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## Sodium Oligomannate (GV-971)

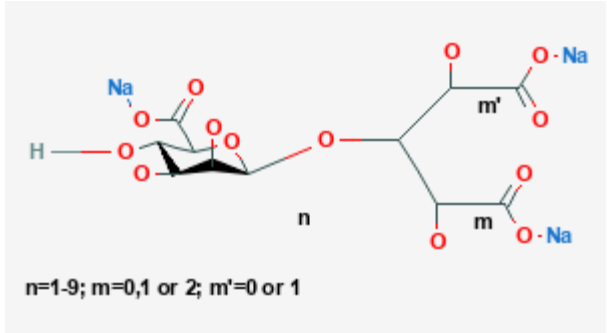
### Evidence Summary

A phase 3 trial of GV-971 improved cognitive functions in Alzheimer's patients and it is approved in China for the treatment of AD. A phase 3 trial in the US/Canada was postponed due to COVID-19.

**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 and reduced neuroinflammation. A phase 3 trial in the US/Canada was postponed due to COVID-19.

**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.

<p><b>Availability:</b> approved in China</p>	<p><b>Dose:</b> The phase 3 trial in mild to moderate Alzheimer's disease patients tested an oral dose of 900 mg/day.</p>	<p><b>Chemical formula:</b> ranges <b>MW:</b> ranges, 670-880 Da</p>
<p><b>Half-life:</b> 11-22 hours</p>	<p><b>BBB:</b> penetrant</p>	 <p>n=1-9; m=0,1 or 2; m'=0 or 1</p>
<p><b>Clinical trials:</b> The phase 3 trial in China included 818 patients with mild to moderate Alzheimer's disease.</p>	<p><b>Observational studies:</b> N/A</p>	

Source: [PubChem](#)

**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 A $\beta$  aggregation, and inhibit neuroinflammation ([Hannan et al., 2020](#); [Wang et al., 2019](#)). Sodium oligomannate modestly 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 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 was initiated, but got suspended/postponed due to COVID-19 ([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 and reduced neuroinflammation. A phase 3 trial in the US/Canada was postponed due to COVID-19.

*Types of evidence:*

- 2 double-blind randomized controlled clinical trials in Alzheimer's patients
- 1 case report of a Burkitt lymphoma patient with cognitive impairment due to CAR-T cell therapy
- 1 pharmacokinetic study in rats and dogs
- 3 reviews
- Several laboratory studies

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

No studies have tested GV-971 for the prevention of dementia or age-related cognitive decline.

Chimeric antigen receptor-T (CAR-T) cell therapy is effective against hematological malignancies, but it is often associated with cytokine release syndrome and neurotoxicity ([Brudno and Kochenderfer, 2016](#)). In a case report of a 22-year-old Burkitt lymphoma patient who experienced CAR-T cell therapy-induced cognitive impairment, sodium oligomannate treatment alone or in combination with rivastigmine partially restored cognitive performance and activities of daily living ([Wang et al., 2022](#)). One month after CAR-T cell infusion, the patient experienced memory loss, then the following month he suffered a grand mal seizure, which led to significant worsening of cognitive impairment (not recognizing family members and common objects). Two months of rehabilitation and hyperbaric oxygen therapy failed to improve symptoms. The patient improved with oral oxiracetam (0.8 g, orally, twice daily) for 5 months, but after discontinuing his medication due to COVID-19 for 10 months, he experienced worse memory decline (forgetfulness, emotional instability, impaired daily living activities). He then started to take sodium oligomannate (450 mg, twice daily), and significant improvements in activities of daily living, emotions, and cognitive functions (measured by MMSE and MoCA) were seen. Later, he was co-administered sodium oligomannate along with rivastigmine (3 mg twice daily), then substituted the oral rivastigmine dose with a 9.5 mg transdermal patch once daily. The patient was stable with no further cognitive improvement.

***Human research to suggest benefits to patients with dementia:***

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).

In the 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).

Some critics have pointed out that the effectiveness of GV-971 in slowing cognitive decline is debatable, as the ADAS-cog12 score difference at week 36 is exaggerated by the precipitous decline in the placebo group from week 24 to week 36 ([Yeo-Teh et al, 2023](#)).

