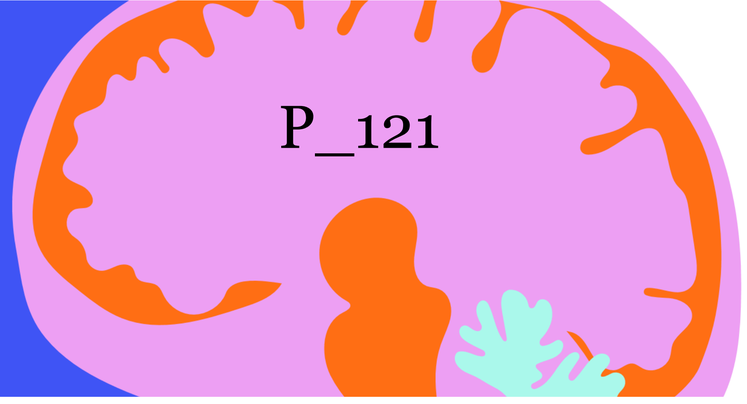
The Phase 2, Randomized, Placebo-Controlled "PRECEDENT" Trial of SAGE-718 in Patients With Parkinson's Disease Cognitive Impairment: Clinical Trial in Progress



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Introduction

- Mild cognitive impairment due to Parkinson's disease (PD-MCI) affects up to 50% of patients with PD[1,2] and leads to difficulty in performing day-to-day tasks, which can impact overall quality of life.[1,3]
- There is a major unmet need for treatment options in PD-MCI.[1]
- *N*-methyl-D-aspartate (NMDA) receptors play a critical role in neuroplasticity and cognitive and behavioral processes.[4-6]
- 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.[7-9]
- 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).**[7]
- 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[7]

Domain	Task	Setting/ frequency	Participants with PD-MCI		
			14-day dosing cohort (part A)	28-day dosing cohort (part B)	
			Trend to day 14[a]	Trend to day 14[a]	Trend to day 28[a]
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[b]	Improvement on delayed only[b]
	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.

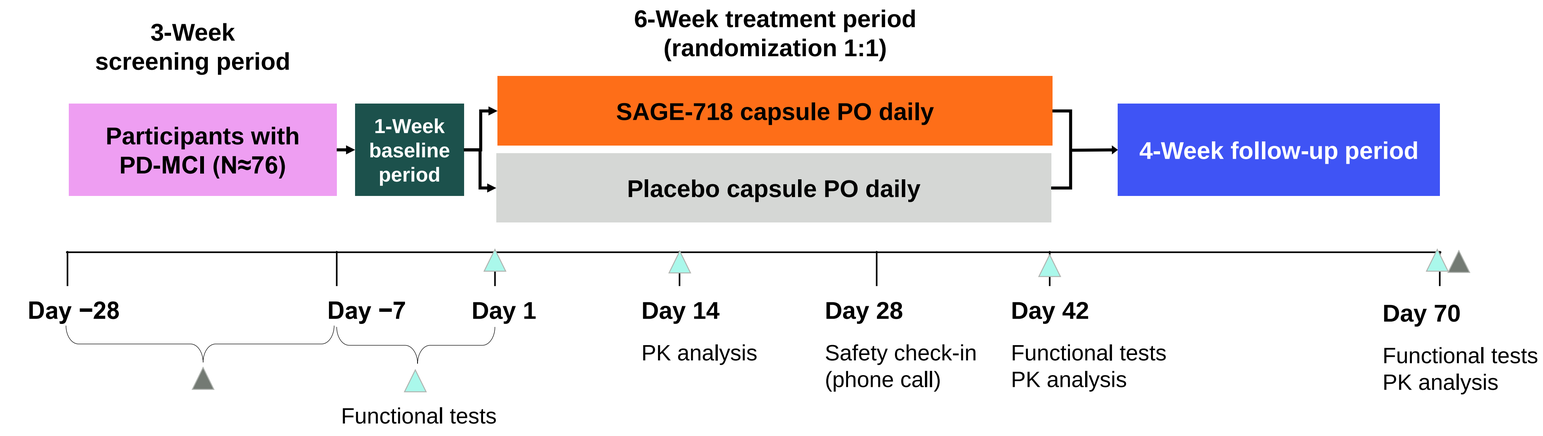
[a] For each task, trends were summarized based on the mean actual value change from baseline to day 14 and 28 in the following key variables: incongruent errors (MTT), mean choices to correct (OTS), total errors (SWM), total correct (DSST), D-prime second condition (2 back), first attempt memory score (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).

