Clinical Trial Results

Research Sponsor: Eisai Ltd.

Drug Studied: Elenbecestat, also called E2609

Short Trial Title: A trial to learn how elenbecestat works and how safe it is in adults with early Alzheimer's disease

Thank you!

You took part in this clinical trial for the trial drug elenbecestat, also called E2609. You and all of the participants helped researchers learn more about whether elenbecestat can help adults with early Alzheimer's disease, also called EAD. People with Alzheimer's disease have problems with memory, thinking, and behavior that affect their activities of daily life. Alzheimer's disease gets worse over time. People with EAD have fewer and milder problems with memory and thinking than people with late Alzheimer's disease. These problems do not always affect their daily lives.

Eisai, a Japanese pharmaceutical company and the sponsor of this trial, thanks you for your help. Eisai is committed to improving health through continuing research in areas of unmet need and sharing with you the results of the trial you participated in. Eisai prepared this summary with a medical and regulatory writing organization called Synchrogenix.

If you participated in the trial and have questions about the results, please speak with the doctor or staff at your trial site.

What has happened since the trial started?

The trial started in December 2016 and ended in January 2020.

The sponsor of the trial reviewed the data collected and created a report of the results. This is a summary of that report.

The trial included 2212 participants from 206 sites in North and South America, Western and Eastern Europe, Japan, China, and other Asian countries.

Of the 2212 participants in this trial, 2209 participants received trial treatment at least once.

Why was the research needed?

Researchers were looking for a different way to treat people who have EAD. At the time of the trial and writing of this summary, there were no medications approved to treat EAD. Researchers thought elenbecestat could help people with EAD.

The researchers in this trial wanted to find out if elenbecestat works in a large number of adults with EAD. They also wanted to find out if people had any medical problems during the trial.

The main questions the researchers wanted to answer in this trial were:

- Did elenbecestat improve participants' memory and thinking compared with placebo after 24 months of treatment when it was measured using the Sum of Box score from the test called the Clinical Dementia Rating scale?
- Did elenbecestat improve participants' memory and thinking compared with placebo after 24 months of treatment when it was measured using combined scores from different tests when put together are called the Alzheimer's Disease Composite Score?
- Did elenbecestat reduce the level of amyloid in the brain compared with placebo after 24 months of treatment?
- What adverse events did participants getting elenbecestat have? An adverse event is a medical problem that may or may not be caused by the trial treatment.

It is important to know that this trial was designed to get the most accurate answers to the questions listed above. There were other questions the researchers wanted to answer to learn more about how elenbecestat works. But, these were not the main questions the trial was designed to answer.

What kind of trial was this?

To answer these questions, researchers asked for the help of men and women like you. The participants in the trial were 50 to 85 years old. Of these participants, 49% were male, and 51% were female.

All of the participants in this trial had EAD. They either had mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease. Cognitive impairment means that a person has trouble remembering, learning, or making decisions that affect their everyday life.

In this trial, each participant needed to have a study partner to complete the questionnaires and talk with the study staff. A study partner is a person who was able to support the participants during the trial and spent at least 8 hours per week with the participants.

This trial was "double-blind". This means that the participants, the study partners, the trial doctors and staff, and the sponsor did not know which trial treatment the participants received.

Participants received either placebo tablet or elenbecestat tablet 50 milligrams, also called mg, taken by mouth once each morning for up to 24 months. A placebo is a pill that looks like the trial treatment but does not have any medicine in it.

The figure below shows how treatment was given during this trial.

What happened during the trial?

During the Screening period, the trial doctors did a full check-up to make sure each participant could join the trial.

The trial doctors or staff also:

- Asked what medications each participant was taking
- Confirmed that the participant had EAD
- Took blood and urine samples
- Took pictures of the brain using a magnetic resonance imaging scan, also called an MRI scan
- Took pictures of the brain using a Positron Emission Tomography scan, also called a PET scan, if the participants agreed to have this done
- Took a small amount of fluid that is around the brain and spinal cord, if the participants agreed to have this done. This test is called a spinal tap. This is done by putting a needle into the area around the spine to collect some of the fluid.
- Checked each participant's heart health using an electrocardiogram, also called an ECG
- Asked participants and their study partners to complete the questionnaires

During the treatment period, the participants were randomly assigned to receive either elenbecestat or a placebo once each morning for up to 24 months.

