UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): July 26, 2023

AMYLYX PHARMACEUTICALS, INC.
(Exact name of Registrant as Specified in Its Charter)

Delaware	**001-41199**	**46-4600503**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

43 Thorndike, St., Cambridge, MA	**02141**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's Telephone Number, Including Area Code: (617) 682-0917

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	AMLX	Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events.

On July 26, 2023, Amylyx Pharmaceuticals, Inc. (the "Company") hosted a conference call with investors and analysts to discuss work in progressive supranuclear palsy ("PSP") and to provide an overview of its Orion Phase 3 clinical trial of AMX0035 in patients with PSP. Selected slides from the investor presentation used during the conference call are attached as Exhibit 99.1 to this Current Report on Form 8-K and are incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits

(d) Exhibits.

Exhibit Number	Description
99.1	Presentation of the Company, dated July 26, 2023
104	Cover Page Interactive Data File (embedded with the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

AMYLYX PHARMACEUTICALS, INC.

Date: July 26, 2023

By: /s/ James M. Frates
James M. Frates
Chief Financial Officer

Exhibit 99.1

AMYLYX

Progressive Supranuclear Palsy (PSP) Investor and Analyst Conference Call

July 26, 2023

On Today's Call

- Welcome
  Lindsey Allen, Head, Investor Relations and Communications, Amylyx
- Opening Remarks
  Josh Cohen and Justin Klee, Co-CEOs, Amylyx
- AMX0035 Scientific Rationale in PSP
  Dr. Jamie Timmons, Head, Global Medical Strategy and Communications, Amylyx
- PSP Treatment Landscape
  Prof. Dr. Günter Höglinger, Director of the Department of Neurology at LMU Hospital, Ludwig-Maximilians-University (LMU) in Munich, Germany
  Primary Investigator for Phase 3 ORION Clinical Trial of AMX0035 in PSP
- Overview of Phase 3 PSP Trial
  Dr. Lahar Mehta, Head, Global Clinical Development, Amylyx
- Q&A Session

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, statements regarding the potential of AMX0035 as a treatment for ALS and the Company’s plans to explore the use of AMX0035 for other neurodegenerative diseases, including progressive supranuclear palsy (PSP) and expectations around the timing of initiation of a Phase 3 clinical trial in PSP and the geographic sites for enrollment; expectations about the market size for PSP; 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 commercial and regulatory strategy, regulatory developments, Amylyx’ ability to fund operations, and the impact that the COVID-19 pandemic may have on Amylyx’ 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, 2022, 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.


