



MARCH 2025

Investor Presentation

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







Raquel, living with Wolfram syndrome

DISCLAIMER

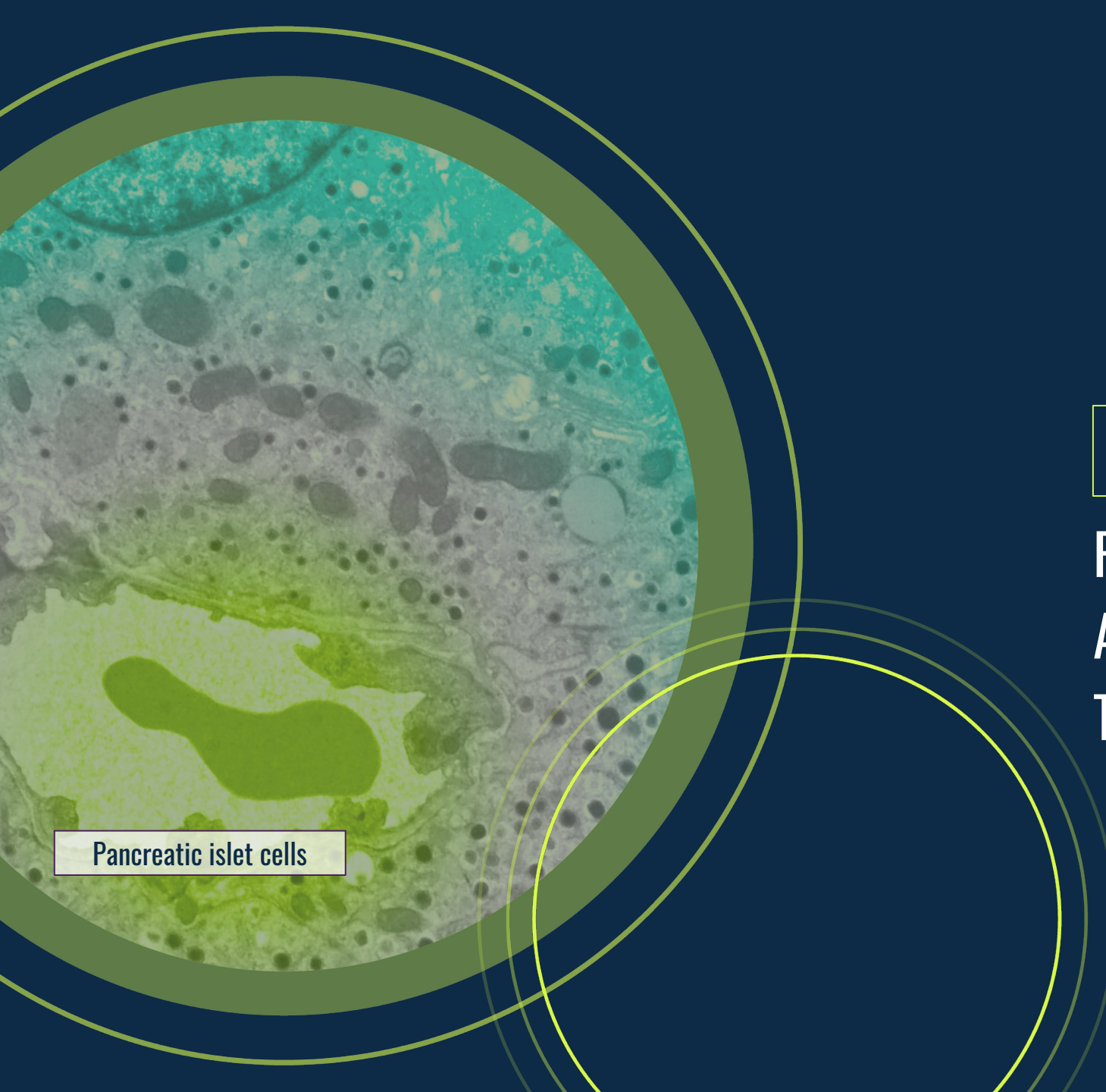
Statements contained in this presentation regarding matters that are not historical facts are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. Because such statements are subject to risks and uncertainties, actual results may differ 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, 2024, 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

			PRECLINICAL	IND	PHASE 1	PHASE 2	PHASE 3	COMMERCIAL
AVEXITIDE GLP-1 receptor antagonist	Post-Bariatric Hypoglycemia (PBH)	<ul style="list-style-type: none"> Phase 3 trial in PBH, with dosing expected to begin in March/April 2025 and data readout anticipated in 1H 2026 Phase 2 trial in PBH showing reduction in hypoglycemia events 				LUCIDITY PHASE 3 CLINICAL TRIAL		
	Congenital Hyperinsulinism (HI)	<ul style="list-style-type: none"> Engaging physician and community experts around next steps for clinical development 						
AMX0035 Sodium phenylbutyrate and taurursodiol (also known as ursodocoltaurine)	Wolfram Syndrome	<ul style="list-style-type: none"> Phase 2 trial in Wolfram Syndrome showed improvement or stabilization across all disease measures at Week 24 (n = 11) and sustained improvement at later timepoints 			HELIOS PHASE 2 CLINICAL TRIAL			
	Progressive Supranuclear Palsy (PSP)	<ul style="list-style-type: none"> Phase 2b/3 ORION trial in PSP underway – showing improvement in PSP symptoms 			ORION PHASE 2b/3 CLINICAL TRIAL			
AMX0114 ASO targeting calpain-2, a protein involved in axonal degeneration	Amyotrophic Lateral Sclerosis (ALS)	<ul style="list-style-type: none"> Preclinical data showed improvement in ALS symptoms Phase 1 trial in ALS with dosing expected to begin in March/April 2025 and early data expected in 2025 			LUMINA PHASE 1 CLINICAL TRIAL			
LONG-ACTING GLP-1 RECEPTOR ANTAGONIST	PBH and other rare diseases	<ul style="list-style-type: none"> Phase 1 trial in PBH to develop a novel long-acting GLP-1 receptor antagonist to enter IND-enabling studies 						

ASO=antisense oligonucleotide; FDA=U.S. Food and Drug Administration; GLP-1=glucagon-like peptide-1; IND=investigational new drug.

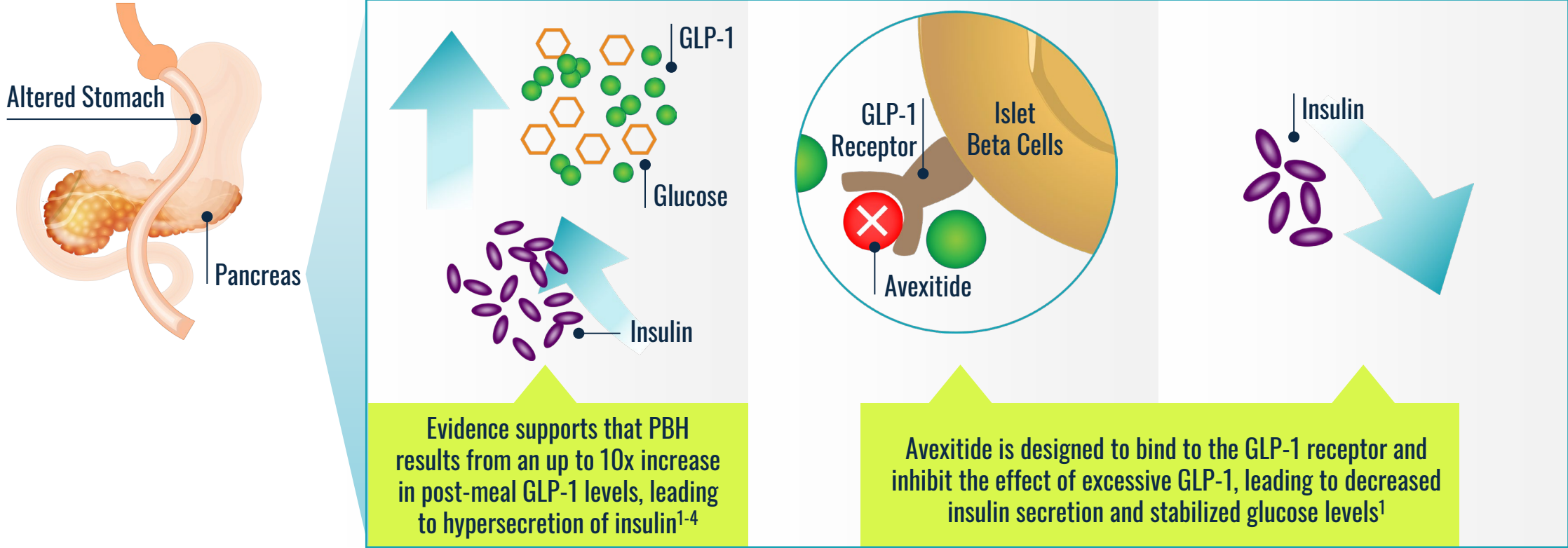


Pancreatic islet cells

AVEXITIDE

First-in-class, Phase 3 GLP-1 Receptor Antagonist with FDA Breakthrough Therapy Designation

