# Summary of Clinical Trial Results

## A study to look at whether gantenerumab works and how safe it is in people with early Alzheimer's disease (GRADUATE I)

See the end of the summary for the full title of the study.

## About this summary

### Contents of the summary



This is a summary of the results of a clinical trial (called a 'study' in this document) – written for:

- Members of the public and
- People who took part in the study

The GRADUATE I study started in June 2018 and finished in December 2022.

This summary of the study was written after the study ended and represents the final study results, which have been fully analysed.

No single study can tell us everything about the risks and benefits of a medicine. It takes lots of people in many studies to find out everything we need to know. The results from this study may be different from those seen in other studies with the same medicine.

**This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.**

### Glossary

- Amyloid protein = a type of protein found in higher amounts in the brains of people with Alzheimer's disease. These proteins can come together to form plaques (or "amyloid plaques") that can damage the brain
- ARIA-E = build-up of fluid or swelling in the brain seen on brain scans, that can occur with or without symptoms
- ARIA-H = bleeding in the brain seen in brain scans, that can occur with or without symptoms
- Care partner = family member, friend or paid helper who regularly looks after someone with a condition
- CDR-SB (Clinical Dementia Rating–Sum of Boxes) = a test to measure how severe the symptoms of dementia are
- Early Alzheimer's disease = mild cognitive impairment due to Alzheimer's disease or mild dementia due to Alzheimer's disease
- Hemosiderin = a substance detected in brain scans that show areas of bleeding
- Mild dementia due to Alzheimer's disease = a stage of the disease when people may still

function independently, but they have significant changes in memory, thinking and problem-solving that affect their day-to-day activities
- Mild cognitive impairment = when people have small changes in memory, thinking and problem-solving but these do not yet significantly affect their day-to-day activities

## Thank you to the people who took part in this study

The people who took part in this study, and their families and care partners, have helped researchers to answer important questions about Alzheimer's disease and the experimental medicine studied – gantenerumab, such as whether gantenerumab worked and was safe for people living with early Alzheimer's disease.

## Key information about this study

- The study (known as GRADUATE I) compared a treatment being investigated, called gantenerumab, with a placebo (a dummy treatment that looked like gantenerumab but had no medicine in it), in people with early Alzheimer's disease.
- GRADUATE I was done to see whether the study medicine, gantenerumab, was effective and safe in treating people living with Alzheimer's disease. Researcher doctors compared the study medicine with a placebo in people with early Alzheimer's disease.
- A total of 985 people, aged between 50 and 90 years, living with early Alzheimer's disease, from 16 countries, took part in the GRADUATE I study.
- Out of the 985 people who took part in the GRADUATE I study, 485 people were randomly chosen to receive a placebo and 499 people were randomly chosen to receive gantenerumab (one person who was due to take part in the study did not receive any treatment).
- The main finding from the GRADUATE I study was that gantenerumab was not effective, and therefore unlikely to help people with early Alzheimer's disease.
- For this reason, other studies that were also investigating gantenerumab were stopped early.
- A total of 41.6% of people (209 out of 503 people) taking gantenerumab had possible adverse reactions, compared to 16.6% of people (80 out of 481 people) taking the placebo. Most of the possible adverse reactions were well tolerated (meaning they were mild to moderate in severity) and the types of possible adverse reactions people experienced were similar to those seen in previous gantenerumab studies. A total of 2.6% of people (13 out of 503 people) taking gantenerumab had serious possible adverse reactions, compared to 1.2% of people (6 out of 481 people) taking the placebo.

# 1. General information about this study

## Why was this study done?

Studies have shown that people with Alzheimer's disease have abnormal levels of amyloid protein, which gathers together to form small clusters (oligomers) and clumps (amyloid plaques) in the brain.

Alzheimer's disease progresses in stages, but everyone experiences it differently. Symptoms progress from mild cognitive impairment due to Alzheimer's disease in the early stages, through to dementia that severely affects daily living in the later stages of the disease.

The GRADUATE I study was done to test whether the study medicine, called gantenerumab, would be effective and well tolerated in slowing down the worsening of symptoms in people with early Alzheimer's disease, and whether it would remove significant amounts of amyloid protein.

## What was the study medicine?

A medicine called 'gantenerumab' was tested in the GRADUATE I study.

- Gantenerumab is a type of monoclonal antibody, meaning that it is a kind of medicine that helps the immune system to specifically recognise and remove the harmful amyloid protein that is linked to Alzheimer's disease.
- Gantenerumab was given to people by injection at home or at a study site.

Gantenerumab was compared to a 'placebo'.

- The placebo looked the same as gantenerumab but did not contain any real medicine. This means it had no medicine-related effect on the body.
- Researchers compared gantenerumab to a placebo so they could show which benefits or adverse reactions were actually caused by the medicine.
- People who received placebo were considered a "control group". Comparing the control group to the group receiving gantenerumab helps better understand if the benefits and possible adverse reactions seen in people receiving gantenerumab were caused by the medicine and not likely to have happened by chance.

