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A study of the effectiveness and safety of gantenerumab in participants at risk for or at the earliest stages of Alzheimer's disease

Submission date
28/01/2022

Recruitment status
Stopped

Registration date
25/04/2022

Overall study status
Stopped

Last Edited
04/12/2023

Condition category
Nervous System Diseases

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Alzheimer's disease is the most common cause of dementia, a general term for memory loss and other cognitive abilities serious enough to interfere with daily life. The aim of this study is to investigate whether gantenerumab can prevent or slow the development of symptoms associated with Alzheimer’s disease in people who are at risk for or in the earliest stages of Alzheimer’s disease. Gantenerumab is a man-made antibody that attaches to amyloid in the brain and mobilizes the immune system to remove it. It is thought that removing brain amyloid may slow down the disease process that underlies Alzheimer’s disease.

Who can participate?
People who are 60-80 years of age (inclusive) who are at risk for or in the earliest stages of Alzheimer’s disease (evidence of amyloid accumulation in the brain, without cognitive deficits)

What does the study involve?
Participants will be randomly assigned to receive either gantenerumab or placebo (dummy drug) by injection. There will be an initial dose-escalation period, followed by a maintenance dosing period. If the participant's cognition declines to a point where they are diagnosed with mild cognitive impairment (MCI) or dementia, they will start a post-progression dose-escalation period followed by maintenance dosing at the target dose where all participants will receive gantenerumab. Gantenerumab/placebo will initially be given in a clinic with equipment and staff who are trained to respond to medical emergencies, during which the participant/study partner may receive observer and dose administration training if willing and capable. At the next four clinic visits, injections will be administered by the participant/study partner under supervision, after which they may administer at home except for mandatory clinic visits. Alternatively, the participant can receive study treatment by a mobile nurse at home (if consented), or in a clinic.

What are the possible benefits and risks of participating?
The participant's health may or may not improve in this study, but the information that is collected may help other people who have a similar medical condition in the future. Assessments will take place more often than they would if participants were not taking part in this study.

Blood collection may cause bruising and discomfort and a risk of infection or blood clots at the site of the collection. Cerebrospinal fluid (CSF) collection may cause pain, nausea, headache, discomfort, bruising, stiffness, and, rarely, infection. It is possible that side-effects that are unknown at this time may occur during the study. New information that may affect participants' health or willingness to take part in the study will be shared with them in a timely manner. There may be a risk in exposing an unborn child to the study drug, and all risks are not known at this time. Women must take precautions to avoid exposing an unborn child to study drugs. Participants will be informed of all of the above risks and will be asked to notify their study doctor or study staff should they experience any side effects, and will be monitored throughout the study in order to minimise risks.

Where is the study run from?
F. Hoffmann-La Roche Ltd (Switzerland)

When is the study starting and how long is it expected to run for?
February 2021 to October 2028

Who is funding the study?
F. Hoffmann-La Roche Ltd (Switzerland)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
2021-001184-25

Integrated Research Application System (IRAS)
1004248

ClinicalTrials.gov (NCT)
NCT05256134

Protocol serial number
WN42444, IRAS 1004248, CPMS 50781

Study information

Scientific Title
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

Acronym
SKYLINE

Study objectives
1. To evaluate the efficacy of gantenerumab compared with control on cognition
2. 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
3. To evaluate the efficacy of gantenerumab compared with control on cognition and/or function
4. To evaluate the safety of gantenerumab compared with placebo
5. To evaluate biomarkers of pharmacodynamics of gantenerumab compared with control

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 22/04/2022, London - West London & GTAC Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham NG1 6FS, UK; +44 (0)207 1048 007; westlondon.rec@hra.nhs.uk), ref: 22/LO/0128

Study design
Randomized double-blind parallel-group placebo-controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Alzheimer's disease

Interventions
Participants will have an equal chance of being placed in the gantenerumab or placebo treatment groups. Study treatment will be given by injection. There will be an initial 9-month dose escalation, where participants will receive increasing volumes of study treatment. From the fifth dose, a mobile nurse can administer study treatment to participants at home. From the eighth dose, the participant can (with training) self-administer study treatment at home, or their study partner can be trained to do this. By the end of the dose-escalation period, the participant will be on a regular weekly or biweekly dosing schedule for the 3 years and 3-month maintenance dosing period. If during the maintenance dosing period the participant's cognitive ability declines to a point the participant is diagnosed with mild cognitive impairment (MCI) or dementia due to Alzheimer’s disease by an independent group of doctors, they will then enter the post-progression dose-escalation period for approximately 9 months. During this period, all participants will undergo a gantenerumab dose-escalation period (mimicked for participants already on gantenerumab to maintain the blind), followed by maintenance dosing at the target dose. The total time on study treatment is approximately 4 years.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Gantenerumab

