

A phase II randomized trial of sodium oligomannate in Alzheimer's dementia

Tao Wang

Shanghai Mental Health Center <https://orcid.org/0000-0003-2153-7328>

Weihong Kuang

West China Hospital of Sichuan University

Wei Chen

Sir Run Run Shaw Hospital affiliated with the Zhejiang University School of Medicine

Liming Zhang

First Affiliated Hospital of Harbin Medical University

Wenwei Xu

Wuxi Mental Health Center

Yingjie Li

The Hospital of 81ST Group Army PLA

Hailin Li

Nanjing Brain Hospital Affiliated to Nanjing Medical University

Ying Peng

Sun Yat-Sen Memorial Hospital

Yangmei Chen

The Second Affiliated Hospital of Chongqing Medical University

Baojun Wang

Baotou Central Hospital

Jinsong Xiao

Zhongnan Hospital of Wuhan University

Honghua Li

Central War Zone General Hospital of the Chinese People's Liberation Army

Chuanzhu Yan

Qilu Hospital of Shandong University

Yifeng Du

Shandong Provincial Hospital

Mouni Tang

Guangzhou Brain Hospital

Zhiyi He

The First Hospital of China Medical University

Haibo Chen

Beijing Hospital

Wei Li

Shanghai Ninth People's Hospital

Hong Lin

Air Force Military Medical University

Shugui Shi

The First Hospital Affiliated to AMU (Southwest Hospital)

Jianzhong Bi

the Second Hospital of Shandong University

Huadong Zhou

Daping Hospital

Yan Cheng

General Hospital Tianjin Medical University

Xiaoping Gao

Hunan Provincial People's Hospital

Yihui Guan

PET Center Huashan Hospital Fudan University

Qiu Huang

Med-X Research Institution

Kewei Chen

Banner Alzheimer's Institute, Translational Genomics Research Institute

Xianliang Xin

Shanghai Green Valley Pharmaceutical Co Ltd

Jian Ding

Shanghai Institute of Materia Medica

Meiyu Geng

Shanghai Institute of Meteria Medica

Shifu Xiao (✉ xiaoshifu@msn.com)

<https://orcid.org/0000-0002-4721-9646>

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Abstract

Background: Sodium oligomannate (GV-971), a marine-derived oligosaccharide, is a novel agent that may improve cognition in AD patients.

Methods: The 24-week multi-center, randomized, double-blind, placebo parallel controlled clinical trial was conducted in AD in China between 24 October 2011 and 10 July 2013. The study included a 4-week screening/washout period, followed by a 24-week treatment period. Patients were randomized 1:1:1 ratio to receive GV-971 900 mg, 600 mg, or placebo capsule in treatment period, respectively. The primary outcome was cognitive improvement as assessed by changes in Alzheimer's Disease Assessment Scale-cognitive subscale 12-item (ADAS-cog12) scores from baseline to week 24. The secondary efficacy outcomes included CIBIC-Plus, ADCS-ADL and NPI at 24 weeks after treatment compared with baseline. A sub-group study was assessment of the change in cerebral glucose metabolism by fluorodeoxyglucose positron emission tomography measurements.

Results: Comparing with placebo group (n=83, change -1.45), the ADAS-Cog12 score change in GV-971 600mg group (n=76) was -1.39 (p=0.89), GV-971 900mg group (n=83) was -2.58 (p=0.30). The treatment responders according to CIBIC-plus assessment was significantly higher in GV-971 900mg group than placebo group (92.77% vs 79.52%, p<0.05). GV-971 900mg subgroup showed a significantly lower cerebral metabolic rate for glucose decline than the placebo subgroup at the left precuneus, right posterior cingulate, and right hippocampus. The respective rates of treatment-related AEs were 5.9%, 14.3%, and 3.5%.

Conclusions: GV-971 was safe and well tolerated. GV-971 900mg was chosen for phase III clinical study.

Trial registration: ClinicalTrials.gov, NCT01453569. Registered 18 October, 2011, <https://clinicaltrials.gov/ct2/show/NCT01453569?term=NCT01453569&draw=2&rank=1>.

Background

Globally, approximately 35.6 million individuals live with dementia, and this number is predicted to double by 2030 and more than triple by 2050¹. The number of people with Alzheimer's disease (AD) was estimated to be 5.69 million in 2010, with the incidence being 6.25 cases/1,000 person-years². The currently available drug treatments for AD target neurotransmitter pathways implicated in disease pathophysiology³. While agents such as acetylcholinesterase inhibitors and *N*-methyl-D-aspartic acid receptor antagonists, including memantine, may stabilize or slow the decline of cognition, function, and behavior in patients with AD, they do not slow down the pathological progression⁴. AD is pathologically characterized by senile plaques, neurofibrillary tangles, reactive astrocytosis, and neuronal cell loss. A major component of senile plaques, implicated in the pathophysiology of AD, is the aggregated β -amyloid (A β) peptide^{5, 6}. Despite the urgent clinical need, in the past decade, disease-modifying therapies such as those targeting amyloid deposition and tau protein have failed to demonstrate clinically relevant efficacy⁷⁻¹⁰.

Certain key amino acid residues and specific domains of the A β peptide reportedly play an important and unique role in A β aggregation^{11,12}. Sodium oligomannate (GV-971) is a marine-derived oligosaccharide¹³; by multitargeting various A β subregions, it inhibits A β aggregation and destabilizes A β aggregates into nontoxic conformers. Moreover, GV-971 can evidently reconstitute the dysbiosis of gut microbiota, reduce metabolite-driven

peripheral infiltration of immune cells into the brain, and inhibit neuroinflammation¹⁴. These effects have been reported to protect synapse integrity and improve cognition *in vitro* and in a transgenic mouse model of AD^{15–18}.

