Report on the Deliberation Results

August 14, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Vorzzz Tablets 2.5 mg Vorzzz Tablets 5 mg Vorzzz Tablets 10 mg
Non-proprietary Name	Vornorexant Hydrate (JAN*)
Applicant	Taisho Pharmaceutical Co., Ltd.
Date of Application	September 12, 2024

Results of Deliberation

In its meeting held on July 31, 2025, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs 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 Condition

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

A committee member made the following comments on precautionary statements and information provision regarding the operation of hazardous machinery such as driving a motor vehicle:

- The draft plan for precautionary statements and information provision regarding the operation of hazardous machinery such as driving a motor vehicle includes the statement that patients should be cautioned about operating hazardous machinery such as driving a motor vehicle. However, precautionary statements and information in the package insert and materials for healthcare professionals and patients should be described in a manner that ensures that the associated risks are adequately understood, and should not lead to the understanding that driving a motor vehicle is acceptable if sufficient caution is exercised.
- To avoid misunderstanding of interpretation of the results from the driving performance assessment, the package insert and materials should include precautionary statements and provide detailed information on the test results. Then, if it is considered that the precautionary statements and information provision regarding the operation of hazardous machinery such as driving a motor vehicle, are based not only on the results of the driving performance assessment test but also on the

characteristics of the product, including subjective daytime sleepiness and assessment results on cognitive function in phase III studies, such information should also be included in the package insert and materials.

Based on the above, the First Committee on New Drugs concluded that precautionary statements and information provision regarding the operation of hazardous machinery such as driving a motor vehicle, should be provided through the package insert and materials reflecting the above comments from the committee members.

This conclusion does not change the results of the review.

**Japanese Accepted Name (modified INN)*

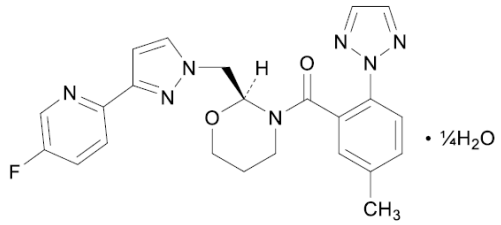
Review Report

July 4, 2025
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	Vorzzz Tablets 2.5 mg Vorzzz Tablets 5 mg Vorzzz Tablets 10 mg
Non-proprietary Name	Vornorexant Hydrate
Applicant	Taisho Pharmaceutical Co., Ltd.
Date of Application	September 12, 2024
Dosage Form/Strength	Uncoated tablets: Each tablet contains 2.525, 5.05, or 10.1 mg of vornorexant hydrate (2.5, 5, or 10 mg of vornorexant).
Application Classification	Prescription drug, (1) Drugs with a new active ingredient

Chemical Structure



Molecular formula: $C_{23}H_{22}FN_7O_2 \cdot 1/4H_2O$

Molecular weight: 451.97

Chemical name: [(2*S*)-2-{[3-(5-Fluoropyridin-2-yl)-1*H*-pyrazol-1-yl]methyl}-1,3-oxazinan-3-yl][5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl]methanone 1/4hydrate

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. 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 dosage is 5 mg of vornorexant orally administered once daily just before bedtime.

The dose may be adjusted according to the patient’s symptoms. The dose 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)

May 27, 2025

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	Vorzzz Tablets 2.5 mg Vorzzz Tablets 5 mg Vorzzz Tablets 10 mg
Non-proprietary Name	Vornorexant Hydrate
Applicant	Taisho Pharmaceutical Co., Ltd.
Date of Application	September 12, 2024
Dosage Form/Strength	Uncoated tablets: Each tablet contains 2.525, 5.05, or 10.1 mg of vornorexant hydrate (2.5, 5, or 10 mg of vornorexant).

Proposed Indication
Insomnia

Proposed Dosage and Administration
The usual adult dosage is 5 mg of vornorexant orally administered once daily just before bedtime.

The dose may be adjusted according to the patient's symptoms. The dose 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

Insomnia is a pathologically hyperarousal condition and represents an inability to fall asleep or maintain sleep associated with an insufficient decline in brain activity from waking to sleep states (*Am J Psychiatry.* 2004;161:2126-9). Orexinergic neurons release orexin A and orexin B as neurotransmitters, which stimulate orexin receptors expressed on the downstream neurons and thereby maintain wakefulness (*Cell.* 1998;92:573-85, *Brain Res.* 2005;1048:138-45, etc.).

The active ingredient of Vorzzz Tablets is vornorexant hydrate (hereinafter referred to as vornorexant), which is an antagonist of orexin receptor type 1 (OX1R) and orexin receptor type 2 (OX2R). By inhibiting signal transduction involved in wakefulness promotion, vornorexant is expected to facilitate the transition from excessive wakefulness to sleep. In Japan, suvorexant, lemborexant, and daridorexant hydrochloride have been approved as OX1R and OX2R antagonists for the indication of insomnia.

The applicant has now submitted a marketing application for this drug based on the results of Japanese phase III studies, which demonstrated efficacy and safety of vornorexant in the treatment of insomnia.

As of May 2025, vornorexant has not been approved in any country or region outside Japan.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance occurs as a white powder. Its general properties, including description, X-ray powder diffraction, solubility, hygroscopicity, melting point, pH, thermal analysis, optical rotation, dissociation constant, partition coefficient, and crystalline polymorphism, have been determined. The drug substance is known to exist in both hydrates and anhydrides, but the commercial manufacturing process is confirmed to produce the drug substance in the hydrate form.

The chemical structure of the drug substance has been elucidated by elemental analysis, ion chromatography, ultraviolet-visible spectrophotometry, infrared spectrophotometry, nuclear magnetic resonance spectroscopy, mass spectrometry, and X-ray crystallography. The drug substance is confirmed to have a single asymmetric carbon atom, which is *S*-configured in terms of absolute configuration.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted][1)] and [redacted][2)] as starting materials.

Quality by design (QbD) approaches were utilized to identify critical quality attributes (CQAs) and critical process parameters (CPPs), and thereby the quality control strategy was developed (Table 1).

1) [redacted]
2) [redacted]

Table 1. Overview of drug substance control strategy

CQA	Method of control
Identification	Manufacturing process and specifications
Content	Manufacturing process and specifications
[redacted]	Manufacturing process and specifications
Related substances	Manufacturing process and specifications
[redacted]	Manufacturing process
[redacted]	Manufacturing process
[redacted]	Manufacturing process
Residue on ignition	Manufacturing process and specifications
[redacted]	Manufacturing process

[redacted][3)] and [redacted] as well as [redacted] have been defined as critical steps. [redacted] has been controlled as a critical intermediate.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (infrared absorption spectroscopy), purity (related substances [high performance liquid chromatography (HPLC)], Impurity X [HPLC]), water content, residue on ignition, and assay (HPLC).

2.1.4 Stability of drug substance

Table 2 shows main stability studies of the drug substance, which was found stable. The photostability study showed that the drug substance is photostable.

Table 2. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 pilot-scale batches	25 ± 2°C	60 ± 5%RH	Double-layered low density polyethylene bags	24 months
Accelerated testing	3 pilot-scale batches	40 ± 2°C	75 ± 5%RH		6 months

Based on the above, a retest period of 36 months has been proposed for the drug substance when stored in double-layered low density polyethylene bags at room temperature in accordance with "Guideline on Evaluation of Stability Data" (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Q1E guideline). The long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is uncoated tablets, each containing 2.525, 5.05, or 10.1 mg of vornorexant hydrate (2.5, 5, or 10 mg of vornorexant) (with score line only for 5 mg tablets). The drug product contains the following excipients: lactose hydrate, microcrystalline cellulose, hydroxypropylcellulose, sodium starch glycolate, magnesium stearate, and yellow ferric oxide (10 mg tablets only).

