

# PRASINEZUMAB'S IMPACT ON NEUROMELANIN- AND IRON-SENSITIVE MRI BIOMARKERS IN PARKINSON'S DISEASE: FINDINGS FROM THE PADOVA PHASE IIB STUDY



Thomas Kustermann<sup>1\*</sup>, Štefan Holiga<sup>1</sup>, Rayo Akande<sup>1</sup>, Judith Anzures-Cabrera<sup>2</sup>, Nathalie Pross<sup>3</sup>, Annabelle Monnet<sup>4</sup>, Tania Nikolcheva<sup>3</sup>, and Gennaro Pagano<sup>1,5</sup>, for the PADOVA Investigators and Prasinezumab Study Group

<sup>1</sup>Roche Pharma Research and Early Development (pRED), Roche Innovation Center, F. Hoffmann-La Roche Ltd, Basel, Switzerland; <sup>2</sup>Roche Products Ltd, Welwyn Garden City, UK; <sup>3</sup>Product Development Neurology, Roche Pharma Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland; <sup>4</sup>Product Development Data Science, F. Hoffmann-La Roche Ltd, Basel, Switzerland; <sup>5</sup>University of Exeter Medical School, London, UK

## What does this mean for the PD community?

- Prasinezumab is a monoclonal antibody that binds extracellular  $\alpha$ -Synuclein and aims to slow down the relentless progression of PD.
- The results of this pre-specified analysis of the phase 2b PADOVA clinical trial data, for the first time, suggest that a drug intended to treat the aggregation of  $\alpha$ Synuclein has altered the biology of Parkinson's Disease.

## Background

Parkinson's Disease (PD) is characterized by the toxic aggregation of  $\alpha$ -synuclein and loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc).

Prasinezumab is a monoclonal antibody designed to bind and clear extracellular aggregated  $\alpha$ -synuclein, thereby aiming to slow the underlying neurodegenerative process. To track disease modification, this study utilized two sensitive MRI-based biomarkers of neuronal integrity in the SNpc:

**Neuromelanin (NM):** A byproduct of dopamine metabolism that sequesters toxic compounds. NM-sensitive MRI serves as a proxy for dopaminergic neuronal health.

**Iron:** Elevated iron levels are associated with oxidative stress and neuroinflammation, contributing to disease progression.

This pre-specified analysis of the PADOVA Phase IIb study evaluated whether prasinezumab could mitigate the loss of NM signal and the accumulation of iron over 76 weeks, potentially reflecting a slowing of the biological disease process.

## Methods

The PADOVA study (NCT04777331) evaluated the efficacy, safety, and pharmacokinetics of 1500 mg IV Q4W prasinezumab in early-stage PD participants on stable monoamine oxidase type B inhibitor or levodopa monotherapy until  $\geq 248$  primary events occurred and all participants completed  $\geq 76$  study weeks.

### Biomarker MRI Endpoints

Endpoints included baseline and Week 76 MRI of the basal ganglia using T1-weighted NM-sensitive sequences and R2\* relaxometry sensitive to iron. These were acquired at investigational sites with required software and sequence available.

### Imaging Pipeline & segmentation

**Processing:** Images underwent T1w non-uniformity correction, BEaST brain extraction, and co-registration of T1nm/R2\* to T1w. Longitudinal alignment utilized subject-specific templates registered to the PD25 standard space.

**Segmentation:** Region of interest (ROI) segmentation (e.g., SNpc, putamen and caudate) was automated using atlas-based and pre-trained model algorithms.

