Summary of Clinical Trial Results

A study to look at whether gantenerumab works in people with early Alzheimer's disease, and if it can be given once a week at home by a care partner (GRADUATION)

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 GRADUATION study started in November 2020 and stopped early in March 2023.

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.
- 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 researchers and participants know the treatment that a person is receiving.
- PET = positron emission tomography; a type of brain scan that creates a 3D image of the inside of the body.

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 GRADUATION) was done to see how a drug called gantenerumab affects the amount of abnormal amyloid protein in the brain when given as an injection under the skin to people with early Alzheimer's disease, once a week for up to 2 years. It also wanted to find out whether gantenerumab was safe and whether care partners were capable of giving gantenerumab at home.
- A total of 192 people, aged between 50 and 90 years, living with early Alzheimer's disease, from 8 countries, took part in the GRADUATION study.
- The amount of abnormal amyloid protein in the brain was measured using a brain scanning method called "PET".
- The main finding from the GRADUATION study was that a decrease in the amount of abnormal amyloid protein in the brain was found in participants receiving gantenerumab.
- A total of 86 out of 192 people (44.8%) taking gantenerumab had a possible adverse reaction. 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 4 out of 192 people (2.1%) taking gantenerumab had a serious possible adverse reaction.
- A total of 130 out of 148 care partners (88%) found giving gantenerumab at home to be easy or very easy. A similarly high number of care partners found giving gantenerumab at home to be convenient or felt confident or satisfied in doing so.
- This study stopped early because other studies found that gantenerumab did not work as well as expected at slowing down the worsening of symptoms in Alzheimer's disease.

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 range from mild cognitive impairment or mild dementia 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 GRADUATION study was done to test whether the study medicine, called gantenerumab, would remove significant amounts of amyloid protein in people with early Alzheimer's disease when given once a week (in the other, main studies with gantenerumab called GRADUATE I and II, it was administered every 2 weeks).

What was the study medicine?

A medicine called 'gantenerumab' was tested in the GRADUATION 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, either by a doctor or nurse or by the participant's care partner.

What did researchers want to find out?

- Previous studies suggested that gantenerumab was effective at reducing the amount of abnormal amyloid protein in the brain.
- Researchers did this study to see if gantenerumab given once a week to people with early Alzheimer's disease was effective at reducing the amount of amyloid protein in the brain over a 2-year period. (The study was originally set up to run for 2 years but was terminated early).
- 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.

- They also wanted to see whether it was feasible for a care partner to give gantenerumab at home, and how confident they were at doing so.

The main questions that researchers wanted to answer were:

1. Does gantenerumab affect the amount of abnormal amyloid protein in the brain when given once a week to people with early Alzheimer's disease for up to 2 years?
2. Is it safe to give gantenerumab once a week, and is it safe and feasible for a care partner to give gantenerumab at home without a doctor or nurse present?

What kind of study was this?

This study was a 'Phase 2' study. This means that gantenerumab had already been tested in other studies in the past with a number of people with Alzheimer's disease prior to starting this study.

In this study, people with early Alzheimer's disease received gantenerumab once a week either at a study site or at home – this was to find out how a weekly dose of gantenerumab affects the amount of abnormal amyloid protein in the brain. This study was done to help understand if gantenerumab could be given once a week as a treatment for early Alzheimer's disease, should it be found effective and safe in other, main studies (GRADUATE I and II).

The study was a 'single arm study'. This means that all participants received gantenerumab.

