Report on the Deliberation Results

December 4, 2019

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Dayvigo Tablets 2.5 mg Dayvigo Tablets 5 mg Dayvigo Tablets 10 mg
Non-proprietary Name	Lemborexant
Applicant	Eisai Co., Ltd.
Date of Application	March 7, 2019

Results of Deliberation

In its meeting held on November 29, 2019, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Approval Conditions

The applicant is required to develop and appropriately implement a risk management plan.

Review Report

November 11, 2019
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name Dayvigo Tablets 2.5 mg
Dayvigo Tablets 5 mg
Dayvigo Tablets 10 mg

Non-proprietary Name Lemborexant

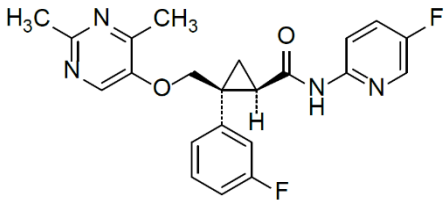
Applicant Eisai Co., Ltd.

Date of application March 7, 2019

Dosage Form/Strength Tablets, each containing 2.5, 5, or 10 mg of lemborexant

Application Classification Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{22}H_{20}F_2N_4O_2$

Molecular weight: 410.42

Chemical name: (1*R*,2*S*)-2-{[(2,4-Dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-*N*-(5-fluoropyridin-2-yl)cyclopropanecarboxamide

Items Warranting Special Mention None

Reviewing Office Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of insomnia and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

Indication Insomnia

Dosage and Administration

The usual adult dose is 5 mg of lemborexant orally administered once daily immediately before going to bed. The dose may be adjusted according to symptoms but should not exceed 10 mg once daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

October 28, 2019

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Dayvigo Tablets 2.5 mg Dayvigo Tablets 5 mg Dayvigo Tablets 10 mg
Non-proprietary Name	Lemborexant
Applicant	Eisai Co., Ltd.
Date of Application	March 7, 2019
Dosage Form/Strength	Tablets, each containing 2.5, 5, or 10 mg of lemborexant
Proposed Indication	Insomnia

Proposed Dosage and Administration

The usual adult dose is 5 mg of lemborexant orally administered once daily immediately before going to bed. The dose may be increased to 10 mg once daily and adjusted according to symptoms. The dose, however, should not exceed 10 mg once daily.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

This tablet product contains lemborexant as an active ingredient. Lemborexant, discovered by Eisai Co., Ltd., is an antagonist at orexin 1 and 2 receptors (OX1R and OX2R).

The axons of orexinergic neurons are nerve nucleus for awakening that project at almost all sites of the central nervous system (CNS). They are known to regulate major awakening neurotransmitters at the upstream (*Sleep and Biological Rhythms*. 2011;9:332). During wakefulness, orexin, an awakening neurotransmitter, binds to the orexin receptors and allows arousal center activity to exceed sleep center activity, and maintains wakefulness (*Nippon Rinsyo.* 2008;66:96-106). The orexin receptor antagonist is expected to induce sleep by improving hyperarousal, thereby shifting to a sleep state.

In Japan, clinical studies began in 2016. The applicant recently filed a marketing application for lemborexant, claiming that the clinical studies demonstrated its efficacy and safety.

In the US, an application was filed in December 2018 for the approval of lemborexant and is currently under review. As of September 2019, lemborexant has not been approved in any country or region.

In Japan, suvorexant was approved in September 2014 as an orexin receptor antagonist for the indication of the treatment of insomnia.

Initially, the brand name "Dayvigo Tablets 2.5 mg, 5 mg, and 10 mg" was spelled differently in Japanese, and it could have been confused with an approved drug "Divigel 1 mg." PMDA, from the viewpoint of risk management, instructed the applicant to modify the spelling. In response, the applicant modified the Japanese spelling to the present one. PMDA accepted the action taken by the applicant.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white powder, and its determined properties include description, solubility, dissociation constant, distribution coefficient, pH, optical rotation, melting point, and hygroscopicity.

The chemical structure of the drug substance has been elucidated by elementary analysis, ultraviolet spectroscopy, infrared spectrophotometry, nuclear magnetic resonance spectrometry (^{1}H- and ^{13}C-NMR), mass spectral analysis, and single-crystal X-ray crystallography. The drug substance has been confirmed to have 2 asymmetric carbon atoms with the first position in the R configuration and the second position in the S configuration.

2.1.2 Manufacturing process

The drug substance is synthesized from [redacted] as starting materials. In the manufacturing process of the drug substance, the step for synthesizing

[redacted], the step for synthesizing [redacted], and the steps for [redacted] of [redacted] were specified as critical steps. In addition, [redacted] are controlled as a critical intermediate.

A quality by design (QbD) approach is applied to the following to formulate the quality control strategy (Table 1).

- Identification of critical quality attributes (CQAs).
- Identification of critical material attributes (CMAs) affecting CQAs
- Risk assessment by the preliminary hazard analysis to identify critical process parameters (CPP) from the process parameters that may affect CQAs, CMAs, or the action limits of process control.
- Establishment of the scope of proof for the CRP as risk management based on the risk assessment of the manufacturing process.

Table 1. Outline of the control strategy for the drug substance

CQA	Control methods
[redacted]	Specifications
[redacted]	Manufacturing process and specifications
[redacted]	Manufacturing process and specifications

2.1.3 Control of drug substance

The proposed specifications for the drug substance include description, identification (infrared spectroscopy and high-performance liquid chromatography [HPLC]), purity (related substances [HPLC] and residual solvents [gas chromatography]), water content, residue on ignition, [redacted], microbial limits, and content (HPLC).

2.1.4 Stability of drug substance

The stability studies of the drug substance are shown in Table 2. The photostability study showed that the drug substance is photostable.

Table 2. Stability studies of the drug substance

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 production batches	30°C	65% RH	Double-layer polyethylene bag	24 months
Accelerated testing	3 production batches	40°C	75% RH		6 months

Accordingly, based on the ICH Q1E Guideline, a re-test period of [redacted] months is proposed for the drug substance when stored in a double-layer polyethylene bag at room temperature. The long-term testing will be continued for up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a tablet containing 2.5, 5, or 10 mg of the drug substance. It contains the following excipients: lactose monohydrate, low-substituted hydroxypropylcellulose,

hydroxypropylcellulose, magnesium stearate, hypromellose, talc, macrogol 6000, titanium oxide, yellow iron sesquioxide (for 5 and 10 mg tablets only), and iron sesquioxide (for 2.5 and 10 mg tablets only).

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of the following steps: [redacted], tableting, coating, filling/packaging/labeling, testing, storage, testing 2, [redacted], filling/packaging/labeling 2, storage 2, and testing 3. The [redacted] step was defined as a critical step, and the process controls were established for the [redacted] and [redacted] steps.

A QbD approach is applied to the following to formulate the quality control strategy (Table 3).

- Identification of CQAs with consideration of effects on the efficacy, safety, and quality target product profile (QTPP).
- The effects of each manufacturing process parameter on the CQAs have been evaluated with a failure mode effects analysis, and the process parameters with moderate to high risk levels have been optimized. Then, the risk is assessed again.

Table 3. Outline of the control strategy for the drug product

CQA	Control methods
[redacted]	Manufacturing process and specifications
[redacted]	Manufacturing process and specifications

2.2.3 Control of drug product

The proposed specifications for the drug product include description, identification (ultraviolet spectroscopy and HPLC), purity (related substance [HPLC]), uniformity of dosage units (content uniformity test [HPLC]), dissolution, microbial limits, and strength (HPLC).

2.2.4 Stability of drug product

The stability studies of the drug product are shown in Table 4. The photostability study showed that the drug product is photostable.

Table 4. Stability studies for the drug product

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 production batches	30°C	65% RH	Blister sheet packaging or high-density polyethylene container/high-density polyethylene cap with low-density polyethylene packing	18 months
Accelerated testing	3 production batches	40°C	75% RH	Blister sheet packaging or high-density polyethylene container/high-density polyethylene cap with low-density polyethylene packing	6 months

Based on the above and in compliance with the ICH Q1E Guideline, a shelf-life of 30 months has been proposed for the drug product when stored at room temperature in the blister packaging with polyvinyl chloride/aluminum foil or a high-density polyethylene container/a high-density polyethylene cap with low-density polyethylene packing. The long-term testing will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Pharmacological data for lemborexant have been submitted from primary pharmacodynamic studies, secondary pharmacodynamic studies, and safety pharmacology studies as pharmacology studies. In addition, 0.5% (w/v) methylcellulose was used as a vehicle in *in vivo* studies, and values are expressed as means or means ± standard errors unless otherwise specified.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Affinity for the orexin receptors

The inhibitory effect of lemborexant (0.6 to 200 nmol/L) on the binding of ^{125}I-orexin A to OX1R and OX2R was investigated with the membrane fraction of Chinese hamster ovary (CHO) cells expressing human OX1R or OX2R. The 50% inhibitory concentration (IC_{50}) and its 95% confidence interval (CI) for human OX1R and OX2R was 6.1 [1.9, 20] nmol/L and 2.6 [1.9, 3.6] nmol/L, respectively (CTD 4.2.1.1.1). The IC_{50} of suvorexant for human OX1R and OX2R was 8.8 ± 2.5 nmol/L and 12.0 ± 2.8 nmol/L, respectively.

The binding kinetics of lemborexant (7 to 28 nmol/L for OX1R; 1 to 10 nmol/L for OX2R) to the OX1R and OX2R was investigated with the membrane fraction of CHO cells expressing human OX1R or OX2R. The binding constant, dissociation constant, dissociation half-life, and its 95% CI for OX1R was 0.0262 [0.0175, 0.0350] $L \cdot nmol^{-1} \cdot min^{-1}$, 0.244 [0.171, 0.317] min^{-1}, and 2.8 [0.9, 4.7] minutes, respectively, and those for OX2R was 0.0496 [0.0463, 0.0528] $L \cdot nmol^{-1} \cdot min^{-1}$, 0.0626 [0.0582, 0.0671] min^{-1}, and 11.1 [10.3, 11.9] minutes, respectively (CTD 4.2.1.1.2 and 4.2.1.1.3).

The effect of lemborexant on the orexin receptors was investigated by using a calcium assay with human embryonic kidney (HEK) 293 cells expressing human, rat, and murine OX1R or OX2R. Lemborexant (0.051 to 13,280 nmol/L) showed no agonistic effects on any receptors. Meanwhile, lemborexant (0.038 to 9,960 nmol/L) showed competitive antagonistic effects on all receptors. The Ki and IC_{50} values of lemborexant for OX1R and OX2R are shown in Table 5 (CTD 4.2.1.1.5).

Table 5. Ki and IC_{50} values for orexin receptors

Animal species	Ki (nmol/L)		IC_{50} (nmol/L)	
	OX1R	OX2R	OX1R	OX2R
Human	8.1 [5.9, 11]	0.48 [0.18, 1.3]	17 [8.1, 37]	1.9 [0.67, 5.6]
Rat	23 [3.2, 170]	1.2, 0.39 a)	56 [5.3, 600]	3.2, 0.94 a)
Mouse	23 [9.1, 59]	0.44 [0.14, 1.3]	89 [21, 370]	1.5 [0.39, 5.9]

Mean [95% CI]; Tested 3 times.
a) Individual values of 2 tests

3.1.1.2 Effects of lemborexant metabolites on orexin receptors (CTD 4.2.1.1.6)

The inhibitory effect of lemborexant metabolites (0.6 to 600 nmol/L) on the binding of ^{125}I-orexin-A to OX1R and OX2R was investigated with the membrane fraction of CHO cells expressing human OX1R or OX2R, and the IC_{50} values are shown in Table 6. It was demonstrated that the 9 metabolites (M3, M4, M7, M8, M9, M10, M13, M14, and M15) have binding affinity for the human orexin receptors, and their binding affinity is comparable to that of lemborexant.

Table 6. IC_{50} values of lemborexant metabolites for OX1R and OX2R

	IC_{50}											
	M2[a)]	M3[b)]	M4[a)]	M7[b)]	M8[b)]	M9[b)]	M10[a)]	M11[c)]	M12[d)]	M13[e)]	M14[e)]	M15[e)]
OX1R	>600	160	12	31	240	19	4.2	>600	>600	380	16	16
OX2R	410	5.2	3.8	4.5	6.3	4.7	2.9	>600	460	12	4.5	6.9

Mean. Tested 3 times.
a) N-oxidated form; b) hydroxylated form; c) amide hydrolyzed form; d) carboxylated form; and e) dioxidized form

3.1.2 *In vivo* studies

3.1.2.1 Effects of lemborexant on sleep in preproorexin knockout mice (CTD 4.2.1.1.9)

Wild-type mice and preproorexin knockout mice[1)] were implanted with electroencephalography (EEG) and electromyography (EMG) electrodes and were given lemborexant (1, 10, and 30 mg/kg for wild-type mice; and 30 mg/kg for preproorexin knockout mice) or a vehicle by voluntary eating[2)] 15 minutes before the dark onset. The effects of lemborexant on sleep time, wake time, and sleep latency[3)] were investigated in a cross-over manner. In the wild-type mice, as compared with the vehicle, lemborexant decreased the sleep latency after administration (130.2 minutes by the vehicle; and 31.3 to 4.7 minutes by lemborexant ≥1 mg) and the percent wake time at 6 hours after the start of administration (73.2% by the vehicle; and 60.2% to 42.0% by lemborexant ≥10 mg) and increased the percent time in non-rapid eye movement (REM) sleep (24.2% by the vehicle; and 36.4% to 50.1% by lemborexant ≥10 mg) and the percent time in REM sleep (2.6% by the vehicle; and 7.8% by lemborexant 30 mg). Meanwhile, in preproorexin knockout mice, lemborexant showed no effects on wake time, non-REM sleep time, or REM sleep time.

3.1.2.2 Effects of lemborexant on sleep in rats (CTD 4.2.1.1.10)

Rats were implanted with EEG and EMG electrodes and were orally given a single dose of lemborexant (3, 10, 30, 100, or 300 mg/kg), zolpidem (3, 10, 30, or 100 mg/kg), or a vehicle 2 to 3 hours after the light onset, and EEG and EMG were measured 2 hours post-dose. The effects on total sleep time[4)] were investigated in a cross-over manner. As compared with the vehicle, lemborexant increased the total sleep time at a 50% effective dose (ED_{50}) of 4.4 mg/kg. In contrast, zolpidem did not increase the total sleep time. As compared with the vehicle, lemborexant showed no effects on the percent time in REM sleep in the total sleep time, but conversely, zolpidem ≥30 mg/kg decreased the percent time in REM sleep in the total sleep time (14.4% by the vehicle, 2.8% to 0% by zolpidem ≥30 mg/kg). After the administration of lemborexant, sleep was entered through non-REM sleep. None of the animals had sleep-onset REM period, which refers to a direct transition from wakefulness to REM sleep without entering through non-REM sleep and is considered to represent a narcolepsy-like symptom.

1) Mice lacking the preproorexin gene, a precursor for orexins A and B
2) Mice were trained to eat artificially-sweetened jelly mixed with lemborexant in 1.5 to 2 minutes.
3) Time to the onset of the initial non-REM sleep (lasting for ≥30 seconds)
4) Combined time of non-REM and REM sleeps

3.1.2.3 Investigation of resistance and rebound insomnia in rats (CTD 4.2.1.1.11)

Rats were implanted with EEG and EMG electrodes and were orally given repeated doses of lemborexant 30 mg/kg/day, zolpidem 100 mg/kg/day, or a vehicle, 2 to 3 hours after the light onset, once daily for 21 days with a 2-day non-treatment period after the completion of the 21-day treatment. EEG and EMG were measured 2 hours post-dose, once every 3 or 4 days during the repeated dosing and both days of the non-treatment period. The effects on sleep latency, total sleep time, and the percentage of REM sleep in the total sleep time were investigated. During the repeated dosing, with the vehicle, lemborexant, and zolpidem, respectively, the sleep latency was 22.6 to 36.7 minutes, 9.4 to 15.7 minutes, and 10.1 to 17.8 minutes, the total sleep time was 56.0 to 84.3 minutes, 89.3 to 104.9 minute, and 74.4 to 85.5 minutes, and the percentage of REM sleep in the total sleep time was 8.4% to 17.7%, 18.8% to 20.4%, and 1.2% to 9.1%. During the repeated dosing, lemborexant decreased the sleep latency and increased the total sleep time, and zolpidem decreased the percentage of REM sleep in the total sleep time. During the non-treatment period, with the vehicle, lemborexant, zolpidem, respectively, the sleep latency was 21.5 to 22.2 minutes, 22.4 to 29.0 minutes, and 20.1 to 59.3 minutes, the total sleep time was 85.1 to 89.1 minutes, 76.5 to 87.2 minutes, and 41.9 to 81.1 minutes, and the percentage of REM sleep in the total sleep time was 17.4% to 19.8%, 16.4% to 17.2%, and 20.0% to 21.1%. Zolpidem prolonged sleep latency and decreased total sleep time.

3.2 Secondary pharmacodynamics

3.2.1 *In vitro* studies

3.2.1.1 Effects on other receptors and enzymes

The binding affinity of lemborexant (1 and 10 μmol/L) for 88 types of receptors, transporters, and ion channels was investigated. Lemborexant 10 μmol/L inhibited binding to the MT1 receptor at 74% (CTD 4.2.1.2.1).

The binding affinity of M4, M9, and M10 (1 and 10 μmol/L), which are metabolites with relatively high exposure in human plasma, for 86 receptors, transporters, and ion channels were investigated. M4, M9, and M10 at 10 μmol/L inhibited binding to the MT1 receptor at 51%, 55%, and 71%, respectively (CTD 4.2.1.2.2).

3.2.1.2 Effects on melatonin receptors (CTD 4.2.1.2.3)

The effects of lemborexant on receptors were investigated with HEK-293 cells expressing human MT1 receptor by using intracellular calcium concentration as an indicator. Lemborexant (0.1 to 30 μmol/L) demonstrated no agonistic effects on the MT1 receptor and instead inhibited the receptors with a Ki of 0.92 μmol/L.

3.2.2 *In vivo* studies

3.2.2.1 Effects of lemborexant in a model of emotion-induced cataplexy (CTD 4.2.1.1.9)

Wild-type mice and preproorexin knockout mice[1)] were implanted with EEG and EMG electrodes. The mice were given lemborexant (1, 10, and 30 mg/kg for wild-type mice; and 30 mg/kg for preproorexin knockout mice) or a vehicle by voluntary eating[2)] 15 minutes before the dark onset and subsequently, were given a special food (chocolate) by voluntary eating at the dark onset. The effects of

lemborexant on cataplexy-like symptoms[5)] were investigated in a cross-over manner. Six hours after the ingestion of the special food, cataplexy was not observed in wild-type mice treated with vehicle but was seen in 3 of 8, 7 of 8, and 8 of 8 mice treated with lemborexant 1, 10, and 30 mg/kg, respectively. In mice treated with lemborexant ≥10 mg/kg, the proportion of duration of cataplexy and the frequency of cataplexy was 0.9% to 3.5% and 5.4 to 12.0, respectively. Meanwhile, in preproorexin knockout mice, the proportion of duration of cataplexy and the frequency of cataplexy at 6 hours post-dose of lemborexant was 10.3% and 41.4, respectively.

3.3 Safety Pharmacology

Results of the safety pharmacology studies with lemborexant and its metabolites are summarized in Table 7. In the cardiovascular system, the IC_{50} of lemborexant for the human ether-à-go-go-related gene (hERG) channel current was 6.1 μmol/L, which was approximately 99 times the C_{max} of lemborexant at the maximum clinical dose.[6)] Furthermore, the C_{max} of lemborexant at its no-observed-effect level (10 mg/kg) in cynomolgus monkeys[7)] was approximately 7 times the C_{max} of lemborexant at the maximum clinical dose.[6)] No effects on the CNS or respiratory system were observed in male Sprague Dawley (SD) rats with lemborexant at doses up to 1,000 mg/kg (CTD 4.2.3.1.2). The C_{max} and $AUC_{0\text{-}24h}$ of lemborexant at 1,000 mg/kg in male rats[8)] was approximately 54 and 107 times the C_{max} and $AUC_{0\text{-}24h}$ of lemborexant at the maximum clinical dose, respectively.[6)]

5) Defined as sudden transition from wakefulness to muscle flaccidity (EEG theta wave of 4 to 9 Hz) and sudden return from muscle flaccidity to wakefulness.

6) The C_{max} and $AUC_{0\text{-}24h}$ of plasma lemborexant at steady state at the clinically recommended maximum dose was 61.6 ng/mL and 441 ng·h/mL, respectively, based on the population pharmacokinetic analysis including data from the phase III clinical studies (Studies E2006-G000-303 and E2006-G000-304).

7) In a study on the effects of lemborexant on the cardiovascular parameters in male cynomolgus monkeys (CTD 4.2.1.3.7), the C_{max} of plasma lemborexant after a single dose of lemborexant 10 mg/kg was 436 ng/mL.

8) In an extended single-dose oral toxicity study in rats (CTD 4.2.3.1.2), the C_{max} and $AUC_{0\text{-}24h}$ of plasma lemborexant after a single dose of 1,000 mg/kg to male rats was 3308 ng/mL and 47016 ng·h/mL, respectively.

Table 7. Outline of results of safety pharmacology studies

System	Animal species	Evaluation item/method	Dosage	Route	Findings	CTD
Central nervous	SD rat (6 males/group)	FOB method [a)]	100, 300, and 1,000 mg/kg	Oral	No effects	4.2.3.1.2
Cardiovascular	CHO cell (5 samples/group)	hERG current	1, 3, and 10 µmol/L	*in vitro*	IC_{50}: 6.1 µmol/L	4.2.1.3.1
	CHO cell (5 to 6 samples/group)	hERG current	M4, M9, and M10: 1, 3, and 10 µmol/L	*in vitro*	M4: IC_{50}, 5.2 µmol/L M9: IC_{50}, 11.2 µmol/L M10: IC_{50}, 9.0 µmol/L	Reference data 4.2.1.3.2
	CHO cell expressing KCNQ1/KCNE1 (6 samples/group)	IKs current	1, 3, 10, and 30 µmol/L	*in vitro*	10 µmol/L: 24.3% inhibition	Reference data 4.2.1.3.3
	Human embryonic stem cell-derived cardiomyocyte (3 samples/group)	FPD current	1, 3, 10, and 30 µmol/L	*in vitro*	10 µmol/L: approx. 10% prolongation [b)]	Reference data 4.2.1.3.4
	Cynomolgus monkey (4 males/group)	Heart rate, electrocardiography, blood pressure	10, 30, and 100 mg/kg	Oral	≥30 mg/kg: Prolongation of QTc interval	4.2.1.3.7
Respiratory	SD rat (6 males/group)	Respiratory rate, tidal volume, minute ventilation [a)]	100, 300, and 1,000 mg/kg	Oral	No effects	4.2.3.1.2

a) Evaluated in an extended single-dose oral toxicity study
b) 9.3% by the Bazzett's correction formula; 10.6% by the Fridericia's correction formula

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of lemborexant

PMDA asked the applicant to explain the action mechanism of lemborexant.

The applicant's explanation:

- The pathophysiology of insomnia has not been completely clarified. However, a study comparing the brain metabolic activity in patients with insomnia with that in healthy adults by using positron emission tomography (PET) demonstrated brain hypermetabolism in patients with insomnia both in the waking and sleep states, suggesting that failure in the mechanism of transition from wakefulness to sleep status causes the difficulty with sleep onset (*Am J Psychiatry*. 2004;161:2126-9). Meanwhile, the orexinergic neurons are thought to play a role in the maintenance of the waking and sleep phases, and sleep is activated by the binding of orexins to the orexin receptors. Orexins are neuropeptides, and there are two types of orexins, orexin-A and -B. The orexin-A selectively binds to an orexin receptor subtype of OX1R, and both orexin-A and -B bind to another receptor subtype of OX2R (*Cell*. 1998:92;573-85).
- Lemborexant binds to both orexin receptors, OX1R and OX2R, and acts as a competitive antagonist for the orexin receptors. Lemborexant is thus expected to exert its sleep-promoting effects by inhibiting the orexin signaling that regulates the sleep-wake rhythm.

PMDA asked the applicant to explain the differences in the pharmacological profiles between lemborexant and suvorexant.

The applicant's explanation:

- The pharmacological profiles of lemborexant and suvorexant for OX1R and OX2R are shown in Table 8. Lemborexant showed competitive antagonistic effects on both OX1R and OX2R and demonstrated a stronger affinity for OX2R than for OX1R. Meanwhile, suvorexant showed a comparative affinity for OX1R and OX2R. Lemborexant bound to and dissociated from OX2R faster than suvorexant.

Table 8. Pharmacological profiles of lemborexant and suvorexant for OX1R and OX2R

Evaluation parameters	Lemborexant		Suvorexant [a)]	
	OX1R	OX2R	OX1R	OX2R
IC_{50} (nmol/L)	6.1	2.6	8.8	12.0
Binding constant ($L \cdot nmol^{-1} \cdot min^{-1}$)	0.0262	0.0496	—	0.0052
Dissociation constant (min^{-1})	0.244	0.0626	—	0.0164
Dissociation half-life (min)	2.8	11.1	—	42.2
Ki (nmol/L)	8.1	0.48	1.4	2.2

Mean

a) *J Pharmacol Exp Ther*. 2017;362:287-95

PMDA considers that the pharmacological characteristics of lemborexant are explained to a certain extent based on the findings currently available.

3.R.2 Safety of lemborexant

3.R.2.1 Cataplexy-like symptoms

Cataplexy-like symptoms were observed in mice after the administration of lemborexant and positive emotional stimuli [see Section 3.2.2.1]. PMDA asked the applicant to explain the mechanism by which cataplexy develops and the possibility of cataplexy in humans.

The applicant's explanation:

- Strong positive emotional stimuli are considered to be related to the development of cataplexy (*Sleep Med.* 2011;12:12-8; *J Neurosci.* 2013;33:9743-51). Orexinergic neurons are projected to the serotonergic neurons in the dorsal raphe nuclei that have both OX1R and OX2R, and the serotonergic neurons receive inhibitory effects from the amygdaloid body that plays an important role in emotional reactions (*J Clin Invest.* 2014;124:604-16; *Nature.* 2015;517:284-92). The amygdaloid body is innervated by the prefrontal area. It has been reported that an emotional stimulus (special food) activated the prefrontal area in mice (*J Neurosci.* 2013:33;9743-51). These findings suggest that orexinergic neurons, the dorsal raphe nuclei serotonergic neurons, and the amygdaloid body form an important pathway for the development of cataplexy (*Proc Natl Acad Sci USA.* 2017;114:E3526-35).
- Cataplexy-like symptoms were observed frequently in orexin knockout mice, whereas the symptoms were seen less frequently in OX2R knockout mice (*Neuron.* 2003;38:715-30). A report from a study using EEG and EMG revealed that the direct transition from wakefulness to REM sleep, which is a characteristic of cataplexy, was observed frequently in OX1R/OX2R knockout mice, whereas it was observed less frequently in OX2R knockout mice. The direct transition did not occur in OX1R knockout mice (*Nat Rev Neurosci.* 2007;8:171-81). These findings suggest that inhibition of both OX1R and OX2R increases the risk of cataplexy and that OX2R has a stronger effect than OX1R.
- Based on the above, lemborexant may cause cataplexy in humans.

PMDA accepted the applicant's explanation and considers that conclusions on the safety in humans should be drawn based on clinical study data.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Non-clinical pharmacokinetic data on the absorption, distribution, metabolism, and excretion of lemborexant in mice, rats, and monkeys were submitted. The concentrations of unchanged lemborexant and metabolites in biospecimens were determined with liquid chromatography-tandem mass spectrometry (LC-MS/MS; lower limit of quantification of 0.3 to 2 ng/mL). In studies using ^{14}C-labeled lemborexant, the concentration of radioactivity in biospecimens was determined by a liquid scintillation counter (lower limit of quantification, 2-fold of background). The following sections summarize only the main pharmacokinetic study data. The values of t_{max} are median and other pharmacokinetic parameter values are mean or mean ± standard deviations unless otherwise specified.

4.1 Absorption

4.1.1 Single-dose studies

4.1.1.1 Single-dose studies in rats

Albino male rats (4/group) were administered a single oral dose of lemborexant 10, 30, or 100 mg/kg under fasting conditions or a single intravenous dose of lemborexant 0.3 or 1 mg/kg under fasting conditions. The pharmacokinetic parameters of unchanged lemborexant and M10 in plasma are shown in Table 9. The absolute bioavailability of unchanged lemborexant in plasma was 2.5% to 22.6% (CTD 4.2.2.2.1).

Table 9. Pharmacokinetic parameters of unchanged lemborexant and M10 in plasma after a single oral or intravenous dose of lemborexant in male rats

Route	Dose (mg/kg)	Unchanged lemborexant				M10			
		C_{max} (ng/mL)	t_{max} (h) [a]	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h) [a]	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)
Intravenous	0.3			1.61 ± 0.17	110 ± 9			—	—
	1			1.64 ± 0.19	353 ± 41			—	—
Oral	10	50.0 ± 32.6	0.25 [0.25, 1.00]	1.49 ± 0.26	87.8 ± 37.6	—	—	—	—
	30	452 ± 324	1.00 [1.00, 2.00]	2.65 ± 1.16	1160 ± 710	1.63 ± 1.19	1.00 [1.00, 2.00]	—	—
	100	964 ± 180	4.50 [1.00, 8.00]	2.24 ± 0.13	7970 ± 1750	3.05 ± 0.39	0.50 [0.25, 1.00]	1.77, 1.63	13.0, 27.9

Mean ± standard deviation; Number of animals evaluated: 4 rats/group. Individual values are shown for a group of ≤2 animals
a) Median [range]

Albino male rats (3/group) were administered a single oral dose of ^{14}C-labeled lemborexant 10 mg/kg under fasting conditions. The C_{max} and $AUC_{0-\infty}$ of radioactivity in plasma (mean ± standard error) was 1,085.6 ± 283.3 ng eq/mL and 11,800 ± 1,300 ng eq·h/mL, respectively (CTD 4.2.2.3.1).

Pigmented male rats (3/group) were administered a single oral dose of ^{14}C-labeled lemborexant 10 mg/kg under fasting conditions. The C_{max} and $AUC_{0-\infty}$ of radioactivity in plasma (mean ± standard error) was 923.0 ± 61.4 ng eq/mL and 10,700 ± 800 ng eq·h/mL, respectively (CTD 4.2.2.3.3).

4.1.1.2 Single-dose studies in monkeys

Male monkeys (4/group) were administered a single oral dose of lemborexant 1, 3, or 10 mg/kg under fasting conditions or a single intravenous dose of lemborexant 0.3 or 1 mg/kg under fasting conditions. The pharmacokinetic parameters of unchanged lemborexant and M10 in plasma are shown in Table 10. The absolute bioavailability of unchanged lemborexant in plasma was 16.1% to 23.4% (CTD 4.2.2.2.2).

Table 10. Pharmacokinetic parameters of unchanged lemborexant and M10 in plasma after single oral or intravenous dose of lemborexant in male monkeys

Route	Dose (mg/kg)	Unchanged lemborexant				M10			
		C_{max} (ng/mL)	t_{max} (h) [a]	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h) [a]	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)
Intravenous	0.3			6.25 ± 3.63	251 ± 30			7.64 ± 9.67	8.89 ± 5.86
	1			5.16 ± 0.49	852 ± 97			1.80 ± 0.39	21.6 ± 4.6
Oral	1	61.7 ± 41.2	1.50 [1.00, 2.00]	3.78 ± 2.34	169 ± 62	12.6 ± 5.1	1.50 [1.00, 2.00]	1.23 ± 0.15	29.6 ± 5.1
	3	110 ± 65	1.00 [1.00, 2.00]	5.23 ± 1.21	420 ± 200	17.9 ± 5.7	1.50 [1.00, 2.00]	1.74 ± 0.60	59.2 ± 11.0
	10	660 ± 404	1.50 [1.00, 2.00]	5.10 ± 1.55	2020 ± 850	65.3 ± 20.9	2.00 [1.00, 2.00]	1.95 ± 1.19	238 ± 60

Mean ± standard deviation; Number of subjects evaluated: 4 animals/group
a) Median [range]

Male monkeys (3/group) were administered a single oral dose of ^{14}C-labeled lemborexant 3 mg/kg under fasting conditions. The C_{max} and $AUC_{0-\infty}$ of radioactivity in plasma (mean ± standard error) was 706.0 ± 128.8 ng eq/mL and 6,640 ± 700 ng eq·h/mL, respectively (CTD 4.2.2.3.2).

4.1.2 Repeated-dose studies

Toxicokinetics of lemborexant was evaluated in repeated oral dose toxicity studies in mice, rats, and monkeys. The pharmacokinetic parameters in individual studies are shown in Tables 11 and 12 (CTD 4.2.3.2.3, 4.2.3.2.8, 4.2.3.2.11, 4.2.3.7.5.1, 4.2.3.7.5.2, and 4.2.3.7.5.3).

Table 11. Pharmacokinetic parameters of unchanged lemborexant in plasma after repeated oral dose of lemborexant

Animal species	Time point	Dose (mg/kg)	Sex (number of animals/group)	C_{max} (ng/mL)	t_{max} (h) [a]	AUC_{0-24h} (ng·h/mL)	CTD
Mouse	Day 28	100	Female (4/point)	1,826	2	18,328	4.2.3.2.3
			Male (4/point)	1,117	4	8,299	
		300	Female (4/point)	1,946	8	27,272	
			Male (4/point)	1,460	4	20,692	
		1,000	Female (4/point)	5,026	4	55,877	
			Male (4/point)	3,628	8	52,509	
Rat	Day 1	30	Female (4)	955 ± 213	1 [1, 1]	1,886 ± 313	4.2.3.2.8
			Male (4)	371 ± 96	1 [1, 1]	609 ± 52	
		100	Female (4)	2,711 ± 707	1 [0.5, 1]	16,661 ± 4,774	
			Male (4)	1,816 ± 875	2.5 [1, 4]	10,233 ± 5,055	
		1,000	Female (4)	7,461 ± 2,669	24 [4, 24]	115,969 ± 36,081	
			Male (4)	4,151 ± 823	6 [4, 8]	67,457 ± 14,948	
	Day 183	30	Female (4)	1,543 ± 488	1 [1, 1]	5,335 ± 1,011	
			Male (4)	690 ± 80	2 [1, 2]	2,330 ± 649	
		100	Female (4)	5,230 ± 2,041	2 [1, 2]	26,486 ± 1,798	
			Male (4)	2,597 ± 1,080	2 [1, 2]	18,015 ± 8,476	
		1,000	Female (4)	13,906 ± 4,305	8 [8, 8][b]	240,344 ± 69,030	
			Male (4)	4,798 ± 940	8 [8, 8]	60,697 ± 10,727	
Monkey	Day 1	10	Female (4)	506 ± 194	1.5 [1, 2]	2,650 ± 691	4.2.3.2-11
			Male (4)	584 ± 406	1 [1, 4]	2,850 ± 1,770	
		100	Female (4)	3,780 ± 1,630	2 [1, 8]	34,600 ± 14,000	
			Male (4)	1,880 ± 819	1 [1, 4]	28,000 ± 13,500	
		1,000	Female (4)	3,640 ± 674	8 [4, 24]	53,500 ± 10,400	
			Male (4)	4,250 ± 1,130	8 [8, 8]	70,700 ± 18,700	
	Day 269	10	Female (4)	1,160 ± 488	1 [1, 1]	4,970 ± 1,390	
			Male (4)	960 ± 109	1 [1, 1]	5,510 ± 1,690	
		100	Female (4)	8,660 ± 2,740	1 [1, 1]	82,800 ± 34,000	
			Male (4)	6,930 ± 1,490	1.5 [1, 4]	82,900 ± 23,300	
		1,000	Female (4)	6,930 ± 3,720	4 [4, 8]	98,200 ± 54,900	
			Male (4)	9,620 ± 3,140	8 [4, 8]	155,000 ± 54,800	

Mean or mean ± standard deviation
a) Median [range]
b) 3 animals. The remaining 1 animal was excluded because its pretreatment value was t_{max}.

