Results from A Phase 2, Open-Label Study Evaluating an Oral, Fixed-Dose Combination of Sodium Phenylbutyrate and Taurursodiol (PB&TURSO) in Wolfram Syndrome (HELIOS)

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Disclosures

Full time employee of and may have stock option ownership in Amylyx Pharmaceuticals, Inc.

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.

Wolfram Syndrome is a Rare, Fatal, Monogenic, Progressive Disorder[1-5]

***WFS1* Gene Mutation**

Progressively impacts multiple organs and systems[1-5]

Childhood-onset Diabetes Mellitus
Elevated blood sugar levels from insulin-producing beta cell death

Gradual Loss of Vision Leading to Blindness
Optic nerve cell death

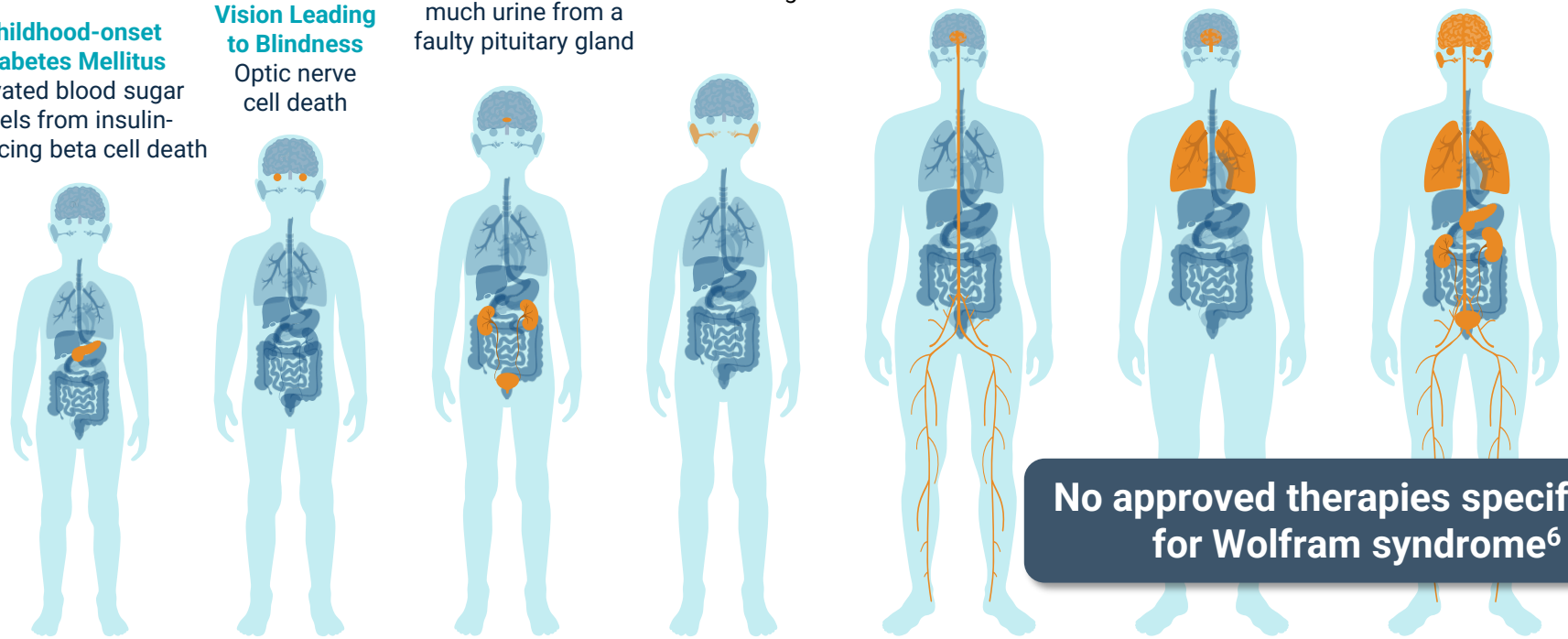
Diabetes Insipidus
Kidneys produce too much urine from a faulty pituitary gland

Hearing Loss
From cranial nerve damage

Balance and Coordination Difficulty
Ataxia from cerebellum damage

Difficulty Breathing
From brain stem damage

Death occurs at a median age range of 25-49 years, **mainly from respiratory failure**



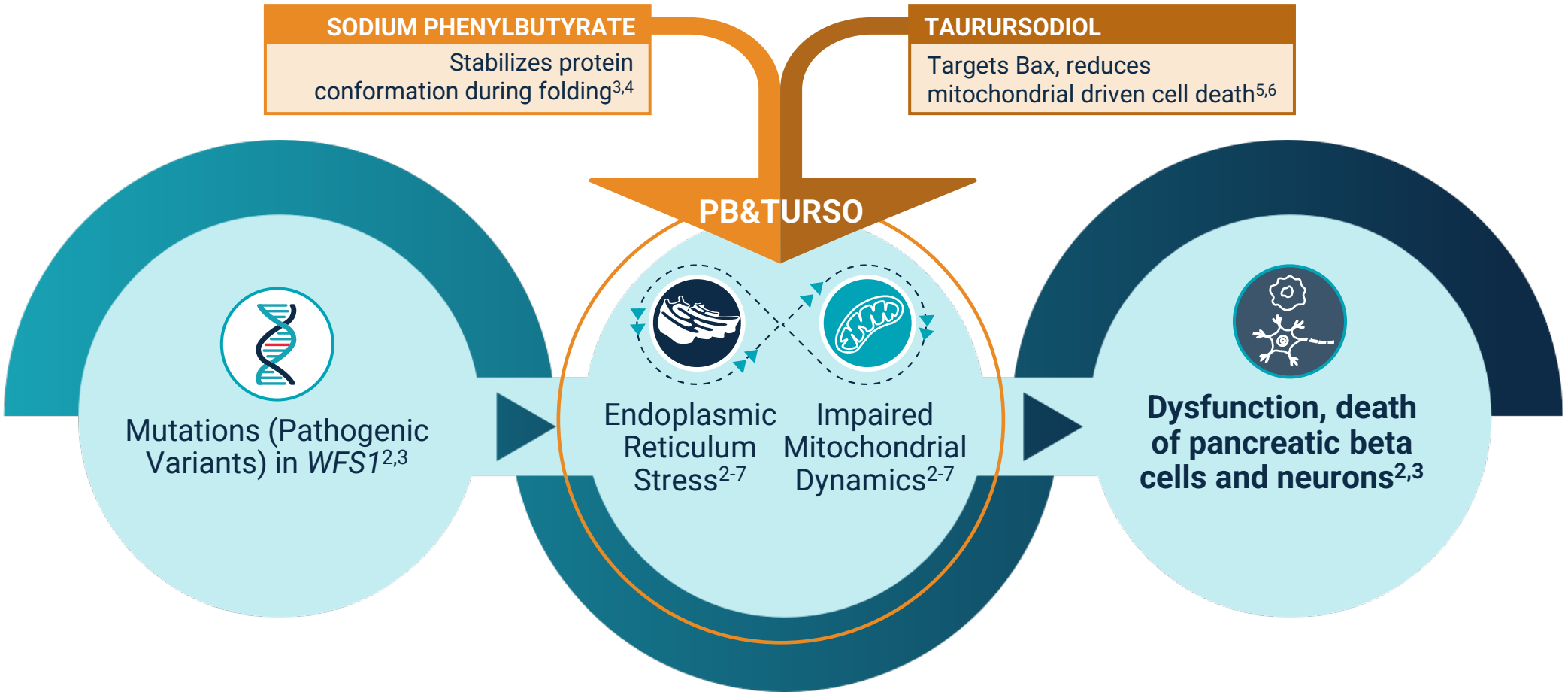
~3,000
people living with Wolfram syndrome in the U.S.[1,2]