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](#)).

This phase 3 trial lacked assessments of Alzheimer's disease biomarkers such as  $A\beta$  and  $p$ -tau, and thus the trial was not able to examine the effects of GV-971 on Alzheimer's pathology ([Yeo-Teh et al, 2023](#)).

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

Neuroprotective mechanisms have been explored in preclinical studies ([Wang et al., 2019](#)), though this publication received criticisms for image duplication ([PubPeer](#)). Subsequent investigation into the senior author of this publication led to a formal criticism of misuse of graphics, but there were no charges of misconduct ([AlzForum](#); [Science](#)).

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 A $\beta$  plaque deposition and tau phosphorylation.

In rats, a single intravenous administration of GV-971 (20 or 40 mg/kg) modestly penetrated the blood-CSF barrier, with a mean peak CSF concentration of 454.4 (with the 20 mg dose) and 1215.4 ng/mL (with the 40 mg dose), a T<sub>max</sub> of 0.5 hours, and a constant area under the concentration-time curve ratio (CSF/plasma) of around 5% ([Lu et al., 2022](#)).

In a biochemical and biophysical study, GV-971 exhibited electrostatic interactions with A $\beta$  and inhibited the formation of A $\beta$  fibrils and A $\beta$  aggregation ([Zhou et al., 2023](#)). However, the ability of GV-971 to affect A $\beta$  aggregation *in vivo* has not been established to date in humans. Given the low bioavailability



and blood-brain barrier permeability of GV-971 after oral administration, it is not clear whether GV-971 levels in the brain are sufficient for the inhibitory actions on A $\beta$  observed *in vitro* ([Yeo-Teh et al, 2023](#)).

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.

*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:*

- 3 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.

In a clinical study of 72 mild-to-moderate Alzheimer's patients, sodium oligomannate treatment resulted in 2 cases of increased stool frequency (5.67%) ([Zhang et al., 2022](#)). There were 2 cases of nausea in the donepezil group (8.33%). The full text of this study was inaccessible, and therefore, details of the study findings could not be evaluated.

Following oral administration, GV-971 crosses the gastrointestinal epithelium through paracellular transport, but oral bioavailability is low in rats (0.6-1.6%) and dogs (4.5-9.3%) ([Lu et al., 2022](#)). Absorbed



GV-971 was mainly present in circulating body fluids in free form. GV-971 excretion was predominantly renal. With only 33.7% (male) and 26.3% (female) of the oral GV-971 dose recovered in the excreta within 96 hours following a single oral administration, some unabsorbed GV-971 was likely ingested by the intestinal flora (as a nutrient).

**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. A phase 3 multi-center randomized double-blind placebo-controlled trial in the US and Canada was initiated in mild to moderate Alzheimer's disease patients, but due to COVID-19, the study was suspended for a later time ([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:**

Based on [ClinicalTrials.gov](#), there are currently 6 ongoing clinical trials testing sodium oligomannate, of which 5 are in Alzheimer's patients and 1 is a study of ischemic stroke prevention. There was a phase 3 multi-center randomized double-blind placebo-controlled trial aimed at testing the efficacy and safety of GV-971 in mild to moderate Alzheimer's disease patients; this study planned to enroll 2,046 participants across 65 study locations in the US and Canada ([NCT04520412](#)). However, the recruitment status has since been changed to "suspended", with a note saying "the quality of the study was seriously affected by COVID-19, so it was decided to suspend the trial and restart" at another time. Green Valley announced in May 2022 that the multi-center phase 3 clinical study of GV-971 underwent early termination, after screening 1308 patients and enrolling 439 patients ([Green Valley press release](#)). They



noted challenges with enrolled subjects not being able to participate in regular visits, high dropout rates, and the increasing research costs.

**Search terms:**

Pubmed, Google: GV-971, oligomannate

Websites visited for GV-971, oligomannate:

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- NIH RePORTER (0)
- DrugAge (0)
- Drugs.com (0)
- [WebMD.com](https://www.webmd.com)
- [PubChem](https://pubchem.ncbi.nlm.nih.gov)
- DrugBank.ca (0)
- Cafepharma (0)
- Pharmapro.com (0)

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