MARKETING AUTHORIZATION APPLICATION FOR POTENTIAL
INSOMNIA DISORDER TREATMENT LEMBOREXANT SUBMITTED IN JAPAN

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that a marketing authorization application has been submitted in Japan for lemborexant, an investigational agent for sleep-wake regulation, seeking approval for use in the treatment of insomnia disorder.

This application was based on the results of two pivotal Phase III clinical studies in patients with insomnia, SUNRISE 1 (Study 304) and SUNRISE 2 (Study 303), enrolling approximately 2,000 patients combined, as well as important safety studies, including assessment of postural stability after middle-of-the-night awakening, and a next-morning driving study (Study 106, Study 108).

SUNRISE 1 was a placebo-controlled 1-month Phase III clinical study evaluating the efficacy and safety of lemborexant versus zolpidem tartrate extended release ("zolpidem ER") in 1,006 male or female adult patients 55 years and older (45% of patients were 65 years and older) with insomnia disorder, which was characterized by difficulty staying asleep. The study objectively assessed sleep latency (time taken between going to bed and falling asleep, primary objective), sleep efficiency and wake after sleep onset (effect on maintaining sleep, secondary objectives) using polysomnography. The results of the study showed that lemborexant 5 mg and 10 mg had statistically significant improvement compared to zolpidem ER 6.25 mg and placebo in sleep parameters evaluated in primary and key secondary objectives. In this study, lemborexant had rates of discontinuation due to adverse events (AEs) comparable to placebo, with the most common AEs in the lemborexant arms being headache and somnolence.

SUNRISE 2 was a placebo-controlled 12-month Phase III clinical study conducted globally including in Japan to evaluate the long-term efficacy and safety of lemborexant in 949 male or female adult participants 18 to 88 years of age with insomnia disorder, which was characterized by difficulty falling asleep and/or staying asleep. During the first six months, patients were administered either lemborexant (5 mg, 10 mg) or placebo. The study evaluated sleep onset latency (primary objective), subjective sleep efficiency, and subjective wake after sleep onset (secondary objectives) by using patient reported (subjective) sleep diaries. From an analysis of results at the end of the six-month, placebo-controlled treatment period, the primary efficacy endpoint and all secondary endpoints were achieved for both lemborexant arms, and statistically significant improvement in sleep onset and sleep maintenance was confirmed for both lemborexant arms compared to placebo during the six-month treatment period. Although the rate of discontinuation due to AEs for lemborexant 5 mg was comparable to placebo, the rate of discontinuation due to AEs for lemborexant 10 mg was higher than placebo. The most common AEs in the lemborexant arms were somnolence, headache and influenza.

Lemborexant acts on the orexin neurotransmitter system and is believed to regulate sleep and wake by dampening wakefulness without impeding the ability to awaken to external stimuli. Lemborexant is being developed for the treatment of multiple sleep-wake disorders, including insomnia disorder. In addition to this marketing authorization application submitted in Japan, a New Drug Application was submitted in the United States to the Food and Drug Administration on December 27, 2018.

Furthermore, a Phase II clinical study of lemborexant in patients with irregular sleep-wake rhythm disorder and mild to moderate Alzheimer's dementia is ongoing.

It is estimated that approximately 1 in every 5 people (over 20 million people) in Japan suffers from a sleep disorder, and the number of patients being examined at medical institutions continues to increase. Eisai is striving to address new unmet medical needs and contribute to further increasing the benefits for patients and their families.

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[Notes to editors]

1. About Lemborexant (development code: E2006)

Lemborexant, an investigational dual orexin receptor antagonist, is Eisai's in-house discovered and developed small molecule compound which inhibits orexin neurotransmission, or signaling, by binding competitively to two subtypes of orexin receptors (orexin receptor 1 and 2). In individuals with sleep-wake disorders, it is possible that the orexin system which regulates wakefulness is not functioning normally. During normal periods of sleep, orexin system activity is suppressed, suggesting it is possible to purposefully counteract inappropriate wakefulness and facilitate the initiation and maintenance of sleep.

