A Phase 2, Randomized, Placebo-Controlled Trial to Evaluate the Effects of SAGE-718 in Patients with Alzheimer's Disease: Study Design

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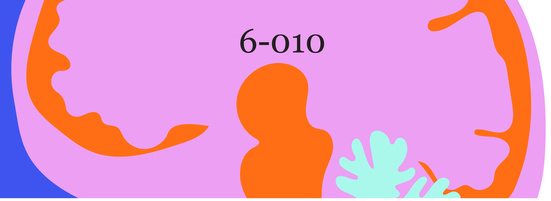


Introduction

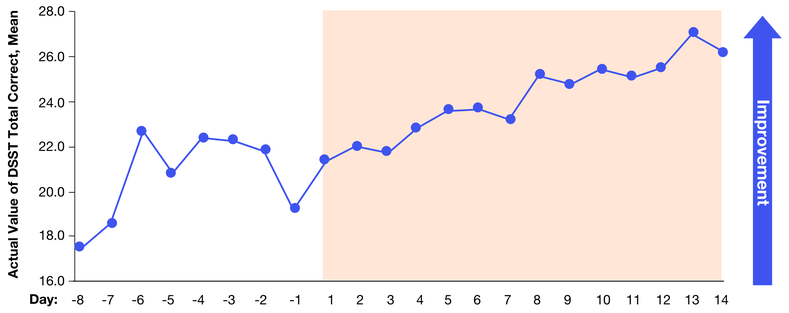
- Alzheimer's disease (AD) is a common neurodegenerative disorder associated with cognitive impairment and loss of independence, accounting for 60% to 70% of cases of dementia globally.[1]
- Both executive functioning (eg, problem solving) and learning and memory deficits associated with AD begin early in the disease course, and, while treatments are available, there remains an unmet need for more effective and better tolerated therapies that address cognitive impairment due to AD.[2-4]
- N-methyl-D-aspartate receptors (NMDARs) are critical for neuronal network stabilization; NMDAR hypofunction has been implicated in multiple neuropsychiatric and neurodegenerative conditions.[5,6]
- SAGE-718 is a novel NMDAR positive allosteric modulator that is being investigated for the treatment of cognitive impairment associated with AD and other neurodegenerative disorders.[7-9]
- Treatment with SAGE-718 improved performance on cognitive tests vs placebo following a ketamine challenge in a study of healthy volunteers.[10,11]
- In the Phase 2, open-label, signal-finding LUMINARY Study (NCT04602624), SAGE-718 was generally well tolerated and associated with improved performance on cognitive tests in patients with mild cognitive impairment (MCI) or mild dementia due to AD (N = 26).[12]
  - SAGE-718 was associated with improvements in measures of learning and memory and improved performance across all tests of executive functioning (**Figure 1A**), including the Digit Symbol Substitution Test (DSST; **Figure 1B**).
  - No appreciable treatment effects were observed on measures of simple attention and/or psychomotor speed, which is consistent with the profile of SAGE-718 observed to date.
- Based on these preliminary results, a randomized, double-blind, placebo-controlled study to evaluate the effect of SAGE-718 on cognitive performance in patients with MCI or mild dementia due to AD was initiated (NCT05619692). The study is currently enrolling and trial design methodology together with key endpoints are detailed in this presentation.
- Note: SAGE-718 is an investigational drug and is not approved by the US Food and Drug Administration (FDA) or any other regulatory agency as safe and effective for any use.

FIGURE 1. PERFORMANCE ON COGNITIVE TESTS WITH SAGE-718 IN THE COMPLETED PHASE 2 LUMINARY STUDY

A.