## What did researchers want to find out?

- Previous studies suggested that gantenerumab was more effective at slowing down the worsening of symptoms in people with early Alzheimer's disease, rather than those with more advanced Alzheimer's disease.
- Researchers did this study to compare gantenerumab with a placebo – to see how well gantenerumab worked if given to people for up to 2 years and 3 months (the study was originally set up to run for 2 years, but this was increased to 2 years and 3 months in case there had been any disruption related to the Covid-19 pandemic). (See section 4 "What were the results of the study?").
- They also wanted to find out how safe gantenerumab was – by checking how many people who received gantenerumab had possible adverse reactions and seeing how serious these were, when compared with the possible adverse reactions seen in people who received placebo.

## What kind of study was this?

This study was a 'Phase 3' study. This means that gantenerumab had been tested in a smaller number of people with Alzheimer's disease before the start of this study

In this study, a larger number of people with Alzheimer's disease either took gantenerumab or a placebo – this was to find out how gantenerumab affects how quickly the symptoms progress in people with early Alzheimer's disease and about the safety of gantenerumab. This study was done to help understand if gantenerumab should be approved for doctors to give to people living with early Alzheimer's disease.

The study was 'randomised'. This means that it was decided by chance if people were receiving the placebo or gantenerumab – like tossing a coin. Randomly choosing which medicine people take, makes it more likely that the types of people in both groups (for example, age, race) will be a similar mix. Apart from the exact medicines being tested in each group, all other aspects of care were the same between the groups.

This study was also 'double-blinded'. This means that neither the people involved in the study nor the researchers knew who was given placebo or gantenerumab. This was done to make sure that the study results were not influenced in any way.

This study looked at the results from people taking a placebo and compared these with the results from people taking gantenerumab.

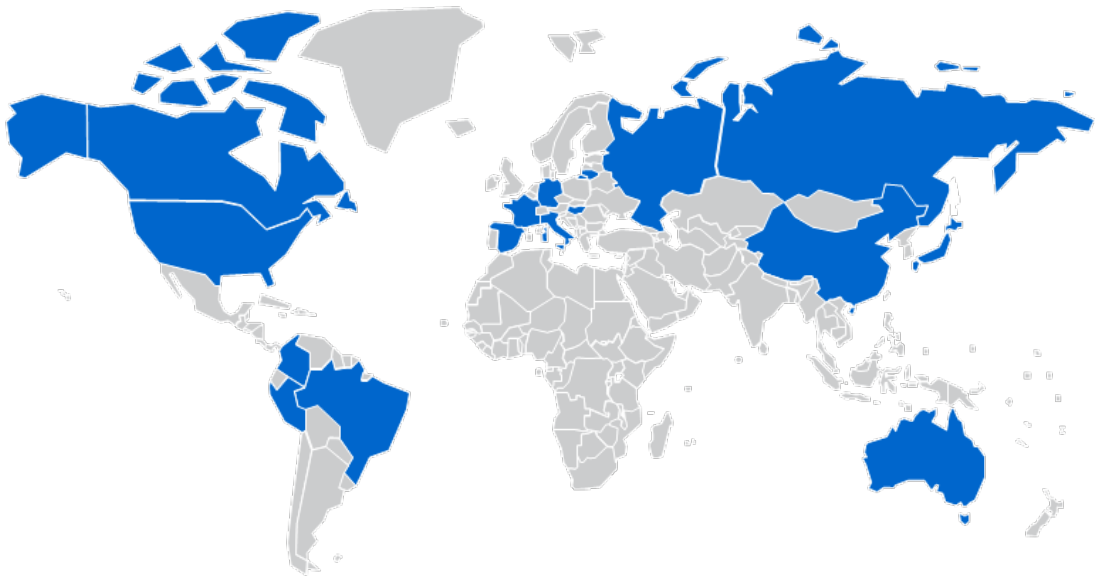
GRADUATE I was conducted at the same time as a separate identical study called GRADUATE II. Different people completed each study.

## When and where did the study take place?

GRADUATE I started in June 2018 and finished in December 2022. This summary was written after the study had ended.

It was conducted in 172 study centres across 16 countries in Asia, Europe, North America, South America, and Australia.