2. About Sleep Disorders

Population studies show that sleep disorders affect many more people worldwide than previously thought.[1] Insomnia disorder is the most common sleep disorder affecting approximately 30% of the adult population worldwide.[1,2] Insomnia disorder is characterized by difficulty falling asleep, staying asleep or both, despite an adequate opportunity to sleep, which can lead to daytime consequences such as fatigue, difficulty concentrating and irritability.[3,4]

Sleeping well is essential for good health, including brain health. Poor sleep is associated with a wide range of health consequences, including an increased risk of hypertension, accidental injury, diabetes, obesity, depression, heart attack, stroke and dementia, as well as adverse effects on mood and behavior.[3,5]

Experimental studies in animals and humans provide evidence of associations between sleep and disease risk factors, diseases and mortality.[6] Studies suggest an optimal sleep duration between seven and eight hours.[7]

Women are 1.4 times more likely than men to suffer from insomnia.[8] Older adults also have higher prevalence of insomnia; aging is often accompanied by changes in sleep patterns, including disrupted sleep, frequent waking and early waking, that can lead to less sleep time.[9]

3. About SUNRISE 1 / Study 304[10]

SUNRISE 1 is a multicenter, randomized, double-blind, placebo-controlled, active comparator, parallel-group Phase III study of the efficacy and safety of lemborexant in 1,006 patients 55 years and older (45% of all patients were aged 65 years and older) with insomnia disorder conducted in North America and Europe. In this study, patients were administered placebo or one of three treatment regimens (lemborexant 5 mg, lemborexant 10 mg, zolpidem ER 6.25 mg).

The primary objective for SUNRISE 1 was to demonstrate using polysomnography that lemborexant at either the 5 mg or 10 mg dose is superior to placebo on objective sleep onset, as measured by latency to persistent sleep after

the last two nights of one month of treatment. Key secondary endpoints included change from baseline in sleep efficiency for both lemborexant doses compared to placebo, wake after sleep onset (WASO) for both lemborexant doses compared to placebo, and WASO in the second half of the night (WASO2H) for both lemborexant doses compared to zolpidem ER, after one month of treatment, measured objectively by polysomnography.

4. About SUNRISE 2 / Study 303[11]

SUNRISE 2 is a 12-month multicenter, global (Japan, North America, South America, Europe, Asia, and Oceania), randomized, placebo-controlled, double-blind, parallel group Phase III study of 949 male or female adult participants (18 to 88 years of age) with insomnia disorder. SUNRISE 2 included a pre-randomization phase of up to 35 days (including a two-week placebo run-in period) and a randomization phase comprised of a six-month placebo-controlled treatment period, a six-month period of only active treatment, and a two-week period without treatment prior to the end-of-study-visit. Lemborexant 5 mg, 10 mg or matching placebo was taken orally in tablet form at home each night immediately before the patient intended to try to sleep for the first six months of study. Patients who received placebo during the first six-month period were administered lemborexant 5 mg or 10 mg for the second six-month period. Patients who received active treatment during the first period continued on the treatment to which they were originally randomized.

The primary outcome measure was mean change from baseline in subjective sleep onset latency after six months of placebo-controlled treatment. Key secondary outcome measures were mean change from baseline in subjective sleep efficiency and subjective wake after sleep onset after six months of placebo-controlled treatment.

5. About Study 106[12,13]

Study 106 was a randomized, double-blind, placebo- and active-controlled, four period, crossover Phase I study to evaluate the effect of lemborexant in 48 healthy adult and elderly volunteers to evaluate on-road driving performance. Participants were treated at bedtime with two out of three dose levels of lemborexant (2.5, 5 or 10 mg) and placebo for eight consecutive days, and zopiclone 7.5 mg as an active control on days one and eight only, with placebo given for the six days in between. The primary endpoint was to evaluate change of standard deviation of lateral position (SDLP) during an on-road driving test conducted after the first (in the morning of Day 2) and last day (in the morning of Day 9) of treatment administration.

6. About Study 108[14]

Study 108 was a randomized, double-blind, four period crossover Phase I study to evaluate the effect of lemborexant on postural stability, auditory awakening threshold, and cognitive performance in 56 healthy volunteers 55 years and older. Participants were treated at bedtime with a single dose of placebo, lemborexant 5 mg, lemborexant 10 mg, or zolpidem ER 6.25 mg. The primary endpoint assessed postural stability when awakened by an alarm approximately four hours after administration of lemborexant compared to zolpidem ER, as measured by stabilometer.

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