ISRCTN17896603 https://doi.org/10.1186/ISRCTN17896603

# A study to evaluate the effect of SAGE-718 on cognitive function in participants with Huntington's Disease

**Submission date**
12/02/2022

**Recruitment status**
No longer recruiting

**Registration date**
16/05/2022

**Overall study status**
Completed

**Last Edited**
31/01/2025

**Condition category**
Nervous System Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

## Plain English summary of protocol

Background and study aims:
Huntington’s disease is a rare, inherited disease causing degeneration of the nerve cells in the brain, leading to gradual impairment in movement, learning abilities, and behavior.
The DIMENSION Study is evaluating the safety and effects of an experimental oral drug, SAGE-718, in adults with early Huntington’s disease (HD). This drug is being tested to see if it can specifically target cognitive symptoms associated with HD.

Who can participate?
Adults aged 25 to 65 years, with Huntington’s disease.
What does the study involve? (what interventions will be compared, will all participants receive the same treatment, what measurements will be taken)
The study lasts up to 20 weeks and includes 9 visits to the study office. The study consists of the following parts: -

a. A screening period of 28 days wherein tests will be done to check if participants are eligible to take part in the study.
b. The treatment period of 84 days wherein participants will be randomly divided into 2 groups to receive either SAGE-718 or placebo, by mouth.
c. A follow-up period of 28 days wherein participants will return to the clinic for check-up visits on Day 98 and Day 112 to help collect continued safety and effectiveness data.

What are the possible benefits and risks of participating?
Benefits:
Based on standardized interviews conducted by Sage, pre-manifest and early manifest HD patients are at high risk of losing employment, their ability to drive and to maintain financial security. In these interviews, care partners observed changes in functioning, and reported that they were beginning to assume some financial or home responsibilities that they previously held by the patient.
SAGE-718 may work to restore aberrant N-methyl-D-aspartate (NMDA) receptor activity in patients with early HD and thereby help to ameliorate cognitive deficits seen in these patients.

Risks:
• The most frequently reported side effects seen after study treatment with SAGE-718 were: Dizziness, Headache, Nausea, Vomiting, Upper respiratory tract infection (common cold), Orthostatic hypotension (drop in blood pressure when standing from laying down), Euphoric mood (feelings of physical and emotional well-being, which become excessive, all consuming, and interfere with daily living), Increased levels of alanine aminotransferase (a liver function test).
• Most side effects were reported as mild or moderate in intensity and got better or went away without stopping study treatment with SAGE-718.
• There was no selective distribution or retention of radioactive SAGE-718 to pigmented tissues and no quantifiable concentration of radioactivity was observed in the eye lens in Long Evans rats, implying that potential risk of phototoxicity is low.

Where is the study run from?
Sage Therapeutics, Inc (USA)

When is the study starting and how long is it expected to run for?
May 2021 to October 2024

Who is funding the study?
Sage Therapeutics, Inc (USA)

Who is the main contact?
Amy Bullock, PhD; amy.bullock@sagerx.com

# Contact information

### Type(s)
Principal investigator

### Contact name
Dr Edward Hugh Galbraith Rickards

### Contact details
25 Vincent Drive
Edgaston
Birmingham
United Kingdom
B15 2FG
+44 121 301 2290
hugh.rickards@nhs.net

### Type(s)
Scientific

### Contact name
Dr Amy Bullock

### Contact details
55 Cambridge Parkway
Cambridge

United States of America
MA 02142
+1 619-949-5151
amy.bullock@sagerx.com

# Additional identifiers

### Clinical Trials Information System (CTIS)
2021-005577-16

### Integrated Research Application System (IRAS)
1004868

### ClinicalTrials.gov (NCT)
NCT05107128

### Protocol serial number
718-CIH-201, IRAS 1004868, CPMS 51899

# Study information

### Scientific Title
A randomized, placebo-controlled, double-blind study to evaluate the effect of SAGE-718 on cognitive function in participants with Huntington's Disease

### Acronym
DIMENSION

### Study objectives
Current study hypothesis as of 31/01/2025:

- To evaluate the effect of SAGE-718 on cognitive performance in participants with HD
- To evaluate the effect of SAGE-718 on cognition and daily function in participants with HD.
- To evaluate the safety and tolerability of SAGE-718 oral capsule in participants with HD.

———

Previous study hypothesis:

- 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.
- To evaluate the safety and tolerability of SAGE-718 oral capsule in participants with HD.

