Summary of Clinical Trial Results

A study, named SCarlet RoAD, to look at how safe gantenerumab is in people with early Alzheimer's disease and whether it works

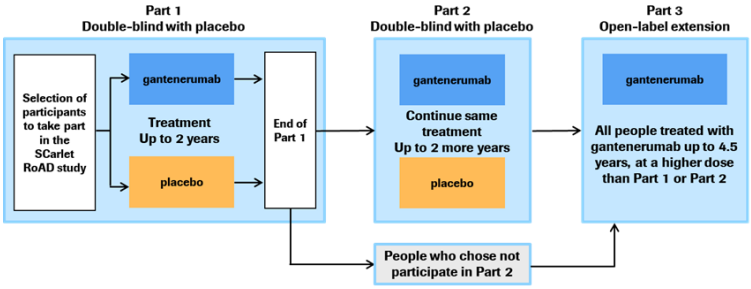
See the end of the summary for the full title of the study.

About this 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 SCarlet RoAD study, which was conducted in 3 parts, started in November 2010 (Part 1) and finished in September 2020 (Part 3). This summary of the study was written after the study ended and represents the final study results for Part 3 of the study, which have been fully analysed.



This study investigated the medicine gantenerumab for the treatment of a disease of the brain that affects memory and other brain functions – called 'Alzheimer's disease'. The original study (Part 1 and Part 2) was a double-blind study, meaning that neither the participants taking part in the study or the study doctors knew if the anyone was taking gantenerumab or placebo. The original study (Part 1 and Part 2) was stopped early – in December 2014. It stopped because a planned analysis (futility) of the medicine's effectiveness during the trial showed that, at the low doses studied, gantenerumab did not work as well as expected compared with a placebo. The study was then changed into a different type of study that tested higher doses of gantenerumab, an open-label study (Part 3).

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.

Contents of the summary

Glossary

- Open-label study = a study where both study doctors and participants know the treatment which the participant is receiving
- ARIA-E = build-up of fluid in the brain seen in imaging, with or without side effects
- ARIA-H = small bleeding in the brain seen using medical imaging techniques, with or without side effects

