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

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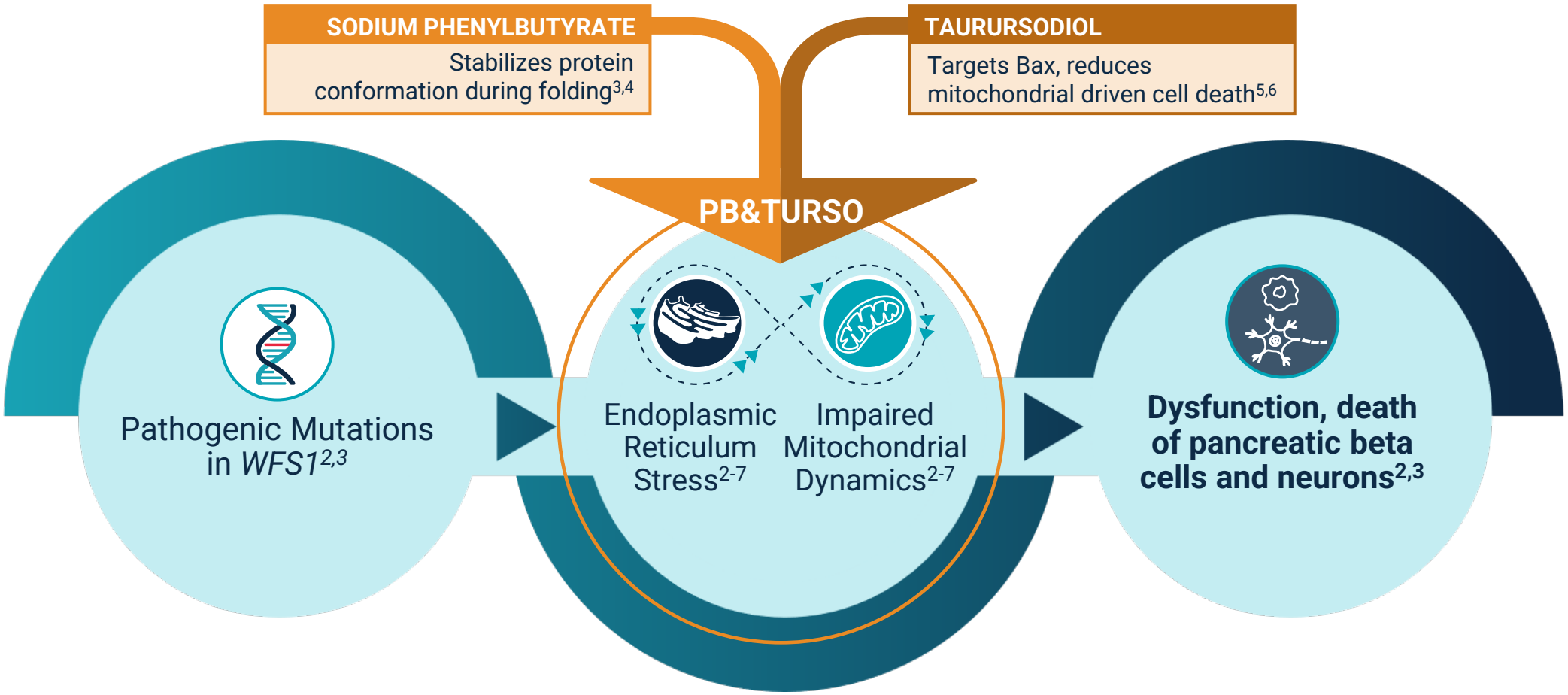
Please Note

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.

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.

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

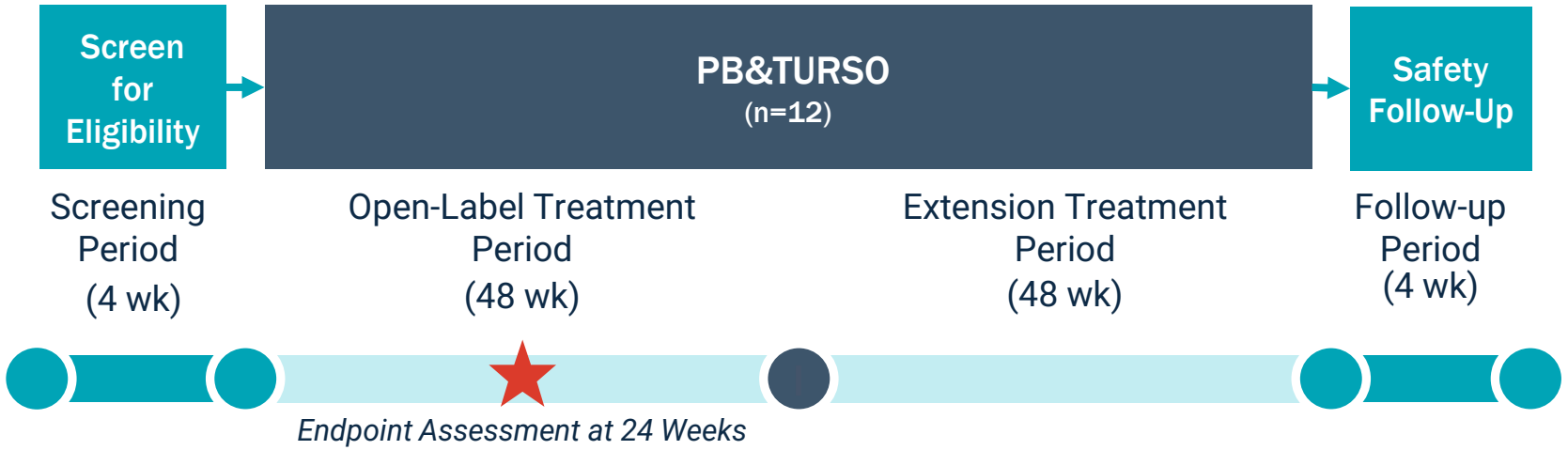
JCI insight

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

HELIOS Trial Design

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)

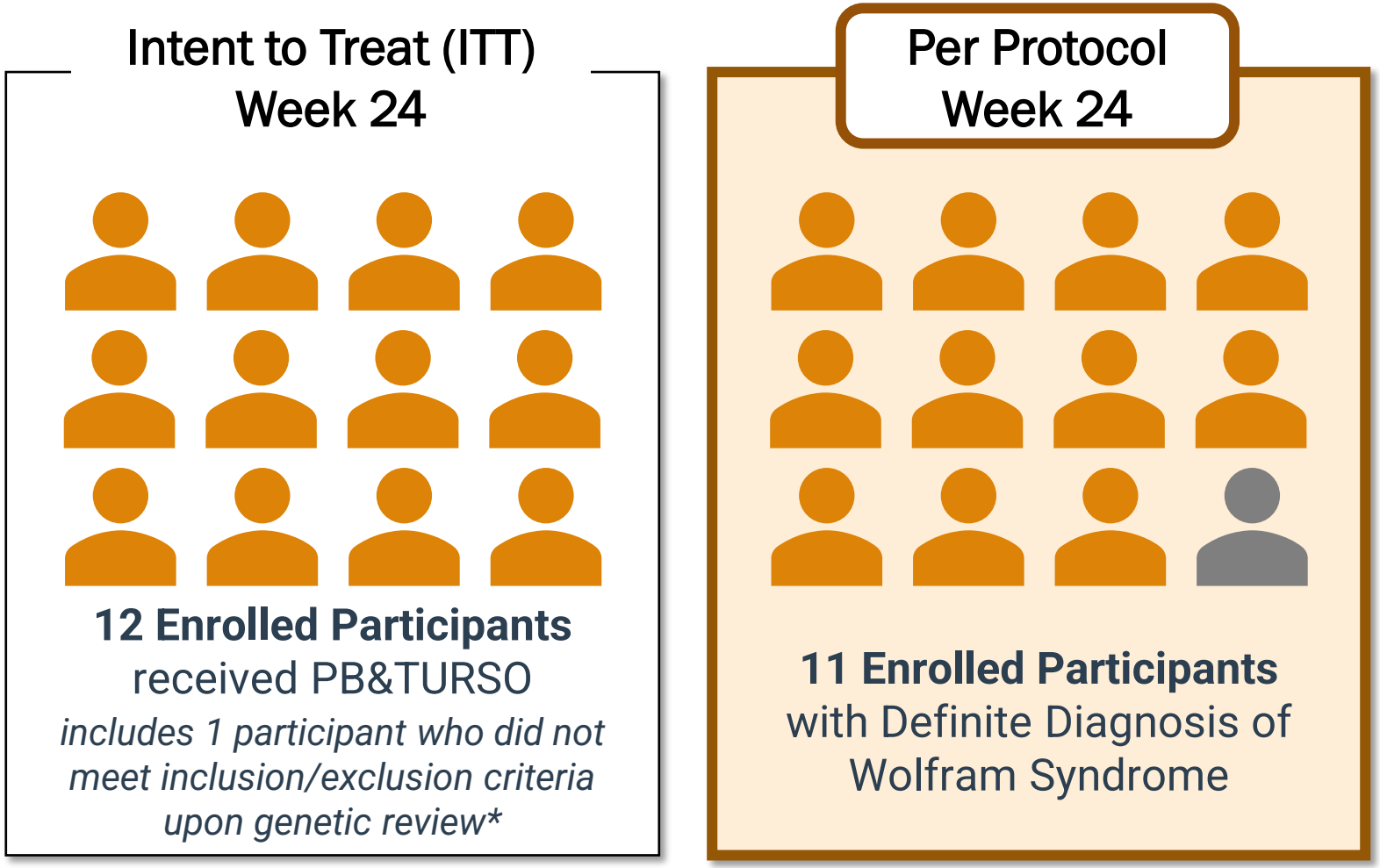
Vision Loss
12 (5 to 29)

