Clinical Trial Results

Research Sponsor: Eisai Inc.

Drug Studied: E2027, also called irsenontrine

Short Trial Title: A trial to learn about how E2027 works and its safety in people with dementia with Lewy bodies or Parkinson's disease dementia with or without amyloid

Thank you!

You and your study partner took part in this clinical trial for the trial drug E2027, also called irsenontrine. You, your study partner, and all of the participants helped the researchers learn more about E2027 to help people with dementia with Lewy bodies, also called DLB, or Parkinson's disease dementia, also called PDD. In DLB or PDD, Lewy bodies are tiny clumps of proteins that develop inside nerve cells of the brain. They prevent the cells from communicating properly, eventually causing cells to die. These changes can lead to difficulties in memory, thinking, movement, concentration, alertness, and hallucination. Hallucination is seeing things that are not there. The symptoms of DLB and PDD get worse over time. Some people with DLB or PDD can also have clumps of protein called amyloid outside of nerve cells in the brain. This is the same amyloid that is found in the brains of people with Alzheimer's disease.

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 Certara 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 February 2021 and ended in January 2022.

The trial included 34 participants from 15 sites in the United States and Canada. All 34 participants received E2027 at least once. There was no placebo used in this study.

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

Why was the research needed?

Researchers were looking for a different way to treat people who have DLB and PDD. At the time of the trial and writing of this summary, there were no medications approved to treat DLB in the United States and European Union. Researchers thought that E2027 could help control the symptoms of people with DLB and PDD, and it might work differently in people with DLB or PDD that also have amyloid in the brain compared to people with DLB or PDD that do not have amyloid in the brain.

The researchers in this trial wanted to find out if E2027 works in people with DLB or PDD differently based on whether or not they also have amyloid. To know this, the researchers measured the levels of a substance called cyclic guanosine monophosphate (or cGMP) in the fluid surrounding the spinal cord, also known as spinal fluid. The substance cGMP is involved in how cells communicate within the brain. E2027 works by increasing cGMP in the brain and spinal fluid.

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 E2027 help increase the level of cGMP in participants with DLB or PDD after 9 weeks of treatment and did the presence of amyloid influence E2027's effect on the cGMP levels?
- What adverse reactions did participants receiving E2027 have? An adverse reaction is a medical problem that may be caused by the trial drug.

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 E2027 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 61 to 84 years old. Of these participants, 62% were male, and 38% were female.

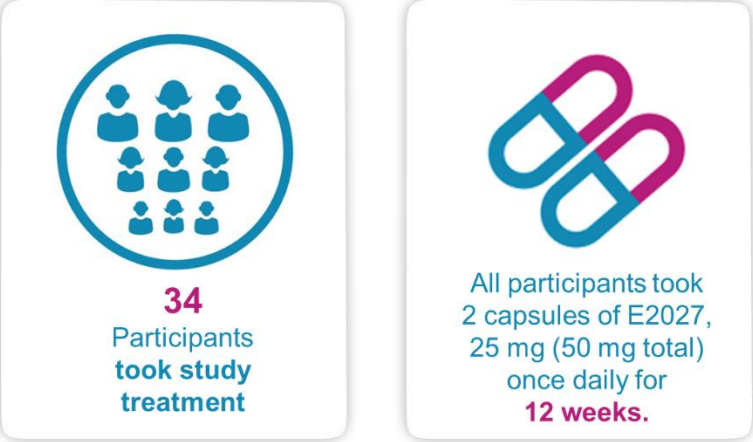
All of the participants in this trial had DLB or PDD. They also had either mild or moderate cognitive impairment. Cognitive impairment means that a person has trouble remembering, learning, or making decisions that affect their everyday life.

All of the participants needed to have a study partner. A study partner was a person who was able to support the participant during the trial and spent at least 20 hours per week with the participant.

For participants with DLB, participants should have experienced visual hallucinations.

This trial was "open-label". This means that the participants, their study partners, the trial doctors and staff, and the sponsor knew that the participants received E2027.

The participants took 2 capsules of E2027 25 milligrams, also called mg, by mouth once daily for 12 weeks. The participants took a total of 50 mg of E2027 daily. The figure below shows how treatment was given in your trial.



What happened during the trial?

Before the trial started, the trial doctors did a full check-up to make sure each participant could join the trial. The trial doctors also:

- Asked what medicines each participant was taking
- Took blood and urine samples
- Checked each participant's heart health
- Asked participants to complete questionnaires with their study partners
- Took pictures of the brain using a magnetic resonance imaging scan, also called an MRI scan

Before the participants started treatment with E2027, the researchers took a sample of the spinal fluid by inserting a needle into the lower spine. The trial doctors then measured the level of cGMP in the participants' spinal fluid.

