ORION

Reflections on the Amylyx ORION Trial: Informing Future PSP Research

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neuro 2026

The PSP and CBD International Research Symposium

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Please Note

- AMX0035 is an investigational drug and has not been approved by any health authority
- This presentation is intended to provide scientific information about AMX0035. The statements and content shared in the presentation have not been evaluated by any health authority

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Every PSP Trial Advances Understanding of the Disease

Clinical trials generate insights beyond efficacy outcomes. ORION provided valuable experience in participant selection, endpoint assessment, and global trial execution that may help inform future PSP research.

DESIGN

- **Population selection**: earlier PSP-RS, for diagnostic confidence
- **Endpoint strategy**: scales chosen under differing regional expectations



CONDUCT

- **Global execution**: 43 sites, 4 countries
- **Participant considerations**: visit burden, accessibility, caregiver role

INTERPRETATION

- **Clinical outcomes**: 24-week results across both primary endpoints
- **Endpoint concordance**: 10-item vs 28-item PSPRS

FUTURE RESEARCH

- **Remaining questions:** Identification, measurement, follow-up duration
- **Opportunities moving forward**: Shared PSP data resources and informed consent considerations

ORION represents one of the largest global interventional PSP studies and provides lessons that extend beyond a single development program.

ORION Learning

PSP-RS, Progressive Supranuclear Palsy-Richardson Syndrome; PSPRS, Progressive Supranuclear Palsy Rating Scale

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The PSP Community Made ORION Possible

ORION was made possible by the collective expertise, perspectives, and commitment of the PSP community.

GLOBAL STEERING COMMITTEE

Providing scientific and strategic guidance across study design, conduct, interpretation, and key program decisions.

- Ikuko Aiba
- Angelo Antonini
- Adam Boxer
- Yaroslau Compta
- Jean-Christophe Corvol
- Lawrence Golbe
- Günter Höglinger
- Anthony E. Lang
- Huw R. Morris
- Per Svenningsson
- Anne-Marie Wills
- Henrik Zetterberg

PSP ADVOCACY GROUPS

curePSP
UNLOCKING THE SECRETS OF BRAIN DISEASE®

PSPA
CREATING A BETTER FUTURE FOR PEOPLE LIVING WITH PSP & CBD

PSP COMMUNITY, TRIAL PARTICIPANTS, AND CAREGIVERS

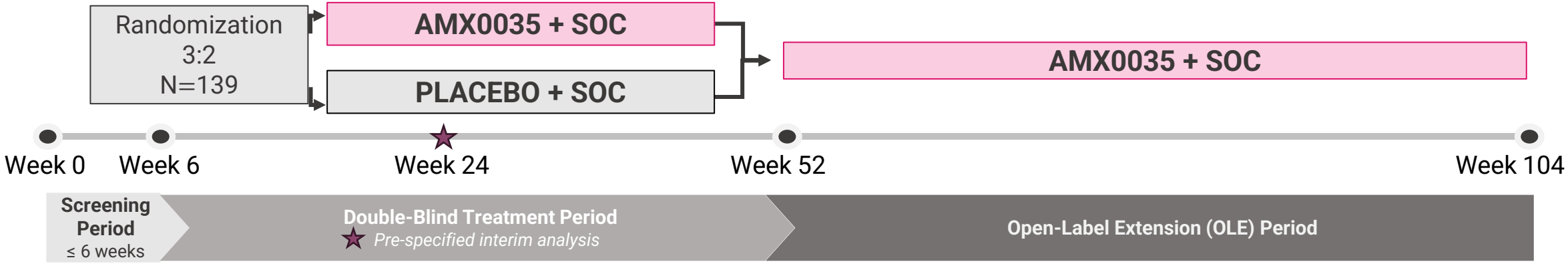
We extend our deepest gratitude to the PSP community members who provided feedback and advice on the study design, and to the trial participants and caregivers whose commitment made ORION possible and advanced PSP research.

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Key Design Choices Shaped ORION

ORION randomized 139 participants 3:2 to AMX0035 or placebo, with an interim analysis at 24 weeks and an open-label extension.



FOUNDATIONAL DESIGN CHOICES

Enrolling earlier in the disease course

Selecting PSP-Richardson syndrome earlier was intended to maximize diagnostic confidence and increase the likelihood of measurable progression during the study period.

Leveraging a seamless Phase 2b/3 design

The seamless design enabled an early assessment of efficacy and operational feasibility before the decision to proceed to Phase 3.

Pairing a controlled period with open-label access in a rapidly progressive condition, guaranteed access to active treatment after the double-blind period and supported enrollment and retention.

