ORION: A Global Phase 2b/3, Randomized, Double-Blind, Placebo-Controlled Trial of AMX0035 in Progressive Supranuclear Palsy (A35-009)

Anne-Marie Wills,[1] Günter Höglinger,[2] Lahar Mehta,[3] Mathias Leinders,[3] Yuehui Wu,[3] Jamie Timmons,[3] Amanda Hayden,[3] Ikuko Aiba,[4] Angelo Antonini,[5] Adam Boxer,[6] Yaroslau Compta,[7] Jean-Christophe Corvol,[8] Anthony E. Lang,[9] Huw R. Morris,[10] Per Svenningsson,[11] Henrik Zetterberg,[12] Lawrence Golbe[13]

[1]Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA; [2]Ludwig-Maximilians-University Hospital, Munich, Germany; [3]Amylyx Pharmaceuticals, Inc., Cambridge, Massachusetts, USA; [4]National Hospital Organization Higashinagoya National Hospital, Nagoya, Japan; [5]University of Padua, Padua, Italy; [6]University of California, San Francisco, California, USA; [7]Hospital Clínic de Barcelona/IDIBAPS/UBNeuro Institute of the University of Barcelona, Barcelona, Catalonia, Spain; [8]Sorbonne Université, Assistance Publicque Hôpitaux de Paris, Paris Brain Institute – ICM, Inserm, CNRS, Department of Neurology, Pitié-Salpêtrière Hospital, Paris, France; [9]Edmond J. Safra Program in Parkinson's Disease and the Rossy PSP Centre, University Health Network and the University of Toronto, Toronto, Canada; [10]University College London Queen Square Institute of Neurology, London, United Kingdom; [11]Karolinska Institutet, Solna, Sweden; [12]University of Gothenburg, Göteborg, Sweden; [13]Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA*

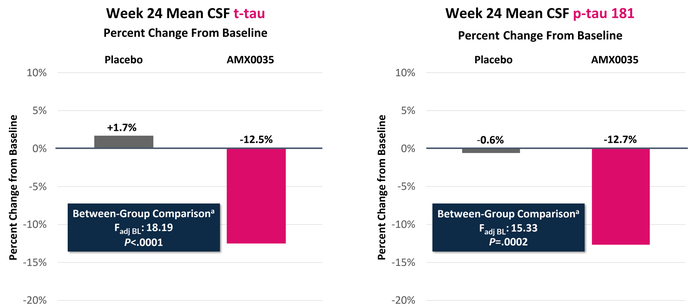
Abstract 636

AMYLYX

BACKGROUND

- AMX0035 is a fixed-dose combination of sodium phenylbutyrate and taurursodiol (also known as ursodoxicoltaurine) hypothesized to simultaneously target endoplasmic reticulum (ER) stress and mitochondrial dysfunction,[1,2] pathways relevant across neurodegenerative diseases, including progressive supranuclear palsy (PSP)[3]
  - Similar to PSP, ER stress and mitochondrial dysfunction are implicated in the pathogenesis of Alzheimer's disease (AD)[3-5]
- The efficacy and safety of AMX0035 has been evaluated in a randomized, placebo-controlled clinical trial in AD[6]
  - Although the primary clinical efficacy endpoint was not met, AMX0035 significantly impacted cerebrospinal fluid (CSF) AD biomarkers, including tau **(Figure 1)**, and markers of synaptic/neuronal degeneration, gliosis, and DNA oxidation[6]
  - AMX0035 was generally well tolerated with an acceptable safety profile; gastrointestinal events occurred with greater frequency in the AMX0035 group[6]
- In June 2024, refinements to the ORION trial design were implemented to allow earlier answers as to whether AMX0035 can slow disease progression in PSP

FIGURE 1. AMX0035 SIGNIFICANTLY LOWERED CSF TAU IN AD[6]



[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.