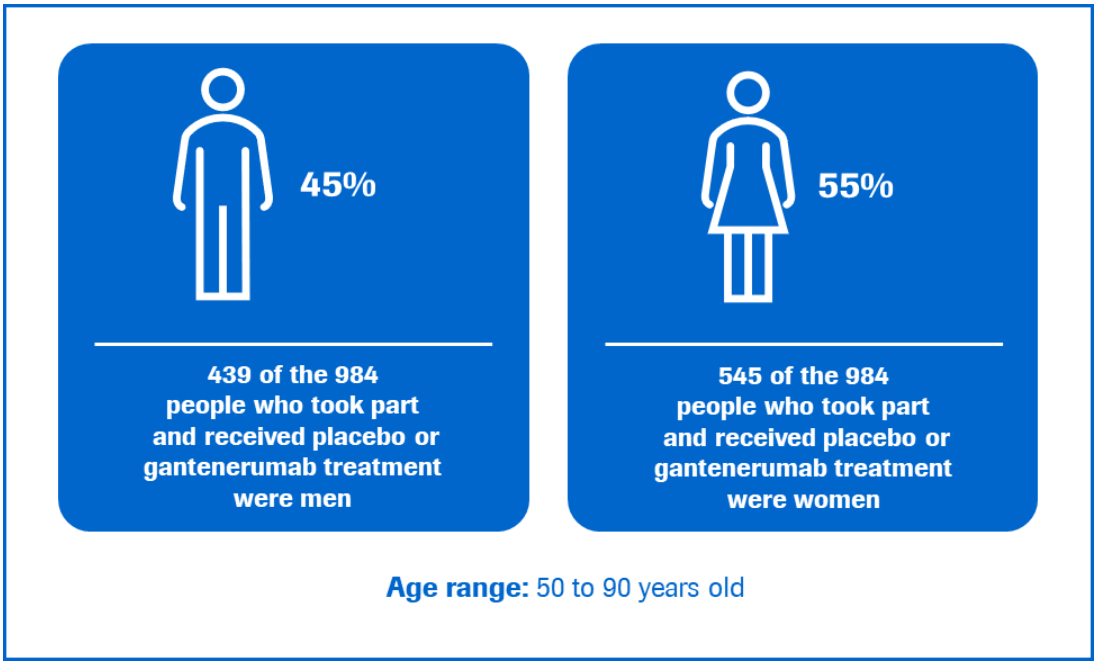
The following map shows the countries where any part of this study took place. The countries were:



- Australia
- Brazil
- Canada
- Colombia
- Mainland China
- Republic of China
- France
- Germany
- Hungary
- Italy
- Japan
- Lithuania
- Peru
- Russian Federation
- Spain
- United States

## 2. Who took part in this study?

A total of 985 adults with early Alzheimer's disease took part in the GRADUATE I study. Of these, 984 people received either placebo or gantenerumab during the study (one person who did not meet all study eligibility criteria was mistakenly enrolled and was withdrawn before receiving any treatment).




People could take part in the study if they:

- were aged between 50 and 90 years at the beginning of the study;
- had memory loss and were diagnosed with early Alzheimer's disease, including people with mild cognitive impairment due to Alzheimer's disease (also known as prodromal Alzheimer's disease) or mild dementia due to Alzheimer's disease (also known as mild Alzheimer's disease);
- had high levels of amyloid in the brain, confirmed by one of the following tests:
    - an analysis of spinal fluid collected from a needle inserted between two spinal bones in the lower back; or
    - a brain scan;
- were in frequent contact with a dedicated study partner who could provide information on the person's progress.

People could not take part in the study if they:

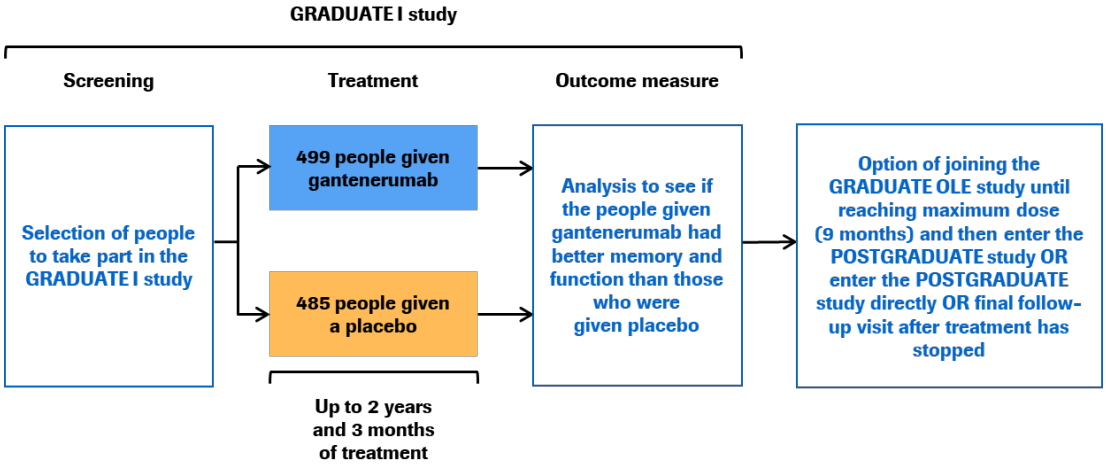
- had other diseases caused by abnormal function of their brain;
- had other diseases such as cancers, as well as heart, liver, immune and metabolic diseases that were not already well controlled.