No approved therapies specifically for Wolfram syndrome[6]

1. Urano, F. *Diabetes*. 2014;63(3):844-846. **2.** Pallotta MT, et al. *J Transl Med*. 2019;17:238. **3.** Lee, E., et al. Front Genet. 2023;14:1198171. **4.** Leslie, M. *Science*. 2021;371(6530): 663-665. **5.** Matsunage et al. *Plos One*. 2014;9(9):106906. **6.** Urano, F. *Curr Diab Rep*. 2016;16(1):

Wolfram Syndrome is a Prototypical Endoplasmic Reticulum Stress Disorder[1]

PB&TURSO targets endoplasmic reticulum stress and related mitochondrial dysfunction pathways

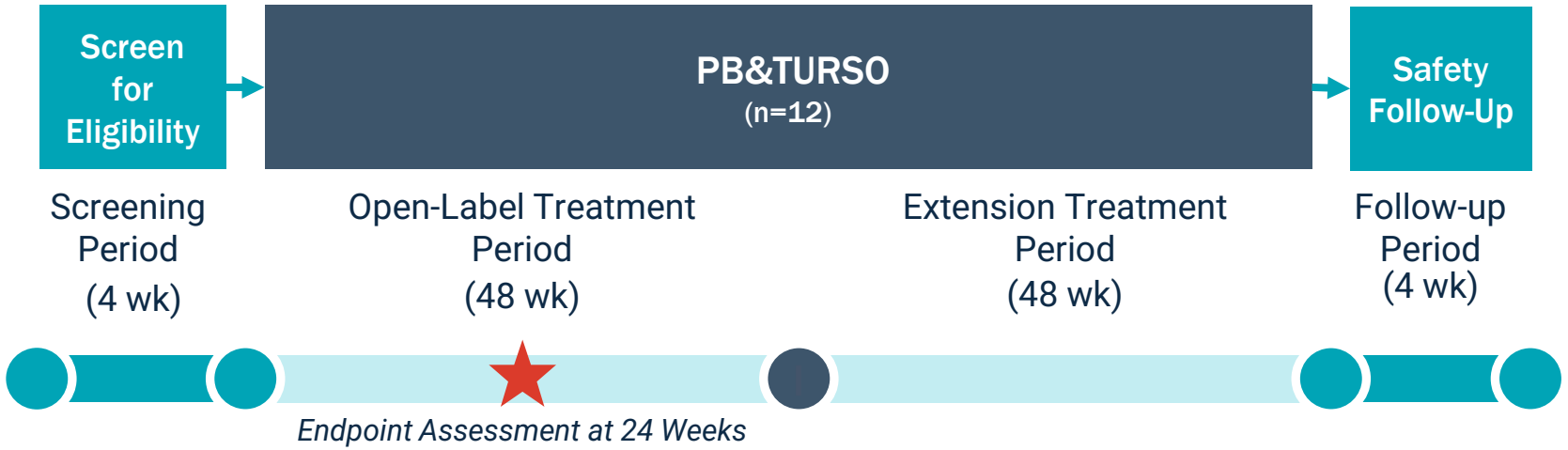


1. Urano, F. *Diabetes*. 2014;63(3):844-846. **2.** Sarmara A, et al. Orphanet J Rare Dis. 2019; 14(1):279. **3.** Pallotta MT, et al. J Transl Med. 2019;7(1):238-249. **4.** Shang L, et al. Diabetes. 2014;63(3):923-933. **5.** Zhou W. J Biol Chem. 2011;286(17):14941-14951. **6.** Rodrigues CM, Steer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

HELIOS Trial Design

Primary Objectives:

- To assess the safety and tolerability of PB&TURSO administered orally for up to 96 weeks
- To evaluate the effect of PB&TURSO on residual beta cell function over 24 weeks by monitoring C-peptide levels



Key inclusion criteria

- Aged ≥17 years
- 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
- 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

Primary Efficacy

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

Key Secondary Efficacy

- 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 in baseline **best-corrected visual acuity** on the LogMAR scale using the Snellen chart

CGM, continuous glucose monitoring. MMTT, mixed meal tolerance test

1. ClinicalTrials.gov identifier: NCT05676034. Updated November 21, 2023. Accessed April 9, 2024. https://www.clinicaltrials.gov/ct2/show/NCT05676034. **2.** Data on File. Amylyx Pharmaceuticals Inc. 2024.

