December 2024

Investor Presentation

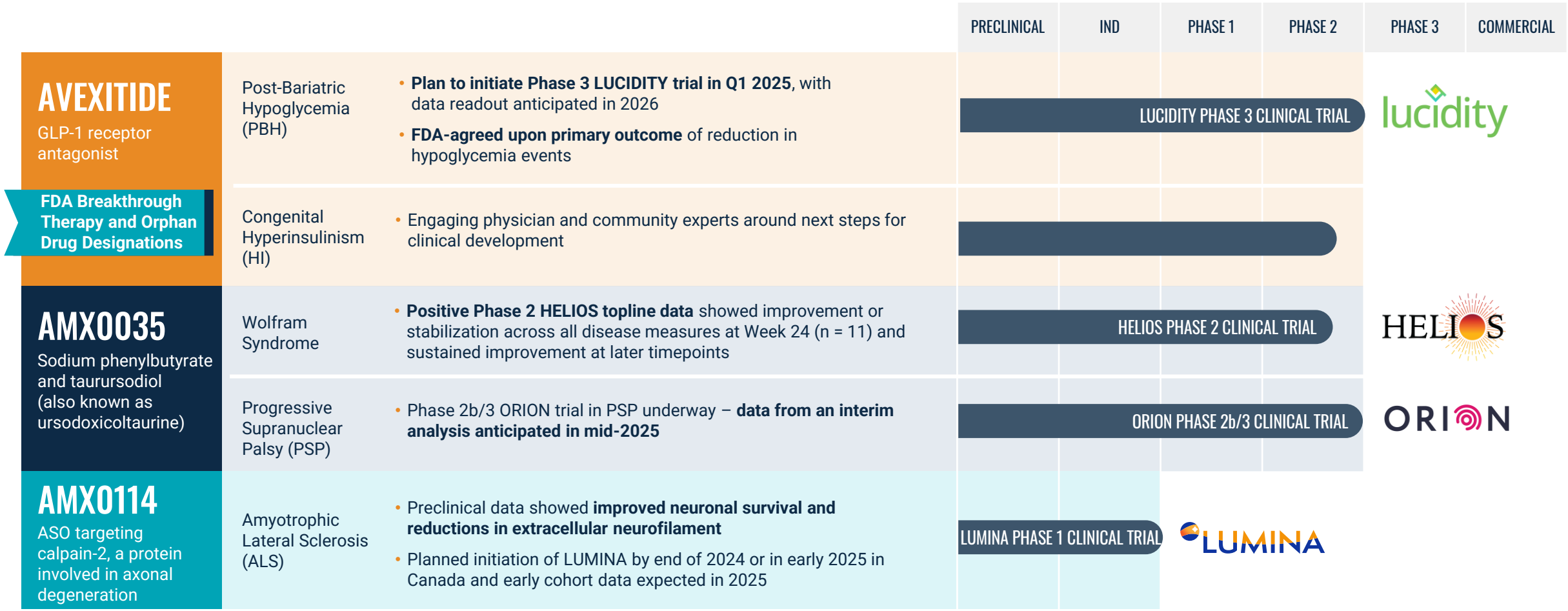
We have an audacious mission to develop novel therapies for diseases with high unmet needs, with a focus on serious and fatal neurodegenerative diseases and endocrine conditions.

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



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

Committed to Developing Treatments for Diseases with High Unmet Needs

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

AVEXITIDE

First-in-class, GLP-1 receptor antagonist with Breakthrough Therapy and Orphan Drug designations

- Designed to bind to the GLP-1 receptor and **inhibit the effect of GLP-1**, decreasing insulin secretion and stabilizing blood glucose levels.
- **Planned initiation of the Phase 3 trial in Q1 2025** to evaluate the efficacy and safety of avexitide in participants with PBH
- FDA guidance and interactions support Phase 3 primary endpoint as **approvable following positive trial results**[1]

AMX0035

Oral, fixed-dose combination of two small molecules, sodium PB and taurursodiol

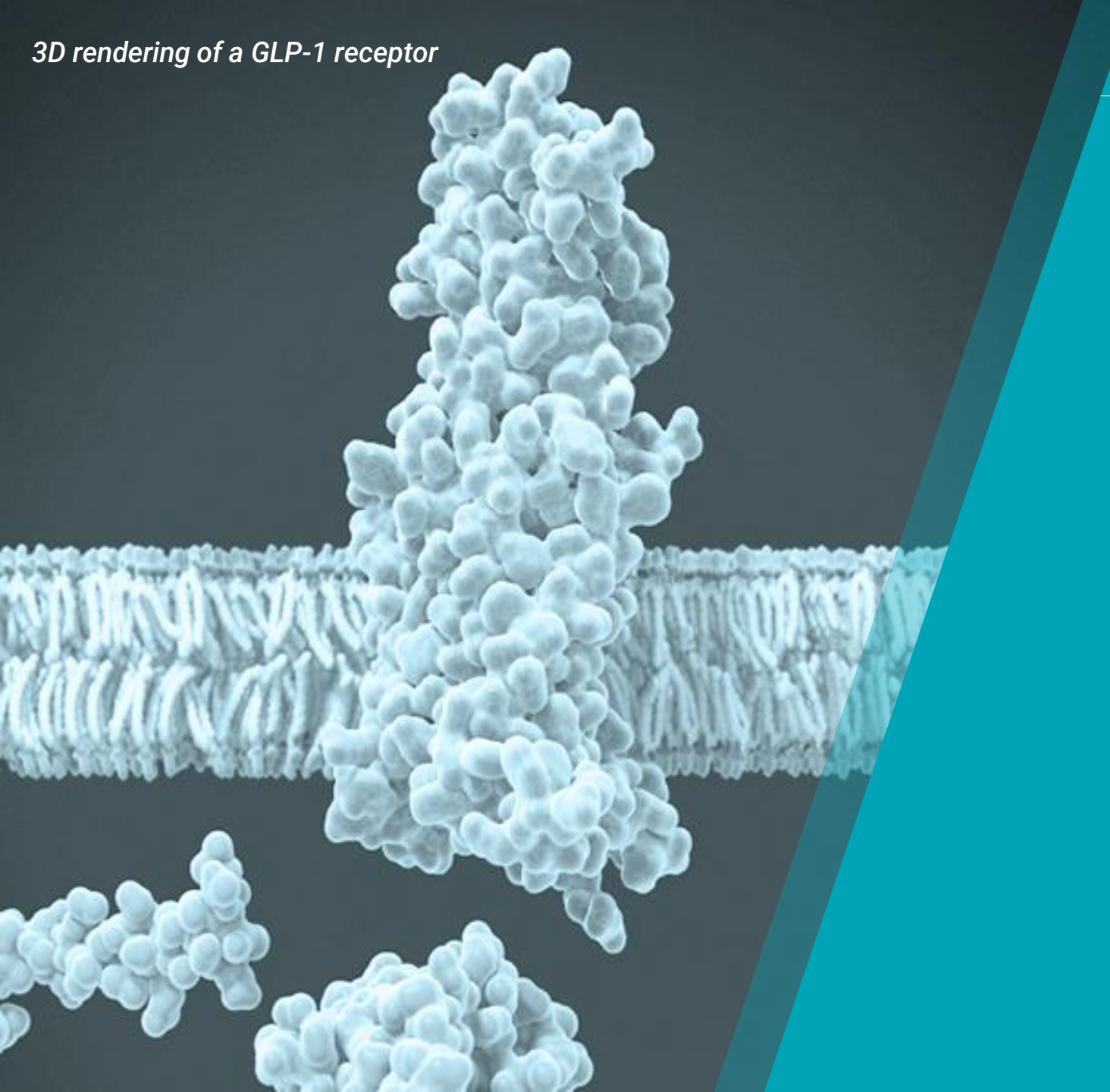
- Designed to **mitigate neurodegeneration by targeting ER stress and mitochondrial dysfunction**, two cellular processes central to neuronal cell death and neurodegeneration
- AMX0035 has **demonstrated clear biological activity** in preclinical and clinical studies
- **Positive Phase 2 HELIOS topline data** showed improvement in pancreatic function following 24 weeks of treatment
- Phase 2b/3 ORION trial in PSP underway

AMX0114

Antisense oligonucleotide designed to target calpain-2, a protein involved in axonal degeneration and neurofilament biology

- Preclinical data demonstrated treatment with AMX0114 showed **rescue of cellular degeneration and neurofilament biology** in multiple cellular experiments
- Phase 1 LUMINA clinical trial, a multicenter, randomized, placebo-controlled, multiple ascending dose trial, will **evaluate the safety and biological activity of AMX0114** in approximately 48 people living with ALS
- Planned **initiation of LUMINA** by the end of 2024 or in the beginning of 2025 in Canada

ALS=amyotrophic lateral sclerosis; ER=endoplasmic reticulum; GLP-1=glucagon-like peptide-1; PB=phenylbutyrate; PBH=post-bariatric hypoglycemia; PSP=progressive supranuclear palsy; **1.** U.S. Food and Drug Administration, FDA-2023-D-0625: Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products (2023).



3D rendering of a GLP-1 receptor

AMYLYX

Avexitide

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

Avexitide: Investigational, First-in-Class GLP-1 Receptor Antagonist

- Avexitide targets known incretin biology
- FDA Breakthrough Therapy Designation and Orphan Drug Designation in hyperinsulinemic hypoglycemia
- Phase 3 LUCIDITY trial is designed to evaluate FDA-agreed upon primary outcome of reduction in hypoglycemia events in PBH
- Highly statistically significant clinical results, including in hypoglycemia outcome planned to be used in Phase 3
  - > Results replicated across clinical studies
- PBH is often a life-altering, orphan condition; ~160,000 prevalent patients
- Strong IP position with patent rights through 2037 and potential for patent term extension
- Leadership team tenured in rare disease; commercial capabilities demonstrated recently with one of the top performing orphan disease drug launches

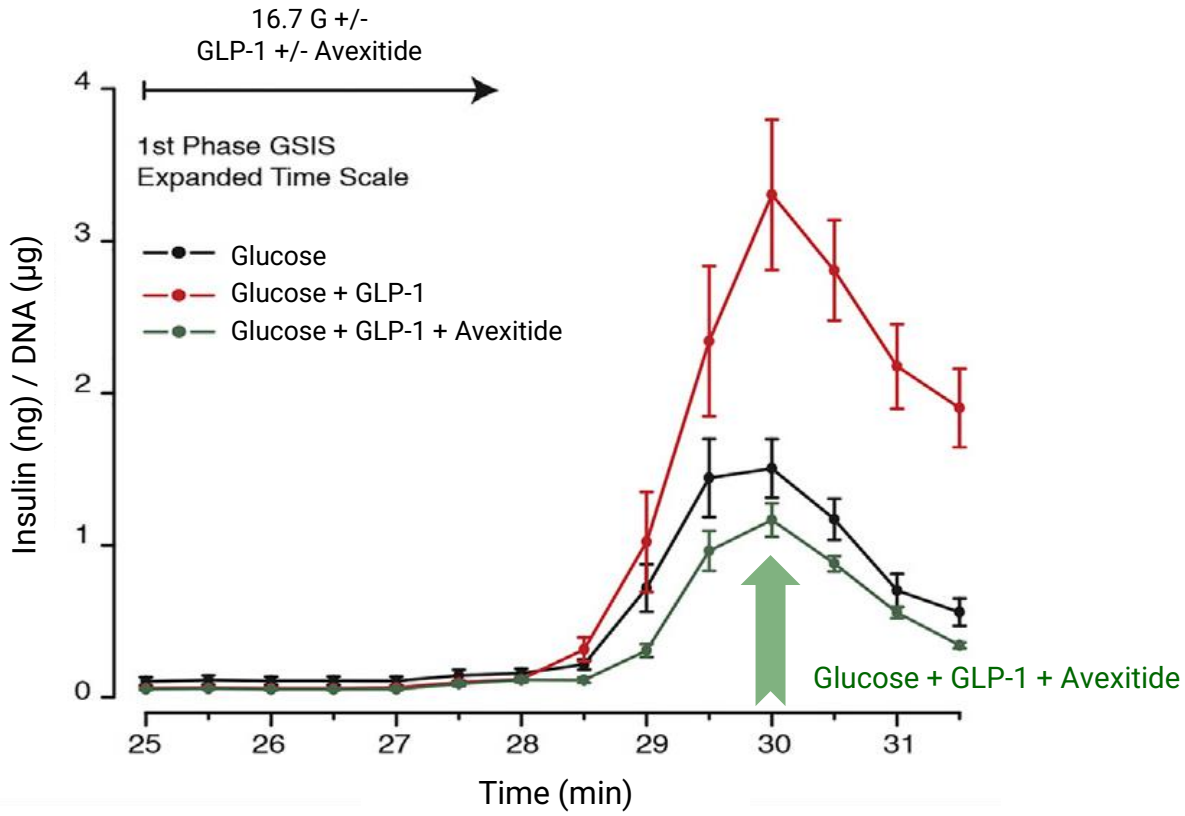
EXPECTED MILESTONES

Q1 2025	2025	2026
Initiate Avexitide Phase 3 Trial in PBH	Complete Enrollment of Avexitide Phase 3 Trial in PBH in 2025	Topline Data from Avexitide Phase 3 Trial in PBH in 2026

Inhibiting Effects of Excessive GLP-1 in PBH to Mitigate Hypoglycemia

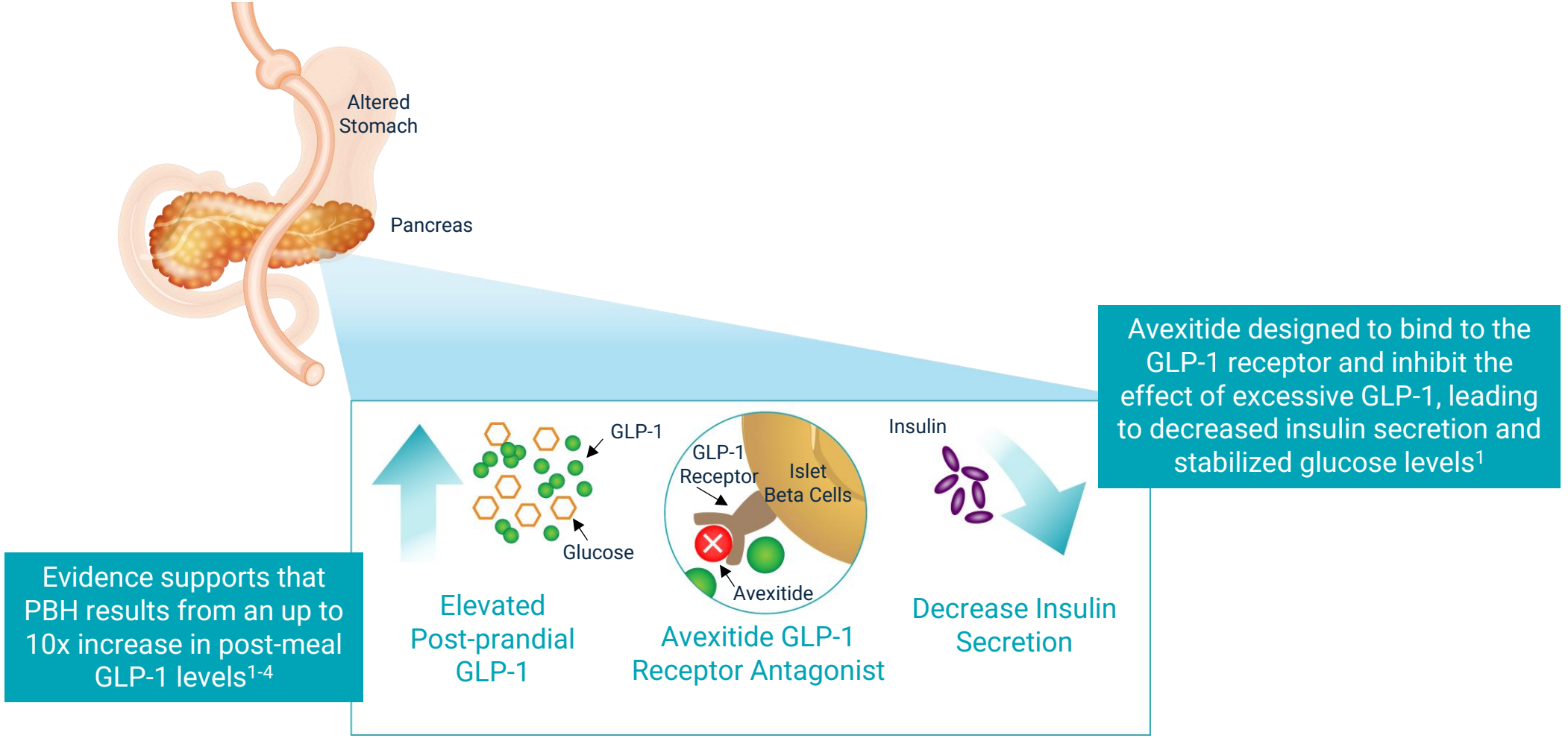
- The GLP-1 receptor is a key regulator of glucose insulin response
- Endogenous GLP-1 secreted in response to a meal to cause insulin secretion and glucose uptake
- Avexitide inhibits endogenous GLP-1 from binding to the GLP-1 receptor, lowering insulin secretion and raising blood glucose levels

GLP-1 receptor antagonism blocks GLP-1 and **decreases insulin response** to glucose in rat pancreatic islet cells[1]



GLP-1=glucagon-like peptide-1; GSIS=glucose-stimulated insulin secretion; PBH=post-bariatric hypoglycemia; **1.** Cabrera O. et al. *The Journal of Biological Chemistry*. 2022;298(2):101484. doi:10.1016/j.jbc.2021.101484.

