Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

SAGE-718

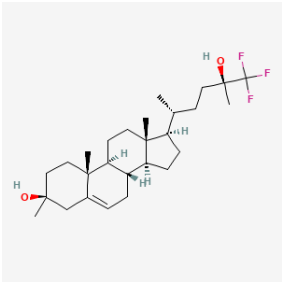
Evidence Summary

A few small clinical trials have tested SAGE-718 in people with neurodegenerative diseases. However, larger placebo-controlled studies are necessary to determine true efficacy.

Neuroprotective Benefit: Several small trials hint at cognitive benefits of SAGE-718 in individuals with neurodegenerative diseases. However, larger controlled studies are necessary to determine true efficacy.

Aging and related health concerns: There is no data or current indication for SAGE-718 outside of the central nervous system.

Safety: Initial small, short-term clinical trials have not reported any serious adverse events. Data from longer placebo-controlled studies is needed.

Availability: in clinical development.	**Dose**: Best dose has not yet been determined. Trials have tested oral doses ranging from 0.9 to 3 mg daily.	**Chemical formula:** $C_{27}H_{43}F_3O_2$ **MW**: 456.6 g/mol 
Half-life: 26.3 hours in plasma and 30.7 hours in brain in rats; specific human data does not appear to have been published yet, though company press releases state it is appropriate for daily dosing.	**BBB**: Penetrant.	
Clinical trials: Has been tested in several Phase 1 and 2 trials; the largest trial enrolled 26 patients. In total, results have been made public from trials comprising a total of 86 patients.	**Observational studies**: There are no observational studies of SAGE-718.	Source: PubChem

What is it?

N-methyl-d-aspartate (NMDA) receptors are a family of ionotropic glutamate receptors that are primarily characterized in the central nervous system. These receptors play an essential role in glutamatergic neurotransmission and are important for the synaptic plasticity and long-term potentiation that underlie learning and memory (Hansen et al., 2020). NMDA receptors can be regulated by a number of compounds, including ones known as positive allosteric modulators (Hackos & Hanson, 2017). An oxysterol known as 24S-hydroxycholesterol (24S-HC), also called cerebrosterol, is a product of brain metabolism of cholesterol. While 24S-HC is known to play a role in cholesterol homeostasis and is a natural ligand of the liver receptor X (LXR) proteins, 24S-HC is also a positive allosteric modulator of NMDA receptors (Gamba et al., 2021, Hill et al., 2022). SAGE-718 is a synthetic compound structurally based on 24S-HC that is under development by Sage Therapeutics (Hill et al., 2022).

NMDA receptors are thought to be involved in a range of neurological diseases, ranging from depression to schizophrenia neurodevelopmental disorders to neurodegenerative diseases (Hansen et al., 2020). Like 24S-HC, SAGE-718 is a positive allosteric modulator of NMDA receptors (Hill et al., 2022, Beckley et al., 2023). It is thought that both hyper- and hypofunction of NMDA receptors can contribute to disease, the former through excitotoxicity and the latter through loss of essential NMDA function (Hansen et al., 2020). SAGE-718 is predicted to mitigate hypofunction of NMDA receptors.

SAGE-718 has been granted orphan drug and fast track status for Huntington's disease (HD) and is being developed for cognitive impairment in AD and Parkinson's disease (PD) as well by Sage Therapeutics. The potential effects of SAGE-718 outside of the brain have largely not been studied and/or reported, at least in part because non-neuronal NMDA receptors exist but are poorly understood (Hogan-Cann & Anderson, 2016).

Neuroprotective Benefit: Several small trials hint at cognitive benefits of SAGE-718 in individuals with neurodegenerative diseases. However, larger controlled studies are necessary to determine true efficacy.

Types of evidence:

- 3 randomized controlled clinical trials in patients with neurodegenerative diseases
- 3 open label studies in patients with neurodegenerative diseases
- 3 observational studies in patients with neurodegenerative diseases
- 3 press releases or investor slides containing data from clinical trials
- 7 reviews
- 4 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

SAGE-718 is under development for treatment of neurodegenerative diseases. Early clinical trials were run in healthy adults, and some tested cognitive effects. The studies were designed using ketamine challenges and so these results may not be applicable for healthy adults without a ketamine challenge. However, they will be included here as they are still results from clinical trials in healthy adults.