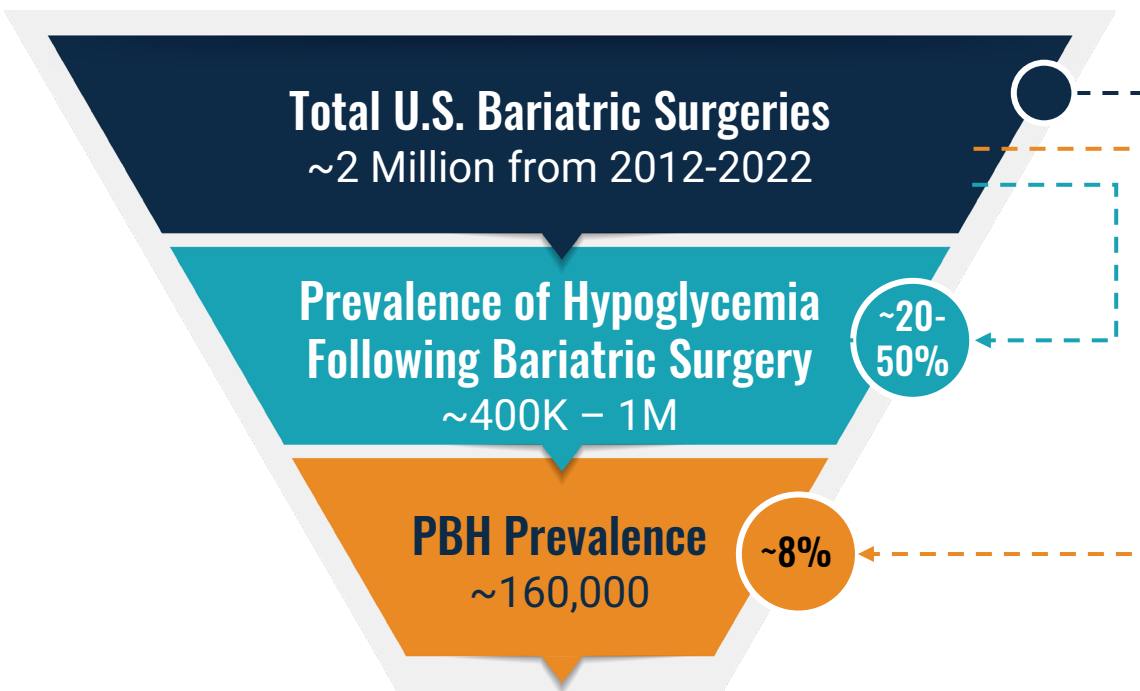
Post-Bariatric Hypoglycemia (PBH) is Believed to be Caused by Excessive GLP-1 Response that Leads to Hyperinsulinemic Hypoglycemia Post-Meal



GLP-1=glucagon-like peptide-1; 1. Craig, C. M. et al. Diabetes, Obesity & Metabolism. 2018;20:352–361. doi.org/10.1111/dom.13078. 2. Jalleh, R. J. et al. Reviews in Endocrine and Metabolic Disorders. 2023;24:1075-1088. doi.org/10.1007/s11154-023-09823-3. 3. van den Broek, M. et al. International Journal of Obesity. 2021;45(3):619-630. doi.org/10.1038/s41366-020-00726-w. 4. Larraufie et al., 2019, Cell Reports 26, 1399–1408. doi.org/10.1016/j.celrep.2019.01.047.

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

Based on representative sample of available studies



1. American Society for Metabolic and Bariatric Surgery (ASMBS). Accessed July 9, 2024. 2. Lupoli R, et al. 2022;32(1):32-39. 3. Fischer LE, et al. 2021;17(10):1787-1798. 4. Belilgoli A, et al. 2017;27:3179-3186. 5. Brix JM, et al. 2019;12:397-406. 6. Lee CJ, et al. 2018;14(6):797-802. 7. de Heide LJM, et al. 2023;25:735-747. 8. Lee CJ, et al. 2016.24(6):1342-1348. 9. Raverdy V, et al. 2016.264(5):878-885. 10. Data on file. 11. Hazelhurst J, et al. 2024;13(5):e230285.

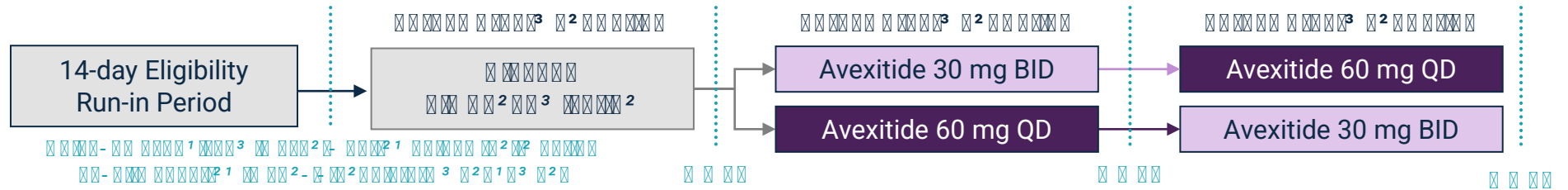
Source	Finding
1. American Society for Metabolic and Bariatric Surgery (ASMBS). Accessed July 9, 2024.	2.4M bariatric surgeries of which 1.9M were either sleeve gastrectomy [SG] or Roux-en-Y gastric bypass [RYGB])
2. Lupoli R, et al. 2022;32(1):32-39.	56.1% prevalence of hypoglycemia in studies specifically examining RYGB and 54.3% in those examining SG (N=280) ²
3. Fischer LE, et al. 2021;17(10):1787-1798.	43.2% prevalence of post-RYGB hypoglycemia symptoms (N=1,448) ³
4. Belilgoli A, et al. 2017;27:3179-3186.	32.8% of participants had at least one OGTT-related hypoglycemia after laparoscopic sleeve gastrectomy (N=186) ⁴
5. Brix JM, et al. 2019;12:397-406.	32.6% showed post-challenge hypoglycemia after RYGB; 22.6% after SG (N=281) ⁵
6. Lee CJ, et al. 2018;14(6):797-802.	29% with new-onset hypoglycemia symptoms post-RYGB or SG (N=341) ⁶
7. de Heide LJM, et al. 2023;25:735-747.	Of 107 individuals with PBH treated with acarbose, 39% had persistent/unacceptable frequency of hypoglycemic events [N/A: Equates to ~8-16% of total bariatric surgery population ^b] (N=120) ⁷
8. Lee CJ, et al. 2016.24(6):1342-1348.	13.1% met criteria for PBH 5 years post-op and 5% of those with PBH had severe symptoms ^c (N=1,206) ⁸
9. Raverdy V, et al. 2016.264(5):878-885.	7.9% met criteria for PBH 5-years post-RYGB (N=177) ⁹
10. Data on file.	Symptoms of PBH requiring hospitalization or ER visit occurred in 2.6-3.6% of people who underwent RYGB at 5 years of follow-up (N=1,448) ³

^aThe 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

Phase 3 LUCIDITY Trial Designed to be Consistent with Phase 2 PREVENT and Phase 2b Trials Evaluating Avexitide for the Treatment of PBH

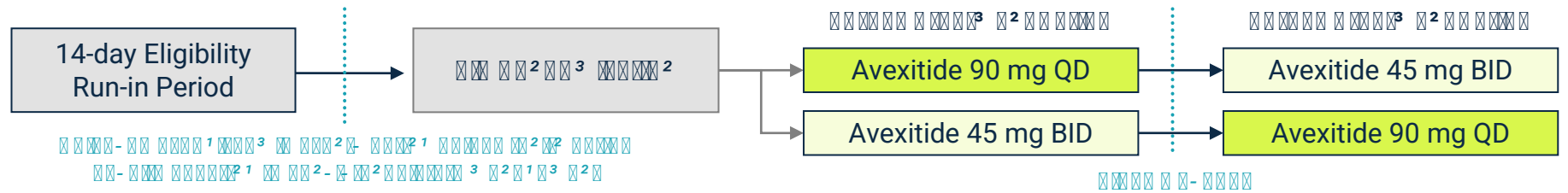
PHASE 2 PREVENT TRIAL DESIGN - 28-day, randomized, placebo-controlled crossover trial (N = 18)

Participants enrolled had Roux-en-Y gastric bypass (RYGB)



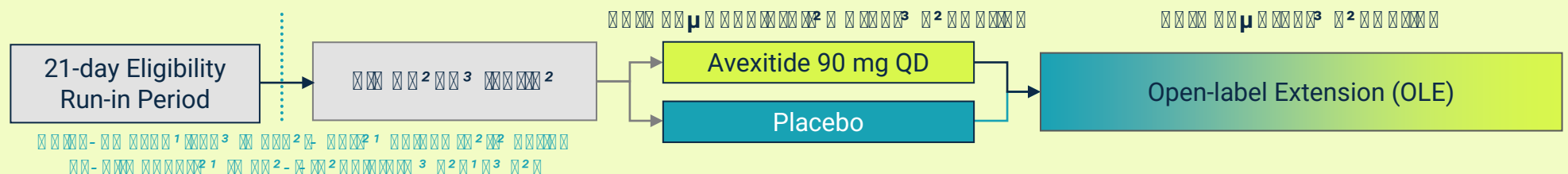
PHASE 2B TRIAL DESIGN - 28-day, open-label, investigator-initiated, crossover trial (N = 16)

Participants enrolled had RYGB, vertical sleeve gastrectomy, esophagectomy, Nissen fundoplication, or gastrectomy



