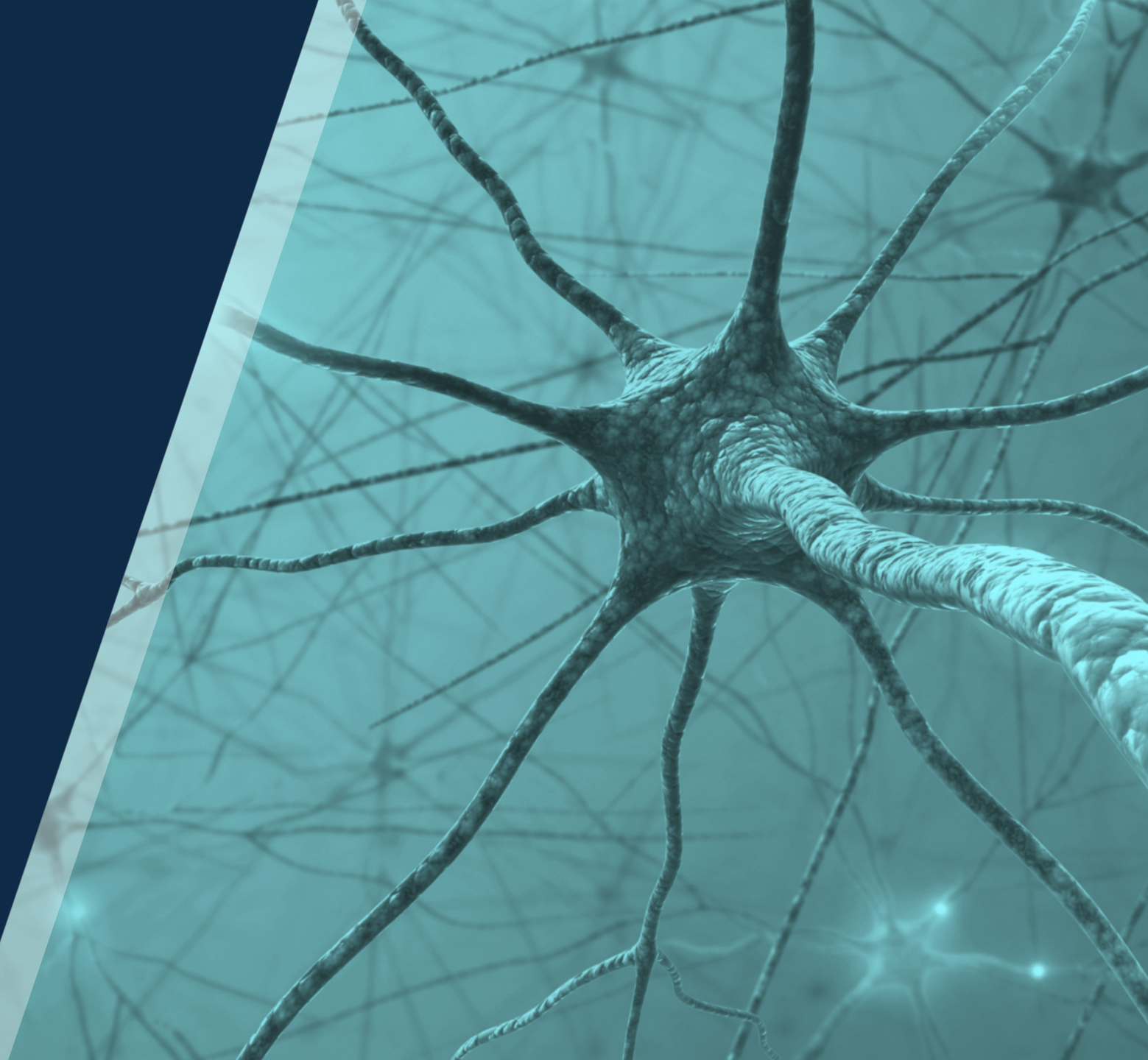
AMYLYX®

Investor Presentation

April 2024



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Committed to Developing Treatments for Neurodegenerative Diseases

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

Novel Neurodegenerative Disease Pipeline Supported by Strong Science

Endoplasmic Reticulum (ER) Stress

Impaired Mitochondrial Dynamics

- **Lead asset AMX0035** shown to target two key neurodegenerative disease pathways by mitigating ER stress and mitochondrial dysfunction, reducing neuronal cell death
- Also reduces markers associated with neurodegenerative diseases

Elevated Calpain-2 Protein Levels

- **AMX0114** shown to target calpain-2, an essential protein in the process of axonal degeneration and linked to neurofilament

Focus on Neurodegenerative Diseases with High Unmet Need

Wolfram Syndrome

- AMX0035 is being studied in Phase 2 HELIOS study in Wolfram syndrome
- Interim analysis demonstrated that AMX0035 had a clinically meaningful effect on key outcomes measuring the progression of diabetes, visual decline, and overall disease burden

Progressive Supranuclear Palsy

- AMX0035 is being studied in Phase 3 ORION study in progressive supranuclear palsy (PSP)
- Biomarker data from Phase 2 PEGASUS trial of AMX0035 in Alzheimer's disease demonstrated a significant reduction in tau, a critical protein implicated in the pathology of PSP

No disease modifying therapies approved for Wolfram syndrome or PSP – current treatment strategies focus on life-sustaining medications, clinical monitoring and symptom management

Amyotrophic Lateral Sclerosis

- AMX0114 was developed to target calpain-2 in ALS and other neurodegenerative diseases where treatment options are limited
- Preclinical data have shown that AMX0114 achieves potent, dose-dependent and durable knockdown of calpain-2 protein levels in human motor neurons and improved survival of iPSC-derived human motor neurons
- Plan to initiate a clinical trial studying AMX0114 in ALS in the second half of this year

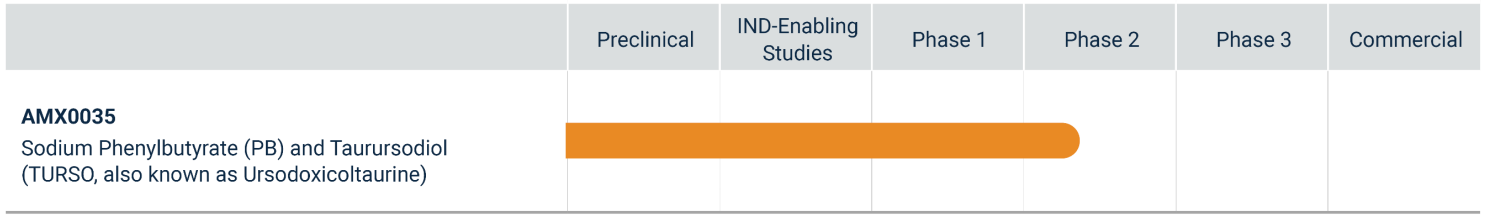
Well Capitalized Through Upcoming Catalysts

$371.4 million in cash, cash equivalents, and short-term investments as of 12/31/23; Expected cash runway into 2026, through anticipated data readouts of AMX0035 in Wolfram syndrome and PSP, and AMX0114 IND filing and forthcoming clinical trial

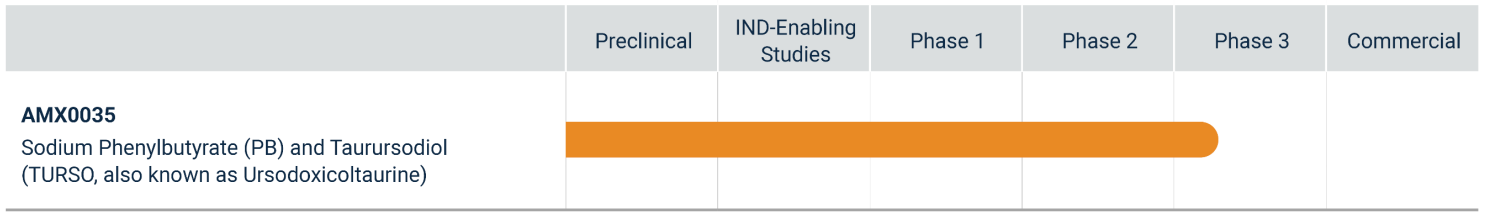
Our mission is to end the suffering caused by neurodegenerative diseases

PIPELINE FOCUSED ON TRANSFORMING THE LIVES OF PEOPLE LIVING WITH NEURODEGENERATIVE DISEASES

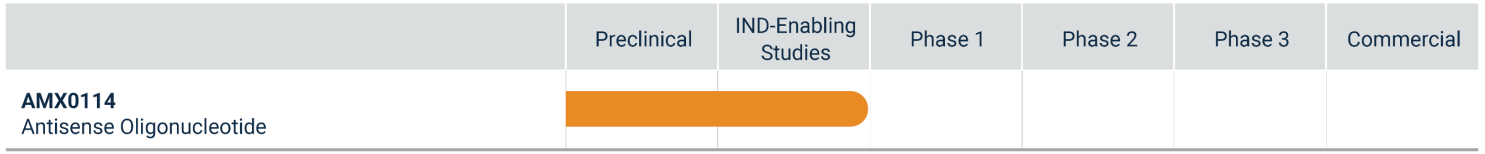
Wolfram Syndrome



Progressive Supranuclear Palsy (PSP)



