Study PRO-101: Experience implementing an ALS community advisory board in early phase drug development

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1. ProJenX, New York, NY | 2. Project ALS, New York, NY | 3. ProJenX Community Advisory Board, New York, NY | 4. Columbia University, New York, NY

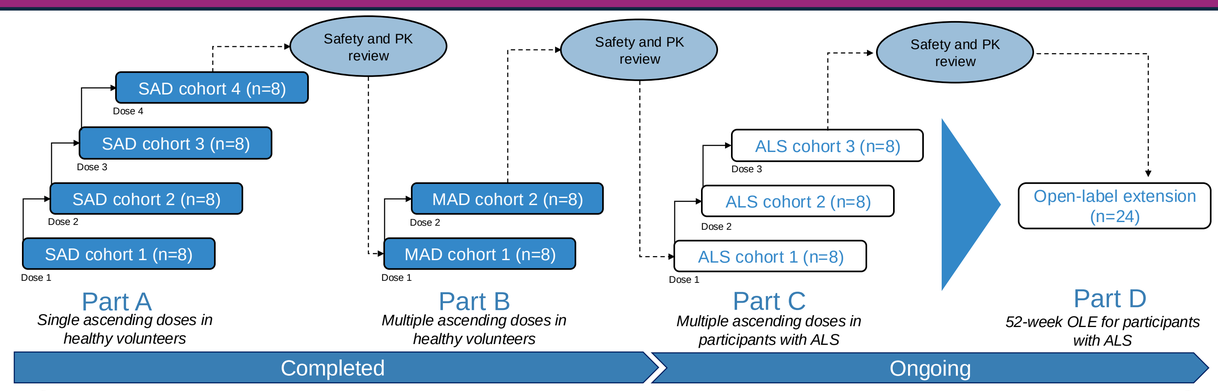
ProJenX

Background

- ProJenX is developing prosetin, a novel, specific, highly potent, CNS-penetrant MAP4K inhibitor, for ALS[1].
- In preclinical models of ALS, prosetin protects motor neurons against endoplasmic reticulum stress and other well-established drivers of ALS disease pathology[1,2].
- We are evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of prosetin in healthy volunteers and people living with ALS in the Phase 1 clinical trial PRO-101 (NCT05279755).
  - Parts A and B, which respectively evaluated the safety, tolerability, and PK of single and multiple (14-day) ascending doses of prosetin in healthy volunteers, have been completed.
  - Part C, a randomized, placebo-controlled, multiple (14-day) ascending dose study in people living with ALS, and Part D, an optional 52-week open label extension for participants who complete Part C, is enrolling at sites in Europe and Canada.
- ProJenX formed a Community Advisory Board (CAB) to provide guidance and expertise from those with lived experience for PRO-101.

1. 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.
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

PRO-101 Study Design



CAB ROLE

Following pre-IND regulatory feedback which necessitated a single dose portion of PRO-101, CAB recommended hybrid study that would enroll people with ALS at a multiple-dose stage, preferably including a long-term OLE.

ProJenX Community Advisory Board

Greg Bauer
ALS gene carrier
Collegeville, PA

Layne Oliff
Dx PLS in 2017, ALS in 2020
Plainfield, NJ

Gwen Petersen
Dx ALS in 2018
Southport, CT

Joseph Porrello
Dx ALS in 2022
Las Vegas, NV

Gretchen Roy
ALS caregiver
Wichita, KS

Nadia Sethi
ALS caregiver
Camarillo, CA

Michele Stellato
Dx ALS in 2020
Nutley, NJ

ProJenX CAB Founding Principles

1. Formed at Inception
No decision has been made in the prosetin preclinical or clinical development program without CAB input.

2. Board Diversity
The CAB includes a diversity of ALS experiences and disease stages, from gene carriers to those living with ALS and caregivers.

3. Transparent Communication
The CAB has access to all core program / study documents and is updated with all key program milestones, including positive news and challenges.

4. Active Role
ProJenX endeavors to incorporate CAB recommendations into the prosetin development program wherever possible.

Key Endpoints: PRO-101 Parts C and D

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

CAB ROLE

CAB advised that LPs can be acceptable if CSF is necessary for more robust scientific readout

CAB provided recommendations for LP best practices, including insights from members' own experience and existing community resources

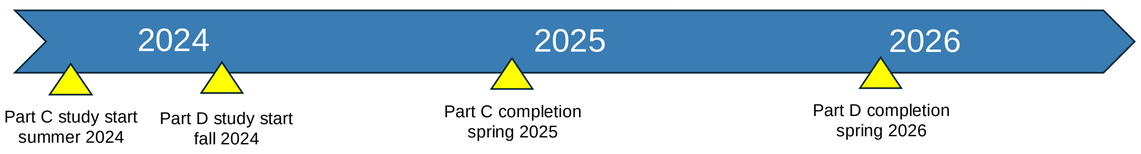
Study Status and Timeline

CAB ROLE

When an initial *partial clinical hold* in the US limited dose levels in PRO-101, the US-based CAB voted to initiate sites in Europe and Canada