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)

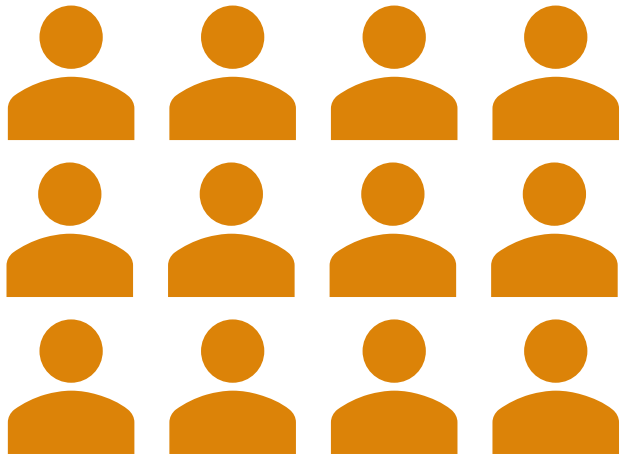
Hearing Loss**
16 (7 to 34)

*N=4; **N=5

Data on File. Amylyx Pharmaceuticals Inc. 2024.

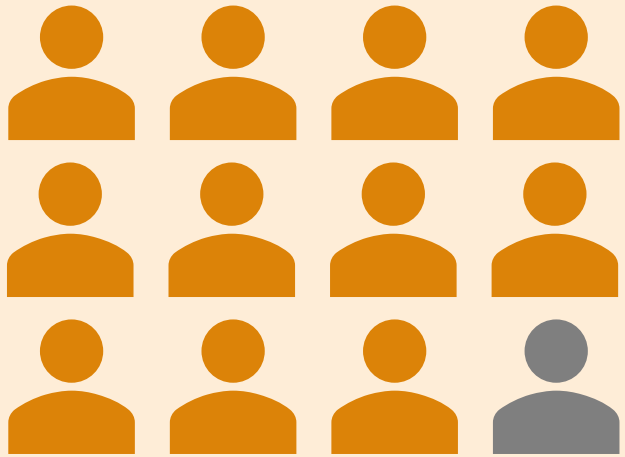
Key Population for Discussion: Participants with Genetically Confirmed Wolfram Syndrome (N=11)

Intent to Treat (ITT) Week 24



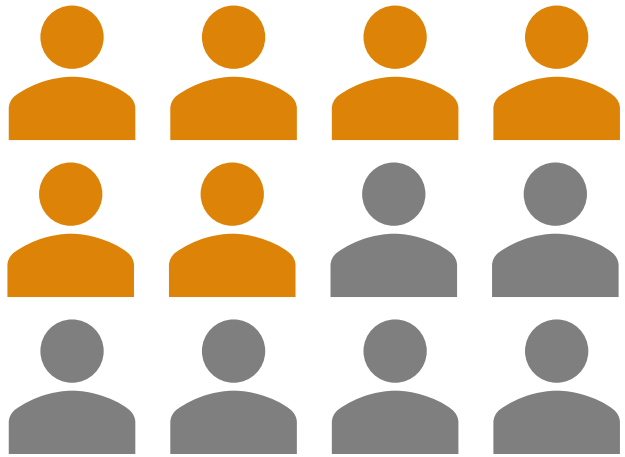
12 Enrolled Participants
received PB&TURSO
*includes 1 participant who did not meet inclusion/exclusion criteria upon genetic review**

Per Protocol Week 24



11 Enrolled Participants
with Definite Diagnosis of Wolfram Syndrome

Available Data Week 48



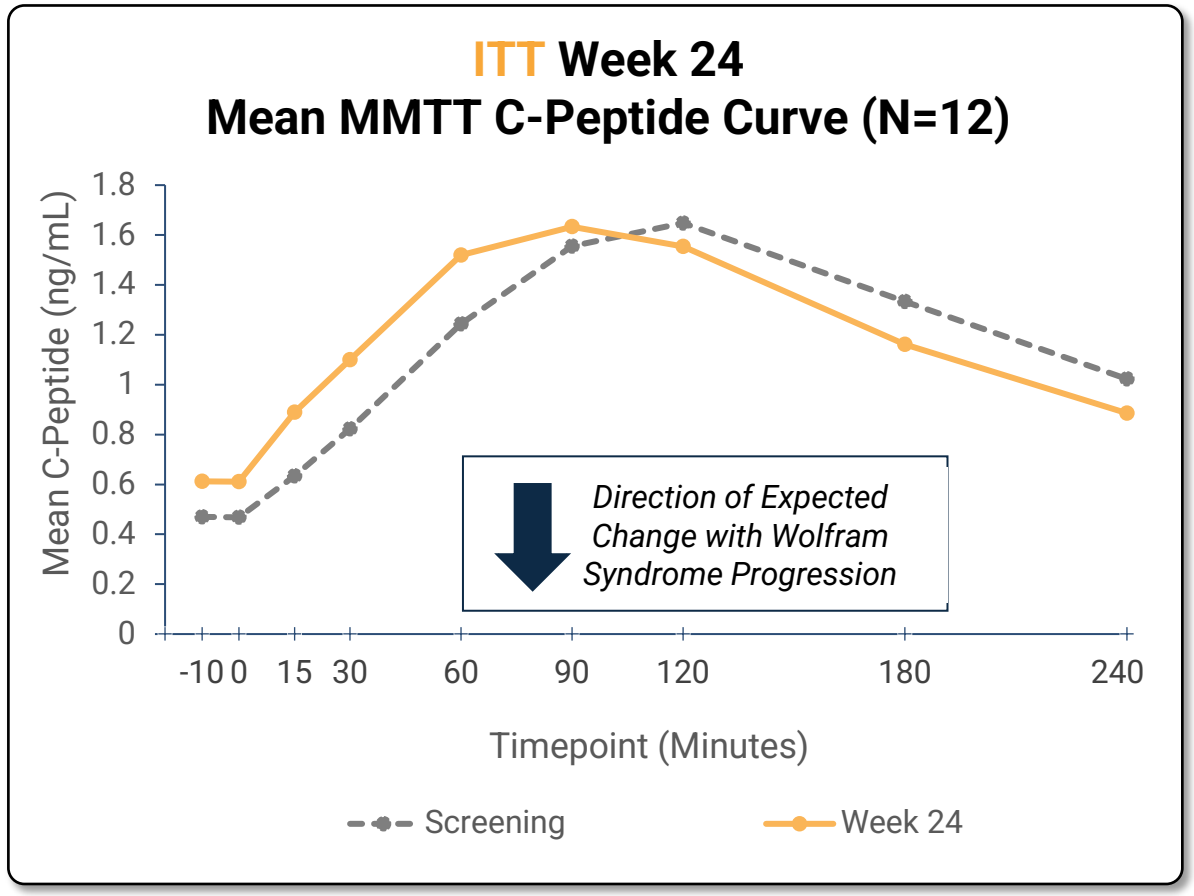
6 Enrolled Participants
with Data Fully Cleaned through Week 48