Table 12. Pharmacokinetic parameters of M10 in plasma after repeated oral dose of lemborexant

Animal species	Time point	Dose (mg/kg)	Sex (number of animals/group)	C_{max} (ng/mL)	t_{max} (h) [a]	$AUC_{0\text{-}24h}$ (ng·h/mL)	CTD
Mouse	Day 28	100	Female (4/point)	365	2.00	3,700	4.2.3.7.5.1
			Male (4/point)	279	2.00	2,000	
		300	Female (4/point)	459	2.00	6,300	
			Male (4/point)	343	2.00	4,630	
		1,000	Female (4/point)	1,000	4.00	12,700	
			Male (4/point)	625	8.00	8,830	
Rat	Day 28	10	Female (4)	0.946 ± 0.232	1 [1, 1]	1.76 ± 0.49	4.2.3.7.5.2
			—	—	—	—	
		30	—	—	—	—	
			Male (4)	3.65 ± 0.62	1.5 [1, 2]	9.85 ± 1.71	
		100	Female (4)	35.1 ± 25.1	2 [2, 2]	204 ± 166	
			Male (4)	17.6 ± 12.1	1.25 [0.5, 2]	74.1 ± 44.4	
		1,000	Female (4)	195 ± 206	6 [4, 8]	3,070 ± 3,890	
			Male (4)	22.9 ± 12.1	8 [4, 8]	259 ± 161	
Monkey	Day 28	10	Female (3)	80.9 ± 36.2	2 [2, 2]	320 ± 142	4.2.3.7.5.3
			Male (3)	63.4 ± 3.7	4 [2, 4]	353 ± 76	
		100	Female (3)	352 ± 195	4 [4, 4]	3,210 ± 1,720	
			Male (3)	403 ± 210	4 [4, 4]	3,650 ± 1,360	
		1,000	Female (3)	357 ± 224	4 [4, 8]	6,780 ± 5,560	
			Male (3)	344 ± 241	4 [4, 4]	2,820 ± 840	

Mean or mean ± standard deviation
a) Median [range]

4.2 Distribution

4.2.1 Tissue distribution

Albino male rats were administered a single oral dose of ^{14}C-labeled lemborexant 10 mg/kg under fasting conditions. The radioactivity concentration peaked 8 hours post-dose in the cecum and large intestine, while it peaked 1 hour after administration, the time of the first sample taking, in other tissues. The radioactivity concentration was ≤1% of the peak or undetectable 336 hours (14 days) after administration (CTD 4.2.2.3.1).

Pigmented male rats were administered a single oral dose of ^{14}C-labeled lemborexant 10 mg/kg. The radioactivity concentration peaked 1 hour after administration in all tissues. The radioactivity concentration was undetectable 336 or 672 hours (28 days) after administration in all tissues other than the lungs and spleen. No accumulation of radioactivity was observed in melanin-containing tissues (skin and eyeball) (CTD 4.2.2.3.3).

Male monkeys were administered a single oral dose of ^{14}C-labeled lemborexant 3 mg/kg under fasting conditions. The radioactivity concentration 336 hours post-dose was highest in the gallbladder bile. Based on the organ weights and radioactivity concentrations, the radioactivity distribution was highest in the liver (CTD 4.2.2.3.2).

Male rats were administered a single oral dose of lemborexant 100 mg/kg under fasting conditions. The unchanged lemborexant, M4, M9, and M10 were rapidly distributed to the brain, and the steady-state ratio of cerebrospinal-fluid (CSF) to plasma unbound drug concentrations for unchanged lemborexant (2 to 8 hours post-dose) was approximately 2.6 to 3.8 times those for M4 and M10, and was comparable to (1.3 times higher than) that for M9 (CTD 4.2.2.2.1).

Male monkeys were administered a single oral dose of ^{14}C-labeled lemborexant 10 mg/kg under fasting conditions. The distribution of unchanged lemborexant, M4, M9, and M10 to the brain nearly reached a steady state 2 hours post-dose. The ratio of CSF to plasma unbound drug concentrations for unchanged lemborexant was approximately 2 (1.9 to 2.3) times those for M4 and M9 and was comparable to (1.1 times) that for M10 (CTD 4.2.2.2.2).

4.2.2 Protein binding and distribution in blood cells

Murine, rat, and monkey plasma was spiked with lemborexant 100 to 1,000 ng/mL to investigate the plasma protein binding ratio of unchanged lemborexant, M4, M9, and M10. The plasma protein binding ratio in mice, rats, and monkeys was determined by an equilibrium dialysis method to be 86.7% to 87.1%, 78.4% to 82.4%, and 82.4% to 83.4%, respectively, for unchanged lemborexant, 64.5% to 66.3%, 53.1% to 55.9%, and 63.1% to 65.0%, respectively, for M4, 71.0% to 74.4%, 74.3% to 74.6%, and 74.2% to 77.2%, respectively, for M9, and 65.2% to 68.4%, 61.3% to 65.3%, and 84.3% to 84.7%, respectively, for M10 (CTD 5.3.2.1.1 and 5.3.2.1.2).

Murine, rat, and monkey blood was spiked with lemborexant 100 to 1,000 ng/mL to investigate the ratio of distribution of unchanged lemborexant, M4, M9, and M10 in blood cells. The ratio of the distribution in blood cells in mice, rats, and monkeys was 0.736 to 0.824, 0.940 to 0.964, 0.816 to 0.879, respectively, for unchanged lemborexant, 0.754 to 0.798, 1.02 to 1.06, and 0.731 to 0.759, respectively, for M4, 0.900 to 0.976, 1.13 to 1.20, and 0.885 to 0.945, respectively, for M9, and 0.842 to 0.890, 0.930 to 0.958, and 0.689 to 0.765, respectively, for M10 (CTD 5.3.2.3.1).

4.2.3 Placental transfer

Pregnant rats on Gestation Day 13 or 18 were administered a single oral dose of ^{14}C-labeled lemborexant 10 mg/kg. The ratio of fetal radioactivity concentration to the plasma radioactivity concentration in dams was 0.19 on Gestation Day 13 and 0.36 on Gestation Day 18. In addition, ≤0.01% of the administered radioactivity was distributed to the fetuses on Gestation Days 13 and 18. An analysis of metabolites showed that lemborexant, M3, and M9 were the main radioactive components in fetuses, fetal plasma, and maternal plasma (CTD 4.2.2.3.4).

4.3 Metabolism

4.3.1 *In vitro* metabolism

Murine, rat, and monkey liver microsomes were spiked with lemborexant 50 µmol/L and were incubated at 37°C for 15 minutes. Hydroxylated forms (M1, M3, M5, M7, M8, and M9), *N*-oxidated forms (M2, M4, and M10), and an oxidized form (M6) were produced (CTD 5.3.2.2.1).

4.3.2 *In vivo* metabolism

Male rats were administered a single oral dose of ^{14}C-labeled lemborexant 10 mg/kg. The following main metabolites were detected: M9 in the plasma and blood cells; glucuronides (mR14, mR26b, and mR31b), a sulfate conjugate (mR31a), and a dihydrodiol form (mR26a) in urine; M1, M12, and mR64 in

feces; M12, a cysteinyl glycine conjugate of H_2O-added metabolite (mR16a), a glutathione conjugate of H_2O-added metabolite (mR16b), an oxidized form of a metabolite conjugated with glucuronide and defluorinated (mR21), and glucuronide of M1 (M16) in bile. No unchanged lemborexant was detected in urine, feces, or bile (CTD 4.2.2.4.1).

Male monkeys were administered a single oral dose of ^{14}C-labeled lemborexant 3 mg/kg. The following main metabolites were detected: M4, dioxidized forms (M13 and M14), and a glucuronide of M1 (M16) in plasma and blood cells; M13, a trioxidized form (mM19c), glucuronides of oxidized forms (M16, M18, and M20), and glucuronides of dioxidized forms (mM19b-1 and mM19b-2) in urine; and M9, M12, and a sulfate conjugate of an oxidized form (mM37a) in feces (CTD 4.2.2.4.2).

4.4 Excretion

4.4.1 Urinary and fecal excretion

Male rats were administered a single oral dose of ^{14}C-labeled lemborexant 10 mg/kg. The cumulative excretion rate of radioactivity in urine and feces (mean ± standard error) up to 168 hours post-dose was 5.9% ± 0.8% and 90.6% ± 1.2% of the total dose of administered radioactivity, respectively. In male rats with bile duct cannulation, the cumulative excretion rate of radioactivity in urine, feces, and bile up to 48 hours post-dose was 1.1% ± 0.2%, 1.2% ± 0.1%, and 100% ± 0.7% of the total dose of administered radioactivity, respectively (CTD 4.2.2.3.1).

Male monkeys were administered a single oral dose of ^{14}C-labeled lemborexant 3 mg/kg. The cumulative excretion rate of radioactivity in urine and feces (mean ± standard error) up to 366 hours post-dose was 22.5% ± 1.6% and 75.1% ± 0.8%, respectively, of the total dose of administered radioactivity (CTD 4.2.2.3.2).

4.4.2 Excretion into milk

Lactating rats were administered a single oral dose of ^{14}C-labeled lemborexant 10 mg/kg. The radioactivity concentration was higher in milk than in plasma at an $AUC_{0-\infty}$ ratio of 3.06. The half-life of radioactivity in milk was 17.3 hours, which was comparable to that in plasma. Results of an analysis of milk samples suggest an excretion of lemborexant, M3, and M9 in milk (CTD 4.2.2.3.4).

4.R Outline of the review conducted by PMDA

PMDA has concluded that no particular problems were found in the submitted non-clinical pharmacokinetic data.

5. Toxicity and Outline of the Review Conducted by PMDA

For evaluation of the toxicity of lemborexant, data were submitted from single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, and other studies (studies on the mechanism of toxicity, studies on dependence, studies on toxicity of metabolites, studies on toxicity of impurities, photosafety studies, and studies on effects on the growth of

Plasmodium). A mixed solution of 1 mol/L hydrochloric acid and 0.5% methylcellulose (a mixing ratio of 1:4, v/v) was used as the vehicle *in vivo* studies unless otherwise specified.

5.1 Single-dose toxicity

A single oral dose toxicity study in rats (CTD 4.2.3.1.1) and extended single-dose oral toxicity studies in rats and cynomolgus monkeys (CTD 4.2.3.1.2 and 4.2.3.1.3) were conducted (Table 13). The approximate lethal dose of oral lemborexant was determined to be >1,000 mg/kg in rats and cynomolgus monkeys.

Table 13. Outline of results of single-dose toxicity studies

Test system	Route	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached CTD
Male and female rat (SD)	Oral	100 [a], 300 [a], 1,000 [a]	No remarkable findings	>1,000	Reference data 4.2.3.1.1
Male and female rat (SD)	Oral	100, 300, 1,000	≥300: increased liver weight (female) 1,000: increased liver weight (male)	>1,000	4.2.3.1.2
Male and female cynomolgus monkey	Oral	100, 300, 1,000	1,000: decreased serum Cl (male), [b] partially closed eye, vomiting, loose stools (male)	>1,000	4.2.3.1.3

a) Vehicle, 0.5% methylcellulose solution
b) Only 1 male experiencing vomiting and loose stools on the following day of administration

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in rats (4, 13, and 26 weeks) and monkeys (4, 13, and 39 weeks) (Table 14). The main target organs included bone and teeth. In the repeated-dose toxicity studies in rats, bone and dental abnormalities were observed. However, these abnormalities were related to fluorosis due to fluoride ions generated during a rat-specific metabolic process for lemborexant, and defluorinated metabolites were detected in rats and in small amount in monkeys, but not in humans (CTD 4.2.2.4.1 to 2, 5.3.2.2.5 and 5.3.2.2.11), suggesting that these findings are not extrapolable to humans. The exposure of lemborexant ($AUC_{0\text{-}24h}$) at the no-observed-adverse-effect level (NOAEL; 100 mg/kg/day for male rats, 30 mg/kg/day for female rats, and 10 mg/kg/day for male and female monkeys) in the repeated-dose toxicity studies in rats (26 weeks) and monkeys (39 weeks) was 41, 12, and 12 times higher in male rats, female rats, and male and female monkeys, respectively, than the exposure (AUC_{ss}: 441 ng·h/mL) after the administration of lemborexant at the maximum clinical dose (10 mg once daily; CTD 5.3.3.5.5).

Table 14. Outline of results of repeated-dose studies

Study	Route	Duration	Dose (mg/kg)	Main findings	NOAEL (mg/kg)	Attached CTD
Male and female rat (SD)	Oral	4 weeks (once daily)	0, 30, 100, and 1,000	1,000: decreased food consumption (female); reduced body weight gain (female); decreased reticulocyte count (female); increased blood urea nitrogen (female); increased blood total protein (female); increased blood total cholesterol (female); increased liver weight (female); centrilobular hepatocellular hypertrophy (female)[a]; femoral pigmentation; decreased hematopoietic cells in the bone marrow (female); and decreased lymphocytes in the thymus (female)	1,000 (male) 100 (female)	4.2.3.2.5 [b] 4.2.3.2.6 4.2.3.2.7 [b]
Male and female rat (SD)	Oral	13/26 weeks[c] (once daily)	0, 30, 100, and 1,000	1,000: deaths [d] (1 of 22 males and 3 of 22 females) 13 weeks ≥30: femoral pigmentation (male) 100: low hematocrit (male), low MCV (male); and low MCH (male) ≥100: whiteness of the incisors; decreased hemoglobin concentration (male); increased serum calcium; increased blood total protein (male); increased liver weight; and pigmentation of the femur (female), tibia and alveolar bone (male), and incisor dentin (male)	100 (male) 30 (female)	4.2.3.2.8

				1,000: decreased food consumption (female); weight loss (female); decreased activity (female); staining of the perioral region (male); no feces; decreased hemoglobin concentration (female); low hematocrit; low MCV; low MCH; increased white blood cell count (female); increased serum potassium (female); increased serum urea nitrogen; increased blood total cholesterol; prolonged APTT (male); hepatocellular hypertrophy; hypertrophy of follicular epithelial cells in the thyroid (female); decreased trabecular bone of the femur (female) and tibia (female); decreased mature lamellar bone of the femur and tibia; pigmentation of the sternum (female), alveolar bone (female), incisor dentin (female), and molar dentin; decreased iron pigment granules in the incisor ameloblasts; and degeneration of incisor ameloblasts 26 weeks ≥30: femoral pigmentation; and whiteness of the incisors (male). ≥100: whiteness of the incisors (female); increased blood total protein; increased blood total cholesterol (female); increased serum calcium (female); decreased serum iron (female); increased liver weight; pigmentation of the tibia, sternum, and incisor dentin; and decreased iron pigment granules in the incisor ameloblasts (female) 1,000: decreased food consumption; weight loss; decreased activity (female); staining of the perioral region (female); no feces; decreased hemoglobin concentration; low hematocrit; low MCV; low MCH; increased reticulocyte count (female); increased white blood cell count (female); increased serum calcium (male); increased serum potassium (female); increased blood urea nitrogen; increased blood total cholesterol (male); prolonged APTT (male); decreased adrenal weight (female); hepatocellular hypertrophy; hypertrophy of follicular epithelial cells in the thyroid (female); decreased trabecular bone of the femur and tibia (female); decreased mature lamellar bone of the femur and tibia; decreased femoral bone density (female); pigmentation of the alveolar bone and molar dentin; decreased iron pigment granules in the incisor ameloblasts; and degeneration of incisor ameloblasts		
Male and female cynomol-gus monkey	Oral	4 weeks (once daily)	0, 30, 100, and 1,000	30: recumbent position (male) ≥100: vomiting; and salivation (male) 1,000: salivation (female); sedation (male); sitting position (male); partially closed eye (male); somnolence (male); decreased red blood cell count; low hematocrit; decreased hemoglobin concentration; and increased reticulocyte count	30	4.2.3.2.9
Male and female cynomol-gus monkey	Oral	13 weeks (once daily)	0, 20, 100, and 1,000	≥100: vomiting; salivation; decreased red blood cell count; low hematocrit; decreased hemoglobin concentration; increased reticulocyte count; blood Howell-Jolly bodies; blood erythroblasts; and malaria infection (including plasmodium in peripheral blood and malaria pigmentation in the spleen, liver, and bone marrow) 1,000: increased serum triglyceride; and increased liver weight	20	4.2.3.2.10
Male and female cynomol-gus monkey	Oral	39 weeks (once daily)	0, 10, 100, and 1,000	≥10: decreased activity; and somnolence 100: increased serum iron (female) ≥100: vomiting; loose stools; liquid stools; low red blood cell count; decreased hemoglobin concentration; low hematocrit; increased reticulocyte count; increased serum triglyceride; increased blood phosphorus; increased blood total iron binding capacity (TIBC); increased blood unsaturated iron binding capacity (UIBC) (female); increased serum iron (male); increased urinary fluoride excretion; increased liver weight; spleen congestion; hemosiderin deposition in the spleen; increased hematopoiesis in the bone marrow; and hemosiderin deposition in the bone marrow 1,000: increased blood UIBC (male); hypertrophy and dark discoloration of the liver; hepatocellular hypertrophy; and pigmentation of the femoral trabeculae	10 [e)]	4.2.3.2.11

a) Moderate to severe induction of hepatic enzymes (CYP1A2, CYP3A1, CYP3A4) was observed.
b) Some parts of the test did not undergo GLP inspection by a foreign regulatory authority and thus GLP compliance remained unconfirmed. However, PMDA considered that the uncertain compliance have minor effect on the safety evaluation.
c) 13 weeks (10 animals/sex/group) or 26 weeks (12 animals/sex/group)
d) A male animal in the 1,000 mg/kg group and female animals in the 1,000 mg/kg group were euthanized for a humanitarian reason due to abnormal gait after the fracture of the hindlimbs. A female animal in the 1,000 mg/kg was euthanized because the animal became moribund on Day 142 of treatment.
e) Decreased activity and somnolence are attributable to the pharmacological effects of lemborexant and were considered by the applicant to be of less toxicological significance.

5.3 Genotoxicity

Bacterial reverse mutation tests, mouse lymphoma tests, and bone marrow micronucleus tests in rats were conducted (Table 15) and demonstrated that lemborexant has no genotoxicity.

Table 15. Outline of results of genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Concentration or dose	Results	Attached CTD
in vitro	Bacterial reverse mutation tests	*Salmonella typhimurium*: TA98, TA100, TA1535, and TA1537 *Escherichia coli*: WP2*uvr*A (pKM101)	S9−	0[a)], 313, 625, 1,250, 2,500, and 5,000 (μg/plate)	Negative	4.2.3.3.1.1
			S9+	0[a)], 313, 625, 1,250, 2,500, and 5,000 (μg/plate)		
	Chromosomal aberration assay with mammalian cultured cells	L5178Y cells derived from mouse lymphoma	S9− (3 hours)	0[a)], 25, 50, 100, 200 (μg/mL)	Negative	4.2.3.3.1.2
			S9− (24 hours)	0[a)], 10, 20, 40, 50, 60, 70, and 80 (μg/mL)		
			S9+ (3 hours)	0[a)], 25, 50, 100, and 200 (μg/mL)		
in vivo	Bone marrow micronucleus tests in rodents	Male rat(SD) Bone marrow		0, 500, 1,000, and 2,000 (mg/kg) (oral, single dose)	Negative	4.2.3.3.2.1

a) Vehicle,: dimethyl sulfoxide (DMSO)

5.4 Carcinogenicity

Carcinogenicity studies were conducted in Tg rasH2 mice and rats and showed no increases in the incidence of tumors in association with administration of lemborexant (Table 16).

Table 16. Outline of results of carcinogenicity studies

Test system	Route	Duration	Main lesion		Dose (mg/kg)					Non-carcinogenic dose	Attached CTD
					0	10	30	100	300		
Male and female mouse (CB6F1-Tg rasH2)	Oral	26 weeks (once daily)		Number of animals	25		25	25	25	500	4.2.3.4.2.1
			Neoplastic lesions	No remarkable findings							
			Non-neoplastic lesions	Centrilobular hepatocellular hypertrophy; femoral pigmentation; and whiteness of the incisors							
Male and female rat (SD)	Oral	104 weeks (once daily)	Main lesion		0	10	30	100	300	300 (male) 100 (female)	4.2.3.4.1.1
				Number of animals	M and F 120[a)]	F 60	M and F 60	M and F 60	M 60		
			Neoplastic lesions	No remarkable findings [b)]							
			Non-neoplastic lesions	Centrilobular hepatocellular hypertrophy; atrophy of the accessory reproductive organs and mammary glands; bone fluorosis (including inflammation of the ankles and toe joints, exostosis, and pigmentation of bone tissues); whiteness of teeth; pigmentation of the bone and incisors; increased frequency of incisor fracture (male); and degeneration of ameloblasts						

a) There were 2 control groups. The data of the 2 control groups were combined in statistical analyses after the confirmation of no significant differences between the control groups.

b) Tumors of the pituitary gland and mammary gland decreased in the female 100 mg/kg group.

5.5 Reproductive and developmental toxicity

Studies of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in rats and rabbits, and a study for effects on pre- and post-natal development, including maternal function, in rats were conducted (Table 17). In the embryo-fetal development study in rats (CTD 4.2.3.5.2.2), membranous ventricular septal defect was observed in the low-dose groups. However, in the embryo-fetal development study in rats (an additional study) (CTD 4.2.3.5.2.3), no dose-relationship was observed. In addition, a study with doses with serious maternal toxicity was conducted to evaluate the reversibility of membranous ventricular septal defect in rats and showed no reproducibility of the results (CTD 4.2.3.5.2.4). In light of these

findings, the applicant considered the changes were not attributable to lemborexant. The exposure to lemborexant ($AUC_{0\text{-}24h}$) at the NOAEL (200 mg/kg/day for rats and 30 mg/kg/day for rabbits) for the development of F1 offspring was 143 and 23 times higher in rats and rabbits, respectively, than the exposure (AUC_{ss}: 441 ng·h/mL) after the administration of lemborexant at the maximum clinical dose (10 mg once daily; CTD 5.3.3.5.5).

Table 17. Outline of results of reproductive and developmental toxicity studies

Study	Test system	Route	Duration	Dose (mg/kg/)	Main findings	NOAEL (mg/kg/day)	Attached CTD
Studies of fertility and early embryonic development to implantation	Male rat (SD)	Oral	From 28 days before mating and during mating period (up to 13 days) (once daily)	0, 30, 100, and 1,000	No remarkable findings	Parental animals (general toxicity): 1,000 Parental animals (fertility): 1,000	4.2.3.5.1.1
	Male rat (SD)	Oral	From 14 days before mating to Gestation Day 6 (once daily)	0, 30, 100, and 1,000	≥100: abnormal estrous cycles; and decreased pregnancy rates. 1,000: decreased food consumption; reduced body weight gain; and decreased number of corpora lutea, implantations, and decreased live embryos	Parental animals (general toxicity): 100 Parental animals (fertility): 30	4.2.3.5.1.2
Embryo-fetal development Studies	Female rat (SD)	Oral	Gestation Days 6 to 17 (once daily)	0, 60, 200, and 600	Parental animals: ≥200: decreased food consumption, reduced body weight gain 600: decreased activity; and staining of the anogenital region. Fetuses: ≥60: membranous ventricular septal defect 600: increased number of dead fetuses; low fetal weight; exomphalos; cleft palate; 14th rib; and incomplete ossification (incomplete ossification of the cervical arch and thoracic centrum).	Parental animals (general toxicity): 60 Embryo-fetal development: < 60	4.2.3.5.2.2
	Female rat (SD)	Oral	Gestation Days 6 to 17 (once daily)	0, 20, 60, and 200	Parental animals: 200: decreased food consumption; and weight loss. Fetuses [a]: 20, 60: membranous ventricular septal defect	Parental animals (general toxicity): 60 Embryo-fetal development: 200	4.2.3.5.2.3
	Female rat (SD)	Oral	Gestation Days 6 to 17 (once daily)	0, 20, 60, 200, and 600	Parental animals: 600: deaths [b] (2 of 55 females) ≥200: decreased food consumption; and weight loss. 600: dehydration; and hunched posture Fetuses: 600: fetal low weight		4.2.3.5.2.4 [c]
	Female rabbit (NZW)	Oral	Gestation Days 7 to 20 (once daily)	0, 10, 30, and 100	Parental animals: ≥10: partially closed eye 100: decreased food consumption; and weight loss Fetuses: 100: cervical rib	Parental animals (general toxicity): 30 Embryo-fetal development: 30	4.2.3.5.2.6
Study for effects on pre- and postnatal development, including maternal function	Female rat (SD)	Oral	Dams: Gestation Day 6 to Postpartum Day 20 (once daily)	0, 30, 100, and 300	Parental animals: 300: decreased food consumption; and reduced body weight gain. F1 offspring: ≥100: Low UIBC and TIBC; and increased bone fluoride levels. 300: fetal low weight: short femoral length; and decrease and prolonged latency in acclimation response to auditory startle stimuli.	Parental animals (general toxicity): 100 F1 offspring development: 300[d]	4.2.3.5.3.2

a) External and visceral examinations on the shapes were performed.
b) Animals with deteriorated general conditions were euthanized on Gestation Day 16 or 17.
c) This study was conducted to confirm the reproducibility of membranous ventricular septal defect observed in the embryo-fetal development studies in rats (CTD 4.2.3.5.2.2 to 3) and the spontaneous closure of the defect after birth. However, no membranous ventricular septal defect was observed in rats treated with lemborexant, and thus no spontaneous closure was confirmed. The laboratory and the rat supplier in this study differed from those in the embryo-fetal development studies in rats (CTD 4.2.3.5.2.2 to 3).
d) Findings of femoral length and acclimation response to auditory startle stimuli are considered to be related to the low body weight. Low neonatal body weight was observed up to Postnatal Day 36, but afterward, no significant differences were observed as compared with the control animals.

5.6 Other studies

5.6.1 Mechanism of toxicity

Studies shown in Tables 18 and 19 were conducted to evaluate the mechanism of the development and reversibility of the bone and dental toxicities observed in the repeated-dose toxicity studies rats. In rats treated with lemborexant, fluoride levels in urine, serum, and bone increased, and findings consistent with fluorosis were observed. These findings showed a trend toward improvement. It was demonstrated that the increase in the urinary fluoride excretion was caused by CYP-mediated metabolism.

Table 18. Outline of results of an oral repeated-dose toxicity study

Test system	Route	Duration	Dose (mg/kg)	Main findings	Attached CTD
Female rat (SD)	Oral	9/14 weeks (once daily) + a 12-week interval	0, 1,000 → 800[a)]	Deaths: 1 in 46 animals[b)] 1,000 decreased to 800: decreased food consumption/weight loss; decreased activity; debility; partially closed eye; hunched posture; increased urinary fluoride excretion; increased bone and serum fluoride concentrations; dental and bone findings related to fluorosis,[c)d)] decreased serum iron,[d)] decreased adrenal weight,[d)] and decreased adrenocorticotropic hormone (ACTH)[d)] Reversibility: observed	4.2.3.7.3.1

a) Since marked weigh loss was observed at Week 2 of administration, lemborexant was interrupted for 7 days from Day 15 and was resumed at the reduced dose of 800 mg/kg on Day 22. After that, 16 animals continued to have marked weight loss and were euthanized at Week 9, and the remaining animals continued with treatment until Week 14.
b) The animal died of renal disorder due to fluorosis on Day 93.
c) Bone findings included decreased femoral bone density, decreased bone density of the lumbar vertebral trabecular bone, decreased trabecular bone at the distal end of the femur, loss of strength of the femur and lumbar vertebra, decreased femoral calcification rate, decreased trabecular bone of the femur and tibia, and decreased mature lamellar bone associated with increased osteoid. Dental findings included discoloration of incisors (whiteness and zonal whiteness), degeneration of incisor ameloblasts, and decreased iron pigment granules of incisors.
d) They were observed at Week 14.

Table 19. Outline of the results of studies on the development of bone and dental toxicities

Study	Test system	Test methods	Main findings	Attached CTD
Study of determination of fluoride after 4-week repeated-dosing in female rats	Female rat (SD)	Fluoride concentrations in urine, serum, and bone were determined after 4-week repeated oral dosing of lemborexant 30, 100, or 1,000 mg/kg/day.	Urinary and bone fluoride concentrations increased in a dose-dependent manner. Serum fluoride concentrations were below the limit of quantitation (<0.5 ppm) in the 30 and 100 mg/kg groups, but slightly high serum fluoride concentrations (up to 1.4 ppm) were observed in some animals in the 1,000 mg/kg group.	Reference data 4.2.3.7.3.2
Study of determination of fluoride in rats concomitantly treated with CYP inhibitors	Male and female rat (SD)	Lemborexant 100 or 1,000 mg/kg was administered twice at a 10-day interval, and urinary fluoride concentrations were determined. Animals were pretreated with 1-aminobenzotriazole (1-ABT)[a)] before the second lemborexant administration.	Urinary fluoride excretion caused by administration of lemborexant was inhibited by treatment with 1-ABT.	Reference data 4.2.3.7.3.3

a) A non-selective CYP inhibitor.

5.6.2 Dependence

The results of dependence studies are summarized in Table 20. Lemborexant induced no physical dependence and was demonstrated to be associated with no psychic dependence.

Table 20. Outline of results of dependence studies

Study	Test system	Test methods	Main findings	Attached CTD
Physical dependence study	Male rat (SD)	Oral lemborexant 100 or 300 mg/kg was administered twice daily for 28 days. After a 7-day washout, rats were monitored for withdrawal syndrome,	No withdrawal syndrome was observed after the interruption of lemborexant, and lemborexant was considered to have no ability to induce no physical dependence.	4.2.3.7.4.1
Self-administration study	Male and female rhesus m onkeys	Lemborexant 0.003, 0.01, 0.03, 0.1, or 0.3 mg/kg was intravenously self-administered to rhesus monkeys trained for self-administration of pentobarbital 1 mg/kg.	The frequency of self-administration did not increase, and lemborexant was considered to have no ability to induce psychic dependence.	4.2.3.7.4.3
Drug discrimination study	Female rat (SD)	Lemborexant or suvorexant 0, 10, 30, 100, or 1,000 mg/kg was orally administered to rats able to discriminate zolpidem 3 mg/kg from a vehicle[a)] to evaluate the discrimination and generalizability.	Lemborexant was considered not to meet the criteria for the generalization from zolpidem, and the discriminative-stimulus effect of lemborexant was considered not similar to that of zolpidem. Meanwhile, suvorexant demonstrated partial generalizability for zolpidem.[b)]	4.2.3.7.4.4

a) 10% polysorbate 80 solution (w/v)
b) Similar data were reported by Born et al. (*Reg Toxicol Pharmacol.* 2017;86:181-192).

5.6.3 Metabolites

M10, one of the metabolites of lemborexant, accounts for >10% of total exposure at the clinically recommended dose and should be characterized in non-clinical studies. In non-clinical safety studies in mice, rats, and monkeys, M10 exceeded the exposure in humans receiving lemborexant 10 mg/day, no individual safety evaluation was considered unnecessary.

5.6.4 Impurities

Bacterial reverse mutation tests were conducted for 10 compounds for synthesized starting materials, intermediates, and related substances (Impurities A, B, C, D, E, F, G, H, I, and J), and Impurities C, D, E, G, and H were tested positive (CTD 4.2.3.7.6.1 to 10). Impurities D and E were found to be well below the threshold of toxicological concern (TTC) in 3 representative batches of the starting materials. Impurities C, G, and H are all controlled below the TTC in the starting materials or critical intermediates.

5.6.5 Photosafety testing

A neutral red uptake assay with BALB/3T3 cells was conducted. Based on the results, lemborexant was considered to show no phototoxicity (CTD 4.2.3.7.7.1 to 2).

5.6.6 Study on the effects of lemborexant on growth of Plasmodium

Malaria relapsed in 1 male monkey receiving lemborexant 1,000 mg/kg in the 13-week repeated-dose toxicity study in monkeys (CTD 4.2.3.2.10). Therefore, a study was conducted to investigate the effects of lemborexant (0.1 to 100 µg/mL) on the growth of Plasmodium (*P. falciparum*) and showed that lemborexant did not accelerate the growth of Plasmodium (CTD 4.2.3.7.7.3).

5.R Outline of the review conducted by PMDA

5.R.1 Reproductive and developmental toxicity

PMDA asked the applicant to explain the relationship between the administration of lemborexant and membranous ventricular septal defect observed in the embryo-fetal development study in rats (CTD 4.2.3.5.2.2) or the embryo-fetal development study in rats (an additional study) (CTD 4.2.3.5.2.3).

The applicant's explanation:

The membranous ventricular septal defect is unlikely to be related directly to the administration of lemborexant for the reasons shown below.

- Although orexin is known to be involved in physiological functions including feeding and sleep cycles during the period before birth to postnatal weaning (*J Chem Neuroanat.* 2004;27:165-81; *J Comp Neurol.* 2001;433:349-63), no physical abnormalities, such as external malformation, have been reported in association with functional disorders induced by orexin.
- The incidences of the membranous ventricular septal defect (≤1.0%) in the groups of lemborexant ≤200 mg/kg in the embryo-fetal development study in rats (CTD 4.2.3.5.2.2) and the embryo-fetal development study in rats (additional study) (CTD 4.2.3.5.2.3) are thought to fall in the range of the incidences of the membranous ventricular septal defect observed spontaneously in wild-type SD rats (the maximum rate, 9.4% per study) (*Congenit Anom.* 2014;54:150-61; *Congenit Anom.* 2018;1-7: https://doi.org/10.1111/cga.12305). The findings suggest that membranous ventricular septal defect can occur accidentally.
- Deteriorated conditions including adverse effects on body weights and food consumption were seen in the dams of the fetuses having membranous ventricular septal defect in the 600 mg/kg group in the embryo-fetal development study in rats (CTD 4.2.3.5.2.2) [see Section 5.5]. Membranous ventricular septal defect may be attributable to the secondary effects of decreased weight and food consumption in dams.
- No dose-relationship was observed in the embryo-fetal development study in rats (additional study) (CTD 4.2.3.5.2.3), and no reproducibility was seen in the study investigating the reversibility of membranous ventricular septal defect with doses with serious maternal toxicity in rats (CTD 4.2.3.5.2.4) [see Section 5.5].

PMDA accepted the above applicant's explanation. PMDA considered that no particular problems were found in the submitted data from other studies.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Data from a study of food effects in non-Japanese healthy adults (CTD 5.3.3.4.2, Study E2006-A001-008 [reference data]) were submitted as reference data. The concentrations of unchanged lemborexant and metabolites in plasma were determined by LC-MS/MS (lower limit of

quantification: 0.0500 to 0.300 ng/mL). Lemborexant 2.5 and 5 mg tablets formulated for clinical studies[9] and lemborexant 10 mg tablets proposed for commercial use were used in phase III studies on lemborexant. Dissolution tests confirmed the bioequivalence among the clinical study formulations with equal strength and among different strengths of the clinical study formulations or commercial formulation.

6.1.1 Food effects (CTD 5.3.3.4.2, Study E2006-A001-008 [reference data])

Non-Japanese healthy adults (24 subjects in the pharmacokinetic analysis) received a single oral dose of lemborexant (the clinical study formulation) 10 mg under fasting conditions or after a high-fat meal to evaluate food effects on the pharmacokinetics of lemborexant in a randomized, open-label, 2-period cross-over study. The C_{max} and $AUC_{0-\infty}$, with ratio of 90% CI, of geometric means (administration after a meal/under fasting conditions) was 0.77 [0.69, 0.87] and 1.18 [1.09, 1.27], respectively.