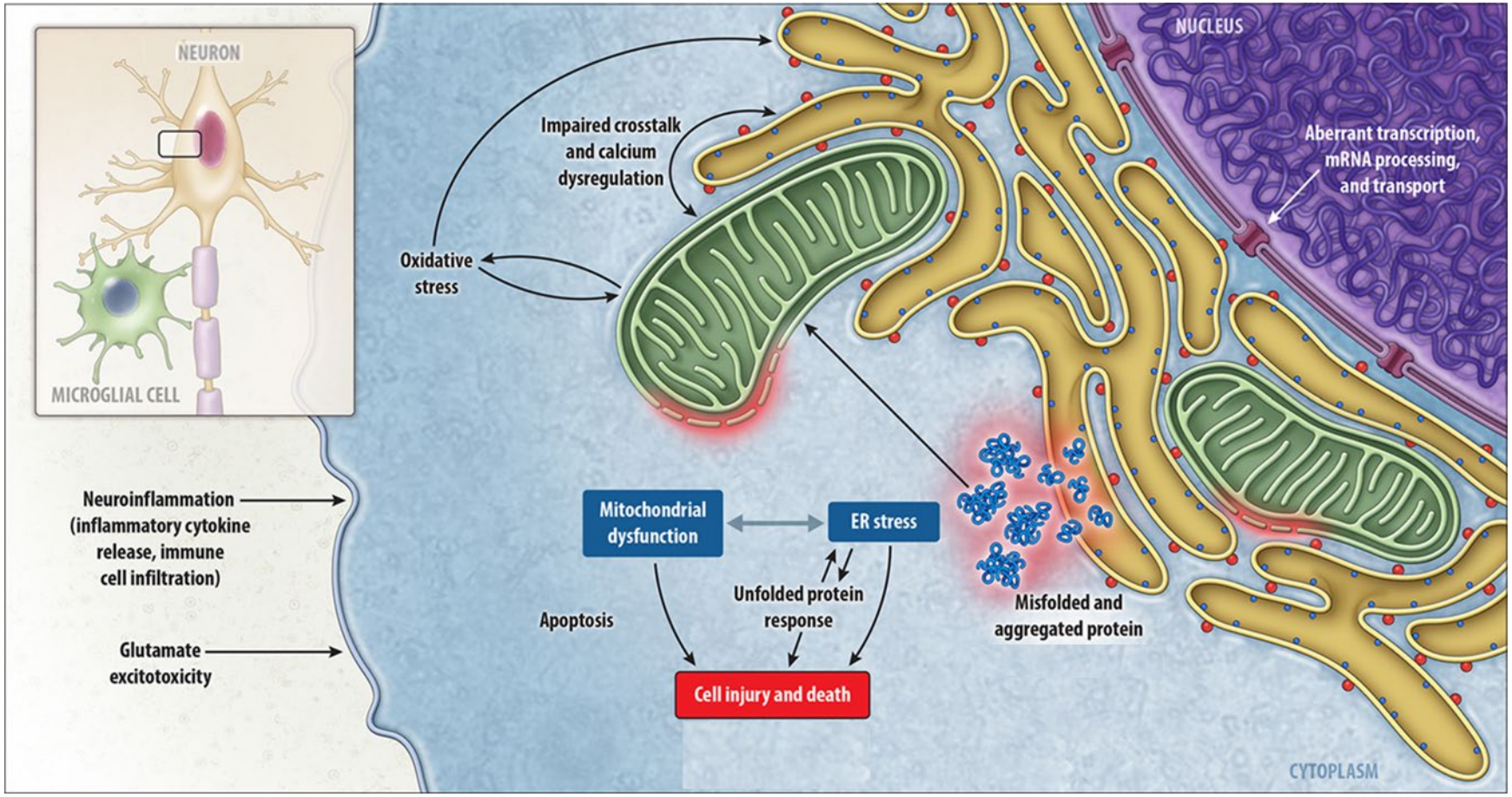
Amyotrophic Lateral Sclerosis (ALS)



Background on AMX0035

AMX0035 — Designed to Reduce Neuronal Cell Death

- AMX0035: Dual unfolded protein response (UPR), mitochondrial apoptosis targeting
  - Reduces endoplasmic reticulum (ER) stress-associated death
  - Reduces mitochondria-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 CM, et al. Biochemistry. 2003;42(10):3070-3080.; Fels JA, et al. Ann Clin Transl Neurol. 2022. doi.org/10.1002/acn3.51648.
The mechanism of action is unknown

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]

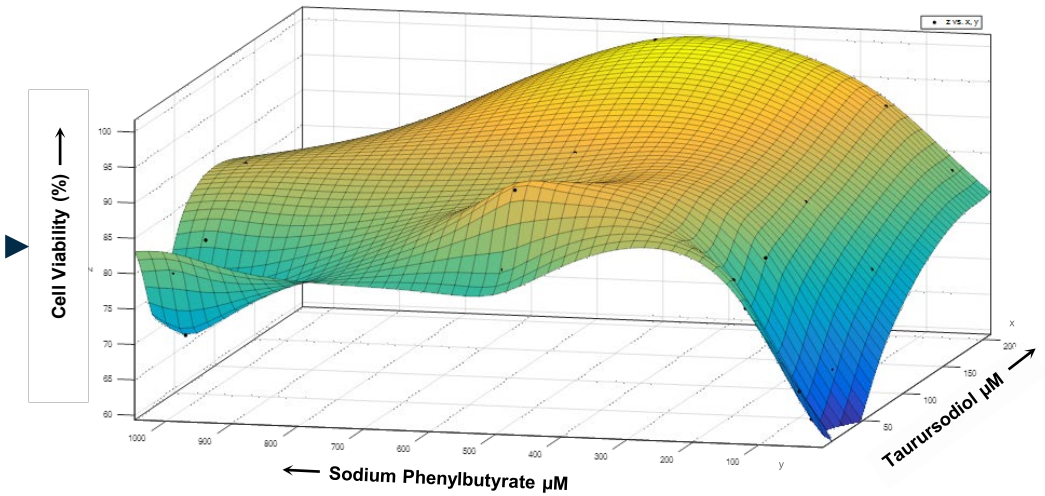


Figure from Cohen J, et al. Clinical trial design for a phase II, randomized, placebo-controlled trial of AMX0035 in amyotrophic lateral sclerosis (CENTAUR). Poster presented at: 28th International Symposium for ALS/MND; December 4–10, 2017; Boston, MA.

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.

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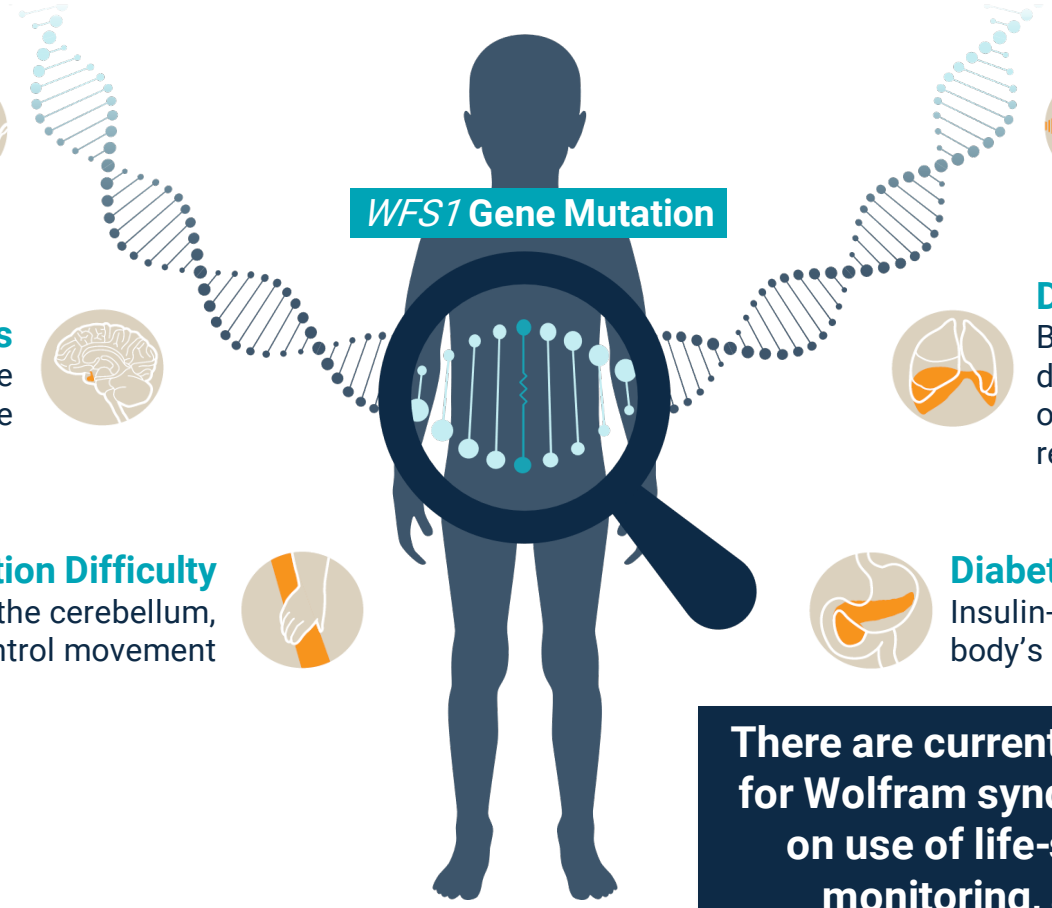
Wolfram Syndrome Program

Raquel, living with Wolfram syndrome.

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 death[1-5]



Loss of Vision
As cells in the optic nerve die, individuals gradually go blind

Diabetes Insipidus
Because of a faulty pituitary gland, the kidneys produce too much urine

Balance and Coordination Difficulty
The disease attacks the cerebellum, hampering the ability to control movement

Deafness
People with Wolfram syndrome usually begin to lose their hearing in their teens

Difficulty Breathing
By damaging the brain stem, the disease can disrupt respiration; death occurs at a mean age of 30 years (range 25-49 years), mainly from respiratory failure

Diabetes Mellitus
Insulin-producing beta cells die, hindering the body's use of sugar as energy

There are currently no disease-modifying therapies for Wolfram syndrome; treatment strategies focus on use of life-sustaining medications, clinical monitoring, and symptom management[6,7]

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

AMYLYX **1**. Urano F. Diabetes. 2014;63(3):844-846. **2.** Pallotta MT, et al. J Transl Med. 2019;17:238. **3.** Lee E, et al. Front Genet. 2023;14:1198171. **4.** Leslie M. Science. 2021;371(6530): 663-665. **5.** Matsunage et al. Plos One. 2014;9(9):106906. **6.** Urano F. Curr Diab Rep. 2016;16(1):6. **7.** Silvestri F, et al. AACE Clinical Case Rep. 2022;8(3):128-130.

Recent Studies Suggest Wolfram Syndrome May be More Common than Previously Estimated[1]

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]**

[a]All U.S. prevalence extrapolations assume a U.S. population of 341,814,420.
[b]Extrapolations 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 monogenic[5] = 384,000 people with monogenic diabetes in U.S.

1. Saint-Martin C, et al. *Diabetes*. 2022;71(3): 578-584. **2.** Fraser FC and T Gunn. *J Med Genet*.1977;14(3): 190-193. **3.** Barrett TG, et al. *Lancet*. 1995;346(8988): 1458-1463. **4.**National Diabetes Statistics Report. Centers for Disease Control and Prevention. Updated November 29, 2023. Accessed April 4, 2024. https://www.cdc.gov/diabetes/data/statistics-report/index.html. **5.** Riddle MC, et al. *Diabetes Care*. 2020;43(12): 3117-3128.

Wolfram Syndrome is a Prototypical Endoplasmic Reticulum Stress Disorder[7]

AMX0035 Targets ER Stress and Mitochondrial Dysfunction, Critical Pathways in Wolfram Syndrome Pathophysiology[1-6]

Pathogenic Mutations in *WFS1*[2,3]

Endoplasmic Reticulum 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]

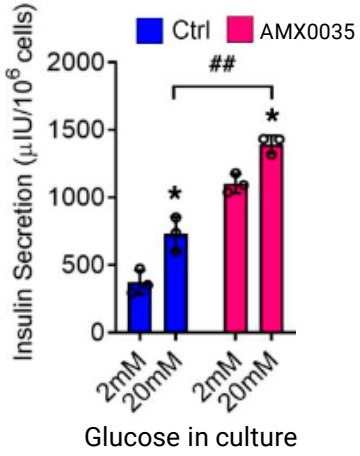
Taurursodiol stabilizes the mitochondrial membrane by reducing the translocation of cell death regulator Bax, improving mitochondrial function and energy production and increasing cell apoptotic threshold[5,6]

1. Mishra R, et al. Ther Adv Rare Dis. 2021:2:26330040211039518. **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.** Urano F. Diabetes. 2014;63(3):844-846.