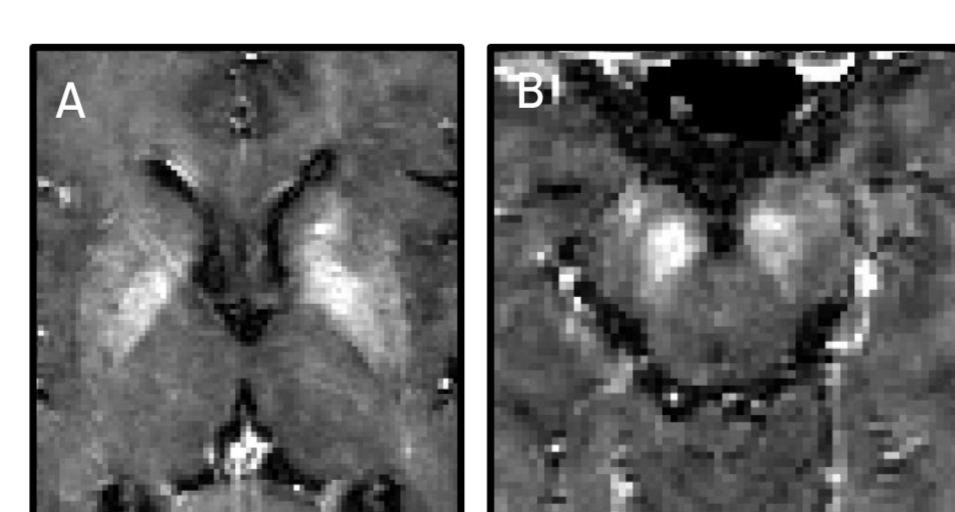
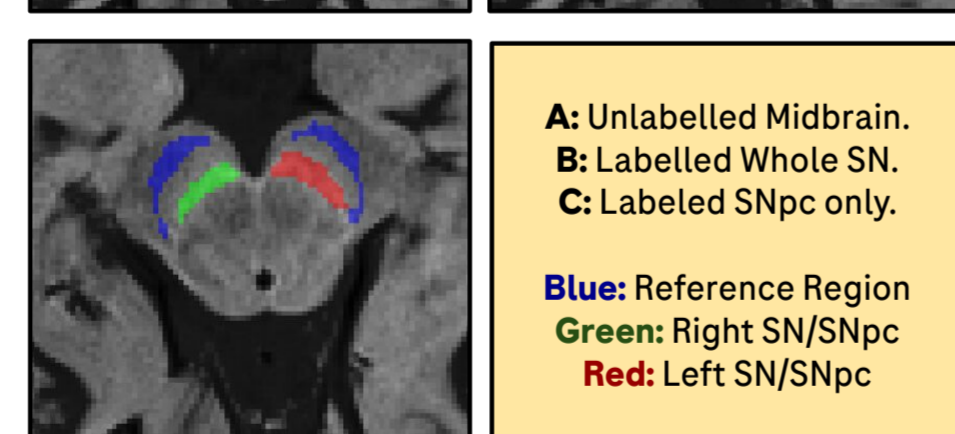
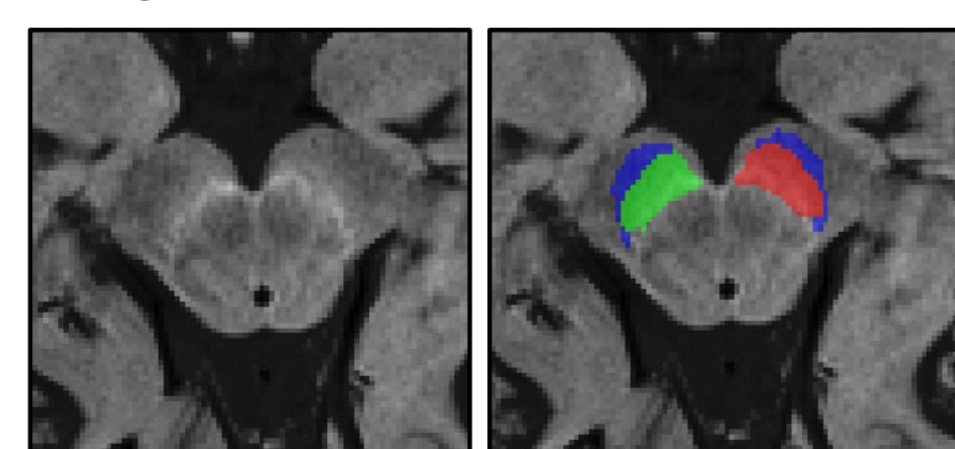
**Morphometry:** Native volumes for all ROIs were determined by normalizing stereotaxic volumes using the linear transformation determinant and a patient-specific head-size scaling factor.

