PRO-101: study design and interim results from a Phase 1 study to evaluate the safety, tolerability, PK, and PD of prosetin in ALS

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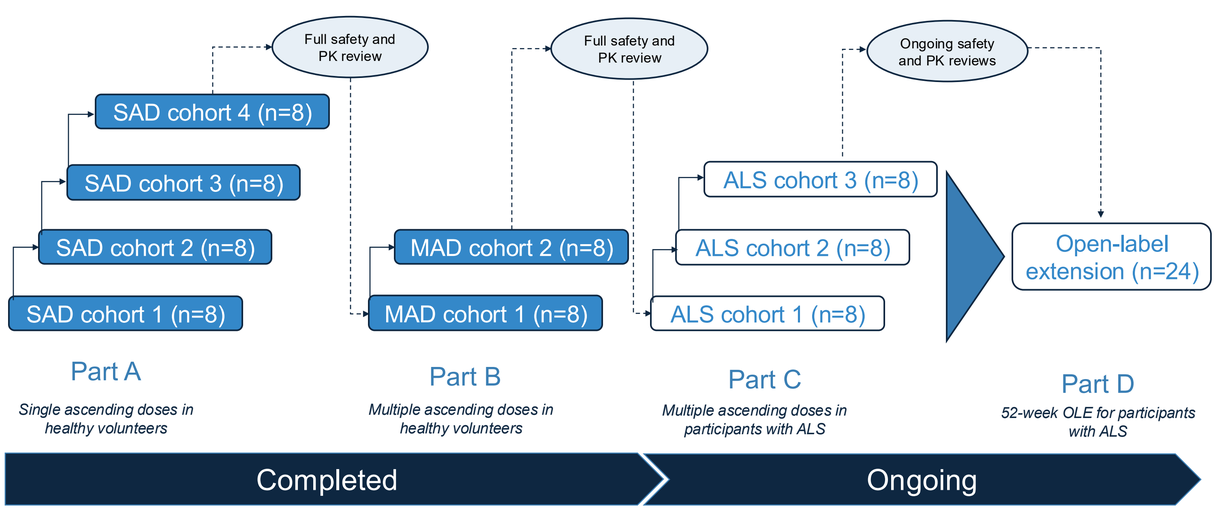
Background

- The genetic and molecular pathways leading to motor neuron degeneration in ALS are not fully understood. To overcome this barrier to discovering meaningful ALS therapies, we developed an unbiased human stem cell-derived drug screening platform to first identify core drivers of neurodegeneration in ALS motor neurons and then screen for compounds that could confer potent neuroprotection against the most critical features of the disease[1].
- With this platform, we found that compounds inducing protein misfolding are selectively toxic to ALS motor neurons and that MAP4K inhibition is strongly neuroprotective against ER stress and other proteostatic stressors involved in ALS motor neuron degeneration[2].
- Previous MAP4K inhibitors demonstrate poor CNS exposure and other unfavorable ADME properties, making them unsuitable drug candidates for ALS.
- To address this challenge, we are developing prosetin, a novel MAP4K inhibitor that is highly potent, metabolically stable, CNS-penetrant, and orally bioavailable[2], for the treatment of ALS.

Methods

- Based on regulatory feedback and to ensure that all ALS participants in this first-in-human study of prosetin can receive long-term access to treatment, ProJenX designed PRO-101 as a hybrid clinical trial.
- In Parts A and B, the safety, tolerability, and plasma pharmacokinetics (PK) of single and multiple (14-day) ascending doses of prosetin were evaluated in healthy volunteers (Worldwide Clinical Trials, Austin, TX, USA).
- Based on supportive safety and PK data from healthy volunteers, the safety, tolerability, and PK of prosetin are being evaluated across dose escalation cohorts (Part C) in participants with ALS. All participants who complete 14 days of double-blind dosing in Part C may continue to Part D, an optional open label extension (OLE).
- PRO-101 employs sentinel dosing at each new dose level and multiple safety reviews, between each dose escalation cohort and at regular timepoints across the OLE.
- Throughout Parts C and D, exploratory endpoints assessing the effects of prosetin on target engagement and ALS-related outcomes will be evaluated in addition to safety, tolerability, and PK.

PRO-101 Study Design



Key Eligibility Criteria: Participants with ALS

Inclusion Criteria	Exclusion Criteria
• Male and female participants ≥ 18 years of age with ALS diagnosis • Slow vital capacity >50% predicted, at Screening • Able to swallow 10mL liquid, in order to ingest the study medication • Not pregnant or breastfeeding, and willing and able to practice effective contraception • If on approved ALS therapies, must be on a stable dose	• Current enrollment in any other investigational drug study • Prior exposure to stem cell or gene therapies (investigational or off-label) for the treatment of ALS • Abnormal laboratory values or safety tests at screening as deemed by the Principal Investigator and/or Medical Monitor • Any medical history of seizures, or episodes of vertigo within 12 months prior to screening

Key Endpoints: Participants with ALS

Primary Endpoint	Secondary Endpoint
• Safety and tolerability of prosetin in people living with ALS	• Plasma and cerebrospinal fluid (CSF) pharmacokinetics of prosetin
Exploratory Endpoints	
• MAP4K target engagement biomarkers in peripheral blood mononuclear cells (PBMCs) • Biomarkers in plasma and CSF: neurofilament light, neuroinflammatory cytokine / chemokine panel • Changes in plasma lipid levels • Clinical outcomes: ALSFRS-R, Slow vital capacity, ALSAQ-5 • Digital twin AI analyses (collaboration with Unlearn)	

Study Status

- PRO-101 is ongoing at three sites, located in Canada, the United States, and the Netherlands.
- Cohorts 1 and 2 are complete. Cohort 3 is ongoing. Participants in the OLE have received up to 9 months of open-label prosetin dosing.
- Clinical safety and PK data are being routinely reviewed by a Safety Review Committee at pre-specified timepoints.