Thank you to the people who took part in this study

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

Key information about this study

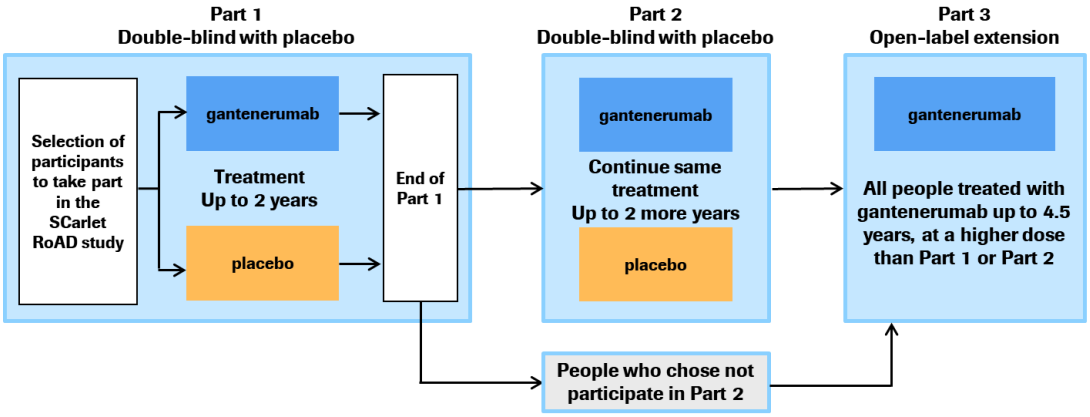
- The study (known as the SCarlet RoAD study) was made up of 3 parts. Part 1 and Part 2 of the study were double-blind and done to compare a new treatment that is being investigated called gantenerumab with a placebo in participants with early Alzheimer's disease. A 'placebo' (plah – see – bo) looks the same as a medicine but does not contain any real medicine. This means that it does not have any medicine-related effect on the body. A placebo is used so that the participants and the doctor do not know whether they are receiving the real medicine or not. This is because knowing can sometimes affect the results of the study.
- Part 3 of the study was an open-label extension, in which participants (from Part 1 or Part 2) were given gantenerumab in higher doses than previously studied in Part 1 and Part 2.
- There were 797 participants who took part and received either gantenerumab or placebo in Part 1 of the SCarlet RoAD study. For those who completed Part 1, participants were offered the option to extend the time receiving either gantenerumab or placebo for up to 2 extra years (Part 2) and 264 participants enrolled into Part 2. A total of 154 participants, between 52 and 84 years, from 24 countries, were included Part 3 of the SCarlet RoAD study.
- A planned analysis of data (futility) from Part 1 and Part 2 was done partway through, before the study was finished. The SCarlet RoAD study was stopped early as this analysis of the double-blind period (Part 1 and Part 2) showed that gantenerumab was safe (side effects experienced in participants who took gantenerumab were similar in those that took the placebo), but also showed that gantenerumab was unlikely to be effective (unlikely to help people with early Alzheimer's disease).
- Additional analyses suggested that higher doses of gantenerumab may be needed to have an effect on people living with Alzheimer's disease, so the study was converted to an open-label extension (Part 3) where participants from Part 1 or Part 2 could be treated with gantenerumab at higher doses.
- Out of the 154 participants in Part 3, 49 participants had previously received a placebo and 105 participants had previously received gantenerumab during Parts 1 and 2 of the study.
- In Part 3 of the study:
  - Treatment with higher doses of gantenerumab was generally well tolerated.
  - In total, 60% of participants who received gantenerumab had at least 1 treatment-related side effect. Most side effects were well tolerated and easy to treat, and the participants recovered.
  - Participants treated with higher doses of gantenerumab showed a decrease in a potentially harmful protein that is linked to Alzheimer's disease, called amyloid, in their brains over time.

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.

This study was initially done to test whether a new drug treatment, called gantenerumab, was effective in slowing down the build-up of amyloid in the brain and how symptoms progressed (Part 1 and Part 2). In Part 3, the study doctors wanted to make sure gantenerumab was still safe at higher doses than were previously studied.



Part 1 and Part 2 of the study were double-blind which means that neither the participants taking part in the study or the study doctors knew which of the study medicines participants were taking. A 'placebo' (plah – see – bo) looks the same as a medicine but does not contain any real medicine. Part 3 was an open-label extension study which means that participants who had participated in Part 1 or Part 2 of the original study carried on taking study medicines. In Part 3, both the participants taking part and the study doctors knew all the participants were taking gantenerumab.

What was the study medicine?

A medicine called gantenerumab was the focus of this study. There were 3 parts to the study. Gantenerumab was compared with a placebo in Part 1 and Part 2 of the study, and in Part 3 gantenerumab alone was tested at higher doses. The medicine was given as a subcutaneous injection, which means that it was delivered through an injection just under the skin.

- Gantenerumab is a type of monoclonal antibody, meaning that it is a kind of medicine that helps the immune system to specifically recognise the harmful amyloid protein that is linked to Alzheimer's disease.
- In Part 1 and Part 2 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. Gantenerumab was compared with a placebo so they could show which benefits or side effects were actually caused by the medicine.

What did researchers want to find out?

- Previous studies suggested that gantenerumab was more effective at treating people with early Alzheimer's disease, rather than those with more advanced disease.
- At the lower doses studied in Part 1 and Part 2, gantenerumab did not work as well as expected compared with a placebo so for Part 3 study doctors wanted to gather long-term information on:
    - How safe gantenerumab was in the long term at the higher dose
    - How people's bodies coped with gantenerumab in the long term

The main questions that researchers wanted to answer were:

1. In Part 3, what are the side effects of gantenerumab when given to participants with early Alzheimer's disease every month up to 4.5 years (Week 236)?
2. In Part 3, how did gantenerumab affect symptoms of Alzheimer's disease and amyloid protein in the brain when given every month up to 4.5 years (Week 236)?

