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

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Note

AMX0035 (sodium phenylbutyrate and taurursodiol [also called ursodoxicoltaurine]; RELYVRIO®) is approved by the US FDA for treatment of ALS and approved with conditions by Health Canada. AMX0035 is an investigational drug for ALS in the European Union and UK and not currently approved for use

PSP and AD are investigational indications for AMX0035; for these indications, AMX0035 has not yet been approved by any health authority (eg, EMA, FDA, PMDA, Health Canada)

This presentation is intended to provide scientific information about AMX0035 and the ORION trial in PSP. The statements and content shared in this presentation have not been evaluated by any health authority

AD, Alzheimer's disease; EMA, European Medicines Agency; US, United States; FDA, US Food and Drug Administration; PSP, progressive supranuclear palsy; PMDA, Pharmaceuticals and Medical Devices Agency (Japan).

About AMX0035

Proprietary fixed-dose combination of 2 small molecules, sodium phenylbutyrate and taurursodiol[1]

- Taurursodiol is the official chemical name for tauroursodeoxycholic acid (TUDCA)[1]
- Ursodoxicoltaurine is the International Nonproprietary Name for TUDCA[2] and is used in Canada and Europe[3,4]

AMX0035 is an oral suspension[1,5]

- Powder packaged in single-use packets
- Stirred into water and administered by mouth

1. Paganoni S, et al. *N Engl J Med*. 2020;383(10):919-930. **2.** Ursodeoxycholic acid. Clinical Drug Experience Knowledgebase. Accessed February 15, 2024. https://www.cdek.liu.edu/api/47109/. **3.** Albrioza. Product monograph. Amylyx Pharmaceuticals Inc; 2023. **4.** Albrioza. European Medicines Agency. Accessed February 15, 2024. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/albrioza. **5.** Paganoni S, et al. Supplementary appendix. *N Engl J Med*. 2020;383(10):919-930. Accessed February 15, 2024. https://www.nejm.org/doi/full/10.1056/nejmoa1916945.

Multiple Pathways Likely Contribute to Tau Dysfunction and Aggregation in PSP[1,2]

A Genetic variants[2]

B ER stress and UPR[3-5]

C Mitochondrial dysfunction[6]

D Neuro-inflammation[7]

E Protein homeostasis defects[3,5]

Pathways implicated with tau dysfunction and aggregation in PSP; exact sequence of events is not yet fully understood

F Tau dysfunction and aggregation[3,7-9]

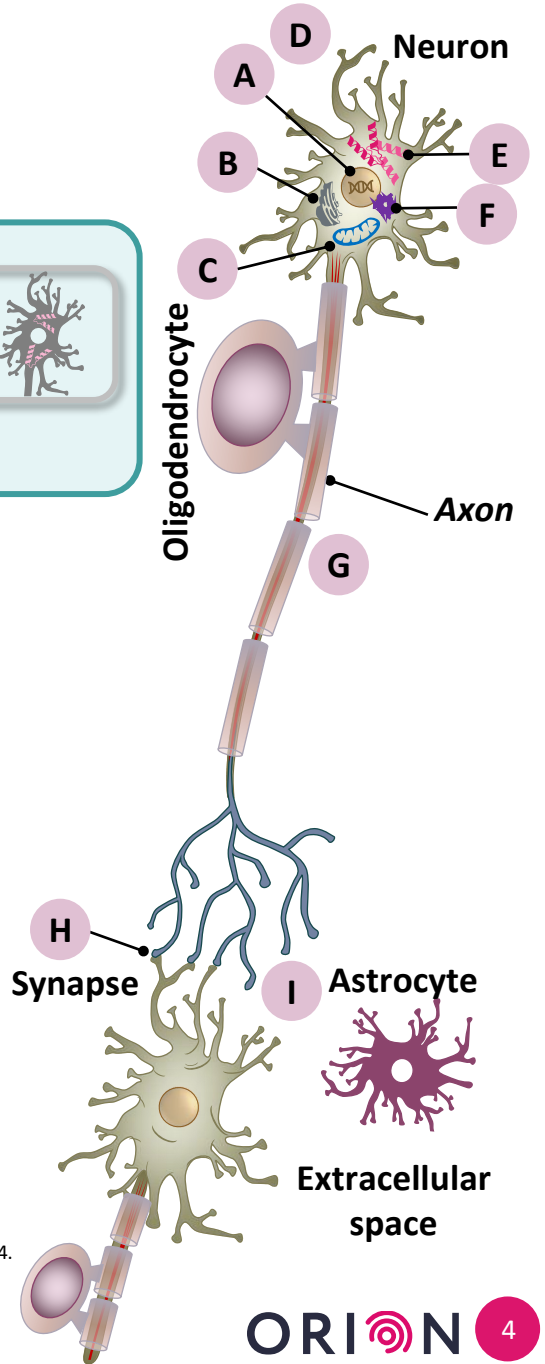
G Axonal defects[8,10]