Herein we report the results of a phase II trial designed to investigate the optimal dose, efficacy, and safety of GV-971 capsules in patients with mild-to-moderate AD.

Methods

Study Design

This 24-week, multicenter, randomized, double-blind, placebo-controlled, phase II trial was conducted in patients with mild-to-moderate AD in geriatric psychiatry, neurology, or geriatrics departments at 24 hospitals (i.e., centers) in China between 24 October 2011 and 10 July 2013. The study included a 4-week screening/washout period, followed by a 24-week treatment period. During the 4-week screening/washout period, all patients received placebo capsules, and during the 24-week treatment period, they underwent the following treatment: three 150-mg GV-971 capsules b.i.d. (900 mg group), two 150-mg GV-971 capsules plus one placebo capsule b.i.d. (600 mg group), or three placebo capsules b.i.d. The trial protocol had two versions: 1.1 and 2.1. The main amendment was the additional clarifications of hypothesis testing in version 2.1 than version 1.1.

The protocol was registered on <https://clinicaltrials.gov/ct2/show/NCT01453569> and approved by the China Food and Drug Administration (approval nos. 2006L02492, 2011L00942). The trial was also approved by the Institutional Review Boards of all participating centers from which the approval of the protocol and all related documents was obtained. The trial protocol can be found in Appendix 1.

Participants

Inclusion Criteria

Patients aged between 50 and 85 years (inclusive) were eligible to participate in this study, regardless of their gender. They should have been educated to primary school level and above, with the ability to complete pertinent cognitive tests and other rating scales. To qualify for the trial, a subject was expected to fulfill the diagnostic criteria of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (1984), with mild-to-moderate stages ($10 \leq$ total Mini-Mental State Examination score ≤ 24)^{19,20}. In addition, the total Hachinski Ischemia Scale²¹ score had to be ≤ 4 and the total 17-item Hamilton Depression Scale²² score had to be ≤ 10 . Furthermore, it was mandatory for each participant to have stable, reliable caregivers who were expected to be with them for at least 4 days/week for at least 2 h each time while the patient was awake. The caregivers were required to provide valuable information on the Clinician Interview Based Impression of Change - Plus (CIBIC-Plus)²³, Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS–ADL)²⁴, and Neuropsychiatric Inventory (NPI)^{25,26} assessments. Prior to implementation of any protocol-related procedure or examination, the subjects were required to sign a written informed consent form. If they were unable to sign the form due to impaired cognition, their legal guardians were asked to sign on their behalf.

Exclusion Criteria

Subjects were excluded if they had participated in any another clinical trial within 30 days prior to the initiation of this study, if they were pregnant or nursing, or if they had dementia due to non-AD causes. Furthermore, they were excluded if they had abnormal laboratory values, including glutamic pyruvic transaminase or glutamic oxaloacetic transaminase > 1.2 times the upper limit of normal; creatinine > 1.2 times the upper limit of normal; white blood cell count, platelet count, or hemoglobin level below the lower limit of normal; and blood glucose level > 1.5 times the upper limit of normal. Patients with systolic blood pressure \geq 160 mmHg or diastolic blood pressure \geq 100 mmHg during screening were also not enrolled. In addition, patients were excluded if they had unstable or severe cardiac, pulmonary, hepatic, renal, or hematopoietic disease; a visual or hearing disorder that prevented completion of the neuropsychological test and scale evaluation; or history of alcohol or drug abuse, psychosis, including severe depression, or use of drugs for AD that could not be stopped. Further details pertaining to the inclusion and exclusion criteria have been provided in Appendix 1.

Randomization and Masking

Patients were randomized in a 1:1:1 ratio to receive 900 mg GV-971, 600 mg GV-971 plus placebo, or placebo during the treatment period via an interactive web response system (IWRS) managed by GCP ClinPlus Co., Ltd. (China). All distributed trial drugs had corresponding numbers. Investigators logged on to IWRS for identifying a participant with the help of a center-specific subject ID and visit ID. The system then distributed the drugs to the designated subject using a system-generated drug number.

Study Assessments

Herein the primary endpoint was cognitive improvement as assessed by changes in Alzheimer's disease Assessment Scale-Cognitive subscale 12-item (ADAS-cog12)²⁷ scores from baseline to week 24. The secondary efficacy outcomes included a global assessment based on CIBIC-Plus, along with improvements in ADCS-ADL and NPI scales at 24 weeks post-treatment as compared with baseline data. An assessment of changes in cerebral glucose metabolism, as evaluated by fluorodeoxyglucose positron emission tomography (FDG-PET) measurements of the cerebral metabolic rate for glucose in the brain regions preferentially affected by AD, was also performed in a subgroup of subjects at two sites in Shanghai and Chengdu; the same inclusion and exclusion criteria were used. Safety assessments included evaluations of adverse events (AEs), serious AEs (SAEs), laboratory test results (routine blood and coagulate function tests), electrocardiography data, and vital signs. The study assessment schedule is provided in Appendix 1.

Statistical Analysis

Sample Size Determination

Data collection and analysis were independently managed by GCP ClinPlus Co., Ltd. (China). Power Analysis and Sample Size software (NCSS, LLC, Utah, USA) was used to calculate the sample size. With 80% power, type-I error of 0.05, and assumed effect size of 0.5 (Δ/δ), we estimated that 70 subjects were needed per group to compare the difference in changes in ADAS-cog12 total scores from baseline to week 24 between the two treatment groups and the placebo group. Considering a drop-off rate of 20%, 84 subjects were expected to be present in each group (total = 252 in the three groups).

