Design of a Global Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial of AMX0035 in Progressive Supranuclear Palsy (A35-009 ORION)

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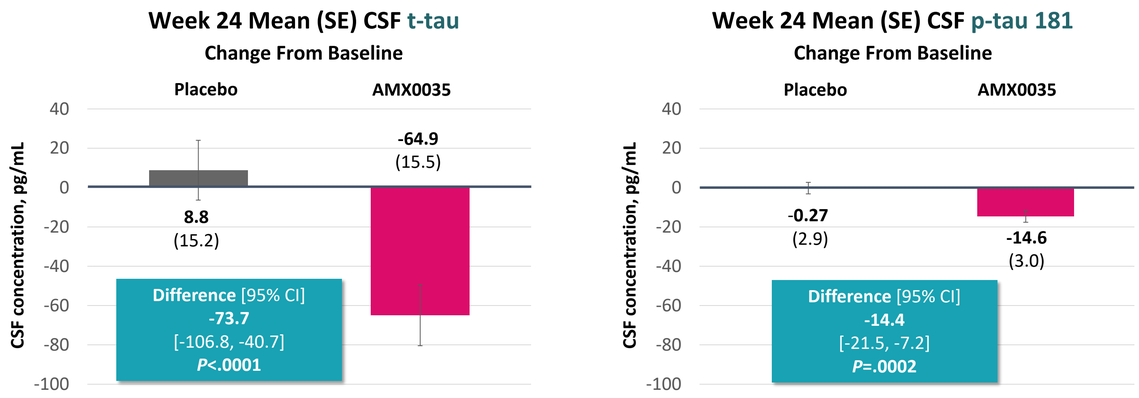
BACKGROUND

- 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 amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD)[2-5]
- The efficacy and safety of AMX0035 has been evaluated in randomized, placebo-controlled clinical trials in ALS and AD[1,6]
  - In ALS, AMX0035 significantly slowed disease progression and prolonged survival[1,7]
  - In AD, although primary end point 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]
  - In both trials, AMX0035 was generally well tolerated with an acceptable safety profile; gastrointestinal events occurred with greater frequency in the AMX0035 group[1,6]

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



OBJECTIVE

- To describe the design of ORION, a phase 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)

STUDY DESIGN

- ORION is a phase 3, double-blind, randomized, placebo-controlled, multicenter, clinical trial **(Figure 2)**
- The ORION trial was designed with the input of the global ORION steering committee and PLWPSP, their caregivers and family members, and advocacy groups **(Table 1)**
- ORION will be conducted in Europe, Japan, and North America, enrolling ≈600 participants at ≈100 sites
  - Trial recruitment is expected to start in late 2023
  - An open-label extension (OLE) phase will be available for continued access to AMX0035 for participants who complete the randomized phase

We would like to acknowledge key global academic leaders, people living with PSP, their caregivers, and industry advocacy groups who contributed to the ORION trial design

TABLE 1. CONTRIBUTORS PROVIDING FEEDBACK ON ORION TRIAL DESIGN

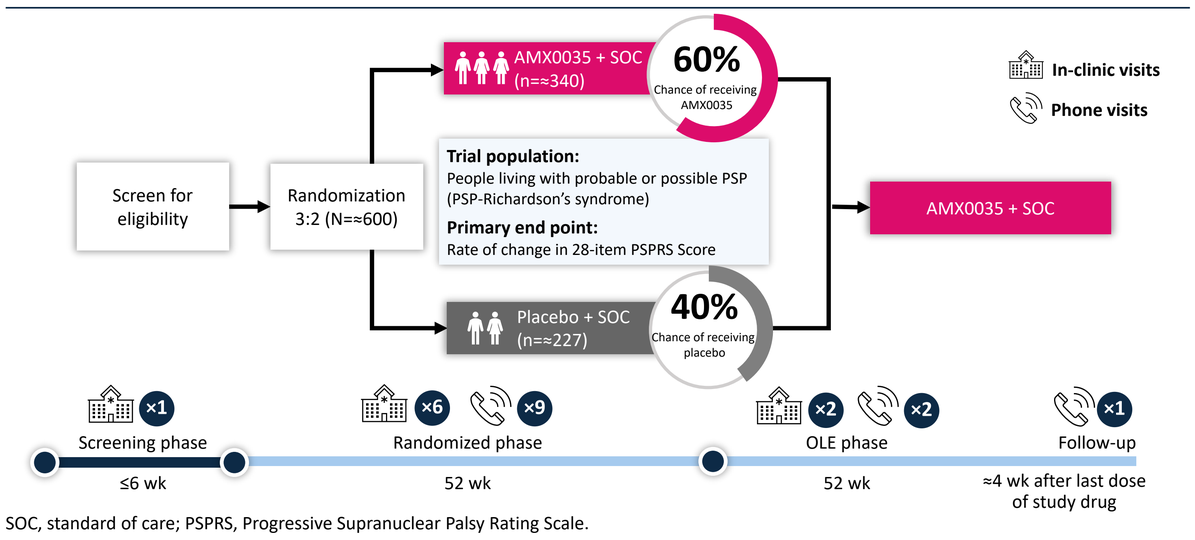
Global Steering Committee		PSP Advocacy Groups	Other Contributors
Ikuko Aiba	Günter Höglinger	curePSP — UNLOCKING THE SECRETS OF BRAIN DISEASE®	• Roger Bowley
Angelo Antonini	Anthony E. Lang	PSPA — CREATING A BETTER FUTURE FOR PEOPLE LIVING WITH PSP & CBD	• Diane and Doug Deaver
Adam Boxer	Huw R. Morris		• Su Hilty
Yaroslau Compta	Per Svenningsson		• Tonya Hudson
Jean-Christophe Corvol	Anne-Marie Wills		• Lori Kinsler
Lawrence Golbe	Henrik Zetterberg		• Thomas Loewald
			• Janet
			• Rob, Lexi, and Chris Naylor
			• Linda and Jack Phillips
			• Tanaka Shirley
			• Virgie Caraway

