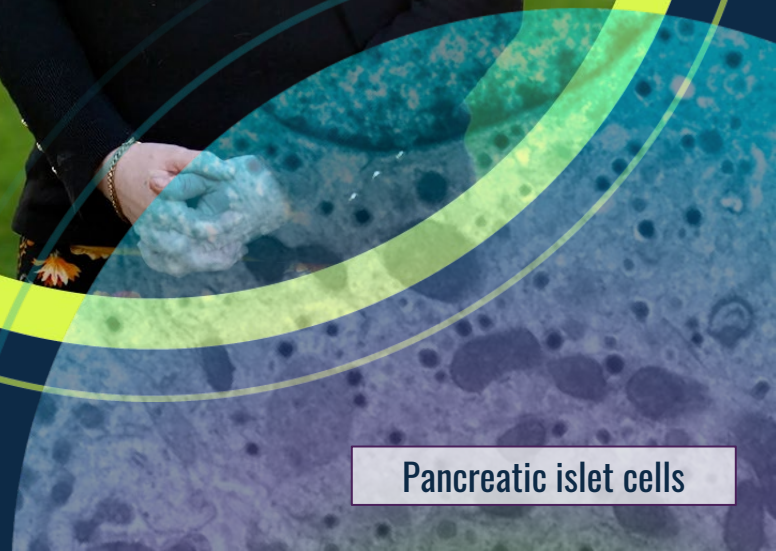
AMYLYX®

SEPTEMBER 2026

We have an audacious mission to develop novel therapies for diseases with high unmet needs, with a focus on serious and fatal endocrine conditions and neurodegenerative diseases.

Maggie, a mom and advocate living with post-bariatric hypoglycemia (PBH).



Pancreatic islet cells

DISCLAIMER

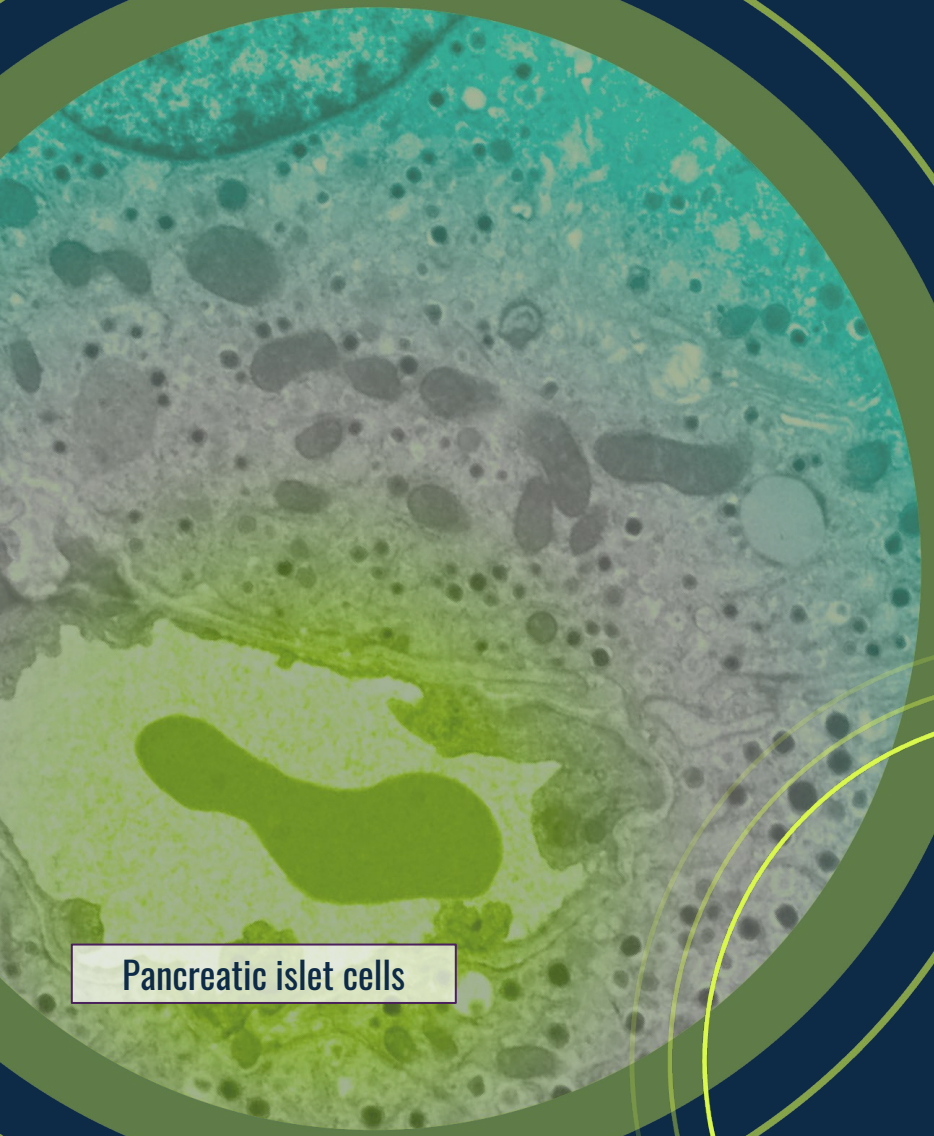
Statements contained in this presentation regarding matters that are not historical facts are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to, the Company’s plans to explore the use of avexitide as a treatment for post-bariatric hypoglycemia (PBH) and congenital hyperinsulinism, AMX0035 for Wolfram syndrome, AMX0114 for ALS, and AMX0318 for PBH and other rare diseases; statements regarding the timing of clinical trials and data readouts for PBH, Wolfram syndrome and/or ALS; expectation for regulatory action, including potential approval of our investigational products; and expectations regarding our longer-term strategy and expected cash runway. Any forward-looking statements in this presentation are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. Risks that contribute to the uncertain nature of the forward-looking statements include: the success, cost, and timing of Amylyx’s program development activities, including ongoing and planned clinical trials, Amylyx’s ability to execute on its development and regulatory strategy, regulatory developments, Amylyx’s cash runway and ability to fund operations, as well as the risks and uncertainties set forth in Amylyx’s United States Securities and Exchange Commission (SEC) filings, including Amylyx’s Annual Report on Form 10-K for the year ended December 31, 2025, and subsequent filings with the SEC. All forward-looking statements contained in this presentation speak only as of the date on which they were made. Amylyx undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

A Growing Pipeline of Therapies to Serve Communities with High Unmet Needs

Led by an experienced team with a proven track record of commercialization in rare diseases

ASO=antisense oligonucleotide; FDA=U.S. Food and Drug Administration; GLP-1=glucagon-like peptide-1; IND=investigational new drug; NDA=New Drug Application; SAE=serious adverse events.

AMYLYX



Pancreatic islet cells

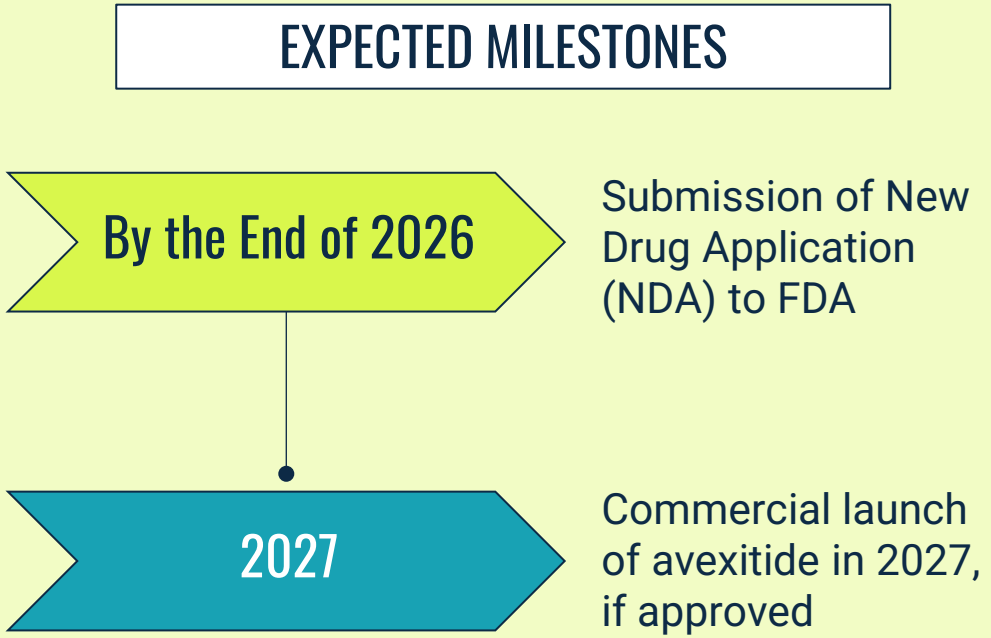
AVEXITIDE

Investigational, First-in-Class GLP-1 Receptor Antagonist with FDA Breakthrough Therapy Designation

lucidity

Avexitide: Investigational, First-in-Class GLP-1 Receptor Antagonist with FDA Breakthrough Therapy Designation in PBH and Orphan Drug Designation

- Phase 3 LUCIDITY trial of avexitide in post-bariatric hypoglycemia (PBH) following RYGB surgery met its primary and all secondary endpoints
  - > 55% reduction in composite rate of Level 2 and Level 3 hypoglycemic events vs. placebo (p=0.000003)
  - > Consistent, highly statistically significant, and clinically meaningful reductions in Level 2 (SMBG and CGM) and Level 3 hypoglycemic events vs. placebo
- Potential to be the first FDA-approved therapy for PBH, a debilitating condition with a profound unmet medical need
  - > ~160,000 prevalent patients
- Strong IP position with patent rights through 2037 and potential for patent term extension

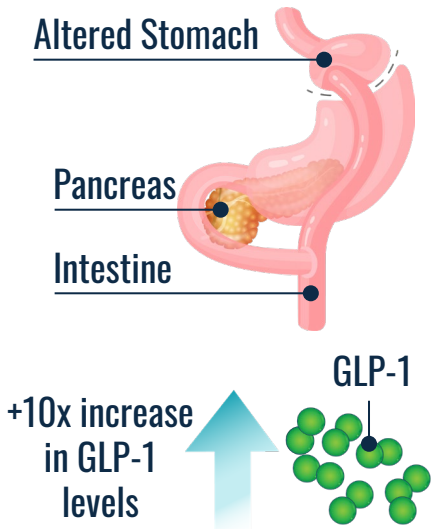


FDA=U.S. Food and Drug Administration; GLP-1=glucagon-like peptide-1; IP=intellectual property; RYGB=Roux-en-Y gastric bypass; SMBG=self-monitoring of blood glucose; CGM=continuous glucose monitoring.

Avexitide, an Investigational, First-in-Class GLP-1 Receptor Antagonist, Targets a Central Pathway of PBH Pathophysiology

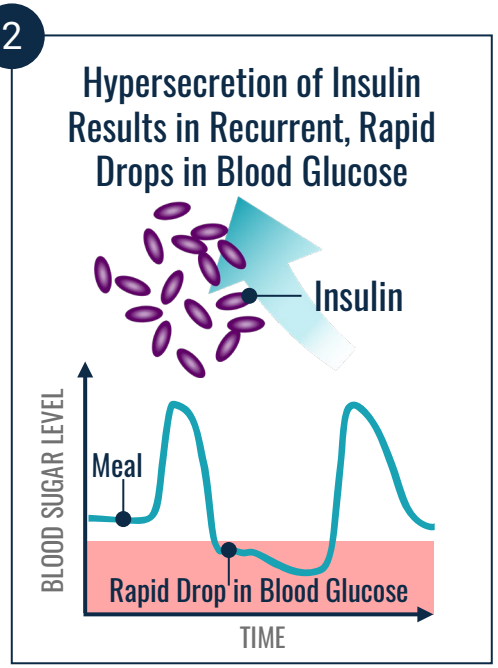
GLP-1 Receptor Antagonism

1



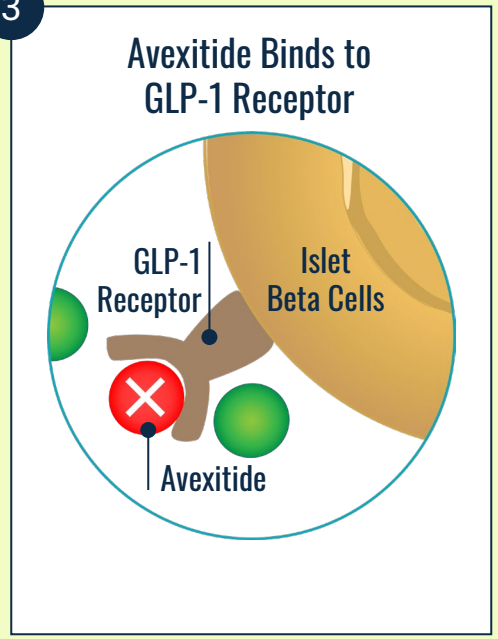
Altered nutrient transit due to anatomical changes associated with bariatric surgery (e.g., Roux-en-Y gastric bypass) leads to **exaggerated GLP-1 secretion** in people with PBH

2



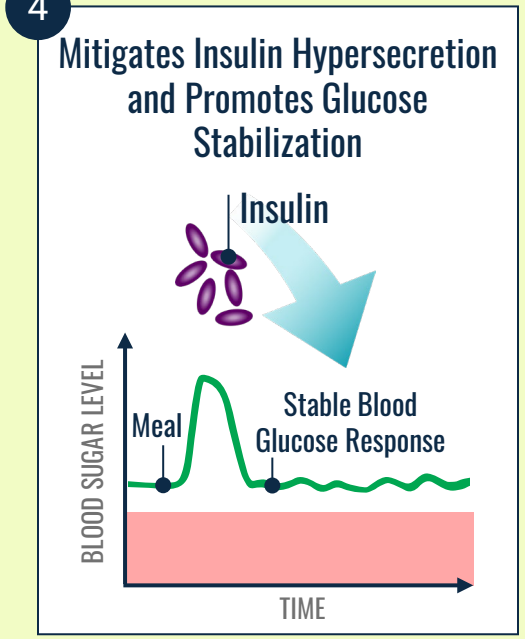
This exaggerated GLP-1 secretion leads to abnormally high insulin levels in the bloodstream, and subsequent hypoglycemia

3



Avexitide binds to the GLP-1 receptor on pancreatic islet beta cells to **inhibit the effect of exaggerated GLP-1**

4

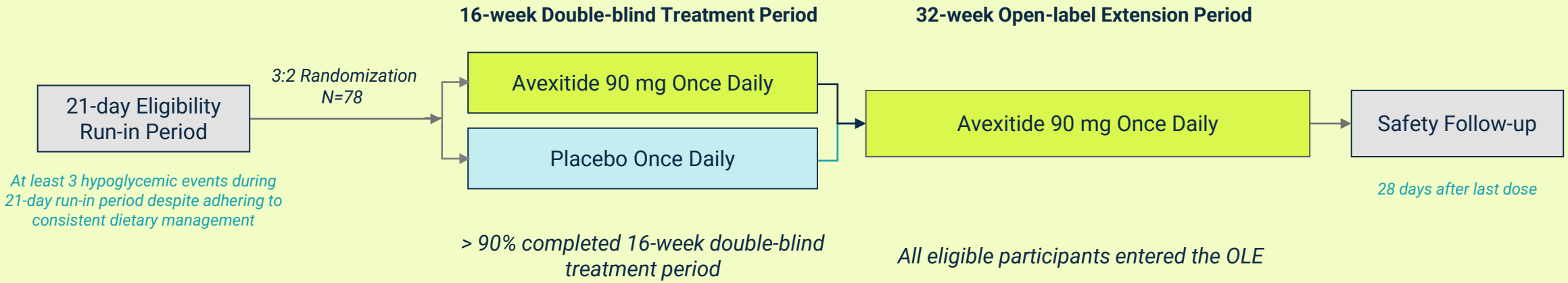


Decreased insulin secretion and stabilized glucose levels resulting from inhibition of the effect of exaggerated GLP-1

GLP-1=glucagon-like peptide-1; PBH=post-bariatric hypoglycemia; **1.** Sheehan A, Patti ME. *Diabetes Metab Syndr Obes*. 2020;13:4469-4482. **2.** Craig CM, et al. *Diabetes Obes Metab*. 2017; 1-10. **3.** Thorens B,. et al. *Diabetes*.1993;42(11):1678-1682. **4.** Craig CM, et al. *Diabetes Obes Metab*. 2018;20(2):352-361. **5.** Smith NK, et al. *Neurochem Int*. 2019;128:94-105. **6.** Meloni AR, et al. *Diabetes Obes Metab*. 2013;15(1):15-27. **7.** Craig CM, et al. *Diabetologia*. 2017;60(3):531-540. **8.** Craig C, et al. *J Endocr Soc*. 2022;6(Suppl 1):A349.

Phase 3 LUCIDITY Trial Design

PHASE 3 LUCIDITY TRIAL DESIGN - Multicenter, randomized, double-blind, placebo-controlled trial (N=78)



Key Trial Entry Criteria

- Has undergone Roux-en-Y gastric bypass (RYGB) at least 12 months prior to screening visit
- Has a clinical diagnosis of PBH

Primary Endpoints

- Composite of Level 2 (SMBG) and Level 3 hypoglycemic events
- Safety and tolerability

Secondary Endpoints

- Level 2 hypoglycemic events (SMBG)
- Level 2 hypoglycemic events (CGM)
- Level 3 hypoglycemic events

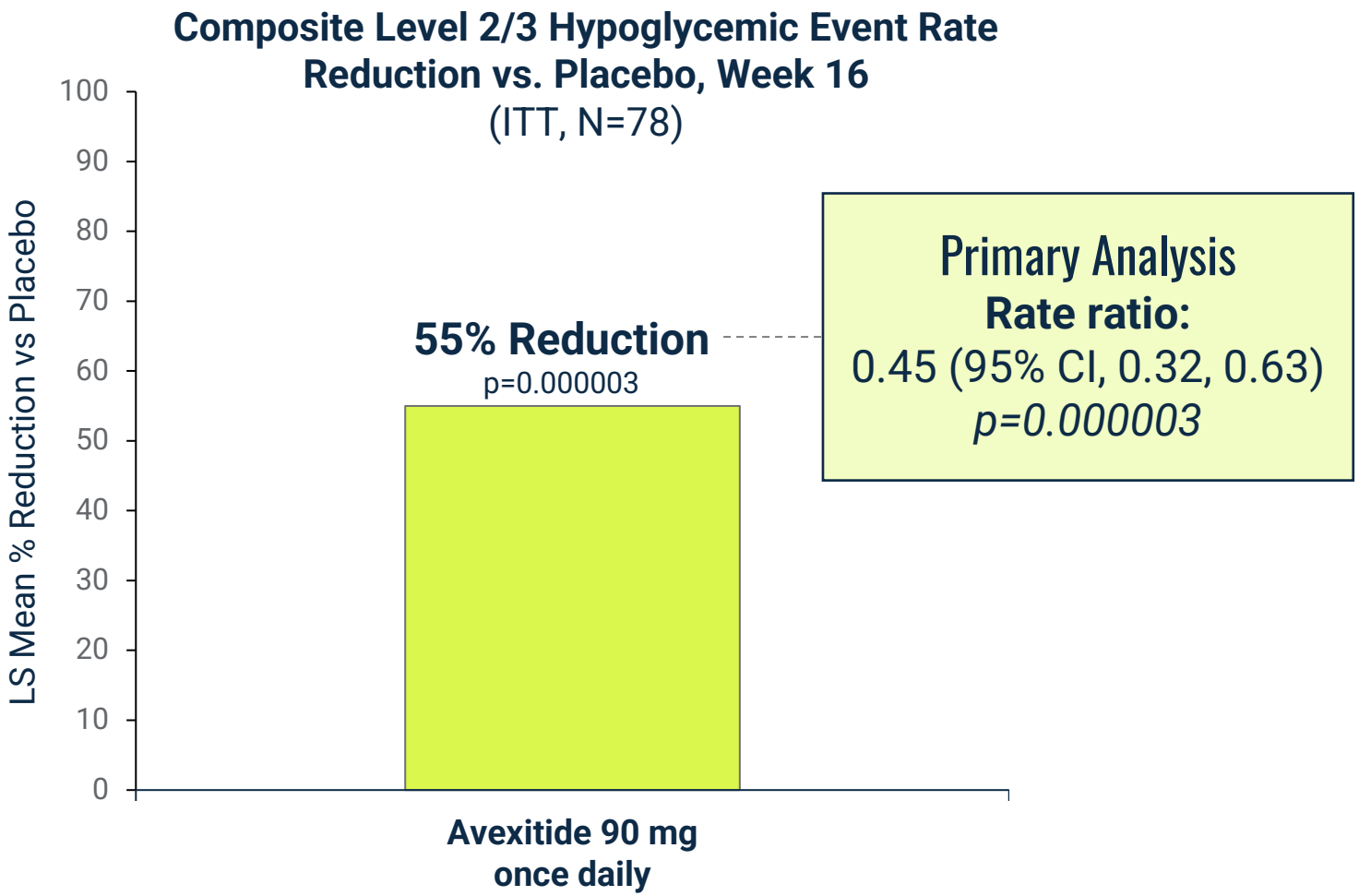
Hypoglycemic Events Definitions

- **Level 2:** glucose <54mg/dL
- **Level 3:** events characterized by altered mental and/or physical function requiring assistance

SMBG: self-monitoring blood glucose; CGM: continuous glucose monitoring.

LUCIDITY Met Primary Endpoint

Statistically significant 55% reduction in composite rate of Level 2 and Level 3 hypoglycemic events compared to placebo



Primary Analysis
Rate ratio:
0.45 (95% CI, 0.32, 0.63)
p=0.000003

LUCIDITY Met All Secondary Endpoints

Consistent, highly statistically significant, and clinically meaningful reductions

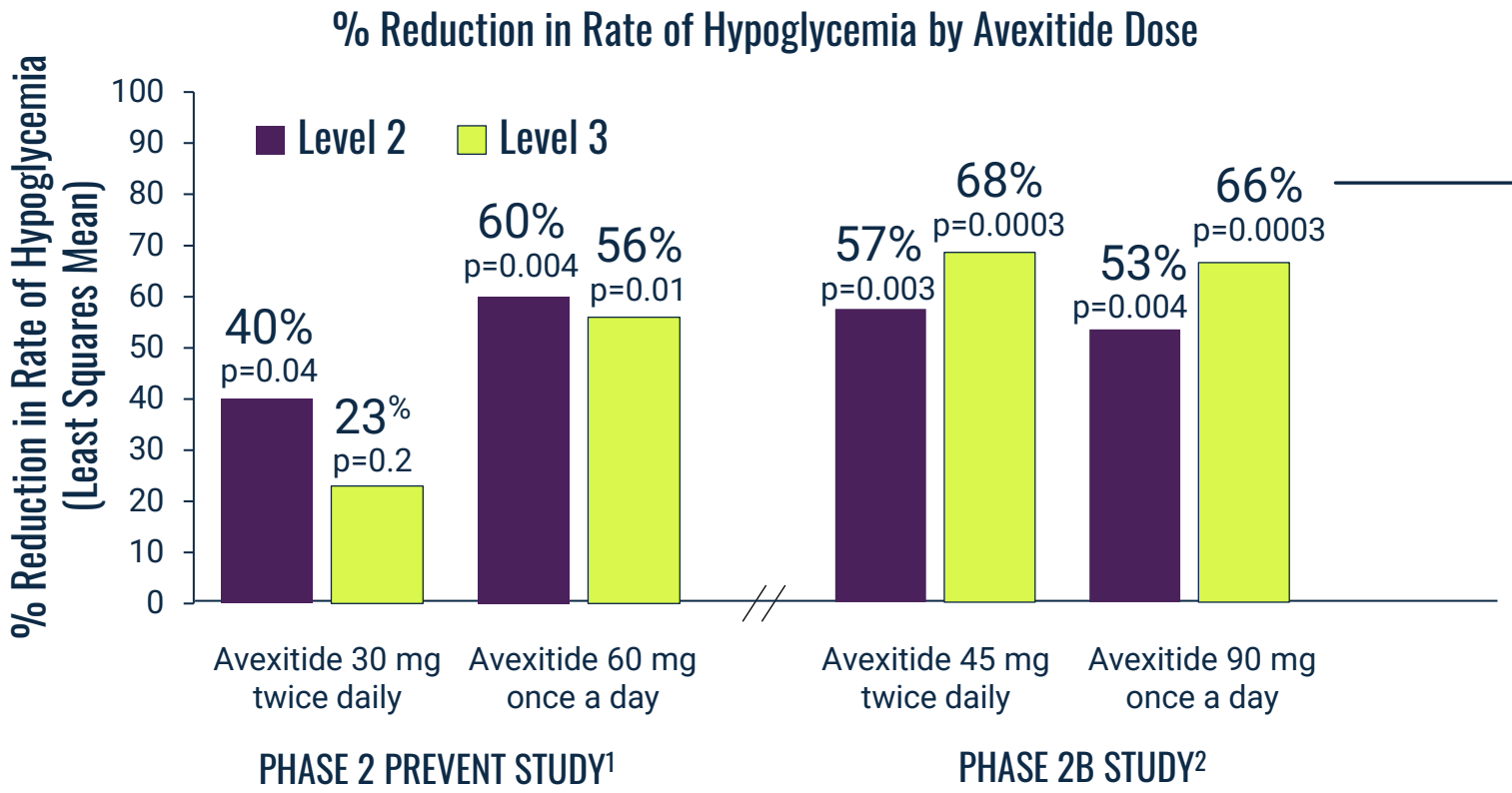
- ✓ Level 2 hypoglycemic events (SMBG)
- ✓ Level 2 hypoglycemic events (CGM)
- ✓ Level 3 hypoglycemic events

Avexitide was Generally Well-Tolerated with a Favorable Safety Profile Through 16 Weeks

- Adverse events were generally mild or moderate
- No treatment-related serious adverse events
- Most common adverse events were diarrhea, injection site erythema, and injection site bruising
- No changes in body weight with avexitide or placebo

Safety profile consistent with that observed across all PBH clinical trials completed to date

Five Clinical Trials of Avexitide Demonstrate Statistically Significant Results in PBH Consistent with LUCIDITY



Avexitide cut rates of hypoglycemic events by

>50%

Treatment effect supported by consistent, dose-dependent effects across Phase 1, SAD, and MAD trials in PBH[3-5]

PBH=post-bariatric hypoglycemia; **1.** Craig, C. M. et al. *The Journal of Clinical Endocrinology & Metabolism*. 2021;106(8):e3235-e3248. doi.org/10.1210/jendso/bvac150.725. **2.** Tan, M. (2022). *Efficacy and Safety of Avexitide for Treatment of Hypoglycemia after Gastrointestinal Surgery: Assessment of Novel Dosing Regimens in an Expanded Indication* [Conference presentation]. **3.** Craig CM, et al. *Diabetologia*. 2017;60(3):531-540. **4**. Craig CM, et al. *Diabetes Obes Metab*. 2018;20:352-361. **5**. Tan M, et al. *Diabetes Obes Metab*. 2020;22(8):1406-1416

[a]Rate defined the weekly number of discrete events during respective treatment periods; [b]Level 2 hypoglycemia: self-monitoring of blood glucose <54 mg/dL[c]Level 3 hypoglycemia: a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery whether an individual receives external assistance or not.

Avexitide has the Potential to be a First FDA-approved Treatment for PBH

Phase 3 LUCIDITY Trial Topline Data Summary

1. **Avexitide met primary and secondary endpoints** demonstrating statistically significant and clinically meaningful reductions in both SMBG and CGM Level 2 and Level 3 hypoglycemic events
2. **Avexitide was generally well-tolerated** with a favorable safety profile across all PBH clinical trials to date
3. **Builds on positive results of five prior clinical trials** of avexitide in PBH, including statistically significant reductions in hypoglycemic events and stabilization of blood glucose

Patient Impact

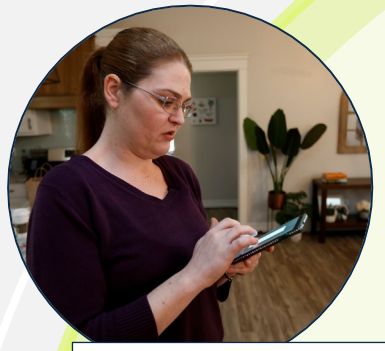
1. **Preventing a single Level 2 or Level 3 hypoglycemic event** could enable someone to care for their child, function independently, and prevent potentially catastrophic consequences, such as a seizure, car accident, or loss of consciousness
2. **High unmet need** for an FDA-approved treatment for PBH, a disease with no approved therapies
3. **~160K people living with PBH in the U.S.** who require medical management despite the current standard of care, nutrition therapy

Post-Bariatric Hypoglycemia (PBH): A Chronic, Debilitating Condition with High Unmet Need

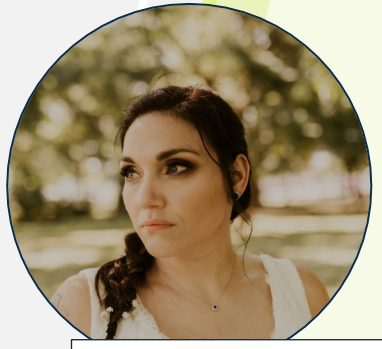
PBH Can be Dangerous and Life-Altering

- Hypoglycemic events can cause cognitive impairment, loss of consciousness, and even seizures because the brain is not getting enough glucose (neuroglycopenia)
- Can feel like a constant cycle of highs and lows with sudden and unpredictable crashes, with limited options to manage it
- Can affect someone's ability to work, drive, function independently, care for others, or even be alone safely
- In one study, over 90% of people with PBH described themselves as living with a disability, speaking to the incredible burden the condition can have on daily living[1]

Maria, living with PBH



Maggie, living with PBH



Jessica, living with PBH

Living with PBH

"It affected my ability to work and take care of my family."

"I pass out multiple times a week. My lows are averaging 4-5 times a day."

"I lost my driver's license since I am unaware of my lows."

"I'm afraid to watch my own kids at the pool because I might pass out."

PBH=post-bariatric hypoglycemia; **1.** Craig CM and McLaughlin TL. *Surg Obes Relat Dis.* 2021 Nov;17(11):1865-1872.

PBH has Significant Unmet Need with no Approved Treatment Options

~160,000 people

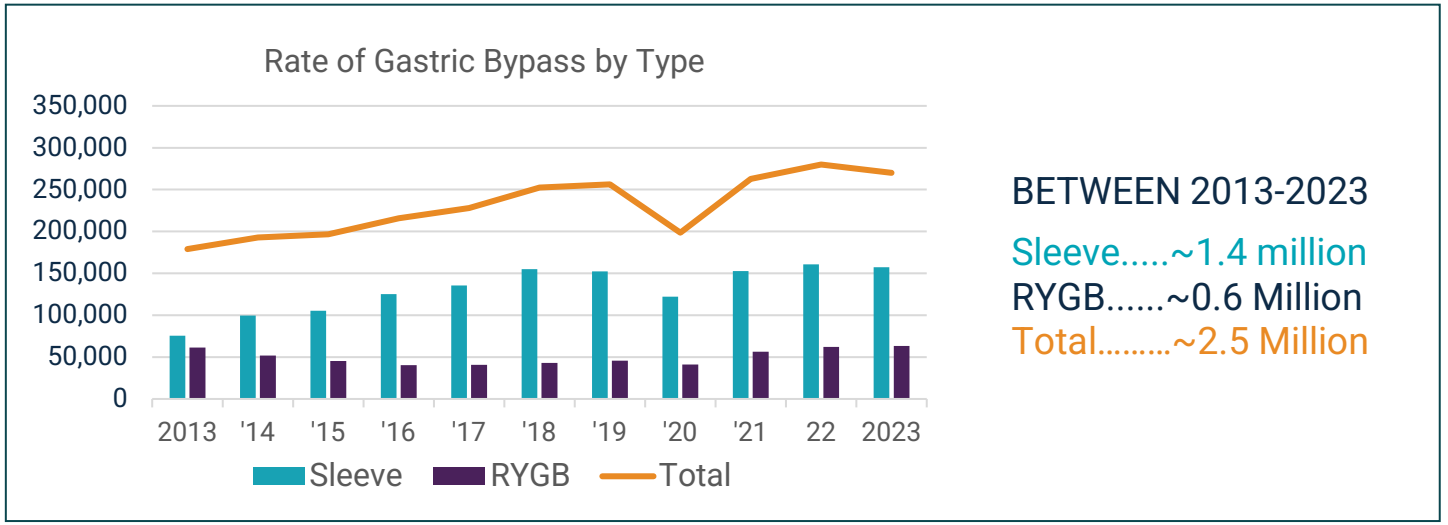
Currently living with PBH in the U.S.[1]

No approved treatment options

~200K new procedures

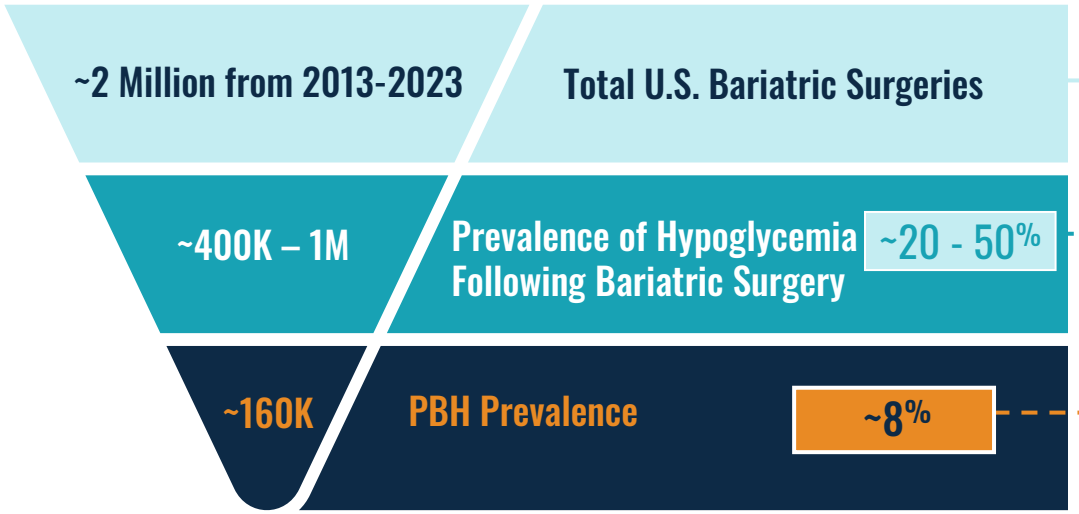
occur annually[2]

PBH develops on average 1-3 years post surgery



PBH=post-bariatric hypoglycemia; RYGB=Roux-en-Y gastric bypass; **1.** Craig CM, et al. *Surg Obes Relat Dis.* 2026;22(6):674-683. **2.** Estimate of Bariatric Surgery Numbers, 2013-2023. American Society for Metabolic and Bariatric Surgery (ASMBS). Accessed May 6, 2026.

~160K People Live With PBH in U.S.



SOURCE	FINDING
ASMBS Registry of Bariatric Surgery[1a]	2.5M bariatric surgeries of which 2M were either sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB)
8-Study Meta-Analysis (N=280)[2]	56.1% prevalence of hypoglycemia in studies specifically examining RYGB and 54.3% in those examining SG
Prospective, Longitudinal Cohort (N=1,448)[3]	43.2% prevalence of post-RYGB hypoglycemia symptoms
Prospective 1-Year Study (N=186)[4]	32.8% of participants had at least one OGTT (oral glucose tolerance test)-related hypoglycemic event after laparoscopic sleeve gastrectomy
Prospective 2-Year Study (N=281)[5]	32.6% showed post-challenge hypoglycemia after RYGB; 22.6% after SG
Retrospective Survey (N=341)[6]	29% with new-onset hypoglycemia symptoms post-RYGB or SG
Retrospective Study (N=120)[7]	Of 107 individuals with PBH treated with acarbose, 37% had persistent/unacceptable frequency of hypoglycemic events [**Note**: Equates to ~8-16% of total bariatric surgery population[b]]
Retrospective Study (N=1,206)[8]	13.1% met criteria for PBH 5 years post-op and 5% of those with PBH had severe symptoms[c]
Prospective, Longitudinal Cohort (N=177)[9]	7.9% met criteria for PBH 5-years post-RYGB
Prospective, Longitudinal Cohort (N=1,448)[3]	Symptoms of PBH requiring hospitalization or ER visit occurred in 2.6-3.6% of people who underwent RYGB after 5 years

ADDITIONAL CORROBORATING DATA

1

Preliminary data from multiple industry-leading medical claims providers align with current literature understanding of ~160K prevalent population[10]

2

Data from a Recent Academic Review[12d]:	Incidence		Prevalence		
	RYGB	SG	RYGB	SG	Total
Any PBH • *>3 hypoglycemia symptoms* • *Neuroglycopenia* • *Need for assistance* ***or*** • *Glucose ≤54 mg/Dl*	27.1%	10.3%	273,996	111,370	385,366
Medically-Important PBH *Visit to inpatient or outpatient facility*	11.8%	4.5%	118,843	48,350	**167,193**

[a]The ASMBS total bariatric procedure numbers are based on the best estimation from available data (BOLD,ACS/MBSAQIP, National Inpatient Sample Data and outpatient estimations) [b] Assumes 20-40% post-surgical hypoglycemic symptom prevalence; [c]Severe symptoms defined as glucose <40 mg/dL or emergency room/hospital visit; [d]Analysis incorporated historical census data dating back to 1993, life expectancy estimates, and disease-state modeling to inform projections

1. Estimate of Bariatric Surgery Numbers, 2013-2023. American Society for Metabolic and Bariatric Surgery (ASMBS). Accessed May 6, 2026. **2.** Lupoli R, et al. *Nutr Metab Cardiovasc Dis.* 2022;32(1):32-39. **3.** Fischer LE, et al. *Surg Obes Relat Dis.*2021;17(10):1787-1798. **4.** Belilgoli A, et al. *Obes Surg.* 2017;27:3179-3186 797-802.**5.** Brix JM, et al. *Obes Facts.* 2019;12:397-406. **6.** Lee CJ, et al. *Surg Obes and Relat Dis*. 2018;14(6):797-802. **7.** de Heide LJM, et al. *Diabetes Obes Metab*.2023;25:735-747.**8.** Lee CJ, et al. *Obesity*.2016.24(6):1342-1348. **9.** Raverdy V, et al. *Annals Surg.* 2016.264(5):878-885.**10.** Data on file. **11.** Hazelhurst J, et al. *Endocr Connect.* 2024;13(5):e230285. **12.** Craig CM, et al. *Surg Obes Relat Dis*. 2026;22(6):674-683.

Phase 3 LUCIDITY Positive Topline Results Advance Potential Commercial Launch of Avexitide

Leadership team tenured in rare disease, global regulatory approval, and commercial launch experience

August 2026

Announced positive topline data

By End of 2026

Expected NDA submission to the FDA

2027

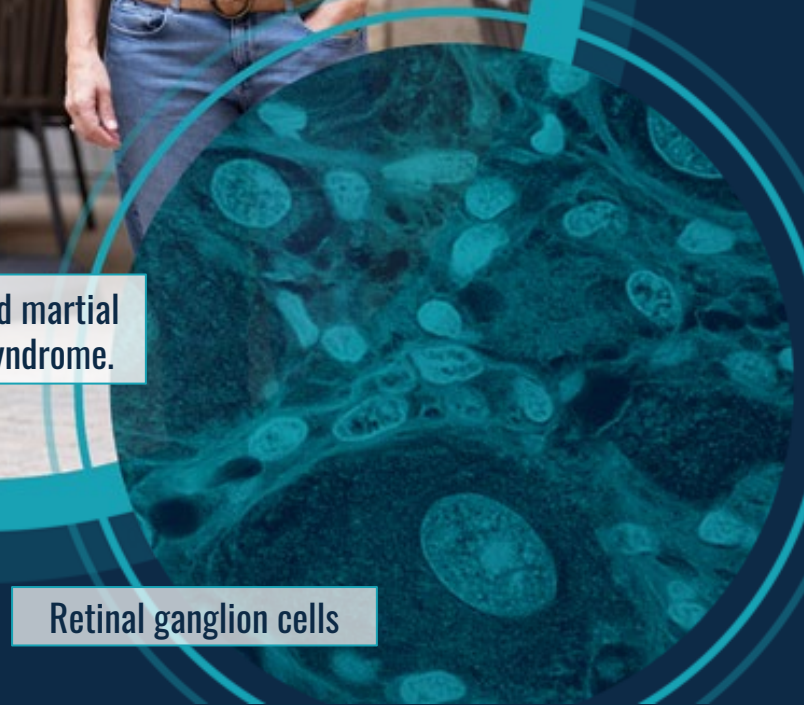
Anticipated commercial launch in 2027, if approved

Strong IP position with **patent rights through 2037**, potential for additional term through Patent Term Extensions

Granted **Orphan Drug designation** and positioned for **NCE exclusivity**

- IP=intellectual property; NCE=new chemical entities.

Raquel, a college student and martial artist living with Wolfram syndrome.



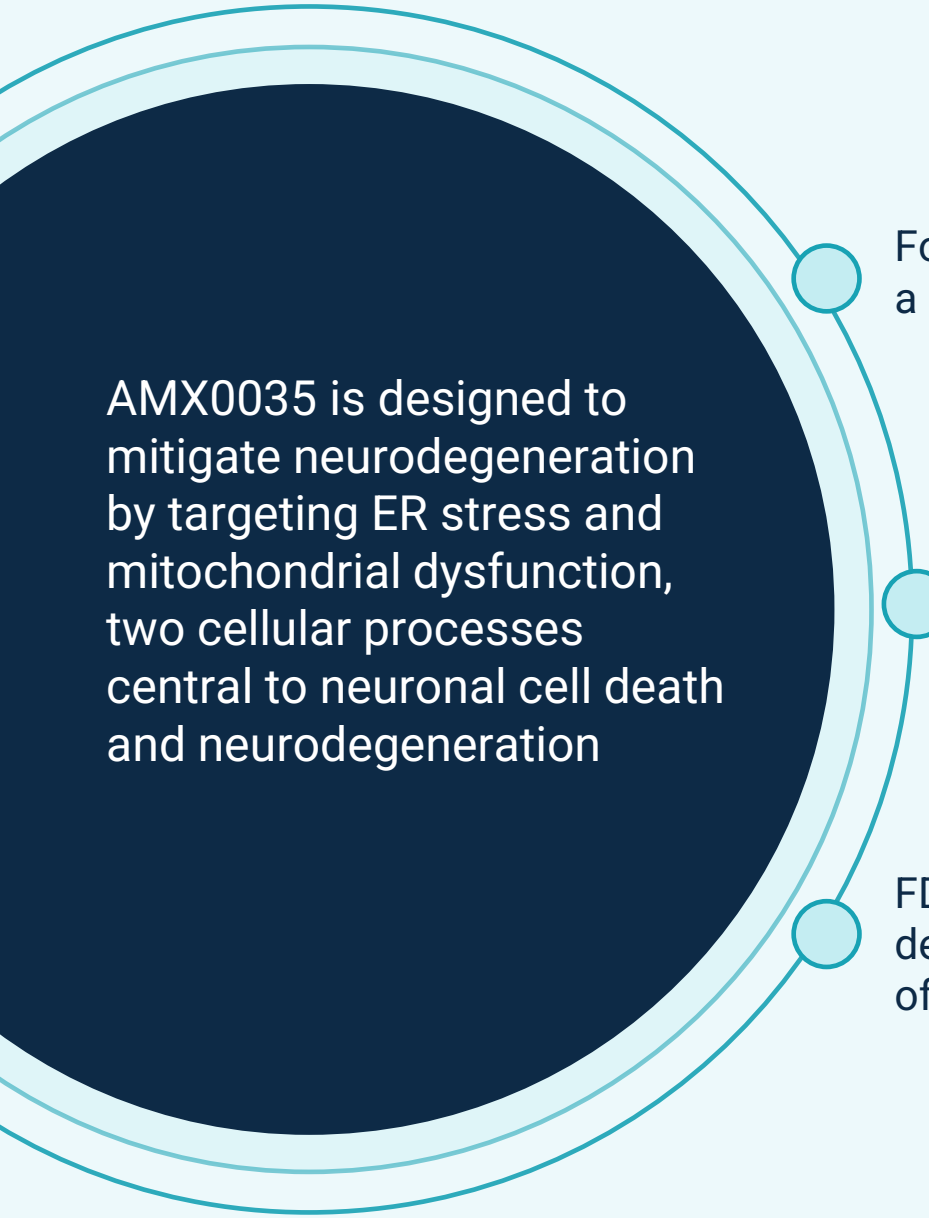
Retinal ganglion cells

AMX0035

Fixed-Dose Combination of Sodium Phenylbutyrate and Taurursodiol Designed to Slow or Mitigate Neurodegeneration

HELIOS

AMX0035 for the Potential Treatment of Wolfram Syndrome



- Focused on studying AMX0035 in Wolfram syndrome, a prototypical ER stress disorder
- Primary efficacy outcome of improvement in pancreatic function at Week 24 met in Phase 2 HELIOS trial; treatment with AMX0035 from Week 24 to Week 48 showed continued stabilization or improvement in multiple outcomes related to disease progression, including pancreatic function, glycemic control, vision, and overall symptom burden
- FDA Orphan drug designation and EU Orphan Drug designation granted to AMX0035 for the treatment of Wolfram syndrome

ER=endoplasmic reticulum.

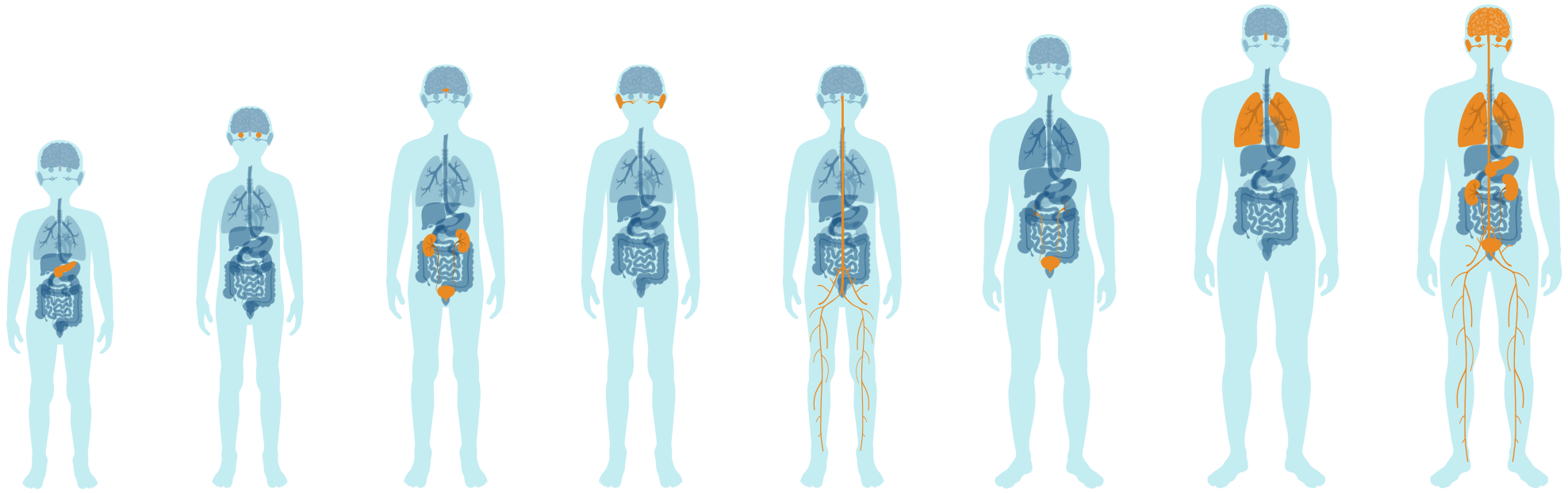
Wolfram Syndrome is a Rare, Fatal, Monogenic, Progressive Disorder[1-5]

WFS1 GENE MUTATION → PROGRESSIVELY IMPACTS MULTIPLE ORGANS AND SYSTEMS[1-5]

~3,000 people

Living with Wolfram Syndrome in the U.S.[1,2]

No approved therapies for Wolfram syndrome[6]



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

Neurogenic bladder
From brainstem and autonomic nervous system damage

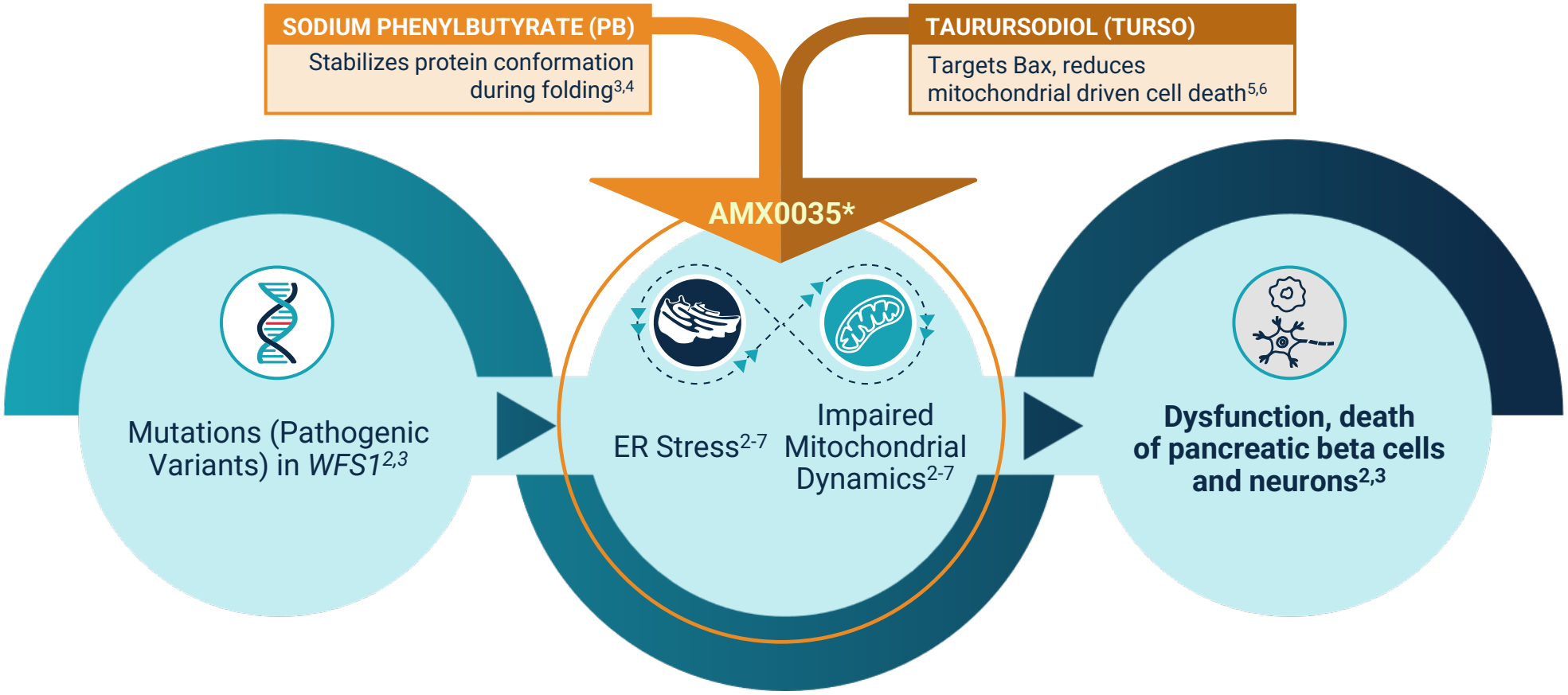
Difficulty Breathing
From brain stem damage

Death occurs at a median age of 30 years (range 25-49 years), **mainly from respiratory failure**

WFS1=Wolfram syndrome type 1 gene; 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. 7. Urano, F. et al. *J Clin Invest*. 2026;136(10):e198519.

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

AMX0035 targets ER stress and related mitochondrial dysfunction pathways



Clear Link of Mechanism of Disease and Mechanism of AMX0035

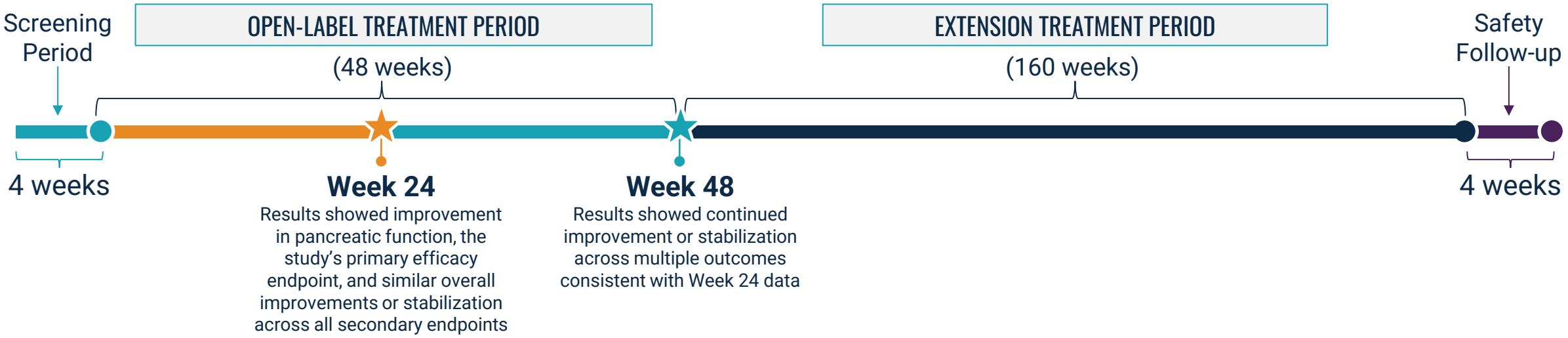
JCI insight

AMX0035 has been extensively studied in Wolfram models including patient-derived cells and mouse model

WFS1=Wolfram syndrome type 1 gene; * 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.

HELIOS Study Design

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



PRIMARY OBJECTIVES

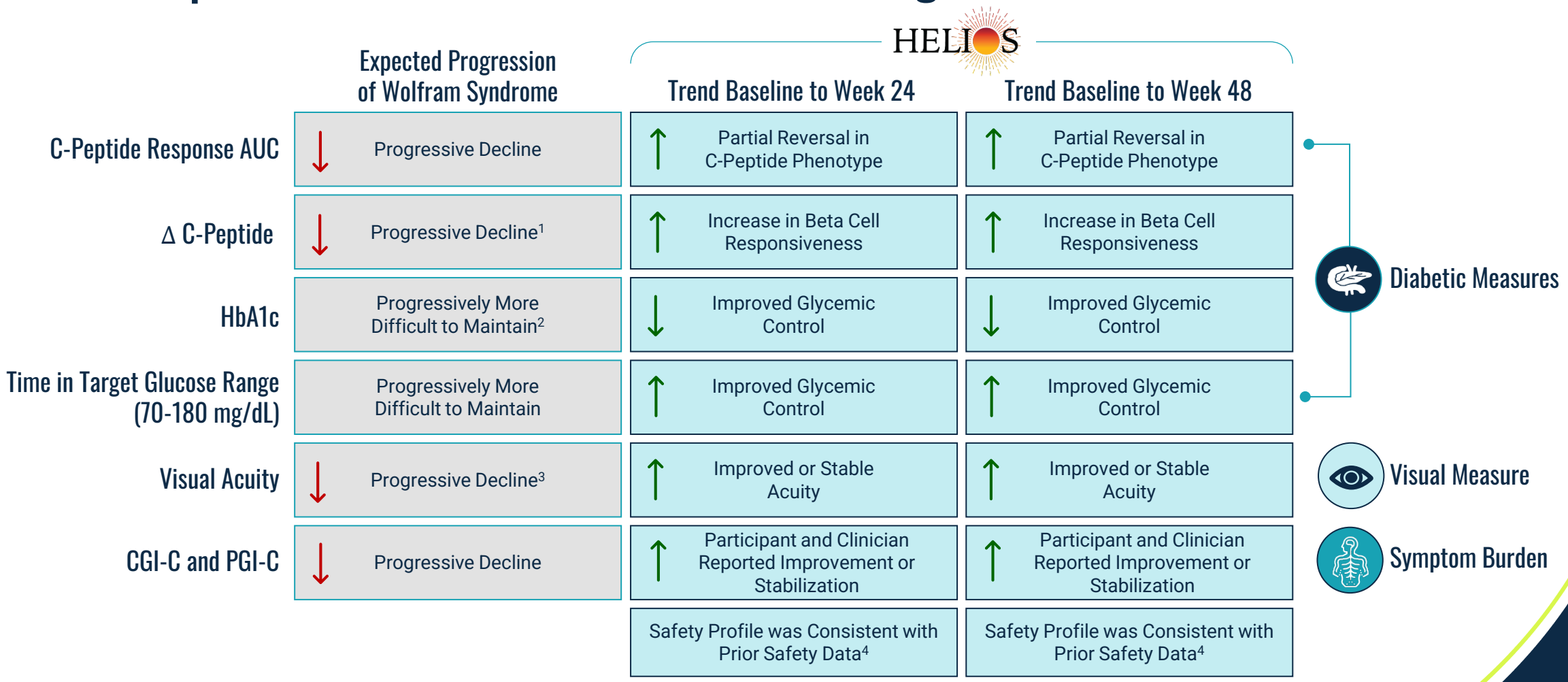
- To assess the safety and tolerability of AMX0035 administered orally for up to 208 weeks
- To evaluate the effect of AMX0035 on residual beta cell function over 24 weeks by monitoring C-peptide levels

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

GLP-1=glucagon-like peptide-1; *WFS1*=Wolfram syndrome type 1 gene; *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. Urano, F. et al. (2025, May 10-13). *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* [Poster presentation]. Joint Congress of ESPE and ESE 2025.

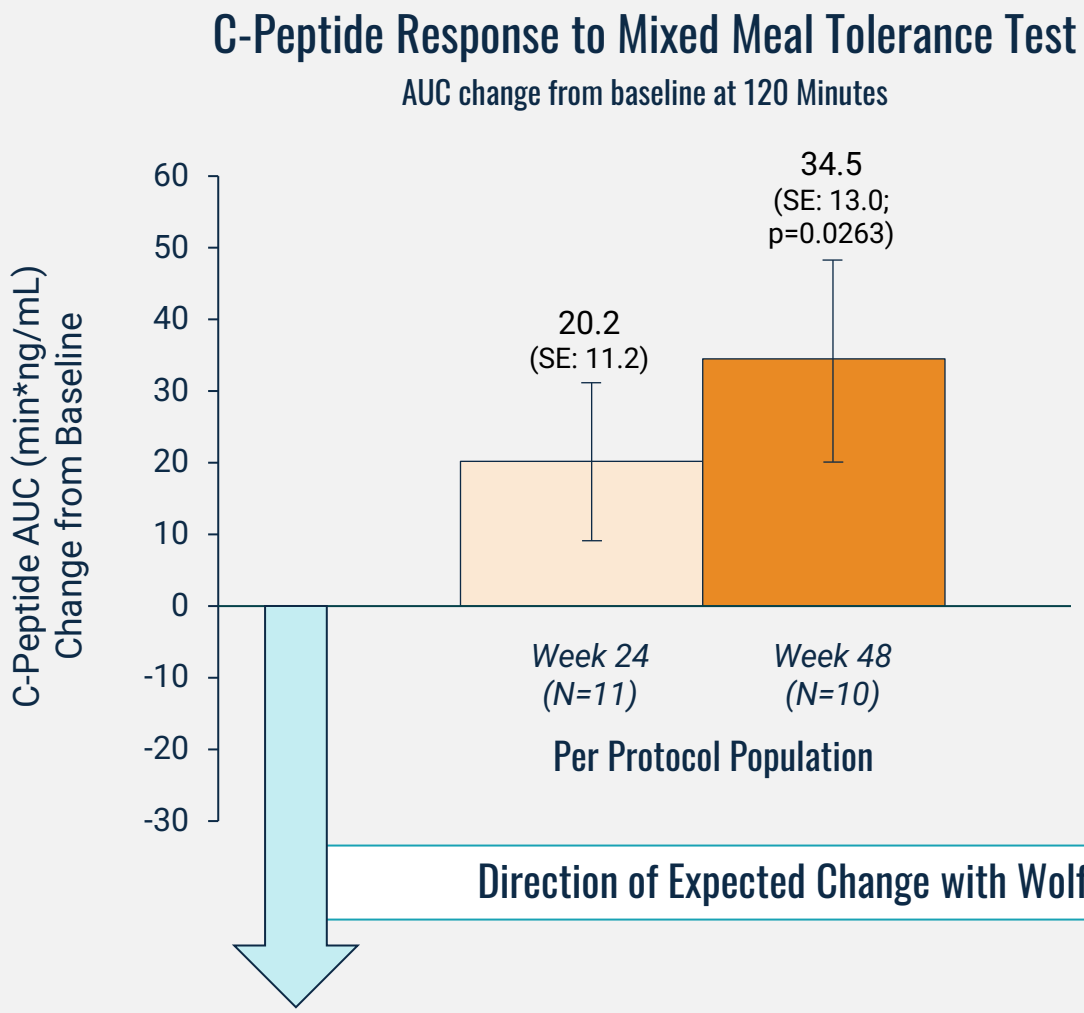
Long-Term Data Suggest Potential Benefit of AMX0035 in Wolfram Syndrome Across Multiple Outcomes Related to Disease Progression



AUC=area under the curve; CGI-C=clinician-reported global impression of change ; HbA1c=glycated hemoglobin A1c; PGI-C=patient-reported global impression of change; Urano, F. et al. (2025, May 10-13). *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* [Poster presentation]. Joint Congress of ESPE and ESE 2025. **1.** Recent natural history study demonstrated C-peptide levels progressively decline in people with Wolfram syndrome. **2.** Recent natural history study demonstrated that average HbA1c increases and time in target glucose range declines in people with Wolfram syndrome. **3.** Recent natural history study demonstrated visual acuity progressively worsens in people with Wolfram syndrome. **4.** AMX0035 was generally well-tolerated. All adverse events (AEs) were mild or moderate, and there were no serious AEs related to AMX0035 treatment.

Primary Endpoint: Improvement in C-Peptide Response Observed

Overall increase in mean C-peptide production from 0-120 minutes during MMTT*



Improvement in C-Peptide Response Observed Compared to Screening

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

JCI The Journal of Clinical Investigation

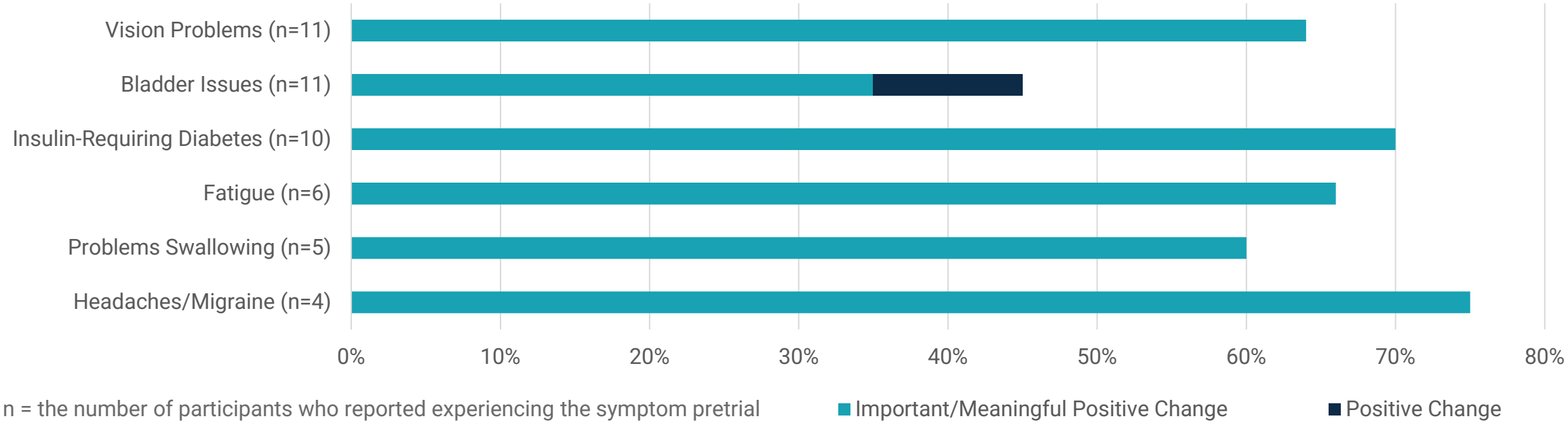
Phase II trial of sodium phenylbutyrate and taurursodiol in Wolfram syndrome

*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. AUC=Area under the curve; ITT=Intent to Treat; Min=Minute; MMTT=mixed meal tolerance testing; ng/mL=Nanograms per milliliter; SE=Standard error; WS=Wolfram syndrome; Urano, F. et al. *J Clin Invest*. 2026;136(10):e198519.

AMX0035 Reduced Overall Symptom Burden at Week 24 and Week 48

Qualitative on-study interview results support potential positive impact of AMX0035 on symptom burden

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



In on-study interviews after at least 24 weeks of treatment, 9 of 11 participants reported improvements in ≥1 Wolfram syndrome-related symptom with all noting the change being meaningful in at least one symptom

Data on File. Urano, F. et al. (2025, May 10-13). *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* [Poster presentation]. Joint Congress of ESPE and ESE 2025.

AMX0035 Safety and Tolerability in HELIOS

- AMX0035 was **generally well-tolerated**
  - > Diarrhea was the most common TEAE (58.3%); 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)

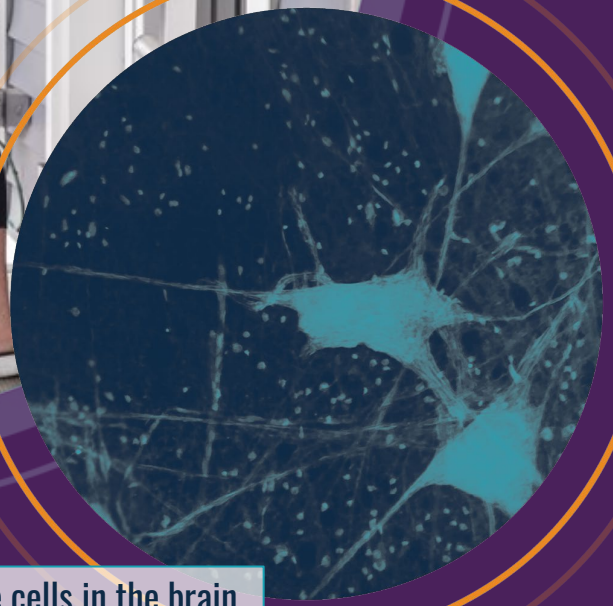
	AMX0035 (N=12)* n (%)
Participants with ≥1 TEAE	11 (91.7)
TEAE related to study drug**	10 (83.3)
Serious adverse events	0 (0)
Drug interrupted owing to TEAE	3 (25.0)
Dose reduced owing to TEAE	3 (25.0)
Drug discontinued owing to TEAE	0 (0)

*All available safety data as of January 10, 2025 included
**Includes those with TEAEs considered at least possibly related to treatment

Urano, F. et al. (2025, May 10-13). *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* [Poster presentation]. Joint Congress of ESPE and ESE 2025.

AMYLYX

In memory of Mick, a husband and father, who was a gifted tattoo artist and musician.



Nerve cells in the brain

AMX0114

Potent Antisense Oligonucleotide (ASO) Targeting Calpain-2

LUMINA

AMX0114: Antisense Oligonucleotide (ASO) Targeting Knockdown of Calpain-2 for the Potential Treatment of ALS

- ALS leads to deteriorating muscle function, inability to move and speak, respiratory paralysis, and death[1,2]
- ALS affects as many as 30,000 adults in the U.S.[3]
  - >90% of people have no family history of disease
- Calpain-2 (*CAPN2*), a protein involved in neurofilament biology, plays an essential role in axonal degeneration, a critical effector in the progression of ALS
- In preclinical studies, treatment with AMX0114 resulted in potent, dose-dependent, and durable reduction in *CAPN2* mRNA and calpain-2 protein levels in disease-relevant cell models of axonal degeneration
- Phase 1 LUMINA trial will evaluate the safety and biological activity of AMX0114 in people living with ALS
- Early data from LUMINA show AMX0114 was generally well-tolerated for participants enrolled in Cohort 1 (n=12), with no treatment-related SAEs
- The FDA granted Fast Track designation to AMX0114 in May 2025 providing eligibility for Priority Review if relevant criteria continue to be met

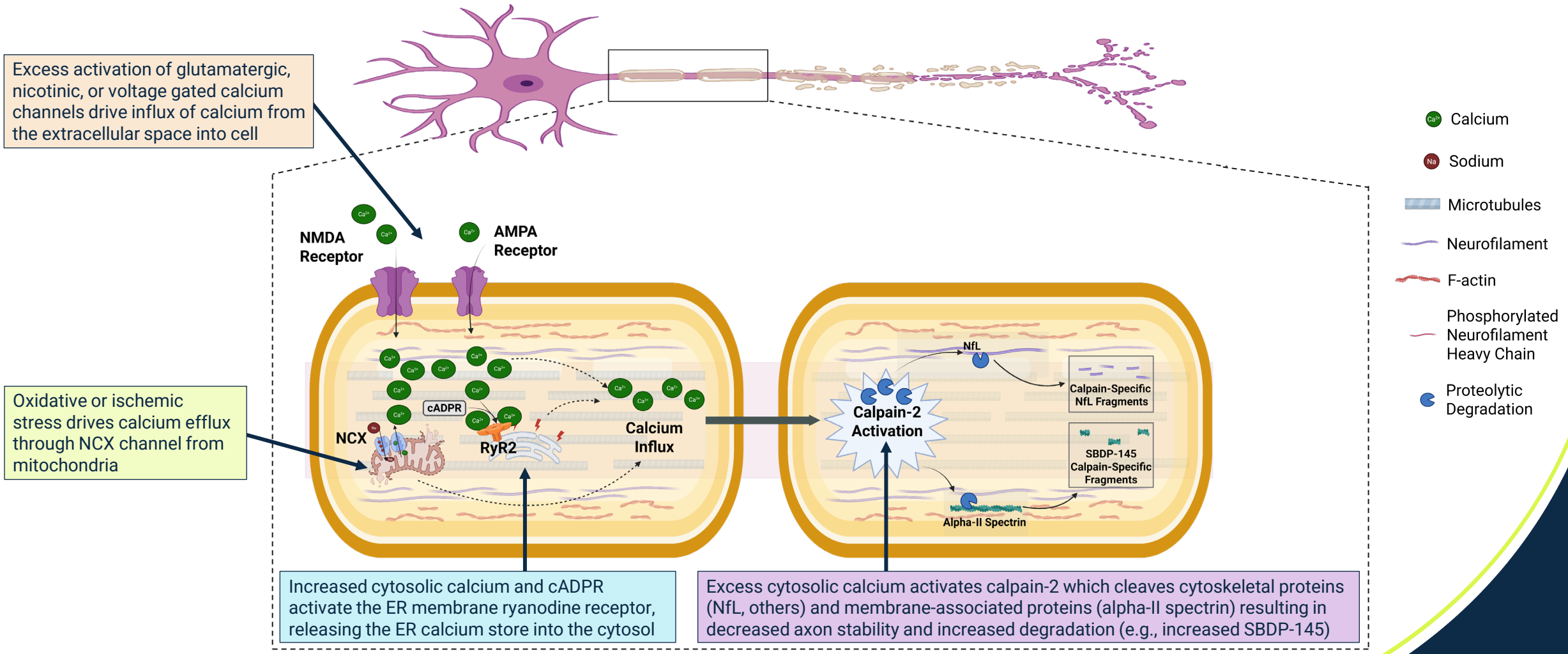
PROGRAM MILESTONES

March 2026 (Complete)	Fully enrolled Cohort 2 (n=12)
1H 2026 (Complete)	Present Cohort 1 data at a medical meeting
August 2026 (Complete)	Fully enrolled Cohort 3 (n=12)

ALS=amyotrophic lateral sclerosis; mRNA=messenger ribonucleic acid; SAE=serious adverse event; **1.** Brown, R. H., Al-Chalabi A. *N Engl J Med*. 2017;377(2):162-172; **2.** Al-Chalabi, A., et al. *Lancet Neurol*. 2016;15(11):1182-1194; **3.** Mehta, P., et al. *Amyotroph Lateral Scler Frontotemporal Degener*. 2023:1-7. doi: 10.1080/21678421.2023.2245858.

