Clinical Trial Results

Research Sponsor: Eisai Ltd.

Drug Studied: Lemborexant, also called Davigo™ or E2006

Short Trial Title: A trial to learn how lemborexant works and how safe it is in adults with Irregular Sleep-Wake Rhythm Disorder and mild to moderate Alzheimer's Disease Dementia

Thank you!

You took part in this clinical trial for the trial drug lemborexant, also called E2006. You and all of the participants helped researchers learn more about whether lemborexant can help adults with Irregular Sleep-Wake Rhythm Disorder, also called ISWRD, and Alzheimer's disease dementia, also called AD-D. People with AD-D have problems with memory, thinking, behavior, and sleep. They can spend much of the night awake, and much of the day time hours asleep. When periods of sleep are spread out over the 24-hour day instead of in a steady period of sleep at night, it is called ISWRD.

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 July 2018.

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 63 participants from 57 sites in Japan, the United Kingdom, and the United States.

Of the 63 participants in this trial, 62 participants got at least 1 dose of trial treatment.

Why was the research needed?

Researchers were looking for a different way to treat people who have ISWRD and mild to moderate AD-D. At the time of the trial, there were no medications approved to treat ISWRD. Lemborexant has been shown to help people who have problems sleeping at night, also called insomnia. These people did not have ISWRD or AD-D. Researchers think lemborexant could help patients with ISWRD sleep better at night and stay awake more in the daytime.

The researchers in this trial wanted to find out if lemborexant works in a large number of adults with ISWRD and mild to moderate AD-D. 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:

- Which dose or doses of lemborexant increased actigraphy-derived sleep efficiency, also called aSE after 4 weeks of treatment?
- Which dose or doses of lemborexant increased the actigraphy-derived wake efficiency, also called aWE after 4 weeks of treatment?
- Which dose or doses of lemborexant increased quiet sleep periods and increased the ability of participants' circadian rhythm to tell the difference between night and day?
- Did any dose or doses of lemborexant make the scores on tests of mental function worse?
- What adverse events did participants getting lemborexant have? An adverse event is a medical problem that may or may not 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 lemborexant 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 64 to 89 years old. 40% of the people were male, and 60% of the people were female.

All of the participants in this trial had ISWRD and mild to moderate AD-D. ISWRD happens often in people with AD-D, and can worsen the problems with memory, thinking, and behavior that are associated with AD-D.

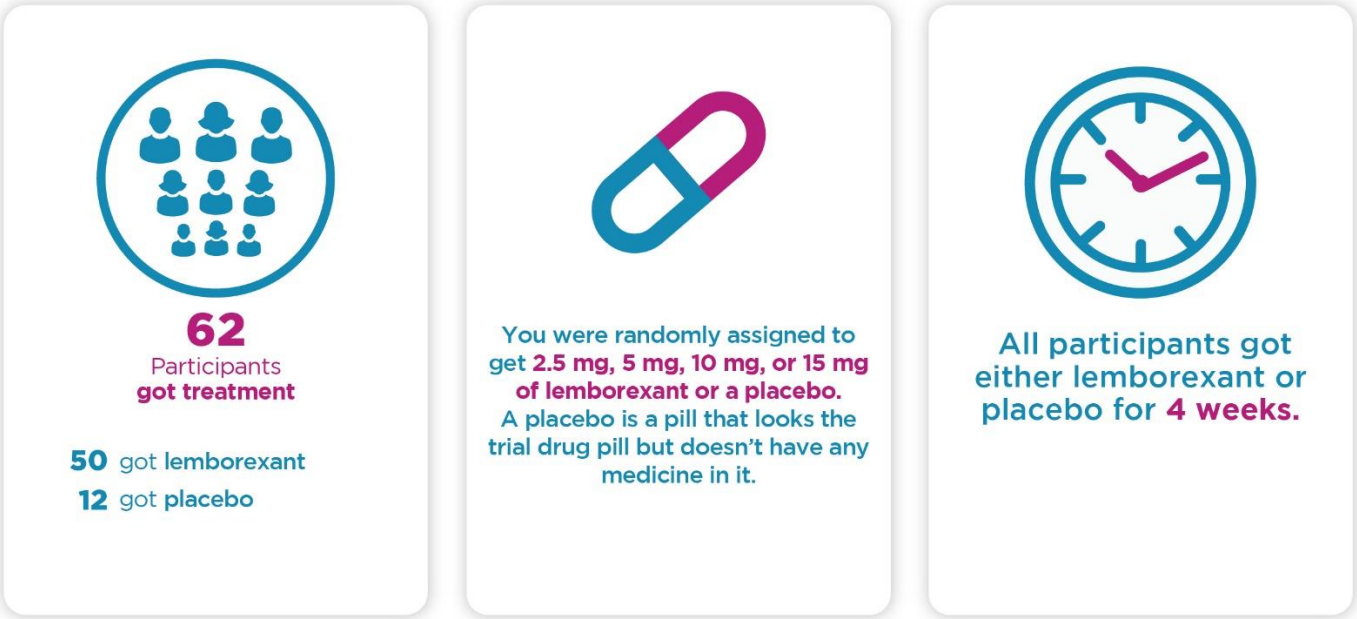
In this trial, since the participants were elderly and had AD-D, their caregivers also enrolled so that they could provide information and complete questionnaires. The