**Neuromelanin** was measured as relative NM intensity (ratio of mean SN or SNpc intensity relative to a reference ROI) and NM volume.

**Iron** accumulation was assessed via mean R2\* signal intensity within the segmented putamen, caudate, globus pallidus and SNpc volumes.

### Statistical analysis

Analysis of covariance (ANCOVA) models of change in MRI endpoints accounted for treatment assignment, sex, age, Hoehn & Yahr, DAT-SPECT, symptomatic treatment and baseline MRI biomarker value.



Iron-sensitive MRI R2\* map of basal ganglia (A) and SN (B).

## Conclusions

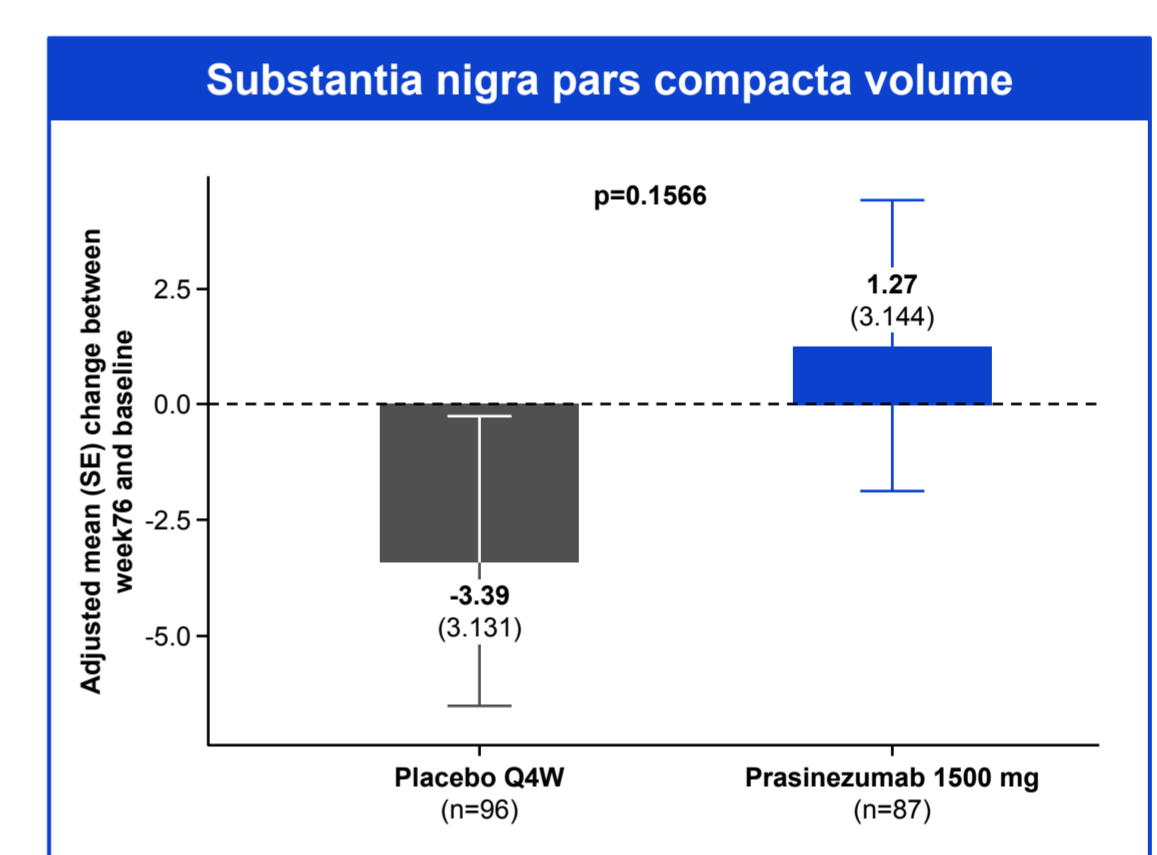
