Results from the HELIOS Trial: A Phase 2 Open-Label Study Evaluating an Oral, Fixed-Dose Combination of Sodium Phenylbutyrate and Taurursodiol in Wolfram Syndrome

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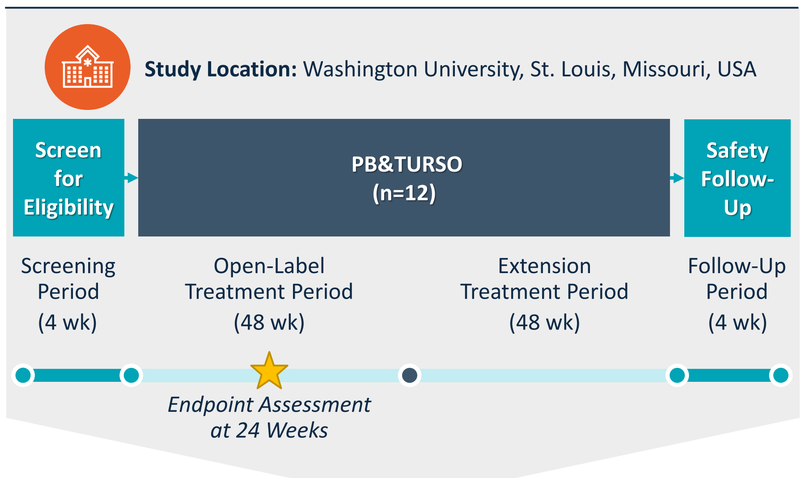
Poster #94

BACKGROUND

- Wolfram syndrome (WS) is a rare, fatal, progressive monogenic disorder characterized by juvenile-onset diabetes mellitus, optic nerve atrophy, diabetes insipidus, sensorineural hearing loss, and neurodegeneration[1-5]
- PB&TURSO is an oral, fixed-dose combination of sodium phenylbutyrate and taurursodiol hypothesized to simultaneously target endoplasmic reticulum (ER) stress and mitochondrial dysfunction[6-7], two pathways critical to the development of Wolfram syndrome[1,8,9]
  - PB&TURSO has demonstrated pre-clinical efficacy in patient-derived cell and mouse WS models[10]
- The phase 2, open-label HELIOS trial is evaluating the safety/tolerability of PB&TURSO and its effects on endocrinologic, neurologic, and ophthalmologic function in Wolfram syndrome

STUDY DESIGN



Key Trial Entry Criteria

- Aged ≥17 years
- Definite diagnosis of Wolfram syndrome[a]
- Stimulated C-peptide level of ≥0.2 ng/mL at Screening
- Insulin-dependent diabetes mellitus due to Wolfram syndrome
- No current GLP-1 agonist use

Trial Efficacy Endpoints

Primary Efficacy Endpoints

- Change from baseline in **C-peptide** (ΔC-peptide, area under the curve [AUC] C-peptide) at Week 24 using 240-minute mixed meal tolerance tests (MMTTs)
  C-peptide is co-secreted in a 1:1 ratio with insulin and is a measure of endogenous insulin secretion and pancreatic beta cell function

Key Secondary Efficacy Endpoints

- Change from baseline in **best-corrected visual acuity** on the LogMAR scale using the Snellen chart
- Change from baseline in **overall time in target glucose** range (70–180 mg/dL) by continuous glucose monitoring (CGM)
- Change from baseline in **hemoglobin A1c (HbA1c)**

Select Exploratory Endpoints

- Clinician-Reported Global Impression of Change[b]
- Patient-Reported Global Impression of Change[b]
- Change from baseline in Most Bothersome Symptom[b]

[a]Documented functionally relevant recessive mutations on both alleles of the *WFS1* gene based on historical test results (if available) or from a qualified laboratory at Screening

[b]Asked to rate participant's change in symptom status since study start using a 7-point scale from 'Very Much Worse' to 'Very Much Improved'