OBJECTIVE

- To describe the refined design of ORION, a phase 2b/3 clinical trial assessing efficacy and safety of AMX0035 in people living with PSP (PLWPSP)

TRIAL DRUG ADMINISTRATION

- Study drug will be provided as a powder packaged in single-use packets to be dissolved in 250 mL or 8 oz of room temperature water and administered orally
- Initially taken once daily in the morning until Week 2 visit; if tolerated, dosage will be increased to twice daily (1 packet in the morning and 1 in the evening)

CONCLUSIONS

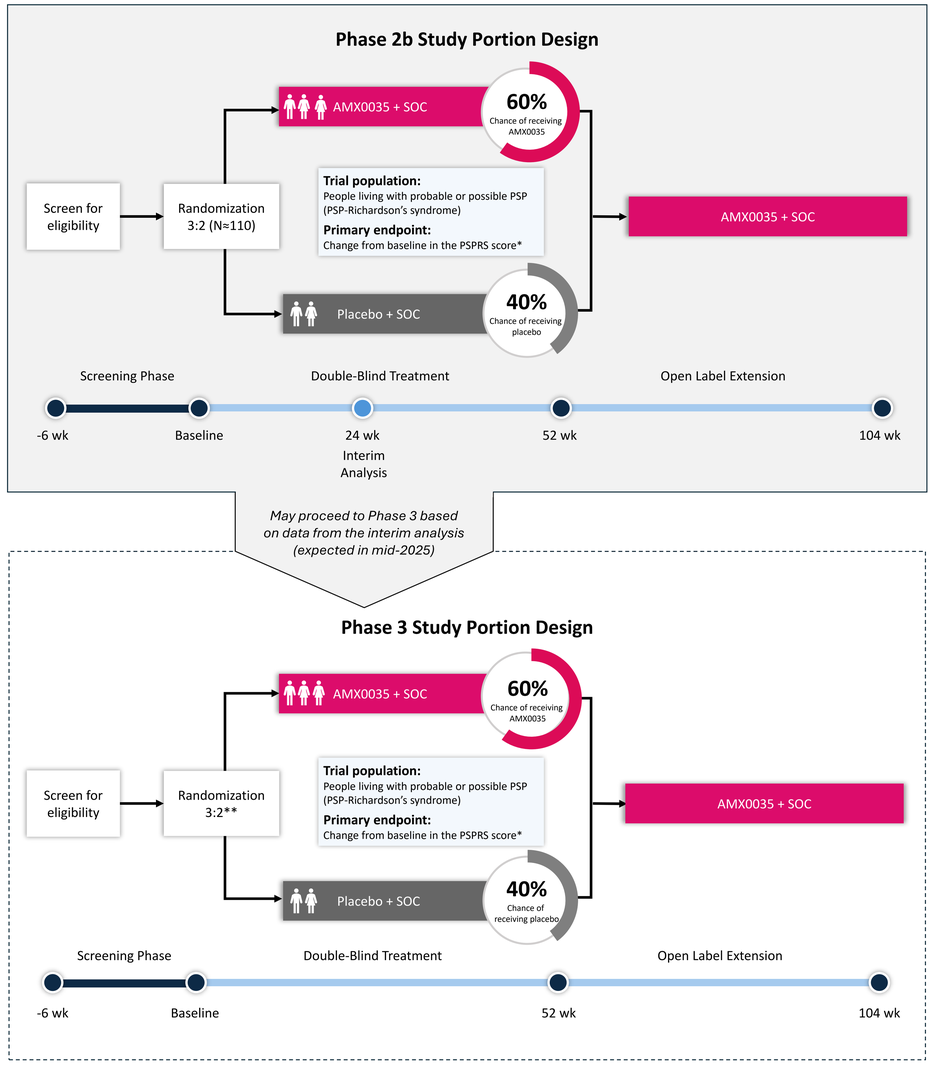
- AMX0035 is proposed to mitigate tau pathology in PSP through multiple pathways
- Refinements of the ORION trial to a seamless phase 2b/3 design will provide answers as to whether AMX0035 can slow disease progression in PSP earlier than originally planned
- Findings from the ORION study may benefit PLWPSP as well as inform the development of therapies for other neurodegenerative diseases
- Global enrollment commenced in late 2023 and is ongoing

AMX0035 is an investigational drug for both PSP and AD and has not been approved for use by any health authority (e.g., the EMA, FDA, PMDA and Health Canada).

