AMX0035 in Wolfram Syndrome: Program Progress and Emerging Insights

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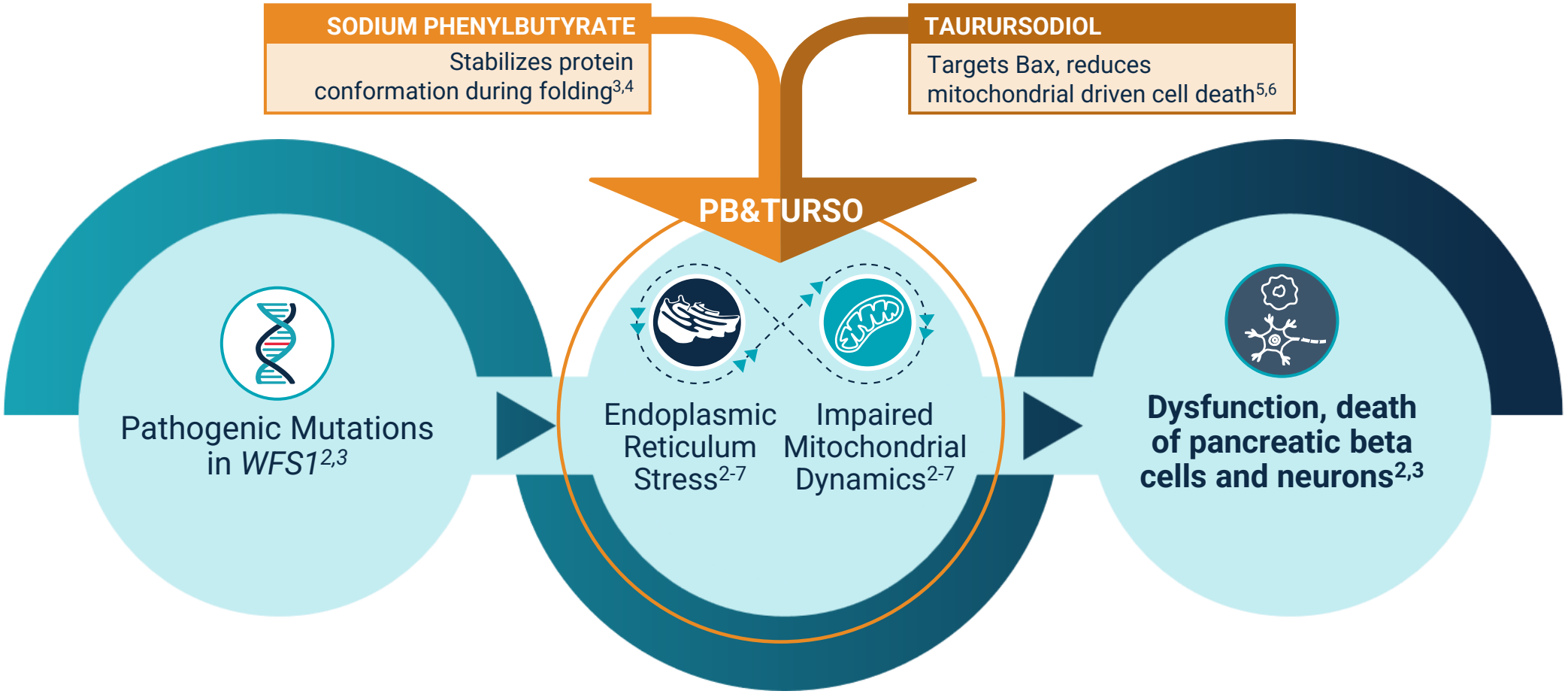
Please Note

PB&TURSO is investigational and is not approved by any health authority.

This presentation is intended to provide scientific information about PB&TURSO and the HELIOS trial in Wolfram syndrome (WS). The statements and content shared in this presentation have not been evaluated by any health authority.

PB&TURSO Targets Endoplasmic Reticulum Stress and Related Mitochondrial Dysfunction Pathways



1. Urano, F. *Diabetes*. 2014;63(3):844-846. **2.** Sarmara A, et al. Orphanet J Rare Dis. 2019; 14(1):279. **3.** Pallotta MT, et al. J Transl Med. 2019;7(1):238-249. **4.** Shang L, et al. Diabetes. 2014;63(3):923-933. **5.** Zhou W. J Biol Chem. 2011;286(17):14941-14951. **6.** Rodrigues CM, Steer CJ. Expert Opin Investig Drugs. 2001;10(7):1243-1253. **7.** Mishra R, et al. Ther Adv Rare Dis. 2021:2:26330040211039518.

Encouraging Preclinical Data Show Therapeutic Potential of PB&TURSO in Wolfram Syndrome

Improvement in Insulin Secretion in Patient-Derived Pancreatic Beta Cells

Improvement in Cell Viability in Patient-Derived Pancreatic Beta Cells

Improvement in Cell Viability in Patient-Derived Neuronal Cells

Statistically Significant Delay in Diabetes Progression in *Wfs1*-deficient Mice

DATA AVAILABLE AT

JCI insight

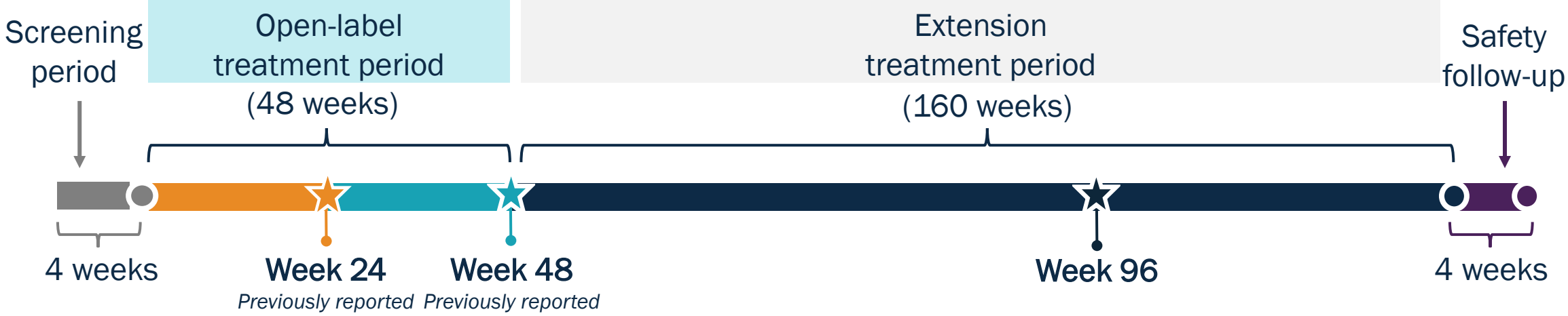
Kitamura RA, et al. *JCI Insight*. 2022;7(18):e156549.