Efficacy Endpoints and Analyses

We finally enrolled 255 cases in this study (n = 85, 84, and 86 in the placebo, 600 mg, and 900 mg groups, respectively). Data were analyzed in the intention-to-treat population and are reported for the full analysis set and

safety set after database lock on August 15, 2013. All data were analyzed using SAS version 9.2. The difference in changes in ADAS-cog12 total scores from baseline to week 24 between the two treatment groups was analyzed using the analysis of covariate model, with baseline ADAS-cog12 total scores serving as the covariate. All results have been expressed as least squares adjusted means and 95% CI. Finally, subjects in the cerebral ^{18}F -FDG-PET small subgroup underwent PET scanning at baseline and week 24. The relative cerebral metabolic rate for glucose was calculated as the standardized uptake value ratio for the brain regions known to be affected by AD, with the whole brain serving as the reference region. The regions of interest included the temporal lobe, hippocampus, posterior cingulate, precuneus, and parietal lobe (all bilateral).

Results

Baseline Characteristics and Overview of Study Subjects

In total, 295 subjects were assessed for eligibility; 255 patients were enrolled and randomly assigned into the placebo (n = 85), 600 mg (n = 84), and 900 mg (n = 86) groups. Patient disposition is shown in Fig. 1. There were 83 patients in the placebo group, 76 in the 600 mg group, and 83 in the 900 mg group who completed the study and were included in the full analysis set. Overall, 32 (12.5%) patients could not continue their participation as they were lost to follow-up, withdrew consent, showed severe complication/symptom deterioration, experienced AEs or allergic reactions, seriously violated the inclusion/exclusion criteria, or showed non-compliance, among other reasons (Fig. 1). There were 7, 9, and 9 patients in the placebo, 600 mg, and 900 mg groups, respectively, who underwent ^{18}F -FDG-PET scans. Baseline demographics were not statistically different among the groups ($P > 0.05$) (Table 1).

Table 1
Baseline patient characteristics and demographics

	Placebo (n = 83)	600 mg (n = 76)	900 mg (n = 83)	P value
Gender				0.5189
Male	31(37.35%)	35(46.05%)	33(39.76%)	
Female	52(62.65%)	41(53.95%)	50(60.24%)	
Age (years)	70.34(8.13)	70.26(8.40)	70.39(8.51)	0.9957
Ethnicity				0.7638
Han Chinese	83(100.00%)	75(98.68%)	82(98.80%)	
Others	0(0.00%)	1(1.32%)	1(1.20%)	
Height (cm)	161.69(8.78)	163.12(7.15)	162.52(7.64)	0.5176
Weight (kg)	57.85(10.40)	60.67(9.88)	58.64(10.03)	0.1986
Education				0.8007
Primary School	31(37.35%)	22(28.95%)	27(32.53%)	
Middle School and above	52(62.65%)	54(71.06%)	56(67.47%)	
Breathing (times/minute)	18.35(1.96)	18.46(2.07)	18.11(2.10)	0.5363
Diastolic Blood Pressure (mmHg)	125.83(12.01)	124.20(11.82)	125.53(11.24)	0.6489
Systolic Blood Pressure (mmHg)	75.67(6.99)	77.62(7.41)	76.12(8.14)	0.2404
Pulse (times/minute)	74.40(10.00)	74.72(8.86)	73.89(8.74)	0.8479
Note: Data represent mean (SD) and were analyzed by t-test; P values were determined using two-tailed t-tests, except gender, ethnicity, and education, which were analyzed using the chi-squared test.				

Primary Efficacy Outcome

The effect of treatment on the primary outcomes in the three groups was not significantly different. For the primary efficacy outcome of cognitive improvement at week 24, as measured using ADAS-cog12 total scores, the mean change from the baseline value was - 1.45 in the placebo group (n = 83), - 1.39 in the 600 mg group (n = 76, P = 0.89 in comparison with the placebo group), and - 2.58 in 900 mg group (n = 83, P = 0.30 in comparison with the placebo group) (Table 2 and Fig. 2). The least squares adjusted mean changes and 95% CI of ADAS-cog12 total scores from baseline to week 24 were as follows: 900 mg group = - 2.53, 95% CI, - 3.91 to - 1.15; 600 mg group = - 1.34, 95% CI, - 2.88 to 0.19; and placebo group = - 1.50, 95% CI, - 2.97 to - 0.03. Though not statistically different, change in ADAS-cog12 scores from baseline to week 24 in the 900 mg group was numerically greater than that in the placebo group.

Table 2
Efficacy analyses for primary outcome of ADAS-cog12 scores with the covariate model

	Placebo (n = 83)	600 mg (n = 76)	900 mg (n = 83)
	Mean (SD)	Mean (SD)	Mean (SD)
Baseline	28.11 (11.99)	26.11 (12.40)	26.16 (11.98)
4 weeks	26.92 (12.10)	24.74 (12.62)	24.66 (12.36)
12 weeks	26.85 (13.27)	24.24 (12.75)	23.97 (12.60)
24 weeks	26.66 (14.48)	24.72 (14.37)	23.58 (13.71)
Change from 24 weeks to baseline	-1.45 (7.00)	-1.39 (6.52)	-2.58 (5.65)
P value	NA	p = 0.886	p = 0.302

Note: P values were derived upon comparison of changes from week 24 to baseline with the placebo group.