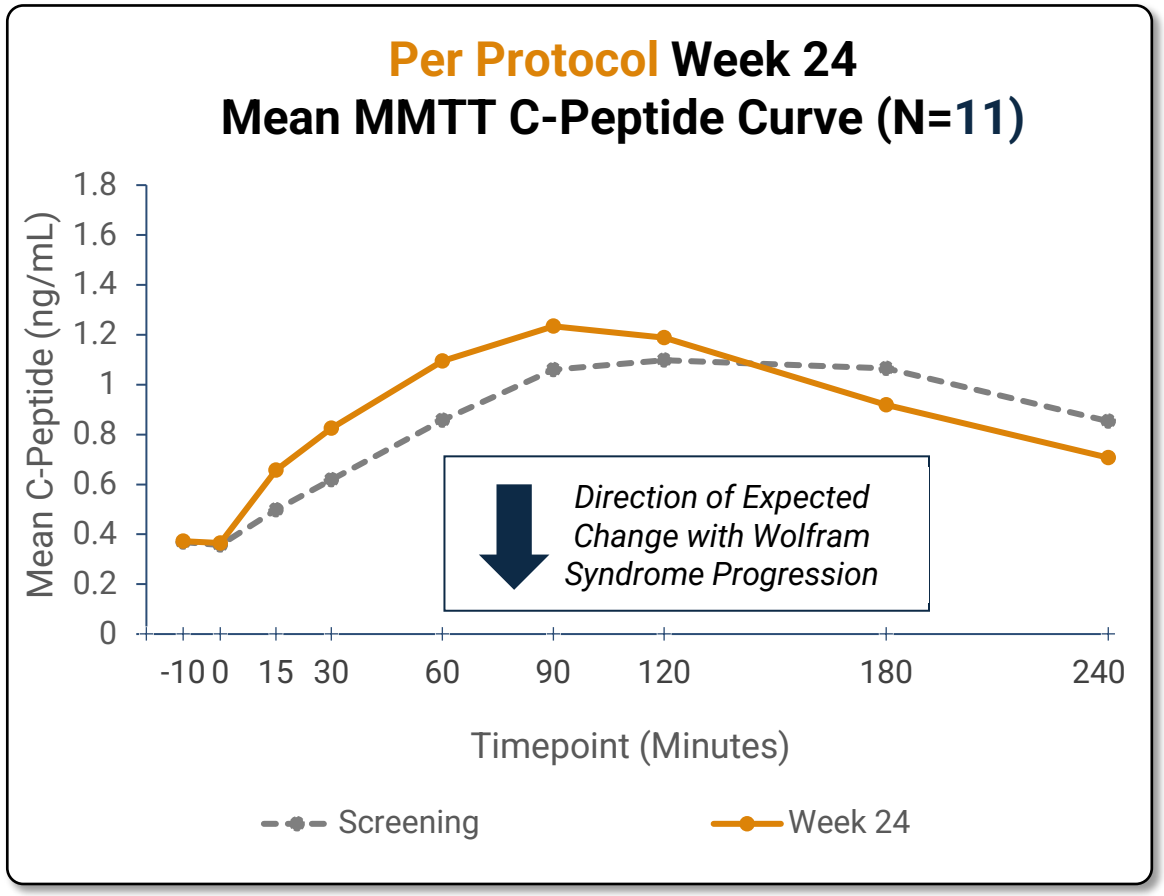
Data on File. Amylyx Pharmaceuticals Inc. 2024.

*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 suggesting lack of typical WS phenotype. In addition, this participant discontinued insulin and was switched to oral anti-diabetic medication.

