Summary of Clinical Trial Results

A study to look at whether long-term treatment with gantenerumab is safe in people with Alzheimer's disease (POSTGRADUATE)

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 (participants)

The POSTGRADUATE study started in January 2021. The study was stopped early in March 2023 because the medicine being studied did not work as well as expected in two other studies (called GRADUATE I and GRADUATE II studies) that were looking at the same medicine in people with early AD.

POSTGRADUATE was an extension study for participants who had previously completed the GRADUATE I and GRADUATE II studies. Some people who completed the GRADUATE I and GRADUATE II studies were able to enter the GRADUATE open-label extension study (OLE). The participants in the GRADUATE OLE had the opportunity to move to POSTGRADUATE study once this was open.

This summary of the study was written after the study was stopped and represents the results at the time the study was stopped, 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
- Early Alzheimer's disease = mild cognitive impairment due to Alzheimer's disease or mild dementia due to Alzheimer's disease
- 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
- 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
- Open-label study = a study where both study doctors and participants know the treatment which a person is receiving
- Study partner = someone who is directly involved in helping a person with a condition take part in a clinical study (this role can be performed by a family member or friend)

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 long-term treatment with gantenerumab was safe for people living with Alzheimer's disease. Since the study was stopped early, learnings from this study are limited.

Key information about this study

- The study (known as the POSTGRADUATE study) was an extension study which investigated a new medicine called gantenerumab in people with Alzheimer's disease who had previously completed either the GRADUATE I or GRADUATE II studies of gantenerumab. Some people who completed the GRADUATE I and GRADUATE II studies were able to enter the GRADUATE open-label extension study (OLE). The participants in the GRADUATE OLE had the opportunity to move to POSTGRADUATE study once this was open.
- The POSTGRADUATE study was done to see whether the study medicine, gantenerumab, was safe for people with Alzheimer's disease over a longer period of time for up to 4 years.
- The POSTGRADUATE study was stopped early, along with other studies investigating gantenerumab, because the main findings from two other studies looking at gantenerumab (GRADUATE I and GRADUATE II studies) showed that gantenerumab was not effective (unlikely to help people with early Alzheimer's disease).
- A total of 1381 people with Alzheimer's disease received gantenerumab in the POSTGRADUATE study.
- People taking part in POSTGRADUATE were from 28 countries out of the 32 countries across GRADUATE I and GRADUATE II.
- Out of these 1381 people, 705 people had previously received a placebo (a dummy treatment that looked like gantenerumab but had no medicine in it) and 676 people had previously received gantenerumab in either the GRADUATE I or GRADUATE II studies.
- A total of 153 out of 705 people (21.7%) who previously received a placebo in GRADUATE I or GRADUATE II had a possible adverse reaction considered to be related to gantenerumab compared to 121 out of 676 people (17.9%) who previously received gantenerumab in GRADUATE I or GRADUATE II. Most possible adverse reactions were well tolerated (meaning mild to moderate in severity), and the types of possible adverse reactions people experienced were similar to those seen in previous gantenerumab studies.

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 and II studies were 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.

The POSTGRADUATE study was done to test whether treatment with gantenerumab would be well tolerated when it was continued to be given over to people with Alzheimer's disease who had completed the GRADUATE I or GRADUATE II studies over a longer period of time. The study was stopped early when data from only up to 2 years and 6 months had been collected. The majority of people received gantenerumab for approximately 10 months on average.

What was the study medicine?

A medicine called 'gantenerumab' was tested in the POSTGRADUATE 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.

What did researchers want to find out?

Researchers did this study to see how safe gantenerumab was when given over a long period of time to people with Alzheimer's disease by checking how many people who previously received gantenerumab in the GRADUATE I and GRADUATE II studies had possible adverse reactions.

The main question that research doctors wanted to answer was:

- What are the possible adverse reactions of gantenerumab when given to people with Alzheimer's disease for up to 4 years?

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, it was planned that a large number of people with Alzheimer’s disease would be given gantenerumab – this was to investigate the possible adverse reactions of gantenerumab given for a long time.

This study was an ‘open label’ study. This means that both the people taking part in the study and the researchers knew all participants were receiving gantenerumab. This is different from GRADUATE I and GRADUATE II where people did not know whether they were taking the study medicine or a placebo. These studies are referred to as “double-blind” studies.