6.2 Clinical pharmacology

Evaluation data were submitted from *in vitro* human biomaterial studies,[10] a pharmacokinetic study in Japanese and non-Japanese healthy adults (CTD 5.3.3.1.3, Study E2006-A001-003), a driving performance study in healthy adults and elderly subjects (CTD 5.3.4.1.3, Study E2006-E044-106), and a dose-response study with polysomnography in patients with chronic insomnia (CTD 5.3.4.2.2, Study E2006-G000-201). Reference data included the results of pharmacokinetic study in non-Japanese healthy adults,[11] studies in special populations,[12] drug interaction studies,[13] and pharmacodynamic studies.[14] For pharmacokinetic parameters, t_{max} indicates median values, and other parameters indicate mean ± standard deviation unless otherwise specified. Only data from the main pharmacokinetic studies are described in the following sections.

6.2.1 Studies using human biomaterials

Human plasma was spiked with lemborexant 100 to 1,000 ng/mL to investigate the plasma protein binding ratio of unchanged lemborexant, M4, M9, and M10 by an equilibrium dialysis method. The plasma protein binding ratio was 87.4% to 88.7% for unchanged lemborexant, 74.3% to 74.4% for M4, 85.3% to 86.2% for M9, and 91.5% to 92.0% for M10 (CTD 5.3.2.1.1, 5.3.2.1.2).

Human blood was spiked with lemborexant 100 to 1,000 ng/mL to investigate the ratio of distribution in blood cells of unchanged lemborexant, M4, M9, and M10. The ratio of concentration in blood cells to that in plasma was 0.610 to 0.656 for unchanged lemborexant, 0.650 to 0.705 for M4, 0.738 to 0.766 for M9, and 0.562 to 0.616 for M10 (CTD 5.3.2.3.1).

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9) The formulation was the same as that for the proposed commercial formulation except for the colorant, a trace ingredient listed.

10) CTD 5.3.2.1.1, Study 12-304; CTD 5.3.2.1.2, Study 16-559; CTD 5.3.2.1.3, Study DMPKT20[redacted]-003; CTD 5.3.2.2.1, Study C[redacted]062; CTD 5.3.2.2.2, Study DMPKT20[redacted]-005; CTD 5.3.2.2.3, Study DMPKT20[redacted]-011; CTD 5.3.2.2.4, Study DMPKT20[redacted]-002; CTD 5.3.2.2.5, Study DMPKT20[redacted]-008; CTD 5.3.2.2.6, Study DMPKT20[redacted]-005; CTD 5.3.2.2.7, Study DMPKT20[redacted]-009; CTD 5.3.2.2.8, Study DMPKT20[redacted]-001; CTD 5.3.2.2.9, Study B[redacted]0772; CTD 5.3.2.2.10, Study 15-131; CTD 5.3.2.2.11, Study AE-7433-G; CTD 5.3.2.3.1, Study 16-560; CTD 5.3.2.3.2, Study DMPKT20[redacted]-010; CTD 5.3.2.3.3, Study KAC36-02-[redacted]0827; and CTD 5.3.2.3.4, Study KAC37-03-[redacted]0827

11) Reference CTD 5.3.3.1.1, Study E2006-A001-001; reference CTD 5.3.3.1.2, Study E2006-A001-002; and reference CTD 5.3.3.1.4, Study E2006-A001-007

12) Reference CTD 5.3.3.3.2, Study E2006-A001-104; and reference CTD 5.3.3.3.3, Study E2006-A001-105

13) Reference CTD 5.3.3.4-1, Study E2006-A001-004; reference CTD 5.3.3.4.4, Study E2006-A001-012; and reference CTD 5.3.3.4.3, Study E2006-A001-009

14) Reference CTD 5.3.3.3.1, Study E2006-A001-102; reference CTD 5.3.4.1.1, Study E2006-A001-108; reference CTD 5.3.4.1.2, Study E2006-A001-103; and reference CTD 5.3.4.2.1, Study E2006-A001-107

Microsomes expressing CYP molecular species (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, and CYP4F12) were spiked with lemborexant, M4, M9, or M10 (100 nmol/L). Lemborexant, M4, M9, and M10 were metabolized mainly by CYP3A (CTD 5.3.2.2.2, Study DMPKT20[redacted]-005; and CTD 5.3.2.2.3, Study DMPKT20[redacted]-011).

The metabolism of lemborexant 300 nmol/L in human liver microsomes was investigated with CYP inhibitors. Lemborexant was nearly completely metabolized by a non-selective CYP inhibitor (1-ABT) and CYP3A inhibitors (troleandomycin and ketoconazole), suggesting that lemborexant is mainly metabolized by CYP3A (CTD 5.3.2.2.4, Study DMPKT20[redacted]-002).

Substrates specific to CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A[15)] were used to investigate the inhibitory capacity and time-dependent inhibitory action of lemborexant (3 to 30 μmol/L) on the CYP molecular species in human liver microsomes. Lemborexant demonstrated reversible inhibition of CYP2A6 and CYP2C19 (IC_{50}, 7.8 and 24.6 μmol/L, respectively). Meanwhile, lemborexant increased the activity of CYP2E1 (125.1% to 212.6% relative to that for a vehicle control). Lemborexant inhibited CYP3A in a time-dependent manner with a 50% inhibitory concentration (Ki) of 25.2 μmol/L at the maximum inactivation rate constant of 0.0503 min^{-1} (CTD 5.3.2.2.8, Study DMPKT20[redacted]-001).

Substrates specific to CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A[15)] were used to investigate the inhibitory capacity and time-dependent inhibitory action of M4, M9, and M10 (3 to 30 μmol/L) on the CYP molecular species in human liver microsomes. M4, M9, or M10 did not clearly demonstrate reversible inhibition of the CYP molecular species (IC_{50}, >30 μmol/L). Meanwhile, the metabolites increased the activity of CYP2E1 (151.0% to 193.5% relative to that for a vehicle control). The metabolites weakly inhibited CYP3A in a time-dependent manner, and the inhibitory activity decreased below 40% at 30 μmol/L (CTD 5.3.2.2.8, Study DMPKT20[redacted]-001; and CTD 5.3.2.2.9, Study B[redacted]0772).

Human hepatocytes were spiked with lemborexant (0.3 to 80 μmol/L), M4, M9, or M10 (1 to 10 μmol/L) to investigate the ability to induce CYP1A2, CYP2B6, and CYP3A4. Lemborexant induced the mRNA of CYP1A2, CYP2B6, and CYP3A4 up to 13.9%, 84.4%, and 79.3% of the positive control, respectively. M4, M9, and M10 induced the mRNA of CYP1A2, CYP2B6, and CYP3A4 up to 7.7%, 41.8%, and 50.8% of the positive control, respectively (CTD 5.3.2.2.10, Study 15-131).

LLC-PK cells expressing P-glycoprotein (P-gp) and MDCKII cells expressing breast cancer resistance protein (BCRP) were spiked with lemborexant or its metabolite (M4, M9, M10, M13, M14, or M15) at 3 μmol/L. The P-gp transport ratio of lemborexant, M4, M9, M10, M13, M14, and M15 (ratio of the transport from the

15) CYP1A2, phenacetin; CYP2A6, coumarin; CYP2B6, bupropion; CYP2C8, paclitaxel; CYP2C9, diclofenac; CYP2C19, S-mephenytoin; CYP2D6, (±)-bufuralol; CYP2E1, chlorzoxazone; and CYP3A4, midazolam, nifedipine, and testosterone.

basement membrane to the brush border membrane to the transport from the brush border membrane to the basement membrane) was 1.47, 16.26, 2.86, 4.41, 17.82, 16.10, and 11.41, respectively. The BCRP transport ratio of lemborexant, M4, M9, M10, M13, M14, and M15 was 1.28, 1.42, 1.04, 0.94, 1.06, 0.85, and 0.79, respectively. The transportation of lemborexant or metabolites was inhibited in the presence of verapamil, a specific inhibitor of P-gp, but was not inhibited in the presence of Ko143, a specific inhibitor of BCRP, indicating that lemborexant is a poor substrate for P-gp and that M4, M9, M10, M13, M14, and M15 are substrates for P-gp. It was also suggested that lemborexant, M4, M9, M10, M13, M14, or M15 was not a substrate for BCRP (CTD 5.3.2.3.2, Study DMPKT20[redacted]-010).

HEK cells expressing OATP1B1 and CHO cells expressing OATP1B3 were spiked with lemborexant or its metabolite (M4, M9, or M10) at 0.5 to 5 µmol/L. Lemborexant or metabolites were not markedly taken by the cells expressing OATP1B1 or OATP1B3, and the extent of uptake by these cells was similar to that for control cells. These findings suggest that lemborexant, M4, M9, and M10 are not substrates for OATP1B1 or OATP1B3 (CTD 5.3.2.3.4, Study KAC37-03-[redacted]0827).

Sf9 cells expressing bile salt export pump (BSEP), CHO cells expressing OATP1B3, OCT1, OCT2, or OAT1, MDCKII cells expressing MATE1 or MATE2-K, and HEK293 cells expressing OAT3 or OATP1B1 were spiked with lemborexant or its metabolite (M4, M9, or M10) at 0.05 to 40 µmol/L. Lemborexant, M4, M9, and M10 did not affect the transport of OAT1. Lemborexant inhibited the transport of BSEP (IC_{50}, 15.8 µmol/L), MATE1 (IC_{50}, 13.2 µmol/L), MATE2-K (IC_{50}, 12.8 µmol/L), OATP1B1 (IC_{50}, 11.1µmol/L), OATP1B3 (IC_{50}, 14.5 µmol/L), OAT3 (IC_{50}, 32.2 µmol/L), OCT1 (IC_{50}, 7.4 µmol/L), and OCT2 (IC_{50},15.8 µmol/L). M4, M9, and M10 also inhibited the transport of these drug transporters, but the extent of inhibition of the metabolites was weaker than that of lemborexant, except for the inhibition of OCT2 by M9 (CTD 5.3.2.3.3, Study KAC36-02-[redacted]0827).

6.2.2 Studies in healthy adults

Non-Japanese healthy adults (64 subjects in the pharmacokinetic analysis) received a single oral dose of lemborexant 1, 2.5, 5, 10, 25, 50, or 100 mg. The pharmacokinetic parameters of unchanged lemborexant in plasma are shown in Table 21 (CTD 5.3.3.1.1, Study E2006-A001-001 [reference data]).

Table 21. Pharmacokinetic parameters of unchanged lemborexant in plasma after a single oral dose of lemborexant in non-Japanese healthy adults

Dose (mg)	Number of subjects evaluated	C_{max} (ng/mL)	t_{max} (h)[a)]	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng ·h/mL)
1	6	5.29 ± 1.25	1.00 [1.00, 1.08]	23.6 ± 21.6	19.8 ± 4.01[b)]
2.5	6	15.9 ± 5.73	1.01 [1.00, 3.00]	31.8 ± 12.7	79.7 ± 42.0[c)]
5	6	22.7 ± 4.39	1.55 [0.92, 3.00]	33.4 ± 6.02	149 ± 34.3[b)]
10	6	36.0 ± 18.7	1.00 [0.57, 2.00]	56.8 ± 12.8	311 ± 90.1
25	6	108 ± 22.0	2.01 [1.00, 3.00]	64.9 ± 6.72	1,540 ± 518
50	6	168 ± 48.7	2.53 [1.00, 3.08]	52.1 ± 14.0	2,150 ± 834
100	6	264 ± 128	3.00 [3.00, 5.00]	61.0 ± 9.08	4,740 ± 1,420
200	6	431 ± 51.1	3.00 [1.00, 9.00]	60.8 ± 17.9	10,500 ± 3,690

Mean ± standard deviation
a) Median [range]; b) 5 subjects; c) 4 subjects

Japanese and non-Japanese healthy adults (32 subjects in the pharmacokinetic analysis) received multiple oral doses of lemborexant 2.5, 10, or 25 mg once daily for 14 days. The pharmacokinetic parameters of unchanged lemborexant and M10 in plasma are shown in Table 22 (CTD 5.3.3.1.3, Study E2006-A001-003).

Table 22. Pharmacokinetic parameters of unchanged lemborexant and M10 in plasma after multiple doses of lemborexant in Japanese and non-Japanese healthy adults

Dose (mg)		Time point	Number of subjects evaluated	Unchanged lemborexant				M10			
				C_{max} (ng/mL)	t_{max} (h)[a]	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)[a]	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
2.5	Japanese	Day 1	6	10.0 ± 1.36	1.54 [1.00, 4.00]	—	54.8 ± 13.1	1.25 ± 0.490	9.00 [2.00, 12.00]	—	21.8 ± 7.99
		Day 14	6	13.2 ± 3.40	1.25 [0.50, 2.00]	50.6 ± 11.4	95.6 ± 21.4	3.12 ± 0.535	3.00 [2.00, 5.00]	46.4 ± 13.2	60.5 ± 9.70
10	Japanese	Day 1	6	46.5 ± 25.8	1.00 [0.50, 6.00]	—	231 ± 40.2	6.26 ± 1.15	3.50 [2.00, 12.00]	—	107 ± 21.6
		Day 14	6	70.2 ± 30.2	1.50 [0.50, 2.00]	47.4 ± 13.9	459 ± 110	14.5 ± 3.66	3.50 [2.00, 12.00]	40.3 ± 19.0	285 ± 75.4
10	Non-Japanese	Day 1	6	47.3 ± 28.1	1.04 [1.00, 3.00]	—	208 ± 83.4	6.45 ± 0.480	4.50 [2.00, 10.00]	—	113 ± 19.3
		Day 14	6	59.4 ± 26.1	1.25 [1.00, 3.00]	43.8 ± 11.0	431 ± 226	13.3 ± 4.31	3.00 [2.00, 12.00]	38.1 ± 12.9	259 ± 110
25	Japanese	Day 1	6	148 ± 56.5	2.50 [1.00, 4.00]	—	750 ± 154	14.0 ± 5.11	11.00 [4.00, 12.00]	—	247 ± 81.8
		Day 14	6	213 ± 66.3	1.00 [1.00, 1.50]	47.1 ± 9.17	1560 ± 559	43.0 ± 15.9	11.00 [1.50, 12.00]	45.2 ± 16.5	881 ± 334

Mean ± standard deviation
a) Median [range]

Non-Japanese healthy adults (8 subjects in the pharmacokinetic analysis) received a single oral dose of ^{14}C-labeled lemborexant 10 mg. By 480 hours post-dose, 29.1% and 57.4% of the total dose of the administered radioactivity was recovered in the urine and feces, respectively, and mainly M12 and M18 (glucuronide of M3) were found in urine and feces. Meanwhile, unchanged lemborexant was not detected in urine, and 13% of the total dose of the administered radioactivity was recovered in feces as unchanged lemborexant (CTD 5.3.3.1.4, Study E2006-A001-007; and CTD 5.3.2.2.11, Study AE-7433-G [reference data]).

6.2.3 Intrinsic ethnic factors

6.2.3.1 Effects of age (CTD 5.3.3.1.2, Study E2006-A001-002 [reference data])

Non-Japanese healthy adults and elderly subjects (11 subjects in the pharmacokinetic analysis) received multiple oral doses of lemborexant 25 mg/day once daily for 14 days. The pharmacokinetic parameters of unchanged lemborexant in plasma are shown in Table 23. The ratio of geometric means (%) [90% CI] of C_{max} and $AUC_{0\text{-}\infty}$ in elderly subjects to that in healthy adults on Day 14 was 118 [77.0, 179] and 112 [76.2, 164], respectively, showing that the C_{max} and $AUC_{0\text{-}24h}$ in the elderly subjects on Day 14 increased by approximately 20% and 10%, respectively, as compared with healthy adults.

Table 23. Pharmacokinetic parameters of unchanged lemborexant in plasma after multiple doses of lemborexant in non-Japanese healthy adults and elderly subjects

	Time point	Number of subjects evaluated	C_{max} (ng/mL)	t_{max} (h)[a]	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
Healthy adults	Day 1	6	92.0 ± 24.0	1.50 [1.00, 5.00]	—	549 ± 104
	Day 14	6	107 ± 38.9	3.00 [1.50, 5.00]	50.6 ± 10.7	1,100 ± 387
Elderly	Day 1	5	79.4 ± 43.1	3.00 [2.00, 5.00]	—	596 ± 347
	Day 14	5	128 ± 47.0	2.00 [1.50, 4.00]	61.8 ± 16.5	1,210 ± 335

Mean ± standard deviation
a) Median [range]

6.2.3.2 Effects of hepatic function (CTD 5.3.3.3.2, Study E2006-A001-104 [reference data])

Non-Japanese subjects with normal hepatic function and subjects with hepatic impairment (8 with normal hepatic function, 8 with a Child-Pugh classification A [mild], and 8 with a Child-Pugh classification B [moderate] in the pharmacokinetic analysis) received a single oral dose of lemborexant 10 mg. The pharmacokinetic parameters of unchanged lemborexant and M10 in plasma are shown in Table 24. The ratio of geometric means (%) [90% CI] of C_{max} and $AUC_{0-\infty}$ of in subjects with hepatic impairment to that in subjects with normal hepatic function was 158 [118, 211] and 125 [88.0, 178], respectively, for subjects with mild hepatic impairment and 122 [91.5, 163] and 154 [106, 222], respectively, for subjects with moderate hepatic impairment. The fraction of unbound lemborexant was 0.0636 in subjects with mild hepatic impairment and 0.0654 in subjects with moderate hepatic impairment, which was comparable to that in subjects with normal hepatic function (0.0603).

Table 24. Pharmacokinetic parameters of unchanged lemborexant and M10 in plasma after a single oral dose of lemborexant in subjects with normal hepatic function and subjects with hepatic impairment

	Number of subjects evaluated	Unchanged lemborexant				M10			
		C_{max} (ng/mL)	t_{max} (h)[a]	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)[a]	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)
Subjects with normal hepatic function[b]	8	41.6 ± 14.1	1.25 [0.50, 4.00]	69.0 ± 16.6	472 ± 124	3.90 ± 1.25	4.00 [4.00, 24.00]	64.3 ± 21.7	342 ± 126
Subjects with mild hepatic impairment	8	65.9 ± 20.0	1.00 [0.50, 1.50]	78.7 ± 27.0[c]	635 ± 366[c]	3.76 ± 1.26	4.00 [2.00, 24.00]	66.6 ± 20.6[d]	314 ± 89.7[d]
Subjects with moderate hepatic impairment	8	51.7 ± 19.9	1.00 [0.50, 3.00]	108 ± 28.3[d]	729 ± 243[d]	3.03 ± 1.26	3.00 [1.00, 4.00]	91.2 ± 21.1[e]	336 ± 56.8[e]

Mean ± standard deviation
a) Median [range]; b) Healthy adults with matching age, sex, and body mass index (BMI) to subjects with hepatic impairment; c) 7 subjects; d) 6 subjects; e) 5 subjects

6.2.3.3 Effects of renal function (CTD 5.3.3.3.3, Study E2006-A001-105 [reference data])

Non-Japanese subjects with normal renal function (8 subjects in the pharmacokinetic analysis) and subjects with severe renal impairment (an estimated glomerular filtration rate [eGFR] of 15 to 29 mL/minute/1.73 m^2, 8 subjects in the pharmacokinetic analysis) received a single oral dose of lemborexant 10 mg. The pharmacokinetic parameters of unchanged lemborexant and M10 in plasma are shown in Table 25. The ratio of geometric means (%) [90% CI] of C_{max} and $AUC_{0-\infty}$ of unchanged lemborexant in subjects with severe renal impairment to that in subjects with normal renal function was 105 [77.4, 142] and 150 [113, 199], respectively. The fraction of unbound lemborexant in subjects with severe renal impairment was 0.0671, which was comparable to that in subjects with normal renal function (0.0715).

Table 25. Pharmacokinetic parameters of unchanged lemborexant and M10 in plasma after a single oral dose of lemborexant in subjects with normal renal function and subjects with severe renal impairment

	Number of subjects evaluated	Unchanged lemborexant				M10			
		C_{max} (ng/mL)	t_{max} (h)[a]	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)[a]	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)
Subjects with normal renal function[b]	8	48.3 ± 13.6	1.00 [1.00, 1.50]	70.0 ± 17.6[c]	475 ± 171[c]	4.21 ± 2.10	3.00 [2.00, 4.00]	64.0 ± 19.1[d]	275 ± 87.3[d]
Subjects with severe renal impairment	8	52.3 ± 19.9	1.00 [0.50, 3.00]	74.8 ± 17.6[c]	683 ± 140[c]	3.07 ± 1.51	5.00 [3.00, 72.17]	64.7 ± 19.5[e]	362 ± 69.7[e]

Mean ± standard deviation
a) Median [range]; b) Healthy adults with matching age, race, sex, and BMI to subjects with renal impairment; c) 7 subjects; d) 5 subjects; e) 6 subjects

6.2.4 Drug interaction

Results of study on the drug interaction between lemborexant and itraconazole, rifampin, ethynyl estradiol, norethindrone, famotidine, fluconazole, ethanol, midazolam, or bupropion are shown in Tables 26 and Table 27.

Table 27

Table 26. Effects of concomitant drugs on pharmacokinetics of lemborexant

Lemborexant	Concomitant drugs	Measured compound in plasma	Number of subjects evaluated	Ratio of geometric means [a] [90% CI]		CTD
				C_{max}	$AUC_{0-\infty}$	
10 mg Single dose	Itraconazole (200 mg, once daily)	Unchanged compound	14	1.36 [1.18, 1.57]	3.70 [3.18, 4.31] [b]	Reference data CTD 5.3.3.4.1: Study E2006-A001-004
10 mg Single dose	Rifampin (600 mg, once daily)	Unchanged compound	15	0.085 [0.067, 0.107]	0.034 [0.026, 0.045] [c]	Reference data CTD 5.3.3.4.1: Study E2006-A001-004
10 mg Once daily	Ethynyl estradiol (30 µg, single dose) Norethindrone (1.5 mg, single dose)	Unchanged compound	20	0.94 [0.84, 1.05]	0.97 [0.94, 1.00] [d]	Reference data CTD 5.3.3.4.4: Study E2006-A001-012
10 mg Single dose	Famotidine (40 mg, single dose)	Unchanged compound	16	0.73 [0.64, 0.84]	1.00 [0.92, 1.09]	Reference data CTD 5.3.3.4.4: Study E2006-A001-012
10 mg Single dose	Fluconazole (200 mg, once daily)	Unchanged compound	14	1.62 [1.34, 1.97]	4.17 [3.83, 4.55] [e]	Reference data CTD 5.3.3.4.4: Study E2006-A001-012
10 mg Single dose	Ethanol (150 mL, single dose)	Unchanged compound	18	1.35 [1.14, 1.60]	1.70 [1.54, 1.89] [f]	Reference data CTD 5.3.3.4.3: Study E2006-A001-009

a) Coadministration/monotherapy; b) 11 subjects; c) 9 subjects; d) AUC_{0-24h}. e) 12 subjects; f) AUC_{0-72h}

Table 27. Effects of lemborexant on pharmacokinetics of concomitant drugs

Lemborexant	Concomitant drugs	Measured compound in plasma	Number of subjects evaluated	Ratio of geometric means [a] [90% CI]		CTD
				C_{max}	$AUC_{0-\infty}$	
10 mg Once daily	Midazolam (2 mg, single dose)	Midazolam	27	1.13 [1.03, 1.24]	1.13 [1.02, 1.25]	Reference data CTD 5.3.3.4.1: Study E2006-A001-004
10 mg Once daily	Bupropion (75 mg, single dose)	S-bupropion	27	0.50 [0.45, 0.55]	0.55 [0.50, 0.59] [b]	Reference data CTD 5.3.3.4.1: Study E2006-A001-004
10 mg Once daily	Bupropion (75 mg, single dose)	Bupropion [S,S]-hydroxylated form	27	0.83 [0.76, 0.91]	0.76 [0.66, 0.86] [c]	Reference data CTD 5.3.3.4.1: Study E2006-A001-004
10 mg Once daily	Ethynyl estradiol (30 µg, single dose)	Ethynyl estradiol	20	1.01 [0.89, 1.14]	1.13 [0.97, 1.31] [c]	Reference data CTD 5.3.3.4.4: Study E2006-A001-012
10 mg Once daily	Norethindrone (1.5 mg, single dose)	Norethindrone	20	1.03 [0.88, 1.20]	0.96 [0.87, 1.06] [d]	Reference data CTD 5.3.3.4.4: Study E2006-A001-012

a) Combination/ lemborexant alone; b) 25 subjects; c) AUC_t; d) 19 subjects

6.2.5 Pharmacodynamics

6.2.5.1 Drug abuse liability study (CTD 5.3.4.1.2, Study E2006-A001-103 [reference data])

Non-Japanese healthy adults with a history of drug abuse[16] (32 patients who completed the treatment period in the pharmacodynamic analysis set of 39 subjects) received a single oral dose of placebo, lemborexant 10, 20, or 30 mg, zolpidem 30 mg, or suvorexant 40 mg. The abuse potential was investigated in a randomized, double-blind, 6-period cross-over study. Based on the visual analog scale (VAS) score of drug liking,[17] the E_{max}[18] (mean ± standard error) of placebo, lemborexant 10, 20, and 30 mg, zolpidem 30 mg, and suvorexant 40 mg was 57.8 ± 2.87, 78.4 ± 3.27, 80.5 ± 3.13, 83.6 ± 3.02, 78.3 ± 2.83, and 76.1 ± 3.15 mm, respectively.

16) Subjects who have used drugs for a recreational but not for therapeutic purpose ≥5 times in the past and on ≥1 occasion within 12 weeks before the screening.
17) 0 mm, least liking; 100, most liking; 50, intermediate liking (neither the most nor least liking)
18) The maximum score recorded during a period from 0.5 to 24 hours post-dose

The E_{max} of the lemborexant doses, zolpidem, and suvorexant significantly increased as compared with placebo, and lemborexant was demonstrated to have liability comparable to zolpidem and suvorexant.

6.2.5.2 Driving performance study (CTD 5.3.4.1.3, Study E2006-E044-106)

Healthy adults and elderly subjects (48 subjects in the pharmacodynamic analysis)[19] received multiple oral doses of placebo or lemborexant 2.5, 5, or 10 mg at bedtime for 8 days and zopiclone 7.5 mg at bedtime on Days 1 and 8 of each period, and underwent a driving test on Days 2 and 9 of each period. The effects on driving ability were investigated in a randomized, double-blind, 4-period cross-over study. The standard deviations of lateral position (SDLP)[20] after the administration of lemborexant 2.5, 5, and 10 mg and zopiclone are shown in Table 28. The percentage of subjects with a difference in SDLP from that for placebo (the SDLP for an active drug − that for placebo) of >2.4 cm and that of <−2.4 cm was compared. In the period of zopiclone treatment, the percentage of subjects with a difference of >2.4 cm was significantly higher than the percentage of <−2.4 cm on both Days 2 and 9, showing a significant difference in the tendency toward deterioration or improvement in driving performance (p <0.0001, McNemar test). During the lemborexant treatment, however, no significant difference was observed between the tendency toward deterioration and that toward improvement in terms of driving performance on both Days 2 and 9 (p >0.07, McNemar test).

Table 28. SDLP in the driving performance study (Study E2006-E044-106)

	Placebo	Zopiclone 7.5 mg/day	Lemborexant 2.5 mg/day	Lemborexant 5 mg/day	Lemborexant 10 mg/day
Number of subjects evaluated	48	48	32	32	32
Day 2					
Least-squares mean ± standard error	17.835 ± 0.4566	19.876 ± 0.4566	17.851 ± 0.5826	18.062 ± 0.5826	18.567 ± 0.5826
Difference from placebo [95% CI]	—	2.041 [0.767, 3.316]	0.016 [−1.444, 1.477]	0.227 [−1.234, 1.688]	0.732 [−0.729, 2.193]
Comparison with placebo (p value)	—	0.019	0.9824	0.7594	0.3240
Day 9					
Least-squares mean ± standard error	17.818 ± 0.4437	19.701 ± 0.4437	18.299 ± 0.5674	18.181 ± 0.5674	18.559 ± 0.5674
Difference from placebo [95% CI]	—	1.883 [0.644, 3.121]	0.480 [−0.941, 1.902]	0.362 [−1.059, 1.784]	0.741 [−0.681, 2.163]
Comparison with placebo (p value)	—	0.0031	0.5056	0.6155	0.3051

Based on a mixed-effect model with age group, treatment sequence, treatment period, time point, and an interaction between the study drug and the treatment timing of the study drug as fixed effects.

6.2.5.3 Drug-alcohol interaction study (CTD5.3.3.4.3, Study E2006-A001-009)

Non-Japanese healthy adults (18 subjects receiving the study drug in all treatment periods in the pharmacodynamic analysis set of 32 subjects) received a single oral dose of placebo, lemborexant 10 mg, alcohol (0.7 g/kg for men and 0.6 g/kg for women), or lemborexant 10 mg plus alcohol (0.7 g/kg for men and 0.6 g/kg for women). The effects of lemborexant plus alcohol on cognitive performance and postural stability were investigated in a randomized, double-blind, 4-period cross-over study. The difference in the change from baseline between lemborexant alone and lemborexant plus alcohol (a value after the administration of lemborexant plus alcohol − a value after the administration of lemborexant alone), in the least-squares means [95% CI] of body sway at 2 hours post-dose[21] was 36.2 [17.6, 54.7], indicating that body

19) The study was conducted in 48 subjects consisting of a Japanese healthy adult, 23 non-Japanese healthy adults, and 24 elderly subjects.

20) The standard deviation of the distance from the lateral line to the car body when the car is driven along the lateral line at a speed of 95 km/h. Based on the impaired driving ability observed at a blood alcohol concentration of 0.5 mg/mL, a difference of mean SDLP from that of placebo of ≥2.4 cm was regarded as a clinically significant deviation (*Int J Gen Med*. 2011;4:359-71).

21) Indicates the ratio of body sway relative to postural stability measured by the Cognitive Drug Research assessment system. Higher values indicate greater body sway (more unstable posture).

sway increased when lemborexant was administered with alcohol. The difference in least-squares means [95% CI] of changes from baseline in the Power of Attention[22] at 0.5 and 6 hours post-dose was 239.2 [23.3, 455.2] and 234.7 [25.8, 443.6] milliseconds, respectively, indicating that the power of attention decreased when lemborexant was administered with alcohol.

6.2.6 PPK analysis (CTD 5.3.3.5.5, CPMS-E2006-004R analysis [reference data])

A population pharmacokinetic (PPK) analysis was performed based on data on plasma concentrations of unchanged lemborexant from 9 phase I studies,[23] a phase II study (CTD 5.3.4.2.2, Study E2006-G000-201), and 2 phase III studies (CTD 5.3.5.1.1, Study E2006-G000-303; and CTD 5.3.5.1.3, Study E2006-G000-304) (12,230 points in 1,892 subjects). The pharmacokinetics of lemborexant was described with a three-compartment model showing the first- and zero-order rate absorption and the first-order elimination from the central compartment. Covariate exploration identified the following statistically significant covariates: drug formulation and treatment duration for the zero-order absorption time; drug formulation and meals for the first-order absorption rate constant; age group, body mass index (BMI), and alkaline phosphatase (ALP) for apparent total clearance; and meals for relevant bioavailability.

6.2.7 Concentration-response analysis for QT/QTc interval (CTD 5.3.3.5.1, tqt-002-003 analysis [reference data])

A concentration-response analysis was performed based on data from 2 phase I studies in Caucasian or Japanese healthy adults (CTD 5.3.3.1.2, Study E2006-A001-002; and CTD 5.3.3.1.3, Study E2006-A001-003). Placebo or lemborexant 2.5, 5, 10, 25, 50, or 75 mg, and placebo or lemborexant 2.5, 10, or 25 mg was administered in Studies E2006-A001-002 and E2006-A001-003, respectively, without a positive control.[24] The similar study design was adopted in Studies E2006-A001-002 and E2006-A001-003, and in these studies, electrocardiography was used for measurements. Data from Studies E2006-A001-002 and E2006-A001-003 were combined and used for the analysis. QT intervals corrected for heart rate of individual subjects (QTcI) were used, and a relationship was investigated between plasma lemborexant concentration and the value obtained by the subtraction of baseline QTcI from QTcI at each point in individual subjects (ΔQTcI). The ΔQTcI was described with a linear mixed-effect model with intercepts including a random effect and categorized factors for plasma drug concentrations, treatment (1 for active drugs and 0 for placebo), and time as fixed effects. The validity of the model was confirmed through the confirmation of the assumption of the model, confirmation of the presence or absence of hysteresis, and the Goodness of Fit Plots. The analysis using the model demonstrated that the difference in placebo-corrected change-from-baseline QTcI (ΔΔQTcI)

22) A composite score of response time (speed) in 3 tests for attention (Simple Reaction Time, Choice Reaction Time, Digit Vigilance) in the Performance assessment battery consisting of 9 tests. Higher values indicate greater decrease in attention response (attention concentration and information processing).

23) CTD 5.3.3.1.1, Study E2006-A001-001 [reference data]; CTD 5.3.3.1.2, Study E2006-A001-002 [reference data]; CTD 5.3.3.1.3, Study E2006-A001-003; CTD 5.3.3.4.1, Studies E2006-A001-004 and E2006-A001-005[reference data]; CTD 5.3.3.4.2, Study E2006-A001-008 [reference data]; CTD 5.3.4.1.3, Study E2006-E044-106 [reference data]; CTD 5.3.4.2.1, Study E2006-A001-107 [reference data]; CTD 5.3.4.1.1, Study E2006-A001-108 [reference data]

24) The geometric mean of C_{max} after the administration of lemborexant 75 mg, the highest dose in this analysis, was 401 ng/mL, which was 6.5 times the C_{max} after the administration of lemborexant at the maximum clinically recommended dose of 10 mg (61.6 ng/mL) and approximately 4.5 times the maximum C_{max} in the special populations and drug interaction (88.3 ng/mL).

after the administration of lemborexant at the highest dose of 75 mg was 1.14 milliseconds (90% CI, −3.49, 5.78), and the upper limit of the 90% CI for ΔΔQTcI was <10 milliseconds.

6.R Outline of the review conducted by PMDA

6.R.1 Comparison of pharmacokinetics between Japanese and non-Japanese subjects

PMDA asked the applicant to explain the pharmacokinetics in Japanese and non-Japanese subjects.

The applicant's explanation:

- The pharmacokinetic parameters of multiple oral doses of lemborexant 10 mg in the foreign phase I study in Japanese and non-Japanese healthy adults (CTD 5.3.3.1.3, Study E2006-A001-003) are shown in Table 22. The ratio of geometric means [90% CI] of C_{max} and $AUC_{0\text{-}24h}$ in Japanese and non-Japanese subjects (Japanese/non-Japanese) was 97% [55%, 172%] and 118% [85%, 162%] on Day 1 and 118% [73%, 191%] and 116% [75%, 179%] on Day 14, respectively. Furthermore, the distribution of individual C_{max} and $AUC_{0\text{-}24h}$ was found to overlap between Japanese and non-Japanese subjects. The above findings from the foreign phase I studies demonstrated no marked differences in pharmacokinetics between Japanese and non-Japanese subjects.
- In the PPK analysis using data on plasma concentrations of unchanged lemborexant in Japanese and non-Japanese subjects, race was a candidate covariate. However, race was not selected as a significant covariate as a result of exploration [see Section 6.2.6].
- Based on the above findings from the foreign phase I studies and the PPK analysis, the pharmacokinetics of lemborexant was not considered to differ markedly between Japanese and non-Japanese subpopulations.

In light of the findings that no marked differences in C_{max} or $AUC_{0\text{-}24h}$ were observed between Japanese and non-Japanese subjects in the foreign phase I studies, PMDA accepted the applicant's explanation that no significant differences in pharmacokinetics exist between Japanese and non-Japanese subpopulations.

6.R.2 Food effects

In the food effect study (CTD 5.3.3.4.2, Study E2006-A001-008 [reference data]), the C_{max} of lemborexant decreased by approximately 23% following a post-prandial dose as compared to that under fasting conditions [see Section 6.1.1]. Given the findings, PMDA asked the applicant to explain the appropriateness of the cautionary advice given on food effects.

The applicant's explanation:

- In the food effect study (Study E2006-A001-008), no deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred in patients treated under fasting conditions, and the severity of all reported adverse events was mild. No marked abnormal laboratory data were observed, or no clinically significant findings were observed in vital signs or electrocardiographic data. Meanwhile, the C_{max} of lemborexant after postprandial dosing decreased by approximately 23% as compared to that under fasting conditions, and the t_{max} was delayed from 1 to 3 hours. These findings suggest that the effect of

lemborexant may be delayed and weakened in the immediate post-prandial dose as compared to the dose given under fasting conditions.

- In the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303) and the foreign phase III study (CTD 5.3.5.1.3, Study E2006-G000-304), it was specified that no meals were allowed within 3 hours before the administration of the study drug.
- The package inserts of drugs for the treatment of insomnia that are known to be affected by food intake (eszopiclone, ramelteon, and suvorexant) give cautions in the "Precautions for Dosage and Administration" section that the drugs should not be taken with or immediately after a meal.
- Accordingly, the package insert of lemborexant should caution not to take the drug with or immediately after a meal in the "Precautions for Dosage and Administration" section.

PMDA accepted the applicant's explanation described above.

6.R.3 Coadministration of lemborexant and CYP3A inhibitors

The applicant's explanation about the coadministration of lemborexant with CYP3A inhibitors:

- Lemborexant was administered concomitantly with a moderate CYP3A inhibitor (fluconazole) or a potent CYP3A inhibitor (itraconazole) (CTD 5.3.3.4.4, Study E2006-A001-012 [reference data]; and CTD 5.3.3.4.1, Study E2006-A001-004 [reference data]). The ratio of geometric means of C_{max} and $AUC_{0-\infty}$ [90% CI] of unchanged lemborexant after the administration of lemborexant alone to those after the coadministration of lemborexant with the inhibitors (coadministration/monotherapy) was 1.62 [1.34, 1.97] and 4.17 [3.83, 4.55] for the moderate CYP3A inhibitor and 1.36 [1.18, 1.57] and 3.70 [3.18, 4.30] for the potent CYP3A inhibitor, respectively, and the AUC and C_{max} of unchanged lemborexant increased by 4 times and 36% to 60%, respectively.
- To investigate the dose of lemborexant in combination with CYP3A inhibitors, the C_{max} and $AUC_{(0-inf)}$ of unchanged lemborexant after coadministration of lemborexant 2.5 mg with CYP3A inhibitors were estimated based on the proportional relationship between the exposure and the dose. The results are shown in Table 29. After the coadministration of lemborexant 2.5 mg with the moderate or potent CYP3A inhibitor, the estimated $AUC_{(0-inf)}$ of unchanged lemborexant was comparable to the measured $AUC_{(0-inf)}$ after the administration of lemborexant 10 mg alone, and the estimated C_{max} of unchanged lemborexant was comparable to the measured C_{max} after the administration of lemborexant 5 mg alone. Therefore, it was estimated that the safety profiles of lemborexant 2.5 mg coadministered with the moderate or potent CYP3A inhibitor are similar to those of lemborexant 10 mg.
- Based on the above, the recommended dose of lemborexant in combination with a moderate or potent CYP3A inhibitor was determined to be 2.5 mg.

Table 29. Estimated C_{max} and $AUC_{0\text{-}inf}$ of unchanged lemborexant after the coadministration of lemborexant 2.5 mg with CYP3A inhibitors and measured values after the administration of lemborexant 5 and 10 mg alone

	Measured value Lemborexant 5 mg alone		Measured value Lemborexant 10 mg		Estimated value [90% CI] Lemborexant 2.5 mg + CYP3A inhibitor	
	C_{max}	$AUC_{0\text{-}inf}$	C_{max}	$AUC_{0\text{-}inf}$	C_{max}	$AUC_{0\text{-}inf}$
Lemborexant alone	22.3 (19.1) [a)]	146 (20.9) [a)]	54.3 (25.2) [b)]	433 (40.3) [b)]	—	—
Coadministration with fluconazole	—	—	88.3 (35.5) [c)]	1480 (29.5) [c)]	22.1 [18.1, 26.9]	370 [308, 445]
Coadministration with itraconazole	—	—	73.9 (18.0) [b)]	1580 (27.9) [b)]	18.9 [17.0, 21.1]	447 [374, 533]

Geometric mean (CV); a) Foreign Study E2006-A001-001; b) Foreign Study E2006-A001-004; c) Foreign Study E2006-A001-012

- A physiologically-based pharmacokinetic (PBPK) model was developed to evaluate the effects of weak CYP3A inhibitors on the pharmacokinetics of lemborexant.[25)] Simcyp version 17.1 was used to analyze the PBPK model. The estimation performance at the development of the model was confirmed with data from the phase I studies (CTD 5.3.3.1.1, Study E2006-A001-001 [reference data]; and CTD 5.3.3.1.2, Study E2006-A001-002 [reference data]), a drug interaction study (Study E2006-A001-004), and the food effect study (Study E2006-A001-008). The estimated and measured values of C_{max} of lemborexant are shown in Table 30.

Table 30. Estimated and measured C_{max} and $AUC_{0\text{-}t}$ of unchanged lemborexant after the administration of lemborexant

Dose	Measured value			Estimated value			Ratio (estimated value/measured value)	
	C_{max}	$AUC_{0\text{-}t}$	t_{max}	C_{max}	$AUC_{0\text{-}t}$	t_{max}	C_{max}	$AUC_{0\text{-}t}$
2.5 mg[a)]	14.9	74.4	1.01	6.79	66.4	1.06	0.46	0.89
10 mg[a)]	32.0	274	1.00	27.1	354	1.06	0.85	1.29
100 mg[a)]	242	4300	3.00	261	3270	1.08	1.08	0.76
10 mg[b)]	54.3	411	1.00	25.3	327	1.06	0.47	0.80
10 mg Day1[c)]	28.0	182	3.25	24.2	168	1.11	0.86	0.92
10 mg Day14[c)]	44.8	321	1.75	32.9	327	1.10	0.73	1.02
10 mg after a meal[d)]	44.1	460	3.00	15.1	327	3.25	0.34	0.71
10 mg under fasting conditions[d)]	57.1	389	1.00	25.5	331	1.08	0.45	0.85

C_{max} and $AUC_{0\text{-}t}$ are expressed as geometric means, and t_{max} is expressed as a median.
a) Foreign Study E2006-A001-001; b) Foreign Study E2006-A001-004; c) Foreign Study E2006-A001-002; d) Foreign Study E2006-A001-008

- The model was validated with the measured values obtained after the coadministration of lemborexant with a CYP3A inhibitor (itraconazole or fluconazole) or a CYP inducer (rifampicin). The estimated and measured C_{max} and $AUC_{0\text{-}t}$ of unchanged lemborexant after the administration of lemborexant 10 mg are shown in Table 31. The developed model was considered to be validated.

Table 31. Estimated and measured C_{max} and $AUC_{0\text{-}t}$ of unchanged lemborexant after the administration of lemborexant 10mg

	Ratio of AUC (coadministered/alone)		Ratio of C_{max} (coadministered/alone)	
	Measured	Estimated	Measured	Estimated
Itraconazole	3.58	3.11	1.36	1.39
Fluconazole	3.76	2.83	1.62	1.37
Rifampicin	0.033	0.19	0.085	0.38

- The effects of a weak CYP3A inhibitor (fluoxetine) was estimated by using the developed PBPK model, and the geometric mean of the ratio of $AUC_{0\text{-}t}$ and C_{max} after the administration of lemborexant alone

25) An advanced dissolution absorption and metabolism (ADAM) model was selected for the lemborexant absorption model, and a full PBPK model was selected for the lemborexant distribution model. The contribution rate of CYP3A4 to metabolism was specified to be 100% based on the results of a mass balance study (CTD 5.3.3.3.1.4, Study E2006-A001-007 [reference data]) and *in vitro* metabolism [see Section 6.2.1]. The CLint of CYP3A4 was estimated from the retrograde model, and renal clearance and clearance by metabolism by other than CYP3A4 were not specified. The default settings of Simcyp were used for the physiological parameters.

and those after the coadministration of lemborexant with the weak CYP3A inhibitor (fluoxetine) (coadministration/monotherapy) was 1.77 and 1.21, respectively.

- In the global study (Study 303) and the foreign study (Study 304), the exposure estimated from the population pharmacokinetic model in 15 subjects receiving lemborexant in combination with a weak CYP3A inhibitor tended to increase as compared with subjects receiving no other concomitant drugs including CYP3A inhibitors. The results were similar to those estimated with the PBPK model.
- Based on the above, lemborexant 5 mg is recommended for the coadministration with a weak CYP3A inhibitor.

PMDA's view on the concomitant use of lemborexant with a potent or moderate CYP3A inhibitor:

- The $AUC_{0-\infty}$ after coadministration of lemborexant with a potent or moderate CYP3A inhibitor increased to 4-fold $AUC_{0-\infty}$ of lemborexant alone. The applicant recommends that only 2.5 mg/day be used in combination with a potent or moderate CYP3A inhibitor, based on its exposure equivalent to that after the administration of lemborexant 10 mg/day. Meanwhile, the applicant proposed the usual dose of 5 mg/day and the maximum dose of 10 mg/day for lemborexant without combination with a CYP3A inhibitor. However, because of the possible increase in a risk of adverse drug reaction such as somnolence associated with dose increase beyond the usual dose, the applicant proposed that the patient's condition be carefully monitored during such dose increase and that the dose be reduced as the symptom subsides [see Section 7.R.6].
- However, the incidences of adverse events such as somnolence and sleep paralysis tended to be higher with lemborexant 10 mg/day than with lemborexant 5 mg/day, and the REM sleep latency shortened with lemborexant 10 mg/day [see Section 7.R.2.].
- Therefore, based on the fact that there is no lemborexant 1.25-mg tablet, to which exposure will be equivalent to that of lemborexant 5 mg/day, the concomitant use of lemborexant with a potent or moderate CYP3A inhibitor should be determined carefully from the safety viewpoint.
- As mentioned above, the concomitant use of lemborexant with a potent or moderate CYP3A inhibitor should be determined carefully. If such treatment is necessary, the dose of lemborexant should be 2.5 mg/day, to which exposure is assumed to be equivalent to that of 10 mg/day. In case of any safety issue, lemborexant should be discontinued.

PMDA's view on the concomitant use of lemborexant with a weak CYP3A inhibitor:

- The applicant recommends only lemborexant 5 mg to be used with a weak CYP3A inhibitor, based on the PBPK model, from which AUC_{0-t} was estimated to be 1.77 times higher after the administration of lemborexant with a weak CYP3A inhibitor (fluoxetine) than lemborexant alone.
- However, the inhibition potency of weak CYP3A inhibitors vary. In the foreign phase II studies where lemborexant was administered at doses up to 25 mg/day, although serious grand mal convulsion occurred in 1 subject receiving lemborexant 25 mg/day, there was no serious adverse event with lemborexant at ≤20 mg/day. In subjects receiving lemborexant ≤20 mg/day, somnolence occurred in a dose-dependent manner. The lemborexant dose may be reduced promptly when somnolence occurs.

- Accordingly, there are no particular problems with the usual dose of lemborexant 5 mg to be used in combination with a weak CYP3A inhibitor, and the dose can be increased to 10 mg if no safety problem, as with lemborexant monotherapy.

PMDA considers that the final conclusion on the appropriateness of the above should be drawn on the basis of comments from the Expert Discussion.

6.R.4 Treatment in patients with renal impairment

In a study investigating the effects of renal function (CTD 5.3.3.3.3, Study E2006-A001-105 [reference data]), non-Japanese subjects with normal renal function and subjects with severe renal impairment received a single oral dose of lemborexant 10 mg. Exposure ($AUC_{0-\infty}$) increased by 50% in subjects with severe renal impairment as compared with subjects with normal renal function. PMDA asked the applicant to explain the safety in patients with renal impairment.

The applicant's explanation:

- In Study E2006-A001-105, the ratio of geometric means (%) [90% CI] of $AUC_{0-\infty}$ of unchanged lemborexant in subjects with severe renal impairment to that in subjects with normal renal function was 150 [113, 199].
- In Study E2006-A001-105, the incidence of adverse events in subjects with normal renal function and subjects with severe renal impairment was 87.5% (7 of 8 subjects) and 62.5% (5 of 8 subjects), respectively, showing no substantial differences in the observed events (subjects with normal renal function, somnolence in 7 subjects; subjects with severe renal impairment, somnolence in 5 subjects and chills in 1 subject). All adverse events, except for moderate somnolence in a subject with normal renal function, were mild in severity. No deaths, serious adverse events, or adverse events leading to discontinuation of the study treatment were reported.
- In a global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303) and a foreign phase III study (CTD 5.3.5.1.3, Study E2006-G000-304), subjects with severe renal impairment were excluded. The occurrence of adverse events by with and without renal impairment in the combined data from these studies is shown in Table 32. The incidences of adverse events did not markedly differ between patients with and without renal impairment both in the lemborexant 5 mg and 10 mg groups.
- Based on the above, adjustment of lemborexant dose is unnecessary for patients with renal impairment.

Table 32. Occurrence of adverse events in patients with and without renal impairment (Combined data from Studies E2006-G000-303 and E2006-G000-304)

	Subjects with renal impairment [a]				Subjects without renal impairment			
	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER
Number of subjects evaluated	20	44	44	28	508	669	661	235
All adverse events	6 (30.0)	19 (43.2)	21 (47.7)	10 (35.7)	247 (48.6)	354 (52.9)	350 (53.0)	83 (35.3)
Main adverse events								
Somnolence	0	1 (2.3)	3 (6.8)	0	9 (1.8)	48 (7.2)	76 (11.5)	4 (1.7)
Headache	0	4 (9.1)	2 (4.5)	2 (7.1)	34 (6.7)	56 (8.4)	43 (6.5)	12 (5.1)
Upper respiratory tract infection	0	2 (4.5)	0	1 (3.6)	14 (2.8)	25 (3.7)	19 (2.9)	1 (0.4)
Influenza	0	1 (2.3)	1 (2.3)	0	17 (3.3)	21 (3.1)	25 (3.8)	1 (0.4)
Urinary tract infection	0	0	3 (6.8)	0	9 (1.8)	13 (1.9)	24 (3.6)	2 (0.9)
Arthralgia	0	2 (4.5)	1 (2.3)	0	9 (1.8)	19 (2.8)	10 (1.5)	1 (0.4)
Fatigue	0	0	0	1 (3.6)	1 (0.2)	16 (2.4)	18 (2.7)	3 (1.3)
Dizziness	1 (5.0)	0	0	0	9 (1.8)	17(2.5)	10 (1.5)	8 (3.4)
Fall	0	0	0	0	10 (2.0)	16 (2.4)	10 (1.5)	0
Nausea	0	0	0	0	5 (1.0)	15 (2.2)	11 (1.7)	5 (2.1)

Number of subjects with events (incidence [%])

a) Subjects with estimated glomerular filtration of <60 mL/minute/1.73 m^2 calculated based on the modification of diet in renal disease (MDRD) before the administration of the study drug

PMDA's view on treatment with lemborexant in patients with renal impairment:

- In Study E2006-A001-105, no substantial differences were seen in adverse events between subjects with normal renal function and subjects with severe renal impairment, and no deaths or serious adverse events occurred.
- Although patients with severe renal impairment were excluded from clinical studies, the data on the occurrence of adverse events in subjects with and without renal impairment (combined data from Studies E2006-G000-303 and E2006-G000-304) showed no marked differences in the incidences of adverse events between patients with and without renal impairment in both lemborexant 5 mg and 10 mg groups.
- In the foreign phase II studies, in which lemborexant was administered at doses up to 25 mg/day, although a serious adverse event of grand mal convulsion occurred in 1 subject receiving lemborexant 25 mg/day, no serious adverse events were observed with lemborexant at doses up to 20 mg/day, and somnolence was a dose-dependent adverse event occurred in subjects receiving lemborexant ≤20 mg/day. The lemborexant dose can be reduced promptly when somnolence occurs.
- In light of the above, although the exposure of subjects with severe renal impairment tended to increase approximately 1.5 times that of subjects with normal renal function, there is no major problem in the applicant's view that the usual dose of lemborexant be 5 mg for patients with renal impairment including those who are severely impaired, as with those who have normal renal function, and that the dose can be increased to 10 mg when there is no safety issue.

PMDA considers that the final conclusion on the appropriateness of the above should be drawn on the basis of comments from the Expert Discussion.

6.R.5 Treatment in patients with hepatic impairment

In the study evaluating the effects of hepatic function, non-Japanese subjects with normal hepatic function and subjects with hepatic impairment received a single oral dose of lemborexant 10 mg, and the exposure ($AUC_{0-\infty}$) increased by 25% in subjects with mild hepatic impairment and 54% in subjects with moderate hepatic

impairment as compared with subjects with normal hepatic function (CTD 5.3.3.3.2, Study E2006-A001-104 [reference data]). PMDA asked the applicant to explain the safety in patients with hepatic impairment.

The applicant's explanation:

- In Study E2006-A001-104, the ratio of geometric means (%) [90% CI] of $AUC_{0-\infty}$ of unchanged lemborexant in subjects with mild and moderate hepatic impairment to that in subjects with normal hepatic function was 125 [88.0, 178] and 154 [106, 222], respectively.
- In Study E2006-A001-104, the incidence of adverse events was 87.5% (7 of 8 subjects) in subjects with normal hepatic function, 87.5% (7 of 8 subjects) in subjects with mild hepatic impairment, and 75.0% (6 of 8 subjects) in subjects with moderate hepatic impairment, and there were no marked differences in the adverse events observed (subjects with normal hepatic function, somnolence in 7; subjects with mild hepatic impairment, somnolence in 7; subjects with moderate hepatic impairment, somnolence in 5, dry mouth, chills, and headache in 1 each). These adverse events were all mild in severity. No deaths, serious adverse events, or adverse events leading to discontinuation of the study treatment were reported.
- Patients with severe hepatic impairment were excluded from the clinical studies. The occurrence of adverse events in patients with and without hepatic impairment (combined data from Studies E2006-G000-303 and E2006-G000-304) is shown in Table 33. In the lemborexant 5 mg group, the incidence of adverse events was higher in subjects with hepatic impairment than in subjects without hepatic impairment. However, only 9 subjects with hepatic impairment were included in the lemborexant 5 mg group, and in the lemborexant 10 mg group, the incidences of adverse events did not markedly differ between subjects with and without hepatic impairment. These findings suggest no safety concerns in patients with hepatic impairment.
- Based on the above, no dose adjustment for lemborexant will be necessary for patients with mild or moderate hepatic impairment. The pharmacokinetics of lemborexant has not been investigated in patients with severe hepatic impairment. However, severe hepatic impairment may increase the plasma concentration of unchanged lemborexant and, in turn, increase the effects of lemborexant markedly. Therefore, lemborexant should be contraindicated in patients with severe hepatic impairment.

Table 33. Occurrence of adverse events in patients with and without hepatic impairment (Combined data from Studies E2006-G000-303 and E2006-G000-304)

	Subjects with hepatic impairment [a]				Subjects without hepatic impairment			
	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER
Number of subjects evaluated	12	9	16	5	516	704	689	258
All adverse events	7 (58.3)	7 (77.8)	10 (62.5)	3 (60.0)	246 (47.7)	366 (52.0)	361 (52.4)	90 (34.9)
Main adverse events								
Somnolence	1 (8.3)	1 (11.1)	2 (12.5)	0	8 (1.6)	48 (6.8)	77 (11.2)	4 (1.6)
Headache	2 (16.7)	0	1 (6.3)	1 (20.0)	32 (6.2)	60 (8.5)	44 (6.4)	13 (5.0)
Upper respiratory tract infection	0	0	1 (6.3)	0	14 (2.7)	27 (3.8)	18 (2.6)	2 (0.8)
Influenza	0	0	1 (6.3)	0	17 (3.3)	22 (3.1)	25 (3.6)	1 (0.4)
Urinary tract infection	0	0	2 (12.5)	0	9 (1.7)	13 (1.8)	25 (3.6)	2 (0.8)
Arthralgia	0	0	1 (6.3)	0	9 (1.7)	21 (3.0)	10 (1.5)	1 (0.4)
Fatigue	0	0	0	0	1 (0.2)	16 (2.3)	18 (2.6)	4 (1.6)
Dizziness	0	0	0	0	10 (1.9)	17 (2.4)	10 (1.5)	8 (3.1)
Fall	0	0	0	0	10 (1.9)	16 (2.3)	10 (1.5)	0
Nausea	0	0	0	0	5 (1.0)	15 (2.1)	11 (1.6)	5 (1.9)

Number of subjects with events (incidence [%])

a) Subjects with events as concurrent or historical conditions included in the following MedDRA (version 21.0) SMQ of Hepatic disorders: Liver related investigations, signs and symptoms (narrow, broad); Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow, broad); Cholestasis and jaundice of hepatic origin (narrow, broad); Hepatitis, non-infectious (narrow, broad); and Liver-related coagulation and bleeding disturbances (narrow)

PMDA's view:

- In light of the fact that lemborexant is metabolized mainly by CYPs, there is no particular objection to the applicant's decision to contraindicate lemborexant in patients with severe hepatic impairment.
- The ratio of geometric means (%) [90% CI] of $AUC_{0-\infty}$ of unchanged lemborexant in subjects with mild and moderate hepatic impairment to that in subjects with normal hepatic function was 125 [88.0, 178] and 154 [106, 222], respectively, showing the degree of increase in exposure differing by severity of hepatic impairment.
- In the foreign phase II studies, in which lemborexant was administered at doses up to 25 mg/day, serious grand mal convulsion occurred in 1 subject receiving lemborexant 25 mg/day, but no serious adverse events were observed with lemborexant at ≤20 mg/day. The observed dose-dependent adverse event in subjects receiving lemborexant ≤20 mg/day was somnolence, for which subsequent doses can be reduced promptly.
- Consequently, although the exposure of subjects with mild hepatic impairment tended to increase approximately 1.25 times that of subjects with normal hepatic function, there is no major problem with the applicant's proposal, i.e., no dose adjustment is required for patients with mild hepatic impairment and the usual dose is 5 mg, as with patients with normal hepatic function; and the dose can be increased to 10 mg when there is no safety issue.
- Patients with moderate hepatic impairment tend to have increased the exposure to unchanged lemborexant depending on the severity of hepatic impairment, and the degree of the increase in exposure in patients with severe hepatic impairment is unknown. The administration of lemborexant in combination with a potent or moderate CYP3A inhibitor increased the exposure 4 times [see Section 6.R.3]. Only a small number of patients with hepatic impairment were evaluated in the clinical studies. Give these, for patients with moderate hepatic impairment, 5 mg should be the maximum dose, unlike for those with normal hepatic function.

PMDA considers that the final conclusion on the appropriateness of the above should be drawn on the basis of comments from the Expert Discussion.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

Data from the clinical studies shown in Table 34 (a foreign phase I study, a foreign phase II study, a global phase III study, and a foreign phase III study) were submitted for the evaluation of the efficacy and safety. Data from the clinical studies conducted outside Japan were also submitted as reference data. Data from the main clinical studies are summarized below.

Table 34. Clinical studies for efficacy and safety

Region	Study CTD	Phase	Subjects	Number of subjects	Outline of dosing regimen	Main endpoints
Foreign	Study E2006-A001-003 5.3.3.1.3	I	Japanese healthy adults	24	Placebo or lemborexant 2.5, 10, or 25 mg was orally administered once daily before bedtime for 14 days.	Safety PK PD
			Caucasian healthy adults	8	Placebo or lemborexant 10 mg was orally administered once daily before bedtime for 14 days.	
	Study E2006-G000-201 5.3.4.2.2	II	Patients with insomnia	291 [a)]	Placebo, or lemborexant 1, 2.5, 5, 10, 15, or 25 mg was orally administered once daily for 15 days, [b)] and then, placebo was orally administered once daily for 2 days. [c)]	Efficacy Safety
Global	Study E2006-G000-303 5.3.5.1.1 5.3.5.1.2	III	Patients with insomnia	971 [a)]	Period 1: Placebo or lemborexant 5 or 10 mg was orally administered once daily for 6 months.	Efficacy Safety PK
					Period 2: Lemborexant 5 or 10 mg was orally administered once daily for 6 months.	
Foreign	Study E2006-G000-304 5.3.5.1.3	III	Patients with insomnia	1,006 [a)]	Placebo, lemborexant 5 or 10 mg, or zolpidem ER 6.25 mg was orally administered once daily for a month.	Efficacy Safety PK

a) Number of patients randomized; b) Double-blind phase; c) Single blind (subject-blinded)
PK, pharmacokinetics; PD, pharmacodynamics.

7.1 Phase I studies

7.1.1 Foreign phase I study (CTD 5.3.3.1.3, Study E2006-A001-003 [December 2013 to May 2014])

A randomized, double-blind, placebo-controlled study was conducted to evaluate the safety, pharmacokinetics, and pharmacodynamics of multiple doses of lemborexant in Japanese healthy adults (target sample size of 24 subjects; 8/dose group [2 in the placebo group and 6 in the lemborexant groups]) and Caucasian healthy adults (target sample size of 8 subjects [2 in the placebo group and 6 in the lemborexant group] [for pharmacokinetics, see Section 6.2.2].

Japanese subjects were treated with placebo or lemborexant 2.5, 10, or 25 mg, while Caucasian subjects received placebo or lemborexant 10 mg. The study drugs were orally administered once daily before bedtime[26)] for 14 days.

All 32 randomized subjects (24 Japanese subjects [6 in the placebo group, 6 in the lemborexant 2.5 mg/day group, 6 in the lemborexant 10 mg/day group, and 6 in the lemborexant 25 mg/day group] and 8 Caucasian subjects [2 in the placebo group and 6 in the lemborexant 10 mg/day group]) were included in the safety analysis set. No patients discontinued the treatment.

26) Within 30 minutes before the normal bedtime

In Japanese subjects, adverse events (including laboratory abnormalities) occurred in 33.3% (2 of 6) of subjects in the placebo group, 16.7% (1 of 6) of subjects in the lemborexant 2.5 mg/day group, 0% (0 of 6) of subjects in the lemborexant 10 mg/day group, and 33.3% (2 of 6) of subjects in the lemborexant 25 mg/day group. In Caucasian subjects, adverse events (including laboratory abnormalities) occurred in 50.0% (1 of 2) of subjects in the placebo group and 50.0% (3 of 6) of subjects in the lemborexant 10 mg/day group. No serious adverse events including death occurred.

A causal relationship between adverse events (including laboratory abnormalities) and the study drug was not ruled out in 33.3% (2 of 6) in the placebo group, 16.7% (1 of 6) in the lemborexant 2.5 mg/day group, 0% (0 of 6) in the lemborexant 10 mg/day group, and 33.3% (2 of 6) in the lemborexant 25 mg/day group of Japanese subjects, and 0% (0 of 2) in the placebo group and 50.0% (3 of 6) in the lemborexant 10 mg/day group of Caucasian subjects. The most common adverse events included somnolence in 5 subjects (1 Japanese in the placebo group, 1 Japanese in the lemborexant 2.5 mg/day group, no Japanese in the lemborexant 10 mg group, 2 Japanese in the lemborexant 25 mg group, no Caucasian in the placebo group, and 1 Caucasian in the lemborexant 10 mg group) and abnormal dreams in 3 subjects (no Japanese in the placebo group, no Japanese in the lemborexant 2.5 mg/day group, no Japanese in the lemborexant 10 mg group, 1 Japanese in the lemborexant 25 mg group, no Caucasian in the placebo group, and 2 Caucasian in the lemborexant 10 mg group).

No clinically significant changes were observed in vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) or electrocardiographic parameters.

7.2 Phase II studies

7.2.1 Foreign phase II study (CTD 5.3.4.2.2: Study E2006-G000-201 [November 2013 to April 2014])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of lemborexant in patients with insomnia[27)] (target sample size, up to 300[28)]).

Placebo or lemborexant 1, 2.5, 5, 10, 15, or 25 mg was orally administered once daily before bedtime[26)] for 15 days (the double-blind period). After that, placebo was orally administered once daily before bedtime for 2 days in a single-blind (subject-blinded) manner (the period for evaluation of rebound insomnia).

27) Patients aged ≥18 and ≤80 years who met all of the following criteria:
a) Patients meeting the following DSM-5 diagnostic criteria for insomnia disorder
・A complaint of dissatisfaction with sleep at night, associated with ≥1 symptoms of difficulty initiating sleep, difficulty maintaining sleep, or early-morning awakening.
・The sleep difficulty occurs ≥3 nights per week and persists for ≥3 months, causing functional impairment in daytime.
b) Patients meeting the following criteria for insomnia subjectively evaluated on the basis of the sleep diary completed on 7 consecutive mornings before PSG at screening and baseline.
・Having subjective sleep latency of ≥30 minutes ≥3 nights per week and having subjective wake after sleep onset of ≥60 minutes ≥3 nights per week.
c) Patients meeting the following criteria for insomnia objectively evaluated by PSG on 2 consecutive nights at screening and baseline.
・Having each sleep latency of ≥15 minutes with a mean of ≥30 minutes, each wake after sleep onset of ≥20 minutes with a mean of ≥30 minutes, and each sleep efficiency of ≤87.5% with a mean of ≤85%.

28) The study employed the Bayesian adaptive design. According to the response adaptive randomization method, the first 105 subjects were evenly assigned to each group, then the allocation rate was changed on the basis of interim analysis results. The first interim analysis was performed for the 105 subjects, and subsequent interim analyses were conducted every 2 weeks. Data were analyzed for the possibility of early termination for efficacy or futility, and subject enrollment was completed because of early termination for efficacy confirmed based on the results of the 5th interim analysis.

All 291 randomized subjects (56 in the placebo group, 32 in the lemborexant 1 mg/day group, 27 in the lemborexant 2.5 mg/day, 38 in the lemborexant 5 mg/day, 32 in the lemborexant 10 mg/day, 56 in the lemborexant 15 mg/day, and 50 in the lemborexant 25 mg/day) were included in the safety analysis set and the full analysis set (FAS) for the efficacy analysis. In the safety analysis set, the study drug was discontinued in 18 subjects (5, 2, 0, 2, 2, 2, and 5). The main reasons for discontinuation included subjects inconvenience in 4 subjects (2, 0, 0, 0, 0, 1, and 1) and lost to follow-up in 2 subjects (0, 1, 0, 0, 0, 0, and 1).

The changes from baseline in sleep efficiency [29)] and KSS scores [30)] objectively evaluated with polysomnography (PSG) at the start and after the end of the administration of the study drug are shown in Tables 35 and 36, respectively.

Table 35. Changes from baseline in sleep efficiency at the start and after the end of the administration of the study drug (FAS)

Group	Baseline [a)]	At the start of administration[b)]		After the end of administration[c)]	
	Observed value	Changes	Difference from the placebo[d)]	Changes	Difference from the placebo[d)]
Placebo	66.56 ± 9.245 (56)	12.61 ± 12.176 (56)		12.33 ± 10.526 (52)	
Lemborexant 1 mg/day	61.69 ± 12.302 (32)	21.11 ± 11.208 (32)	4.57 [1.19, 7.94]	17.46 ± 13.615 (31)	0.34 [−3.22, 3.90]
Lemborexant 2.5 mg/day	61.33 ± 14.707 (27)	21.28 ± 14.105 (27)	4.44 [0.86, 8.01]	20.73 ± 14.665 (27)	3.94 [0.22, 7.66]
Lemborexant 5 mg/day	63.09 ± 12.478 (38)	21.15 ± 13.196 (38)	5.74 [2.54, 8.93]	21.00 ± 15.433 (37)	5.76 [2.40, 9.12]
Lemborexant 10 mg/day	65.11 ± 11.748 (32)	21.88 ± 11.924 (32)	8.09 [4.73, 11.45]	21.72 ± 13.369 (31)	7.78 [4.24, 11.32]
Lemborexant 15 mg/day	65.12 ± 12.193 (56)	23.84 ± 12.216 (56)	10.06 [7.20, 12.93]	21.17 ± 12.922 (54)	7.89 [4.86, 10.92]
Lemborexant 25 mg/day	66.57 ± 10.941 (50)	22.74 ± 10.981 (50)	10.13 [7.18, 13.08]	21.42 ± 9.956 (46)	8.87 [5.72, 12.02]

Mean ± standard deviation. (Number of subjects evaluated)
a) Mean of measurements for 2 days in the period from 9 to 3 days before administration. b) Mean of measurements on Days 1 and 2 of administration. c) Mean of measurements on Days 14 and 15 of administration. d) Based on a model of analysis of covariance with changes between groups [95% CI] and group as factors and baseline value as a covariate.

29) Sleep efficiency (%) = (total sleep time (minutes) /total time in bed (minutes)) ×100
30) A self-assessment scale for sleepiness consisting of 9 points from 1 (“extremely alert”) to 9 (“extremely sleepy – fighting sleep”)

Table 36. Changes from baseline in KSS scores at the start and after the end of the administration of the study drug (pharmacodynamic analysis set[a])

Group	Baseline[b]	At the start of administration[c]		After the end of administration[d]	
	Observed value	Changes	Difference from the placebo[e]	Changes	Difference from the placebo[e]
Placebo	3.96 ± 2.009 (55)	−0.20 ± 1.271 (55)		−0.22 ± 1.433 (51)	
Lemborexant 1 mg/day	4.03 ± 1.823 (32)	−0.20 ± 0.966 (32)	0.02 [−0.49, 0.54]	0.27 ± 1.217 (31)	0.51 [−0.03, 1.06]
Lemborexant 2.5 mg/day	4.00 ± 1.593 (27)	−0.28 ± 1.003 (27)	−0.06 [−0.61, 0.48]	−0.09 ± 1.118 (27)	0.13 [−0.44, 0.70]
Lemborexant 5 mg/day	4.29 ± 1.609 (38)	−0.13 ± 1.536 (38)	0.20 [−0.29, 0.68]	0.07 ± 1.385 (37)	0.43 [−0.09, 0.94]
Lemborexant 10 mg/day	3.81 ± 1.768 (32)	0.02 ± 1.505 (32)	0.16 [−0.36, 0.67]	−0.15 ± 1.566 (31)	0.01 [−0.54, 0.55]
Lemborexant 15 mg/day	4.14 ± 1.911 (56)	0.05 ± 1.589 (56)	0.32 [−0.11, 0.76]	0.09 ± 1.724 (54)	0.38 [−0.08, 0.85]
Lemborexant 25 mg/day	3.72 ± 1.762 (50)	0.37 ± 1.362 (50)	0.47 [0.02, 0.93]	0.58 ± 1.509 (46)	0.68 [0.19, 1.17]

Mean ± standard deviation. (Number of subjects evaluated)
a) A subgroup of patients with ≥1 pharmacodynamic parameter; b) Measurement 1 hour after waking on Day 1 of administration; c) Mean of measurements 1 hour after waking on Days 2 and 3 of administration; d) Mean of measurements 1 hour after waking on Days 15 and 16 of administration; e) Based on a model of analysis of covariance with changes between groups [95% CI] and group as factors and baseline value as a covariate

The incidence of adverse events (including laboratory abnormalities) and those for which a causal relationship to the study drug was not ruled out is shown in Table 37. No deaths occurred. Serious adverse events other than death were reported in 1 subject in the placebo group (hyperkalemia) and 1 subject in the lemborexant 25 mg/day group (grand mal convulsion). A causal relationship to the study drug was not ruled out for grand mal convulsion reported in the subject in the lemborexant 25 mg/day.