Primary Endpoint: C-Peptide Response

Improvement in average beta cell responsiveness at Week 24 compared to Screening

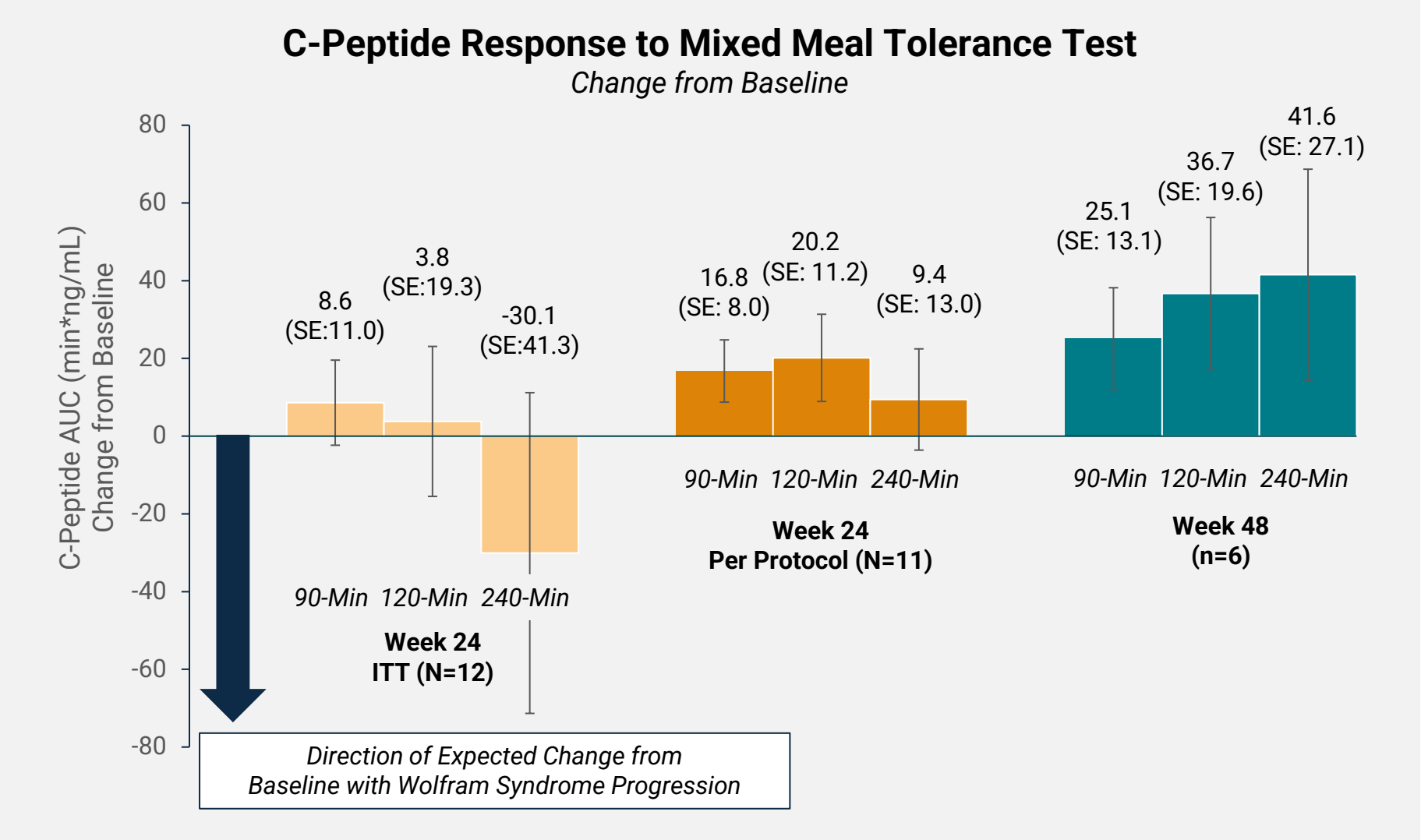




MMTT, mixed-meal tolerance test

Data on File. Amylyx Pharmaceuticals Inc. 2024.

Primary Endpoint: C-Peptide Response

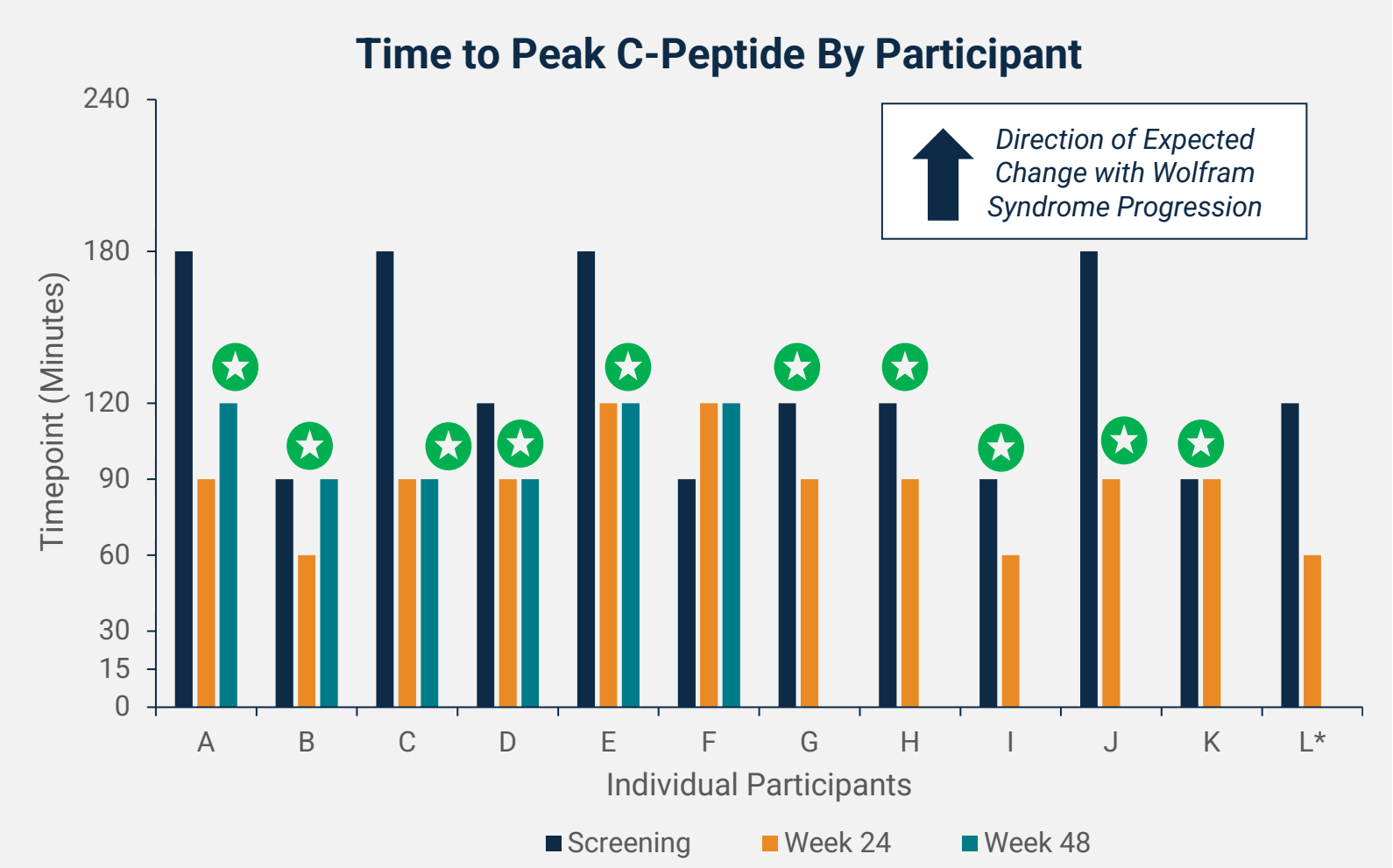


Improvement in in C-Peptide Response Observed at Week 24 Compared to Screening

AUC: Area under the curve; SE: Standard error

Data on File. Amylyx Pharmaceuticals Inc. 2024.