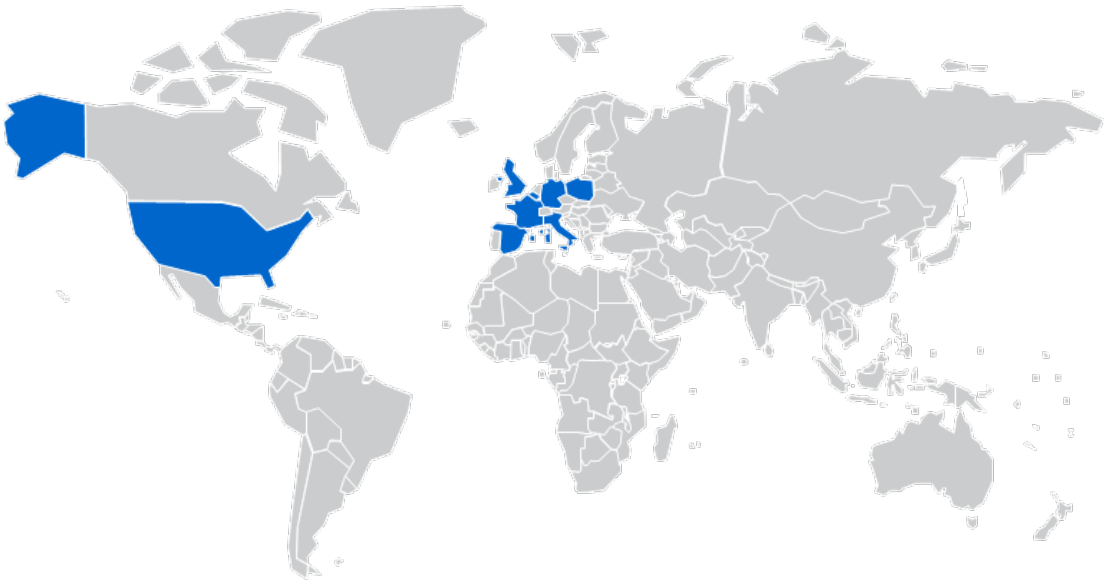
This study was "open-label" which means both the research doctors and participants knew which treatment, in this case gantenerumab, the participant was receiving.

When and where did the study take place?

GRADUATION started in November 2020 and was stopped early in March 2023 because gantenerumab did not work as well as expected in the other, main studies called GRADUATE I and II. This summary was written after the study had ended.

It was conducted in 33 study centres across 8 countries in Europe and North America.

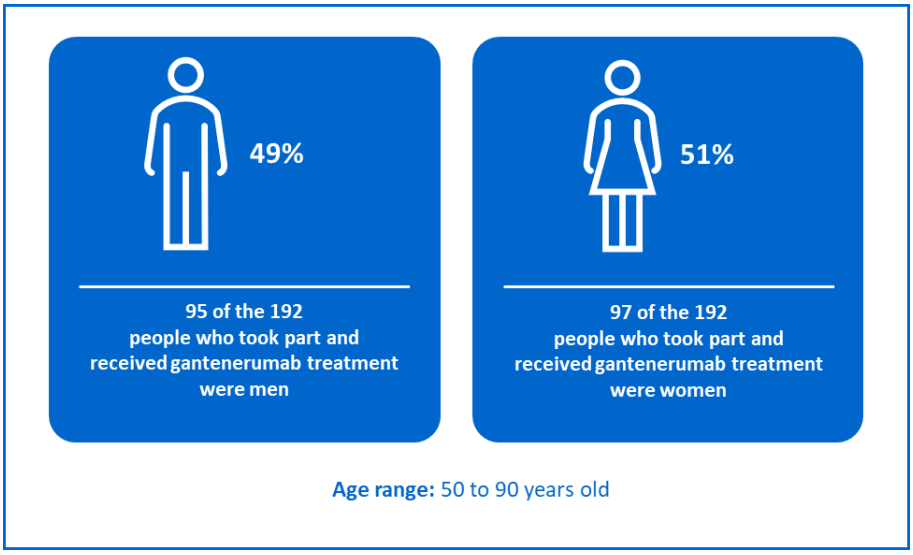
The following map shows the countries where any part of this study took place. The countries were:



- Belgium
- France
- Germany
- Italy
- Poland
- Spain
- United Kingdom
- United States

2. Who took part in this study?

A total of 192 adults with early Alzheimer's disease took part in the GRADUATION study. Of these, 164 people received gantenerumab for at least a year before the study was stopped (28 people did not receive gantenerumab for at least a year before the study was stopped).