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



Evidence supports that PBH results from an up to 10x increase in post-meal GLP-1 levels[1-4]

Avexitide designed to bind to the GLP-1 receptor and inhibit the effect of excessive GLP-1, leading to decreased insulin secretion and stabilized glucose levels[1]

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.

PBH Can Be Life-Threatening and There Are No Approved Treatment Options

Hypoglycemia from PBH is Often Dangerous and Life-Altering

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

Living with PBH

"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."

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

~160,000 people

currently living with symptomatic PBH in the U.S.[1-3]

No approved treatment options

>200K

new procedures are happening annually[1]

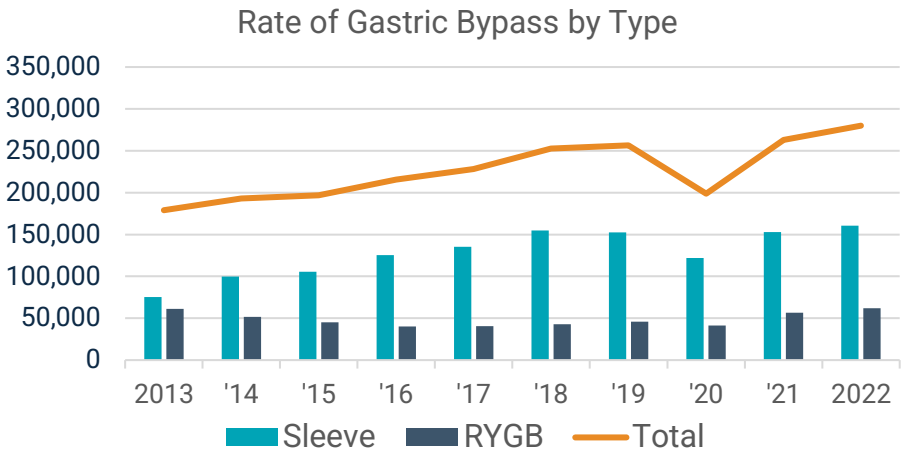
PBH occurs on average 1-3 years post surgery

BETWEEN 2013-2022

Sleeve.....~1.3 million

RYGB.....~0.5 Million

Total.....~2.3 Million



PBH=post-bariatric hypoglycemia; RYGB=Roux-en-Y gastric bypass; **1.** Estimate of Bariatric Surgery Numbers, 2011-2022. American Society for Metabolic and Bariatric Surgery (ASMBS). Accessed July 9, 2024. **2.** Raverdy V. et al. *Annals of Surgery*. 2016;264(5):878-885. doi:10.1097/SLA.0000000000001768. **3.** de Heide, L. J. M. et al. *Diabetes, Obesity, & Metabolism*. 2023;25:735-747. doi.org/10.1111/dom.14920.

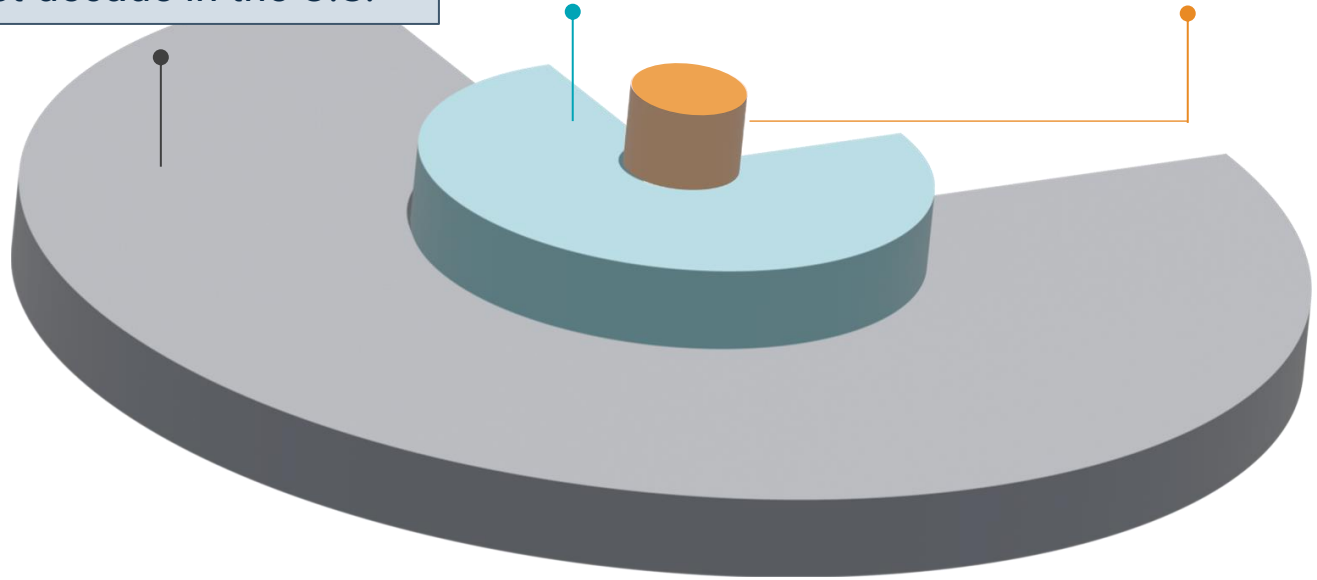
~160,000 People Are Currently Living With Symptomatic PBH in the U.S.[1-3]

PREVALENCE

~2 million people have previously undergone the two most common types* of bariatric surgery in the past decade in the U.S.[1]

~20-40% of bariatric surgery patients develop hypoglycemia[5-7]

~160,000 people are currently living with symptomatic PBH in the U.S.[1-3]



*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]

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

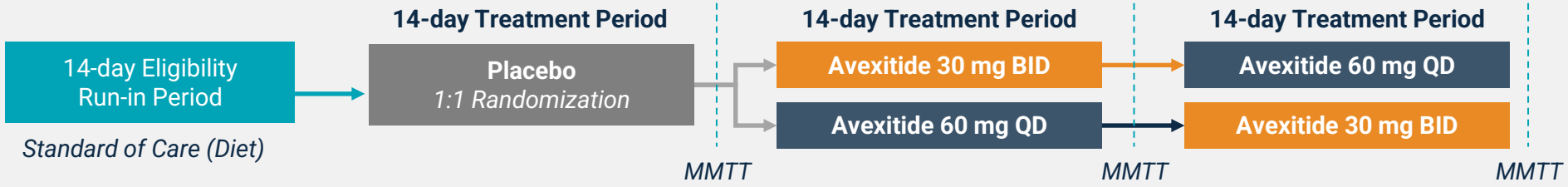
PBH=post-bariatric hypoglycemia; **1.** Estimate of Bariatric Surgery Numbers, 2011-2022. American Society for Metabolic and Bariatric Surgery (ASMBS). Accessed July 9, 2024. **2.** Raverdy V. et al. *Annals of Surgery*. 2016;264(5):878-885. doi:10.1097/SLA.0000000000001768. **3.** de Heide, L. J. M. et al. *Diabetes, Obesity, & Metabolism*. 2023;25:735-747. doi.org/10.1111/dom.14920. **4.** Hazlehurst, J. et al. *Endocrine Connections*. 2024;13(5), e230285. doi:10.1530/EC-23-0285. **5.** Lee CJ, et al. Surg Obes and Relat Dis. 2018;14(6):797-802. **6.** Brix JM, et al. Obes Facts. 2019;12:397-406. **7.** Fischer LE, et al. Surg Obes Relat Dis.2021;17(10):1787-1798.

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)

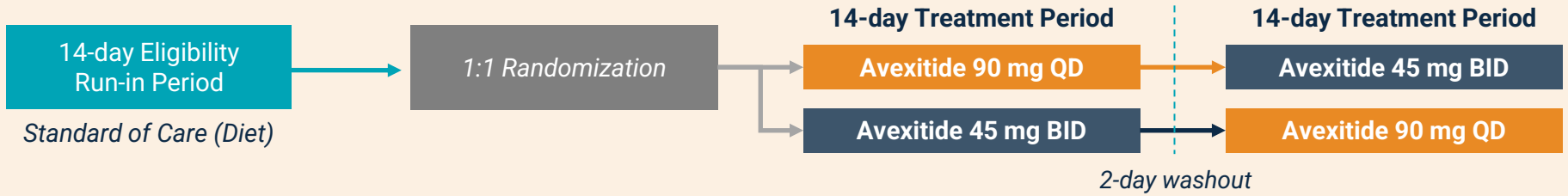
Participants enrolled had Roux-en-Y gastric bypass (RYGB)



Phase 2b Trial Design

28-day, open-label, investigator-initiated, crossover trial (N = 16)

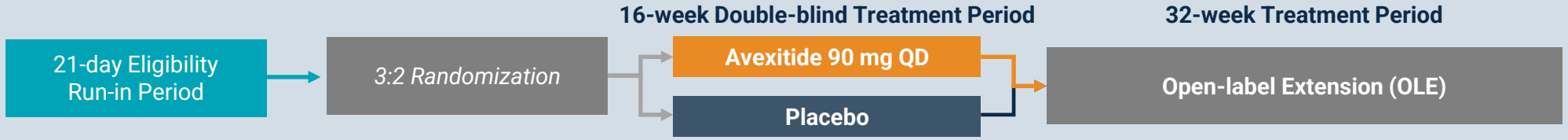
Participants enrolled had RYGB, vertical sleeve gastrectomy, esophagectomy, Nissen fundoplication, or gastrectomy



Phase 3 LUCIDITY Trial Design

Multicenter, randomized, double-blind, placebo-controlled trial (N = ~75)

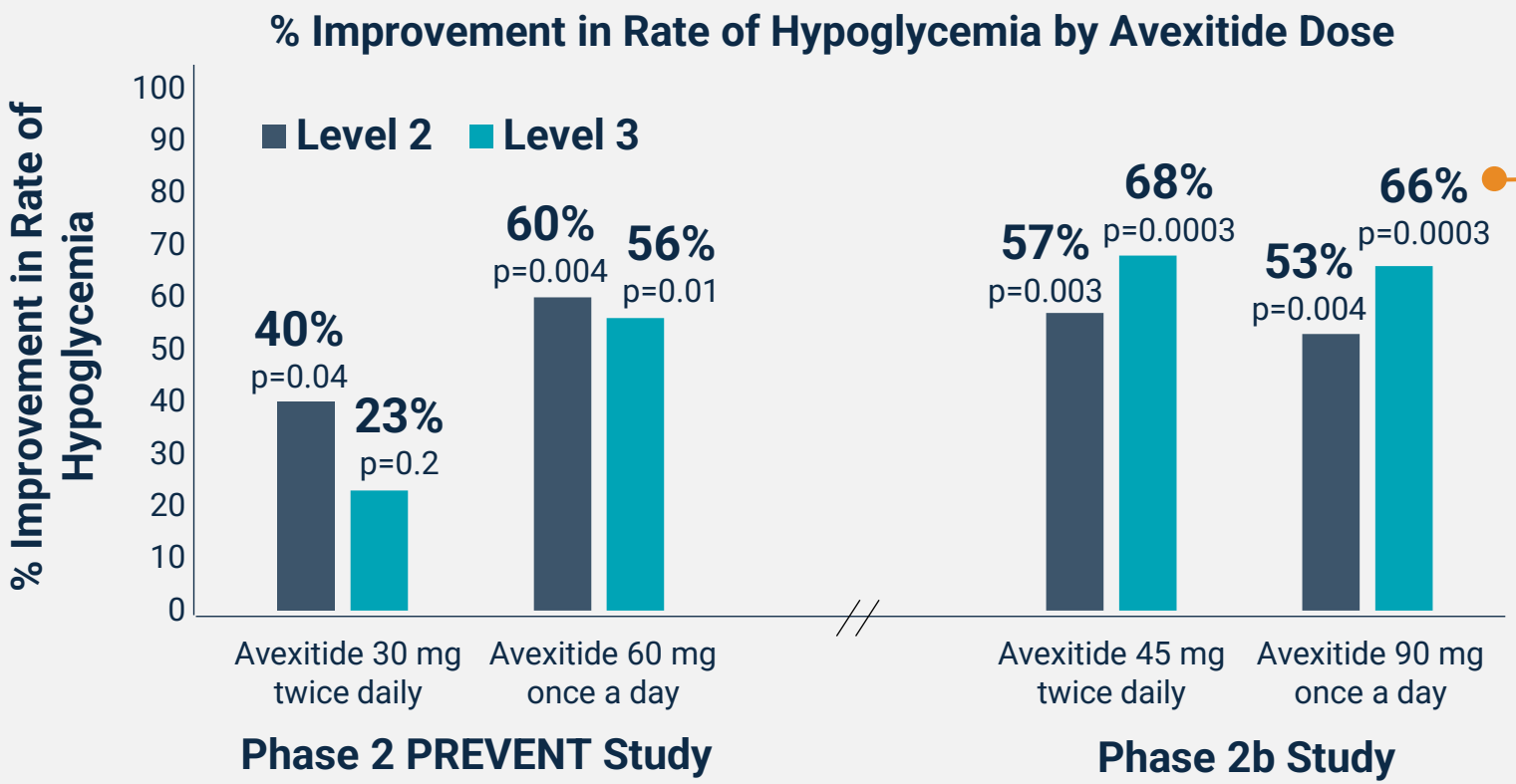
Participants enrolled had RYGB



AMYLYX

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



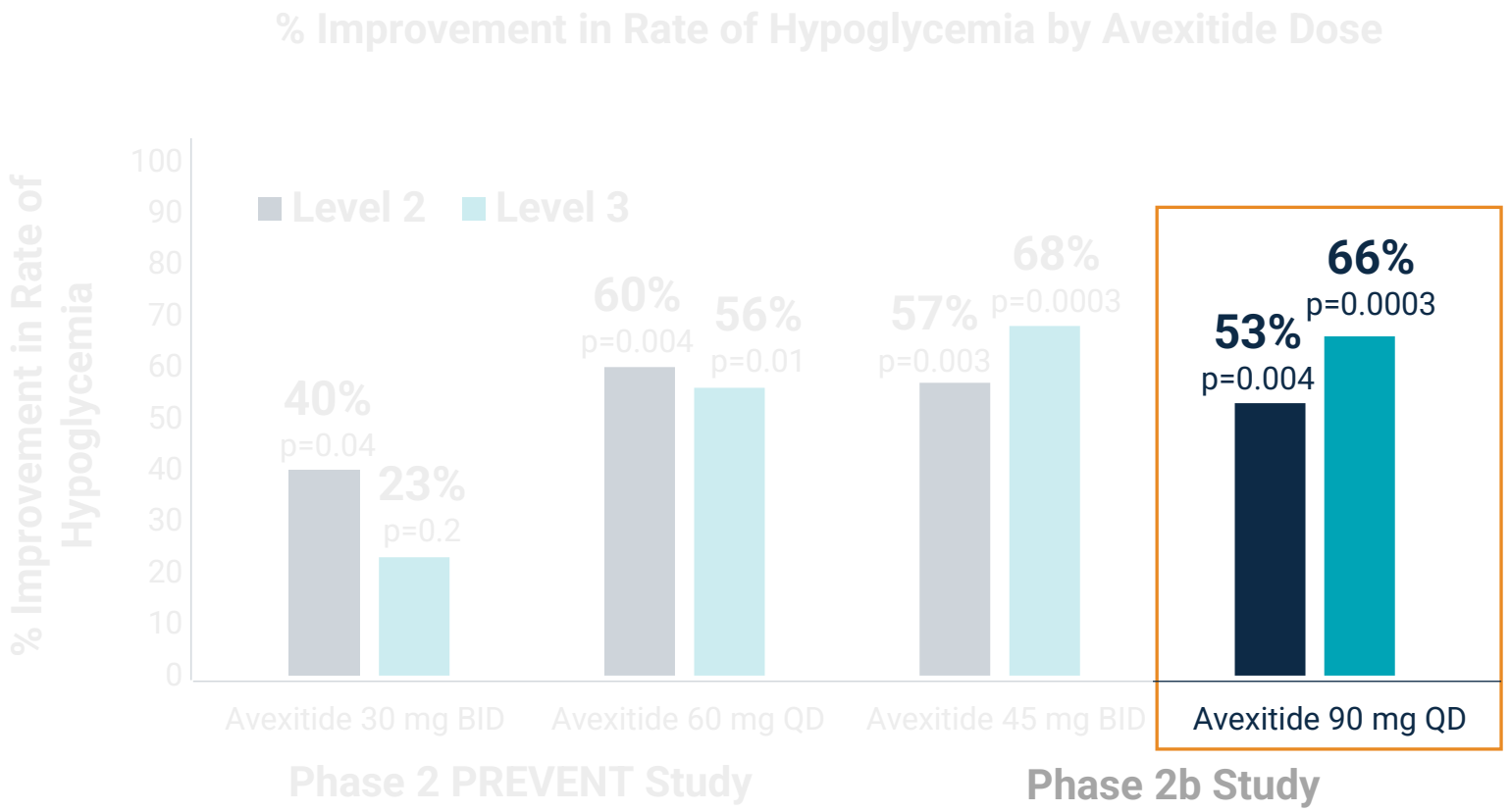
Avexitide 90 mg QD demonstrated a half-life of ~3 hours, a Tmax ranging from 6-9 hours, and therapeutic exposure through 24 hours.