H Intercellular tau spread[3]

I Glial-mediated spread[3]

Widespread neuronal cell death and neurodegeneration[8,10]

PSP



ER, endoplasmic reticulum; UPR, unfolded protein response.

1. Boxer AL, et al. *Lancet Neurol*. 2017;16(7):552-563. **2.** Coughlin DG, Litvan I. *Parkinsonism Relat Disord*. 2020;73:105-116. **3.** Rösler TW, et al. *Prog Neurobiol*. 2019;180:101644. **4.** Bruch J, et al. *EMBO Mol Med*. 2017; 9:371-384. **5.** Ghemrawi R and Khair M. *Int J Mol Sci*. 2020;21(17):6127. **6.** Stamelou M, et al. *Brain*. 2010;133(6):1578-90. **7.** Park HK, et al. *J Mov Disord*. 2021;14(2):103-113. 8. Stamelou M, et al. *Nat Rev Neurol*. 2021;17(10):601-620. **9.** Shoeibi A, et al. *Front Neurol*. 2019; 10:1125. **10.** Sarkar S, 2018. *J Genet*. 2018; 97(3):783-793.

AMX0035 Proposed MOA in PSP

A Genetic mutations[1]

B ER stress and UPR[2-4]

C Mitochondrial dysfunction[5]

D Neuro-inflammation[6]

E Protein homeostasis defects[2,4]

Pathways implicated with tau dysfunction and aggregation in PSP; exact sequence of events is not yet fully understood

F Tau dysfunction and aggregation[2,6-8]

G Axonal defects[7,9]

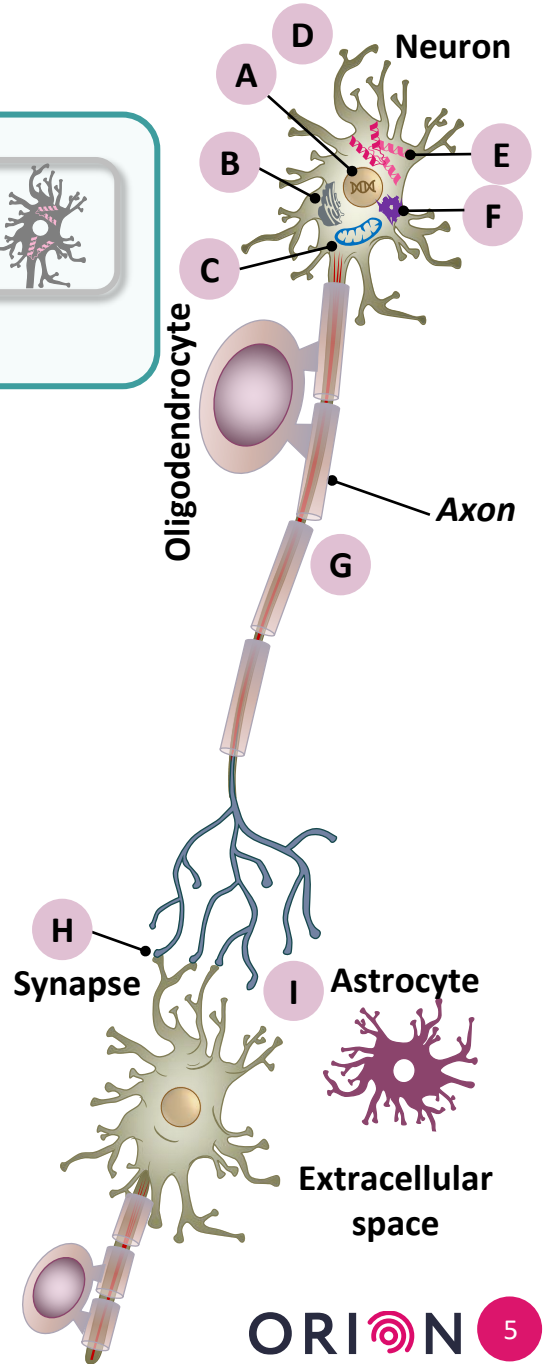
H Intercellular tau spread[2]