Axonal Degeneration Disrupts Neural Connectivity and is a Key Early Contributor to the Pathogenesis of ALS

Mechanisms of Axonal Degeneration



AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; cADPR=cyclic adenosine diphosphate ribose; ER=endoplasmic reticulum; NCX=sodium-calcium exchanger; NfL=neurofilament light chain; NMDA=N-methyl-D-aspartate; RyR2=ryanodine receptor 2; SBDP-145=alpha-II spectrin breakdown product 145 kDa; Created in BioRender. Fontaine, R. (2026).

Calpain-2, a Protein Involved in Neurofilament Biology, Plays an Essential Role in Axonal Degeneration, a Critical Effector in the Progression of ALS

Evidence for Targeting Calpain-2 in ALS[1-4]

Multiple injury paradigms and hypotheses of axonal degeneration converge on calpain-2

- Calpain-2 levels are elevated in people with ALS
- Calpain-2 inhibition increases overall survival and delays disease onset in ALS mouse model
- Calpain-2 substrates include neurofilament and TDP-43
- AMX0114 has shown efficacy in preclinical ALS models

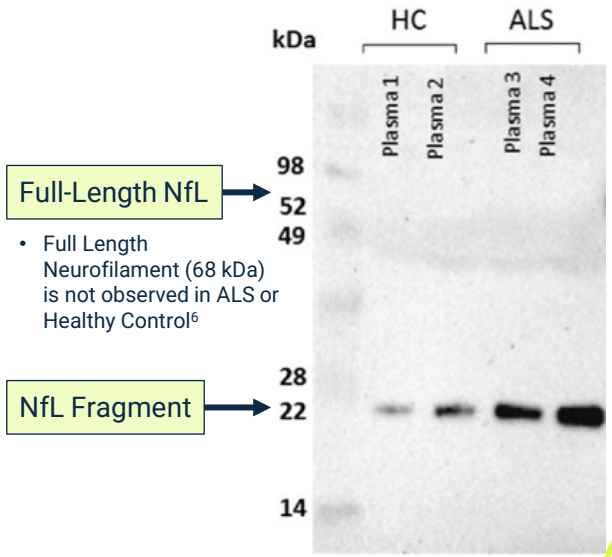
Genetic Support for Calpain-2 as a Target

Calpain-2 genetic variant found to be associated with ALS

~30K data set

(~20K with ALS / ~10K controls)[7]

NfL is Cleaved by Calpain-2, with Increased NfL Fragments Seen in ALS

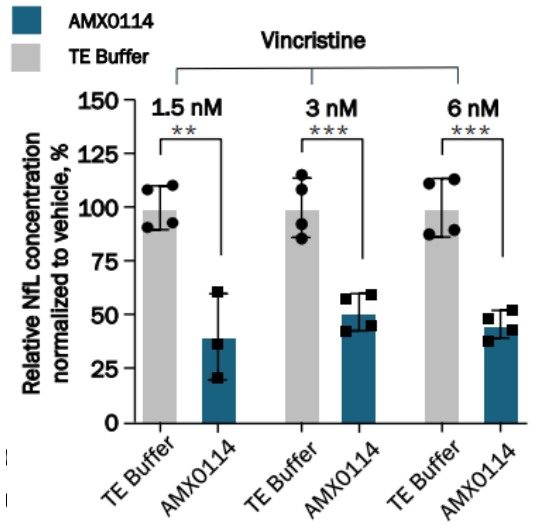


- Full Length Neurofilament (68 kDa) is not observed in ALS or Healthy Control[6]

ALS=amyotrophic lateral sclerosis; **1.** Ueyama H et al. *J Neurol Sci*. 1998;155(2):163-169. **2.** Yamashita T et al. *Nat Commun*. 2012;3:1307. **3.** Rao MV, et al. *J Neurochem*. 2016;137(2):253-65. **4.** Ma M, et al. *Neurobiol Dis*. 2013;56:34-46. **5.** Asakawa, K., Handa, H., Kawakami, K. Multi-phaseted problems of TDP-43 in selective neuronal vulnerability in ALS. *Cell Mol Life Sci*. 2021;78(10):4453-4465. doi:10.1007/s00018-021-03792-z **6.** Lombardi, V., Carassiti, D., Giovannoni, G. *et al. Sci Rep* 10, 97 (2020). doi:10.1038/s41598-019-54310-y; **7.** Hop et al. *Nat Genet* (2026). doi:10.1038/s41588-026-02535-9.

AMX0114 Reduces Extracellular NfL Levels in Multiple Models of Trigger-Induced Neuronal Injury and Improves Survival in Relevant Models

Pretreatment with AMX0114 Reduces Extracellular NfL in Vincristine Treated Neurons

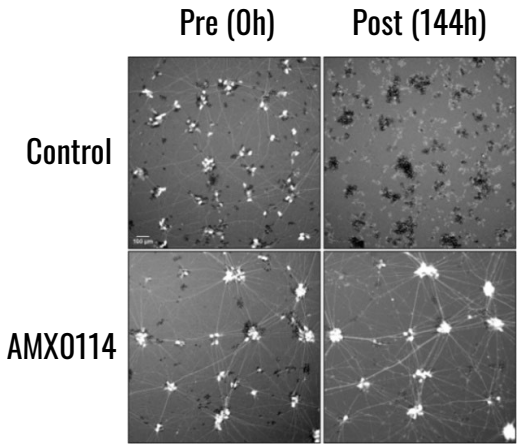


Similar NfL Reduction in Rotenone and Colchicine iPSC models

Bars represent mean (SD) Nfl concentrations relative to vehicle. Overlying symbols represent individual replicate values.
NS= P>.05.
* = P<.05.
** = P<.01,
*** = P<.001,
**** = P<.0001.
NfL, neurofilament light chain; NS, not significant; TE, tris ethylenediaminetetraacetic acid.

Pretreatment with AMX0114 improves motor neuron survival following oxidative stress (or H_2O_2 exposure)

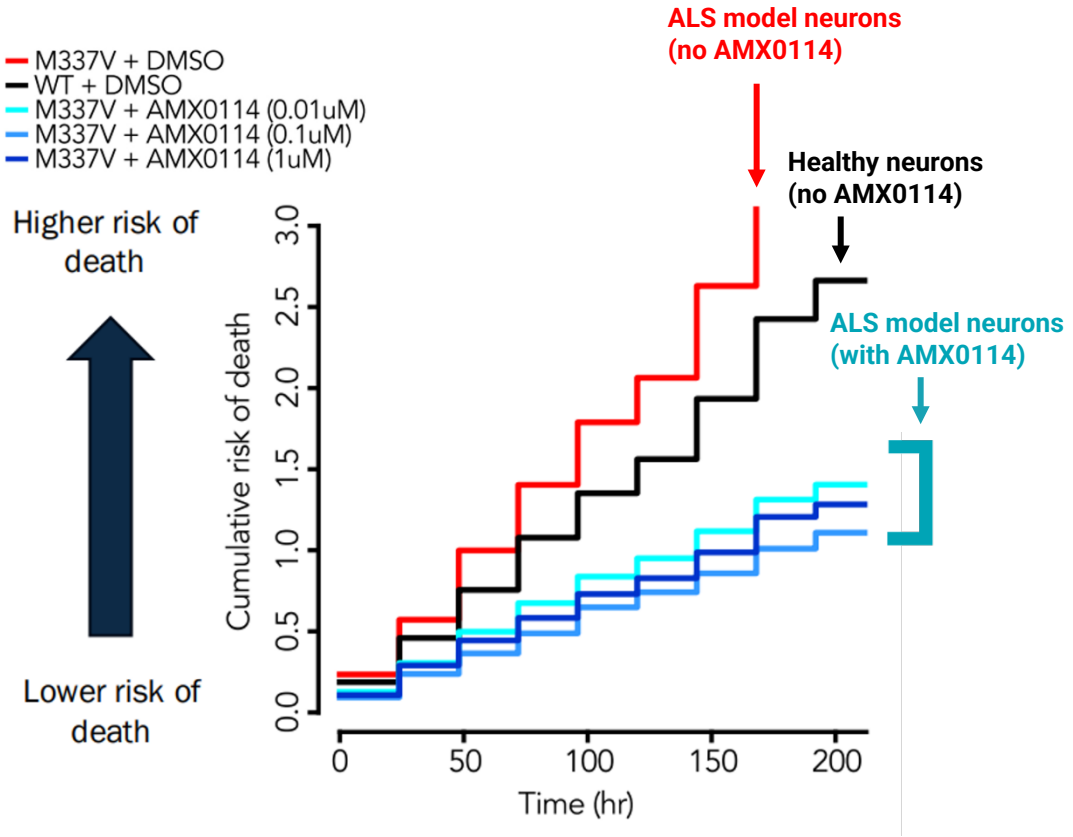
Representative Images of Motor Neurons Pre- and Post-Exposure to H_2O_2



Presented at ALS ONE

AMX0114 Treatment Improves Motor Neuron Survival in TDP43 ALS iPSC Model

TDP-43 ALS Model



Induced pluripotent stem cell (iPSC)-derived motor neurons were exposed to varying concentrations of the neurotoxic compounds vincristine, rotenone, and colchicine after pretreatment with AMX0114.

ALS=amyotrophic lateral sclerosis; NfL=neurofilament light chain; Data on File. Amylyx Pharmaceuticals Inc. 2024; Survival analyses performed in the lab of Dr. Sami Barmada at the University of Michigan Medical School by Dr. Michael Bekier.