Secondary Efficacy Outcomes

The assessment of the secondary efficacy outcomes showed that significantly more patients were classified as treatment responders based on CIBIC-Plus at week 24 in the 900 mg group than in the placebo group (Fig. 3). Treatment responders were defined as those with marked improvement, moderate improvement, minimum improvement, or no change on CIBIC-Plus. The difference in the percentage of treatment responders was significant between the 900 mg and placebo groups (92.77% vs. 79.52%; $P = 0.01$), but insignificant between the 600 mg and placebo groups (68.42% vs. 79.52%; $P = 0.11$). For other secondary outcome measures, i.e., the effect of the study drug at week 24 on ADCS-ADL and NPI scales, no significant differences were found between the two treatment groups and the placebo group (Appendix 2).

¹⁸F-FDG-PET Scan Subgroup Analysis

The effect of GV-971 on cerebral glucose metabolism, as measured using ¹⁸F-FDG-PET, was evaluated in 7, 9, and 9 patients from the placebo, 600 mg, and 900 mg groups, respectively. Differences, not corrected for multiple comparisons, before and after treatment were noted in the brain regions known to be affected by AD in the 900 mg group, such as the left precuneus ($P = 0.0026$), right posterior cingulate cortex ($P = 0.002$), right hippocampus region ($P = 0.004$), and lower part of the left orbitofrontal gyrus ($P = 0.002$) (Fig. 4 and Fig. 5).

Safety Analysis

The AE profile of GV-971 is summarized in Table 3 and Appendix 2. Most AEs were mild to moderate and needed no treatment. The total rate of AEs was 77.6%, 76.2%, and 59.3% in the placebo, 600 mg, and 900 mg groups, respectively, while the rates of treatment-related AEs were 5.9%, 14.3%, and 3.5% in the aforementioned groups, respectively. The discontinuation rates due to AEs were 1.2% in the placebo group, 3.6% in the 600 mg group, and 3.5% in the 900 mg groups. There were 14 reported SAEs (seen as 15 case-events), including six SAEs in the placebo group (six case-events, 7.1%), five in the 600 mg group (six case-events, 6.0%), and three in the 900 mg group (three case-events, 3.5%). Thirteen SAEs, including four in the 600 mg group, three in the 900 mg group, and six in the placebo group, were evaluated by investigators to be definitely unrelated to the study drug. One SAE, behavioral and psychiatric symptoms of dementia, in the 600 mg group was possibly related to the study drug.

The assessment of vital signs and physical examination results yielded essentially no abnormalities or intergroup differences. Laboratory test results and ECG findings were similar between the groups at 24 weeks post-treatment as compared with the baseline data.

Table 3
Summary of adverse events (AEs) and serious AEs (SAEs)

Items	Placebo (N = 85)				600 mg (N = 84)				900 mg (N = 86)			
	case	%	event	%	case	%	event	%	case	%	event	%
AEs	35	41.2	66	77.6	31	36.9	64	76.2	24	27.9	51	59.3
NR Med	32	37.7	61	71.8	26	30.9	52	61.9	21	24.4	48	55.8
RE Med*	3	3.5	5	5.9	5	6.0	12	14.3	3	3.5	3	3.5
SAEs	6	7.1	7	8.2	5	6.0	6	7.1	3	3.5	3	3.5
NR Med	6	7.1	7	8.2	4	4.8	5	6.0	3	3.5	3	3.5
RE Med*	0	0.0	0	0.0	1	1.2	1	1.2	0	0.0	0	0.0
Drop-off due to AE	1	1.2	1	1.2	3	3.6	5	6.0	3	3.5	3	3.5

Note: [□]AEs RE Med (medication-related AEs): definitely, probable, possible, and suspiciously.

Discussion

In this phase II study, as compared with placebo, the oral administration of GV-971 at 600 mg or 900 mg/day for 24 weeks did not have any significant positive effects on the primary endpoint in patients with mild-to-moderate AD. However, the trial results provided useful information pertaining to the clinical efficacy of GV-971. We used ADAS-cog12 scores as the primary endpoint and found a non-significant trend in cognitive function improvement in subjects in the 900 mg group at 24 weeks as compared to those in the placebo group. The secondary efficacy outcome based on CIBIC-Plus also proved that administering 900 mg GV-971 improved the global function in patients with mild-to-moderate AD; further, the percentage of treatment responders was significantly higher for those in the 900 mg group as compared to those in the placebo group.

AD is clinically characterized by progressive cognitive impairment, which is associated with impaired cerebral glucose metabolism²⁸. In fact, cerebral glucose hypometabolism occurs during early AD, and ¹⁸F-FDG-PET studies have consistently reported reductions in progressive cerebral glucose metabolism, the extent and topography of which correlate with symptom severity²⁹. In this 24-week, double-blind, randomized, placebo-controlled trial, we employed FDG-PET to assess the effects of GV-971 on regional neuronal activity in patients with mild-to-moderate AD. We realized that our analysis was exploratory and did not survive multiple comparison correction; thus, our findings should be interpreted with caution. ¹⁸F-FDG-PET data showed that treatment with GV-971 at 900 mg/day

slowed the impairment of cerebral glucose metabolism in several AD-associated brain regions. Our results imply that the effects of GV-971 on neuronal function are not simply compensatory in the brain regions affected by AD. More generally, we postulate that AD-modifying treatments have a relatively early effect on neuronal activity and that FDG-PET, for this very reason, may offer better sensitivity to detect the effects of treatment^{30,31}.