Throughout the trial, the trial doctors or staff:

- Continued to check the participants' health, asked what medications they were taking, and took blood and urine samples
- Asked participants how they were feeling and if they had any adverse events
- Checked each participant's heart health
- Checked the participant's brain using an MRI scan
- Asked participants and their study partners to complete the questionnaires

During the trial, the study doctor asked the participants to stop receiving trial treatment if they had:

- Low numbers of white blood cells in the body
- Certain problems with their liver or skin
- Seizure
- Severe infection

They do this to protect the participants' health and well-being.

After a 24-month period, participants could continue to receive elenbecestat for another 24 months if they wanted to. But the trial was stopped early by the sponsor, so no participants received elenbecestat after the first 24 months.

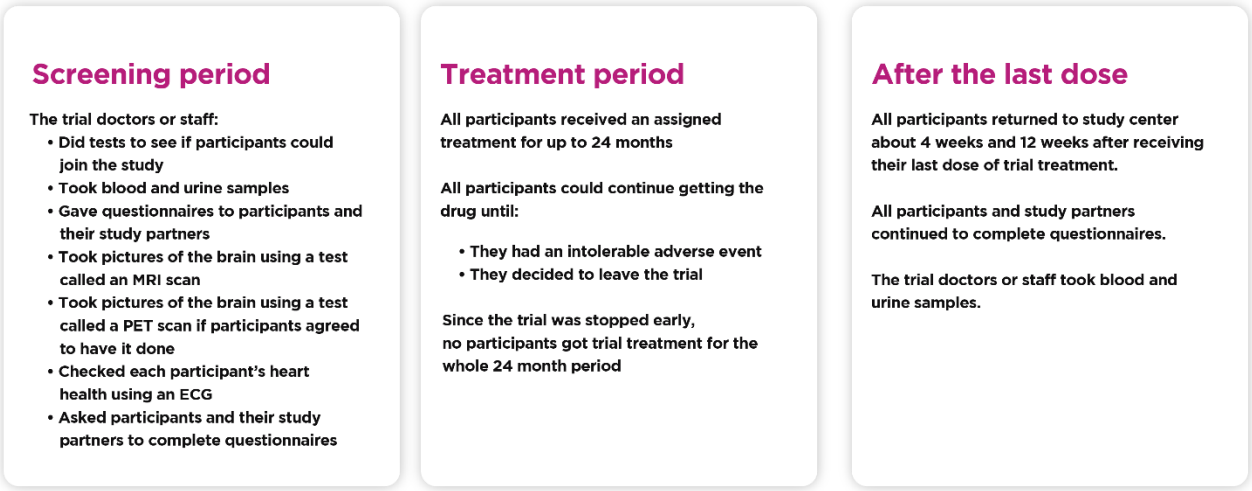
After their last dose, all participants returned to the study center about 4 weeks and 12 weeks later.

The participants:

- Had their blood and urine samples taken
- Continued to complete the questionnaires along with their study partners

The figure below shows how the trial was done.

How did this trial work?



What were the results of the trial?

This is a summary of the main results of this trial. The results each participant had might be different and are not in this summary. But the results each participant had are part of the summary of results. A full list of the questions researchers wanted to answer can be found on the websites listed at the end of this summary. When a scientific report of this clinical trial is available, it can be found on the websites listed at the end of this summary.

Researchers look at the results of many trials to decide which treatment options may work best and are well tolerated. Other trials may provide new information or different results. Always talk to a doctor before making any treatment decisions.

The information below includes results from the participants in 2 trials that were done the same way. The results from the participants in the 2 trials were combined to get enough information to see if the trial treatment helped to reduce participants' EAD symptoms. But both trials were stopped early by the sponsor once they learned that elenbecestat was not helpful in reducing EAD symptoms.

Did elenbecestat improve participants' memory and thinking compared with placebo after 24 months of treatment when it was measured using the Sum of Box score from the test called the Clinical Dementia Rating scale?