Sage Therapeutics ran 3 Phase 1 randomized blinded studies of healthy adults. Participants were assigned to either SAGE-718 or placebo by mouth once daily, with durations and doses varying between trials. All SAGE-718 dosing was by mouth. All participants also received a low-dose ketamine challenge; ketamine is an NMDA receptor blocker and therefore mimics NMDA receptor hypofunction and allows for a readout of SAGE-718 target engagement. The studies assessed safety, tolerability, target engagement as assessed by ECG and MRI, and included some cognitive assessments.

According to a poster presentation at the 58th Annual Meeting of the American College of Neuropsychopharmacology (ANCP) in 2019, one study of 40 participants found that those who received 1 mg SAGE-718 and low-dose ketamine for 10 days had statistically significant improvements over the course of the trial in working memory and complex problem solving than those who received placebo and low-dose ketamine at the same dose and duration as the treatment group. The cognitive results were significantly or trended towards significantly associated with the maximum concentrations of SAGE-718 in blood. It is worth nothing that the study was 10 days long and testing appears to have occurred every other day, so a practice effect may be at play (ANCP 58th Annual Meeting, Poster Session 1: Koenig et al., 2019, M143). This result seems to be associated with the following clinical trial: NCT03771586.

Another study involved a randomized crossover design with a 10-day washout period. Participants received either placebo or 3 mg SAGE-718, and then either electrophysiological recordings or MRI assessments were done. The participants then received a 0.25 mg/kg ketamine infusion over the course of an hour, during which they received another electrophysiological reading session or MRI that included measures of blood oxygenation level (BOLD) changes and functional connectivity. The study had 13 subjects with completed data for the MRI portion and 18 completed subjects with valid data from the electrophysiological reading section. The authors report that SAGE-718 attenuated the ketamine-induced brain changes as measured by MRI and electrophysiological readings (ANCP 58th Annual Meeting, Poster Session 1: Murck at el., 2019, M144). These results appear to be associated with ClinicalTrials.gov registries: NCT03844906 and NCT03770780.

Human research to suggest benefits to patients with dementia:

SAGE-718 is under investigation in ongoing trials for HD, AD, and PD. Some early phase data is available.

LUMINARY is an open-label study of SAGE-718 in patients with MCI or mild dementia. The study enrolled 26 participants aged 50 to 80 years. Participants took 3 mg of SAGE-718 by mouth daily for 14 days and received cognitive and functional assessments. The authors report that they observed improvements in measures of overall function, executive function, learning, and memory between baseline and day 14. They also report a statistically significant improvement in cognition as assessed by Montreal Cognitive Assessment (MoCA) between baseline and day 28. Due to the study design (lack of placebo control group), placebo effects and practice effects cannot be ruled out. Full data is not yet available for this study (Koenig et al., 2022).

Results from an open-label study in patients with PD with cognitive impairment were presented at AD/PD in 2022. This study involved a Part A with 11 participants and a Part B with 7 participants. All participants received 3 mg of SAGE-718 by mouth daily; Part A participants took SAGE-718 for 14 days, whereas Part B participants took SAGE-718 for 28 days. The patients in Part A received cognitive assessments at baseline, 14 days, and 28 days. The investigators announced that they observed improvements in measures of executive function, and potential improvements on measures of learning and memory, when comparing Day 14 to baseline results. They also announced that the benefits appeared to be sustained until at least Day 28 (Press release). Due to the study design, placebo effects and practice effects cannot be ruled out.

SAGE-718 has also been evaluated in an open-label study of 6 patients with HD. The patients received 1 mg of SAGE-718 for 14 days. Outcome measures included assessments of cognitive function. Sage Therapeutics reports that patients had statistically significantly improved performance on assessments of executive function as compared to baseline. It is important to note that this was an open label study and participants were tested every other for 2 weeks, meaning that practice effects cannot be ruled out (Sage Therapeutics Press Release; Sage Therapeutics FutureCast Slide Deck, Slide 16).

Overall, initial results show potential for cognitive improvement when taking SAGE-718. However, most of these studies were open-label or involved repeated testing. It also should be noted that many of these results were published in posters or announced in press releases and have not yet been published in peer-reviewed journals, making some of the findings difficult to fully assess. Data from the ongoing longer, placebo-controlled trials are needed to evaluate the efficacy of SAGE-718.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Brain NMDA receptors are a class of ionotropic glutamate that play important roles in synaptic plasticity and long-term potentiation, and therefore in learning and memory. Most NMDA receptors are coincidence detectors – that is, they detect coincident events. In order to open many NMDA channels to ion flow, glutamate and a co-agonist (typically glycine or serine) must bind. Additionally, at neuronal membrane resting potential, most NMDA receptors are blocked by Mg2+ ions. Only upon membrane depolarization is the blockade lifted and can the co-agonist binding allow the channel to open to Ca2+ ions. The frequency and length of Ca2+ inflow can lead to long-term potentiation or long-term depression through many downstream signaling effects (Hansen et al., 2020).