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 (previously known as prodromal Alzheimer's disease) or mild dementia due to Alzheimer's disease (previously known as mild Alzheimer's disease);
- had high levels of amyloid in the brain, confirmed by 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:

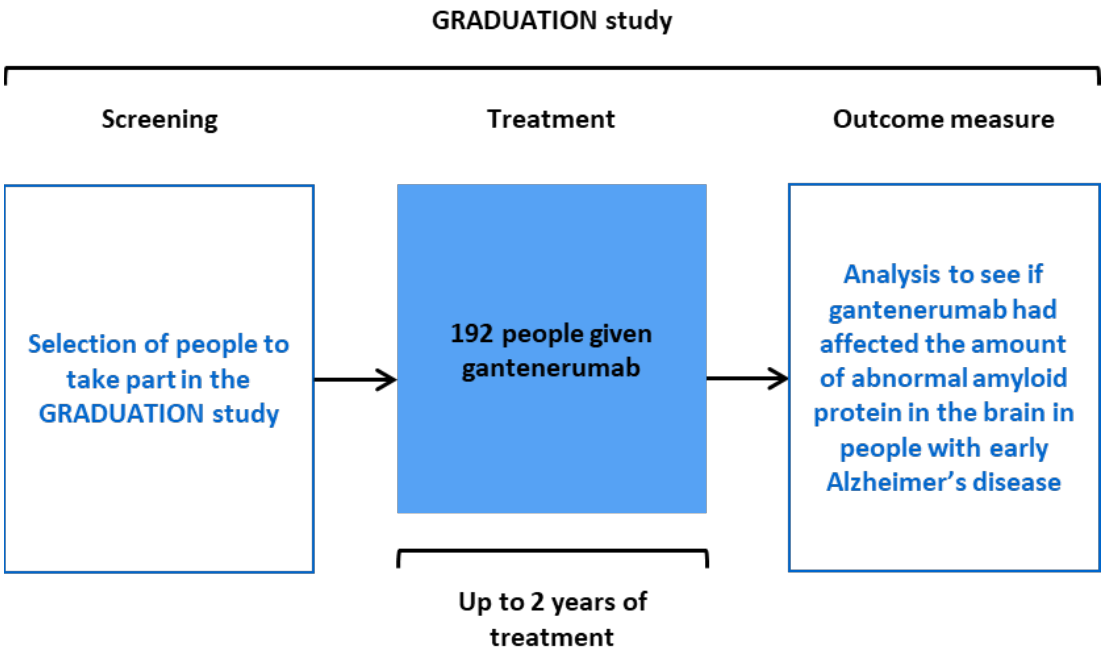
- had other diseases caused by abnormal function of their brain;
- had other diseases such as cancers, as well as heart, liver, immune and metabolic diseases that were not already well controlled.

3. What happened during the study?

GRADUATION study

During the GRADUATION study, people received gantenerumab as a single injection once weekly. The frequency of gantenerumab doses was slowly increased from once every 4 weeks to once every week over a period of about 36 weeks. This slow increase in the frequency of dose was done to reduce the chances of people experiencing adverse reactions. Before every increase in the frequency of dose, people went through safety checks to make sure they were not experiencing any adverse reactions from the medicine they were taking.

The study stopped early because gantenerumab did not work as well as expected in the GRADUATE I and II studies. After people finished taking their medicine for this study, they were asked to go back to their study centre for more visits to check their overall health. The study flowchart shows all stages planned for the study. Most people received gantenerumab for a year or more.



4. What were the results of the study?

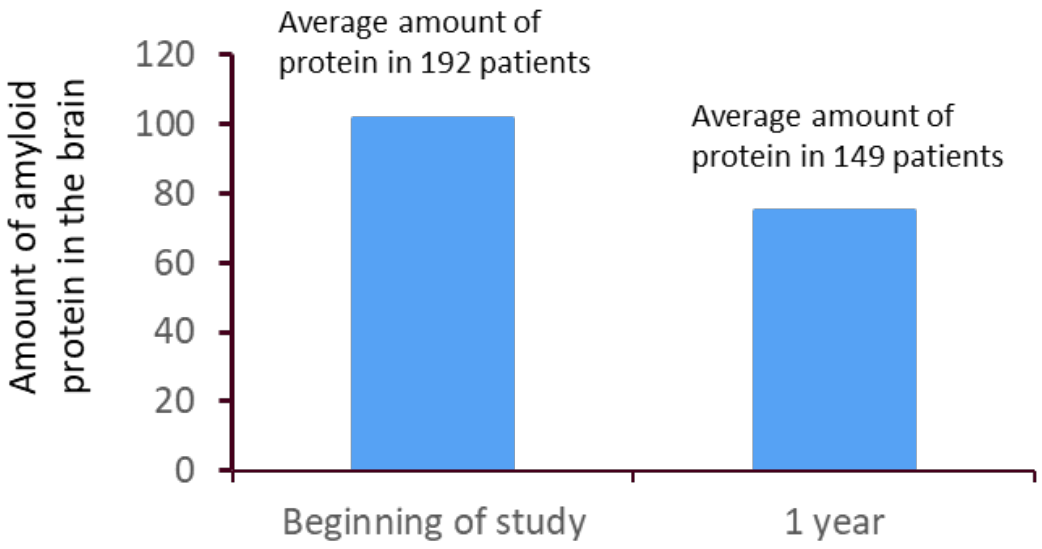
Question 1. Does gantenerumab affect the amount of abnormal amyloid protein in the brain when given once a week to people with early Alzheimer's disease for up to 2 years?