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

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

MAD=multiple ascending dose; PBH=post-bariatric hypoglycemia; QD=once daily; SAD=single ascending dose; **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]. ENDO Annual Symposium.

Phase 3 Endpoint Met in Phase 2 and Phase 2b



Phase 3 program 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 Breakthrough Therapy Designation

FDA=U.S. Food and Drug Administration; PBH=post-bariatric hypoglycemia; QD=once daily; **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]. ENDO Annual Symposium.

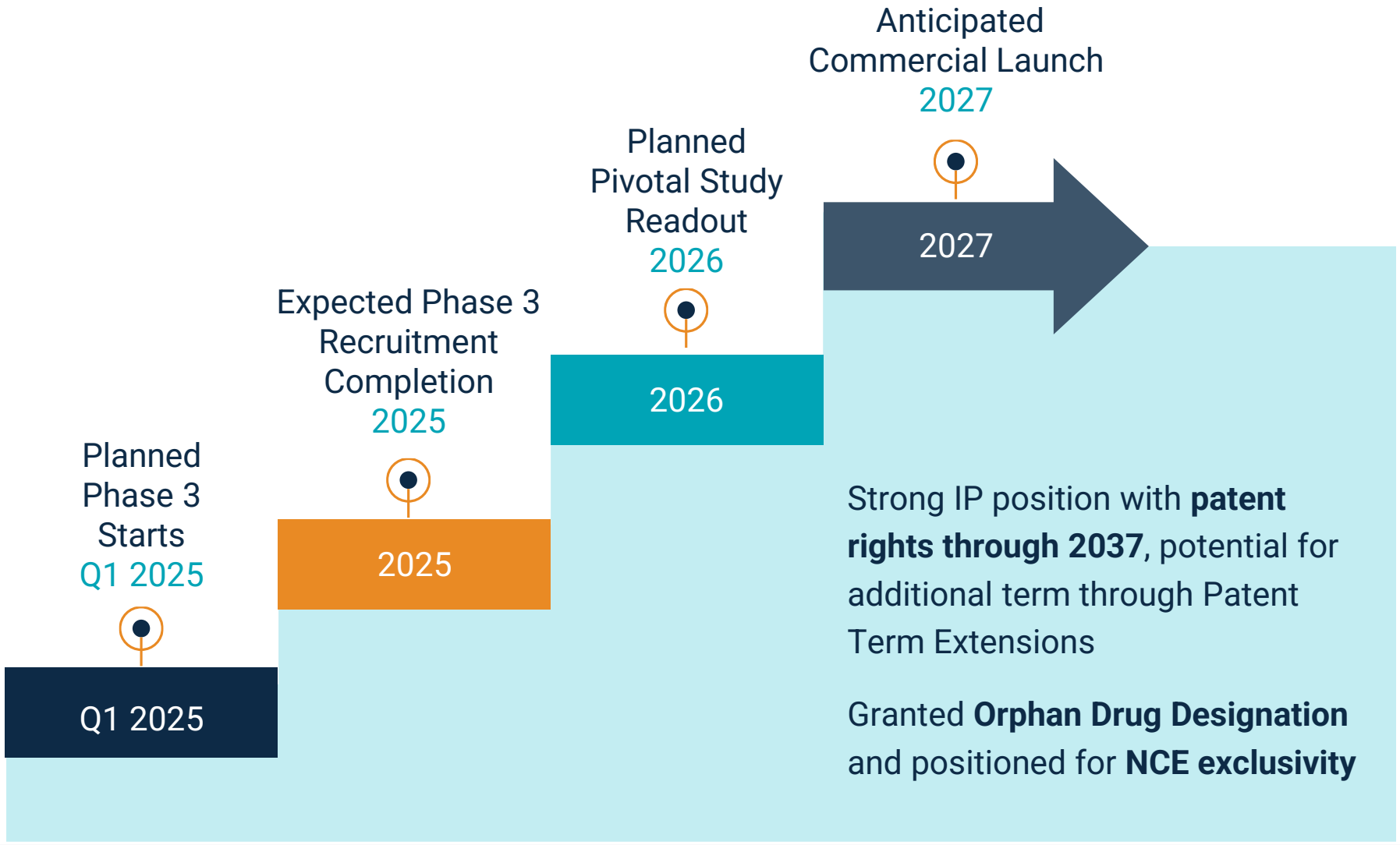
Avexitide was Generally Well-Tolerated with a Favorable Safety Profile Across Both Phase 2 Trials

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 • 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

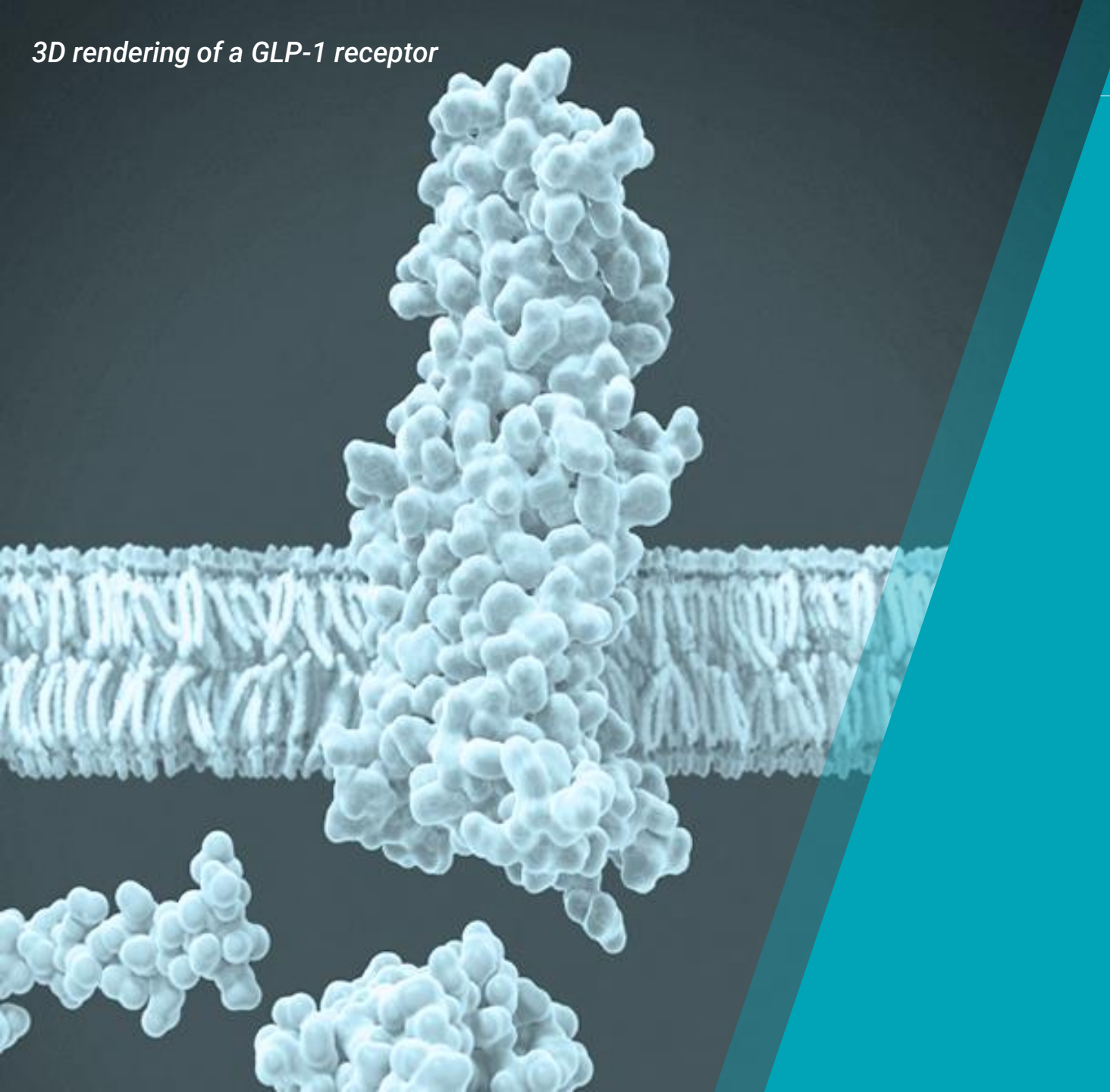
No clinically relevant increases were observed in fasting or peak postprandial plasma glucose levels (i.e., no hyperglycemia observed)

AE=adverse event; **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]. ENDO Annual Symposium.

Phase 3 to Begin Q1 2025, Readout in 2026



NCE=new chemical entities.



3D rendering of a GLP-1 receptor

AMYLYX

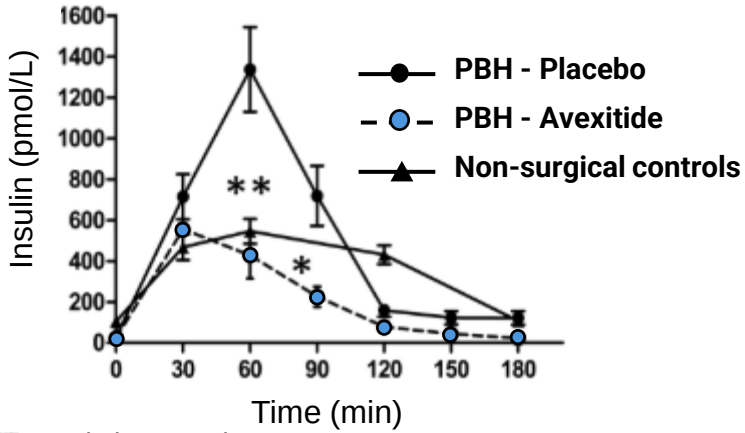
Additional Avexitide Clinical Data in PBH

Avexitide Significantly Decreased Post-Meal Insulin Levels

PHASE 1, SAD, MAD

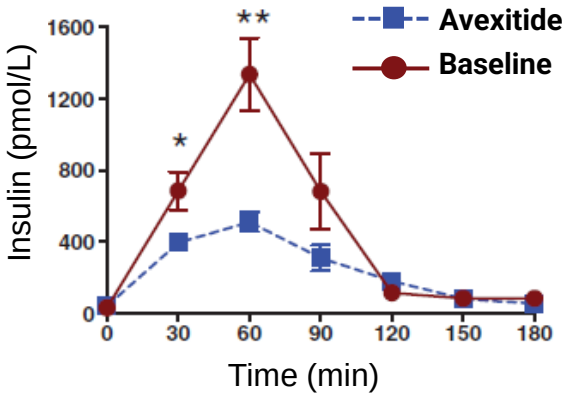
Phase 1, IV infusion[1]

Single Dose, N=8, OGTT



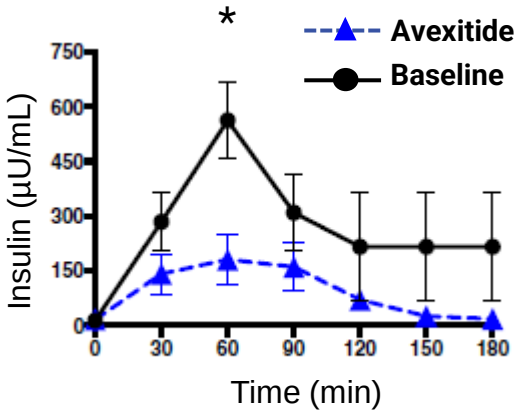
SAD, SC injection[2]

Single Dose, N=8, OGTT



MAD, SC injection[3]

BID Dosing, N=19, OGTT



Consistent and significant decrease in insulin levels across Phase 1, SAD, and MAD trials in people with PBH[1-3]

***p≤0.05, **p≤0.01**

OGTT = oral glucose tolerance test

PREVENT PHASE 2

PREVENT

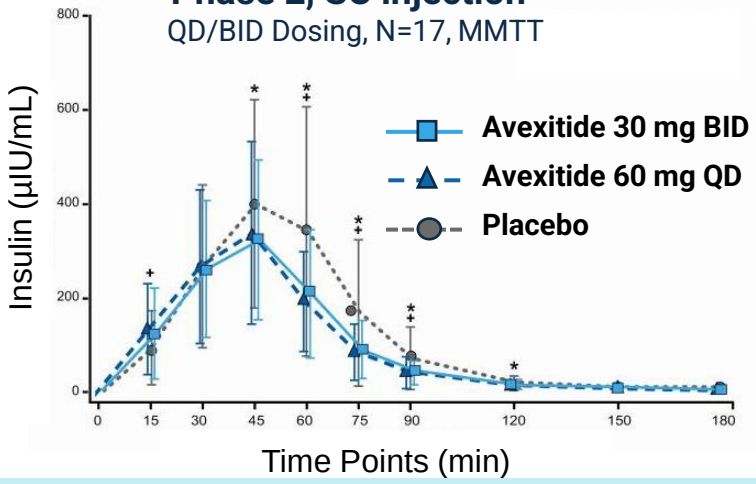
For PREVENT (vs placebo)

30 mg BID: *p<0.05

60 mg QD: +p<0.05

Phase 2, SC injection[4]

QD/BID Dosing, N=17, MMTT



Peak insulin was reduced by 23% (p=0.029) and 21% (p=0.042) following avexitide 30 mg BID and 60 mg QD, respectively, compared with placebo in the Phase 2 PREVENT trial in people with PBH[4]

MMTT = mixed meal tolerance test

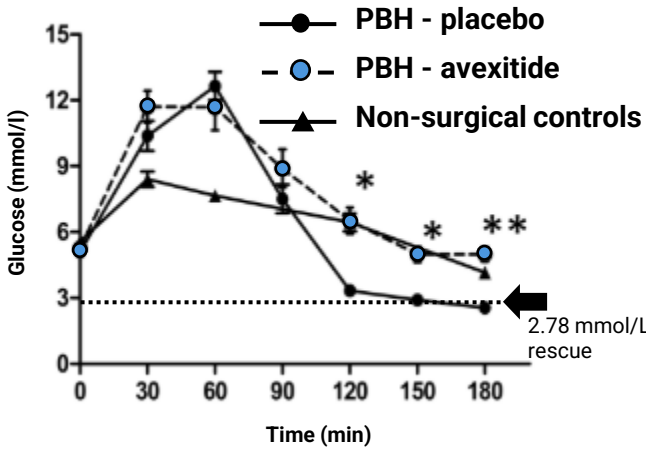
BID=twice daily; IV=intravenous; MAD=multiple ascending dose; PBH=post-bariatric hypoglycemia; QD=once daily; SAD=single ascending dose; SC=subcutaneous; **1.** Craig, C. M. et al. *Diabetologia*. 2017;60(3):531-540. doi:10.1007/s00125-016-4179-x; **2.** Craig, C. M. et al. *Diabetes, Obesity & Metabolism*. 2018;20:352–361. doi.org/10.1111/dom.13078; **3.** Tan, M. et al. *Diabetes, Obesity & Metabolism*. 2020;22(8):1406-1416. doi:10.1111/dom.14048; **4.** Craig, C. M. et al. *The Journal of Clinical Endocrinology & Metabolism*. 2021;106(8):e3235-e3248. doi:10.1210/clinem/dgab103.