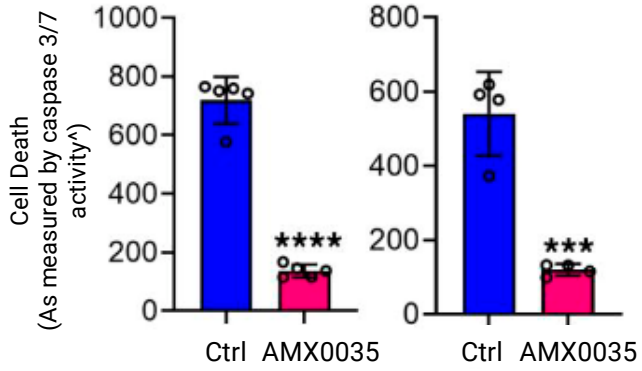
AMX0035 has been Extensively Studied in Wolfram Models including patient Derived Cells and Mouse Model

Effect of AMX0035 in Preclinical Studies[1]

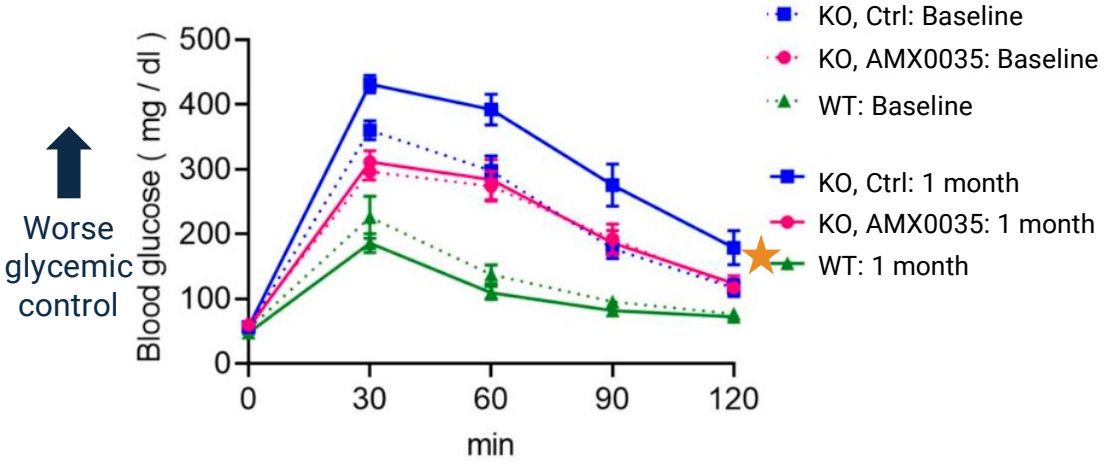
Improved WFS1 Mutant Insulin Secretion in Two Patient-Derived Cell Lines (P<0.05)



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

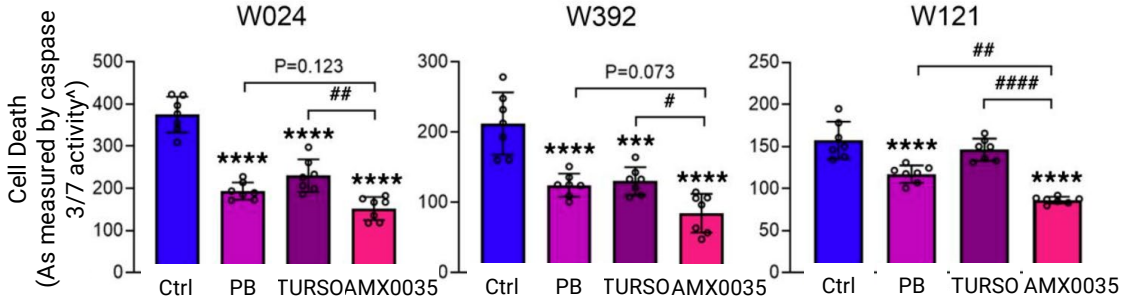


AMX0035-Treated Mice Showed Better Glycemic Control (P<0.001) than Untreated After 1 Month with Minimal to No Diabetes Progression Based on Glucose Tolerance Test (GTT)



*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

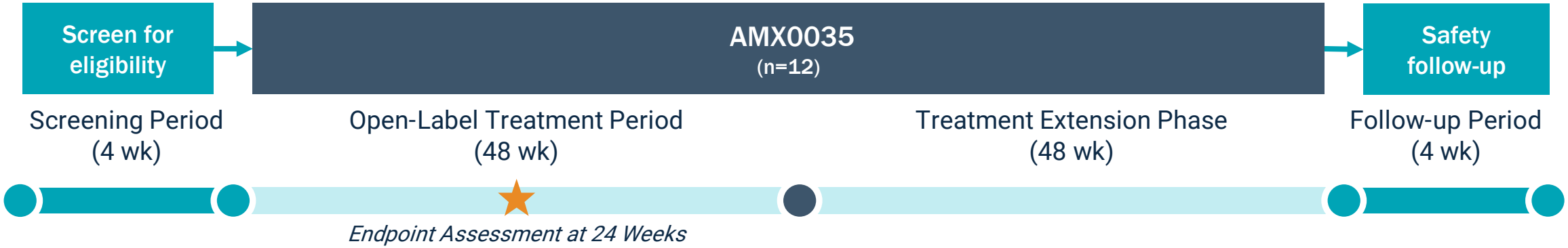
1. Kitamura RA, et al. *JCI Insight*. 2022;7(18):e156549.

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.

[a]Documented functionally relevant recessive mutations on both alleles of the *WFS1* gene based on historical test results (if available) or from a qualified laboratory at screening

1. ClinicalTrials.gov identifier: NCT05676034. Updated November 21, 2023. Accessed April 9, 2024. https://www.clinicaltrials.gov/ct2/show/NCT05676034. **2.** Data on File. Amylyx Pharmaceuticals Inc. 2024.

HELIOS Endpoints

Primary Efficacy

- Change from baseline in C-peptide (ΔC-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)

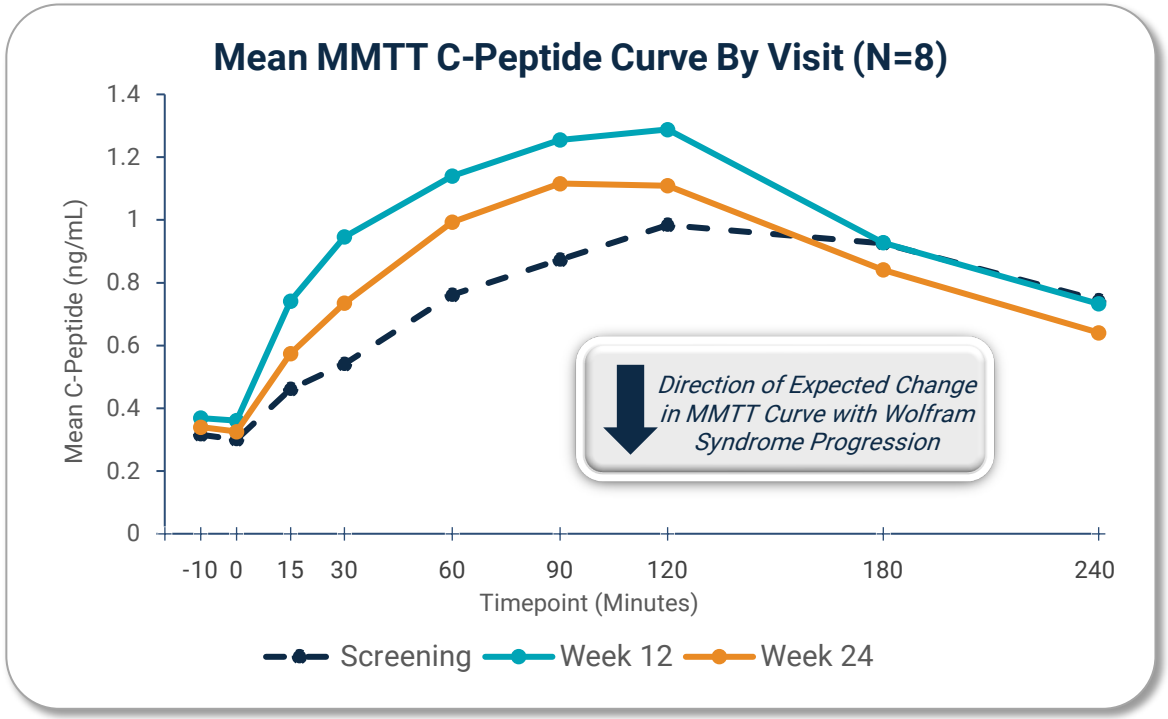
- Final Week 24 data will report all 12 participants and include additional assessments

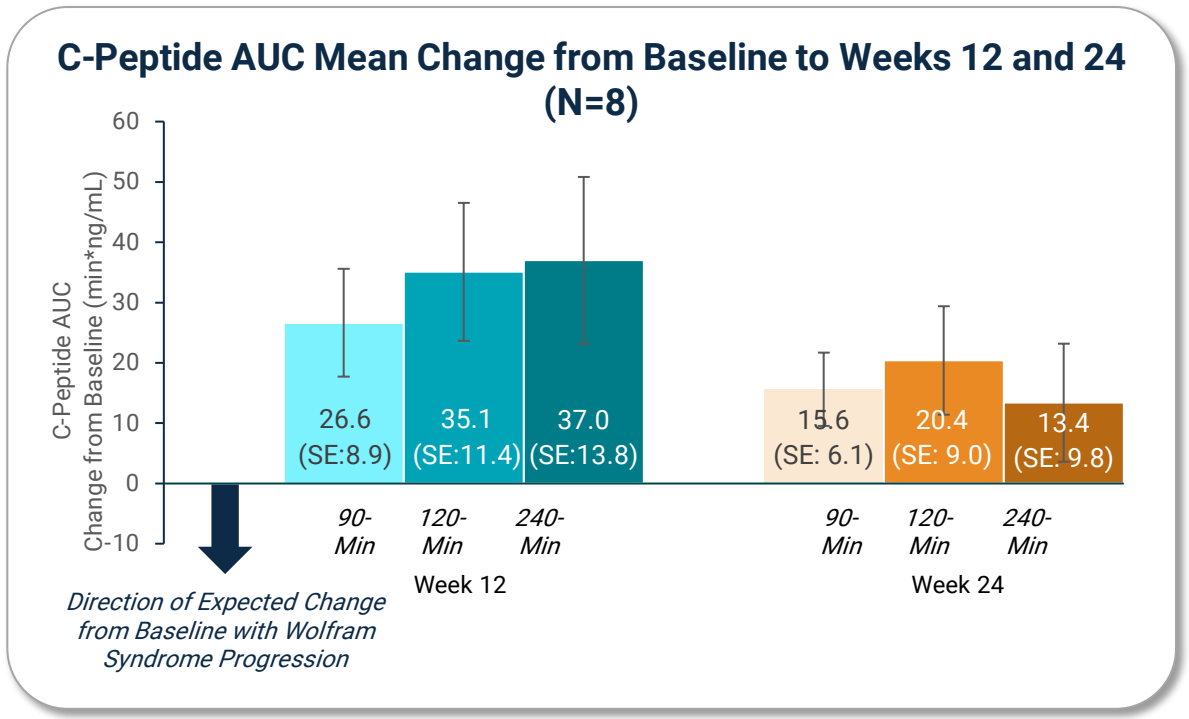
AUC, area under the curve; MMTT, mixed-meal tolerance test.

