
Investor Presentation

September 2024



Everything we do is centered around those living with diseases with high unmet needs and their loved ones.

We are on a mission to discover and develop innovative treatments and to help support and create more moments for these communities.

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 neurodegenerative diseases, including progressive supranuclear palsy (PSP) and Wolfram syndrome (WS), AMX0114 for ALS; statements regarding the timing of clinical trials for PBH, PSP, WS and/or ALS; and expectations regarding our longer-term strategy. 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’ program development activities, including ongoing and planned clinical trials, Amylyx’ ability to execute on its development and regulatory strategy, regulatory developments, Amylyx’ cash runway and ability to fund operations, as well as the risks and uncertainties set forth in Amylyx’ United States Securities and Exchange Commission (SEC) filings, including Amylyx’ Annual Report on Form 10-K for the year ended December 31, 2023, 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 proven track record of commercialization in rare diseases

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							Engaging with FDA based on interim data; planning for a single Phase 3 clinical trial and will share details once finalized Report 24-week topline data in Fall 2024
Progressive Supranuclear Palsy (PSP)							Data from interim analysis expected 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

Key Upcoming Milestones



Engaging with FDA based on interim data reported from Phase 2 HELIOS trial of AMX0035 in **Wolfram syndrome** and anticipate sharing plans for a single Phase 3 clinical trial once finalized



HELIOS topline data for all participants expected **fall of 2024**

Planning to initiate avexitide Phase 3 program in **PBH** in **Q1 2025**



Planning to initiate a multiple ascending dose clinical trial of AMX0114 in people living with **ALS** in **second half of 2024**



Phase 3 ORION trial of AMX0035 in **PSP** – data from an interim analysis anticipated in **mid-2025**



Expecting to complete enrollment of avexitide Phase 3 program in **PBH** in **2025**



Topline data from avexitide Phase 3 program in **PBH** anticipated in **2026**



Post-Bariatric Hypoglycemia Program

- Avexitide is a phase 3-ready, first-in-class GLP-1 receptor antagonist with potential to treat hyperinsulinemic hypoglycemia including PBH

Avexitide is a Compelling Asset with FDA Breakthrough Therapy Designation

Novel, first-in-class GLP-1 receptor antagonist with the potential to treat hyperinsulinemic hypoglycemia



Debilitating orphan indications with no approved treatment options; Symptomatic PBH affects ~160,000 people in U.S.



Clear match of mechanism of disease (hyperinsulinemic hypoglycemia) and mechanism of potential treatment



Highly statistically significant and clinically meaningful data with well-tolerated safety profile replicated across five clinical trials of PBH



Builds on Amylyx' endocrine and neuroscience expertise

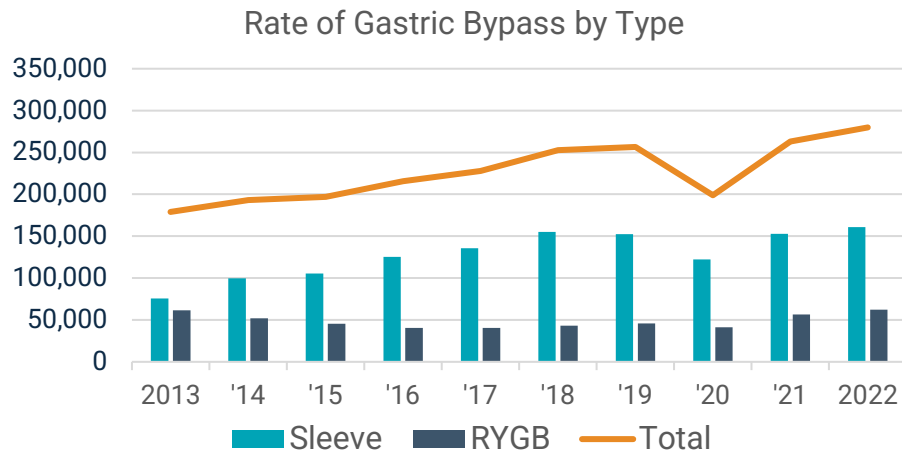


Rapid path to Phase 3 based on outcomes met in Phase 2 and Phase 2b; Plan to utilize FDA-agreed upon primary endpoint in Phase 3

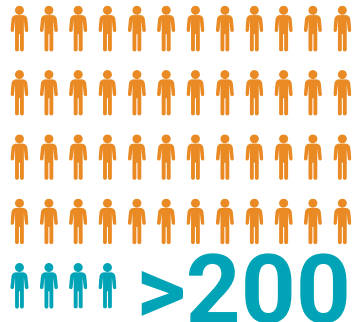
Data from pivotal post-bariatric hypoglycemia (PBH) Phase 3 program expected in 2026, planning for commercial launch in 2027

Bariatric Surgery is a Cornerstone of Weight Loss Therapy

With millions of people having undergone surgery



~2M
people living in the
U.S. have received
bariatric surgery in
the past 10 years¹



new procedures are
happening annually¹

Bariatric Surgery Results in Substantial Weight Loss

- 20-30% reduction in bodyweight, with some participants losing even more^{2,3}
- Higher BMI associated with higher total weight loss⁴
- Bariatric surgery shows benefits for other conditions including in direct comparison to medical management for **Type 2 diabetes**⁵ and **cardiovascular disease**^{6,7}

Millions of People Have Already Benefited From Bariatric Surgery

Expected to remain a cornerstone of weight loss therapy despite the introduction of GLP-1 receptor agonists for weight loss



Bariatric surgery is likely more effective and more sustainable for weight loss^{1,6} and evidence suggest reduced risk of cardiovascular events and MASLD (previously known as NAFLD)^{2,3}



Bariatric surgery is cost-effective and covered by insurance⁴



Bariatric surgery and GLP-1 agonists may be combined, especially for people with higher BMIs⁵

There are already millions of people who have undergone bariatric surgery

MASLD = metabolic dysfunction-associated steatotic fatty liver disease
NAFLD = nonalcoholic fatty liver disease



1. Sarma, S. et al. *Obesity (Silver Spring)*. 2022;30(11):2111-2121. doi:10.1002/oby.23563 2. Cohen, E. et al. *The American Journal of Gastroenterology*. 2023;118(10S):p S1237. doi: 10.14309/01.ajg.0000956248.42228.0d 3. Adekolu, A. et al. *The American Journal of Gastroenterology*. 2023;118(10S):p S971. doi: 10.14309/01.ajg.0000954768.41220.8b4. 4. Haseeb, M. et al. *JAMA Netw Open*. 2024;7(4):e246221. doi:10.1001/jamanetworkopen.2024.6221 5. Weight-loss drugs are increasingly paired with bariatric surgery, 2023. *Axios*. 6. Jenkins, M. et al. (2024, June 9-13). *Effectiveness and durability of common weight loss methods* [Poster]. ASBMS Annual Meeting, San Diego, CA, United States. [Link to access](#).

Post-Bariatric Hypoglycemia (PBH) is a Condition Affecting People Who Have Undergone Bariatric Surgery

- Occurs on average 1-3 years post bariatric surgery¹
- Characterized by hyperinsulinemic (inappropriately high insulin levels) hypoglycemia (low blood sugar) after a meal²
- Current management approaches are insufficient
 - > Symptoms persist for many despite dietary modification and off-label use of acarbose, octreotide, and/or diazoxide³
 - > Patient typically managed by endocrinologist/diabetologist

Living with PBH

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

“I lost my driver’s license since I am unaware of my lows.”

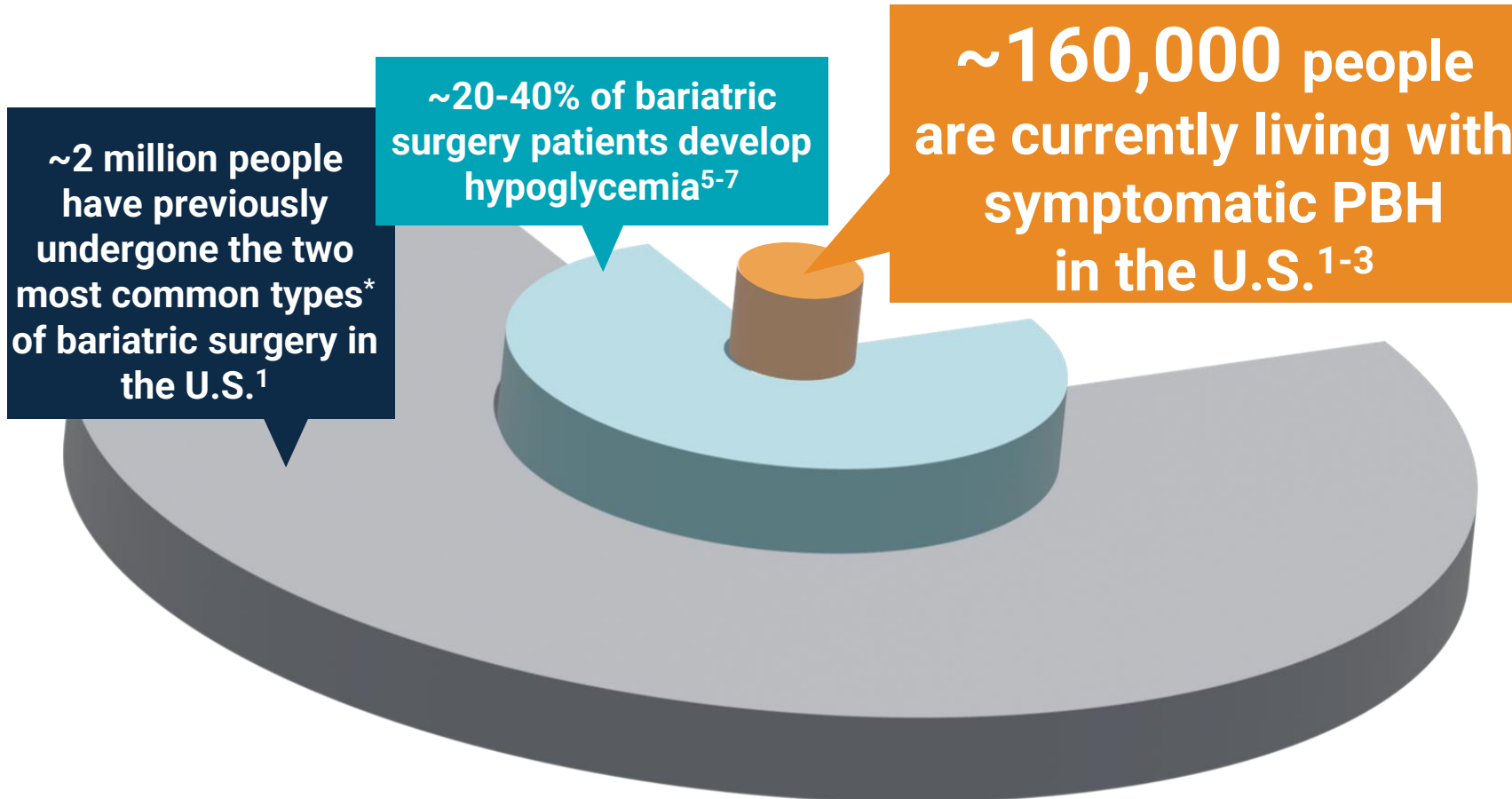
“I pass out multiple times a week. My lows are averaging 4-5 times a day.”