Table 37. Incidence of adverse events and those for which a causal relationship to the study drug could not be ruled out (safety analysis set)

		Placebo	Lemborexant					
			1 mg/day	2.5 mg/day	5 mg/day	10 mg/day	15 mg/day	25 mg/day
Number of subjects evaluated		56	32	27	38	32	56	50
All adverse events		21 (37.5)	11 (34.4)	11 (40.7)	16 (42.1)	19 (59.4)	31 (55.4)	30 (60.0)
Adverse events for which a causal relationship to the study drug was not ruled out		11 (19.6)	8 (25.0)	9 (33.3)	12 (31.6)	15 (46.9)	24 (42.9)	24 (48.0)
Main events[a]	Somnolence	0 0	1 (3.1) 1 (3.1)	1 (3.7) 1 (3.7)	2 (5.3) 2 (5.3)	4 (12.5) 3 (9.4)	10 (17.9) 9 (16.1)	11 (22.0) 11 (22.0)
	Headache	3 (5.4) 2 (3.6)	3 (9.4) 2 (6.3)	3 (11.1) 2 (7.4)	3 (7.9) 1 (2.6)	3 (9.4) 2 (6.3)	6 (10.7) 3 (5.4)	5 (10.0) 3 (6.0)
	Sleep paralysis	0 0	0 0	0 0	1 (2.6) 1 (2.6)	3 (9.4) 3 (9.4)	4 (7.1) 4 (7.1)	2 (4.0) 2 (4.0)
	Rapid eye movements sleep abnormal	2 (3.6) 2 (3.6)	0 0	2 (7.4) 2 (7.4)	1 (2.6) 1 (2.6)	1 (3.1) 1 (3.1)	3 (5.4) 3 (5.4)	2 (4.0) 2 (4.0)
	Nightmare	0 0	0 0	0 0	1 (2.6) 1 (2.6)	3 (9.4) 3 (9.4)	4 (7.1) 4 (7.1)	0 0
	Abnormal dreams	0 0	2 (6.3) 2 (6.3)	0 0	1 (2.6) 1 (2.6)	3 (9.4) 2 (6.3)	0 0	0 0
	Myalgia	0 0	0 0	0 0	3 (7.9) 2 (5.3)	1 (3.1) 0	1 (1.8) 1 (1.8)	0 0

Number of subjects with events (incidence [%])
a) Upper row, adverse events; lower row, adverse events for which a causal relationship to the study drug was not ruled out

No clinically significant changes were observed in vital signs (heart rate, diastolic blood pressure, systolic blood pressure, respiratory rate, and body temperature). Electrocardiographic findings after the administration of the study drug were QTcF increased from baseline by >30 milliseconds in 13 subjects (2 in the placebo group,

2 in the lemborexant 1 mg/day group, 1 in the lemborexant 2.5 mg/day group, none in the lemborexant 5 mg/day group, 3 in the lemborexant 10 mg/day group, 4 in the lemborexant 15 mg/day group, and 1 in the lemborexant 25 mg/day group) and by >60 milliseconds in 1 subject (0, 0, 0, 0, 0, 0, and 1). After the administration of the study drug, QTcF was >450 milliseconds in 13 subjects (4, 2, 2, 2, 1, 2, and 0), but no subjects had a QTcF of >480 milliseconds.

7.3 Phase III studies

7.3.1 Global phase III study (CTD 5.3.5.1.1, 5.3.5.1.2: Study E2006-G000-303 [November 2016 to January 2019])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with insomnia[31)] (target sample size, 900; 300/group) in 12 countries[32)] to evaluate the efficacy and safety of lemborexant.[33)]

In Period 1, placebo or lemborexant 5 or 10 mg was orally administered once daily just before bedtime[34)] for 6 months. In Period 2, patients receiving lemborexant 5 or 10 mg in Period 1 continued with the treatment regimen, and patients receiving placebo in Period 1 were switched to oral lemborexant 5 or 10 mg administered once daily just before bedtime[34)] for 6 months.

In Period 1, 971 subjects were randomized (325 to the placebo group, 323 to the lemborexant 5 mg/day group, and 323 to the lemborexant 10 mg/day group). Of these, 959 (321, 319, and 319) received the study drug. After the study treatment, of the 959 subjects, 947 (319, 314, and 314) were evaluated for safety at least once and were included in the safety analysis set, and 949 (318, 316, and 315) were evaluated for efficacy at least once and were included in the FAS for efficacy analysis. In Period 1, 189 subjects (58, 51, and 80) discontinued the treatment, and the main reasons for discontinuation included consent withdrawal in 43 subjects (13, 10, and 20), inconvenience in 43 subjects (15, 11, and 17), inadequate response in 37 subjects (17, 9, and 11), and adverse events in 30 subjects (8, 7, and 15).

The primary endpoint was changes from baseline in the subjective sleep latency at Month 6 in the FAS. The results are shown in Table 38, demonstrating statistically significant differences between the lemborexant 5 or 10 mg/day groups and the placebo group.

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31) Patients aged ≥18 years who met all of the following criteria:
   a) Patients meeting the following DSM-5 diagnostic criteria for insomnia disorder
   ・A complaint of dissatisfaction with sleep at night, associated with ≥1 symptoms of difficulty initiating sleep, difficulty maintaining sleep, or early-morning awakening
   ・The sleep difficulty occurs ≥3 nights per week and persists for ≥3 months, causing functional impairment in daytime
   b) Patients confirmed to have subjective sleep latency of ≥30 minutes ≥3 nights per week and/or to have subjective wake after sleep onset of ≥60 minutes ≥3 nights per week 4 weeks before the screening, before the run-in period, and before the baseline
   c) Patients confirmed to have a regular total time in bed of 7 to 9 hours, a regular sleep between 21:00 and 01:00, and regular wakeup time between 5:00 to 10:00 in the screening period (before the run-in period and before the baseline) and an ISI score of ≥15 at the screening period and baseline
32) U.S., Canada, Mexico, Finland, Germany, Italy, Poland, Romania, Spain, New Zealand, Japan, and South Korea
33) The study had a placebo lead-in period, in which placebo was administered in a single-blind manner for 2 weeks before Period 1 to confirm the eligibility.
34) Just before the time to sleep (trying to sleep) every night (≤5 minutes)

Table 38. Change from baseline in the subjective sleep latency at Month 6 (Period 1: FAS)

Group	Subjective sleep latency		Change from baseline [a, b]	Ratio relative to placebo (Lemborexant/placebo)	
	Baseline	Month 6		Intergroup ratio [95% CI] [c]	*p* value [c]
Placebo	64.03 ± 45.209 (316) 44.99 55.86 (31.14, 78.93)	46.47 ± 45.010 (251) 27.42 34.29 (16.43, 60.00)	0.618 [0.559, 0.684]		
Lemborexant 5 mg/day	62.19 ± 45.674 (314) 42.97 53.57 (32.86, 75.71)	29.49 ± 26.685 (247) 18.62 22.29 (12.86, 35.43)	0.453 [0.408, 0.502]	0.732 [0.636, 0.843]	<0.0001
Lemborexant 10 mg/day	64.97 ± 44.020 (312) 45.05 55.71 (33.57, 85.07)	33.09 ± 32.167 (230) 19.35 23.57 (12.86, 40.71)	0.433 [0.389, 0.483]	0.701 [0.607, 0.810]	<0.0001

Unit, minute. Upper row, mean ± standard deviation (number of subjects evaluated); middle row, geometric mean; lower row, median (quartile point [Q1, Q3])

a) Least-squares ratio of geometric means of subjective sleep latency at each point (Month 6/baseline) [95% CI]

b) Based on an analysis of log-transformed subjective sleep latency by the MMRM (using the unstructured covariance matrix) adjusted for age group (<65/≥65 years of age), region, baseline value, treatment group, evaluation point, and interaction between treatment group and evaluation point. Missing values were imputed by the multiple imputation assuming missing not at random (MNAR) using complete case missing value pattern (CCMV).

c) The multiplicity of the test was adjusted by the gate-keeping method: a comparison was performed between the placebo group and the lemborexant 5 mg/day group with a significant level of 5% (two-sided) only if a significant difference was identified between the placebo group and the lemborexant 10 mg/day group with the significant level of 5% (two-sided).

Important secondary endpoints were changes from baseline in the subjective sleep efficiency and subjective wake after sleep onset at Month 6 in the FAS and are shown in Table 39, demonstrating improvement in the lemborexant 5 and 10 mg/day group as compared with the placebo group.

Table 39. Changes from baseline in subjective sleep efficiency and subjective wake after sleep onset at Month 6 (Period 1: FAS)

	Group	Baseline	Month 6	Change from baseline [a, b]	Difference from the placebo group (Lemborexant −placebo) [95% CI] [b]
Subjective sleep efficiency	Placebo	61.34 ± 17.836 (307)	71.40 ± 18.314 (247)	9.640 ± 0.844	
	Lemborexant 5 mg/day	63.14 ± 18.231 (302)	78.55 ± 16.244 (245)	14.189 ± 0.863	4.549 [2.236, 6.861]
	Lemborexant 10 mg/day	62.03 ± 17.248 (299)	76.53 ± 17.987 (228)	14.307 ± 0.872	4.667 [2.373, 6.960]
Subjective wake after sleep onset	Placebo	132.49 ± 80.198 (314)	103.15 ± 82.294 (251)	−29.276 ± 3.605	
	Lemborexant 5 mg/day	132.77 ± 82.518 (313)	81.79 ± 76.803 (247)	−46.750 ± 3.658	−17.474 [−27.306, −7.643]
	Lemborexant 10 mg/day	136.83 ± 87.391 (311)	86.38 ± 77.793 (229)	−41.947 ± 3.694	−12.671 [−22.378, −2.964]

Unit: % (sleep efficiency), minute (wake after sleep onset), mean ± standard deviation (number of subjects evaluated)

a) Estimated least-squares mean ± standard error

b) Based on an analysis by the MMRM (using the unstructured covariance matrix) adjusted for age group (<65/≥65 years of age), region, baseline value, treatment group, evaluation point, and interaction between treatment group and evaluation point. Missing values were imputed by the multiple imputation assuming MNAR using the CCMV.

Adverse events (including laboratory abnormalities) occurred in 62.7% (200 of 319) of subjects in the placebo group, 61.1% (192 of 314) of subjects in the lemborexant 5 mg/day group, and 59.6% (187 of 314) of subjects in the lemborexant 10 mg/day group. No deaths occurred. Serious adverse events other than deaths occurred in 5 subjects in the placebo group (tibia fracture/arthritis bacterial, pneumonia, goiter and cyst, pelvic fracture/ rib fracture and jaw cyst/jaw fistula in 1 each), 7 subjects in the lemborexant 5 mg/day group (fall/lower limb fracture, chest pain, postoperative wound infection, hydrosalpinx, diabetic retinopathy/diabetic neuropathy, angina pectoris, and hypertension in 1 each), and 9 subjects in the lemborexant 10 mg/day group (cerebrovascular accident, osteoarthritis, deep vein thrombosis, intraductal proliferative breast, disturbance in attention, cystitis, type 2 diabetes mellitus, cholestasis and hepatotoxicity,

chronic obstructive pulmonary disease in 1 each). A causal relationship to the study drug was not ruled out for disturbance in attention in the subject in the lemborexant 10 mg/day.

A causal relationship between adverse events (including laboratory abnormalities) and the study drug was not ruled out in 13.8% (44 of 319) of subjects in the placebo group, 24.8% (78 of 314) of subjects in the lemborexant 5 mg/day group, and 29.0% (91 of 314) of subjects in the lemborexant 10 mg/day group. Major events included somnolence (4 in the placebo group, 27 in the lemborexant 5 mg/day group, and 40 in the lemborexant 10 mg/day group), headache (11, 12, and 12), fatigue (1, 10, and 8), abnormal dreams (5, 7, and 4), and nightmare (1, 3, and 7).

Clinically significant changes in vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body weight) were blood pressure systolic increased in 2 subjects (the placebo group); blood pressure diastolic decreased in 1 subject (the placebo group), blood pressure diastolic increased in 4 subjects (1 in the placebo group, 3 in the lemborexant 5 mg/day group, and 0 in the lemborexant 10 mg/day group), respiratory rate decreased in 3 subjects (0, 2, and 1); weight increased (16, 14, and 12); and weight loss (7, 5, and 9). Electrocardiographic findings after the administration of the study drug included increased QTcF from baseline by >30 milliseconds in 52 subjects (19, 12, and 21) and by >60 milliseconds in no subjects. After the administration of the study drug, QTcF was >450 milliseconds in 32 subjects (14, 9, and 9), but no subjects had a QTcF of >500 milliseconds.

After the administration of lemborexant, 884 subjects underwent safety evaluation at least once during Periods 1 and 2 of the lemborexant treatment (447 subjects in the lemborexant 5 mg/day arm consisting of those receiving lemborexant 5 mg/day in both Periods 1 and 2 and those receiving placebo in Period 1 and lemborexant 5 mg/day in Period 2, and 437 subjects in the lemborexant 10 mg/day arm consisting of those receiving lemborexant 10 mg/day in both Periods 1 and 2 and those receiving placebo in Period 1 and lemborexant 10 mg/day in Period 2). The 884 subjects were included in the safety analysis set. Of these, 884 subjects (444 in the lemborexant 5 mg/day arm and 437 in the lemborexant 10 mg/day arm) underwent efficacy evaluation at least once and were included in the FAS. Among 728 subjects entering Period 2 (384 and 344), the study drug was discontinued in 75 subjects (38 and 37), and the main reasons for discontinuation included inconvenience (11 and 8), consent withdrawal (5 and 5), and adverse events (7 and 16).

Changes over time in the subjective sleep latency up to Month 12 of the treatment with lemborexant are shown in Table 40.

Table 40. Changes over time in the subjective sleep latency up to Month 12 of lemborexant treatment (Periods 1 and 2: FAS)

	Lemborexant 5 mg/day			Lemborexant 10 mg/day		
	Mean ± standard deviation. (Number of subjects evaluated)	Geometric mean	Median (quartile point [Q1, Q3])	Mean ± standard deviation. (Number of subjects evaluated)	Geometric mean	Median (quartile point [Q1, Q3])
Baseline [a)]	57.25 ± 46.279 (442)	37.21	48.10 (27.86, 72.50)	60.23 ± 45.123 (434)	39.41	52.14 (30.00, 77.14)
Month 1	39.47 ± 35.834 (417)	24.70	30.00 (17.14, 52.50)	40.08 ± 35.352 (415)	25.19	30.00 (15.71, 55.71)
Mont 3	33.98 ± 33.602 (388)	20.72	23.57 (13.88, 40.71)	35.96 ± 37.255 (377)	21.87	24.29 (13.57, 47.14)
Month 6	29.97 ± 29.251 (354)	18.24	21.57 (12.14, 35.71)	33.80 ± 36.999 (332)	19.05	22.86 (12.14, 40.00)
Month 9	28.42 ± 27.052 (234)	16.79	19.80 (11.43, 35.00)	29.47 ± 31.520 (214)	17.08	20.61 (10.00, 36.67)
Month 12	28.04 ± 26.376 (217)	16.85	20.00 (11.33, 34.29)	30.65 ± 40.148 (205)	17.33	21.20 (10.71, 39.17)

Unit, minute.

a) For subjects who were assigned to lemborexant in Period 1, baseline value in Period 1; for subjects who were assigned to placebo in Period 1, baseline value in Period 2

Changes over time in the subjective sleep efficiency and subjective wake after sleep onset up to Month 12 of the treatment with lemborexant are shown in Table 41.

Table 41. Changes over time in the subjective sleep efficiency and subjective wake after sleep onset up to Month 12 of lemborexant treatment (Periods 1 and 2: FAS)

	Subjective sleep efficiency		Subjective wake after sleep onset	
	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Lemborexant 5 mg/day	Lemborexant 10 mg/day
Baseline [a)]	65.34 ± 19.110 (430)	64.66 ± 17.914 (421)	124.75 ± 82.827 (441)	126.48 ± 88.090 (433)
Month 1	72.52 ± 18.438 (410)	72.27 ± 17.472 (408)	104.14 ± 81.293 (416)	104.18 ± 80.234 (412)
Month 3	76.70 ± 16.527 (381)	75.50 ± 17.277 (371)	89.78 ± 78.235 (388)	93.25 ± 82.477 (376)
Month 6	77.73 ± 17.073 (352)	76.42 ± 18.126 (329)	84.69 ± 77.556 (354)	87.10 ± 79.303 (331)
Month 9	78.96 ± 17.012 (231)	77.82 ± 17.606 (213)	78.73 ± 78.906 (234)	80.34 ± 75.573 (214)
Month 12	80.01 ± 14.630 (215)	78.15 ± 17.473 (203)	74.03 ± 69.990 (217)	79.97 ± 74.527 (205)

Unit, % (sleep efficiency), minute (wake after sleep onset), mean ± standard deviation (number of subjects evaluated)

a) For subjects who were assigned to lemborexant in Period 1, baseline value in Period 1; for subjects who were assigned to placebo in Period 1, baseline value in Period 2

In Period 2 alone, adverse events (including laboratory abnormalities) occurred in 50.8% (195 of 384) of subjects in the lemborexant 5 mg/day arm and 52.3% (180 of 344) subjects in the lemborexant 10 mg/day arm. No deaths occurred. Serious adverse events other than deaths occurred in 12 subjects in the lemborexant 5 mg/day arm (breast reconstruction/pneumonia/gastrointestinal inflammation, hiatus hernia/and osteoarthritis, inflammation/dermal cyst, non-cardiac chest pain, erysipelas, diabetic neuropathy, alcoholic pancreatitis, intentional overdose, ankle fracture, hand fracture, atrial fibrillation, and floppy eyelid syndrome in 1 each) and 8 subjects in the lemborexant 10 mg/day arm (nephrolithiasis/fall/ankle fracture, meniscus injury/osteoarthritis, gastrointestinal haemorrhage, osteoarthritis, rib fracture, extrasystoles, pharyngeal inflammation, and acute myocardial infarction in 1 each). A causal relationship to the study drug was ruled out for all events.

A causal relationship between adverse events (including laboratory abnormalities) and the study drug was not ruled out in 12.8% (49 of 384) of subjects in the lemborexant 5 mg/day arm and 12.8% (44 of 344) of subjects in the lemborexant 10 mg/day arm. Major events were somnolence (12 subjects in the lemborexant 5 mg/day arm and 19 subjects in the lemborexant 10 mg/day arm), headache (8 and 4), fatigue (2 and 6), sleep paralysis (7 and 4), dizziness (5 and 3), weight increased (4 and 3), and abnormal dreams (2 and 3).

In Period 2, clinically significant changes in vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body weight) were blood pressure systolic increased (0 in the lemborexant 5 mg/day arm and 1 subject in the lemborexant 10 mg/day arm), blood pressure diastolic increased (1 and 0), blood pressure diastolic decreased (1 and 0), pulse rate decreased (1 and 0), pulse rate increased (0 and 1), respiratory rate decreased (1 and 1), weight increased (22 and 33), and weight loss (22 and 11). Electrocardiographic findings after the administration of the study drug in Period 2 included increased QTcF from baseline by >30 milliseconds in 44 subjects (25 in the lemborexant 5 mg/day arm and 19 in the lemborexant 10 mg/day arm) and >60 milliseconds in 1 subject (1 and 0). After the administration of the study drug in Period 2, QTcF was >450 milliseconds in 20 subjects (9 and 11), but no subjects had a QTcF of >500 milliseconds.

7.3.2 Foreign phase III study (CTD 5.3.5.1.3: Study E2006-G000-304 [May 2016 to January 2018])

A placebo- and active-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of lemborexant in patients with insomnia[35)] (target sample, 950; 200 in the placebo group, 250 in the zolpidem ER[36)] group, 250 in the lemborexant 5 mg/day group, and 250 in the lemborexant 10 mg/day groups).[37)]

Placebo, lemborexant 5 or 10 mg, or zolpidem ER 6.25 mg was orally administered, once daily, just before bedtime [34)] for 30 days.

All 1,006 randomized subjects (208 in the placebo group, 266 in the lemborexant 5 mg/day group, 269 in the lemborexant 10 mg/day group, and 263 in the zolpidem ER group) were included in the safety analysis set and the FAS for efficacy analysis. The study treatment was discontinued in 44 subjects (10, 8, 9, and 17) in the safety analysis set, and the main reasons for discontinuation included adverse events in 13 subjects (2, 2, 3, and 6) and consent withdrawal in 11 subjects (2, 1, 2, and 3).

The primary endpoint was changes from baseline in the sleep latency assessed by PSG at the end of treatment in the FAS[38)] and are shown in Table 42, demonstrating statistically significant differences between the lemborexant 5 or 10 mg/day group and the placebo group.[39)]

35) Men aged ≥65 years or women aged ≥55 years who met all of the following criteria:
a) Patients meeting the following DSM-5 diagnostic criteria for insomnia disorder
・A complaint of dissatisfaction with sleep at night, associated with difficulty maintaining sleep and/or early-morning awakening (with or without difficulty initiating sleep)
・・The sleep difficulty occurs ≥3 nights per week and persists for ≥3 months, causing functional impairment in daytime.
b) Patients confirmed to have the subjective wake after sleep onset of ≥60 minutes 4 weeks before the screening, before the run-in period, and before baseline, and to have the wake after sleep onset of ≥60 minutes ≥3 nights per week before baseline
c) Patients confirmed to have a regular total time in bed of 7 to 9 hours, a regular sleep between 21:00 and 01:00, and regular wakeup time between 5:00 to 10:00 in the screening period and an ISI score of ≥13 at the screening period and baseline
36) Zolpidem tartrate sustained-release tablets 6.25 mg (unapproved in Japan)
37) A placebo lead-in period was specified, in which placebo was administered in a single-blind manner for 7 to 16 days before the double-blind period to confirm the eligibility.
38) Time from lights off to the first epoch (30 s/1 epoch) of 20 consecutive epochs of non-wakefulness, calculated with PSG
39) The lemborexant 5 and 10 mg/day groups were compared with the placebo group in the primary endpoint analysis.

Table 42. Changes from baseline in sleep latency assessed by PSG at the end of treatment (FAS)

Group	Sleep latency		Change from baseline [b, c)]	Ratio relative to placebo [95% CI] (Active drug/placebo)	
	Baseline	End of administration [a)]		Intergroup ratio [95% CI] [d)]	p value [d)]
Placebo	43.89 ± 33.596 (208) 33.61 33.63 (20.75, 59.50)	36.04 ± 32.090 (200) 24.88 25.75 (14.75, 44.25)	0.699 [0.625, 0.783]		
Lemborexant 5 mg/day	44.86 ± 36.528 (266) 32.98 33.13 (20.25, 62.25)	25.84 ± 24.253 (260) 18.87 18.75 (11.75, 31.00)	0.541 [0.489, 0.597]	0.773 [0.672, 0.889]	0.0003
Lemborexant 10 mg/day	44.61 ± 32.986 (269) 33.31 38.50 (17.75, 62.00)	22.75 ± 17.460 (260) 17.49 19.25 (11.25, 29.25)	0.506 [0.458, 0.559]	0.723 [0.628, 0.832]	<0.0001
Zolpidem ER	44.52 ± 38.349 (262) 30.96 31.50 (17.50, 61.25)	37.11 ± 28.397 (251) 27.88 28.50 (17.00, 52.25)	0.852 [0.770, 0.943]	1.218 [1.057, 1.403]	—[e)]

Unit, minute. Upper row, mean ± standard deviation (number of subjects evaluated); middle row, geometric mean; lower row, Median (quartile point [Q1, Q3])

a) Mean of values on Days 29 and 30

b) Least-squares ratio of geometric means of sleep latency at each point (end of treatment/baseline) [95% CI]

c) Based on an analysis of log-transformed sleep latency by the MMRM (using the unstructured covariance matrix) adjusted for age group (<65/≥65 years of age), region, baseline value, treatment group, evaluation point, and interaction between group and evaluation point. Missing values were imputed by the multiple imputation assuming the MNAR using the CCMV.

d) The multiplicity of the test was adjusted by the gate-keeping method (A comparison was performed between the placebo group and the lemborexant 5 mg/day group with a significant level of 5% [two-sided] only if a significant difference was identified between the placebo group and the lemborexant 10 mg/day group with the significant level of 5% [two-sided]).

e) The comparison between the zolpidem ER and placebo groups was not included in the primary analysis.

Secondary endpoints were changes from baseline in the subjective sleep latency and the sleep efficiency and wake after sleep onset assessed by PSG at the end of treatment and are shown in Tables 43 and 44, respectively.

Table 43. Changes from baseline in subjective sleep latency at the end of treatment (FAS)

Group	Subjective sleep latency		Change from baseline[b, c)]	Ratio relative to placebo[c)] [95% CI] (Active drug/placebo)
	Baseline	End of administration[a)]		
Placebo	55.90 ± 37.389 (206) 44.07 49.29 (28.86, 70.71)	47.60 ± 32.765 (197) 37.11 38.57 (22.14, 65.00)	0.826 [0.756, 0.902]	
Lemborexant 5 mg/day	65.79 ± 43.530 (263) 53.77 58.57 (35.71, 81.43)	38.80 ± 28.028 (254) 30.10 30.36 (17.50, 57.86)	0.619 [0.572, 0.669]	0.750 [0.671, 0.837]
Lemborexant 10 mg/day	60.88 ± 42.514 (269) 48.43 53.57 (29.29, 80.00)	36.51 ± 31.059 (258) 27.12 27.50 (15.71, 50.00)	0.569 [0.526, 0.615]	0.689 [0.618, 0.769]
Zolpidem ER	60.54 ± 36.350 (258) 49.96 53.21 (33.57,77.86)	43.64 ± 30.649 (251) 33.99 37.50 (21.43, 58.33)	0.792 [0.648, 0.760]	0.850 [0.761, 0.949]

Unit, minute. Upper row, mean ± standard deviation (number of subjects evaluated); middle row, geometric mean; lower row, Median (quartile point [Q1, Q3])

a) Mean of values on the last 7 days.

b) Least-squares ratio of geometric means of the subjective sleep latency at each point (the end of treatment /baseline) [95% CI]

c) Based on an analysis of log-transformed subjective sleep latency with the MMRM (using the unstructured covariance matrix) adjusted for treatment group, age group (<65/≥65 years of age), region, baseline value, evaluation point, and interaction between treatment group and evaluation point. Missing values were imputed by the multiple imputation assuming the MNAR using the CCMV.

Table 44. Changes from baseline in sleep efficiency and wake after sleep onset assessed by PSG at the end of treatment (FAS)

	Group	Baseline	End of treatment[a)]	Changes from baseline[b, c)]	Difference from the placebo group[c)] [95% CI] (lemborexant −placebo)
Sleep efficiency	Placebo	68.89 ± 9.639 (208)	74.49 ± 9.848 (200)	6.34 ± 0.599	
	Lemborexant 5 mg/day	68.36 ± 11.268 (266)	81.29 ± 8.800 (260)	13.42 ± 0.533	7.07 [5.61, 8.54]
	Lemborexant 10 mg/day	67.85 ± 10.849 (269)	81.99 ± 8.801 (260)	14.37 ± 0.535	8.03 [6.57, 9.49]
	Zolpidem ER	68.13 ± 11.419 (262)	77.17 ± 10.185 (251)	9.50 ± 0.547	3.15 [1.67, 4.63]
Wake after sleep onset	Placebo	111.75 ± 37.179 (208)	92.09 ± 40.965 (200)	−21.43 ± 2.464	
	Lemborexant 5 mg/day	113.44 ± 38.953 (266)	69.10 ± 34.533 (260)	−45.40 ± 2.185	−23.96 [−29.98, −17.95]
	Lemborexant 10 mg/day	114.83 ± 39.997 (269)	68.60 ± 35.200 (260)	−46.78 ± 2.193	−25.35 [−31.36, −19.34]
	Zolpidem ER	114.31 ± 39.922 (262)	77.71 ± 39.932 (251)	−37.68 ± 2.217	−16.25 [−22.31, −10.18]

Unit: % (sleep efficiency), minute (wake after sleep onset), mean ± standard deviation (number of subjects evaluated)
a) Mean of values on Days 29 and 30
b) Estimated least-squares mean ± standard error
c) Based on an analysis by the MMRM (using the unstructured covariance matrix) adjusted for treatment group, age group (<65/≥65 years of age), region, baseline value, evaluation point, and interaction between treatment group and evaluation point. Missing values were imputed by the multiple imputation assuming MNAR using CCMV.

Adverse events (including laboratory abnormalities) occurred in 25.4% (53 of 209) of subjects in the placebo group, 27.8% (74 of 266) of subjects in the lemborexant 5 mg/day group, 30.6% (82 of 268) of subjects in the lemborexant 10 mg/day group, and 35.4% (93 of 263) of subjects in the zolpidem ER group. No deaths occurred. Serious adverse events other than deaths occurred in 2 subjects in the lemborexant 5 mg/day group (gastroenteritis viral and abdominal hernia in 1 each) and 4 subjects in the zolpidem ER group (peripheral vascular disorder/coronary artery disease/pneumonia, small intestinal obstruction, back pain, and chest pain in 1 each). A causal relationship to the study drug was ruled out for all the serious events.

A causal relationship between adverse events (including laboratory abnormalities) and the study drug was not ruled out in 7.7% (16 of 209) of subjects in the placebo group, 11.3% (30 of 266) of subjects in the lemborexant 5 mg/day groups, 14.6% (39 of 268) of subjects in the lemborexant 10 mg/day group, and 15.2% (40 of 263) of subjects in the zolpidem ER group. Major events included somnolence (3, 10, 17, and 4), headache (4, 9, 8, and 6), and dizziness (3, 2, 1, and 7).

Clinically significant changes in vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body weight) were blood pressure systolic decreased (0 in the placebo group, 0 in the lemborexant 5 mg/day group, 0 in the lemborexant 10 mg/day group, 1 in the zolpidem ER group); blood pressure systolic increased (1, 1, 1, and 0); blood pressure diastolic decreased (0, 1, 0, and 0); blood pressure diastolic increased (0, 1, 1, and 0); pulse rate decreased (1, 3, 2, and 2); respiratory rate increased (1, 4, 3, and 0); weight increased (1, 3, 4, and 1); and weight loss (1, 2, 2, and 2). Electrocardiographic findings included increased QTcF from baseline by >30 milliseconds in 73 subjects (17, 23, 18, and 15) and by 60 milliseconds in 1 subject in the placebo group. QTcF was >450 milliseconds in 54 subjects (8, 11, 23, and 12) and >500 milliseconds in 1 subject in the lemborexant 10 mg/day group.

7.R Outline of the review conducted by PMDA

7.R.1 Evaluation based on data from the global study

7.R.1.1 Intrinsic and extrinsic ethnic factors

PMDA asked the applicant to explain how the applicant examined the intrinsic and extrinsic ethnic factors affecting the efficacy and safety of lemborexant for the implementation of the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303).

The applicant's response:

The effects of intrinsic and extrinsic ethnic factors on the efficacy and safety of lemborexant were considered small based on the following findings, justifying the implementation of the phase III study as a global study.

- The diagnosis of insomnia is confirmed based on standard diagnostic guidelines such as DSM-5 and ICSD-3 both in Japan and overseas, and thus, no marked differences exist.
- For the treatment of insomnia, use of benzodiazepines or nonbenzodiazepine hypnotics is recommended as appropriate pharmacotherapy in Japan (Guidelines for the Proper Use and Cessation of Hypnotics 2014), and pharmacotherapy with benzodiazepines and nonbenzodiazepine hypnotics is recommended also in the US (NIH Consensus and State-of-the-Science Statements 2005; June 13-15, 22(2):1-30). The classification and choice of hypnotics are similar between Japan and overseas.
- Prior to the implementation of Study E2006-G000-303, training on the proper use of sleep diary and monitoring methods was provided to the study sites to uniform the evaluation. The study sites then provided patients with training so that they would keep a sleep diary appropriately according to a manual. The recording in the diary was monitored regularly, and patients were re-trained if necessary.
- In the foreign phase I study conducted in Japanese and Caucasian healthy adults (CTD 5.3.3.1.3: Study E2006-A001-003), the distribution of serum lemborexant concentrations was found to overlap between Japanese and non-Japanese subjects [see Section 6.R.1]. The PPK analysis demonstrated that race had no effects on the pharmacokinetics of lemborexant [see Section 6.2.6]. These findings suggest that the pharmacokinetics of lemborexant do not differ substantially between Japanese and non-Japanese subpopulations.

PMDA accepted the applicant's explanation above.

7.R.1.2 Differences in efficacy and safety between Japanese and non-Japanese subjects in the global phase III study

PMDA asked the applicant to explain the similarities in the efficacy and safety of lemborexant between Japanese and non-Japanese subjects at evaluation points including short-term ones in the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303).

The applicant's explanation:

- The Guidelines for the Clinical Evaluation of Hypnotic Drugs (PFSB/ELD Notification No. 1213-1, dated December 13, 2011) state that "An evaluation parameter either of sleep latency, time or number of wake after sleep onset, or total sleep time should be specified as primary endpoints in a rational way."

According to the guidelines, the subjective sleep latency was specified as the primary endpoint, and the subjective wake after sleep onset and subjective sleep efficiency were specified as the secondary endpoints in Study E2006-G000-303. The guidelines also state that "it is appropriate to conduct a placebo-controlled, randomized, double-blind, parallel-group study with a 2- to 4-week treatment duration as a confirmatory study of drugs for the treatment of insomnia" and that "The treatment in a long-term treatment study should be ≥6 months in principle because of possible chronicity." Accordingly, the evaluation was performed at Day 7 and Months 1, 3, and 6 in Study E2006-G000-303.

- Tables 45, 46, and 47 show changes over time from baseline in the subjective sleep latency, subjective sleep efficiency, and subjective wake after sleep onset, respectively, in Japanese and non-Japanese subpopulations in Study E2006-G000-303. Similar tendencies were observed between the Japanese subpopulation and the entire study population. At Month 1 in the Japanese subpopulation, the degree of improvement in changes from baseline in the subjective sleep latency and subjective sleep efficiency in the lemborexant 5 mg/day group and the subjective wake after sleep onset in the lemborexant 5 and 10 mg/day groups was not greater than that in the placebo group. However, Japanese subjects (159) was smaller in number than non-Japanese subjects (783), resulting in low accuracy in estimation. In addition, the degree of improvement at Months 3 and 6 in the lemborexant 5 and 10 mg/day was greater than that in the placebo group in the Japanese subpopulation. These facts suggest that the results on the efficacy are consistent between the Japanese and non-Japanese subpopulations.