I Glial-mediated spread[2]

Widespread neuronal cell death and neurodegeneration[7,9]

PSP

AMX0035 is hypothesized to simultaneously mitigate ER stress/unfolded protein response and mitochondrial dysfunction[10-13]



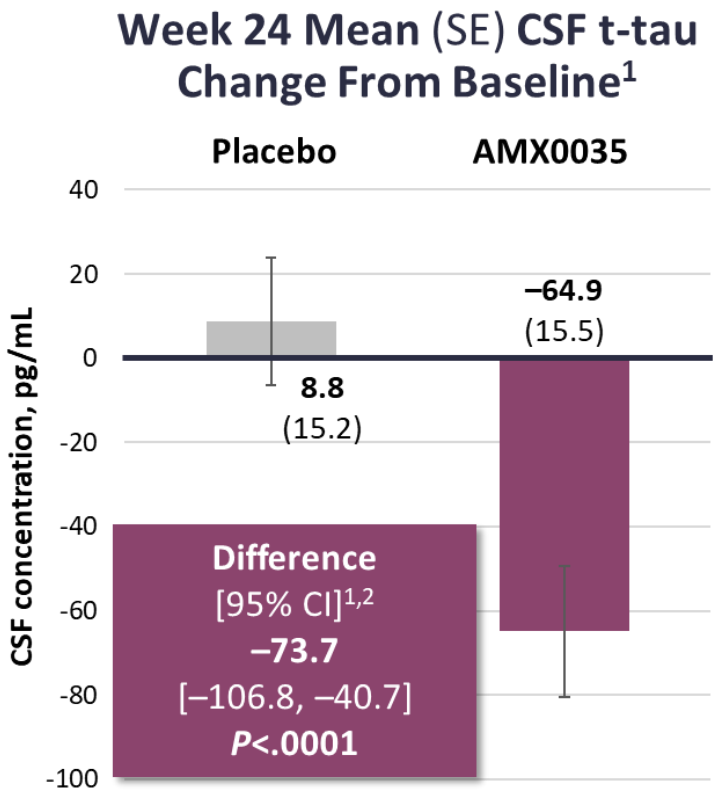
MOA, mechanism of action.