Some treatments similar to gantenerumab work by reducing the amount of abnormal amyloid protein in the brains of people with Alzheimer's disease.

As the study was stopped early, the results only look at the effect of gantenerumab on the amount of abnormal amyloid protein in the brain for up to a year, instead of the 2 years originally planned.

The amount of abnormal amyloid protein in the brain was measured using a type of brain scan called "PET".

Although some amyloid protein was removed from the brain in people after 1 year of being given gantenerumab, most people still had substantial levels of amyloid protein at the end of the study.



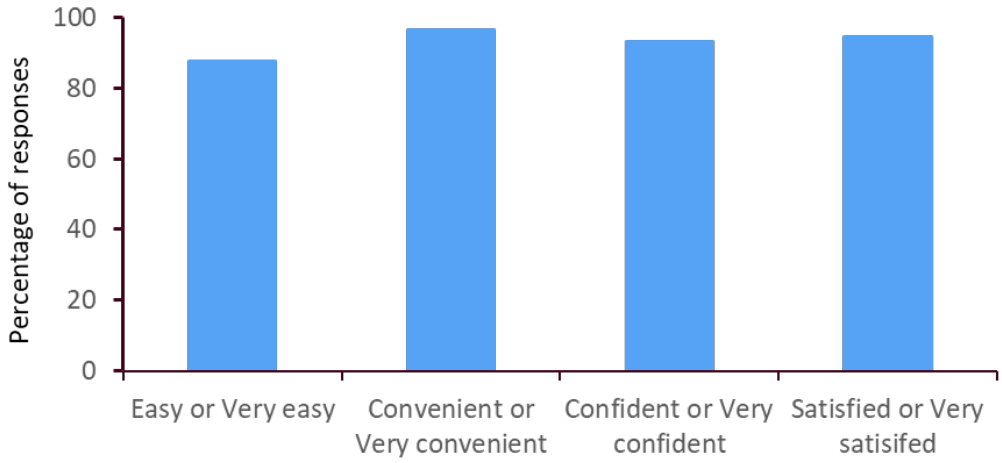
Note: The amount of amyloid protein shown in this figure is the average of the data collected and is presented in units called centiloids.

Question 2. Is it safe to give gantenerumab once a week, and is it safe and feasible for a care partner to give gantenerumab at home without a doctor or nurse present?

Another piece of information that researchers collected was about how safe gantenerumab was and whether it can be given by a care partner at home, for up to 2 years, the duration of the GRADUATION study.

The capability of home administration was measured by a questionnaire given to care partners about their experience of giving the drug to people with early Alzheimer's disease. After 1 year, 148 care partners answered the questionnaire.

The majority of care partners found it easy and convenient to give gantenerumab at home and were confident and satisfied in doing so.



- The study showed that gantenerumab was well tolerated at the dose studied.
    - As reported in other studies of gantenerumab, people in this study were likely to experience amyloid-related imaging abnormalities (ARIA) after receiving gantenerumab treatment.
        - ARIA are abnormalities in the brain seen during magnetic resonance imaging scans, sometimes experienced by people receiving gantenerumab and drugs similar to gantenerumab. These can occur with or without the person having any symptoms.
        - There are two types of ARIA: 1) ARIA-E, which is the build-up of fluid or swelling in the brain, and 2) ARIA-H, which is a small bleeding in or on the surface of the brain.
    - The study drug was given as an injection under the skin and people reported reactions at the site of the injection such as redness, rash or swelling. This is known as an injection site reaction.

      Other types of possible adverse reactions were reported during this study (for example, headaches and disorientation).

