May 26, 2021

Dear Families Living with CDKL5 Deficiency Disorder,

While some of you may already know our company from previous presentations at scientific meetings, we are now pleased to provide your community with a more formal communication regarding Ultragenyx's research on CDKL5 deficiency disorder (CDD).

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

We have completed key efficacy studies in both the mouse model and a model of human neurons derived from induced pluripotent stem cells (iPSCs) from CDD patients. IPSCs can be generated by reprogramming skin cells from patients into pluripotent stem cells that can then be differentiated into many different types of cells including neurons. Our iPSC model is a very powerful tool because it enables us to directly test our potential drug product in neurons from CDD patients. We have seen that our AAV9 vector is efficacious in both model systems, which gives us confidence as we move forward toward our non-clinical safety studies. We are also working hard to improve the efficiency of gene transfer to neurons across the brain by conducting studies in non-human primates. These studies are critically important because they will help us understand what we need to do to enable widespread gene transfer in a much larger brain (such as a human brain) compared to the rodent.

To complement UX055 efforts, as well as the important work being done by the International CDKL5 Clinical Research Network (ICCRN) and others in the academic and advocacy communities, Ultragenyx has partnered with Allstripes, a research platform dedicated to rare diseases, earlier this year. Together, we are conducting a research study using the de-identified data shared by the Allstripes CDKL5 community. Two key goals of this study are to better understand what it's like living with CDD and how patients interact with and use the healthcare system. For example, some of the key research questions we hope to answer include:

- How are people living with CDD diagnosed?
- What is the medical journey of people living with CDD?
- What are the types of medical tests used to diagnose, monitor and manage CDD?
- What symptoms, health complications and other conditions are associated with CDD?
- What medications are commonly used by patients and what treatment plans do people living with CDD follow?
- What types of healthcare providers and specialists do patients visit, and how often?

Through this research, we will be studying up to 35 patients from the Allstripes CDKL5 community who live in North America. We thank those families for their contributions, as well as the International Foundation for CDKL5 Research (IFCR), which has been actively involved in helping AllStripes conduct research on CDD.

Both AllStripes and Ultragenyx strongly believe it's important that participants in research studies like this have the opportunity to learn about the research results and track their impact. We are committed to sharing learnings with the CDKL5 community and will provide updates on the progress of this study as we are able to. Research takes time, so we expect it may be a little while until we have information to report.

In addition, our Clinical Outcomes Research and Evaluation (CORE) team is conducting a landscape review of completed and ongoing research in CDD and, to the extent permitted by applicable regulations, will also soon conduct 1:1 interviews with CDD experts and families living with CDD. The purpose of the landscape review is to understand and acknowledge the important research already being conducted in CDD and determine additional work that might be needed to support Ultragenyx's clinical program. The interviews will also build upon existing research in CDD, as well as help Ultragenyx to advance the development of a CDD Conceptual Model that will support our interactions with regulatory agencies. The CDD Conceptual Model will include all of the important concepts in CDD related to signs, symptoms and physical, social and emotional impacts to daily living that are discovered through the literature and discussions with clinical experts and families living with CDD. We will inform the community when the potential opportunity to participate in the interviews becomes available.

We are also proud that three Ultragenyx team members were invited to participate as members of the External Advisory Committee for the NIH/NINDS funded U01 U01NS114312 "*Multi-Site Validation of Biomarkers and Core Clinical Outcome Measures for Clinical Trials Readiness in CDKL5 Deficiency Disorder*" project. This project involves the ICCRN, a network that aims to develop appropriate tools for future clinical trials in CDD. Specifically, the goals of the project are to refine and validate appropriate quantitative clinical outcome measures and biomarkers and conduct a multi-site clinical trial readiness study through the ICCRN to ensure that they can be successfully implemented.

While this may not have been widely known, Ultragenyx has been committed to discovering and developing a potential new treatment for CDD for the last 3 years. Advancing our program through the collaboration with Allstripes and the work being led by our CORE team are in line with our continued commitment to CDD.

We look forward to updating you periodically and thank you for everything you do to support the CDD community and advance the awareness and knowledge of CDD. These efforts will be key for any future success in developing treatments.

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,

DocuSigned by:
Jessica Riviere
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Jessica Riviere

Vice President of Patient Advocacy and Patient Engagement