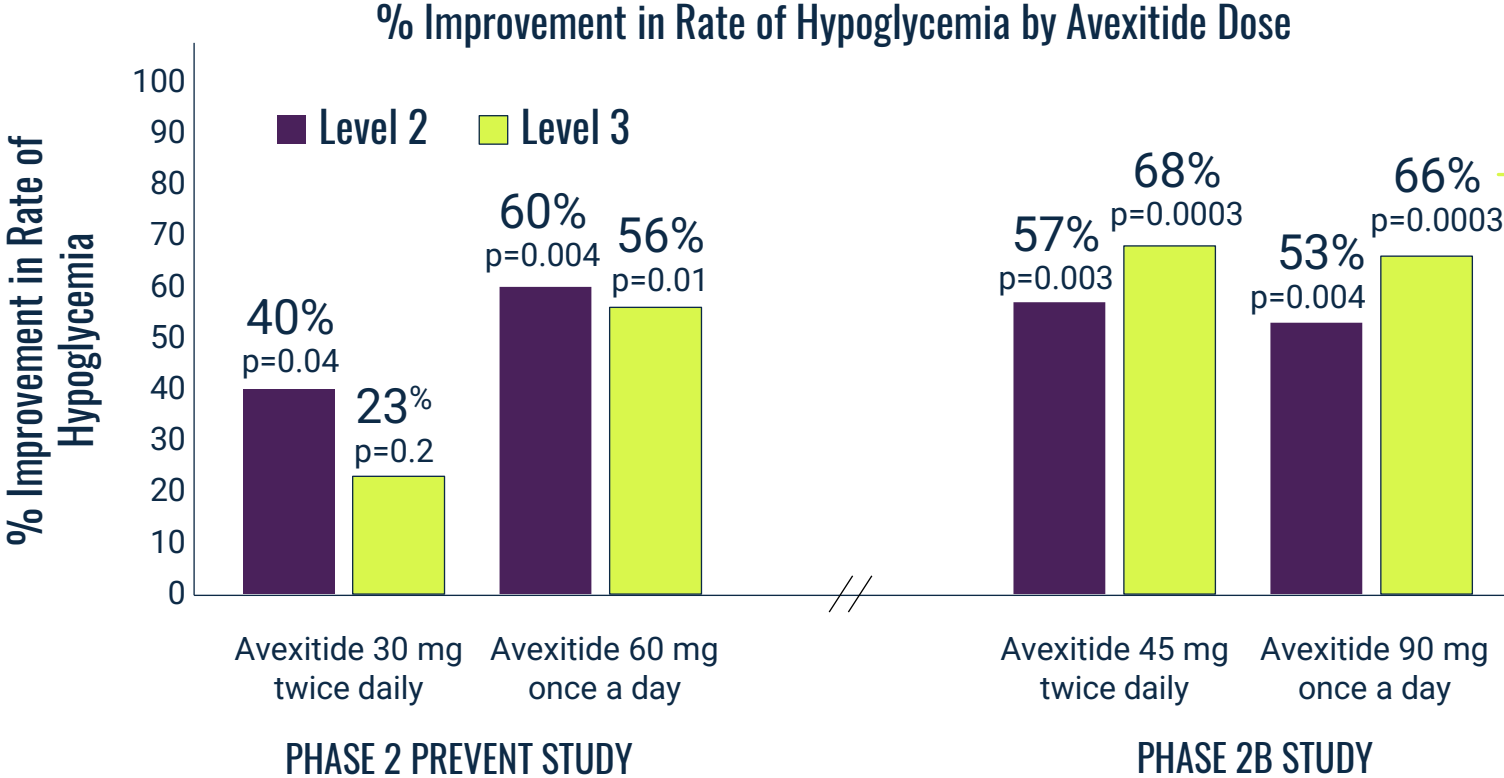
PHASE 3 LUCIDITY TRIAL DESIGN - Multicenter, randomized, double-blind, placebo-controlled trial (N = ~75)

Participants to be enrolled will have had RYGB



BID=twice daily; MMTT=mixed meal tolerance testing; PBH=post-bariatric hypoglycemia; QD=once daily.

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



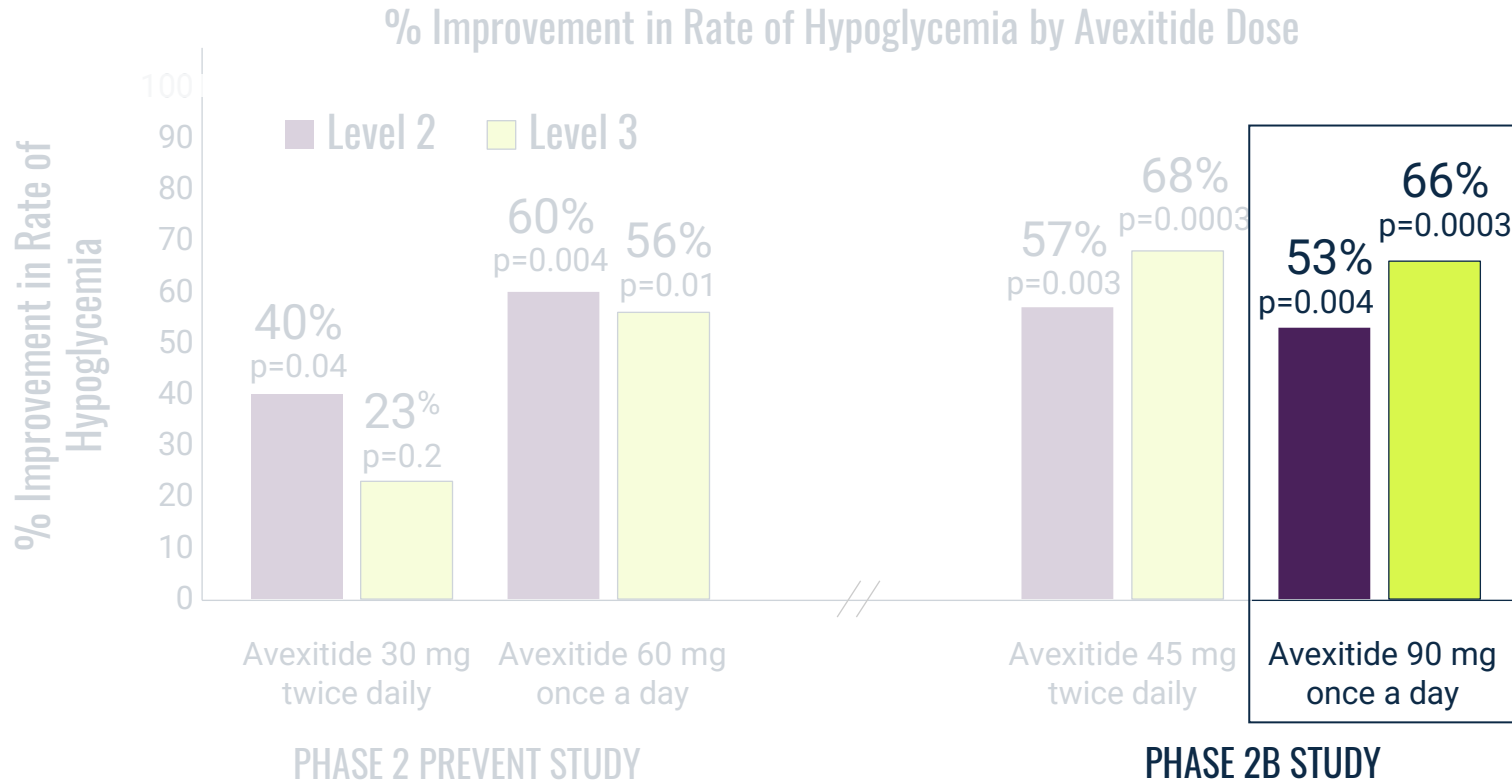
Avexitide cut rates of hypoglycemia events by **>50%**

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

Avexitide 90 mg QD demonstrated a half-life of ~3 hours, a Tmax ranging from 6-9 hours, and therapeutic exposure through 24 hours.

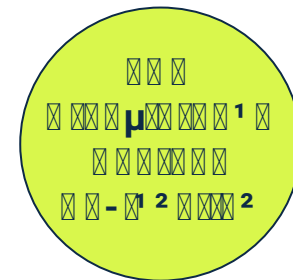
MAD= multiple ascending dose; PBH=post-bariatric hypoglycemia; QD=once daily; SAD=single ascending dose; Tmax=time to peak drug concentration; 1. Craig, C. M. et al. *Diabetes Care* 2021;106(8):e3235-e3248. doi.org/10.1210/jendso/bvac150.725. 2. Tan, M. (2022). *Diabetes Care* [Conference presentation]. ENDO Annual Symposium.

Phase 3 Endpoint Met in Phase 2 and Phase 2b



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

FDA-agreed upon primary endpoint: Composite of Level 2 and Level 3 Hypoglycemia events



FDA=U.S. Food and Drug Administration; PBH=post-bariatric hypoglycemia; QD=once daily; 1. Craig, C. M. et al. *Diabetes Care* 2021;106(8):e3235-e3248. doi.org/10.1210/jendso/bvac150.725. 2. Tan, M. (2022). *Diabetes Care* 2022;45(1):100-101. [Conference presentation]. ENDO Annual Symposium.