Primary outcome(s)
Severity of cognitive decline measured using Preclinical Alzheimer's Cognitive Composite-5 (PACC-5) score at baseline to Year 4

Key secondary outcome(s))
1. Time from randomization to clinical progression to MCI or dementia due to Alzheimer's disease (AD) based on the diagnosis of the independent Clinical Adjudication Committee (iCAC), measured at baseline to Year 4 (Week 211)
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, measured at baseline to Year 4 (Week 211)
3. Impairment in daily activities assessed using the Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version (A-IADL-Q-SV) and the Cognitive Function Instrument acute (CFIa) at baseline to Year 4 (Week 211)
4. Stage/severity of Alzheimer dementia and mild cognitive impairment (MCI) assessed using the Clinical Dementia Rating Sum of Boxes (CDR-SB) at baseline to Year 4 (Week 211)
5. Nature, frequency, severity, and timing of adverse events, serious adverse events, and adverse events of special interest measured using PI/clinical assessment at baseline to Week 227 (or 15 weeks after Early Term Visit) (Note: The primary comparison for safety will be between active gantenerumab and placebo)
6. Physical examinations (including neurological systems), vital signs, blood tests, electrocardiograms (ECGs), and suicidal ideation measured using the Columbia-Suicide Severity Rating Scale (C-SSRS) measured at baseline to Week 227 (or 15 weeks after Early Term Visit) (Note: The primary comparison for safety will be between active gantenerumab and placebo)
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) measured at baseline to Week 227 (or 15 weeks after Early Term Visit) (Note: The primary comparison for safety will be between active gantenerumab and placebo)
8. Nature, frequency, severity, and timing of injection-site reactions (ISRs) measured using PI /clinical assessment at baseline to Week 227 (or 15 weeks after Early Term Visit) (Note: The primary comparison for safety will be between active gantenerumab and placebo)
9. Presence of anti-drug antibodies (ADAs) during the study relative to the presence of ADAs at baseline measured using laboratory blood test at baseline to Week 227 (or 15 weeks after Early Term Visit) (Note: The primary comparison for safety will be between active gantenerumab and placebo)
10. Brain amyloid measured by amyloid positron emission tomography (PET) in a subset of participants at baseline to week 211
11. Brain tau load measured by tau PET in a subset of participants at baseline to week 211
12. Cerebrospinal fluid (CSF) biomarkers, including, but not limited to, Aβ1-42, Aβ1-40, NfL, pTau, and tTau measured using laboratory analysis of CSF in a subset of participants measured at baseline to week 211
13. Blood-based biomarkers, including, but not limited to, Aβ1-42, Aβ1-40, NfL, pTau, and tTau measured using laboratory plasma sample test in a subset of participants at screening, baseline, weeks 25, 53, 79, 105, 157, 211, follow-up safety assessment, early termination visit (if applicable)
14. Magnetic resonance imaging (MRI)-derived measurements, including, but not limited to, volumetric changes in whole-brain, ventricles, hippocampus, or other structures in all participants measured at baseline to Week 227 (or 15 weeks after Early Term Visit)

Completion date
13/10/2028

Reason abandoned (if study stopped)
Objectives no longer viable

Eligibility

Key inclusion criteria
Main study:
1. Age 60-80 years (inclusive) at the time of signing the ICF
2. Cognitively unimpaired with a screening Clinical Dementia Rating Global Score (CDR-GS) of 0, and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Delayed Memory Index (DMI) ≥80
3. Show evidence of cerebral amyloid accumulation
4. Have an available person (referred to as a "study partner" throughout the protocol) who:
4.1. Has frequent and sufficient contact with the participant, and is willing and able to provide accurate information regarding the participant's cognitive and functional abilities, signs the necessary ICF(s), and has sufficient cognitive capacity to accurately report on the participant's cognitive and functional abilities
4.2. Is in sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the participant and participation in study procedures throughout the duration of the study
4.3. Is fluent in the language of the tests used at the study site
4.4. Every effort should be made to have the same study partner participate throughout the duration of the study
5. Are fluent in the language of the tests used at the study site
6. Have adequate visual and auditory acuity, sufficient to perform neuropsychological testing
7. 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
8. Have agreed not to participate in other interventional research studies for the duration of this trial
9. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods during the treatment period and for at least 17 weeks after the final dose of study treatment

Optional blood-based biomarker prescreening procedure:
1. Age 60-80 years (inclusive) at the time of signing the Blood-Based Biomarker Prescreening Informed Consent Form (ICF)
2. Do not have a known clinical diagnosis of cognitive impairment, MCI, prodromal AD, or any form of dementia