HELIOS Trial Design

Sodium Phenylbutyrate and Taurursodiol (PB&TURSO)

N=12 (ITT) | n=11 (Per-Protocol)

Eligible adults had genetically confirmed Wolfram syndrome, insulin-requiring diabetes, and residual β-cell function



Key Inclusion Criteria

- Aged ≥17 years
- Documented functionally relevant recessive mutations on both alleles of the *WFS1* gene
- Stimulated C-peptide level of ≥0.2 ng/mL at screening
- Insulin-dependent diabetes mellitus due to Wolfram syndrome
- No current GLP-1 receptor agonist use

1. ClinicalTrials.gov identifier: NCT05676034. Updated April 14,2026. Accessed May 1,2026. https://www.clinicaltrials.gov/ct2/show/NCT05676034. **2.** Data on File. Amylyx Pharmaceuticals Inc. 2026.

HELIOS Trial Design - Endpoints

Primary Efficacy

- Change from baseline in **C-peptide** (ΔC-peptide, AUC C-peptide) at Week 24 measured during 240-minute MMTTs

Key Secondary Efficacy

- **C-peptide AUC response** to a 240-minute MMTT at Week 48
- Change from baseline in **HbA1c level**
- Change from baseline in **exogenous insulin dose**
- Change from baseline in **overall time in target glucose range (70–180 mg/dL)**
- Change from baseline in **best-corrected visual acuity** on the LogMAR scale using the Snellen chart

MMTT, mixed meal tolerance test

1. ClinicalTrials.gov identifier: NCT05676034. Updated April 14,2026. Accessed May 1,2026. https://www.clinicaltrials.gov/ct2/show/NCT05676034. **2.** Timmons J. Virtual trial update: 48-week HELIOS trial. Presented at: Wolfram Syndrome UK and Snow Foundation Virtual Global Research and Trial Update; November 15, 2025.

Participant Baseline Characteristics

Median Age:
25 years (range: 18 to 39)

Male:
2 (17%)

Female:
10 (83%)

Median Time Since WS Diagnosis:
5 years (range: 0.4 to 15)

Median Age at Diagnosis
21 (range: 8 to 36)

Median Age of Symptom Onset, Years (Range)

Diabetes Mellitus
9 (3 to 33)

Diabetes Insipidus*
11 (8 to 24)

Vision Loss
12 (5 to 29)

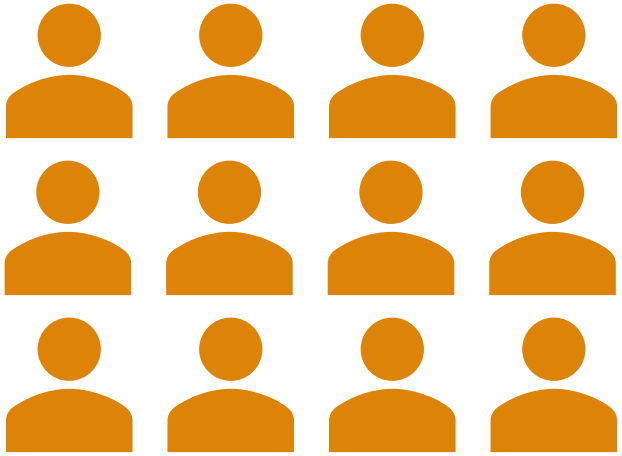
Hearing Loss**
16 (7 to 34)

*N=4; **N=5

Timmons J. Virtual trial update: 48-week HELIOS trial. Presented at: Wolfram Syndrome UK and Snow Foundation Virtual Global Research and Trial Update; November 15, 2025.

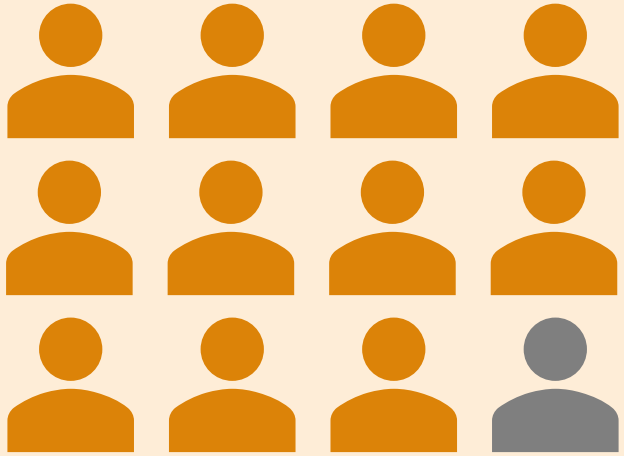
Key HELIOS Analysis Populations

Intent to Treat (ITT)



12 Enrolled Participants
received PB&TURSO
*includes 1 participant who did not meet inclusion/exclusion criteria upon genetic review**

Per Protocol (PP)