What kind of study was this?

This study was a 'Phase 3' study. This means that gantenerumab had been already tested in other studies in the past with a smaller number of people with Alzheimer's disease prior to starting this study.

In Part 1 and Part 2 of the study, a larger number of participants with Alzheimer's disease took gantenerumab to find out about the side effects of gantenerumab and if gantenerumab worked to improve the symptoms of Alzheimer's disease. Part 1 and Part 2 were stopped early as the analysis showed that gantenerumab was unlikely to be effective (unlikely to help people with early Alzheimer's disease). Part 3 of the study was an 'open-label extension' study. This means that participants in Part 1 or Part 2 of the Phase 3 study could carry on taking gantenerumab at higher doses.

When and where did the study take place?

SCarlet RoAD started in November 2010 and was completed in July 2020.

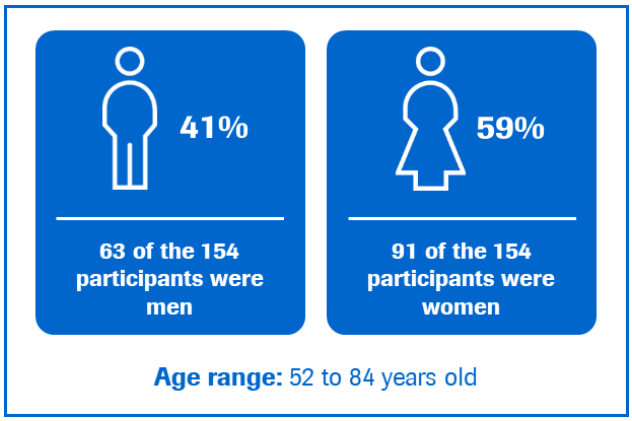
Part 1 and Part 2 of the study took place at approximately 128 sites across 24 countries in Asia, Europe, and the Americas. Of the original 128 sites, 53 took part in Part 3 of the study.

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

2. Who took part in this study?

In double-blind Part 1 of the Study, 797 participants with early Alzheimer's disease received treatment with either gantenerumab or placebo. Double-blind means that neither the participants taking part in the study or the study doctors knew which of the study medicines participants were taking. 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. Participants had the option to continue double-blind treatment in Part 2.

A total of 154 adults with early Alzheimer's disease who participated in Part 1 or Part 2 chose to participate in Part 3 of the study. Part 3 of the study was an 'open-label extension' study. As an 'open-label' study, both the participants taking part and the study doctors knew all participants were taking gantenerumab. Participants in Part 3 of the study were between 52 and 84 years of age. In Part 3, 105 of the participants taking part (68%) previously received gantenerumab, and 49 participants (32%) had previously received the placebo during Part 1 or Part 2.



Participants could take part in the open-label extension (Part 3) if they met these criteria:

- Had early Alzheimer's disease and were between 50 and 85 years old at the beginning of Part 1.
- Had received treatment during Part 1 or Part 2 of SCarlet RoAD before the planned futility analysis partway through the study.
- Had at least one follow-up visit after participating in Part 1 or Part 2.

