48-Week 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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Abstract P22

BACKGROUND

- Wolfram syndrome (WS) is a rare, fatal, progressive monogenic disorder characterized by juvenile-onset insulin-requiring 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 endocrinological, neurological, and ophthalmological function in Wolfram syndrome

STUDY DESIGN

Study Location: Washington University, St. Louis, Missouri, USA

Screen for Eligibility	PB&TURSO (n=12)		Safety Follow-Up
Screening Period (4 wk)	Open-Label Treatment Period (48 wk)	Extension Treatment Period (96 wk)	Follow-Up Period (4 wk)

Week 24 and 48 Analyses

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[b]

Primary Efficacy

- **C-peptide** (ΔC-peptide, area under the curve [AUC] C-peptide) change from baseline 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

- **HbA1c** change from baseline
- **Daily exogenous insulin dose** change from baseline
- **Time in target glucose range** (70–180 mg/dL) change from baseline by continuous glucose monitoring (CGM)
- **Best-corrected visual acuity (BCVA)** change from baseline on the LogMAR scale using the Snellen chart

Select Exploratory

- Clinician-Reported Global Impression of Change (CGI-C)[c]
- Patient-Reported Global Impression of Change (PGI-C)[c]
- Participant experience from on-study qualitative interviews

[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]All statistical summaries (including p-values) are descriptive in nature; p-values based on two-sided t-tests
[c]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

- Due to the progressive nature of Wolfram syndrome, pancreatic β-cell function, glycemic control, visual function, and overall symptom burden typically worsen over time[11,12]
- At Week 24, treatment with PB&TURSO instead showed overall stabilization or improvement relative to baseline
- At Week 48, treatment with PB&TURSO showed sustained stabilization and/or improvement of pancreatic function, glycemic control, vision, and symptom burden
- Treatment with PB&TURSO in HELIOS is ongoing
- Results will inform planned Phase 3 program

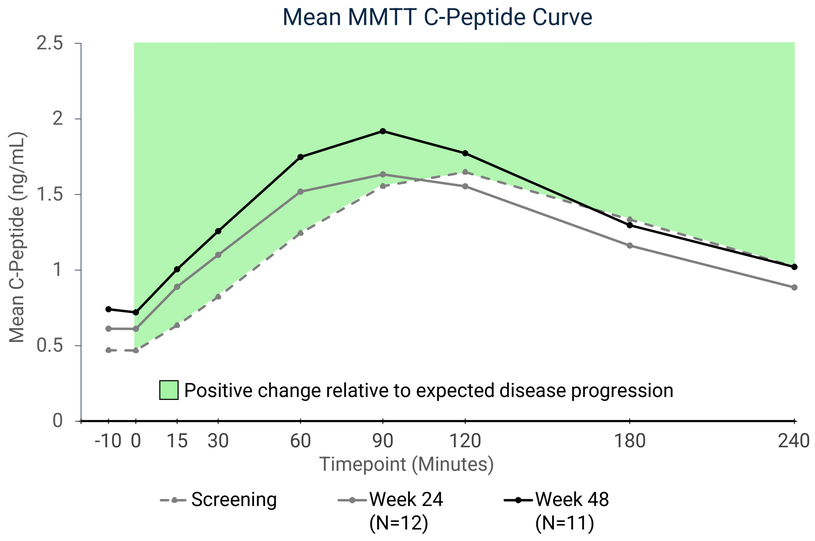
PB&TURSO is an investigational drug for Wolfram syndrome and has not been approved for use by any health authority (e.g., the FDA and EMA).