Additional MMTT Analyses: Time to Peak C-Peptide

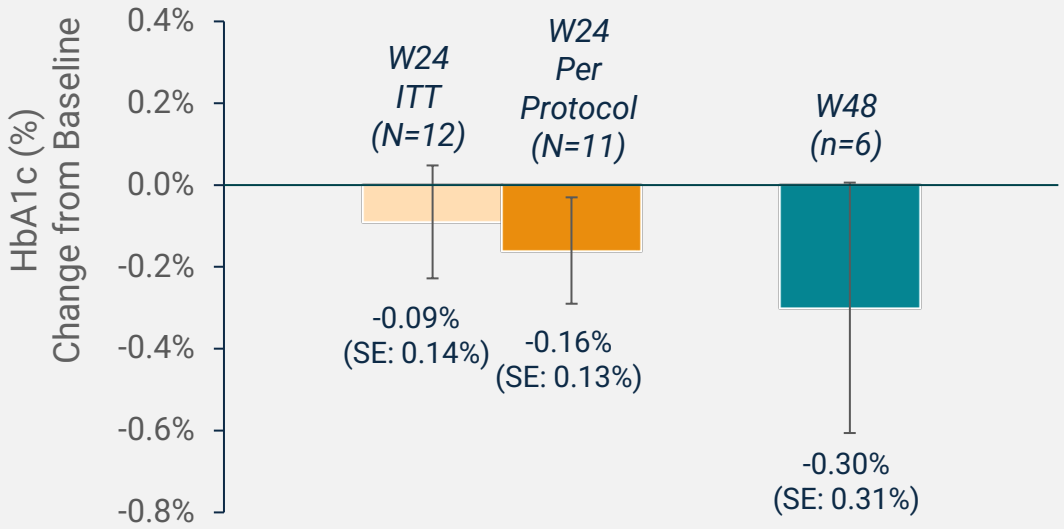


10 of 11 in Per Protocol maintained or decreased time to peak C-peptide at Week 24 compared to screening, suggesting improved pancreatic function

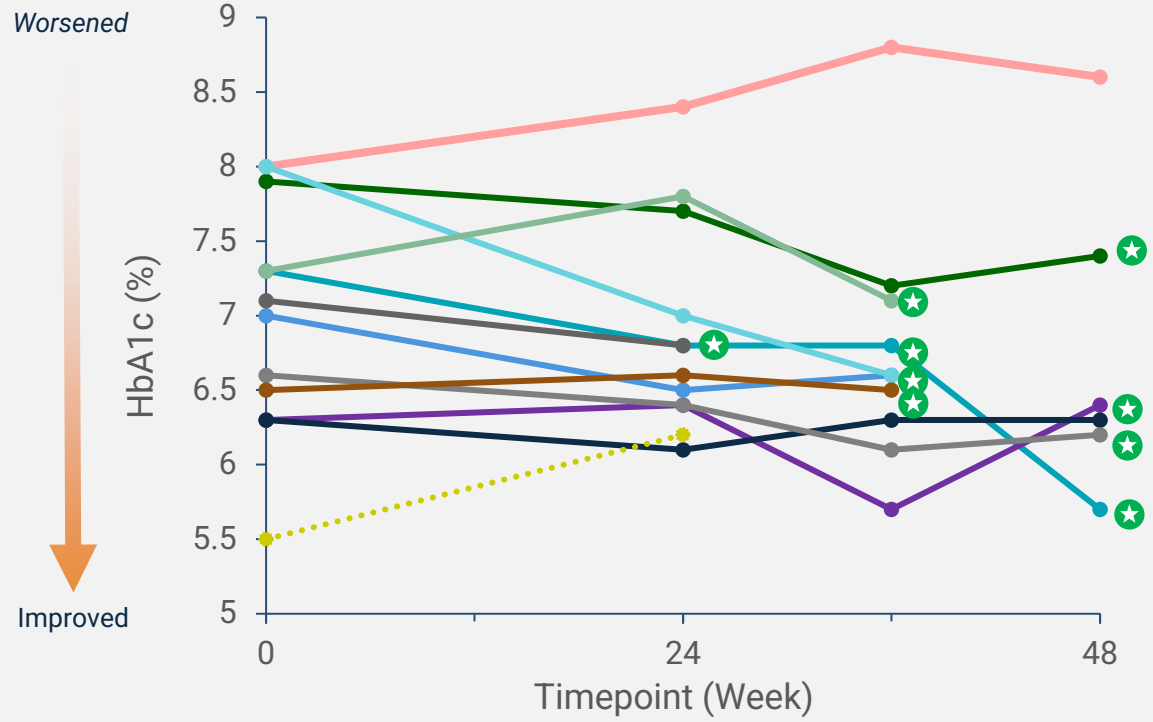
Data on File. Amylyx Pharmaceuticals Inc. 2024.
*Participant not included in the Per Protocol population.

Secondary Endpoint: HbA1c

HbA1c Mean Change from Baseline



HbA1c By Participant



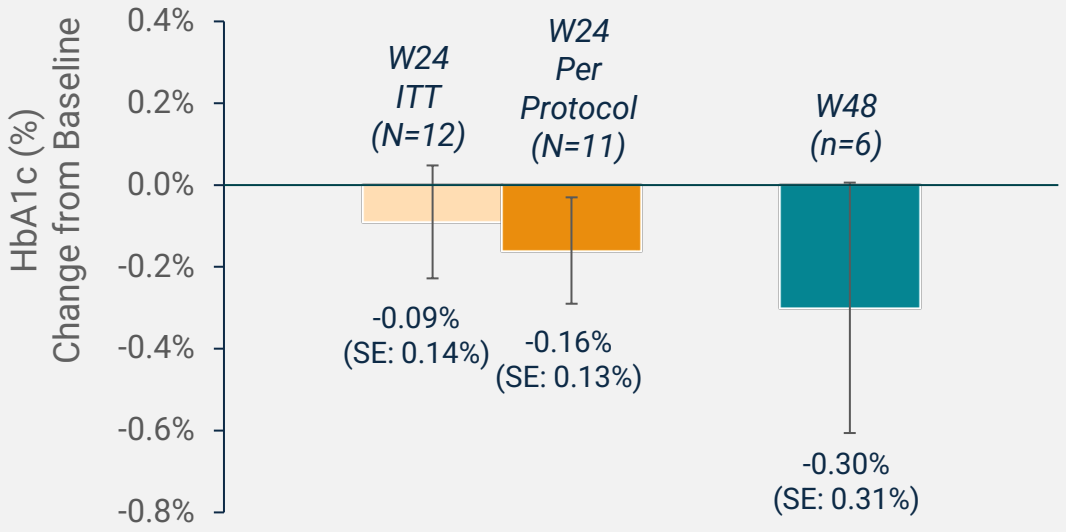
Improved Glycemic Control as Measured by HbA1c at Week 24 Compared to Screening