To answer the question, researchers interviewed participants and their study partner using the test called the Clinical Dementia Rating scale, or CDR. This test is used to look at a participant's memory and thinking. Each question in the CDR is given a score. One of the scores is called the Sum of Boxes, or SB. A decrease in the CDR-SB score means that EAD symptoms were improving.

The researchers recorded the participants' CDR-SB score before they received the trial treatment and then recorded the change in participants' CDR-SB score after 24 months of receiving trial treatment.

The researchers found that elenbecestat did not improve EAD symptoms compared with placebo after 24 months of treatment. Participants who received elenbecestat and participants who received placebo had increased CDR-SB score after 24 months of trial treatment.

Since the trial was stopped early, not all of the participants were able to complete the CDR-SB after 24 months of treatment. So, the results of the CDR-SB score are not available for all of the participants.

The table below shows the average change in participants' CDR-SB score after 24 months of treatment.

Average change in CDR-SB score after 24 months of treatment

	Out of 98 participants who completed 24 months of placebo	Out of 91 participants who completed 24 months of elenbecestat
Average change in CDR-SB score after 24 months of treatment	2.17	1.99

Did elenbecestat improve participants' memory and thinking compared with placebo after 24 months of treatment when it was measured using combined scores from different tests when put together are called the Alzheimer's Disease Composite Score?

To answer the question, researchers used different sets of tests to check the participants' memory and thinking. Each question in these tests is given a score. Some of the scores from these tests were combined to make the Alzheimer's Disease Composite Score, or ADCOMS. A decrease in the ADCOMS means that the EAD symptoms were improving.

The researchers recorded the participants' ADCOMS before they received the trial treatment and then recorded the change in participants' ADCOMS after 24 months of receiving trial treatment.

The researchers found that elenbecestat did not improve EAD symptoms compared to placebo after 24 months of treatment. Participants who received elenbecestat and participants who received placebo had increased ADCOMS after 24 months of treatment.

Since the trial was stopped early, not all of the participants were able to complete the tests needed for ADCOMS after 24 months of treatment. So, the results of the ADCOMS scores are not available for all of the participants.

The table below shows the average change in participants' ADCOMS after 24 months of treatment.

Average change in ADCOMS after 24 months of treatment

	Out of 128 participants who completed 24 months of placebo	Out of 115 participants who completed 24 months of elenbecestat
Average change in ADCOMS after 24 months of treatment	0.24	0.23