Hearing Loss**
16 (7 to 34)

*N=4; **N=5

Data on File. Amylyx Pharmaceuticals Inc. 2024.

Key HELIOS Analysis Populations



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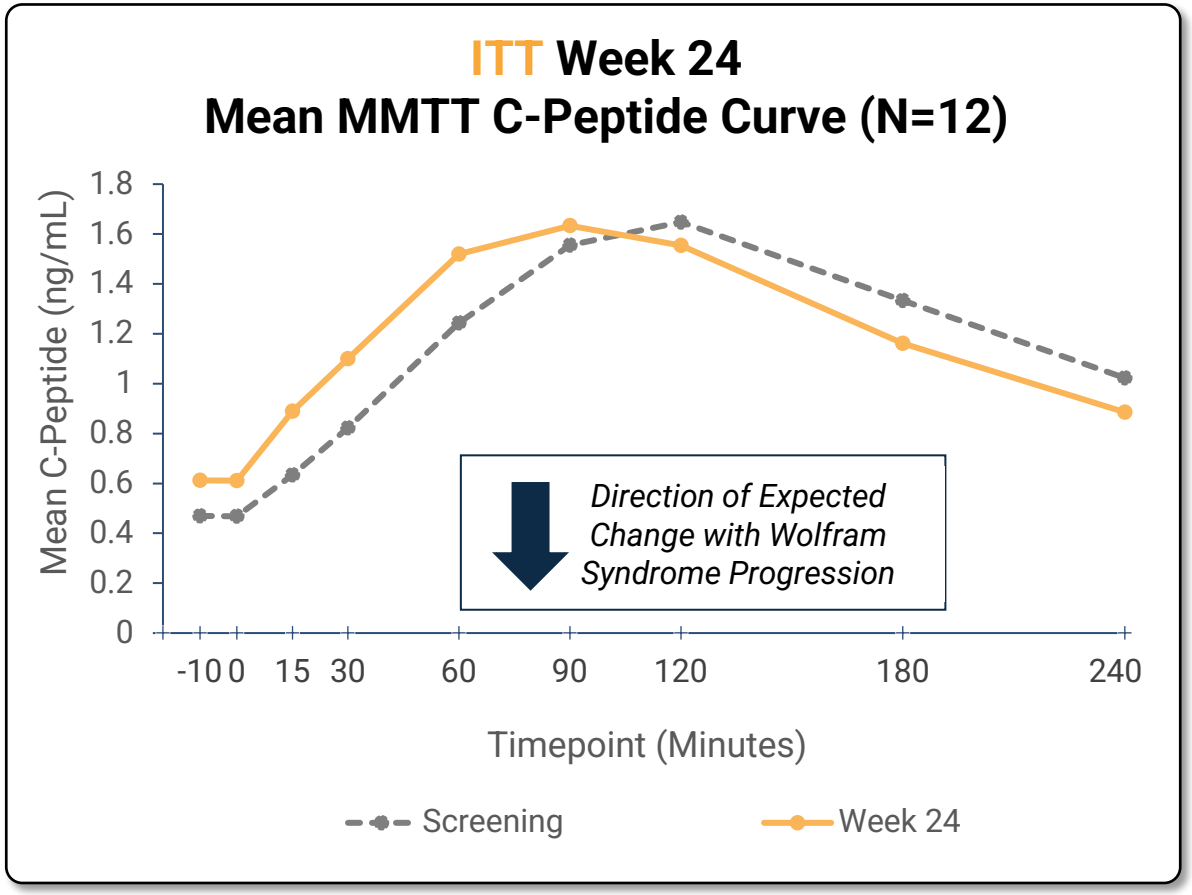
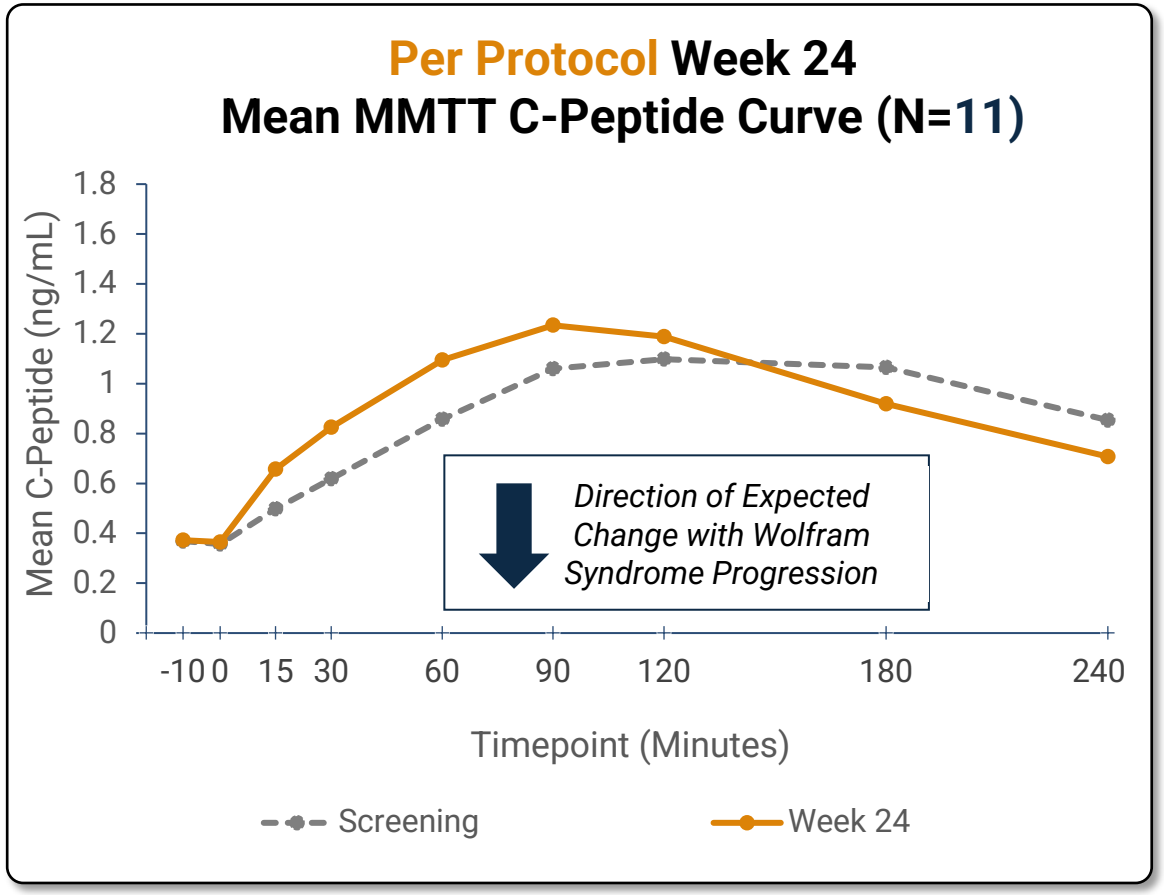
*Participant found to have an autosomal recessive mutation confirmed to be pathogenic on just one of the two alleles and variant of uncertain significance on the other allele. Participant was within normal range for C-peptide, glycemic measures, and vision throughout suggesting lack of typical WS phenotype.In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

