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A study to investigate the processing by the body, safety, and side effects of gantenerumab in healthy Chinese participants following a single dose

Submission date
17/05/2021

Recruitment status
No longer recruiting

Registration date
25/06/2021

Overall study status
Completed

Last Edited
15/09/2022

Condition category
Other

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Alzheimer's disease (AD) is the most common form of dementia, accounting for 60%–70% of cases. The prevalence of AD increases with age, with a global prevalence of 5%– 8% in people 60 years and older. Because of its increasing prevalence, long duration, and high cost of care, AD is expected to be a major public health problem for decades to come.
AD is thought to be caused by an abnormal build-up of proteins in the brain resulting in a loss of brain cells. Treatments targeting the processing and deposition of protein may alter the progression of AD. Gantenerumab (RO4909832) is an antibody that binds specifically to amyloid-beta (a brain protein fragment and prime suspect in AD), promoting its clearance. This single-dose study in healthy participants has been designed to support the development of gantenerumab for the treatment of patients with AD in China.

Who can participate?
Healthy Chinese male and female volunteers

What does the study involve?
On day one, participants will receive a single dose of gantenerumab as two injections, one in the lower quadrant and one in the upper quadrant of the abdomen. Blood levels of gantenerumab are measured at pre-dose, Day 1, 2, 3, 4, 5, 6, 7, 8, 12, 21, 29, 43, 64 and 85.

What are the possible benefits and risks of participating?
Gantenerumab has been well-tolerated in patients with AD. The dosage is within the range of recently conducted clinical trials in healthy participants; all tested doses were considered safe and well-tolerated. There are two identified risks for the compound: amyloid-related imaging abnormalities (ARIA) are abnormal differences seen in brain imaging of AD patients, observed following repeated treatment in patients with AD, and integrated stress response (ISR). In previous single-dose studies of gantenerumab, in participants with AD, ARIA has not been observed. As with any medicinal product, the potential for a hypersensitivity reaction with

gantenerumab cannot be excluded. Therefore, the participants will be closely monitored during injection and for 24 hours after treatment, and medications for the treatment of hypersensitivity reactions will be available. Overall, based on previous studies with gantenerumab and the careful monitoring of safety parameters within this study, the risks for the participants in this study are considered acceptable.
No therapeutic benefit is anticipated for the participants participating in this study. The results from this study may guide the future development of gantenerumab for the treatment of patients with AD.

Where is the study run from?
Huashan Hospital Affiliated to Fudan University (China)

When is the study starting and how long is it expected to run for?
June 2020 to October 2021

Who is funding the study?
Genentech, Inc. (USA)

Who is the main contact?
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Contact information

Type(s)
Public

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
YP40254

Study information

Scientific Title

A single-center, open-label, Phase I study to investigate the pharmacokinetics, safety, and tolerability of gantenerumab in healthy Chinese participants following single subcutaneous administration of a high-concentration liquid formulation in the abdomen

Study objectives
The aim is to investigate the pharmacokinetics, safety, and tolerability of gantenerumab in healthy Chinese participants following a single subcutaneous administration of a high-concentration liquid formulation in the abdomen.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/01/2021, Ethics Review Committee of Huashan Hospital Affiliated to Fudan University (c/o Caihong Li, Office of Scientific Research Office, 10th Floor, Outpatient Clinic, No. 12 Middle Wulumuqi Road, Jing 'an District, Shanghai, China; +86 (0)21 52888921; licaihong199505@163.com), ref: 2020 Review No. 1208

Study design
Single-center open-label Phase I study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Pharmacokinetics, safety, and tolerability of gantenerumab

Interventions
The only arm in the YP40254 study is the treatment arm. Participants will be administered with 510 mg gantenerumab subcutaneous (SC) in the abdominal area. Participants will be confined at the study site from the time of check-in (Day -1) until clinic discharge on Day 3 (at least 48 hours after study drug administration). On day one, participants will receive a single SC dose of 510 mg of gantenerumab HCLF administered as two injections (2 × 255 mg [1.7 ml]).