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
Approved 05/05/2022, London-Riverside Research Ethics Committee (Temple Quay House, 2 The Square, Bristol Research Ethics Committee Centre, Bristol, BS1 6PN, UK; +44(0)207 104 8150; riverside.rec@hra.nhs.uk), ref: 22/LO/0177

## Study design
Interventional double-blind randomized placebo-controlled trial

## Primary study design
Interventional

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
Huntington's disease

## Interventions
Current interventions as of 25/10/2022:

The intervention model is parallel assignment with two arms. Eligible participants will be randomized 1:1 to receive either SAGE-718 (oral softgel lipid capsules) or placebo (SAGE-718-matching oral softgel lipid capsules) for 84 days. After completing the treatment period, participants will return to the clinic for follow-up visits at on Day 98 and Day 112 to collect continued safety and efficacy data.

Participants are randomized via an IRT system.

_____

Previous interventions:

The intervention model is parallel assignment with two arms. Eligible participants will be randomized 1:1 to receive either SAGE-718 (oral capsules) or placebo (SAGE-718-matching oral capsules) for 84 days. After completing the treatment period, participants will return to the clinic for follow-up visits at on Day 98 and Day 112 to collect continued safety and efficacy data.

Subjects are randomized via an IRT system.

## Intervention Type
Drug

## Phase
Phase II

## Drug/device/biological/vaccine name(s)
SAGE-718

## Primary outcome(s)
Current primary outcome measure as of 31/01/2025:

Change from baseline to day 84 in the cognitive function assessed using the Symbol Digit Modalities Test (SDMT)

_____

Previous primary outcome measure:

Change from baseline to day 84 in the cognitive function assessed using Huntington's Disease Cognitive Assessment Battery (HD-CAB) Composite Score

### Key secondary outcome(s))
Current secondary outcome measures as of 31/01/2025:

1. Change from baseline to day 84 in the functional capacity assessed using Unified Huntington's Disease Rating Scale (UHDRS) - Independence Scale
2. Change from baseline to day 84 in the cognitive function assessed using the Trail Making Test Part B
3. Change from baseline to day 84 in the cognitive function assessed using the One Touch Stockings of Cambridge (OTS)
4. Change from baseline to day 84 in the motor function assessed using the Paced Tapping Test (PTAP)
5. Change from baseline to day 84 in the functioning difficulty assessed using the Huntington’s Disease Everyday Functioning (Hi-DEF) Home subdomain score
6. Change from baseline to day 84 in the cognitive function assessed using the Clinical Global Impression – Severity (CGI-S) Cognitive Status subdomain score
7. Percentage of Participants with Treatment-emergent Adverse Events (TEAEs) up to approximately 112 days

_____

Previous secondary outcome measures:

1. Change from baseline to day 84 in the functional capacity assessed using Unified Huntington's Disease Rating Scale (UHDRS) - Independence Scale
2. Change from baseline to day 84 in the motor function assessed using UHDRS - Total Motor Score (TMS)
3. Percentage of Participants with Treatment-emergent Adverse Events (TEAEs) up to approximately 112 days

### Completion date
03/10/2024

## Eligibility

### Key inclusion criteria
Current inclusion criteria as of 31/01/2025:

1. Meet all the following criteria for HD at Screening (Days -28 to -2):
1.1. Genetically confirmed disease with huntingtin gene CAG expansion ≥36.
1.2. At Screening, UHDRS-Total Functional Capacity (TFC) score >6 and <13 suggesting no more than a moderate level of functional impairment.
1.3. No features of juvenile HD.
2. Score of 15 to 25 (inclusive) on the Montreal Cognitive Assessment (MoCA) at screening indicating the presence of cognitive impairment.
3. 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.

4. Be ambulatory (use of assistance devices such as a walker or cane is acceptable as is occasional use of wheelchair, as judged by the investigator. Individuals requiring a wheelchair on a regular basis are excluded), able to travel to the study center, and, as judged by the investigator, is likely to be able to continue to travel to the study center to complete study visits for the duration of the study.
5. Completion of HD-CAB Trail Making-B Test in <240 seconds at Screening (Days -28 to -2).

_____

Previous inclusion criteria as of 20/05/2024:

1. Meet all the following criteria for HD at Screening (Days -28 to -2):
1.1. Genetically confirmed disease with huntingtin gene CAG expansion ≥36.
1.2. At Screening, UHDRS-Total Functional Capacity (TFC) score >6 and <13 suggesting no more than a moderate level of functional impairment.
1.3. No features of juvenile HD.
2. Score of 15 to 25 (inclusive) on the Montreal Cognitive Assessment (MoCA) at screening indicating the presence of cognitive impairment.
3. 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.
4. Be ambulatory (use of assistance devices such as a walker or cane is acceptable as is occasional use of wheelchair, as judged by the investigator. Individuals requiring a wheelchair on a regular basis are excluded), able to travel to the study center, and, as judged by the investigator, is likely to be able to continue to travel to the study center to complete study visits for the duration of the study.