3) [redacted]

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of the following steps: granulation, drying, sizing, blending, tableting, packaging, and testing/storage. [redacted] has been defined as the critical step. Process control items and action limits have been established for the [redacted], [redacted], and [redacted] steps.

QbD approaches were utilized to identify CQAs and CPPs, and thereby the quality control strategy was established (Table 3).

Table 3. Overview of drug product control strategy

CQA	Method of control
Strength	Manufacturing process and specifications
Description	Specifications
Identification	Specifications
Related substances	Manufacturing process and specifications
Uniformity of dosage units	Manufacturing process and specifications
Dissolution	Manufacturing process and specifications
[redacted]	Manufacturing process

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (HPLC, ultraviolet spectroscopy), purity (related substances [HPLC]), uniformity of dosage units (content uniformity test [HPLC]), dissolution, and assay (HPLC). Purity (related substances [HPLC]) was established in the course of the review.

2.2.4 Stability of drug product

Table 4 shows main stability studies of the drug product, which was found stable. The photostability study showed that the drug product is photostable.

Table 4. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 pilot-scale batches	25 ± 2°C	60 ± 5%RH	Blister pack/ aluminum foil bag	24 months
Accelerated testing	3 pilot-scale batches	40 ± 2°C	75 ± 5%RH		6 months

Based on the above, a shelf life of 36 months has been proposed for the drug product when blister packs (polypropylene film/aluminum foil) of the tablets are packaged in aluminum foil bags and stored at room temperature in accordance with the ICH Q1E guidelines. 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 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

The applicant submitted non-clinical pharmacology data for vornorexant in the form of results from primary pharmacodynamic studies, secondary pharmacodynamic studies, and safety pharmacology

studies. Non-clinical pharmacology studies included investigations of vornorexant's metabolites (M1[4] and M3[5]), but exposures to these metabolites in humans were both confirmed to be below 10% of the total plasma exposure after oral administration of vornorexant [see Section 6.2.5].

Unless otherwise specified, 0.5%(w/v) methylcellulose aqueous solution was used as a vehicle in *in vivo* studies.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding capacity to orexin receptors (CTD 4.2.1.1-1)

Membrane preparations from cells expressing recombinant human OX1R or OX2R were used to investigate the inhibitory effects of vornorexant and its metabolites (M1 and M3) on OX1R and OX2R in radioligand-receptor binding assays. Table 5 shows the investigation results.

Table 5. Inhibitory effects on human OX1R and OX2R

Binding inhibition constant (nmol/L)					
Vornorexant		M1		M3	
OX1R	OX2R	OX1R	OX2R	OX1R	OX2R
0.460	0.374	2.08	2.72	2.22	3.39

Mean of triplicate assays

3.1.1.2 Effects on orexin receptors (CTD 4.2.1.1-2, 4.2.1.1-3, 4.2.1.1-4, 4.2.1.1-7, 4.2.1.1-8, 4.2.1.1-9, and 4.2.1.1-10)

Chinese hamster ovary (CHO) cells expressing recombinant human or rat OX1R or OX2R were used to investigate agonistic effects of vornorexant and its metabolites (M1 and M3) (0.01-10000 nmol/L for each) on OX1R and OX2R based on the maximum change in fluorescence intensity of a calcium-sensitive fluorescent dye (calcium indicator) incorporated in the cells. None of them exhibited agonistic effects on human OX1R or OX2R. Inhibitory effects of vornorexant and its metabolites (M1 and M3) on an increase in intracellular Ca^{2+} concentration induced by [Ala$^{6,\ 12}$]Orexin-A (Ala-OXA) was investigated. All inhibited the increase in a concentration-dependent manner. Table 6 shows their equilibrium dissociation constant.

Table 6. Inhibitory effects of vornorexant and its metabolites on OX1R and OX2R

	Equilibrium dissociation constant (nmol/L)					
	Vornorexant		M1		M3	
	OX1R	OX2R	OX1R	OX2R	OX1R	OX2R
Human	0.67	0.84	2.22	3.27	1.52	1.69
Rat	0.44	0.80	1.13	2.40	1.09	1.97

Mean of triplicate assays

3.1.2 *In vivo* study

3.1.2.1 Effects on sleep (CTD 4.2.1.1-5, 4.2.1.1-6, and 4.2.1.1-11)

A single dose of vehicle, vornorexant (1, 3, or 10 mg/kg), or metabolite M3 (0.1, 1, or 10 mg/kg) was orally administered to rats just before the start of a dark phase to investigate the effects of vornorexant on sleep as assessed by EEG and EMG. Compared with vehicle, vornorexant at any dose shortened sleep

4) Vornorexant's metabolite with the hydroxylated methyl group of the methylphenyl moiety
5) Vornorexant's metabolite with the dehydrogenated oxazinane ring

latency and increased REM sleep percentage up to 2 hours post dose, non-REM sleep percentage, and total sleep percentage. Compared with vehicle, metabolite M3 at 10 mg/kg shortened sleep latency and increased REM sleep percentage up to 2 hours post dose.

3.2 Secondary pharmacodynamics

3.2.1 Study for off-target effects (CTD 4.2.1.2-1, 4.2.1.2-2, and 4.2.1.2-3)

A binding study using 90 types of target molecules (receptors, transporters, and ion channels) was conducted to investigate binding capacity of vornorexant (1 and 10 μmol/L) and metabolite M3 (1 and 10 μmol/L).

Vornorexant inhibited the NK_1 receptor, dopamine transporter, and sigma 2 receptor by ≥50%. Metabolite M3 inhibited the NK_1 receptor by ≥50%. The applicant explained that the observed off-target effects would not cause a problematic trend in clinical use because the concentrations of vornorexant and metabolite M3 which result in 50% inhibition (IC_{50}) values were 22 and 290 times higher than exposures to their unbound forms at the maximum clinical dose of vornorexant (10 mg/day).

3.2.2 Effects on motor coordination (CTD 4.2.1.2-4 and CTD 4.2.1.2-5)

A single dose of vehicle, vornorexant (3, 10 or 30 mg/kg), or zolpidem (10 mg/kg) alone was orally administered to rats, and motor coordination was investigated by rotarod test. Zolpidem caused motor coordination disorders, but vornorexant at any dose had no effects. When orally administered to rats treated with ethanol (1 g/kg), a single dose of zolpidem (3 mg/kg) caused motor coordination disorders, but a single dose of vornorexant (30 mg/kg) had no effects.

3.3 Safety pharmacology

Table 7 shows a summary of safety pharmacology studies.