11 Enrolled Participants
with Definite Diagnosis of Wolfram Syndrome

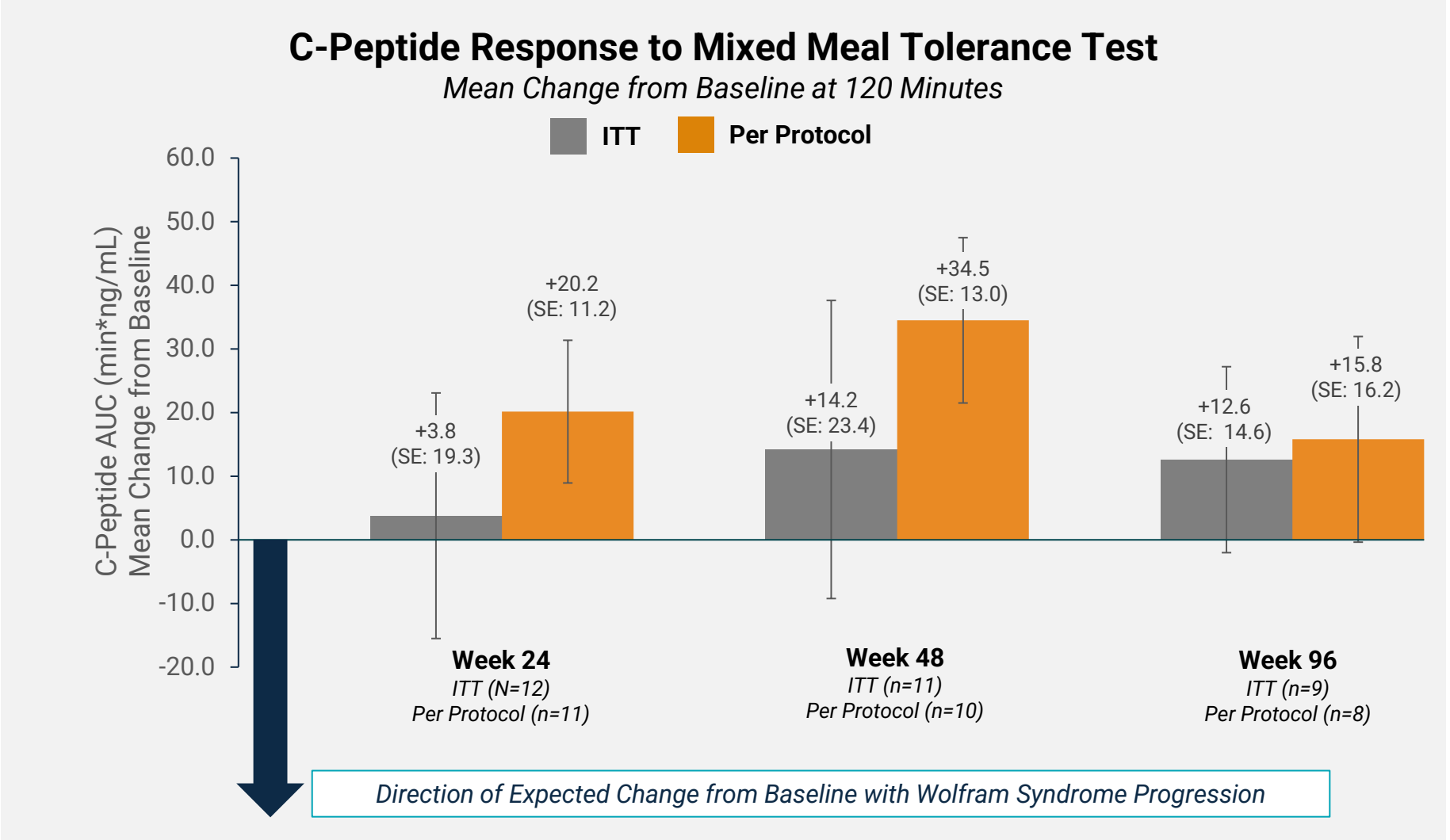
Participant numbers in analyses reflect available data at each timepoint:

Week 24: ITT N=12, PP n=11;
Week 48: ITT n=11, PP n=10
Week 96: ITT n=9, PP n=8

*Participant found to have an autosomal recessive mutation confirmed to be pathogenic on just one of the two alleles and variant of uncertain significance on the other allele. Participant was within normal range for C-peptide, glycemic measures, and vision throughout suggesting lack of typical WS phenotype.In addition, this participant discontinued insulin ~ 3 months after enrolling in the trial, and continues longstanding oral anti-diabetic medication.

Timmons J. Virtual trial update: 48-week HELIOS trial. Presented at: Wolfram Syndrome UK and Snow Foundation Virtual Global Research and Trial Update; November 15, 2025.

Primary Endpoint: C-Peptide Response (AUC of Levels)