Treatment with GV-971 was safe and well tolerated. Most AEs were either infections, gastrointestinal disorders, or nervous system disorders. Moreover, as compared with the placebo group, none of the AEs were more prevalent in the active treatment groups. Although the primary output measure did not reach statistical significance, findings from this phase II trial are still informative. First, our results suggest that GV-971 dosage should be 900 mg/day whenever a new phase III study is being conducted. Second, the trending difference between the placebo and 900 mg groups suggests that the trial duration should be > 24 weeks in the future to comprehensively assess the efficacy of GV-971.

According to our results, in the future, a phase III trial of GV-971 should be able to reduce the ADAS-cog12 score from baseline by at least 1.4, which, together with variability information, can be converted to an effect size (Δ/δ) of 0.23. Assuming the two-arm design (placebo vs. 900 mg GV-971), such a study can be conducted with 315 subjects/group with 80% power to detect differences in the change between the GV-971 and placebo groups, with a two-sided α -level of 0.05.

This phase II study has three important limitations. First, biomarkers associated with AD were not included as a part of the inclusion/exclusion criteria for AD diagnosis at the protocol design and to serve as possible additional output measures. The lack of biomarkers may thus lead to some bias in AD diagnosis. Second, there could have been an evaluation bias at few sites as investigators were not continuously trained to ensure consistency in assessing cognitive test data. Third, there was a trend of continuous improvement in the 900 mg group at endpoint, so the 24-week treatment duration may not be long enough to witness the effectiveness of GV-971. Therefore, it is necessary to increase the treatment duration in future phase III trials of GV-971.

Conclusion

In conclusion, this phase II trial provided the evidence that GV-971 was safe and well tolerated. GV-971 900 mg was chosen for phase III clinical study.

Abbreviations

GV-971: Sodium oligomannate; AD: Alzheimer's disease; ADAS-cog12: Alzheimer's Disease Assessment Scale-cognitive subscale 12-item; CIBIC-Plus: Clinician Interview Based Impression of Change – Plus; ADCS-ADL: Alzheimer's Disease Cooperative Study–Activities of Daily Living; NPI: Neuropsychiatric Inventory; A β : β -amyloid; b.i.d.: bis in die; IWRS: interactive web response system; ID: Identity document; FDG-PET: fluorodeoxyglucose positron emission tomography; AE: adverse event; SAE: serious AE; CI: Confidence interval.

Declarations

Ethics approval and consent to participate

The trial protocol was approved by the Ethics Review Board of Shanghai Mental Health Center (Shanghai, China). The trial protocol was approved by the Institutional Review Boards of all participating sites. All participants or their

representatives provided written informed consent before participation in the trial.

Consent for publication

All authors approved the final version of the manuscript for submission.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Competing interests

SFX has been provisional consultant of Pfizer, Lilly, Novartis, GSK, Johnson & Johnson, Lundbeck and Green Valley and received honorariums. Part of the results of this paper were presented at the 7th Clinical Trials Conference on Alzheimer's Disease (CTAD) November 20 - 22, 2014, Philadelphia, Pennsylvania, USA.

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Authors' contributions

SFX was the principle investigator. TW was the sub-principle investigator. SFX, TW, XLX, JD, and MYG were involved in study design. SFX, TW, WHK, WC, WWX, LMZ, YJL, HLL, YP, YMC, BJW, JSX, HHL, CZY, YFD, MNT, ZYH, HBC, WL, HL, SGS, JZB, HDZ, YC, XPG carried out the study. TW, YHG, QH, KWC, XLX, JD, MYG, and SFX were involved in the data analysis and interpretation. TW drafted the manuscript. All authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

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Author details

¹ Department of Geriatric Psychiatry, Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai, China; Alzheimer's disease and Related Disorders Center of Shanghai Jiaotong University, Shanghai, China

² Department of Psychiatry, West China Hospital of Sichuan University, Chengdu, Sichuan, China

³ Department of Neurology, Sir Run Run Shaw Hospital, affiliated with the Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

⁴ Department of Geriatric Psychiatry, Wuxi Mental Health Center, Wuxi, Jiangsu, China

- ⁵ Department of Neurology, First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China
- ⁶ Department of Neurology, The Hospital of 81ST Group Army PLA, Zhangjiakou, Hebei, China
- ⁷ Department of Geriatric Psychiatry, Nanjing Brain Hospital Affiliated to Nanjing Medical University, Nanjing, Jiangsu, China
- ⁸ Department of Neurology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University
- ⁹ Department of Neurology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China
- ¹⁰ Department of Neurology, Baotou Central Hospital
- ¹¹ Department of Neurology, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China
- ¹² Department of Neurology, Central War Zone General Hospital of the Chinese People's Liberation Army, Wuhan, Hubei, China
- ¹³ Department of Neurology, Qilu Hospital of Shandong University, Jinan, Shandong, China
- ¹⁴ Department of Neurology, Shandong Provincial Hospital, Jinan, Shandong, China
- ¹⁵ Department of Geriatric Psychiatry, Guangzhou Brain Hospital, Guangzhou, Guangdong, China
- ¹⁶ Department of Neurology, The First Hospital of China Medical University, Shenyang, Liaoning, China
- ¹⁷ Department of Neurology, Beijing Hospital, Beijing, China
- ¹⁸ Department of Neurology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
- ¹⁹ Department of Neurology, Air Force Military Medical University, xi'an, Shanxi, China
- ²⁰ Department of Neurology, The First Hospital Affiliated to AMU (Southwest Hospital), Chongqing, China
- ²¹ Department of Neurology, the Second Hospital of Shandong University, Jinan, Shandong, China
- ²² Department of Neurology, Daping Hospital, Chongqing, China
- ²³ Department of Neurology, General Hospital, Tianjin Medical University, Tianjin, China
- ²⁴ Department of Neurology, Hunan Provincial People's Hospital, Changsha, Hunan, China
- ²⁵ PET Center Huashan Hospital Fudan University, Shanghai, China
- ²⁶ Med-X Research Institution, Shanghai Jiao Tong University, Shanghai, China
- ²⁷ Banner Alzheimer's Institute, Translational Genomics Research Institute, University of Arizona, and Arizona Alzheimer's Consortium, Phoenix, AZ