[b] 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.

TABLE 2. KEY INCLUSION AND EXCLUSION CRITERIA

Key inclusion criteria[a]	Key exclusion criteria[a]
- Aged between 50 and 75 years (inclusive). - Meet the following criteria for PD-MCI: • Confirmed idiopathic PD diagnosis per 2015 Movement Disorder Society (MDS) clinical diagnostic criteria. • MCI in PD per MDS Task Force criteria (excluding requirement for United Kingdom PD Brain Bank diagnostic criteria). - Meet the following criteria for Montreal Cognitive Assessment (MoCA): • For level 1 PD-MCI criteria, have an MoCA score of 20 to 25 (inclusive). • For level 2 (within the last year), have an MoCA score of 18 to 25 (inclusive). - Have mild to moderate motor severity per modified Hoehn and Yahr stage I to III criteria. - Have stable motor symptoms for ≥4 weeks prior to screening. - Able to complete Color Trails Test 1 and expected to be capable of engaging in prolonged cognitive testing for the duration of the study.	- Have a diagnosis of dementia of any etiology, including but not limited to dementia with Lewy bodies, Alzheimer's dementia, and vascular dementia. - Have any parkinsonism other than PD, including secondary parkinsonism or atypical parkinsonism. - In the opinion of the investigator, be experiencing fluctuations in motor symptoms associated with PD that will interfere with completing study procedures. - Have any ongoing central nervous system condition (other than PD) that could influence the outcome of the study. - Have a history, presence, and/or current evidence of: • Brain surgery, deep brain stimulation, or hospitalization due to a brain injury. • Clinically relevant intracranial abnormality. • Seizures or epilepsy, except for a single episode of childhood febrile seizures. - Experienced significant psychotic symptoms, including hallucinations or delusions, within the past 3 months, in the opinion of the investigator.

[a] 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.[10,11]

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** 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).

References

1. Goldman JG, Litvan I. *Minerva Med*. 2011;102(6):441-459.
2. Goldman JG, et al. *NPJ Parkinsons Dis*. 2018;4:19.
3. Barone P, et al. *Mov Disord*. 2009;24(11):1641-1649.
4. Kantrowitz JT, Javitt DC. *Brain Res Bull*. 2010;83(3-4):108-121.
5. Lin C, et al. *Curr Pharm Des*. 2014;20(32):5169-5179.
6. Newcomer JW, Krystal JH. *Hippocampus*. 2001;11(5):529-542.
7. Koenig A, et al. Poster presented at: ECNP 2022; October 15-18, 2022; Vienna, Austria. Poster 0147.
8. Koenig A, et al. Oral presentation at: AAN 2022 Annual Meeting; April 2-7, 2022; Seattle, Washington.
9. Koenig A, et al. Poster presented at: CHDI Foundation Annual Meeting; February 24-27, 2020; Palm Springs, CA.
10. Jaeger J. *J Clin Psychopharmacol*. 2018;38(5):513-519.
11. Pearson. *Advanced Clinical Solutions for the WAIS-IV and WMS-IV*. Pearson; 2009.

Acknowledgements

We would like to thank the participants and their families for helping us reimagine brain health. We would also like to thank Sara Boattini and Emily Freitag for their contributions to the study. The PRECEDENT study is sponsored by Sage Therapeutics, Inc. Medical writing and editorial support were provided by Meditech Media, Ltd, and funded by Sage Therapeutics, Inc.

Disclosures: AB, AK, KP, JW, SP, MQ, JP, and JD are employees of Sage Therapeutics, Inc, and may hold stock and/or stock options.

IAPRD 2023 World Congress, Chicago, Illinois, USA
May 13 – May 16, 2023

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MRC-718-00433

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