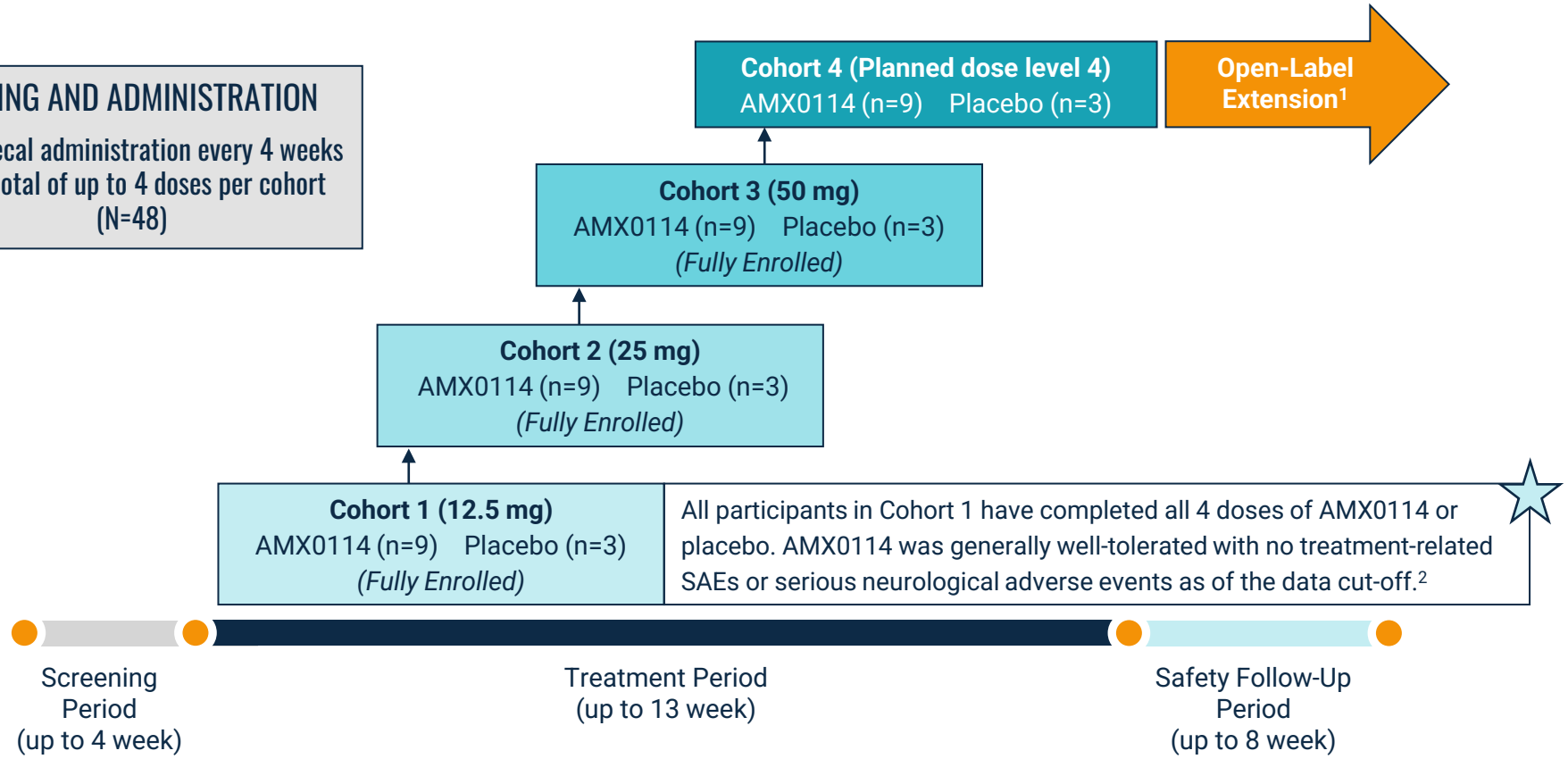
LUMINA: Phase 1 Clinical Trial of AMX0114 in ALS

PRIMARY OBJECTIVE: To assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AMX0114 in people living with ALS

- Will assess ALS biomarkers, including change from baseline in neurofilament light (NfL) levels

DOSING AND ADMINISTRATION

Intrathecal administration every 4 weeks for a total of up to 4 doses per cohort (N=48)



ALS=amyotrophic lateral sclerosis; SBDP-145=spectrin breakdown product-145.
1. The open-label extension may be implemented if safety and efficacy data support a positive benefit-risk profile **2.** As of March 11, 2026.

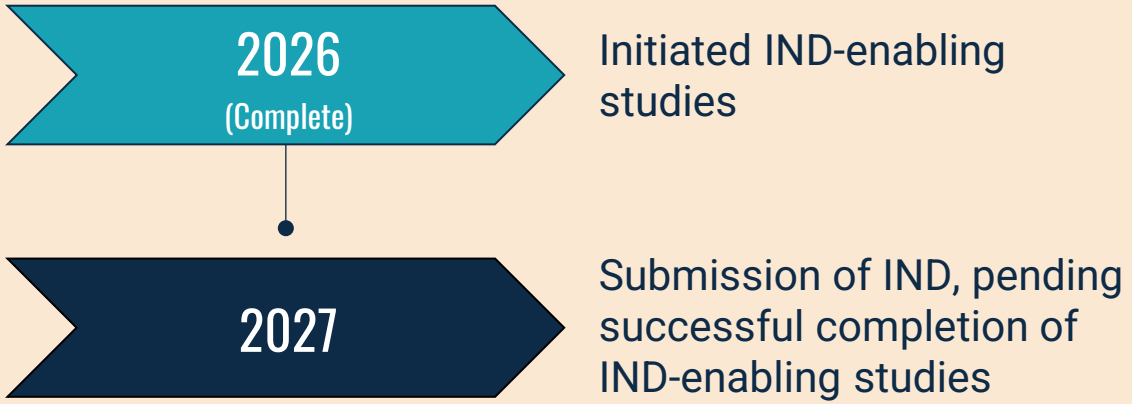
AMX0318

Novel, Long-Acting GLP-1 Receptor Antagonist

AMX0318: A Novel, Long-Acting Glucagon-Like Peptide-1 (GLP-1) Receptor Antagonist

- Entered into a collaboration with Gubra A/S in December 2024 to develop a long-acting GLP-1 receptor antagonist and in January 2026, AMX0318 was nominated as a development candidate
- AMX0318 completed an extensive preclinical evaluation in collaboration with Gubra A/S
- In preclinical studies, AMX0318 met key preclinical criteria for a long-acting GLP-1 receptor antagonist, including:
  - > Robust chemical stability profile
  - > High solubility
  - > Strong *in vitro* potency
  - > Evidence of *in vivo* activity and tolerability
  - > Favorable pharmacokinetic profile consistent with a long-acting peptide

EXPECTED MILESTONES

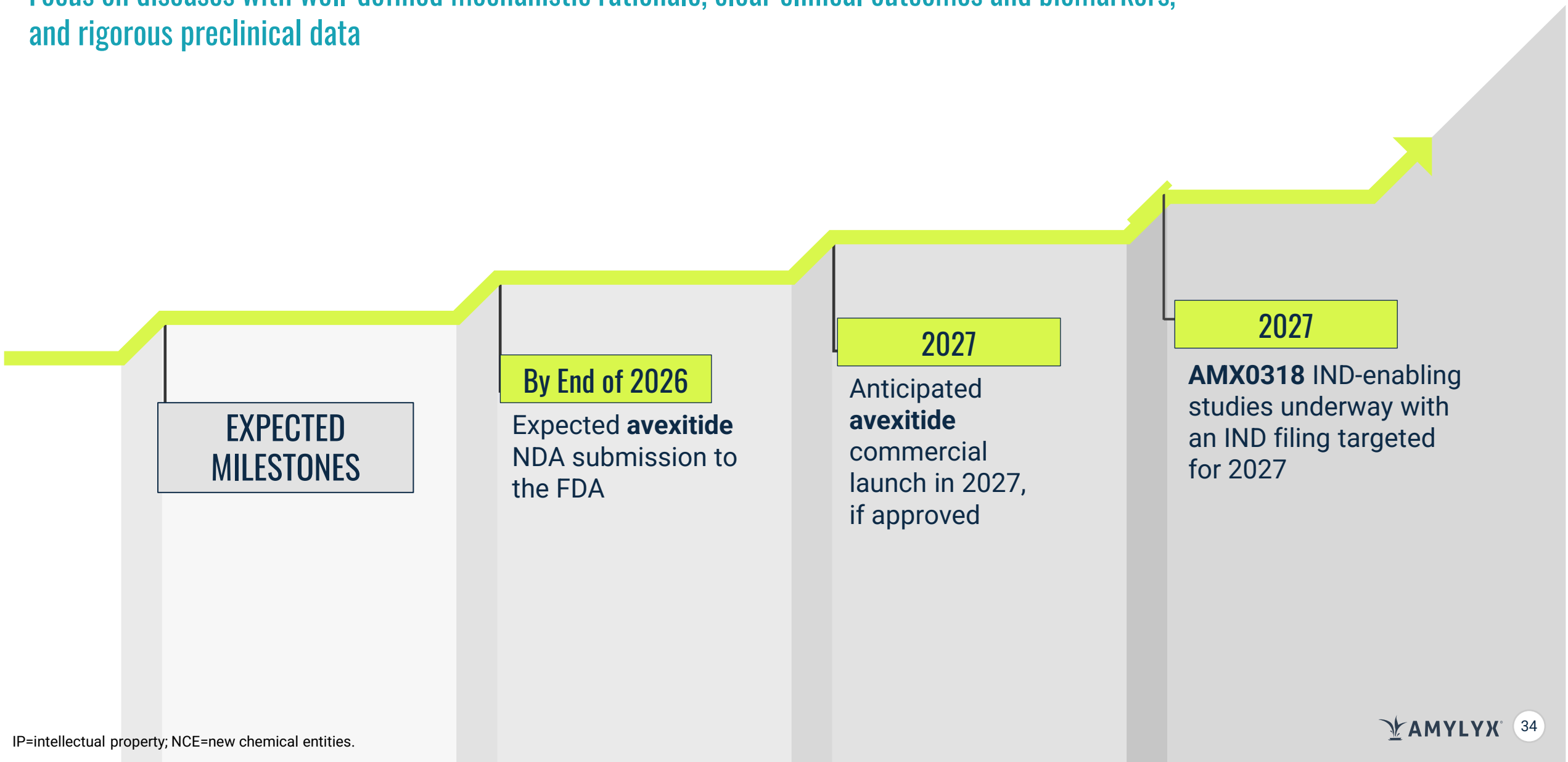


IND=investigational new drug.

Key Corporate Highlights

Advancing Novel Therapies for Diseases with High Unmet Needs

Focus on diseases with well-defined mechanistic rationale, clear clinical outcomes and biomarkers, and rigorous preclinical data



IP=intellectual property; NCE=new chemical entities.

Avexitide, AMX0035, and AMX0114 are Protected by Robust Global IP Portfolio

AVEXITIDE

>250 granted patents and over 40 pending applications worldwide*

- Granted US patent rights through 2037
  - > **Additional patent term potentially available through patent term extension**
- Positioned for NCE exclusivity
- Granted Orphan Drug designation for the treatment of hyperinsulinemic hypoglycemia

AMX0035

>80 granted patents and over 50 pending applications worldwide

- Granted US patent rights through 2040
- Granted Orphan Drug designation for the treatment of Wolfram syndrome

AMX0114

Pending composition of matter patent provides potential patent term through 2043 if granted

- Positioned for NCE exclusivity

FISH & RICHARDSON

* Includes in-licensed patents

NCE=new chemical entities.

Public Offering
Closed on August 21, 2026

Net Proceeds
$544.5M

As of June 30, 2026

$250.8M
in cash, cash equivalents and marketable securities

PRO FORMA SHARES OUTSTANDING AFTER OFFERING* **127.6M**

*As noted in Form 424B5 filed Aug. 20, 2026

Team

Leadership Team Tenured in Rare Disease with Commercial and Clinical Development Capabilities

Joshua Cohen, BSE
Co-CEO and Director

Co-founded Amylyx, Co-CEO since 2013. Track record: preclinical and clinical development, as well as commercial launch; successful execution of Phase 3 trial for avexitide; transformative business development

Justin Klee, ScB
Co-CEO and Director

Co-founded Amylyx, Co-CEO since 2013. Track record: preclinical and clinical development, as well as commercial launch; successful execution of Phase 3 trial for avexitide; transformative business development

Jim Frates
Chief Financial Officer

22-year CFO at Alkermes; grew to >$1B in annual revenue and >2,000 employees worldwide

Camille L. Bedrosian, MD
Chief Medical Officer

Nearly 30 years of experience within the biotech industry; Former CMO at Ultragenyx, Alexion, and ARIAD

Dan Monahan
Chief Commercial Officer

20+ years of commercial leadership experience; Former commercial lead for multiple industry-leading medicines at Otsuka, Novartis, and Sanofi

Tom Holmes
Chief Technical Operations Officer

More than 25 years of biotech experience; Former Head of Global External Manufacturing at Biogen

Gina M. Mazzariello
Chief Legal Officer and General Counsel

20+ years of corporate and commercial legal experience within the healthcare industry, including at Boehringer Ingelheim

Linda Arsenault
Chief Human Resources Officer

25+ years of global HR experience at multibillion-dollar life sciences and technology companies, including at Sumitomo Pharma America Holdings (SMPA)

Ushering in a New Era for Treating Diseases with High Unmet Needs

AMYLYX®