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

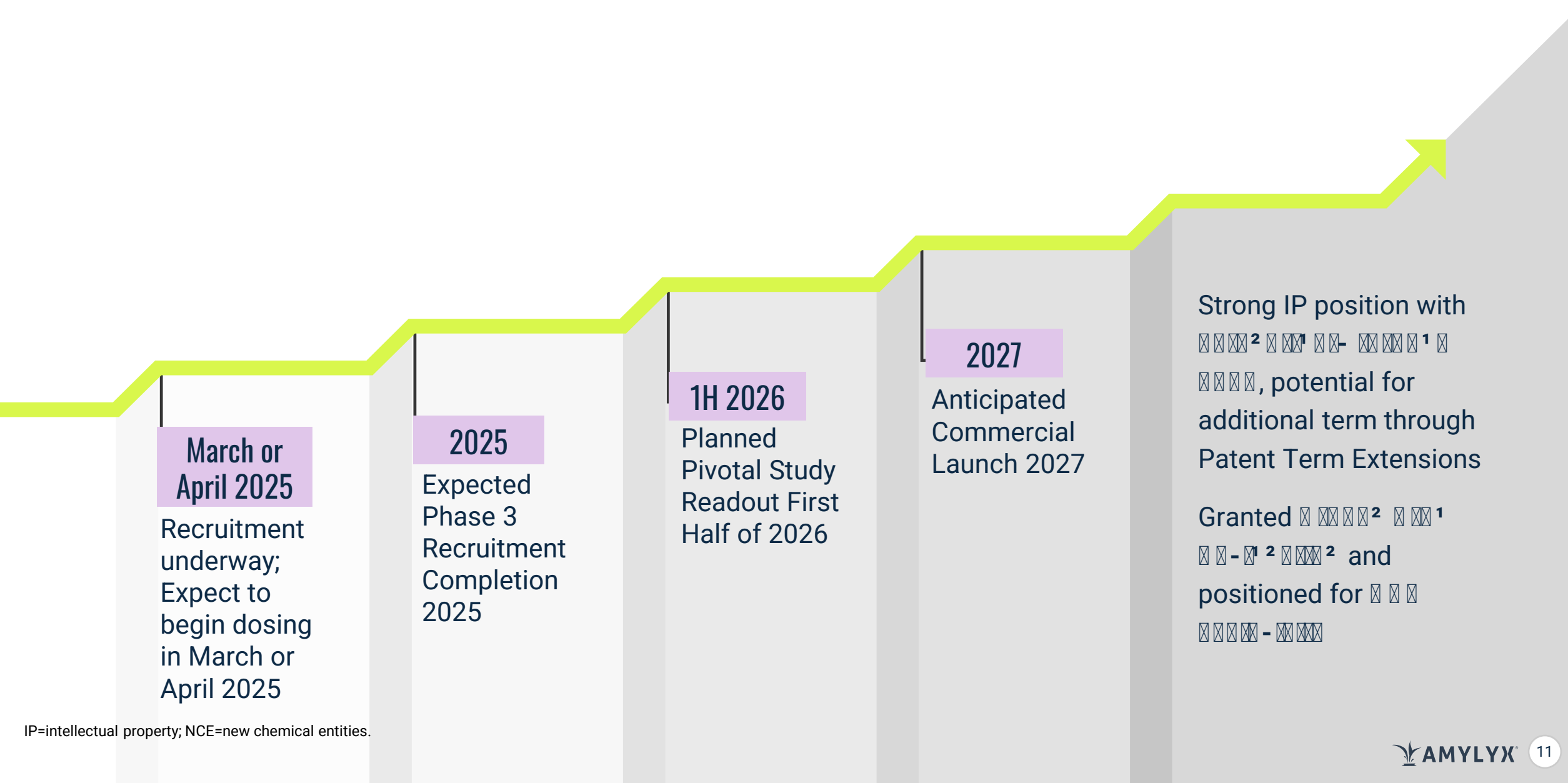
Phase 2 PREVENT Study ¹	Phase 2b Study ²
AEs generally mild to moderate and transient	AEs generally mild to moderate and transient
No treatment-related serious AEs <ul style="list-style-type: none"> • 1 serious adverse event (presyncope during avexitide 60 mg once daily) occurred; reported as unrelated 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 discontinuations	No participant discontinuations

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

*Injection site reactions generally mild and transient with no grade 3 events or resulting discontinuations

AE=adverse event; 1. Craig, C. M. et al. *Diabetes Care* 2021;106(8):e3235-e3248. doi.org/10.1210/jendso/bvac150.725. 2. Tan, M. (2022). *Diabetes Care* [Conference presentation]. ENDO Annual Symposium.

Phase 3 LUCIDITY Trial Underway, Readout in First Half of 2026



IP=intellectual property; NCE=new chemical entities.

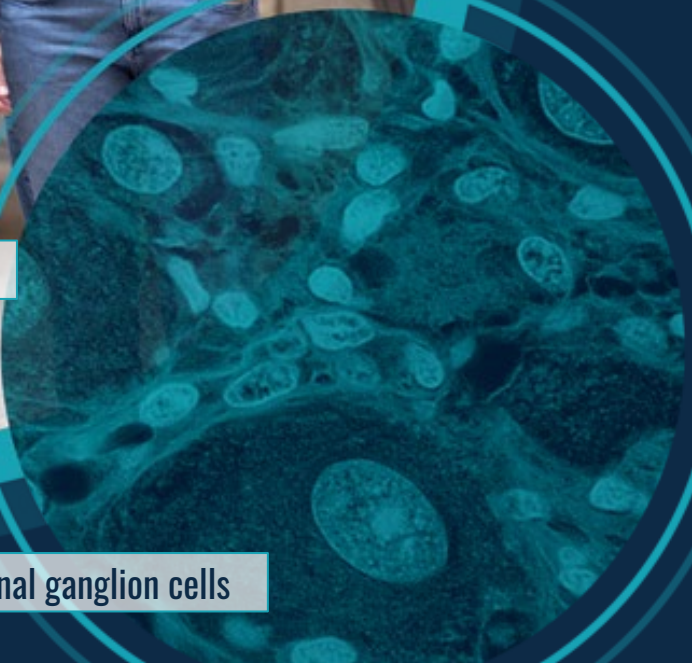
A decorative graphic on the left side of the slide consisting of several overlapping circles and arcs in shades of teal and light blue. One large teal circle is prominent in the foreground, with other lighter circles and arcs behind it.

AMX0035

Fixed-dose combination of sodium phenylbutyrate and taurursodiol designed to slow or mitigate neurodegeneration



Wolfram Syndrome Program



Raquel, living with Wolfram Syndrome

Retinal ganglion cells

Wolfram Syndrome is a Rare, Fatal, Monogenic, Progressive Disorder¹⁻⁵



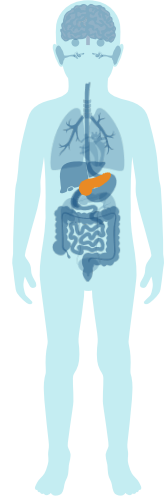
WFS1 GENE MUTATION

PROGRESSIVELY IMPACTS MULTIPLE ORGANS AND SYSTEMS¹⁻⁵

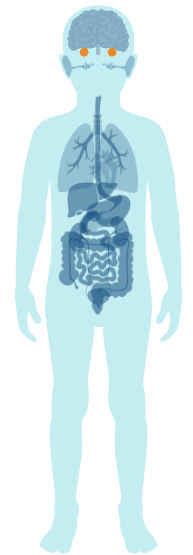
~3,000 people

Living with Wolfram Syndrome in the U.S.^{1,2}

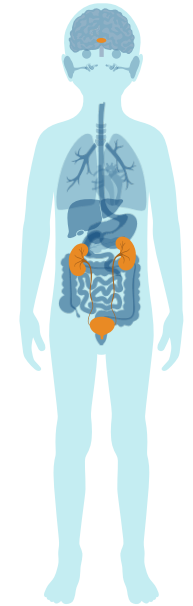
No approved therapies for Wolfram syndrome⁶



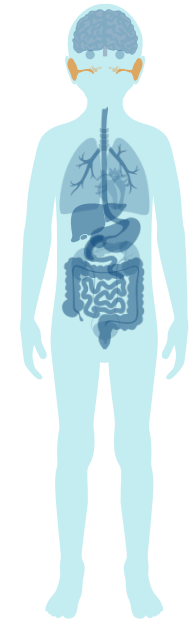
Childhood-onset Diabetes Mellitus
Elevated blood sugar levels from insulin-producing beta cell death



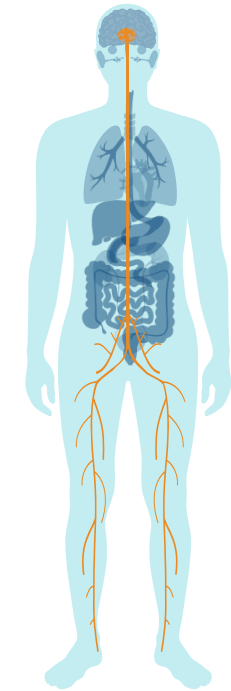
Gradual Loss of Vision Leading to Blindness
Optic nerve cell death



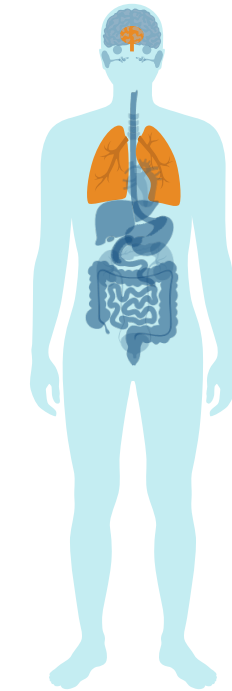
Diabetes Insipidus
Kidneys produce too much urine from a faulty pituitary gland



