A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER*S DISEASE

Published: 01-05-2018
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This study will evaluate the efficacy and safety of gantenerumab compared with placebo in patients with early (prodromal to mild) Alzheimer's disease (AD).

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON50345

Source
ToetsingOnline

Brief title
WN39658 / Graduate II

Condition

- Other condition

Synonym
Alzheimer disease, dementia

Health condition

neurologische aandoeningen, Alzheimer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: effectiviteit, gantenerumab, prodromaal en mild AD, veiligheid

Outcome measures

Primary outcome

Primary efficacy objective of main study: To evaluate the efficacy of

gantenerumab administered by SC injection compared with placebo

The change from baseline (Day 1) to Week 104 in global outcome, as measured by

the CDR-SOB

Primary efficacy objective of the OLE period: To evaluate the long-term safety

and tolerability of SC gantenerumab in patients with early AD

Protocol version 4: endpoint timeline become week 116

The ongoing impact of the COVID-19 pandemic on the study procedures will be

closely monitored, and if necessary, the double-blind treatment period will be

further extended by another 12 weeks and times will be adjusted accordingly.

Secondary outcome

Secundary efficacy objective: To evaluate the efficacy of gantenerumab versus

placebo on cognition and function

The change from baseline to Week 104 in cognition

and/or function, as measured by:

* MMSE total score

* ADAS-Cog11 and ADAS-Cog13

* Verbal Fluency Task

* Coding

* FAQ

* ADCS-ADL total score and instrumental score

Protocol version 4: change of endpoint timelines to week 116.

Study description

Background summary

Gantenerumab (or RO4909832) is a fully human anti Amyloid beta (Ab) peptide antibody developed by in vitro selection utilizing aggregated Ab and in vitro maturation within a complete human Ig, subclass-1 framework (IgG1). Gantenerumab recognizes a conformational epitope
of Ab present in aggregated Ab and that is demonstrated for both major species of Ab that is, Ab*1*40 and Ab 1*42. Gantenerumab has a molecular mass of 146.3 kDa. In vitro, gantenerumab recognizes synthetic aggregated Ab fibrils and Ab oligomers with high nanomolar affinity. Based on additional in vitro studies and studies in animal models, the pharmacologic profile suggests that in humans gantenerumab may prevent, inhibit, and reduce accumulation of Ab, which is

believed to play an important role in the pathogenesis of AD.

Study objective

This study will evaluate the efficacy and safety of gantenerumab compared with placebo in patients with early (prodromal to mild) Alzheimer's disease (AD).

Study design

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gantenerumab in patients with early (prodromal to mild) AD. The planned number of patients for the global enrollment phase for the study is approximately 760 patients: randomized in a 1:1 ratio to receive gantenerumab and placebo (380 patients randomized to gantenerumab and 380 randomized to placebo). For more information, see section 16 of the study protocol.

Protocol version 4: increase of included participants of 1016

Intervention

Gantenerumab (target dose 510 mg) or placebo will be administered by SC injection to all patients.

Study burden and risks

SIDE EFFECTS KNOWN TO BE ASSOCIATED WITH GANTENERUMAB
As of 31 May 2019, approximately 1400 patients have been exposed to gantenerumab. Gantenerumab is still being studied, and the side effects associated with this treatment are not completely known yet. The most frequent risks associated with gantenerumab, which have been identified to date, are effects on brain and injection-site reactions as described below.
EFFECTS ON THE BRAIN
Some patients who received gantenerumab or other investigational drugs similar to gantenerumab had some changes in their MRI brain scans. These may include swelling. Other changes include something called *microbleeds,* which are very small areas in the brain where a nearby blood vessel may have leaked. Microbleeds can occur spontaneously and are sometimes seen in people who did not receive gantenerumab or similar drugs. These MRI changes occurred more frequently in people who have a certain type of *APOE* gene.
In previous and ongoing studies, approximatively 1400 patients have received gantenerumab on doses ranging from 105-1200 mg. In some of these patients, MRI changes compatible with brain swelling were observed. Swelling was also observed in very few patients who received placebo. The vast majority of patients reported no symptoms at the time of brain swelling and the swelling resolved spontaneously when the study drug was withheld. In few cases,

patients developed symptoms, which were mostly of mild intensity (for example, headache) and sometimes serious (for example, confusion or seizure/epilepsy). Overall, such events did not occur more frequently than expected in the AD population; however, it cannot be excluded that the presence of brain swelling contributed to or triggered the onset of the symptoms.
INJECTION-SITE REACTIONS
Gantenerumab may cause a reaction when given as a subcutaneous (under the skin) injection. To date, the most common events occurring more frequently with gantenerumab than with placebo were local injection reactions such as reddening of the skin at the site of injection. Most of these events were of mild intensity and resolved without treatment.

TO DATE, THERE HAVE BEEN NO REPORTS OF SERIOUS ALLERGIC REACTIONS TO GANTENERUMAB.
For other risks please see paragraph 5 of the main ICF and safety setions in the protocol.

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

- Age 50-90 years
- Meets National Institute on Aging/Alzheimer's Association (NIAAA) core clinical criteria for probable AD dementia or prodromal AD (consistent with the NIAAA diagnostic criteria and guidelines for mild cognitive impairment)
- Evidence of AD pathological process, as confirmed by cerebrospinal fluid or amyloid positron emission tomography scan
- Demonstrate abnormal memory function
- MMSE score between 22-30 (inclusive)
- Clinical Dementia Rating Global Score of 0.5 or 1.0
- Availability of a reliable study partner who accepts to participate in study procedure throughout the study duration
- If receiving symptomatic AD medication the dosing regimen must have been stable for 3 months prior to screening

Exclusion criteria

- Any evidence of a condition other than AD that may affect cognition
- History or presence of clinically evident systemic vascular disease that in the opinion of the investigator has the potential to affect cognitive function
- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder
- Unstable or clinically significant cardiovascular, kidney or liver disease
- At risk of suicide in the opinion of the investigator
- Alcohol or substance abuse in past 2 years
- Relevant brain hemorrhage, bleeding disorder and cerebrovascular abnormalities
- Any contraindications to brain magnetic resonance imaging
- Uncontrolled hypertension

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):	04-10-2018
Enrollment:	8
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	01-05-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-08-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-09-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-12-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-02-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-07-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-07-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-08-2019
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-08-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-08-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-09-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-09-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-03-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-03-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-07-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	14-07-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-09-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-09-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-09-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-12-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-12-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	24-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2017-001365-24-NL
ClinicalTrials.gov	NCT03443973
CCMO	NL65034.100.18