A PHASE III, MULTICENTER, RANDOMIZED, PARALLEL-GROUP, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF GANTENERUMAB IN PARTICIPANTS AT RISK FOR OR AT THE EARLIEST STAGES OF ALZHEIMER*S DISEASE

Published: 20-06-2022
Last updated: 05-04-2024

The primary objective of this secondary prevention study is to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of gantenerumab, an anti-amyloid antibody, in amyloid-positive, cognitively unimpaired participants at risk for or...

Ethical review	Not approved
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON50277

Source
ToetsingOnline

Brief title
WN42444/ Skyline

Condition

- Other condition

Synonym
Alzheimer's disease, dementia

Health condition

Neurologisch; ziekte van Alzheimer

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Alzheimer's Disease, Gantenerumab, Phase III, preventive

Outcome measures

Primary outcome

Primary objective: To evaluate the efficacy of gantenerumab compared with

control on cognition

Primary endpoint:

Change from baseline to Year 4 in the Preclinical Alzheimer's Cognitive

Composite-5 (PACC-5) score

Secondary outcome

Secundary objectives:

* To evaluate the efficacy of gantenerumab compared with control on clinical

progression based on time from randomization to clinical progression to mild

cognitive impairment (MCI) or dementia and time to onset of confirmed clinical

progression

* To evaluate the efficacy of gantenerumab compared with control on cognition and/or function

* To evaluate the safety of gantenerumab compared with placebo

* To evaluate biomarkers of pharmacodynamics of gantenerumab compared with control

Secundary endpoints:

1. Time from randomization to clinical progression to MCI or dementia due to AD based on the diagnosis of the independent Clinical Adjudication Committee (iCAC)
2. Time to onset of confirmed clinical progression, defined as the time from randomization to the first occurrence of two consecutive visits (approximately 6 months apart) with a CDR-GS >0
3. Change from baseline to Year 4 in the Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version (A-IADL-Q-SV) and the Cognitive Function Instrument acute (CFIa)
4. Change from baseline to Year 4 in the Clinical Dementia Rating Sum of Boxes (CDR-SB)
5. Nature, frequency, severity, and timing of adverse events, serious adverse events, and adverse events of special interest
6. Physical examinations (including neurological systems), vital signs, blood tests, electrocardiograms (ECGs), and Columbia-Suicide Severity Rating Scale (C-SSRS)
7. Nature, frequency, severity, and timing of MRI findings: amyloid related

imaging abnormality-edema/effusion (ARIA-E) and amyloid related

imaging abnormality-hemosiderin deposition (ARIA-H)

8. Nature, frequency, severity, and timing of injection-site reactions (ISRs)

9. Presence of anti-drug antibodies (ADAs) during the study relative to the

presence of ADAs at baseline

10. Change in brain amyloid load over time, as measured by amyloid positron

emission tomography (PET) in a subset of participants

11. Change in brain tau load over time, as measured by tau PET in a subset of

participants

12. Change in cerebrospinal fluid (CSF) biomarkers, including, but not limited

to, A*1-42, A*1-40, NfL, pTau, and tTau in a subset of participants

13. Change in blood-based biomarkers biomarkers, including, but not limited to,

A*1-42, A*1-40, NfL, pTau, and tTau in a subset of participants

14. Change in magnetic resonance imaging (MRI)-derived measurements over time,

including, but not limited to, volumetric changes in whole brain,

ventricles, hippocampus, or other structures in all participants

Study description

Background summary

Alzheimer*s disease, a debilitating and progressive neurodegenerative disease, represents a significant unmet medical need with no fully approved therapeutics to halt, slow, or prevent the onset of symptoms. The currently available treatment options primarily include symptomatic medications and are only approved for the overtly symptomatic stages of AD. The amyloid hypothesis postulates that amyloid may be an early, key driver of AD pathophysiology. If this hypothesis is true, then early intervention at the amyloid-positive, cognitively unimpaired stage (i.e., at-risk stage of

disease), may result in a high efficacy potential for an anti-amyloid antibody (i.e., gantenerumab), to slow the disease process and preserve the cognitive and functional abilities of affected individuals. This is the main hypothesis Study WN42444 (SKYLINE) aims to test.