CONCLUSIONS

- AMX0035 is proposed to mitigate tau pathology in PSP through multiple pathways
- Findings from the ORION study may benefit PLWPSP as well as inform the development of therapies for other neurodegenerative diseases
- Global enrollment commences in late 2023

AMX0035 is an investigational drug for both PSP and AD and has not been approved for use by any health authority (eg, the EMA, FDA, PMDA and Health Canada).
AMX0035 is an investigational drug in the European Union, UK, and Switzerland and not currently approved for use in ALS.

FIGURE 2. ORION TRIAL DESIGN



SOC, standard of care; PSPRS, Progressive Supranuclear Palsy Rating Scale.

SELECT ELIGIBILITY CRITERIA

Key Eligibility Criteria

- ✓ Adults aged 40-80 years
- ✓ Meet criteria for the diagnosis of **probable or possible PSP (see below)**
- ✓ Presence of PSP symptoms for <5 years
- ✓ Be able to walk 5 steps with minimal assistance (stabilization of 1 arm)
- ✓ PSPRS total score (28-item) <40
- ✓ Live outside of a nursing home or dementia care facility
- ✓ 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
- ✓ Participants must NOT require the use of feeding tube

Criteria for diagnosis **probable or possible PSP** (PSP-Richardson's syndrome) according to International Parkinson and Movement Disorder Society (MDS) Criteria 2017[8]

- Gradually progressive disorder with age at disease onset ≥40 years
- Either or both of the following 2 items are met:
  - **Probable PSP-Richardson's syndrome**: (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)
  - **Possible PSP-Richardson's syndrome**: Slow velocity of vertical saccades AND postural instability with >2 steps backward on the pull-test within 3 years

Participants should be willing/able to undergo a brain magnetic resonance imaging (MRI) and lumbar puncture twice during randomized phase and 1 additional time during OLE phase

ENDPOINTS

*Secondary end points
**Exploratory end points

Week 52

Disease Progression

- **Total PSP Rating Scale (PSPRS, 28-items): PRIMARY END POINT**
  - PSPRS is a clinician-rated instrument designed to assess disability and severity in PLWPSP using 28 items across 6 domains and is used as a primary end point in many therapeutic trials in PSP[9]
- Modified 10-item PSPRS score*

Activities of Daily Living

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

Safety and Tolerability

- Frequency of treatment-emergent adverse events and serious adverse events*

Burden and Quality of Life

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

Brain Atrophy

- Brain regional volumes as measured by MRI**

Biomarkers

- CSF and plasma biomarkers of neuronal injury and neuroinflammation**

Survival

- Overall survival (from randomization to death)**

Acknowledgments
The authors would like to thank the members of the global steering committee for the ORION trial as well as PLWPSP, their caregivers and family members, and advocates for providing feedback and advice on the study design. Medical writing support for this presentation was provided by PRECISIONscientia under direction of the authors and funded by Amylyx.
This study is sponsored by Amylyx Pharmaceuticals, Inc.

Disclosures
GH, IA, AA, AB, YC, 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.

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Presented at Neuro2023: The PSP and CBD International Research Symposium; October 19-20, 2023; London, United Kingdom