SOC, standard of care

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ORION Enrolled a Well-Defined PSP Cohort

*The enrolled population closely reflected the intended trial population balanced across treatment groups. Mean PSPRS and SE-ADL values were consistent with **less** disease burden than davunetide and/or tilavonemab trials.*

Parameter	AMX0035 (n = 83)	Placebo (n = 56)
Time Since PSP Diagnosis (Months)		
Mean (SD)	16.68 (12.67)	15.04 (12.06)
Protocol-defined PSP Richardson Diagnosis*, n (%)		
Probable	80 (96.4)	55 (98.2)
Possible	3 (3.6)	1 (1.8)
Baseline use of Parkinson medication, n (%)		
Yes	52 (62.7)	39 (69.6)
No	31 (37.3)	17 (30.4)
PSPRS (28-item) Total Score		
Mean (SD)	29.7 (6.51)	29.7 (6.77)
PSPRS (10-item) Total Score		
Mean (SD)	8.6 (3.05)	8.3 (3.19)
SE-ADL by Rater		
Mean (SD)	64.5 (18.56)	68.1 (16.33)
CSF Neurofilament Light Chain (NfL, pg/mL)	n=75	n=50
Mean (SD)	2466.77 (2209.27)	2194.63 (950.613)

Mean values consistent with **less** disease burden than davunetide and/or tilavonemab trials

* Protocol defined PSP-RS based on MDS criteria from Höglinger et al 2017. PSPRS, Progressive Supranuclear Palsy Rating Scale; SE-ADL, Schwab and England Activities of Daily Living Scale; CSF, cerebrospinal fluid. Data on File. Amylyx Pharmaceuticals, Inc.

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Lessons from Global Trial Operations

Screening 220 participants across 43 sites in four countries surfaced practical lessons in site training, participant support, and community engagement.

Engagement across participants, caregivers, and the community

Participant engagement

- Audio-administered materials supported participants with oculomotor impairment who could not reliably complete written assessments.

Caregiver partnership

- In a rapidly progressive condition, caregivers supported longitudinal participation and provided essential context for day-to-day function. Maintaining a consistent informant across visits reduced variability in caregiver-reported outcomes.

Community input

- Advocacy and participant feedback on visit burden and assessment sequencing informed protocol refinements.

Site training and selection

Site training and reinforcing consistent screening criteria were critical to reliable assessments and standardized trial execution.

Country	Sites	Screened	Screen Failed	Randomized
Germany	2	5	1	4
Italy	4	26	5	21
Spain	5	15	1	14
USA	32	174	74	100
TOTAL	**43**	**220**	**81**	**139**

European sites screened after the US and applied US training experience. Screen failure fell from 43% to 15%, supported by strong waiting lists at activation.

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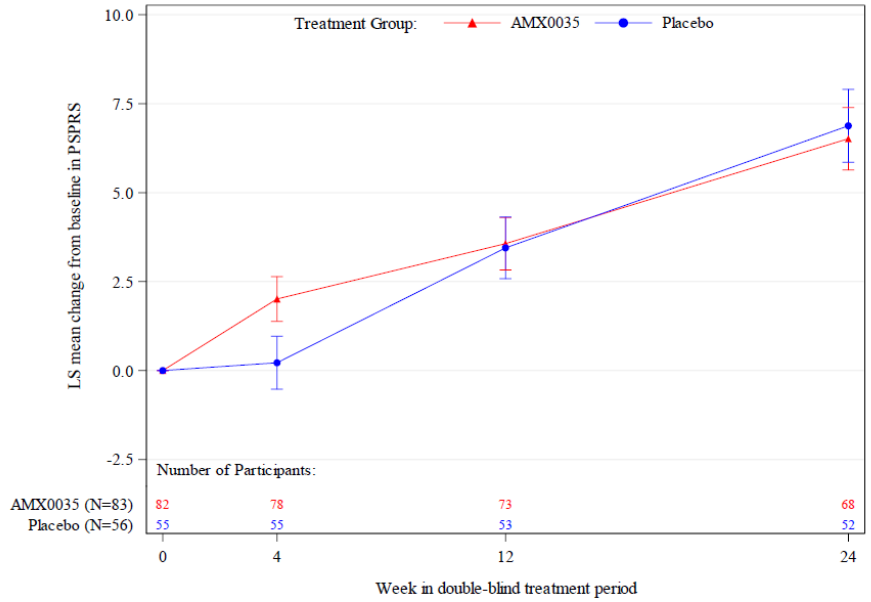
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Consistent Results with Different PSPRS Endpoints