Avexitide Significantly Stabilized Post-Meal Glucose Levels

PHASE 1, SAD, MAD

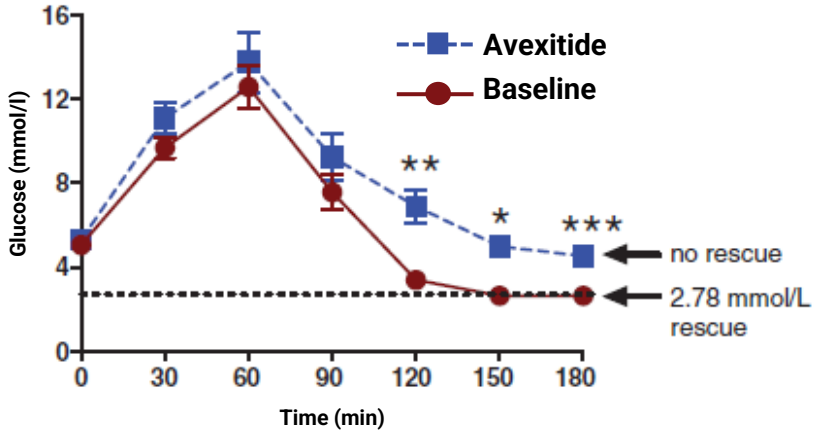
Phase 1, IV infusion[1]

Single Dose, N=8, OGTT



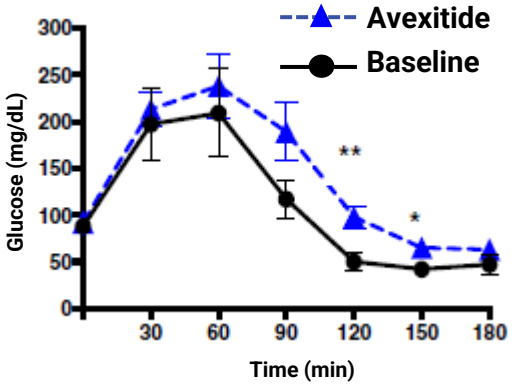
SAD, SC injection[2]

Single Dose, N=8, OGTT



MAD, SC injection[3]

BID Dosing, N=19, OGTT



Consistent and significant stabilization in plasma glucose nadir across Phase 1, SAD, and MAD trials in people with PBH[1-3]

OGTT = oral glucose tolerance test

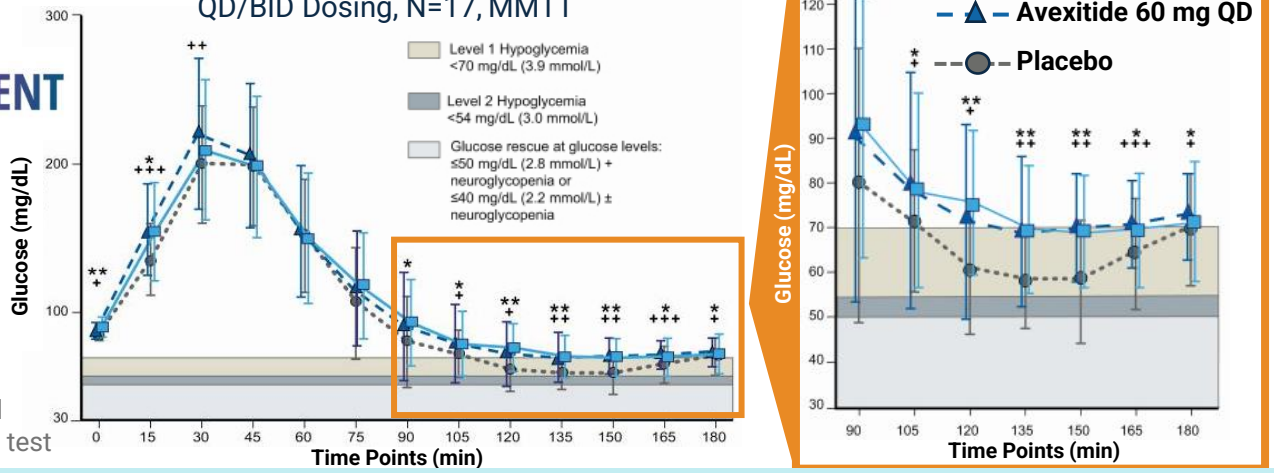
***p≤0.05, **p≤0.01, ***p≤0.001**

PREVENT PHASE 2

Phase 2, SC injection[4]

QD/BID Dosing, N=17, MMTT

PREVENT



MMTT = mixed meal tolerance test

Mean plasma glucose nadir (prespecified primary endpoint) increased by 21% (p=0.001) and 26% (p=0.0002) following avexitide 30 mg BID and 60 mg QD, respectively, compared with placebo in the Phase 2 PREVENT trial in people with PBH[4]

- Corresponded to 50% and 75% fewer participants requiring rescue, respectively

For PREVENT (vs placebo): **30 mg BID:** *p<0.05, **p<0.01, ***p<0.001
60 mg QD: +p<0.05, ++p<0.01, +++p<0.001

AMYLYX

BID=twice daily; IV=intravenous; MAD=multiple ascending dose; PBH=post-bariatric hypoglycemia; QD=once daily; SAD=single ascending dose; SC=subcutaneous; **1.** Craig, C. M. et al. Diabetologia. 2017;60(3):531-540. doi:10.1007/s00125-016-4179-x; **2.** Craig, C. M. et al. Diabetes, Obesity & Metabolism. 2018;20:352–361. doi.org/10.1111/dom.13078; **3.** Tan, M. et al. Diabetes, Obesity & Metabolism. 2020;22(8):1406-1416. doi:10.1111/dom.14048; **4.** Craig, C. M. et al. The Journal of Clinical Endocrinology & Metabolism. 2021;106(8):e3235-e3248. doi:10.1210/clinem/dgab103.

Patients Report Being Able to Feel Benefit in Structured Interviews

AVEXITIDE STUDY TEAM

Termeh Shamloo
Stanford University School of Medicine

Dalia Perelman, RD
Stanford University School of Medicine

Colleen Craig, MD
Eiger BioPharmaceuticals, Inc.

Tracey McLaughlin, MD, MS
Stanford University School of Medicine

STUDY PARTICIPANTS

"My husband noted I'm in a much better mood, and my nocturnal hypoglycemia was all gone."

"Experience was amazing…"

"I felt great and normal after a very long time - very happy."

"I'm back to practicing as a [professional] with full cognitive functioning."

"Feeling protected, mood is much better, the explosive behavior has been much better."

"Memory loss and recall improved."

"I feel like myself again after a very long time."

Stanford MEDICINE

EIGER BIOPHARMACEUTICALS

These are individual experiences and not necessarily representative of all clinical trial participants.

Image source: 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]. ENDO Annual Symposium.

AMX0035

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

AMX0035: Fixed-dose Combination of Sodium Phenylbutyrate and Taurursodiol Designed to Slow or Mitigate Neurodegeneration

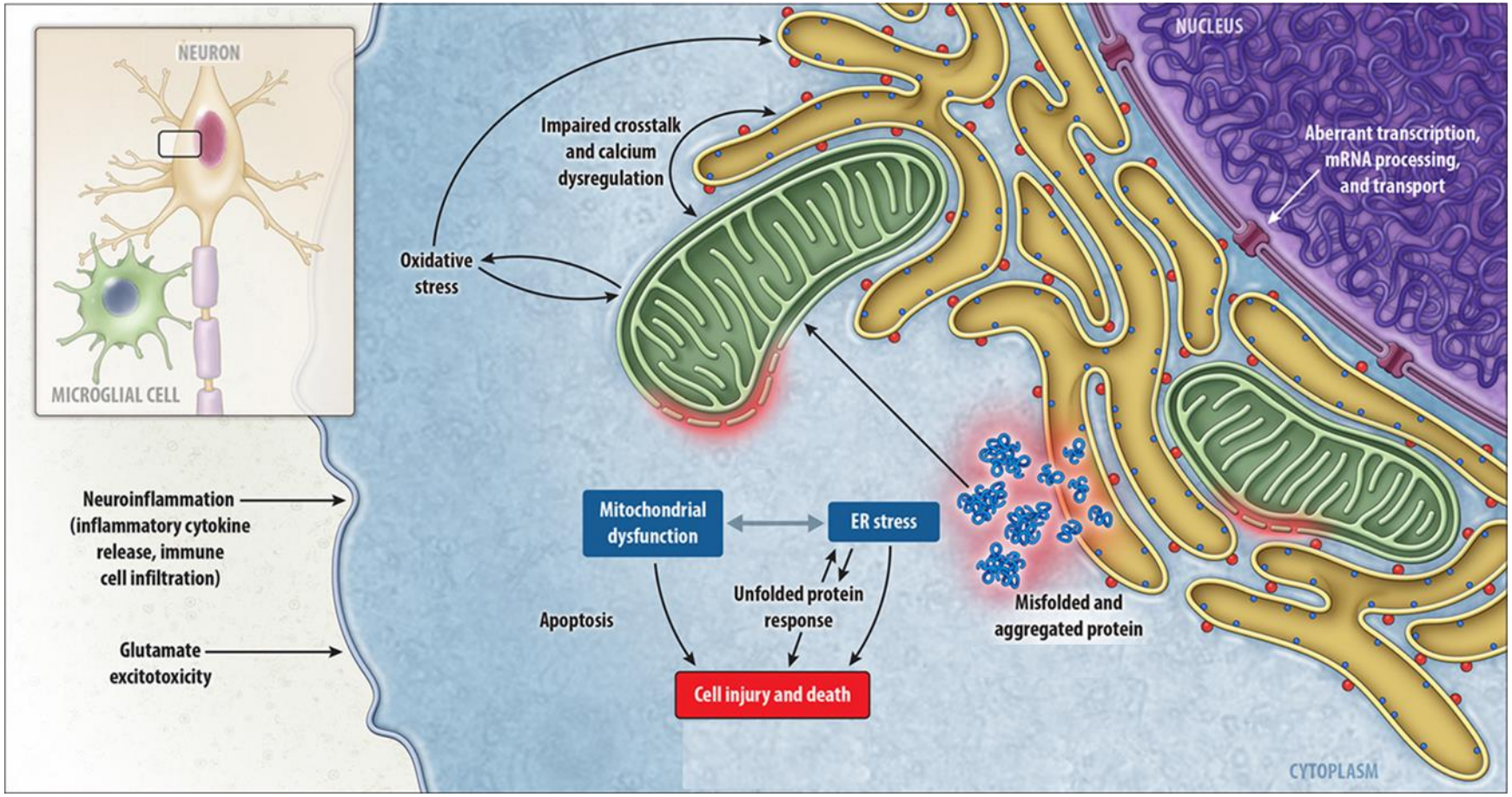
- AMX0035 is designed to mitigate neurodegeneration by targeting ER stress and mitochondrial dysfunction, two cellular processes central to neuronal cell death and neurodegeneration
- Proprietary combination of PB and TURSO allows for synergistic targeting of abnormal cell death to better prevent neurodegeneration than either agent alone
- Focused on diseases in which ER stress and mitochondrial dysfunction are known contributors, including Wolfram syndrome and PSP
  - > Positive Phase 2 HELIOS topline data showed improvement in pancreatic function following 24 weeks of treatment and sustained improvement over time
  - > Phase 2b/3 ORION trial in PSP underway

EXPECTED MILESTONES

2025	Mid-2025
Provide an update on a Phase 3 program in Wolfram syndrome	Data from interim analysis of Phase 2b/3 ORION trial in PSP

AMX0035 — Designed to Reduce Cell Death

- AMX0035: Dual unfolded protein response (UPR), mitochondrial apoptosis targeting
  - Reduces endoplasmic reticulum (ER) stress- associated death
  - Reduces mitochondrial-dysfunction-associated death



AMX0035 has broad applicability across neurodegenerative diseases

Zhou, W. J Biol Chem. 2011;286(17):14941-14951.; Rodrigues CM, Steer CJ. Expert Opin Investig Drugs. 2001;10(7):1243-1253.; Rodrigues, C. M., et al. Biochemistry. 2003;42(10):3070-3080.; Fels, J. A., et al. Ann Clin Transl Neurol. 2022. doi.org/10.1002/acn3.51648.

AMX0035 Targets ER Stress and Mitochondrial Dysfunction Simultaneously to Prevent or Slow Cell Death

AMX0035 Effect in Relevant Preclinical Models

- Glutamate excitotoxicity model showing favorable effects on neuronal survival[1]
- Models of primary mitochondrial disease showing restoration of mitochondrial functions[1]
- Protection against neuronal death in model of primary cortical neuron damage[2]

AMX0035 demonstrates synergistic* protection of cortical neurons against peroxide-mediated neuronal death in a range of ratios[2]

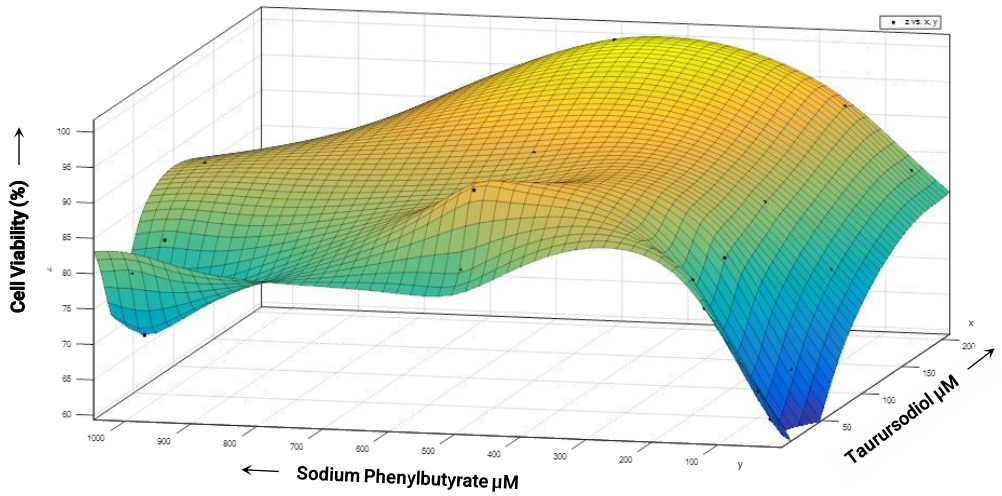


Figure from Cohen J, et al. Clinical trial design for a phase II, randomized, placebo-controlled trial of AMX0035 in amyotrophic lateral sclerosis (CENTAUR). Poster presented at: 28th International Symposium for ALS/MND; December 4–10, 2017; Boston, MA.

* Results for AMX0035 are synergistic relative to PB or TURSO alone.

PB=sodium phenylbutyrate; TURSO=taurursodiol; **1.** Data on File. Amylyx Pharmaceuticals. **2.** 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.

AMYLYX

Wolfram Syndrome Program

HELIOS

Raquel, living with Wolfram syndrome.

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

***WFS1* Gene Mutation**

Progressively impacts multiple organs and systems[1-5]

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

Gradual Loss of Vision Leading to Blindness
Optic nerve cell death

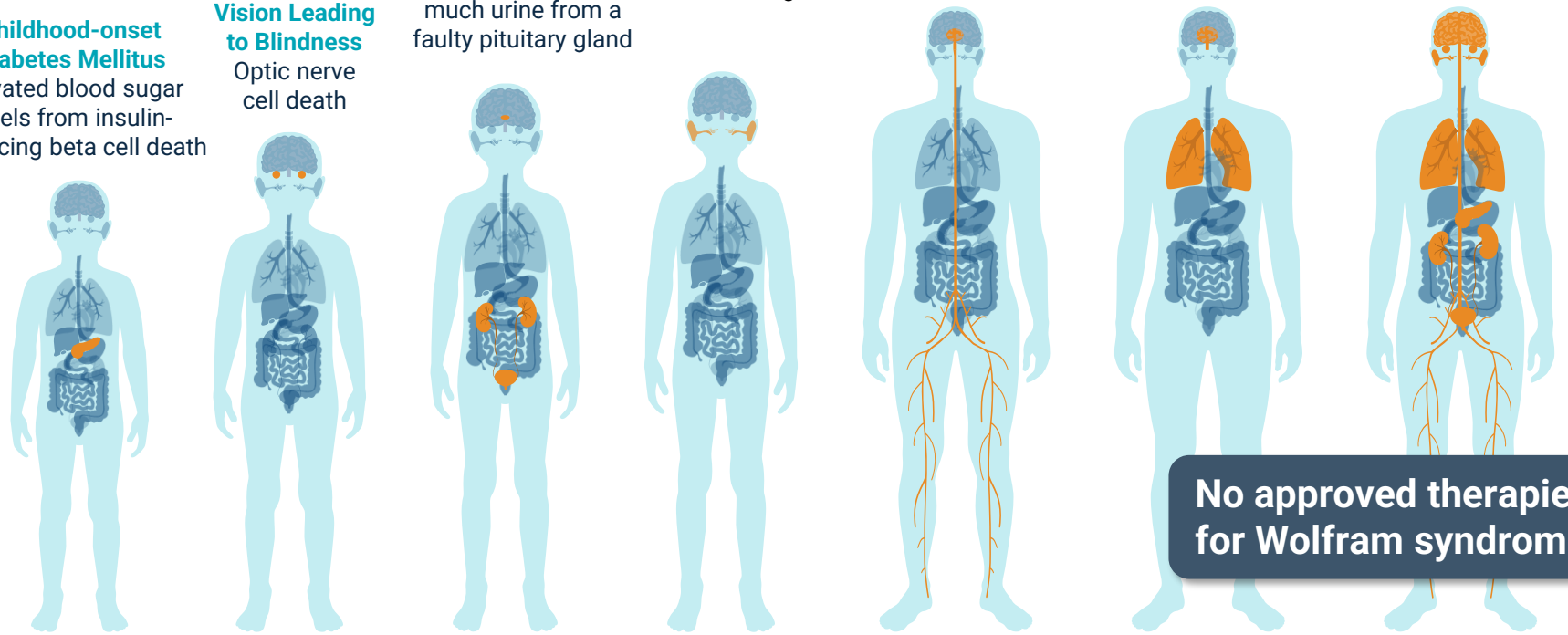
Diabetes Insipidus
Kidneys produce too much urine from a faulty pituitary gland

Hearing Loss
From cranial nerve damage

Balance and Coordination Difficulty
Ataxia from cerebellum damage

Difficulty Breathing
From brain stem damage

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



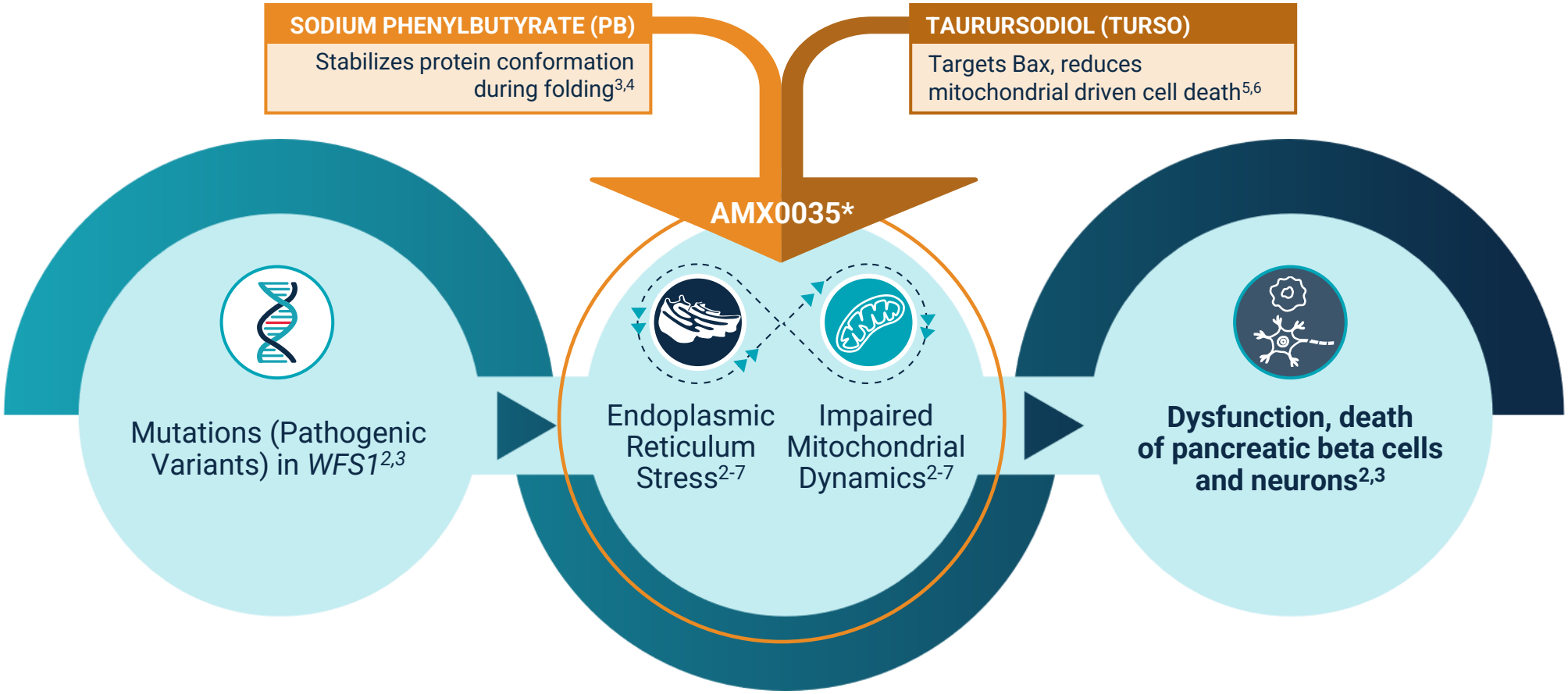
~3,000
people living with Wolfram syndrome in the U.S.[1,2]

No approved therapies for Wolfram syndrome[6]

1. Urano, F. *Diabetes*. 2014;63(3):844-846. **2.** Pallotta MT, et al. *J Transl Med*. 2019;17:238. **3.** Lee, E., et al. Front Genet. 2023;14:1198171. **4.** Leslie, M. *Science*. 2021;371(6530): 663-665. **5.** Matsunage et al. *Plos One*. 2014;9(9):106906. **6.** Urano, F. *Curr Diab Rep*. 2016;16(1):6.