Table 45. Change over time from baseline in subjective sleep latency (Study E2006-G000-303, Period 1, FAS)

			Entire study population	Japanese subpopulation	Non-Japanese subpopulation
Baseline	Placebo	Observed value[a)]	64.03 ± 45.209 (316) 44.99, 55.86 (34.14, 78.93)	60.78 ± 44.005 (54) 42.33, 49.14 (34.29, 65.71)	64.70 ± 45.507 (262) 45.55, 58.57 (33.86, 79.29)
	Lemborexant 5 mg/day	Observed value[a)]	62.19 ± 45.674 (314) 42.97, 53.57 (32.86, 75.71)	59.40 ± 59.591 (52) 42.62, 49.64 (35.71, 70.36)	62.74 ± 42.497 (262) 43.04, 55.71 (32.86, 78.57)
	Lemborexant 10 mg/day	Observed value[a)]	64.97 ± 44.020 (312) 45.05, 55.71 (33.57, 85.07)	70.37 ± 53.247 (53) 48.78, 53.57 (33.57, 90.00)	63.87 ± 41.919 (259) 44.32, 55.71 (33.57, 84.43)
Day 7	Placebo	Changes[b,c)]	0.931 [0.879, 0.986]	0.852 [0.755, 0.961]	0.933 [0.877, 0.993]
	Lemborexant 5 mg/day	Changes[b,c)]	0.728 [0.687, 0.771]	0.776 [0.685, 0.880]	0.706 [0.663, 0.751]
		Intergroup ratio of changes[c,d)]	0.781 [0.725, 0.842]	0.912 [0.775, 1.072]	0.756 [0.695, 0.823]
	Lemborexant 10 mg/day	Changes[b,c)]	0.701 [0.661, 0.742]	0.685 [0.607, 0.775]	0.692 [0.650, 0.736]
		Intergroup ratio of changes[c,d)]	0.752 [0.698, 0.811]	0.805 [0.684, 0.946]	0.741 [0.681, 0.807]
Month 1	Placebo	Changes[b,c)]	0.786 [0.731, 0.845]	0.704 [0.608, 0.815]	0.794 [0.734, 0.859]
	Lemborexant 5 mg/day	Changes[b,c)]	0.637 [0.592, 0.685]	0.757 [0.651, 0.880]	0.604 [0.558, 0.653]
		Intergroup ratio of changes[c,d)]	0.810 [0.735, 0.893]	1.076 [0.879, 1.316]	0.760 [0.681, 0.848]
	Lemborexant 10 mg/day	Changes[b,c)]	0.605 [0.563, 0.650]	0.593 [0.512, 0.688]	0.598 [0.552, 0.647]
		Intergroup ratio of changes[c,d)]	0.770 [0.698, 0.848]	0.843 [0.690, 1.031]	0.753 [0.674, 0.840]
Month 3	Placebo	Changes[b,c)]	0.673 [0.617, 0.734]	0.574 [0.472, 0.698]	0.687 [0.624, 0.756]
	Lemborexant 5 mg/day	Changes[b,c)]	0.524 [0.480, 0.572]	0.550 [0.450, 0.672]	0.514 [0.466, 0.566]
		Intergroup ratio of changes[c d)]	0.778 [0.690, 0.878]	0.958 [0.729, 1.259]	0.748 [0.654, 0.856]
	Lemborexant 10 mg/day	Changes[b,c)]	0.518 [0.474, 0.567]	0.509 [0.418, 0.619]	0.512 [0.464, 0.565]
		Intergroup ratio of changes[c,d)]	0.770 [0.681, 0.869]	0.886 [0.675, 1.162]	0.745 [0.651, 0.854]
Month 6	Placebo	Changes[b,c)]	0.618 [0.559, 0.684]	0.592 [0.477, 0.735]	0.616 [0.547, 0.692]
	Lemborexant 5 mg/day	Changes[b,c)]	0.453 [0.408, 0.502]	0.508 [0.407, 0.635]	0.436 [0.388, 0.491]
		Intergroup ratio of changes[c,d)]	0.732 [0.636, 0.843]	0.858 [0.633, 1.164]	0.709 [0.601, 0.836]
	Lemborexant 10 mg/day	Changes[b,c)]	0.433 [0.389, 0.483]	0.420 [0.337, 0.522]	0.431 [0.382, 0.487]
		Intergroup ratio of changes[c,d)]	0.701 [0.607, 0.810]	0.709 [0.524, 0.960]	0.701 [0.593, 0.829]

a) Unit, minute. Upper row, mean ± standard deviation (number of subjects evaluated); middle row, geometric mean; lower row, Median (quartile point [Q1, Q3])
b) Least-squares ratio of geometric means of subjective sleep latency at each point (evaluation point/baseline) [95% CI]
c) Based on an analysis of log-transformed subjective sleep latency by the MMRM (using the unstructured covariance matrix) adjusted for age group (<65/≥65 years of age), region (for the entire study population only), baseline value, treatment group, evaluation point, and interaction between group and evaluation point. For the entire study population, missing values were imputed by the multiple imputation assuming the MNAR using the CCMV. For the Japanese and non-Japanese subpopulations, missing values were not imputed assuming the missing at random (MAR).
d) Ratio to the placebo group [95% CI]

Table 46. Changes over time from baseline in subjective sleep efficiency (Study E2006-G000-303, Period 1, FAS)

			Entire study population	Japanese subpopulation	Non-Japanese subpopulation
Baseline	Placebo	Observed value[a)]	61.34 ± 17.836 (307)	62.06 ± 18.257 (54)	61.18 ± 17.778 (253)
	Lemborexant 5 mg/day	Observed value[a)]	63.14 ± 18.231 (302)	65.04 ± 18.124 (52)	62.74 ± 18.264 (250)
	Lemborexant 10 mg/day	Observed value[a)]	62.03 ± 17.248 (299)	66.03 ± 15.205 (51)	61.21 ± 17.553 (248)
Day 7	Placebo	Changes[b,c)]	2.097 ± 0.635	2.797 ± 1.254	2.177 ± 0.688
	Lemborexant 5 mg/day	Changes[b,c)]	6.396 ± 0.642	4.630 ± 1.299	7.077 ± 0.692
		Intergroup difference in changes[c,d)]	4.299 [2.638, 5.961]	1.834 [−1.562, 5.229]	4.901 [3.041, 6.760]
	Lemborexant 10 mg/day	Changes[b,c)]	7.889 ± 0.655	6.759 ± 1.304	8.330 ± 0.695
		Intergroup difference in changes[c,d)]	5.793 [4.133, 7.452]	3.963 [0.566, 7.360]	6.154 [4.295, 8.013]
Month 1	Placebo	Changes[b,c)]	5.536 ± 0.730	6.667 ± 1.429	5.511 ± 0.811
	Lemborexant 5 mg/day	Changes[b,c)]	7.763 ± 0.739	5.820 ± 1.472	8.535 ± 0.814
		Intergroup difference in changes[c,d)]	2.227 [0.307, 4.146]	−0.847 [−4.745, 3.052]	3.024 [0.816, 5.231]
	Lemborexant 10 mg/day	Changes[b,c)]	9.151 ± 0.757	9.018 ± 1.468	9.582 ± 0.824
		Intergroup difference in changes[c,d)]	3.615 [1.635, 5.595]	2.352 [−1.544, 6.247]	4.071 [1.854, 6.289]
Month 3	Placebo	Changes[b,c)]	8.578 ± 0.803	9.272 ± 1.478	8.857 ± 0.899
	Lemborexant 5 mg/day	Changes[b,c)]	12.801 ± 0.798	12.045 ± 1.504	13.217 ± 0.912
		Intergroup difference in changes[c,d)]	4.222 [2.068, 6.377]	2.773 [−1.241, 6.787]	4.359 [1.888, 6.830]
	Lemborexant 10 mg/day	Changes[b,c)]	12.939 ± 0.798	11.495 ± 1.505	13.627 ± 0.929
		Intergroup difference in changes[c,d)]	4.361 [2.220, 6.501]	2.223 [−1.797, 6.242]	4.769 [2.276, 7.262]
Month 6	Placebo	Changes[b,c)]	9.640 ± 0.844	9.122 ± 1.678	10.417 ± 0.963
	Lemborexant 5 mg/day	Changes[b,c)]	14.189 ± 0.863	12.708 ± 1.715	14.785 ± 0.974
		Intergroup difference in changes[c,d)]	4.549 [2.236, 6.861]	3.586 [−1.022, 8.193]	4.369 [1.719, 7.018]
	Lemborexant 10 mg/day	Changes[b,c)]	14.307 ± 0.872	12.041 ± 1.712	15.382 ± 1.001
		Intergroup difference in changes[c,d)]	4.667 [2.373, 6.960]	2.919 [−1.686, 7.525]	4.966 [2.281, 7.651]

a) Unit: minute, mean ± standard deviation (number of subjects evaluated)
b) Unit: minute, least-squares mean ± standard error
c) Based on an analysis by the MMRM (using the unstructured covariance matrix) adjusted for age group (<65/≥65 years of age), region (for the entire study population only), baseline value, group, evaluation point, and interaction between group and evaluation point. For the entire study population, missing values were imputed by the multiple imputation assuming the MNAR using the CCMV. For the Japanese and non-Japanese subpopulations, missing values were not imputed assuming the MAR.
d) Difference from the placebo group [95% CI]

Table 47. Changes over time from baseline in subjective wake after sleep onset (Study E2006-G000-303, Period 1, FAS)

			Entire study population	Japanese subpopulation	Non-Japanese subpopulation
Baseline	Placebo	Observed value[a)]	132.49 ± 80.198 (314)	121.62 ± 80.844 (54)	134.74 ± 80.035 (260)
	Lemborexant 5 mg/day	Observed value[a)]	132.77 ± 82.518 (313)	113.23 ± 73.174 (52)	136.67 ± 83.840 (261)
	Lemborexant 10 mg/day	Observed value[a)]	136.83 ± 87.391 (311)	99.03 ± 81.932 (53)	144.59 ± 86.595 (258)
Day 7	Placebo	Changes[b,c)]	−4.770 ± 2.735	−2.020 ± 5.607	−5.853 ± 2.947
	Lemborexant 5 mg/day	Changes[b,c)]	−19.098 ± 2.750	−6.516 ± 5.769	−22.277 ± 2.949
		Intergroup difference in changes[c,d)]	−14.328 [−21.411, −7.245]	−4.497 [−19.757, 10.764]	−16.423 [−24.368, −8.478]
	Lemborexant 10 mg/day	Changes[b,c)]	−21.489 ± 2.748	−11.856 ± 5.668	−24.186 ± 2.960
		Intergroup difference in changes[c,d)]	−16.720 [−23.813, −9.626]	−9.836 [−25.064, 5.392]	−18.332 [−26.291, −10.374]
Month 1	Placebo	Changes[b,c)]	−17.178 ± 3.097	−17.425 ± 6.128	−17.912 ± 3.378
	Lemborexant 5 mg/day	Changes[b,c)]	−22.692 ± 3.080	−9.749 ± 6.292	−26.027 ± 3.363
		Intergroup difference in changes[c,d)]	−5.514 [−13.568, 2.540]	7.675 [−9.089, 24.439]	−8.115 [−17.264, 1.034]
	Lemborexant 10 mg/day	Changes[b,c)]	−24.183 ± 3.068	−17.331 ± 6.188	−27.454 ± 3.407
		Intergroup difference in changes[c,d)]	−7.005 [−15.098, 1.088]	0.094 [−16.635, 16.823]	−9.542 [−18.749, −0.336]
Month 3	Placebo	Changes[b,c)]	−26.828 ± 3.319	−23.486 ± 5.723	−28.606 ± 3.847
	Lemborexant 5 mg/day	Changes[b,c)]	−40.253 ± 3.354	−36.508 ± 5.824	−43.137 ± 3.887
		Intergroup difference in changes[c,d)]	−13.424 [−22.218, −4.631]	−13.022 [−28.510, 2.466]	−14.531 [−25.085, −3.977]
	Lemborexant 10 mg/day	Changes[b,c)]	−36.907 ± 3.441	−27.452 ± 5.715	−41.722 ± 3.960
		Intergroup difference in changes[c,d)]	−10.079 [−19.053, −1.104]	−3.966 [−19.414, 11.481]	−13.115 [−23.772, −2.459]
Month 6	Placebo	Changes[b,c)]	−29.276 ± 3.605	−22.337 ± 6.456	−33.357 ± 4.279
	Lemborexant 5 mg/day	Changes[b,c)]	−46.750 ± 3.658	−41.986 ± 6.646	−50.787 ± 4.304
		Intergroup difference in changes[c,d)]	−17.474 [−27.306, −7.643]	−19.648 [−37.397, −1.900]	−17.430 [−29.186, −5.674]
	Lemborexant 10 mg/day	Changes[b,c)]	−41.947 ± 3.694	−26.156 ± 6.539	−47.932 ± 4.426
		Intergroup difference in changes[c,d)]	−12.671 [−22.378, −2.964]	−3.819 [−21.517, 13.879]	−14.574 [−26.502, −2.647]

a) Unit, minute. Mean ± standard deviation (number of subjects evaluated)
b) Unit, minute. Least-squares mean ± standard error
c) Based on an analysis by the MMRM (using the unstructured covariance matrix) adjusted for age group (<65/≥65 years of age), region (for the entire study population only), baseline value, treatment group, evaluation point, and interaction between treatment group and evaluation point. For the entire study population, missing values were imputed by the multiple imputation assuming the MNAR using the CCMV. For the Japanese and non-Japanese subpopulations, missing values were not imputed assuming the MAR.
d) Difference from the placebo group [95% CI]

- The occurrence of adverse events in the entire study population, Japanese subpopulation, and non-Japanese subpopulation in Period 1 of Study E2006-G000-303 is shown in Table 48. No distinct differences in the safety of lemborexant are observed between Japanese and non-Japanese subpopulations.

Table 48. Occurrence of adverse events in Japanese and non-Japanese subpopulations (Study E2006-G000-303, Period 1)

	Entire study population			Japanese subpopulation			Non-Japanese subpopulation		
	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day
Number of subjects evaluated	319	314	314	54	53	54	265	261	260
Adverse events	200 (62.7)	192 (61.1)	187 (59.6)	26 (48.1)	13 (24.5)	26 (48.1)	174 (65.7)	179 (68.6)	161 (61.9)
Adverse events resulting in death	0	0	0	0	0	0	0	0	0
Serious adverse events	5 (1.6)	7 (2.2)	9 (2.9)	0	0	0	5 (1.9)	7 (2.7)	9 (3.5)
Adverse events leading to treatment discontinuation	12 (3.8)	13 (4.1)	26 (8.3)	0	0	2 (3.7)	12 (4.5)	13 (5.0)	24 (9.2)
Main adverse events									
Somnolence	5 (1.6)	27 (8.6)	41 (13.1)	0	4 (7.5)	6 (11.1)	5 (1.9)	23 (8.8)	35 (13.5)
Nasopharyngitis	40 (12.5)	30 (9.6)	29 (9.2)	11 (20.4)	7 (13.2)	11 (20.4)	29 (10.9)	23 (8.8)	18 (6.9)
Headache	21 (6.6)	28 (8.9)	21 (6.7)	1 (1.9)	1 (1.9)	1 (1.9)	20 (7.5)	27 (10.3)	20 (7.7)
Influenza	15 (4.7)	15 (4.8)	16 (5.1)	3 (5.6)	1 (1.9)	0	12 (4.5)	14 (5.4)	16 (6.2)
Upper respiratory tract infection	10 (3.1)	13 (4.1)	11 (3.5)	0	0	0	10 (3.8)	13 (5.0)	11 (4.2)
Fatigue	1 (0.3)	12 (3.8)	11 (3.5)	0	0	0	1 (0.4)	12 (4.6)	11 (4.2)
Back pain	8 (2.5)	12 (3.8)	9 (2.9)	2 (3.7)	0	0	6 (2.3)	12 (4.6)	9 (3.5)
Arthralgia	9 (2.8)	14 (4.5)	3 (1.0)	0	0	0	9 (3.4)	14 (5.4)	3 (1.2)
Urinary tract infection	7 (2.2)	4 (1.3)	9 (2.9)	0	0	0	7 (2.6)	4 (1.5)	9 (3.5)
Gastroenteritis	4 (1.3)	5 (1.6)	7 (2.2)	1 (1.9)	0	0	3 (1.1)	5 (1.9)	7 (2.7)
Nausea	3 (0.9)	8 (2.5)	4 (1.3)	2 (3.7)	0	0	1 (0.4)	8 (3.1)	4 (1.5)
Abnormal dreams	6 (1.9)	7 (2.2)	4 (1.3)	0	0	0	6 (2.3)	7 (2.7)	4 (1.5)
Nightmare	1 (0.3)	4 (1.3)	7 (2.2)	0	0	1 (1.9)	1 (0.4)	4 (1.5)	6 (2.3)
Fall	10 (3.1)	5 (1.6)	5 (1.6)	0	0	0	10 (3.8)	5 (1.9)	5 (1.9)
Sinusitis	8 (2.5)	4 (1.3)	3 (1.0)	0	0	0	8 (3.0)	4 (1.5)	3 (1.2)

Number of subjects with events (incidence [%])

- The above findings suggest that the efficacy and safety of lemborexant can be evaluated on the basis of the data of the overall study population in Study E2006-G000-303 conducted as a global study.

PMDA accepted the above applicant's explanation.

7.R.2 Efficacy

7.R.2.1 Efficacy of lemborexant for difficulty with sleep onset

PMDA asked the applicant to explain the efficacy of lemborexant for difficulty with sleep onset.

The applicant's explanation:

- The clinical practice guideline of the American Academy of Sleep Medicine states that the clinical significance thresholds for changes in sleep latency are reduction in PSG sleep latency by ≥10 minutes and reduction in the subjective sleep latency by ≥20 minutes as compared with placebo (*J Clin Sleep Med.* 2017;13:307-49).
- In the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303), statistically significant differences were observed in the primary endpoint, i.e., changes from baseline in the subjective sleep latency at Month 6 between the lemborexant 5 and 10 mg/day groups and the placebo group (Table 38). Table 49 shows the percentage of subjects achieving clinical improvement, who were defined as "subjects with baseline subjective sleep latency of >30 minutes and that of ≤20 minutes at each evaluation point." The results demonstrate clinical improvement observed from the beginning of the treatment with lemborexant as compared with placebo.

Table 49. Percentage of subjects with clinical improvement in subjective sleep latency at each evaluation point (Study E2006-G000-303, FAS)

		Number of subjects evaluated	Number of applicable subjects (Percentage %) [a)]	Difference from the placebo group [95% CI]
Day 7	Placebo	254	13 (5.1)	
	Lemborexant 5 mg/day	250	31 (12.4)	7.28 [2.39, 12.17]
	Lemborexant 10 mg/day	249	28 (11.2)	6.25 [1.50, 10.99]
Month 1	Placebo	254	26 (10.2)	
	Lemborexant 5 mg/day	250	40 (16.0)	5.71 [−0.19, 11.61]
	Lemborexant 10 mg/day	249	54 (21.7)	11.49 [5.13, 17.85]
Month 3	Placebo	254	45 (17.7)	
	Lemborexant 5 mg/day	250	69 (27.6)	9.72 [2.48, 16.96]
	Lemborexant 10 mg/day	249	74 (29.7)	12.18 [4.81, 19.56]
Month 6	Placebo	254	45 (17.7)	
	Lemborexant 5 mg/day	250	78 (31.2)	13.67 [6.24, 21.10]
	Lemborexant 10 mg/day	249	75 (30.1)	12.53 [5.20, 19.86]

a) Subjects with missing evaluation at each point due to early discontinuation, etc. were regarded as not improved.

- As shown in Table 45 "changes over time in subjective sleep latency in Study E2006-G000-303," subjective sleep latency decreased even early in the treatment course and improved at all evaluation points in the lemborexant 5 and 10 mg/day groups as compared with the placebo group.
- For changes from baseline in PSG sleep latency on Days 29 and 30, the primary endpoint in the foreign phase III study (CTD 5.3.5.1.3: Study E2006-G000-304), statistically significant differences were observed between the lemborexant 5 and 10 mg/day groups and the placebo group (Table 42). The difference [95% CI] in the least-squares means of the changes relative to the placebo group was −10.52 [−14.69, −6.35] minutes for the lemborexant 5 mg/day group and −13.23 [−17.41, −9.06] minutes for the lemborexant 10 mg/day group, showing improvement of ≥10 minutes, which is the clinical significance threshold for changes recommended by the clinical practice guideline of the American Academy of Sleep Medicine (*J Clin Sleep Med*. 2017;13:307-49).
- The above findings indicate that the efficacy of lemborexant has been demonstrated to be clinically significant for both subjective and objective assessments of difficulty with sleep onset. When Study E2006-G000-303 was being planned, the efficacy and safety of lemborexant were planned to be evaluated objectively by PSG at Month 1 of treatment in another global phase III study in subjects including Japanese subpopulation. However, the planned phase III study with PSG was canceled when the Study E2006-G000-303 was underway, and at that point the participation in the foreign phase III study, which employed the PSG-based objective evaluation, was difficult for Japanese patients (CTD 5.3.5.2.1, Study E2006-G000-304). As a result, objective evaluation of difficulty with sleep onset was not possible in Japanese patients.

PMDA accepted the above applicant's explanation.

7.R.2.2 Efficacy for difficulty with sleep maintenance

PMDA asked the applicant to explain the efficacy of lemborexant in difficulty with sleep maintenance.

The applicant's explanation:

- According to the clinical practice guideline of the American Academy of Sleep Medicine, improvement in the sleep efficiency of ≥5% or 10% and wake after sleep onset of ≥20 or 30 minutes relative to those

with placebo according to subjective parameters and PSG-based objective parameters are the clinical significance threshold for these changes (*J Clin Sleep Med.* 2017;13:307-49).

- Changes from baseline in the subjective sleep efficiency and subjective wake after sleep onset at Month 6 in the FAS were specified as important secondary endpoints in the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303). These changes from baseline improved with both lemborexant 5 and 10 mg/day as compared with placebo (Table 39). Changes over time from baseline in the subjective sleep efficiency and subjective wake after sleep onset at each evaluation point in Study E2006-G000-303 are shown in Tables 46 and 47. The subjective sleep efficiency and subjective wake after sleep onset began to improve early in the treatment course and showed improvement at all evaluation points in both lemborexant 5 and 10 mg/day groups as compared with the placebo group.
- Table 50 shows the percentage of subjects who had clinical improvement defined as "the subjective wake after sleep onset of ≥60 minutes at baseline and the mean of ≤60 minutes for the subjective wake after sleep onset at an evaluation point with a decrease of >10 minutes from baseline."

Table 50. Percentage of subjects with clinical improvement in difficulty with sleep maintenance at evaluation points (Study E2006-G000-303, FAS)

		Number of subjects evaluated	Number of applicable subjects (Percentage %) [a)]	Difference from the placebo group [95% CI]
Day 7	Placebo	250	31 (12.4)	
	Lemborexant 5 mg/day	263	46 (17.5)	5.15 [−1.04, 11.33]
	Lemborexant 10 mg/day	257	45 (17.5)	5.04 [−1.14, 11.22]
Month 1	Placebo	250	47 (18.8)	
	Lemborexant 5 mg/day	263	59 (22.4)	3.67 [−3.39, 10.73]
	Lemborexant 10 mg/day	257	60 (23.3)	4.52 [−2.61, 11.64]
Month 3	Placebo	250	50 (20.0)	
	Lemborexant 5 mg/day	263	84 (31.9)	11.95 [4.38, 19.53]
	Lemborexant 10 mg/day	257	70 (27.2)	7.37 [0.01, 14.72]
Month 6	Placebo	250	51 (20.4)	
	Lemborexant 5 mg/day	263	92 (35.0)	14.65 [6.97, 22.33]
	Lemborexant 10 mg/day	257	77 (30.0)	9.82 [2.29, 17.35]

a) Subjects with missing evaluation data at each point due to early discontinuation, etc. were regarded as not improved.

- In the foreign phase III study (CTD 5.3.5.1.3, Study E2006-G000-304), the difference [95% CI] in the least-squares means of changes from baseline in wake after sleep onset assessed by PSG at the end of treatment at Month 1 relative to the placebo group was −23.96 [−29.98, −17.95] minutes in the lemborexant 5 mg/day group and −25.35 [−31.36, −19.34] minutes in the lemborexant 10 mg/day group, showing improvement in both the lemborexant 5 and 10 mg/day groups as compared with the placebo group. The difference from the placebo group was >20 minutes, which is defined as the clinical significance threshold for the changes in wake after sleep onset in the clinical practice guideline of the American Academy of Sleep Medicine (*J Clin Sleep Med.* 2017;13:307-49).
- The above findings indicate that the clinically significant efficacy of lemborexant has been demonstrated in both subjective and objective assessments of difficulty with sleep maintenance. At the time of designing of Study E2006-G000-303, a global phase III study was planned to be conducted in subjects including Japanese subpopulation to objectively evaluate the efficacy and safety of lemborexant in difficulty with sleep maintenance. However, the planned global phase III study was canceled when Study E2006-G000-303 was underway. Therefore, objective evaluation of difficulty with sleep maintenance could not be objectively evaluated in Japanese patients [see Section 7.R.2.1].

PMDA accepted the above applicant's explanation.

7.R.2.3 Effects of lemborexant on daytime functioning

PMDA asked the applicant to explain the effects of lemborexant on daytime functioning because the Guidelines for the Clinical Evaluation of Hypnotic Drugs (PFSB/ELD Notification No. 1213-1, dated December 13, 2011) recommend that the efficacy profiles of an investigational drug should be evaluated for next-day physical and psychiatric dysfunction.

The applicant's explanation:

- Changes from baseline in the Insomnia Severity Index (ISI) daily functioning score (Items 4 to 7)[40] in the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303) and the foreign phase III study (CTD 5.3.5.1.3, Study E2006-G000-304) are shown in Table 51, indicating improvement in both the lemborexant 5 and 10 mg/day groups as compared with the placebo group.

Table 51. Changes from baseline in ISI daily functioning scores (Items 4 to 7) (Studies E2006-G000-303 and Study E2006-G000-304, FAS)

Evaluation point	Placebo	Lemborexant 5 mg/day		Lemborexant 10 mg/day	
	Change	Change	Difference from placebo [a]	Change	Difference from placebo [a]
Study E2006-G000-303					
Month 1	−3.1 ± 3.41 (296)	−4.1 ± 3.66 (300)	−0.71 [−1.27, −0.15]	−4.2 ± 4.8 (286)	−0.94 [−1.51, −0.38]
Month 3	−3.7 ± 3.55 (283)	−5.2 ± 3.88 (274)	−1.16 [−1.75, −0.57]	−5.2 ± 4.05 (259)	−1.36 [−1.96, −0.76]
Month 6	−4.3 ± 3.66 (257)	−6.0 ± 3.76 (258)	−1.30 [−1.90, −0.71]	−5.7 ± 4.00 (234)	−1.32 [−1.92, −0.71]
Study E2006-G000-304					
Month 1	−3.9 ± 3.56 (198)	−4.8 ± 3.59 (257)	−1.10 [−1.73, −0.47]	−4.8 ± 3.74 (253)	−1.08 [−1.71, −0.46]

Mean ± standard deviation. (Number of subjects evaluated)

a) Difference from the placebo group [95 %CI]: In Study E2006-G000-303, based on the MMRM (using the unstructured covariance matrix) adjusted for age group (<65/≥65 years of age), region, baseline value, treatment group, evaluation point, and interaction between treatment group and evaluation point. Missing values were not imputed assuming the missing at random (MAR). In Study E2006-G000-304, based on the model of analysis of covariance with age group (<65/≥65 years of age), region, and treatment group as factors and baseline value as a covariate.

- Subjective sleepiness/wake levels were assessed based on the sleep diary to evaluate carryover effect subjectively.[41] Changes from baseline in the subjective sleepiness/wake levels are shown in Table 52, indicating improvement in the sleepiness/wake levels in the lemborexant 5 and 10 mg/day groups as compared with the placebo group.

40) The ISI is a self-report questionnaire to assess the nature, severity, and impact of insomnia: severity of difficulty with sleep onset comprising 7 items to be assessed, i.e., sleep maintenance, early morning awakening, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties (*Sleep Med.* 2001;2:297-307). In addition to the overall ISI score with the maximum total score of 28 (0 to 4 points for each item), the total score of Items 4 to 7 is used as the ISI daily functioning score.

41) A 9-point scale (1, "very bad" to 9, "very good")

Table 52. Changes from baseline in subjective sleepiness/wake levels based on the sleep diary (Studies E2006-G000-303 and E2006-G000-304, FAS)

Evaluation point	Placebo	Lemborexant 5 mg/day		Lemborexant 10 mg/day	
	Change	Change	Difference from placebo [a)]	Change	Difference from placebo [a)]
Study E2006-G000-303					
First 7 days	0.15 ± 0.991 (314)	0.36 ± 0.964 (310)	0.205 [0.057, 0.353]	0.33 ± 1.018 (310)	0.171 [0.023, 0.320]
Month 1	0.44 ± 1.233 (300)	0.53 ± 1.172 (298)	0.077 [−0.107, 0.261]	0.55 ± 1.298 (297)	0.073 [−0.111, 0.258]
Month 3	0.62 ± 1.366 (280)	0.74 ± 1.325 (268)	0.074 [−0.141, 0.289]	0.90 ± 1.452 (264)	0.255 [0.039, 0.471]
Month 6	0.79 ± 1.392 (249)	0.98 ± 1.463 (245)	0.144 [−0.089, 0.378]	1.05 ± 1.524 (229)	0.261 [0.026, 0.497]
Study E2006-G000-304					
First 7 days	0.51 ± 1.156 (202)	0.78 ± 1.366 (261)	0.27 [0.05, 0.48]	0.81 ± 1.300 (266)	0.25 [0.04, 0.47]
First 7 days	0.85 ± 1.409 (196)	1.24 ± 1.497 (253)	0.39 [0.13, 0.64]	1.18 ± 1.534 (258)	0.30 [0.05, 0.56]

Mean ± standard deviation (number of subjects evaluated)

a) Difference from the placebo group [95% CI]: Based on the MMRM (using the unstructured covariance matrix) adjusted for age group (<65/≥65 years of age), region, baseline value, treatment group, evaluation point, and interaction between treatment group and evaluation point. Missing values were not imputed assuming the MAR.

- The above findings indicate that lemborexant is effective in daytime functioning in patients with insomnia as well.

PMDA accepted the applicant's explanation described above. However, the effects of lemborexant on daytime functioning should be evaluated from a viewpoint safety, not only efficacy, and be further discussed in Section 7.R.3.2.

7.R.2.4 Effects on sleep architecture

PMDA asked the applicant to explain the effects of lemborexant on sleep architecture, in light of the importance of investigating the effect of study drugs on sleep structure from both efficacy and safety viewpoints, which is mentioned in the Guidelines for the Clinical Evaluation of Hypnotic Drugs (PFSB/ELD Notification No. 1213-1, dated December 13, 2011).

The applicant's explanation:

- Table 53 shows the percentage of the duration of each sleep stage in the total sleep time and the changes from baseline for each sleep stage in the foreign phase III study (CTD 5.3.5.1.3, Study E2006-G000-304). In the lemborexant groups, the percentages in the non-REM sleep stages decreased and the percentages of REM sleep tended to increase as compared with the placebo group. Since they did not markedly differ from the reported percentages of REM sleep in healthy adults (mean ± standard deviation; 18.2% ± 5.2% to 21.0% ± 3.9%; *Sleep.* 2009;32:139-49), the differences from the placebo group were thought to be clinically insignificant.

Table 53. Percentage of the duration of each sleep stage to total sleep time and changes from baseline for each sleep stage (Study E2006-G000-304, FAS)

	Placebo		Lemborexant 5 mg/day		Lemborexant 10 mg/day		Zolpidem ER	
	Percentage[a)]	Change[b)]	Percentage[a)]	Change[b)]	Percentage[a)]	Change[b)]	Percentage[a)]	Change[b)]
Number of subjects evaluated[c)]	208/208/200		266/266/260		269/269/260		263/263/251	
Non-REM sleep Stage 1 (%)								
Baseline	11.02 ± 6.060		10.84 ± 5.996		12.36 ± 6.465		10.85 ± 5.843	
Start of treatment[d)]	11.03 ± 6.500	−0.34 ± 0.282	10.05 ± 5.806	−1.18 ± 0.253	10.61 ± 5.473	−1.66 ± 0.253	9.27 ± 4.779	−1.98 ± 0.256
End of treatment[e)]	10.49 ± 6.134	−0.84 ± 0.306	10.72 ± 5.527	−0.52 ± 0.272	11.92 ± 6.551	−0.33 ± 0.273	9.78 ± 4.935	−1.56 ± 0.277
Non-REM sleep Stage 2 (%)								
Baseline	57.18 ± 9.335		56.51 ± 8.752		57.47 ± 8.733		57.43 ± 9.231	
Start of treatment[d)]	57.02 ± 9.316	0.19 ± 0.465	56.50 ± 8.133	0.07 ± 0.416	56.28 ± 7.214	−0.75 ± 0.416	59.90 ± 9.717	2.97 ± 0.421
End of treatment[e)]	58.40 ± 9.282	1.58 ± 0.487	57.77 ± 7.768	1.20 ± 0.433	57.30 ± 7.176	0.24 ± 0.434	61.00 ± 9.377	4.12 ± 0.441
Non-REM sleep Stage 3 (%)								
Baseline	12.21 ± 8.128		13.53 ± 9.147		11.45 ± 7.965		12.10 ± 8.122	
Start of treatment[d)]	12.09 ± 8.145	−0.11 ± 0.376	12.53 ± 8.359	−0.65 ± 0.337	10.17 ± 7.361	−1.45 ± 0.337	12.32 ± 9.169	0.10 ± 0.340
End of treatment[e)]	11.86 ± 8.670	−0.32 ± 0.388	11.76 ± 7.827	−1.34 ± 0.346	9.71 ± 6.783	−1.90 ± 0.346	10.47 ± 8.465	−1.80 ± 0.351
REM sleep (%)								
Baseline	19.59 ± 5.222		19.12 ± 5.515		18.72 ± 5.366		19.61 ± 6.015	
Start of treatment[d)]	19.86 ± 5.362	0.35 ± 0.349	20.92 ± 5.508	1.65 ± 0.312	22.94 ± 5.380	3.88 ± 0.312	18.52 ± 5.814	−0.97 ± 0.316
End of treatment[e)]	19.25 ± 5.245	−0.33 ± 0.357	19.75 ± 5.180	0.55 ± 0.317	21.08 ± 5.674	2.02 ± 0.318	18.76 ± 5.328	−0.65 ± 0.323

a) Mean ± standard deviation
b) Change from baseline (least-squares mean ± standard error)
Based on an analysis by the MMRM (using the unstructured covariance matrix) adjusted for age group (<65/≥65 years of age), region, baseline value, treatment group, evaluation point, and interaction between treatment group and evaluation point. Missing values were not imputed assuming the MAR.
c) Baseline/start of treatment[d)]/end of treatment[e)]
d) Mean of values on Days 1 and 2
e) Mean of values on Days 29 and 30

- Table 54 shows the percentage of subjects in whom the change from baseline in REM sleep latency and the REM sleep latency was 15 minutes.[42)] As compared with the placebo group, the REM latency in the lemborexant groups was reduced, and the percentage of subjects with the REM sleep latency of <15 minutes tended to be higher in the lemborexant groups.

Table 54. Changes from baseline in REM sleep latency and percentage of subjects with REM sleep latency of <15 minutes (Study E2006-G000-304, FAS)

	Changes in REM sleep latency[a)]				Percentage of subjects with the REM sleep latency of <15 minutes[b)]			
	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER
Baseline					0.5 (1/208)	0.8 (2/266)	1.1 (3/269)	0.4 (1/261)
Start of treatment[c)]	−6.85 ± 54.490 (208)	−42.55 ± 53.896 (266)	−49.57 ± 52.941 (269)	0.22 ± 54.155 (261)	1.4 (3/208)	8.3 (22/266)	11.9 (32/269)	0.4 (1/263)
End of treatment[d)]	−7.65 ± 62.296 (200)	−30.68 ± 55.663 (260)	−37.70 ± 56.173 (259)	−3.99 ± 56.389 (249)	1.5 (3/200)	3.1 (8/260)	3.9 (10/259)	1.2 (3/251)

a) Unit: minute, mean ± standard deviation (number of subjects evaluated)
b) Percentage (%) (number of subjects thereof /number of subjects evaluated)
c) Mean of values on Days 1 and 2
d) Mean of values on Days 29 and 30

42) Diagnostic criteria for narcolepsy. Narcolepsy is confirmed when the following are both observed with the next-day multiple sleep latency test after PSG at night (bedtime of ≥6 hours): "mean daytime sleep latency of ≤8 minutes" and "REM sleep after sleep onset (REM sleep within 15 minutes after sleep onset) in ≥2 of 5 naps."