The trial doctors also did a blood test to check whether participants were more or less likely to have amyloid in the brain.

On the day before the start of treatment, the participants were categorized into 4 study groups based on whether they had DLB or PDD with or without amyloid.

Group A: DLB without amyloid	Group B: DLB with amyloid	Group C: PDD without amyloid	Group D: PDD with amyloid
10 participants	11 participants	10 participants	3 participants

During the trial, the participants took 2 capsules of E2027 25 mg by mouth, a total of 50 mg, once daily for a total of 12 weeks.

Throughout the trial, the trial doctors:

- Continued to check the participants' health, took blood and urine samples, and checked their heart health
- Asked participants how they were feeling, if they had any medical problems, and what medicines they were taking
- Asked participants to complete questionnaires with their study partners
- Took another sample of the spinal fluid on Week 9 and measured the cGMP levels in the spinal fluid again

Four weeks after their last dose, all participants and their study partners returned to the trial center

The participants:

- Were asked how they were feeling, if they had any medical problems, and what medicines they were taking
- Were checked for their heart health
- Continued to complete questionnaires with their study partners

The figure below shows how the trial was done:

How did this trial work?

Before the trial

The trial doctors or staff:

- Confirmed that the participants had DLB or PDD
- Checked the participants' overall health and asked them to complete questionnaires with their study partners
- Took a picture of the brain
- Took a sample of the spinal fluid and measured cGMP level in spinal fluid
- Did a blood test to check for amyloid, and categorized the participants into 4 study groups

During the trial

All participants who could join the trial took E2027 for 12 weeks.

The trial doctors or staff:

- Continued to check participants' health and asked if they had medical problems
- Asked participants to complete questionnaires with their study partners
- Took another sample of the spinal fluid at Week 9 and measured cGMP level again

After their last dose

All participants returned to study center about 4 weeks after receiving their last dose of E2027.

The trial doctors or staff checked the participants' health and asked how they were feeling. All participants and continued to complete questionnaires with their study partners.

What were the results of the trial?

The results each person had might be different and are not in this summary. But the results each person 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. If a full report of the trial results is available, it can also be found on these websites.

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.

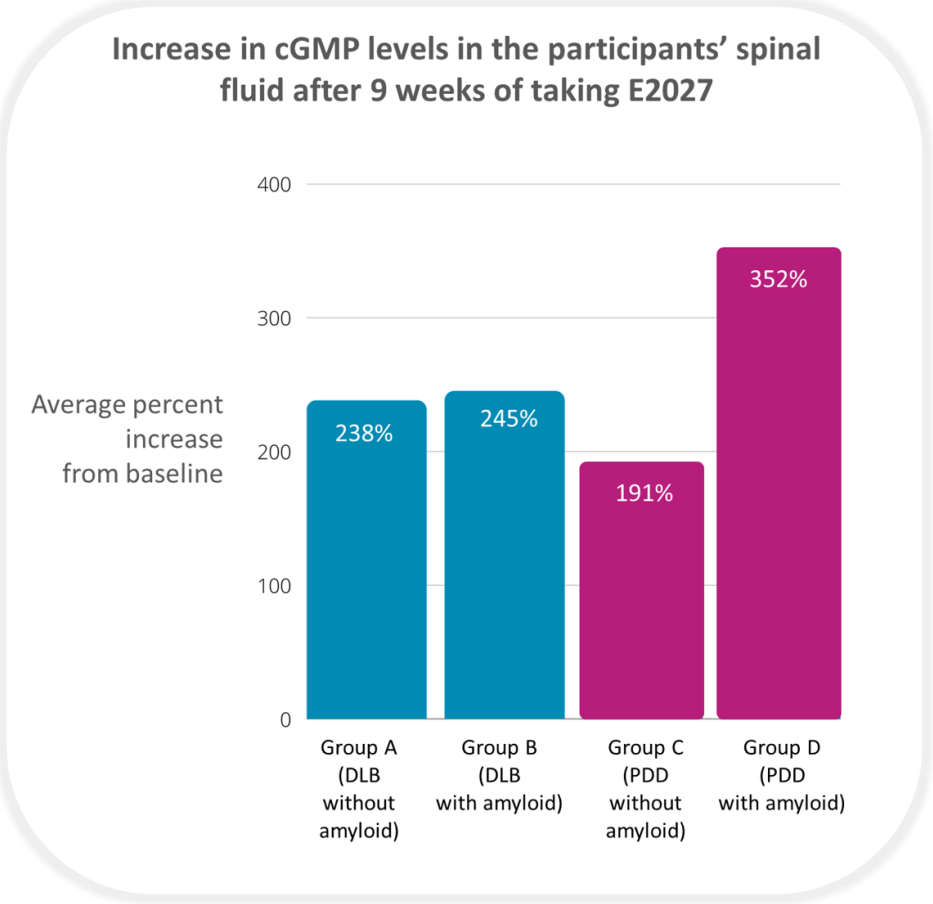
Did E2027 help increase the level of cGMP in participants with DLB or PDD after 9 weeks of treatment and did the presence of amyloid influence E2027's effect on the cGMP levels?