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Sex
All

Key exclusion criteria

Exclusions related to central nervous system (CNS) disorders:
Participants who:
1. Show any evidence of an underlying neurological or neurodegenerative condition that may lead to cognitive impairment other than AD
2. Have a clinical diagnosis of MCI, prodromal AD, or any form of dementia
3. Have a history or presence of intracranial or intracerebral vascular malformations, aneurysm, subarachnoid hemorrhage, intracerebral macrohemorrhage, or posterior reversible encephalopathy syndrome
4. Have a history of ischemic stroke with clinical symptoms or an acute event that is consistent with a transient ischemic attack or severe, clinically significant CNS trauma
5. Have a history or presence of intracranial mass lesion that could potentially impair cognition or lead to progressive neurological deficits
6. Have infections that may affect brain function or a history of infections that resulted in neurologic sequelae
7. Have a history of major depression, schizophrenia, schizoaffective disorder, or bipolar disorder
8. Are at risk for suicide
9. Have a history of alcohol and/or substance abuse or dependence

Exclusions related to imaging findings:
Participants who:
1. According to the MRI central reader, show MRI evidence of any of the following:
1.1. >1 lacunar infarcts
1.2. Any territorial infarct >1 cm3
1.3. Any white matter lesion that corresponds to an Overall Fazekas score of 3
2. Have a combined number of microbleeds and areas of leptomeningeal hemosiderosis on the MRI of >5
3. Have a presence of any other significant cerebral abnormalities
4. Are not able to tolerate MRI procedures or have a contraindication to MRI

Exclusions related to cardiovascular disease:
Participants who:
1. Have a history or presence of clinically significant systemic vascular disease or atrial fibrillation
2. Experienced unstable or clinically significant cardiovascular disease
3. Have a history or presence of heart failure- Have had uncontrolled hypertension

Exclusions related to hepatic and renal disorders:
Participants who:
1. Have chronic kidney disease or confirmed and unexplained impaired hepatic function

Exclusions related to infections and immune disorders:
Participants who:
1. Have a history of, or are known to currently have an HIV infection, or hepatitis B or hepatitis C virus infection or spirochete infection of the CNS
2. Have a history or presence of systemic autoimmune disorders
3. Have systemic immunosuppression or immunomodulation
4. Have a current COVID-19 infection

Exclusions related to metabolic and endocrine disorders:
Participants who:
1. Have abnormal thyroid function

2. Show evidence of folic acid deficiency or vitamin B-12 deficiency
3. Have a screening hemoglobin A1c (HbA1c) >8% or poorly controlled insulin-dependent diabetes with hypoglycemic episodes

Exclusions related to medications:
1. Any previous administration of:
1.1. Gantenerumab
1.2. Active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
1.3. Passive immunotherapy (Ig) or another long-acting biologic agent to prevent or postpone cognitive decline
2. Any other investigational treatment within 5 half-lives or 6 months
3. Any previous administration of sodium oligomannate (GV-971)
4. Any previous treatment with medications specifically intended to treat symptoms related to Parkinson's disease or any other neurodegenerative disorder
5. Anticonvulsant medications, typical and atypical antipsychotic or neuroleptic medications, anticoagulation medications
6. Psychedelic drugs and substances, recreational cannabis and illicit use of opioids or ketamine
7. Medical marijuana, chronic use of prescribed opiates or opioids for pain management and chronic use of prescribed benzodiazepines, barbiturates and hypnotic medications, medical food supplements are allowed if on a stable dose for at least 1 month prior to screening
8. Nootropics and stimulant medications
9. Any previous treatment with cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists

Additional exclusions:
Participants who:
1. Are pregnant or breastfeeding, or intending to become pregnant
2. Have a deformity of the lumbosacral region of the spine, clinically significant abnormal screening blood, CSF or urine results, impaired coagulation, history of cancer, severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, hypersensitivity to any gantenerumab excipients
3. Have any other severe or unstable medical conditions that could be expected to progress, recur, or change to such an extent that it could put the participant at special risk, interfere with the participant's ability to complete the study assessments, or would require the equivalent of institutional or hospital care
4. Reside in a skilled nursing facility such as a convalescent home or long-term care facility
5. Planned or recent exposure to ionizing radiation that exceeds recommended local guidelines

Date of first enrolment
05/09/2022

Date of final enrolment
15/03/2024

Locations

Countries of recruitment
United Kingdom

England

Scotland

Argentina

Australia

Belgium

Canada

France

Germany

Ireland

Italy

Japan

Netherlands

New Zealand

Poland

Russian Federation

Spain

Sweden

Study participating centre
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Study participating centre
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Study participating centre
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DD1 9SY

Study participating centre
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Sponsor information

Organisation
Roche (Switzerland)

ROR
https://ror.org/00by1q217

Funder(s)

Funder type
Industry

Funder Name
Roche

Alternative Name(s)
F. Hoffmann-La Roche Ltd, F. Hoffmann-La Roche & Co, F. Hoffmann-La Roche AG, Roche Holding AG, Roche Holding Ltd, Roche Holding, Roche Holding A.G., Roche Holding, Limited, F. Hoffmann-La Roche & Co., Roche Holdings, Inc.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes