A Phase 3, multi-center, randomized, double-blind, parallel-group, placebo-controlled clinical trial to evaluate the efficacy and safety of sodium oligomannate (GV-971) in treatment of mild to moderate Alzheimer's disease (GREEN MEMORY: GREen Valley 971 EvaluatioN Memory)

Published: 05-02-2021
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To assess the efficacy of GV-971 compared with placebo on cognition and global function in participants with mild to moderate Alzheimer's disease (AD).

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mental impairment disorders
Study type	Interventional

Summary

ID

NL-OMON51880

Source
ToetsingOnline

Brief title
GV971-007

Condition

- Mental impairment disorders

Synonym

Alzheimer's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Green Valley (Shanghai) Pharmaceuticals Co., Ltd.
Source(s) of monetary or material Support: Shanghai Green Valley Pharmaceutical Co.;Ltd.

Intervention

Keyword: Alzheimer's Disease, Phase 3, Sodium Oligomannate

Outcome measures

Primary outcome

1 Change from baseline to End of Double-blind Study (EODB) in Alzheimer's

Disease Assessments Scale * cognitive subscale/11-item (ADAS-cog/11) score.

2 Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change

(ADCS-CGIC) scale total score at EODB.

Secondary outcome

1. Change from baseline to Weeks 36, and 52 in Neuropsychiatric

Inventory (NPI) score.

2. Change from baseline to EODB in Mini Mental State Examination

(MMSE) score.

3. End point

* Change from baseline to Weeks 36 and 52 in Alzheimer's Disease

Cooperative Study * Activities of Daily Living; 23-item Scale (ADCSADL23).

* Change from baseline to Weeks 36 and 52 in Amsterdam Instrumental

Activities of Daily Living scale (A-IADL).

4. Change from baseline to Weeks 12, 24, and 36 in ADAS-cog/11 and

ADCS-CGIC scores.

5. end point

* Incidence of treatment emergent adverse events (TEAEs) and SAEs

* Vital signs

* Clinical laboratory values

* Physical exam findings

* Electrocardiogram (ECG)

* Brain magnetic resonance imaging (MRI)

* Columbia-Suicide Severity Rating Scale (C-SSRS)

* Change from baseline in Zarit Burden Interview (ZBI).

* Change from baseline in NPI caregiver items.

6. End point

* Change from baseline in the primary and secondary caregiver time

components of the Resource Utilization in Dementia (RUD) * Lite Version

* The change from baseline in the RUD-Lite total score

7. Changes from baseline through End of Study (EOS) and from Week 52

to Week 78 in:

o ADAS-cog/11,

o ADCS-CGIC,

o NPI,

o MMSE,

o ADCS-ADL23,

o A-IADL,

o Incidence of adverse events (AEs),

o Vital signs,

o Clinical laboratory values,

o Physical exam findings,

o Electrocardiogram (ECG),

oMRI - for safety,

o Columbia-Suicide Severity Rating Scale (C-SSRS).

Study description

Background summary

This is a 52-week, multi-center, randomized, double-blind, 2-arm, parallel-group, placebo-controlled, monotherapy Phase 3 study, to evaluate the efficacy and safety of GV-971 in the treatment of mild to moderate Alzheimer*s disease dementia participants (Mini Mental State Examination [MMSE] score 11 to 24, inclusive; with regional stratification [North America, China, Europe/Australia/rest of world] and at least 75% of participants with MMSE scores < 20). Participants who successfully complete the double-blind treatment period may continue in the 26-week open-label extension (OLE) period.

Alzheimer*s disease (AD) represents both one of the greatest development challenges as well as an area of urgent and rapidly increasing unmet need. Symptomatic therapies available for the last 20 years for the treatment of AD include acetylcholinesterase inhibitors (AChEI) and memantine. Because of the limited duration of efficacy associated with current standard of care and safety, there is an urgent unmet need for drugs that demonstrate long-term efficacy, good tolerability, and safety in patients with mild to moderate AD. GV-971 in a Phase 3 study conducted in China (Study 971-III) showed a pattern of rapid initial gains with sustained improvement over the 36-week study period. This study is designed to provide further data including biomarkers and long-term efficacy and safety analyses that will show GV-971 effect on AD progression.

The proposed study will involve 2046 subjects with mild to moderate Alzheimer*s disease. The recruitment will take place globally across approximately 200 investigative sites. All eligible subjects will be randomized in a 1:1 ratio to receive GV-971 or placebo capsules at a dose of 900 mg per day orally. The clinical study design has taken into consideration the recommendations included in the scientific advice documents requested by the sponsor from the European

Medicines Agency (EMA).

Study objective

To assess the efficacy of GV-971 compared with placebo on cognition and global function in participants with mild to moderate Alzheimer's disease (AD).

