November 16, 2022

Dear Families Living with CDKL5 Deficiency Disorder,

First and foremost, we hope this update finds you and your families continuing to stay safe and healthy.

Ultragenyx recently provided updates about our CDKL5 Deficiency Disorder (CDD) research program to the scientific community at the 2022 CDKL5 Forum in Boston, and we have enclosed these updates to ensure all that families and patient organizations also have access to this information. We will host a webinar with the International Foundation for CDKL5 Research (IFCR) to expand upon these updates and answer your questions as part of our commitment to providing the community with timely information.

What is the status of UX055?

Ultragenyx remains in the pre-clinical stage of development for UX055, our investigational gene therapy program for CDD. UX055 is designed to deliver a fully functioning copy of the human *CDKL5* gene to neurons. The goal is for those neurons to use the new gene to produce functional CDKL5 protein. We are using Adeno-Associated Vector Serotype 9 (AAV9) to transport the *CDKL5* gene into neurons in the brain.

Pre-clinical research is required to assess the safety and potential efficacy of a therapeutic candidate, and this research phase needs to be successfully completed before any human trials can begin. Dr. Sharyl Fyffe-Maricich, the UX055 non-clinical lead, presented learnings from studies recently conducted in animal models that aimed to understand key research questions, including 1) What factors lead to the maximal targeting and transduction of neurons across the brain after AAV9 delivery? and 2) What routes of administration best target neurons across the brain when delivering AAV9 gene therapy? Dr. Fyffe-Maricich will discuss these results at the upcoming webinar.

Pending the outcome of additional non-clinical studies, we expect to submit an Investigational New Drug (IND) application to the US Food and Drug Administration (FDA) in 2023. An IND is required before any clinical trials involving patients can be conducted. The submission and approval of an IND is an iterative process that requires input from regulatory agencies. In addition, gene therapy manufacturing is a critical component to ensure that we can produce safe and efficacious therapies to the patients that need it most. Until all pre-clinical and manufacturing testing has been completed, we cannot be assured the program will advance into clinical testing.

When and where will clinical trials take place?

Importantly, an IND submission does not guarantee that clinical studies will occur. Ultimately, sponsor companies must seek approval for their submission from a regulatory agency (such as the FDA) to conduct a first-in-human clinical trial. A regulatory agency may not approve an IND as it was submitted, and additional regulatory interactions may be required following the initial review of the IND. If an IND is approved, ethical review and approval of the final clinical trial design is required from each clinical site running the study, which also takes time; in other words, the first patient enrolled does not occur immediately following IND approval.

Since patients with any rare disease are by definition uncommon in most populations, this typically requires that we conduct trials in multiple countries. It is common for most clinical development programs to begin in a smaller number of countries and then expand into other countries.

How are CDD families informing our research?

Our team has been focused on several initiatives that involve learning from patients, caregivers, and advocates and these efforts are actively shaping our research. Recent examples include hosting three insights meetings with caregivers and patient advocates, as well as one-on-one interviews with ten caregivers. These efforts are helping us to understand the experiences of the CDD community, including:

- Perceptions and thoughts on what life is like for a person living with CDD and how symptoms of CDD may impact daily life
- Perspectives on current treatment, potential treatment, unmet medical needs, and how these perspectives have shifted since diagnosis, with a focus on building upon information published in "The Voice of the Patient Report: CDD"
- Expectations of gene therapy and goals for a new treatment option
- Knowledge of and perspectives on gene therapy and clinical trials, including what information families may need to consider to participate in an early-stage investigational study
- Knowledge of and perspectives on different routes of administration to deliver AAV9 gene therapy

The Ultragenyx CDD team would like to express our sincere gratitude to those families who have helped us deepen our understanding of CDD. We know that time is invaluable in the lives of rare disease patients and families and our goal is to advance research as efficiently and fast as possible while ensuring development of a safe treatment option for CDD. As Dr. Emil Kakkis, Ultragenyx's CEO and Founder, expressed at the Forum, the development of new treatments for rare diseases is hard, and we will all be in this together. Many unforeseen challenges will occur that we must solve to advance research and getting to a safe and effective drug will take time, fortitude, and collaboration with the community.

We understand that you may have questions and look forward to expanding on this letter in a future webinar with IFCR. We will be in touch with the community with more information as the webinar planning advances. In the meantime, please visit our Patient Advocacy website at UltraRareAdvocacy.com to access rare disease education and tools and follow us on Facebook at Facebook.com/Ultragenyx.

Sincerely,

Kristin Voorhees

Director, Patient Advocacy