Study objective

The primary objective of this secondary prevention study is to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of gantenerumab, an anti-amyloid antibody, in amyloid-positive, cognitively unimpaired participants at risk for or at the earliest stages of Alzheimer*s disease (AD).

Study design

Study WN42444 is a 4-year and 9-month phase III multicenter, randomized, double-blind, placebo-controlled, parallel group study.
Eligible participants will be randomized in a 1:1 ratio to receive either gantenerumab or placebo.
If, in the course of the study, a participant progresses to a clinical diagnosis of mild cognitive impairment (MCI) or dementia due to AD, a *post-progression dose escalation* period will commence.
During the post-progression dose escalation period, participants who were randomized to placebo will switch to gantenerumab in a double-blinded manner.
Participants who were randomized to gantenerumab will continue with gantenerumab (255 mg SC every 1 week [Q1W] or 510 mg SC every 2 weeks [Q2W]).
All participants who progress to a clinical diagnosis of MCI or dementia due to AD must comply with all aspects of the post-progression dose escalation schedules of activities.

The study treatment duration is 211 weeks regardless of the dosing regimen (i.e., Q1W or Q2W) or whether a participant progresses to a clinical diagnosis of MCI or dementia due to AD.
The primary comparison for efficacy will be between the following arms:
- Experimental arm: participants randomized to gantenerumab at the beginning of the study
- Control arm: participants randomized to placebo at the beginning of the study, irrespective of whether they progressed during the study and thus, started gantenerumab

Intervention

The treatment period consists of a dose escalation period and a study dose period.
Dose escalation (approximately 9 months):

During dose escalation (approximately 9 months), the subject receives increasing amounts of gantenerumab (group 1) or placebo (group 2).
* Step 1: One injection of 0.8 ml (120 mg gantenerumab or placebo) every 4 weeks for 3 months thereafter
* Step 2: One injection of 1.7 ml (255 mg gantenerumab or placebo) every 4 weeks for 3 months thereafter
then
* Step 3:
1. Two injections of 1.7 ml (510 mg gantenerumab or placebo) every 4 weeks
OR
2. One injection of 1.7 ml (255 mg gantenerumab or placebo) every 2 weeks for 3 months based on your choice thereafter
* Step 4:
1. Two injections of 1.7 ml (510 mg gantenerumab or placebo) every 2 weeks
OR
2. One injection of 1.7 ml (255 mg gantenerumab or placebo) every other week until the end of the treatment period based on your choice

During the maintenance dose period (approximately 3 years and 3 months), the injection of the study compound is done once a week or once every 2 weeks, depending on the dosing regimen chosen by the subject.

If progression:
The subject will receive gantenerumab anyway. A new dose escalation period of 9 months is completed; QW or Q2W according to schedule.
The dose escalation after progression is followed by a maintenance dose with the target dose and will not extend the total time in the treatment period (approximately 4 years).

Study burden and risks

Known Side Effects of Gantenerumab
* Brain microbleeds detected on MRI scans.
* Brain microbleeds can occur spontaneously and are sometimes seen in people who did not receive gantenerumab or similar drugs. Brain microbleeds are expected to occur more frequently in people who have a certain type of *APOE* gene.
* Brain swelling detected on MRI scans
* The vast majority of patients who developed brain swelling while being treated with gantenerumab reported no symptoms, and the swelling resolved spontaneously when the study drug was withheld. In a few cases, patients developed symptoms, which were of mild intensity (for example, headache) and sometimes serious (for example, confusion or seizure/epilepsy). Brain swelling is expected to occur more frequently in people who have a certain type of *APOE* gene.
* Injection site reactions; Injection-site reactions are non-serious, largely mild to moderate in severity, and self-resolving. Potential Side Effects

* Injection-related or allergic reaction with symptoms such as fever, chills, low blood pressure, rash, headache, nausea, or vomiting.
* Immune system might develop antibodies to the study drug

An iDMC will evaluate safety data on a regular basis from Study WN42444 in an unblinded fashion, including the incidence, severity, and nature of adverse events, serious adverse events, ARIA-E and ARIA-H, ISRs, adverse events of special interest, ECGs, laboratory abnormalities, and the Mini Mental State Examination (MMSE).