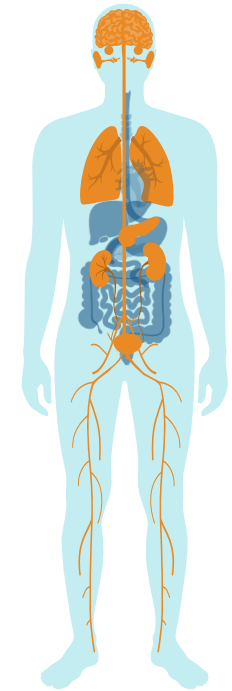
Hearing Loss
From cranial nerve damage



Balance and Coordination Difficulty
Ataxia from cerebellum damage



Difficulty Breathing
From brain stem damage

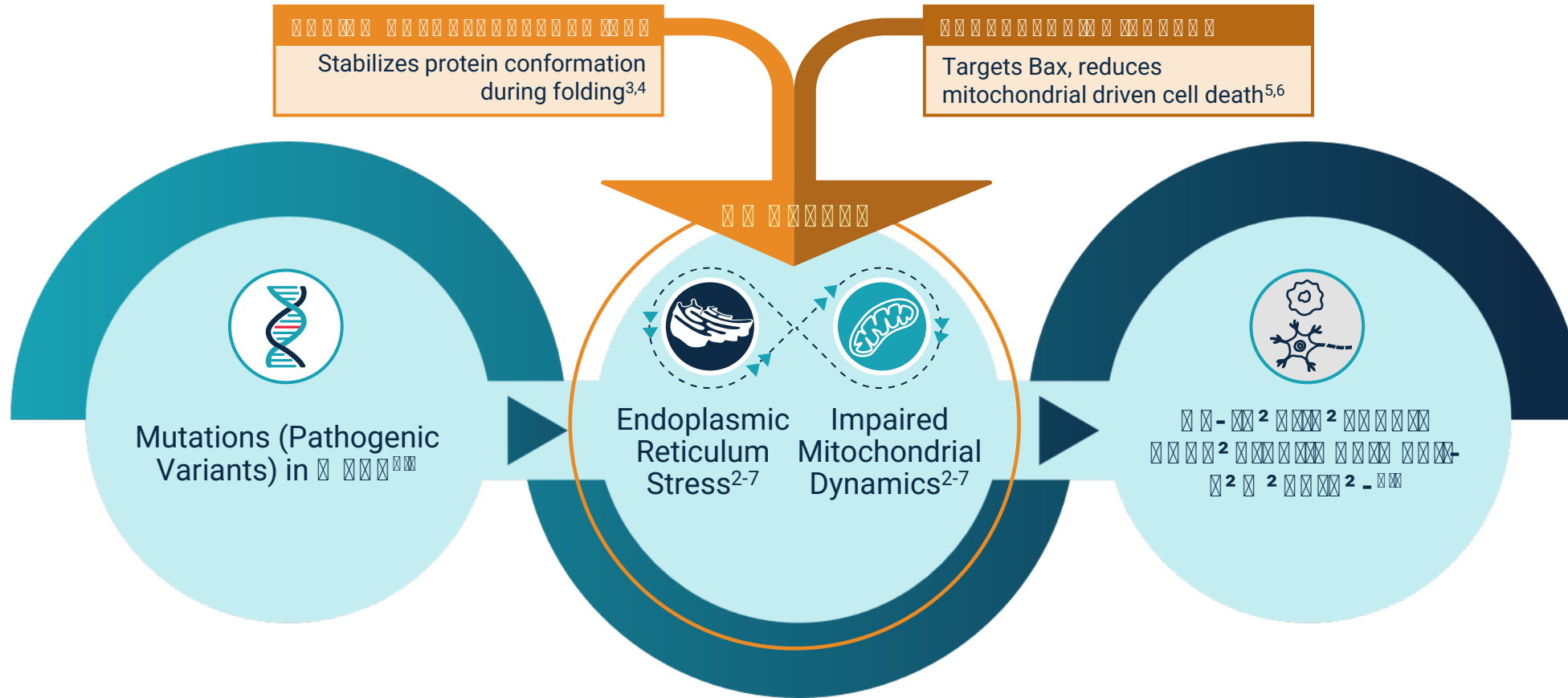


Death occurs at a median age of 30 years (range 25-49 years), mainly from respiratory failure

WFS1=Wolfram syndrome type 1 gene; 1. Urano, F. *Diabetes*. 2014;63(3):844-846. 2. Pallotta MT, et al. *Diabetes*. 2019;17:238. 3. Lee, E., et al. *Front Genet*. 2023;14:1198171. 4. Leslie, M. *Diabetes*. 2021;371(6530):663-665. 5. Matsunaga et al. *Diabetes*. 2014;9(9):106906. 6. Urano, F. *Diabetes*. 2016;16(1):6.

Wolfram Syndrome is a Prototypical Endoplasmic Reticulum Stress Disorder¹

AMX0035 targets endoplasmic reticulum stress and related mitochondrial dysfunction pathways



JCI insight

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

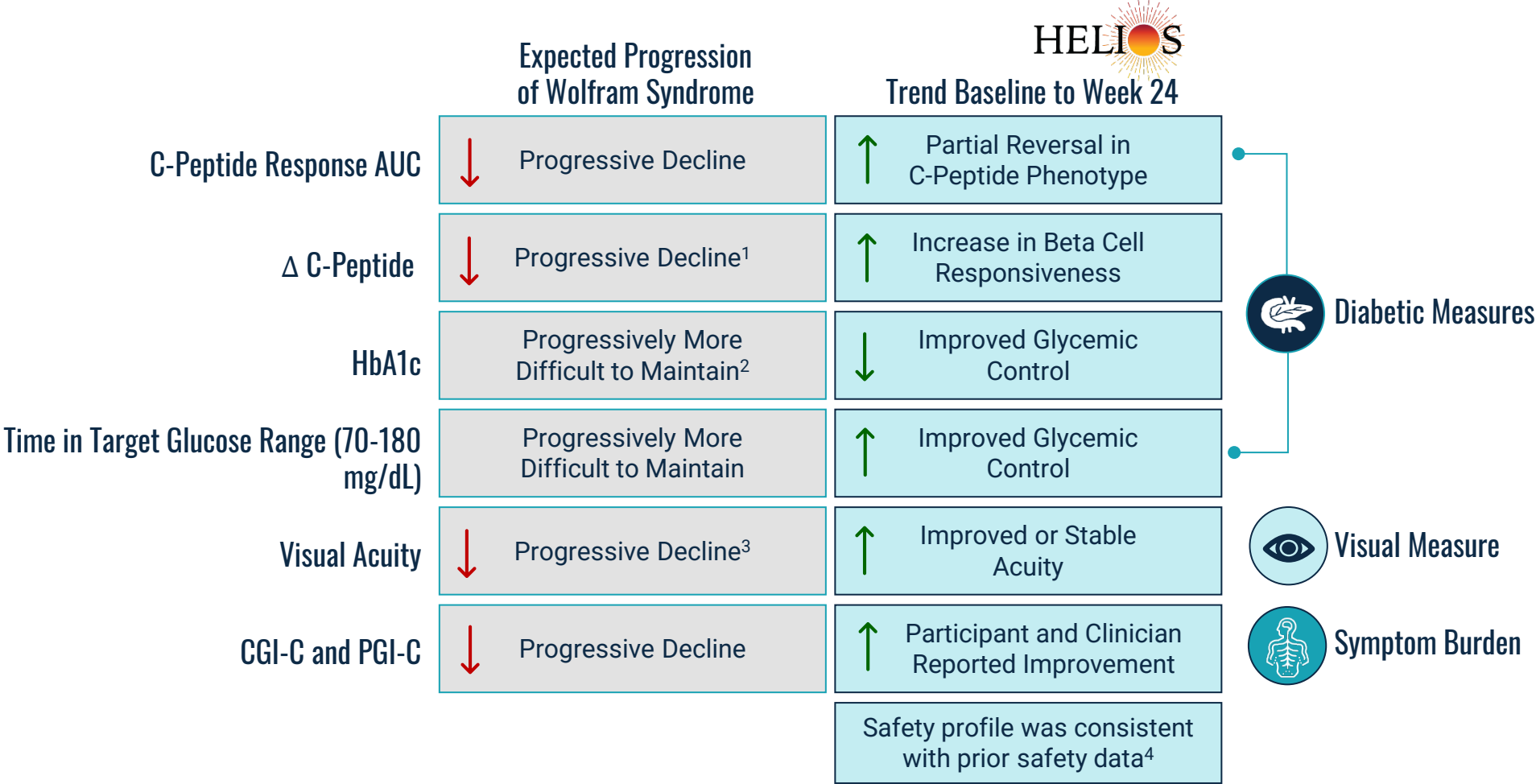


Clear Link of Mechanism of Disease and Mechanism of AMX0035

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.

Topline Data Suggest Potential Benefit of AMX0035 in Wolfram Syndrome

Improvements across disease measures observed in open-label, single-arm clinical trial (N = 12)



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; Data on File. Amylyx Pharmaceuticals Inc. 2024. 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.