Please see the next section (Section 5) for full details of the possible adverse reactions people had during the GRADUATION 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 a headache) 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 GRADUATION, 4 of 192 people (2.1%) who were given gantenerumab had at least one serious possible adverse reaction that the study doctor thought might have been related to their study treatment.

The table below shows all of the serious possible adverse reactions considered to be related to the study treatment by the study doctors. 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	Proportion of people who experienced this reaction
ARIA-E	**1.6%** (3 out of 192)
ARIA-H	**0.5%** (1 out of 192)
Partial seizure (when nerve cells in a part of the brain are involved)	**0.5%** (1 out of 192)
Convulsive seizure (muscle stiffening, jerking or twitching)	**0.5%** (1 out of 192)

One person died due to an infection of the valves of the heart during the study. This death was not considered by study doctors to be caused by treatment with gantenerumab.

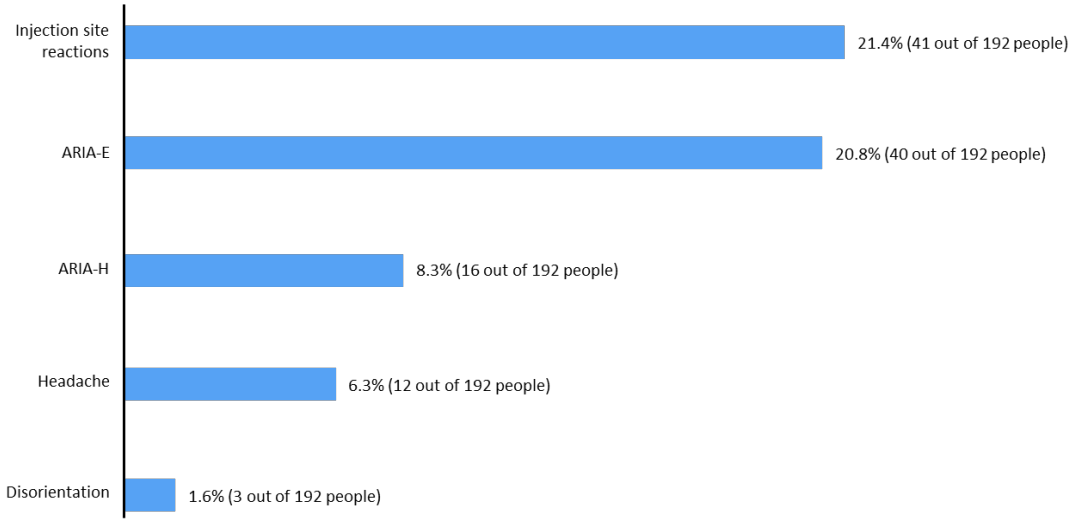
During the study, some people decided to stop taking their medicine because of possible adverse reactions:

- Because of ARIA-H, 10 out of 192 people (5.2%) stopped taking their medicine.
- Because of ARIA-E, 2 out of 192 people (1.0%) 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 five most common possible adverse reactions for people who received gantenerumab. Some people had more than one possible adverse reaction – this means that they are included in more than one bar in the figure.



In total, 44 people experienced ARIA-E. New ARIA-H were found in 44 people. The graph above shows only those cases of ARIA-E and ARIA-H that the researchers considered as possible adverse reactions.

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 given once a week under the skin at home by a care partner to people with early Alzheimer's disease, was well tolerated, manageable and convenient. These results helped researchers learn more about how this approach could possibly reduce the number of times that a patient would have to go to hospital for treatment and provide more flexible options for giving a drug to treat Alzheimer's disease.

The information presented here is from a single study of 192 people with early Alzheimer's disease that was stopped early.

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/NCT04592341
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001384-87/results
- https://forpatients.roche.com/

If you would like to find out more about the results of this study, the relevant scientific paper is due to be published in the near future.

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-pharmacodynamic--pd--effects-of-20860.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 Study to Evaluate the Pharmacodynamic (PD) Effects of Once Weekly Administration of Gantenerumab in Participants With Early Alzheimer's Disease (AD)”.

The study is known as GRADUATION.

- The protocol number for this study is: WN29722.
- The ClinicalTrials.gov identifier for this study is: NCT04592341.
- The EudraCT number for this study is: 2020-001384-87.