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.

Sodium Oligomannate (GV-971)

Evidence Summary
In China, a phase 3 trial of GV-971 improved cognitive functions in Alzheimer’s patients and it was approved for the treatment of Alzheimer’s disease in 2019. A phase 3 trial in the US/Canada is ongoing.

**Neuroprotective Benefit:** GV-971 improved cognitive functions in Alzheimer’s patients in a phase 3 trial in China. In mice, GV-971 altered gut microbiota, decreased brain infiltration of Th1 cells, reduced neuroinflammation, and improved cognitive function.

**Aging and related health concerns:** No studies have evaluated GV-971 for age-related diseases other than Alzheimer’s disease.

**Safety:** Adverse events for GV-971 are generally mild to moderate and their incidence is comparable to that for placebo. GV-971 may cause nasopharyngitis, dry mouth, hematuria, and elevations in liver enzymes and LDL cholesterol.
**What is it?** Sodium oligomannate (GV-971) is derived from brown algae and is a mixture of linear, acidic oligosaccharides with a degree of polymerization ranging from dimers to decamers. After oral administration, most of the ingested sodium oligomannate is retained in the gut and its proposed mechanism of action is to reconstitute the gut microbiota, reduce bacterial metabolite-driven peripheral infiltration of immune cells into the brain, inhibit Aβ aggregation, and inhibit neuroinflammation in the brain (Hannan et al., 2020; Xiao et al., 2021). Sodium oligomannate penetrates the blood-brain barrier through transporters including the glucose transporter GLUT1 (Syed, 2020).

Sodium oligomannate was co-discovered and co-developed by Ocean University of China, Chinese Academy of Sciences’s Shanghai Institute of Materia Medica, and Shanghai Green Valley Pharmaceuticals. Shanghai Green Valley Pharmaceuticals acquired licensing rights for sodium oligomannate in 2009 (Syed, 2020). In November 2019, sodium oligomannate received its approval in China for the treatment of mild-to-moderate Alzheimer’s disease to improve cognitive function. In the US and Canada, a phase 3 multi-center randomized double-blind placebo-controlled trial testing the efficacy and safety of GV-971 in mild to moderate Alzheimer’s disease patients is currently ongoing (NCT04520412).
Neuroprotective Benefit: GV-971 improved cognitive functions in Alzheimer’s patients in a phase 3 trial in China. In mice, GV-971 altered gut microbiota, decreased brain infiltration of Th1 cells, reduced neuroinflammation, and improved cognitive function.

Types of evidence:
- 2 double-blind randomized controlled clinical trials in Alzheimer’s patients
- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:
None available.

Human research to suggest benefits to patients with dementia:
In a phase 3 double-blind randomized controlled trial of 818 patients with mild to moderate Alzheimer’s disease, treatment with GV-971 (900 mg/day) for 36 weeks resulted in a significant difference in cognitive functions as measured by ADAS-Cog12 favoring GV-971 at all time-points after 4 weeks and continuing to 36 weeks (Xiao et al., 2021). This clinical trial was conducted at 34 participating sites in the psychiatry, neurology, and geriatric departments of hospitals in several regions of China. One limitation of this trial was the lack of requirement for a diagnostic amyloid biomarker at screening, thus likely including participants who had dementia that was not due to Alzheimer’s disease; however, approximately 50% of the participants were APOE4 carriers with higher likelihood of amyloid deposition.

The mean changes from baseline at week 36 were −2.70 points for the GV-971 group and −0.16 points for the placebo group, with an unadjusted group difference of −2.54 points. The mean modeled difference between the groups on the change from baseline to week 36 was −2.15 points (95% CI, −3.07 to −1.23; p < 0.0001, with Cohen’s d effect size=0.531, using analysis of covariance).

There were no statistically significant treatment effects for prespecified secondary outcomes, which the authors noted that they were underpowered to show as the sample size was calculated based on the primary endpoint (Xiao et al., 2021). The p-value for Clinician’s Interview-Based Impression of Change with caregiver input (CIBIC+) was 0.059 between the groups. The activities of daily living score (ADCS-ADL) was directionally in favor of GV-971 but was not statistically different between the groups (p=0.57). The neuropsychiatric inventory (NPI) scores at baseline were very low (average score=3 points), with little room to show measurable improvement.
In pre-planned exploratory analyses based on baseline MMSE scores 11-14, 15-19, and 20-26, the adjusted difference values of the primary outcome in ADAS-Cog12 were 4.55, 2.96, and 1.66, respectively (Xiao et al., 2021), suggesting that improvements with GV-971 appeared greater in people with lower cognitive scores.

