Summary of Clinical Trial Results

A study to find out if a new medicine (semorinemab) is effective and safe for people with Alzheimer's disease

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).

This summary is written for:

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

This summary is based on information known at the time of writing.

The study started in October 2017 and the second part of the study (open-label extension) was stopped early – in May 2021 – because the medicine being studied did not work as well as expected.

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

Thank you to the people who took part in this study

The people who took part have helped researchers answer important questions about early Alzheimer's disease and the medicine that was studied – "semorinemab".

Key information about this study

- This study was done to find out if a new medicine was effective for people with early Alzheimer's disease.
- In this study, people were given either the medicine being studied (semorinemab) or a placebo – it was decided by chance which treatment each person was given.
- This study included 457 people in 13 countries.
- The main finding was that semorinemab was not effective for people with early Alzheimer's disease.
- Two people (0.6%) out of 311 who got semorinemab had a serious side effect, compared to none (0%) of the 130 who got placebo.
- Early results showed that semorinemab did not work as well as expected for people with early Alzheimer's disease. As a result, the second part of the study (open-label extension) was stopped early.

1. General information about this study

Why was this study done?

Alzheimer's disease is the most common cause of dementia. It affects about 4.5 million people in the United States and 26.6 million people around the world.

People with Alzheimer's disease undergo changes to brain cells. "**Plaques**" form between cells and "**tangles**" form inside cells.

Plaques are sticky clusters of protein fragments that build up between nerve cells. They contain a protein called "**beta-amyloid**". Tangles are twisted protein strands inside cells. The tangles contain a protein called "**tau**".

In healthy people, the tau protein keeps strands straight (parallel), but tau collapses and is tangled up in people with Alzheimer's disease. When tangles form, it disrupts the smooth flow of supplies inside cells, and causes cell death.

The **different stages of Alzheimer's disease** are diagnosed based on how well the patient functions and his/her reasoning ability – functional and cognitive decline. Available medicines can improve the symptoms of Alzheimer's disease for some people, but do not slow the progression of the disease.

Semorinemab is a new medicine. It is an antibody against tau. Semorinemab binds to all six forms (isoforms) of tau found outside the cell. It could stop or slow down the cell-to-cell spread of the toxic effects of tau.

This study was done to find out if semorinemab could be used to treat diseases that are related to tau, such as Alzheimer's disease. People who participated in the study had early ("prodromal" or "mild") Alzheimer's disease.

What were the study medicines?

This study looked at 2 treatments and a radio-labeled chemical:

- **Semorinemab** is a new medicine that could be useful for treating people with Alzheimer's disease. It is an antibody that binds to tau protein outside cells – semorinemab could prevent these tau proteins from causing tangles inside cells.
- Some people got a "**placebo**" treatment. The placebo looked similar to semorinemab, but did not contain any real medicine. By comparing the effects of semorinemab to the placebo, researchers could figure out the real effect of the medicine.
- People had brain scans – called "positron emission tomography" or "PET" scans. They were given a radio-labeled chemical – **[^{18}F]GTP1** - before the brain scan. The [^{18}F]GTP1 label binds to tau, and was used to measure the amount and location of tau tangles in the PET scans.

What did researchers want to find out?

The main questions that researchers wanted to answer were:

1. Was there any improvement in early Alzheimer's disease symptoms for people who got semorinemab treatment in comparison to those who got placebo?
2. Was semorinemab safe and tolerable in comparison to placebo?

What kind of study was this?

There are several ways to describe this study.

- **Phase 2 study**
  Phase 2 studies are carried out to find out if the study medicines are effective for people with specific diseases. It also means that semorinemab had previously been tested and found to be safe for use in healthy volunteers – in an earlier phase 1 study.
- **Randomized study**
  A computer randomly decided which person joined which medicine group and which person joined the placebo group. Researchers and people had no control over this.
- **Double-blind study**
  The researchers and people in the study did not know who was getting the study medicine and who was getting the placebo. That made this a double-blind study.
- **Placebo-controlled study**
  Some people got the real medicine while others got a placebo. This was done so that everyone got a treatment, and the real effect of the medicine could be compared against the placebo.
- **Parallel-group study**
  A parallel group study compares two or more treatments. People are randomly assigned to treatment groups. After the study is completed, results for the different treatment groups are compared.

When and where did the study take place?

The study started in October 2017 and stopped early because semorinemab did not work as well as expected in early Alzheimer's disease. This summary presents the results of the study up until it was stopped in May 2021.

