

A Longitudinal Quantitative Assessment of Phosphorylated Alpha-Synuclein Deposition in Dementia with Lewy Bodies

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Background

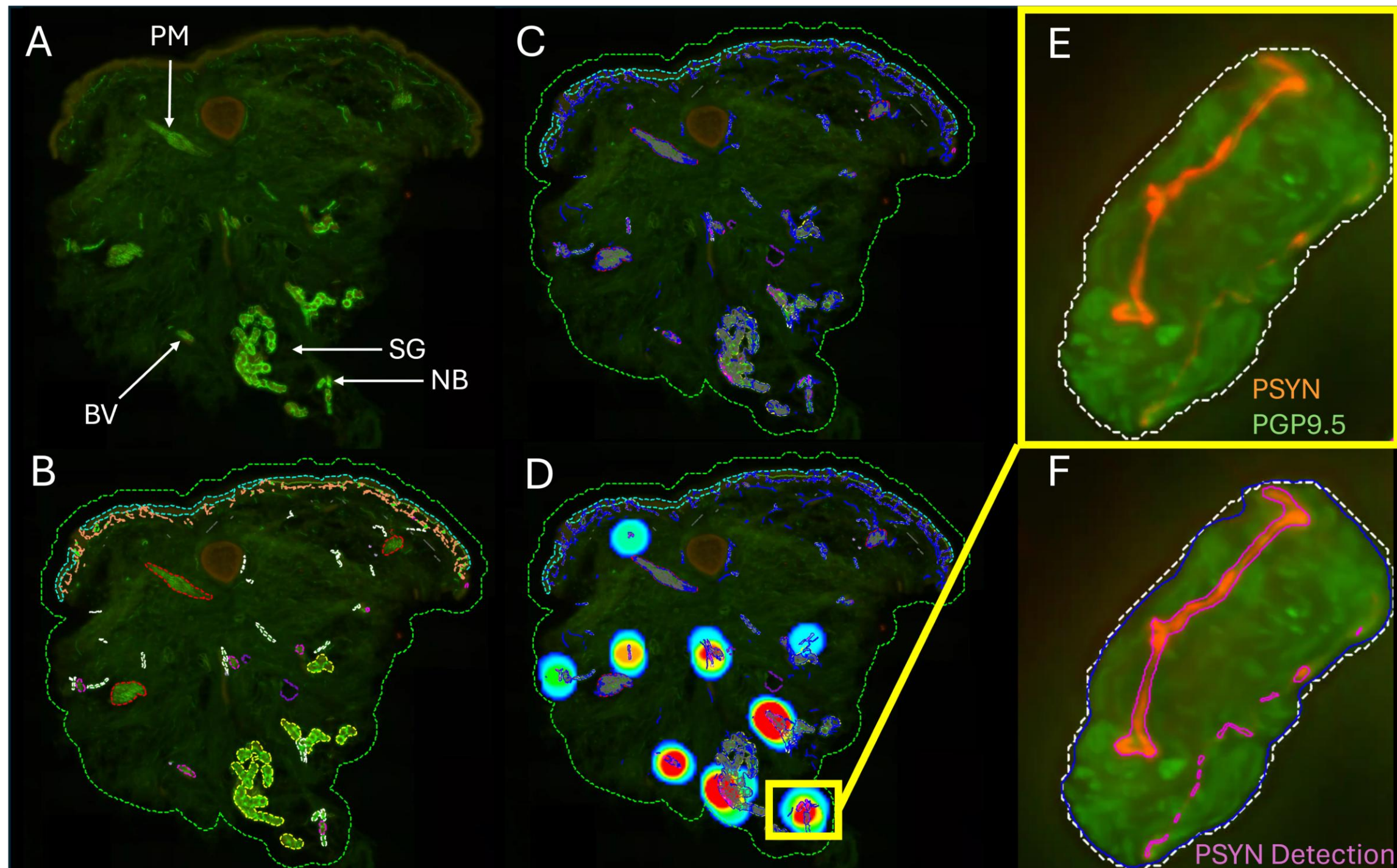
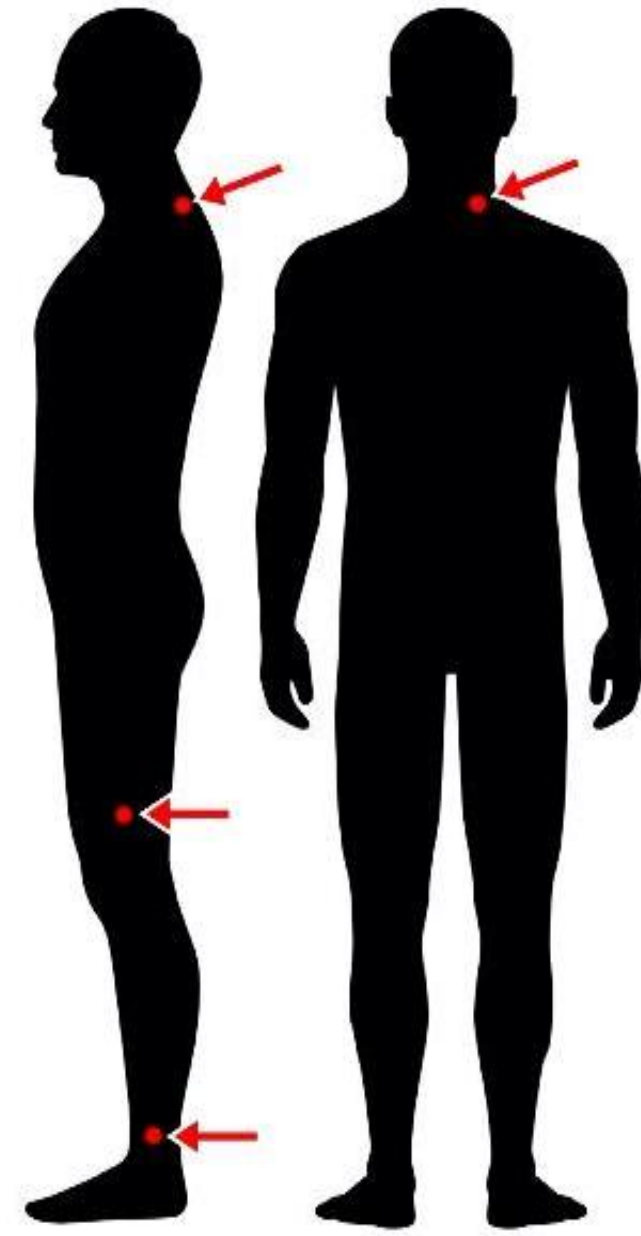
- Dementia with Lewy bodies (DLB) is a neurodegenerative disease characterized by the progressive accumulation of misfolded protein, phosphorylated alpha-synuclein (PSYN), which can be quantified from standard punch biopsies
- At present, there are no surrogate endpoint biomarkers and no in vivo human measure of target engagement