AMX0035 Scientific Rationale in PSP
Dr. Jamie Timmons
Head, Global Medical Strategy and Communications, Amylyx
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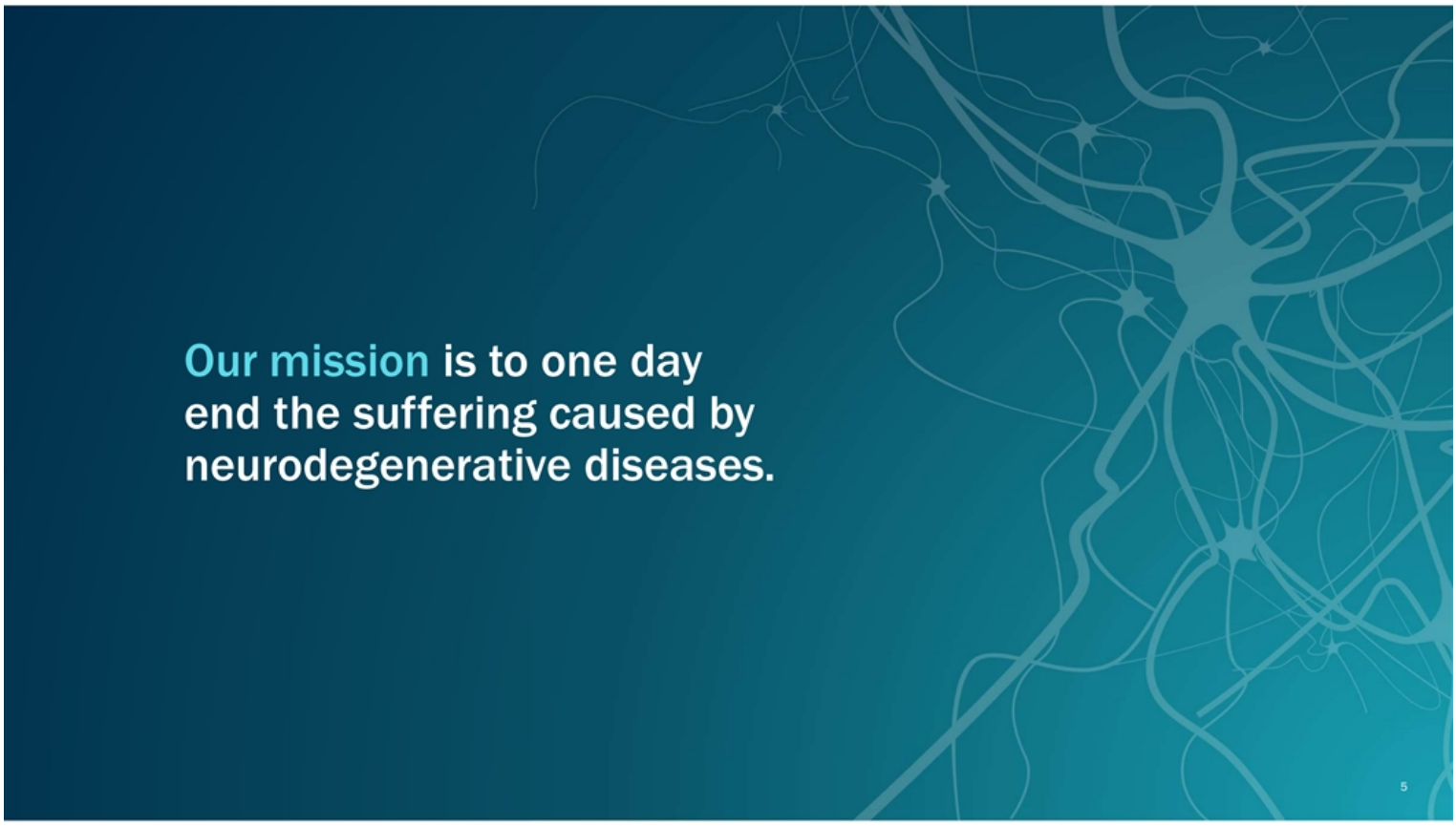
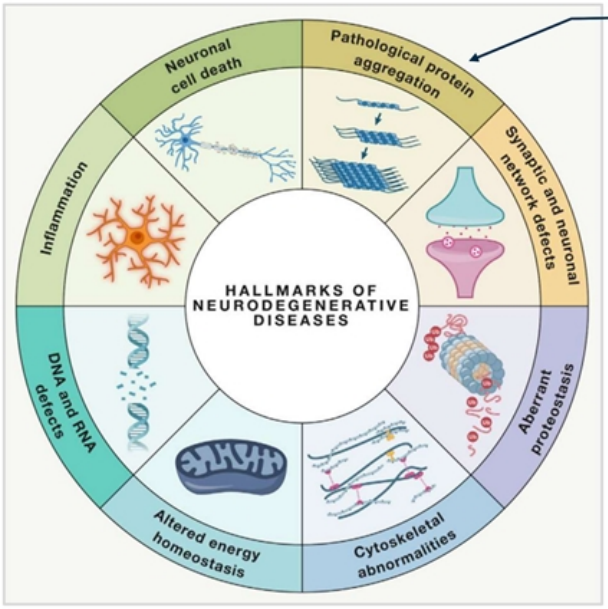

Our mission is to one day
end the suffering caused by
neurodegenerative diseases.
5

Neurodegenerative Diseases Share Interconnected, Hallmark Pathological Pathways



Pathological Protein Aggregation

Amyotrophic Lateral Sclerosis (ALS)
- TDP43, tau, SOD1, FUS, DPRs

Tauopathies; e.g., Progressive Supranuclear Palsy (PSP)
- tau

Alzheimer's Disease
- tau, Aβ

The interconnectedness of these pathways highlights the need for multi-pathway therapy

Wilson DM 3rd, et al. *Cell*. 2023 Feb 16;186(4):693-714.

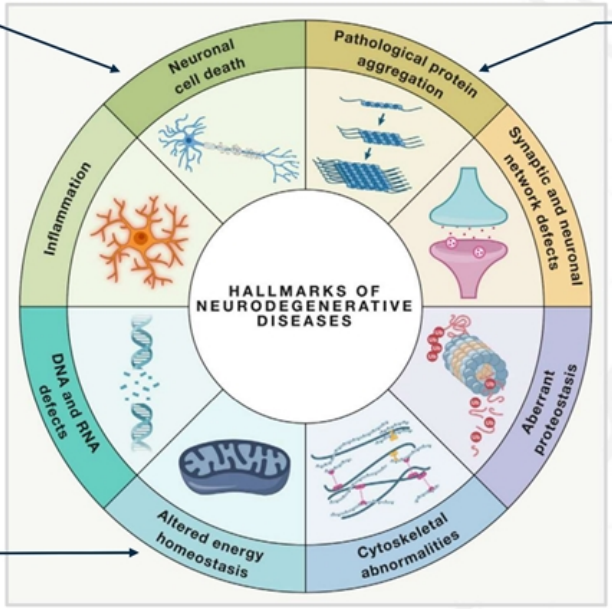
AMX0035 (Sodium Phenylbutyrate and Taurursodiol) Acts on Several Shared Hallmark Pathways to Reduce Neuronal Cell Death[1-9]

Neuronal Cell Death

- In vitro evidence of protecting neurons from death[2]
- Affects key pathways leading to cell death, including intrinsic apoptosis via the mitochondria and unfolded protein response[3-5]

Altered Energy Homeostasis

- Stabilizes mitochondrial membrane, improves mitochondrial function, increasing energy production of the cell[4,5]



Pathological Protein Aggregation

- Reduces tau in neurodegenerative disease cell and mouse models and in Alzheimer's disease clinical trial[6-9]

1. Wilson DM 3rd, et al. Cell. 2023 Feb 16;186(4):693-714. 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.

PSP is a Rare, Progressive and Fatal Tauopathy

- Rare neurological disorder affecting body movements, walking and balance, and eye movement.
- Lack of 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]

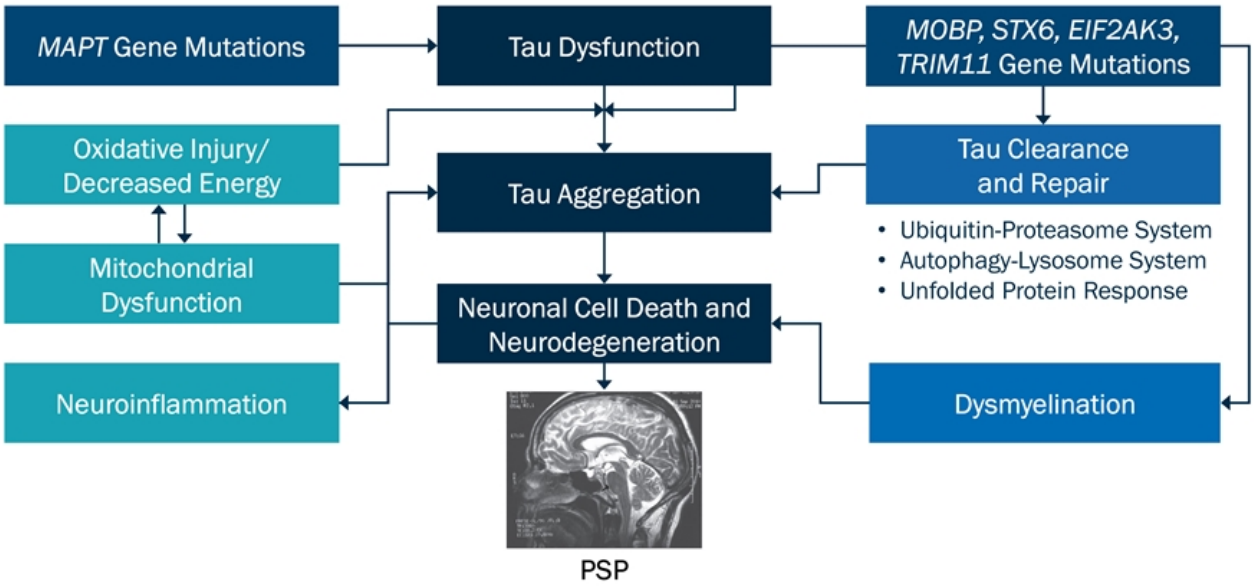
ESTIMATED INCIDENCE:

0.81 in 100,000 worldwide[2]

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

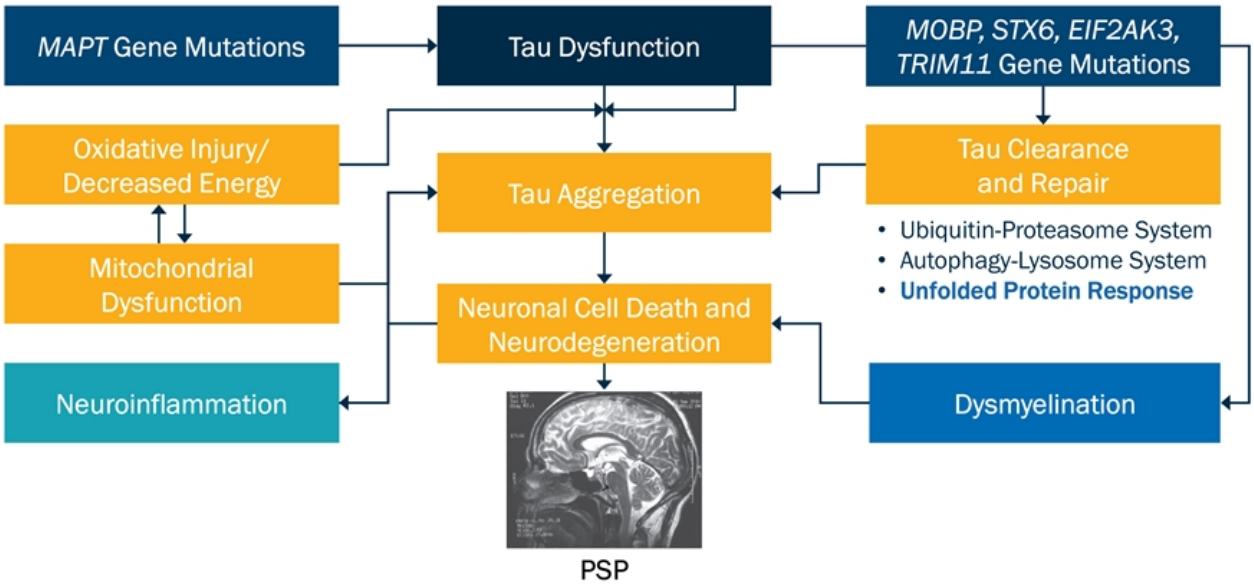
1. Swallow DMA, et al. Mov Disord Clin Pract. 2022 Jun 28;9(5):604-613. doi: 10.1002/mdc3.13489. 2. Lyons S, et al. J Neurol.2023;June 8. epub ahead of print. 3. Stamelou M, et al. Nat Rev Neurol. 2021;17(10):601-620. 4. Viscidi E, et al. Front Neurol. 2021;12:571800. 5. Golbe and Ohman-Strickland. Brain.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

Pathophysiologic Changes Underlying PSP Provide Multiple Pathways to Target



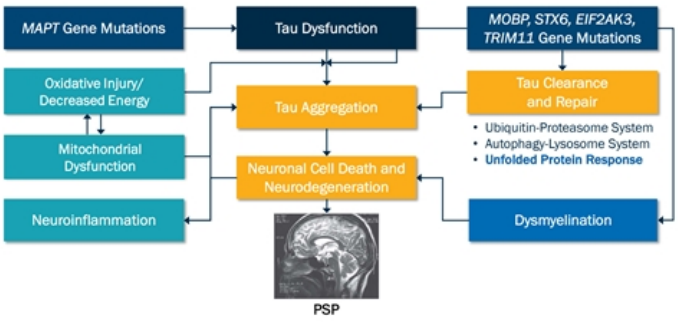
Park HK, et al. J Mov Disord. 2021; 14(2):103-113.

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.

Preclinical Data Support Sodium Phenylbutyrate (PB) for Potential Treatment of PSP



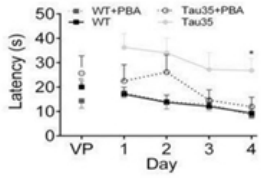
Sodium phenylbutyrate upregulates and recruits chaperone proteins, stabilizes protein folding, and reduces ER stress and the unfolded protein response (UPR) in vitro[1-4]

PB is Effective in PSP Mouse Model, Reduced Tau in AD Mouse Model

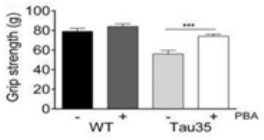
PB reduced tau pathology and improved cognitive and motor function measures in relevant mouse models[5,6]

- Alzheimer's APP/PS1 mouse model: reduced tau phosphorylation and improved cognition[5]
- Tau35 PSP mouse model (shown): reduced tau phosphorylation and improved cognition and motor function[6]

Morris Water Maze[6]

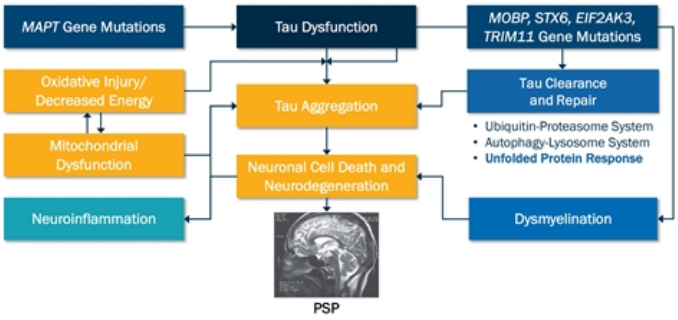


Grip Strength[6]



1. Zhou W. J Biol Chem. 2011;286(17):14941-14951. 2. Wiley JC, et al. PLoS One. 2010;5:e9135. 3. Mimori S, et al. Biol Pharm Bull. 2012;35:84-90. 4. Cho JA, et al. PLoS One 2014;9:e110086. 5. Ricobaraza A, et al. Neuropsychopharmacology. 2009;34(7):1721-1732. 6. Bondulich MK, et al. Brain. 2016;139(8):2290-2306.

Preclinical Data Support Taurursodiol (TURSO) for Potential Treatment of PSP

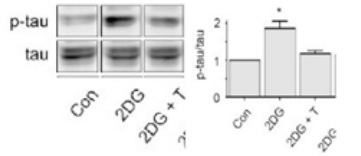


Taurursodiol stabilizes the mitochondrial membrane by reducing the translocation of cell death regulator Bax, improving mitochondrial function and energy production and increasing cell apoptotic threshold[1,2]

TURSO reduced p-tau in cellular model of metabolic stress[3]

Taurursodiol (TURSO) reduced tau phosphorylation in vitro[3]

Reduced p-tau with TURSO[3]

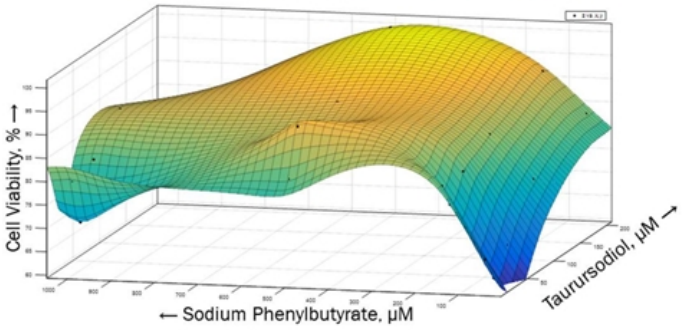


- 2 deoxy glucose (2DG) induced metabolic stress in neuronal cell model resulting in increased p-tau levels[3]
- TURSO (T) reduced increase in p-tau levels[3]

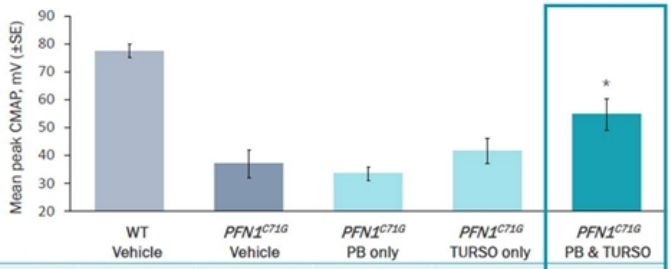
1. Rodrigues CM, Steer CJ. Expert Opin Investig Drugs. 2001;10(7):1243-1253. 2. Rodrigues CM, et al. Biochemistry. 2003;42(10):3070-3080. 3. van der Harg JM, et al. Cell Death Dis. 2014;5(8):e1393.

Numerous Preclinical Studies Show that AMX0035 Combination Targets Multiple Pathways Simultaneously to Prevent or Slow Cell Death

Dose-Matrix Study: Primary Cortical Neuron Damage Model[1]



Profilin Mouse Model of ALS[2]



	WT Vehicle	*PFN1*^{C71G} Vehicle	*PFN1*^{C71G} PB only	*PFN1*^{C71G} TURSO only	*PFN1*^{C71G} PB & TURSO
Mean peak CMAP (SE)	77.4 mV (2.5)	36.9 mV (5.1)	33.4 mV (2.4)	41.5 mV (4.6)	54.6 mV (5.7)

*P<.05 compared with *PFN1*^{C71G} vehicle.
CMAP, compound muscle action potential; PB, sodium phenylbutyrate; *PFN1*, profilin 1; TURSO, ursodoxicoltaurine; WT, wild type.

In vitro, AMX0035 combination demonstrated synergistic protection of cortical neurons against peroxide-mediated neuronal cell death

- Either PB or TURSO administration alone prevented a moderate percentage of neuronal cell death in vitro
- AMX0035 combination prevented nearly 100% of neuronal death _in vitro_

In mouse model of ALS, AMX0035 combination demonstrated synergistic decrease in motor function decline

- AMX0035 combination significantly decreased motor function decline in a mouse model of ALS
- This benefit was only seen when combining PB and TURSO and not with individual PB or TURSO treatment

1. 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. 2. Timmons J, et al. Efficacy of Sodium Phenylbutyrate and Ursodoxicoltaurine Combination in Transgenic Mice Displaying Progressive Motor Neuron Degeneration Phenotype. Poster presented at ENCALS Meeting 2023; July 12-14, 2023; Barcelona, Spain.

Numerous Preclinical Studies Show that AMX0035 Combination Targets Multiple Pathways Simultaneously to Prevent or Slow Cell Death

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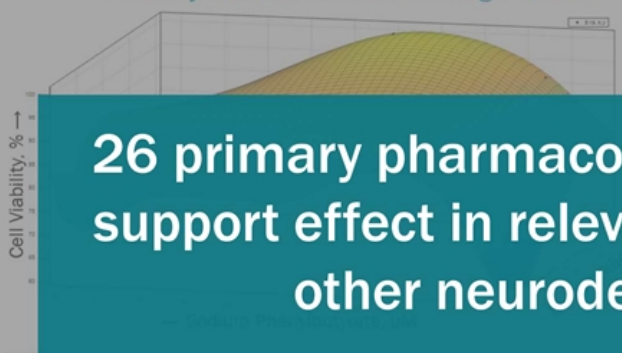


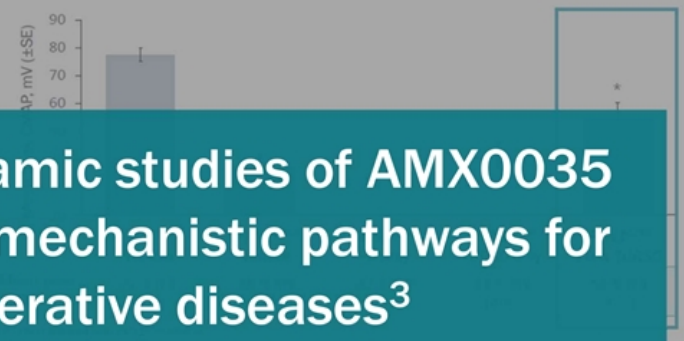
26 primary pharmacodynamic studies of AMX0035 support effect in relevant mechanistic pathways for other neurodegenerative diseases[3]

3. Data on File

In vitro, AMX0035 combination demonstrated synergistic **protection of cortical neurons against peroxide-mediated neuronal cell death**

- Either PB or TURSO administration alone prevented a moderate percentage of neuronal cell death in vitro
- AMX0035 combination prevented nearly 100% of neuronal death *in vitro*

Profilin Mouse Model of ALS[2]