Dysfunction of NMDA receptors can contribute to disease. Overactivation of NMDA receptors can result in excitotoxicity. Drugs like memantine, an NMDA receptor blocker that is commonly prescribed to AD patients, are designed to counteract this hyperfunction. Direct NMDA agonists can lead to the same issue. However, NMDA receptor hypofunction has also been linked to psychiatric symptoms and cognitive impairment (Hansen et al., 2020, Hakos & Hanson, 2017). Other NMDA regulators, including positive allosteric modulators such as 24S-HC, pregnenolone sulfate, and SAGE-718, are therefore of interest to the community (Hakos & Hanson, 2017, Geoffroy et al., 2022).

Levels of 24S-HC have been found to be associated with neurodegenerative disease and/or degree of cognitive impairment. Lower levels of 24S-HC have been observed in patients with symptomatic HD as compared to pre-manifest HD patients or healthy controls (Leoni et al., 2008). Data has also been presented that found levels of 24S-HC to be positively correlated with cognitive tests in individuals in TRACK-HD, a longitudinal biomarker study that includes healthy controls, individuals with pre-manifest HD, and HD patients. The authors report that 24S-HC levels only correlated with cognitive tasks, not motor symptoms (ANCP 58th Annual Meeting, Poster Session 1: Lewis et al., 2019, M147). 24S-HC is also a player in cholesterol homeostasis, and cholesterol dysregulation is a feature of HD and other diseases (Beckley et al., 2023). These data have led to the hypothesis that the lower 24S-HC levels result in lower NMDA activation, and that compensating for the lower 24S-HC levels through other positive allosteric modulators of NMDA receptors like SAGE-718 may improve cognitive function.

It should be noted that the role of 24S-HC in AD is controversial. Some studies have found that 24S-HC levels do not correlate with disease or found opposite correlations; it has also been suggested that increased or decreased levels of 24S-HC in blood could reflect breakdown of neuronal cellular

membranes, thus releasing more of this lipid into the blood. 24S-HC has also been proposed to mediate disease-promoting effects such as neuroinflammation, Aβ peptide production, oxidative stress, and cell death. However, many of these actions are proposed to occur through 24S-HC-mediated activation of LXR or the renin-angiotensin system (RAS) (Hansen et al., 2020). SAGE-718 did not appear to act as an agonist or otherwise affect LXRs based on cellular and enzymatic assays as well as functional nuclear hormone receptor assays (Beckley et al., 2023).

SAGE-718 is a positive allosteric modulator of NMDA receptors and is thought to increase the chance of NMDA channel opening. In a setting of NMDA receptor hypofunction, this would be predicted to help restore NMDA function and could have positive impacts on cognitive function. In preclinical models, SAGE-718 administration improved deficits that were induced by NMDA hypofunction (Beckley et al., 2023).

There are many NMDA receptors in the overall family. There are seven known subunits: GluN1, GluN2A-D, and GluN3A-B. NMDA receptors are obligatory heterotetramers. Typically, they consist of two GluN1 and two GluN2 subunits; as there are 4 different GluN2 subunits, GluN1/2 receptors can be a variety of combinations. GluN 1/2/3 and GluN1/3 receptor combinations also exist. NMDA receptors can also be found at the synaptic (synaptic NMDA receptors) but can also be located outside the synapse (extrasynaptic NMDA receptors) (Hansen et al., 2020). With different subunit compositions, subcellular localizations, neuronal subtypes, and localizations in the brain, NMDA receptors can have different behavior including response to ligands and downstream effects (Hansen et al., 2020; Geoffroy et al., 2022). SAGE-718 is reported to act as a positive allosteric modulator for all GluN1/2 NMDA receptors, albeit with different potencies. As NMDA receptor positive allosteric modulators only increase receptor activity in the presence of co-agonists, which mainly occurs at the synpase, Iit is hypothesized that SAGE-718 would be more specific for synaptic NMDA receptors as opposed to extrasynaptic NMDA receptors (Hill et al., 2022, Beckley et al., 2023). While the difference between NMDA receptors is appreciated and the different potency of SAGE-718 for various recombinant NMDA receptors in a laboratory setting is known, the clinical significance of this, if any, is another layer of complexity to be watched in future studies.