In subgroup analyses, significant intergroup differences were found for: APOE4 carriers/noncarriers, age (< 65; > 65 years) groups, sexes, education levels (< 6; > 6 years), and MMSE score (3 terciles) (Xiao et al., 2021). In a post hoc subgroup analysis, significant intergroup differences were detected for CIBIC+ outcome in participants with the most severe cognitive decline (MMSE scores between 11-14)(p=0.017), with an effect size of 1.3.

In the [18F]-FDG-PET study where 41 (10.5%) participants in the GV-971 group and 31 (7.7%) participants in the placebo group were assessed, no intergroup differences in predefined global relative cerebral metabolic rate were observed after 36 weeks of treatment (Xiao et al., 2021).

In the phase 2 double-blind randomized controlled trial of 255 mild to moderate Alzheimer’s patients, treatment with GV-971 for 24 weeks resulted in numerically better (but not statistically significant) cognitive scores compared to those receiving the placebo (Wang et al., 2020). ADAS-Cog12 score changes in the GV-971 600 mg daily dose group was −1.39 (p = 0.89) and the GV-971 900 mg daily dose group was −2.58 (p = 0.30), compared to the placebo group which showed a change of −1.45. The percentage of treatment responders according to CIBIC+ assessment was significantly higher in the GV-971 900-mg group than the placebo group (92.77% vs. 79.52%; p < 0.05), while not significant between the 600-mg group and placebo. In an [18F]-FDG-PET study including 7, 9, and 9 patients from the placebo, 600-mg, and 900-mg groups, the GV-971 900-mg group showed a lower decline of cerebral metabolic rate for glucose than the placebo subgroup at the left precuneus (p=0.003), right posterior cingulate (p=0.005), bilateral hippocampus (p=0.006, 0.003, for right and left, respectively), and bilateral inferior orbital frontal cortex (p=0.02, 0.0008, for right and left, respectively). However, p-values were not corrected for multiple comparisons, and after correction, none of these changes were significant. For other secondary outcome measures (ADCS-ADL, NPI scales), no significant differences were found between the treatment groups and placebo.

One limitation of this phase 2 trial was that biomarkers for Alzheimer’s were not included as an inclusion/exclusion criteria, similar to the phase 3 trial. The study was sponsored by Shanghai Green Valley Pharmaceutical Co., Ltd., and supported by the National Major Scientific and Technological
Special Project (grant 2011ZX09101-003-01) and the National High Technology Research and Development Program of China (grant 2006AA090501).

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

Neuroprotective mechanisms have been explored in preclinical studies. In mouse models of Alzheimer’s disease, alterations in the gut microbiota composition led to peripheral accumulation of phenylalanine and isoleucine, which stimulated the differentiation and proliferation of proinflammatory T helper 1 (Th1) cells, whereas GV-971 treatment reversed these effects (Wang et al., 2019). Enterotype analysis showed a clustering effect in the gut microbiome, with the transgenic mouse model of Alzheimer’s (5xFAD mice) clustering under the family of Muribaculaceae and wild-type mice clustering into the Lactobacillus genus. Principal component analysis revealed a shift in the gut microbiota composition during Alzheimer’s progression in 5xFAD mice, while few changes were observed in wild-type mice. The changes in gut microbiome with pathology were associated with the infiltration of peripheral immune cells and neuroinflammation.

In contrast, when an antibiotic cocktail (ampicillin, streptomycin, colistin) was used to ablate the gut microbiota, there was marked reduction in microbial abundance, along with a reduction in infiltrating pro-inflammatory Th1 cells and proinflammatory microglia in the brain.

In a mouse model of Alzheimer’s disease (9-month-old APP/PS1 mice), treatment with GV-971 (100 mg/kg/day, oral gavage) for 3 months significantly ameliorated cognitive impairment, as measured by spatial learning and memory performance on the Morris Water Maze task (Wang et al., 2019). GV-971 treatment also significantly improved performance on the Y maze task. In parallel, GV-971 treatment significantly reduced Aβ plaque deposition and tau phosphorylation.