Table 7. Summary of safety pharmacology studies

Item	Animal species	Evaluation items and methods	Dose of vornorexant	Route of administration	Findings	CTD
Central nervous system	SD rat (6 males/group)	Modified Irwin method	0, 100, 300, 1000 mg/kg	Oral	0, 100 mg/kg: No effects 300, 1000 mg/kg: Abnormal posture	4.2.1.3-1
Cardiovascular system	HEK293 cells (5 preparations/ group)	hERG current	0, 3, 10, 30 μmol/L	*In vitro*	0, 3, 10 μmol/L: No effects 30 μmol/L: Inhibited by 23.2%	4.2.1.3-2
	Dog (4 males)	Blood pressure, heart rate, electrocardiogram	0, 0.4, 2, 10 mg/kg	Oral	2, 10 mg/kg: Decreased heart rate 0.4, 2, 10 mg/kg: QT interval prolonged, QTc interval prolonged	4.2.1.3-3
Respiratory system	SD rat (8 males/group)	Tidal volume, respiratory rate, and minute ventilation	0, 100, 300, 1000 mg/kg	Oral	No effects	4.2.1.3-4

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effects of vornorexant

The applicant's explanation about the pharmacological effects of vornorexant:
Orexin plays an important role in stabilization and control of sleep and wakefulness (*Protein, Nucleic Acid and Enzyme.* 2007;52:1840-8), and 2 neuropeptides, orexin A and orexin B, have been identified. Orexin receptor has 2 subtypes, OX1R and OX2R, both of which are expressed on neurons that maintain wakefulness in the brain (*Nat Rev Neurosci.* 2007;8:171-81, *J Comp Neurol.* 2001;435:6-25). Orexin A has similar affinity to OX1R and OX2R, but orexin B has higher affinity to OX2R than to OX1R (*Cell.* 1998;92:573-85).

The submitted pharmacology data showed that vornorexant selectively bound to OX1R and OX2R and inhibited these receptors [see Sections 3.1.1 and 3.2.1]. In addition, vornorexant shortened sleep latency and increased the percentage of REM and non-REM sleep up to 2 hours post dose in rats [see Section 3.1.2].

Based on the above, the applicant considers that vornorexant can be expected to be effective in the treatment of insomnia.

Based on the submitted data on primary pharmacodynamics, PMDA considers that vornorexant is demonstrated to have certain effects on sleep and wakefulness.

3.R.2 Safety pharmacology

The applicant's explanation about the mechanism of occurrence of findings in the central nervous and cardiovascular systems (decreased heart rate, QT interval prolonged, and corrected QT [QTc] interval prolonged) observed in the safety pharmacology studies:
Abnormal postures (stretched posture without and with limb extension) observed in rats were considered attributable to sleep behavior associated with the sleep-inducing effect of vornorexant, because the doses studied exceeded the sleep-inducing dose in rats. In clinical studies of vornorexant, adverse events in the central nervous system such as somnolence were also observed.

The decreased heart rate observed in dogs was within the range of physiological responses during sleep in dogs (*Animals [Basel].* 2018;8:107, *Front Behav Neurosci.* 2019;13:207, etc.). Although orexin A and orexin B have been reported to increase heart rate as an effect on the cardiovascular system (*Am J Physiol.* 1999;277:R1780-5), heart rates in orexin A and orexin B-knockout mice and orexin neuron-deficient rats were similar to those in wild-type animals (*J Appl Physiol.* [1985] 2010;109:1053-63, etc.). Thus, the inhibitory effects of vornorexant on OX1R and OX2R, its pharmacological effect, is considered not to affect heart rate. The QT interval and QTc interval prolonged observed in dogs were similar to physiological responses during sleep in dogs (*J Toxicol Sci.* 2005;30:229-37) in terms of their extent and showed neither correlation with plasma vornorexant concentrations nor a dose-response relationship. Based on the above, the findings in the cardiovascular system were all considered attributable to sleep behavior associated with the sleep-inducing effect of vornorexant. For the following reasons, the applicant considered that adverse events involving the cardiovascular system in clinical use of vornorexant are unlikely to pose clinical problems: (a) in a Japanese long-term treatment study (Study

302 [Japanese phase III study (Study TS142-302)]), a clinical study of vornorexant in patients with insomnia, adverse events involving the cardiovascular system were atrial fibrillation, bradycardia and ventricular extrasystoles (1 patient each) in the vornorexant 5 mg group and extrasystoles and palpitations (1 patient each) in the vornorexant 10 mg group; however, all of the events, except atrial fibrillation, were mild, and none of them were observed in the other clinical studies; and (b) QT/QTc evaluation study revealed that vornorexant is unlikely to affect QT/QTc [see Section 6.2.6].

PMDA accepted the applicant's explanation about the mechanism of occurrence of findings in the central nervous and cardiovascular systems.

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

The applicant submitted data on absorption, distribution, metabolism, and excretion of vornorexant in mice, rats, rabbits, and dogs in the form of results from non-clinical pharmacokinetic studies. Concentrations of vornorexant and its metabolites (M1 and M3) in biological samples were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS), and the lower limit of quantification was 0.1 ng/mL for plasma concentrations in rats and dogs, 0.5 ng/mL for brain concentrations in rats, and 0.2 ng/mL for cerebrospinal fluid (CSF) concentrations in rats. The [^{14}C]vornorexant used was a [pyrazole ring-^{14}C]vornorexant and/or [carbonyl -^{14}C]vornorexant. Main study results are provided below.

4.1 Absorption

4.1.1 Single-dose studies

A single dose of vornorexant was orally or intravenously administered to male and female rats in the fasted state. Table 8 shows pharmacokinetic parameters of vornorexant and its metabolites (M1 and M3) (CTD 4.2.2.2-4). Both C_{max} and $AUC_{0-\infty}$ of vornorexant and its metabolites (M1 and M3) after an oral or intravenous administration tended to be higher in females than in males. However, the applicant explained that the difference was attributable to sex-related differences in cytochrome P450 (CYP) expression and metabolic activity in rats.

Table 8. Plasma pharmacokinetic parameters in male and female rats after a single-dose administration of vornorexant

Analyte	Sex	Route of administration	Dose of vornorexant (mg/kg)	No. of animals	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	Bioavailability[a)] (%)
Vornorexant	Male	Oral	3	3	55.4 ± 36.5	0.67 ± 0.29	107 ± 66	0.96 ± 0.43	7.6
		Intravenous	1	3	-	-	467 ± 34	0.37 ± 0.07	
	Female	Oral	3	3	392 ± 32	1.0 ± 0.0	752 ± 31	0.75 ± 0.30	33.3
		Intravenous	1	3	-	-	753 ± 150	0.43 ± 0.03	
M1	Male	Oral	3	3	82.5 ± 46.5	0.83 ± 0.29	176 ± 100	1.1 ± 0.2	
		Intravenous	1	3	41.7 ± 8.3	0.25 ± 0.00	36.4 ± 9.1	1.1 ± 0.2	
	Female	Oral	3	3	493 ± 23	1.0 ± 0.0	1700 ± 90	2.4 ± 0.2	
		Intravenous	1	3	231 ± 33	0.83 ± 0.29	559 ± 155	1.8 ± 0.7	
M3	Male	Oral	3	3	30.9 ± 14.9	1.0 ± 0.0	69.2, 103[b)]	1.1, 1.3[b)]	
		Intravenous	1	3	18.0 ± 1.1	0.25 ± 0.00	16.9 ± 1.6	0.58 ± 0.15	
	Female	Oral	3	3	92.6 ± 30.0	1.0 ± 0.0	211 ± 63	0.80 ± 0.13	
		Intravenous	1	3	37.7 ± 16.7	0.83 ± 0.29	34.5, 86.2[b)]	0.71, 0.78[b)]	

-, Not calculated
Mean ± standard deviation (SD)
a) ($AUC_{0-\infty}$ after oral administration/oral dose)/($AUC_{0-\infty}$ after intravenous administration/intravenous dose) × 100
b) Individual values from 2 animals

A single dose of vornorexant was orally or intravenously administered to male dogs in the fasted state. Table 9 shows pharmacokinetic parameters of vornorexant and its metabolites (M1 and M3) (CTD 4.2.2.2-8).