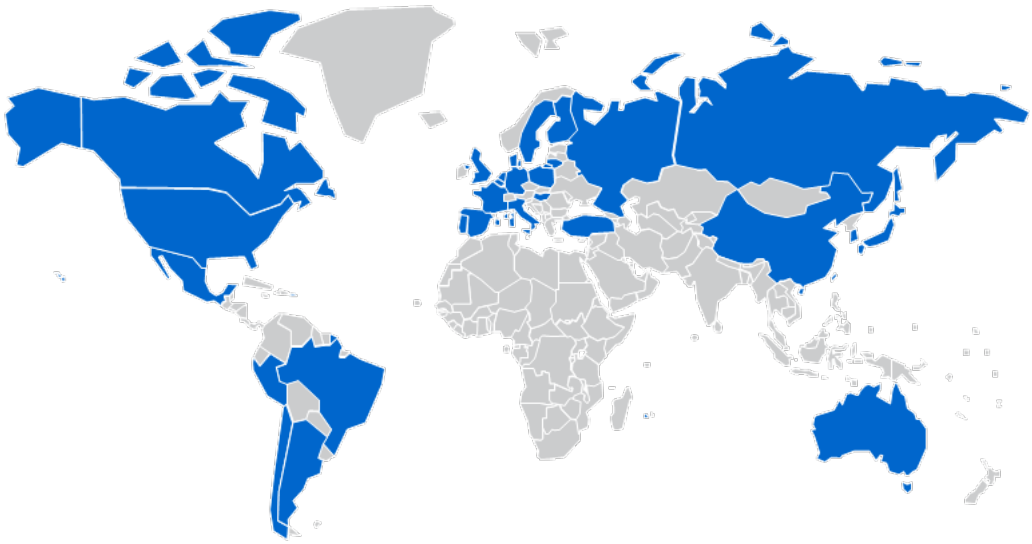
This study was a ‘rollover’ study. This means that only the participants that completed the previous related study, namely the GRADUATE I and GRADUATE II studies, were offered the opportunity to participate in the POSTGRADUATE study.

When and where did the study take place?

The POSTGRADUATE study started in January 2021 and was stopped early because gantenerumab did not work as well as expected in two other studies (called GRADUATE I and GRADUATE II studies) that were looking at gantenerumab in people with early Alzheimer's disease. This summary presents the results of the study up until March 2023.

This study took place at 258 study centres across 28 countries in Asia, Australia, Europe, North America, and South America.

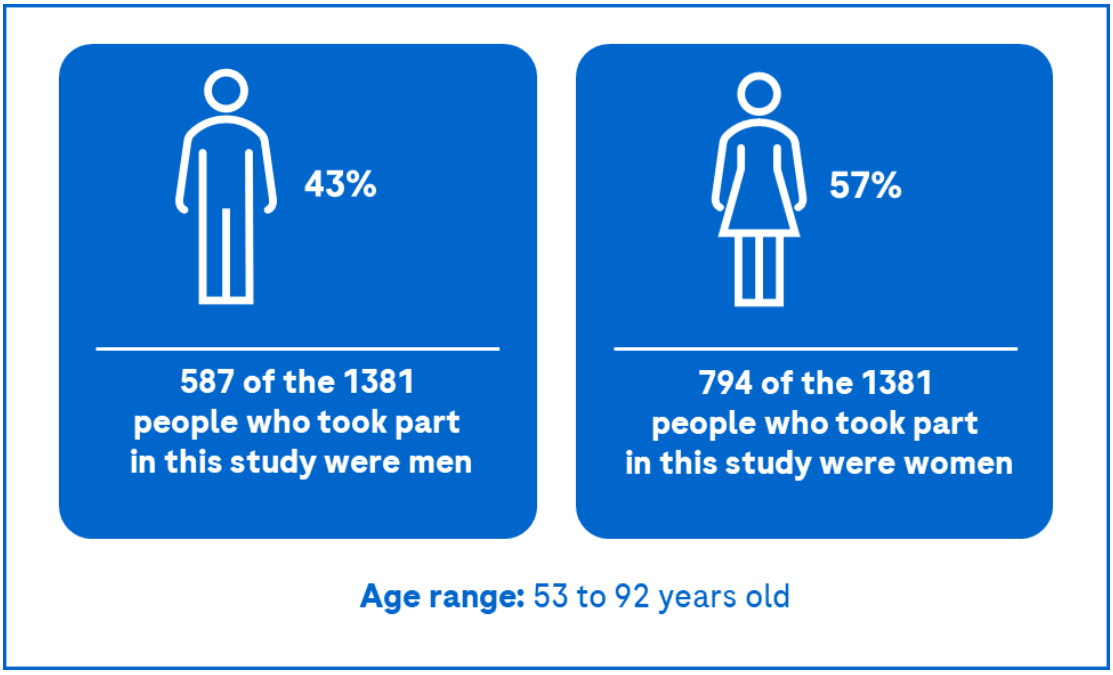
The following map shows the countries where any part of this study took place. The countries were:



- Argentina
- Australia
- Belgium
- Brazil
- Canada
- Chile
- China
- Denmark
- Finland
- France
- Germany
- Hungary
- Italy
- Japan
- Republic of Korea
- Lithuania
- Mexico
- Netherlands
- Peru
- Poland
- Portugal
- Russian Federation
- Spain
- Sweden
- Taiwan
- Turkey
- United Kingdom
- United States

2. Who took part in this study?

A total of 1381 adults with Alzheimer's disease took part in the POSTGRADUATE study and received gantenerumab during the study.



People could take part in the study if they:

- had completed the GRADUATE I or GRADUATE II studies, and did not discontinue the study medicine early;
- were in frequent contact with a dedicated study partner who could provide information on the person's progress;
- agreed not to donate blood for the duration of the study and for 1 year after completion of the study; and
- were willing and able to complete all parts of the study, either by themselves or with the help of a care partner.

People could not take part in the study if they:

- had not previously taken part in the GRADUATE I or GRADUATE II studies, or discontinued the study medicine early;
- had any medical conditions that the study doctors considered may affect the person's safety if they continued to receive the study medicine; or
- received any other investigational medicine other than the study medicine during or since completion of GRADUATE I or GRADUATE II.

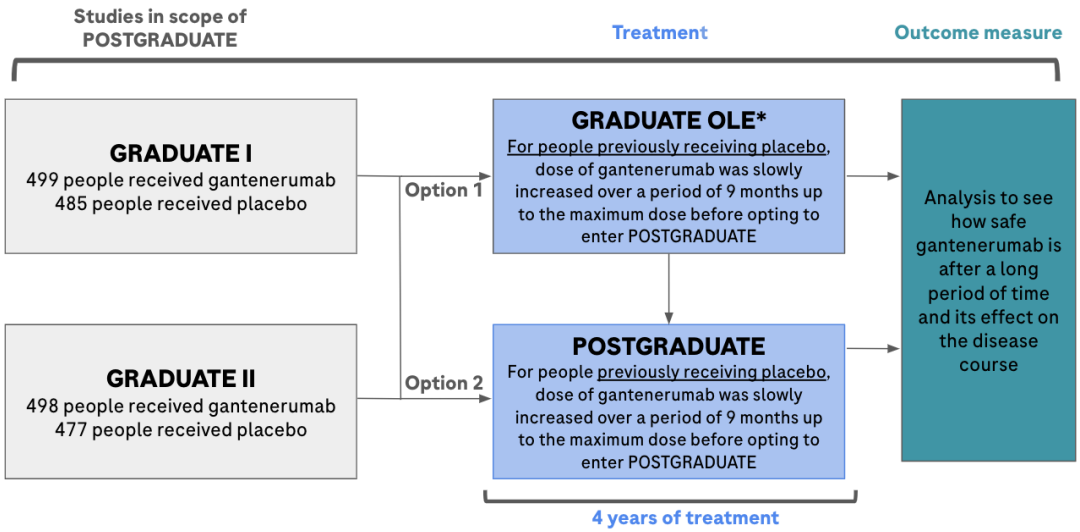
3. What happened during the study?