## 3. What happened during the study?

### GRADUATE I study

During the GRADUATE I study, people were split randomly into two groups and given either placebo or gantenerumab. Neither the people taking part in the study nor the researchers involved knew which group was receiving a placebo and which group was receiving gantenerumab.

The dose of gantenerumab was slowly increased over a period of 9 months up to the maximum dose that the researchers wanted to study. This slow increase in dose was done to reduce the chances of people experiencing ARIA, an adverse reaction associated with anti-amyloid antibody treatments like gantenerumab. People went through safety checks to make sure that the dose could be safely increased.




### GRADUATE open-label extension (OLE) part or POSTGRADUATE study

People who finished the GRADUATE studies were invited to take part in the GRADUATE OLE study until reaching maximum dose (9 months) and then enter the POSTGRADUATE study, or enter the POSTGRADUATE study directly, or go back to their study centre for a final visit up to 1 year (50 weeks) after they stopped treatment.

'Open label' means that all the people in the study received gantenerumab and knew that they were doing so.

This study was also a 'rollover' study. This means that the people involved in the study had previously taken part in another study (either GRADUATE I or GRADUATE II), and were able to continue their involvement into this new study.

The POSTGRADUATE study was done to see if gantenerumab would still be safe after a longer period of time.

Results from the POSTGRADUATE study will be shared in a separate summary.

## 4. What were the results of the study?

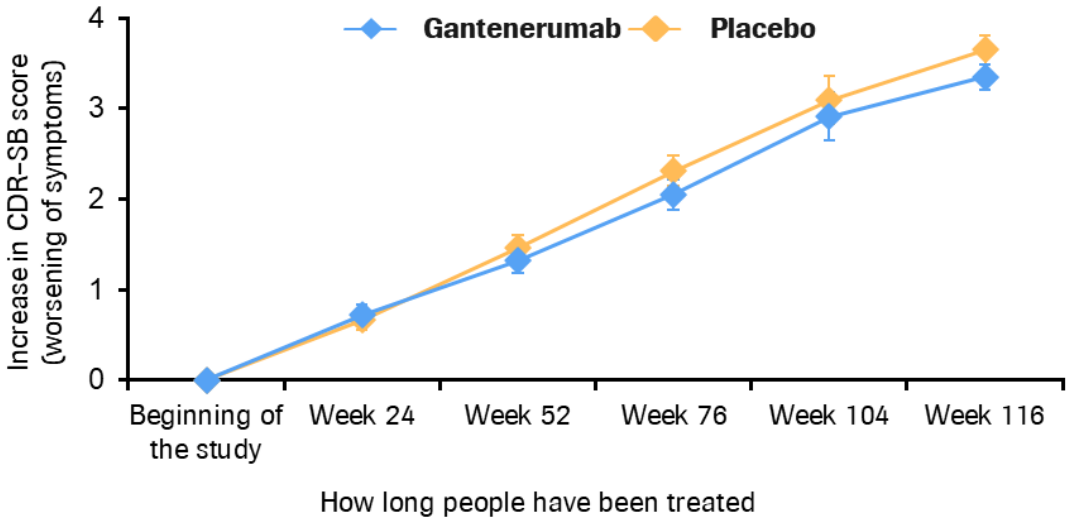
### **Question 1:** Does gantenerumab slow down the worsening of symptoms when given to people with early Alzheimer's disease for up to 2 years and 3 months?

Research doctors used a test called the Clinical Dementia Rating–Sum of Boxes (CDR-SB) test to measure the change in people's Alzheimer's disease symptoms over 2 years and 3 months.

The CDR is a questionnaire that measures how severe the symptoms of dementia are. It looks at symptoms of dementia in six categories (memory; orientation; judgement and problem-solving; community affairs; home and hobbies; and personal care). Each category is scored on a scale from 0 (no symptoms) to 3 (severe symptoms). Scores are added together to give a total out of 18, with higher scores meaning worse symptoms.

The figure below shows the changes in CDR-SB score in people treated with placebo or gantenerumab over 2 years and 3 months (Week 116 = 2 years and 3 months), until the study ended.

**There were very small differences not considered meaningful in the changes in CDR-SB scores in people who were given gantenerumab for up to 2 years and 3 months, compared with those who were given placebo.**




Researchers also used a range of other tests to measure changes in the Alzheimer's disease symptoms in people taking part in the study. This included information given by the care partners about the memory and thinking skills of the people in the study through questionnaires that were completed during clinic visits.
Three additional tests used to measure the change in symptoms in people with Alzheimer's disease during the study were:

1. The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 13) = an assessment of a person's mental function and abilities including attention and