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. 2022.

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



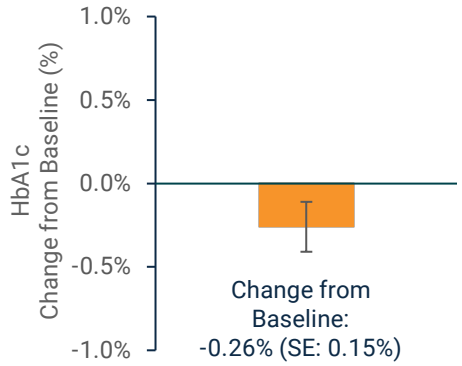


Partial Reversal in C-peptide Phenotype Observed at Weeks 12 and 24 Compared to Screening

Data on File. Amylyx Pharmaceuticals Inc. 2024.

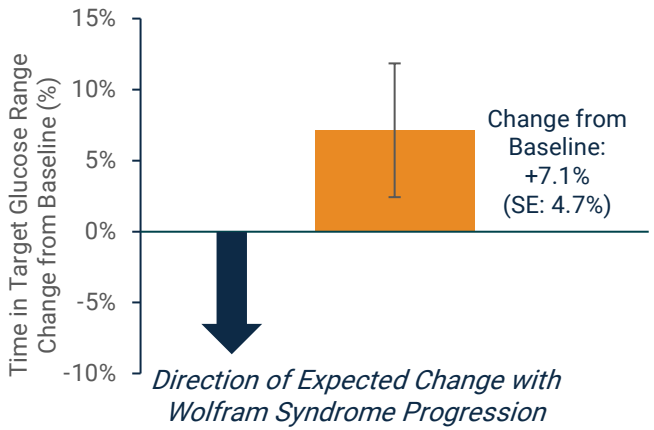
Secondary Endpoints: HbA1c, Overall Time in Target Glucose Range, Best Corrected Visual Acuity (BCVA)

HbA1c Mean Change from Baseline to Week 24 (N=8)



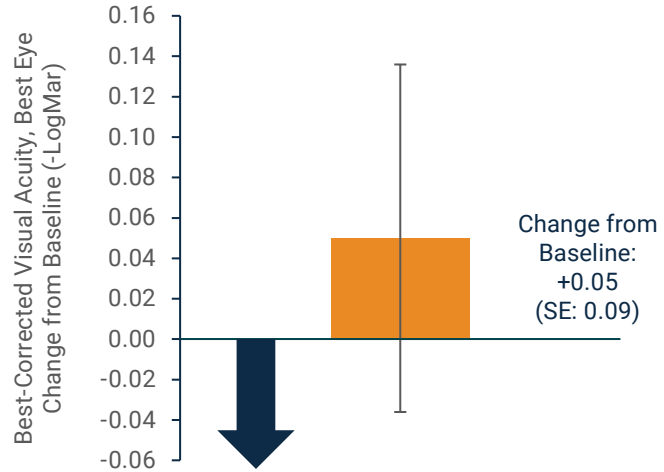
Improved Glycemic Control as Measured by HbA1c at Week 24 Compared to Screening

Time in Target Glucose Range Change from Baseline to Week 24 (N=8)



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

BCVA, Best Eye Mean Change from Baseline to Week 24 (N=8)



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

Data on File. Amylyx Pharmaceuticals Inc. 2024.

*Goal as defined by Recommendations from the International Consensus on Time in Range (Battelino T, et al. *Diabetes Care.* 2019;42(8):1593-1603.)

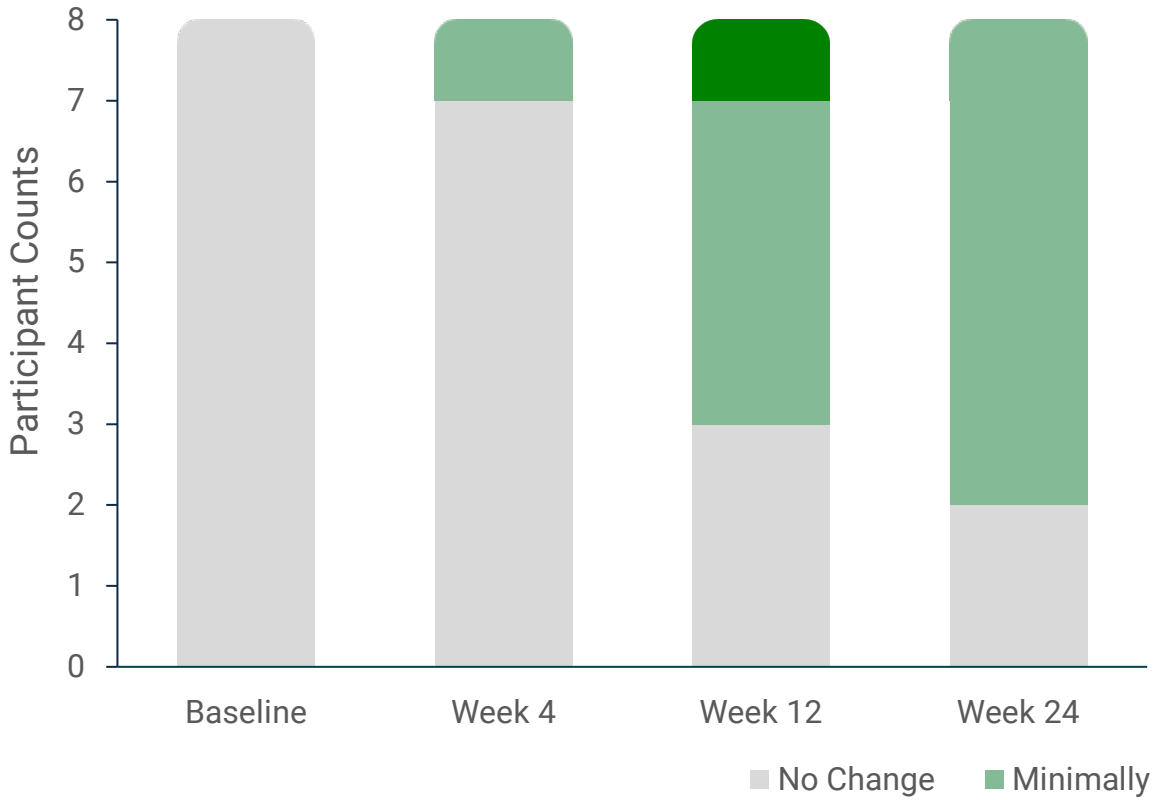
Data on File. Amylyx Pharmaceuticals Inc. 2024.

Exploratory Endpoint: PGI-C and CGI-C

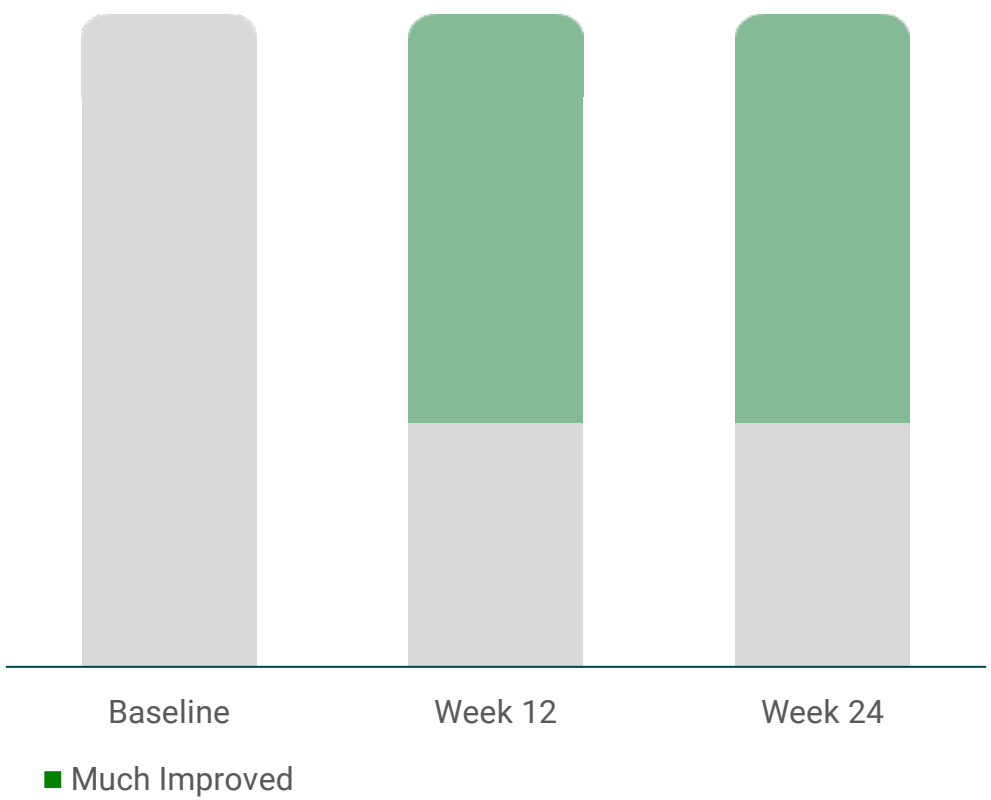
100% of Participants Met Responder Criteria by Self and Clinician Assessment

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)



Data on File. Amylyx Pharmaceuticals Inc. 2024.

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

Data on File. Amylyx Pharmaceuticals Inc. 2024.