Intervention Type
Drug

Phase
Phase I

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

Primary outcome(s)
Pharmacokinetics:
Plasma concentration of gantenerumab measured using enzyme-linked immunosorbent assay (ELISA) at pre-dose, Day 1, 2, 3, 4, 5, 6, 7, 8, 12, 21, 29, 43, 64 and 85

Added 15/09/2022: Area under the concentration–time curve of gantenerumab measured using noncompartmental analysis from time 0 to infinity (AUC[0-inf]) at pre-dose, Day 1, 2, 3, 4, 5, 6, 7, 8, 12, 21, 29, 43, 64 and 85

Safety:
1. Nature, incidence, severity and causal relationship of adverse events (AEs) recorded through case report form (CRF) during the AE reporting period (defined as from screening to 85 days after the dose of study drug)
2. Local pain assessed using the visual analog scale (VAS) and verbal rating scale (VRS) at the following timepoint: after first needle insertion, immediately post-dose (second injection), 5 minutes, 10 minutes, 20 minutes, 1 hour, 6 hours, 24 hours and 48 hours post-dose (and at additional regular intervals at the investigator's discretion if an adverse reaction associated with local tolerability and pain is observed)
3. Incidence of injection site reactions (ISRs) recorded through the CRF during the AE reporting period (defined as from screening to 85 days after the dose of study drug)

Immunogenicity:
Anti-drug antibodies (ADAs) to gantenerumab measured using ELISA on baseline and Day 85

Key secondary outcome(s))
Added 15/09/2022:
1. Area under the concentration–time curve of gantenerumab measured using noncompartmental analysis from time 0 to 672 hours [AUC(0-672)], at pre-dose, Day 1, 2, 3, 4, 5, 6, 7, 8, 12, 21, 29, 43, 64 and 85
2. Area under the concentration–time curve of gantenerumab from time 0 to the time of the last quantifiable concentration [AUC(0-last)] measured using noncompartmental analysis at pre-dose, Day 1, 2, 3, 4, 5, 6, 7, 8, 12, 21, 29, 43, 64 and 85
3. Apparent terminal elimination half-life (t1/2) of gantenerumab measured using noncompartmental analysis at pre-dose, Day 1, 2, 3, 4, 5, 6, 7, 8, 12, 21, 29, 43, 64 and 85
4. Apparent systemic clearance (CL/F) after SC dosing of gantenerumab measured using noncompartmental analysis at pre-dose, Day 1, 2, 3, 4, 5, 6, 7, 8, 12, 21, 29, 43, 64 and 85
5. Apparent volume of distribution following SC dosing of gantenerumab based on the terminal phase (Vz/F) measured using noncompartmental analysis at pre-dose, Day 1, 2, 3, 4, 5, 6, 7, 8, 12, 21, 29, 43, 64 and 85
6. Time to maximum observed plasma concentration (tmax) of gantenerumab measured using noncompartmental analysis at pre-dose, Day 1, 2, 3, 4, 5, 6, 7, 8, 12, 21, 29, 43, 64 and 85
7. Apparent terminal rate constant (λz) of gantenerumab measured using noncompartmental analysis at pre-dose, Day 1, 2, 3, 4, 5, 6, 7, 8, 12, 21, 29, 43, 64 and 85

Completion date
30/10/2021

Eligibility

Key inclusion criteria
1. Healthy Chinese male and female subjects who are 18 to 60 years of age, inclusive, at the time of signing informed consent form (ICF)
2. Healthy status is defined by the absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead electrocardiogram (ECG), hematology, blood chemistry, coagulation, serology, and

urinalysis. Some medical conditions are allowed that are well controlled by stable medication.
3. A body mass index (BMI) between 18.0 and 30.0 kg/m², inclusive
4. A body weight between 50 to 100 kg, inclusive
5. For women of reproductive potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures as defined below:
5.1. Women must remain abstinent or use contraceptive methods that result in a failure rate of <1% per year for at least 17 weeks after dosing.
5.2. A woman is considered to be of reproductive potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of reproductive potential may be adapted for alignment with local guidelines or requirements.
5.3. Examples of contraceptive methods that result in a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
9. Able to participate and willing to give written informed consent and to comply with the study restrictions