Hypoglycemia from PBH is Often Dangerous and Life-Altering

- General fatigue, confusion
- Risk of falls, seizures, vehicle accidents
- Job and income loss

~160,000 People Are Currently Living With Symptomatic PBH in the U.S.¹⁻³

Prevalence

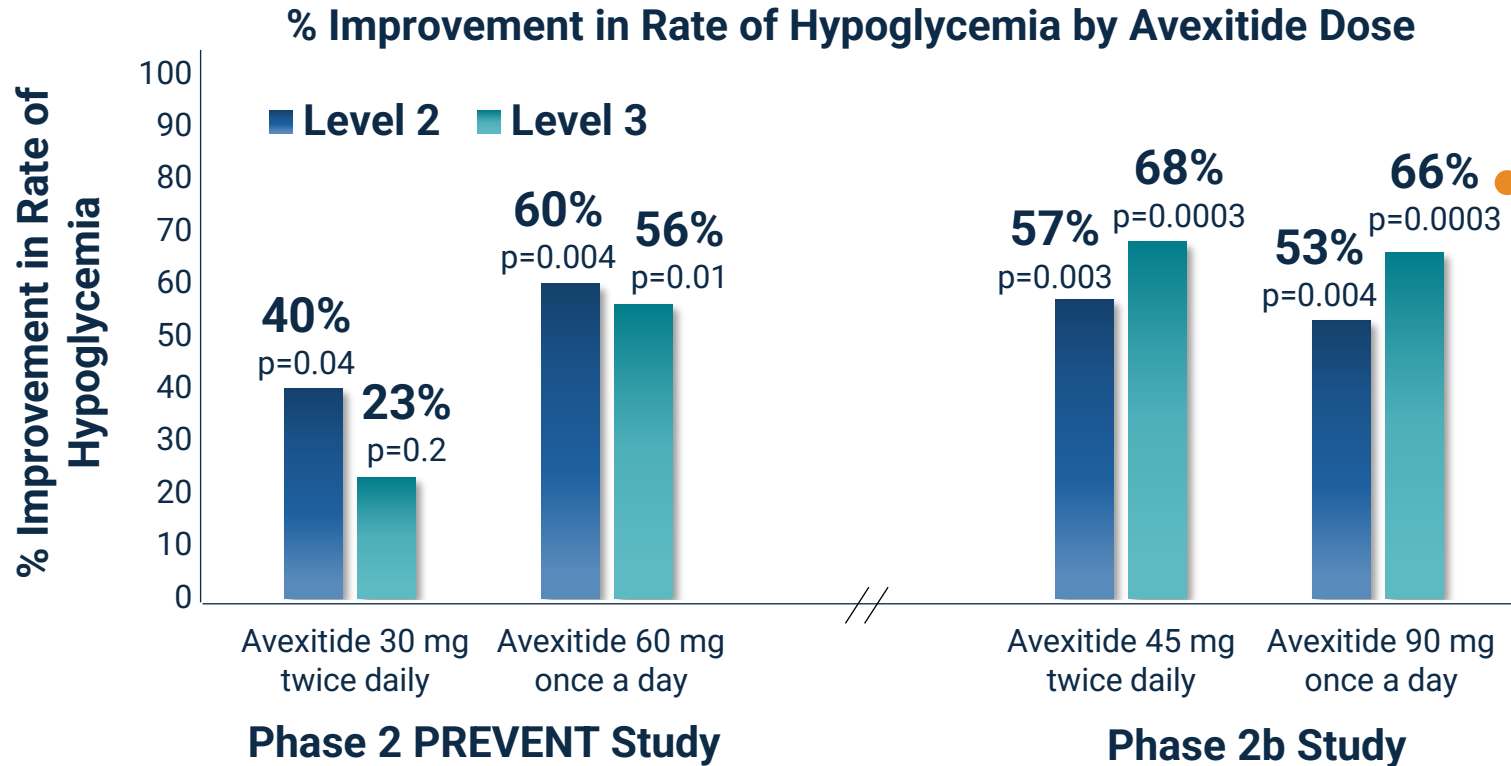


Characteristics of symptomatic PBH from literature:²⁻⁴

- Current guidelines suggest PBH defined as clinically significant hypoglycemia (experiencing a Level 2 event as defined as <54 mg/dL after bariatric surgery)
- Postprandial neuroglycopenic symptoms: difficulty speaking, blurred vision, confusion, drowsiness, impaired consciousness, coma, seizures, traffic accidents, requiring ER visit or hospitalization

*According to 2022 bariatric surgery estimates from the American Society for Metabolic and Bariatric Surgery (ASMBS), more than 75% of bariatric surgeries in the U.S. are either sleeve gastrectomy (57%) or Roux-en-Y gastric bypass (22%).¹

Avexitide Significantly Reduced Daily Rates of Hypoglycemia in Two Phase 2 Clinical Trials in PBH

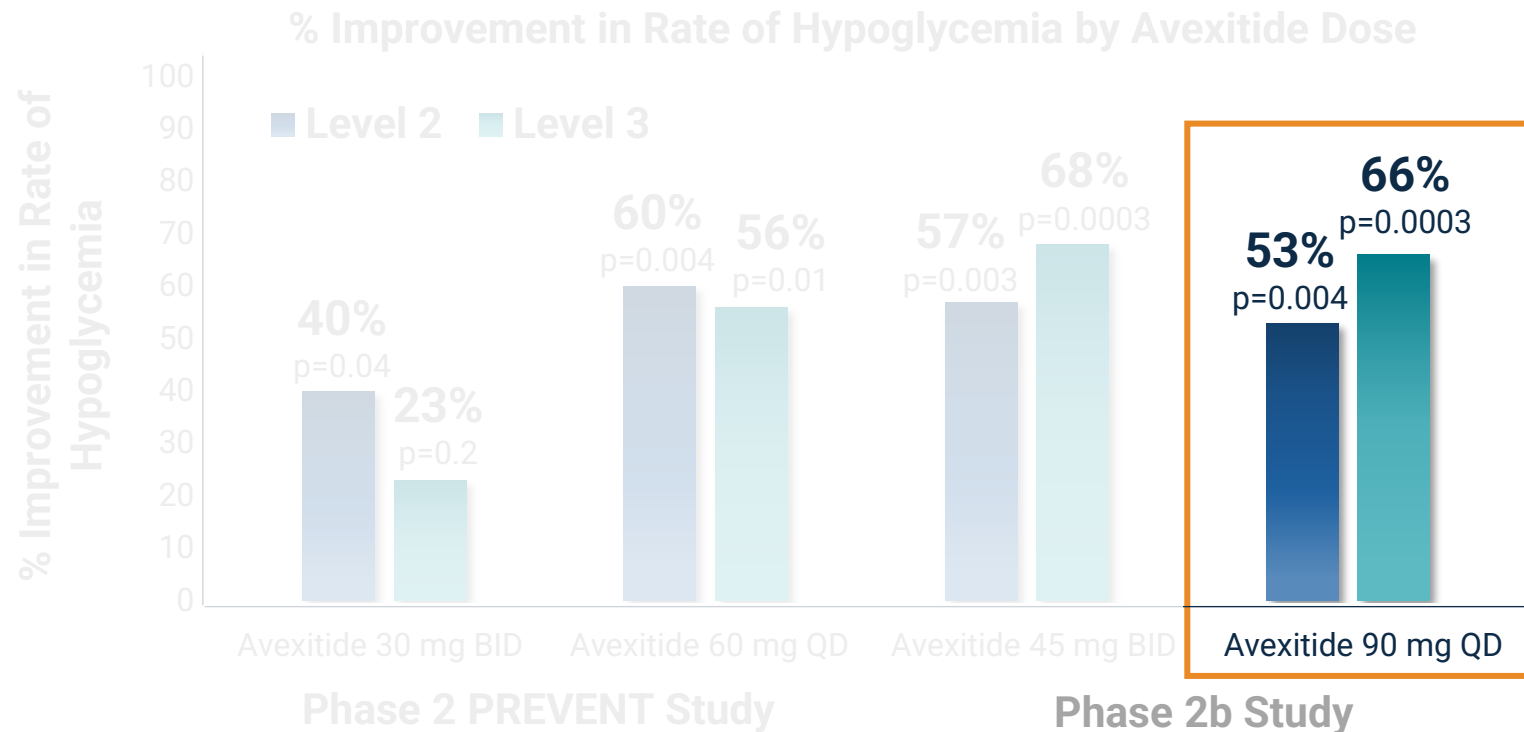


Avexitide cuts rates of hypoglycemia events by **>50%**

Treatment effect supported by significant results across Phase 1, SAD, and MAD trials in PBH

Planned Phase 3 Designed To Leverage Success from Phase 2 and Phase 2b

Consistent, dose-dependent effects enable dose selection for evaluation in planned Phase 3 program in PBH



Phase 3 program will evaluate 90 mg QD in people living with PBH

FDA-agreed upon primary endpoint: Reduction in the composite of Level 2 and Level 3 hypoglycemia events

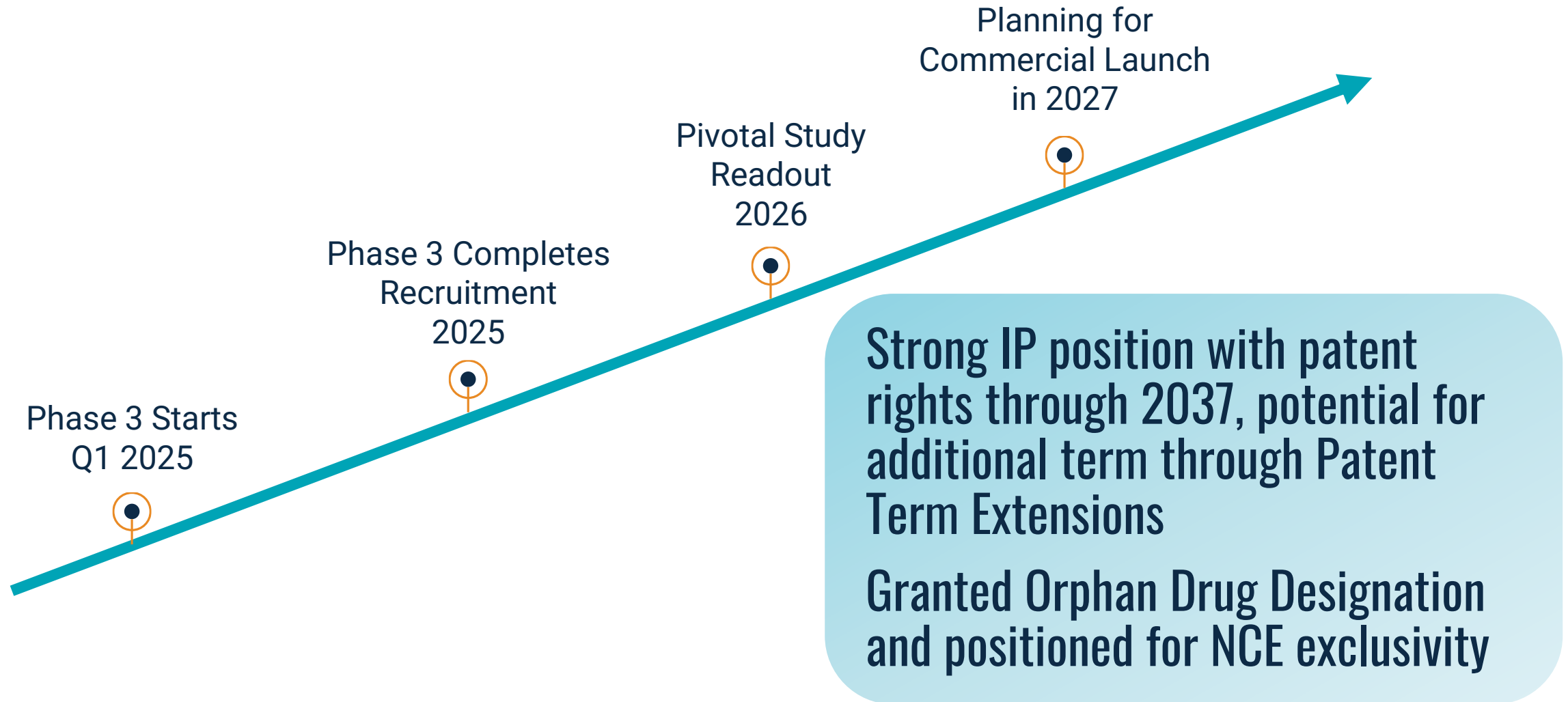
FDA Breakthrough Therapy Designation

Avexitide was Generally Well-Tolerated with a Favorable Safety Profile Across Both Phase 2 Trials

Phase 2 PREVENT Study ¹	Phase 2b Study ²
AEs generally mild to moderate and transient	AEs generally mild to moderate and transient
No treatment-related serious AEs <ul style="list-style-type: none"> • 1 serious adverse event (presyncope during avexitide 60 mg once daily) occurred; reported as unrelated to study drug and self-limited 	No serious AEs
Most common AEs were injection site bruising, headache, and nausea	Most common AEs were diarrhea, headache, bloating, and injection site reaction/bruising
No participant withdrawals	No participant withdrawals

No clinically relevant increases were observed in fasting or peak postprandial plasma glucose levels (i.e., no hyperglycemia observed)

Phase 3 to Begin Q1 2025, Readout in 2026

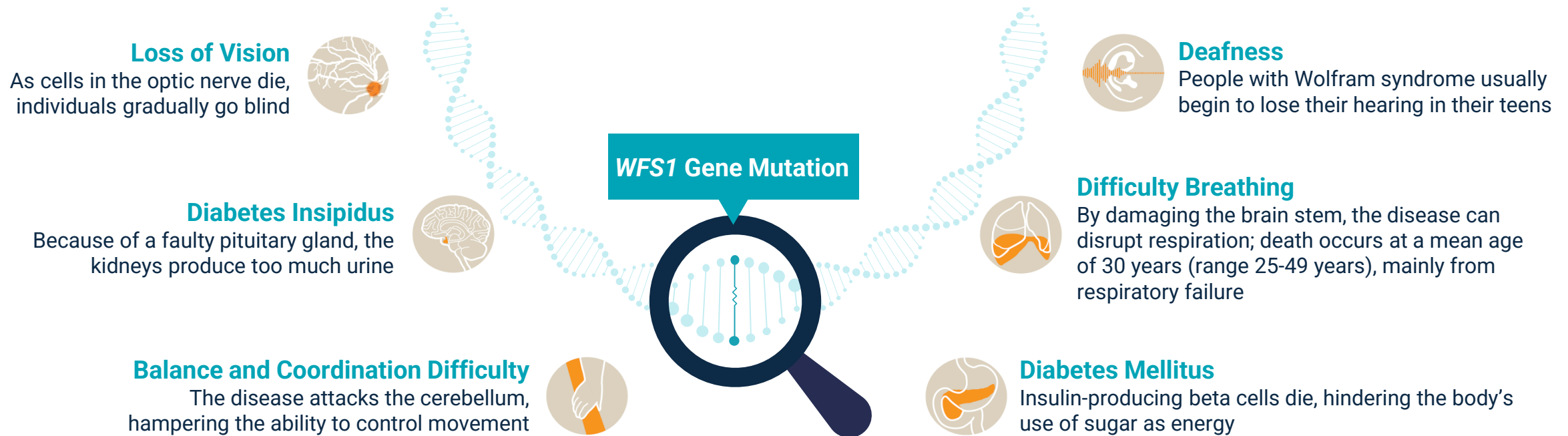


Wolfram Syndrome Program



Wolfram Syndrome Is a Rare and Fatal Genetic Disorder^{1,5}

Characterized by childhood-onset diabetes mellitus, optic nerve atrophy, deafness, diabetes insipidus, and neurodegeneration, eventually resulting in premature death¹⁻⁵



No approved therapies for Wolfram syndrome. Individuals are supported with the use of life-sustaining medications, clinical monitoring, and symptom management.^{6,7}

Image adapted from Leslie M. SAcience. 2021;371(6530):663-665.

Recent Studies Suggest Wolfram Syndrome May be More Common than Previously Estimated¹

Wolfram Syndrome Impacts ~3,000 People in the U.S.

Older Literature Estimates Anywhere Between ~500 to ~3,400 People Living with Wolfram syndrome in U.S.^{2,3}

Studies Pre-Dating Molecular Genetic Testing	Prevalence Estimate	Extrapolated U.S. Prevalence Estimate ^a
1977 Publication Extrapolating Wolfram Prevalence Based on Frequency in Juvenile Diabetes in North America ²	1:100,000 Individuals	~3,400 cases
1995 Prevalence Study in the U.K. ³	1:770,000 Individuals	~500 cases

Studies Evaluating Genetic Causes of Diabetes	Prevalence Estimate	Extrapolated U.S. Prevalence Estimate ^a
2023 Diabetes Study Evaluating Monogenic Diabetes in France ¹	WFS1 mutations found in 3% of monogenic diabetes cases (monogenic diabetes = ~1% of diabetes cases in U.S.)	~11,000 cases ^b

^aAll U.S. prevalence extrapolations assume a U.S. population of 341,814,420.

^bExtrapolations to U.S. prevalence from diabetes population are illustrative only to show potential trends in higher prevalence and should not be considered exact numbers. Extrapolation for monogenic diabetes assumes 38.4 million cases of diabetes in U.S.⁴; 1% of those cases are monogenic⁵ = 384,000 people with monogenic diabetes in U.S.

Wolfram Syndrome is a Prototypical Endoplasmic Reticulum Stress Disorder⁷

AMX0035 Targets ER Stress and Mitochondrial Dysfunction, Critical Pathways in Wolfram Syndrome Pathophysiology¹⁻⁶



Pathogenic Mutations in *WFS1*^{2,3}



Endoplasmic Reticulum (ER) Stress

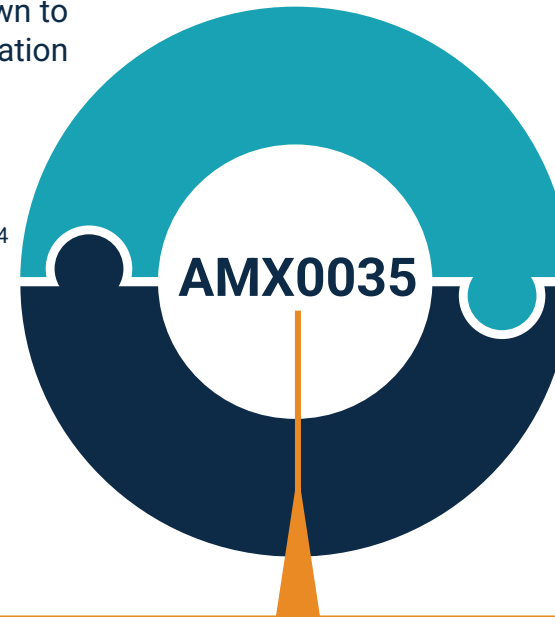


Impaired Mitochondrial Dynamics



Dysfunction and apoptosis of cells, including pancreatic beta cells and neurons^{2,3}

Sodium phenylbutyrate is a chemical chaperone shown to stabilize protein conformation during folding, decrease trafficking of mutant proteins, and restore normal insulin secretion in Wolfram mutant cells^{3,4}



Taurursodiol stabilizes the mitochondrial membrane by reducing the translocation of cell death regulator Bax, improving mitochondrial function and energy production and increasing cell apoptotic threshold^{5,6}

- **FDA Orphan Drug Designation** for AMX0035 in Wolfram syndrome granted in 2020
- **European Commission Orphan Drug Designation** for AMX0035 for the treatment of Wolfram syndrome granted in 2024

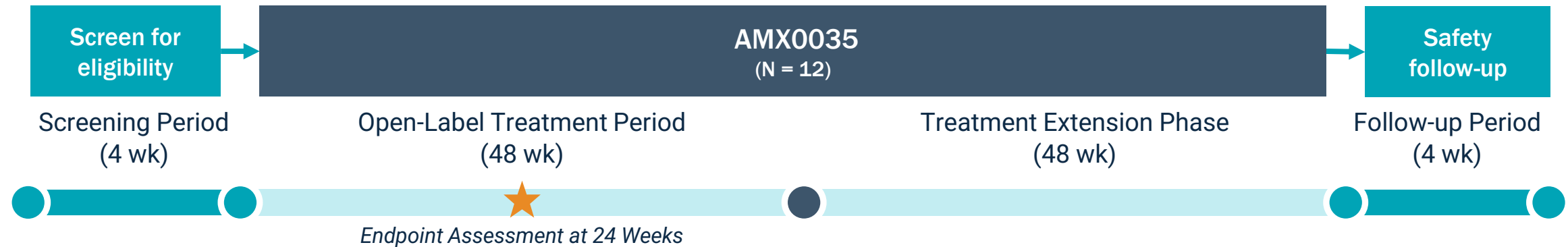
HELIOS Study Design^{1,2}



Primary Goal of HELIOS:
Achieve slowing of Wolfram syndrome progression

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^a
- Stimulated C-peptide level of ≥ 0.2 ng/mL at screening
- Insulin-dependent diabetes mellitus due to Wolfram syndrome
- Must be willing to wear a CGM device for the study duration
- No GLP-1 Agonist Use

CGM = continuous glucose monitoring.

HELIOS Endpoints

Primary Efficacy

- Change from baseline in C-peptide (Δ C-peptide, AUC C-peptide)

Secondary Efficacy

- Change in baseline **best-corrected visual acuity** on the LogMar scale using the Snellen chart
- Change from baseline in **exogenous insulin dose**
- Change from baseline in **overall time in target glucose range (70–180 mg/dL)**
- Change from baseline in **HbA1c level**

Exploratory



General

- Wolfram United Rating Scale
- Clinician-reported Global Impression of Change
- Patient-reported Global Impression of Change
- Most bothersome symptom



Visual

- Visual Functioning Questionnaire–25
- Optical Coherence Tomography measurements

Additional Pancreatic



- Diabetic measurements, including fasting glucose, fasting proinsulin, AUC C-peptide/ AUC glucose, delta proinsulin
- Change from Week 96 to Week 100 in C-peptide levels

Neurological



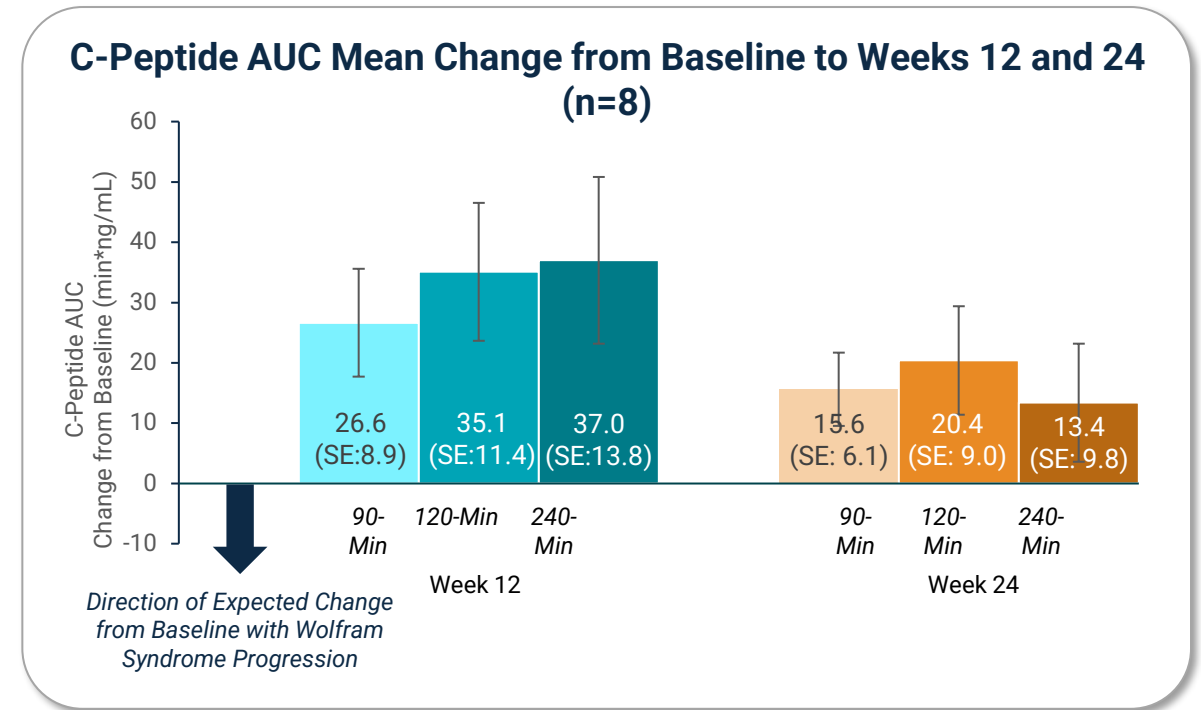
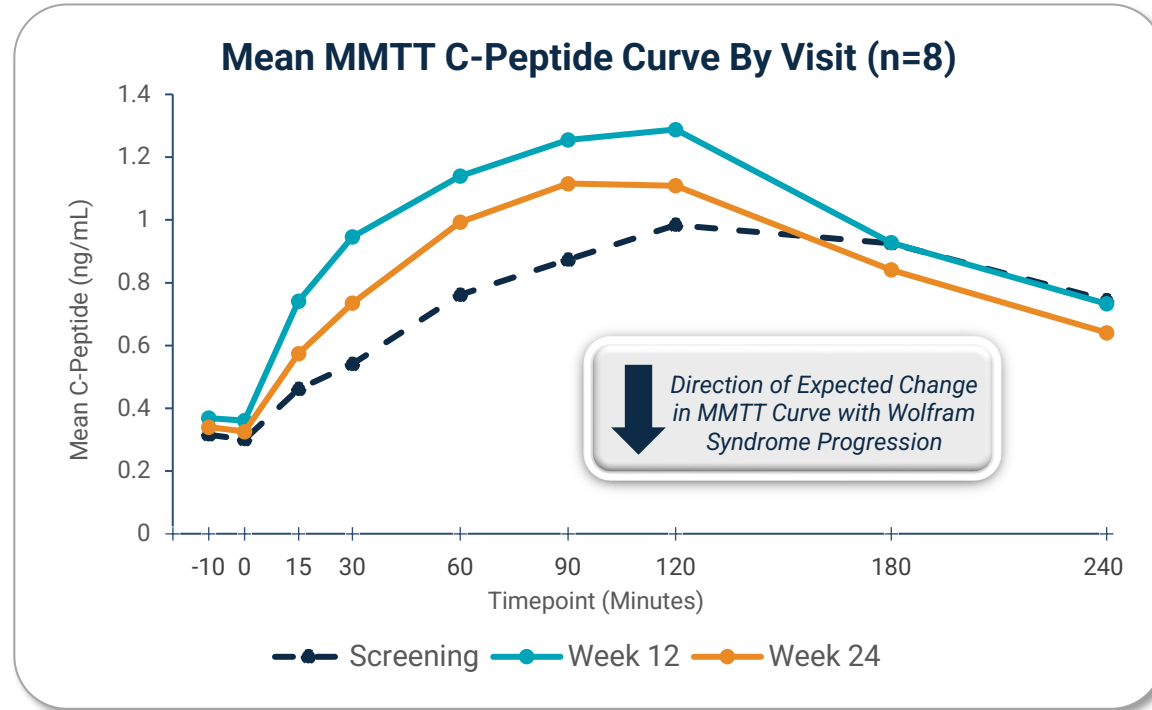
- Blood biomarker (panel) levels of neurodegeneration and neuroinflammation
- Scale for the Assessment of Rating Ataxia

Interim Analysis Results Focus on Diabetes and Vision Assessments in 8 participants (Week 24)
• Final Week 24 data will report all 12 participants and include additional assessments

AUC = area under the curve; MMTT = mixed-meal tolerance test.