9 of 11 Per Protocol participants demonstrated reduced or unchanged HbA1c from Screening to the latest available time point

Data on File. Amylyx Pharmaceuticals Inc. 2024.
Dotted line in By Participant graph indicates the participant not included in the Per Protocol population

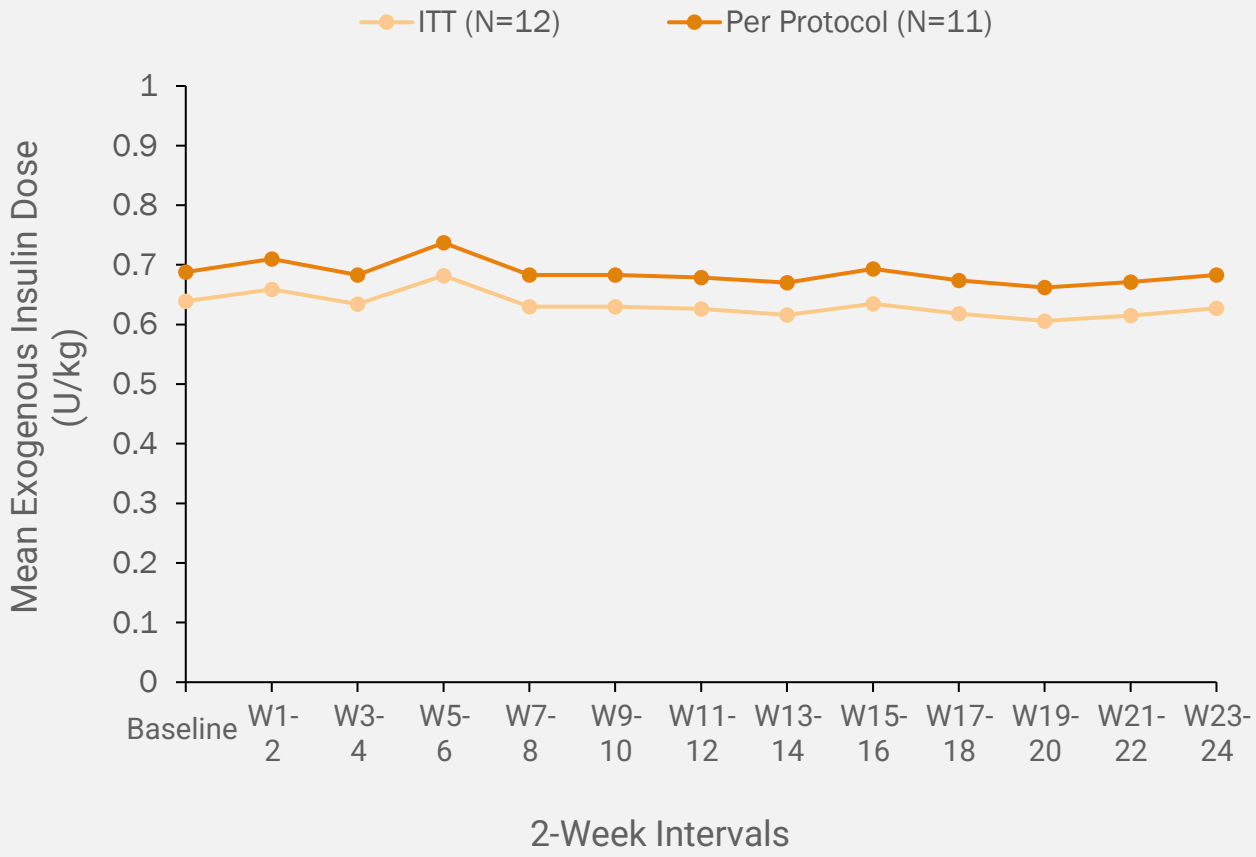
Secondary Endpoint: HbA1c and Exogenous Insulin Dose

HbA1c Mean Change from Baseline



Improved Glycemic Control as Measured by HbA1c at Week 24 Compared to Screening Despite Consistent Insulin Use

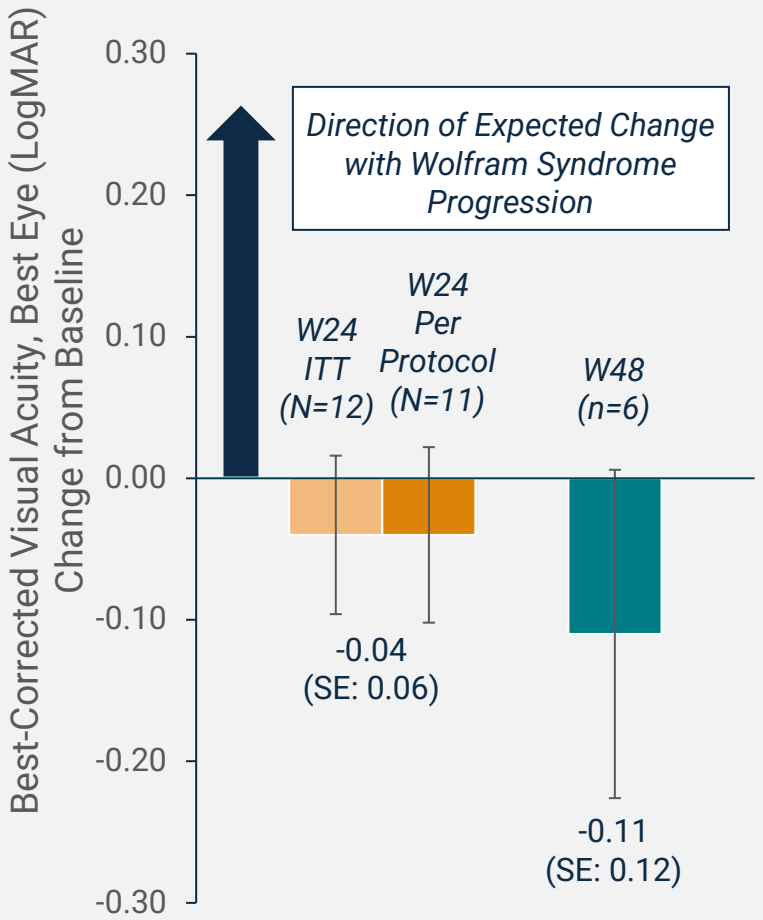
Mean Exogenous Insulin Dose
per kg body weight