3. What happened during the study?

SCarlet RoAD Study – Part 1

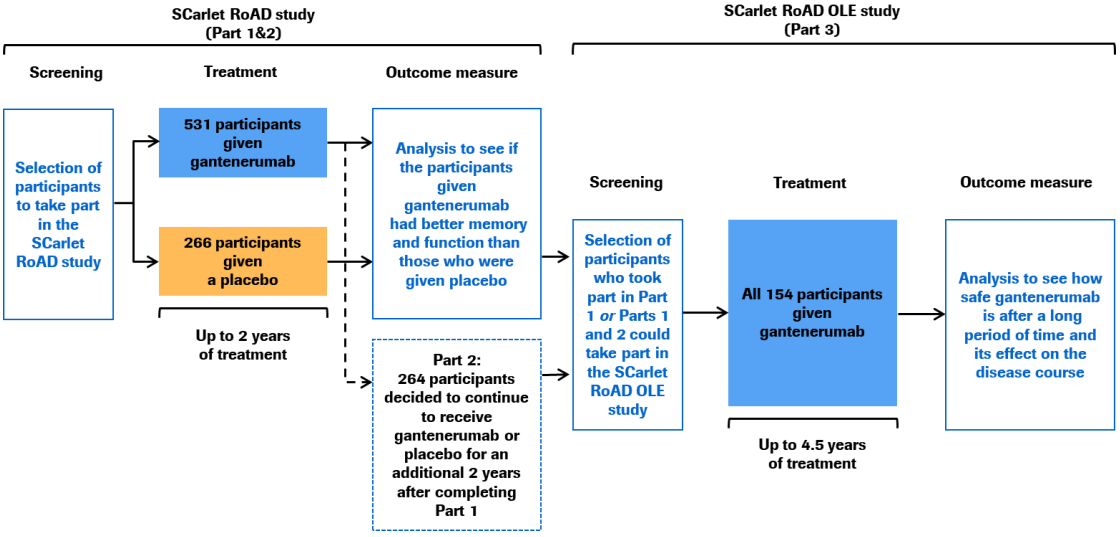
During Part 1 of the SCarlet RoAD study, participants were split randomly into 2 groups and given either gantenerumab or a placebo. As this was a double-blind study, nobody taking part in the study knew which group they were in. This was done to make sure that those participating in the study and the study doctors involved could not sway the results of the study.

SCarlet RoAD Study – Part 2

Participants from Part 1 of the study were given the choice to enter Part 2 of the study, where they would continue double-blind treatment for an additional 2 years. Participation in Part 2 of the study was optional, and the participants and study doctors remained unaware of who was receiving gantenerumab and who was receiving a placebo.

SCarlet RoAD Open-Label Extension (OLE) Study – Part 3

Participants previously in Part 1 or Part 2 of the SCarlet RoAD study were invited to take part in Part 3 of the study, and everyone who participated was given gantenerumab. The study was done to see if gantenerumab would still be safe after a longer period of time and at a higher dose, and to see how gantenerumab affects the course of Alzheimer's disease at a higher dose than in Part 1 and Part 2 of the original study. The dose of gantenerumab that the participants received was gradually increased (up-titrated) until they reached the higher doses that the study doctors wanted to investigate for this study. Part 3 of the study was open-label, meaning that both the participants and the study doctors involved in the study knew that all participants were given gantenerumab in this part of the study.



OLE stands for open-label extension. Participants in Canada and Russia could only participate in Part 3 for up to 3 years.

4. What were the results of the study?

Question 1: In Part 3, what are the side effects of gantenerumab when given to participants with early Alzheimer's disease every month up to 4.5 years (Week 236)?

The SCarlet RoAD study investigated the safety of gantenerumab by recording the number of side effects or 'adverse events', and particularly the number of serious side effects, that participants had during the study.

'Side effects', or 'adverse events', are unwanted medical problems (such as a headache) that may happen to participants receiving study medications or a placebo.

'Serious side effects' are side effects that are life-threatening or require immediate treatment or hospitalisation.

Side effects and serious side effects are not necessarily related to the use of a specific treatment.

In some cases, side effects may be related to study treatment. These are the ones that occur during the study period and which the study doctors think might have been related to the treatment received.

The study showed that gantenerumab was well tolerated at the doses studied. All types of side effects reported during this study were similar to those reported in other studies of gantenerumab.