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

AMX0035 targets endoplasmic reticulum 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

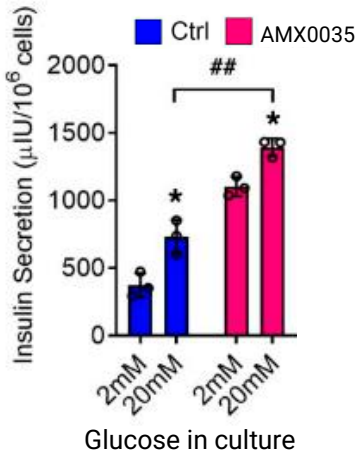
* Results for AMX0035 are synergistic relative to PB or TURSO alone. Supported by data on file with Amylyx & Cohen. J., et al. Clinical trial design for a phase II, randomized, placebo-controlled trial of AMX0035 in amyotrophic lateral sclerosis (CENTAUR). Poster presented at: 28th International Symposium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

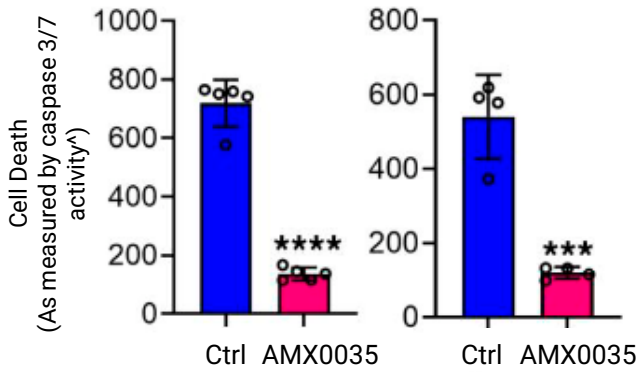
AMX0035 has been Extensively Studied in Wolfram Models including Patient-Derived Cells and Mouse Model

Effect of AMX0035 in Preclinical Studies[1]

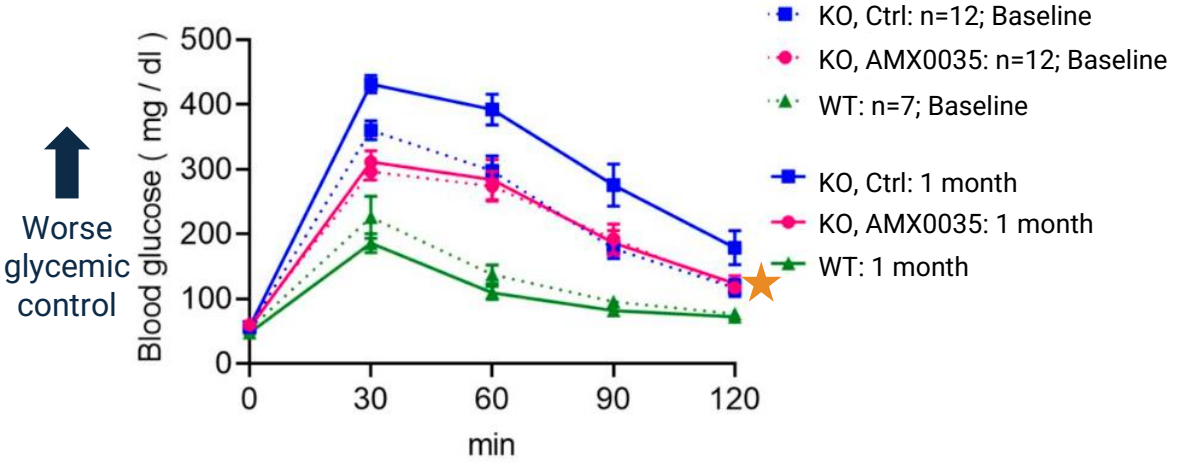
Improved WFS1 Mutant Insulin Secretion in Two Patient-Derived Cell Lines (P<0.05)



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

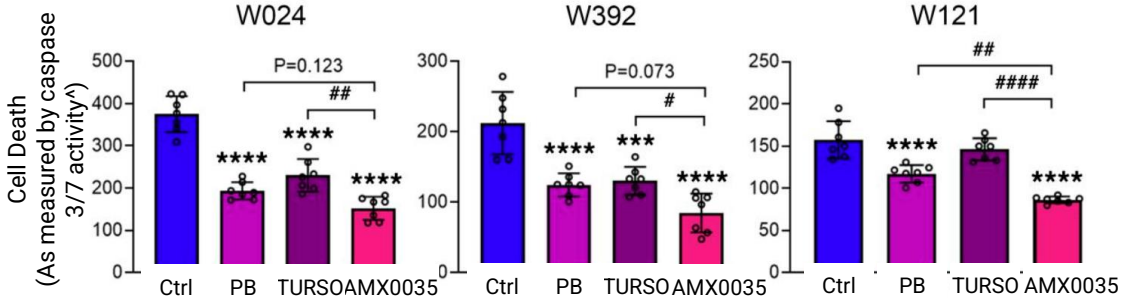


AMX0035-Treated Mice Showed Better Glycemic Control (P<0.001) than Untreated After 1 Month with Minimal to No Diabetes Progression Based on Glucose Tolerance Test (GTT)



*P<0.05 by unpaired *t* test compared with Ctrl; ***P<0.001 and ****P<0.0001 by unpaired *t* test compared with Ctrl; #P<0.05 and ##P<0.01 by 2-way unpaired *t* test; ^Normalized by cell viability

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

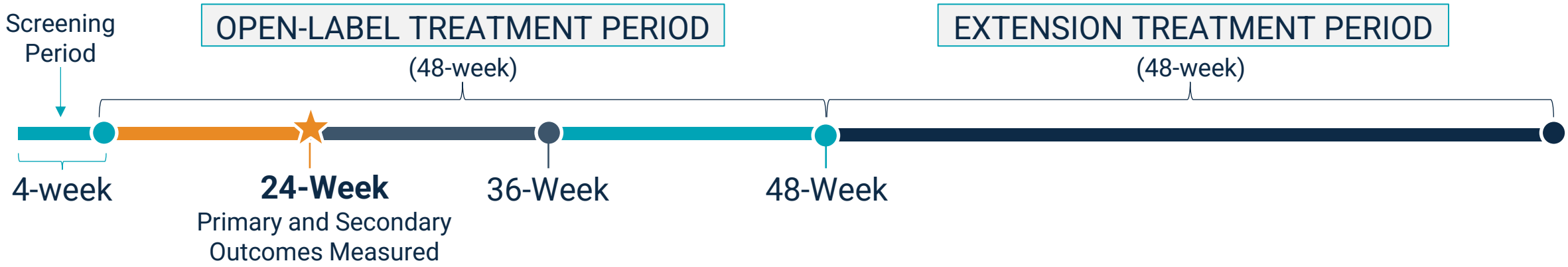


W024, W392, W121 indicate cell lines from specific patients; **PB**, sodium phenylbutyrate; **TURSO**, taurursodiol. ***P<0.001 and ****P<0.0001 by 1-way ANOVA compared with Ctrl; #P<0.05, ##P<0.01, and ###P<0.0001 by 1-way ANOVA; ^Normalized by cell viability

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

HELIOS Study Design[1,2]

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



PRIMARY OBJECTIVES:

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

KEY TRIAL ENTRY CRITERIA[1,2]

- Aged ≥17 years
- Definite diagnosis of Wolfram syndrome defined by documented pathogenic mutations in *WFS1* gene*
- Stimulated C-peptide level of ≥0.2 ng/mL at screening
- Insulin-dependent diabetes mellitus due to Wolfram syndrome
- No current GLP-1 agonist use

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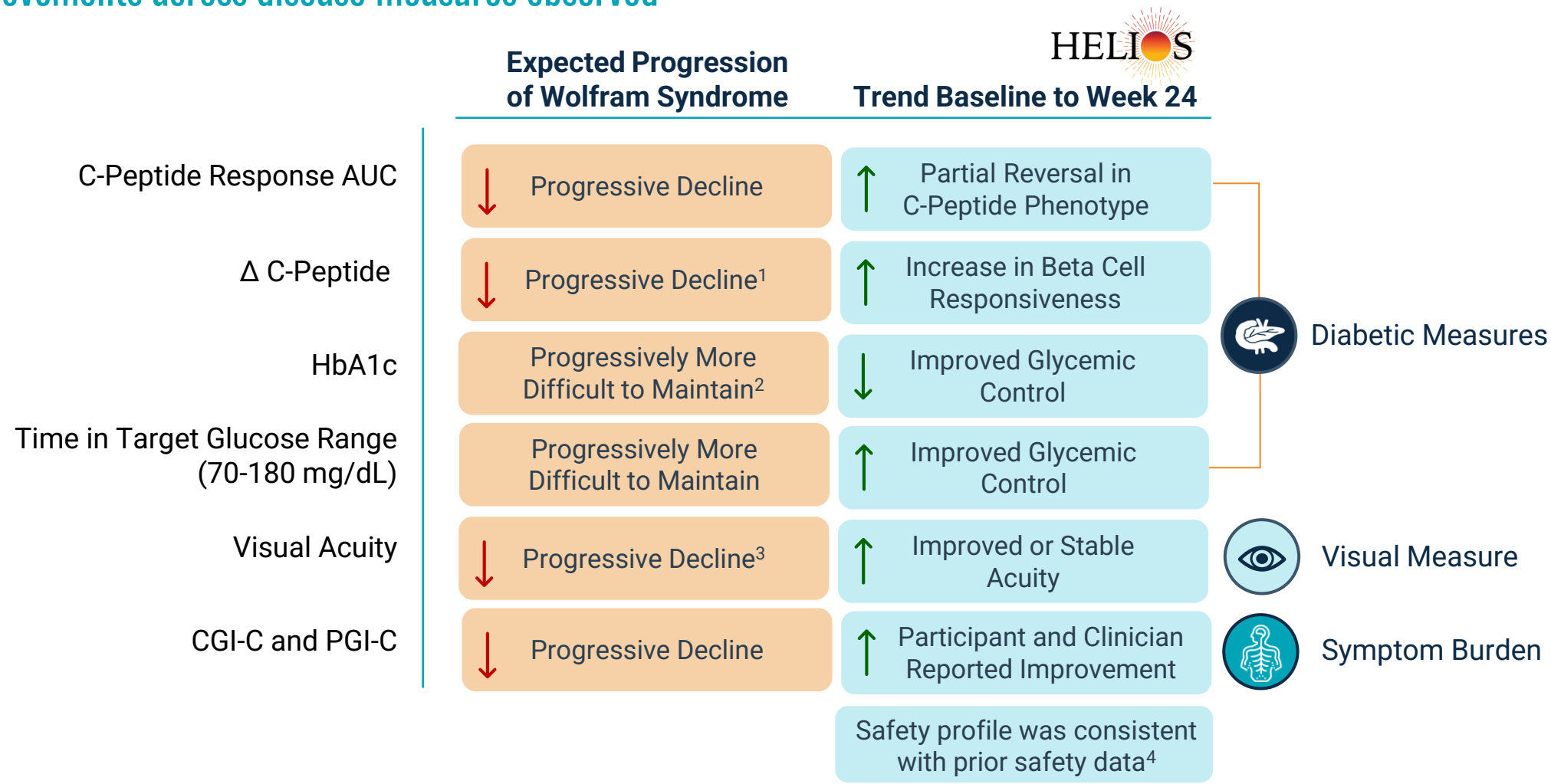
GLP-1=glucagon-like peptide-1; *Documented functionally relevant recessive mutations on both alleles of the *WFS1* gene based on historical test results (if available) or from a qualified laboratory at screening;
1. ClinicalTrials.gov identifier: NCT05676034. Updated November 21, 2023. Accessed April 9, 2024. https://www.clinicaltrials.gov/ct2/show/NCT05676034. **2.** Data on File. Amylyx Pharmaceuticals Inc. 2024.

Topline Data Suggest Potential Benefit of AMX0035 in Wolfram Syndrome

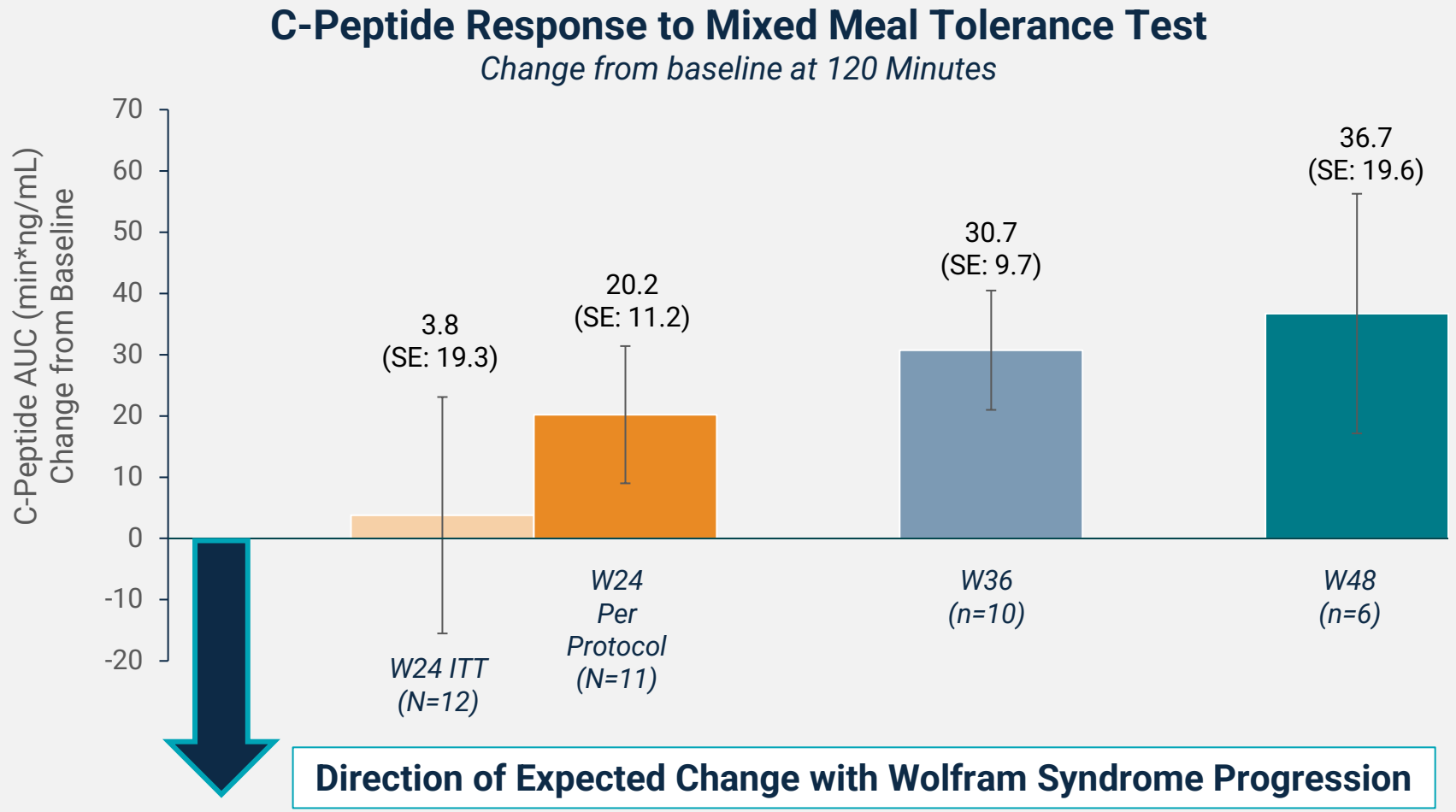
Improvements across disease measures observed



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.

