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Phase 2 HELIOS Topline Data in Wolfram Syndrome

October 17, 2024

Raquel, living with Wolfram syndrome.

Disclaimer

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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

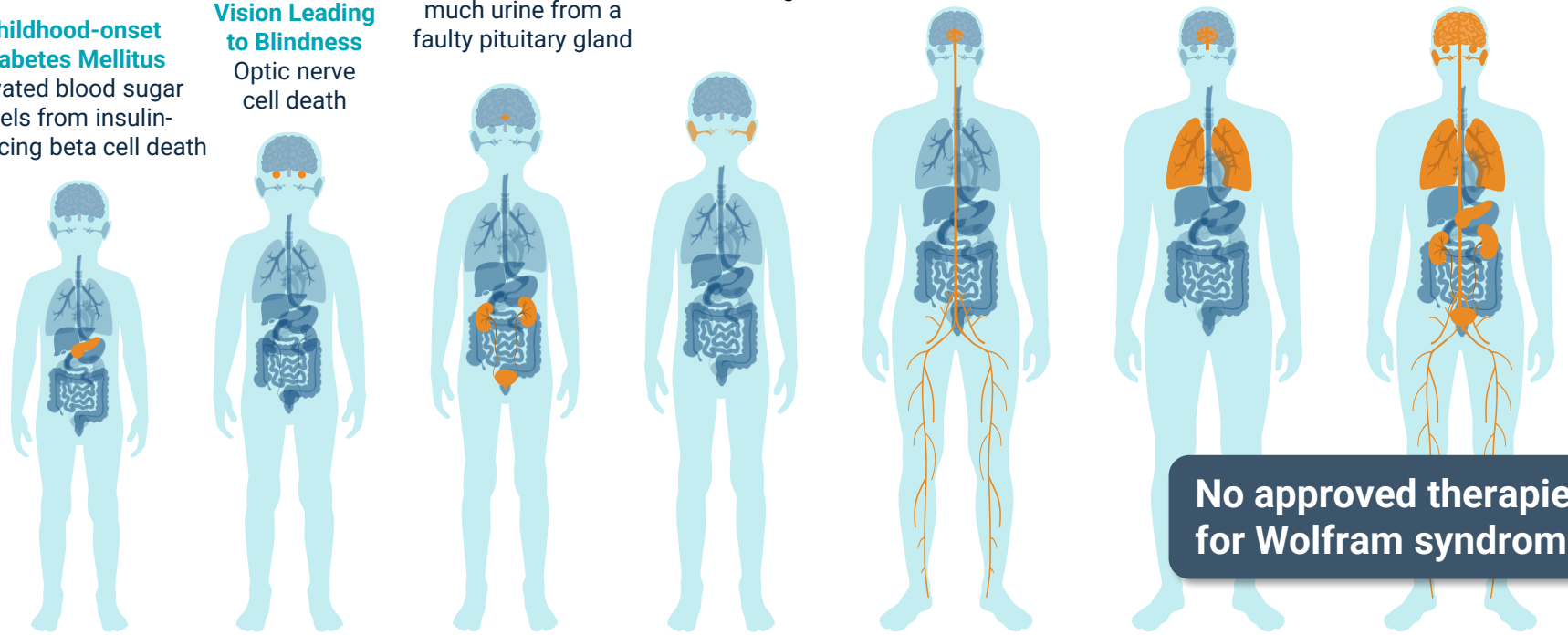
Diabetes Insipidus
Kidneys produce too much urine from a faulty pituitary gland

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 of 30 years
(range 25-49 years), **mainly from respiratory failure**

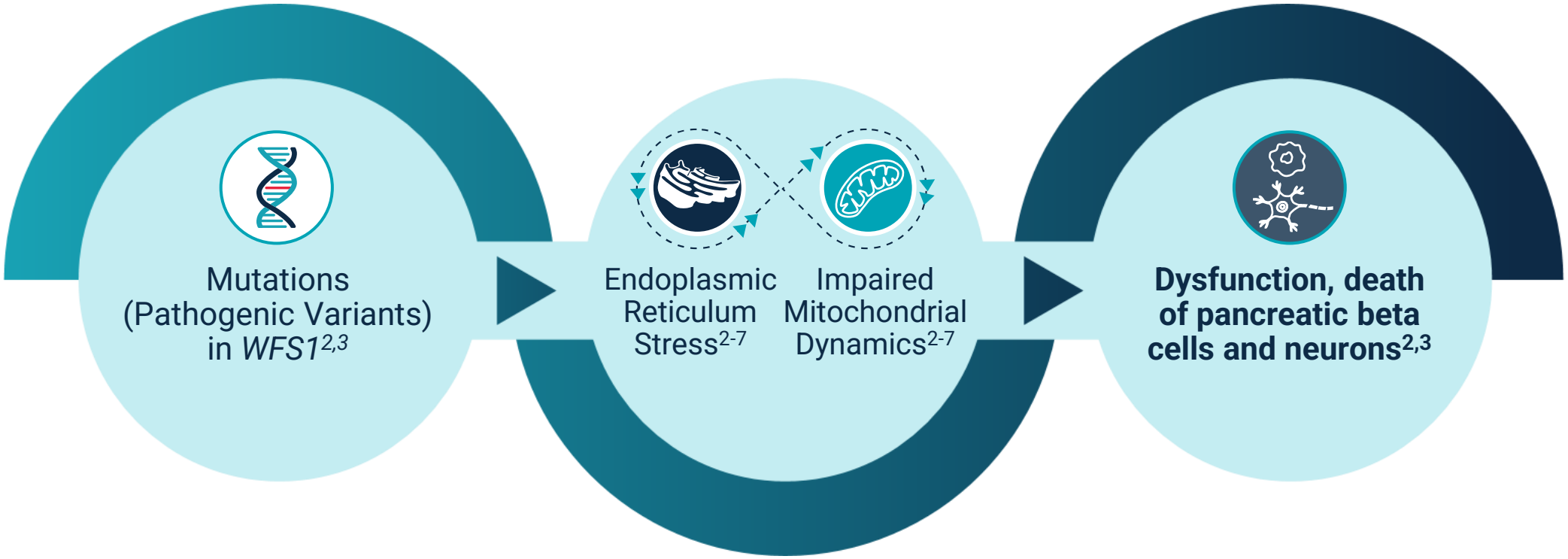


~3,000
people living with Wolfram syndrome in the U.S.[1,2]

No approved therapies 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):6.

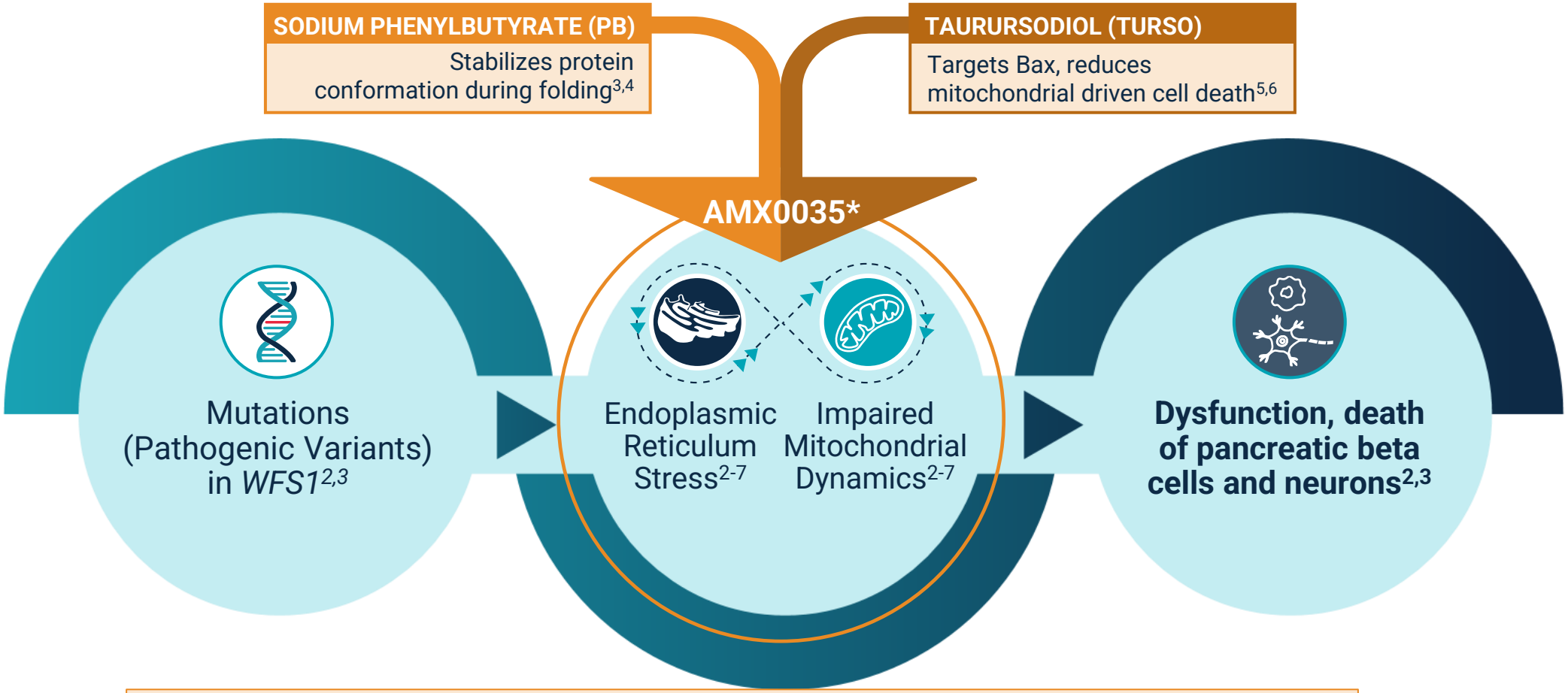
Wolfram Syndrome is a Prototypical Endoplasmic Reticulum Stress Disorder[1]



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.

