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The Honorable Members of the Application Review Subcommittee (ARS)
Independent Citizens Oversight Committee (ICOC)
California Institute for Regenerative Medicine (CIRM)
601 Gateway Blvd, Suite 400
South San Francisco, CA 94080

Subject: Response to Review Summary and Support for PDEV-19154 Application (An UNC13A Targeting Antisense Oligonucleotide (ASO) Treatment for ALS)

We appreciate the comprehensive review of our PDEV plan, which confirms the project's proportionate scope, strong chemistry, relevant preclinical data, and suitable vendor selection. Our responses below focus on clarifying project details and mitigating moderate vulnerabilities related to clinical execution, quality systems, and regulatory readiness.

I. Regulatory and Technical Readiness (CMC & Biomarkers)
We have received positive pre-submission advice from both the FDA and BfArM, clearing the path for both IND and CTA submissions. Our GMP manufacturing is guided by two expert CMC consultants: Marc Lemaitre (Drug Substance) and Geertje van Beeck (Drug Product), who bring many years of ASO development experience.

- Analytical/Biomarker Vulnerability Clarification: As part of our TRAN1 (TRAN1-16013) project activities: the analytical method qualifications for the Drug Substance (DS) are complete, and Drug Product (DP) qualifications are underway; both with very competent CDMOs. The biomarker plan includes built-in redundancy via a synapse-focused CSF protein panel, ensuring an independent and validated assay will be ready without competing for CMC resources. The biomarker/bioanalytical assays are being developed by two very experienced CROs.
- DS Pooling Strategy: The process of combining fractions from two synthesis batches into a master pool is a standard processing method. Purity is strictly controlled through in-process testing prior to ultrafiltration, ensuring a homogenous, GMP-compliant batch and will not create regulatory risk.
- DP Aseptic Process: The aseptic process for manufacturing the active and placebo GMP batches is qualified by routine media fill validation covering worst-case conditions, which are repeated twice annually at the selected GMP facility.
- IND filing timeline: We appreciate the feedback and plan to formally extend the IND submission timeline to 6 months. The positive pre-IND and BfArM feedback has already significantly de-risked the submission process. Bryan Boggs (Head of Regulatory/Project Lead) will be responsible for the regulatory strategy, supported by a dedicated full-time Regulatory Affairs Writer, ensuring timely completion.

II. Operational Execution and Bandwidth Mitigation

The concern regarding organization size and the clarity of clinical operations execution skills is addressed by targeted hiring and strategic outsourcing:

- Clinical Leadership: We are actively recruiting a full-time VP of Clinical Operations (a budgeted position) to assume sole responsibility for all execution, managing CROs, site contracting, and routine trial management.
- Team Strength: Our success is validated by the successful partnering of our PIKFYVE ASO program with Takeda. Clinical and regulatory decisions are governed by the VP of Clinical Operations and Bryan Boggs, Head of Regulatory/Project Lead, ensuring experienced oversight.
- CMO/CRO Network: We have selected a clinical CRO who will be responsible for both California and international site clinical selection and activation, leveraging the expertise of two experienced CDMOs and CROs for deployment of the drug supply and validated clinical biomarker assays. This model for small biotechs entering Phase I is proven. We have already engaged with a candidate Chief Medical Officer (CMO) on a consulting basis, to be hired full time as the program advances in clinical development.

III. Quality and Regulatory Compliance

- Quality/QMS Mitigation: To address the vulnerability in our still-developing internal QA/QMS capacity, we have proactively contracted a firm for dedicated QMS services and budgeted for an independent QA Consultant. This robust, external framework provides compliance oversight during the IND build phase.

IV. Clinical Site Strategy and Diversity

Our clinical operational plan is clear, and our commitment to diversity is fully operationalized:

- Site Strategy: US site activation will target the CIRM Alpha Clinics Network (e.g., UC Irvine, USC + CHLA). We will file the EU CTA via the CTIS system. For European sites, we will work with the TRICALS consortium.
- Diversity Outreach: To ensure inclusive intent translates to proportional participation, our strategy leverages CIRM's Patient Support Program (PSP) & Community Care Center of Excellence (CCCE) for recruiting patients from historically underrepresented groups. We also maintain close relationships with national advocacy groups, including The ALS Association and ALS Network, whose extensive reach ensures a broad and diverse patient base.

With best regards,

Sam Alworth, MBA, MS
CEO and Co-founder, AcuraStem, Inc.