Table 9. Plasma pharmacokinetic parameters in male dogs after a single-dose administration of vornorexant

Analyte	Route of administration	Dose of vornorexant (mg/kg)	No. of animals	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	Bioavailability[a)] (%)
Vornorexant	Oral	3	3	2360 ± 460	1.3 ± 0.6	10700 ± 1800	2.7 ± 0.8	58.0 ± 9.9
	Intravenous	0.5	3	-	-	3100 ± 380	1.3 ± 0.4	
M1	Oral	3	3	491 ± 77	2.0 ± 0.0	3500 ± 340	4.6 ± 0.6	
	Intravenous	0.5	3	170 ± 34	1.7 ± 0.6	944 ± 129	3.5 ± 0.7	
M3	Oral	3	3	134 ± 33	2.0 ± 0.0	1250 ± 370	5.2 ± 2.5	
	Intravenous	0.5	3	48.2 ± 12.8	1.7 ± 0.6	321 ± 51	3.5 ± 1.2	

-, Not calculated
Mean ± SD
a) ($AUC_{0-\infty}$ after oral administration/oral dose)/($AUC_{0-\infty}$ after intravenous administration/intravenous dose) × 100

A single dose of [^{14}C]vornorexant was orally administered to male rats and male dogs in the fasted state. Table 10 shows pharmacokinetic parameters of radioactivity in plasma (CTD 4.2.2.2-1, 4.2.2.2-2, and 4.2.2.2-3).

Table 10. Pharmacokinetic parameters of radioactivity in plasma after single oral administration of vornorexant

Test article	Animal species	Route of administration	Dose of vornorexant (mg/kg)	No. of animals	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	Oral absorption rate[a)] (%)
[pyrazole ring-^{14}C] vornorexant	Rat	Oral	3	3	2900 ± 250	0.25 ± 0.00	3890 ± 460	44 ± 8	83.7
		Intravenous	1	3	-	-	1550 ± 30	58 ± 4	
[carbonyl-^{14}C] vornorexant	Rat	Oral	3	3	1780 ± 820	0.25 ± 0.00	4480 ± 1370	67 ± 54	78.6
		Intravenous	1	3	-	-	1900 ± 110	61 ± 5	
	Dog	Oral	3	3	5950 ± 370	1.0 ± 0.0	54800 ± 12400	170 ± 40	74.9
		Intravenous	0.5	3	-	-	12200 ± 4000	170 ± 50	

-, Not calculated
Mean ±SD
a) ($AUC_{0-\infty}$ after oral administration/oral dose)/($AUC_{0-\infty}$ after intravenous administration/intravenous dose) × 100

4.1.2 Repeated-dose studies

4.1.2.1 Repeated-dose study in rats

In a toxicity study, vornorexant was orally administered to male and female rats for 26 weeks on a repeated-dose regimen to investigate the toxicokinetics. Table 11 shows pharmacokinetic parameters of vornorexant and its metabolites (M1 and M3) (CTD 4.2.3.4.1-1). C_{max} and AUC_{0-24h} of vornorexant and its metabolites (M1 and M3) generally increased in a dose-proportional manner, and no accumulation was observed after repeated administration at any dose. C_{max} and AUC_{0-24h} of vornorexant and its metabolites (M1 and M3) tended to be higher in females than in males. However, the applicant explained that the difference was attributable to sex-related differences in CYP expression and metabolic activity in rats.

Table 11. Plasma pharmacokinetic parameters in rats which orally received vornorexant on a repeated-dose regimen for 26 weeks

Sex	Dose of vornorexant (mg/kg/day)	Sampling time point	No. of animals	Vornorexant			M1			M3		
				C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng·h/mL)
Male	300	Day 1	3	859 ± 86	3.3 ± 1.2	7180 ± 1460	698 ± 83	3.3 ± 1.2	5800 ± 1220	324 ± 58	2.7 ± 1.2	2980 ± 850
		Week 26	3	578 ± 292	6.7 ± 2.3	7750 ± 3640	615 ± 136	1.8 ± 1.9	7240 ± 2480	185 ± 52	4.2 ± 3.8	2510 ± 730
	1000	Day 1	3	1110 ± 750	4.0 ± 0.0	10400 ± 8100	772 ± 362	3.3 ± 1.2	6970 ± 4450	389 ± 283	3.3 ± 1.2	3830 ± 3140
		Week 26	3	424 ± 358	5.3 ± 2.3	4710 ± 3920	397 ± 268	5.3 ± 2.3	4250 ± 2610	156 ± 100	5.3 ± 2.3	1800 ± 1080
	1500	Day 1	3	2750 ± 1450	4.0 ± 0.0	26500 ± 10100	1760 ± 830	4.0 ± 0.0	18500 ± 6800	841 ± 342	4.0 ± 0.0	10300 ± 3500
		Week 26	3	1180 ± 450	6.7 ± 2.3	14800 ± 5200	948 ± 323	3.3 ± 1.2	11900 ± 3800	314 ± 93	6.7 ± 2.3	4470 ± 1190
Female	30	Day 1	3	1740 ± 690	2.7 ± 1.2	10800 ± 1900	1290 ± 260	2.7 ± 1.2	8630 ± 690	252 ± 118	2.7 ± 1.2	1960 ± 800
		Week 26	3	1390 ± 440	2.0 ± 0.0	8380 ± 2570	1270 ± 230	2.0 ± 0.0	8920 ± 940	334 ± 41	2.0 ± 0.0	2780 ± 1080
	100	Day 1	3	2890 ± 350	3.3 ± 1.2	18900 ± 1300	4000 ± 1050	4.0 ± 0.0	30500 ± 11700	309 ± 78	3.3 ± 1.2	3050 ± 830
		Week 26	3	2060 ± 740	3.5 ± 4.0	18500 ± 12600	2860 ± 900	4.7 ± 3.1	29100 ± 12100	531 ± 321	4.2 ± 3.8	5710 ± 4360
	300	Day 1	3	5440 ± 1270	4.0 ± 0.0	40100 ± 8300	4580 ± 830	4.0 ± 0.0	36200 ± 9300	512 ± 104	5.3 ± 2.3	5390 ± 2230
		Week 26	3	1860 ± 250	6.7 ± 2.3	19000 ± 1800	2270 ± 720	5.3 ± 2.3	24900 ± 5400	493 ± 114	5.3 ± 2.3	6100 ± 1400

Mean ± SD

4.1.2.2 Repeated-dose study in dogs

In a toxicity study, vornorexant was orally administered to male and female dogs for 39 weeks on a repeated-dose regimen to investigate the toxicokinetics. Table 12 shows pharmacokinetic parameters of vornorexant and its metabolites (M1 and M3) (CTD 4.2.3.2-7). C_{max} and AUC_{0-24h} of vornorexant and its metabolites (M1 and M3) generally increased in a dose-proportional manner and tended to be slightly higher at Week 39 than on Day 1; however, due to large inter-animal variability, no clear accumulation was observed after repeated administrations. Pharmacokinetics of vornorexant did not differ substantially between males and females.