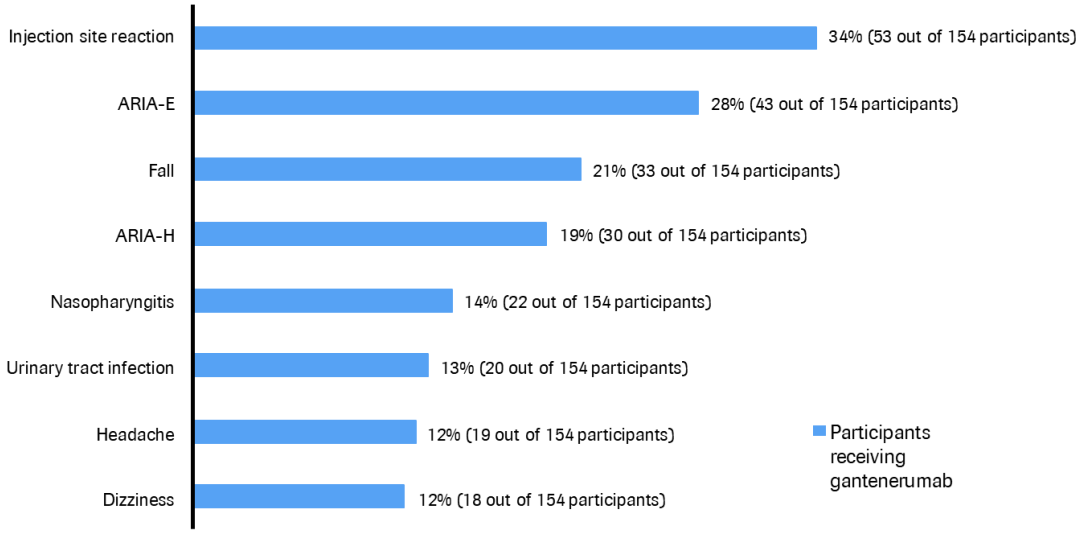
Most side effects were mild or moderate (such as headache or dizziness) meaning that they were easy to treat if necessary, and participants recovered.

Overall, out of 154 participants in Part 3, 146 participants (95%) who received gantenerumab had at least 1 side effect (see the table and graph below for the number, types of side effects and most common side effects that occurred in more than 10% of participants in this study). A total of 1750 side effects occurred in 146 participants who received gantenerumab. During Part 3, the side effects reported were similar in participants who were previously treated with gantenerumab or a placebo (in Part 1 or Part 2).

Number of participants who had side effects in this study

	Participants who received gantenerumab in OLE	**In the 49 participants who received a placebo in Part 1 or Part 2**	**In the 105 participants who received gantenerumab in Part 1 or Part 2**
At least 1 side effect	**95%** (146 out of 154)	**94%** (46 out of 49)	**95%** (100 out of 105)
Serious side effects	**30%** (46 out of 154)	**37%** (18 out of 49)	**27%** (28 out of 105)
Side effects considered related to study treatment by the study doctors	**60%** (92 out of 154)	**57%** (28 out of 49)	**61%** (64 out of 105)

Most common side effects in this study (reported in more than 10% of participants)



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

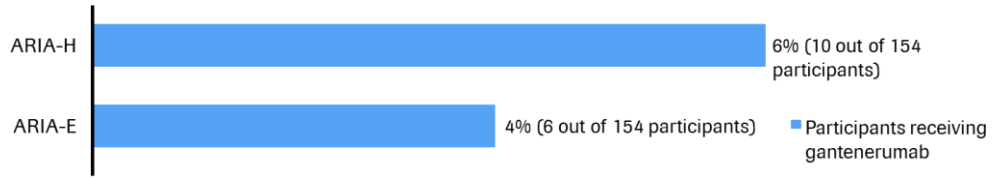
Amyloid-related imaging abnormalities (ARIA) are a class of side effect sometimes experienced by participants receiving drugs similar to gantenerumab, which are visible in the brain during MRI (magnetic resonance imaging) scans. The two types of ARIA are ARIA-E, which is the build-up of fluid in the brain, and ARIA-H, which is small bleeding in the brain. In this study, ARIA-E did not always cause side effects. When side effects of ARIA-E occurred, they were non-serious.

'Nasopharyngitis' is a swelling in the passages of the nose and throat –commonly known as a 'cold'.