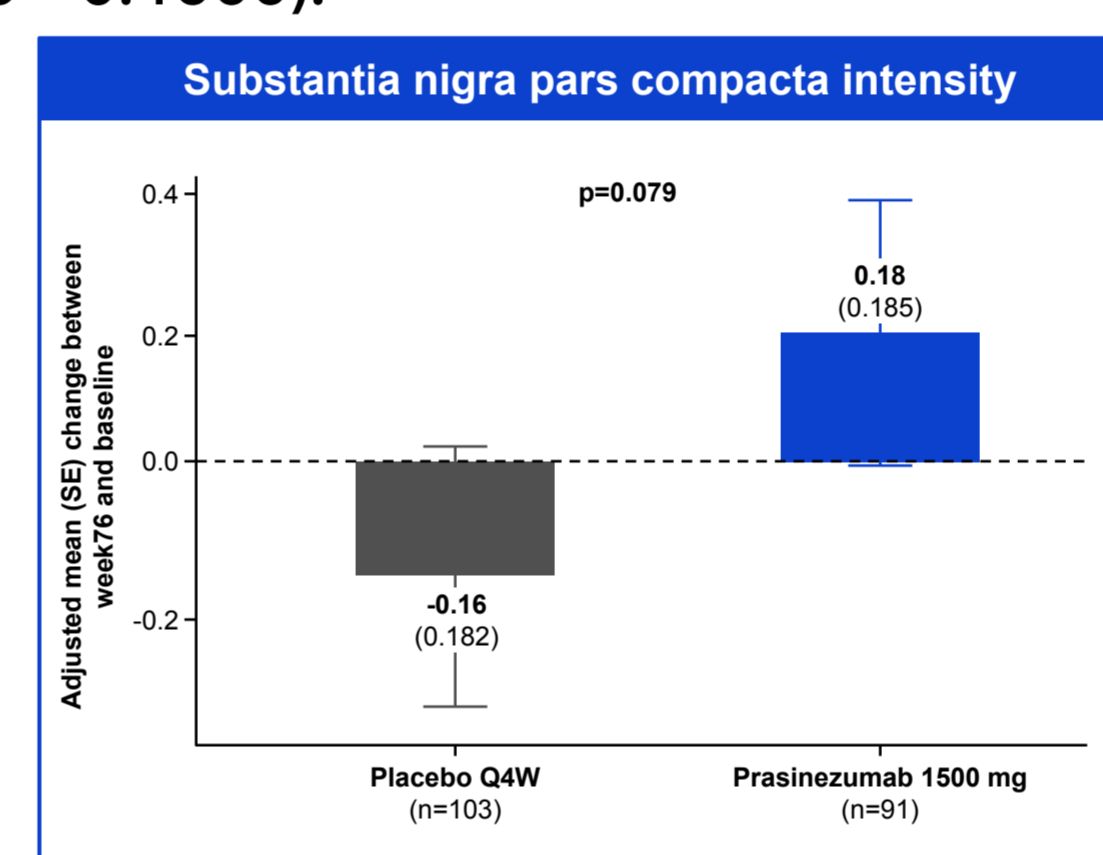
- PADOVA biomarker data suggests prasinezumab is biologically active and slows neurodegenerative processes in early PD.
- Prasinezumab slowed the loss of NM signal in the SNpc and significantly reduced iron accumulation in the putamen versus placebo.
- Structural imaging changes correlated with MDS-UPDRS Part III scores, linking biological impact to clinical motor progression

## Results

Of 586 enrolled participants, 194 provided longitudinal NM-MRI scans and 202 provided iron-sensitive MRI scans which could be included in the analysis.

