Summary of Clinical Trial Results

A study to look at whether gantenerumab works and how safe it is in people at risk for developing Alzheimer's disease or in the earliest stages of Alzheimer's disease (SKYLINE)

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 SKYLINE study started in April 2022. It 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.

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
- People at risk or at earliest stages of Alzheimer's disease = people who have abnormal levels of amyloid protein in the brain that may or may not experience very subtle changes in thinking ability and memory and that do not yet meet the criteria needed for a doctor to diagnose mild cognitive impairment due to Alzheimer's disease. These

people may or may not progress to show symptoms of Alzheimer's disease in their lifetime

- 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
- PACC-5 = a test to measure deterioration in thinking and memory (=cognition) in the earliest stages of Alzheimer's disease
- 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 study partners, were ready to help 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 at risk for developing Alzheimer's disease or in the earliest stages of 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 SKYLINE study) compared a new experimental treatment being investigated, called gantenerumab, with a placebo (a dummy treatment that looked like gantenerumab but had no medicine in it), in people at risk for developing Alzheimer's disease or who are in the earliest stages of Alzheimer's disease.
- SKYLINE was done to see whether the study medicine, gantenerumab, was effective and safe in preventing or slowing down the development of symptoms associated with Alzheimer's disease in people at risk for developing Alzheimer's disease or in the earliest stages of Alzheimer's disease. Research doctors wanted to compare the study medicine with a placebo.
- The SKYLINE study was stopped early after careful consideration of all available information 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 25 people of the planned 1200, aged between 60 and 80 years, at risk for developing Alzheimer's disease or at the earliest stages of Alzheimer's disease, from 3 countries, took part in the SKYLINE study before the study was stopped early.
- Out of 25 people who took part in the SKYLINE study, 12 people were randomly chosen to receive a placebo and 13 people were randomly chosen to receive gantenerumab.
- Possible adverse reactions were experienced by 1 out of 13 people (7.7%) taking gantenerumab and 1 out of 12 (8.3%) people taking a placebo. All possible adverse reactions were well tolerated (meaning they were mild in severity) and the types of possible adverse reactions people experienced were similar to those seen in previous gantenerumab studies. No-one taking gantenerumab or a placebo had a serious possible adverse reaction.

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.

Some people have abnormal levels of amyloid protein but no or very subtle changes in their thinking ability and memory (=cognition). These people are considered to be at risk for Alzheimer's disease or may be in the earliest stages of Alzheimer's disease

The SKYLINE study was done to test whether the study medicine, called gantenerumab, would prevent or slow the development of symptoms associated with Alzheimer's disease in people at risk for Alzheimer's disease or in the earliest stages of Alzheimer's disease. The study was stopped early when data from only a limited number of people (25) receiving study drug up to 27 weeks, either gantenerumab or a placebo, had been collected.

What was the study medicine?

A medicine called 'gantenerumab' was tested in the SKYLINE 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 possible adverse reactions could actually be 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?

- Abnormal levels of amyloid in the brain are associated with Alzheimer's disease. Previous studies suggested that gantenerumab was effective at removing the amyloid protein in the brain, which was hypothesised to prevent or slow the development of symptoms associated with Alzheimer disease. Researchers did this study to compare gantenerumab with a placebo – to see how well gantenerumab might work if given to older people with abnormal levels of amyloid in the brain, yet no or only very subtle changes in thinking ability and memory (=cognition), i.e., in people considered to be at risk for Alzheimer's disease or in the earliest stages of Alzheimer's disease, for up to 4 years. (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 would experience possible adverse reactions and seeing how serious these were, when compared with the possible adverse reactions seen in people who received placebo.

The main questions that research doctors wanted to answer were:

1. Does gantenerumab prevent or slow down the development of symptoms associated with Alzheimer's disease when given to people at risk for developing Alzheimer's disease or in the earliest stages of Alzheimer's disease for up to 4 years?
2. What are the possible adverse reactions of gantenerumab when given to people at risk for developing Alzheimer's disease or in the earliest stages of 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 approximately 1200 people at risk of developing Alzheimer's disease or in the earliest stages of Alzheimer's disease would take either gantenerumab or a placebo. This was to find out if gantenerumab prevents or slows down the development of symptoms associated with Alzheimer's disease in people at risk of developing Alzheimer's disease or in the earliest stages of Alzheimer's disease, and about the safety of gantenerumab. However, as the study was stopped early, only 25 people actually received gantenerumab or a placebo.

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 study medications 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 done to compare the results from people taking a placebo with the results from people taking gantenerumab.