A 'urinary tract infection', or UTI, is an infection that affects the kidney, bladder or the tubes in which participants pass water from the body.

A total of 92 participants (60%) receiving gantenerumab experienced side effects that were considered related to the study treatment (see graph below for the most common side effects related to the stopping of study treatment).

Side effects which made more than 1 participant stop study treatment



A total of 29 participants (19%) receiving gantenerumab experienced a total of 42 side effects that made them stop treatment. The only side effects that caused more than 1 person to stop treatment were ARIA-E and ARIA-H. Ten participants experienced ARIA-H and 6 participants experienced ARIA-E. Among these participants, 4 reported ARIA-H and ARIA-E

at the same time. Participants with too many ARIA-H within 1 year had to stop treatment because of study guidelines.

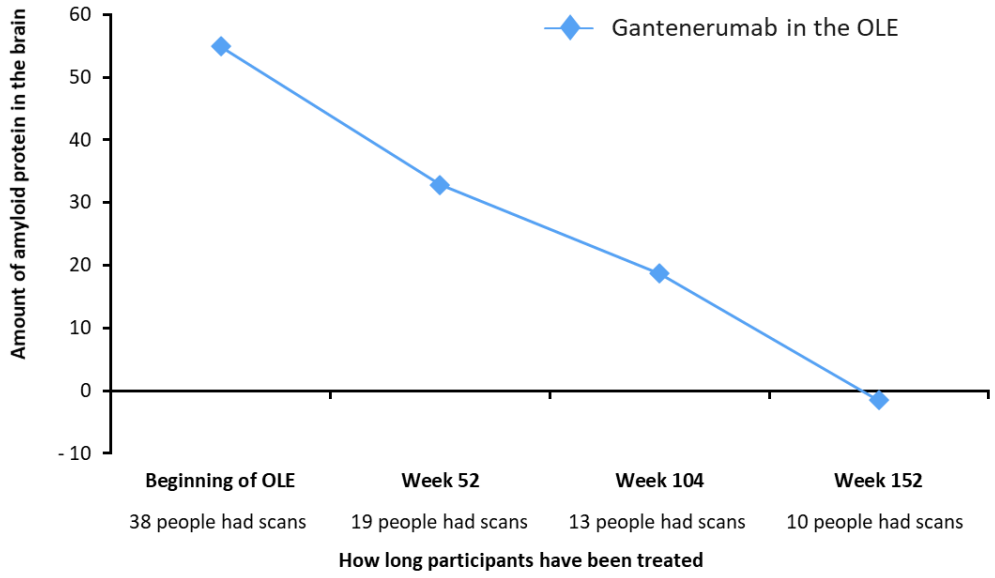
A total of 4 participants died during the study. None of the deaths that occurred were considered by study doctors to be caused by treatment with the study drug.

Question 2: In Part 3, how did gantenerumab affect symptoms of Alzheimer's disease and amyloid protein in the brain when given every month up to 4.5 years (Week 236)?

Study doctors looked at results from several tests to measure the change in participants' symptoms over the study period. The participants' memory and understanding declined over the 3 years of the study. However, since there was no placebo group during Part 3 and not everyone who took part in Part 1 and Part 2 continued to Part 3, we do not know if treatment with gantenerumab had an effect on changes in understanding.

A small number of participants from Part 3 voluntarily took part in an imaging substudy looking at the amount of amyloid protein in the brain over time. The amount of amyloid protein within participants' brains lowered over time, which may be beneficial to some people. The protein levels left after Week 104 of Part 3 were similar to levels seen in people without Alzheimer's disease.

Reduction in amyloid protein in the brain over 3 years



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 side effects?

Side effects are medical problems (such as feeling dizzy) that happen during the study.

- They are described in this summary because the study doctor believes the side effects were related to the treatments in the study.
- Not all the participants in this study had all the side effects.
- Side effects may be mild to very severe and can be different from person to person.
- It is important to be aware that the side effects reported here are from this single study. Therefore, the side effects shown here may be different from those seen in other studies.
- Serious and common side effects considered related to gantenerumab treatment according to the study doctor are listed in the following sections.