- The occurrence of adverse events in subjects with a REM sleep latency of <15 minutes or ≥15 minutes is shown in Table 55. There was no marked differences in safety between the subject groups with the mentioned REM sleep latency.

Table 55. Occurrence of adverse events in subjects with REM sleep latency of <15 minutes or ≥15 minutes (Study E2006-G000-304, safety analysis set)

	Subjects with REM sleep latency of 15 minutes				Subjects with REM sleep latency of ≥15 minutes			
	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER
Number of subjects evaluated	6	26	38	4	203	240	230	259
Adverse events	1 (16.7)	9 (34.6)	10 (26.3)	2 (50.0)	52 (25.6)	65 (27.1)	72 (31.3)	91 (35.1)
Serious adverse events	0	0	0	0	0	2 (0.8)	0	4 (1.5)
Adverse events leading to treatment discontinuation	0	0	1 (2.6)	1 (25.0)	2 (1.0)	2 (0.8)	2 (0.9)	6 (2.3)
Main adverse events								
Headache	1 (16.7)	3 (11.5)	5 (13.2)	0	12 (5.9)	14 (5.8)	8 (3.5)	14 (5.4)
Somnolence	0	2 (7.7)	3 (7.9)	0	4 (2.0)	9 (3.8)	16 (7.0)	4 (1.5)
Fatigue	0	1 (3.8)	1 (2.6)	0	0	1 (0.4)	0	4 (1.5)
Fall	0	2 (7.7)	0	0	0	2 (0.8)	0	0
Narcolepsy-related adverse events								
Sleep paralysis	0	0	1 (2.6)	0	0	1 (0.4)	2 (0.9)	0

Number of subjects with events (incidence [%])

- As discussed above, the REM sleep latency in the lemborexant groups was reduced as compared with the placebo group, and the percentage of subjects with a REM sleep latency of <15 minutes tended to be higher in the lemborexant groups than in the placebo group. However, no marked differences in safety were identified between subject groups with a REM sleep latency of <15 minutes or ≥15 minutes. Therefore, reduced REM sleep latency in association with lemborexant will not pose a clinically significant concern.

PMDA's view:

- In light of the percentage of each sleep stage observed in Study E2006-G000-304 that did not markedly differ from that of REM sleep reported in healthy adults, there are no marked problems in the applicant's view that the reduced REM sleep latency with lemborexant is unlikely to be of clinical significance.
- However, there were limited number of subjects experiencing reduced REM sleep latency in Study E2006-G000-304, precluding a definitive conclusion on the effects of the reduced REM sleep latency caused by lemborexant. Narcolepsy and associated conditions in the use of lemborexant should be further discussed in Section 7.R.3.1, because reduced REM sleep latency is observed in patients with in narcolepsy and lemborexant may theoretically induce narcolepsy.

7.R.2.5 Patients with secondary insomnia

The Guidelines for the Clinical Evaluation of Hypnotic Drugs (PFSB/ELD Notification No. 1213-1, dated December 13, 2011) state that "In patients with secondary insomnia, the possibility cannot be ruled out that their primary disease may affect efficacy and safety evaluation. In general, therefore, exploratory and confirmatory studies should target patients with primary insomnia, and when patients with secondary insomnia are to be targeted, another study should be designed for them, separately from those with primary insomnia."

In light of the fact that the global phase III study (CTD 5.3.5.1.1, 5.3.5.1.2: Study E2006-G000-303) included both patients with primary insomnia and those with secondary insomnia, PMDA asked the applicant to explain the efficacy and safety of lemborexant in patients with primary insomnia or secondary insomnia individually.

The applicant's explanation:

- Both patients with primary insomnia and those with secondary insomnia were included in Study E2006-G000-303 for the following reason. Before the publication of the DSM-IV, "primary insomnia" was differentiated from "secondary insomnia (sleeping disorders related to diseases comorbid with insomnia)." However, with the revision to the DSM-5 (2013) and ICSD-3 (2014), they are not differentiated from each other and are proposed to be called insomnia disorder or insomnia. When Study E2006-G000-303 was underway, the DSM-5 was already used as the diagnostic criteria for insomnia. The DSM-5 states that insomnia disorder is diagnosed without a distinction between primary and secondary insomnia. Furthermore, according to the DSM-5, even if insomnia is comorbid with other diseases, it is unnecessary to elucidate the causal relationship between the 2 clinical conditions, and both conditions are the therapeutic targets. Therefore, Study E2006-G000-303 was conducted in both patients with primary insomnia and patients with secondary insomnia.
- Tables 56 and 57 show the results of a subgroup analysis of changes in the subjective sleep latency, subjective sleep efficiency, and subjective wake after sleep onset by the comorbidities (depression, anxiety disorder, gastroesophageal reflux, migraine, hypertension, diabetes mellitus, and renal impairment) in Study E2006-G000-303. There were no marked differences in the efficacy between subjects with and without respective comorbidities.

Table 56. Changes from baseline in subjective sleep latency by comorbidity (Study E2006-G000-303 Period 1, FAS)

	Treatment	Subjective sleep latency		Change[a, b)]	Ratio to the placebo group [95% CI] [b, c)]
		Baseline	Month 6		
With comorbidity	Placebo	63.95 ± 43.914 (144) 45.98 51.43 (33.57,77.50)	45.90 ± 45.786 (120) 27.66 31.14 (16.14, 60.00)	0.648 [0.564, 0.744]	
	Lemborexant 5 mg/day	65.14 ± 44.103 (146) 45.83 59.29 (34.29, 77.86)	32.57 ± 29.780 (110) 20.19 23.93 (13.57, 38.57)	0.458 [0.397, 0.529]	0.707 [0.583, 0.858]
	Lemborexant 10 mg/day	64.50 ± 44.447 (174) 44.73 59.64 (32.14, 84.29)	33.40 ± 32.524 (127) 20.39 22.86 (12.86, 40.71)	0.450 [0.394, 0.514]	0.695 [0.576, 0.837]
Without comorbidity	Placebo	64.10 ± 46.394 (172) 44.17 58.57 (34.29, 79.50)	47.00 ± 44.456 (131) 27.20 35.71 (16.80, 60.00)	0.587 [0.501, 0.687]	
	Lemborexant 5 mg/day	59.62 ± 46.976 (168) 40.63 51.13 (32.86, 73.29)	27.02 ± 23.735 (137) 17.45 20.00 (11.71, 31.43)	0.441 [0.376, 0.517]	0.751 [0.604, 0.934]
	Lemborexant 10 mg/day	65.57 ± 43.631 (138) 45.45 54.23 (35.71, 86.43)	32.70 ± 31.876 (103) 18.14 24.14 (11.57, 39.43)	0.406 [0.341, 0.484]	0.692 [0.550, 0.872]

Unit, minute. Upper row, mean ± standard deviation (number of subjects evaluated); middle row, geometric mean; lower row, median (quartile point [Q1, Q3])

a) Least-squares ratio of geometric means of the sleep latency at each point (Month 6 /baseline) [95% CI]

b) Based on an analysis of log-transformed sleep latency by the MMRM (using the unstructured covariance matrix) adjusted for age group (<65/≥65 years of age), region, baseline value, treatment group, evaluation point, and interaction between treatment group and evaluation point. Missing values were not imputed assuming the MAR.

c) Intergroup ratio of changes (lemborexant/placebo)

Table 57. Changes from baseline in subjective sleep efficiency and subjective wake after sleep onset by comorbidity (Study E2006-G000-303 Period 1, FAS)

	Group	Subjective sleep efficiency		Change[a,b)]	Difference from placebo [95% CI][b,c)]
		Baseline	Month 6		
With comorbidity	Placebo	62.98 ± 16.968 (139)	73.83 ± 18.463 (117)	10.370 ± 1.255	
	Lemborexant 5 mg/day	61.52 ± 18.999 (140)	77.83 ± 15.517 (108)	14.231 ± 1.302	3.861 [0.467, 7.254]
	Lemborexant 10 mg/day	62.82 ± 16.951 (165)	76.15 ± 17.982 (126)	14.030 ± 1.220	3.660 [0.373, 6.947]
Without comorbidity	Placebo	59.98 ± 18.464 (168)	69.22 ± 17.971 (130)	9.806 ± 1.213	
	Lemborexant 5 mg/day	64.54 ± 17.478 (162)	79.12 ± 16.830 (137)	14.276 ± 1.223	4.470 [1.253, 7.686]
	Lemborexant 10 mg/day	61.06 ± 17.622 (134)	76.99 ± 18.072 (102)	15.263 ± 1.334	5.457 [2.070, 8.844]
	Group	Subjective wake after sleep onset		Changes[a,b)]	Difference from placebo [95% CI][b,c)]
		Baseline	Month 6		
With comorbidity	Placebo	126.15 ± 79.513 (143)	99.36 ± 89.974 (120)	−31.063 ± 5.307	
	Lemborexant 5 mg/day	138.81 ± 84.739 (146)	85.82 ± 76.931 (110)	−47.799 ± 5.454	−16.736 [−31.067, −2.406]
	Lemborexant 10 mg/day	134.75 ± 84.421 (173)	89.22 ± 77.224 (127)	−43.988 ± 5.081	−12.925 [−26.783, 0.933]
Without comorbidity	Placebo	137.79 ± 80.615 (171)	106.63 ± 74.751 (131)	−30.211 ± 5.469	
	Lemborexant 5 mg/day	127.49 ± 80.410 (167)	78.56 ± 76.828 (137)	−48.392 ± 5.509	−18.181 [−32.710, −3.652]
	Lemborexant 10 mg/day	139.44 ± 91.221 (138)	82.85 ± 78.734 (102)	−41.406 ± 6.026	−11.195 [−26.547, 4.157]

Unit, minute. Mean ± standard deviation (number of subjects evaluated)
a) Least-squares mean ± standard error
b) Based on an analysis with the MMRM (using the unstructured covariance matrix) adjusted for age group (<65/≥65 years of age), region, baseline value, group, evaluation point, and interaction between group and evaluation point. Missing values were not imputed assuming the MAR.
c) Intergroup difference in changes (lemborexant − placebo)

- Subjective sleep latency, subjective sleep efficiency, and subjective wake after sleep onset were evaluated by presence or absence of these comorbidities. No marked differences were observed by presence or absence of these comorbidities.
- The occurrence of adverse events by comorbidity in Study E2006-G000-303 is shown in Table 58, indicating no clear differences among the groups. Even in Study E2006-G000-303 (Periods 1 and 2), the incidences of adverse events and serious adverse events were slightly higher in subjects with comorbidity than in subjects without comorbidity. In the subgroup of patients with comorbidity, the incidence of somnolence tended to be higher in subjects receiving lemborexant 10 mg/day than in those receiving lemborexant 5 mg/day, but no obvious differences were observed in the incidence of other adverse events by dose.

Table 58. Occurrence of adverse events by comorbidity (Study E2006-G000-303, safety analysis set)

	Period 1						Periods 1 and 2			
	Subjects with comorbidity			Subjects without comorbidity			Subjects with comorbidity		Subjects without comorbidity	
	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Lemborexant 5 mg/day	Lemborexant 10 mg/day
Number of subjects evaluated	147	144	175	172	170	139	207	234	240	203
Adverse events	98 (66.7)	103 (71.5)	111 (63.4)	102 (59.3)	89 (52.4)	76 (54.7)	158 (76.3)	164 (70.1)	141 (58.8)	125 (61.6)
Serious adverse events	4 (2.7)	4 (2.8)	8 (4.6)	1 (0.6)	3 (1.8)	1 (0.7)	12 (5.8)	14 (6.0)	6 (2.5)	2 (1.0)
Adverse events leading to treatment discontinuation	4 (2.7)	6 (4.2)	14 (8.0)	8 (4.7)	7 (4.1)	12 (8.6)	10 (4.8)	26 (11.1)	13 (5.4)	15 (7.4)
Major adverse events										
Somnolence	4 (2.7)	9 (6.3)	25 (14.3)	1 (0.6)	18 (10.6)	16 (11.5)	15 (7.2)	33 (14.1)	23 (9.6)	27 (13.3)
Nasopharyngitis	14 (9.5)	11 (7.6)	15 (8.6)	26 (15.1)	19 (11.2)	14 (10.1)	23 (11.1)	24 (10.3)	28 (11.7)	24 (11.8)
Headache	12 (8.2)	13 (9.0)	12 (6.9)	9 (5.2)	15 (8.8)	9 (6.5)	21 (10.1)	21 (9.0)	22 (9.2)	11 (5.4)
Influenza	5 (3.4)	10 (6.9)	8 (4.6)	10 (5.8)	5 (2.9)	8 (5.8)	12 (5.8)	12 (5.1)	10 (4.2)	14 (6.9)
Upper respiratory tract infection	4 (2.7)	8 (5.6)	7 (4.0)	6 (3.5)	5 (2.9)	4 (2.9)	11 (5.3)	9 (3.8)	10 (4.2)	9 (4.4)
Fatigue	1 (0.7)	5 (3.5)	7 (4.0)	0	7 (4.1)	4 (2.9)	6 (2.9)	10 (4.3)	8 (3.3)	7 (3.4)
Back pain	2 (1.4)	9 (6.3)	7 (4.0)	6 (3.5)	3 (1.8)	2 (1.4)	13 (6.3)	9 (3.8)	7 (2.9)	4 (2.0)
Arthralgia	2 (1.4)	12 (8.3)	3 (1.7)	7 (4.1)	2 (1.2)	0	18 (8.7)	6 (2.6)	2 (0.8)	4 (2.0)
Urinary tract infection	6 (4.1)	4 (2.8)	7 (4.0)	6 (3.5)	5 (2.9)	4 (2.9)	9 (4.3)	13 (5.6)	1 (0.4)	5 (2.5)
Gastroenteritis	2 (1.4)	5 (3.5)	4 (2.3)	2 (1.2)	0	3 (2.2)	6 (2.9)	5 (2.1)	2 (0.8)	5 (2.5)
Nausea	0	4 (2.8)	2 (1.1)	3 (1.7)	4 (2.4)	2 (1.4)	6 (2.9)	6 (2.6)	6 (2.5)	3 (1.5)
Abnormal dreams	3 (2.0)	5 (3.5)	3 (1.7)	3 (1.7)	2 (1.2)	1 (0.7)	5 (2.4)	4 (1.7)	4 (1.7)	3 (1.5)
Nightmare	0	3 (2.1)	5 (2.9)	1 (0.6)	1 (0.6)	2 (1.4)	4 (1.9)	5 (2.1)	1 (0.4)	3 (1.5)
Fall	8 (5.4)	2 (1.4)	5 (2.9)	2 (1.2)	3 (1.8)	0	4 (1.9)	8 (3.4)	8 (3.3)	2 (1.0)
Sinusitis	3 (2.0)	3 (2.1)	3 (1.7)	5 (2.9)	1 (0.6)	0	5 (2.4)	6 (2.6)	5 (2.1)	1 (0.5)

Number of subjects with events (incidence [%])

- The package insert of a similar drug (suvorexant) gives caution that the efficacy or safety of suvorexant has not been established for secondary insomnia. However, the above results indicate that there are no marked differences in the efficacy and safety of lemborexant between patients with insomnia with and without comorbidities. Therefore, such caution is not necessary in the package insert of lemborexant.

PMDA's view:

- The Guidelines for the Clinical Evaluation of Hypnotic Drugs (PFSB/ELD Notification No. 1213-1, dated December 13, 2011) state that clinical studies should target patients with primary insomnia in general and that clinical studies in patients with secondary insomnia, if necessary, should be conducted separately from patients with primary insomnia. In contrast, the diagnostic criteria manuals published later, such as DSM-5 and ICSD-3, do not discriminate secondary from primary insomnia.
- In Study E2006-G000-303, in which both patients with primary and secondary insomnia were included, no marked differences in the efficacy of lemborexant were observed between patients with and without comorbidities. The incidence of adverse events tended to be higher in patients with comorbidities than in those without comorbidities. However, the events observed in patients with comorbidities were seen commonly in subjects receiving lemborexant, against which cautionary advices will be given in the package insert.

- The package insert of the similar drug notes that "the efficacy or safety has not been established for secondary insomnia" for which studies have been conducted in patients with primary insomnia alone and not in patients with secondary insomnia.
- Accordingly, there are no major problems in the applicant's opinion that it is unnecessary to give caution in the package insert on unestablished efficacy or safety of lemborexant for secondary insomnia.

PMDA considers that the final conclusion on the appropriateness of the above should be drawn on the basis of comments from the Expert Discussion.

7.R.3 Safety

7.R.3.1 Central nervous system events

PMDA asked the applicant to explain the occurrence of CNS adverse events in association with the use of lemborexant.

The applicant's explanation:

(a) Occurrence of CNS adverse events

- Table 59 shows the occurrence of CNS adverse events[43)] in the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303) and the foreign phase III study (CTD 5.3.5.1.3: Study E2006-G000-304). The incidences of CNS adverse events tended to be higher in the lemborexant groups than in the placebo group. Major adverse events leading to treatment discontinuation included somnolence in 14 subjects (2 in the placebo group, 3 in the lemborexant 5 mg/day group, and 9 in the lemborexant 10 mg/day group) and nightmare in 5 subjects (0, 1, and 4) in Period 1 of Study E2006-G000-303 and somnolence in 23 subjects (7 in the lemborexant 5 mg/day arm and 16 in the lemborexant 10 mg/day arm), nightmare in 6 subjects (2 and 4), and dizziness in 5 subjects (3 and 2) in Study E2006-G000-303 (Periods 1 and 2). The first onset of these events was relatively frequently observed on Days 1 to 7.
- Severe somnolence occurred in 1 subject in the placebo group in Period 1 of Study E2006-G000-303, 2 subjects in the lemborexant 10 mg/day arm in Periods 1 and 2 of Study E2006-G000-303, and 1 subject in the lemborexant 10 mg/day group of Study E2006-G000-304. The severity of somnolence was mild or moderate in most cases.
- Somnolence may influence daytime functioning. Due caution will be given against somnolence through the package insert, etc., and the risk factors for somnolence influential to daytime functioning will be investigated in the post-marketing setting.

43) Events included in the MedDRA SOCs "Nervous system disorders" or "Psychiatric disorders."

Table 59. Occurrence of CNS adverse events (Studies E2006-G000-303 and E2006-G000-304)

	Study E2006-G000-303					Study E2006-G000-304			
	Period 1 alone			Periods 1 and 2					
	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER
Number of subjects evaluated	319	314	314	447	437	209	266	268	263
CNS adverse events	52 (16.3)	77 (24.5)	85 (27.1)	120 (26.8)	124 (28.4)	21 (10.0)	33 (12.4)	39 (14.6)	41 (15.6)
Serious adverse events	0	1 (0.3)	2 (0.6)	2 (0.4)	2 (0.5)	0	0	0	0
Adverse events leading to treatment discontinuation	8 (2.5)	7 (2.2)	19 (6.1)	16 (3.6)	27 (6.2)	1 (0.5)	2 (0.8)	2 (0.7)	2 (0.8)
Major adverse events									
Somnolence	5 (1.6)	27 (8.6)	41 (13.1)	38 (8.5)	60 (13.7)	4 (1.9)	11 (4.1)	19 (7.1)	4 (1.5)
Headache	21 (6.6)	28 (8.9)	21 (6.7)	43 (9.6)	32 (7.3)	13 (6.2)	17 (6.4)	13 (4.9)	14 (5.3)
Nightmare	1 (0.3)	4 (1.3)	7 (2.2)	5 (1.1)	8 (1.8)	1 (0.5)	2 (0.8)	1 (0.4)	0
Sleep paralysis	0	0	5 (1.6)	8 (1.8)	8 (1.8)	0	1 (0.4)	3 (1.1)	0
Dizziness	6 (1.9)	5 (1.6)	4 (1.3)	14 (3.1)	8 (1.8)	4 (1.9)	3 (1.1)	2 (0.7)	8 (3.0)
Abnormal dreams	6 (1.9)	7 (2.2)	4 (1.3)	9 (2.0)	7 (1.6)	1 (0.5)	0	4 (1.5)	3 (1.1)

Number of subjects with events (incidence [%])

(b) Occurrence of parasomnia-related adverse events

- Table 60 shows the occurrence of parasomnia-related adverse events[44)] in Studies E2006-G000-303 and E2006-G000-304. No obvious differences were observed among the groups, and the events were non-serious, suggesting no clear risks of parasomnia-related adverse events in association with the treatment with lemborexant.

Table 60. Occurrence of parasomnia-related adverse events (Studies E2006-G000-303 and E2006-G000-304)

	Study E2006-G000-303					Study E2006-G000-304			
	Period 1 alone			Periods 1 and 2					
	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER
Number of subjects evaluated	319	314	314	447	437	209	266	268	263
Parasomnia-related adverse events	7 (2.2)	10 (3.2)	11 (3.5)	13 (2.9)	15 (3.4)	2 (1.0)	2 (0.8)	6 (2.2)	3 (1.1)
Serious adverse events	0	0	0	0	0	0	0	0	0
Adverse events leading to treatment discontinuation	1 (0.3)	1 (0.3)	5 (1.6)	3 (0.7)	5 (1.1)	0	1 (0.4)	0	0
Major adverse events									
Nightmare	1 (0.3)	4 (1.3)	7 (2.2)	5 (1.1)	8 (1.8)	1 (0.5)	2 (0.8)	1 (0.4)	0
Abnormal dreams	6 (1.9)	7 (2.2)	4 (1.3)	9 (2.0)	7 (1.6)	1 (0.5)	0	4 (1.5)	3 (1.1)
Rapid eye movements sleep abnormal	0	0	0	0	0	0	0	1 (0.4)	0

Number of subjects with events (incidence [%])

(c) Occurrence of narcolepsy-related adverse events (including cataplexy)

- Table 61 shows the occurrence of narcolepsy-related adverse events[45)] in Studies E2006-G000-303 and E2006-G000-304. Narcolepsy-related adverse events occurred only in the lemborexant groups. However, they were all mild or moderate in severity and non-serious. No specific tendency was identified in the time of the first onset.

44) Events included in the MedDRA HLT "Parasomnia."
45) Events included in the MedDRA HLT "Narcolepsy and associated conditions," except for cataplexy-related adverse events.

Table 61. Occurrence of narcolepsy-related adverse events (Studies E2006-G000-303 and E2006-G000-304)

	Study E2006-G000-303					Study E2006-G000-304			
	Period 1 alone			Periods 1 and 2					
	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER
Number of subjects evaluated	319	314	314	447	437	209	266	268	263
narcolepsy-related adverse events	0	1 (0.3)	7 (2.2)	9 (2.0)	11 (2.5)	0	1 (0.4)	3 (1.1)	0
Serious adverse events	0	0	0	0	0	0	0	0	0
Adverse events leading to treatment discontinuation	0	0	0	1 (0.2)	0	0	0	0	0
Major adverse events									
Sleep paralysis	0	0	5 (1.6)	8 (1.8)	8 (1.8)	0	1 (0.4)	3 (1.1)	0
Hypnagogic hallucination	0	1 (0.3)	2 (0.6)	1 (0.2)	5 (1.1)	0	0	0	0
Hypnopompic hallucination	0	0	1 (0.3)	0	1 (0.2)	0	0	0	0

Number of subjects with events (incidence [%])

- Table 62 shows the occurrence of cataplexy-related adverse events[46)] in Studies E2006-G000-303 and E2006-G000-304. A serious adverse event, fall, occurred in 1 subject receiving lemborexant 5 mg/day and 1 subject receiving lemborexant 10 mg/day, but a causal relationship to lemborexant was ruled out for the event of both cases.

Table 62. Occurrence of cataplexy-related adverse events (Studies E2006-G000-303 and E2006-G000-304)

	Study E2006-G000-303					Study E2006-G000-304			
	Period 1 alone			Periods 1 and 2					
	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER
Number of subjects evaluated	319	314	314	447	437	209	266	268	263
Cataplexy-related adverse events	10 (3.1)	8 (2.5)	9 (2.9)	15 (3.4)	17 (3.9)	1 (0.5)	5 (1.9)	2 (0.7)	0
Serious adverse events	0	1 (0.3)	0	1 (0.2)	1 (0.2)	0	0	0	0
Adverse events leading to treatment discontinuation	0	1 (0.3)	0	1 (0.2)	2 (0.5)	0	0	0	0
Major adverse events									
Fall	10 (3.1)	5 (1.6)	5 (1.6)	12 (2.7)	10 (2.3)	0	4 (1.5)	0	0
Muscular weakness	0	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	0	1 (0.4)	1 (0.4)	0
Syncope	0	2 (0.6)	1 (0.3)	2 (0.4)	3 (0.7)	0	0	0	0
Cataplexy	0	0	1 (0.3)	0	1 (0.2)	0	0	0	0
Dysarthria	0	0	1 (0.3)	0	1 (0.2)	0	0	0	0

Number of subjects with events (incidence [%])

- Lemborexant's inhibitory effect on the orexin neurotransmission may induce narcolepsy and associated clinical conditions [see Section 3.R.2.1]. In Study E2006-G000-304, REM sleep latency tended to decrease in the lemborexant groups as compared with the placebo group, and the percentage of subjects with the sleep-onset REM period (REM sleep latency of <15 minutes), which is used in the narcolepsy diagnostic criteria, was higher in the lemborexant groups than in the placebo group. The percentage was higher especially on Days 1 and 2 in the lemborexant 10 mg/day group [see Section 7.R.2.4]. These findings suggest a possible risk for narcolepsy-related adverse events.
- As mentioned above, in Study E2006-G000-303, narcolepsy-related adverse events were observed only in the lemborexant groups. However, the incidence was low, and no severe or serious adverse events were observed. These findings suggest that narcolepsy-related adverse events (including cataplexy) of lemborexant are unlikely to pose a significant safety concern.

46) Events corresponding to the following MedDRA PTs:
Cataplexy, fall, drop attacks, clonus, consciousness fluctuating, depressed level of consciousness, diplopia, eyelid myoclonus, heteronymous diplopia, homonymous diplopia, hypotonia, loss of consciousness, muscle fatigue, muscle tone disorder, muscular weakness, myoclonus, opsoclonus myoclonus, presyncope, reversible ischaemic neurological deficit, slow speech, syncope, transient global amnesia, transient ischaemic attack, dysarthria, paralysis, circulatory collapse, and eyelid ptosis

- Nevertheless, the risk of narcolepsy-related adverse events cannot be completely ruled out, and the possibility of worsening of these symptoms also cannot be ruled out. Therefore, cautionary advice will be given against these events in the "Careful Administration" section of the package insert.

(d) Occurrence of suicide-related adverse events

- The risk of suicide was reported to increase in patients receiving hypnotics as compared with the general population (*Arch Suicide Res.* 2014;18:170-80). There are risks of deaths, etc. resulting from abnormal behavior in association with the use of nonbenzodiazepine hypnotics for the treatment of insomnia. Therefore, the U.S package inserts of eszopiclone, zolpidem, and zaleplon warn about the risks.
- The incidence of suicide-related adverse events[47)] in Period 1 of Study E2006-G000-303 was 0.3% (1 of 319) in the placebo group, 0.6% (2 of 314) in the lemborexant 5 mg/day group, and 0% (0 of 314) in the lemborexant 10 mg/day group. The event reported from all these subjects was non-serious intentional overdose. The reported overdose level of lemborexant was 10 mg, and the possibility of a suicide attempt was thus unlikely. The incidence of suicide-related adverse events in Study E2006-G000-303 (Periods 1 and 2) was 0.9% (4 of 447) in subjects receiving lemborexant 5 mg/day and 0% (0 of 437) in subjects receiving lemborexant 10 mg/day. The event reported from these subjects was intentional overdose. The event was assessed as serious in 1 subject but was considered unrelated to the study drug.
- In Study E2006-G000-304, no suicide-related adverse events occurred.
- Suicidal ideation in Period 1 of Study E2006-G000-303 was evaluated by the Columbia-Suicide Severity Rating Scale (C-SSRS). The baseline incidence of suicidal ideation was 0.9% (3 of 319) in the placebo group, 1.0% (3 of 314) in the lemborexant 5 mg/day group, and 1.3% (4 of 314) in the lemborexant 10 mg/day group, and at the end of treatment, 0.3% (1 of 318) in the placebo group, 0.3% (1 of 313) in the lemborexant 5 mg/day group, and 0.6% (2 of 312) in the lemborexant 10 mg/day group. There was no trend toward increased incidence with prolonging treatment duration or increasing lemborexant dose.
- Suicidal ideation in Study E2006-G000-304 was evaluated by the C-SSRS. The baseline incidence was 0% (0 of 204) in the placebo group, 1.1% (3 of 252) in the zolpidem ER group, 0.4% (1 of 255) in the lemborexant 5 mg/day group, and 0.7% (2 of 254) in the lemborexant 10 mg/day group. At the end of treatment, 0% (0 of 193) in the placebo group, 0.8% (2 of 242) in the zolpidem ER group, 0% (0 of 249) in the lemborexant 5 mg/day group, and 0% (0 of 252) in the lemborexant 10 mg/day group. There was no trend toward increased incidence with prolonging treatment duration or increasing lemborexant dose.
- Suicidal ideation was evaluated by the C-SSRS after the treatment of lemborexant. No suicidal behavior or self-injury was found in Studies E2006-G000-303 and E2006-G000-304.
- Currently, the package insert of the similar drug (suvorexant) gives no cautionary advice against suicide.
- Accordingly, the risk of suicide-related adverse events in association with the use of lemborexant is unlikely to be a clinical concern.

PMDA's view:

47) Events included in the MedDRA SMQ "Suicide/self-injury (SMQ)."

- Among CNS adverse events including parasomnia, somnolence is highly associated with the efficacy of lemborexant that is a drug for the treatment of insomnia. In Studies E2006-G000-303 and E2006-G000-304, the incidence of somnolence and sleep paralysis was higher in the lemborexant 10 mg/day group than in the lemborexant 5 mg/day group. In Study E2006-G000-303, the incidence of treatment discontinuation due to somnolence or nightmare tended to increase in the lemborexant 10 mg/day group as compared with the lemborexant 5 mg/day group.
- In terms of narcolepsy, REM sleep latency decreased after treatment with lemborexant [see Section 7.R.2.4], and narcolepsy-related adverse events (sleep paralysis, hypnagogic hallucination, and hypnopompic hallucination) were observed only in the lemborexant groups. In Study E2006-G000-304, fracture associated with falls was reported in the lemborexant groups.
- Given these observations, the incidence of CNS adverse events including parasomnia and narcolepsy-related events tended to be higher in the lemborexant 10 mg/day group than in the lemborexant 5 mg/day group. Dose increase to 10 mg requires prudence and caution against these adverse events. Information on CNS events including parasomnia and narcolepsy-related events should be further collected in the post-marketing setting.
- Suicide-related adverse events showed no marked differences in the incidences among groups in the clinical study data or no trend toward increase with prolonging treatment or increasing dose of lemborexant in the C-SSRS evaluation. However, the risk of suicide is known to increase by the use of hypnotics, information on suicide should be further collected in the post-marketing setting.

PMDA considers that the final conclusion on the appropriateness of the view above should be drawn on the basis of comments from the Expert Discussion.

7.R.3.2 Risk of carryover effect

PMDA asked the applicant to explain the carryover effect with treatment with lemborexant.

The applicant's explanation:

(a) Evaluation of postural stability,[48)] power of attention,[49)] quality of memory (retention and retrieval of memory)[50)] in healthy adults aged ≥55 years.

- A foreign phase I study was conducted to evaluate the physical and cognitive performance at awakening at night (4 hours post-dose) and on the following day (8 hours post-dose) (CTD 5.3.4.1.1, Study E2006-A001-108, a randomized cross-over study [reference data]).
- Table 63 shows changes from baseline in body sway, power of attention, and quality of memory (retention and retrieval of memory). The changes from baseline in body sway exceeded the clinically significant threshold (7 U) at 4 hours post-dose of lemborexant 10 mg/day and zolpidem ER. The changes from baseline in the power of attention exceeded the clinically significant threshold (48.8 milliseconds)

48) Body sway and postural stability were assessed by using the Cognitive Drug Research posture assessment device. Higher values indicate greater body sway and a more unstable posture.
49) A combined score for response time in attention test in the cognitive performance assessment battery. Higher values indicate greater decrease in the power of attention.
50) Assessed with a combined score for accuracy of memory in 2 working memory tests and 4 episode-memory tests. Lower values indicate greater decrease in the quality of memory.

at 4 hours post-dose of all tested drugs including placebo and at 8 hours post-dose of lemborexant 10 mg/day. No marked differences in quality of memory (retention and retrieval of memory) were observed at 4 hours post-dose of lemborexant 5 mg/day as compared with placebo, but quality of memory tended to decrease after the administration of lemborexant 10 mg/day. No marked differences were observed at 8 hours post-dose among these groups.

Table 63. Changes in body sway, power of attention, and quality of memory at 4 and 8 hours post-dose (Study E2006-A001-108, pharmacodynamic analysis set)

Parameters	Study drug	Number of subjects evaluated	4 hours post-dose		8 hours post-dose	
			Change from baseline	Difference from placebo [95% CI][a)]	Change from baseline	Difference from placebo [95% CI][a)]
Body sway (U)	Placebo	56	−1.1 ± 14.21		−2.2 ± 16.77	
	Lemborexant 5 mg/day	56	5.8 ± 18.45	6.8 [1.21, 12.34]	0.4 ± 20.86	2.4 [−3.13, 8.00]
	Lemborexant 10 mg/day	56	8.1 ± 19.46	9.3 [3.72, 14.84]	−0.4 ± 18.54	1.8 [−3.78, 7.34]
	Zolpidem ER	56	20.4 ± 25.53	21.4 [15.79, 26.92]	5.0 ± 21.18	7.0 [1.47, 12.60]
Power of attention (millisecond)	Placebo	56	50.9 ± 99.05		−7.7 ± 162.11	
	Lemborexant 5 mg/day	56	127.9 ± 209.94	73.0 [−28.46, 174.51]	36.7 ± 238.80	40.5 [−60.99, 141.97]
	Lemborexant 10 mg/day	56	252.5 ± 672.59	202.2 [100.76, 303.68]	72.7 ± 338.38	81.1 [−20.35, 182.57]
	Zolpidem ER	56	135.5 ± 1633.26	82.6 [−18.89, 184.03]	1.0 ± 161.80	6.7 [−94.73, 108.19]
Quality of memory (U)	Placebo	56	6.71 ± 56.786		−2.25 ± 56.511	
	Lemborexant 5 mg/day	56	−6.01 ± 74.244	−12.65 [−30.377, 5.080]	4.75 ± 57.225	7.07 [−10.661, 24.795]
	Lemborexant 10 mg/day	56	−27.85 ± 87.309	−34.57 [−52.295, −16.847]	4.26 ± 62.822	6.50 [−11.223, 24.225]
	Zolpidem ER	56[b)]	−35.01 ± 54.877	−41.87 [−59.698, −24.046]	6.27 ± 55.623	8.31 [−9.411, 26.037]

Mean ± standard deviation

a) Difference in least-squares means based on a crossover mixed-effect model temporal measurement with study drug, treatment sequence, treatment period, baseline value, time point, an interaction between study drug and time point, and an interaction between baseline value and time point as fixed effects and subject as a random effect

b) A total of 55 subjects were evaluated at 4 hours post-dose (including a subject with missing data).

(b) Effects of lemborexant on driving performance

- In a driving performance study (CTD 5.3.4.1.3, Study E2006-E044-106), effects of placebo, lemborexant 2.5, 5, and 10 mg, and zopiclone 7.5 mg on driving performance were evaluated. A single dose or multiple doses of lemborexant did not affect subjects' driving performance in the following morning [see Section 6.2.5.2].