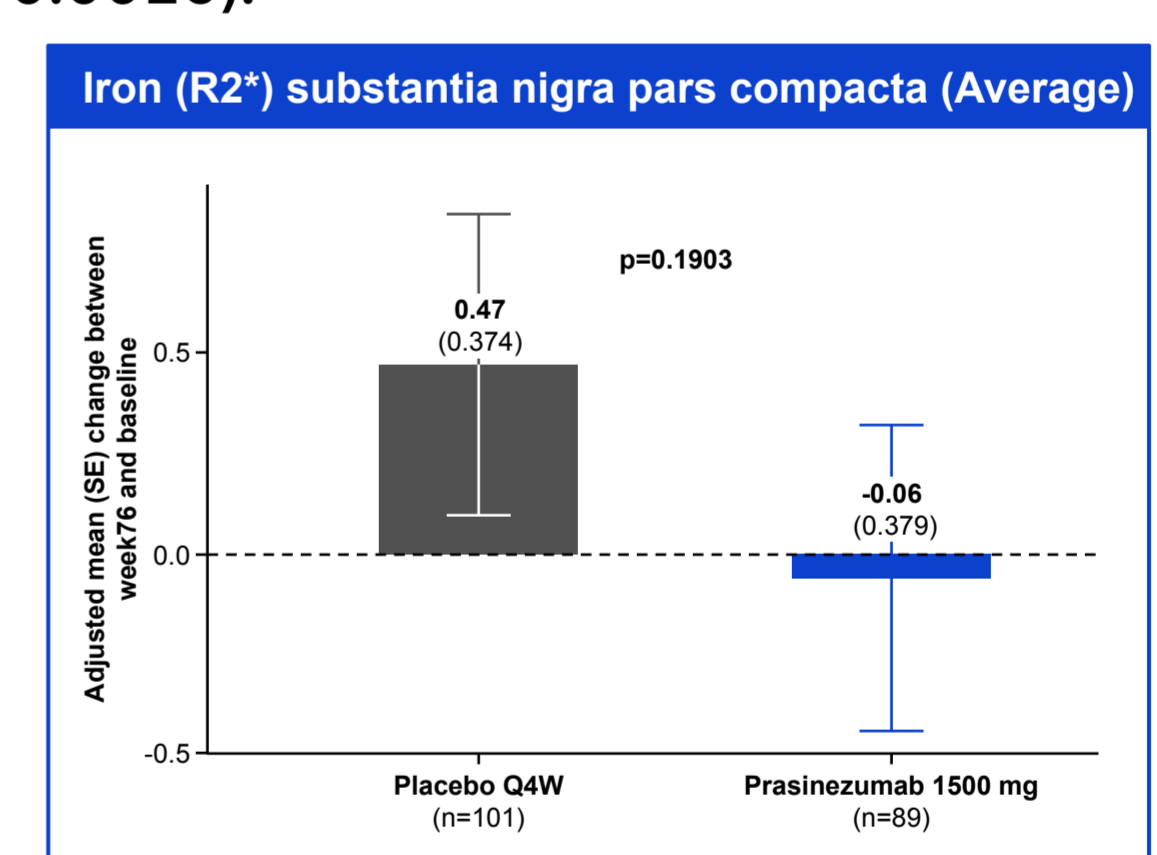