APOE4 interactions:

Whether SAGE-718 and APOE4 status interact is not yet known. Theoretically, they could interact; APOE is involved in cholesterol transport and SAGE-718 is derived from 24-S-hydroxycholesterol, a cholesterol

metabolite produced in the brain. Plasma levels of 24S-HC have been reported to be increased in patients who carry an APOE4 allele (Papassotiropoulos et al., 2000). Whether this is clinically significant and whether and how the APOE4 allele influences drug action, or vice versa, is not known.

Aging and related health concerns: There is no data or current indication for SAGE-718 outside of the central nervous system.

Types of evidence:

- 1 review

There is no information available about the clinical effects of SAGE-718 on aging or related health concerns outside of the central nervous system. There are non-neuronal NMDA receptors that may or do participate in a variety of aging related diseases, such as diabetes, cancer, and osteoporosis (reviewed by Hogan-Cann & Anderson, 2016). However, this receptor family is not well understood, and it is not known whether or how SAGE-718 would interact with these peripheral NMDA receptors.

Safety: Initial small, short-term clinical trials have not reported any serious adverse events. Data from longer placebo-controlled studies is needed.

Types of evidence:

- 2 open label studies
- 2 randomized controlled trials
- 2 press releases or investor slides containing data from clinical trials
- 2 laboratory studies

LUMINARY was an open label study of 3 mg daily SAGE-718 in 26 patients with MCI or mild dementia. The authors report that there were no serious adverse evets or deaths. There were eight mild or moderate treatment-emergent adverse effects in seven participants; six of them were judged to be treatment related. The nature of the adverse events was not reported (Koenig et al., 2022).

NCT04476017 was a two part open label study looking at the safety and tolerability of SAGE-718 in patients with PD-MCI. The study enrolled 18 participants. The 11 participants in Part A of the study took

3 mg of SAGE-718 once a day for 14 days, whereas the 7 participants in Part B took 3 mg of SAGE-718 once a day for 28 days. All participants took SAGE-718 by mouth with food in the morning. The results were posted on the 'Results' tab of the clinicaltrials.gov study page. Of the 18 participants, all but 1 participant in Part A completed the study. In Part 4, 5 of the 11 participants (45.5%) reported at least one treatment-emergent adverse event; in Part B, 1 of the 7 participants (14.3%) reported at least one treatment-emergent adverse event. There were no clinically significant changes in vital signs, laboratory assessments, or ECG. There were no deaths or serious adverse events, including any suicidal behavior or ideation. No adverse event affected more than one participant. The full list of adverse events can be seen in the 'Results' tab; the investigators do not report which, if any, they deemed to be potentially treatment related.

Sage Therapeutics reported on the outcomes of early phase trials of SAGE-718 through poster presentations at the ANCP meeting in 2019.

- Poster M143 involved a randomized blinded study of 40 healthy adults who received either 1 mg SAGE-718 or placebo daily for 10 days. The study was a ketamine challenge paradigm, so all participants also received low dose ketamine. There were no serious adverse events or deaths. There were no discontinuations or dose reductions of SAGE-718 due to treatment-emergent adverse events. The most frequently reported treatment-emergent adverse events were mild and 'numerically similar' to the placebo group [6 (31.6%) of the treatment group and 7 (33.3% of the placebo group)].
- Poster M144 involved a crossover-study design and ketamine challenge paradigm wherein the healthy adult participants received one dose of either placebo or 3 mg SAGE-718 and then ketamine hours later and received MRI or electrophysiological assessments. The authors report assessment results from 13 subjects with valid data from the MRI portion, and 18 subjects with valid data from the electrophysiological portion. There were no serious adverse events or deaths. Treatment-emergent adverse events reported before ketamine administration were 'mild and infrequent', and included headache (n=1) and fatigue (n=1). There were no discontinuations or dose reductions of SAGE-718 due to adverse events, and no significant changes in laboratory assessments, vital signs, or physical exams.

Sage Therapeutics reported on the results of a 14-day open-label study of SAGE-718 in HD patients. The 6 patients received 1 mg of SAGE-718 daily. In a press release and investor slide presentation, the company reported that there had been no serious adverse events or deaths, and that 'most treatment-

emergent adverse events [had] been mild in severity' (Sage Therapeutics Press Release; Sage Therapeutics FutureCast Slide Deck, Slide 16).