To answer this question, researchers measured the level of cGMP in the participants' spinal fluid before taking E2027 (also called baseline cGMP level) and again after 9 weeks of taking E2027. Researchers then looked at how much the levels of cGMP increased at Week 9 compared to baseline. This is called the "percent increase from baseline" in cGMP levels.

Then, the researchers compared the results of participants in Group A (DLB without amyloid) with Group B (DLB with amyloid), then Group C (PDD without amyloid) with Group D (PDD with amyloid) to help understand the possible influence of amyloid on the effect of E2027 on cGMP levels.

Overall, all participants had an increase in the cGMP levels. However, the percent increase in cGMP levels was similar among the participants who had DLB with and without amyloid. In participants with PDD, a greater increase in cGMP levels was seen in those with amyloid than those without it, although the number of participants in this group was too small for a clear comparison with the other groups.

The chart below shows the average percent increases in cGMP levels in the participants' spinal fluid.



What medical problems did participants have?

Medical problems that happen in clinical trials are called “adverse events”. An adverse event that the trial doctors thought was caused by the trial drug is called an “adverse reaction”. An adverse reaction 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 reactions that happened during this trial.

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.

How many participants had adverse reactions?

In this trial, 6 out of 34 participants (18%) had adverse reactions. Two participants stopped treatment with E2027 because of adverse reactions.

The table below shows how many participants had adverse reactions.

Adverse Reactions in This Trial

	Out of 10 participants in Group A (DLB without amyloid)	Out of 11 participants in Group B (DLB with amyloid)	Out of 10 participants in Group C (PDD without amyloid)	Out of 3 participants in Group D (PDD with amyloid)	Out of all 34 participants who received E2027
How many participants had adverse reactions?	2 (20%)	1 (9%)	1 (10%)	2 (67%)	6 (18%)
How many participants had serious adverse reactions?	0	0	0	0	0
How many participants stopped receiving the trial drug because of adverse reactions?	1 (10%)	0	1 (10%)	0	2 (6%)

What were the most common serious adverse reactions?

None of the participants had a serious adverse reaction in this trial.

No participant died due to adverse reactions in this trial. One participant who had DLB without amyloid died in this trial, but the death was not thought by the trial doctors to be related to E2027. The death occurred after the 12-week treatment period.

What were the most common adverse reactions?

In this trial, 6 out of 34 participants (18%) had an adverse reaction. All adverse reactions were experienced by 1 participant each. The following were the adverse reactions experienced during the trial.

- Nausea
- Sensitivity to temperature
- Feeling restless or difficulty sitting still
- Dizziness
- Feeling aggressive
- Feeling agitated
- Hallucination
- Changes in mental status
- Restlessness
- Feeling dizzy upon sitting up or standing up

How has this trial helped patients and researchers?

In this trial, researchers learned more about how E2027 may help people with DLB or PDD.

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 this one trial. Other trials may provide new information or different results.

Further clinical trials with E2027 are not planned.

There was 1 clinical trial completed by Eisai with E2027 that focused on learning about how E2027 works and its safety in patients with dementia with Lewy bodies. Details about this clinical trial are:

Full Title	A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Study to Evaluate the Efficacy, Safety and Tolerability of E2027 in Subjects With Dementia With Lewy Bodies
Protocol number	E2027-G000-201
US Study number	NCT03467152
https://clinicaltrials.gov/ct2/show/NCT03467152	

Where can I learn more about the trial?

You can find more information about this trial on the websites listed below. If a full report of the trial results is available, it can also be found here:

- http://www.clinicaltrials.gov - Once you are on the website, type **NCT04764669** into the search box and click "**Search**".

Full trial title: An Open-Label Study To Evaluate the Pharmacodynamic Effects, Efficacy, Safety, and Tolerability of E2027 in Subjects With Dementia With Lewy Bodies or Parkinson's Disease Dementia With or Without Amyloid Copathology

Protocol number: E2027-A001-203

Eisai, the sponsor of this trial, has headquarters in Tokyo, Japan, and regional headquarters in Nutley, 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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