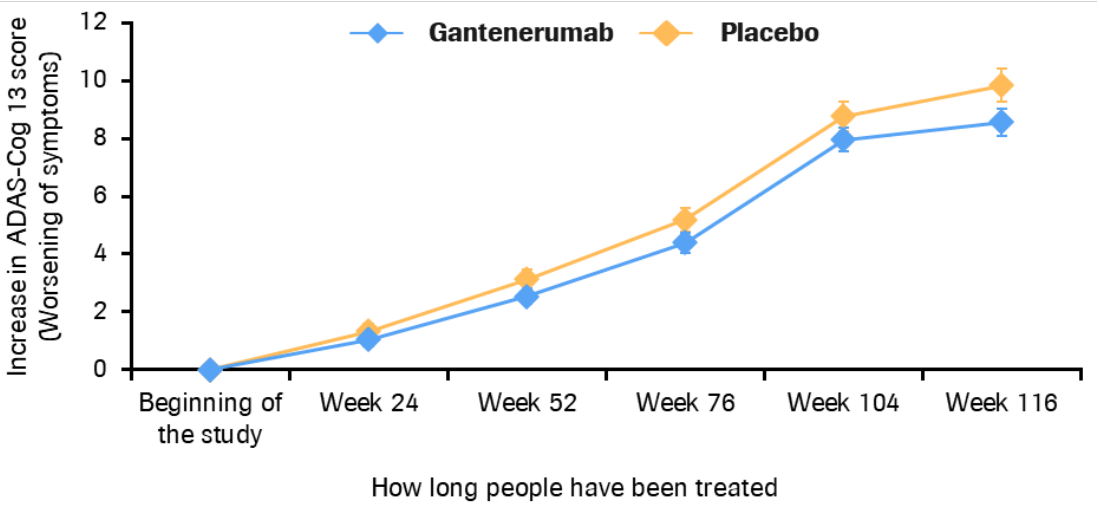
concentration, word recall and memory. Scores are added together to give a total out of 85, with higher scores meaning worse symptoms.

2. The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) = a questionnaire that looks at a person's ability to complete 23 activities of daily living, such as eating, getting dressed, using the telephone and managing personal finances. Scores are added together to give a total out of 78, with lower scores meaning worse symptoms.

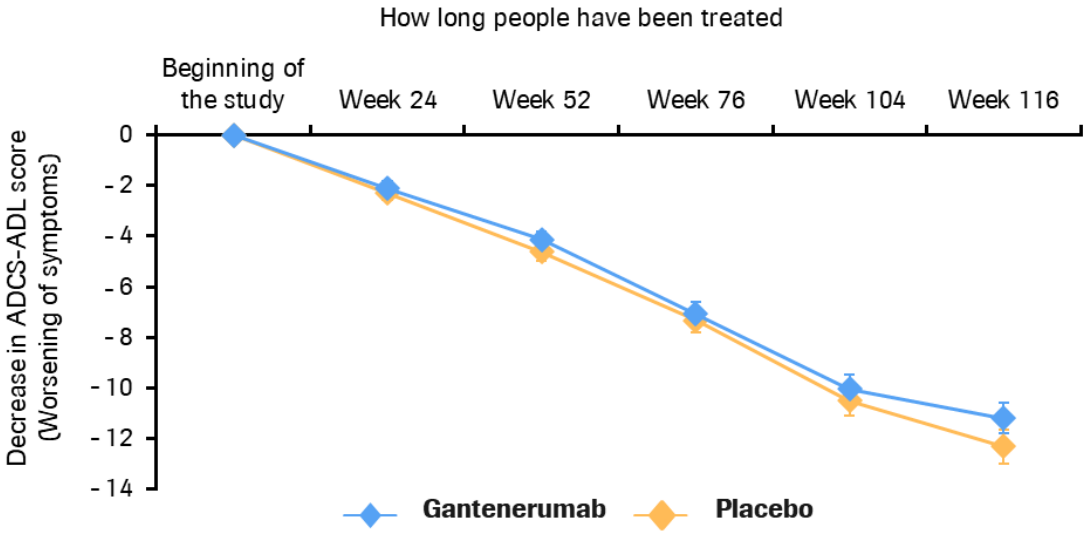
3. The Functional Activities Questionnaire (FAQ) = a way to measure a person's ability to carry out more complex activities of daily living, such as managing personal finances and preparing balanced meals. Scores are added together to give a total out of 30, with higher scores indicating worse symptoms.

Even when looking at other tests there were no differences between the placebo and gantenerumab groups over time.

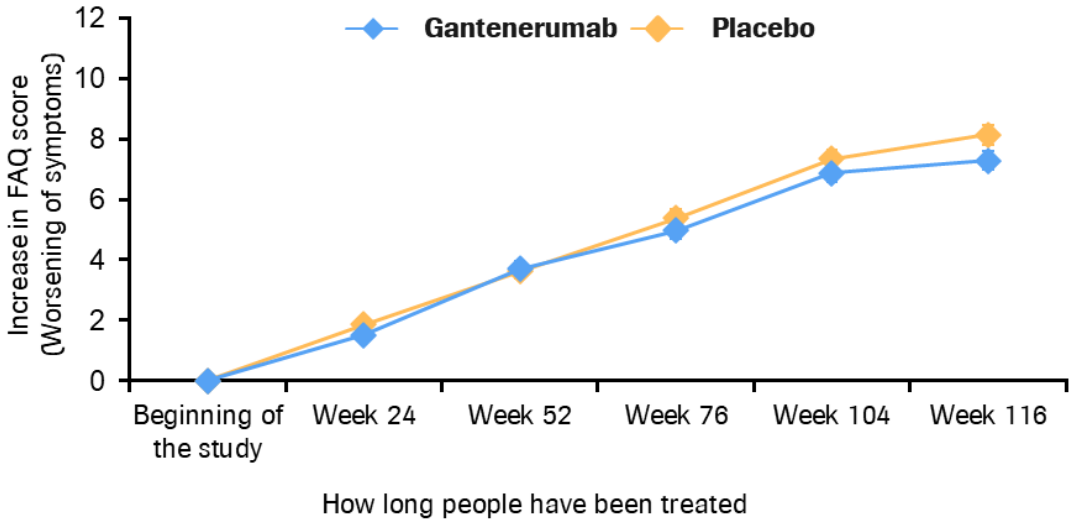
**There were very small differences not considered meaningful in the changes in ADAS-Cog 13 scores in people who were given gantenerumab for up to 2 years and 3 months, compared with those who were given placebo.**



**There were very small differences not considered meaningful in the changes in ADCS-ADL scores in people who were given gantenerumab for up to 2 years and 3 months, compared with those who were given placebo.**




**There were very small differences not considered meaningful in the changes in FAQ scores in people who were given gantenerumab for up to 2 years and 3 months, compared to those who were given placebo.**

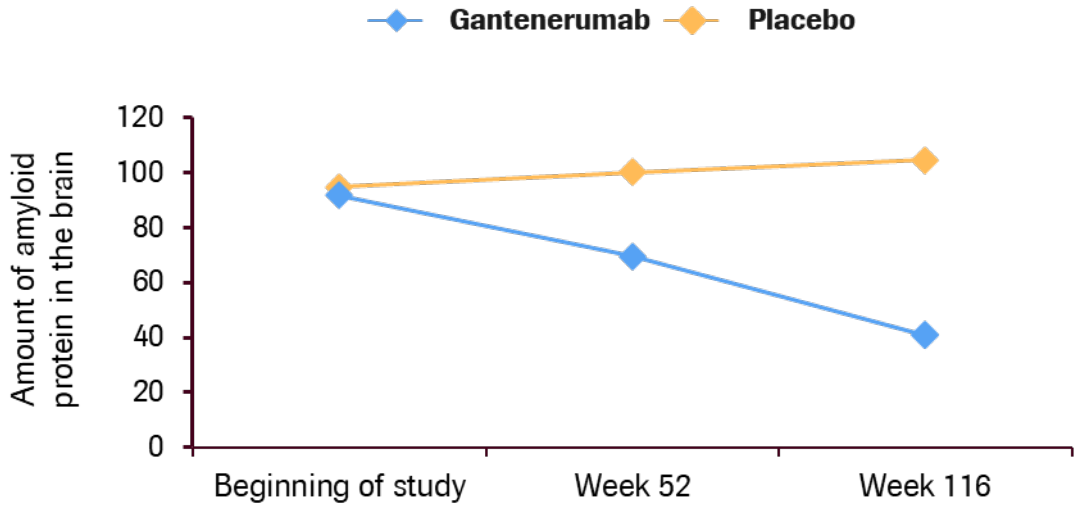


## **Question 2:** How does gantenerumab affect the amount of abnormal amyloid protein in the brain when given to people with early Alzheimer's disease for up to 2 years and 3 months?

Researchers think treatments such as gantenerumab work by reducing the amount of the abnormal amyloid protein in the brains of people with Alzheimer's disease.

A total of 161 people who took part in GRADUATE I also took part in a smaller substudy looking at the change in the amount of amyloid protein in the brain over time when being given gantenerumab.

**Although amyloid was removed from the brain in people after 2 years and 3 months of being given gantenerumab, most people still had substantial levels of amyloid protein at the end of the study.**




Note: The amount of amyloid protein shown in this figure is the mean average of the data collected in units called centiloids.

## **Question 3:** How safe was gantenerumab when given to people with early Alzheimer's disease for up to 2 years and 3 months?

Another piece of information that researchers collected was about how safe gantenerumab was when given for up to 2 years and 3 months, the duration of the GRADUATE I study.

- The study showed that gantenerumab was well tolerated in this study at the dose studied.
    - As reported in other studies of gantenerumab, ARIA was more likely to occur in people receiving gantenerumab treatment compared to placebo.
    - The study drug was given as an injection under the skin and more people who received gantenerumab than placebo reported reactions at the site of the injection such as redness, rash or swelling.
    - Other types of possible adverse reactions reported during this study in people who received gantenerumab were similar to those reported in people who received placebo (for example, headaches and falls)

Please see the next section (Section 5) for full details of the possible adverse reactions people had during the GRADUATE I study.

This section only shows the key results from this study. You can find information about all other results on the websites at the end of this summary (see section 8).

## 5. What were the possible adverse reactions?

Possible adverse reactions are medical problems (such as feeling dizzy) that happened during the study.

- They are described in this summary because the study doctors believed these possible adverse reactions were related to the treatments in the study.
- Not all of the people in this study had all of the possible adverse reactions.
- Possible adverse reactions may be mild to very serious and can be different from person to person.
- It is important to be aware that the possible adverse reactions reported here are from this single study. Therefore, the possible adverse reactions shown here may be different from those seen in other studies.
- Serious and common possible adverse reactions are listed in the following sections.

### Serious possible adverse reactions

A possible adverse reaction is considered 'serious' if it is life-threatening, needs hospital care, or causes lasting problems.

During the GRADUATE I study, 13 of 503 people (2.6%) who were given gantenerumab and 6 of 481 people (1.2%) who were given placebo had at least one serious possible adverse reaction.

The table below shows the most frequent serious possible adverse reactions (considered to be related to the study treatment by the study doctors) across both placebo and gantenerumab groups. Some people had more than one serious possible adverse reaction – this means that they are included in more than one row in the table.

**Serious possible adverse reactions that study doctors considered may have been related to the study treatment**

| Serious possible adverse reactions reported in this study | People who received placebo | People who received gantenerumab |
|---|---|---|
| ARIA-E | **0%** (0 out of 481) | **1.4%** (7 out of 503) |
| ARIA-H | **0%** (0 out of 481) | **0.4%** (2 out of 503) |
| Not able to speak or write and not able to understand spoken or written words (aphasia) | **0%** (0 out of 481) | **0.2%** (1 out of 503) |
| Decreased oxygen in brain (cerebral ischemia) | **0.2%** (1 out of 481) | **0%** (0 out of 503) |
| Seizure | **0%** (0 out of 481) | **0.2%** (1 out of 503) |
| Damage to the brain | **0%** (0 out of 481) | **0.2%** (1 out of 503) |
| Partial blindness (temporary) | **0%** (0 out of 481) | **0.2%** (1 out of 503) |
| Quick, uncontrollable jerking | **0%** (0 out of 481) | **0.2%** (1 out of 503) |
| Decreased oxygen in a part of the brain called “thalamus” | **0%** (0 out of 481) | **0.2%** (1 out of 503) |
| Unusual heartbeat (atrial fibrillation) | **0%** (0 out of 481) | **0.2%** (1 out of 503) |
| Heart attack (myocardial infarction) | **0.2%** (1 out of 481) | **0%** (0 out of 503) |
| Stomach ache | **0%** (0 out of 481) | **0.2%** (1 out of 503) |
| Bleeding in the large intestine | **0.2%** (1 out of 481) | **0%** (0 out of 503) |
| Anxiety | **0.2%** (1 out of 481) | **0%** (0 out of 503) |
| Confusion | **0%** (0 out of 481) | **0.2%** (1 out of 503) |
| Slowing down of mental and physical activities | **0%** (0 out of 481) | **0.2%** (1 out of 503) |
| Blood clot in lungs (pulmonary embolism) | **0.2%** (1 out of 481) | **0.2%** (1 out of 503) |
| Build-up of blood between the skull and the surface of the brain | **0.2%** (1 out of 481) | **0%** (0 out of 503) |
| Sudden and severe increase in blood pressure | **0%** (0 out of 481) | **0.2%** (1 out of 503) |

A total of 13 people (3 people taking gantenerumab and 10 people taking the placebo) died during the study data collection period. None of the deaths that occurred were considered by study doctors to be caused by treatment with gantenerumab.

During the study, some people decided to stop taking their medicine because of possible adverse reactions:

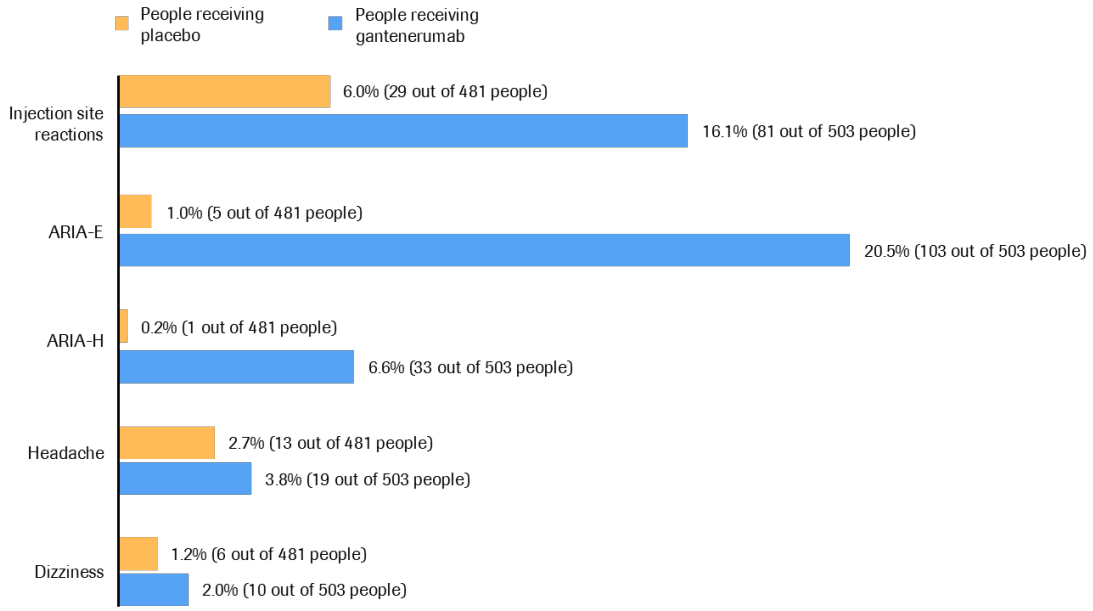
- In the gantenerumab group, 36 out of 497 people (7.2%) stopped taking their medicine.
- In the placebo group, 3 out of 476 people (0.6%) stopped taking their medicine.

People most commonly had to stop treatment because of ARIA-H. Not all people who had an ARIA-H had to stop treatment.

## Most common possible adverse reactions

The most common possible adverse reactions are shown in the following figure – these are the 5 most common possible adverse reactions across both treatment groups. Some people had more than one possible adverse reaction – this means that they are included in more than one row in the table.

**Most common possible adverse reactions in the study**




An injection site reaction is a reaction at the place where a medicine is injected under the skin, and can include redness, rash or swelling.

Amyloid-related imaging abnormalities (ARIA) are findings in the brain during magnetic resonance imaging (MRI) scans, sometimes experienced by people receiving gantenerumab

and drugs similar to gantenerumab. These can occur with and without the person having any symptoms.

There are two types of ARIA: 1) ARIA-E, which involves transient build-up of fluid in the brain, and 2) ARIA-H, which is small bleeding in or on the surface of the brain.

In total, eight people receiving placebo and 119 receiving gantenerumab experienced an ARIA-E. New ARIA-H were found in 59 people receiving placebo and in 118 people receiving gantenerumab. The graph above shows only those cases of ARIA-E and ARIA-H that the researchers considered met the reporting criteria specified in the study.

### Other possible adverse reactions

You can find information about other possible adverse reactions (not shown in the sections above) on the websites listed at the end of this summary – see section 8.

## 6. How has this study helped research?

Gantenerumab was not effective as a treatment for people with early Alzheimer's disease because it did not slow down the progression of their Alzheimer's disease symptoms. These results helped researchers learn more about Alzheimer's disease and the link between removing amyloid from the brain and slowing down the progression of symptoms.

The information presented here is from a single study of 985 people with early Alzheimer's disease.

No single study can tell us everything about the risks and benefits of a medicine. It takes lots of people in many studies to find out everything we need to know. The results from this study may be different from other studies with the same medicine.

- **This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.**

## 7. Are there plans for other studies?

No other studies of gantenerumab are planned at this time.

## 8. Where can I find more information?

You can find more information about this study on the websites listed below:

- https://clinicaltrials.gov/ct2/show/results/NCT03444870
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-019895-66/results
- https://forpatients.roche.com/

If you would like to find out more about the results of this study, the full title of the relevant scientific paper is: Two Phase 3 Trials of Gantenerumab in Early Alzheimer's Disease.

If you would like to find out more about the results of the POSTGRADUATE study, please contact a representative at your local Roche office or visit the ForPatients platform using the web address above.

### Who can I contact if I have questions about this study?

If you have any further questions after reading this summary:

- Visit the ForPatients platform and fill out the contact form – https://forpatients.roche.com/en/trials/neurodegenerative-disorder/ad/efficacy-and-safety-study-of-gantenerumab-in-participants-with-e.html

- Contact a representative at your local Roche office.

If you took part in this study and have any questions about the results:

- Speak with the research doctor or staff at the study hospital or clinic.

If you have questions about your own treatment:

- Speak to the doctor in charge of your treatment.

### Who organised and paid for this study?

This study was organised and paid for by F. Hoffmann-La Roche Ltd who have their headquarters in Basel, Switzerland.

### Full title of the study and other identifying information

The full title of this study is: "A Phase III, Multicentre, Randomized, Double-blind, Placebo-controlled, Parallel-Group Efficacy and Safety Study of Gantenerumab in Patients With Early (Prodromal to Mild) Alzheimer's Disease".

The study is known as GRADUATE I.

- The protocol number for this study is: WN29922.
- The ClinicalTrials.gov identifier for this study is: NCT03444870.
- The EudraCT number for this study is: 2017-001364-38.