	2	5	24
Multiple*	-	2	-	-	-	-	2
Ethnicity							
Hispanic/Latino	3	5	1	5	2	4	20
Not Hispanic/Latino	5	3	7	3	6	4	28

*In Cohort A2, two subjects recorded two races, Black/White and Asian/Black.

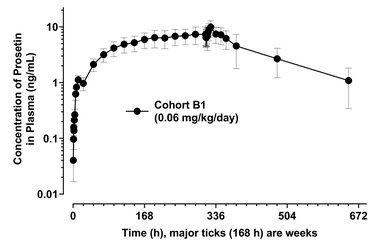
Pharmacokinetic profile of prosetin following single and multiple doses

SINGLE DOSE PLASMA PHARMACOKINETICS



Healthy volunteers (n=6/cohort) were administered a single dose of prosetin at 0.03, 0.06, 0.12, or 0.24 mg/kg dose levels. Plasma levels of prosetin increased with dose in a modestly supra-proportional manner (2-fold increases in dose resulted in 2.4 to 3.4-fold increases in exposure). Low intra-subject variability and clear separation in exposure between each dose level was observed. In later cohorts, the sampling time frame was extended to capture terminal elimination given the long plasma half-life of prosetin.

MULTIPLE DOSE PLASMA PHARMACOKINETICS (INTERIM RESULTS)



Healthy volunteers (n=6) were administered prosetin at 0.06 mg/kg/day over 14 days. As expected given the long single-dose plasma half-life of prosetin, exposure increased over time. Low intra-subject variability was observed, and steady state was reached or nearly reached at 14 days.

Discussion and Conclusions

- The primary goal of PRO-101 is to assess the safety and tolerability of prosetin, which is to our knowledge the first brain penetrant MAP4K inhibitor to be studied in clinical trials.
- In doses studied to date, prosetin is safe and well-tolerated, with a predictable and consistent pharmacokinetic profile.
- Higher doses, and longer durations of dosing, will be studied in people living with ALS in Part 1c of PRO-101.
- Data from PRO-101, in tandem with nonclinical safety and efficacy data, support the further evaluation of prosetin as a potential treatment for ALS.

Acknowledgements and Disclosures

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EF is an employee and shareholder of ProJenX. ERL, AZ, BS, and HW are shareholders of and consultants to ProJenX. JA serves as a consultant to AL-S Pharma, Amylyx, Biogen, Cytokinetics, Denali, Orphazyme, Novartis, Sanofi, UCB, and Wave Therapeutics.

PROJECT ALS THERAPEUTICS CORE AT COLUMBIA