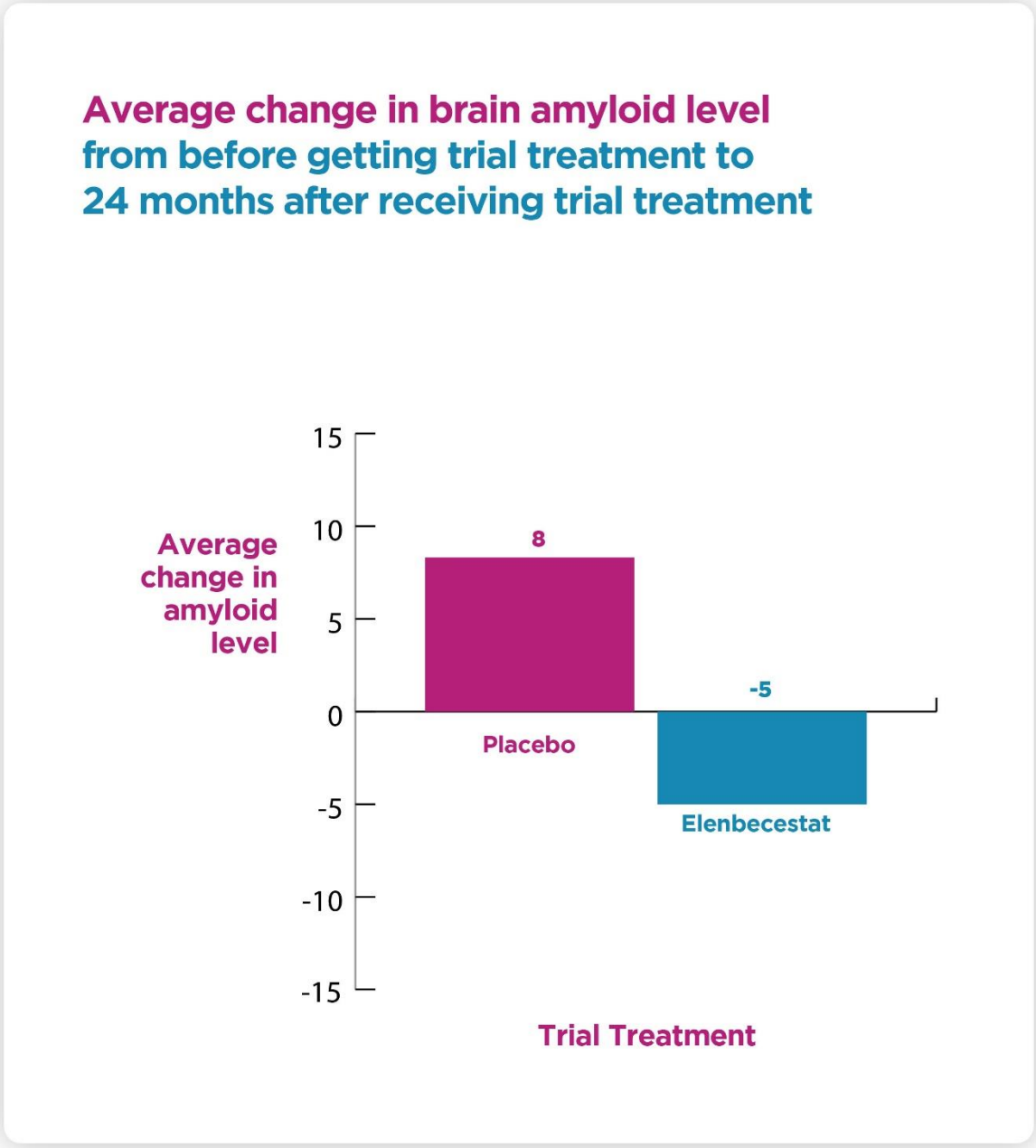
Did elenbecestat reduce the level of amyloid in the brain compared with placebo after 24 months of treatment?

Amyloid is a protein that can collect between the nerve cells in the brain as deposits of plaque. Too much amyloid is found in the brain among all people with Alzheimer's disease. The level of amyloid in the brain was measured using PET scan. A PET scan is a test that shows the inside of the brain, nerve cells, and the amount of amyloid in the brain.

To answer the question, researchers measured the participants' amyloid level using PET before they received the trial treatment and then recorded the change in participants' amyloid level after 24 months of receiving trial treatment.

After 24 months of trial treatment, the level of amyloid in the brain was significantly decreased in participants who received elenbecestat, while it was increased in participants who received placebo.

The chart below shows the average change in brain amyloid level after 24 months of trial treatment. A lower number means that there is less amyloid in the brain.



What medical problems did participants have?

Medical problems that happen in clinical trials are called “adverse events”. An adverse event is called “serious” when it is life threatening, causes lasting problems, or the participant needs to be admitted to a hospital.

This section is a summary of the adverse events that happened during this trial. These medical problems may or may not be caused by the trial drug. The websites listed at the end of this summary may have more information about the medical problems that happened in this trial. A lot of research is needed to know whether a drug causes a medical problem.

The results of all 2204 participants are included below. They received trial treatment at least once and were checked by trial doctors for medical problems at least once.

How many participants had adverse events?

In this trial,

- 807 out of 1105 participants (73%) who received the placebo had adverse events.
- 853 out of 1099 participants (78%) who received elenbecestat had adverse events.

The table below shows how many participants had adverse events in this trial while on treatment.

Adverse events in this trial

	Out of 1105 participants who received placebo	Out of 1099 participants who received elenbecestat
How many participants had adverse events?	807 (73%)	853 (78%)
How many participants had serious adverse events?	117 (11%)	134 (12%)
How many participants stopped receiving the trial drug because of adverse events?	68 (6%)	129 (12%)

What were the most common serious adverse events?

In this trial, 251 out of 2204 participants (11%) had serious adverse events while on treatment.

- 117 out of 1105 participants (11%) who received placebo had serious adverse events.
- 134 out of 1099 participants (12%) who received elenbecestat had serious adverse events.