One of the mechanisms in which GV-971 inhibits neuroinflammation is possibly by regulating amino acid metabolism (Wang et al., 2019). Phenylalanine and isoleucine were the top amino acids that were different between wild-type and Alzheimer’s transgenic mice, with correlations to disease progression. The concentrations of phenylalanine and isoleucine were significantly higher in the feces of transgenic mice compared to wild-type mice, and GV-971 treatment significantly reduced their concentrations to levels comparable to those of wild-type mice. Similar changes in blood levels of phenylalanine and isoleucine were found. Exposure to either phenylalanine or isoleucine significantly enhanced Th1 cell differentiation, while this effect was inhibited by GV-971 treatment.
These findings were also confirmed in people—phenylalanine and isoleucine concentrations as well as Th1 cell frequency in the blood were higher in people with mild cognitive impairment compared to age-matched healthy controls.

Dysbiosis of the gut microbiota can lead to the infiltration of various peripheral immune cells into the brain. Preclinical findings suggest that the abnormal production of phenylalanine and isoleucine by gut microbiota in Alzheimer’s disease models promotes Th1 cell differentiation, leading to passage of Th1 cells through the blood-brain barrier, causing neuroinflammation and differentiation of microglia to a proinflammatory phenotype (Wang et al., 2019). In contrast, GV-971 reconditioned gut microbiota, decreased the concentration of phenylalanine and isoleucine in the feces and blood, and reduced Th1-related neuroinflammation in the brain. Thus, the therapeutic effect of GV-971 may be driven by the reconstitution of gut microbiome.

**APOE4 interactions:** Unknown.

**Aging and related health concerns:** No studies have evaluated GV-971 for age-related diseases other than Alzheimer’s disease.

*Types of evidence:*
- No studies

There have not been any preclinical or clinical studies testing sodium oligomannate for age-related diseases. However, based on its mechanism of action of improving the gut microbiome, there could be theoretical benefits for various conditions such as metabolic disease and inflammation.

**Safety:** Adverse events for GV-971 are generally mild to moderate and their incidence is comparable to that for placebo. GV-971 may cause nasopharyngitis, dry mouth, hematuria, and elevations in liver enzymes and LDL cholesterol.

*Types of evidence:*
- 2 double-blind randomized controlled clinical trials in Alzheimer’s patients
- 1 review
In a safety analysis of sodium oligomannate (577 for sodium oligomannate, 495 for placebo), the overall incidence of adverse reactions did not differ significantly between the sodium oligomannate and placebo groups (14.6% vs. 18.0%) (Syed, 2020). Adverse reactions associated with sodium oligomannate were generally mild to moderate in severity, with severe adverse reactions reported in just 1 patient (0.2%, pneumonia). Seven (1.2%) patients discontinued treatment because of adverse reactions (1 case each of decreased platelet count, type 2 diabetes, acid reflux, irritability and rash; 2 cases of abnormal liver function). The most common (incidence greater than 1-10%) adverse reactions that were more frequent in sodium oligomannate than placebo group were dry mouth (1.0% vs. 0.4%), hematuria (1.0% vs. 0.2%) and elevated alanine aminotransferase (1.9% vs. 0.4%), aspartate aminotransferase (1.7% vs. 0.8%), bilirubin (1.2% vs. 0.2%) and LDL-cholesterol (1.2% vs. 1.0%) levels.

In a phase 3 double-blind randomized controlled trial of 818 patients with mild to moderate Alzheimer’s disease, treatment with GV-971 (900 mg/day) for 36 weeks resulted in incidences of treatment-emergent adverse events that were comparable between the treatment and placebo groups (73.9% versus 75.4% had at least 1 event) (Xiao et al., 2021). Two deaths occurred in the GV-971 group (due to metastatic lung cancer and brain stem encephalitis) but were determined to be unrelated to drug effects. The most common treatment-emergent adverse events (occurring in 5% or more subjects) included hyperlipidemia and nasopharyngitis, which were higher in the GV-971 group (7.1% and 7.4%, respectively) than in the placebo group (3.4% and 5.6%, respectively). All other common adverse events were not statistically significantly different between the GV-971 and placebo groups. Seventy-six participants (18.7%) in the GV-971 group and 86 participants (20.9%) in the placebo group reported a treatment-emergent adverse event that was related or possibly related to the trial drug according to an investigator. Fourteen participants (3.4%) in the GV-971 group and 9 participants (2.2%) in the placebo group had a treatment-emergent adverse event that led to their discontinuation from the trial.