RESULTS

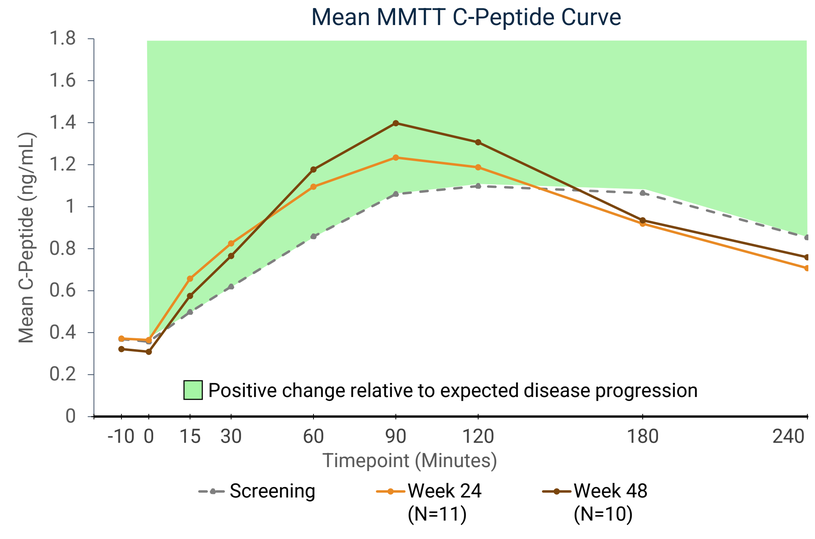
- The main analysis performed includes Week 24 data for all 12 participants (the Intent-to-Treat [ITT] population) and for the 11 participants with genetically confirmed Wolfram syndrome (the Per Protocol population)
  - Upon genetic review, one participant was determined not to meet inclusion/exclusion criteria; this participant had a pathogenic autosomal recessive mutation on one allele and a variant of uncertain significance on the other
  - Data was available for 11 participants at Week 48; one participant discontinued for reasons unrelated to safety
- 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 (**Figure 3**)
- 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 (58.3% in ITT); all cases were of mild severity
  - Dose reduction or drug interruption due to TEAE occurred in only 25% of participants and no TEAEs led to drug discontinuation

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

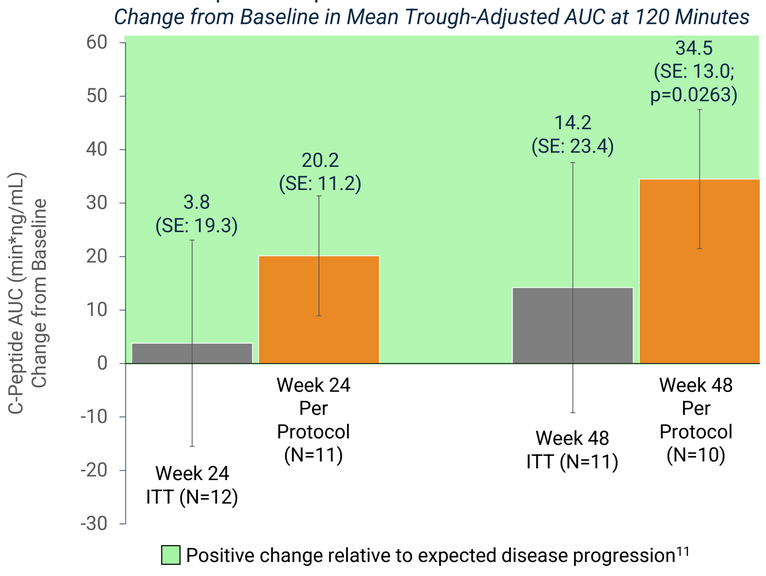
ITT Week 24 and 48
Mean MMTT C-Peptide Curve



Per Protocol Week 24 and 48
Mean MMTT C-Peptide Curve



C-Peptide Response to Mixed Meal Tolerance Test
Change from Baseline in Mean Trough-Adjusted AUC at 120 Minutes



Key Diabetic Outcomes in Per Protocol Population

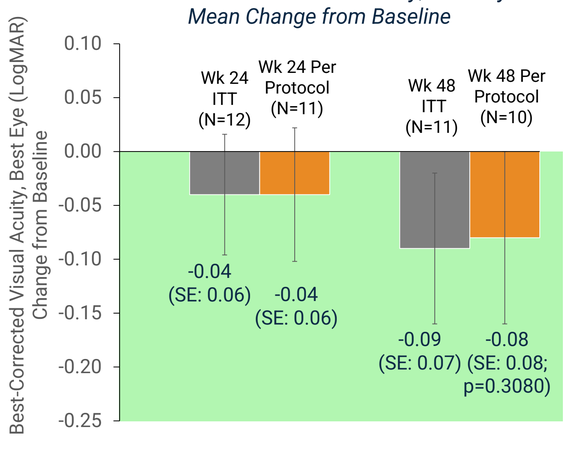
Pancreatic Function *See graphs above*
- ↑ **Improved C-Peptide Response**
- **Faster Time to Peak C-Peptide**

