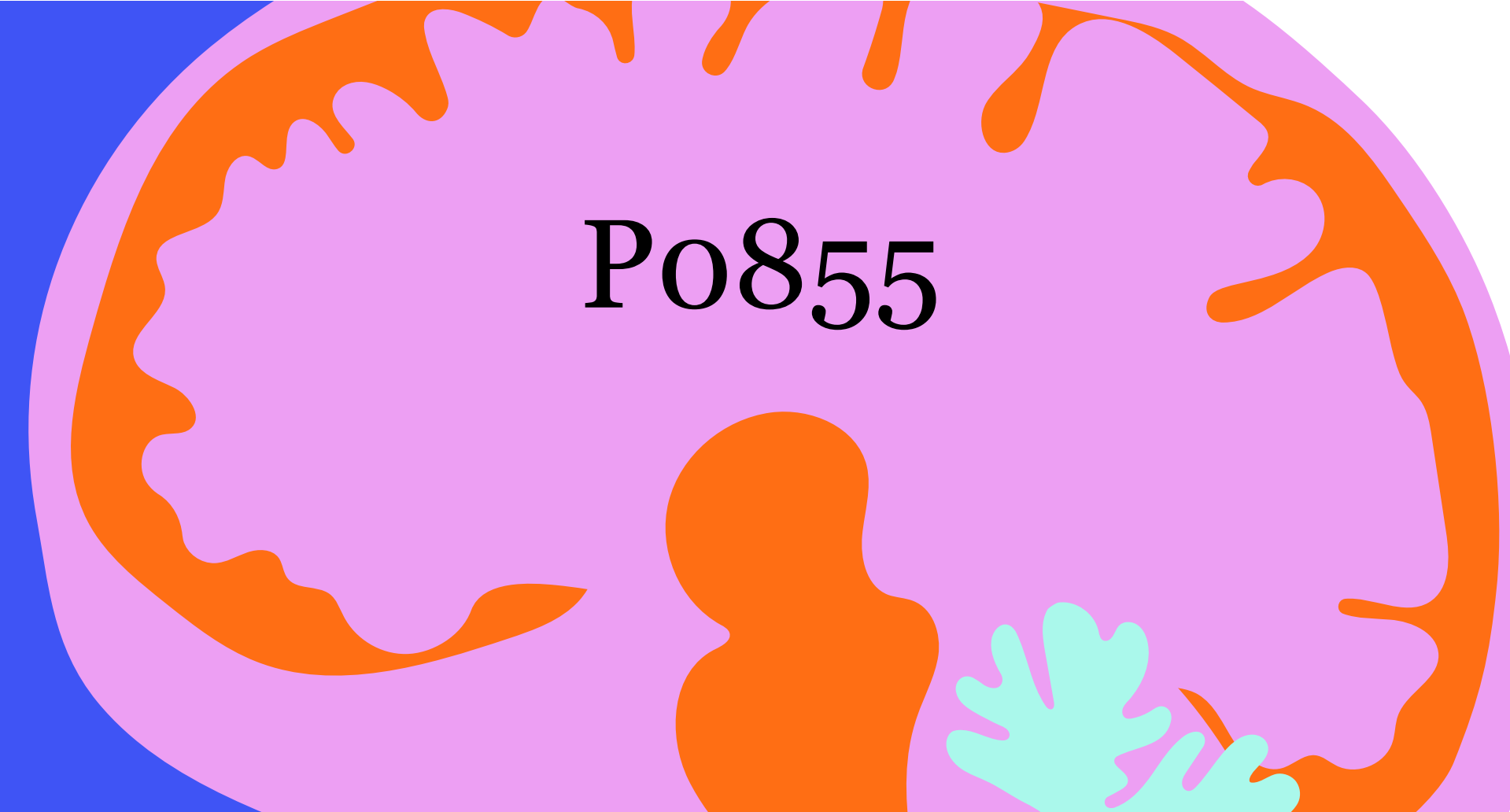


# The Phase 2, Randomized, Placebo-Controlled “PRECEDENT” Trial of SAGE-718 in Patients With Parkinson’s Disease Cognitive Impairment: Clinical Trial in Progress

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## Introduction

- Mild cognitive impairment due to Parkinson’s disease (PD-MCI) affects up to 50% of patients with PD<sup>1,2</sup> and leads to difficulty in performing day-to-day tasks, which can impact overall quality of life.<sup>1,3</sup>
- There is a major unmet need for treatment options in PD-MCI.<sup>1</sup>
- N-methyl-D-aspartate (NMDA) receptors play a critical role in neuroplasticity and cognitive and behavioral processes.<sup>4-6</sup>
- SAGE-718, an investigational NMDA receptor–positive allosteric modulator, has been associated with improved cognitive performance in prior clinical studies in patients with PD or other neurodegenerative diseases.<sup>7-9</sup>
- In the phase 2 open-label PARADIGM study (NCT04476017), SAGE-718 was generally well tolerated and associated with improved performance on tests of executive functioning and learning and memory in patients with PD-MCI (Table 1).<sup>7</sup>
- The PRECEDENT study (NCT05318937) is designed to evaluate the efficacy, safety, and tolerability of SAGE-718 as a potential treatment for cognitive impairment due to PD. Trial methodology and key endpoints are described in this presentation.
- Note: SAGE-718 is an investigational drug and is not approved by the US Food and Drug Administration or any other regulatory agency as safe and effective for any use.