With regards to serious adverse events, 33 participants (8.1%) in the GV-971 group and 29 participants (7.1%) in the placebo group reported at least one serious adverse event (Xiao et al., 2021). For the GV-971 group, infectious pneumonia reported by 1 participant was determined as being possibly related to the trial drug by investigators. The remaining severe adverse events were determined to be not related or possibly related to the trial drug.

In a phase 2 double-blind randomized controlled trial of 255 mild to moderate Alzheimer’s patients, treatment with GV-971 (600 or 900 mg/day) for 24 weeks resulted in treatment-related adverse event incidences of 5.9%, 14.3%, and 3.5% for placebo, 600 mg, and 900 mg GV-971 (Wang et al., 2020). The total rate of adverse events (including those not related to the treatment) was 77.6%, 76.2%, and 59.3%.
in the placebo, 600 mg, and 900 mg GV-971 groups, respectively. Overall, 32 (12.5%) patients failed to complete the study as they were lost to follow-up, withdrew consent, showed severe complication/symptom deterioration, experienced adverse events or allergic reactions, seriously violated the inclusion/exclusion criteria, or showed non-compliance, among other reasons. Most adverse events were mild to moderate and required no treatment. The discontinuation rates due to adverse events were 1.2% in the placebo group, 3.6% in the 600 mg group, and 3.5% in the 900 mg group. There were 14 reported severe adverse events, including 6 SAEs in the placebo group (7.1%), 5 in the 600 mg GV-971 group (6.0%), and 3 in the 900 mg GV-971 group (3.5%). Of the 14, 13 serious adverse events (4 in the 600 mg GV-971 group, 3 in the 900 mg GV-971 group, and 6 in the placebo group) were evaluated by investigators to be definitely unrelated to the study drug. One serious adverse event, behavioral and psychiatric symptoms of dementia, in the 600 mg GV-971 group was possibly related to the study drug. No abnormalities or intergroup differences were observed in the vital signs and physical examination results. Laboratory test results and ECG findings were similar between the groups after 24 weeks of treatment as compared with the baseline data.

**Drug interactions**: Drug interactions have not been studied with sodium oligomannate. Based on its mechanism of action, it is possible that sodium oligomannate may interact with probiotics or other products affecting the gut microbiome. Although no dose adjustment is required for patients with mild hepatic or renal impairment, in patients with more serious hepatic or renal impairment, monitoring of hepatic or renal function is required during treatment with sodium oligomannate ([Syed, 2020](#)).

**Sources and dosing**: Sodium oligomannate (GV-971) is marketed in China by Shanghai Green Valley Pharmaceuticals. In November 2019, sodium oligomannate received its approval in China for the treatment of mild-to-moderate Alzheimer’s disease to improve cognitive function. It is not marketed outside of China, but a phase 3 multi-center randomized double-blind placebo-controlled trial in the US and Canada is currently testing GV-971 in mild to moderate Alzheimer’s disease patients ([NCT04520412](#)).

Sodium oligomannate comes in capsule form for oral intake. The dose used in the phase 3 trial in China that showed cognitive benefits in mild to moderate Alzheimer’s disease was 900 mg/day (3 capsules of 150 mg, taken twice daily) ([Xiao et al., 2021](#)).

**Research underway**: A phase 3 multi-center randomized double-blind placebo-controlled trial testing the efficacy and safety of GV-971 in mild to moderate Alzheimer’s disease patients is currently ongoing ([NCT04520412](#)). This study is enrolling 2,046 participants across 65 study locations in the US and Canada.
Canada. Primary outcomes are change from baseline in the ADAS-cog11 score and change from baseline in the Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC) scale total score. This trial is expected to be completed in October 2026.

Search terms:
Pubmed, Google: GV-971, oligomannate

Websites visited for GV-971, oligomannate:
- Clinicaltrials.gov (1)
- NIH RePORTER (0)
- DrugAge (0)
- Drugs.com (0)
- WebMD.com
- PubChem
- DrugBank.ca (0)
- Labdoor.com (0)
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- Pharmapro.com (0)

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