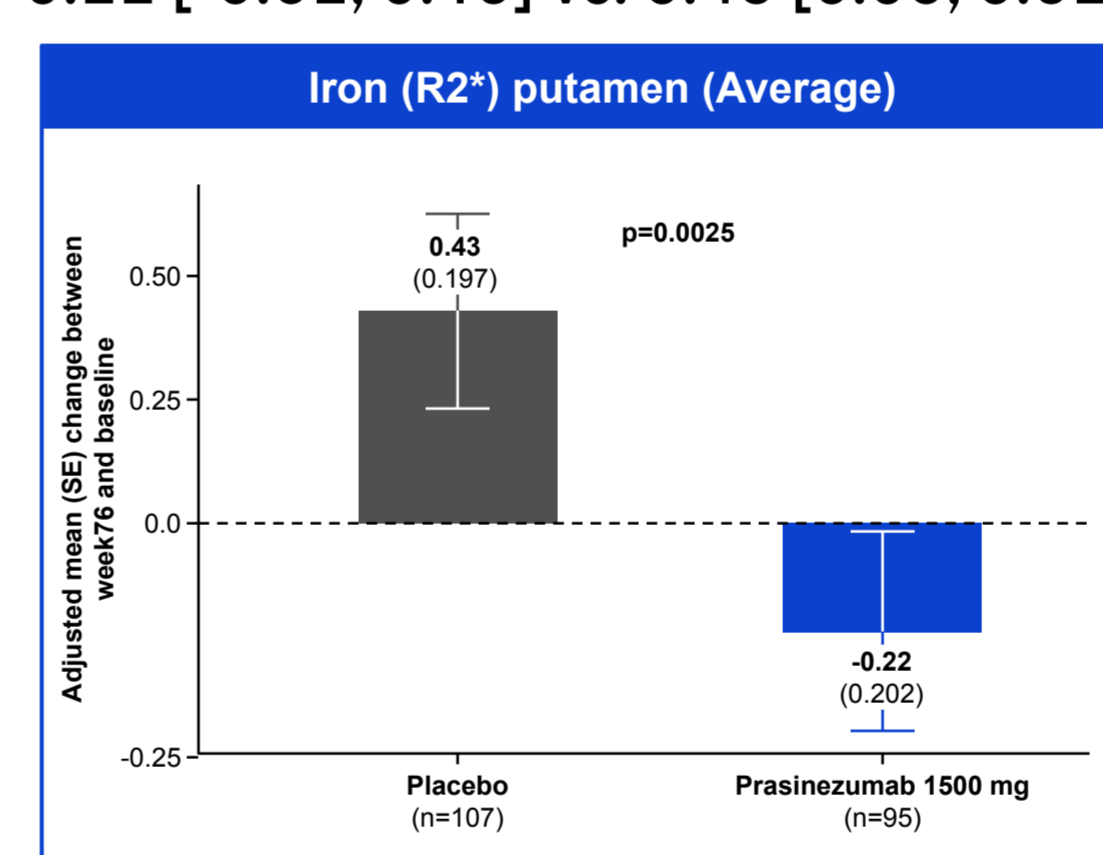
### Neuromelanin