Serious side effects

A side effect is considered 'serious' if it is life-threatening, needs hospital care or causes lasting problems.

During Part 3 of this study, 6 of 154 participants (4%) had at least one serious side effect that was related to gantenerumab treatment according to the study doctor. These were:

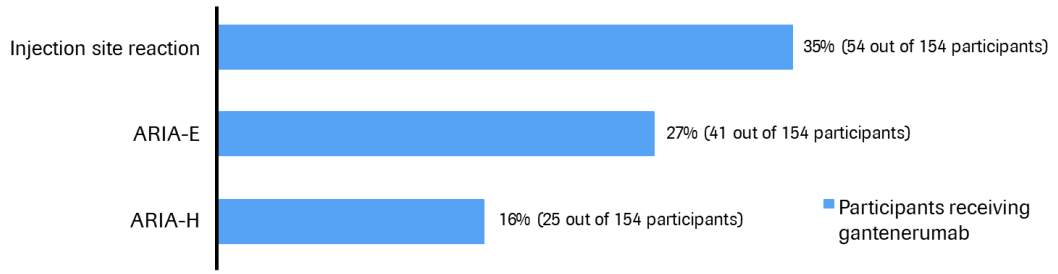
- 1 person with ARIA-E (build-up of fluid in the brain) and epilepsy (a seizure disorder)
- 1 person with ARIA-E with confusional state (build-up of fluid in the brain with confusion)
- 1 person with a cerebral haemorrhage (bleeding in the brain)
- 1 person with cerebral haematoma (collection of blood within the skull)
- 1 person with generalised tonic-clonic seizure (seizure with stiffening, twitching or jerking of muscles)
- 1 person with epilepsy (a seizure disorder)

A total of 4 participants died during the study. None of the deaths that occurred were considered by study doctors to be caused by treatment with the study drug.

Most common side effects

During Part 3 of this study, around 6 out of every 10 participants (60%) had a side effect that was related to gantenerumab according to the study doctor. The most common side effects are shown in the following picture.

Most common side effects related to gantenerumab treatment



Other side effects

You can find information about other side effects (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?

The information presented here is from the open-label extension of a single study of 154 participants with Alzheimer's disease. These results have helped researchers learn more about Alzheimer's disease and gantenerumab. This study has shown that higher doses of gantenerumab are both safe and well tolerated by participants with 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?

Studies with gantenerumab are still happening, and further studies are planned. These studies include investigation into:

- Participants with early Alzheimer's disease (ClinicalTrials.gov Identifiers; NCT03444870 and NCT03443973)
- Participants with or at risk for inherited familial Alzheimer's disease (ClinicalTrials.gov Identifier; NCT01760005)
- Long-term safety studies for those who have completed other trials (ClinicalTrials.gov Identifiers; NCT04374253 and NCT04339413)
- At-home administration (ClinicalTrials.gov Identifier; NCT04592341)

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/NCT01224106
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-019895-66/results
- https://forpatients.roche.com/en/trials/neurodegenerative-disorder/ad/a-study-of-gantenerumab-in-participants-with-prodromal--48625.html

If you would like to find out more about the results of Part 1 and Part 2 of this study, the full title of the relevant scientific paper is: "A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease". The authors of the scientific paper are: Susanne Ostrowitzki, Robert A. Lasser, Ernest Dorflinger, Philip Scheltens, Frederik Barkhof, and others. The paper was published in 2017 in the journal *Alzheimer's Research & Therapy*, volume number 9(1), on pages 1–15.

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-of-gantenerumab-in-participants-with-prodromal--48625.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 study 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 of Gantenerumab in Participants With Prodromal Alzheimer's Disease”.

The study is known as SCarlet RoAD.

- The protocol number for this study is: WN25203.
- The ClinicalTrials.gov identifier for this study is: NCT01224106.
- The EudraCT number for this study is: 2010-019895-66.