The POSTGRADUATE study was an extension study for people with Alzheimer's disease who finished the GRADUATE I or GRADUATE II studies, to receive gantenerumab for up to 4 years. People who took part had previously taken part in the GRADUATE I and GRADUATE II studies where they received either placebo or gantenerumab during the trial. Some people who completed the GRADUATE I and GRADUATE II studies were able to enter the GRADUATE open-label extension study (OLE). The participants in the GRADUATE OLE had the opportunity to move to POSTGRADUATE study once this was open.

Because the study was stopped early, people in this study only received gantenerumab up to approximately 2 years and 6 months (with most people receiving gantenerumab for an average of 10 months) after completing GRADUATE I or GRADUATE II. People in the study had a follow-up visit 14 weeks after their last dose.

For people taking part in the POSTGRADUATE study, who had previously received placebo in the GRADUATE I or GRADUATE II studies, 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. People on gantenerumab in the GRADUATE I and GRADUATE II studies continued to receive the maximum dose of gantenerumab in the POSTGRADUATE study until the study was stopped.

Study design of the POSTGRADUATE study



There were 50 people who entered the GRADUATE OLE, of which 43 were able to join the POSTGRADUATE study. For more details on this please go to section 5.

4. What were the results of the study?

Question: What are the possible adverse reactions of gantenerumab when given to people with Alzheimer's disease for up to 4 years?

The POSTGRADUATE study investigated the safety of gantenerumab by recording the number of possible adverse reactions, and particularly the number of serious possible adverse reactions, that people had during the study. The study showed that:

- gantenerumab was well tolerated in this study at the dose tested;
- gantenerumab was given as an injection under the skin and some people reported reactions at the site of the injection such as redness, rash or swelling;
- as reported in other studies of gantenerumab, ARIA were mostly asymptomatic and clinically manageable; and
- all types of possible adverse reactions reported during this study were similar to those reported in other studies of gantenerumab.

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

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.

The number of people who had one or more possible adverse reactions was similar in the group who had previously received a placebo and the group who had previously received gantenerumab in the GRADUATE I or GRADUATE II studies.

In the POSTGRADUATE study, overall, 153 out of 705 people (21.7%) who previously received placebo in GRADUATE I or GRADUATE II, and 121 out of 676 people (17.9%) who received gantenerumab in GRADUATE I or GRADUATE II had at least one possible adverse reaction. In total, 695 possible adverse reactions were reported.

Most possible adverse reactions were mild or moderate meaning that they were easy to treat if necessary, and people recovered quickly.

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 POSTGRADUATE study, 6 of 705 (less than 1%) people in the group that previously received a placebo in GRADUATE I or GRADUATE II, and 1 out of 676 (less than 1%) people in the group that previously received gantenerumab in GRADUATE I or GRADUATE II, had at least one serious possible adverse reaction.

The table below shows all of the serious possible adverse reactions (considered to be related to the study treatment by the study doctors across participants who previously received placebo or gantenerumab in GRADUATE I or GRADUATE II. 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 previously received placebo in GRADUATE I or GRADUATE II	People who previously received gantenerumab in GRADUATE I or GRADUATE II
Build-up of fluid in the brain (ARIA-E)	**Less than 1%** (3 out of 705)	**0%** (0 out of 676)
Build-up of fluid in cavities called ventricles deep within the brain (hydrocephalus)	**Less than 1%** (1 out of 705)	**0%** (0 out of 676)
Short-term loss of consciousness	**Less than 1%** (1 out of 705)	**0%** (0 out of 676)
Build-up of blood between the skull and the surface of the brain	**Less than 1%** (1 out of 705)	**0%** (0 out of 676)
Cancer of a type of white blood cells known as myeloid cells	**Less than 1%** (0 out of 705)	**Less than 1%** (1 out of 676)
Confusional state	**Less than 1%** (1 out of 705)	**0%** (0 out of 676)
Delusion	**Less than 1%** (1 out of 705)	**0%** (0 out of 676)

A total of 10 people died during the POSTGRADUATE study data collection period: five deaths in the group that received a placebo in GRADUATE I or GRADUATE II and five deaths in the group that received gantenerumab in GRADUATE I or GRADUATE II. None of the deaths that occurred were considered by study doctors to be caused by treatment with the study medicine.