Table 12. Plasma pharmacokinetic parameters in dogs which orally received vornorexant on a repeated-dose regimen for 39 weeks

Sex	Dose of vornorexant (mg/kg/day)	Sampling time point	No. of animals	Vornorexant			M1			M3		
				C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng·h/mL)
Male	60	Day 1	3	5550 ± 670	1.5 ± 0.9	33200 ± 3600	1650 ± 170	3.3 ± 1.2	15200 ± 1500	406 ± 59	4.0 ± 0.0	4660 ± 680
		Week 39	3	8260 ± 1140	1.7 ± 0.6	49000 ± 4200	2500 ± 730	2.7 ± 1.2	29200 ± 9300	372 ± 75	5.3 ± 2.3	4740 ± 550
	300	Day 1	3	8000 ± 4570	1.3 ± 0.6	36300 ± 24700	2780 ± 1450	2.7 ± 1.2	18800 ± 14200	308 ± 61	3.3 ± 1.2	2780 ± 1480
		Week 39	3	7930 ± 2600	1.3 ± 0.6	43200 ± 15900	3150 ± 1820	2.0 ± 0.0	29000 ± 18600	366 ± 142	2.0 ± 2.0	4570 ± 1550
	1000	Day 1	5	7700 ± 1840	5.8 ± 10.2	65600 ± 23100	2650 ± 1760	7.2 ± 9.4	29100 ± 23000	582 ± 154	8.0 ± 8.9	9020 ± 4030
		Week 39	5	19100 ± 7700	1.8 ± 0.4	158000 ± 83000	5100 ± 2010	2.8 ± 1.1	59300 ± 26200	1450 ± 1110	4.8 ± 3.3	23300 ± 18400
Female	60	Day 1	3	5580 ± 3230	2.0 ± 0.0	45700 ± 34400	1240 ± 410	3.3 ± 1.2	16700 ± 10800	311 ± 104	4.0 ± 0.0	4310 ± 2460
		Week 39	3	8140 ± 4500	1.3 ± 0.6	60700 ± 42700	2140 ± 1040	4.0 ± 0.0	25800 ± 14500	439 ± 260	5.3 ± 2.3	5830 ± 3850
	300	Day 1	3	7620 ± 1150	1.0 ± 0.9	57200 ± 17000	1430 ± 130	2.7 ± 1.2	18400 ± 1700	480 ± 215	10 ± 12	6640 ± 3330
		Week 39	3	10500 ± 3000	1.3 ± 0.6	90100 ± 42800	2160 ± 670	3.3 ± 1.2	28500 ± 9200	675 ± 361	5.3 ± 2.3	10500 ± 6200
	1000	Day 1	5	10500 ± 2700	1.4 ± 0.5	59200 ± 14700	4150 ± 2650	2.8 ± 1.1	30600 ± 12900	483 ± 142	3.2 ± 1.1	5900 ± 1550
		Week 39	5	11700 ± 2800	1.6 ± 0.5	94800 ± 28500	3710 ± 1100	3.6 ± 0.9	44100 ± 14200	691 ± 386	4.8 ± 1.8	10200 ± 5300

Mean ± SD

4.2 Distribution

4.2.1 Tissue distribution in rats

A single dose of [^{14}C]vornorexant 3 mg/kg was orally administered to male rats, and radioactivity concentrations in each tissue[6)] at 0.5, 2, 6, 24, 72, 168, and 336 hours post-dose were determined (CTD 4.2.2.3-1). When [carbonyl-^{14}C]vornorexant was administered, radioactivity concentrations peaked in the small intestine and mesenteric lymph node at 2 hours post-dose and in the other tissues at 0.5 hours post-dose. When [pyrazole ring-^{14}C]vornorexant was administered, the radioactivity concentration in all tissues peaked at 0.5 hours post-dose. Tissues in which the radioactivity concentration at 0.5 hours post-dose was higher than that in blood were bladder, liver, kidney, stomach, small intestine, lung, and adrenal gland after administration of [pyrazole ring-^{14}C]vornorexant, and the liver and kidney after administration of [carbonyl-^{14}C]vornorexant. For either radioactive compound administered, radioactivity concentrations decreased over time and were not detected in any tissue at 336 hours post-dose.

A single dose of vornorexant 3 mg/kg was orally administered to male rats, and its transfer into the central nervous system up to 4 hours post-dose was investigated (CTD 4.2.2.2-4). Concentrations of vornorexant and its metabolites (M1 and M3) in the brain and CSF remained lower than plasma concentrations at any time point.

6) Radioactivity concentrations in the following tissues were determined: Blood, cerebellum, cerebrum, medulla oblongata, pituitary gland, eye ball, Harderian gland, submandibular gland, thyroid, spinal cord, thymus, heart, lung, liver, adrenal gland, kidney, spleen, pancreas, prostate gland, testis, epididymis, vesicular gland, aorta, bladder, bone, bone marrow, skeletal muscle, white skin, pigmented skin, white fat, brown fat, mesenteric lymph node, stomach, small intestine, cecum, and large intestine.

4.2.2 Protein binding

Plasma protein binding of [carbonyl-^{14}C]vornorexant (0.05-20 μg/mL as vornorexant hydrate) and metabolite M3 (0.05-10 μg/mL) was investigated using plasma specimens from mice, rats, rabbits, and dogs. The mean protein binding was 91.6% to 92.9%, 89.4% to 92.6%, 86.6% to 88.4%, and 93.6% to 97.7% for [carbonyl-^{14}C]vornorexant and 96.0% to 97.1%, 96.2% to 97.1%, 94.5% to 95.3%, and 96.4% to 98.7% for metabolite M3, respectively. For either compound, no concentration dependency was observed (CTD 4.2.2.3-2 and CTD 4.2.2.3-3).

4.2.3 Placental and fetal transfer

A single dose of [carbonyl-^{14}C]vornorexant 3 mg/kg was orally administered to pregnant rats on Gestation Day 18, and radioactivity concentrations in maternal and fetal tissues[7)] were investigated (CTD 4.2.2.3-5). In all the maternal and fetal tissues in which radioactivity concentrations were determined (except amniotic fluid), the concentrations peaked at 0.5 hours post-dose and then decreased over time. The detection of radioactivity in fetal tissues suggested that vornorexant crosses the placenta and is transferred to the fetus.

4.3 Metabolism

4.3.1 *In vitro* metabolism

Incubation of [^{14}C]vornorexant or vornorexant with rat and dog hepatocytes resulted in production of various metabolites including the primary metabolites of vornorexant, M1 and M3, in both animal species (CTD 4.2.2.4-5).

4.3.2 *In vivo* metabolism

A single dose of [^{14}C]vornorexant 3 mg/kg was orally administered to male rats to determine the percentages of vornorexant and its metabolites in plasma, urine, and feces, and to bile duct-cannulated male rats to determine the percentages of vornorexant and its metabolites in bile (CTD 4.2.2.4-1-3). Among vornorexant and 12 metabolites structurally identified or estimated in plasma, M10 was the most abundant at 0.5 hours after administration of [pyrazole ring-^{14}C]vornorexant (51.2% of the total radioactivity in plasma), whereas M12 was the most abundant after administration of [carbonyl-^{14}C]vornorexant (26.2% of the total radioactivity in plasma). At 4 hours after administration of [pyrazole ring-^{14}C]vornorexant, only M10 was detected (66.2% of the total radioactivity in plasma), whereas at the same time point after administration of [carbonyl-^{14}C]vornorexant, none were detected. In urine up to 8 hours post-dose, vornorexant was not detected, and 4 metabolites were detected. After administration of [pyrazole ring-^{14}C]vornorexant, M10 was the most abundant (47.6% of the administered radioactivity), whereas after administration of [carbonyl-^{14}C]vornorexant, M12 was the most abundant (13.7% of the administered radioactivity). In feces up to 24 hours post-dose, vornorexant was not detected, and 8 metabolites were detected. After administration of either [pyrazole ring-^{14}C]vornorexant or [carbonyl-^{14}C]vornorexant, M5 was the most abundant (11.7% or 10.2% of the administered radioactivity, respectively). In bile up to 8 hours post-dose, vornorexant was not detected,

7) Radioactivity concentrations in the following tissues were determined: Maternal blood, brain, heart, lung, liver, kidney, ovary, uterus, placenta, amniotic fluid, embryonic membrane, and mammary gland; and fetal whole body, blood, brain, heart, lung, liver, and kidney.

and 7 metabolites were detected (the most abundant metabolite accounted for 10.6% of the administered radioactivity).