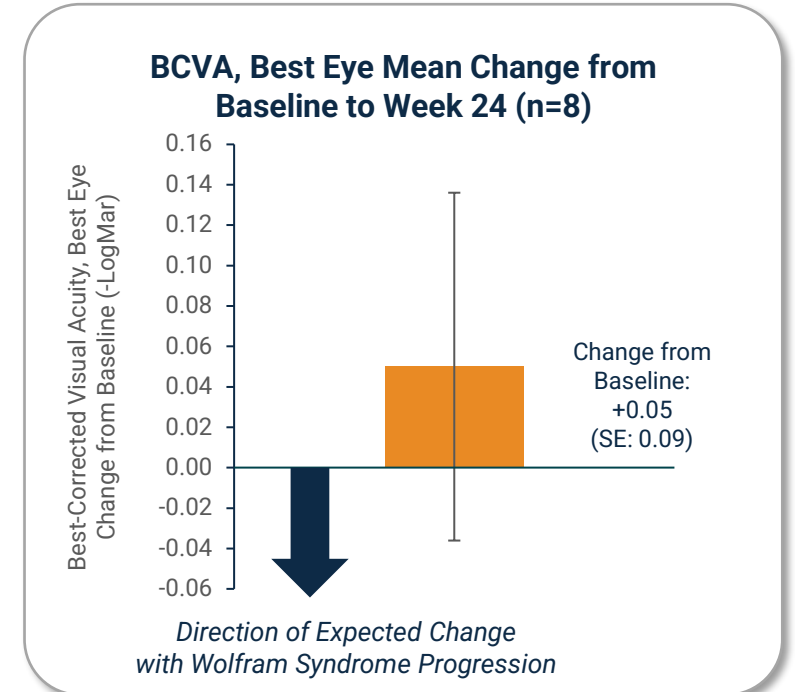
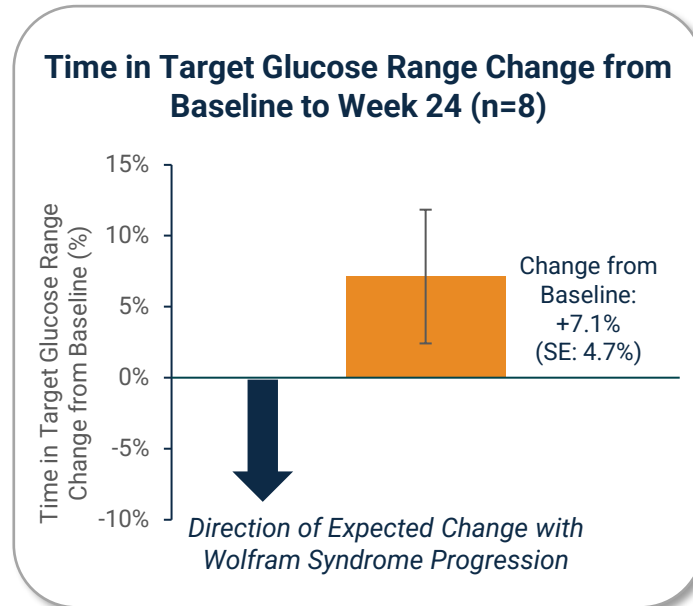
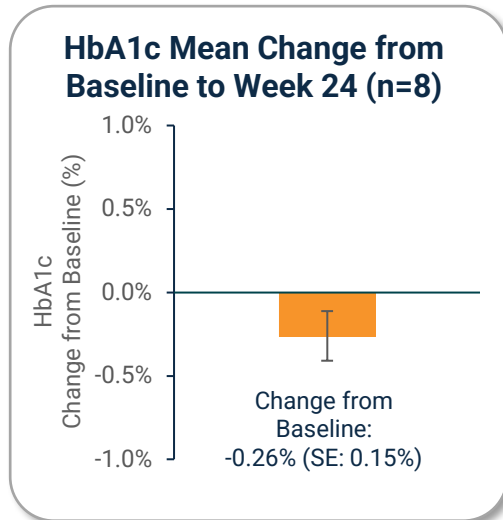
Primary Endpoint: Improvement in C-Peptide Response at Weeks 12 and 24

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



Partial Reversal in C-peptide Phenotype Observed at Weeks 12 and 24 Compared to Screening

Secondary Endpoints: HbA1c, Overall Time in Target Glucose Range, Best Corrected Visual Acuity (BCVA)



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

Improved Glycemic Control as Assessed by Continuous Glucose Monitoring at Week 24 Compared to Screening

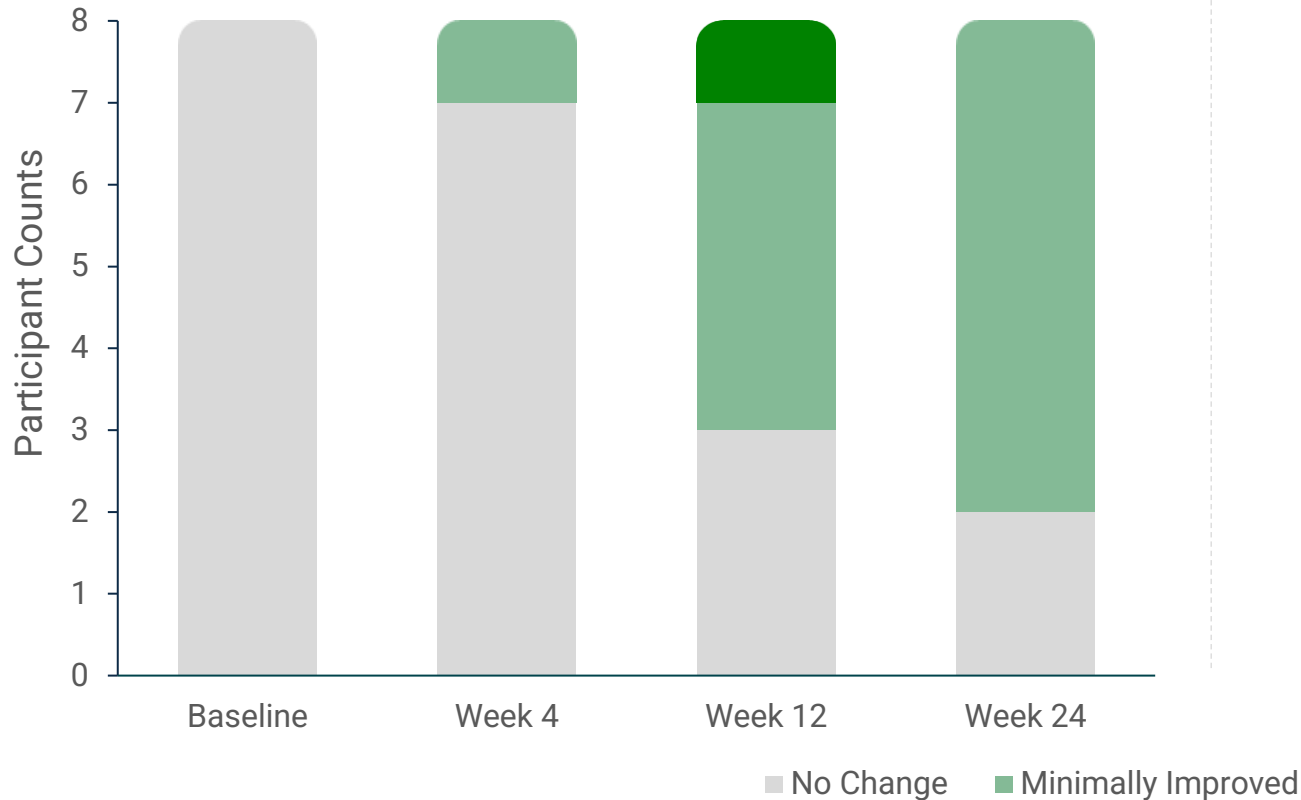
Trend Indicating Potential Visual Acuity Improvement at Week 24 Compared to Screening

Exploratory Endpoint: PGI-C and CGI-C

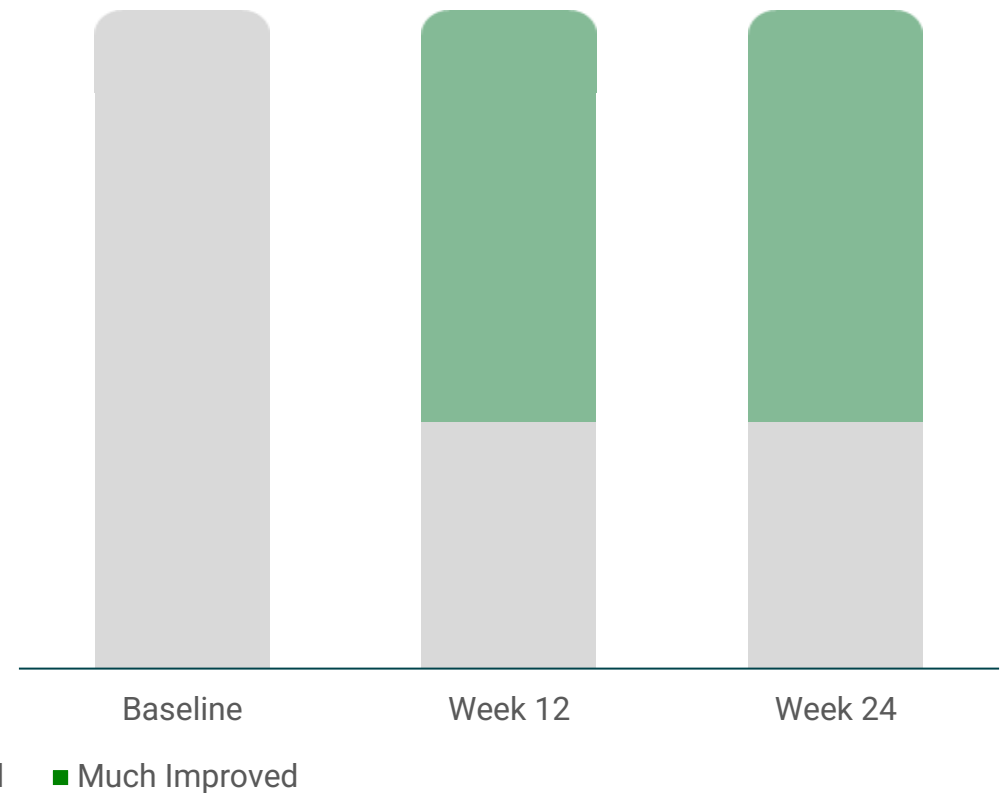
100% of Participants Met Responder Criteria by Self and Clinician Assessment