Study design

This is a 52-week, multi-center, randomized, double-blind, 2-arm, parallel-group, placebo-controlled, monotherapy Phase 3 study, to evaluate the efficacy and safety of GV-971 in the treatment of mild to moderate AD dementia participants (Mini Mental State Examination [MMSE] score 11 to 24, inclusive; with regional stratification [North America, China, Europe/Australia/rest of world] and at least 75% of participants with MMSE scores < 20). Participants who successfully complete the double-blind treatment period may continue in the 26-week open-label extension (OLE) period.

Intervention

All eligible participants will be randomized in a 1:1 ratio to GV-971 and placebo groups.
Both GV-971 and placebo will be administered orally, twice a day.
The dose of the product will be 450mg twice a day.

Study burden and risks

Subject*s participation in this study will last 1 year and 10 months and consists of 4 periods: a screening period (8 weeks), double blind treatment period (52 weeks), open label treatment period (26 weeks) and a safety follow-up period (4 weeks). During the treatment periods, subjects will need to visit the study site every 12 weeks.
4 weeks after discontinuation of treatment subjects will visit the study site 1 time.

Aside from the intervention described above, participation in this study involves blood draws at multiple visits and might involve radiation exposure through CT, in case MRI is contraindicated for medical reasons. Participants will be subjected to:
- ECG 7 times
- MRI 3 times

Taking into account the study drug's tolerability close to placebo, the measures taken to minimize any risk to study participants, the potential risks identified in association with the study drug are justified by the anticipated

benefits that may be afforded to participants with mild to moderate AD. Based on 9 clinical studies performed, the safety and tolerability profile of the study drug strongly suggests a favorable risk/benefit profile given the promising efficacy results of the Phase 2 and 3 studies.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male and female participants aged 50 to 85 years (inclusive) at the time of screening.
2. Willing and able to give informed consent by GCP and local guidance. If the study participant is not competent to give informed consent, in the opinion of the principal investigator, a legally authorized representative (per applicable laws, rules, and regulations) must provide informed consent on his/her behalf,

and the participant must provide assent (or local equivalent).
3. Mild to moderate AD as characterized by the following clinical, cognitive, and functional criteria per National Institute on Aging - Alzheimer's Association (NIA-AA) diagnostic criteria (refer to Section 11.5 for additional details).
a. Clear history of cognitive and functional decline over at least 1 year that is either (1) documented in medical records or (2) documented by history taken from a study partner or other person who knows the participant well (eg, personal physician).
b. MMSE scores between 11 and 24, inclusive, at screening and at baseline.
Note: Screening MMSE must be performed after obtaining consent.
4. Have a study partner/caregiver who has known the participant for at least 1 year and assists the participant regularly at least 3 times per week and has intimate knowledge of the participant's cognitive, functional, and emotional states and of the participant's personal care. The study partner must be willing to accompany the participant to all study visits, assure that all of the participant's medications and the
study drug are stored and dispensed safely, and report adverse events. The study partner must be willing and able to give informed consent for their own participation, be able to read and write, and be capable of providing partner responses to scales such as ADL scales, ADCS-CGIC, and NPI.
Note: Use of the same study partner/caregiver during the study period is encouraged. Any change in study partner/caregiver should be recorded with reasons detailed in the medical chart and case report form (CRF). Informed consent must be obtained from the new study partner/caregiver.
5. Investigator confirmation of participant's ability to complete efficacy assessments and have physical, cognitive, hearing, speech, literacy, and language capacity to participate in all testing.
6. A brain magnetic resonance imaging (MRI) scan during screening. All imaging is evaluated by a central reader vendor (refer to imaging manual for details). MRI will have oblique coronal hippocampus scan and must show the highest possibility of AD, including:
a. Medial temporal lobe atrophy visual rating scale (MTA) * grade 2 by central read;
b. Fazekas scale for white matter lesions grade < 3;
NOTE: Computerized tomography (CT) may be substituted with similar review by central reading when there are MRI contraindications such as heart valve replacement, pacemaker or implants, if medical monitor approves. CT unlike MRI would not be repeated in double-blind or OLE period (see Section 8.2.7.4).
7. Female participants should be postmenopausal (menopause > 24 months), surgically sterilized, or of childbearing potential who agree to take highly effective contraceptive measures throughout the study (see Section 9 for details regarding contraception).
Women of childbearing potential (WOCBP) must undergo a urine pregnancy test at screening and baseline and result must be negative.
8. May use allowed/permitted concomitant medications at screening and during the study (see Table 6-1). These medications must keep stable dosing at least

30 days before randomization and the regimens must be planned to remain constant throughout the study.
9. Participants previously enrolled in an AD clinical study involving a disease modifying or symptomatic therapeutic agent may enroll in this study if:
(1) AD vaccine last dose > 12 months before baseline visit;
(2) monoclonal antibodies last dose > 6 months before baseline visit; and
(3) last symptomatic therapeutic agent ended > 4 weeks or 5 half-lives (whichever is longer) before baseline visit.
These restrictions do not apply if the participant was assigned to placebo treatment, which is documented in the source documents.