The study took place at 97 study centers – across 13 countries:

- Australia (4 study sites)
- Belgium (3 study sites)
- Canada (6 study sites)
- Denmark (2 study sites)
- France (8 study sites)
- Germany (5 study sites)
- Great Britain (2 study sites)
- Italy (4 study sites)
- Netherlands (2 study sites)
- Poland (10 study sites)
- Spain (12 study sites)
- Sweden (2 study sites)
- United States (37 study sites)

2. Who took part in this study?

Four hundred and fifty-seven people with early Alzheimer's disease took part in this study.

- They were between 50 and 81 years old.
- Half of the people on the study were over 71 years old and half were below this age (median age = 71 years old).
- There were 253 women and 204 men who took part in the study.

The people in this study joined 4 treatment groups:

	Placebo	Semorinemab 1500 mg	Semorinemab 4500 mg	Semorinemab 8100 mg
Number of people who joined the study	135	94	136	92
Number of women	75	51	79	48
Number of men	60	43	57	44
Youngest age (years)	50	51	50	51
Oldest age (years)	81	81	81	80
Most common age (median years)	71	71	71	71

People could take part in the study if:

- They were between 50 and 80 years old.
- They met the medical criteria for "mild Alzheimer's disease" or "prodromal Alzheimer's disease".
- They tested positive for Alzheimer's disease through a brain scan (PET scan) or "CSF test". The CSF (cerebrospinal fluid) test uses fluid collected from the spine to look for proteins associated with Alzheimer's disease.
- Memory tests indicated poor memory function.

People could not take part in the study if:

- They could not tolerate imaging procedures (magnetic resonance imaging – MRI).
- They could not tolerate both of these procedures – PET scan and CSF test.
- They did not meet the height-weight ratio (body mass index greater than 40).
- They were hospitalized recently – before the study started.
- They had a planned procedure or surgery that would interfere with the study.
- They recently received a blood transfusion or had one planned for the near future.
- They had a history of certain kinds of cancer, infections, or immune problems.
- They had other types of brain or mental health disorders.

3. What happened during the study?

There were two treatment phases, a double-blind study followed by an open-label extension.

Double-blind study: 457 people were selected by chance to get one of 4 treatments.

- A computer selected the treatment for each person at random.
- In every round, 3 people joined the placebo group, 2 people joined semorinemab 1500 mg, 3 people joined semorinemab 4500 mg, and 2 people joined semorinemab 8100 mg.
- The computer program balanced out (stratified) the 4 groups so that the same proportion of people in each group had:
    - The same level of disease (mild Alzheimer's disease or prodromal Alzheimer's disease).
    - The same level of genetic risk (presence of *APOE* gene associated with Alzheimer's disease).
- People got their treatment through an IV (intravenously).
    - They were treated once every two weeks for the first 3 doses.
    - Starting with the fourth dose, they were treated once every 4 weeks.
- People were treated for 68 weeks. They could receive a total of 19 doses.
- A doctor saw everyone at 12 weeks after his or her last treatment. Some people joined a second treatment phase and their last doctor visit came much later.

Open-label extension (OLE) study: 360 people who completed the double-blind study joined a second treatment phase – the OLE study.

- Everyone got the same treatment (semorinemab 4500 mg, once every 4 weeks, by IV) in the OLE study.
- People could be treated for up to 96 weeks during the OLE phase.
- A doctor saw everyone at 12 weeks after his or her last treatment.

People who provided results about whether the treatment worked:

- They received at least one dose of the treatment and had at least one measurement of their disease after treatment. The "Clinical Dementia Rating Scale – Sum of Boxes" (CDR-SB) test was used for measuring whether they experienced any improvements. The test measured how well a person was able to remember, process information, and perform their everyday activities.

People who provided results about whether the treatment was safe:

- They received at least one dose of semorinemab, placebo, or [^{18}F]GTP1.

Details for the treatment groups:

	Placebo	Semorinemab 1500 mg	Semorinemab 4500 mg	Semorinemab 8100 mg
People who joined group	135	94	136	92
People who provided results about whether the medicine worked	126	86	126	84
People who provided results about whether the medicine was safe	130	89	132	90

4. What were the results of the study?

Question 1: Was there any improvement in Alzheimer's disease symptoms for people who got semorinemab treatment in comparison to those who got placebo?

Early results showed that semorinemab did not work as well as expected in early Alzheimer's disease. As a result of this, the OLE phase of the study was stopped by the sponsor in May 2021.