²⁸ Shanghai Green Valley Pharmaceutical Co Ltd

²⁹ State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China

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Figures

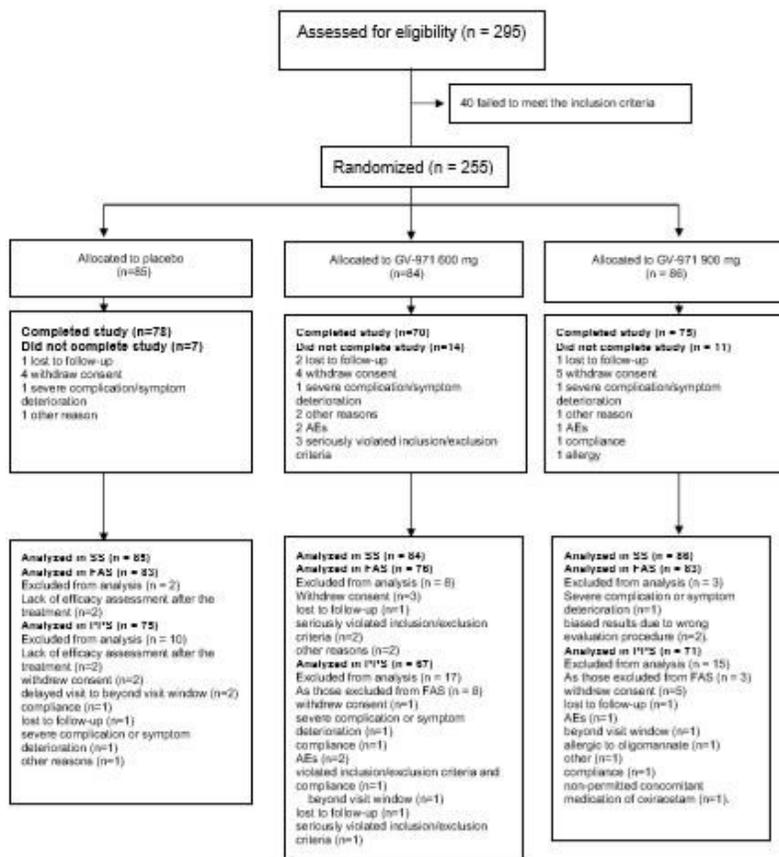


Figure 1

Patient disposition.