Exclusion criteria

1. Diagnosis of a dementia-related central nervous system disease other than AD (eg, Parkinson's Disease, Huntington's Disease, frontotemporal dementia, multi-infarct dementia, dementia with Lewy bodies, normal pressure hydrocephalus).
2. Abnormally low folate, thyroid, and/or vitamin B12 values or evidence of hypothyroidism thought to be the cause of or to contribute to the severity of the participant's dementia.
3. Abnormalities found on brain MRI, including ischemic and hemorrhagic infarctions, hydrocephalus, and brain tumors will be flagged for discussion with the Medical Monitor. The NIA-AA criteria will be applied to determine if vascular lesions are exclusionary.
NOTE: CT scan may be substituted, with similar review by central reading when there are MRI contraindications such as heart valve replacement, pacemaker, or implants, if medical monitor approves. CT, unlike MRI, would not be repeated in double-blind or OLE period (see Section 8.2.7.4).
4. Mental/psychiatric illness determined by Diagnostic and Statistical Manual of Mental Disorders (DSM) V criteria, that is unstable within 12 months, or would interfere with study assessments, including schizophrenia or other psychotic disorders, bipolar disorder, severe depression, or delirium.
5. History of suicidal actions within the past 12 months or current suicide risk determined by a positive response ('Yes') to either Question 4 or Question 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.
6. DSM V diagnosis of alcohol or other substance abuse dependence within the last 12 months.
7. Gastrointestinal illness that may substantially impact absorption such as gastric bypass or recurrent diarrhea.
8. History within the last 12 months or current diagnosis of clinically significant cardiovascular or cerebrovascular diseases/disorders such as serious cardiac arrhythmias, heart rate abnormalities, myocardial infarction, well-documented transient ischemic attack, or cerebrovascular accident, uncompensated congestive heart failure New York Heart Association class III and

IV.
9. A resting heart rate of < 50 beats per minute (bpm) by pulse or ECG, after 5 minutes of rest in sitting or supine position unless deemed not clinically significant by the Principal Investigator.
10. Major medical illness or unstable medical condition within 6 months of screening that in the opinion of the investigator may interfere with the participant's ability to comply with study procedures and abide by study restrictions, or with the ability to interpret safety data, including any physical disability (eg, blindness, deafness, non-AD-related speech impairment, sensory or motor dysfunction) that would prevent completion of study procedures or assessments.
11. Cancer except:
a. Cancer that has been in remission (no evidence of recurrence) for > 3 years from the screening.
b. Basal cell or stage 1 squamous cell carcinoma of the skin or stable untreated cancer such as prostate or meningioma.
c. Chronic carcinomas that do not require treatment (eg, prostate carcinoma restricted to the prostate).
12. Any participants who have previously been treated with GV-971 but discontinued due to safety issues or lack of efficacy.
13. Any participants who have taken any dose of GV-971 within 6 months prior to screening.
14. Use of antibiotics
a. For more than 10 consecutive days in the last 12 weeks prior to baseline
b. When it is expected that participant will receive a treatment for more than 10 days.
c. Extended frequent use (eg, chronic every other day use), unless approved by Medical Monitor.
Note: This refers to those antibiotics which are expected to act in the GI tract, blood system, or an internal organ system and excludes topical agents, which may not be absorbed systemically or come in contact with the GI tract.
15. Use of AChEI, memantine or aducanumab within 4 weeks prior to the first day of screening, within 8 weeks prior to baseline and throughout the study.
16. Use of over-the-counter or prescription medication (including herbal medications) not in compliance with Table 6-1
17. Participants are excluded if they:
a. have participated in any other clinical study (excluding non-drug interventional clinical study) within 4 weeks prior to screening visit
b. have participated in another GV-971 clinical study at any time
c. plan to take part in another clinical study during this study.
18. Geriatric Depression Scale-15 (GDS-15) total score > 7 at screening
19. Inadequate hepatic function, defined in protocol
20. Substantial laboratory abnormalities, defined in protocol
21. After resting for at least 5 minutes in the supine position, 3 averaged ECG shows clinically significant abnormalities or QTcF > 450 ms for male participants and > 470 ms female participants. Exclusion applies if the average of the 3 exceeds these limits.

22. After at least 5 minutes of rest in sitting or supine position (unless deemed not clinically significant by the Principal Investigator):
a. systolic blood pressure (BP) > 180 mmHg
b. diastolic BP > 100 mmHg or < 50 mmHg
23. Poor venous access for blood samples
24. Female participants who are pregnant or lactating. NOTE: Does not apply to female partners of male participants.
25. Wherever residing, participants who do not have a reliable caregiver/study partner and are not able to perform basic ADL (eg, washing and eating) without nursing supervision.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-09-2021
Enrollment:	45
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sodium Oligomannate
Generic name:	Sodium Oligomannate

Ethics review

Approved WMO Date:	05-02-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-09-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-001755-41-NL
ClinicalTrials.gov	NCT04520412
CCMO	NL75788.056.21