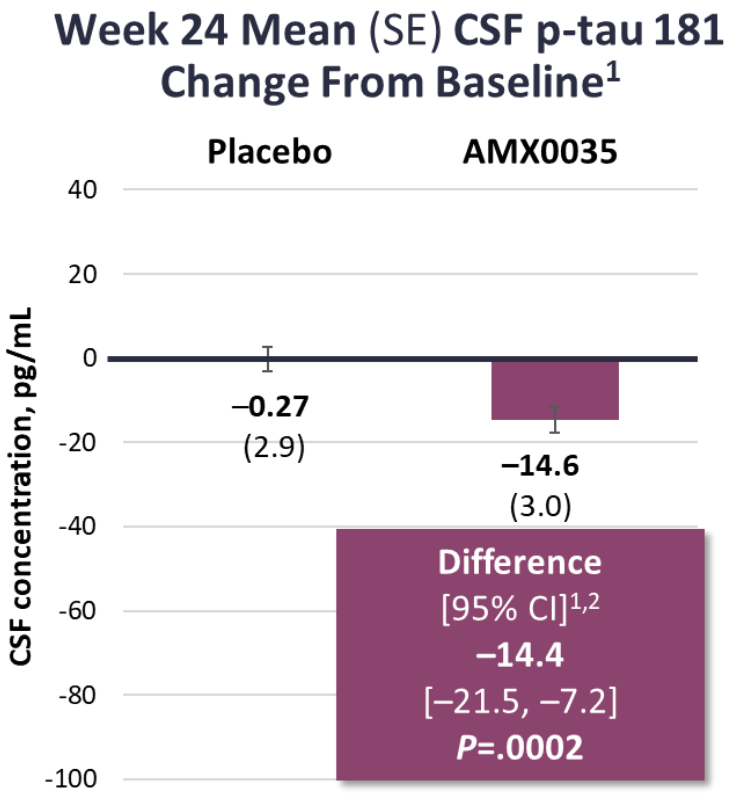
1. Coughlin DG, Litvan I. *Parkinsonism Relat Disord*. 2020;73:105-116. **2.** Rösler TW, et al. *Prog Neurobiol*. 2019;180:101644. **3.** Bruch J, et al. *EMBO Mol Med*. 2017; 9:371-384. **4.** Ghemrawi R and Khair M. *Int J Mol Sci*. 2020;21(17):6127. **5.** Stamelou M, et al. *Brain*. 2010;133(6):1578-90. **6.** Park HK, et al. *J Mov Disord*. 2021;14(2):103-113. Zhou W. *J Biol Chem*. 2011;286(17):14941-14951. **7.** Stamelou M, et al. *Nat Rev Neurol*. 2021;17(10):601-620. **8.** Shoeibi A, et al. *Front Neurol*. 2019; 10:1125. **9.** Sarkar S, 2018. *J Genet*. 2018; 97(3):783-793. **10.** Zhou W. *J Biol Chem*. 2011;286(17):14941-14951. **11.** Rodrigues CM, Steer CJ. *Expert Opin Investig Drugs*. 2001;10(7):1243-1253. **12.** Rodrigues CM, et al. *Biochemistry*. 2003;42(10):3070-3080. **13.** Khalaf K, et al. *Transl Neurodegener*. 2022;11(1):33.

Clinical efficacy and safety outcomes of AMX0035 in other neurodegenerative diseases that share common pathophysiology with PSP support further investigation of AMX0035 in PSP[1,2]

1. Paganoni S, et al. *N Engl J Med*. 2020;383(10):919-930. **2.** Arnold SE. Presented at: 15th Clinical Trials on Alzheimer's Disease Conference; November 29-December 2, 2022; San Francisco, CA.

• In the **phase 2a PEGASUS trial**, AMX0035 significantly lowered phospho-tau181 and total tau in the cerebrospinal fluid of people living with **AD**[1,2]





Tau Biomarkers Correlate With Proteomics[2]

- Analysis evaluated impact of AMX0035 on proteomic changes and how these changes correlated with the observed biomarker changes
- 288 proteins were quantified from PEGASUS samples
- AMX0035 affected 17 proteins spanning multiple pathways, but primarily those related to **tau and neurodegeneration**

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

SE, standard error; CSF, cerebrospinal fluid

1. Arnold SE, et al. J Prev Alzheimers Dis. 2022;9(suppl 1):S40-S41. CTAD abstract LB11. **2.** Cullen N, et al. Poster presented at the 16th Clinical Trials on Alzheimer's Disease (CTAD) Conference; October 24-27, 2023; Boston, Massachusetts.

- In the **phase 2 CENTAUR** trial, AMX0035 significantly slowed functional decline compared to placebo in people living with **ALS**[1]
  - In a post hoc exploratory analysis, a longer median survival was observed in the participants originally randomized to AMX0035[2]

Function[1]
ALSFRS-R total score

Difference of

2.32 points

at the end of 6-mo placebo-controlled period

0.42 point-per-month difference
(95% CI, 0.03–0.81; *P*=.03)

Survival[2,a]
ITT population

Originally randomized to **AMX0035** (n=89)

Originally randomized to **placebo** (n=48)

4.8-mo

LONGER MEDIAN SURVIVAL in the group originally randomized to AMX0035

36%

LOWER RISK OF DEATH in the group originally randomized to AMX0035;
HR, 0.64 (95% CI, 0.42–1.00; *P*=.048)

AMX0035 is an investigational drug in the European Union, UK, and Japan and not currently approved for use in ALS.