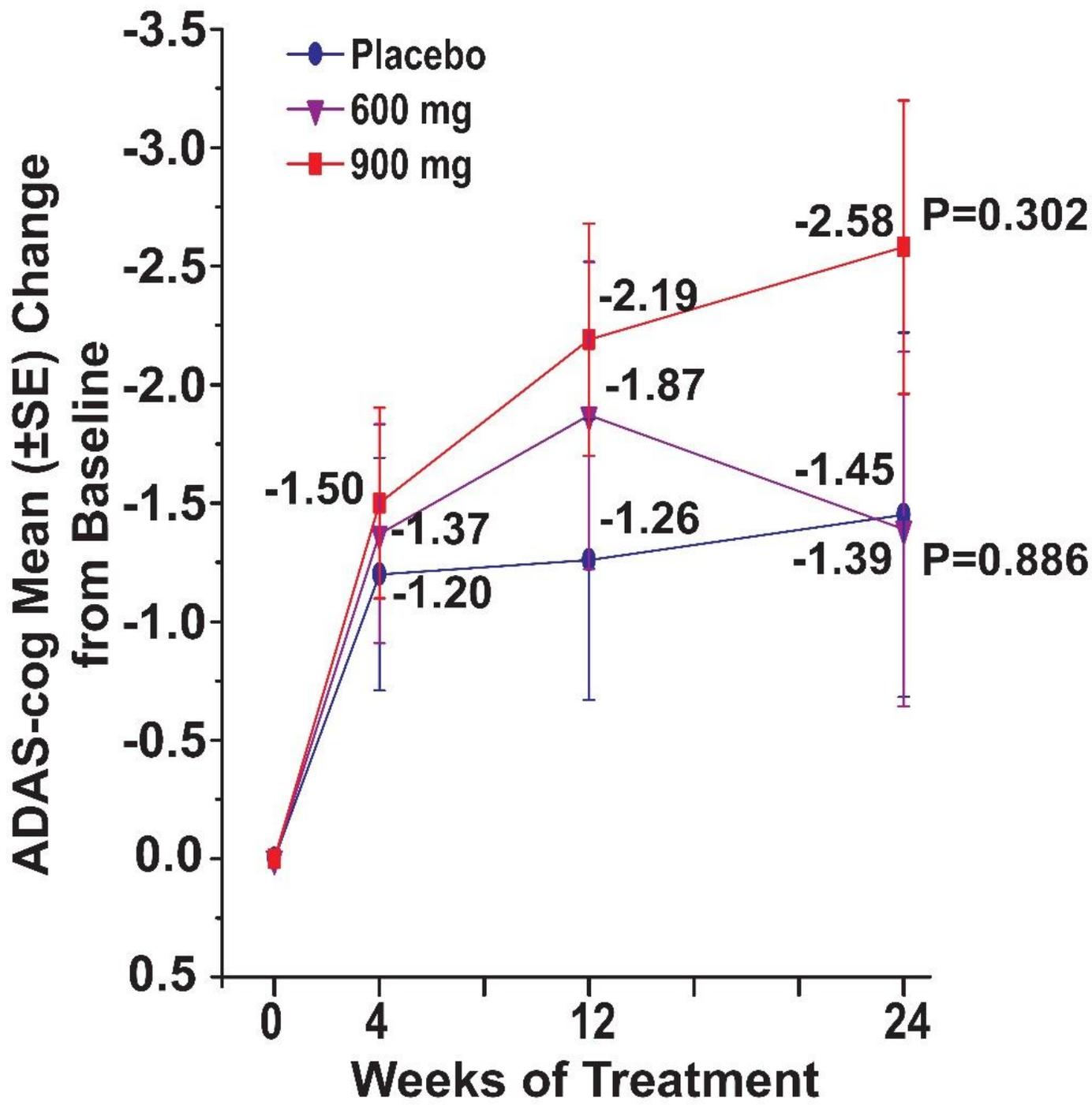
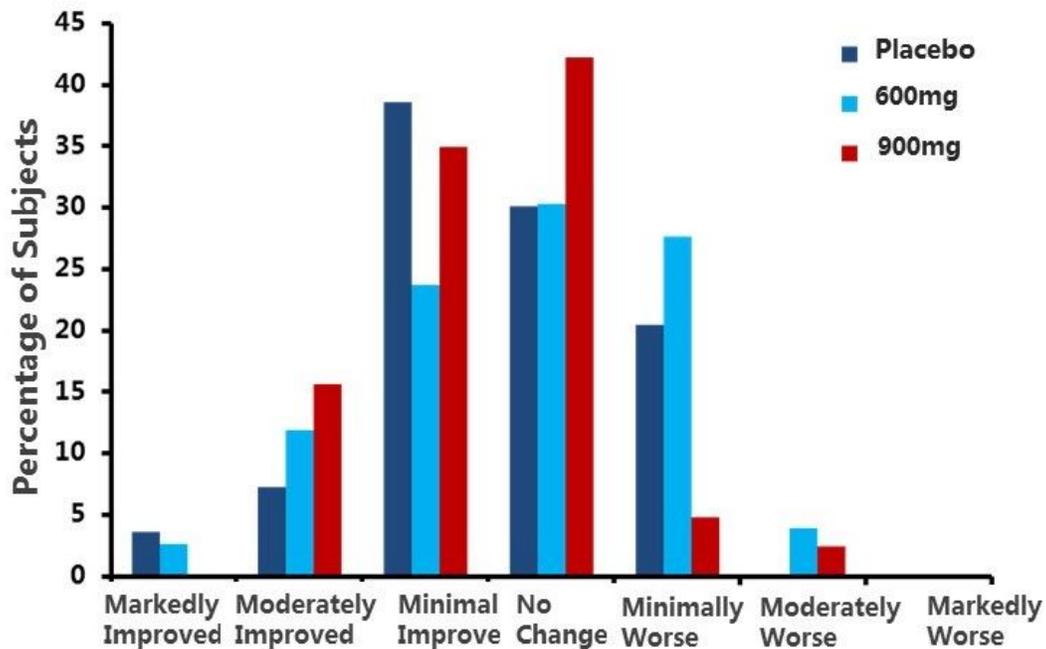


Figure 2

Full analysis set of primary efficacy outcome of ADAS-cog12 change scores from baseline to week 24 among the three groups.

Global Function Assessment : CIBIC-plus



➤ **Group 900mg showed significant improvement for patients' global function (P=0.0135)**

*Effective Percentage of Subjects = (Markedly Improved + Moderately Improved + Minimally Improved + No Change) * n / N_{total}*

Figure 3

Full analysis set of Second efficacy outcome of CIBIC-Plus change score from baseline to week 24 among groups

