February 16, 2024

Dear Friends,

With Rare Disease Day approaching, I want to take a moment to recognize the incredible strength of the Wolfram syndrome community. The increasing number of patients referred to us highlights the urgency of our work in developing effective treatments. Every day, I receive messages from patients and families looking for updates, which reinforces the importance of our research. This day is an opportunity to raise awareness, push for progress, and reaffirm our dedication to improving care and finding better treatments. I am pleased to share the latest updates with you.

Ongoing Clinical Trial of AMX0035 in patients with Wolfram Syndrome
https://clinicaltrials.gov/study/NCT05676034

We continue working with Amylyx Pharmaceuticals to evaluate AMX0035, an encouraging oral medication aimed at slowing the progression of Wolfram syndrome. The Phase 2 clinical trial began in April 2023, with interim results announced in April and October 2024. The latest analysis in October included assessments at Week 48 and continued to show encouraging outcomes. Among the eight participants evaluated, sustained improvements were observed in pancreatic beta cell function, blood sugar control, and neurological symptoms. C-peptide levels, a marker of pancreatic beta cell function, remained stable or improved in most participants, which contrasts with the typical decline seen in Wolfram syndrome. Encouragingly, measures of vision function also showed stabilization or modest improvement in several individuals. Importantly, AMX0035 continued to be well tolerated, with no new safety concerns reported. These findings reinforce the potential of AMX0035 as a disease-modifying therapy for Wolfram syndrome. Ongoing discussions with Amylyx and the U.S. FDA will determine the next steps toward further development and potential regulatory pathways.
For more details, please visit: https://www.amylyx.com/news/amylyx-pharmaceuticals-announces-positive-topline-results-from-phase-2-helios-clinical-trial-demonstrating-sustained-improvements-with-amx0035-in-people-living-with-wolfram-syndrome

Gene-Editing Therapy

We are making steady progress in developing gene-editing therapies to target the underlying cause of Wolfram syndrome. Our focus is on second- and third-generation gene-editing technologies: base editing and prime editing. These methods offer precise correction of genetic variants with increasing efficiency and safety. To enhance effectiveness, we are testing base editing with engineered DNA-free virus-like particles (eVLPs) and dual adeno-associated virus (AAV) systems. Our research uses brain cells differentiated from patient iPSCs and rodent models carrying WFS1 variants. One of the new variants being studied is WFS1 c.1672C>T (p.Arg558Cys) associated with a mild form of Wolfram syndrome commonly seen in the Ashkenazi-Jewish population. Our goal is to develop a gene-editing therapy that could be available within five to ten years.

Regenerative Therapy for Optic Nerve Atrophy

As most of you know, vision loss from optic nerve atrophy is a major challenge in Wolfram syndrome. We are developing regenerative therapies, especially the use of a neurotrophic factor called MANF. MANF has protective effects against ER stress, a key driver of Wolfram syndrome, and helps support stressed nerve cells. Pre-clinical studies, including experiments with humanized mouse models of Wolfram syndrome, show encouraging results. We are currently refining methods to deliver MANF effectively to the eye. To accelerate this work, we are collaborating with patient organizations to gather input and drive the development of this therapy. By working closely with these organizations, we aim to incorporate patient perspectives into our research and clinical trial design. This collaborative approach strengthens our commitment to making regenerative therapy a viable option

for individuals with Wolfram syndrome. We aim to begin clinical trials for this therapy within the next five to seven years.

Wolfram Syndrome and Related Disorders Clinic

To enhance care for patients with Wolfram syndrome and WFS1-related disorders, we operate the multi-disciplinary Wolfram Clinic at Washington University Medical Center. This clinic delivers expert care to patients from across the United States and worldwide. I am grateful to the Snow Foundation, the Ellie White Foundation, Unravel Wolfram Syndrome, Wolfram Syndrome UK, and the various Wolfram syndrome support groups for their support in connecting patients with our clinic. We offer comprehensive services, including genetic evaluations, counseling, and personalized management plans developed in collaboration with specialists across multiple disciplines. We warmly welcome both international and out-of-state patients.
For more information, please visit our website: https://wolframsyndrome.wustl.edu/

Introducing a Nurse Navigator for Wolfram Syndrome

I am pleased to introduce Ashley Raterman, RN, as our new nurse navigator for the Wolfram syndrome clinic and research programs. She will coordinate our multidisciplinary clinic at Washington University Medical Center, oversee the International Registry for Wolfram Syndrome, and work closely with patient organizations. For any questions, she can be reached at 314-477-1527 or via email at wolframsyndrome@wustl.edu.

Thank you for your ongoing support. We remain committed to advancing research and improving care for those affected by Wolfram syndrome.

Sincerely,
Fumi

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