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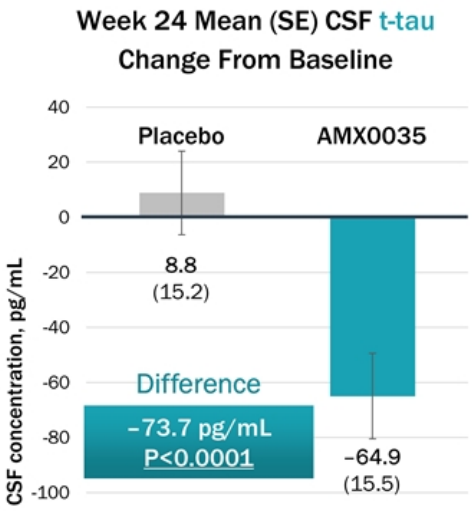
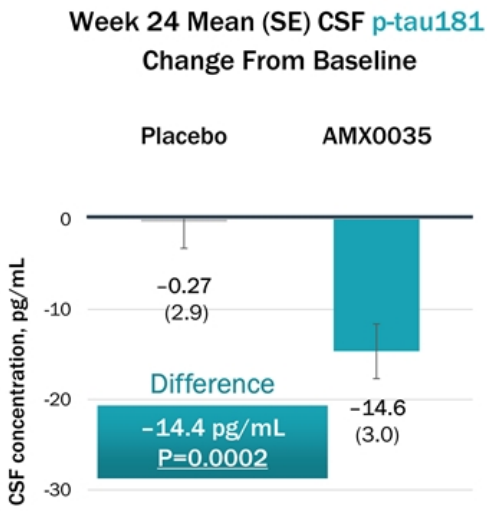
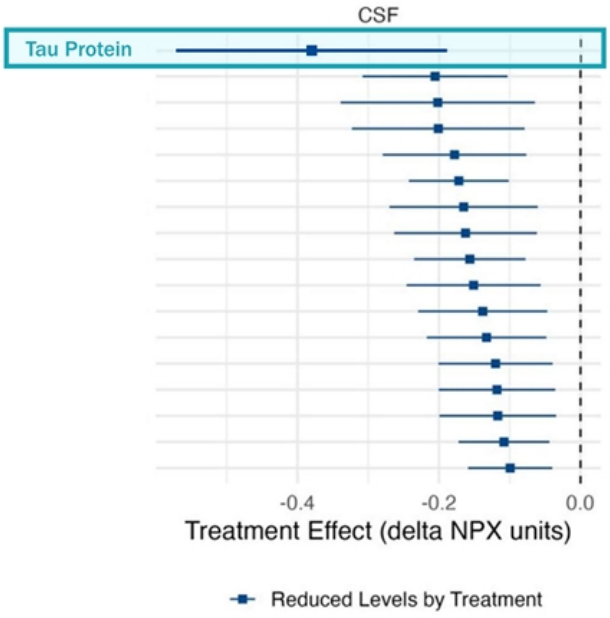
AMX0035 Significantly Lowered CSF Tau and p-Tau in Randomized Placebo Controlled Trial in People with Alzheimer's Disease





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 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. Data on File
The Proteomic analysis was a pre-specified, exploratory analysis in the PEGASUS trial of AMX0035 for the treatment of Alzheimer's disease.

AMX0035 Slowed Disease Progression and Prolonged Survival in ALS[1,2]

ALS and PSP Share Several Phenotypic Features and Shared Disease Mechanisms[3-5]
Suggests that a Drug Effective for ALS May be Effective for PSP[3]

Shared Disease Mechanisms[3]	Shared Phenotypic Features[4,5]
Unfolded protein response	Swallowing difficulty
Mitochondrial dysfunction	Respiratory dysfunction
Neuroinflammation	Speech disturbance
Protein misfolding and aggregation	Impaired cognition

1. Paganoni S, et al. N Engl J Med. 2020;383(10):919-930. 2. RELYVRIO. Prescribing information. Amylyx Pharmaceuticals, Inc.; 2022. 3. Wilson DM 3rd, et al. Cell. 2023 Feb 16;186(4):693-714. 4. Viscidi E, et al. *Front Neurol.* 2021;12:571800. 5. Brown RH, Al-Chalabi A. N Engl J Med. 2017;377(2):162-172.

Key Takeaways

- PSP is a tauopathy associated with tau dysfunction, tau aggregation and widespread neurodegeneration.
- Multiple pathways, are implicated in tau pathology in PSP.
- AMX0035 is proposed to mitigate tau pathology in PSP through multiple pathways.
- Pre-clinical and clinical evidence supports that AMX0035 can reduce tau pathology.