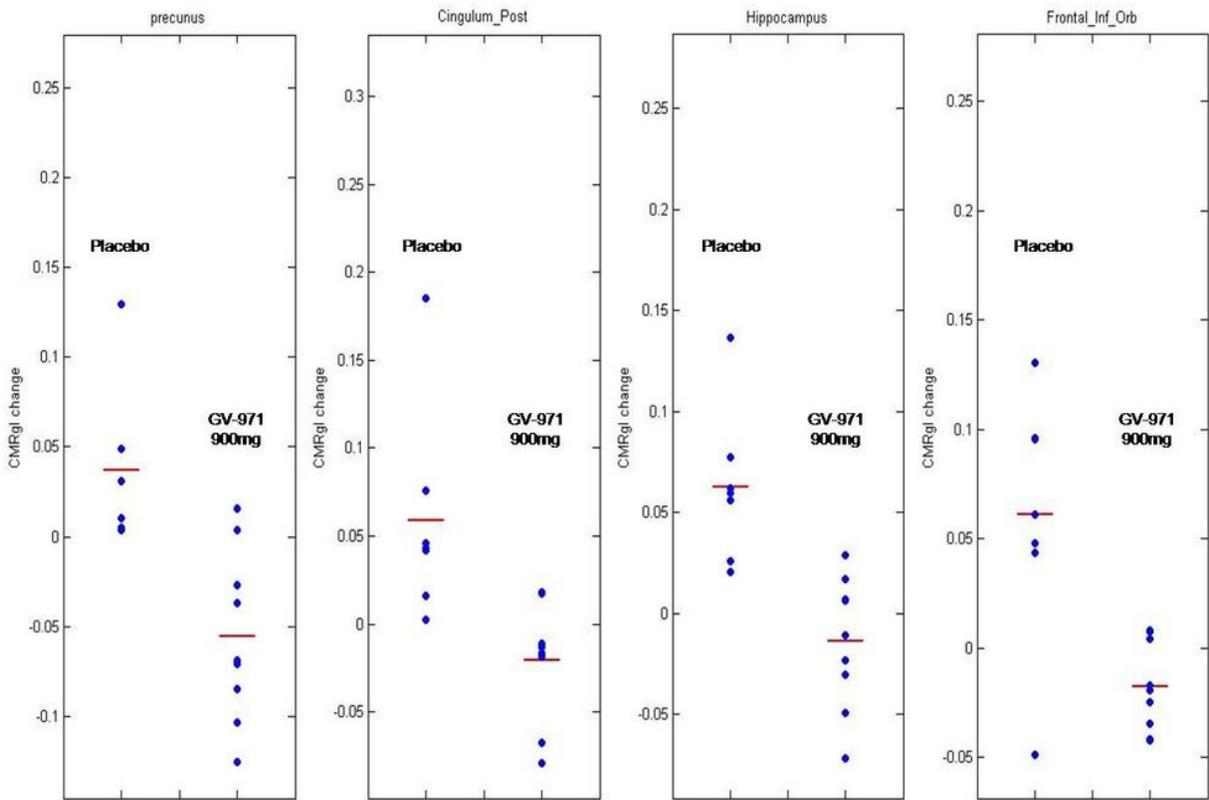


Figure 4

Brain regions where ¹⁸F-FDG-PET measured changes in cerebral glucose metabolism (baseline – follow-up), revealing an improvement or slower decline in the 900 mg group than in the placebo group. Uncorrected P < 0.005

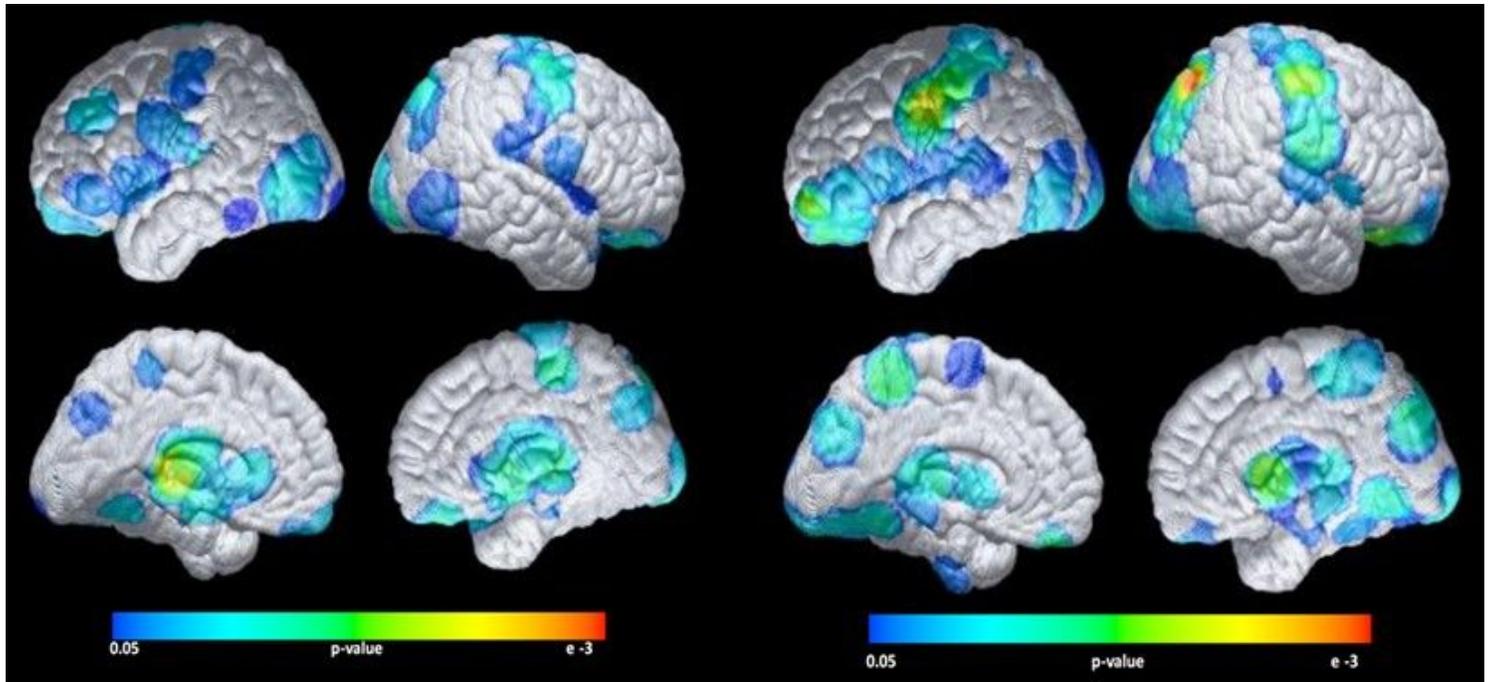


Figure 5

Brain regions where ¹⁸F-FDG-PET measured changes in cerebral glucose metabolism (baseline – follow-up), revealing an improvement or slower decline in the GV-971 group than in the placebo group. Uncorrected P < 0.05. Left: 600 mg vs placebo group. Right: 900 mg vs placebo group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Appendix2.CSRofPhasellinChinesepreppedENGUS.doc](#)
- [Appendix1.EN971phasellclinicaltrialprotocol.doc](#)