**TABLE 1. PERFORMANCE ON COGNITIVE TESTS WITH SAGE-718 IN THE COMPLETED PHASE 2 PARADIGM STUDY<sup>7</sup>**

Domain	Task	Setting/frequency	Participants with PD-MCI		
			14-day dosing cohort (part A)	28-day dosing cohort (part B)	
			Trend to day 14 <sup>a</sup>	Trend to day 14 <sup>a</sup>	Trend to day 28 <sup>a</sup>
Executive functioning	Multitasking	Clinic/weekly	Improvement	Improvement	Improvement
	One Touch Stockings	Clinic/weekly	Improvement	Improvement	Improvement
	Spatial working memory	Clinic/weekly	Improvement	No improvement	No improvement
	DSST	Mobile/daily	Improvement	Improvement	Improvement
	2 back	Clinic/weekly	Improvement	Improvement	Improvement
Learning and memory	Paired associates	Clinic/weekly	Improvement	No improvement	Improvement
	Pattern recognition (immediate and delayed)	Clinic/weekly	Improvement	Improvement on delayed only <sup>b</sup>	Improvement on delayed only <sup>b</sup>
	Verbal memory	Clinic/weekly	Improvement	No improvement	No improvement
	Spatial span	Clinic/weekly	No improvement	No improvement	No improvement

DSST, Digit Symbol Substitution Test; MTT, Multitasking Test; OTS, One Touch Stockings; PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; SSP, Spatial Span; SWM, Spatial Working Memory.

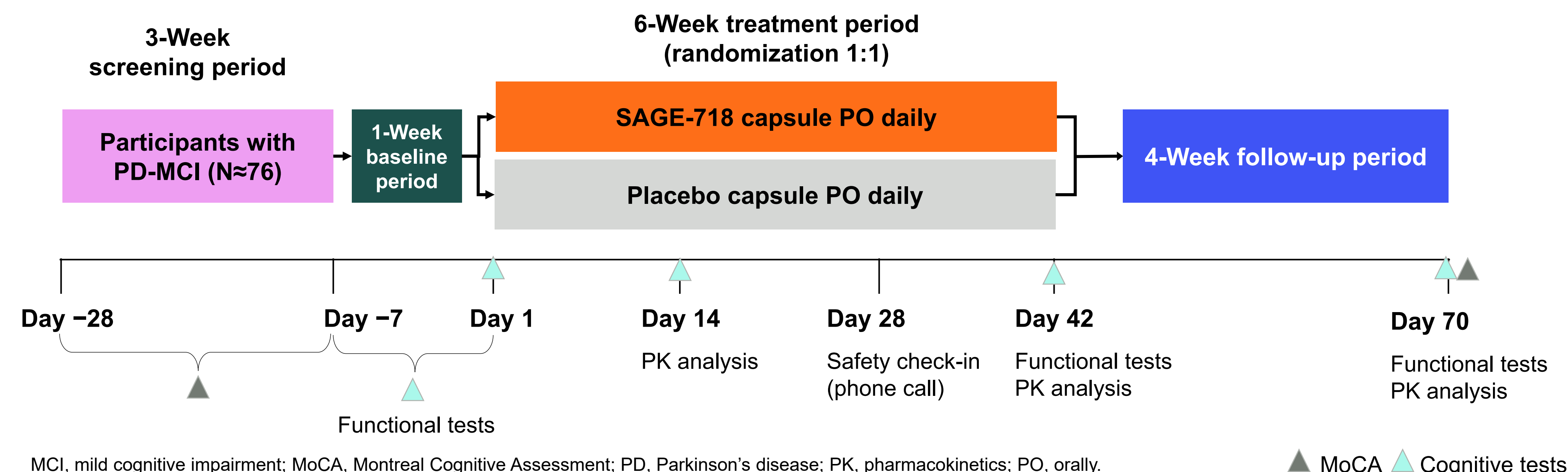
<sup>a</sup> For each task, trends were summarized based on the mean actual value change from baseline to day 14 and 28 in the following key variables: incongruent errors (MTT), mean choices to correct (OTS), total errors (SWM), total correct (DSST), D-prime second condition (2 back), first attempt memory score (PAL), percent correct (PRM), free recall (VRM), and forward span length (SSP). In total, 11 participants received SAGE-718 in part A, and 7 participants received SAGE-718 in part B (N varied per time point per test).

<sup>b</sup> Although improvement from baseline was observed in the PRM delayed, this improvement will need to be further evaluated due to high prebaseline measures.