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

AMX0035 targets endoplasmic reticulum stress and related mitochondrial dysfunction pathways



CLEAR LINK OF **MECHANISM OF DISEASE** AND **MECHANISM OF AMX0035**

* Results for AMX0035 are synergistic relative to PB or TURSO alone. Supported by data on file with Amylyx & Cohen. J., et al. Clinical trial design for a phase II, randomized, placebo-controlled trial of AMX0035 in amyotrophic lateral sclerosis (CENTAUR). Poster presented at: 28th International Symposium for ALS/MND; December 4–10, 2017; Boston, MA **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 AMX0035 in Wolfram Syndrome

Clear Improvement in Insulin Secretion in Patient-Derived Beta Cells

Data available in appendix, slide 26

Clear Improvement in Cell Viability in Patient-Derived Beta Cells

Data available in appendix, slide 26

Clear Improvement in Cell Viability in Patient-Derived Neuronal Cells

Data available in appendix, slide 27

Highly Statistically Significant Delay in Diabetes Progression in Wolfram Syndrome Mice

Data available in appendix, slide 28

DATA AVAILABLE AT

JCI insight

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

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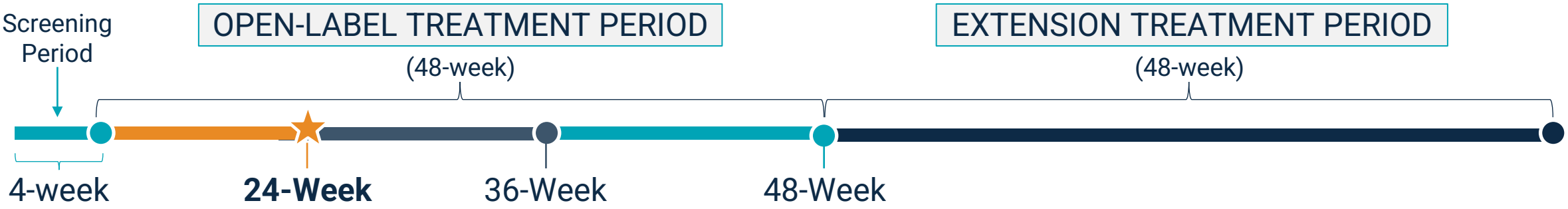
Phase 2 HELIOS Clinical Trial Design and Patient Baseline Characteristics

HELIOS Study Design[1,2]

Open-label clinical trial of AMX0035 in people with Wolfram syndrome, enrolling up to 12 participants



PRIMARY OBJECTIVES:

- To assess the safety and tolerability of AMX0035 administered orally for up to 96 weeks
- To evaluate the effect of AMX0035 on residual beta cell function over 24 weeks by monitoring C-peptide levels

KEY TRIAL ENTRY CRITERIA[1,2]

- Aged ≥17 years
- Definite diagnosis of Wolfram syndrome defined by documented pathogenic mutations in *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 agonist use

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*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

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.

HELIOS Endpoints in Context of Wolfram Syndrome Natural History Expectations

Primary Endpoint: C-Peptide

C-peptide progressively **decreases**

Average C-Peptide Decline:*

First ~2 years after Diabetes Onset

-0.37 ng/mL per year

After the first ~2 years

-0.13 ng/mL per year

Secondary Endpoints: HbA1c & Time in Target Glucose Range

HbA1c and time in target range gets **more challenging to control**

Average HbA1c Increase and Time in Target Glucose Range Decline (Worsening):

If blood glucose is well-controlled, HbA1c and time in target glucose range may remain stable; however, may become more difficult for levels to remain stable as the disease progresses[1,2]

Secondary Endpoint: Best Corrected Visual Acuity

Visual acuity progressively **worsens**

Average Visual Acuity Decline:**

All Participants (n=38)

0.059 logMAR/year

Rapid Decline Subset (26%)

0.16 logMAR/year

* Based on recent natural history study; as measured by 30-minute mixed meal tolerance test—120 min AUC not evaluated in this natural history study[2]
** Based on recent 10-year analysis of 38 individuals with Wolfram syndrome[3]

1. Kondo M, et al. *Diabetologia*. 2018;61(10);2189-2201. **2.** Ray MK, et al. *Pediatr Diabetes*. 2022;23(2):212-218. **3**. O'Bryhim BE, et al. Am J Opthalmol. 2022:243:10-18.

Patient 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)

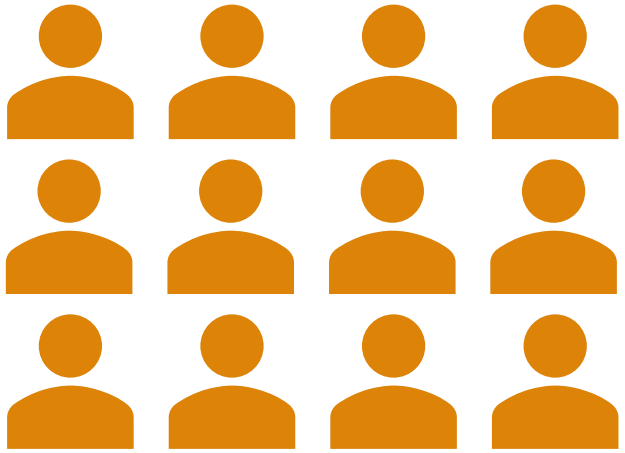
Vision Loss
12 (5 to 29)

Hearing Loss**
16 (7 to 34)

*N=4; **N=5

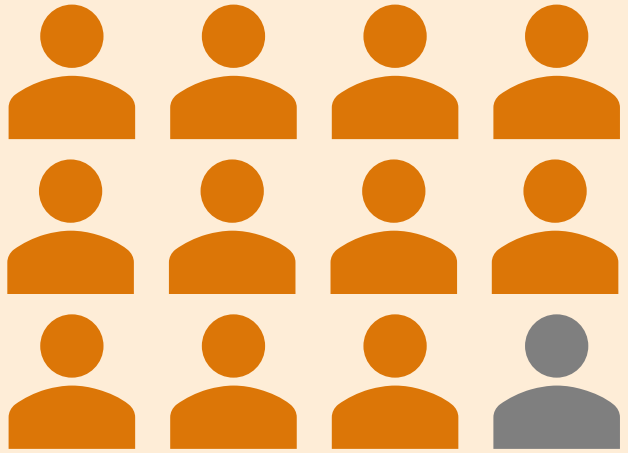
Key Population for Discussion: Participants With Genetically Confirmed Wolfram Syndrome (N=11)

Intent to Treat (ITT)
Week 24 (N=12)



12 Enrolled Participants
received AMX0035
*includes 1 participant who did not meet inclusion/exclusion criteria upon genetic review**

Per Protocol
Week 24 (N=11)



