SAGE-718
Ongoing Study Designs
March 2022
**DIMENSION Study - SAGE-718**

*Placebo-controlled study in patients with early Huntington’s disease*

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**STUDY OVERVIEW**

<table>
<thead>
<tr>
<th>Status</th>
<th>Enrolling</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Huntington’s Disease Cognitive Impairment</td>
</tr>
<tr>
<td><strong>Phase</strong></td>
<td>Phase 2</td>
</tr>
<tr>
<td><strong>Arms</strong></td>
<td>Double-blind, randomized: 1:1</td>
</tr>
<tr>
<td>- SAGE-718, placebo</td>
<td></td>
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<tr>
<td><strong>Dosing Regimen</strong></td>
<td>1.2 mg oral daily from days 1 to 27; 0.9 mg oral daily from days 28 to 84</td>
</tr>
</tbody>
</table>
| **Objectives**  | • To evaluate the effect of SAGE-718 on cognitive performance in participants with HD  
• To evaluate the effect of SAGE-718 on daily function in participants with HD |
| **Primary Endpoint** | • Change from baseline in Composite score of the Huntington’s Disease Cognitive Assessment Battery (HD-CAB) |
| **Key Secondary Endpoint** | • UHDRS Independence Scale  
• Be at least 25 years old but no older than 65 years of age at Screening  
• Meet all the following criteria for HD:  
  • Genetically confirmed disease with huntingtin gene CAG expansion ≥36  
  • UHDRS-Total Functional Capacity (TFC) score >6 and <13  
  • No features of juvenile HD  
• Score <26 on the Montreal Cognitive Assessment (MoCA) at screening  
• Be willing to invite a study partner, if available, who is reliable, competent, and at least 18 years of age to participate in the study  
• Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 180 days or 5 half-lives (whichever is longer), unless the patient participated solely in the placebo arm of the study  
• Have a diagnosis of an ongoing neurodegenerative condition other than HD, including but not limited to, Alzheimer's Disease, vascular dementia, dementia with Lewy bodies, or Parkinson's Disease |

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**Inclusion Criteria**

- Be at least 25 years old but no older than 65 years of age at Screening  
- Meet all the following criteria for HD:  
  - Genetically confirmed disease with huntingtin gene CAG expansion ≥36  
  - UHDRS-Total Functional Capacity (TFC) score >6 and <13  
  - No features of juvenile HD  
- Score <26 on the Montreal Cognitive Assessment (MoCA) at screening  
- Be willing to invite a study partner, if available, who is reliable, competent, and at least 18 years of age to participate in the study  
- Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 180 days or 5 half-lives (whichever is longer), unless the patient participated solely in the placebo arm of the study  
- Have a diagnosis of an ongoing neurodegenerative condition other than HD, including but not limited to, Alzheimer's Disease, vascular dementia, dementia with Lewy bodies, or Parkinson's Disease
**SURVEYOR Study - SAGE-718**

*PBO-controlled study in patients with early HD, with Healthy Participant (HP) Comparator Arm*

**STUDY OVERVIEW**

**Status**
Start-up

**Objectives**
- To assess the magnitude of the baseline difference between participants with early Huntington’s Disease (HD) and healthy participants (HP) with respect to measures of cognitive performance.
- To evaluate the effect of SAGE-718 on cognition and functioning outcomes in participants with HD

**Indication**
Huntington’s Disease Cognitive Impairment

**Primary Endpoint**
Baseline measures of the Huntington’s Disease Cognitive Assessment Battery (HD-CAB) cognitive composite score.

**Phase**
Phase 2

**Secondary Endpoints**
- Change from Baseline to Day 28 on HD-CAB, VRFCAT, other endpoints.
- Safety and tolerability of SAGE-718

**Arms**
Double-blind, randomized: 1:1 (HD)
- SAGE-718, placebo
Assessment-only comparator arm (HP)

**Inclusion Criteria (HD Participants)**
- Be at least 25 years old but no older than 65 years of age at Screening
- Meet all the following criteria for HD:
  - Genetically confirmed disease with huntingtin gene CAG expansion ≥36
  - UHDRS-Total Functional Capacity (TFC) score >6 and <13
  - No features of juvenile HD
- Score <26 on the Montreal Cognitive Assessment (MoCA) at screening
- Be willing to invite a study partner, if available, who is reliable, competent, and able to participate in the study

**Exclusion Criteria (HD Participants)**
- Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 90 days or 5 half-lives (whichever is longer), unless the patient participated solely in the placebo arm of the study
- Have a diagnosis of an ongoing neurodegenerative condition other than HD, including but not limited to, Alzheimer’s Disease, vascular dementia, dementia with Lewy bodies, or Parkinson’s Disease

**Dosing Regimen**
1.2 mg oral daily
**STUDY OVERVIEW**

**Status**
Start-up

**Indication**
Mild Cognitive Impairment (MCI) due to Parkinson's Disease

**Phase**
Phase 2

**Arms**
Double-blind, randomized: 1:1
- SAGE-718, placebo

**Dosing Regimen**
1.2 mg oral daily

**Objectives**
- To evaluate the effect of SAGE-718 on cognitive performance in participants with Parkinson’s Disease (PD) Mild Cognitive Impairment (MCI)
- To evaluate the safety and tolerability of SAGE-718 oral capsule in participants with PD-MCI

**Primary Endpoint**
- Change from Baseline to Day 42 in the Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding test

**Key Secondary Endpoint**
- Proportion of participants experiencing treatment emergent adverse events (TEAEs) and severity of TEAEs.
- Number of participants who withdraw due to adverse events (AEs).

**Inclusion Criteria**
- Be between the ages of 50 and 75 at Screening
- Meet all the following criteria for PD-MCI:
  - Have a confirmed diagnosis of idiopathic PD according to 2015 MDS clinical diagnostic criteria, and
  - Meet MDS Task Force Criteria for MCI in PD (excluding requirement for UK PD Brain Bank diagnostic criteria).
- For participants meeting Level 1 PD-MCI criteria, have a MoCA score of 20 to 25 (inclusive) at Screening
- Meet criteria for modified Hoehn and Yahr Stage I to III (mild to moderate motor severity) at Screening
- Have stable motor symptoms for at least 4 weeks prior to Screening, in the opinion of the investigator
- Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 180 days or 5 half-lives (whichever is longer), unless the patient participated solely in the placebo arm of the study

**Exclusion Criteria**
- Have a diagnosis of dementia of any etiology, including but not limited to: Dementia associated with PD (probable or possible), Dementia with Lewy Bodies, Alzheimer's Dementia, and Vascular Dementia
- Have any parkinsonism other than PD, including secondary parkinsonism or atypical parkinsonism