## Methods

- PRECEDENT is an ongoing, randomized, double-blind, placebo-controlled trial of SAGE-718 in participants with PD-MCI (Figure 1).
- Up to 76 participants will be enrolled from 30 sites in the United States.
- Eligible participants are randomized 1:1 to receive a daily oral dose of SAGE-718 or matching placebo for up to 42 days.
- At scheduled visits during the treatment period, safety, efficacy, PK, and adherence procedures are performed.
- Key study eligibility criteria are described in Table 2.

**FIGURE 1. STUDY DESIGN**



MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; PD, Parkinson’s disease; PK, pharmacokinetics; PO, orally. ▲ MoCA ▲ Cognitive tests

**TABLE 2. KEY INCLUSION AND EXCLUSION CRITERIA**

Key inclusion criteria <sup>a</sup>	Key exclusion criteria <sup>a</sup>
<ul style="list-style-type: none"> <li>Aged between 50 and 75 years (inclusive).</li> <li>Meet the following criteria for PD-MCI: <ul style="list-style-type: none"> <li>Confirmed idiopathic PD diagnosis per 2015 Movement Disorder Society (MDS) clinical diagnostic criteria.</li> <li>MCI in PD per MDS Task Force criteria (excluding requirement for United Kingdom PD Brain Bank diagnostic criteria).</li> </ul> </li> <li>Meet the following criteria for Montreal Cognitive Assessment (MoCA): <ul style="list-style-type: none"> <li>For level 1 PD-MCI criteria, have an MoCA score of 20 to 25 (inclusive).</li> <li>For level 2 (within the last year), have an MoCA score of 18 to 25 (inclusive).</li> </ul> </li> <li>Have mild to moderate motor severity per modified Hoehn and Yahr stage I to III criteria.</li> <li>Have stable motor symptoms for ≥4 weeks prior to screening.</li> <li>Able to complete Color Trails Test 1 and expected to be capable of engaging in prolonged cognitive testing for the duration of the study.</li> </ul>	<ul style="list-style-type: none"> <li>Have a diagnosis of dementia of any etiology, including but not limited to dementia with Lewy bodies, Alzheimer’s dementia, and vascular dementia.</li> <li>Have any parkinsonism other than PD, including secondary parkinsonism or atypical parkinsonism.</li> <li>In the opinion of the investigator, be experiencing fluctuations in motor symptoms associated with PD that will interfere with completing study procedures.</li> <li>Have any ongoing central nervous system condition (other than PD) that could influence the outcome of the study.</li> <li>Have a history, presence, and/or current evidence of: <ul style="list-style-type: none"> <li>Brain surgery, deep brain stimulation, or hospitalization due to a brain injury.</li> <li>Clinically relevant intracranial abnormality.</li> <li>Seizures or epilepsy, except for a single episode of childhood febrile seizures.</li> </ul> </li> <li>Experienced significant psychotic symptoms, including hallucinations or delusions, within the past 3 months, in the opinion of the investigator.</li> </ul>

<sup>a</sup> Additional inclusion and exclusion criteria will apply.

### PRIMARY ENDPOINT

- Change from baseline (CFB) to Day 42 in the Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding Test.
- The Coding Test from the WAIS-IV requires the participant to identify symbols matched to numbers using a key within a specific time frame and is used to monitor changes in cognitive function over time and for early detection of cognitive impairment.<sup>10,11</sup>

### SECONDARY ENDPOINTS

- Proportion of participants experiencing treatment-emergent adverse events (TEAEs), TEAE severity, and number of participants who withdraw due to AEs.

### OTHER ENDPOINTS

- Additional assessments of safety and tolerability, PK, motor symptoms, cognitive performance, and functioning.

### STATISTICAL ANALYSIS

- The endpoints for each cognitive and functional outcome will be analyzed by a mixed-effects model for repeated measures.
- The model will include CFB scores as the dependent variable; treatment, visit, and visit by treatment interaction as fixed effects; participants as random effects; and baseline cognitive test scores as a covariate. Model-based point estimates at each time point (visit) will be reported.
- Descriptive statistics of scores and CFB scores will be summarized based on the full analysis set (all participants in the safety set who have baseline and ≥1 postbaseline efficacy evaluation).

## Conclusions

- The ongoing, randomized, double-blind, placebo-controlled PRECEDENT trial is designed to evaluate the efficacy, safety, and tolerability of SAGE-718 in participants with PD-MCI.
- PRECEDENT is currently enrolling at sites in the United States (please see [PrecedentStudy.com](http://PrecedentStudy.com) for more information).
- These data are expected to inform the potential of SAGE-718 as a treatment for cognitive impairment due to PD.
- Ongoing trials currently investigating the effects of SAGE-718 on cognitive function in other neurodegenerative disorders include:
  - A randomized, double-blind, placebo-controlled study evaluating SAGE-718 in participants with MCI or mild dementia due to Alzheimer’s disease (LIGHTWAVE: NCT05619692).
  - Two phase 2 randomized controlled trials evaluating SAGE-718 in participants with Huntington’s disease (SURVEYOR: NCT05358821 and DIMENSION: NCT05107128, both part of the PERSPECTIVE Clinical Developmental Program).

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