caregivers completed the sleep logs and questionnaires on behalf of the participants.

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

You got lemborexant or a placebo by mouth once each night before bedtime for 4 weeks. A placebo is a pill that looks like the trial drug pill but does not have any medicine in it.

The figure below shows how treatment was given during your 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. This period lasted for up to 6 weeks.

The trial doctors or staff also:

- Asked what medications each participant was taking
- Confirmed that the participant had ISWRD and mild to moderate AD-D
- Asked participants to wear an actigraph, which is a device that measures body movement
- Took blood and urine samples
- Checked each participant's heart health using an electrocardiogram, also called an ECG
- Asked caregivers to complete questionnaires on behalf of the participants
- Asked caregivers to complete sleep logs on behalf of the participants

During the treatment period, participants were randomly assigned to get either 2.5 mg, 5 mg, 10 mg, or 15 mg of lemborexant or a placebo each night for 4 weeks. Participants wore an actigraph during the treatment period.

Throughout the trial, the trial doctors or staff:

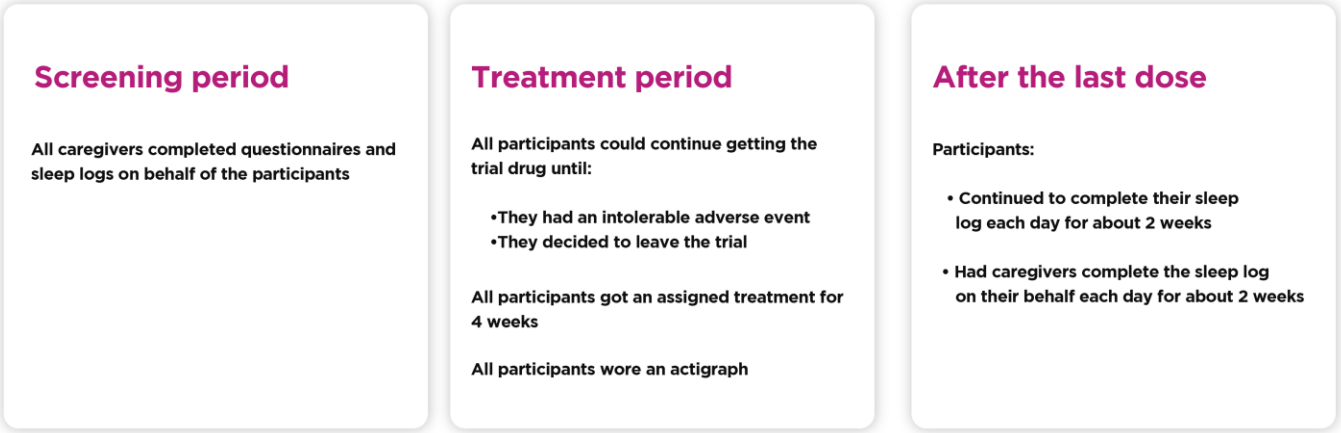
- Continued to check the participants' health, asked what medications they were taking, and took blood and urine samples
- Asked caregivers about how participants were feeling and if they had any adverse events
- Asked caregivers to complete questionnaires on behalf of participants
- Asked caregivers to complete sleep logs on behalf of participants
- Checked each participant's heart health

After their last dose, all participants:

- Continued to wear the actigraph
- Had caregivers complete questionnaires and the sleep logs on their behalf
- Returned to the clinic approximately 2 weeks later for their final visit and tests

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 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.