CAB unanimously recommended conducting PRO-101 at limited # of well-established Ph. 1 clinical sites, then expand to geographic access at Ph. 2

Study Sites in Canada, Europe, US



CAB Recommendations and Considerations

1. Transparency
Set clear expectations for:
(1) CAB role: what is the scope of the board? What can the board change?
(2) Development program: advisors need to understand potential risks (regulatory challenges, safety risks, etc.) to give effective input.

2. Leveraging Community Experience
ProJenX community advisors bring concrete expertise to their role. Integrating best practices—and avoiding worst practices—based on advisors' extensive clinical research experience can improve recruitment, retention, and quality of data in ALS clinical studies.

3. Education
Removing the "black box" feeling of drug development is essential for advisors to be effective. The CAB should be able to understand the scientific rationale behind eligibility criteria, study procedures, etc., in PRO-101 in order to advocate more broadly. Education builds trust.

4. Regular Updates & Meetings
The CAB meets biannually, and ad-hoc meetings are held to discuss emerging data and events. To ensure accessibility, meetings are held virtually and are 60-90 minutes long. Meetings are recorded, with opportunities to provide written feedback if attendance is not possible.

5. Integration with ProJenX Team
Community advice should be heard beyond a patient advocacy team. To ensure that CAB advice is integrated into the prosetin development program, CAB meetings include the ProJenX CEO, scientific founders, and regulatory and clinical consultants as relevant.

PRO-101 Interim Data: Parts A and B

To date, 48 healthy volunteers have completed study PRO-101. Of these, 36 received either single or multiple doses of prosetin. No participants discontinued the trial prematurely.

Safety assessments, which were performed at pre-specified timepoints throughout the study, are summarized in Table 1. Single and multiple dose pharmacokinetic data is summarized in Figure 1.

Table 1. SAFETY ASSESSMENTS: PARTS A AND B

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

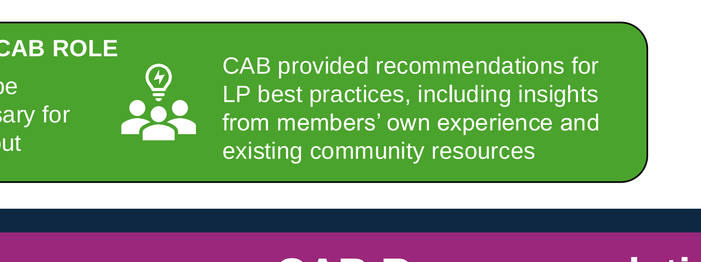


Figure 1. SINGLE AND MULTIPLE DOSE PLASMA PHARMACOKINETICS

Healthy volunteers (n=6/cohort) were administered (a) a single dose of prosetin at 0.03, 0.06, 0.12, or 0.24 mg/kg dose levels, or (b) a single daily dose of prosetin at 0.06 or 0.10 m/kg dose levels once daily over 14 days. Plasma levels of prosetin increased with dose in a modestly supra-proportional manner. Low intra-subject variability and clear separation in exposure between each dose level was observed.

CAB ROLE

CAB reviewed this data in real-time alongside ProJenX team and scientific/clinical advisors, to fully understand the drug profile prior to people living with ALS being treated with prosetin.

Discussion and Future Directions

- PRO-101 is 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 doses studied to date, prosetin is safe and well-tolerated, with a predictable and consistent pharmacokinetic profile.
- The ProJenX CAB has provided concrete feedback to help steer critical decisions in the phase development of prosetin.
- As the prosetin clinical development program continues, ProJenX will grow the CAB to integrate new perspectives, including the addition of members from geographic regions beyond the United States.
- A formal CAB that provides regular review and feedback can be efficient, effective, and can help overcome challenges along the drug development pathway. Future drug development programs would benefit from early partnership with a CAB.

Acknowledgements and Disclosures

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EF is an employee and shareholder of ProJenX. VE is a Board Director at ProJenX. MS, AR, and HW are consultants to ProJenX. GB is an advisor to Abbvie. NS is a consultant to Biogen, Cytokinetics, Sanofi, ALS TDI, Ionis, and Merck, and is past employee of ALS TDI. JA has participated on an advisory board for ProJenX, Neurosense, and Akava, a previous consultant to Biogen, Amylyx, Cytokinetics, Appellis, Wave, and Revalasio , and declares research funding (paid to their institution) from Biogen, Cytokinetics, Amylyx, Prilenia, Denali, and Calico.