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.

When and where did the study take place?

The SKYLINE study started in April 2022 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 it was stopped in March 2023.

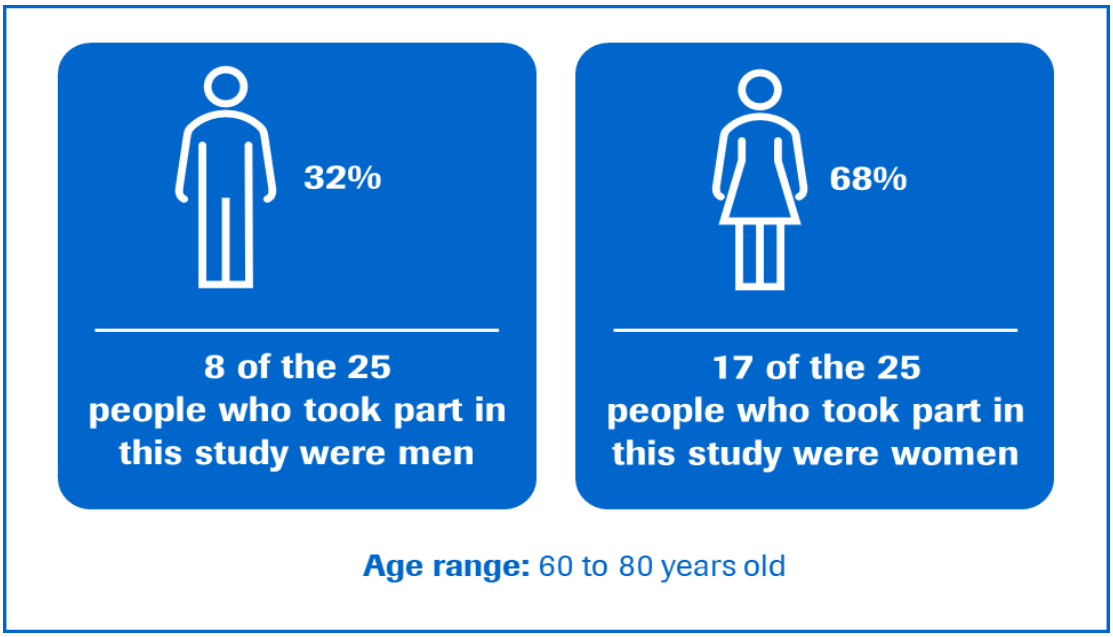
Because of the early stop, the SKYLINE study was only conducted in 12 study centres across 3 countries in Australia and North America. More countries and sites were originally planned to be part of the study.

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

- Australia
- Canada
- United States of America

2. Who took part in this study?

A total of 25 of the planned 1200 adults at risk of developing Alzheimer's disease or in the earliest stages of Alzheimer's disease took part in the SKYLINE study and received either gantenerumab or a placebo during the study.



People could take part in the study if they:

- were aged between 60 and 80 years at the beginning of the study;
- had abnormal levels of amyloid protein 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;
- had no symptoms of Alzheimer's disease and had not been diagnosed with early Alzheimer's disease (including people with mild cognitive impairment due to Alzheimer's disease or mild dementia due to Alzheimer's disease); and
- 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; or
- 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?

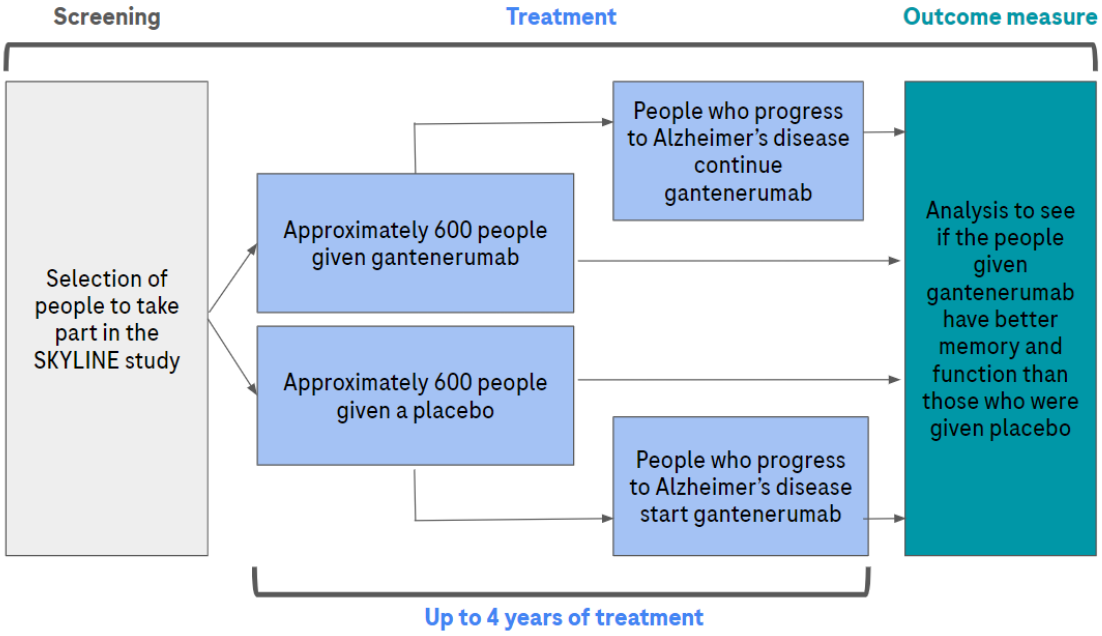
During the SKYLINE study, people were split randomly into two groups and given either a placebo or gantenerumab. Neither the people taking part in the study nor the researchers involved knew which group was receiving a placebo and which group was receiving gantenerumab.