75% of participants claim to improve on AMX0035;
clinician reports 62.5% of patients improving

Patient-Reported Global Impression of Change (PGI-C) (n=8)



Clinician-Reported Global Impression of Change (CGI-C) (n=8)



AMX0035 Safety and Tolerability in HELIOS (N=12)

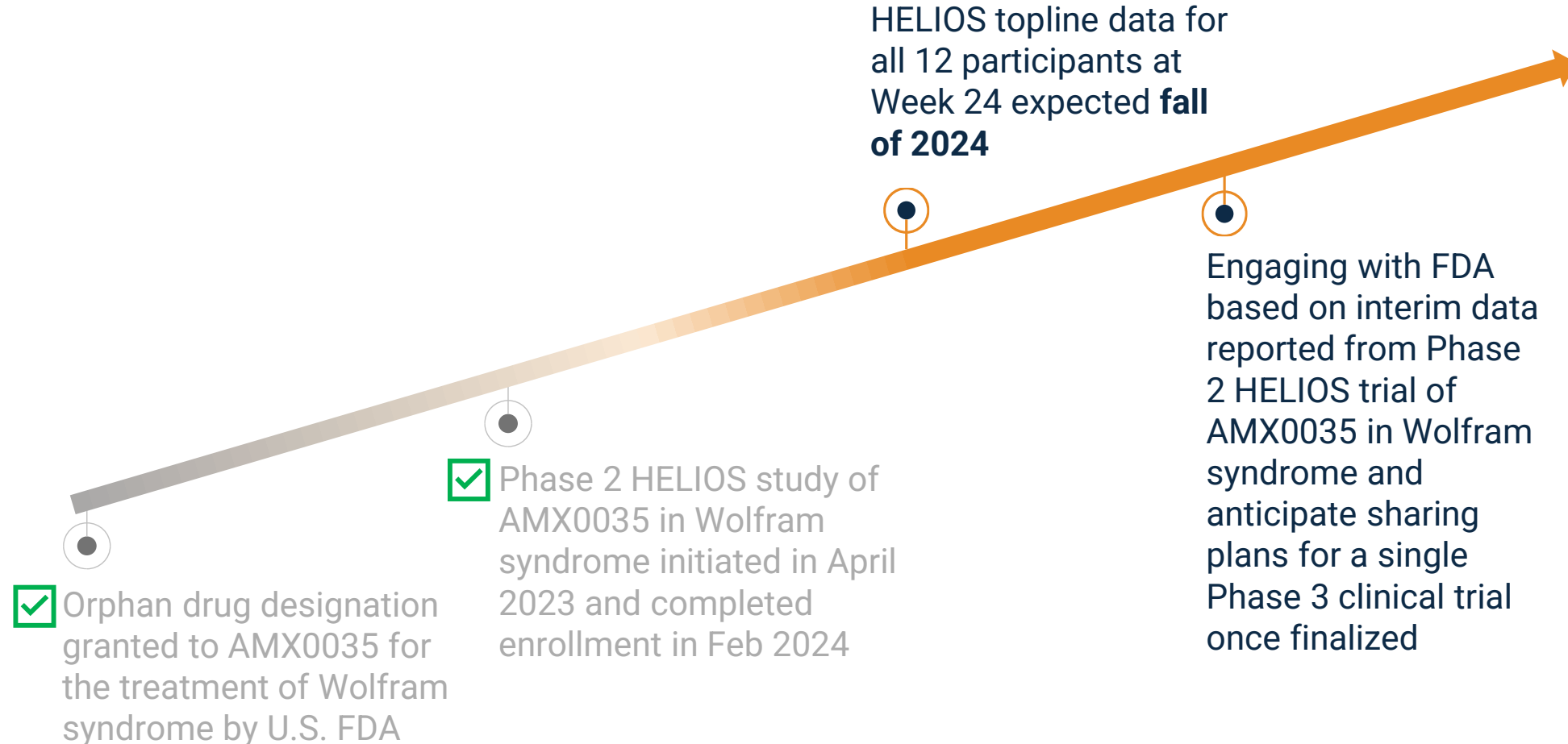
- AMX0035 was **generally well tolerated**
 - Diarrhea was the most common TEAE (41.7%)
- **No new safety signals** were identified
- Nearly all participants reported ≥ 1 TEAE during the trial
 - Most did not lead to modification or interruption of AMX0035 dosing and **none led to drug discontinuation**

Summary of Treatment Emergent Adverse Events (TEAEs)

	AMX0035 (N=12)
Participants with ≥ 1 TEAE – n (%)	11 (91.7%)
TEAE related to study drug – n (%)	7 (58.3%)
Treatment-emergent serious adverse events – n (%)	0 (0%)
Drug interrupted owing to TEAE – n (%)	2 (16.7%)
Dose reduced owing to TEAE – n (%)	1 (8.3%)
Drug discontinued owing to TEAE – n (%)	0 (0%)

**N=8 with data through 24 weeks; For remaining 4, all available safety data as of March 5, 2024 used

AMX0035 Wolfram Syndrome Program Next Steps



Progressive Supranuclear Palsy (PSP) Program

ORION

PSP is a Rare, Progressive, and Fatal Tauopathy

- Rare neurological disorder affecting body movements, walking and balance, and eye movement
- No disease modifying therapies creates significant unmet need
- PSP is a tauopathy associated with tau dysfunction, tau aggregation and widespread neurodegeneration



ESTIMATED PREVALENCE:

7 in 100,000 worldwide^{1,2}

U.S. PREVALENCE:

Approximately 23,000

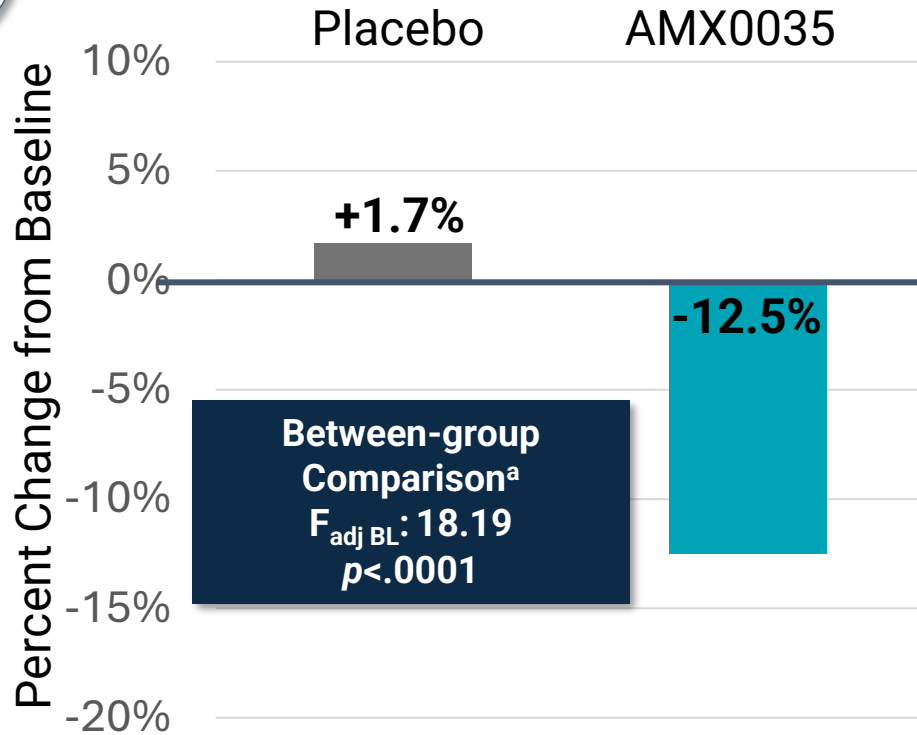


**PSP is typically fatal within
6-8 years from symptom onset³⁻⁶**

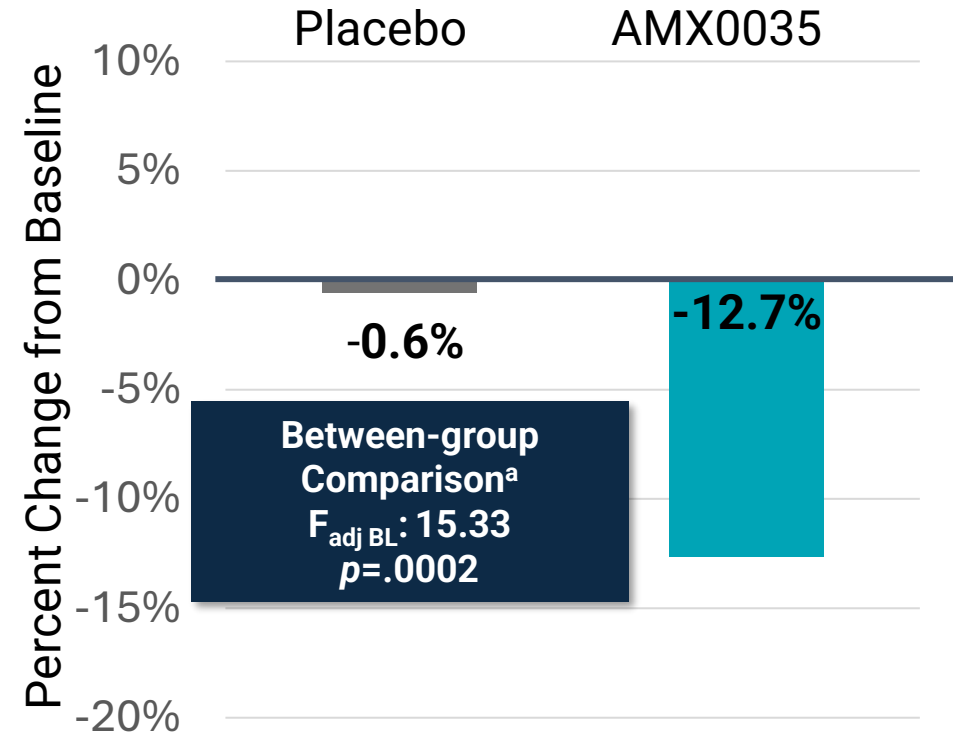
AMX0035 Significantly Lowered CSF Tau and p-Tau in Randomized Placebo Controlled Phase 2 PEGASUS Trial in People with Alzheimer's Disease