Objective

To report the quantitative change in cutaneous phosphorylated alpha-synuclein (P-SYN) in patients with dementia with Lewy bodies (DLB) over 6 months of longitudinal follow-up in a blinded clinical trial

Methods

- Participants and Procedures:** Individuals aged 50-85 with mini-mental status examination scores in the 18-27 range who met diagnostic criteria for Probable DLB
- After signing consent, participants completed neurologic examinations (MDS-UPDRS III), medical history review, cognitive evaluation (MOCA), and skin biopsies at baseline visit and 6 months later
- Treatment trial with CT1812, a sigma-2 receptor antagonist that displaces oligomers bound to neuronal receptors, potentially improving cognition by reducing downstream toxicity
- Skin Biopsies:** Skin biopsies (3mm) were taken from the distal leg, distal thigh, and posterior cervical regions at baseline and 6 months, with quantitation of P-SYN and intraepidermal nerve fiber density



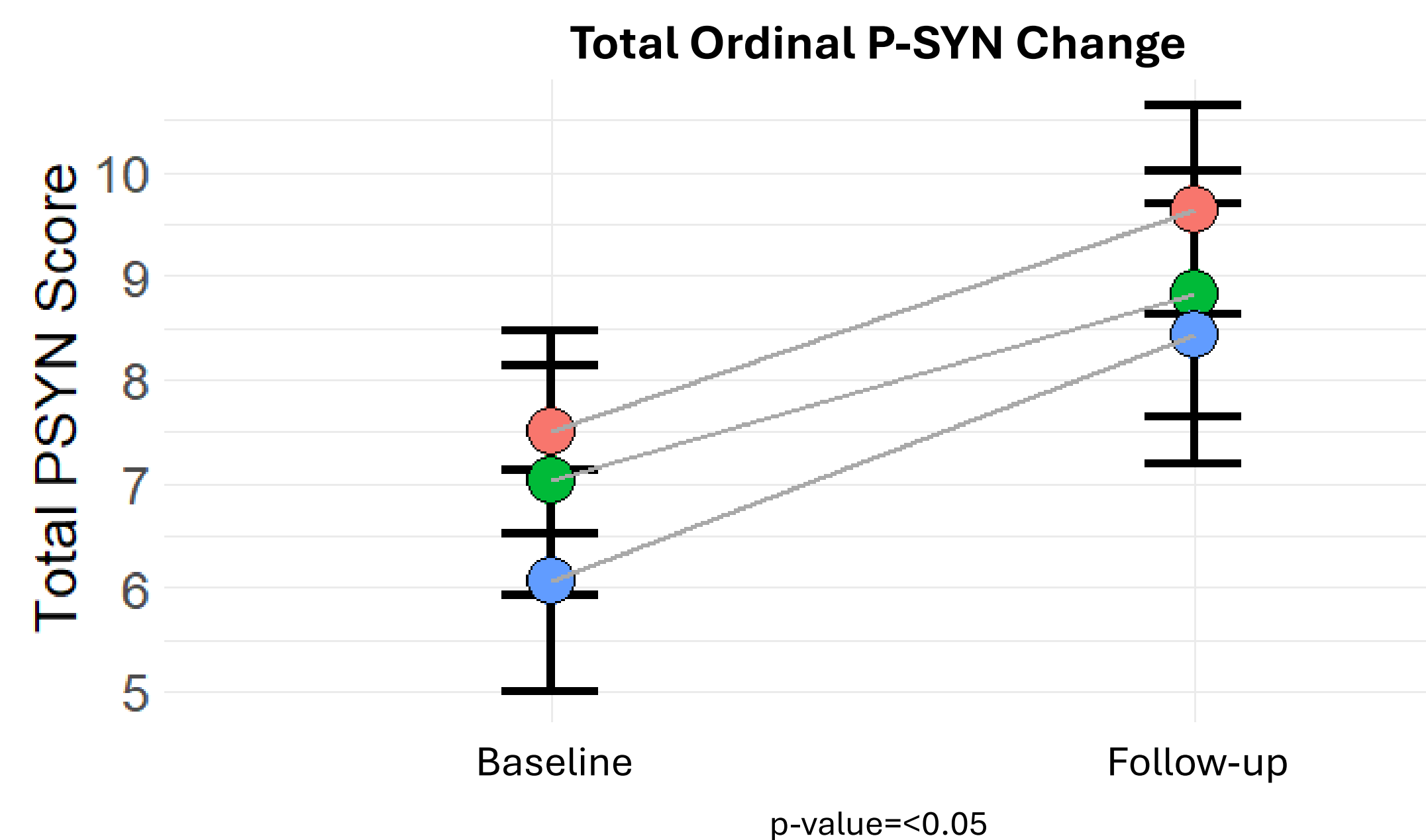
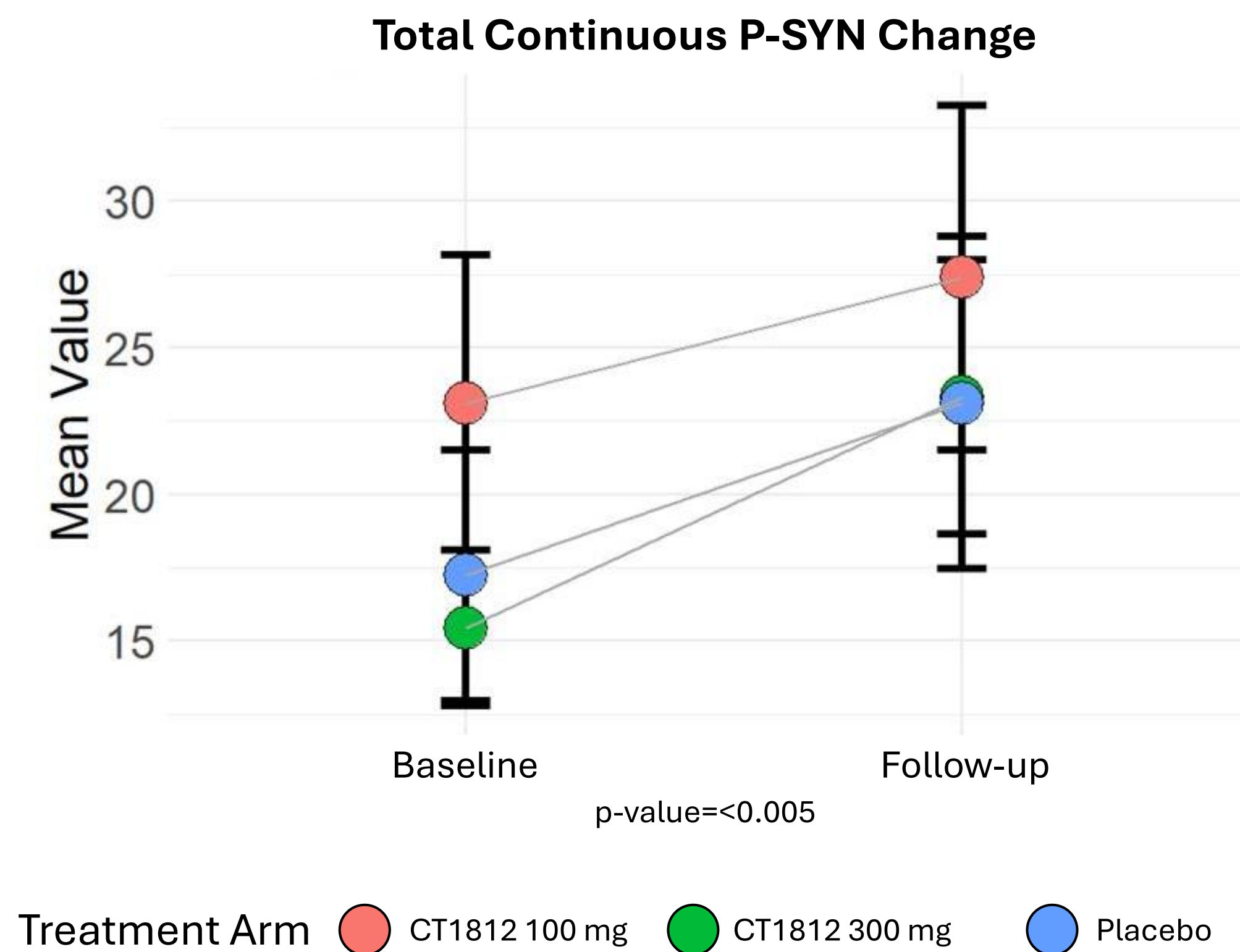
- (A) Protein gene product 9.5 (PGP9.5) and phosphorylated alpha-synuclein (PSYN) immunostained skin biopsy section with identifiable substructures (pilomotor muscles, PM; nerve bundles, NB; sweat glands, SG; blood vessels, BV).
- (B) Tissue has undergone complete confocal imaging, and artificial intelligence supported tissue detection.
- (C) Nerve fibers are identified and quantified (faint blue lines superimposed on the image).
- (D) The presence of intra-axonal PSYN is displayed by a heat-map overlay of the image. Blue circles display smaller amounts of PSYN. Brighter yellow and red circles indicating larger deposits of PSYN.
- (E) A nerve bundle is displayed containing PSYN.
- (F) The digitally captured area of PSYN deposition is represented.