AMX0035 Safety and Tolerability in HELIOS

- AMX0035 was ¹ χ^2 χ^2 χ^2 χ^2 χ^2 χ^2
 - > Diarrhea was the most common TEAE (50.0%); all cases were of mild severity
 - > All TEAEs were graded mild or moderate
- χ^2 χ^2 - χ^2 χ^2 - χ^2 χ^2 were identified
- Nearly all participants reported ≥ 1 TEAE during the trial
 - > Most did not lead to modification or interruption of AMX0035 dosing and ² χ^2 χ^2 χ^2 χ^2 ¹ χ^2 - χ^2 ² χ^2 χ^2 χ^2 ²

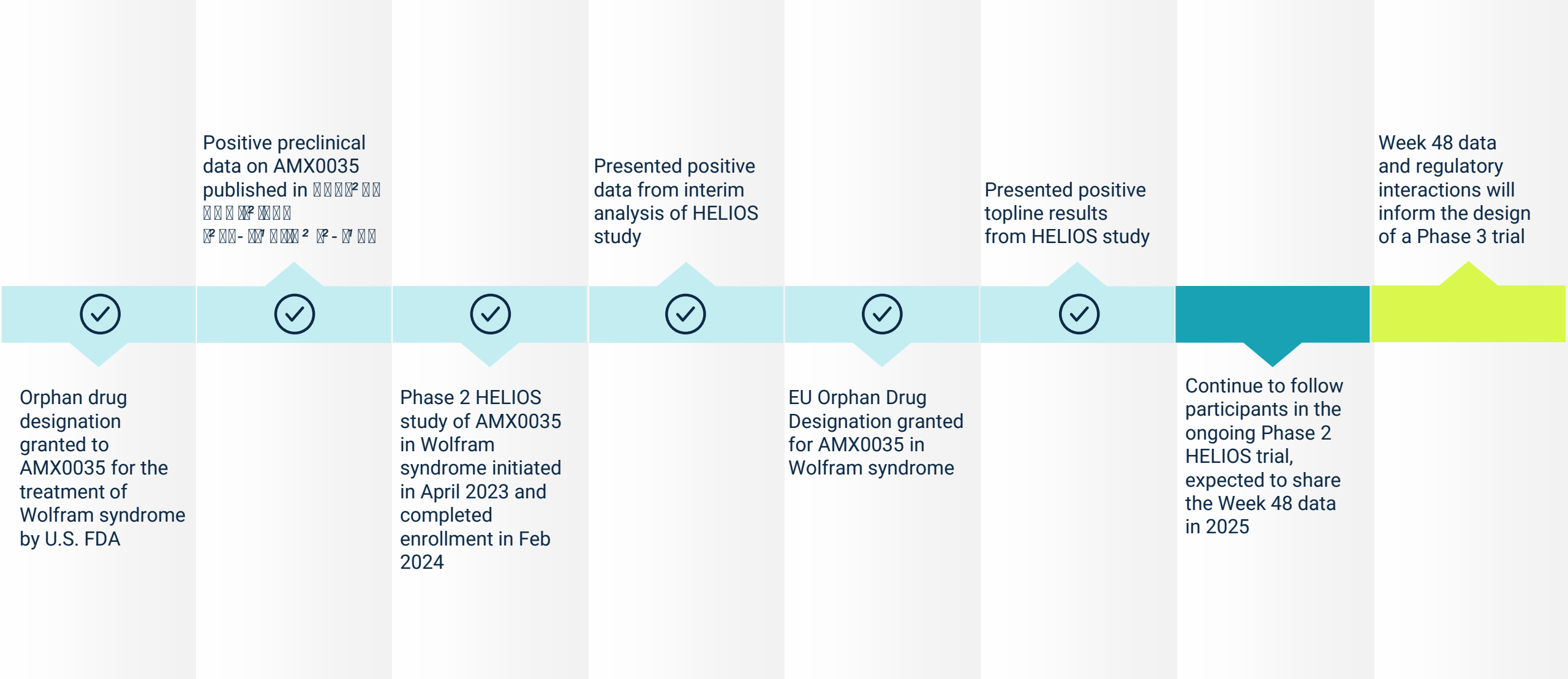
Summary of Treatment Emergent Adverse Events (TEAEs)

	AMX0035 (N=12)* n (%)
Participants with ≥ 1 TEAE	11 (91.7)
TEAE related to study drug**	9 (75.0)
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 July 31, 2024 included

**Includes those with TEAEs considered possibly related to treatment; none considered “probably related” or “definitely related”

AMX0035 Wolfram Syndrome Program Next Steps



EU=European Union; FDA=U.S. Food and Drug Administration.

Progressive Supranuclear Palsy (PSP) Program

ORION

Purkinje nerve cell in the cerebellum

PSP is a Rare, Progressive, and Fatal Tauopathy

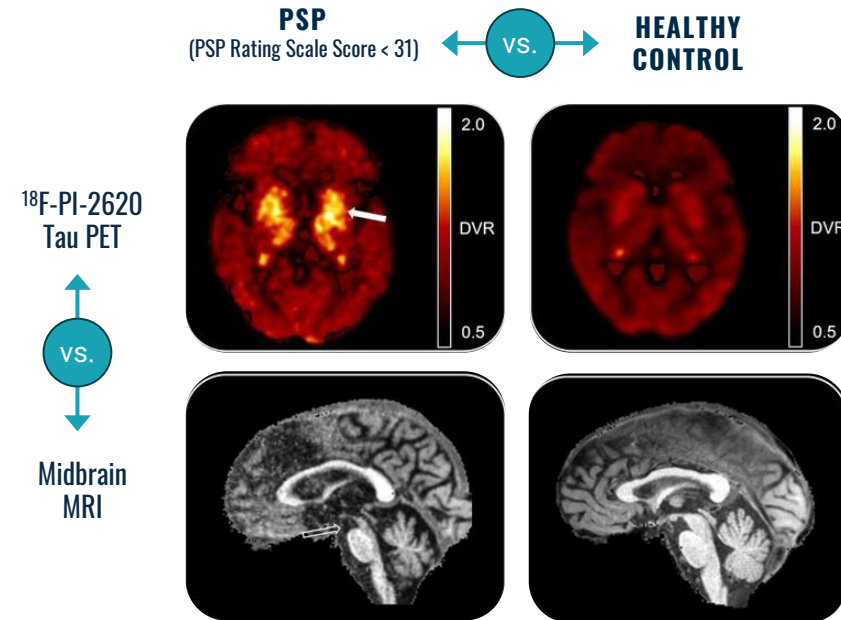
- PSP affects body movements, including balance and eye movements
- No disease-modifying therapies approved
- PSP is considered a tauopathy based on the strong genetic link between tau variants and disease development and the presence of abnormal tau protein deposits in the brain
- Biomarker data from Phase 2 trial of AMX0035 in Alzheimer's disease demonstrated a significant reduction in tau

PSP
is typically fatal

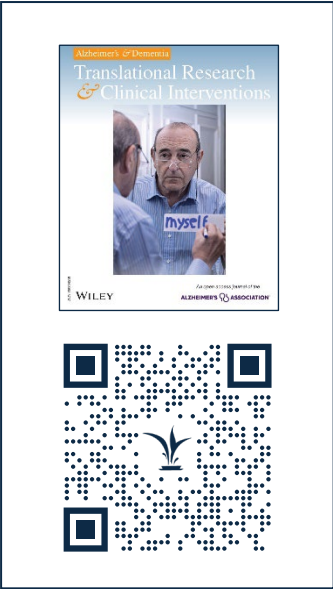
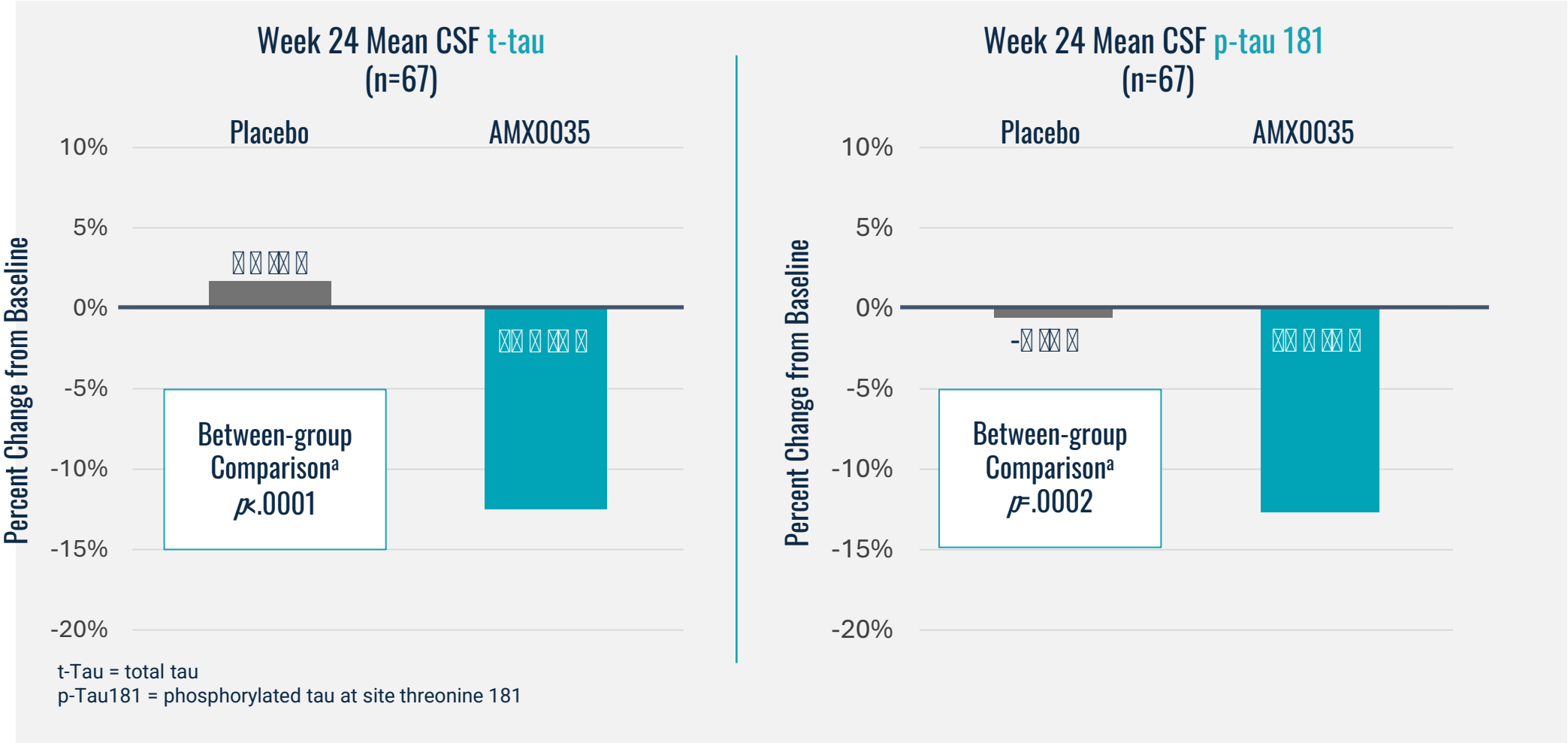
Within 6-8 years from symptom onset³⁻⁶