(c) Evaluation by the mixed-effect model repeated measurement

- A foreign phase I study was conducted to investigate the carryover effect of lemborexant in patients with insomnia (CTD 5.3.4.2.1, Study E2006-A001-107, a randomized crossover study [reference data]). Table 64 shows changes from baseline in sleep latency as assessed by the mixed-effect model repeated measurement (M-MSLT). The lower limit of the 95% CI for the differences in changes between lemborexant 5 and 10 mg and placebo exceeded −6 minutes, the predefined value having no carryover effect, suggesting that lemborexant 5 and 10 mg have no clinically significant effects on carryover effect.

Table 64. Changes from baseline in sleep latency as assessed by M-MSLT (Study E2006-A001-107, FAS)

	Baseline	Post-dose	
		Changes [a)]	Difference from placebo [Lower limit of the one-side 95% CI]
Placebo	18.25 ± 2.621 (68)	−3.44 ± 0.564	
Lemborexant 5 mg	18.28 ± 2.61 (69)	−4.58 ± 0.561	−1.15 [−2.12]
Lemborexant 10 mg	18.25 ± 2.621 (68)	−6.92 ± 0.564	−3.48 [−4.46]

Mean ± standard deviation (Number of subjects evaluated)
a) Least-squares mean ± standard error
Based on a crossover mixed-effect model with study drug, treatment period, site, and treatment sequence as fixed effects, baseline value as a covariate, and subject as a random effect

(d) Assessment of daily functioning in the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2: Study E2006-G000-303) and the foreign phase III study (CTD 5.3.5.1.3, Study E2006-G000-304)

- In Studies E2006-G000-303 and E2006-G000-304, improvement was observed in subjective sleepiness/awakening levels[41)] based on the ISI daily functioning score (Items 4 to 7)[40)] and sleep diary in the lemborexant 5 and 10 mg/day groups as compared with the placebo group [see Section 7.R.2.3].
- Table 65 shows the occurrence of carryover effect-related adverse events.[51)] The incidence of somnolence was higher in the lemborexant 10 mg/day group than in the lemborexant 5 mg/day group. Serious disturbance in attention, for which a causal relationship with lemborexant was not ruled out, occurred in a subject in the lemborexant 10 mg/day group in Period 1 of Study E2006-G000-303. However, the subject was found to have experienced abdominal pain, which was determined by the investigator to have been caused by lemborexant, other medication, and alcohol taken. After that, the subject did not have adverse events of similar type. The majority of other events were mild or moderate in severity.

Table 65. Occurrence of carryover effect-related adverse events (Studies E2006-G000-303 and E2006-G000-304)

	Study E2006-G000-303					Study E2006-G000-304			
	Period 1			Periods 1 and 2					
	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER
Number of subjects evaluated	319	314	314	447	437	209	266	268	263
Adverse events related to carryover effect	7 (2.2)	41 (13.1)	53 (16.9)	54 (12.1)	78 (17.8)	6 (2.9)	13 (4.9)	22 (8.2)	10 (3.8)
Serious adverse events	0	0	1 (0.3)	0	1 (0.2)	0	0	0	0
Adverse events leading to treatment discontinuation	3 (0.9)	4 (1.3)	10 (3.2)	9 (2.0)	17 (3.9)	1 (0.5)	1 (0.4)	1 (0.4)	1 (0.4)
Main adverse events									
Somnolence	5 (1.6)	27 (8.6)	41 (13.1)	38 (8.5)	60 (13.7)	4 (1.9)	11 (4.1)	19 (7.1)	4 (1.5)
Fatigue	1 (0.3)	12 (3.8)	11 (3.5)	14 (3.1)	17 (3.9)	0	2 (0.8)	1 (0.4)	4 (1.5)

Number of subjects with events (incidence [%])

- In Study E2006-G000-303 (Period 1), road traffic accidents[52)] occurred in 0.3% (1 of 319) of subjects in the placebo group, 0% (0 of 314) of subjects in the lemborexant 5 mg/day group, and 0.3% (1 of 314) of subjects in the lemborexant 10 mg/day group. The events were mild or moderate, and a causal relationship with the study drug was ruled out. In Study E2006-G000-304, road traffic accidents occurred in 0% (0 of 209) of subjects in the placebo group, 0% (0 of 266) of subjects in the lemborexant 5 mg/day group, 0% (0 of 268) of subjects in the lemborexant 10 mg/day group, and 0.4% (1 of 263) of

51) Events corresponding to the following MedDRA PTs:
Fatigue; feeling abnormal; sluggishness; amnesia; aphasia; balance disorder; cognitive disorder; coordination abnormal; depressed level of consciousness; disturbance in attention; dysarthria; lethargy; memory impairment; retrograde amnesia; sedation; somnolence; stupor; bradyphrenia; distractibility; and mental status changes.
52) Events corresponding to the MedDRA PT "road traffic accident."

subjects in the zolpidem ER group. The event was mild or moderate, and a causal relationship with the study drug was ruled out.

The applicant's view on the carryover effect of lemborexant based on (a) to (d):

- Data from Studies E2006-G000-303 and E2006-G000-304 demonstrate improvement in subjective sleepiness/awakening levels based on daily functioning evaluation and sleep diary in the lemborexant 5 and 10 mg/day groups as compared with the placebo group, and the majority of carryover effect-related adverse events were mild or moderate in severity.
- Data from Study 106 suggest that the administration of lemborexant 5 or 10 mg does not affect driving performance in the following morning.
- As shown above, the risk of carryover effect with lemborexant is considered unlikely to be a significant concern.
- In the clinical setting, there are patients with various backgrounds who drive cars in different situations. Physicians should inform patients of drowsiness caused by lemborexant, and patients should exercise due caution in car driving and the operation of other hazardous machines. Furthermore, physicians should advise patients not to drive or operate hazardous machines when the have drowsiness.

PMDA's view on carryover effect:

- In Study E2006-E044-106, the difference in SDLP for car driving performance between the lemborexant groups and the placebo group increased in a dose-dependent manner, suggesting that lemborexant 10 mg is associated with a higher risk for effects on driving performance as compared with lemborexant 5 mg. The highest dose used in the driving performance study was 10 mg, and the exposure to lemborexant is increased by a drug interaction and in special patient populations [see Section 6.R]. Therefore, the carryover effect of increased exposure is unknown.
- No major problems were found with ISI and daily functioning scores in Studies E2006-G000-303 and E2006-G000-304. However, in these studies, the incidence of carryover effect-related adverse events including somnolence tended to increase in the lemborexant 5 and 10 mg group in a dose-dependent manner as compared with the placebo group.
- Currently, the possibility cannot be ruled out that lemborexant causes narcolepsy or cataplexy.
- The above findings suggest that the risk of accidents may increase when somnolence, narcolepsy, or cataplexy occurs with the use of lemborexant. Therefore, the operation of hazardous machines including car driving should be prohibited, and this should be highlighted in the package insert as practiced for the similar drug.

PMDA considers that the final conclusion on the appropriateness of the above should be drawn on the basis of comments from the Expert Discussion.

7.R.3.3 Effects of lemborexant on respiratory function

PMDA asked the applicant to explain the effects of treatment with lemborexant on respiratory function.

The applicant's explanation:

- Table 66 shows the occurrence of respiratory function-related adverse events[53)] in the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2: Study E2006-G000-303) and the foreign phase III study (CTD 5.3.5.1.3, Study E2006-G000-304). There was no trend toward increased incidences with prolonging treatment or increasing lemborexant dose. Sleep apnoea syndrome in Period 2 of Study E2006-G000-303 led to treatment discontinuation but was assessed as unrelated to the study drug, and dyspnoea and respiratory failure subsided.

Table 66. Occurrence of respiratory function-related adverse events (Studies E2006-G000-303 and E2006-G000-304, safety analysis set)

	Study E2006-G000-303					Study E2006-G000-304			
	Period 1			Periods 1 and 2					
	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Placebo	Lemborexant 5 mg/day	Lemborexant 10 mg/day	Zolpidem ER
Number of subjects evaluated	319	314	314	447	437	209	266	268	263
Respiratory function-related adverse events	0	0	3 (1.0)	2 (0.4)	4 (0.9)	3 (1.4)	1 (0.4)	0	1 (0.4)
Serious adverse events	0	0	0	0	0	0	0	0	0
Adverse events leading to treatment discontinuation	0	0	0	0	1 (0.2)	0	0	0	1 (0.4)
Main adverse events									
Dyspnoea	0	0	2 (0.6)	1 (0.2)	2 (0.5)	2 (1.0)	1 (0.4)	0	0
Hyperventilation	0	0	1 (0.3)	0	1 (0.2)	0	0	0	0
Tachypnoea	0	0	0	0	0	0	0	0	1 (0.4)

Number of subjects with events (incidence [%])

- In Study E2006-G000-303, although no increase in respiratory rate (>30 breaths/minute with an increase by ≥10 breaths/minute from baseline) was seen, decreased respiratory rate (<8 breaths/minute with a change from baseline of ≥4 breath/minute) was observed in none in the placebo group, 0.7% (2 of 314) of subjects in the lemborexant 5 mg/day group, and 0.3% (1 of 314) of subjects in the lemborexant 10 mg/day group. The decreased respiratory rate in these subjects was transient and clinically insignificant. In Study E2006-G000-304, respiratory rate increased in 0.5% (1 of 209) of subjects in the

53) Events corresponding to the following MedDRA PTs:
Platypnoea; dyspnoea exertional; nocturnal dyspnoea; anoxia; apnoeic attack; apnoea; chronic respiratory failure; trepopnoea; tachypnoea; anaemic hypoxia; dyspnoea paroxysmal nocturnal; alveolar aeration excessive; brain hypoxia; hypocapnia; hypoxia; hypoventilation; cyanosis central; suffocation feeling; asphyxia; sleep apnoea syndrome; upper airway resistance syndrome; bradypnoea; hypercapnia; hyperoxia; grunting; mouth breathing; respiratory depression; respiratory paralysis; respiratory failure; respiratory arrest; respiratory alkalosis; respiratory acidosis; respiratory depth increased; respiratory depth decreased; painful respiration; dyspnoea; respiratory gas exchange disorder; respiratory distress; respiration abnormal; prolonged expiration; hypopnoea; acute respiratory failure; orthopnoea; hyperventilation; dyspnoea at rest; Pickwickian syndrome; Cheyne-Stokes respiration; Kussmaul respiration; cardiopulmonary failure; cardio-respiratory distress; cardio-respiratory arrest; cyanosis; hypoxic-ischaemic encephalopathy; central-alveolar hypoventilation; respiratory dyskinesia; breath holding; breathing-related sleep disorder; expiratory reserve volume increased; expiratory reserve volume decreased; expiratory reserve volume abnormal; rhinomanometry abnormal; alveolar oxygen partial pressure decreased; alveolar oxygen partial pressure increased; alveolar oxygen partial pressure abnormal; pulmonary function challenge test abnormal; pulmonary function test decreased; pulmonary function test increased; pulmonary function test abnormal; spirometry abnormal; vital capacity decreased; vital capacity abnormal; carbon dioxide increased; carbon dioxide decreased; carbon dioxide abnormal; forced expiratory volume increased; forced expiratory volume decreased; forced expiratory volume abnormal; PCO2 decreased; PCO2 increased; PCO2 abnormal; pH body fluid decreased; pH body fluid increased; pH body fluid abnormal; total lung capacity increased; total lung capacity decreased; total lung capacity abnormal; ciliary function test abnormal; venous oxygen saturation decreased; venous oxygen saturation increased; venous oxygen saturation abnormal; venous oxygen partial pressure decreased; venous oxygen partial pressure increased; venous oxygen partial pressure abnormal; inspiratory capacity increased; inspiratory capacity decreased; inspiratory capacity abnormal; oxygen saturation decreased; oxygen saturation immeasurable; oxygen saturation increased; oxygen saturation abnormal; oxygen consumption increased; oxygen consumption decreased; acid base balance abnormal; maximal voluntary ventilation increased; maximal voluntary ventilation decreased; maximal voluntary ventilation abnormal; peak expiratory flow rate increased; peak expiratory flow rate decreased; peak expiratory flow rate abnormal; airway peak pressure increased; end-tidal CO2 increased; end-tidal CO2 decreased; end-tidal CO2 abnormal; blood lactic acid increased; blood lactic acid decreased; blood lactic acid abnormal; blood gases abnormal; blood pH decreased; blood pH increased; blood pH abnormal; functional residual capacity increased; functional residual capacity decreased; functional residual capacity abnormal; base excess positive; base excess increased; base excess decreased; base excess negative; base excess abnormal; carbon monoxide diffusing capacity decreased; capnogram abnormal; anion gap increased; anion gap decreased; anion gap abnormal; PO_2 decreased; PO_2 increased; PO_2 abnormal; and PaO_2/FiO_2 ratio decreased

placebo group, 1.5% (4 of 266) of subjects in the lemborexant 5 mg/day group, and 1.1% (3 of 268) of subjects in the lemborexant 10 mg/day group. Meanwhile, there was no decreased respiratory rate.

- Based on the above, cautionary advice against effects on respiratory function is unnecessary.

PMDA accepted the applicant's explanation.

7.R.3.4 Rebound insomnia and withdrawal syndrome due to treatment discontinuation

PMDA asked the applicant to explain the rebound insomnia and withdrawal syndrome due to discontinuation of lemborexant.

The applicant's explanation:

- Rebound insomnia-related adverse events[54)] did not occur in Period 1 of the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303). In Study E2006-G000-303 (Periods 1 and 2), rebound insomnia-related adverse event was reported in 0.2% (1 of 447 subjects, insomnia) of subjects receiving lemborexant 5 mg/day. In the foreign phase III study (CTD 5.3.5.1.3, Study E2006-G000-304), no rebound insomnia-related adverse events occurred. Insomnia observed after the administration of lemborexant was non-serious and mild, and resolved without intervention.
- In Period 1 of Study E2006-G000-303, withdrawal syndrome-related adverse events[55)] occurred in 0% (0 of 319) of subjects in the placebo group, 0.3% (1 of 314) of subjects in the lemborexant 5 mg/day group, and 0.6% (2 of 314) of subjects in the lemborexant 10 mg/day group. Reported events were anxiety (the lemborexant 5 mg/day group), aphasia (lemborexant 10 mg/day), ataxia (lemborexant 10 mg/day), cerebrovascular accident (lemborexant 10 mg/day), and somnolence (lemborexant 10 mg/day). A serious adverse event occurred in 1 subject in the lemborexant 10 mg/day group (cerebrovascular accident) but was unrelated to the study drug. In Study E2006-G000-304, withdrawal syndrome-related adverse events occurred in 2.9% (6 of 209) of subjects in the placebo group, 3.0% (8 of 266) of subjects in the lemborexant 5 mg/day group, and 1.5% (4 of 268) of subjects in the lemborexant 10 mg/day group. Major adverse events included headache (3 subjects each in the placebo, lemborexant 5 mg/day, and lemborexant 10 mg/day groups). All these events were non-serious and did not lead to treatment discontinuation.
- As shown above, the incidence of rebound insomnia and withdrawal syndrome-related adverse events leading to discontinuation of lemborexant was low and did not substantially differ among the placebo and the lemborexant groups, suggesting that these events are unlikely to be a clinical concern.

PMDA accepted the applicant's explanation.

7.R.3.5 Risk of abuse and dependence

PMDA asked the applicant to explain the risk of abuse and dependence in association with lemborexant.

54) Events corresponding to the MedDRA PTs "insomnia," "middle insomnia," "initial insomnia," "hyposomnia," and "terminal insomnia."
55) Events included in the MedDRA SOCs "psychiatric disorders," "nervous system disorders," and "general disorders and administration site conditions," except for adverse events related to rebound insomnia.

The applicant's explanation:

- In the dependence studies in rats and rhesus monkeys, lemborexant did not induce physical dependence or psychic dependence [see Section 5.6.2].
- In the drug abuse liability study in non-Japanese healthy adults with a history of drug abuse, E_{max} of the Drug Liking VAS score for lemborexant was higher than that for placebo and was comparable to those for the positive controls (zolpidem 30 mg and suvorexant 40 mg) [see Section 6.2.5.1].
- The incidence of drug abuse liability-related adverse events[56)] in Period 1 of the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303) was 0.3% (1 of 319) in the placebo group, 0.6% (2 of 314) in the lemborexant 5 mg/day group, and 0% (0 of 314) of subjects in the lemborexant 10 mg/day group. In all cases, the reported adverse event was intentional overdose. In Study E2006-G000-303 (Periods 1 and 2), drug abuse liability-related adverse event occurred in 1.1% (5 of 447) of subjects receiving lemborexant 5 mg/day and 0% (0 of 437) of subjects receiving lemborexant 10 mg/day. Adverse events reported in subjects receiving lemborexant 5 mg/day were intentional overdose (4 subjects) and accidental overdose (1 subject). In Study E2006-G000-304, drug abuse liability-related adverse event occurred in 0% (0 of 209) of subjects in the placebo group, 0.4% (1 of 263) of subjects in the zolpidem ER group, 0% (0 of 266) of subjects in the lemborexant 5 mg/day group, and 0.4% (1 of 268) of subjects in the lemborexant 10 mg/day group. In all cases, the reported adverse event was accidental overdose.
- As shown above, the risk of dependence on or abuse of lemborexant is unlikely. The results of Study E2006-A001-103, however, will be communicated through the package insert.

PMDA's view:

While the non-clinical studies and Studies E2006-G000-303 and E2006-G000-304 showed no risk for dependence on or abuse of lemborexant, Study E2006-A001-103 in non-Japanese subjects with a history of drug abuse showed an increase in drug preference similar to that observed in those who were using the similar drug. In the clinical setting, lemborexant is expected to be used in patients with a risk of dependence on or abuse of hypnotics with various characteristics, the applicant's action to provide information via the package insert, as practiced for the similar drug, is acceptable.

7.R.4 Clinical positioning

PMDA asked the applicant to explain the clinical positioning of lemborexant.

The applicant's explanation:

- Typical pharmacotherapy for insomnia is generally classified into benzodiazepines, nonbenzodiazepine hypnotics, melatonin receptor agonists, and orexin receptor antagonists, according to their mechanism of action.

56) Events included in the MedDRA SMQ "Drug abuse, dependence and withdrawal" (broad).

- Some benzodiazepines or nonbenzodiazepine hypnotics have anxiolytic effects in addition to hypnotic effects and are effective in patients with severe insomnia-related anxiety (Guidelines for the Proper Use and Cessation of Hypnotics 2014). However, they are not always effective for difficulty with sleep maintenance (*Ann Clin Psychiatry*. 2006;18:49-56). These drugs are also known to cause lightheadedness (*ORL J Otorhinolaryngol Relat Spec*. 2005;67:106-12) and have a higher risk of fall and fracture, and are therefore not recommended for elderly patients from the safety point of view (Guidelines for the Proper Use and Cessation of Hypnotics 2014). In addition, benzodiazepines are reported to be associated with physical dependence or resistance even within the range of their approved dose (https://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000156323.pdf).
- Melatonin receptor agonists, despite low safety concerns, are not indicated for difficulty with sleep maintenance in Japan. Their package inserts note that efficacy or safety has not been established in patients with a history of prior treatment with other anti-insomnia drugs.
- Orexin receptor antagonists show no clinical significance in the development of resistance or dependence in long-term use as compared with benzodiazepines and nonbenzodiazepine hypnotics (*P T*. 2014;39:264-6). The clinical practice guideline of the American Academy of Sleep Medicine recommends orexin receptor antagonists for the treatment of difficulty with sleep maintenance (*J Clin Sleep Med.* 2017;13:307-49). Note that the Japanese clinical practice guideline (Guidelines for the Proper Use and Cessation of Hypnotics. 2014) does not mention orexin receptor antagonists because the currently available version was published before the market launch of the first orexin receptor antagonist.
- In the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303), lemborexant proved to be effective for onset and maintenance of sleep at Month 6 in Period 1 and is expected to be effective in long-term use including the use in Period 2 of the study [see Sections 7.3.1 and 7.R.2]. No withdrawal symptoms or rebound insomnia were observed after the completion of treatment in the clinical studies [see Section 7.R.3.5], and there was no increase in the risk of falls [see Section 7.R.3.1]. Furthermore, lemborexant proved to be effective even in patients with insomnia who have concurrent conditions as with patients with primary insomnia, and no factors affecting the efficacy of lemborexant have been identified [see Section 7.R.2.5].
- The above findings suggest that lemborexant can offer a therapeutic option for the treatment of insomnia.

PMDA accepted the applicant's explanation and considers that lemborexant can offer a therapeutic option for both difficulty with sleep onset and difficulty with sleep maintenance in treatment of insomnia.

7.R.5 Indication

PMDA asked the applicant to explain the appropriateness of the proposed indication.

The applicant's explanation:

- In the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303), lemborexant 5 and 10 mg/day proved to be effective for subjective sleep latency, subjective sleep efficiency, and subjective wake after sleep onset [see Sections 7.3.1 and 7.R.2].

- In the foreign phase III study (CTD 5.3.5.1.3, Study E2006-G000-304), lemborexant 5 and 10 mg/day proved to be effective for PSG-assessed sleep latency, sleep efficiency, and wake after sleep onset [see Section 7.3.2].
- Lemborexant was suggested to be effective to a certain level in the treatment of both primary and secondary insomnia [see Section 7.R.2.5].
- The above findings suggest it appropriate that lemborexant is indicated for "insomnia."

PMDA accepted the applicant's explanation and found no problem with the proposed indication.

7.R.6 Dosage and administration

PMDA asked the applicant to explain the rationale for the dosing regimen used in the global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303).

The applicant's explanation for the use of lemborexant 5 and 10 mg in Study E2006-G000-303:

- In the foreign phase II study in patients with insomnia (CTD 5.3.4.2.2, Study E2006-G000-201), placebo and lemborexant 1, 2.5, 5, 10, 15, and 25 mg/day were evaluated for sleep efficiency and sleep latency. Lemborexant showed dose-dependence, with improvement at ≥2.5 mg/day as compared with placebo. Meanwhile, the effect on change from baseline in next-day somnolence at 1 hour after awakening were observed in the lemborexant 25 mg/day group as compared with the placebo group (Table 36). The change from baseline [95% CI] at 2 hours after awakening in the placebo and lemborexant 1, 2.5, 5, 10, 15, and 25 mg/day group was −0.10 [−0.58, 0.38], −0.06 [−0.56, 0.45], 0.18 [−0.27, 0.63], 0.01 [−0.47, 0.48], 0.51 [0.10, 0.92], and 0.68 [0.26, 1.10], respectively, on Day 2 to 3 and 0.15 [−0.39, 0.69], 0.12 [−0.44, 0.69], 0.34 [−0.17, 0.85], 0.15 [−0.39, 0.69], 0.37 [−0.10, 0.83], and 0.59 [0.10, 1.07], respectively, on Day 15 to 16, indicating that lemborexant affects next-day somnolence at a dose of ≥15 mg.
- The foreign phase I study (Study E2006-A001-107) was conducted to evaluate the carryover effect of lemborexant in patients with insomnia. The study data suggest that the risk of carryover effect of lemborexant 5 and 10 mg is unlikely to pose a significant concern [see Section 7.R.3.2 (a)].
- The driving performance study (Study E2006-E044-106) was conducted in healthy elderly subjects and healthy adults (including a Japanese subject). The results demonstrated that lemborexant 2.5, 5, or 10 mg did not markedly affect driving performance on the following day [see Sections 6.2.5.2 and 7.R.3.2 (b)].
- Based on the above findings, the lemborexant doses of 5 and 10 mg were decided to be used in the phase III study.

PMDA asked the applicant to explain the appropriateness of the dosing regimens for lemborexant.

The applicant's explanation:

- The global phase III study (CTD 5.3.5.1.1 and 5.3.5.1.2, Study E2006-G000-303) demonstrated the efficacy of lemborexant 5 and 10 mg/day in the subjective sleep parameters (subjective sleep latency,

subjective sleep efficiency, and subjective wake after sleep onset) of patients with insomnia [see Sections 7.R.2.1 to 7.R.2.2].

- The foreign phase III study (CTD 5.3.5.1.3, Study E2006-G000-304) demonstrated the efficacy of lemborexant 5 and 10 mg/day in the objective sleep parameters assessed by PSG at Month 1 (including sleep latency, sleep efficiency, wake after sleep onset) and subjective sleep parameters (subjective sleep latency, subjective sleep efficiency, and subjective wake after sleep onset) [see Section 7.3.2].
- In Studies E2006-G000-303 and E2006-G000-304, the incidence of events including somnolence was higher in the lemborexant 10 mg/day group than in the placebo and lemborexant 5 mg/day groups [see Section 7.R.3.1]. However, these events were all non-serious. Furthermore, no marked differences in the occurrence of all adverse events or serious adverse events were observed among groups [see Section 7.3].
- In general, because of individual variability in response and symptoms of insomnia, dose increase to 10 mg/day may be effective even in patients with inadequate response to 5 mg/day.
- Thus, the recommended usual dose of lemborexant should be 5 mg/day. However, the dose increase to 10 mg/day as necessary is unlikely to pose a clinically significant concern. Given that the incidence of somnolence following lemborexant treatment was higher in the lemborexant 10 mg/day group than in the placebo and lemborexant 5 mg/day groups in Study E2006-G000-303, somnolence and other adverse reactions may increase when lemborexant dose is increased beyond the usual dose, and the dose increase should be carefully decided while the patient's condition is closely monitored, and the dose should be reduced when symptoms ameliorate. This should be advised in the "Precautions for Dosage and Administration" section of the package insert.

PMDA's view:

- The submitted clinical study data suggest no major problem in the applicant's proposal recommending the usual dose of lemborexant 5 mg/day.
- However, the incidence of adverse events such as somnolence and sleep paralysis tended to be higher in subjects receiving lemborexant 10 mg/day than in subjects receiving lemborexant 5 mg/day, and REM sleep latency decreased in patients receiving lemborexant 10 mg/day [see Section 7.R.2.4]. Given these, the dose should not be increased without careful consideration.
- Therefore, dose increase to 10 mg/day should be determined carefully. The lemborexant dose should be increased to 10 mg/day only for patients having an inadequate response to 5 mg/day and no safety concerns with the dose increase to 10 mg/day.
- The applicant explains that advice will be given so that a dose increase is implemented with careful consideration under close monitoring of patient condition, in light of somnolence and other adverse reactions that may occur more frequently at the increased dose, and efforts are made to reduce the increased dose when symptoms ameliorate. There is no major problem with the applicant's view.

PMDA considers that the final conclusion on the appropriateness of the above should be drawn on the basis of comments from the Expert Discussion.

7.R.7 Post-marketing investigations

The applicant plans to conduct a drug use-results survey as an additional pharmacovigilance activity focusing on the evaluation of risk factors for the effect of somnolence on daily functioning.

PMDA considers that the final conclusion on the appropriateness of post-marketing investigations should be drawn on the basis of comments from the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspection and data integrity assessment

Compliance assessment is now under way. The results and PMDA's conclusion will be reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

Compliance assessment is now under way. The results and PMDA's conclusion will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that lemborexant has efficacy in the treatment of insomnia and that lemborexant has acceptable safety in view of its benefits. Lemborexant is clinically meaningful because it offers a new treatment option for patients with insomnia. PMDA considers that the safety of lemborexant for CNS adverse events, the risk of carryover effect, and the appropriateness of investigations in the post-marketing surveillance should be further discussed and reviewed in the Expert Discussion.

PMDA has concluded that lemborexant may be approved if lemborexant is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 19, 2019

Product Submitted for Approval

Brand Name	Dayvigo Tablets 2.5 mg
	Dayvigo Tablets 5 mg
	Dayvigo Tablets 10 mg
Non-proprietary Name	Lemborexant
Applicant	Eisai Co., Ltd.
Date of Application	March 7, 2019

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusions in the "7.R.2.5 Patients with secondary insomnia," "7.R.3.1 Central nervous system events," "7.R.5 Indication," and "7.R.6 Dosage and administration" sections in the Review Report (1).

PMDA further discussed the following matters and took necessary actions.

1.1 Risk of carryover effect

PMDA's view on carryover effect:

- In Study E2006-E044-106, the difference from the placebo group in SDLP in driving performance was greater in subjects receiving lemborexant 10 mg than those receiving lemborexant 5 mg. This suggests that lemborexant 10 mg has higher risk of affecting driving performance than lemborexant 5 mg. The highest dose used in the driving performance study was 10 mg, and the exposure to lemborexant increases in the presence of drug interaction or in special patient populations [see Section 6.R]. The carryover effect of increased exposure is unknown.
- No significant problems were found for the ISI and daily functioning scores in Studies E2006-G000-303 and E2006-G000-304. However, in Studies E2006-G000-303 and E2006-G000-304, the incidence of

carryover effect-related adverse events including somnolence tended to be higher than the placebo group in the lemborexant 5 and 10 mg groups in a dose-dependent manner.

- At present, the possibility cannot be ruled out that lemborexant may induce narcolepsy or cataplexy.
- The above findings suggest that the risk of accidents may increase when somnolence, narcolepsy, or cataplexy is caused by lemborexant. Therefore, driving and the operations of hazardous machines should be prohibited through the package insert as practiced for the approved hypnotics.

The above PMDA's view was generally supported by the expert advisors. Meanwhile, some of the expert advisors made comments about cautionary advice concerning the driving performance study:

- High doses of lemborexant enhance its carryover effect and may increase risks in driving. Given this, the prohibition of driving and the operation of other hazardous machines is reasonable, as practiced for the use of other hypnotics. At the same time, the prohibition of driving on the day after a dose of hypnotic will discourage patients from receiving the drug therapy, and whether it is appropriate to allow previously untreated patients with insomnia to drive remains questionable from a viewpoint of medical care.
- The Guidelines for Psychiatrists for Driving by Patients (the Japanese Society of Psychiatry and Neurology, dated June 2014) has the following explanation about antipsychotics, antidepressants, anxiolytics, hypnotics, anticonvulsants, etc.: "These drugs may induce drowsiness and other adverse reactions that clearly affect driving performance, and therefore, caution should be given against them. … However, adverse drug reactions develop in diverse ways in each patient, and there is no solid medical basis to prohibit all patients on these drugs from driving. In fact, patients receiving these drugs engage in driving, and the prohibition of driving does not suit the real situation. More practical measures taken by prescribing physicians should be to instruct patients prior to treatment or dose increase to avoid driving for the first several days of treatment and to see if they have drowsiness, etc. carefully before the resumption of driving. Afterward, physicians should continue to give caution to the patient as needed." In the driving performance study (CTD 5.3.4.1.3, Study E2006-E044-106), driving performance at 9 hours post- lemborexant 10 mg dose tended to decrease mildly as compared with lemborexant 5 mg but showed no statistically significant effect as compared with placebo [see Section 6.2.5.2], suggesting that lemborexant may offer a safer therapeutic option for patients with insomnia for whom driving is inevitable.

In response to the above comments from the expert advisors, PMDA explained that, as reported in the Review Report (1), giving cautionary advice on lemborexant, which would be similar to those for the similar drug, is considered appropriate, in light of the carryover effect increased with a high dose of lemborexant, no sufficient data on the carryover effect with increased exposure, and prohibited car driving and other machine operations in the use of available hypnotics. The expert advisors accepted the PMDA's view.

Accordingly, PMDA requested the applicant to provide the following advice in the "Important Precautions" section of the package insert, and the applicant responded appropriately.

Important Precautions

The effect of lemborexant may persist until the next morning or later and may induce drowsiness and a decrease in attention, concentration, or reflex movement ability. Patients should be warned not to engage in driving and the operation of other hazardous machines.

1.2 Risk management plan (draft)

In view of the discussion presented in Section "7.R.7 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion that parasomnia, narcolepsy-related events, suicidal ideation, and suicidal behavior, as well as somnolence, should be investigated in the post-marketing setting, PMDA requested the applicant to investigate the these items through the post-marketing surveillance. The applicant agreed.

Further, in view of the discussion above, PMDA has concluded that the current risk management plan (draft) for lemborexant should include the safety specifications presented in Table 67 and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 68.

Table 67. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
・Sleep paralysis ・Somnolence	・Narcolepsy symptoms ・Parasomnia ・Possibility of abuse ・Suicidal ideation and suicidal behavior	None
Efficacy specification		
None		

Table 68. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
・Early post-marketing phase vigilance ・General use-results survey	・Preparation, revision, and provision of materials for healthcare professionals (proper use guide) ・Preparation, revision, and provision of materials for patients

In light of the above, PMDA instructed the applicant to conduct post-marketing surveillance to investigate the issues shown above.

The applicant responded that a general use-results survey (Table 69) will be conducted in patients with insomnia.

Table 69. Outline of a general use-results survey (draft)

Objective	To investigate the safety of lemborexant in clinical practice
Survey method	Central registration
Population	Patients with insomnia
Observation period	Up to 6 months
Planned sample size	300 patients
Main survey items	Patient characteristics (including age, sex, concurrent diseases, renal impairment/hepatic impairment, and insomnia symptom types) Details of treatment with lemborexant, previous pharmacotherapy for insomnia, concomitant drugs, and adverse events.

PMDA accepted the applicant's plan and considers that data obtained from the survey should be immediately provided to healthcare professionals.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.1 and 5.3.5.1.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and the dosage and administration modified as shown below, with the following condition. The product is a drug with a new active ingredient, and the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication Insomnia

Dosage and Administration

The usual adult dose is 5 mg of lemborexant orally administered once daily immediately before going to bed. The dose may be adjusted according to symptoms but should not exceed 10 mg once daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

List of Abbreviations

1-ABT	1-Aminobenzotriazole
ACTH	Adrenocorticotropic hormone
ALP	Alkaline phosphatase
AUC	Area Under Concentration-time Curve
BMI	Body mass index
CCMV	Complete case missing value
CHO	Chinese Hamster Ovary
CI	Confidence interval
CMA	Critical Material Attribute
C_{max}	Maximum Concentration
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DMSO	Dimethyl Sulfoxide
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ED_{50}	Effective Dose, 50%
EEG	Electroencephalogram
eGFR	estimated Glomerular Filtration Rate
E_{max}	Maximum effect
EMG	Electromyogram
ER	Extended Release
FAS	Full analysis set
FOB	Functional observational battery
FPD	Field potential duration
HEK	Human Embryonic Kidney
hERG	human Ether-à-go-go-related Gene
[redacted]	[redacted]
[redacted]	[redacted]
HPLC	High performance liquid chromatography
IC_{50}	Half Maximal (50%) Inhibitory Concentration
ICH Q1E Guidelines	Evaluation for Stability Data (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ICSD-3	International Classification of Sleep Disorders, version 3
IKs	Slow component of delayed rectifier potassium current
ISI	Insomnia Severity Index
K_i	Inhibitory Constant
KSS	Karolinska Sleepiness Scale
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
MAR	Missing at random
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MMRM	Mixed effect model repeated measurement
M-MSLT	Modified-Multiple Sleep Latency Test
MNAR	Missing not at random
MT1	Melatonin 1

NMR	Nuclear Magnetic Resonance Spectroscopy
NZW	New Zealand White
OX1R	Orexin receptor 1
OX2R	Orexin receptor 2
PET	Positron Emission Tomography
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population Pharmacokinetics
PSG	Polysomnography
PTP	Press Through Packaging
QbD	Quality by Design
QTcF	Fridericia-corrected QT
QTcI	QT interval corrected for individual heart rate
QTPP	Quality Target Product Profile
RH	Relative Humidity
SD	Sprague Dawley
SDLP	Standard deviation of lateral position
SNRI	Serotonin-Noradrenaline Reuptake Inhibitor
$t_{1/2}$	Elimination Half-life
TIBC	Total Iron Binding Capacity
t_{max}	Time to Reach Maximum Concentration
TTC	Threshold of Toxicological Concern
UIBC	Unsaturated Iron Binding Capacity
VAS	Visual Analog Scale