Primary Endpoint: C-Peptide Response

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

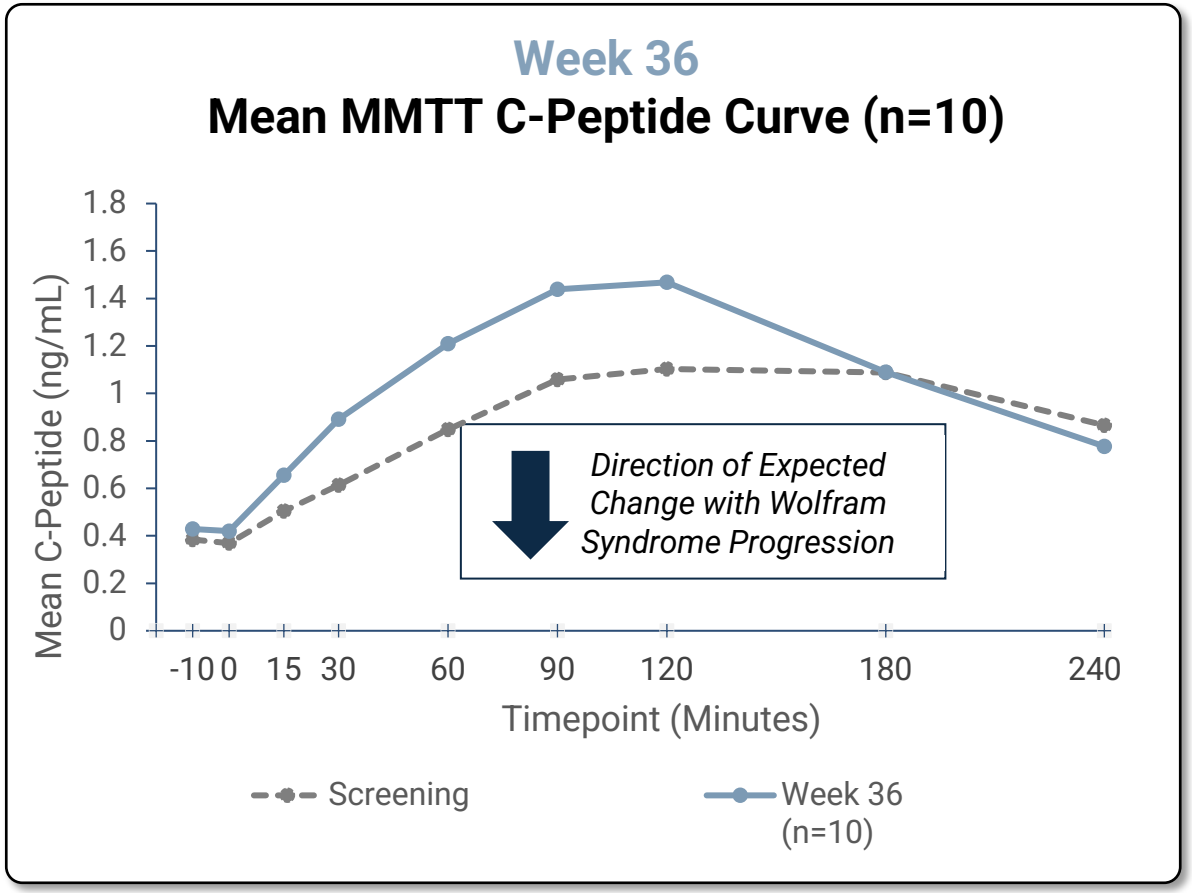


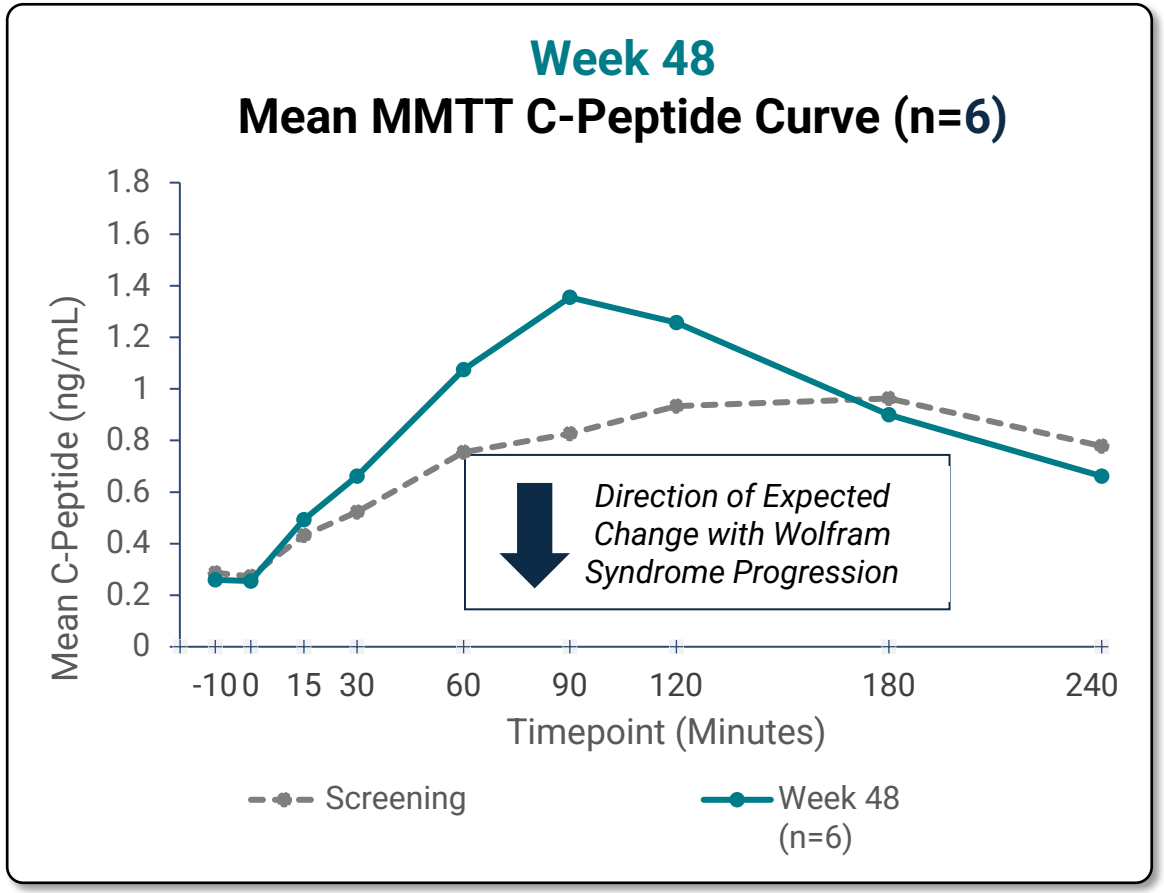


MMTT, mixed-meal tolerance test

Data on File. Amylyx Pharmaceuticals Inc. 2024.

Primary Endpoint: C-Peptide Response





MMTT, mixed-meal tolerance test

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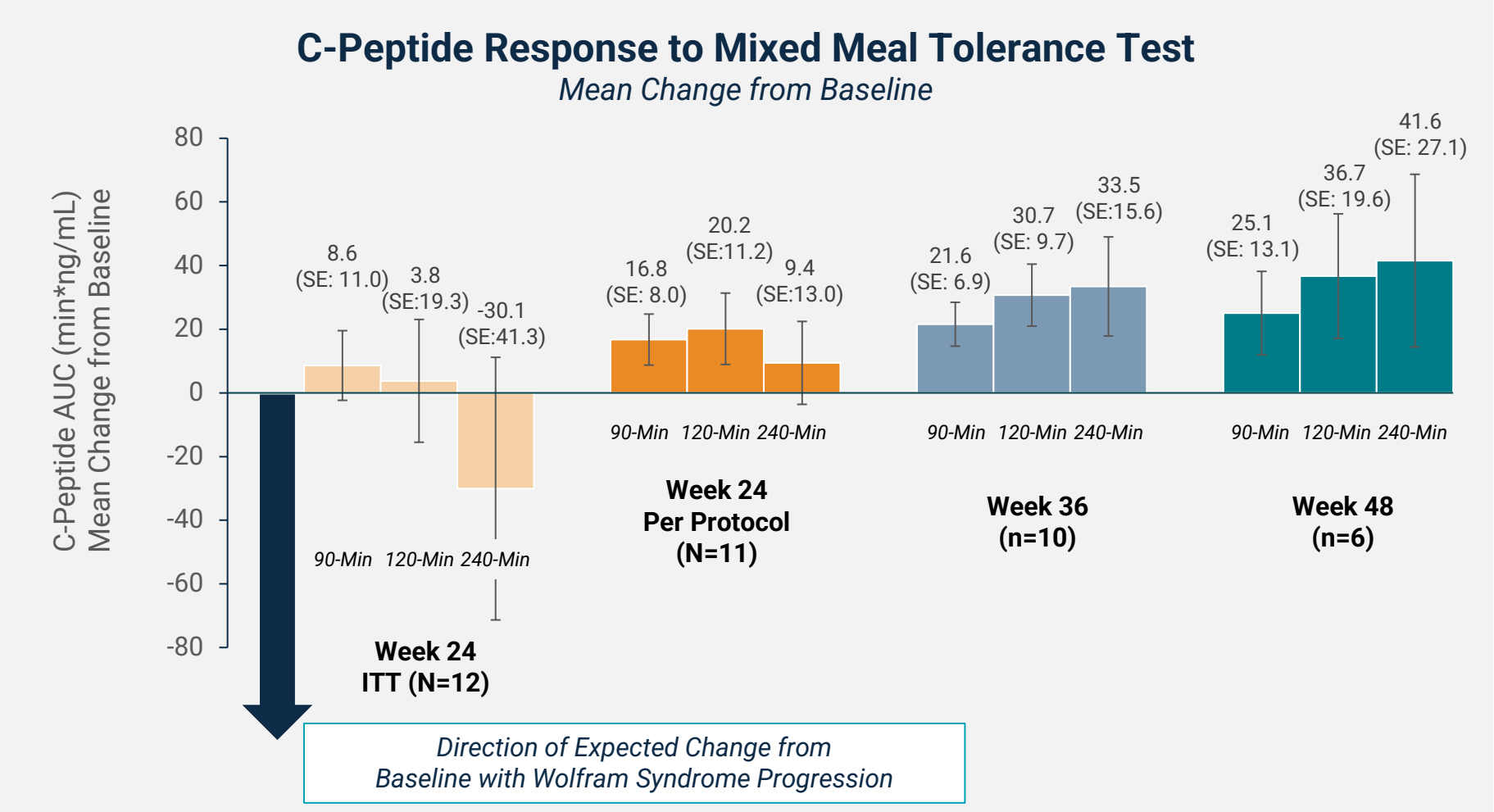
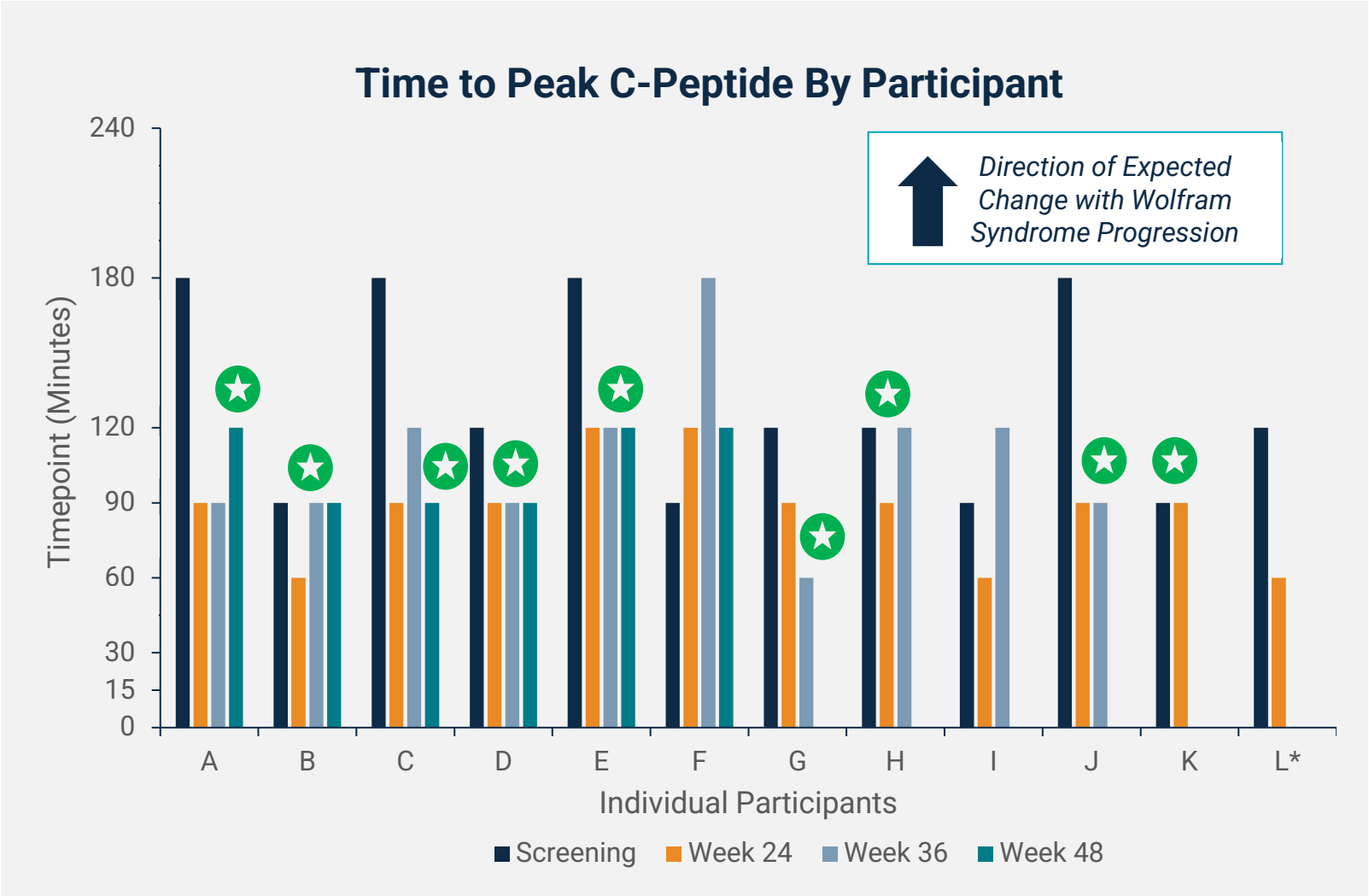
Primary Endpoint: C-Peptide Response (AUC of Levels)



Improvement in in C-Peptide Response Observed Compared to Screening

AUC, Area under the concentration time curve
Data on File. Amylyx Pharmaceuticals Inc. 2024.

Additional MMTT Analyses: Time to Peak C-Peptide



9 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

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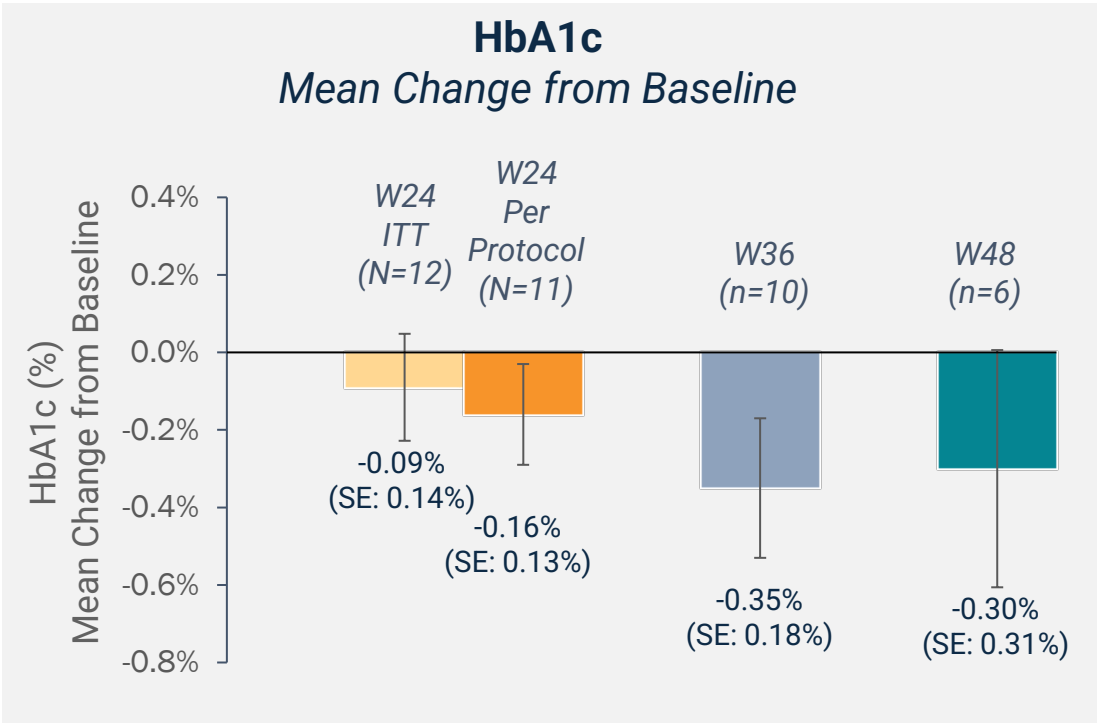
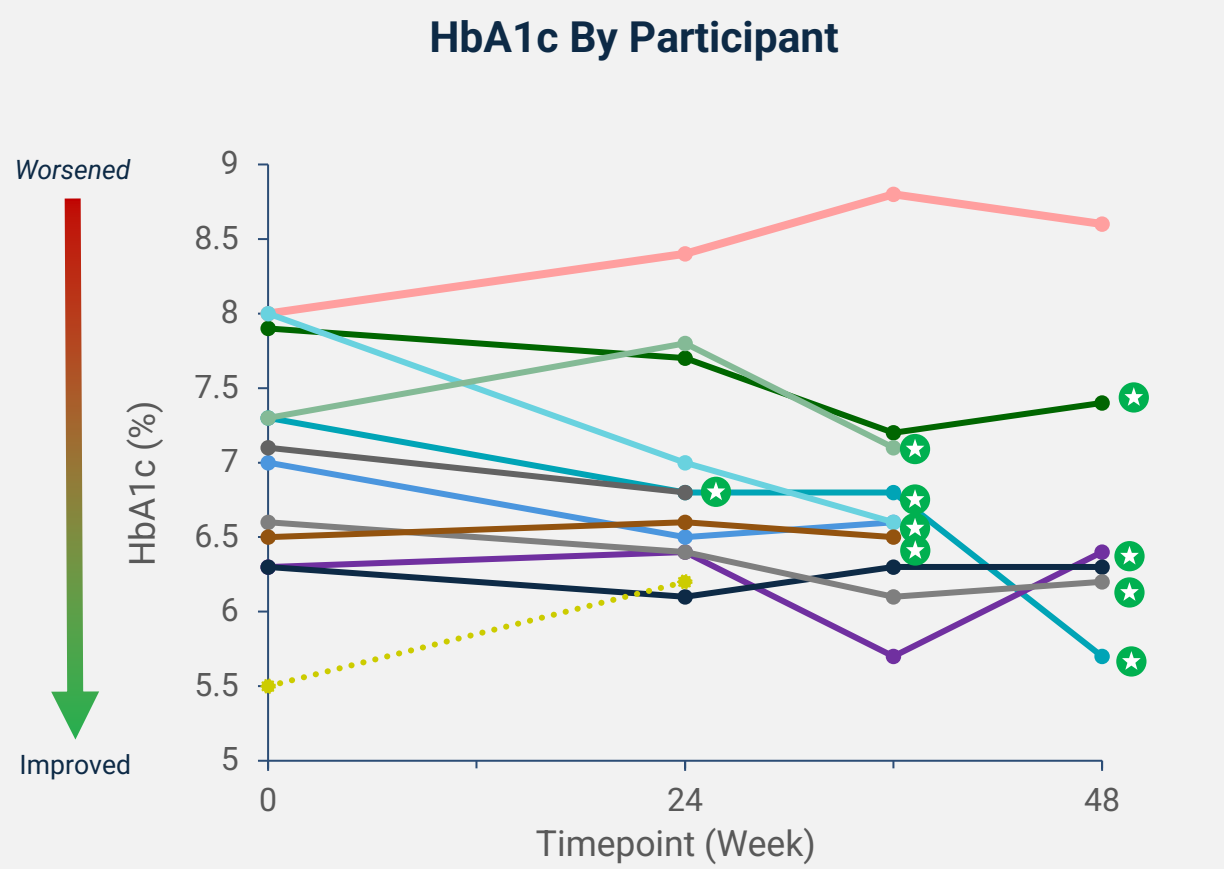
Secondary Endpoint: HbA1c



Improved Glycemic Control as Measured by HbA1c Compared to Screening

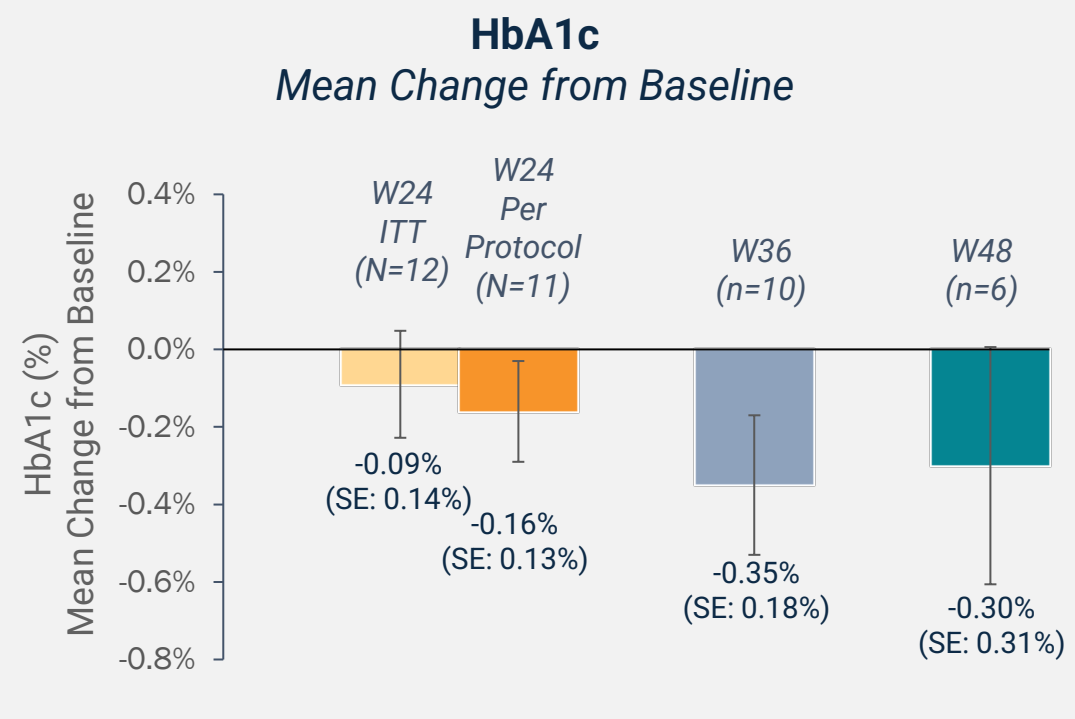


9 of 11 Per Protocol participants demonstrated reduced or stable HbA1c from Screening to the latest available time point

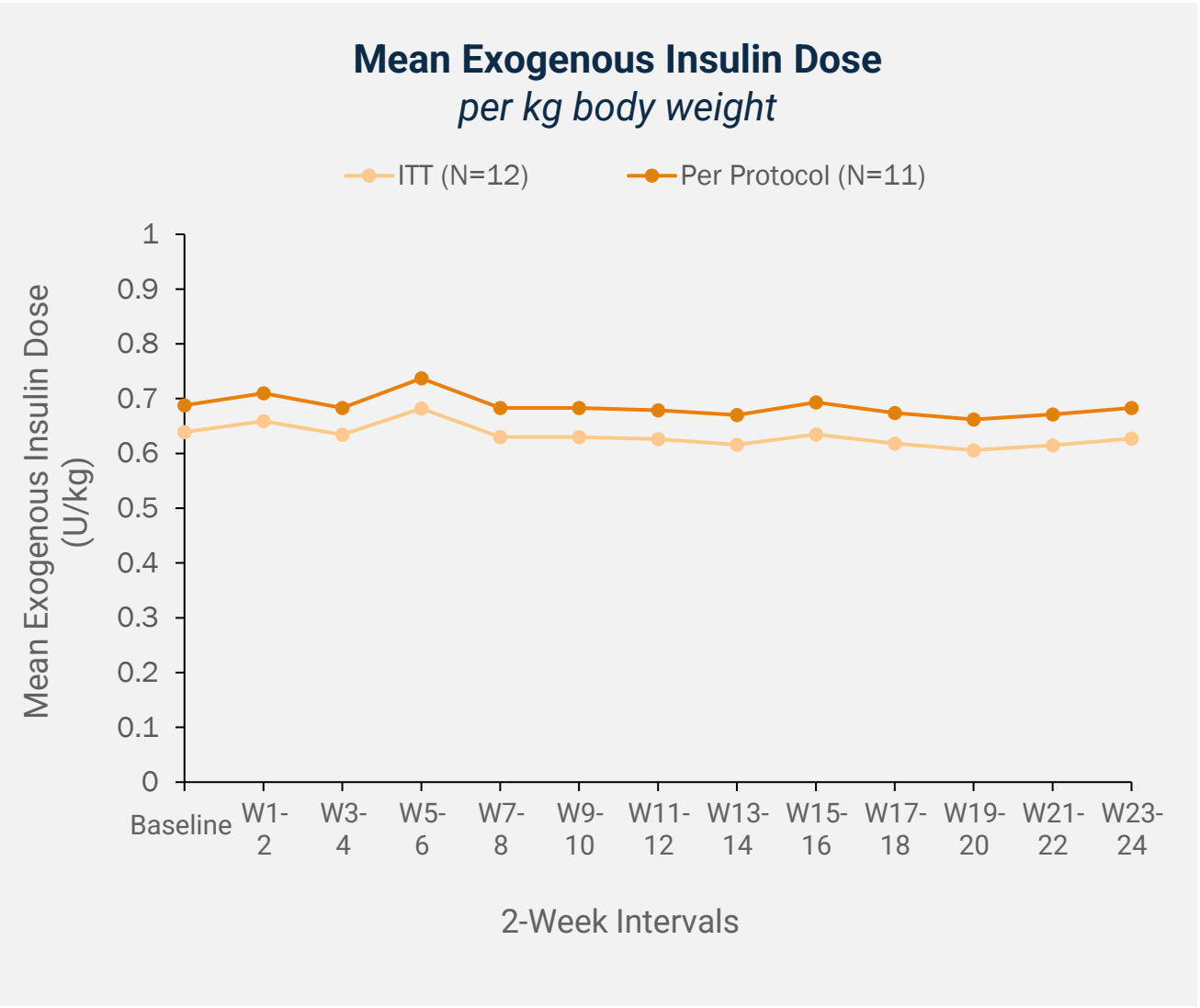
Dotted line in By Participant graph indicates the participant not included in the Per Protocol population

Data on File. Amylyx Pharmaceuticals Inc. 2024.

Secondary Endpoint: HbA1c and Exogenous Insulin Dose

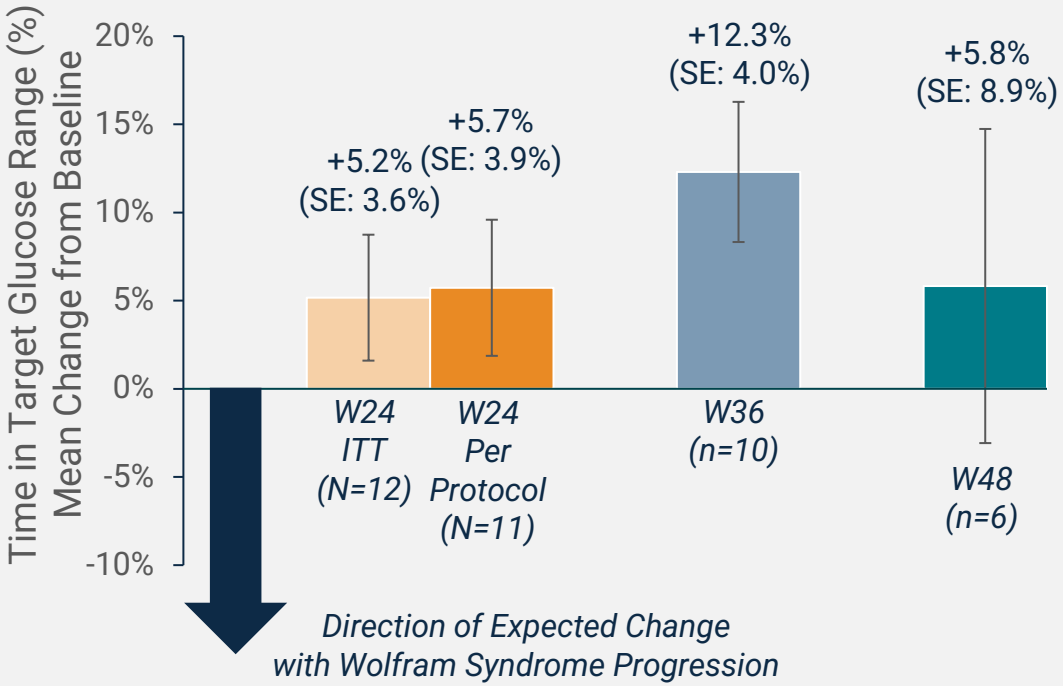


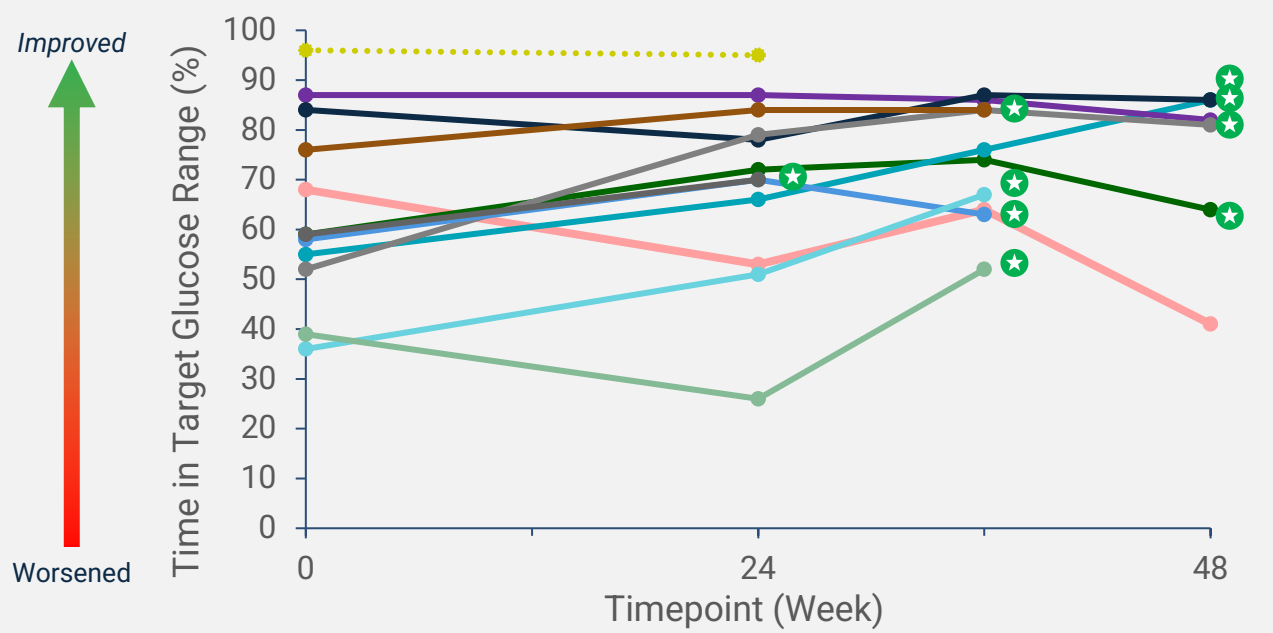
Improved Glycemic Control as Measured by HbA1c at Week 24 Compared to Screening Despite Consistent Insulin Use



Data on File. Amylyx Pharmaceuticals Inc. 2024.