AMX0035 Wolfram Syndrome Program Next Steps

Orphan drug designation granted to AMX0035 for the treatment of Wolfram syndrome by U.S. FDA

Phase 2 HELIOS study of AMX0035 in Wolfram syndrome initiated in April 2023 and completed enrollment in Feb 2024

Continue to progress the Phase 2 HELIOS study and evaluate options for future development

Planning to engage with regulatory authorities to align on the development path

Topline data for all 12 participants at Week 24 are expected in the second half of 2024

Members of the Wolfram syndrome community

Progressive Supranuclear Palsy (PSP) Program

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]

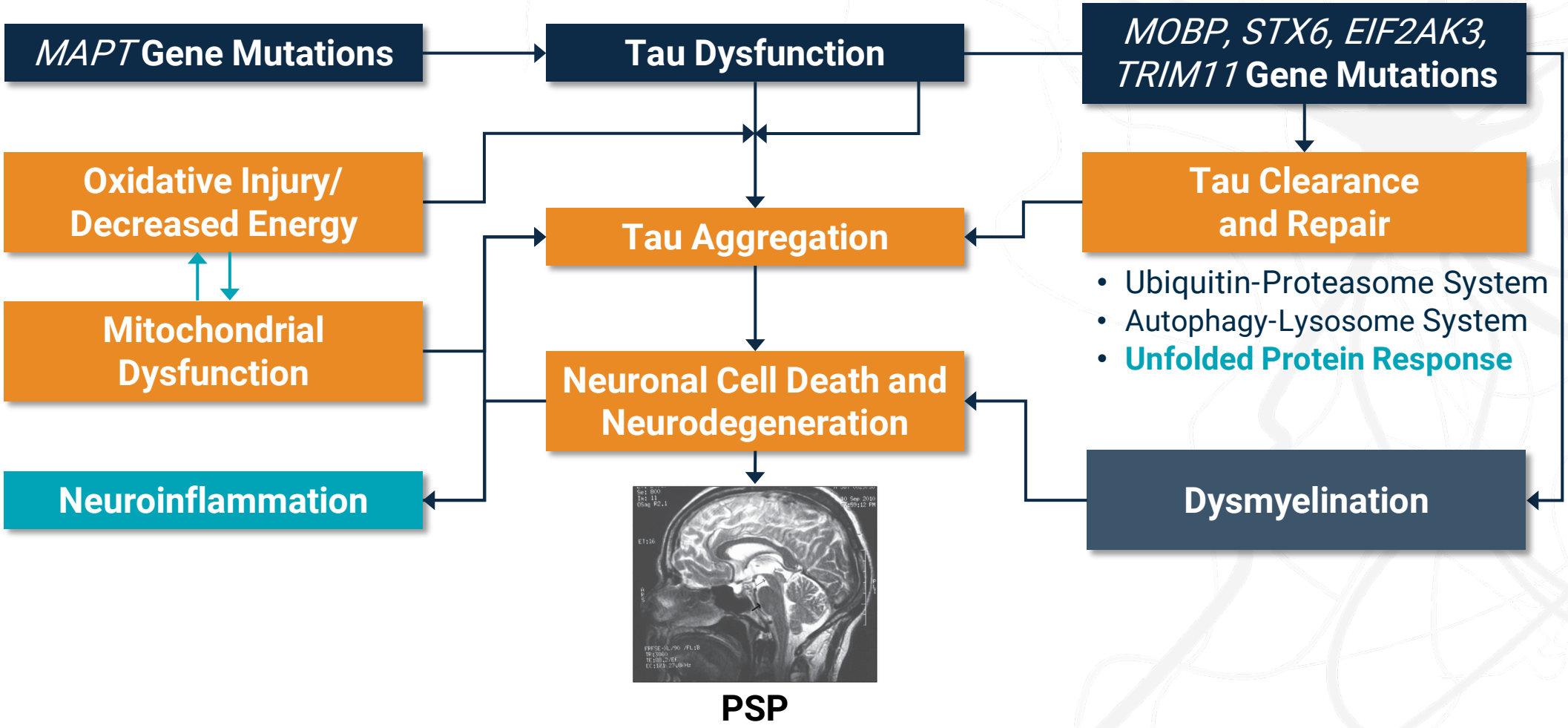
ESTIMATED INCIDENCE:

0.81 in 100,000 worldwide[2]

PSP is typically fatal within 6-8 years from symptom onset[3-6]

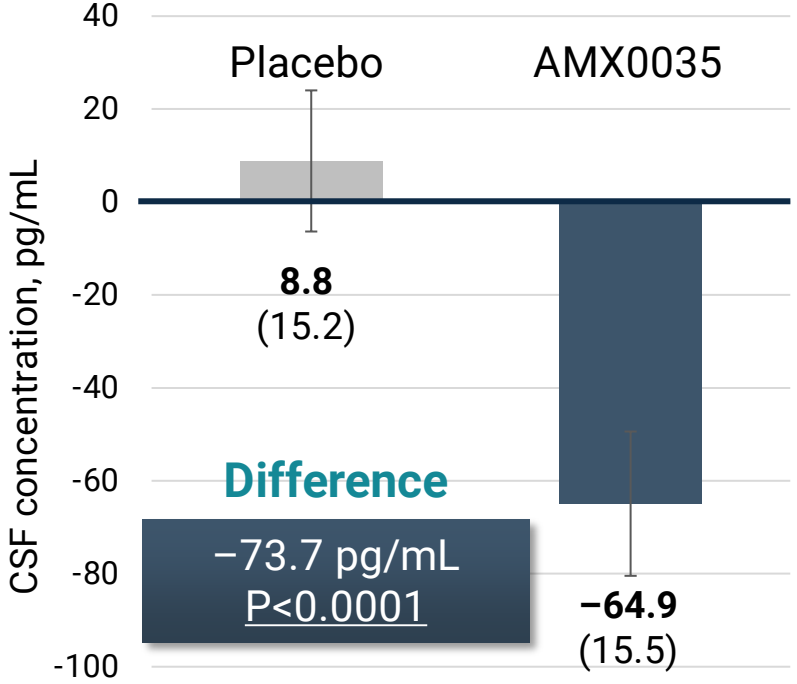
1. Swallow DMA, et al. Mov Disord Clin Pract. 2022 Jun 28;9(5):604-613. doi: 10.1002/mdc3.13489. **2.** Lyons S, et al. J Neurol.2023; June 8. epub ahead of print. **3.** Stamelou M, et al. Nat Rev Neurol. 2021;17(10):601-620. **4.** Viscidi E, et al. Front Neurol. 2021;12:571800. **5.** Golbe and Ohman-Strickland.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

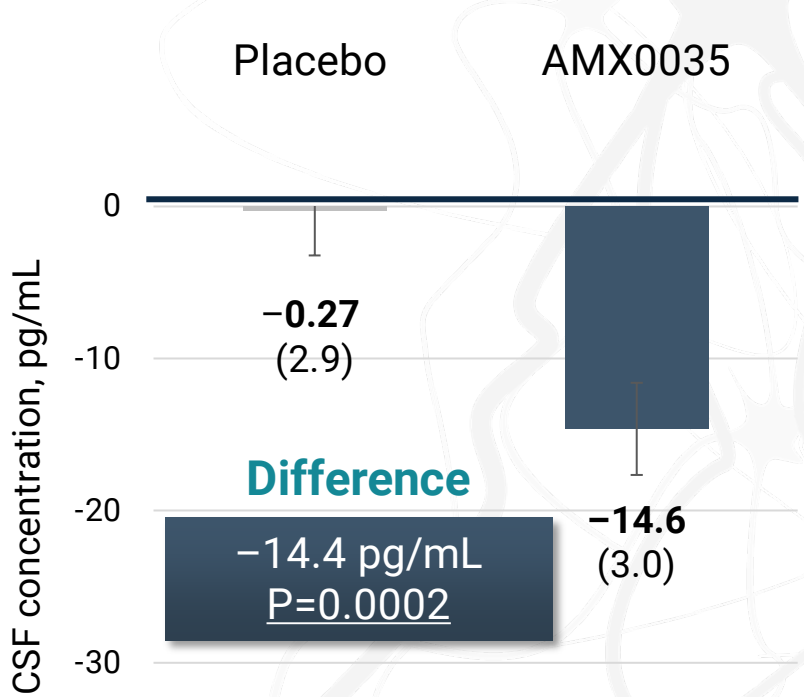
AMX0035 May Influence PSP Tau Pathology Through Multiple Mechanisms[1-9]



1. Park HK, et al. J Mov Disord. 2021; 14(2):103-113. **2.** Cohen J, et al. Poster presented at: 28th International Symposium for ALS/MND; December 4-10, 2017; Boston, MA. **3.** Zhou W. J Biol Chem. 2011;286(17):14941-14951. **4.** Rodrigues CM, Steer CJ. Expert Opin Investig Drugs. 2001;10(7):1243-1253. **5.** Rodrigues CM, et al. Biochemistry. 2003;42(10):3070-3080. **6.** Ricobaraza A, et al. Neuropsychopharmacology. 2009;34(7):1721-1732. **7.** Bondulich MK, et al. Brain. 2016;139(8):2290-2306. **8.** van der Harg JM, et al. Cell Death Dis. 2014;5(8):e1393. **9.** Arnold SE, et al. Poster presented at: 15th Clinical Trials on Alzheimer's Disease; November 29-December 2, 2022; San Francisco, CA.

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

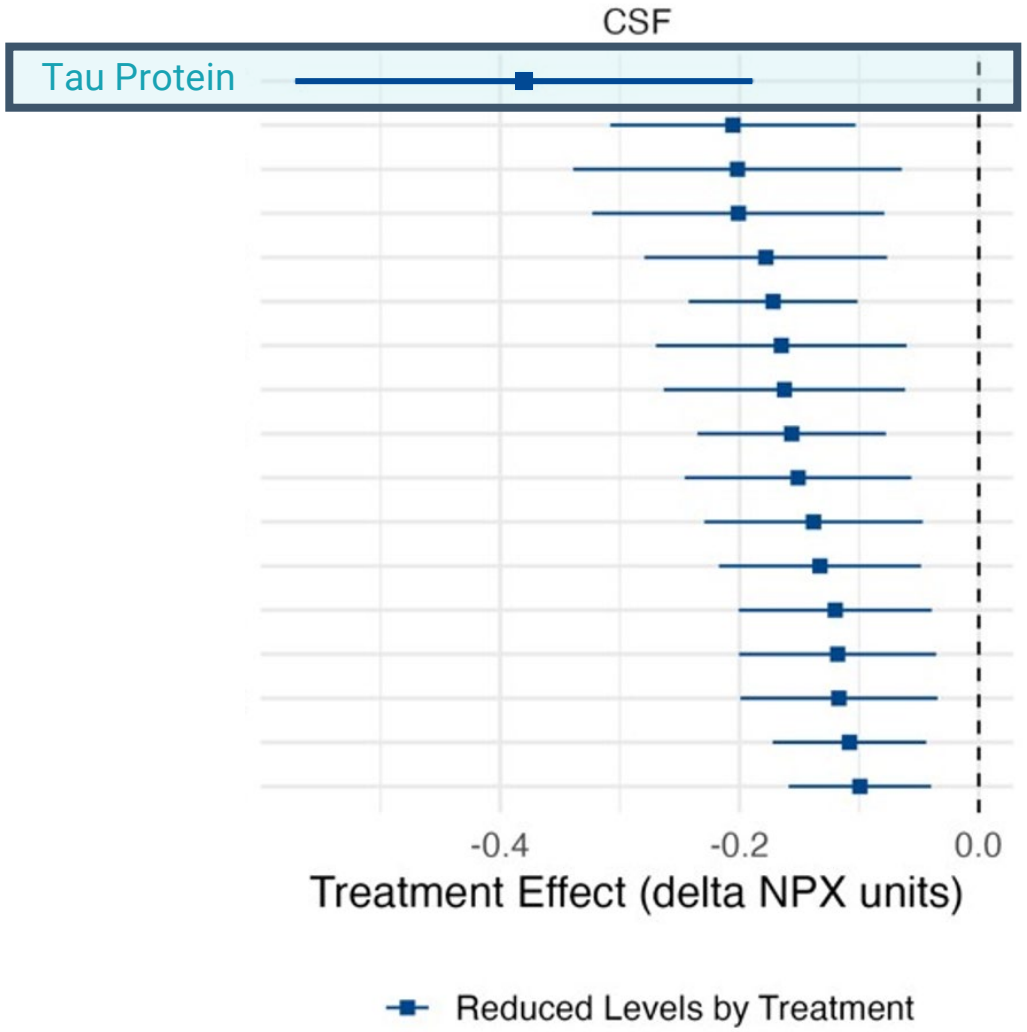




Arnold SE, et al. Cerebrospinal Fluid Biomarker Effects From a Fixed-Dose Combination of Sodium Phenylbutyrate and Taurursodiol in Alzheimer's Disease:Results From the PEGASUS Trial. Poster presented at: 15th Clinical Trials on Alzheimer's Disease CTAD, November 29-Dec2; California.