Based on the available information, no interactions between gantenerumab and the COVID-19 vaccines are expected to occur, and no other safety concerns have been identified that would prohibit the vaccination of participants enrolled in the studies where gantenerumab is being
investigated for the treatment of Alzheimer*s disease. COVID-19 vaccins will be considered as co-medication

The adverse reactions associated with florbetaben are indicated on the SmPC (Eu).

There are potential risks associated with the study related assessment / procedures, as described in the ICF.

Contacts

Public
Roche Nederland B.V.

Beneluxlaan 2A
Woerden 3446 GR
NL
Scientific
Roche Nederland B.V.

Beneluxlaan 2A
Woerden 3446 GR
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Ability to provide written informed consent and has signed the Informed Consent Form
* Age 60-80 years old (inclusive) at time of signing the Informed Consent Form
* Willingness and ability to comply with the study protocol, and complete all aspects of the study (including cognitive and functional assessments, physical and neurological examinations, MRI, CSF collection, genotyping, and PET imaging)
* Cognitively unimpaired with a screening CDR-GS of 0, MoCA score 26 or > 26 and RBANS DMI 85 -115
* Evidence of cerebral amyloid accumulation, as confirmed by a combined measure of quantitative and qualitative amyloid PET or CSF pTau/A(-42 ratio
* Availability of a person ("study partner* throughout the study) in the investigator's judgment
- Participants who are fluent in the language of the tests used at the study site
- Participants who have adequate visual and auditory acuity, sufficient to perform
neuropsychological testing (eye glasses and hearing aids are permitted)
- Participants who have agreed not to donate blood or blood products for transfusion
for the duration of the study and for 1 year after the final dose of study drug
- Participants who have agreed not to participate in other interventional research
studies for the duration of this trial
- For women of childbearing potential: agreement to remain abstinent (refrain from
heterosexual intercourse) or use contraceptive methods that result in a failure rate
of < 1% per year during the treatment period and for at least 17 weeks after the final
dose of study treatment

Exclusion criteria

- Exclusions Related to CNS Disorders:
- Any evidence of an underlying neurological or neurodegenerative condition that may
lead to cognitive impairment other than AD, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson*s disease, corticobasal syndrome, Creutzfeldt-Jakob disease, progressive
supranuclear palsy, frontotemporal lobar degeneration, Huntington disease, normal
pressure hydrocephalus, seizure disorder, delirium, hypoxia, or encephalopathy related to prior COVID-19 infection
- Clinical diagnosis of MCI, prodromal AD, or any form of dementia
- History or presence of intracranial or intracerebral vascular malformations, aneurysm, subarachnoid hemorrhage, or intracerebral macrohemorrhage
- History or presence of posterior reversible encephalopathy syndrome
- History of ischemic stroke with clinical symptoms or an acute event that is consistent
with a transient ischemic attack within 12 months of screening
- History of severe, clinically significant (i.e., resulting in persistent neurologic deficit
or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial mass lesion (e.g., glioma, meningioma) that could
potentially impair cognition or lead to progressive neurological deficits
- Infections that may affect brain function or a history of infections that resulted in
neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, and viral or bacterial
meningitis and encephalitis)
- History of major depression, schizophrenia, schizoaffective disorder, or bipolar
disorder
History or presence of major depression is acceptable if the participant is considered to be in remission or depression is controlled by treatment and the participant has had no episode of major depression within 12 months of screening.
- At risk for suicide
- History of alcohol and/or substance abuse or dependence (according to the criteria
specified in the Diagnostic and Statistical Manual of Mental Disorders, Version 5)
within 2 years of screening
- Exclusions Related to Imaging Related Criteria
- Exclusions Related to Cardiovascular Disorders

- Exclusions Related to Hepatic and Renal Disorders
- Exclusions Related to Infections and Immune Disorders
- Exclusions Related to Metabolic and Endocrine Disorders
- Exclusions Related to Medications
- Other Exclusions

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:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	60
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Gantenerumab
Generic name:	Gantenerumab

Ethics review

Approved WMO

Date:	20-06-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Not approved Date:	17-10-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2021-001184-25-NL
CCMO	NL79192.100.21