A Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety study of Gantenerumab in patients with Mild Alzheimer*s disease; part II: open-label extension for participating patients

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Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON45187

Source
ToetsingOnline

Brief title
WN28745 / Marguerite RoAD

Condition

- Other condition

Synonym
Alzheimer disease, dementia

Health condition

centraal zenuwstelsel aandoeningen: neurologische aandoeningen

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, Open label, Subcutaneous

Outcome measures

Primary outcome

The co-primary efficacy measures for part 1 of this study were as follows:

* Mean change from baseline at Week 104 in ADAS Cog13

* Mean change from baseline at Week 104 in ADCS-ADL score

Secondary outcome

The key secondary efficacy measures for part 1 of this study were the following:

* Time to clinical decline as measured by

* Confirmed (at two consecutive visits) > or = 2-point decline on MMSE, and

* Loss of > or =1 points on one or more basic ADL, as assessed with the

ADCS-ADL or

* Loss of > or = 2 points on one or more IADL, as assessed with the ADCS-ADL

* Change from baseline at week 104 in CDR-SB

* ADAS-Cog responder

* Change from baseline (i.e., collected at screening) to Week

104 in CSF t-tau, p-tau, and ABeta1-42 levels

The secondary biomarker outcome measures for this study were as follows:

* Change from baseline (screening visit) to Week 104 in MRI

volumetry, as assessed on structural MRI:

* Change from baseline in hippocampal volume

* Change from baseline in whole brain volume

* Change from baseline in cortical thickness

* Change in baseline in ventricular volume

* Changes in brain and heart (not applicable in the Netherlands) amyloid load

over time using florbetapir, a PET radioligand selective to Beta-amyloid in

patients treated with gantenerumab or placebo

Additional secondary efficacy outcome measures for part 1 of this study were

the mean change from baseline at Week 104 in the following:

* CDR-GS

* ADAS-Cog13 scores

* NPI total and domain scores (neuropsychiatric behavior)

* MMSE total score (cognition)

* Clinical composite endpoint (prespecified items from the ADAS-Cog, MMSE, and

CDR)

* QOL-AD (global score)

* SymptomGuide* Facilitated GAS (change in symptoms and goal achievement)

* DS (global score, and Cognitive Support and Assistance and Elder Active

scales)

* RUD-Lite (resource utilization, time care-giving, caregiver productivity, and

institutionalization)

* ZCI-AD (domains and global scores)

Efficacy measures in Part 2 are exploratory and will include both clinical

outcome measures (ADAS-Cog, MMSE, CDR, and ADCS-ADL) and biomarker measures.

Study description

Background summary

The clinical benefit of an anti-amyloid therapy is expected to be most beneficial early in the disease course when brain amyloid is still accumulating and subsequent neuronal damage may not have progressed significantlyAs described in Section 1.3.2, clinical data supporting the use of gantenerumab in AD come from the analysis of the NN19866 PET study that demonstrated a robust biologic effect in the brain. In this study, brain amyloid was decreased in a dose-dependent manner in patients with mild to moderate AD who received doses of gantenerumab IV (200 mg or 60 mg) every 4 weeks (q4w) compared with placebo (Ostrowitzki et al. 2012). The purpose of Study WN28745 is to establish the efficacy and safety of gantenerumab as a disease-modifying treatment in patients with mild AD who may or may not be treated concurrently with approved treatments for AD.

Part 2:On the basis of results of the WN25203 study and the PRIME study, the doses of 105 and 225 mg gantenerumab can now be considered to be sub-therapeutic. Therefore, the double-blind period of the study (part 1) will be suspended and replaced by the OLE (part 2) with increased dose up to 1200 mg.

Study objective

The primary efficacy objective for this study was to evaluate the efficacy of gantenerumab compared with placebo administered to patients by subcutaneous (SC) injection over 100 weeks as measured by the following co-primary endpoints (final outcome assessment 4 weeks after the final dose):
* Cognition, as measured by the ADAS-Cog (13-item)
* Function, as assessed by ADCS-ADL

Secondary objectives:
Evaluate the efficacy, safety, tolerability of Gantenerumab versus placebo administered as subcutaneous injections.

Part 2:
The main objective of the 2-year OLE is to evaluate the safety and tolerability of gantenerumab at higher doses focusing on physical and neurologic examinations, vital signs, blood safety tests, ECGs, and adverse event monitoring. All patients previously enrolled and ongoing in the study will be eligible to receive active gantenerumab and will be up-titrated gradually to the highest possible dose up to 1200 mg.