There are a few theoretical safety considerations of SAGE-718:

- One main concern is whether modulation of NMDA receptors would lead to excessive glutamatergic signaling and thus aberrant neuronal activity such as seizure and/or excitotoxicity. In preclinical studies using cell and animal models, SAGE-718 did not increase network activity associated with epileptiform activity and did not have any anti- or pro-convulsant activity. (Beckley et al., 2023).
- NMDA receptors are also hypothesized to play a role in tumor progression, and NMDA receptor blockade has been suggested as a potential chemotherapeutic. Potential oncogenic activity is therefore another potential safety effect to watch for.

It is important to note that these issues have not been observed or reported in preclinical or clinical trials, and there is preclinical data that suggests some of these concerns are unfounded. Beckley et al., 2023 included a 6-month toxicology study in rats and reported no effects of SAGE-718 on survival or adverse events.

Drug interactions:

The drug interactions of SAGE-718 are not fully elucidated. As SAGE-718 is a positive allosteric modulator of NMDA receptors, SAGE-718 could theoretically interact with other medications that affect NMDA receptors (Beckley et al., 2023). For instance, a preclinical paper indicated that SAGE-718 could affect ketamine-NMDA receptor dynamics in cell culture and animal models. The clinical significance and extent of these interactions remain to be determined.

Research underway:

There are five ongoing trials on SAGE-718 that are registered on clinicaltrials.gov: one in AD patients, one in PD patients, and three in HD patients.

NCT05619692 is an ongoing study of SAGE-718 in patients with MCI or mild AD. The randomized, controlled, blinded study plans to enroll 150 patients. Participants will take 1.2 mg of SAGE-718 orally

for 6 weeks, and then take 0.9 mg SAGE-718 orally for the remaining 6 weeks, or matching placebo. The primary outcome is cognitive function as assessed by the Wechsler Adult Intelligence Scale IV (WAIS-IV) Coding Test. Secondary outcomes include safety as assessed by incidence of treatment-emergent adverse events and withdrawal from the study due to adverse events.

NCT05318937 is an ongoing study of SAGE-718 in patients with PD and MCI. The randomized, controlled, blinded study will enroll 76 patients. Patients will take either SAGE-718 or placebo by mouth once a day for 6 weeks. The primary outcome is cognitive function as assessed by the Wechsler Adult Intelligence Scale IV (WAIS-IV) Coding Test. Secondary outcomes include safety as assessed by incidence of treatment-emergent adverse events and withdrawal from the study due to adverse events.

Three remaining studies are assessing the utility of SAGE-718 in HD populations.

NCT05107128 is evaluating the effects of SAGE-718 on cognitive function in 178 HD patients 25 to 65 years of age. This randomized, controlled, blinded trial will involve participants taking either SAGE-718 or placebo by mouth every day for 12 weeks. The primary outcome of the trial is the change in cognitive function as assessed by the composite score of the Huntington's Disease Cognitive Assessment Battery (HD-CAB). Secondary outcomes include changes in measures of functional capacity as measured by the Independence Scale item of the Unified Huntington's Disease Rating Scale (UHDRS), changes in motor function based on motor score from the UHDRS, and safety assessments based on the incidence of treatment-emergent adverse events.

NCT05358821 is evaluating the extent of changes in cognitive performance from baseline in patients with early HD compared to healthy controls, all 25 to 65 years of age. This randomized, controlled, blinded study will enroll 80 participants. The participants will take 1.2 mg of SAGE-718 or matching placebo once a day by mouth for up to 4 weeks. The primary outcome will be the change from baseline in HD-CAB score between participants with HD vs. healthy controls. Secondary outcomes focus on measures of safety, such as incidence of adverse events and incidence of clinically significant changes in either vital sign measurements or laboratory tests. Other outcome measures include other assessments of cognitive function and activities of daily living and will also compare participants with HD in the SAGE-718 arm to HD patients in the placebo arm.

NCT05655520 plans to enroll 300 HD patients who are 25 to 65 years of age. This open-label safety study will function as a long-term extension study for HD patients in the two trials discussed above

(NCT05107128 and NCT05358821) as well as a de novo cohort. Participants in this study will take SAGE-718 every day by mouth for up to 1 full year. The outcomes of this study focus on safety, assessed by incidence of treatment-emergent adverse events, number of participants who withdraw due to adverse events, incidence of changes in laboratory tests or physical examinations, and changes in a measure of suicidal ideation and behavior.

Search terms:

Pubmed, Google: SAGE-718, 24S-HC, 24-S-hydroxycholesterol, NMDA receptor positive allosteric modulator

- Dementia, neurodegenerative disease, HD, PD, AD, diabetes, APOE, cardiovascular

Websites visited for SAGE-718:

- Clinicaltrials.gov
- PubChem
- Cafepharma