Question 2: Was semorinemab safe and tolerable in comparison to placebo?

Semorinemab was safe enough and tolerable for people at all the doses tested.

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 happened during the study.

- They are described in this summary because the study doctor believes the side effects were potentially related to the treatments in the study.
- Not all of the people in this study had all of the side effects.
- Side effects may be mild to very serious 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, or those that appear on the medicine leaflet.
- Serious and common side effects 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 the double-blind phase of the study:

- Two people out of 311 who were treated with semorinemab had a serious side effect thought to be potentially caused by the study treatment. Both persons were in the 4500 mg treatment group. The serious side effects were:
  - One person experienced slowing of the heart rate (bradycardia).
  - One person experienced feeling very sad (major depression).
- None of the 130 people who were treated with placebo had any serious side effects thought to be potentially caused by the treatment

During the OLE phase of the study:

- None of the 360 people had any serious side effects potentially thought to be caused by treatments (semorinemab or placebo).

Deaths:
Five people died while on the study. None of the deaths were thought to be related to the study treatments.

- Four people died during the double-blind phase of the study due to:
  - COVID-19 infection.
  - Euthanasia - the person chose to end his life with the help of medical professionals in a part of the world where this act is legally.
  - Road traffic accident.
  - Sudden death.
- One person died during the OLE phase of the study. The cause of death was:
  - Bacterial infection in the blood - Staphylococcal bacteremia.

Stopping treatment due to side effects:
During the study, some people decided to stop taking their medicine because of side effects:

- In the semorinemab treatment groups, 14 out of 311 people (4.5%) stopped their treatment.
- In the placebo treatment group, 8 out of 130 people (6.2%) stopped their treatment.

Most common side effects

Double-blind treatment phase:

During the double-blind treatment phase, 71 people had a side effect that was not considered serious but was potentially thought to be caused by the study treatment. This included:

- Sixteen people (12.3%) in who received placebo treatments.
- Fifty-five people (17.7%) who received semorinemab treatments.

While many of the side effects were only seen in one person, we will list the most common side effects – those seen in two or more people in the study.

These are the common side effects seen during the double-blind treatment phase:

	Placebo treatment (130 people)	Semorinemab treatment (311 people)
Side effect:	**People with side effect:**	**People with side effect:**
Reaction to the IV infusion	3 (2.3%)	25 (8.0%)
Headache	1 (0.8%)	3 (1.0%)
"Hemosiderin" deposit in the brain	1 (0.8%)	2 (0.6%)
Feeling dizzy	1 (0.8%)	2 (0.6%)
Abnormal blood test (live function test increased)	1 (0.8%)	1 (0.3%)
Blood pressure increased	1 (0.8%)	1 (0.3%)
Feeling tired	1 (0.8%)	1 (0.3%)
Small bleed in the brain (cerebellar microhemorrhage)	1 (0.8%)	1 (0.3%)

OLE treatment phase:
Eleven of the 360 people (3.1%) in the OLE treatment phase had a side effect. The most common side effect was reaction to the IV infusion seen in 5 people (1.4%). The other side effects were not common and only seen in one person each.

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 a single study of 457 people with early Alzheimer's disease. These results helped researchers learn more about early Alzheimer's disease and semorinemab.

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.**
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7. Are there plans for other studies?

At the time of writing this summary, another study looking at semorinemab in more advanced Alzheimer's disease was ongoing.

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/NCT03289143

https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-001800-31

https://forpatients.roche.com/en/trials/neurodegenerative-disorder/ad/a-study-to-evaluate-the-efficacy-and-safety-of-ro7105705-in-pati.html

If you would like to find out more about the results of this study:

The full title of the relevant scientific paper is: "A Phase 2 randomized trial of semorinemab in prodromal-to-mild Alzheimer's disease ".

The authors of the scientific paper are: Edmond Teng, Paul T. Manser, Karen Pickthorn, Flavia Brunstein, Mira Blendstrup, and others.

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/About.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 organized and paid for this study?

This study was organized and paid for by Genentech, Inc., South San Francisco, CA, USA. Genentech is part of F. Hoffmann-La Roche Ltd., with headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is:

> "A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, and Safety Study of MTAU9937A in Patients with Prodromal to Mild Alzheimer's Disease".

- The protocol number for this study is GN39763.
- The ClinicalTrials.gov identifier for this study is NCT03289143.
- The EudraCT number for this study is 2017-001800-31.