11 Enrolled Participants
with Definite Diagnosis of Wolfram Syndrome

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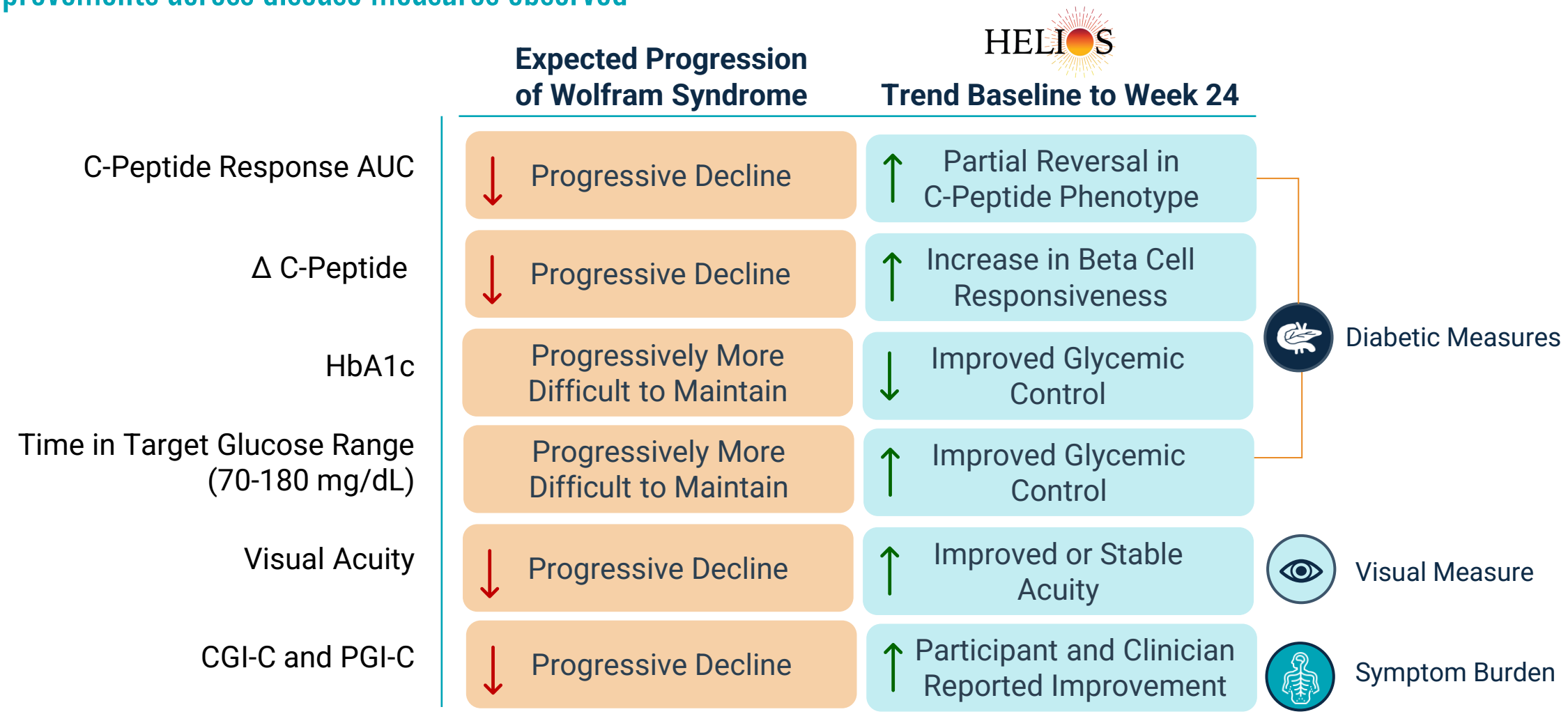
*Participant found to have an autosomal recessive mutation confirmed to be pathogenic on just one of the two alleles and variant of uncertain significance on the other allele. Participant was within normal range for C-peptide, glycemic measures, and vision suggesting lack of typical Wolfram syndrome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

Topline Efficacy and Safety Results of AMX0035 in Wolfram Syndrome

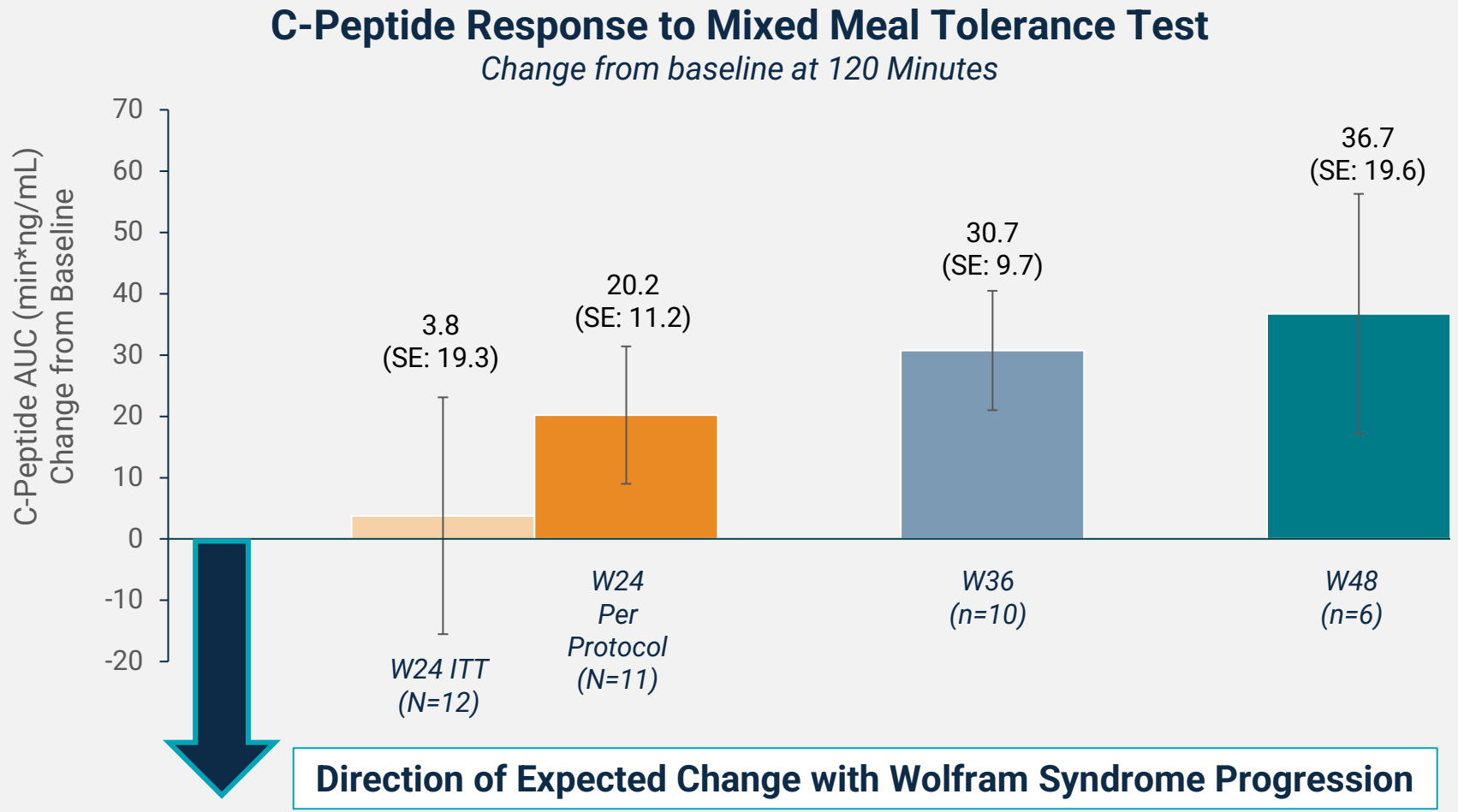
Topline Data Suggest Potential Benefit of AMX0035 in Wolfram Syndrome

Improvements across disease measures observed



Primary Endpoint: Improvement in C-Peptide Response Observed

Overall increase in mean C-peptide production at 120 minutes*



Improvement in C-Peptide Response Observed Compared to Screening

Please refer to appendix for alternative visualizations of C-peptide response from HELIOS

WS NATURAL HISTORY EXPECTATIONS:
C-peptide progressively **decreases**

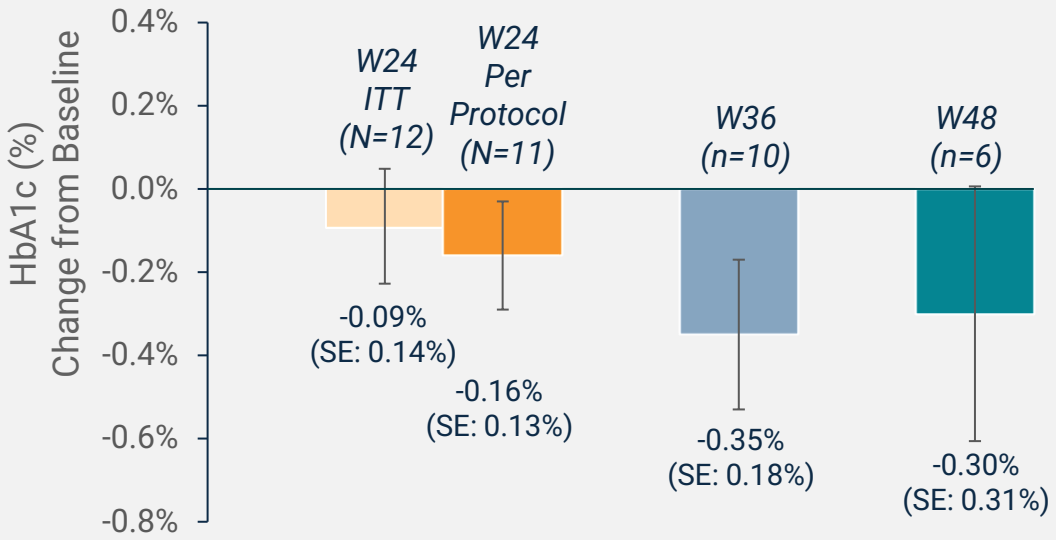
ITT: Intent to Treat; SE: Standard error; AUC: Area under the curve; Min: Minute; ng/mL: Nanograms per milliliter
Data on File. Amylyx Pharmaceuticals Inc. 2024.

*In non-diabetic individuals, C-peptide peaks after a meal at approximately ~30 minutes; in Wolfram Syndrome, peak is slower but generally was at or before 120 minutes in HELIOS. AUC over 120 minutes after meal challenge reflects beta cell response to a meal. Amylyx is currently planning to focus on 120-min AUC as the C-peptide measure for future studies.