ESTIMATED PREVALENCE
7 in 100,000
Worldwide^{1,2}

U.S. PREVALENCE
23,000
Approximately



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



Arnold SE, Hendrix S, Nicodemus-Johnson J, et al. Biological effects of sodiumphenylbutyrate and taurursodiol in Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2024;10:e12487. <https://doi.org/10.1002/trc2.12487>.

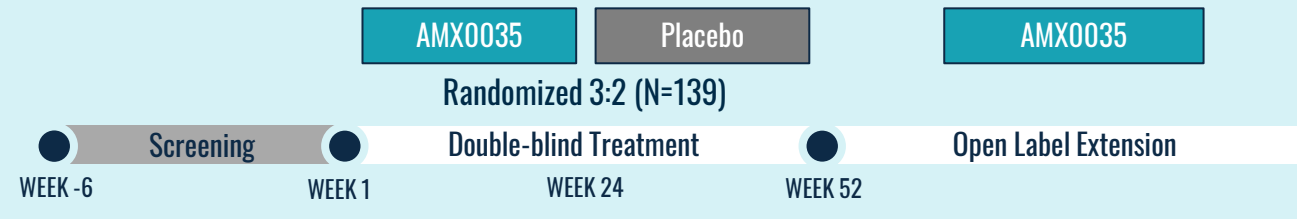
ORION: Operationally Seamless Phase 2b/3 Clinical Trial Underway

★ INTERIM ANALYSIS EXPECTED IN Q3 2025



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

PHASE 2B STUDY PORTION DESIGN



Interim Analysis expected in mid-2025

Proceed to Phase 3 if Data are Strong



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

Primary Endpoint

- PSPRS score*

Secondary Endpoints

- PSPRS score*
- MDS-UPDRS Part II score

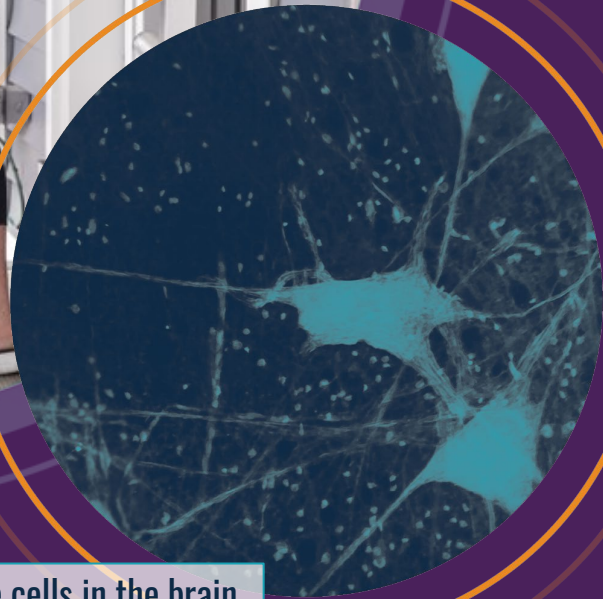
Additional Endpoints

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

*Given regional evidentiary requirements, the 10-item PSPRS is the primary endpoint in the U.S. and the 28-item PSPRS is the primary endpoint outside of the U.S.; for each region, the other form of the PSPRS is considered a secondary endpoint. MDS, Movement Disorders Society; MMSE, mini-mental status exam; PSPRS, Progressive Supranuclear Palsy Rating Scale; MRI, magnetic resonance imaging; QoL, quality of life; CSF, cerebrospinal fluid ¶ Gradually progressive disorder, with age at disease onset ≥ 40 years ¶¶ Either or both of the following two items are met: i. Vertical supranuclear gaze palsy OR slow velocity of vertical saccades AND postural instability with repeated unprovoked falls within 3 years OR tendency to fall on the pull-test within 3 years ii. Slow velocity of vertical saccades AND postural instability with more than two steps backward on the pull-test within 3 years. 1,2. Höglinger et al. Movement Disorders 2017. ¶¶ Ability to walk 5 steps with minimal assistance (stabilization of one arm).



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



Nerve cells in the brain

AMX0114 PROGRAM

Potent antisense oligonucleotide (ASO) targeting calpain-2

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

Evidence for Targeting Calpain-2 in ALS¹⁻⁴



Calpain-2 levels are elevated in people with ALS



Inhibition of calpain-2 has shown benefit in ALS mouse model



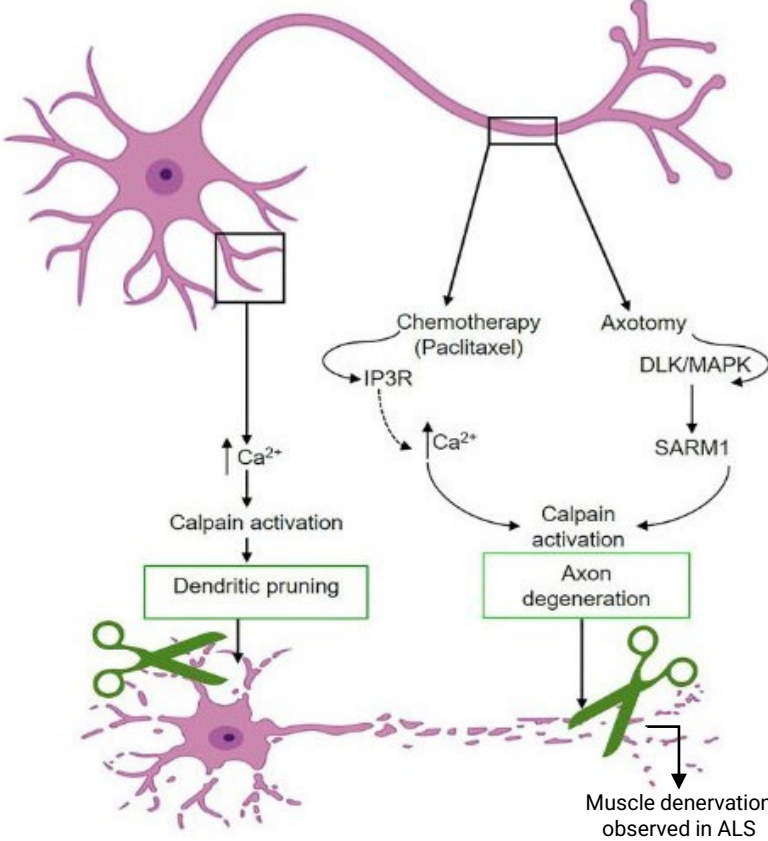
Calpain-2 substrates include neurofilament and TDP-43



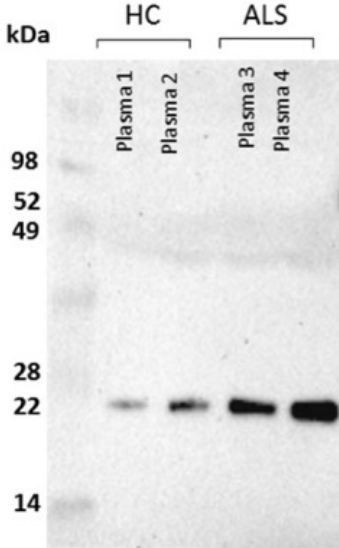
AMX0114 has shown efficacy in pre-clinical ALS models