Primary Endpoint: Improvement in C-Peptide Response Observed

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



Improvement in C-Peptide Response Observed Compared to Screening

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

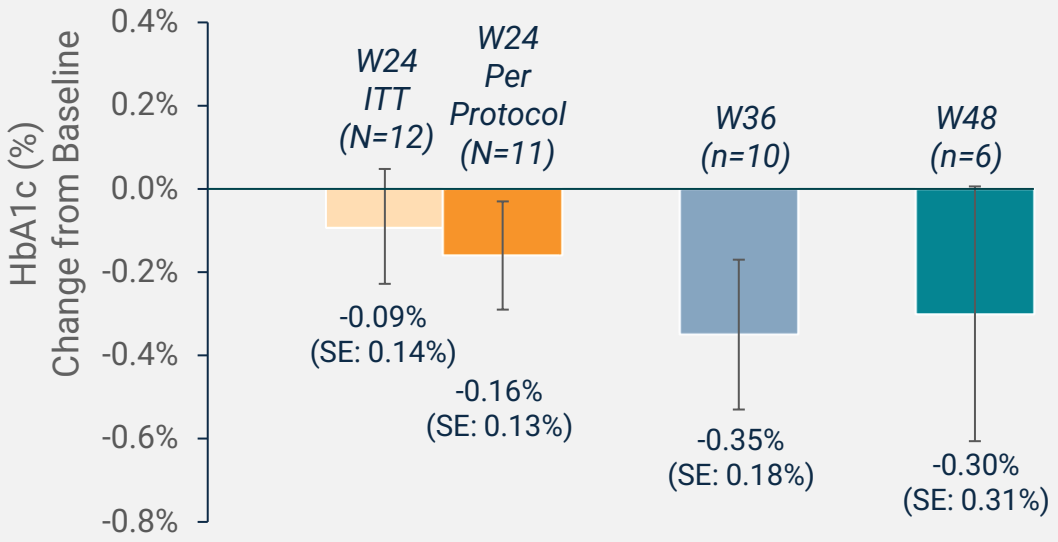
AMYLYX

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

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

Secondary Endpoint: Improved Glycemic Control

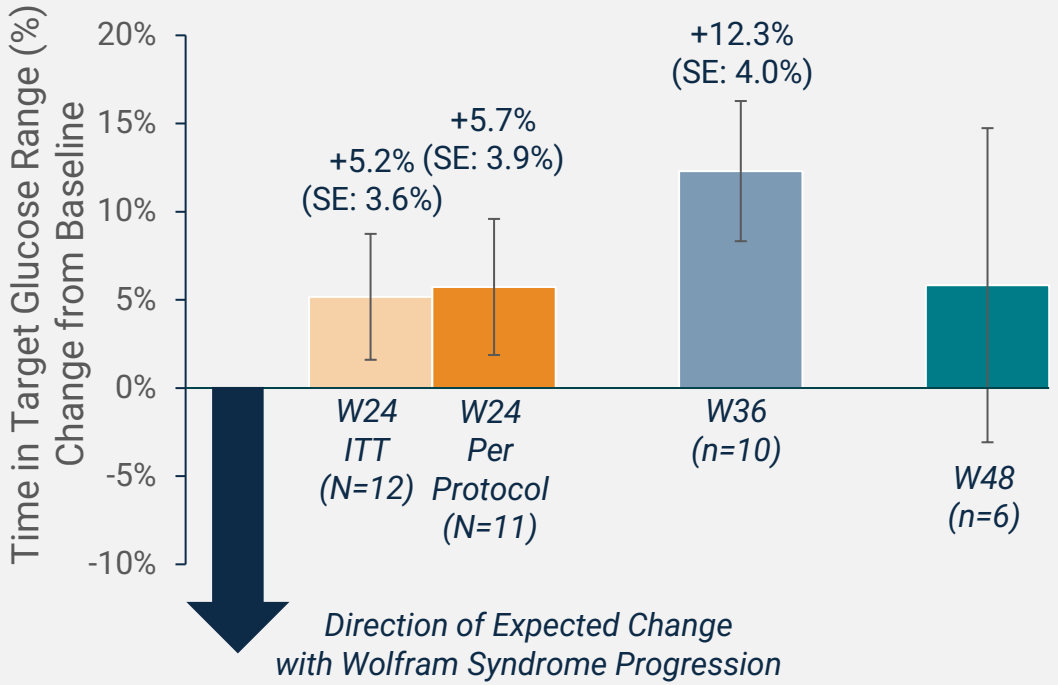
HbA1c Mean Change from Baseline



Improved Glycemic Control
as Measured by HbA1c Compared to Screening

Lower HbA1c is associated with improved metabolic function

Mean Time in Target* Glucose Range Change from Baseline



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

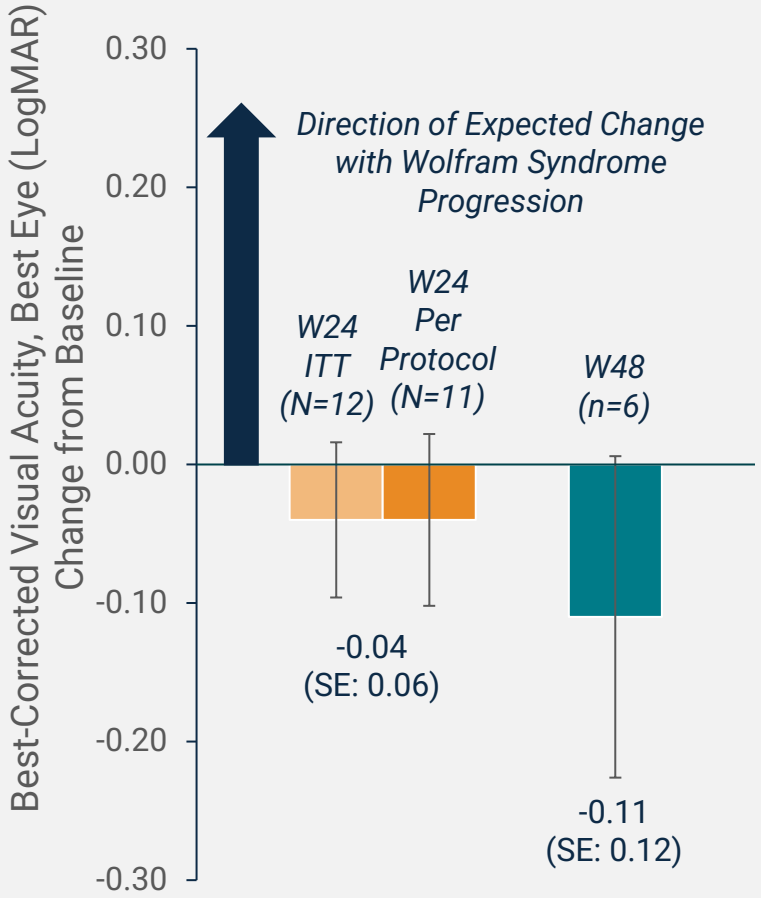
AMYLYX

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

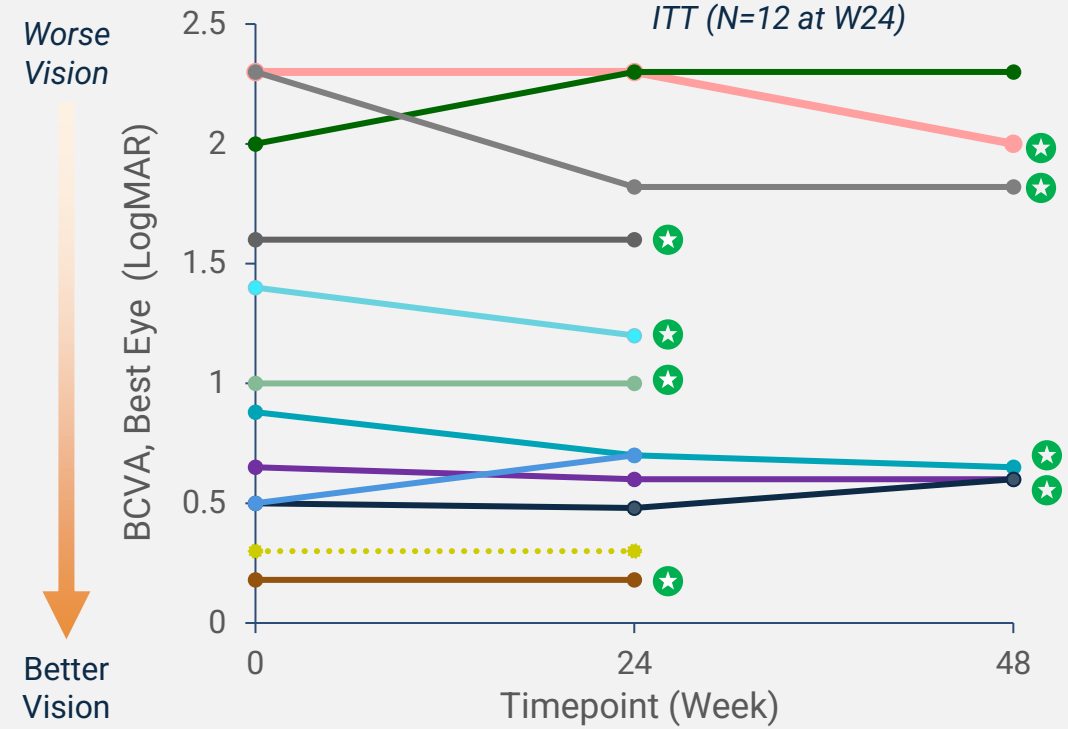
*Time in target was measured by continuous glucose monitoring (CGM). Good range defined as glucose recording between 70 and 180 mg/dL.

Secondary Endpoint: Trends Indicating Potential Visual Acuity Improvement or Stabilization

BCVA, Best Eye Mean Change from Baseline



Best Corrected Visual Acuity (BCVA), Best Eye by Participant



8 of 11 in Per Protocol demonstrated improved or stable visual acuity in their best eye from Screening to latest available timepoint

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

Of remaining participants:

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

Trends Indicating Potential Visual Acuity Improvement or Stabilization Compared to Screening

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

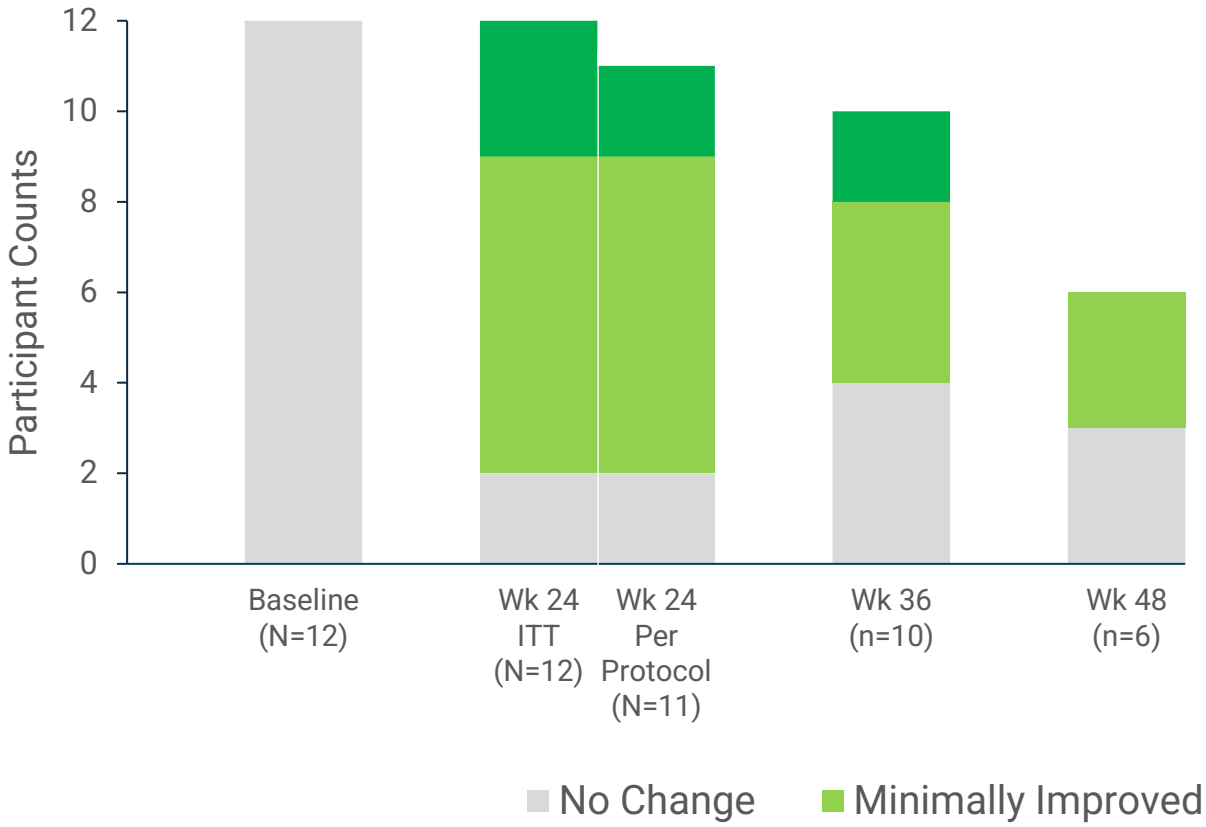
ITT: Intent to Treat; SE: Standard Error
Dotted line in By Participant graph indicates participant not included in the Per Protocol population.
Data on File. Amylyx Pharmaceuticals Inc. 2024.

Exploratory Endpoint: PGI-C and CGI-C

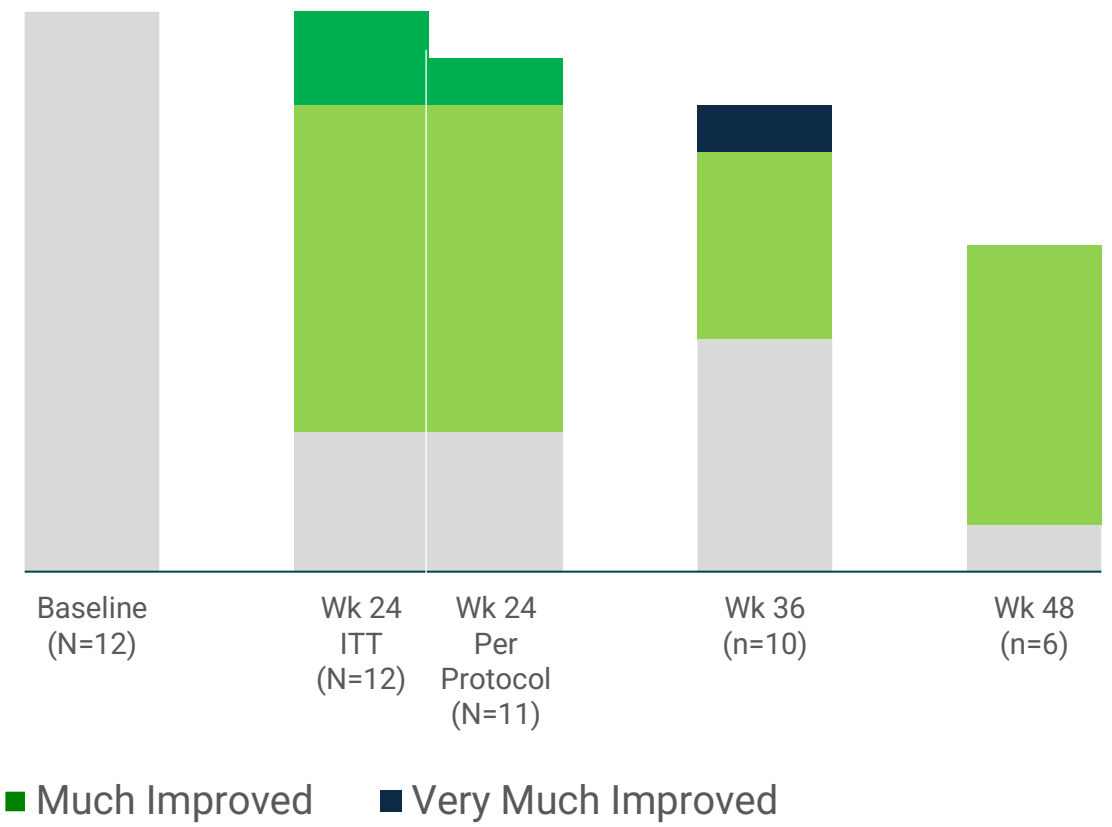
100% of Participants Met Responder* Criteria by Self and Clinician Assessment

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

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



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



No Change Minimally Improved Much Improved Very Much Improved

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

AMX0035 Safety and Tolerability in HELIOS

- AMX0035 was **generally well tolerated**
  - Diarrhea was the most common TEAE (50.0%); all cases were of mild severity
  - All TEAEs were graded mild or moderate
- **No new safety signals** were identified
- Nearly all participants reported ≥1 TEAE during the trial
  - Most did not lead to modification or interruption of AMX0035 dosing and **none led to drug discontinuation**