Secondary Endpoint: Improved Glycemic Control as Measured by HbA1c

Lower HbA1c is associated with improved metabolic function

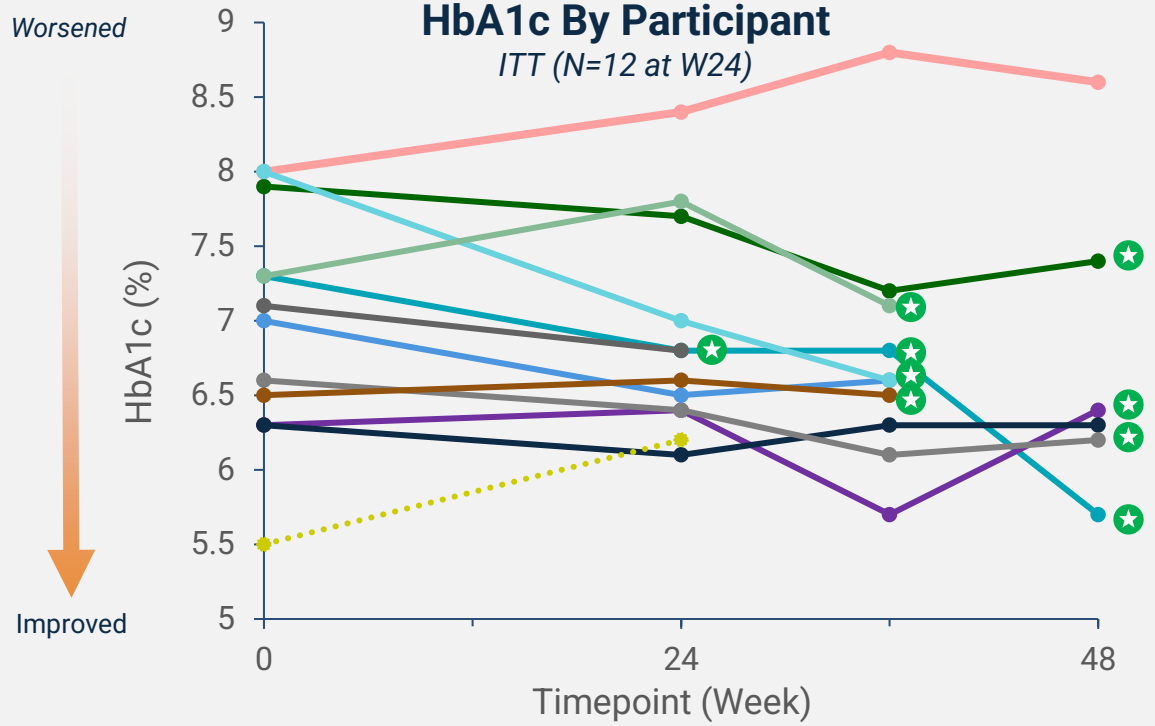
HbA1c Mean Change from Baseline



Improved Glycemic Control
as Measured by HbA1c Compared to Screening

HbA1c By Participant

ITT (N=12 at W24)



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

WS NATURAL HISTORY EXPECTATIONS:
HbA1c gets **more challenging to control** over time

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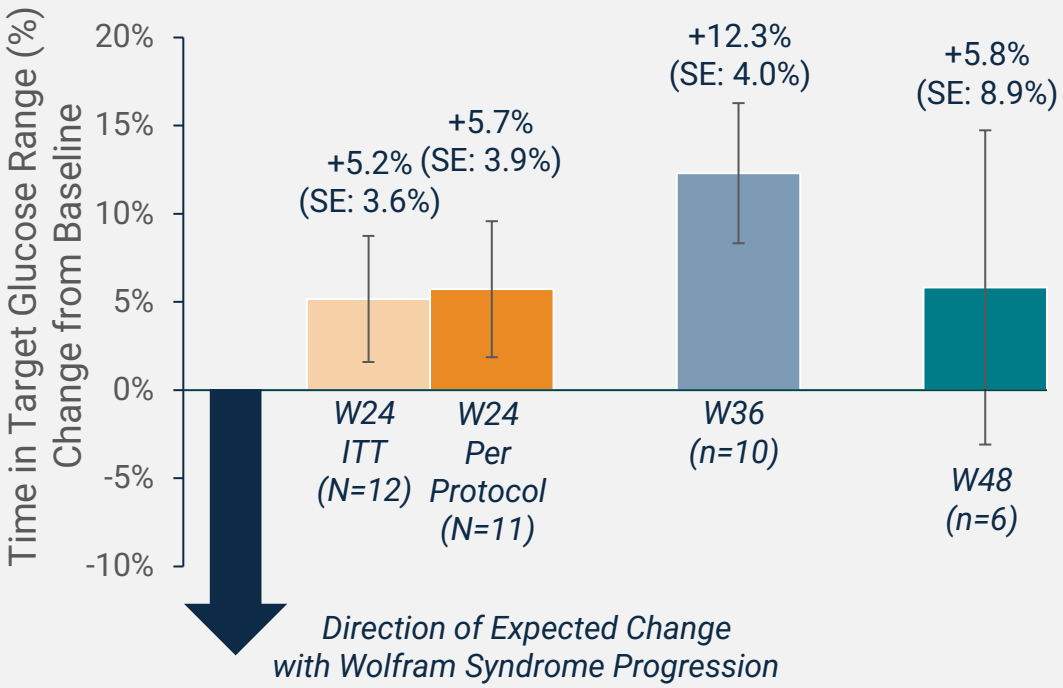
ITT: Intent to Treat; SE: Standard Error
Dotted line in By Participant graph indicates participant not included in the Per Protocol population.
Data on File. Amylyx Pharmaceuticals Inc. 2024.

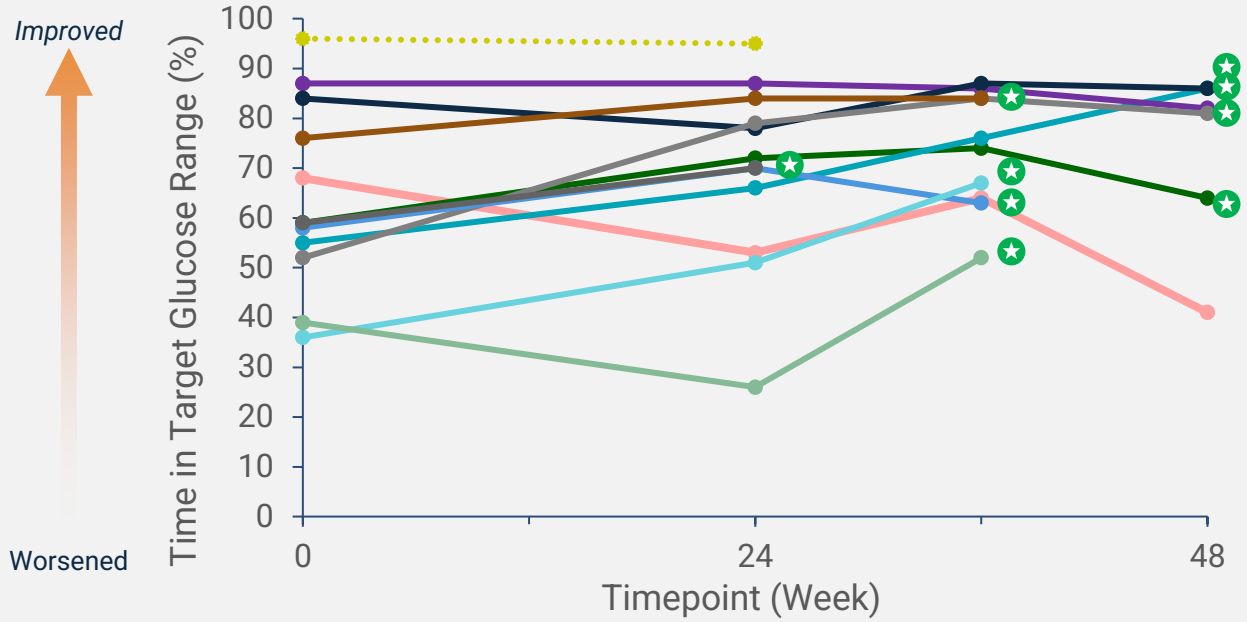
Secondary Endpoint: Improved Glycemic Control as Measured by Time in Target Glucose Range*

Mean Time in Target Glucose Range Change from Baseline



Time in Target Glucose Range by Participant

ITT (N=12 at W24)



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

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

WS NATURAL HISTORY EXPECTATIONS:
Time in range **more challenging to control** over time

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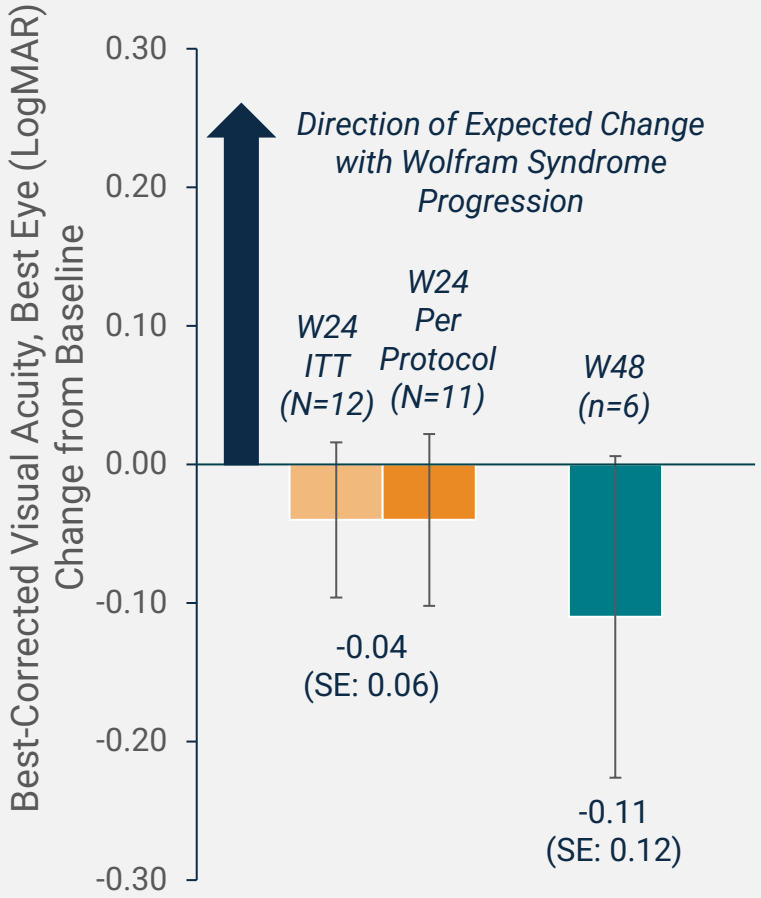
ITT: Intent to Treat
SE: Standard Error
Data on File. Amylyx Pharmaceuticals Inc. 2024.

