October 6, 2021

Dear Members and Friends of the Association for Creatine Deficiencies (ACD),

We hope this update finds you and your families safe and healthy.

We have received questions from the community about the status of our CTD clinical development program and wanted to ensure that you have access to timely information. Thank you for your interest in our CTD development program and ongoing research.

UX068

As you know, Ultragenyx has been conducting pre-clinical studies over the past several years to assess the safety of an intravenous (IV) formulation for treatment of patients with CTD. This small molecule prodrug is designed to carry creatine across membranes and into neurons in the absence of a functional creatine transporter molecule. Our goal is to maximize delivery of intact prodrug into the brain in order to boost functional cerebral creatine levels.

An important update is that we have decided to expand our research to study an oral formulation. We made this decision as a direct result of insights collected from patients and families that an oral formulation would be preferrable. We learned this through a series of advisory discussions in 2020 and 2021 aimed at understanding the experiences and perspectives of caregivers. Pre-clinical work is ongoing to determine the magnitude of creatine that we can safely deliver via this route of administration.

Part of this research includes working to identify a dose of an oral formulation that is both safe and likely to provide optimal efficacy, and this is a very important time in the pre-clinical phase. Some of the questions we're currently focused on answering as part of this expanded pre-clinical work include:

- What is the best way to deliver enough prodrug into the brain to achieve optimal levels of cerebral creatine?
- What oral formulation is the safest for patients and best tolerated?
- How does the drug get absorbed, distributed, metabolized, and/or excreted?
- What are potential dosing ranges?

Now that we have shifted our focus to an oral administration option, the timeline of our pre-clinical work and, ultimately, a future IND submission is significantly impacted. (An Investigational New Drug application, or IND, is a necessary step before patients can be dosed with an investigational drug treatment as part of a clinical trial.) We currently do not have an updated timeline for our IND submission based on this new course of

action. This stage of drug development requires extensive testing, and it is very common for pre-clinical work to take a year or longer to complete.

We understand that this news is disappointing and may be unexpected due to previous information communicated to the CTD community. Drug development is a dynamic process that takes time and requires flexibility, given the number of variables involved and the nature of early pre-clinical research. Despite these delays, we remain firmly committed to the CTD community and the UX068 program and we are full speed ahead in terms of our dedication to the program. Our relationship with ACD and the CTD community is of the utmost importance, and we will share new information once we have results from ongoing studies.

Ultragenyx is grateful to caregivers for sharing information that has informed our therapeutic development. We are in the process of establishing a CTD Caregiver Leadership Council to help guide the advancement of Ultragenyx CTD research and patient advocacy and patient engagement efforts. The Leadership Council will help us to further understand the family perspective and identify knowledge gaps, educational needs, and opportunities for Ultragenyx to partner with the CTD community. We look forward to sharing more information about this initiative in the future.

We are committed to advancing CTD research, conducting the ongoing Vigilan study and preparing the Vigilan study's first manuscript. (You can read a recent update about the Vigilan study here.) We will share future updates with you as new information becomes available. In the meantime, you can access and download rare disease education and tools on our Patient Advocacy website at UltraRareAdvocacy.com and follow us on Facebook at Facebook.com/Ultragenyx.

Sincerely,

DocuSigned by:
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Vice President of Patient Advocacy and Patient Engagement