Domain	Task	LUMINARY (N=26) Trend to Day 14*
Executive Functioning	Multitasking	Improvement
	One Touch Stockings	Improvement
	Spatial Working Memory	Improvement
	Digit Symbol Substitution Test (DSST)	Improvement
	2-Back	Improvement
Learning and Memory	Pattern Recognition (Delayed)	Improvement
	Verbal Memory	Improvement
Attention and Psychomotor Speed	Reaction Time	No change
	Psychomotor Vigilance	No change
Global	Montreal Cognitive Assessment (MoCA)	Improvement

B. DIGIT SYMBOL SUBSTITUTION TEST,† TOTAL CORRECT DAILY, MOBILE-BASED[12]



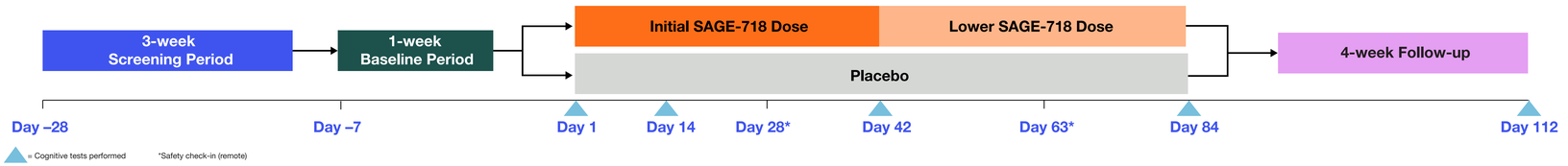
*For each task, trends were summarized based upon the mean actual value change from baseline to Day 14 in the following key variables; incongruent errors (MTT), mean choices to correct (OTS), total errors (SWM), total correct (DSST), percent correct (PRM), free recall (VRM), median 5-choice reaction time (RTI), reaction latency (PVT), and MoCA CFB (measured at Day 28).
†Both the DSST and the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) require the participant to transcribe a digit-symbol code using a key.
Shaded area denotes time on treatment.
For DSST, n=2 at Day –8, n≥8 at all other pre-treatment timepoints, and n≥18 at all timepoints during treatment.
CFB = change from baseline.

Methods

STUDY DESIGN AND PATIENT POPULATION

- Approximately 150 patients will be enrolled across 40 sites in the United States. Eligible patients aged 50 to 80 years who meet the diagnostic criteria for AD (baseline Montreal Cognitive Assessment [MoCA] score of 15 to 25, baseline Clinical Dementia Rating [CDR] score of 0.5 to 1.0 [inclusive], and memory box score ≥0.5) are randomized to receive either oral SAGE-718 or placebo.
- The study design includes a 3-week screening period, a 1-week baseline period, a 12-week treatment period, and a 4-week follow-up period (**Figure 2**). During the initial 6 weeks of the treatment period, patients in the SAGE-718 arm receive an initial dose of SAGE-718 (Days 1 to 42), then during the next 6 weeks of treatment receive a lower dose of SAGE-718 (different dose; Days 43 to 84). Matching placebo is given throughout the entire treatment period (12 weeks).
  - The dose regimen has been selected to provide optimal pharmacokinetic exposures, similar to those achieved in prior studies that demonstrated target engagement.
  - At scheduled clinic visits during the treatment period, cognitive performance, safety, efficacy, and adherence are assessed.

FIGURE 2. STUDY DESIGN



Key Inclusion Criteria*

- Aged between 50 and 80 years, inclusive, at Screening.
- Meet the following criteria for MCI or mild dementia due to AD at Screening:
  - A memory complaint reported by the participant or their study partner.
  - A CDR score of 0.5 to 1.0 (inclusive) with a memory box score ≥0.5.
  - Essentially preserved activities of daily living, in the opinion of the investigator.
  - Brain MRI report, obtained within the 2 years preceding the Baseline Period, which is consistent with the diagnosis of AD and with no clinically significant findings of non-AD pathology that could account for the observed cognitive impairment.
- A score of 15 to 25 (inclusive) on the MoCA at Screening.
- A study partner who is willing and able to provide informed consent and reliably support study-specific activities.
- On stable concomitant medication usage (dose and frequency) for at least 4 weeks prior to the first IP administration, and for the duration of the study.