Results

A total of 130 individuals were enrolled in the study
Subjects were randomized 1:1:1 to drug (low dose, drug (high dose) or placebo

	Dose 1 (low dose N=44)	Dose 2 (high dose N=44)	Placebo (N=42)	Total (N=130)
Age – years	72.6 (7.8)	72.1 (5.9)	73.7 (6.3)	72.8 (6.7)
Sex (% Male)	79.5	86.4	78.6	81.5
MMSE	24.6 (2.6)	23.6 (2.6)	23.8 (2.7)	24 (2.7)
MoCA	19.5 (4.3)	17.8 (5.4)	17.9 (4.6)	18.4 (4.9)
MDS-UPDRS III	29.2 (13.9)	25.4 (12.9)	28.1 (13.4)	27.6 (13.4)

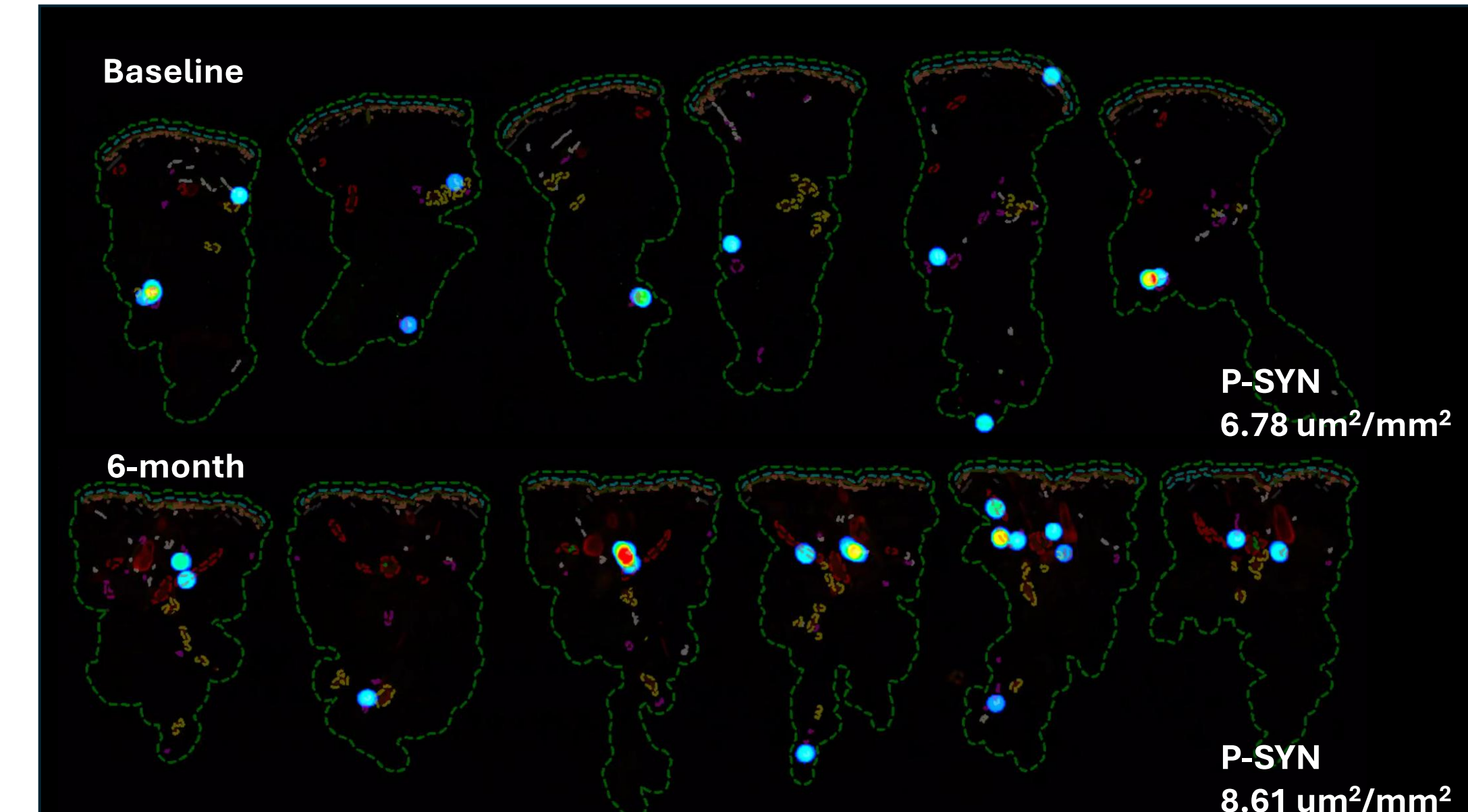
P-SYN significantly increased from baseline to follow up



- Placebo group had a significant increase in P-SYN over 6 months (P<0.01)
- No significant difference between groups
- P-SYN increased by 24.2% over 6 months across all 3 study groups (P<0.001)

Results

Example Quantitative Analysis of Phosphorylated Alpha-Synuclein



Conclusion

- In this phase 2 clinical trial, 95/109 (87%) of individuals with a suspected diagnosis of DLB had P-SYN present on skin biopsy
- These results mirror a recent publication where P-SYN was detected in 89% of cases referred with a diagnosis of DLB
 - Study design included an independent expert review panel blinded to pathology to confirm DLB diagnosis
 - PSYN detection rate increased to 96% with an independent expert panel review to ensure clinical criteria were strictly adhered to
- These results support the use of cutaneous P-SYN detection as a biomarker to improve patient homogeneity in clinical trials of DLB
- We also successfully demonstrate longitudinal quantitative analysis of P-SYN in patients with DLB
- Cutaneous P-SYN levels increased by 24.2% over 6 months across all treatment groups
 - These results confirm that the beneficial clinical effects seen with CT1812 are not synuclein dependent
- Pathologic detection and quantitation of cutaneous phosphorylated alpha-synuclein provides a novel technique to monitor changes in synuclein deposition over time
- These results support skin biopsy detection of P-SYN as a biomarker for target engagement and disease modification in therapies that modify synuclein deposition or clearance

References

Gibbons CH, et al Skin Biopsy Detection of Phosphorylated α-Synuclein in Patients With Synucleinopathies. JAMA. 2024