CONCLUSIONS

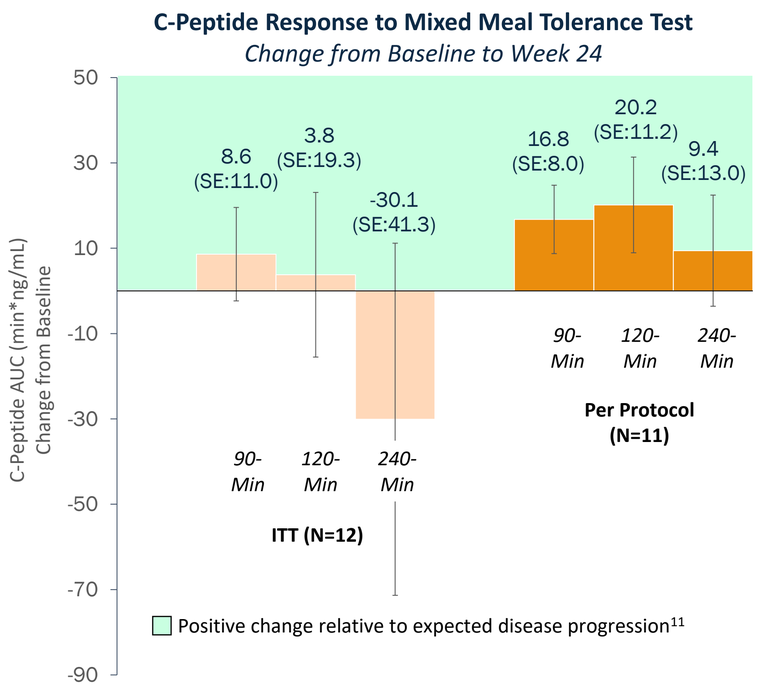
- While the natural history of Wolfram syndrome would suggest pancreatic β-cell function, glycemic control, visual function, and overall symptom burden should worsen over time[11,12], treatment with PB&TURSO instead showed overall stabilization or improvement relative to baseline
- Analyses once all 12 participants have completed Week 48 assessments will provide additional insight
- Results will inform planned Phase 3 program

PB&TURSO is an investigational drug for Wolfram syndrome and has not been approved for use by any health authority (eg, the FDA and EMA).

RESULTS

- The main analysis performed includes Week 24 data for all 12 participants (the Intent-to-Treat [ITT] population) and for the 11 participants with genetically confirmed Wolfram syndrome (the Per Protocol population)
  - Upon genetic review, one participant was determined not to meet inclusion/exclusion criteria; this participant had a pathogenic autosomal recessive mutation on one allele and a variant of uncertain significance on the other
- Treatment with PB&TURSO showed overall stabilization or improvement relative to baseline on multiple outcomes across organ systems typically affected in Wolfram syndrome[1], including endocrine function (**Figure 1**), ophthalmologic function (**Figure 2**), and overall symptom burden **(Figures 3 and 4)**
- PB&TURSO was generally well tolerated with no serious adverse events and all treatment-emergent adverse events (TEAEs) graded mild or moderate
  - Diarrhea was the most common TEAE (50% in ITT); all cases were of mild severity
  - Most TEAEs did not lead to modification or interruption of PB&TURSO dosing and none led to drug discontinuation

FIGURE 1. Improved Pancreatic Function, Beta Cell Responsiveness, and Glycemic Control

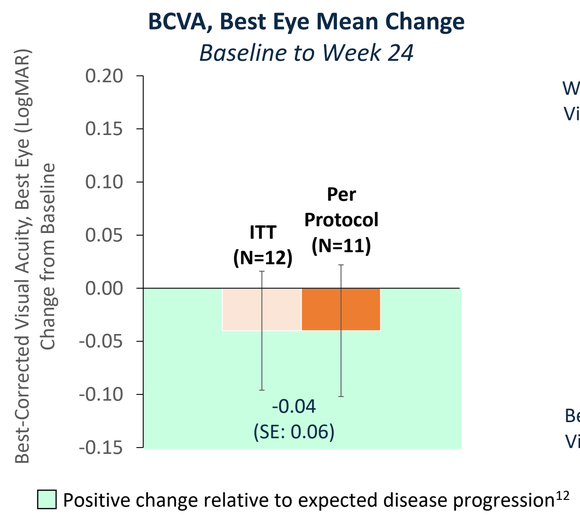


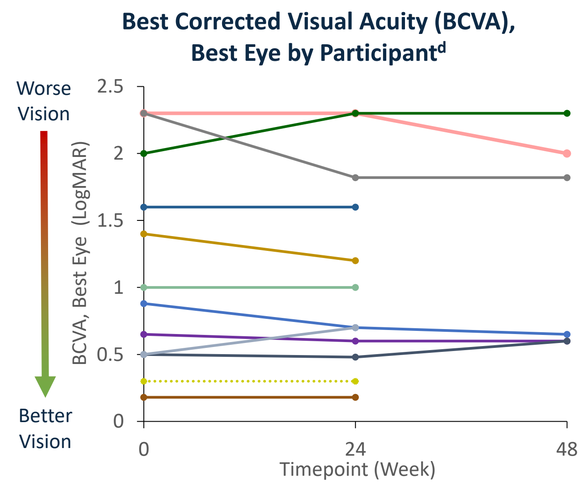
Key Diabetic Outcomes in Per Protocol Population