Which dose or doses of lemborexant increased aSE after 4 weeks of treatment?

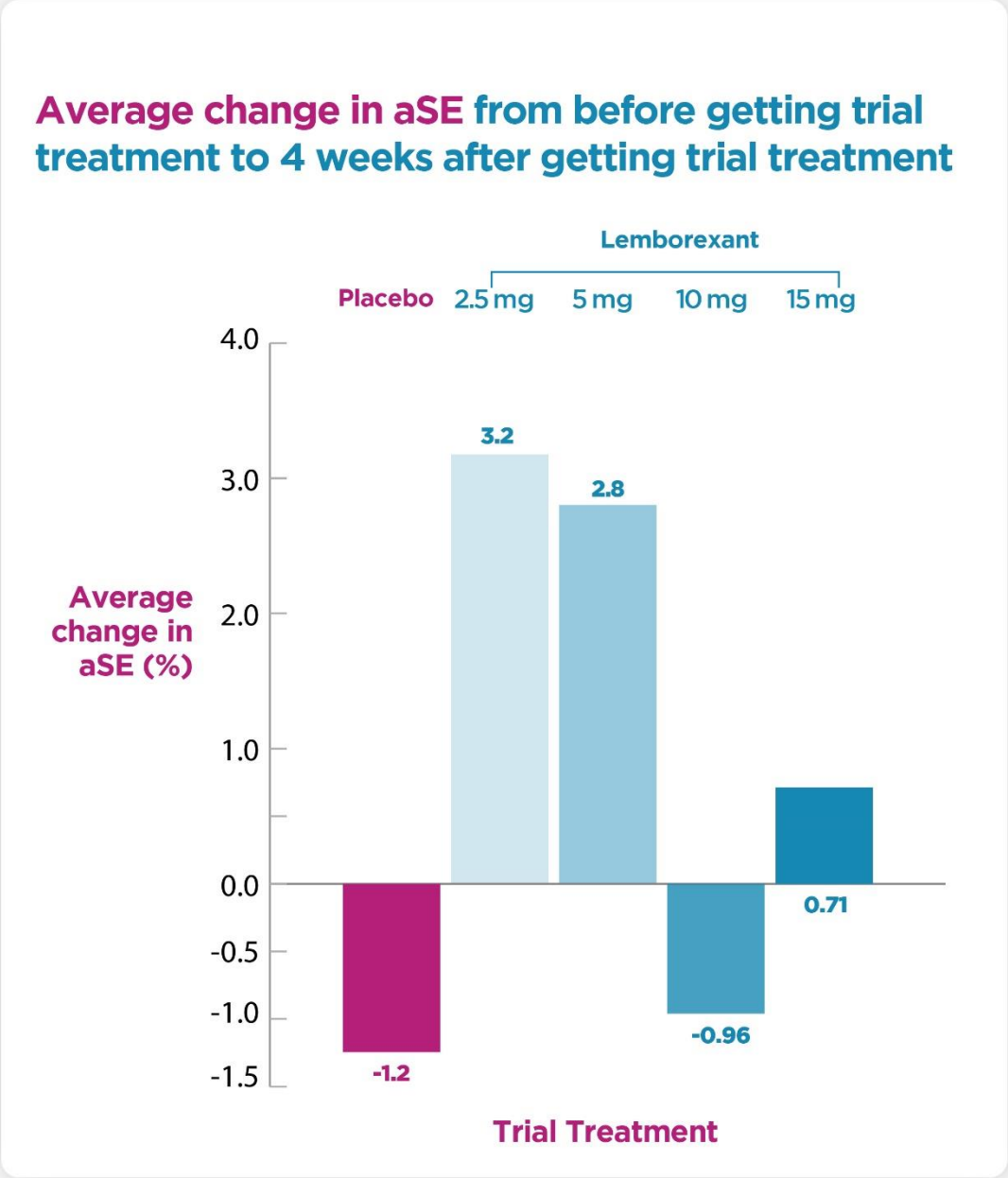
To see if participants' aSE increased after getting the trial treatment, researchers measured the participants' aSE before they got the trial treatment and then measured the average change in participants' aSE after 4 weeks of getting trial treatment.

aSE is the amount of time a person is actually asleep during the time spent in bed trying to sleep. This was measured by the actigraph that the participants wore.