Interim Data

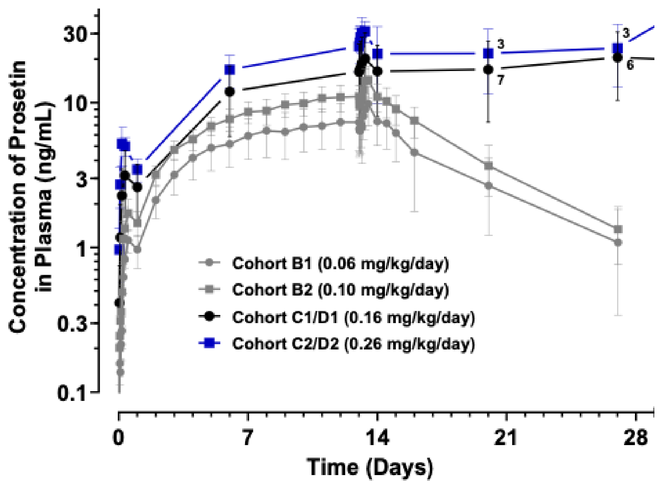
- Baseline characteristics of study participants represent a heterogenous ALS population, consistent with the broad eligibility criteria of the study.

Cohort 1 Baseline Characteristics

Participant	Age	Sex	S/S onset (months)	ALSFRS-R Total Score	SVC % pred.	Riluzole Y/N	Edaravone Y/N
1	71	Female	30	36	82%	Y	N
2	65	Female	23	28	50%	Y	N
3	57	Female	26	36	69%	Y	N
4	70	Male	17	40	110%	N	N
5	56	Female	22	38	80%	Y	N
6	49	Male	15	23	41%	N	N
7	55	Male	15	37	95%	Y	Y
8	66	Male	13	39	91%	Y	N

Cohort 2 Baseline Characteristics

Participant	Age	Sex	S/S onset (months)	ALSFRS-R Total Score	SVC % pred.	Riluzole Y/N	Edaravone Y/N
1	69	Female	27	34	73%	Y	N
2	68	Male	11	43	64%	Y	Y
3	62	Male	30	42	86%	Y	N
4	63	Female	20	35	51%	Y	Y
5	69	Female	25	35	84%	Y	N
6	64	Male	33	39	95%	Y	N
7	52	Male	18	35	77%	Y	Y
8	63	Female	7	43	81%	Y	Y



- Safety data from Cohorts 1 and 2, in tandem with PK data, have supported dose escalations to higher doses of prosetin.
- To date, plasma levels of prosetin have increased in a predictable, dose-related manner in both healthy volunteers and ALS participants. Open-label dosing in Part D has shown steady state is achieved.
- A recently completed compatibility study will allow participants ongoing in Part D to switch to feeding tube administration, if needed.

Discussion and Conclusions

- A growing body of literature suggests that MAP4K inhibition can broadly prevent ALS motor neuron degeneration under both exogenous and endogenous stress conditions[2,3,4].
- Prosetin is a potent, orally available, CNS-penetrant MAP4K inhibitor being evaluated in a hybrid Phase 1 clinical trial designed to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of prosetin in healthy volunteers and people living with ALS.
- In Parts A and B of PRO-101, in single and multiple ascending doses in healthy volunteers, prosetin was safe and well-tolerated with a predictable and consistent pharmacokinetic profile.
- Parts C and D are ongoing at sites in Canada, the United States, and the Netherlands. Dose escalations have been supported by clinical safety and PK data from Cohorts 1 and 2. Next steps will be determined based on review of completed Cohort 3 safety and PK data.

Acknowledgements and Disclosures

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EF & DS are employees and shareholders of ProJenX. EL, AZ, BS, and HW are shareholders of and consultants to ProJenX. AR, KS, HW, and JQ are consultants to ProJenX. ID serves as the study Medical Monitor. AG and LvdB are Investigators on Parts C and D, and members of the Clinical Advisory Board.

References

1. 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.
2. 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.
3. Wu, C et al. MAP4K4 Activation Mediates Motor Neuron Degeneration in Amyotrophic Lateral Sclerosis
Cell Rep (2019) doi: 10.1016/j.celrep.2019.01.019
4. Liu, M. et al. Screens in aging-relevant human ALS-motor neurons identify MAP4Ks as therapeutic targets for the disease. Cell Death Dis (2024) doi: 10.1038/s41419-023-06395-7