Pancreatic Function *See graph to left*	↑ **Improved C-Peptide Response**	**Faster Time to Peak C-Peptide**
Glycemic Control	↓ **HbA1c** -0.16% (SE: 0.13%)[c]	**Time in Target Glucose Range** +5.7% (SE: 3.9%)[c]

[c]Mean change from baseline to Week 24
SE: Standard Error

FIGURE 2. Trend Toward Visual Acuity Stabilization at Week 24 Compared to Baseline

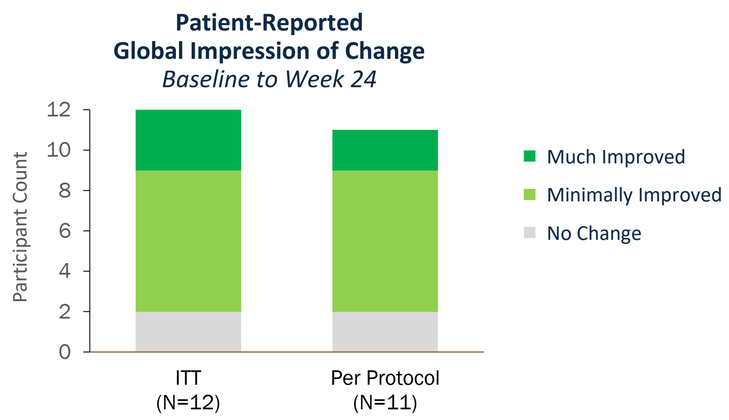


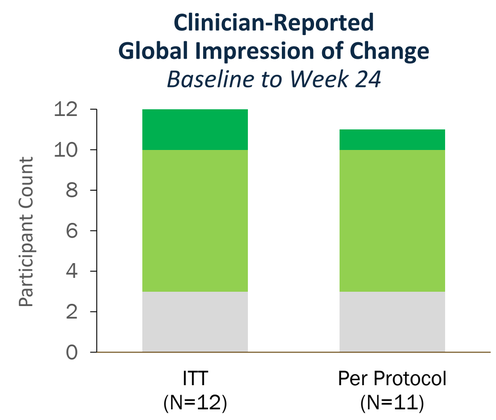


- 8 of 11 Per Protocol participants demonstrated improved or stable visual acuity in their best eye from baseline to the latest available timepoint
- Of remaining participants:
  - 2 stable in one eye
  - 1 worsened

[d]All available data shown for individual participants, including 12 participants with data at Week 24 and 6 participants with data at Week 48; dotted line indicates participant excluded from Per Protocol

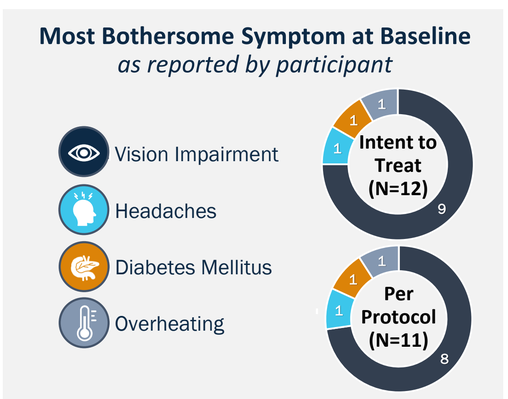
FIGURE 3. Reduced Overall Symptom Burden at Week 24 by Clinician and Patient Report

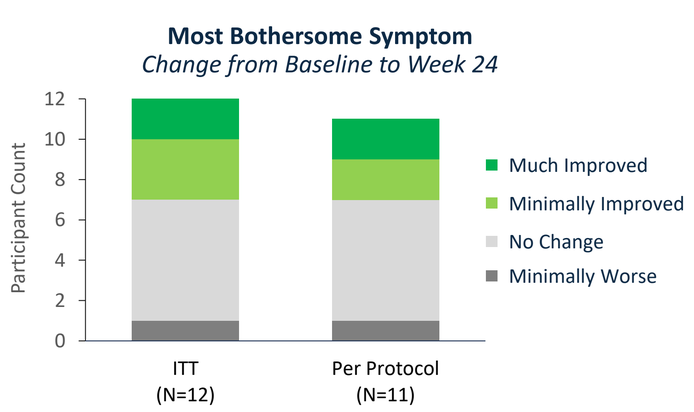




Interpretation of PGI-C and CGI-C:
HELIOS defines a "responder" on both scales as no change or improvement given the progressive nature of Wolfram syndrome

FIGURE 4. Stabilization or Improvement in Most Bothersome Symptom at Week 24





- 91% of Per Protocol participants reported stabilization or improvement from baseline in their most bothersome symptom

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Disclosures
NE, KC, ML, JP, and **LM** are or were full-time employees of Amylyx who may have had stock option/ownership in Amylyx Pharmaceuticals, Inc. at the time of the study.

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