The secondary objectives will include the following:
* To evaluate the effect of higher doses of gantenerumab on imaging biomarkers (PET and MRI) on CSF biomarkers and on clinical outcome measures (cognition and function) over time
* To explore pharmacokinetics at the higher gantenerumab doses

Study design

Study WN28745 is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of gantenerumab in patients with mild AD. Patients with mild AD will be selected on the basis of clinical diagnosis of probable mild AD according to the National Institute of Neurological and Communicative Disorders and Stroke/ Alzheimer*s Disease and Related Disorders Association (NINCDS/ADRDA) criteria or probable major neurocognitive disorder (NCD) due to AD-mild severity using the Diagnostic and Statistical Manual of Mental Disorders, Version 5 (DSM-5) criteria, and biomarker evidence for increased amyloid burden. Approximately 175 centers will participate.

Part 2:
All patients (approximately 350 patients) who are actively enrolled in Study WN28745 (i.e., not discontinued from study drug) will be invited to participate in the OLE study. Patients will receive open-label gantenerumab up to1200 mg by SC injection q4w for up to a maximum of
100 weeks (26 doses). Patients will also have follow-up visits at 4, 16 and 52 weeks after the final dose for safety and limited efficacy.

In addition to the initial 2 years in OLE, patients will be given the option to continue receiving open label gantenerumab treatment until the end of 2020, at which time anticipated results from other relevant monoclonal antibody treatments will be available. Patients who discontinue study drug at any time during OLE, or who complete the first 2 years of OLE only will be asked to complete follow up visits at 4 and 16 weeks from their last dose (Follow Up 1 and 2, respectively).

Intervention

Test Product
Gantenerumab will be administered via subcutaneous injection to all subjects randomized to active, regardless of ApoE genotype, at a dose of 225 mg every 4 weeks for up to a total of 20 doses. Injections will be administered as one 1-mL SC injection to the abdomen.

Comparator
Placebo of similar physical characteristics and identical volume to gantenerumab will be administered via subcutaneous injection to all subjects randomized to placebo with the same frequency and administration.

Part 2: Patients participating in Part 2 will receive open-label gantenerumab administered as SC injections to the abdomen every q4w either as one or multiple injections from a PFS or extracted from a vial and administered either by a syringe (300 mg) or a syringe pump (for 450 mg doses and higher).Starting dose will be 225mg up to 600 mg dependent of ApoE4 genotype and dosage received durig part 1 of the trial. Dosage will increase over time up to 1200 mg.

Study burden and risks

Subjects may have side effects from the drugs or procedures used in this study. Side effects can vary from mild to very serious and may vary from person to person. Everyone taking part in the study will be watched carefully for any side effects. However, Roche, the study doctor, and other doctors do not know all of the side effects that could occur.

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

- Adult patients, 50 to 90 years of age, inclusive;- Clinical diagnosis of probable mild Alzheimer disease (AD) based on NINCDS/ADRDA criteria or major neurocognitive disorder due to AD of mild severity whether or not receiving AD approved medication;- Availability of a person ('caregiver') who in the investigator's judgment has frequent and sufficient contact with the patient, and is able to provide accurate information regarding the patient's cognitive and functional abilities;- Fluency in the language of the tests used at the study site;- Willingness and ability to complete all aspects of the study ;- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted);- Agreement not to participate in other research studies for the duration of the trial and its associates substudies;- All patients who have been randomized and are actively participating in the study at the time of the amendment approval in their respective country will be eligible to participate in the OLE.

Exclusion criteria

- Dementia or NCD due to a condition other than AD, including, but not limited to, frontotemporal dementia, Parkinson disease, dementia with Lewy bodies, Huntington disease, or vascular dementia;- History or presence of clinically evident vascular disease potentially affecting the brain that in the opinion of the investigator has the potential to affect cognitive function;- History or presence of stroke within the past 2 years or documented history of transient ischemic attack within the last 12 months;- History or presence of systemic autoimmune disorders potentially causing progressive neurologic disease with associated cognitive deficits ;- History of schizophrenia, schizoaffective disorder, or bipolar disorder;- Alcohol and/or substance use disorderd (according to the DSM-5) within the past 2 years (nicotine use is allowed);- History or presence of atrial fibrillation ;- Within the last 2 years, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction, angina pectoris, cardiac failure New York Heart Association Class II or higher);- Uncontrolled

hypertension;- Chronic kidney disease ;- Impaired hepatic function ;- Patients who have been discontinued from the study will not be allowed to enroll in the OLE.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-07-2014
Enrollment:	8
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	14-01-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2014

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-11-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-12-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-02-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-04-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	04-08-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-11-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-04-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-08-2018
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-09-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-05-2020
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	EUCTR2013-003390-95-NL
ClinicalTrials.gov	NCT02051608
CCMO	NL46633.056.13

Study results

Date completed:	29-01-2021
Results posted:	20-12-2021

First publication
01-12-2021