The dose of gantenerumab was slowly increased over a period of 9 months up to the maximum dose of 1020 mg per month that the researchers wanted to study. This slow increase in dose was done in an effort 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 taking part in the study could choose to receive the study medicine once a week or every two weeks, and to receive the study medicine at home or at the study centre before completing 25 weeks in the study.

People who progressed to the symptomatic stage of Alzheimer disease would receive gantenerumab, regardless of receiving gantenerumab or placebo since the beginning of the study.

Study design of the SKYLINE study



4. What were the results of the study?

Question 1: Does gantenerumab prevent or slow down the development of symptoms associated with Alzheimer's disease when given to people at risk for developing Alzheimer's disease or in the earliest stages of Alzheimer's disease for up to 4 years?

In the SKYLINE study, research doctors were going to use a test called the Preclinical Alzheimer's Cognitive Composite-5 (PACC-5) test to measure how well gantenerumab worked in preventing or slowing down the development of symptoms associated with Alzheimer's disease for people at risk for developing Alzheimer's disease or in the earliest stages of Alzheimer's disease over 4 years.

The PACC-5 test score is calculated by using a combination of scores from 5 different tests that measure the memory and function of people who are at risk for developing Alzheimer's disease in the earliest stages of Alzheimer's disease. These 5 tests include the Wechsler Memory Scale, Free and Cued Selective Reminding Test, Wechsler Adult Intelligence Scale, Mini-Mental State Examination, and Category fluency test. The PACC-5 test score ranges from −3 to 3, with higher scores meaning a person has better memory and function.

As the SKYLINE study was stopped early, not enough people had taken part, no-one was dosed for more than 27 weeks and therefore people who were randomly receiving gantenerumab did not reach the maximum dose. For this reason, no conclusions can be made on the efficacy measure in this study.

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.

Overall, 1 out of 13 (7.7%) people who received gantenerumab had at least one possible adverse reaction compared to 1 out of 12 (8.3%) people who received a placebo.

All possible adverse reactions were mild (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.

No serious possible adverse reactions occurred during the study. No one had to stop taking the study medicine due to possible adverse reactions. No deaths occurred during the study.

Most common possible adverse reactions

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

Two possible adverse reactions were considered related to the study medicine. These possible adverse reactions were general pain (reported by one person receiving a placebo) and an injection site reaction (reported by one person receiving gantenerumab).

An injection site reaction is a reaction at the place where a medicine is injected under the skin. The person experiencing the injection site reaction had rash and 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.

No one who took part in the study had an ARIA-E event. One person who received gantenerumab had an ARIA-H event after the start of the study which did not present any symptoms, with no further actions needed.

6. How has this study helped research?

Since the SKYLINE study was stopped early, learnings are limited and no conclusions can be made on whether gantenerumab would be effective in preventing or slowing down the development of symptoms associated with Alzheimer's disease in people at risk for developing Alzheimer's disease or in the earliest stages of 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/NCT05256134
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-001184-25/ES
- https://forpatients.roche.com/

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-efficacy-and-safety-of-gantener-84528.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, 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”.

The study is known as SKYLINE.

- The protocol number for this study is: WN42444.
- The ClinicalTrials.gov identifier for this study is: NCT06256134.
- The EudraCT number for this study is: 2021-001184-25.