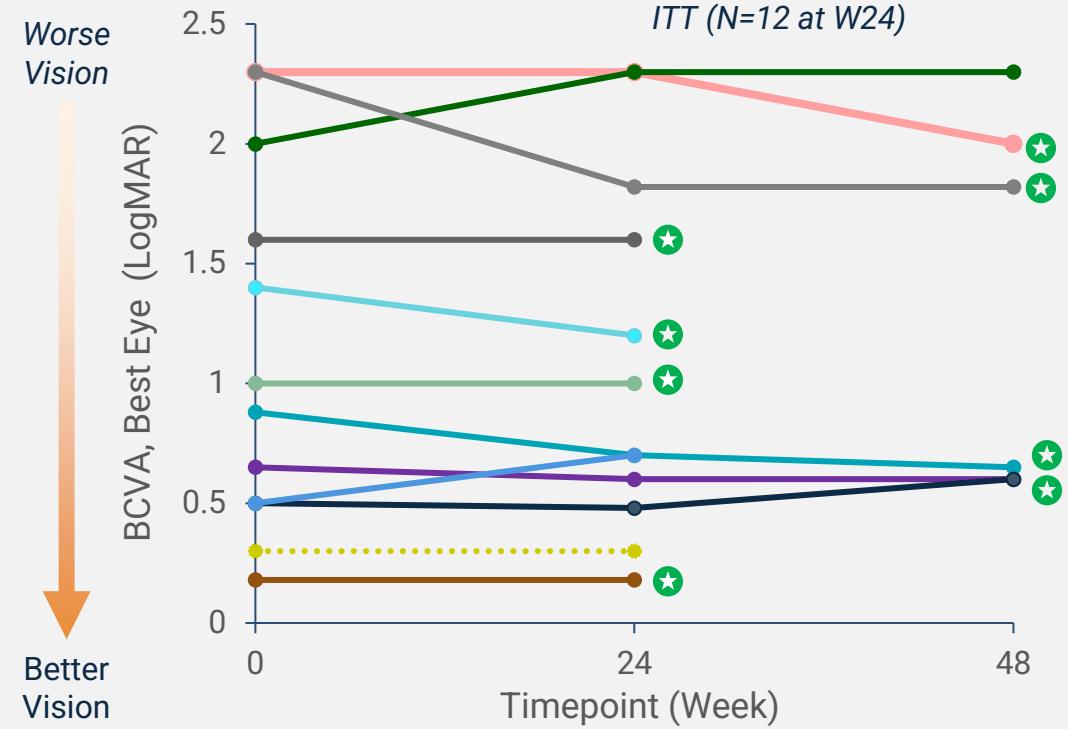
*Time in range was measured by continuous glucose monitoring (CGM). Good range defined as glucose recording between 70 and 180 mg/dL
Dotted line in By Participant graph indicates participant not included in the Per Protocol population.

Secondary Endpoint: Trends Indicating Potential Visual Acuity Improvement or Stabilization

BCVA, Best Eye Mean Change from Baseline



Best Corrected Visual Acuity (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

Includes 2 participants blind at baseline who now have some vision in one eye

Of remaining participants:

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

Trends Indicating Potential Visual Acuity Improvement or Stabilization Compared to Screening

WS NATURAL HISTORY EXPECTATIONS: Visual acuity progressively **worsens (increasing LogMAR)**

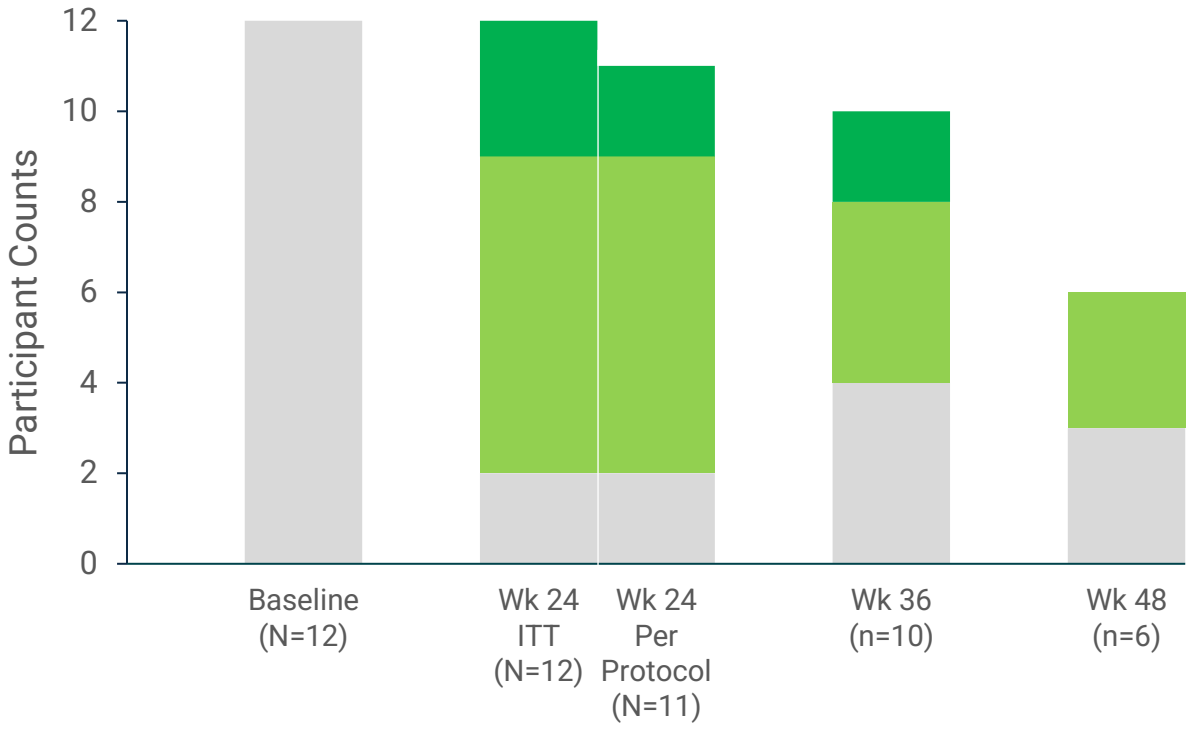
ITT: Intent to Treat; SE: Standard Error
Dotted line in By Participant graph indicates participant not included in the Per Protocol population.
Data on File. Amylyx Pharmaceuticals Inc. 2024.

Exploratory Endpoint: PGI-C and CGI-C

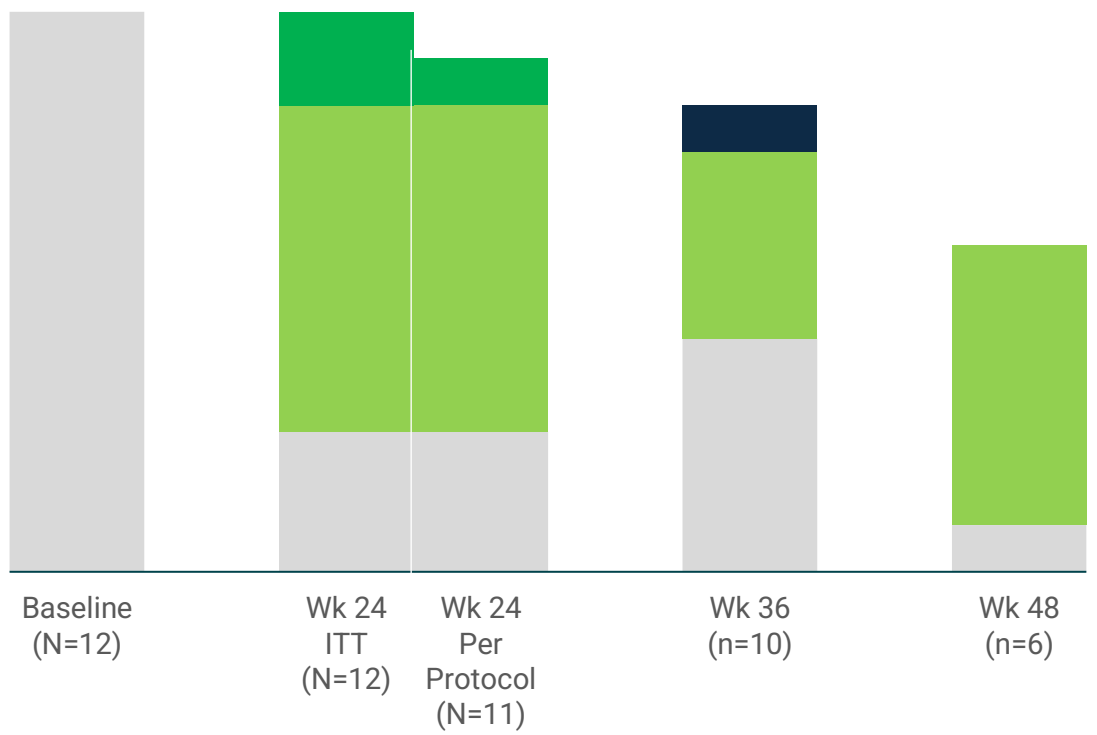
100% of Participants Met Responder* Criteria by Self and Clinician Assessment

At Week 24, 82% of Per Protocol participants claimed to have improved on AMX0035; 73% improved based on clinician report

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



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



No Change Minimally Improved Much Improved Very Much Improved

*HELIOS defines a "responder" on both scales as no change or improvement given the progressive nature of Wolfram syndrome
ITT: Intent to Treat
Data on File. Amylyx Pharmaceuticals Inc. 2024.