Actigraphy is a way to measure sleep time and wake time by recording the amount of movement a person has while in bed or while awake during the day time. An actigraph, which looks like watch, is worn on the wrist to record this information.

None of the doses of lemborexant significantly increased participants' aSE more than placebo after 4 weeks of trial treatment. But, the 2.5 mg and 5 mg doses of lemborexant increased aSE more than the other doses and placebo did. The placebo and 10 mg dose of lemborexant decreased aSE, but the decrease was not significant.

The chart below shows the average change in participants' aSE after 4 weeks of trial treatment. Higher numbers mean that there is more improvement in aSE.



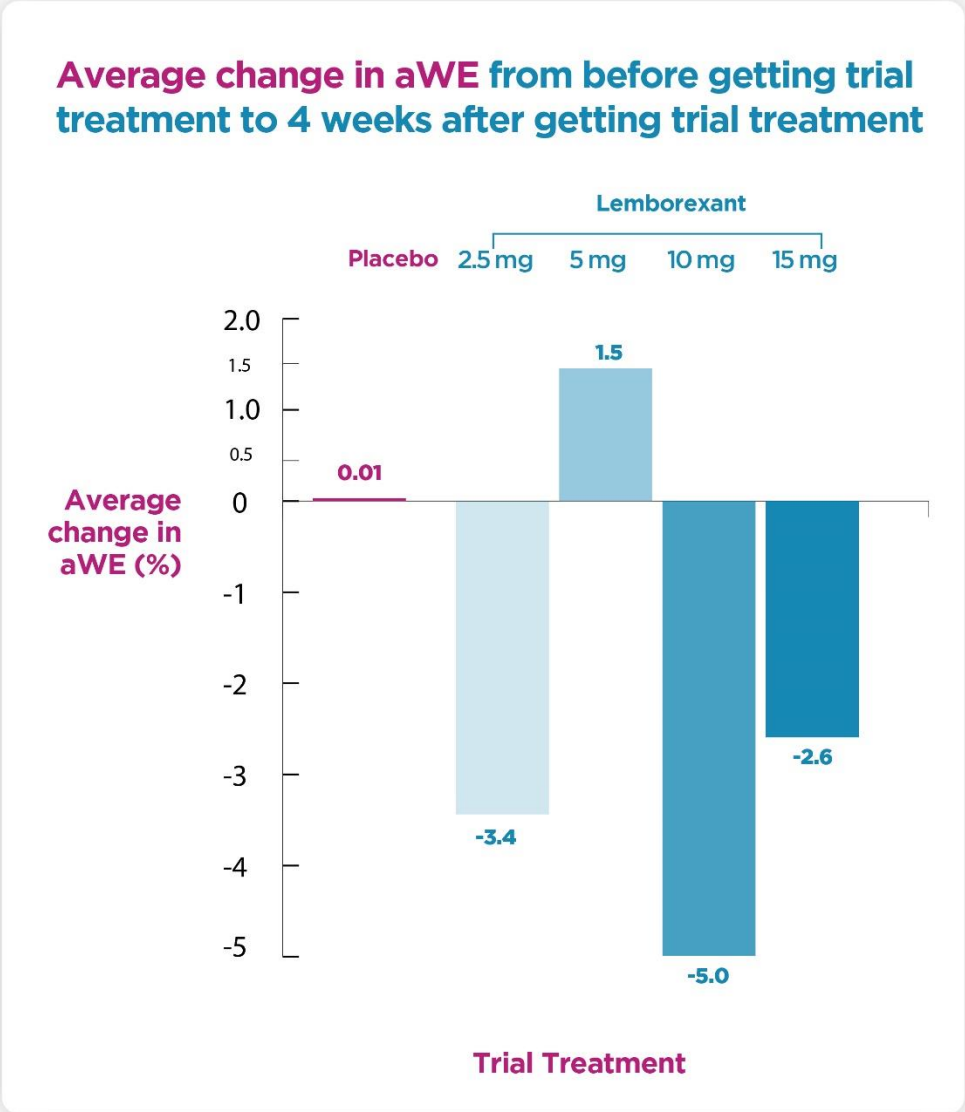
Which dose or doses of lemborexant increased aWE after 4 weeks of treatment?