ORION Phase 3 PSP Trial Design
Dr. Lahar Mehta
Head, Global Clinical Development, Amylyx
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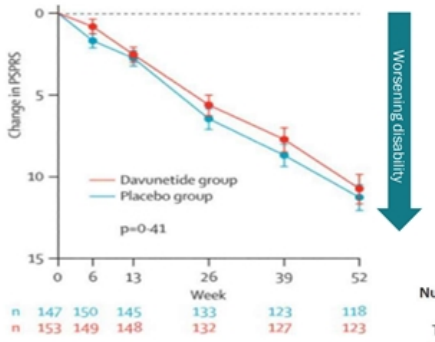
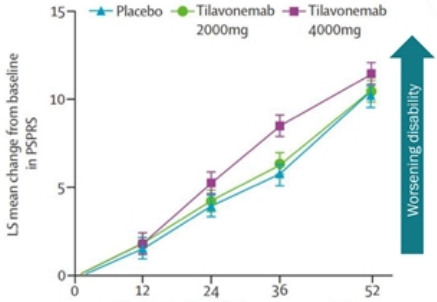
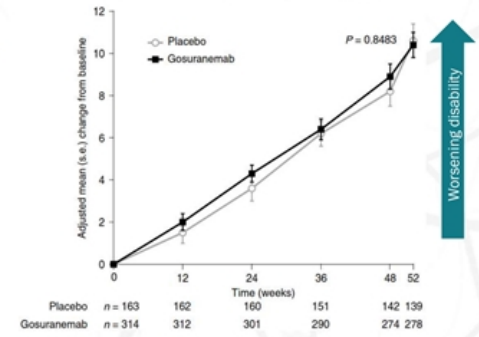
Completed PSP Clinical Studies Exhibit Consistent and Measurable Progression on Validated Endpoint



Boxer et al 2014.



Höglinger et al 2021.



Dam et al 2021.

Three large, global clinical trials conducted to date show consistent progression of ~10 points/year on Progressive Supranuclear Palsy Rating Scale (PSPRS) with relative low noise

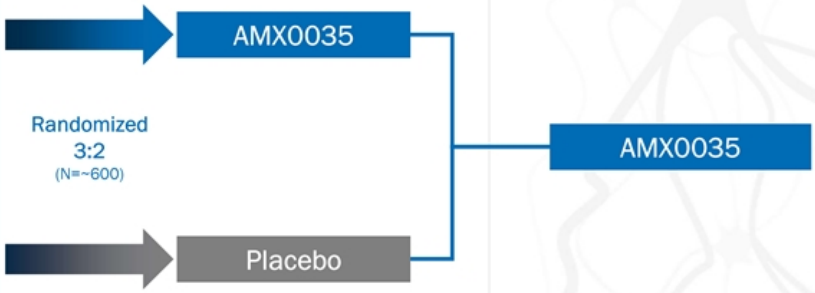
ORION: Phase 3 Clinical Trial of AMX0035 in PSP

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

ORION

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



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

MDS, Movement Disorders Society; MMSE, mini-mental status exam; PSPRS, Progressive Supranuclear Palsy Rating Scale

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).

ORION Clinical Trial Endpoints

Primary Endpoint	**Disease Progression** • Total PSPRS[1] score (28-item)	
Secondary Endpoints	**Disease Progression** • Modified 10-item PSPRS[1] score	**Motor Aspects of Activities of Daily Living** • MDS-UPDRS[2] Part II score
Additional Endpoints	**Brain Atrophy** • Brain volume (MRI)[3] **Burden and Quality of Life** • Participant QoL[4] and caregiver burden	**Biomarkers** • CSF[5] and plasma biomarkers of neuronal injury and neuro-inflammation **Overall Survival**

Plan to initiate trial by year-end 2023

Plan to enroll sites in U.S., Canada, Europe, and Japan

1. PSPRS, Progressive Supranuclear Palsy Rating Scale 2. MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale 3. MRI, magnetic resonance imaging 4. QoL, quality of life
5. CSF, cerebrospinal fluid

PSP Meets Rigorous Criteria for Our Next Potential Indication for AMX0035

- ☑ Clear unmet need
- ☑ Strong scientific rationale
- ☑ Biomarker evidence
- ☑ Adjacencies and synergies with ALS
- ☑ Existing and robust understanding of the natural history of the disease
- ☑ Interest and support from KOLs and advocacy groups

AMYLYX

Q&A Session