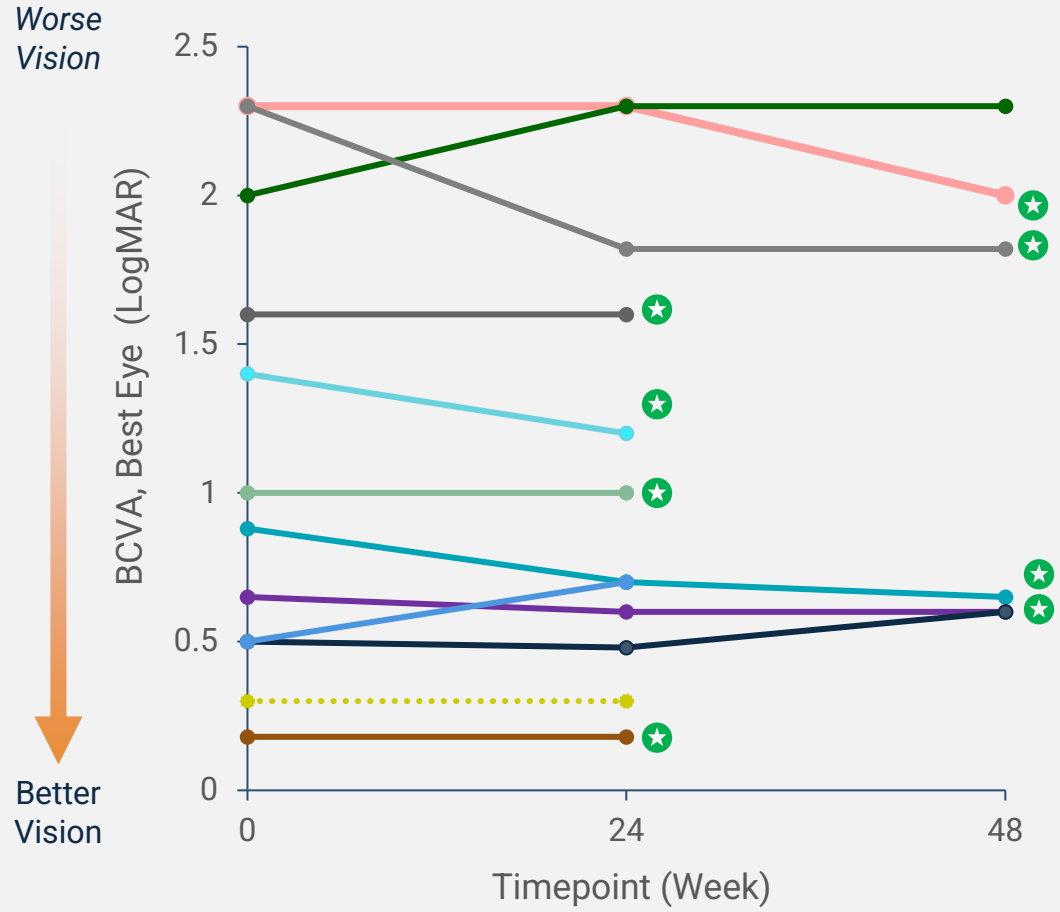
Data on File. Amylyx Pharmaceuticals Inc. 2024.

Secondary Endpoint: Best Corrected Visual Acuity (BCVA)

BCVA, Best Eye Mean Change from Baseline



BCVA, Best Eye by Participant



8 of 11 in Per Protocol demonstrated improved or stable visual acuity in their best eye from Screening to latest available timepoint

Of remaining participants:

- *2 stable in one eye*
- *1 worsened*

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

Data on File. Amylyx Pharmaceuticals Inc. 2024.

PB&TURSO Safety and Tolerability

- PB&TURSO was **generally well tolerated**
  - Diarrhea was the most common TEAE (50.0%); all cases were of mild severity
  - All TEAEs were graded mild or moderate
- **No new safety signals** were identified
- Nearly all participants reported ≥1 TEAE during the trial
  - 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 (91.7%)
TEAE related to study drug** – n (%)	9 (75.0%)
Serious adverse events – n (%)	0 (0%)
Drug interrupted owing to TEAE — n (%)	3 (25.0%)
Dose reduced owing to TEAE — n (%)	3 (25.0%)
Drug discontinued owing to TEAE — n (%)	0 (0%)

*All available safety data as of July 31, 2024 included
**Includes those with TEAEs considered possibly related to treatment; none considered “probably related” or “definitely related”

Data on File. Amylyx Pharmaceuticals Inc. 2024.

Key Takeaways

- Wolfram syndrome is a progressive, genetic disease caused by mutations in *WFS1* that cause **endoplasmic reticulum (ER) stress and impaired mitochondrial dynamics**
- There are currently **no disease-modifying therapies** for Wolfram syndrome
- PB&TURSO has been shown to mitigate ER stress and mitochondrial dysfunction
- HELIOS analysis demonstrated **improvement in pancreatic function and glycemic control**, as measured by C-peptide and other markers of glucose metabolism
- **Improvements were also seen in secondary and exploratory endpoints** though the degree of benefit was variable
- Analyses once all participants have completed Week 48 will provide more insight
- Results will inform **planned phase 3 program**

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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