ALS, amyotrophic lateral sclerosis; CI, confidence interval; HR, hazard ratio
[a]Post-randomization follow up duration ≤ 42 months

1. Paganoni S, et al. *N Engl J Med*. 2020;383(10):919-930. **2.** Paganoni S, et al. *Muscle Nerve*. 2022;66:136-141.

• AMX0035 was generally well-tolerated in both **ALS** and **AD** clinical trials; diarrhea was most common adverse event[1-4]

		ALS[1,2]		AD[3,4]	
		AMX0035 (n=89)	Placebo (n=48)	AMX0035 (n=51)	Placebo (n=44)
Most common AEs, % (>5% of AMX0035 and ≥5% greater than placebo)	Diarrhea	21	19	16	7
	Abdominal pain	8	6	N/A[a]	N/A[a]
	Nausea	19	12		
	URTI	4	6		
	Fatigue	10	6		
	Salivary hypersecretion	10	2		
	Dizziness	12	6		
SAEs, %		12	19	6	2
Deaths, n (%)		5 (6)	2 (4)	0	0

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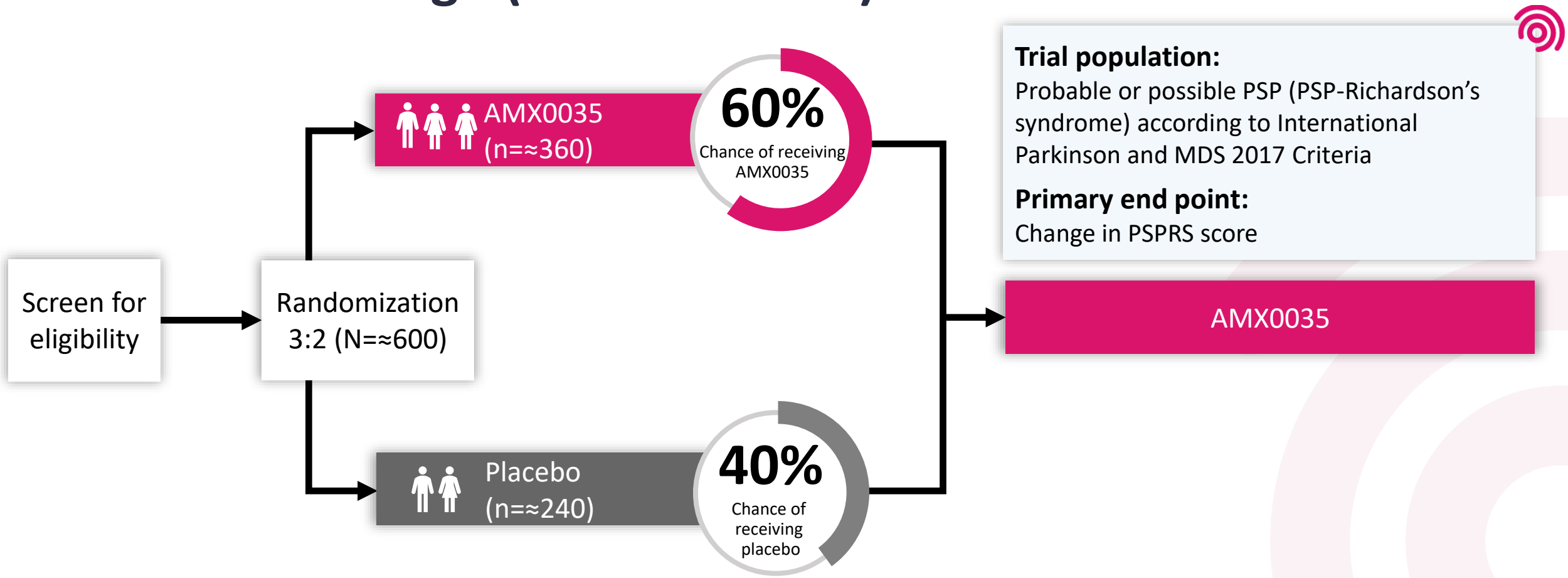
AMX0035 is an investigational drug in the European Union, UK, and Japan and not currently approved for use in ALS.

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AE, adverse reaction; SAE, serious adverse reaction; URTI, upper respiratory tract infection.
[a]>5% of AMX0035 and ≥5% greater than placebo threshold did not apply so not classified as most common AEs

1. Paganoni S, et al. *N Engl J Med*. 2020;383(10):919-930. **2.** Paganoni S, et al. *N Engl J Med.* 2020;383(10):919-930 (supplementary information). **3.** Arnold SE, Presented at CTAD 2022; December 1, 2022; San Francisco, CA.
4. Arnold SE, et al. Supplementary appendix. *J Prev Alzheimers Dis*. 2021;8;S125-S126.