During the POSTGRADUATE study, a total of 28 of 705 people (4.0%) in the group that received a placebo in GRADUATE I or GRADUATE II and 15 of 676 people (2.2%) in the group that received gantenerumab in GRADUATE I or GRADUATE II stopped taking gantenerumab because of possible adverse reactions. People most commonly had to stop treatment because of ARIA-H. Not all people who had an ARIA-H had to stop treatment.

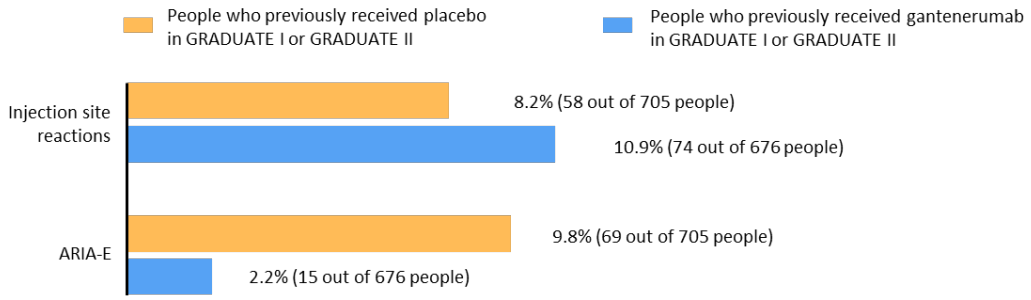
There were 56 people who entered the GRADUATE OLE study. Of these, a total of 11 people did not complete the GRADUATE OLE period and therefore did not enter the POSTGRADUATE study. One participant died of a brain haemorrhage after a head trauma, which was considered unrelated to the study drug by the research doctor. The other did not complete the study due to multiple reasons, including but not limited to personal circumstances and research doctor recommendation.

Most common possible adverse reactions

Most possible adverse reactions were mild or moderate, meaning that they were easy to treat if necessary, and people recovered quickly.

The most common possible adverse reactions are shown in the following figure – these are the 2 most common possible adverse reactions. Some people had more than one possible adverse reaction – this means that they could be included in more than one row in the figure.

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.

A total of 110 people who received a placebo in the GRADUATE I or GRADUATE II, and 32 people who received gantenerumab in GRADUATE I or GRADUATE II had an ARIA-E. The graph above shows only those cases of ARIA-E that the researchers considered as possible adverse reactions. New ARIA-H were found in 88 people who received a placebo in GRADUATE I or GRADUATE II and 44 people who received gantenerumab in GRADUATE I or GRADUATE II.

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?

While the POSTGRADUATE study was stopped early because gantenerumab did not work as well as expected in GRADUATE I and GRADUATE II, this study provided an opportunity to collect long-term safety data to add to the body of evidence on the safety profile of the medicine tested in this study. Furthermore, these results help researchers and doctors better understand ARIA-E and ARIA-H which are abnormalities in the brain that can develop spontaneously in patients with Alzheimer's disease and that may occur with treatments similar to gantenerumab.

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://classic.clinicaltrials.gov/ct2/show/NCT04374253
- https://www.clinicaltrialsregister.eu/ctr-search/search?query=WN42171
- https://forpatients.roche.com/

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.

If you would like to find out more about the results for the GRADUATE I and GRADUATE II studies, these are reported in separate summaries:

- GRADUATE I:
  https://forpatients.roche.com/en/trials/neurodegenerative-disorder/ad/efficacy-and-safety-study-of-gantenerumab-in-participants-with-e.html

- GRADUATE II:
  https://forpatients.roche.com/en/trials/neurodegenerative-disorder/ad/safety-and-efficacy-study-of-gantenerumab-in-participants-with-e.html

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/a-study-to-evaluate-the-safety--tolerability--and-effic-66535.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: “An Open-Label, Multicentre, Rollover Study to Evaluate the Safety, Tolerability, and Efficacy of Long-Term Gantenerumab Administration in Participants With Alzheimer's Disease”.

The study is known as POSTGRADUATE.

- The protocol number for this study is: WN42171.
- The ClinicalTrials.gov identifier for this study is: NCT04374253.
- The EudraCT number for this study is: 2020-000766-42.