Disease Worsening

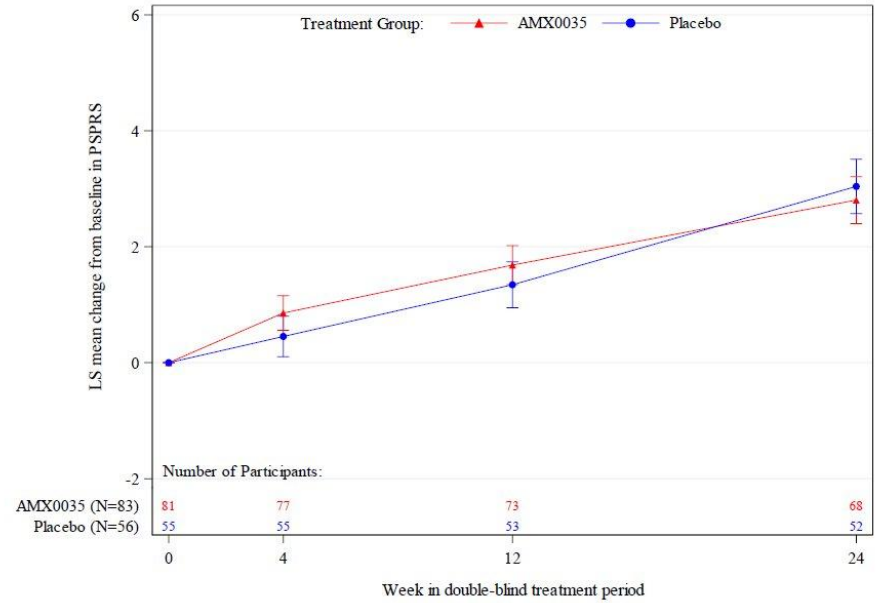
28-Item PSPRS

Primary outside of the United States



10-Item PSPRS

Primary in the United States



Different regional endpoint strategies led to a consistent conclusion

Regional regulatory feedback led to different primary endpoints in each region, with the alternate version designated secondary. Both scales produced similar conclusions at 24 weeks.

PSPRS: Progressive Supranuclear Palsy Rating Scale. Data on File. Amylyx Pharmaceuticals, Inc.

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Remaining Challenges in PSP Clinical Development



Earlier Identification

How can appropriate participants be identified earlier and with greater diagnostic confidence?



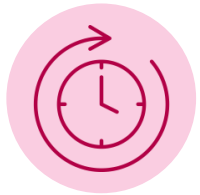
Measuring Clinical Change

Which outcomes can sensitively and consistently capture meaningful progression?



Biomarker Integration

Can fluid measures complement clinical scales in PSP trials?



Determining Optimal Follow-Up

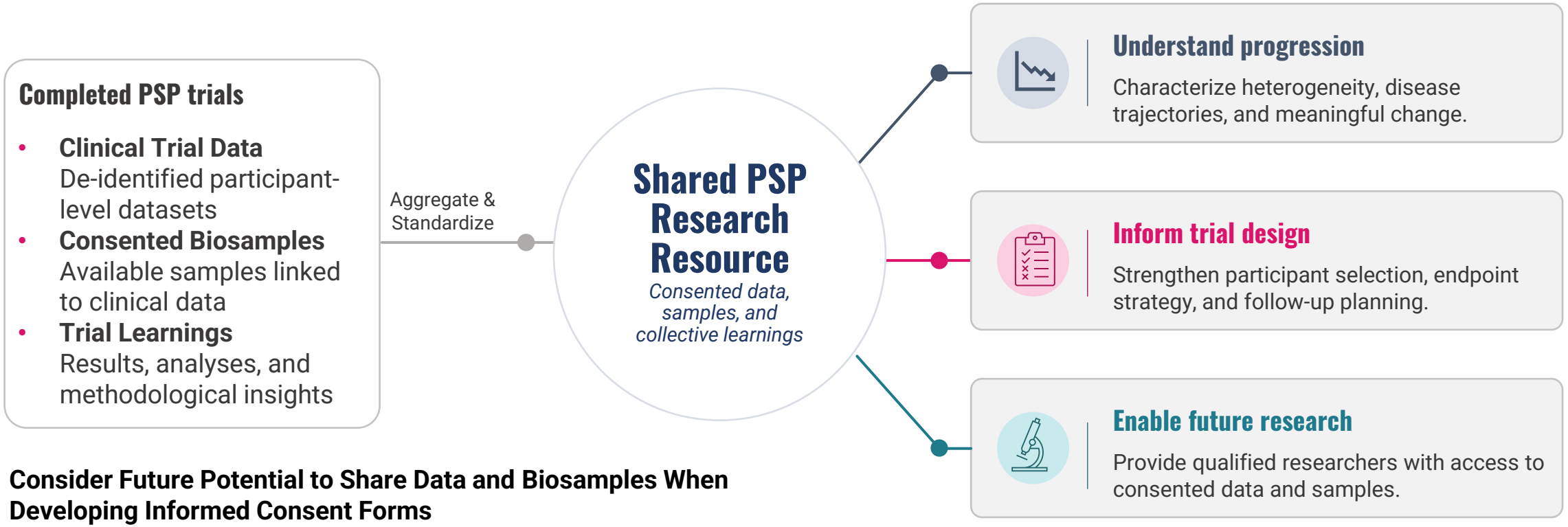
How long is needed to detect clinically meaningful change or a treatment effect?

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A Shared PSP Research Resource Could Accelerate the Field

Data from completed trials, including those that did not meet their endpoints, retain substantial value for the field.



Consider Future Potential to Share Data and Biosamples When Developing Informed Consent Forms

A MODEL FROM ALS

PRO-ACT

The Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database aggregates and standardizes data from public and private trials into a common structure, enabling open-science collaboration across the ALS field.

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THANK YOU

Questions & Discussion

We extend our sincere gratitude to the ORION investigators, participants, and caregivers, the Global Steering Committee, advocacy organizations, and people living with PSP and their caregivers, whose insights, feedback, and guidance were instrumental in shaping the study design.

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