To see if participants' aWE increased after getting the trial treatment, researchers measured the participants' aWE before they got the trial treatment and then measured the average change in participants' aWE after 4 weeks of getting trial treatment.

aWE is the amount of time a person is actually awake during the time spent out of bed during the day time.

Only the 5 mg dose of lemborexant increased participants' aWE. The 10 mg dose of lemborexant significantly decreased participants' aWE more than placebo after 4 weeks of trial treatment.

The chart below shows the average change in participants' aWE after 4 weeks of trial treatment. Higher numbers mean that there is more improvement in aWE.



Which dose or doses of lemborexant increased quiet sleep periods and increased the ability of participants' circadian rhythm to tell the difference between night and day?

Circadian rhythm refers to a 24-hour body clock that is running in the background of the brain, and cycles between sleepiness and alertness at regular periods of time. It is also called the sleep/wake cycle. Circadian rhythm helps to set the difference between activity levels during the night and day.

To see if participants increased quiet sleep periods and an increase in the difference between activity levels during the night and day after getting the trial treatment, the researchers did different tests before the participants got the trial treatment to measure their quiet sleep periods and the difference between activity levels during the night and day. Then, the researchers measured the average change in participants' quiet sleep periods and the difference between activity levels during the night and day after 4 weeks of trial treatment

All doses of lemborexant increased participants' quiet sleep periods and increased the participants' circadian rhythm more than placebo after 4 weeks of trial treatment. This means that there was more difference in activity between night and day.

Did any dose or doses of lemborexant make the scores on tests of mental function worse?

To see if participants had worse scores on tests of mental function after getting the trial treatment, researchers measured the scores of 2 tests of mental function before the participants got trial treatment and then measured the average change in participants' test scores after 4 weeks of getting trial treatment.

Mental function refers to memory, ability to recognize words, name objects, and follow commands.

None of the doses of lemborexant made the participants' mental function test scores worse after 4 weeks of trial treatment.

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.

How many participants had adverse events?

In the trial,

- 4 out of 12 participants (33.3%) who got the placebo had adverse events.
- 16 out of 50 participants (32.0%) who got lemborexant had adverse events.

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

	Placebo (N=12) n (%)	Lemborexant			
		2.5 mg (N=12) n (%)	5 mg (N=13) n (%)	10 mg (N=13) n (%)	15 mg (N=12) n (%)
How many participants had adverse events?	4 (33.3%)	3 (25.0%)	3 (23.1%)	4 (30.8%)	6 (50.0%)
How many participants had serious adverse events?	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
How many participants stopped receiving the trial drug because of adverse events?	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

N is the number of participants in each group.
% is the percentage of participants with the adverse event in each group.
n is the number of participants with the adverse event in each group.

None of the participants had serious adverse events during the trial.

None of the participants died during the trial.

What were the most common adverse events?

In this trial, 20 out of 62 participants (32.2%) had adverse events

The most common adverse events were constipation, feeling sleepy, joint pain, headache, and nightmare.

The table below shows the adverse events in the trial that happened in at least 2 participants who got trial treatment. There were other adverse events, but these happened in fewer participants.

Most Common Adverse Events in This Trial

	Placebo (N=12) n (%)	Lemborexant			
		2.5 mg (N=12)	5 mg (N=13)	10 mg (N=13)	15 mg (N=12)
Constipation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	2 (16.7%)
Feeling sleepy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	2 (16.7%)
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (16.7%)
Infection of nose and throat	1 (8.3%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)
Joint pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (16.7%)
Nightmare	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (15.4%)	0 (0.0%)

N is the number of participants in each group.
% is the percentage of participants with the adverse event in each group.
n is the number of participants with the adverse event in each group.

How has this trial helped patients and researchers?

In this trial, researchers learned more about whether lemborexant may have helped people with ISWRD and mild to moderate AD-D.

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 lemborexant are planned.

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 **NCT03001557**into the search box and click "**Search**".
- http://www.clinicaltrialsregister.eu – Once you are on the website, type **2017-003306-40** into the search box and click "**Search**".

Full trial title: A Multicenter, Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Phase of the Efficacy and Safety of Lemborexant in Subjects with Irregular Sleep-Wake Rhythm Disorder and Mild to Moderate Alzheimer's Disease Dementia

Protocol number: E2006-G000-202

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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