Week 24 Mean CSF t-tau
(n=67)



Week 24 Mean CSF p-tau 181
(n=67)

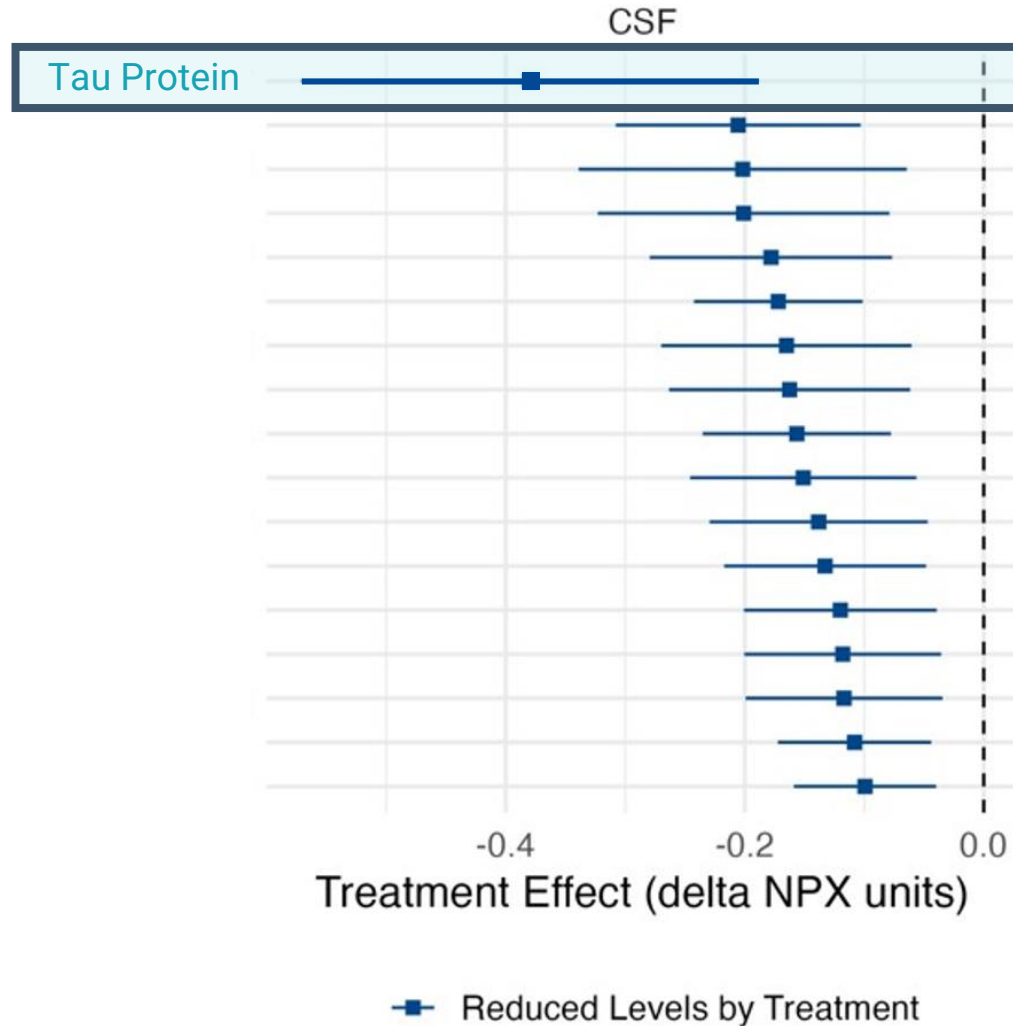


t-Tau = total tau

p-Tau181 = phosphorylated tau at site threonine 181

^aFrom a linear regression model with Week-24 biomarker level as the response variable and treatment group and baseline biomarker levels as explanatory variables.

AMX0035 Shown to Reduce Tau Protein in Proteomic Analysis



288

Of 288 proteins measured in CSF and plasma, tau protein was the most significantly changed protein by AMX0035¹

NPX = normalized protein eXpression units

ORION: Operationally Seamless Phase 2b/3 Clinical Trial Underway

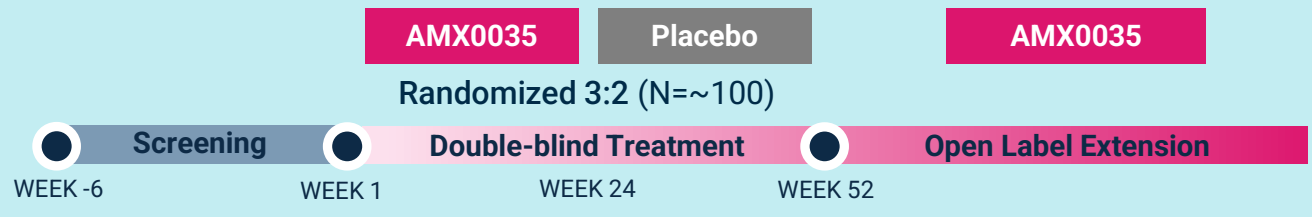


Primary Objective: To assess the impact of AMX0035 compared to placebo on disease progression rate as measured by PSPRS

Key Eligibility Criteria

- Adults 40-80 years old
- Possible or Probable PSP (Steele-Richardson-Olszewski Syndrome) according to MDS 2017 criteria^{1,2}
- Presence of PSP symptoms < 5 years
- Able to walk independently or with minimal assistance³
- PSPRS total score < 40
- MMSE score ≥ 24
- Study partner required
- No feeding tube use

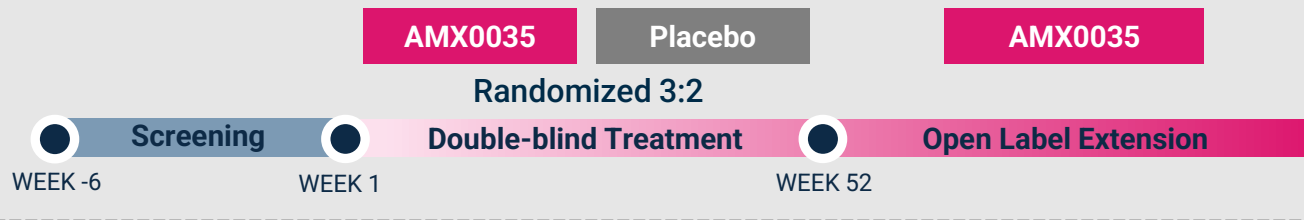
PHASE 2B STUDY PORTION DESIGN



Interim Analysis expected in mid-2025

Proceed to Phase 3 if Data are Strong

PHASE 3 STUDY PORTION DESIGN



Primary Endpoint

- PSPRS score*

Secondary Endpoints

- PSPRS score*
- MDS-UPDRS Part II score

Additional Endpoints

- Brain volume (MRI)
- Participant QoL and caregiver burden
- CSF and plasma biomarkers of neuronal injury and neuro-inflammation
- Overall survival

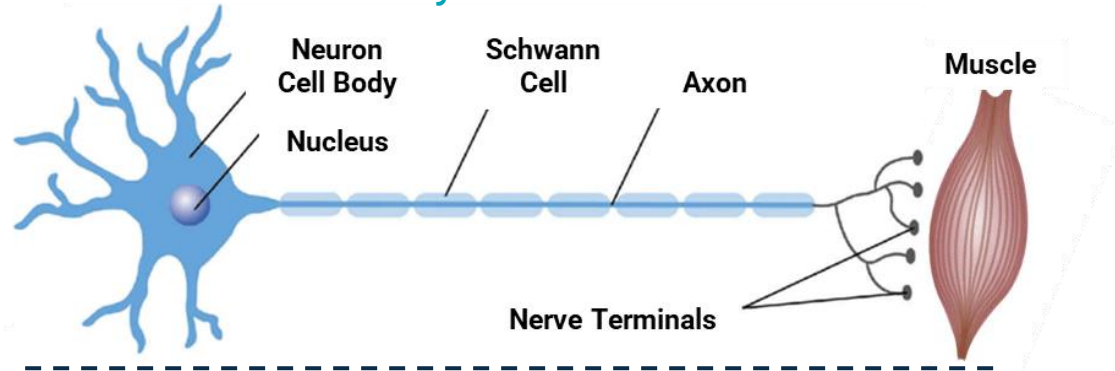
ALS Program

- AMX0114 is a potent antisense oligonucleotide (ASO) targeting inhibition of calpain-2