Summary of Treatment Emergent Adverse Events (TEAEs)

	AMX0035 (N=12)*
Participants with ≥1 TEAE— n (%)	11 (91.7%)
TEAE related to study drug** – n (%)	9 (75.0%)
Serious adverse events – n (%)	0 (0%)
Drug interrupted owing to TEAE — n (%)	3 (25.0%)
Dose reduced owing to TEAE — n (%)	3 (25.0%)
Drug discontinued owing to TEAE — n (%)	0 (0%)

*All available safety data as of July 31, 2024 included
**Includes those with TEAEs considered possibly related to treatment; none considered “probably related” or “definitely related”

AMX0035 Wolfram Syndrome Program Next Steps

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

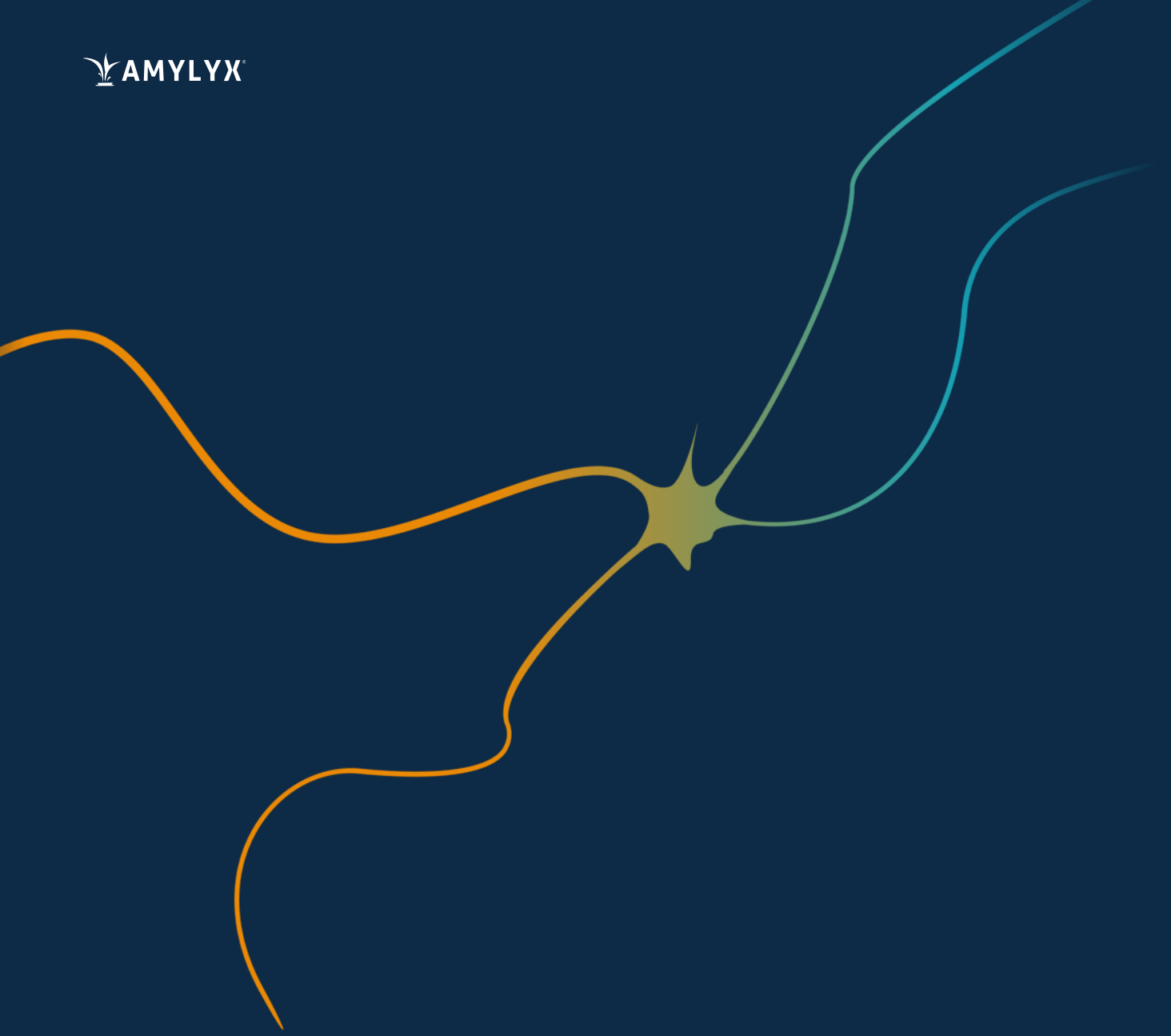
HELIOS

Raquel, living with Wolfram syndrome.

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

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

AMYLYX

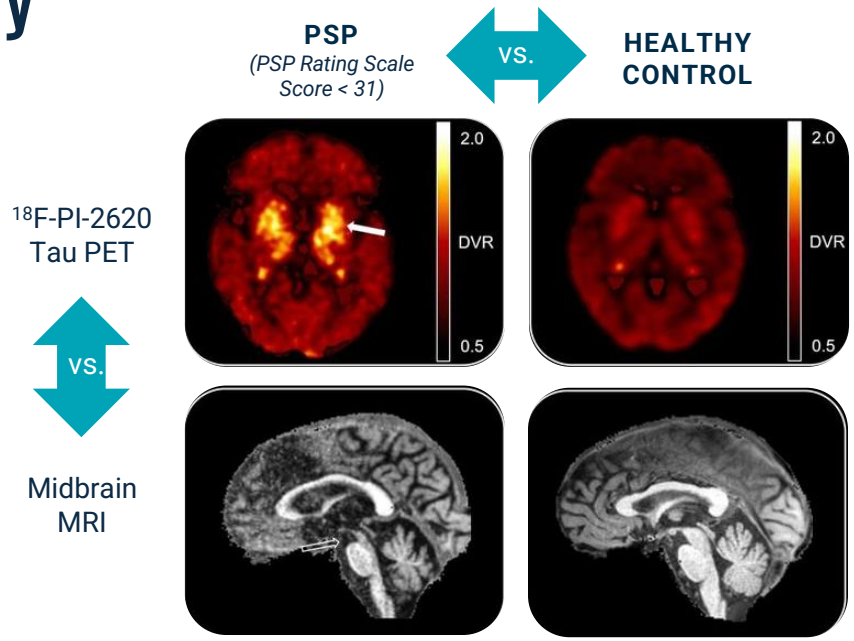


Progressive Supranuclear Palsy (PSP) Program

ORION

PSP is a Rare, Progressive, and Fatal Tauopathy

- PSP is 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
- Alterations to the structure of tau drive neurodegeneration
- Similar to other neurodegenerative diseases, pathophysiologic changes underlying PSP are likely multifactorial, including genetic mutations, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and neuroinflammation
- 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 onset[3-6]

ESTIMATED PREVALENCE:

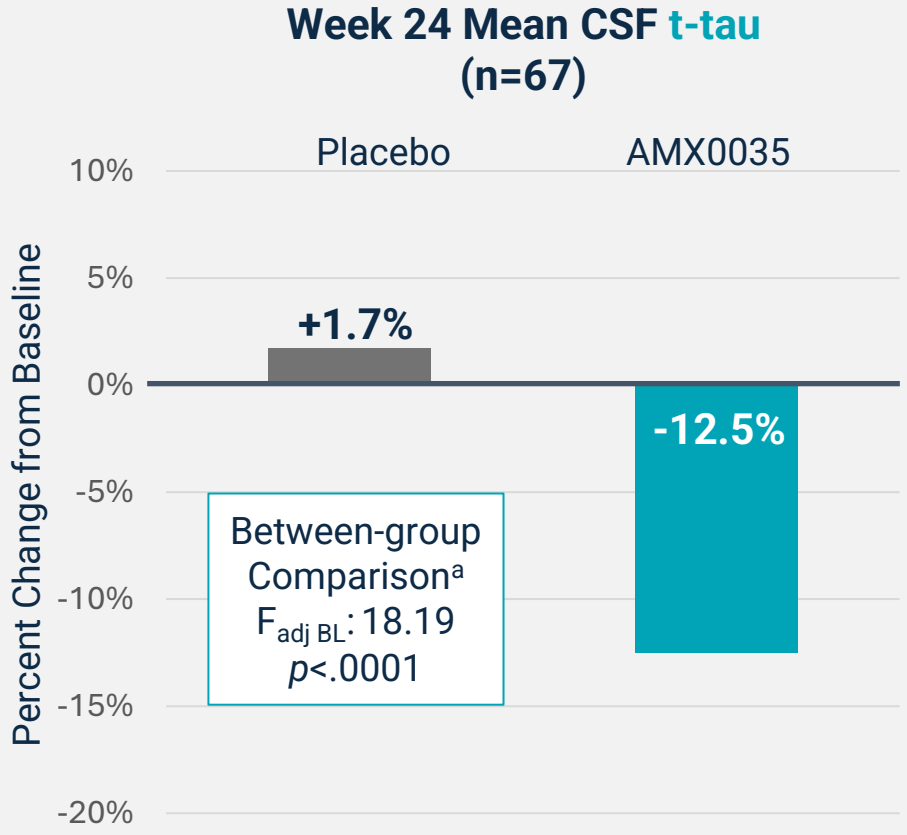
7 in 100,000 worldwide[1,2]

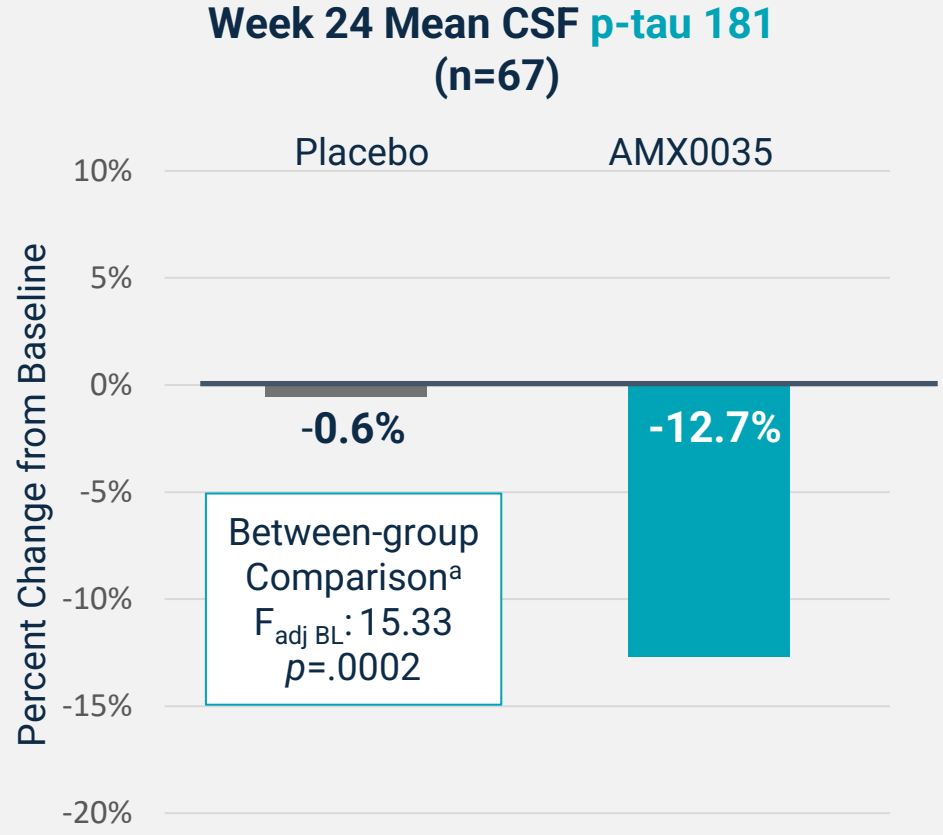
U.S. PREVALENCE:

Approximately 23,000

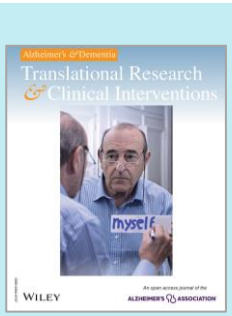
MRI=magnetic resonance imaging; PET=positron emission tomography; PSP=progressive supranuclear palsy; **1.** Swallow, D. M. A., et al. *Mov Disord Clin Pract*. 2022 Jun 28;9(5):604-613. doi: 10.1002/mdc3.13489. **2.** Lyons, S., et al. *J Neurol*. 2023; June 8. epub ahead of print. **3.** Stamelou, M., et al. *Nat Rev Neurol*. 2021;17(10):601-620. **4.** Viscidi, E., et al. *Front Neurol*. 2021;12:571800. **5.** Golbe and Ohman-Strickland. *Brain*. 2007;130(6):1552-65. **6.** Swallow and Counsell. *J Neurol*. 2023;270(7):3464-3474

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





t-Tau = total tau
p-Tau181 = phosphorylated tau at site threonine 181
[a]From a linear regression model with Week-24 biomarker level as the response variable and treatment group and baseline biomarker levels as explanatory variables.



Arnold SE, Hendrix S,Nicodemus-Johnson J, et al. Biological effects of sodiumphenylbutyrate and taurursodiol in Alzheimer's disease. *Alzheimer's Dement.* 2024;10:e12487.https://doi.org/10.1002/trc2.12487;
AMX0035 a met the primary endpoint of safety and tolerability in the PEGASUS trial of AMX0035 for the treatment of Alzheimer's disease. The 6-month trial was not powered to evaluate differences between groups in efficacy outcomes and no differences were seen in the primary efficacy outcome, a newly developed composite outcome of cognitive, functional, and imaging measures, or secondary efficacy outcomes of cognition, function, and imaging.

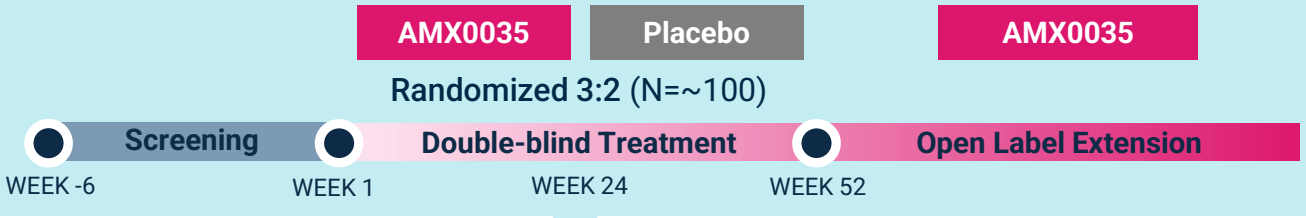
★ Interim analysis expected in mid-2025

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

ORION

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

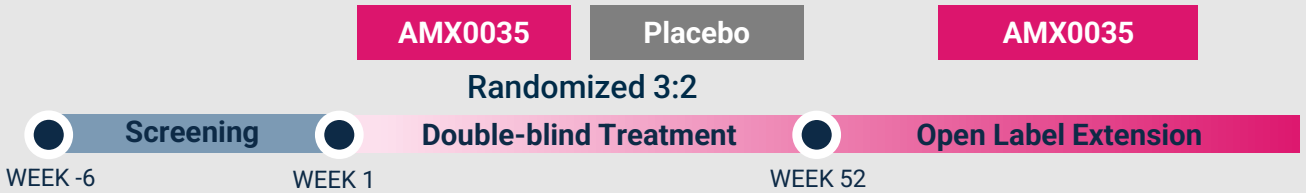
PHASE 2B STUDY PORTION DESIGN



Interim Analysis expected in mid-2025

Proceed to Phase 3 if Data are Strong

PHASE 3 STUDY PORTION DESIGN



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 assistance[3]
- 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

AMYLYX

*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 **1.** Gradually progressive disorder, with age at disease onset ≥ 40 years **2.** 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. **3.** Ability to walk 5 steps with minimal assistance (stabilization of one arm).

In memory of Eric, a husband and father, who was a courageous skydiver and Army veteran.

AMX0114 Program

- Potent antisense oligonucleotide (ASO) targeting calpain-2

AMX0114: Antisense Oligonucleotide (ASO) Targeting CAPN2 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
- 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

EXPECTED MILESTONES

By End of 2024 or Q1 2025	2025
Initiate Phase 1 LUMINA trial of AMX0114 in people living with ALS	Early cohort data for the Phase 1 LUMINA trial expected

AMX0114 was developed in-house as part of our larger R&D strategy to discover and develop novel therapies

ALS=amyotrophic lateral sclerosis; **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.