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.

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 AMX0035[1]

1. Poster presented at 16th Annual CTAD Meeting; October 24-27, 2023.
The Proteomic analysis was a pre-specified, exploratory analysis in the PEGASUS trial of AMX0035 for the treatment of Alzheimer's disease.

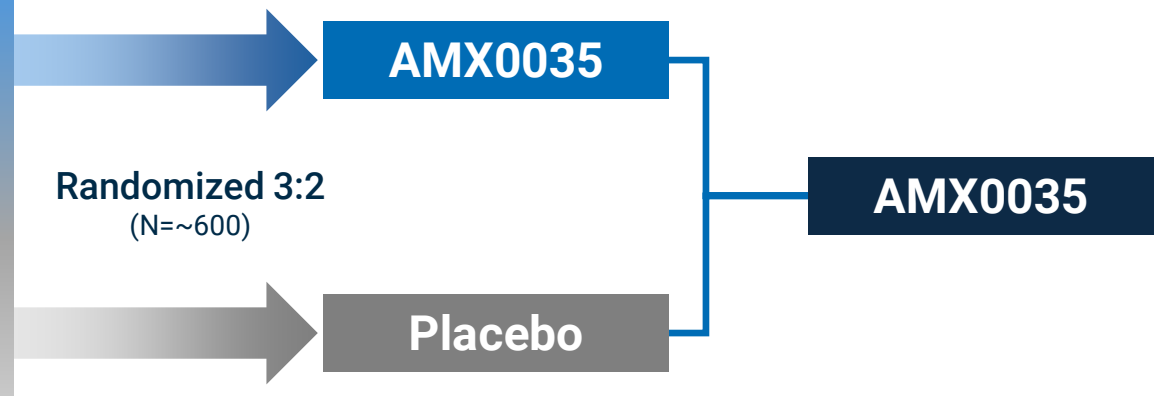
ORION: Phase 3 Clinical Trial of AMX0035 in PSP

ORION

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 assistance[3]
- PSPRS total score < 40
- MMSE score ≥ 24
- Study partner required
- No feeding tube use



Screening	Double-Blind Treatment	Open Label Extension
≤ 6 weeks	52 weeks	52 weeks

Primary Endpoint

- Total PSPRS score (28-item)

Secondary Endpoints

- Modified 10-item 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

First participant dosed in December 2023

Interim analysis expected in mid-2025

AMYLYX

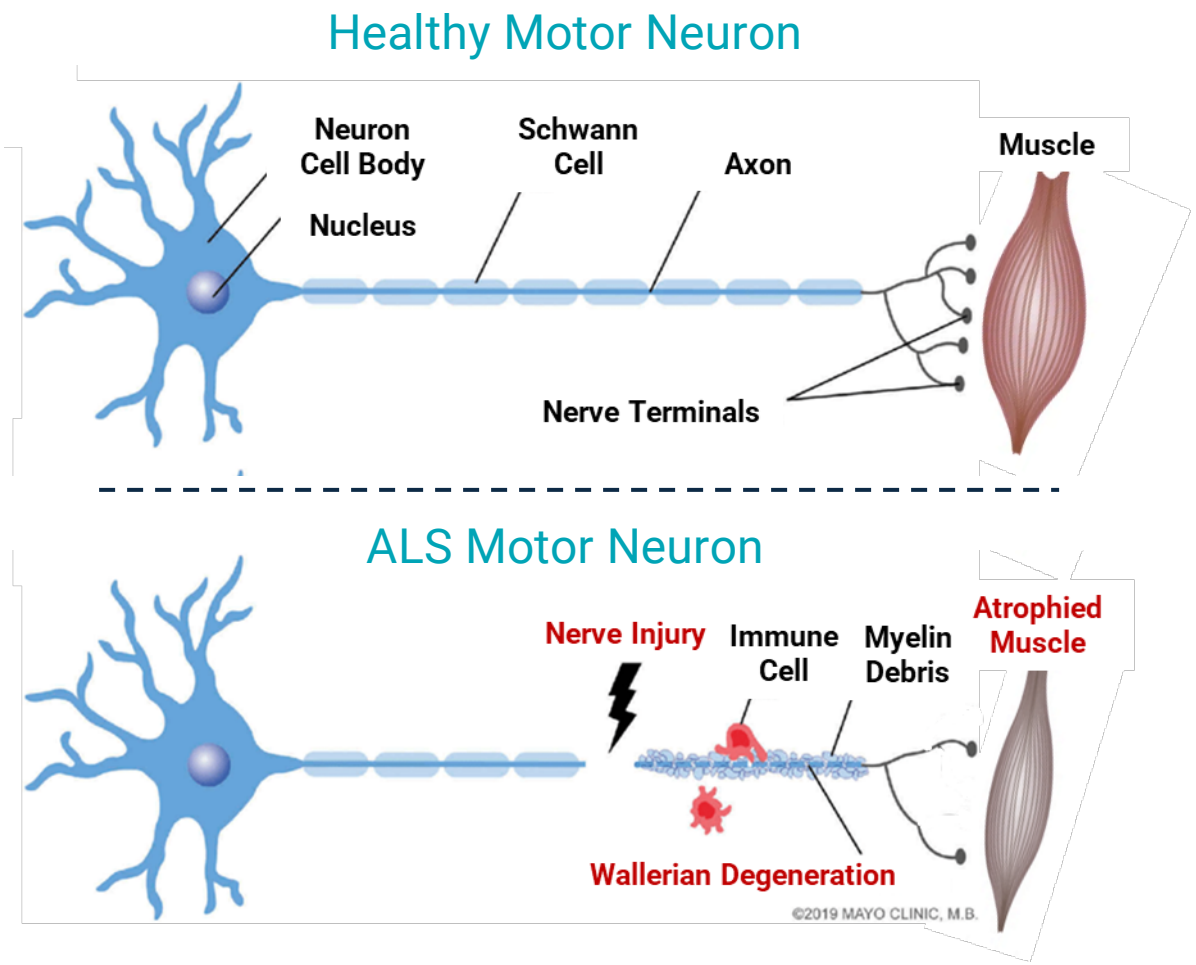
MDS, Movement Disorders Society; MMSE, mini-mental status exam; PSPRS, Progressive Supranuclear Palsy Rating Scale; MRI, magnetic resonance imaging; QoL, quality of life; CSF, cerebrospinal fluid
1. Gradually progressive disorder, with age at disease onset ≥ 40 years **2.** Either or both of the following 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).

AMYLYX

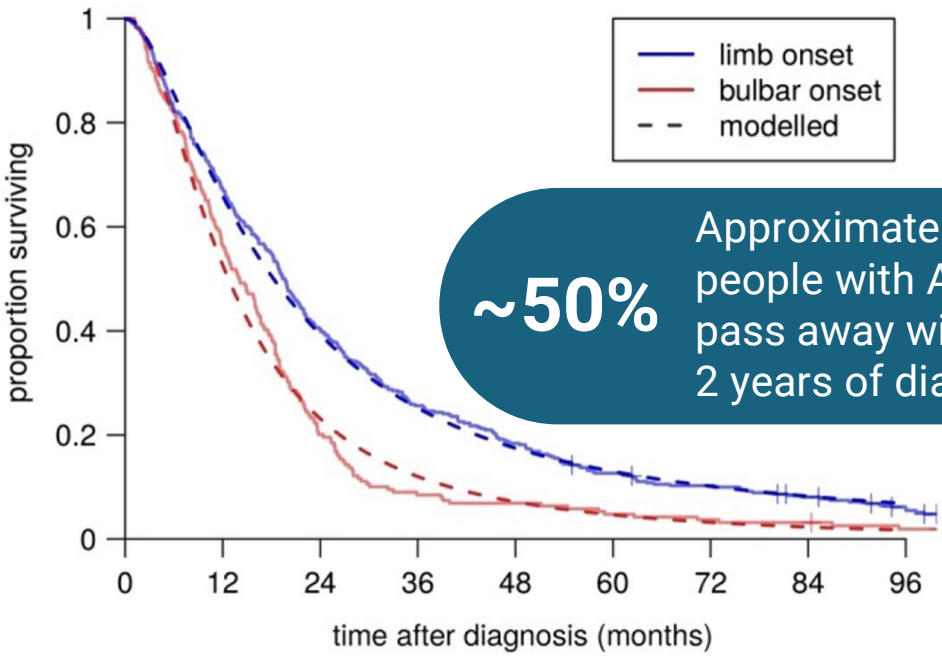
AMX0114 Program
An Antisense Oligonucleotide (ASO) Inhibitor of Calpain-2

- Expect to initiate a clinical trial studying AMX0114 in ALS in the second half of this year

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]
- Diagnosis is usually between ages 40 and 75
- >90% of patients have no family history of the disease



~50% Approximately half of people with ALS will pass away within 2 years of diagnosis[3]

1. Brown RH, 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.** Knibb JA, Keren N, Kulka A, et al. J Neurol Neurosurg Psychiatry. 2016;87(12):1361-1367.

