# A Phase 1 Study to Determine the Safety, Tolerability, Pharmacokinetics, and Cognitive Effects of SAGE-718

**Aaron Koenig, MD, Kevin Moynihan, BA, Sigui Li, MS, Jeffrey Wald, PhD, Ludmila Kryzhanovska, MD, PhD, Irena Webster, MPH, MA, Mike Lewis, PhD, Helen Colquhoun, MD, Stephen J. Kanes, MD, PhD, James Doherty, PhD**

**Sage Therapeutics, Inc., Cambridge, MA, USA**

## Introduction

Huntington’s Disease (HD) is a neurodegenerative disorder that manifests with motor, cognitive, and psychiatric symptoms. An estimated 20,000 (18,600 to 30,000) adults (7.3 to 11.8 per 100,000) are diagnosed with HD in the United States. Decreased N-methyl-D-aspartate receptor (NMDAR) function has been implicated in the pathogenesis of HD, and enhancement of NMDAR-related neurotransmission may offer a potential therapeutic approach.

In recent studies, SAGE-718, a novel, investigational, oxysterol-based NMDAR positive allosteric modulator, demonstrated functional NMDAR engagement and positive cognitive effects in healthy volunteers.

In a Phase 1 study of SAGE-718 (oral solution), healthy volunteers were evaluated in double-blind, placebo-controlled, multiple-ascending dose cohorts, while patients with HD received SAGE-718 in an open-label cohort (NCT03787758). The safety, tolerability, pharmacokinetics (PK), and cognitive effects of SAGE-718 were evaluated.

## Methods

- Participants of both sexes, ages 18-65 (healthy volunteers) and ages 18-70 (patients with HD), were eligible for this study.
- Cohorts 1 and 2 enrolled healthy volunteers (N=12 each), and Cohort 3 enrolled HD patients (N=6) positive for mutant HTT gene (CAG repeats ≥36 units), with qualifying cognitive and motor assessments: Total Functional Capacity score of >6, and a Montreal Cognitive Assessment (MoCA) score of ≥22.
- Exclusion criteria included clinically significant findings during physical examination, heart rate <50 or >100 beats per minute, systolic blood pressure <90 or >140 mmHg, or diastolic blood pressure <60 or >90 mmHg.
- Healthy volunteers were randomized 3:1 to SAGE-718: placebo in Cohorts 1 (0.5 mg) and 2 (1.0 mg), and Cohort 3 received open-label SAGE-718 1.0 mg. All patient cohorts were administered SAGE-718 daily for 14 days in a mixed inpatient and outpatient setting, with follow-up through Day 21.

## Results

### DEMOGRAPHICS & BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Race</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>37.5 (8.3)</td>
<td>39.2 (3.9)</td>
<td>9 (100.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>HD - 0.5 mg</td>
<td>39.2 (3.9)</td>
<td>9 (100.0%)</td>
<td>9 (100.0%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>HD - 1.0 mg</td>
<td>38.2 (3.9)</td>
<td>9 (100.0%)</td>
<td>9 (100.0%)</td>
<td>2 (33.3%)</td>
</tr>
</tbody>
</table>

### HD PATIENT ASSESSMENTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean PK Profiles Across Cohorts</th>
<th>LS Mean (SE) Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>UHDRS Motor score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two-Back Test score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### PERFORMANCE ON COGNITIVE BATTERY IN HD PATIENTS

**COGNITIVE TESTS**

<table>
<thead>
<tr>
<th>Test</th>
<th>Cognitive Domain and Instructions</th>
<th>Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection Test*</td>
<td>Psychomotor Function</td>
<td>&quot;Hit the card turned right&quot;</td>
</tr>
<tr>
<td>One-Back Test*</td>
<td>Working Memory</td>
<td>&quot;Is the card the same as the previous card?&quot;</td>
</tr>
<tr>
<td>Stop Signal Reaction Time (STOP) Test*</td>
<td>Response Inhibition</td>
<td>&quot;Impulse control&quot;</td>
</tr>
<tr>
<td>Two-Back Test*</td>
<td>Working Memory</td>
<td>&quot;Is the card the same as the card 2 cards ago?&quot;</td>
</tr>
</tbody>
</table>

**DETECTION TEST (PSYCHOMOTOR FUNCTION)**

- No changes from baseline were observed on assessment of psychomotor speed (Detection Test).

**ONE-BACK TEST (SIMPLE WORKING MEMORY)**

- No significant changes from baseline were observed on assessment of simple working memory (One-Back Test).

**STOP TEST (RESPONSE INHIBITION)**

- No significant changes from baseline were observed in assessment of response inhibition (STOP Test).

**TWO-BACK TEST (WORKING MEMORY)**

- HD subjects improved on the Two-Back Test at all post-baseline visits, and demonstrated statistically-significant (p < 0.05) improvement compared to baseline on Days 8, 10, 12, and 14.

**GROTON MAZE TEST (EXECUTIVE FUNCTION)**

- HD subjects displayed a trend towards improvement on the Groton Maze Test post-baseline, excluding Day 4.

## Conclusions

- SAGE-718 was generally well-tolerated, with no serious AEs or AEs leading to treatment discontinuation reported for any cohort.
- SAGE-718 was associated with improvements in measures of executive functioning on the Two-Back Test, reaching statistical significance at Days 8, 10, 12 and 14. There was a trend towards improvement as measured by the Groton Maze Test (with the exception of Day 4), both of which reflect the core cognitive deficits observed in patients with HD.
- These cognitive improvements did not appear to be driven by changes in psychomotor speed or simple attentional processes.
- These findings support further investigation of SAGE-718 in the treatment of cognitive deficits in HD.

## References