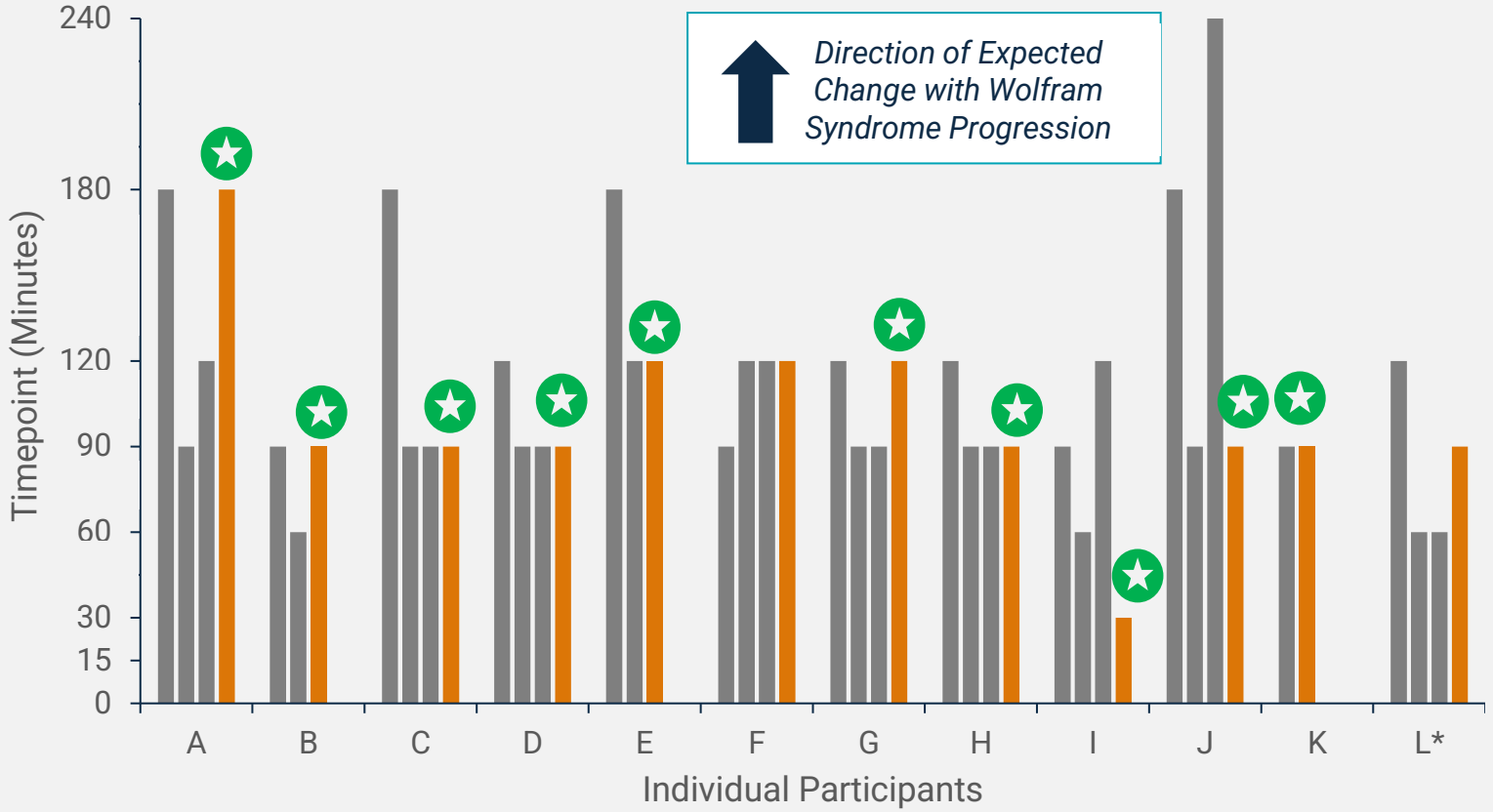


20%, 52% and 14% increases vs baseline at Weeks 24, 48, and 96, respectively, based on geometric mean ratios (0-120 min), in the Per Protocol population

AUC, Area under the concentration time curve

Data on File. Amylyx Pharmaceuticals Inc. 2026.

Additional MMTT Analyses: Time to Peak C-Peptide