SNpc NM intensity showed a trend towards an increase in the prasinezumab group (adjusted mean change [95% confidence interval]: 0.18 [-0.18, 0.55]), compared to a decline in the placebo group (-0.16 [-0.52, 0.20];  $p=0.0792$ ). A similar pattern was evident for volume (prasinezumab: -3.39 [-9.57, 2.79] vs placebo: 1.27 [-4.93, 7.48],  $p=0.1566$ ).

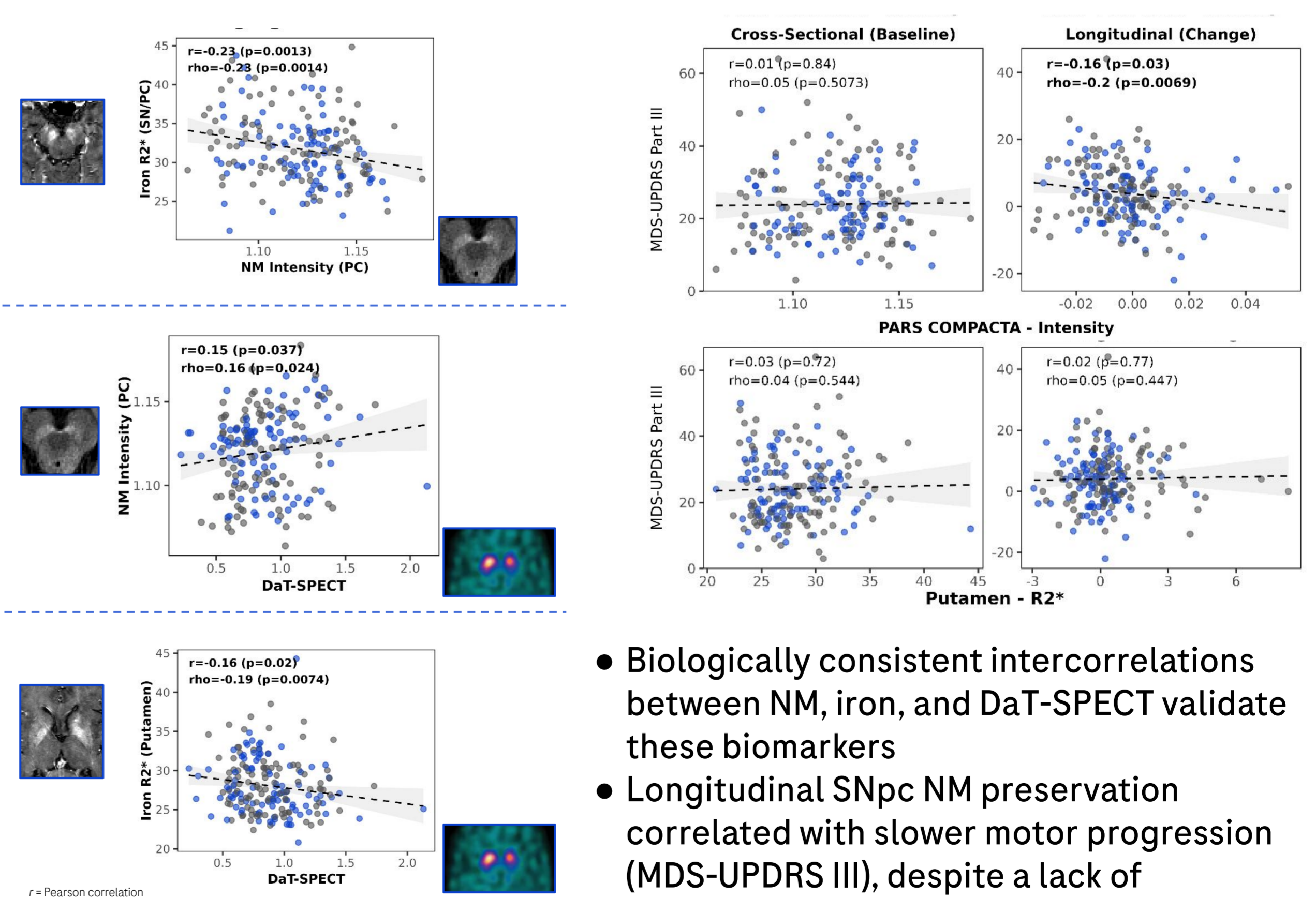


### Iron

Prasinezumab treatment was also associated with a decrease in SNpc iron, with concurrent progressive iron accumulation in the placebo group (-0.06 [-0.80, 0.69] vs. 0.47 [-0.26, 1.21],  $p=0.1903$ ). This pattern was more pronounced in the putamen (-0.22 [-0.62, 0.18] vs. 0.43 [0.05, 0.82],  $p=0.0025$ ).



## Imaging biomarker & clinical endpoint analysis



- Biologically consistent intercorrelations between NM, iron, and DaT-SPECT validate these biomarkers
- Longitudinal SNpc NM preservation correlated with slower motor progression (MDS-UPDRS III), despite a lack of cross-sectional correlations

## Conclusions

The results suggest that prasinezumab may impact the underlying disease biology of Parkinson's Disease by mitigating the degeneration of the substantia nigra pars compacta and reducing pathological iron accumulation in the putamen. Significant intercorrelations between NM, iron, and DAT-SPECT, combined with the specific link between longitudinal NM and MDS-UPDRS III changes, advocating for incorporation of these exploratory imaging measures in future clinical trials in PD.

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## Disclosures

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