Secondary Endpoint: Overall Time in Target Glucose Range*





Improved Glycemic Control as Assessed by Continuous Glucose Monitoring (CGM) Compared to Screening

★ *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
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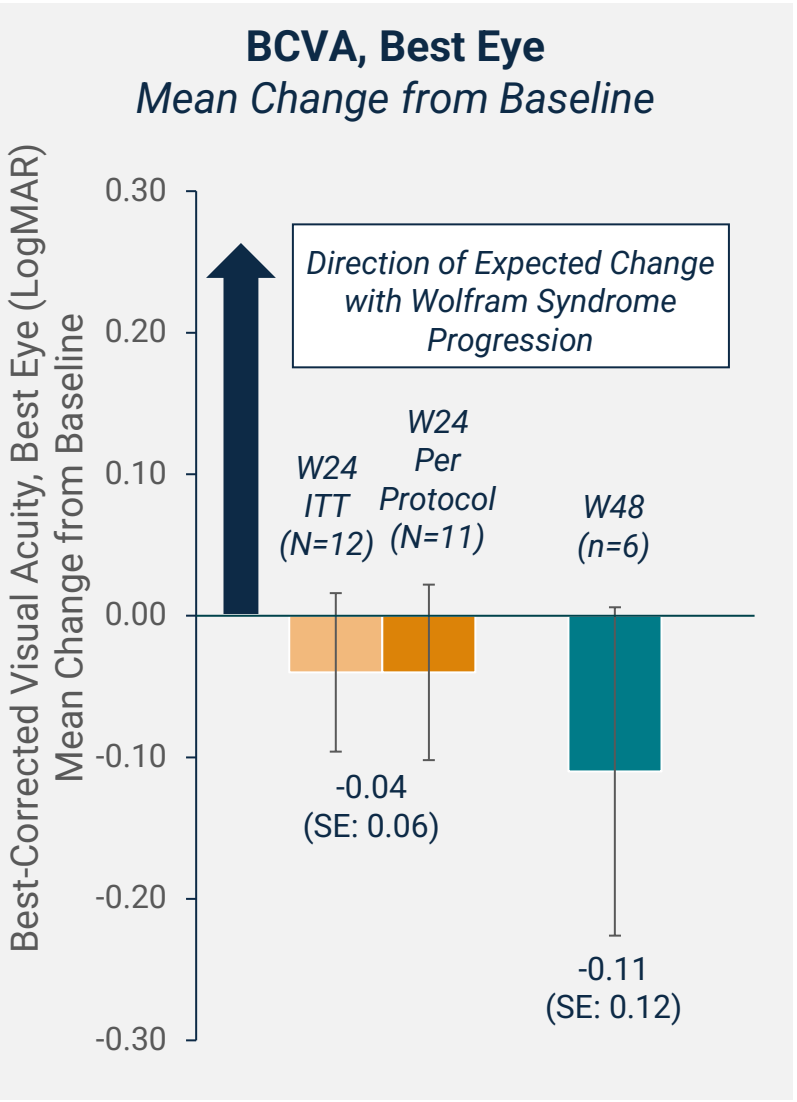
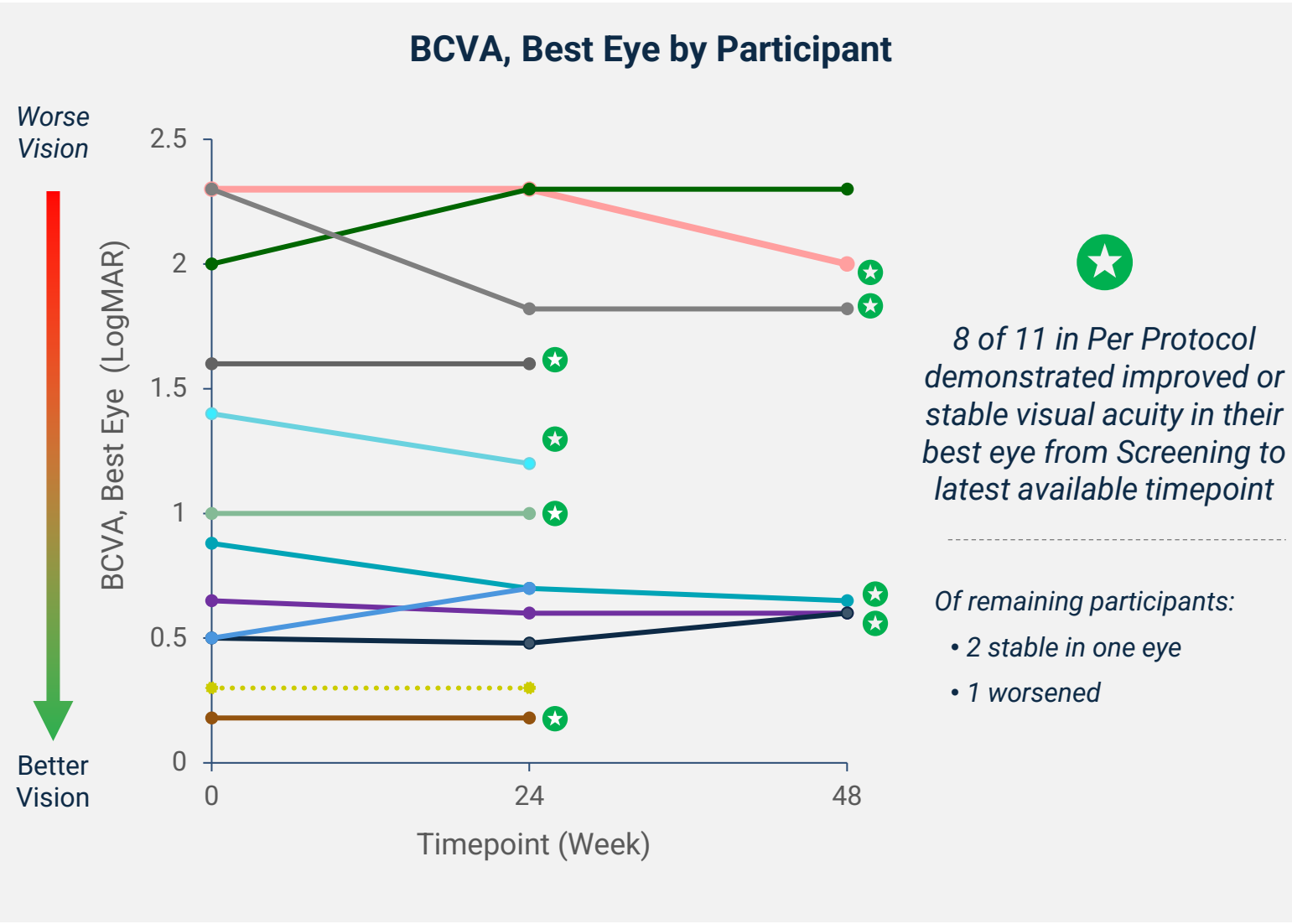
Secondary Endpoint: Best Corrected Visual Acuity (BCVA)





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.