AMX0035 Safety and Tolerability in HELIOS

- AMX0035 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 AMX0035 dosing and **none led to drug discontinuation**

Summary of Treatment Emergent Adverse Events (TEAEs)

	AMX0035 (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”

- C-peptide continuously declines in Wolfram syndrome.
- The data indicate that participants experienced improvements in both C-peptide and HbA1c levels.
  - Suggests reduced beta cell stress and improved beta cell function.
  - Implies that AMX0035 reduced ER stress, including in different neuron populations such as retinal ganglion cells.
- Impact on diabetes-related measures and visual acuity suggest AMX0035 is impacting multiple systems.
- The PGI improvement seems to surpass a placebo effect.

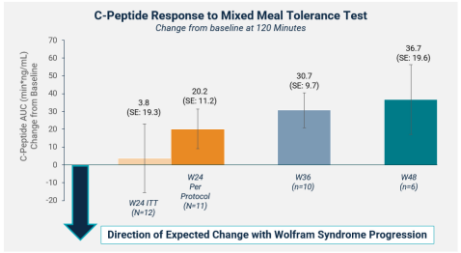
Key Takeaways

Strong Scientific Rationale

***WFS1* Gene Mutation**

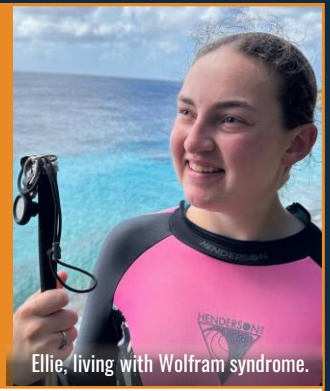
- Wolfram syndrome is a progressive, genetic disease caused by mutations in *WFS1* that cause endoplasmic reticulum (ER) stress and impaired mitochondrial dynamics
- AMX0035 has been shown to simultaneously mitigate ER stress and mitochondrial dysfunction
- Preclinical data have demonstrated the efficacy of AMX0035 in cell lines, patient-derived cells, and mouse models

Open-label, Single-arm Phase 2 Data Support AMX0035's Potential in Wolfram Syndrome



- Available natural history shows progressive decline in C-peptide and vision for people with Wolfram syndrome
- Topline data from 12-participant open-label, single-arm study demonstrated improvements or stabilization on glycemic and vision scales in additional to patient and physician impression of change
- AMX0035 was generally well-tolerated in all participants

Urgent Unmet Need



Ellie, living with Wolfram syndrome.

- There are currently no disease-modifying therapies for Wolfram syndrome
- Wolfram syndrome impacts ~3,000 people in the U.S. and results in premature death

AMX0035 Wolfram Syndrome Program Next Steps

- Orphan drug designation granted to AMX0035 for the treatment of Wolfram syndrome by U.S. FDA
- Positive preclinical data on AMX0035 published in *Journal of Clinical Investigation Insight*
- Phase 2 HELIOS study of AMX0035 in Wolfram syndrome initiated in April 2023 and completed enrollment in Feb 2024
- Presented positive data from interim analysis of HELIOS study
- EU Orphan Drug Designation granted for AMX0035 in Wolfram syndrome
- Presented positive topline results from HELIOS study
- Plans to meet with the FDA and other stakeholders to inform a Phase 3 program
- Continue to gather longer term data from the Phase 2 HELIOS study

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Raquel, living with Wolfram syndrome.

In memory of Lauren, a beautiful daughter and passionate Wolfram syndrome warrior.

Key Upcoming Anticipated Company Milestones

AVEXITIDE GLP-1 RECEPTOR ANTAGONIST	PRECLINICAL	IND-ENABLING STUDIES	PHASE 1	PHASE 2	PHASE 3	COMMERCIAL	EXPECTED UPCOMING MILESTONE(S)
Post-Bariatric Hypoglycemia (PBH)				FDA BREAKTHROUGH DESIGNATION ★			Phase 3 program begins in Q1 2025; completes recruitment in 2025; readout 2026, planning for commercial launch in 2027
Congenital Hyperinsulinism (HI)				FDA BREAKTHROUGH DESIGNATION ★			Engaging physician and community experts around next steps for clinical development

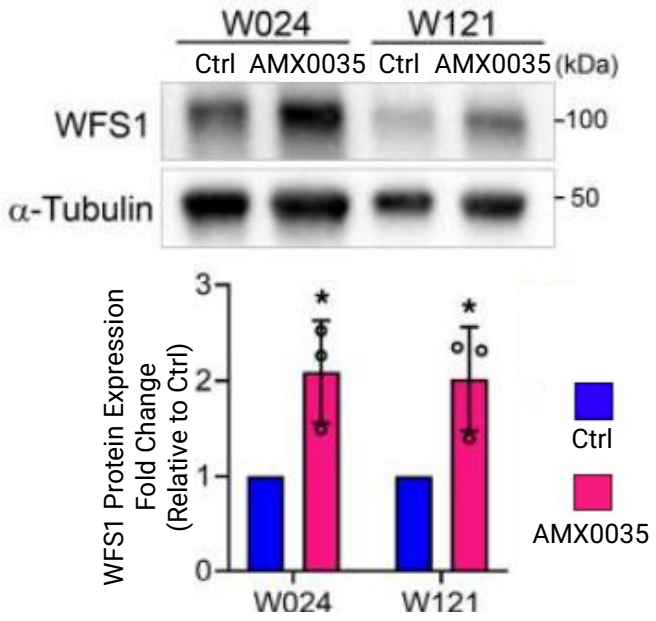
AMX0035 SODIUM PHENYLBUTYRATE (PB) AND TAURURSODIOL (TURSO, ALSO KNOWN AS URSODOXICOLTAURINE)	PRECLINICAL	IND-ENABLING STUDIES	PHASE 1	PHASE 2	PHASE 3	COMMERCIAL	EXPECTED UPCOMING MILESTONE(S)
Wolfram Syndrome							Planning to meet with the FDA and other stakeholders to inform a Phase 3 program and expects to provide an update in 2025
Progressive Supranuclear Palsy (PSP)							Expecting data from interim analysis in mid-2025

AMX0114 ANTISENSE OLIGONUCLEOTIDE	PRECLINICAL	IND-ENABLING STUDIES	PHASE 1	PHASE 2	PHASE 3	COMMERCIAL	EXPECTED UPCOMING MILESTONE(S)
Amyotrophic Lateral Sclerosis (ALS)							Initiating multiple ascending dose clinical trial in people with ALS in second half of 2024

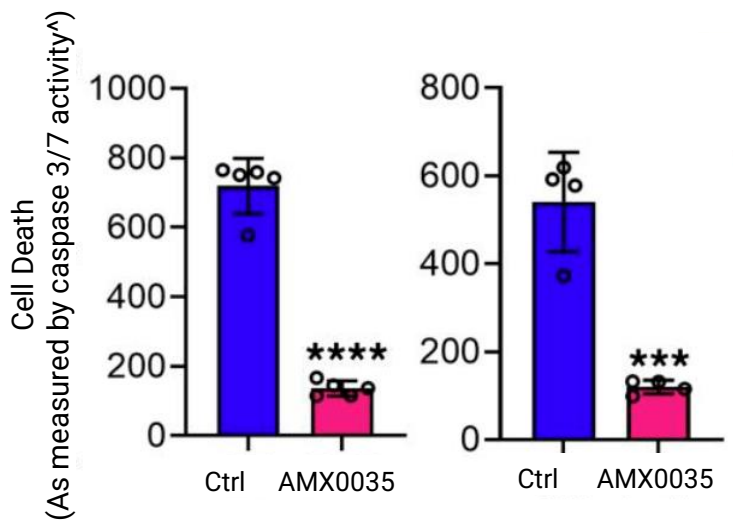
Appendix

AMX0035 Improved WFS1 Protein Expression, Increased Insulin Secretion, and Inhibited Beta Cell Death