Global, Phase 3, Double-Blind, Placebo-Controlled, Multicenter Trial to Evaluate AMX0035 in PSP

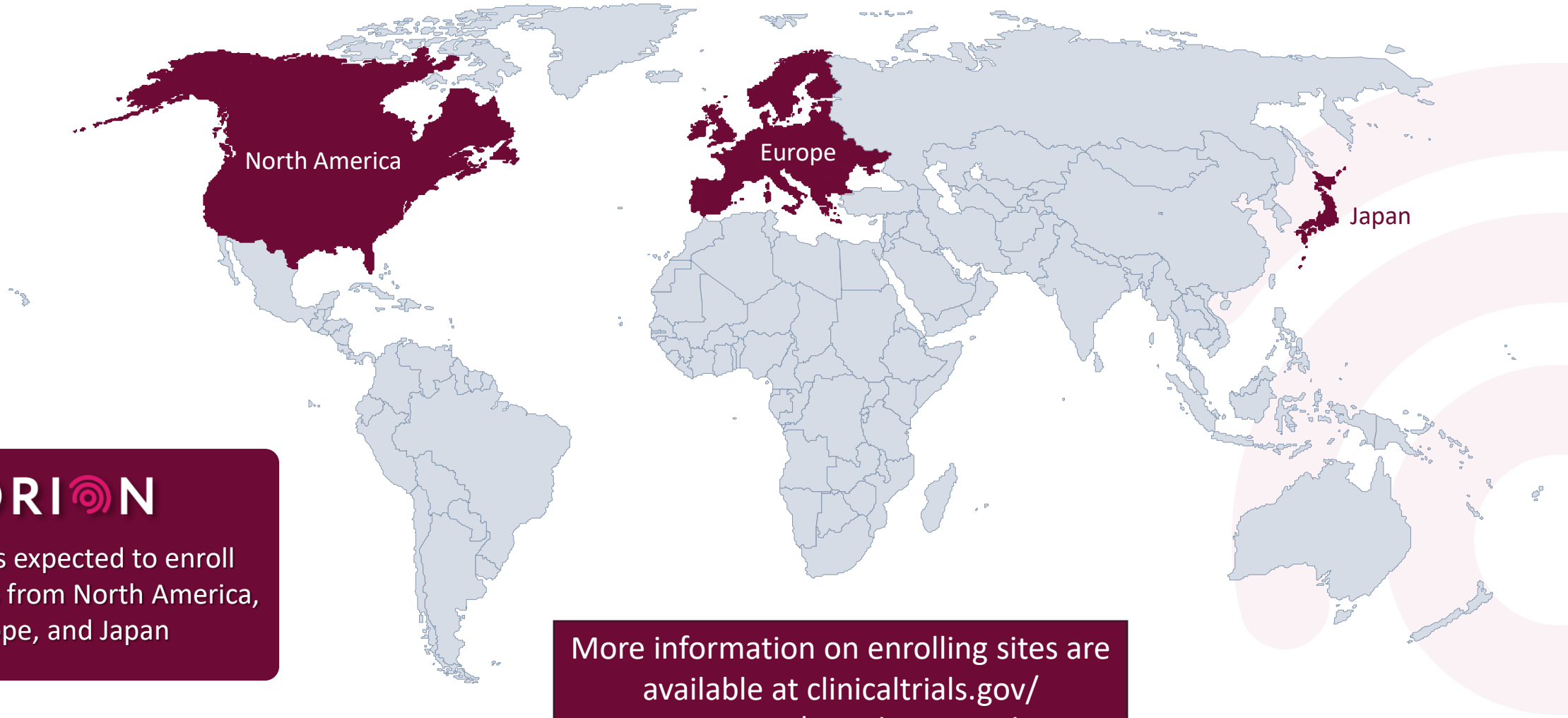
ORION Trial Design (NCT06122662)



OLE, open-label extension; SOC, standard of care; PSPRS, progressive supranuclear palsy rating scale

Clinicaltrials.gov https://clinicaltrials.gov/study/NCT06122662?intr=NCT06122662&rank=1. Accessed Nov 15, 2023