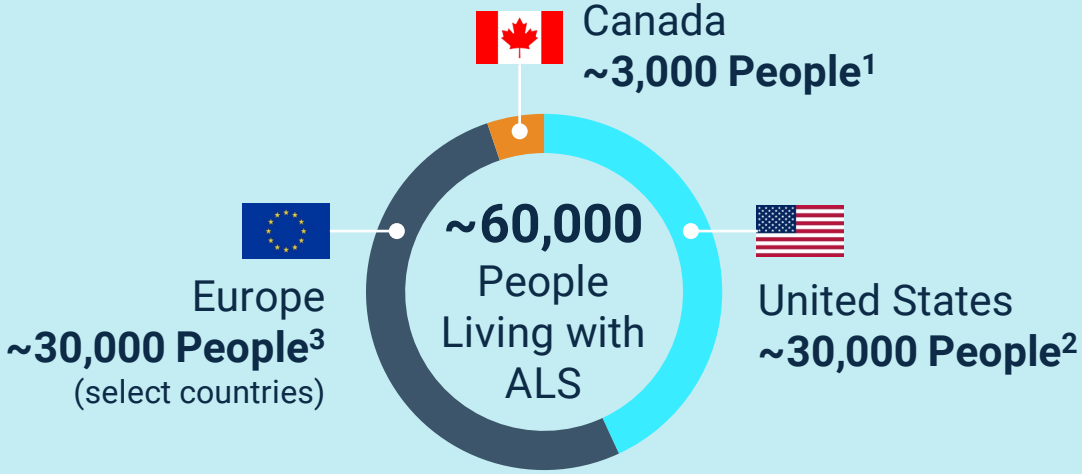
There is Clear and Urgent Unmet Need in ALS[1]

ALS is a global orphan disease affecting at least

300,000

people worldwide[4]

regardless of ethnic, geographic, or racial background



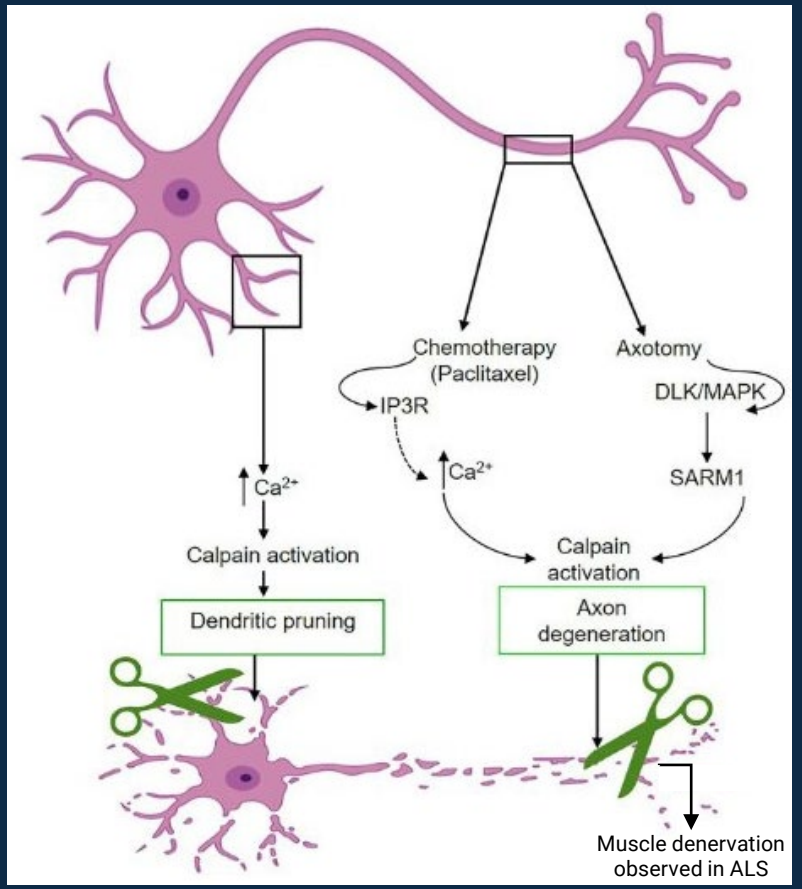
Urgent unmet need for new and effective treatment options – currently approved therapies are limited

1. Shoesmith C, et al. CMAJ. 2020;192(46):E1453-E1468. **2.** Mehta P, et al. Amyotroph Lateral Scler Frontotemporal Degener. 2023:1-7. doi: 10.1080/21678421.2023.2245858. **3.** Brown CA, et al. Neuroepidemiology. 2021;55(5):342-353. **4.** GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Lancet. 2017 Sep 16;390(10100):1211-1259.

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

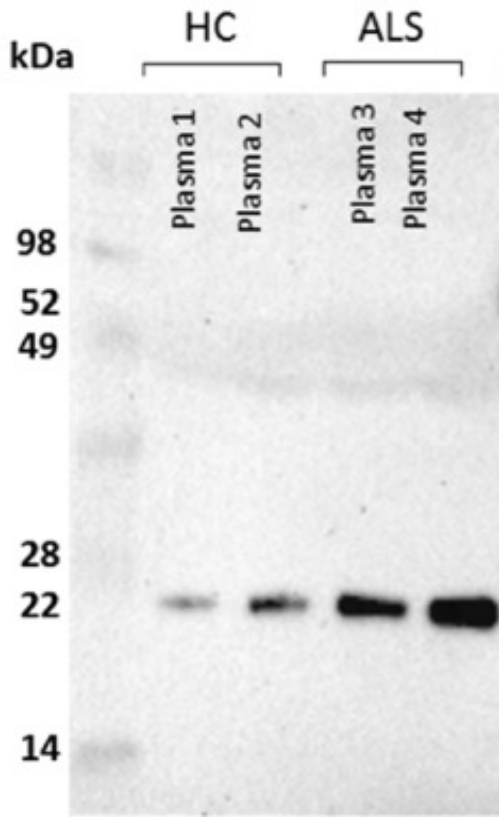


Multiple injury paradigms and hypotheses of axonal degeneration converge on calpain-2

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

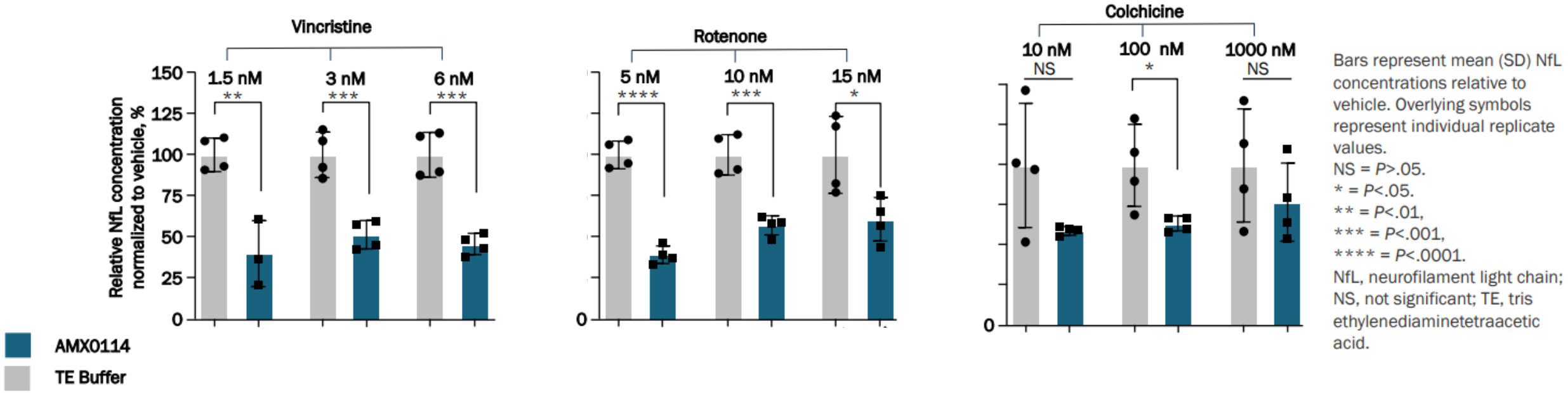
Calpain-2 Activation Leads to Neurofilament Proteolysis

- Neurofilaments are broadly researched biomarkers in ALS related to axonal degeneration and neurofilament was reported as a substrate for calpain-2 proteolysis as early as 1982[1]
- Calpain-2 cleaves neurofilament to produce 22 kDa, 40 kDa, and 55 kDa fragments[2]
- No full-length neurofilament light chain (NfL) is detected in ALS cerebrospinal fluid (CSF) or plasma, and the 22 kDa fragment is the NfL fragment which predominates in ALS[3]
  - This suggests a major role for calpain-2 in producing the NfL signal detected in ALS
- In *in vitro* models of neurodegeneration, treatment with AMX0114 has reduced extracellular NfL levels



1. Zimmerman, et. Al., 1982 2. Ma et al., 2013 3. Lombardi et al., 2020

AMX0114 Reduces Neurofilament in Cellular Models



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

Data on File. Amylyx Pharmaceuticals Inc. 2024.

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

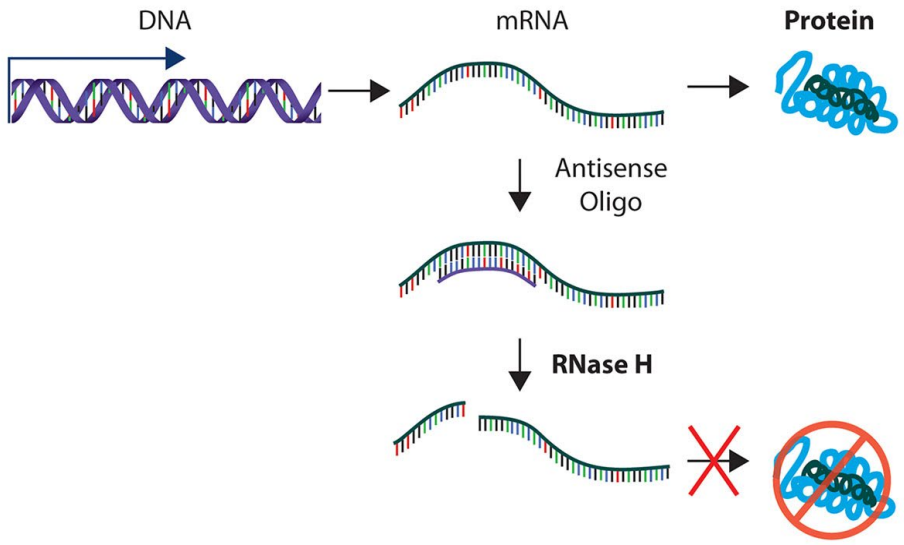
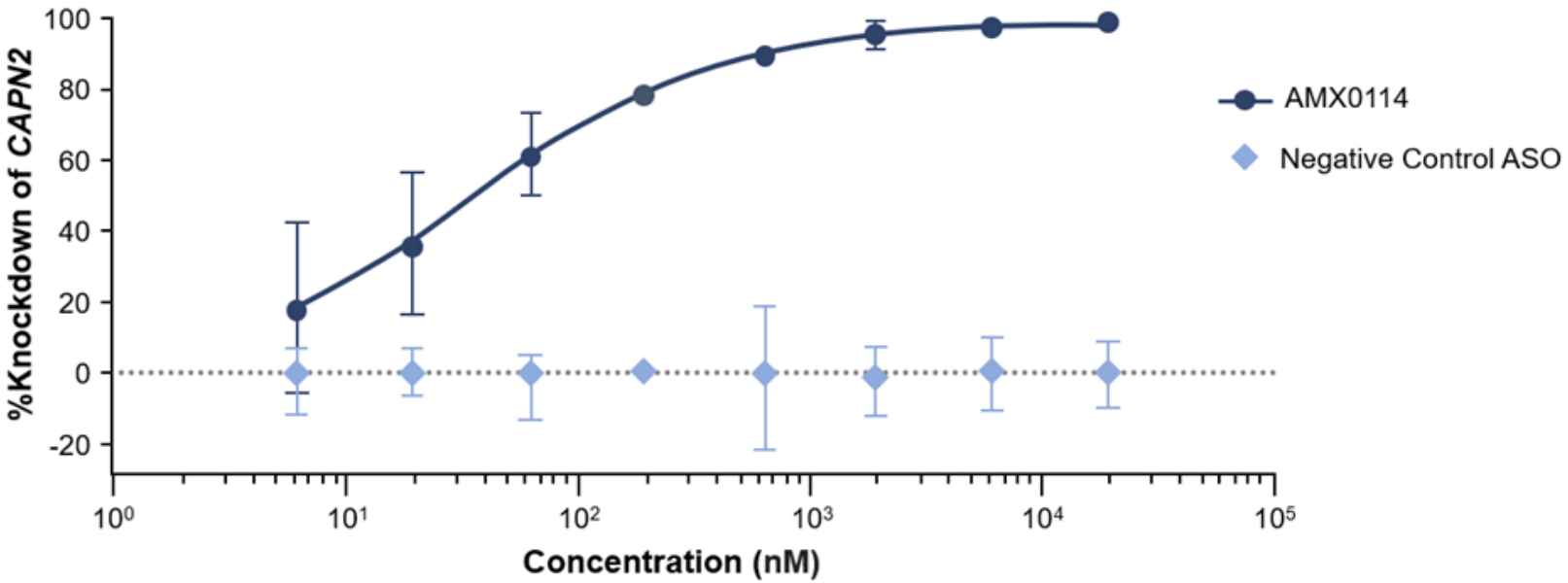