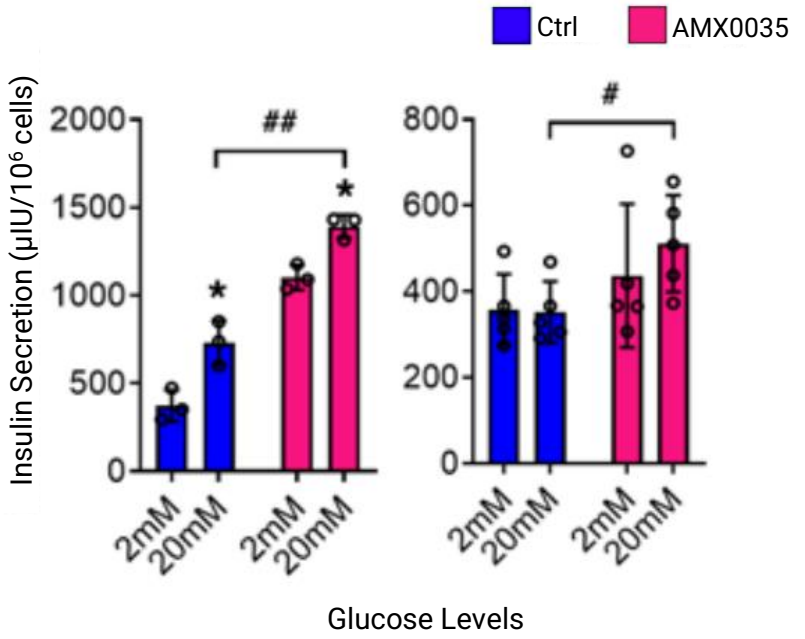
Increased WFS1 Protein Levels in Patient-Derived Beta Cells (P<0.05)



Rescued *WFS1* Mutant Islet Cell Viability in Patient-Derived Beta Cells (P<0.001)



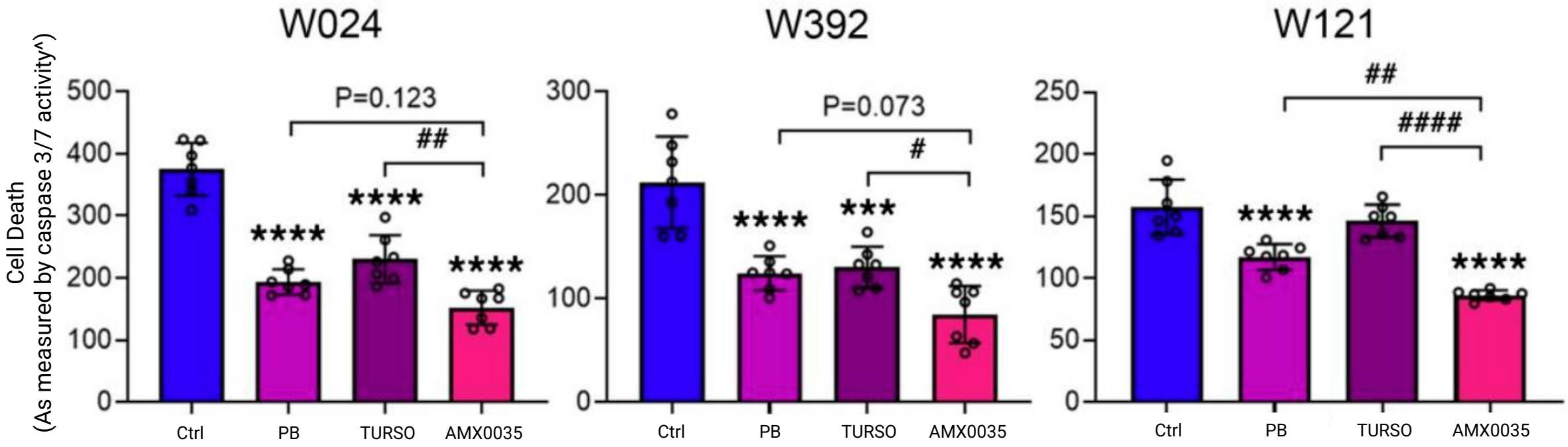
Improved *WFS1* Mutant Insulin Secretion in Two Patient-Derived Cell Lines (P<0.05)



W024 and W121 indicate cell lines from specific patients
*P<0.05 by unpaired *t* test compared with Ctrl; ***P<0.001 and ****P<0.0001 by unpaired *t* test compared with Ctrl; #P<0.05 and ##P<0.01 by 2-way unpaired *t* test; ^Normalized by cell viability

AMX0035 Prevented Cell Death in Patient-Derived Neuronal Cell Models

AMX0035 Prevented Cell Death (P<0.0001)
In Three Different Patient-Derived Neuronal Cell Models

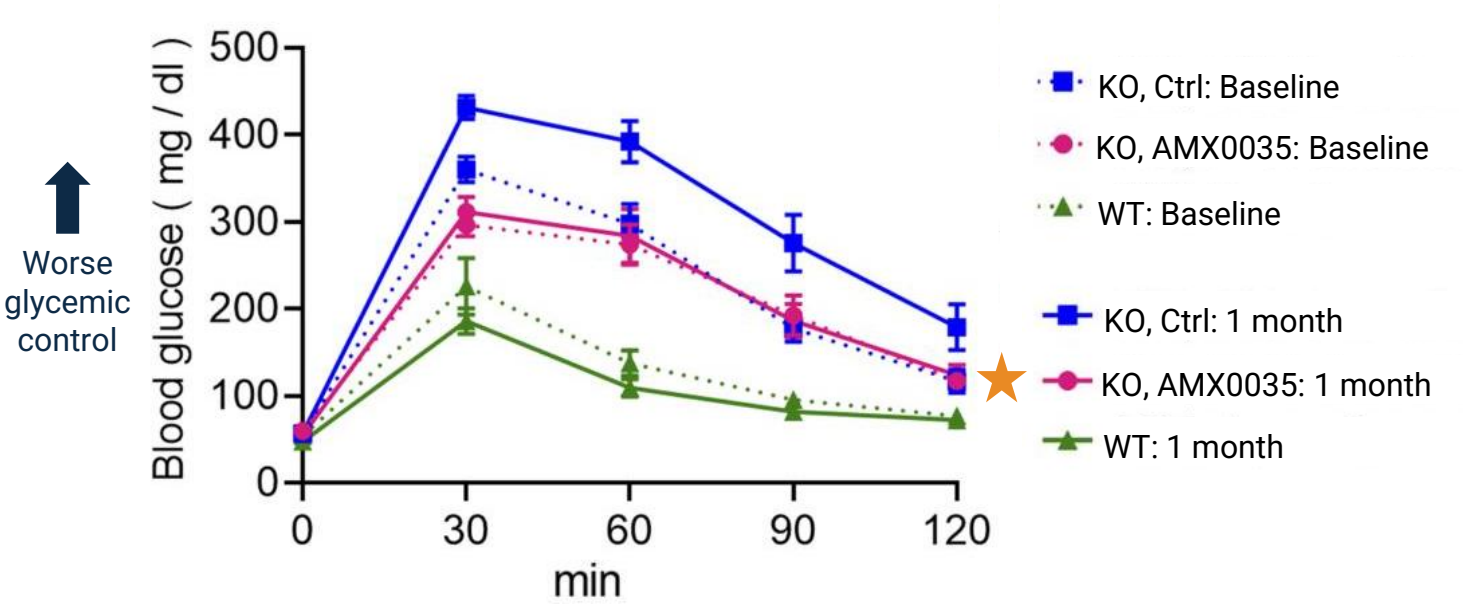


W024, W392, W121 indicate cell lines from specific patients; **PB**, sodium phenylbutyrate; **TURSO**, taurursodiol.
***P<0.001 and ****P<0.0001 by 1-way ANOVA compared with Ctrl; #P<0.05, ##P<0.01, and ####P<0.0001 by 1-way ANOVA; ^Normalized by cell viability

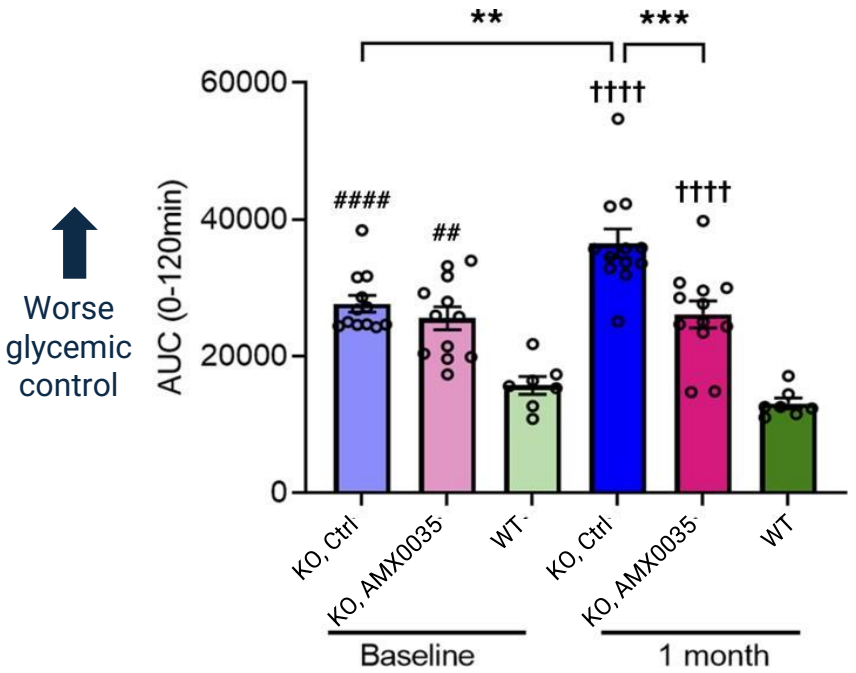
AMX0035 Significantly Delayed Onset of Diabetic Phenotypes in *Wfs1*-deficient mice