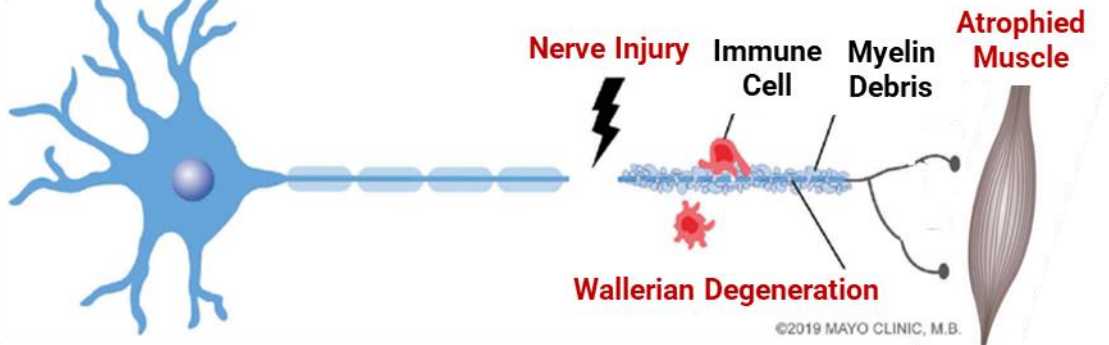
ALS is a Relentlessly Progressive, Debilitating, and Universally Fatal Disease Caused by Motor Neuron Loss

ALS leads to deteriorating muscle function, inability to move and speak, respiratory paralysis, and death^{1,2}

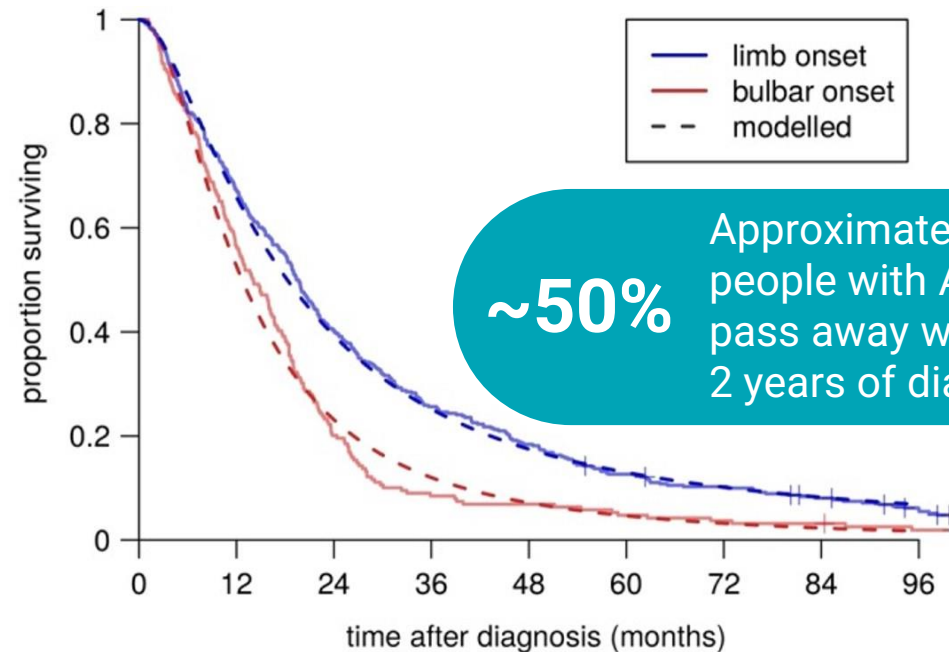
Healthy Motor Neuron



ALS Motor Neuron



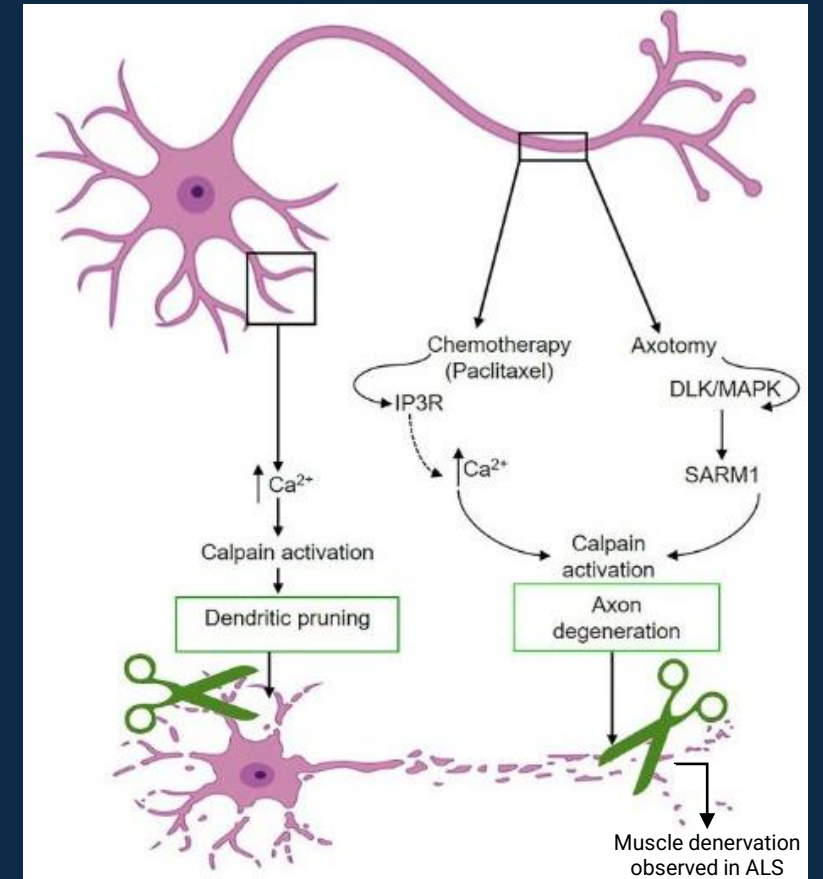
- **Urgent unmet need** for new and effective treatment options – currently approved therapies are limited
- Impacts ~30,000 people in the U.S.³
- Diagnosis is usually between ages 40 and 75
- >90% of patients have no family history of the disease



Calpain-2 Plays a Critical Role in Axonal Degeneration, a Key Mechanism Underlying ALS Pathophysiology

- Calpains are a family of Ca^{2+} -dependent proteases that target substrates within the axonal cytoskeleton
- There are over a dozen calpain isoforms, but activation of calpain-2 has shown the clearest association with axonal degeneration
- Following injury-induced Ca^{2+} dyshomeostasis, proteolysis mediated by calpain-2 results in cytoplasmic TDP-43 aggregates, defective axonal transport, and ultimately muscle denervation observed in ALS

Mechanisms of Axonal Degeneration



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

AMX0114: An Antisense Oligonucleotide (ASO) Inhibitor of Calpain-2

Selectivity of the ASO modality offers distinct advantages over earlier, small molecule-based approaches to targeting calpain-2

- ✓ Specifically inhibits calpain-2 without disrupting the function of other calpains or calpastatin
- ✓ Designed to downregulate expression of the calpain-2 gene (*CAPN2*)
- ✓ Targets an exon in the active site of the calpain-2 protease
- ✓ Lowers levels of *CAPN2* mRNA transcript through RNase H-mediated degradation, subsequently lowering levels of functional calpain-2 protein in the cell
- ✓ Pre-clinical data demonstrated that AMX0114
 - ✓ Achieves potent, dose-dependent, and durable knockdown of *CAPN2* mRNA and Calpain-2 Protein
 - ✓ Improves survival in relevant models

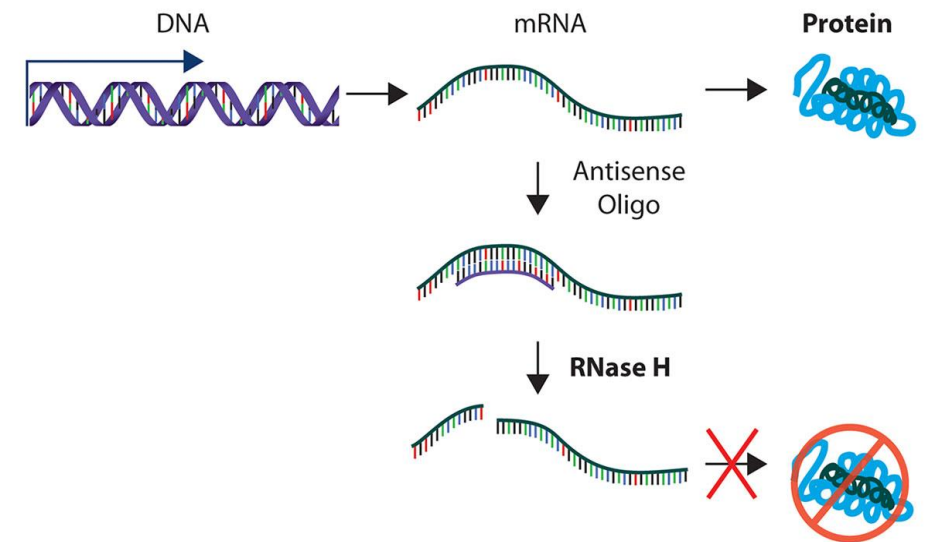


Image Credit: *Online Biology Notes*

Next Steps in AMX0114 Program

- Planning to initiate a multiple ascending dose clinical trial of AMX0114 in people living with ALS in the second half of 2024

Avexitide, AMX0035, and AM0114 are Protected by Robust Global IP Portfolio

AVEXITIDE

>150

granted patents and over 30 pending applications worldwide*

- Granted US patent rights through 2037**
- Positioned for NCE exclusivity
- Granted Orphan Drug Designation for the treatment of hyperinsulinemic hypoglycemia

AMX0035

>70

granted patents and over 60 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

* Includes in-licensed patents

** Additional patent term potentially available through patent term extension

Expected Cash Runway into 2026

\$309.8M in cash, cash
equivalents, and short-term
investments as of 6/30/24



Every day, we strive for
better therapies.

