ASSOCIATION FOR CREATINE DEFICIENCIES

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Ultragenyx Town Hall Follow-Up Questions

Thank you to Ultragenyx for providing the following answers to questions submitted during ACD's December 2021 virtual town hall discussion with Ultragenyx. Answers to all other questions submitted before the town hall were addressed during the event which can be viewed on ACD's YouTube channel.

1. When we attended a symposium in Rotterdam a few years ago, the researchers confirmed to us that an oral drug could not cross the Blood Brain Barrier. How would Ultragenyx medical treatment be efficient?

   In general, it is challenging to design a drug which can cross the blood-brain barrier (BBB) efficiently, however it is not accurate to suggest that an oral drug could not cross the BBB (as there are many examples of small molecule treatments which are able to pharmacologically impact brain target selectively1). Our investigational UX068 prodrug was developed with this challenge in mind and was designed to enable diffusion across the BBB and into the brain. We have been able to demonstrate the brain distribution with our prodrug in animal studies which have been visualized through imaging, as well as quantified bioanalytically.

   [1] ***Nau 2010, Clin Microbiol Rev.***

2. What do we need to do to start a communication with Ultragenyx to provide our input regarding our experiences and progress of our child with CTD. Our child (son) has been a part of the NIH family history study and we are committed to help the community to find solutions/progress for this disease. What do we need to do to help provide data/information to Ultragenyx directly to help in data collection of a person with CTD (SLC6A8)?

   Thank you for your interest in sharing your experiences with Ultragenyx. We are grateful for all contributions to the Vigilan study – it would not be possible to study the natural history of CTD without participation from families like yours - and we also appreciate your willingness to find other ways to participate in the research process.

   Ultragenyx established a CTD Caregiver Leadership Council in the fall of 2021 with the goal to glean insights from the CTD patient/caregiver community to help guide the advancement of Ultragenyx CTD research and patient advocacy and patient engagement efforts. It's important that the Council reflects the diverse perspectives of people living with CTD across different age ranges in both males and females and that Council members represent various global regions. There is currently an opening on the Council for a caregiver of an adolescent male or female who is living in Canada or Europe. Please contact Kristin Voorhees at kvoorhees@ultragenyx.com if you are interested in learning more.

In addition, Ultragenyx will soon conduct one on one interviews with caregivers who speak English and live in the US to explore the symptoms and daily impacts of CTD, build on existing data from all previous Ultragenyx CTD research and inform long-term endpoint development strategy. Please contact Natasha, Clinical Outcomes Solutions Study Coordinator, by phone at 520-325-9510 or by email at natasha.schumacher@clinoutsolutions.com if you are interested in learning more.

We are also in the early stages of determining appropriate and timely opportunities to work with ACD to leverage their CCDS registry and include topics and questions that may help to inform Ultragenyx's research. We look forward to sharing more information in the future as the discussions progress.

3. How close to IND application was the IV route of drug research?

   Ultragenyx did not file an IND for the UX068 program. Ultragenyx has been actively working towards an IND submission, which included interacting with the FDA through a pre-IND meeting. The purpose of this interaction was to gather FDA feedback on general programmatic questions related to manufacturing and plans for non-clinical and future clinical development and took place throughout 2020 and 2021. This type of pre-IND meeting is standard for many drug development programs of this stage.

   Importantly, the decision that Ultragenyx made to focus on an oral route of administration instead of IV (and thus an impact on a future IND filing) was not part of this regulatory correspondence. There was still a considerable amount of work needed prior to filing an IND when the change was made. While the switch to an oral formulation may have impacted our IND submission somewhat, we anticipate that it will result in an overall smoother path towards IND filing.

4. Will there be liquid oral or will it be powder or pill or chewable?

   This decision has not yet been made. We are currently in the process of selecting the optimal formulation (such as a capsule, tablet, powder, or other possible oral formulation) and this important decision will be based on patient population and disease characteristics. This work is led by our Chemistry, Manufacturing, Controls (CMC) team and is executed in close collaboration with Clinical Development, Patient Advocacy and Clinical Outcomes Research and Evaluation (CORE) to ensure that patient and family perspectives are incorporated whenever possible. We shared

examples of how we will collect patient and family perspectives regarding the oral formulation of investigational UX068 in the town hall on December 17, 2021; you may consider reviewing some of that information to learn more about how we will collect community feedback.

5. In saying if it hits one neuron who's to say that that is the only neuro it hits or will there be a way to target different neurons

   The investigational UX068 prodrug distributes throughout the brain by passive diffusion, so one "dose" of prodrug is anticipated to reach many neurons per treatment. However, the lack of creatine transporter protein in CTD neurons unfortunately prevents any creatine recycling or re-uptake to different neurons once it is released. This suggests that a neuron is expected to benefit from the energy production associated with the prodrug's delivery of creatine in that instance, but once absorbed within a neuron, this creatine is unlikely to go on to help other neurons because of its inability to cross without transporter proteins being present.

The recording of the town hall event can be found on ACD's YouTube Channel.