AMX0035-Treated Mice Showed Better Glycemic Control (P<0.001) than Untreated After 1 Month with Minimal to No Diabetes Progression Based on Glucose Tolerance Test (GTT)

IP-GTT with WT or Wfs1-KO Mice at Baseline and 1 Month



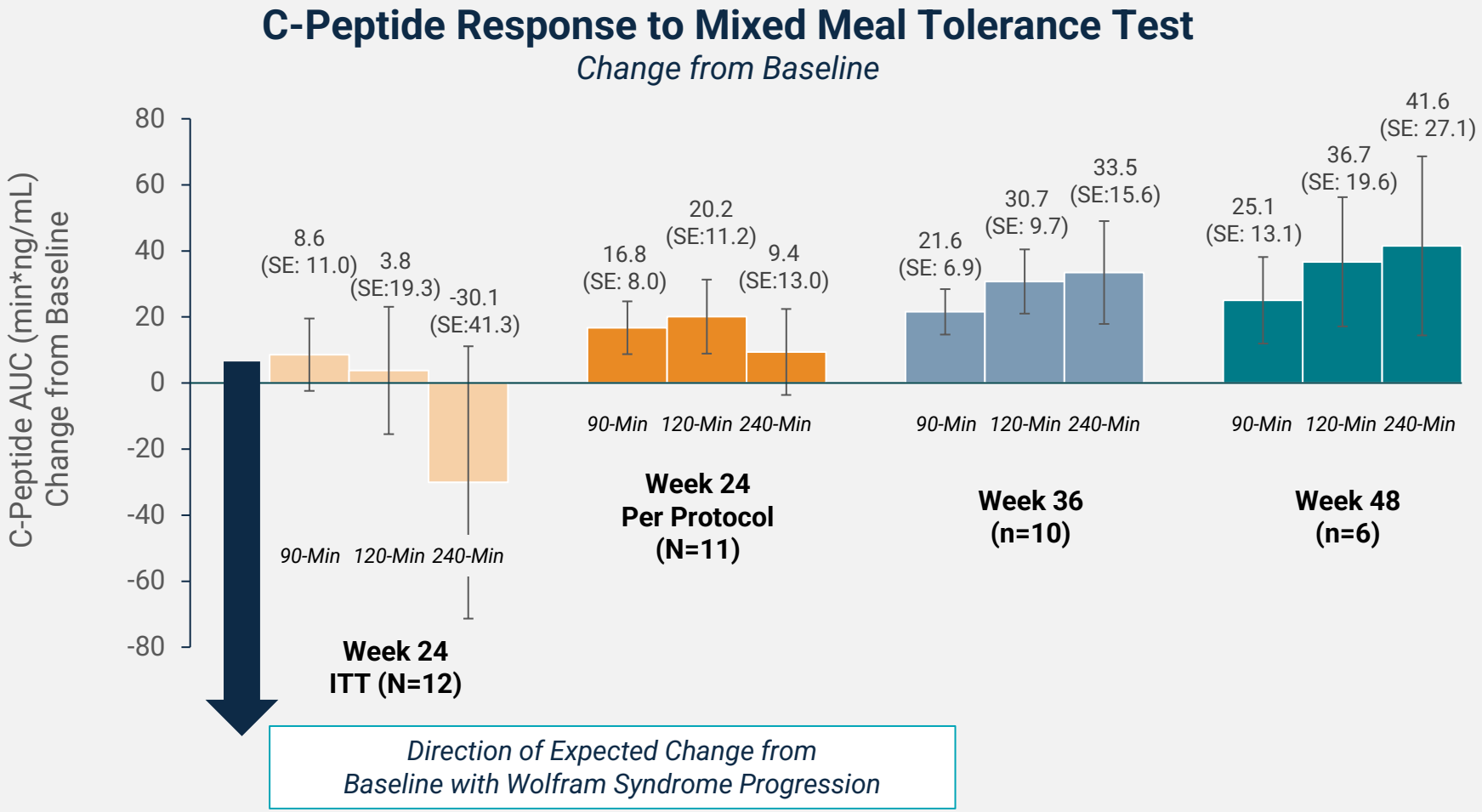
Area Under the Curve of the Glucose Tolerance Test



IP-GTT, intraperitoneal glucose tolerance test (IP-GTT)
**P < 0.01 and ***P < 0.001 by 1-way ANOVA; ##P < 0.01 and ####P < 0.0001 by 1-way ANOVA compared with WT: Baseline; ††††P < 0.0001 by 1-way ANOVA compared with WT: 1 month)

Primary Endpoint: Improvement in C-Peptide Response at Week 24

Overall increase in mean C-peptide (Area Under Curve) when decrease expected



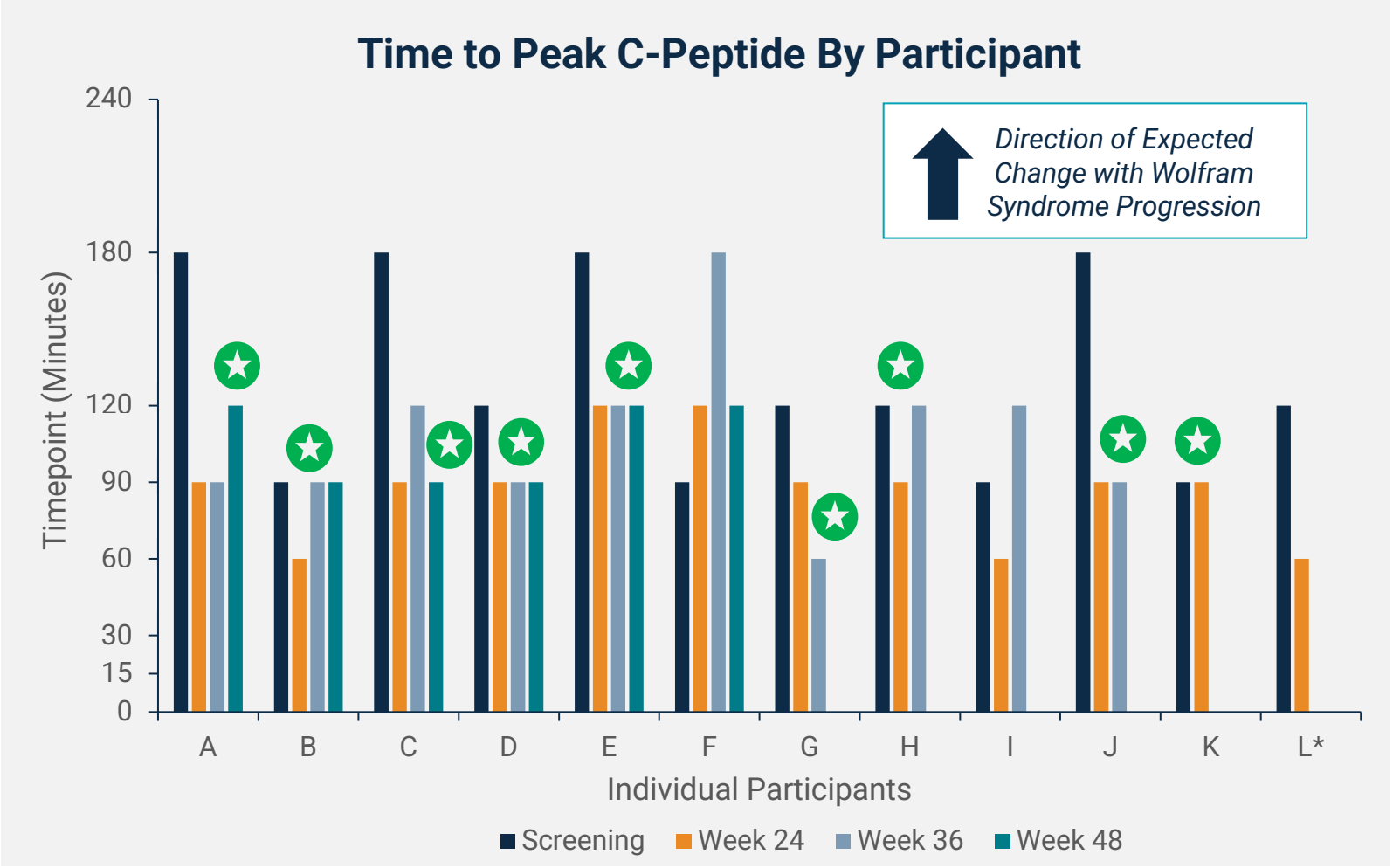
Improvement in C-Peptide Response Observed Compared to Screening

WS NATURAL HISTORY EXPECTATIONS:
C-peptide progressively **decreases**

ITT: Intent to Treat; SE: Standard error; AUC: Area under the curve;
Min: Minute; ng/mL: Nanograms per milliliter
Data on File. Amylyx Pharmaceuticals Inc. 2024.

Primary Endpoint: Time to Peak C-Peptide Improved with AMX0035

Shorter time to peak C-peptide suggesting more rapid beta-cell response to glucose challenge



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

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