A single dose of [carbonyl-^{14}C]vornorexant 3 mg/kg was orally administered to male dogs to determine percentages of vornorexant and its metabolites in plasma, urine, and feces (CTD 4.2.2.4-4). In plasma at 1 and 4 hours post-dose, vornorexant was the most abundant (55.1% and 33.5% of the total radioactivity in plasma, respectively). In urine up to 24 hours post-dose, vornorexant was not detected, and 6 metabolites were detected with M12 being the most abundant (27.4% of the administered radioactivity). In feces up to 48 hours post-dose, vornorexant was not detected, and 13 metabolites were detected (the most abundant metabolite accounted for 5.7% of the administered radioactivity).

4.4 Excretion

4.4.1 Excretion into urine, feces, and expired air in rats and dogs

A single dose of [pyrazole ring-^{14}C]vornorexant was orally administered at 3 mg/kg or intravenously administered at 1 mg/kg to male rats. Excretion rates of radioactivity in urine, feces, and expired air up to 168 hours post-dose were 56.9%, 41.8%, and 0.3% after the oral administration and 57.4%, 39.6%, and 0.4% after the intravenous administration (CTD 4.2.2.2-1), respectively.

A single dose of [carbonyl-^{14}C]vornorexant was orally administered at 3 mg/kg or intravenously administered at 1 mg/kg to male rats. Excretion rates of radioactivity in urine and feces up to 168 hours post-dose were 35.1% and 58.9% after the oral administration and 40.0% and 58.0% after the intravenous administration, respectively, and no radioactivity was excreted in expired air (CTD 4.2.2.2-2).

A single dose of [carbonyl-^{14}C]vornorexant was orally administered at 3 mg/kg or intravenously administered at 0.5 mg/kg to male dogs. Excretion rates of radioactivity in urine and feces up to 168 hours post-dose were 51.1% and 45.3% after the oral administration and 44.5% and 52.9% after the intravenous administration, respectively (CTD 4.2.2.2-3).

4.4.2 Excretion into bile in rats

A single dose of [pyrazole ring-^{14}C]vornorexant was orally administered at 3 mg/kg or intravenously administered at 1 mg/kg to bile duct-cannulated male rats. Excretion rates of radioactivity in bile, urine, and feces up to 48 hours post-dose were 42.1%, 50.5%, and 7.8% after the oral administration and 44.8%, 50.2%, and 2.7% after the intravenous administration, respectively (CTD 4.2.2.2-1).

A single dose of [carbonyl-^{14}C]vornorexant was orally administered at 3 mg/kg or intravenously administered at 1 mg/kg to bile duct-cannulated male rats. Excretion rates of radioactivity in bile, urine, and feces up to 48 hours post-dose were 59.8%, 31.0%, and 6.4% after the oral administration and 68.4%, 27.3%, and 3.7% after the intravenous administration, respectively (CTD 4.2.2.2-2).

4.4.3 Excretion into milk

A single dose of [carbonyl-^{14}C]vornorexant 3 mg/kg was orally administered to female rats 10 days postpartum, and excretion into milk was investigated at 0.5, 2, 6, 24, and 48 hours post-dose. The

radioactivity concentration in milk peaked at 0.5 hours post-dose (0.723 times the plasma radioactivity concentration [mean of 3 animals]) and then decreased over time. Vornorexant was shown to be transferred into milk (CTD 4.2.2.3-5).

4.R Outline of the review conducted by PMDA

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

5. Toxicology and Outline of the Review Conducted by PMDA

The applicant submitted toxicity data on vornorexant in the form of results from repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies (dependence, phototoxicity, and genotoxicity of impurities).

Unless otherwise specified, 0.5% (w/v) methylcellulose aqueous solution was used as the vehicle in *in vivo* studies.

5.1 Single-dose toxicity

No single-dose toxicity studies of vornorexant were conducted. Acute toxicity and the approximate lethal dose in rats and dogs were evaluated based on clinical signs after the first dose in a micronucleus assay in rats and a repeated-dose toxicity study in dogs (1 month) (Table 13).

Table 13. Summary of acute toxicity evaluation

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	CTD
Male and female rats (SD)	Oral	0, 500, 1000, 2000	None	>2000	4.2.3.3.2-1
Male and female dogs (beagle)	Oral	0, 60, 300, 1000	≥60: Somnolence 1000: Feces containing white matter	>1000	4.2.3.2-5

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies in rats (1 month and 26 weeks) and dogs (1 month, 13 and 39 weeks) were conducted (Table 14).

In repeated oral dose studies in rats (26 weeks) and dogs (39 weeks), the no observed adverse effect level (NOAEL) was 1000 mg/kg for both species. At the NOAEL, $AUC_{0\text{-}24h}$ of unbound vornorexant was 378 ng·h/mL in male rats and 2230 ng·h/mL in female rats as well as 4740 ng·h/mL in male dogs and 2840 ng·h/mL in female dogs.[8)] The corresponding plasma exposures in rats and dogs were 9.5 and ≥72 times higher, respectively, than that of unbound vornorexant ($AUC_{0\text{-}24h}$, 39.6 ng·h/mL)[9)] in human subjects who received a single oral dose of vornorexant at the maximum clinical dose (10 mg).

8) Calculated from plasma exposure to vornorexant (4290 ng·h/mL in male rats, 25300 ng·h/mL in female rats, [for data in dogs, see Section 4.1.2.2]) and protein binding (91.2% in rats, 97.0% in dogs).
9) Calculated from plasma exposure to vornorexant in a phase I study in healthy adults [see Section 6.1.1] and protein binding (94.5%).

Table 14. Summary of repeated oral dose toxicity studies

Test system	Duration of treatment	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Male and female rats (SD)	1 month (QD) + 1 month of recovery	0, 100, 300, 1000	1000: Food consumption decreased, prothrombin time prolonged Reversible	1000[a)]	4.2.3.2-2
Male and female rats (SD)	26 weeks (QD) + 4 weeks of recovery	0, 100, 300, 1000	1000: Body weight and food consumption increased Not reversible	1000[a)]	4.2.3.2-3
Male and female dogs (beagle)	1 month (QD) + 1 month of recovery	0, 60, 300, 1000	≥60: Somnolence 1000: AST and albumin decreased, ALP increased Reversible	1000[a)]	4.2.3.2-5
Male and female dogs (beagle)	13 weeks (QD) + 4 weeks of recovery	0, 60, 300, 1000	≥60: Somnolence Reversible	1000[a)]	4.2.3.2-6
Male and female dogs (beagle)	39 weeks (QD) + 4 weeks of recovery	0, 60, 300, 1000	≥60: Somnolence Reversible	1000[a)]	4.2.3.2-7

a) Somnolence is caused by the pharmacological effect, and other findings were considered of little toxicological significance because no abnormalities were observed in related parameters.

5.3 Genotoxicity

A bacterial reverse mutation assay and a mammalian cell micronucleus assay were conducted as *in vitro* studies, and a rat bone marrow micronucleus assay was conducted as an *in vivo* study (Table 15).