ORION: Study Locations



ORION

The trial is expected to enroll participants from North America, Europe, and Japan

More information on enrolling sites are available at clinicaltrials.gov/NCT06122662 | amylyxpsptrial.com

US, United States.
Clinicaltrials.gov https://clinicaltrials.gov/study/NCT06122662?intr=NCT06122662&rank=1. Accessed Nov 15, 2023

ORION: Key Eligibility Criteria

Key Eligibility Criteria[1]

- Adults aged 40 to 80 years
- Meet criteria for diagnosis of **probable or possible PSP** (PSP-Richardson's syndrome) according to International Parkinson and MDS 2017 Criteria
- Presence of PSP symptoms for <5 years
- Be able to walk 5 steps with minimal assistance
- PSPRS total score (28-item) of <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, can accompany study visits, and can provide information on abilities
- Participants must NOT require the use of feeding tube

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

Criteria for Diagnosis of Probable or Possible PSP According to MDS Criteria 2017[2]

- Gradually progressive disorder with age at disease onset ≥40 years
- Either or both of the following 2 criteria 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

MRI, magnetic resonance imaging.

Clinicaltrials.gov https://clinicaltrials.gov/study/NCT06122662?intr=NCT06122662&rank=1. Accessed Nov 15, 2023 **2.** Höglinger GU, et al. *Mov Disord.* 2017;32(6):853-64.

ORION: Trial End Points

Evaluating Function

Week 52

Disease Progression

P Total PSPRS

- A clinician-rated instrument designed to assess disability and severity in PSP

Activities of Daily Living

S MDS-UPDRS Part II Score

- A measure of motor aspects of experiences of daily living across 13 domains assessed by an approved trained rater

E SEADL score

- A measure composed of a self-report questionnaire of activities of daily living and an assessment of motor function by a clinician

P Primary End Point

S Secondary End Point

E Exploratory End Point

MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; SEADL, Schwab and England Activities of Daily Living.

Clinicaltrials.gov https://clinicaltrials.gov/study/NCT06122662?intr=NCT06122662&rank=1. Accessed Nov 15, 2023

ORION: Trial End Points

Evaluating Burden and Health-Related QoL

Burden and QoL

Week 52

- **E** EuroQoL 5-Dimension 5-Level (EQ5D-5L)
  - A patient-reported measure of 5 items to determine health state
- **E** Zarit Burden Interview (ZBI)
  - A 22-item assessment of caregiver burden
- **E** Clinical Global Impression of Severity and Change
  - A clinician rating of severity of illness (CGI-S) and improvement (CGI-C)
- **E** Montreal Cognitive Assessment (MoCA)
  - A screening instrument to assess general cognitive status
- **E** Medical Resource Utilization
  - Assessment of medical resource utilization associated with medical encounters

E Exploratory End Point

CGI-C, Clinical Global Impressions Scale-Change; CGI-S, Clinical Global Impressions Scales–Severity; QoL, quality of life.
Clinicaltrials.gov https://clinicaltrials.gov/study/NCT06122662?intr=NCT06122662&rank=1. Accessed Nov 15, 2023

ORION: Trial End Points

Evaluating Brain Atrophy and Biomarkers

Week 52

Brain Atrophy

E Brain regional volumes

- Measured by MRI (whole brain and volumes of third ventricle, midbrain, and frontal lobe as combined imaging readout)

Biomarkers

E CSF and plasma biomarkers of neuronal injury and neuroinflammation

E Exploratory End Point

CSF, cerebral spinal fluid

Clinicaltrials.gov https://clinicaltrials.gov/study/NCT06122662?intr=NCT06122662&rank=1. Accessed Nov 15, 2023

ORION: Trial End Points

Evaluating safety and overall survival

Day 1 until 28 ± 7 d after final dose

Safety and Tolerability

- (S) Frequency of TEAEs and SAEs

Randomization to death

Overall Survival

- (E) Ongoing reporting of survival status will be recorded until time of death or end of study is announced

