60 Leveroni Court
Novato, CA 94949
Phone: 415-483-8800

January 30, 2025

Dear CIRM Independent Citizens' Oversight Committee (ICOC),

Re: Letter of support for CLIN2 17091

I am writing on behalf of Ultragenyx, a California-based biopharmaceutical company committed to bringing novel products to patients for the treatment of serious rare and ultrarare genetic diseases. We have built a diverse portfolio of approved therapies and product candidates aimed at addressing diseases with high unmet medical need and clear biology for treatment, for which there are typically no approved therapies treating the underlying disease.

I strongly support this Committee to reassess the review of the CLIN2 17091 and urgently approve the grant of a transformative gene therapy program for Spastic Paraplegia 50 (SPG 50) to treat children in California.
While CIRM has assured the community of its support, recent actions, such as the rejection of a transformative gene therapy program for SPG50, tell a different story. SPG50 is a devastating neurodegenerative disorder that causes paralysis and severe developmental challenges, yet remarkable grassroots efforts started by a loving father have led to promising treatments, including an upcoming Phase III trial. Despite this, CIRM's review process lacked expertise in gene therapy and rare diseases, undermining the program and the patients it aims to help.

Elpida Therapeutics, a California-based organization born out of CIRM's initial encouragement, has become a leader in rare disease research, employing Californians and collaborating with world-class institutions like Cedars-Sinai, Boston Childrens Hospital, UT Southwestern Medical Center and the NIH, and have also committed per your request an additional $10 million to match.
Yet, the denial of Elpida's funding application sends a troubling message: that CIRM no longer prioritizes rare diseases or brain-targeted gene therapies.

The cost of the grant request Elpida proposed for the Phase III trial, with 8x dosed patients and 16x controls is appropriate and necessary.

- This is a Phase III study designed to lead to BLA and requires a commercial-grade vector which is much more than most trials leverage for earlier phases but is required for FDA approval.
- The 16x control patients must be followed for five years, just like the treated patients.
- The regulatory and operational rigor of a Phase III trial is significantly higher, necessitating a CRO.
- The cost estimates account for the full scope of compliance, long-term follow-up, and manufacturing at scale, ensuring trial feasibility.

Enrolling patients will be possible with a small indication.

- Elpida provided a real-world matching document with de-identified names of exact matches to the controls and 8x patients.
- There are over 20 children globally who meet the enrollment criteria, and they continue to identify 2-3 new patients each month.

Elpida should continue advancing to Phase III and not be further delayed.

- Rare disease leaders recognize that slowly progressing diseases have a single shot at approval, requiring innovative trial designs.
- The FDA has already approved the Phase III trial to proceed.
- Waiting until the full completion of Phase I/II would delay Phase III by another four years, which is why we are moving forward now.
- Advancing directly to Phase III maximizes the potential for early intervention and regulatory alignment, expediting patient access to treatment.

I have been involved in the development of this program alongside my colleagues from its inception, contributing to both the pre-clinical and clinical aspects. The successful execution of the Phase 1/2 trial has paved the way for the development of a Phase III trial, with the goal of seeking regulatory approval for this therapy, thereby making it accessible to all patients, not just those enrolled in the clinical trial.

As a consortium of drug developers for rare diseases, we dedicated years of work to meticulously designing trials, engaging in multiple discussions with the FDA to refine the clinical design and select appropriate endpoints. Having a Phase III trial approved by the FDA for a rare indication is a significant achievement, marking a remarkable milestone not only in the advancement of this therapy but also in demonstrating the flexibility of regulatory authorities.

I respectively urge approval of the SPG50 grant. Without action, children with SPG50 in California could lose access to life-changing treatments, and the rare disease community could lose faith in one of its most vital supporters.

A sincere thank you for your leadership and commitment to rare disease patients.

Dr. Emil Kakkis
President, CEO and Founder, Ultragenyx