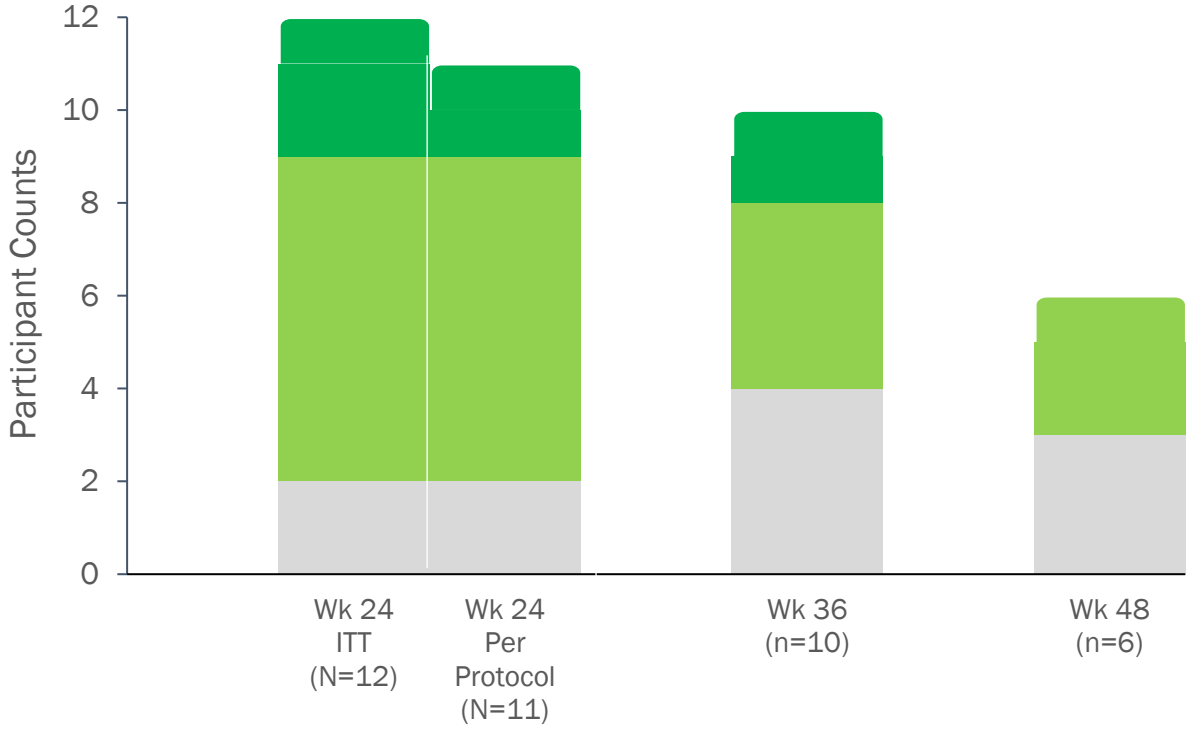
Exploratory Endpoint: PGI-C and CGI-C

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

At Week 24, 82% of Per Protocol participants claimed to have improved on PB&TURSO; 73% improved based on clinician report

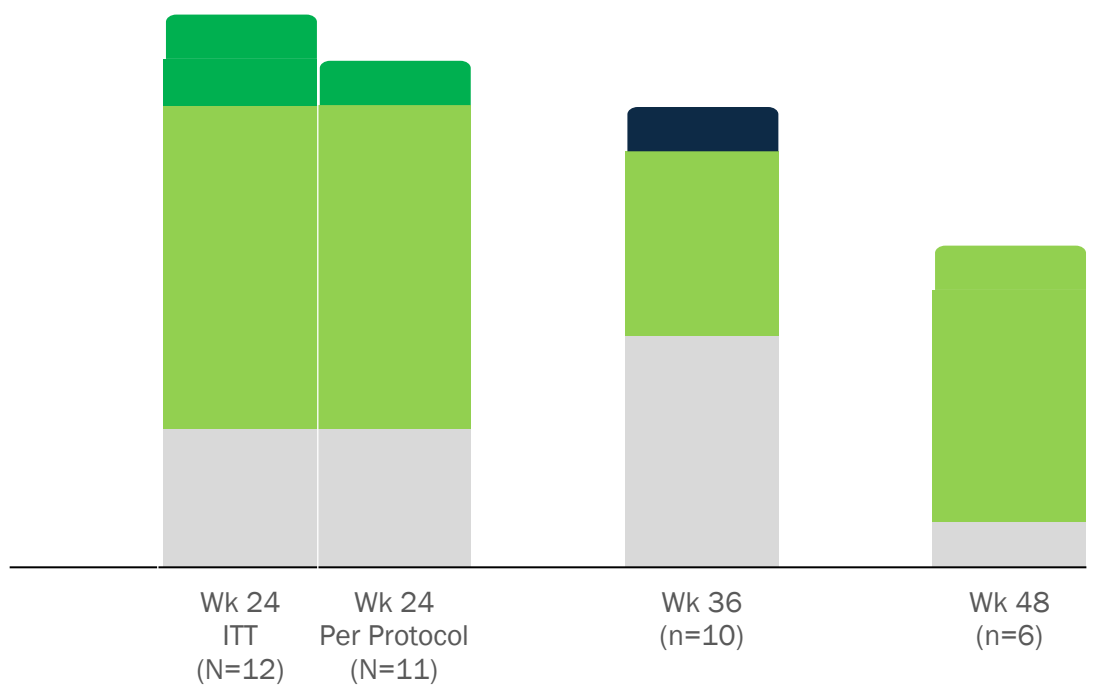
Patient-Reported Global Impression of Change (PGI-C)

Change from Baseline



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

Change from Baseline



Very Much Improved Much Improved Minimally Improved No Change

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

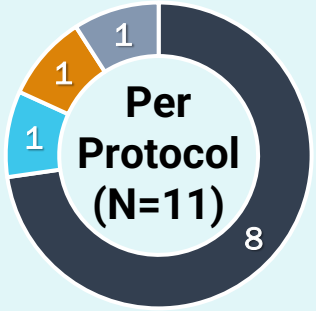
Data on File. Amylyx Pharmaceuticals Inc. 2024.

Exploratory Endpoint: Most Bothersome Symptom

Most Bothersome Symptom at Baseline

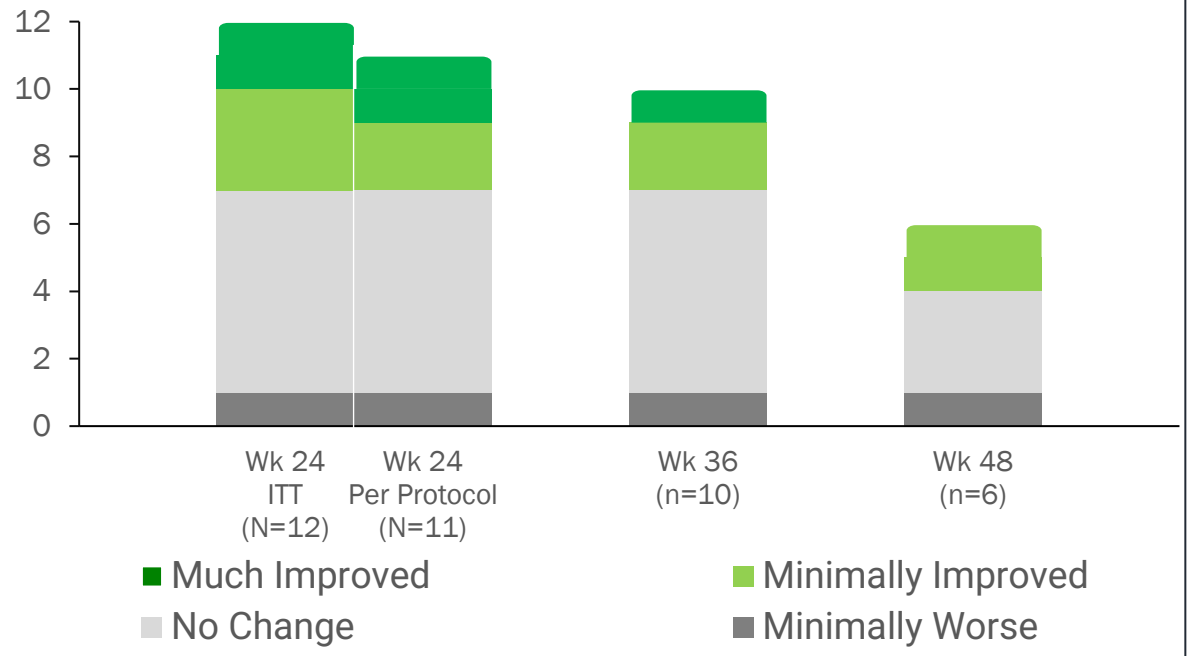
as reported by participant

- Vision Impairment
- Headaches
- Diabetes Mellitus
- Overheating



Most Bothersome Symptom

Change from Baseline



At Week 24, 91% of Per Protocol participants reported stabilization or improvement from baseline in their most bothersome symptom

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.

Limitations

- Open-label, single-arm study
- 12 adult participants
- Clinical heterogeneity in individuals with Wolfram syndrome (e.g., based on the severity of the *WFS1* gene variants)
- Developing understanding of the genetics of Wolfram syndrome (e.g., classification of variants of uncertain significance)

Data on File. Amylyx Pharmaceuticals Inc. 2024.

Key Takeaways

- Wolfram syndrome is a progressive, genetic disease caused by pathogenic variants 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 interim analysis demonstrated **improvement in pancreatic function and glycemic control**, as measured by C-peptide and other markers of glucose metabolism
- **Improvements were also seen across secondary and exploratory endpoints** though the degree of benefit was variable
- Analyses once all participants have completed Week 48 will provide additional 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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