Pretzel Therapeutics: POLG Foundation Summit Questions from the Community

How can POLG pediatric families be strategic partners and help support the PX578 program?

There are several ways families and partners can help support the PX578 program:

- Participating in registries, such as MitoShare with UMDF, and natural history studies, such as the PIONEER study we initiated in collaboration with UMDF and the POLG Foundation.
- Keeping the lines of communication open through events and forums, such as the recent POLG Summit and other opportunities for dialogue between industry and patients, families and advocates.
- An important event will be the externally-led POLG Patient Focused Drug Development meeting on Nov 17, put together by MitoAction and POLG Foundation. This is meeting features the patient voice to educate the FDA on POLG disease and ensure they hear a first-hand account of the impact this condition has on families and what aspects of POLG disease have the most impact on quality of life.
- And more generally, taking opportunities to voice your experiences living with POLG disease is helpful for everyone, for us as sponsors, for regulatory authorities, etc. At Pretzel, we view patients and caregivers as experts in their own right.

How is Pretzel thinking about the inclusion of children with POLG disease in future development plans, particularly younger children and those with more rapidly progressive disease?

We know that the earlier the age of onset, the greater the severity of POLG disease progression and understand the urgent need to treat young children. We are committed to developing PX578 for ***all*** patients, especially pediatric patients. Within this context, it's important to understand the considerations that factor into our stepwise approach:

- Drug companies typically test investigational treatments in adults before studying them in children to meet regulatory requirements, ensure safety, and generate foundational data.
- Specifically, first-in-class, novel investigational medicines, like PX578, are held to high standards because there are more unknowns. This includes but is not limited to creating appropriate drug product formulations depending on the patient population, conducting adult and juvenile animal safety tests, as well as cell-based and animal efficacy studies, and trials in adults, and then moving to trials in younger age groups.
- Regulatory authorities (e.g., U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA)), generally require initial safety data in adults before pediatric studies can begin. This reflects a long-standing framework designed to protect children as a more vulnerable population.
- Adults provide an acceptable starting point to understand how a therapy behaves in the body and to identify potential side effects. These data inform dosing and safety monitoring for pediatric trials. Children are not "small adults." Because their bodies are still developing, drugs can work differently and carry risks. Studying treatments in adults before dosing pediatric patients may help reduce uncertainty before introducing them in children.
- While PX578 has been tested in healthy adults, we will test it in adults living with POLG disease first, so we understand its actions in the body and gain data on benefits and risks. We then determine how best to dose younger patients to help ensure the dose is safe and can provide benefit.

Even in rare diseases, this stepwise approach helps reduce risk in pediatric research and improve trial design, which increases the likelihood that children receive treatments that are both safe and effective.

What biomarkers or outcome measures are being explored for POLG disease, and how will meaningful clinical benefit for children be measured?

Pretzel follows the science and listens to the patient voice.

- Outcome measures for POLG patients includes ataxia, gait and mobility, peripheral neuropathy, ptosis, seizure frequency and type, loss of independence/activities of daily living and quality of life. For pediatric patients, seizure onset, liver function, development regression, feeding dependance, growth failure and failure to thrive are measures that important to evaluate.

- Biomarkers, such as Growth Differentiation Factor 15 (GDF-15), Fibroblast Growth Factor 21 (FGF-21) and circulating stress-responsive biomarkers of mitochondrial dysfunction can be assessed.

Understanding how these measures change over time may help us understand what is clinically relevant over the course of the disease. In turn, this informs us on what measures to use in various patient populations (including children) and how much time it may take to see a meaningful difference between a treatment's effects on those specific outcomes over time.

How important are POLG registries and natural history studies to Pretzel's development strategy, and are there specific types of patient data families can contribute that would be most helpful?

Registries and natural history studies provide important information to prepare for interventional clinical studies. For example, the POLG Foundation and UMDF recently launched a prospective natural history study of patients with POLG disease (the PIONEER study).

- Pretzel Therapeutics is sponsoring part of the PIONEER natural history study, taking place at sites in the U.S., to characterize biomarkers and clinical outcomes related to disease progression of POLG disease in patients.

- Patients interested in participating in the PIONEER study should register with MitoShare, UMDF's patient driven registry.

What milestones for PX578 should the POLG community realistically be watching for over the next 1–3 years?

- We expect to complete the Phase 1 healthy volunteer study to generate safety and pharmacokinetic data in support of clinical advancement.

- We will initiate a Phase 2 study in adult patients living with POLG disease. We will continue work towards registration & approval, as well as expanding our clinical study activities.

It's important to note that our engagements with global regulatory authorities inform and shape our clinical development path in patients to support approvals and ensure a first- and best-in-class profile with meaningful improvements in clinical and patient reported outcomes.

What if patients are on experimental or unapproved investigational medicines, can one still participate in PX578 clinical trial?

As with most clinical trials, other experimental medications are excluded to ensure a proper understanding of the effects of the investigational medicine being studied.