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

Mechanisms of Axonal Degeneration⁵

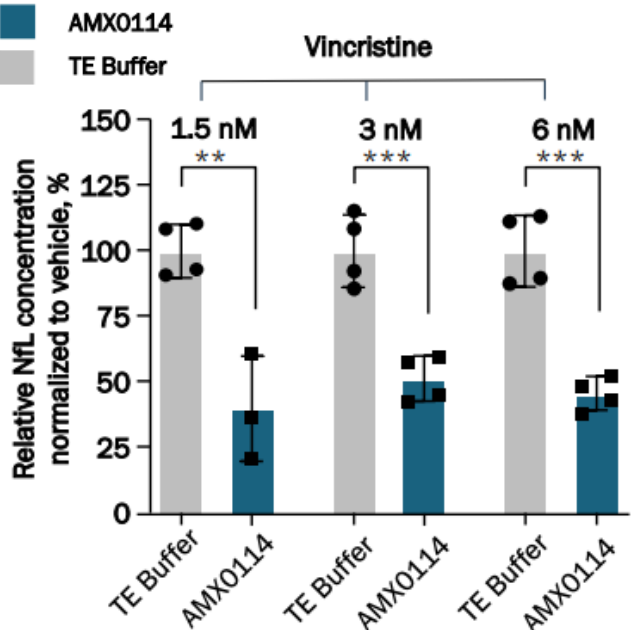


Full Length Neurofilament (68 kDa) is not observed in ALS or Healthy Control

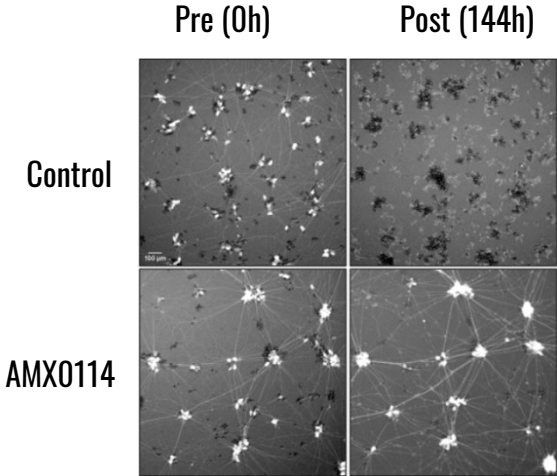


ALS=amyotrophic lateral sclerosis; 1. Ueyama H et al. J Neurol Sci. 1998;155(2):163-169. 2. Yamashita T et al. Nat Commun. 2012;3:1307. 3. Rao MV, et al. J Neurochem. 2016;137(2):253-65. 4. Ma M, et al. Neurobiol Dis. 2013;56:34-46. 5. Asakawa, K., Handa, H., Kawakami, K. Multi-phaseted problems of TDP-43 in selective neuronal vulnerability in ALS. *Neurosci Lett*. 2021;78(10):4453-4465. doi:10.1007/s00018-021-03792-z

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



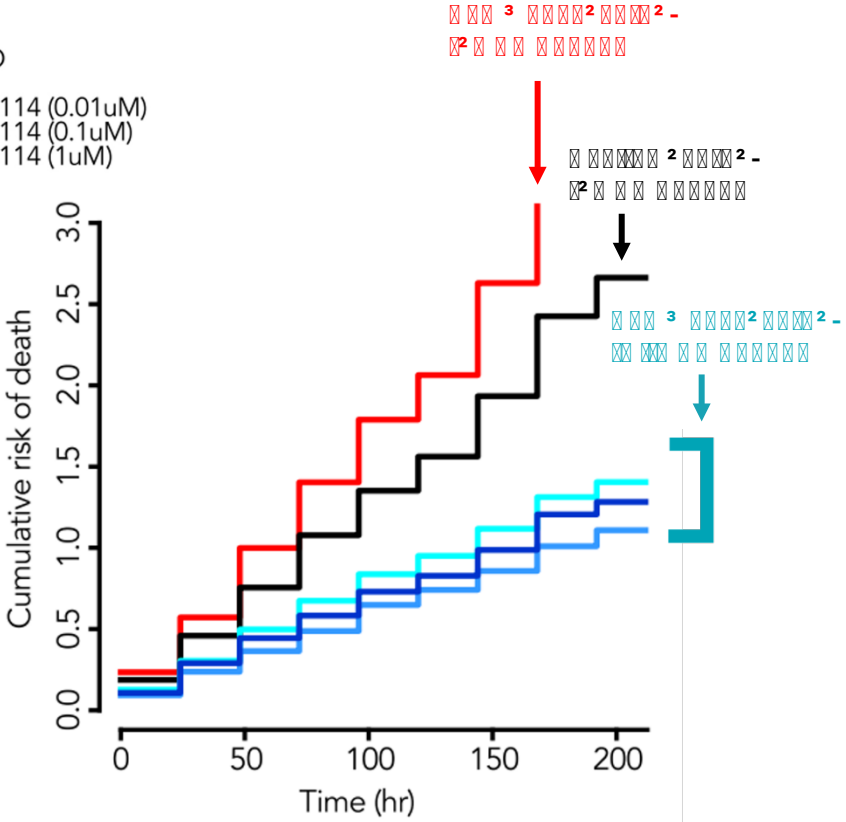
Representative Images of Motor Neurons Pre- and Post-Exposure to H₂O₂



TDP-43 ALS Model

- M337V + DMSO
- WT + DMSO
- M337V + AMX0114 (0.01uM)
- M337V + AMX0114 (0.1uM)
- M337V + AMX0114 (1uM)

Higher risk of death
↑
Lower risk of death



Similar NfL Reduction in Rotenone and Colchicine models

NS = P>.05.
* = P<.05.
** = P<.01,
*** = P<.001,
**** = P<.0001.
NfL, neurofilament light chain;
NS, not significant; TE, tris ethylenediaminetetraacetic acid.

Presented at

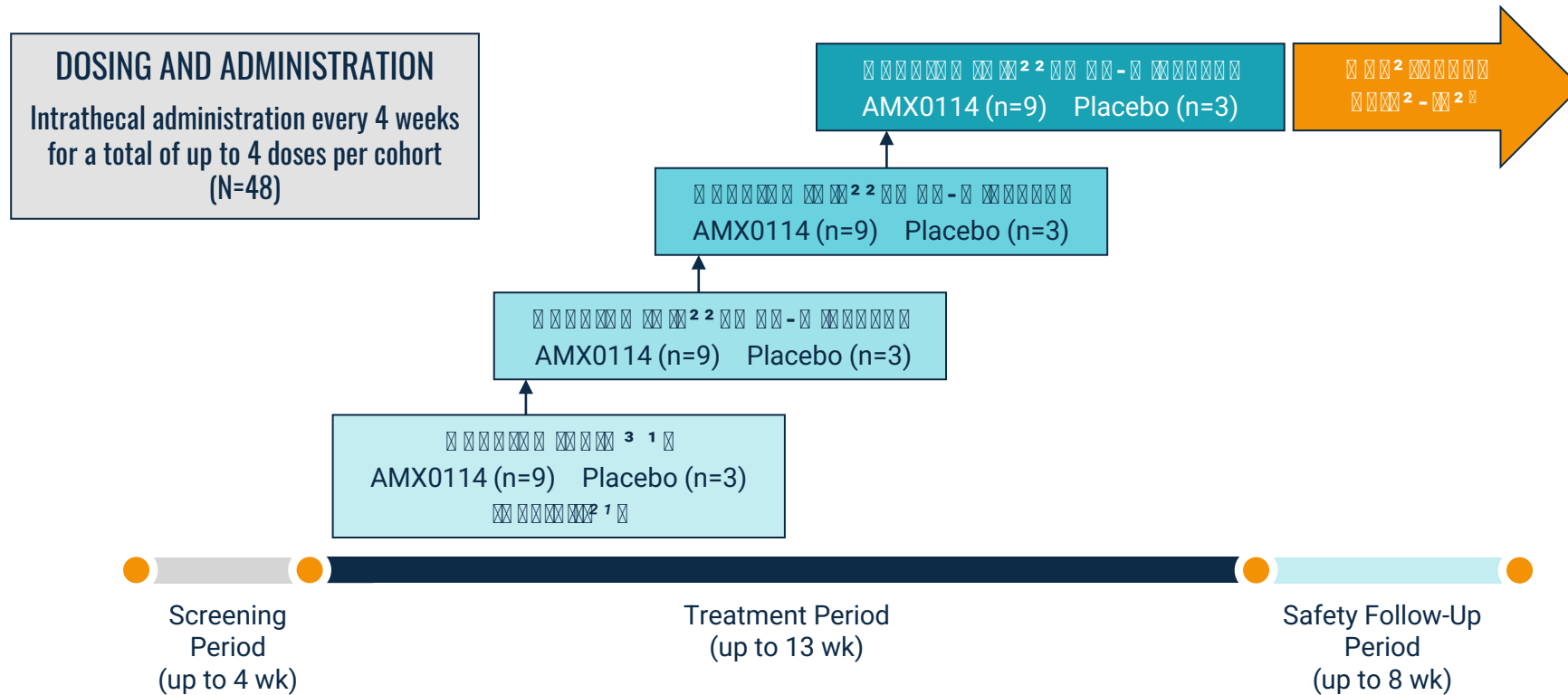
ALS=amyotrophic lateral sclerosis; NfL=neurofilament light chain; Data on File. Amylyx Pharmaceuticals Inc. 2024; Survival analyses performed in the lab of Dr. Sami Barmada at the University of Michigan Medical School by Dr. Michael Bekier.

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



EARLY COHORT DATA EXPECTED IN 2025

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.



Key Corporate Highlights

EXPECTED CASH THROUGH THE END OF 2026¹

As of Dec. 31, 2024

\$176.5M in cash, cash equivalents,
and short-term investments

Public Offering

Closed on January 13, 2025

SHARES ISSUED

19.7MM

NET PROCEEDS

\$65.5MM

¹ Cash guidance based on current operating plan including proceeds from Jan. 13, 2025 offering.

Ushering in a new era for treating
diseases with high unmet needs