_____

Previous inclusion criteria as of 25/10/2022:

1. Meet all the following criteria for HD:
1.1. Genetically confirmed disease with huntingtin gene CAG expansion ≥36.
1.2. UHDRS-Total Functional Capacity (TFC) score >6 and <13.
1.3. No features of juvenile HD.
2. Score <26 on the Montreal Cognitive Assessment (MoCA) at screening.
3. 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.
4. Be ambulatory (use of assistance devices such as a walker or cane is acceptable as is occasional use of wheelchair, as judged by the investigator. Individuals requiring a wheelchair on a regular basis are excluded), able to travel to the study center, and, as judged by the investigator, is likely to be able to continue to travel to the study center to complete study visits for the duration of the study.

_____

Previous inclusion criteria:

1. Meet all the following criteria for HD:
1.1. Genetically confirmed disease with huntingtin gene CAG expansion ≥36.
1.2. UHDRS-Total Functional Capacity (TFC) score >6 and <13.
1.3. No features of juvenile HD.
2. Score <26 on the Montreal Cognitive Assessment (MoCA) at screening.

3. 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.
4. Be ambulatory (use of assistance devices such as a walker or cane is acceptable; individuals requiring a wheelchair are excluded), able to travel to the study center, and, as judged by the investigator, is likely to be able to continue to travel to the study center to complete study visits for the duration of the study.

**Participant type(s)**
Patient

**Healthy volunteers allowed**
No

**Age group**
Adult

**Lower age limit**
25 years

**Upper age limit**
65 years

**Sex**
All

**Total final enrolment**
189

**Key exclusion criteria**
Current exclusion criteria as of 20/05/2024:

1. Have participated in a previous clinical study of SAGE-718, have previous exposure to gene therapy or have participated in any HD investigational drug, biologic, or device trial within 180 days or a non-HD drug, biologic, or device trial within 30 days or 5 half-lives (whichever is longer) (Note: Participants with confirmation of enrollment in the placebo arm of these trials would not be excluded.)
2. 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

———

Previous exclusion criteria as of 25/10/2022:

1. Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have participated in any other drug, biologic, or device trial within 30 days or 5 half-lives (whichever is longer), unless the participant participated solely in the placebo arm of the study. Additionally, participants who have received treatment with antisense oligonucleotides (ASOs) or a messenger ribonucleic acid (mRNA) splicing modifier will be excluded.
2. 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

_____

Previous exclusion criteria:

1. Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have participated 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.
2. 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.

### Date of first enrolment
05/11/2021

### Date of final enrolment
11/06/2024

## Locations

### Countries of recruitment
United Kingdom

England

Scotland

Australia

Canada

United States of America

### Study participating centre
**Birmingham and Solihull Mental Health NHS Foundation Trust**
Unit 1
50 Summer Hill Road
Birmingham
United Kingdom
B15 2FG

### Study participating centre
**Re-Cognition Health**
Unit 2

5 Research Way
Plymouth
United Kingdom
PL6 8BT

**Study participating centre**
**Unit 3**
Aberdeen
United Kingdom
AB25 2ZA

**Study participating centre**
**Unit 4**
Cardiff
United Kingdom
CF10 3AX

**Study participating centre**
**Unit 5**
Leeds
United Kingdom
LS1 3X

**Study participating centre**
**Unit 6**
Leeds
United Kingdom
LS7 4SA

**Study participating centre**
**Unit 7**
Newcastle Upon Tyne
United Kingdom
NE6 4QD

**Study participating centre**

**Unit 8**
Southampton
United Kingdom
SO16 6YD

**Study participating centre**
**Unit 9**
Tooting
London
United Kingdom
SW17 0QT

# Sponsor information

**Organisation**
Sage Therapeutics, Inc.

# Funder(s)

**Funder type**
Industry

**Funder Name**
Sage Therapeutics, Inc

# Results and Publications

**Individual participant data (IPD) sharing plan**
The datasets generated during and/or analysed during the current study are not expected to be made available due to participant-level data not being a regulatory requirement.

**IPD sharing plan summary**
Not expected to be made available

**Study outputs**

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| HRA research summary | | | 28/06/2023 | No | No |
| Participant information sheet | Participant information sheet | 11/11/2025 | 11/11/2025 | No | Yes |