In this trial, 5 out of 2204 participants (0.2%) died due to serious adverse events while on treatment. Out of these 5 participants who died, 2 participants received elenbecestat and 3 participants received placebo.

The table below shows the serious adverse events in the trial that happened in at least 0.2% of participants in either group while on treatment. There were other adverse events, but these happened in fewer participants.

Most common serious adverse events in this trial

	Out of 1105 participants who received placebo	Out of 1099 participants who received elenbecestat
Fall	4 (0.4%)	7 (0.6%)
Pneumonia	3 (0.3%)	5 (0.5%)
Flu	2 (0.2%)	5 (0.5%)
Fainting	1 (0.1%)	4 (0.4%)
Urinary tract infection	2 (0.2%)	3 (0.3%)
Broken hip	1 (0.1%)	3 (0.3%)
Cloudiness over lens of the eye	1 (0.1%)	3 (0.3%)
Broken thighbone	0	3 (0.3%)
Chest pain	3 (0.3%)	2 (0.2%)
Pain in joints of the body	6 (0.5%)	1 (0.1%)
Breast cancer	3 (0.3%)	1 (0.1%)
Pain in abdomen	3 (0.3%)	1 (0.1%)
Sudden heart attack	3 (0.3%)	1 (0.1%)
Heart attack	3 (0.3%)	0

What were the most common adverse events?

In this trial, 1660 out of 2204 participants (75%) had adverse events while on treatment.

The most common adverse events were common cold, infection of nose, throat, or voice box, urinary tract infection, dizziness, fall, and accidental overdose.

The table below shows the adverse events in the trial that happened in at least 5% of participants in either group while on treatment. There were other adverse events, but these happened in fewer participants.

Most common adverse events in this trial

	Out of 1105 participants who received placebo	Out of 1099 participants who received elenbecestat
Common cold	67 (6%)	71 (7%)
Lower numbers of white blood cells in the body	18 (2%)	71 (7%)
Fall	64 (6%)	67 (6%)
Accidental overdose	55 (5%)	66 (6%)
Rash	22 (2%)	61 (6%)
Infection of nose, throat, or voice box	50 (5%)	58 (5%)
Dizziness	46 (4%)	58 (5%)
Abnormal dreams	36 (3%)	57 (5%)
Urinary tract infection	56 (5%)	46 (4%)

How has this trial helped patients and researchers?

In this trial, researchers learned more about whether elenbecestat may have helped people with EAD.

Researchers look at the results of many trials to decide which treatment options may work best and are well tolerated. This summary shows only the main results from the 2 trials. Other trials may provide new information or different results.

Further clinical trials with elenbecestat are not planned.

Where can I learn more about the trial?

You can find more information about this trial on the websites listed below. When a scientific report of this clinical trial is available, it can be found on the websites listed below:

- http://www.clinicaltrials.gov - Once you are on the website, type **NCT03036280** into the search box and click "**Search**".
- http://www.clinicaltrialsregister.eu – Once you are on the website, type **2016-004128-42** into the search box and click "**Search**".

Full trial title: A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease

Protocol number: E2609-G000-302

Eisai, the sponsor of this trial, has headquarters in Tokyo, Japan, and regional headquarters in Woodcliff Lake, New Jersey, USA and Hatfield, Hertfordshire, UK. The phone number for general information is 44-845-676-1400.

Thank you

Eisai would like to thank you for your time and interest in participating in this clinical trial. Your participation has provided a valuable contribution to research and improvement in health care.

Eisai Co., Ltd. is a global research and development-based pharmaceutical company headquartered in Japan. We define our corporate mission as "giving first thought to patients and their families and to increasing the benefits health care provides," which we call our human health care (hhc) philosophy. With over 10,000 employees working across our global network of R&D facilities, manufacturing sites, and marketing subsidiaries, we strive to realize our hhc philosophy by delivering innovative products in multiple therapeutic areas with high unmet medical needs, including Oncology and Neurology. For more information, please visit http://www.eisai.com.

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Synchrogenix Headquarters 2951 Centerville Road, Suite 100 Wilmington, DE 19808
http://www.synchrogenix.com • 1-302-892-4800