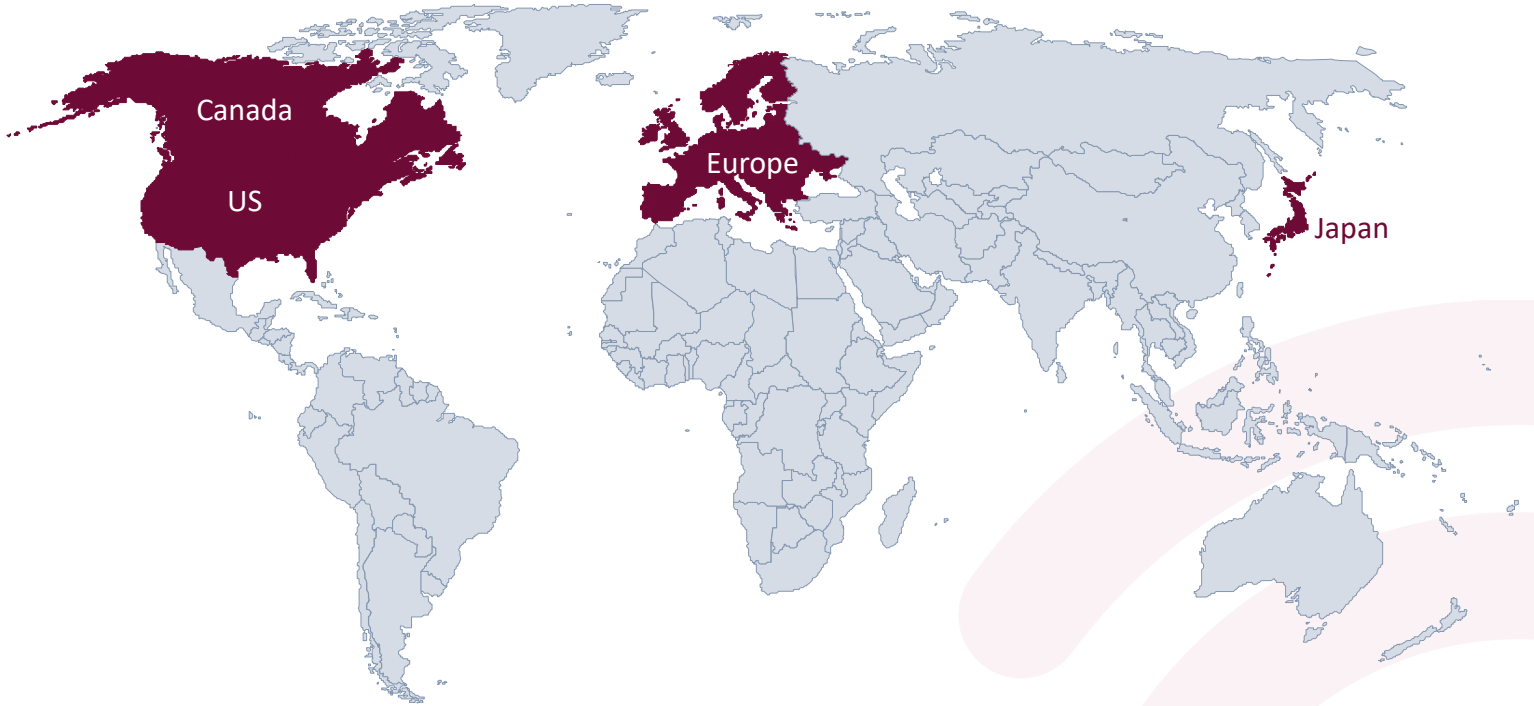
(S) Secondary End Point

(E) Exploratory End Point

TEAE, treatment-emergent adverse events; SAE, serious adverse events

Clinicaltrials.gov https://clinicaltrials.gov/study/NCT06122662?intr=NCT06122662&rank=1. Accessed Nov 15, 2023

ORION Trial: Summary



Number of participants:
≈600

Location:
North America, Europe, and **Japan**

Key eligibility criteria:
Adults aged 40 to 80 years; meet criteria for the diagnosis of probable or possible PSP (PSP-Richardson's syndrome)

Primary end point:
Change in the PSPRS score

For more information:
clinicaltrials.gov/NCT06122662 | amylyxpsptrial.com

Clinicaltrials.gov https://clinicaltrials.gov/study/NCT06122662?intr=NCT06122662&rank=1. Accessed Nov 15, 2023

Thank you!

Global Steering Committee

- 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

Other Contributors

People living with PSP and their caregivers