STUDY DESIGN

- ORION is a phase 2b/3, double-blind, randomized, placebo-controlled, multicenter clinical trial **(Figure 2)**
- The primary objective of the ORION trial is to assess the impact of AMX0035 compared to placebo on disease progression rate as measured by the Progressive Supranuclear Palsy Rating Scale (PSPRS)
- The phase 2b portion of ORION will be conducted in the United States and Europe
  - Trial recruitment started in late 2023 and is ongoing
  - A total of ≈110 participants will be enrolled in the phase 2b study portion
- The phase 3 portion of ORION may be initiated based on results of the phase 2b interim analysis, which is expected to be completed in mid-2025
  - The study design and endpoints for the phase 3 portion are analogous to those of the phase 2b portion
- An open-label extension (OLE) phase will be available for continued access to AMX0035 for participants who complete the randomized phase of either study portion

FIGURE 2. ORION TRIAL DESIGN



SOC, standard of care; PSPRS, Progressive Supranuclear Palsy Rating Scale.
*Given regional regulatory feedback, the 10-item PSPRPS is the primary endpoint in the United States and the 28-item PSPRS is the primary endpoint outside of the US; for each region, the other form of the PSPRS is considered a secondary endpoint
**Participants in the Phase 2b study portion will not be eligible to take part in the Phase 3 portion

Key Eligibility Criteria

- ✓ Adults aged 40-80 years
- ✓ Meet criteria for the diagnosis of **possible or probable PSP,** also known as PSP-Richardson syndrome, based on International Parkinson and Movement Disorder Society 2017 criteria[7]
- ✓ Presence of PSP symptoms for <5 years
- ✓ Able to walk 5 steps with minimal assistance (stabilization of 1 arm)
- ✓ PSPRS total score (28-item) <40
- ✓ Minimum score of 24 on the Mini Mental State Examination
- ✓ Stable dosing of antiparkinsonian drugs for 60 days and other drugs for 30 days
- ✓ Have a trial partner who has ≥10 hours per week of contact with the participant, and who can attend study visits and provide information on participant abilities

Endpoints

(P) Primary Endpoint (S) Secondary Endpoint (E) Exploratory Endpoint

Week 52

Disease Progression
- (P) Total PSP Rating Scale (PSPRS) score (28-item)*
  - The PSPRS is a clinician-rated instrument designed to assess disability and severity in PLWPSP and is used as a primary endpoint in many therapeutic trials in PSP[8]
- (S) Modified 10-item PSPRS score*

Activities of Daily Living
- (S) MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II score (motor aspects of activities of daily living)
- (E) Schwab and England Activities of Daily Living (SEADL) Scale

Safety and Tolerability
- (S) Frequency of treatment-emergent adverse events and serious adverse events

Burden and Quality of Life
- (E) Clinical Global Impression of Severity (CGI-S) and Change (CGI-C)
- (E) Montreal Cognitive Assessment score
- (E) EuroQuality of Life (EQ5D-5L)
- (E) Zarit Burden Interview (caregiver burden)
- (E) Medical resource utilization parameters

Brain Atrophy
- (E) Brain regional volumes as measured by MRI

Biomarkers
- (E) CSF and plasma biomarkers of neuronal injury and neuroinflammation

Survival
- (E) Overall survival (from randomization to death)

Scan to Learn More about the ORION Trial

Contact Info: Nathalie Erpelding
nathalie_erpelding@amylyx.com

Acknowledgments
The authors would like to thank the members of the global steering committee for the ORION trial as well as people living with PSP, their caregivers and family members, and advocacy organizations CurePSP and PSPA for providing feedback and advice on the study design.
This study is sponsored by Amylyx Pharmaceuticals, Inc.

Disclosures
AW, GH, IA, AA, AB, YC, JCC, AL, HM, PS, AW, HZ, LG are members of the Steering Committee for the ORION trial.
LM, ML, YW, JT, and **AH** are full-time employees of and may have stock option ownership in Amylyx Pharmaceuticals, Inc.

References
1. Paganoni S, et al. *N Engl J Med.* 2020;383(10):919-930. **2.** Paganoni S, et al. Supplemental appendix. *N Engl J Med.* 2020;383(10):919-930. Accessed October 2, 2023. https://www.nejm.org/doi/full/10.1056/nejmoa1916945. **3.** Coughlin DG, Litvan I. *Parkinsonism Relat Disord.* 2020;73:105-116. **4.** Agrawal I, Jha S. *Front Aging Neurosci.* 2020;12:252. **5.** Hashimoto S, Saido TC. *Open Biol.* 2018;8(4):180024. **6.** Arnold SE, et al. *Alzheimer's Dement.* 2024; 10:e12487. **7.** Höglinger GU, et al. *Mov Disord.* 2017;32(6):853-64. **8.** Golbe LI, Ohman-Stricland PA. *Brain.* 2007;160(Pt 6):1552-65.

Presented at The International Congress of Parkinson's Disease and Movement Disorders; September 27 – October 1, 2024; Philadelphia, PA, US