May 21, 2021

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

We hope this update finds you and your families continuing to stay safe and healthy. Below please find important updates related to our program for creatine transporter deficiency (CTD).

UX068

Ultragenyx remains focused on crafting the clinical development program for UX068, our investigational treatment for CTD. Information learned directly from families living with CTD and clinicians managing CTD is actively informing our clinical development program, which includes decisions related to the potential design of a future clinical trial. For example, our Clinical Outcomes Research and Evaluation team concluded its caregiver burden of disease survey last summer and this survey data will be coupled with a literature review and 1:1 interviews with clinicians and caregivers focused on signs, symptoms and impacts of CTD. We also conducted an advisory board and interviews with caregivers to achieve a broad understanding of patient and family perspectives across different age ranges.

In addition, one of the primary areas of work for the UX068 team has been and continues to be conducting the mandatory safety activities which the U.S. Food and Drug Administration requires in order for us to move into the clinic. Pending the results of the safety studies, we plan to file an Investigational New Drug (IND) application in 2021. This application is a necessary step before patients can be dosed with an investigational drug treatment as part of a clinical trial.

Vigilan Study

Vigilan, an observational study focused on understanding the natural history of CTD over a period of 48 months, currently has 50 patients enrolled at nine sites, including one in Canada and eight in the U.S. The following chart describes the participant breakdown of each site. Please note that Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio was previously a study site, and closed on 08/28/2019. However, Dr. Kim Cecil, a spectroscopist at the University of Cincinnati Department of Pediatrics continues to lend her expertise to the study. Currently, Duke is in the process of closing their site and we are working closely with Duke to help ensure families who are interested in continuing with the study can be transferred to another site.

If you are enrolled in Vigilan and have questions about the study, please contact your site directly.

Study Site	Number of Patients Enrolled
University of California San Diego, La Jolla, California	5
University of Utah, Salt Lake City, Utah	1
Texas Children's Hospital, Houston, Texas	6
Rush University Medical Center, Chicago, Illinois	6
Duke University Medical Center, Durham, North Carolina	5
National Institutes of Health Clinical Center, Bethesda, Maryland	9
Children's Hospital of Philadelphia, Philadelphia, Pennsylvania	7
Boston Children's Hospital, Boston, Massachusetts	4
The Hospital for Sick Children, Toronto, Ontario, Canada	7

We know that some families have had questions about the impact of COVID-19 on Vigilan. During the height of the COVID-19 pandemic, all sites were closed for non-interventional studies such as Vigilan, to ensure the safety of patients. As the pandemic has evolved, Vigilan has experienced some minor impacts. This was expected due to the impact of COVID-19 on the overall healthcare system, such as hospital staff being reassigned to meet COVID-19 needs. As parts of North America begin to re-open and adjust to a new sense of normalcy based on state and institutional policies, the impacts of COVID-19 on Vigilan sites continue to be dynamic and fluid, however we do not expect COVID-19 to have any major impact on Vigilan.

Ultragenyx is currently focused on analyzing Vigilan data in preparation for the development of the study's first manuscript. We will provide the community with a plain language summary of the scientific publication once the manuscript has been published and look forward to sharing additional updates in the coming months.

Once all participants have completed the Vigilan study, the study records and test results of all the participants will be analyzed together. Ultragenyx will review the results of the study and create a report of the results. Aggregated, de-identified study results will be provided to study participants and available to the public approximately one year after the study has completed.

Scientific Publications

We would also like to share our progress in making information available to the research and family communities.

First, we presented the poster *"Path to Diagnosis and the Caregiver's Perspective on the Impact of Creatine Transporter Deficiency"* at the 2021 American College of Medical Genetics (ACMG) Annual Clinical Genetics Meeting in April. This poster shared results from our caregiver burden of disease survey and a virtual advisory board. In addition, the survey results were presented as a poster titled *"Caregiver Perspectives on the Humanistic Burden of Creatine Transporter Deficiency"* at the Professional Society for Health Economics and Outcomes Research (ISPOR) 2021 meeting in May. This poster included data on seizure frequency and hospitalizations, developmental milestones, receptive and expressive communication and gross and fine motor skills. We provided the CTD community with a summary of the survey results earlier this year and you can access that summary on ACD's website **here**. Ultragenyx plans to publish the full results of the survey in the future.

Ultragenyx is proud of the progress we have made over the past several months and grateful to those members of the CTD community who have contributed to our understanding of CTD through participation in Vigilan and other Ultragenyx research efforts: we could not advance CTD research without you. We are committed to continuing to advance CTD research and look forward to sharing 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:
Jessica Riviere
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Jessica Riviere
Vice President of Patient Advocacy and Patient Engagement