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
20

Key exclusion criteria
1. History of any clinically significant gastrointestinal, renal, hepatic, broncho-pulmonary, neurological, psychiatric, cardiovascular, endocrinological, hematological or allergic disease, metabolic disorder, cancer, or cirrhosis
2. History or suspicion of drug abuse and/or drug addiction
3. History or suspicion of alcohol abuse and/or alcohol addiction. Consumption of alcohol will not be allowed from 48 hours before dosing until the end of the residential period (Day 3) and should be limited to a maximum of 14 drinks per week for males and 7 drinks per week for females (1 drink = 12 g of pure alcohol) during the out-clinic period until follow-up.
4. Smokers who smoke more than 10 cigarettes per day or an equivalent amount of tobacco as determined by history. Healthy volunteers must be able to abstain from smoking from 48 hours

before dosing until the end of the residential period (Day 3).
5. Pregnant or breastfeeding, or intending to become pregnant during the study or within 17 weeks after the last dose of study drug
6. Positive serum pregnancy test result at screening or Day –1 for women of childbearing potential
7. Known human immunodeficiency virus (HIV) infection or positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or HIV-1 antibody
8. Any familial history of early onset of AD
9. Participants who are >49 years of age with a MoCA score lower than 26
10. Confirmed (may use an average of ≤3 blood pressure measurements), supine systolic blood pressure (SBP) <90 mmHg or >140 mmHg or diastolic blood pressure (DBP) <50 mmHg or >90 mmHg at screening or Day –1
11. Pulse rate (PR) >90 beats per minute or <45 beats per minute (at screening only)
12. History or presence of clinically significant ECG abnormalities (e.g., PQ/PR interval > 220 milliseconds, Fridericia's correction [QTcF] > 450 milliseconds) or cardiovascular disease (e.g., cardiac insufficiency, coronary artery disease, cardiomyopathy, congestive heart failure, family history of congenital long QT syndrome, family history of sudden death)
13. Use of prohibited medications or herbal remedies
14. Prior administration of gantenerumab
15. Clinically significant abnormalities (as judged by the investigator) in laboratory test results (including complete blood count, chemistry panel, and urinalysis)
16. Any major illness within 1 month before the screening examination or any febrile illness within 1 week prior to screening and up to the first administration of study drug 17. Impaired hepatic function as indicated by screening AST or ALT ≥3 × or total bilirubin ≥2 × the upper limit of normal (ULN)
18. Participation in an investigational drug medicinal product or medical device study within 30 days before dosing or within seven times the elimination half-life, whichever is longer
19. Donation of blood over 500 ml within 3 months before screening, for the duration of the study, and until 1 year after dosing
20. Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study
21. Any clinically relevant history of hypersensitivity or allergic reactions, either spontaneous or following drug administration, or exposure to foods or environmental agents
22. Known hypersensitivity to gantenerumab or to any of the excipients in the gantenerumab formulation
23. Any abnormal skin conditions or potentially obscuring tattoos, pigmentation, or lesions in the area intended for SC injection
24. Evidence of clinically significant brain magnetic resonance imaging (MRI) findings (as judged by the investigator), including lacunar infarct, territorial infarct or macroscopic hemorrhage, 3 microbleeds or areas of leptomeningeal hemosiderosis (not localized in the same area), or deep white matter lesions corresponding to an overall Fazekas score of ≥ 2
25. Claustrophobia, as well as the presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan

Date of first enrolment
02/06/2021

Date of final enrolment
13/06/2021

Locations

Countries of recruitment
China

Study participating centre
Huashan Hospital Affiliated to Fudan University
China
200040

Sponsor information

Organisation
Genentech, Inc.

Funder(s)

Funder type
Industry

Funder Name
Genentech

Alternative Name(s)
Genentech, Inc., Genentech USA, Inc., Genentech USA

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available due to participant-level data not being a regulatory requirement for Phase I studies.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			15/09/2022	No	No