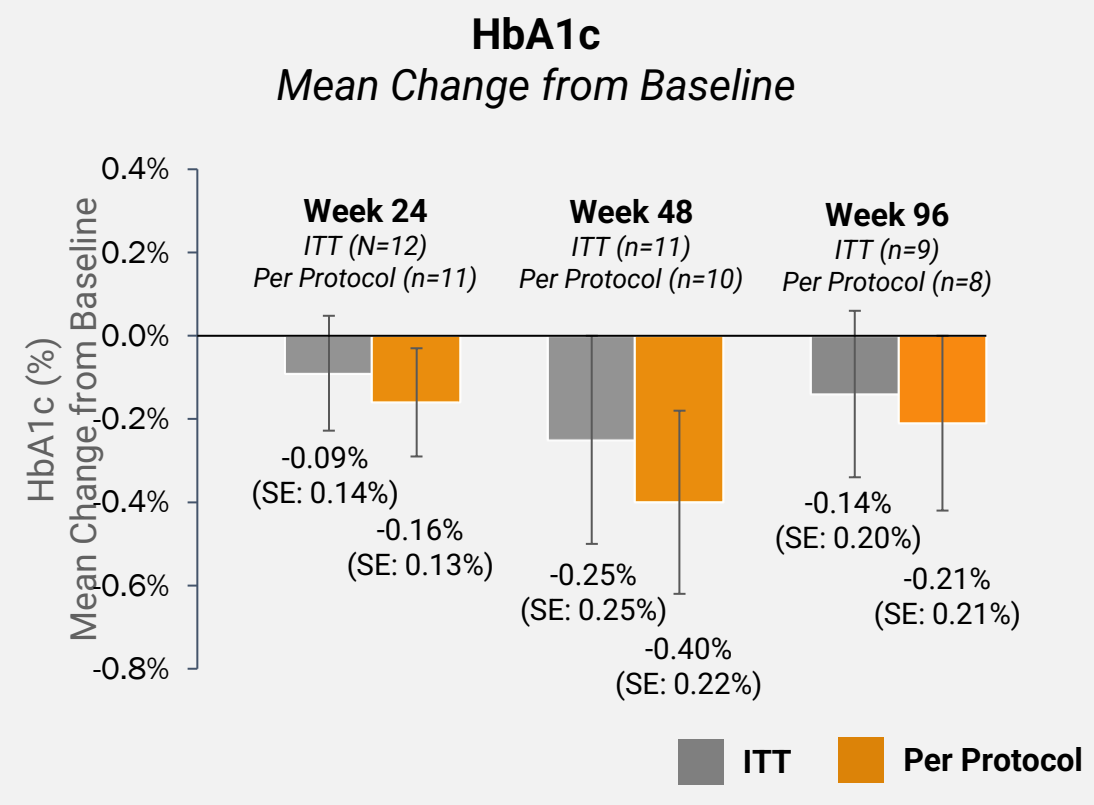
Bars represent, for each participant, Screening (bar 1), Week 24 (bar 2), Week 48 (bar 3), and Week 96 (bar 4).

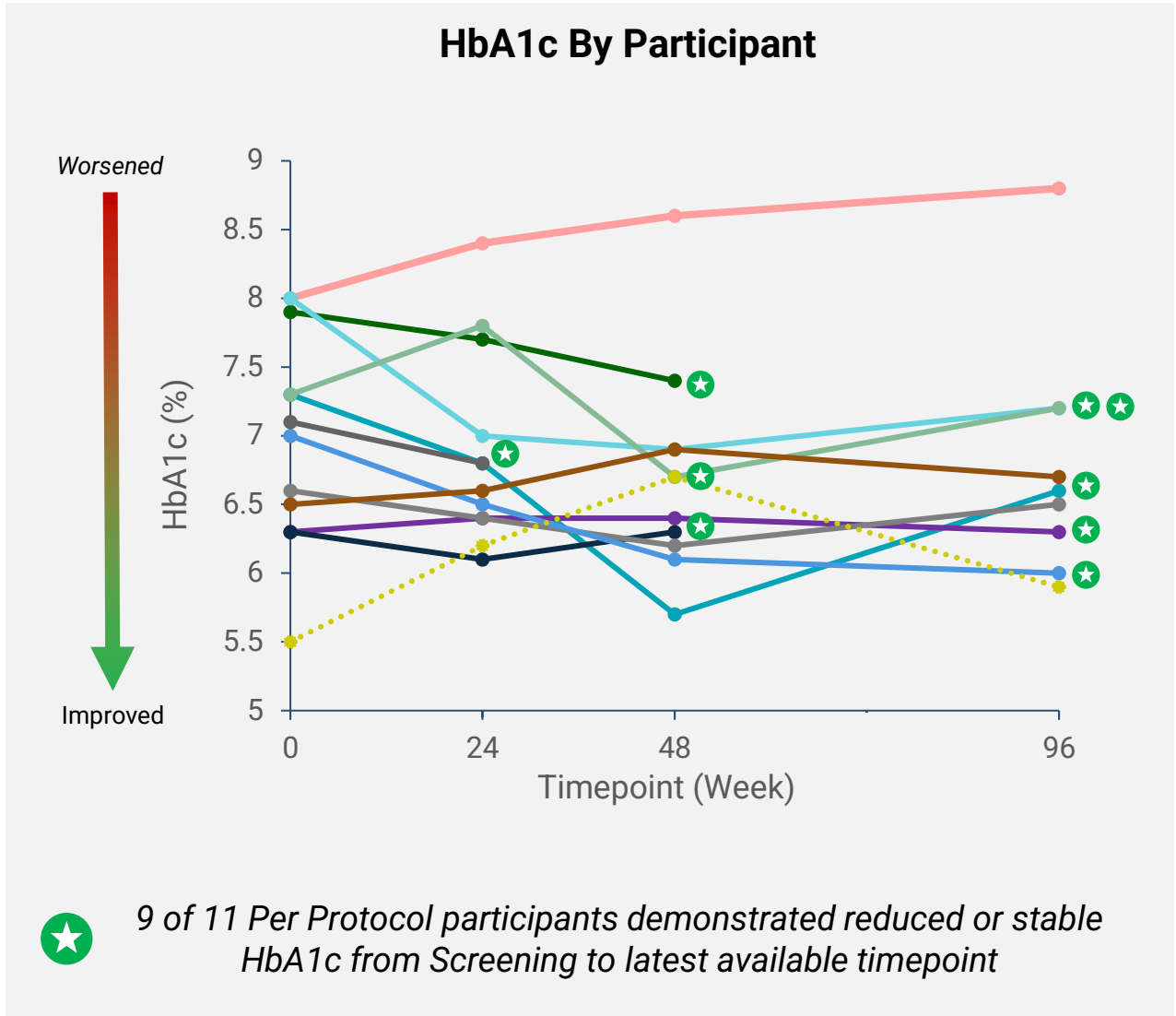
10 of 11 Per Protocol Participants Demonstrated Stable or Improved Pancreatic Function at Latest Available Timepoint Compared to Screening as Measured by Time to Peak C-Peptide

*Participant not included in the Per Protocol population

Data on File. Amylyx Pharmaceuticals Inc. 2026.

Secondary Endpoint: HbA1c



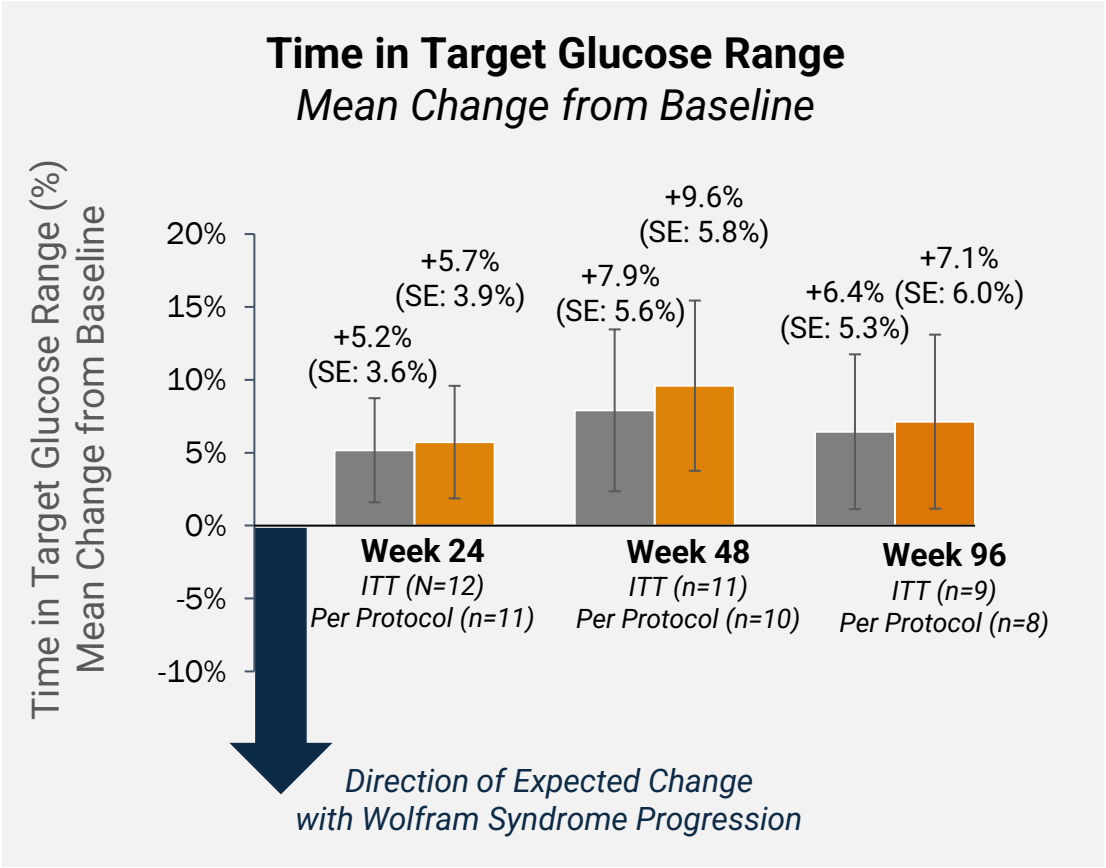


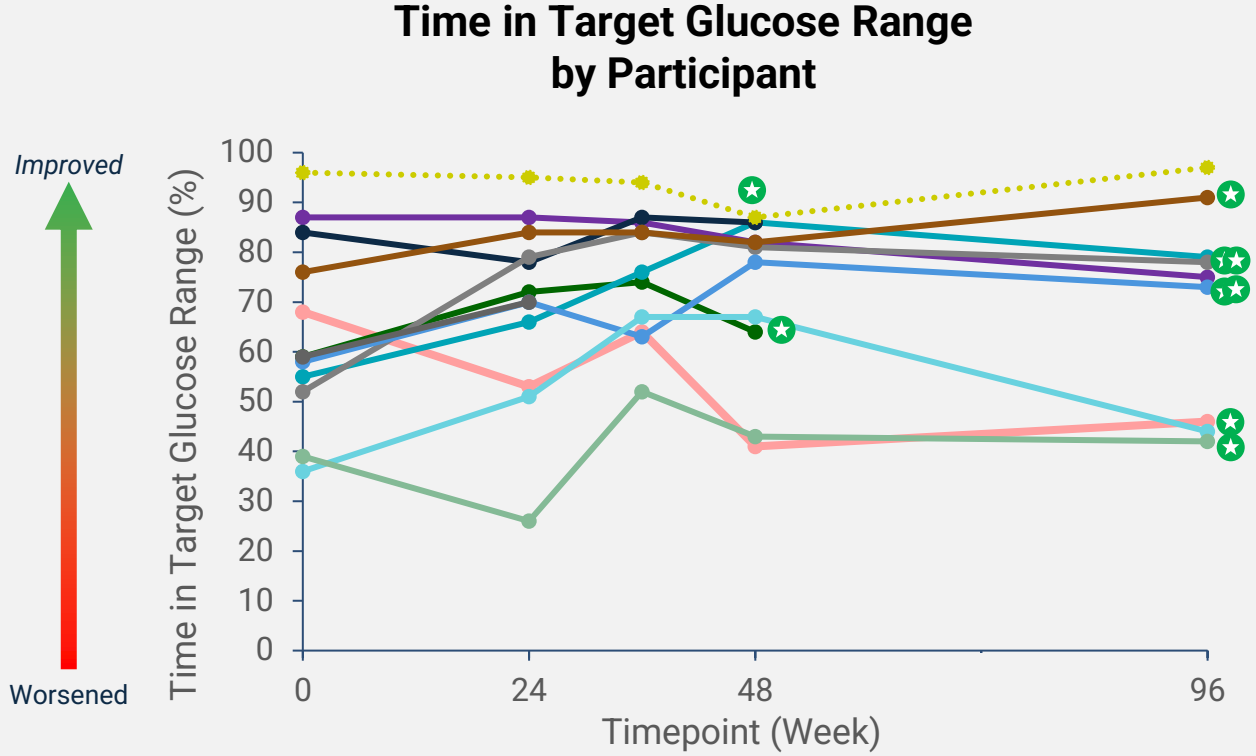
9 of 11 Per Protocol participants demonstrated reduced or stable HbA1c from Screening to latest available timepoint

Dotted line in By Participant graph indicates the participant not included in the Per Protocol population

Data on File. Amylyx Pharmaceuticals Inc. 2026.

Secondary Endpoint: Overall Time in Target Glucose Range*

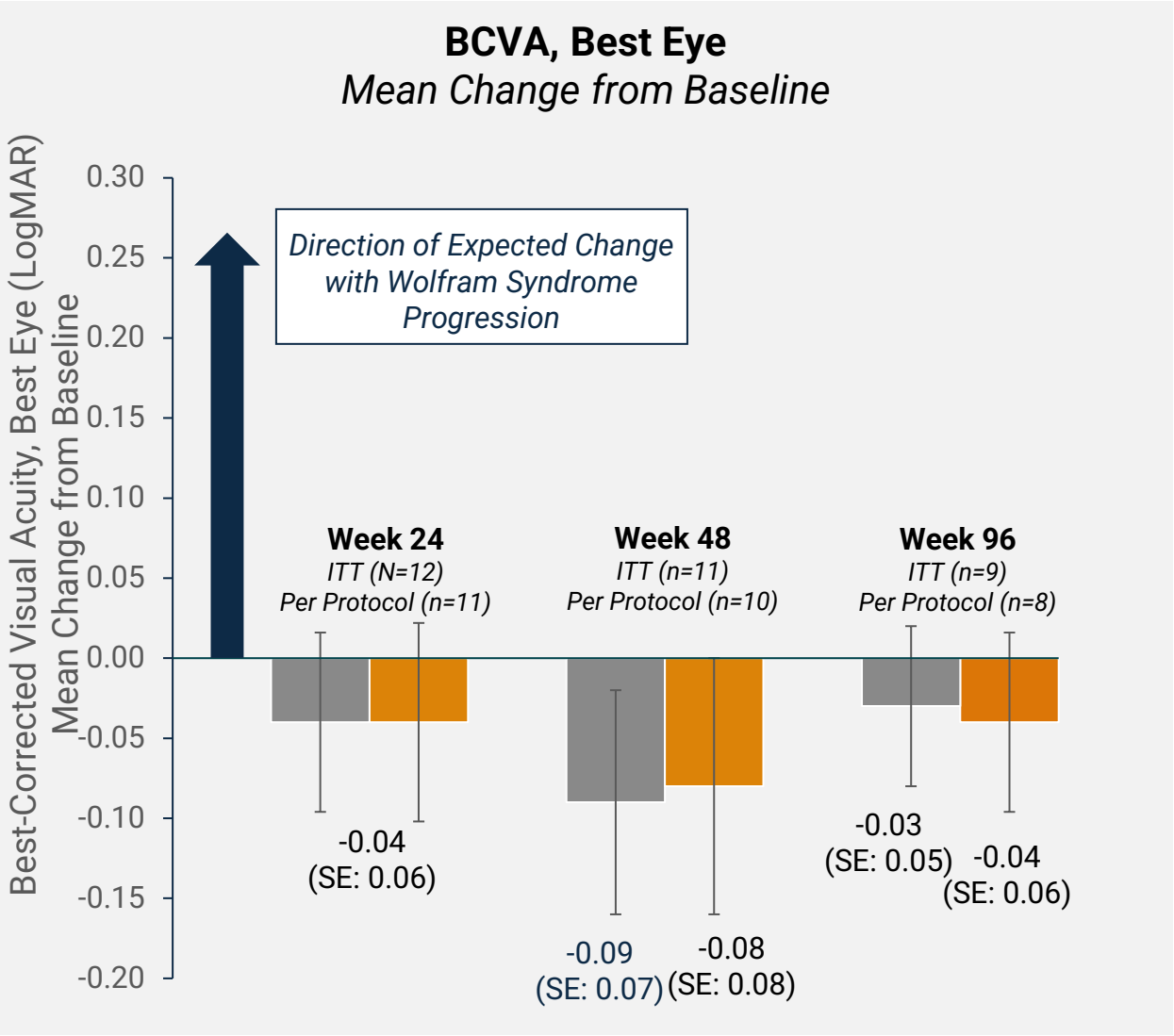


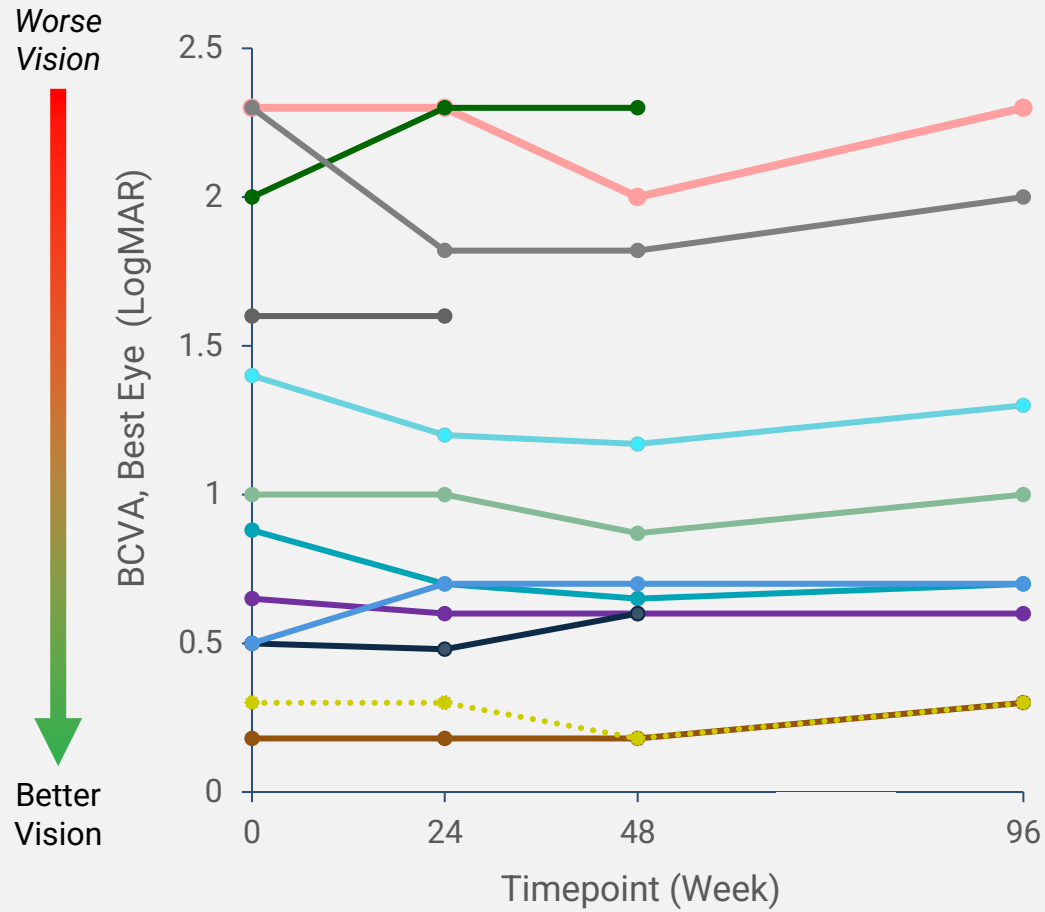


★ *9 of 11 Per Protocol participants demonstrated stable or increased time in target glucose range from Screening to latest available timepoint*

*Time in range was measured by continuous glucose monitoring (CGM). Good range defined as glucose recording between 70 and 180 mg/dL
Dotted line in By Participant graph indicates the participant not included in the Per Protocol population
Data on File. Amylyx Pharmaceuticals Inc. 2026.

Secondary Endpoint: Best Corrected Visual Acuity (BCVA)





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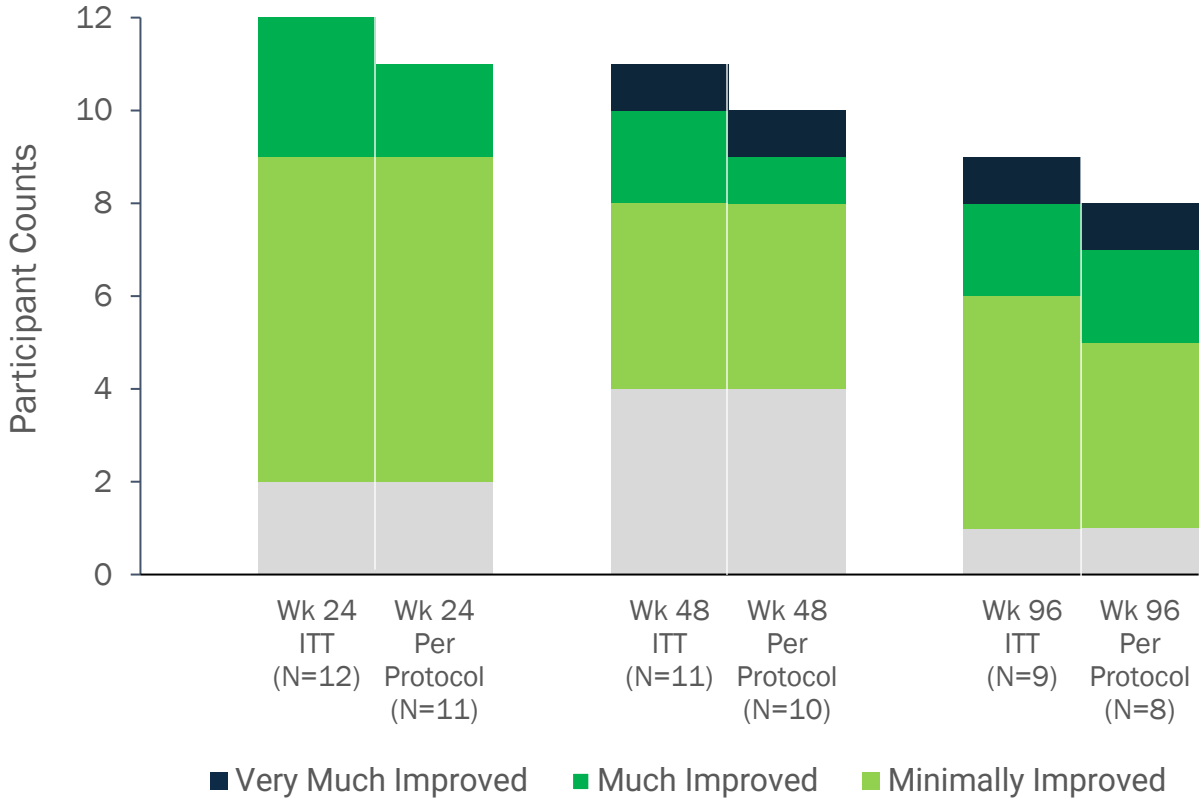
Exploratory Endpoint: PGI-C and CGI-C

100% of Participants Met Responder* Criteria by Self and Clinician Assessment

At Week 96, 7 of 8 Per Protocol participants claimed to have improved on PB&TURSO; 7 of 8 improved based on clinician report

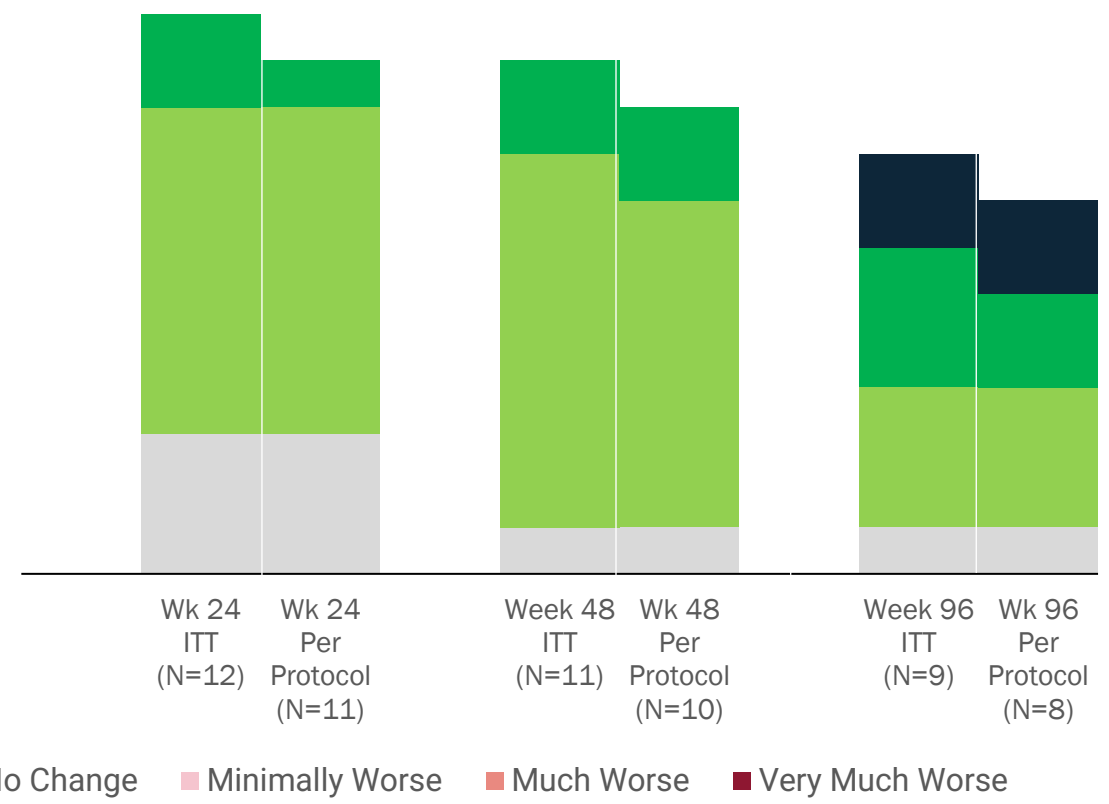
Patient-Reported Global Impression of Change (PGI-C)

Change from Baseline



Clinician-Reported Global Impression of Change (CGI-C)

Change from Baseline



*HELIOS defines a "responder" on both scales as no change or improvement given the progressive nature of Wolfram syndrome

Data on File. Amylyx Pharmaceuticals Inc. 2026.

PB&TURSO Safety and Tolerability

- PB&TURSO continues to be **generally well tolerated**
  - One serious adverse event, considered unlikely related to treatment
  - All TEAEs assessed as at least possibly related to AMX0035 were gastrointestinal in nature and mild (Grade 1)
- **No new safety signals** were identified
- Nearly all participants reported ≥1 TEAE
  - Diarrhea was the most common TEAE (58%); all cases were of mild severity
  - Most did not lead to modification or interruption of PB&TURSO dosing and **none led to drug discontinuation**

Summary of Treatment Emergent Adverse Events (TEAEs)

	PB&TURSO (N=12)*
Participants with ≥1 TEAE— n (%)	11 (92%)
TEAE related to study drug** – n (%)	10 (83%)
Serious adverse events – n (%)	1 (8%)
Drug interrupted owing to TEAE — n (%)	4 (33%)
Dose reduced owing to TEAE — n (%)	3 (25%)
Drug discontinued owing to TEAE — n (%)	0 (0%)

*All available safety data as of February 2026 included
**Includes those with TEAEs at least possibly related to treatment; 10 possibly related, 1 probably related

Data on File. Amylyx Pharmaceuticals Inc. 2026.

Limitations

- Open-label, single-arm design
- 12 adult participants (aged ≥17 years)
- Genetic heterogeneity within WFS1-associated Wolfram syndrome, with >200 known WFS1 variants and incomplete genotype–phenotype correlations

Looking Ahead: Building the Next Trial in Wolfram Syndrome

We are actively shaping the next trial through multidisciplinary engagement.

Illustrative Questions Under Consideration

What to Measure

- How do we best capture **progression across pancreatic beta cell (endocrine) and neuronal cell (visual, urological) domains** in a multi-system disease?
- What is the optimal balance between **objective biomarkers** and **patient-centered outcomes**?
- How can endpoints reflect **clinically meaningful outcomes?**

Who to Study

- What elements predict a population that is most likely to benefit from treatment in the duration of a clinical trial?

How to Study It

- What trial designs can deliver **robust, interpretable results in an ultra-rare disease setting**?
- How can we **minimize placebo burden** while maintaining **scientific validity** and supporting recruitment?
- What approaches can reduce **study burden (e.g., visits, procedures, travel)** while preserving data quality?

Key Takeaways

- **New Week 96 HELIOS data extend previously reported Week 24 and 48 findings**, providing longer-term follow-up on efficacy and safety outcomes in adults with Wolfram syndrome treated with PB&TURSO
- **At Week 96, measures of pancreatic function and glycemic control were stable or improved relative to baseline in most participants**; results were directionally consistent with earlier timepoints, though with a smaller magnitude of change
  - **Secondary and exploratory endpoints at Week 96**, including visual acuity and patient- and clinician-reported outcomes, **showed patterns consistent with disease stabilization**, with interpretation limited by the open-label, single-arm design and small sample size
- **PB&TURSO continued to be generally well tolerated with longer-term administration**, with no new safety concerns identified based on available data
- Amylyx continues to discuss next steps with Wolfram Syndrome experts and multidisciplinary specialists

We extend our deepest gratitude to the HELIOS trial participants, their loved ones, Dr. Fumi Urano, the Washington University site team, and the entire Wolfram Syndrome community for their support of this trial.

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