Table 15. Summary of genotoxicity study results

Type of test		Test system	Metabolic activation (treatment)	Concentrations or doses	Study result	CTD
in vitro	Bacterial reverse mutation	*Salmonella typhimurium,* TA98, TA100, TA1535, TA1537; *Escherichia coli,* WP2*uvrA*	Rat S9+/-	0,[a)] 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 µg/plate	Negative	4.2.3.3.1-1
	Mammalian cell micronucleus	Chinese hamster lung cells	Rat S9+/- (6 hours)	0,[a)] 112, 224, 448 µg/mL	Negative	4.2.3.3.1-2
			Rat S9- (26 hours)	0,[a)] 50, 100, 150, 200 µg/mL	Negative	
in vivo	Rat bone marrow micronucleus	Male and female rats (SD) bone marrow		0, 500, 1000, 2000 mg/kg (QD for 2 days)	Negative	4.2.3.3.2-1

a) Dimethyl sulfoxide (DMSO)

5.4 Carcinogenicity

A 26-week carcinogenicity study in Tg mice was conducted (Table 16). At the non-carcinogenic dose (1500 mg/kg) , plasma exposure to unbound vornorexant[10)] ($AUC_{0\text{-}24h}$) was 560 ng·h/mL in male mice

[10)] Calculated from plasma exposure to vornorexant ($AUC_{0\text{-}24h}$, 7780 ng·h/mL in male mice, 20600 ng·h/mL in female mice) and protein binding (92.8%).

and 1480 ng·h/mL in female mice. The corresponding plasma exposures in male and female mice were 14 and 37 times higher than that of unbound vornorexant ($AUC_{0\text{-}24h}$, 39.6 ng·h/mL)[9)] in human subjects who received a single oral dose of vornorexant at the maximum clinical dose (10 mg) .

Table 16. Summary of carcinogenicity study in mice

Test system	Route of administration	Duration of treatment	Main lesions		Dose (mg/kg/day)				Non-carcinogenic dose (mg/kg/day)	CTD
					0	100	500	1500		
				Sex	M and F	M and F	M and F	M and F		
				n	25 each	25 each	25 each	25 each		
Male and female mice (CB6F1-Tg rasH2)	Oral	26 weeks (QD)	Neoplastic lesions: None Non-neoplastic lesions: None						1500	4.2.3.4.2-3

A 24-month carcinogenicity study in rats was conducted (Tables 17 and 18). In male rats, the incidences of islet cell adenoma and the combined incidences of islet cell adenoma and adenocarcinoma showed significant dose-responses, and the incidence of islet cell adenoma in the 1500 mg/kg group was significantly higher than that in the control group. In female rats, islet cell tumors were observed, but the increase in incidence was not statistically significant.

At the maximum dose (1500 mg/kg in male rats and 300 mg/kg in female rats), $AUC_{0\text{-}24h}$ of unbound vornorexant[11)] was 1300 ng·h/mL and 1670 ng·h/mL, respectively. The corresponding plasma exposures in male and female rats were 33 and 42 times higher than that of unbound vornorexant[9)] ($AUC_{0\text{-}24h}$, 39.6 ng·h/mL) in human subjects who received a single oral dose of vornorexant at the maximum clinical dose (10 mg).

Table 17. Summary of carcinogenicity study in male rats

Test system	Route of administration	Duration of treatment	Main lesions		Dose (mg/kg/day)				Non-carcinogenic dose (mg/kg/day)	CTD
					0	300	1000	1500[a)]		
				n	60	60	60	59		
Male rats (SD)	Oral	24 months (QD)	Neoplastic lesions						-	4.2.3.4.1-1
			Islet cell adenoma		8	14	14	24		
			Islet cell adenocarcinoma		1	3	2	3		
			Islet cell adenoma + adenocarcinoma		9	17	16	26		
			Other findings							
			Islet hypercellularity		0	0	1	2		

a) Selected as the limit dose corresponding to the maximum clinical dose of <500 mg/day

11) Calculated from plasma exposure to vornorexant [see Section 4.1.2.1] and protein binding (91.2%).

Table 18. Summary of carcinogenicity study in female rats

Test system	Route of administration	Duration of treatment	Main lesions		Dose (mg/kg/day)				Non-carcinogenic dose (mg/kg/day)	CTD
					0	30	100	300[a)]		
				n	60	60	60	60		
Female rats (SD)	Oral	24 months (QD)	Neoplastic lesions						300	4.2.3.4.1-1
				Islet cell adenoma	3	3	6	4		
				Islet cell adenocarcinoma	1	1	0	0		
				Islet cell adenoma + adenocarcinoma	4	4	6	4		
			Other findings							
				Islet hypercellularity	0	2	2	0		

a) Selected as the upper boundary corresponding to the maximum clinical dose <500 mg/day

5.5 Reproductive and developmental toxicity

A study for fertility and early embryonic development to implantation in rats, embryo-fetal development studies in rats and rabbits as well as a study for prenatal and postnatal development, including maternal function in rats were conducted (Table 19).

The NOAEL for reproductive and developmental toxicity was 1000 mg/kg in both rats and rabbits. At the NOAEL, $AUC_{0\text{-}24h}$ of unbound vornorexant[12)] was 6200 ng·h/mL in rats and 2360 ng·h/mL in rabbits. The corresponding plasma exposures in rats and rabbits were 160 and 60 times higher than that of unbound vornorexant[9)] ($AUC_{0\text{-}24h}$, 39.6 ng·h/mL) in human subjects who received a single oral dose of vornorexant at the maximum clinical dose (10 mg).

12) Calculated from plasma exposure to vornorexant ($AUC_{0\text{-}24h}$, 70400 ng·h/mL in rats and 18600 ng·h/mL in rabbits) and protein binding (91.2% in rats and 87.3% in rabbits).

Table 19. Summary of reproductive and developmental toxicity studies

Type of test	Test system	Route of administration	Duration of treatment	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Fertility and early embryonic development to implantation	Male and female rats (SD)	Oral	Male: 42 days from 2 weeks before mating through 1 day before necropsy (QD) Female: 23-35 days from 2 weeks before mating through Gestation Day 7 (QD)	0, 100, 300, 1000	Parent animal (general toxicity): None Parent animal (reproductive performance): None	Parent animal (general toxicity): 1000 Parent animal (reproductive performance): 1000 Early embryonic development: 1000	4.2.3.5.1-1
Embryo-fetal development	Female rats (SD)	Oral	Gestation Days 7 through 17 (QD) Cesarean section: Gestation Day 20	0, 100, 300, 1000	Maternal animal: None Embryo-fetal development: None	Maternal animal (general toxicity): 1000 Embryo-fetal development: 1000	4.2.3.5.2-2
Embryo-fetal development	Female rabbits (NZW)	Oral	Gestation Days 7 through 19 (QD) Cesarean section: Gestation Day 29	0, 100, 300, 1000	Maternal animal ≥100: Abortion Embryo-fetal development: None	Maternal animal (general toxicity): 1000[a)] Embryo-fetal development: 1000	4.2.3.5.2-5
Prenatal and postnatal development, including maternal function	Female rats (SD)	Oral	Maternal animal: Gestation Day 7 through 20 days postpartum (QD)	0, 100, 300, 1000	Maternal animal (general toxicity): None Prenatal and postnatal development: None F1 (development and reproductive performance): None	Maternal animal (general toxicity): 1000 Prenatal and postnatal development: 1000 F1 (development and reproductive performance): 1000	4.2.3.5.3-1

a) Abortions observed in the 100 and 1000 mg/kg/day groups were considered unrelated to vornorexant in view of the historical incidence of spontaneous abortions at the laboratory, food consumption in each dose group, and occurrence state of the abortions.