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

Evidence for Targeting Calpain-2 in ALS[4-7]

Calpain-2 levels are elevated in people with ALS

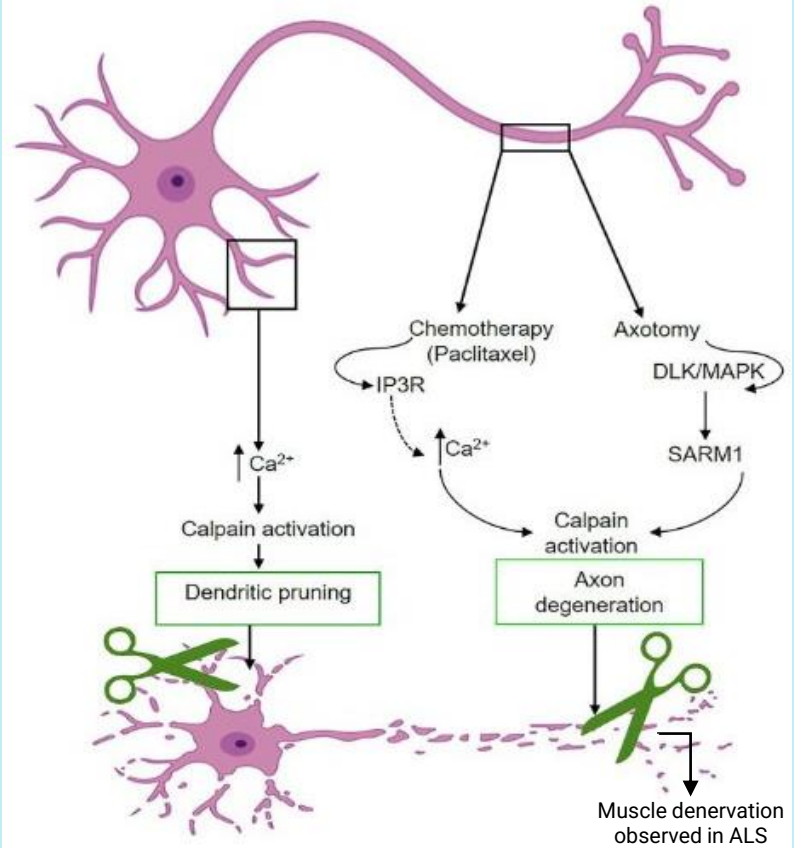
Inhibition of calpain-2 has shown benefit in ALS mouse model

Calpain-2 substrates include neurofilament and TDP-43

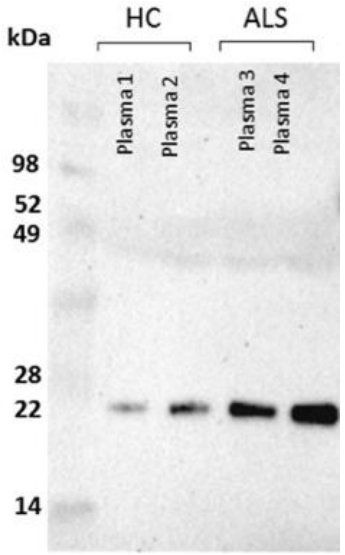
AMX0114 has shown efficacy in pre-clinical ALS models

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

Mechanisms of Axonal Degeneration[8]



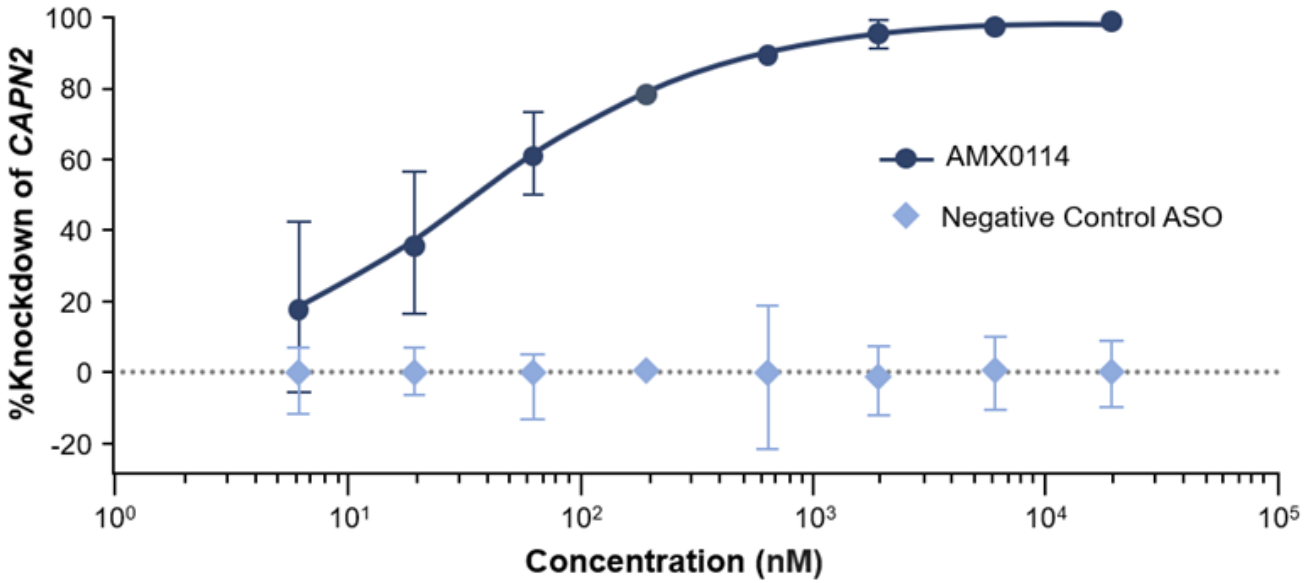
Full Length Neurofilament (68 kDa) is not observed in ALS or Healthy Control



ALS=amyotrophic lateral sclerosis; **1.** Fischer LR, Glass JD. Neurodegenerative Dis 2007;4:431–442. **2.** Ono Y, Saido TC, Sorimachi H. Nat Rev Drug Discov. 2016;15(12):854-876. **3.** Ma M. Neurobiol Dis. 2013;60:61-79. **4.** Ueyama H et al. J Neurol Sci. 1998;155(2):163-169. **5.** Yamashita T et al. Nat Commun. 2012;3:1307. **6.** Rao MV, et al. J Neurochem. 2016;137(2):253-65. **7.** Ma M, et al. Neurobiol Dis. 2013;56:34-46. **8**. 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

AMX0114 Achieves Potent, Dose-Dependent, and Durable Knockdown of *CAPN2* mRNA and Calpain-2 Protein

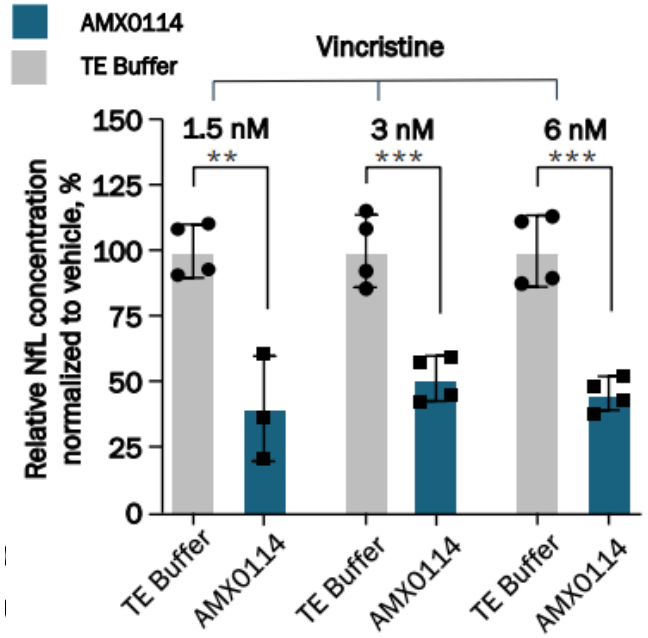
Demonstrated across multiple disease-relevant cell types and preclinical models of axonal degeneration



- mRNA reduction >90% at a concentration of 20x10^3 nM (20 µM) in human motor neurons
- Potency (half-maximal effective concentration or EC_{50}) ≈ 40-100 nM

ASO=antistreptolysin O.

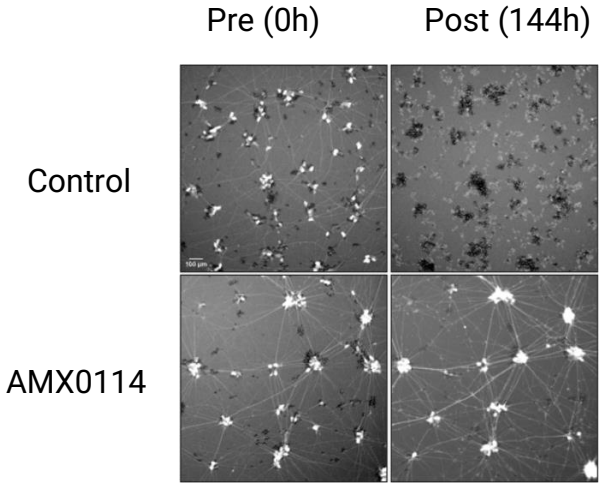
AMX0114 Reduces Extracellular NfL Levels in Multiple Models of Trigger-Induced Injury Neuronal Injuect and Improves Survival in Relevant Models



Similar NfL Reduction in Rotenone and Colchicine models

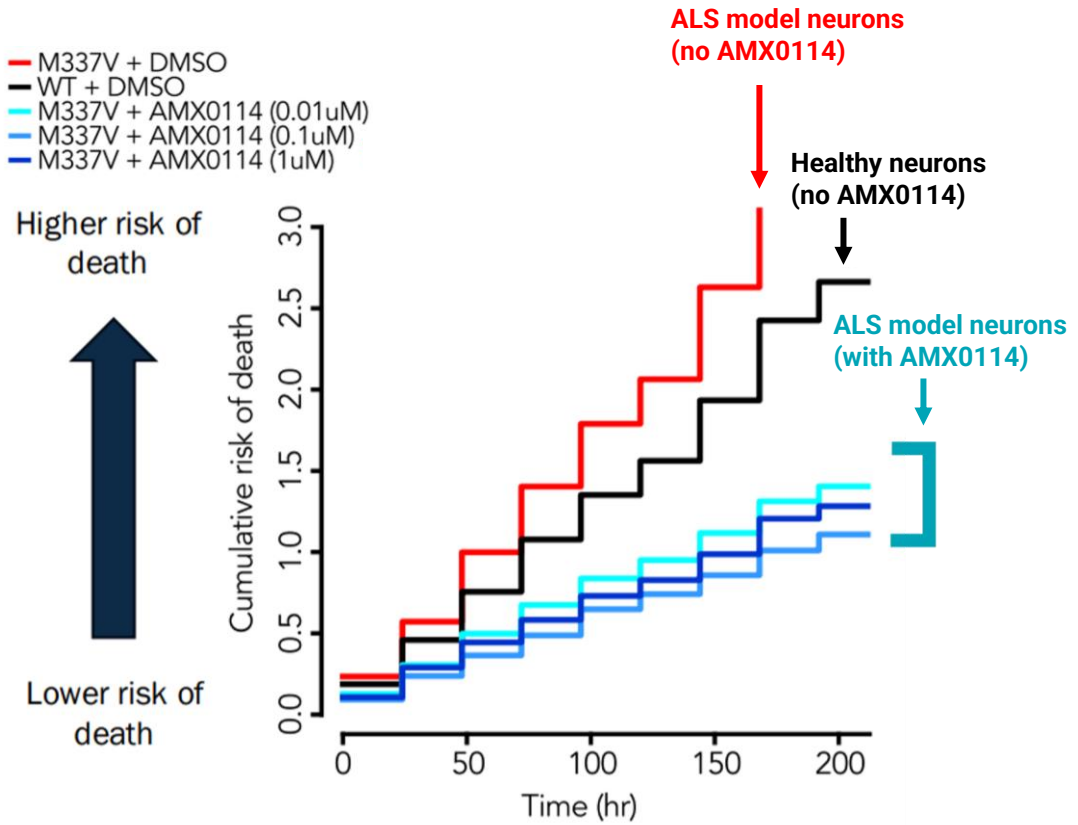
NS = $P>.05$.
* = $P<.05$.
** = $P<.01$,
*** = $P<.001$,
**** = $P<.0001$.
NfL, neurofilament light chain; NS, not significant; TE, tris ethylenediaminetetraacetic acid.

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



Presented at ALS ONE

TDP-43 ALS Model

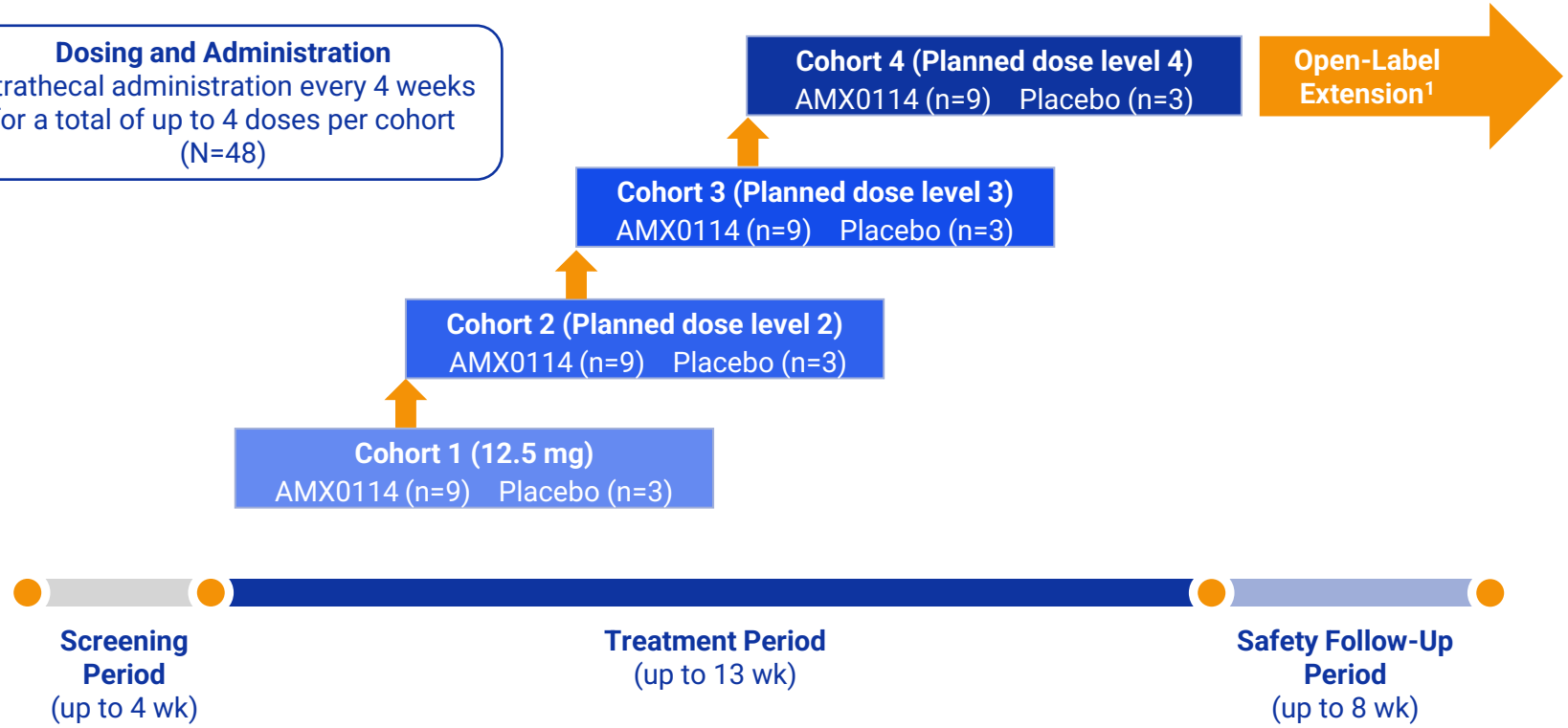


LUMINA: Phase 1 Clinical Trial of AMX0114 in ALS

Plan to initiate LUMINA in Canada by end of 2024 or in early 2025; early cohort data expected in 2025

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

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



Key Eligibility Criteria

- Aged ≥18 years
- Diagnosis of clinically definite or clinically probable ALS, based on El Escorial criteria
- Time since onset of first symptom of ALS <24 months
- Slow vital capacity (SVC) > 75%
- Stable dose of ALS approved treatments for at least 30 days prior to baseline visit

Primary Endpoint

- Safety and tolerability

Secondary Endpoints

- PK concentrations

Additional Endpoints

- Change from baseline of plasma and CSF pharmacodynamic measures of ALS and markers of target engagement (e.g., calpain-2 levels, NfL, SBDP-145)
- Change from baseline of ALS Functional Rating Scale – Revised (ALSFRS-R) and slow vital capacity (SVC)

ALS=amyotrophic lateral sclerosis; NfL=neurofilament light chain; 1. The open-label extension may be implemented if safety and efficacy data support a positive benefit-risk profile.

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

AVEXITIDE	AMX0035	AMX0114
>150 granted patents and over 30 pending applications worldwide*	>70 granted patents and over 60 pending applications worldwide	Pending composition of matter patent provides potential patent term through 2043 if granted
• Granted US patent rights through 2037** • Positioned for NCE exclusivity • Granted Orphan Drug Designation for the treatment of hyperinsulinemic hypoglycemia	• Granted US patent rights through 2040 • Granted Orphan Drug Designation for the treatment of Wolfram syndrome	• Positioned for NCE exclusivity

** Includes in-licensed patents*
*** Additional patent term potentially available through patent term extension*

FISH & RICHARDSON

Expected Cash Runway into 2026

$234.4M in cash, cash equivalents, and short-term investments as of 9/30/24

Team

Experienced Executive Team to Oversee Clinical Development and Execution

Joshua Cohen, BSE

Co-CEO and Director

Co-Founded Amylyx, Co-CEO since 2013, led preclinical, clinical and commercial development of Relyvrio as well as IPO and ~$1B in financing

Justin Klee, ScB

Co-CEO and Director

Co-Founded Amylyx, Co-CEO since 2013, led preclinical, clinical and commercial development of Relyvrio as well as IPO and ~$1B in financing

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

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®