Key Exclusion Criteria*

- Participated in a previous clinical study of SAGE-718, a previous gene therapy study, or received other study treatment within 30 days or 5 half-lives (whichever is longer), unless the participant participated solely in the placebo arm of the study. Additionally, those who have received treatment with antisense oligonucleotides will be excluded.
- Clinically significant comorbid medical conditions or a chronic condition that is unstable, or who are taking concomitant medications that may make them unsuitable for inclusion.
- Any medical or neurological condition (other than AD) that might be contributing to their cognitive impairment or history of cognitive decline.
- A history, presence, and/or current evidence of a clinically significant intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion, or other non-AD pathology) that is likely to call into question a primary clinical diagnosis of AD.
- A history, presence, and/or current evidence of:
  - Brain surgery, deep brain stimulation, or any history of hospitalization due to a brain injury.
  - Possible or probable cerebral amyloid angiopathy, according to Boston Criteria.[13]
  - Received treatment with an anti-amyloid therapy (including biologics) without subsequent MRI that demonstrated the absence of amyloid-related imaging abnormalities.
  - Seizures or epilepsy, with the exception of childhood febrile seizures.
- Receiving any of the following prohibited medications:
  - Medications with potent effects at the NMDA receptor, including memantine, within 4 weeks of investigational product administration and during the entire course of the study.
  - Medications that inhibit cholesterol absorption (eg, ezetimibe).
  - Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine).
  - Other medications or supplements given at doses, frequencies, or in combinations that are likely to have a deleterious effect on cognitive performance.
  - Cannabis or other tetrahydrocannabinol-containing substances, regardless of whether or not they are prescribed.

*Additional inclusion/exclusion criteria will apply

PRIMARY ENDPOINT

- The primary endpoint is the change from baseline (CFB) at Day 84 in the Coding Test (total correct) from the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV).
  - The Coding Test from the WAIS-IV requires the participant to identify symbols matched to numbers using a key within a specific timeframe, and is used to monitor changes in cognitive function over time and for early detection of cognitive impairment.[14-16]

SECONDARY ENDPOINTS

- The secondary endpoints are the proportion of patients experiencing treatment-emergent adverse events (TEAEs), the severity of TEAEs, and number of study withdrawals due to AEs.
  - AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

OTHER ENDPOINTS

- Other exploratory cognitive and functional endpoints will also be evaluated.

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 dependent variables; treatment, visit, and visit-by-treatment interaction as fixed effects; patients as random effects; and baseline cognitive test scores as a covariate. Model-based point estimates (ie, least squares mean, 95% confidence intervals, and associated p values) at each time point (visit) will be reported where applicable.
- Descriptive statistics of scores and CFB scores will be summarized based on the Full Analysis Set (all patients in the Safety Set who have baseline and at least 1 postbaseline efficacy evaluation).

Conclusions

- This ongoing, randomized, double-blind, placebo-controlled study (NCT05619692) is designed to evaluate the safety and effects on cognitive performance of SAGE-718 in patients with MCI or mild dementia due to AD.
- These data are expected to inform the potential of SAGE-718 for the treatment of cognitive impairment associated with AD.
- SAGE-718 is being investigated in other neurodegenerative diseases, as outlined here:
  - The PERSPECTIVE Clinical Development Program includes 2 ongoing Phase 2 randomized, controlled trials for patients with cognitive impairment associated with Huntington's disease (HD)[17]:
    - DIMENSION (NCT05107128): 12-week treatment period.
    - SURVEYOR (NCT05358821): 4-week treatment period.
    - Patients who complete the Phase 2 DIMENSION or SURVEYOR Studies will be eligible to enroll in a planned Phase 3, open-label, safety trial. A de novo cohort of patients with HD and a Total Functioning Capacity score of 13 and/or a MoCA score of ≥26 will also be eligible to enroll.
  - PRECEDENT (NCT05318937) is a Phase 2, randomized, double-blind, placebo-controlled trial in patients with Parkinson's disease that is currently enrolling.

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AK, TL, JJ, SP, SL, JW, KP, MQ, and **JD** are employees of Sage Therapeutics, Inc., and hold stock or stock options.

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