Glycemic Control
- ↓ **HbA1c**
  Wk 24: -0.16% (SE: 0.13%)[c]
  Wk 48: -0.40% (SE: 0.22%; p=0.0998)[c]
- ↑ **Time in Target Glucose Range**
  Wk 24: +5.7% (SE: 3.9%)[c]
  Wk 48: +9.6% (SE: 5.8%; p=0.1350)[c]

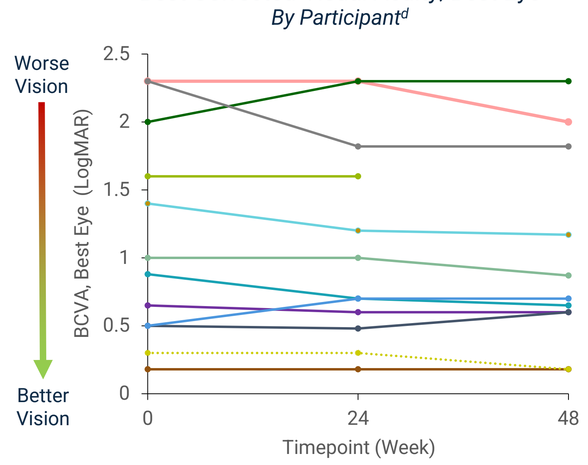
[c]Mean change from baseline to indicated timepoint
SE: Standard Error

FIGURE 2. Visual Acuity Stabilization and Trend Toward Improvement at Week 24 and 48 Compared to Baseline

Best Corrected Visual Acuity, Best Eye
Mean Change from Baseline



Best Corrected Visual Acuity, Best Eye
By Participant[d]

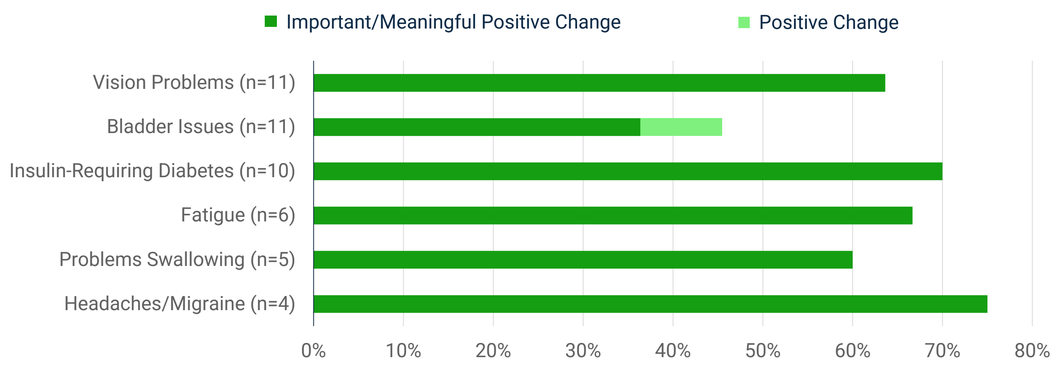


- 8 of 11 Per Protocol participants demonstrated improved or stable visual acuity in their best eye from baseline to the latest available timepoint
- Of remaining participants:
  - 1 stable in one eye
  - 2 worsened from Baseline to Week 24 but stabilized from Week 24 to 48

[d]Dotted line indicates participant excluded from Per Protocol analysis set

FIGURE 3. Reduced Overall Symptom Burden at Week 24 and 48 by Clinician and Participant Report

Positive Changes in WS-Related Symptoms by Participant Report in On-Study Interviews



n = the number of participants who reported experiencing the symptom pretrial

- In on-study interviews after at least 24 weeks of treatment, 9 of 11 reported improvements in ≥1 WS-related symptom with all noting the change being meaningful in at least one symptom
- 100% of participants met responder criteria by self and clinician assessment (no change or improvement on PGI-C and CGI-C) at Week 24 and 48
- At Week 48, 6 of 10 Per Protocol participants reported improvement on PB&TURSO; 9 of 10 improved based on clinician report

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Disclosures
NE, KF, 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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