Image Credit: *Online Biology Notes*

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

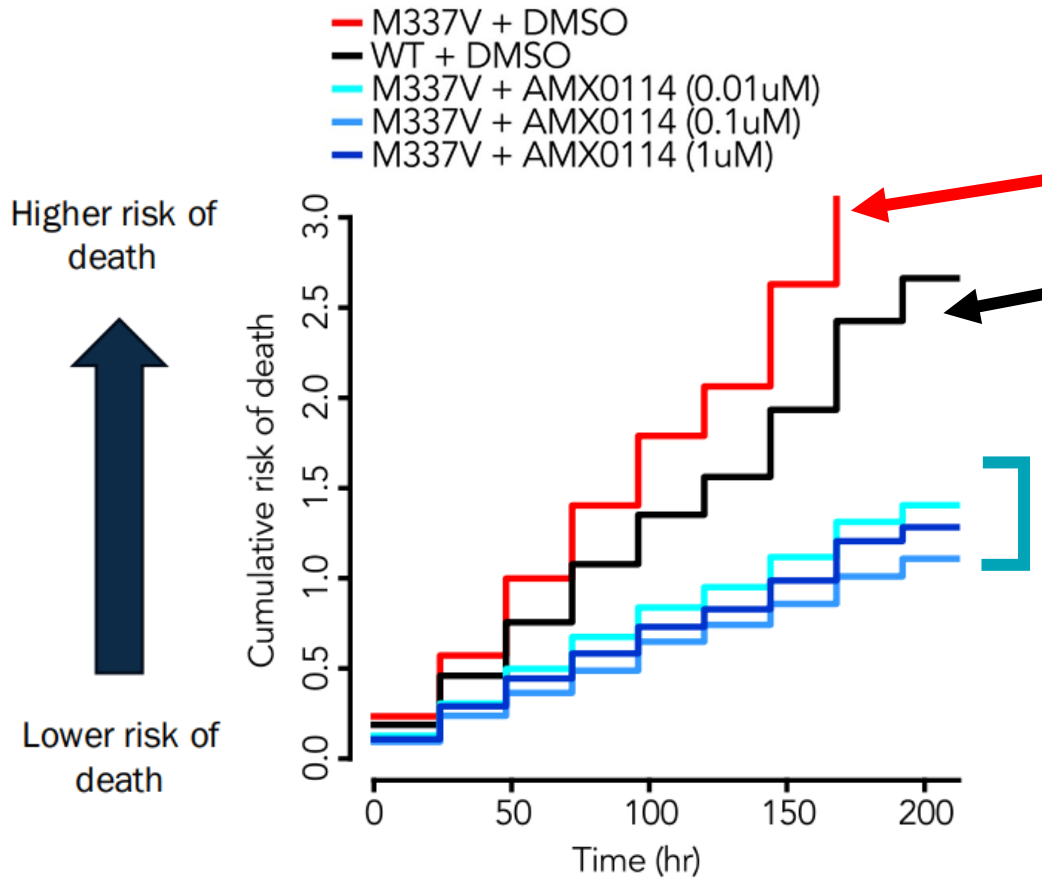


Days After AMX0114 Removal	CAPN2 mRNA Knockdown (Reduction vs. Control)	Calpain-2 Protein Knockdown (Reduction vs. Control)
0	94.47%	3.25%
3	87.12%	23.32%
7	84.36%	45.47%
10	82.16%	31.39%
14	83.80%	51.07%
21	77.25%	40.75%

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

- Reduction in *CAPN2* mRNA and calpain-2 protein levels following treatment with AMX0114 is rapid, robust, and stable over at least 21 days in a disease-relevant cell model.

AMX0114 Improves Survival in a Model of TDP-43 ALS



ALS model neurons (no AMX0114)

Healthy neurons (no AMX0114)

ALS model neurons (with AMX0114)

- TDP-43(M337V) is an ALS-linked mutation resulting in **increased risk of cell death**
- Treatment with as little as 0.01 µM AMX0114:
  - Reduced cell death by nearly **60%** relative to untreated M337V neurons ($p<0.0001$)
  - Reduced cell death by **>30%** relative to untreated wild-type neurons ($p<0.0001$)

Survival analyses performed in the lab of Dr. Sami Barmada at the University of Michigan Medical School by Dr. Michael Bekier

Corporate Highlights

Team

Experienced Executive Team to Oversee Clinical Development and Execution

Joshua Cohen, BSE

Co-CEO and Director

Co-invented AMX0035, dedicated to ALS/neurodegenerative research since 2013, co-designed CENTAUR study, co-led development of AMX0035 as 3-person company for 6 years, then built Amylyx team

Justin Klee, ScB

Co-CEO and Director

Co-invented AMX0035, dedicated to ALS/neurodegenerative research since 2013, co-designed CENTAUR study, co-led development of AMX0035 as 3-person company for 6 years, then built Amylyx team

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)

Strong Global IP Position

IP Portfolio Provides Robust Protection of Pipeline

>60

issued patents worldwide

>70

additional patents pending

+

potential for additional filings

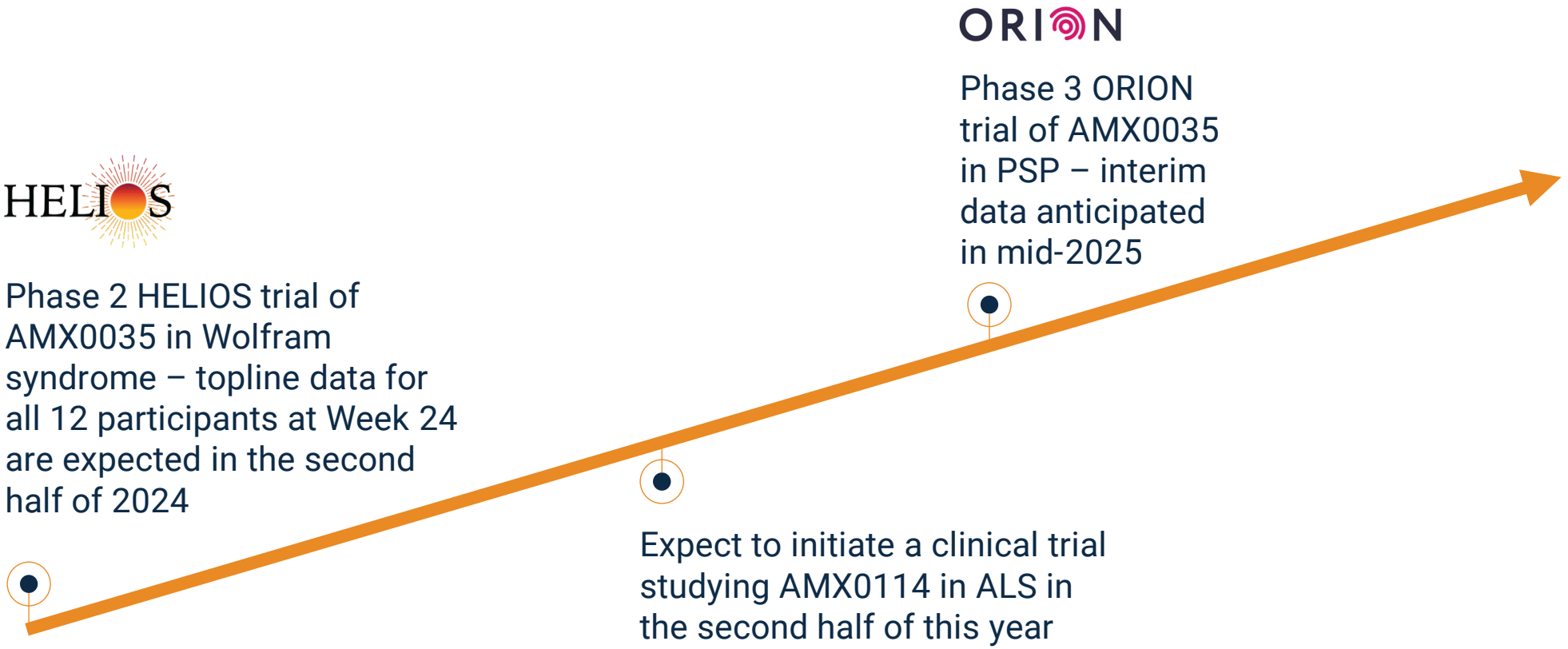
FISH & RICHARDSON

IP Portfolio includes:

- Granted patents directed to AMX0035 in U.S. expiring between 2033 – 2040
- Coverage of PB & TURSO composition of matter and its use in treating neurodegenerative diseases, as well as related formulations, combinations and manufacturing processes
- Orphan Drug Designation for treatment of Wolfram syndrome with AMX0035
- Coverage of AMX0114 composition of matter and its use in treating neurodegenerative diseases

Expected Cash Runway into 2026, Through Key Upcoming Milestones

$371.4M in cash, cash equivalents, and short-term investments as of 12/31/23



Thank you.

AMYLYX®