5.6 Other studies

5.6.1 Dependency

A self-administration study in rats was conducted, and vornorexant was shown not to induce psychic dependence (Table 20).

Table 20. Summary of dependency study

Type of test	Test system	Test method	Main findings	CTD
Self-administration	Male rats (SD)	Rats trained to self-administer ketamine hydrochloride intravenously underwent intravenous self-administration of vornorexant at 0,[a)] 0.003, 0.01, 0.03, 0.1, or 0.3 mg/kg/dose to evaluate the reinforcing effect.	The number of self-administration actions was not increased.	4.2.3.7.4-2

a) Solution containing 1 v/v% DMSO, 0.1 mol/L HCl, and 20% sulfobutyl ether β-cyclodextrin (SBEβCD)

Furthermore, evaluation of effects on the central nervous system in rats [see Section 3.3] and clinical signs in repeated-dose toxicity studies in rats and dogs [see Section 5.2] did not show any findings related to activation of dopaminergic neurons (stereotyped behavior, increased locomotor activity), which are suggestive of psychic dependence (*Behav Pharmacol.* 2001;12:603-11, *Psychopharmacology [Berl].* 1997;130:183-8, etc.). During a recovery period of the repeated-dose toxicity studies, neither clinical signs nor changes in body weight suggestive of withdrawal syndrome were observed [see Section 5.2], and thus vornorexant was not suggested to induce physical dependence.

5.6.2 Phototoxicity evaluation

Because vornorexant was shown to absorb light at 290 to 320 nm in its ultraviolet-visible absorption spectroscopy, a reactive oxygen species (ROS) assay was performed (Table 21).

Table 21. Summary of photoreactivity study

Test system	Test method	Main findings	CTD
ROS assay	Vornorexant 200 μmol/L was exposed to artificial sunlight for 1 hour, and generated reactive oxygen species were measured.	No photoreactivity	4.2.3.7.7-1

5.6.3 Genotoxicity study of impurities

To evaluate the mutagenicity of potential impurities in the drug substance, 4 compounds of Impurities A, B, C,[13)] and D of vornorexant were subjected to a bacterial reverse mutation assay. Impurity A was found to be mutagenic, while the other 3 compounds were not. Impurity A, a mutagenic impurity, was controlled in the manufacturing process of the drug substance to ensure that the acceptable intake (1.5 μg/day) for drugs with a duration of treatment from >10 years to lifetime would not be reached or exceeded, in accordance with Option 3 for control of mutagenic impurities in the ICH M7 guideline.

5.R Outline of the review conducted by PMDA

5.R.1 Islet cell tumors observed in carcinogenicity study in rats

Concerning the finding of islet cell tumors in the carcinogenicity study in rats, PMDA asked the applicant to explain the mechanism of development of the finding and the carcinogenicity risk of vornorexant in clinical use.

The applicant's explanation:

For the following reasons, the islet cell tumors in rats were not attributable to vornorexant and are considered to have developed spontaneously and occurred incidentally more frequently in high-dose groups.

- Vornorexant was negative for genotoxicity [see Section 5.3].
- Drug-induced islet cell tumors in rats are known to develop in association with glucose metabolism disorders, hyperglycemia, and hyperprolactinemia (*Academic Press.* 2018;695-704, etc.); however, in the vornorexant dose groups in the repeated-dose toxicity and carcinogenicity studies in rats, no hyperglycemia, increased food consumption, or increased pituitary or mammary gland tumors suggestive of prolactin hypersecretion was observed [see Sections 5.2 and 5.4].

13) [redacted]

- In rats, spontaneous proliferative lesions of pancreatic cells occur more frequently with aging (*Toxicol Pathol.* 1994;22:48-55). In SD rats, the incidence of islet cell tumors is higher in males than in females (*Toxicologic Histopathology*. Nishimura Co., Ltd; 2017.p723).
- The incidence of islet cell adenoma in males treated with vornorexant at 1500 mg/kg/day (41%) was higher than the laboratory historical control data from the past 5 years (16%-25%) but was generally similar to the upper bound of a range of the incidences reported in literature (8.00%-40.00%) (*Toxicologic Histopathology*. Nishimura Co., Ltd; 2017.p723).
- If islet cell tumors are drug-induced, such proliferative lesions of the pancreatic islet in rats would increase in females as well (*Toxicol Pathol.* 1993;21:502-8, etc.). However, proliferative lesions of islet cells did not increase in female rats treated with vornorexant (100 and 300 mg/kg), although the plasma exposure to vornorexant in these females was higher than that in male rats (1500 mg/kg).

Based on the following points in addition to the above, a carcinogenicity risk of vornorexant is considered to be limited.

- The increased incidence of islet cell adenoma was observed in male rats treated with vornorexant at 1500 mg/kg; in these animals, plasma exposure to unbound vornorexant was 33 times higher than that in human subjects who received a single oral dose of vornorexant at the maximum clinical dose (10 mg) [see Section 5.4]. The "Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals" (ICH S1 guideline) states that "positive results for carcinogenicity in rodents at exposures ≥25 times the clinical exposure do not suggest a carcinogenic risk in humans."
- In clinical studies of vornorexant, no islet cell tumors have been observed, and a causal relationship to vornorexant was ruled out for the other tumor lesions observed.

PMDA's view:

Given that the increase in the incidence of islet cell tumors in male rats was significant in both the trend test and pairwise comparisons, it is difficult to conclude that the islet cell tumors occurred spontaneously. Therefore, it is appropriate that the relevant study results be included in the package insert to provide the information to healthcare professionals. However, in view of the difference in exposure between the carcinogenic dose and the clinical dose, the applicant's conclusion that the carcinogenicity risk in humans is limited is acceptable.

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

Plasma concentrations of vornorexant and its metabolites (M1 and M3) were determined by LC-MS/MS. For any analyte, the lower limit of quantification was 0.1 ng/mL.

Of formulations used in Japanese phase III studies, the 2.5 mg and 5 mg formulations were the same as the respective proposed formulations, and the 10 mg formulation was confirmed to be bioequivalent to the proposed formulation by dissolution tests. The formulations among different strengths were also confirmed to be bioequivalent by dissolution tests.

Unless otherwise specified, each dose represents an amount of vornorexant.

6.1.1 Phase I study (food effect) (CTD 5.3.1.1-1, Study TS142-304)

Japanese healthy adults (12 subjects included in pharmacokinetic analysis) orally received a single dose of vornorexant 10 mg tablets (proposed formulation) in the fasted state or after breakfast (approximately 510 kcal), and the food effect on pharmacokinetics of vornorexant was investigated in a crossover manner.

Table 22 shows pharmacokinetic parameters after administration of vornorexant in the fasted or fed state. Food did not greatly change C_{max} of vornorexant, but the administration in the fed state increased $AUC_{0-\infty}$ of vornorexant and delayed t_{max} compared with those after administration in the fasted state.

Table 22. Pharmacokinetic parameters after administration of vornorexant in the fasted state and fed state

Meal condition	No. of subjects	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	Geometric mean ratio [90% CI] (fed/fasted)	
						C_{max}	$AUC_{0-\infty}$
Fasted	12	279 ± 96.7	0.50 [0.50, 3.00]	720 ± 237	2.13 ± 0.185	0.96 [0.76, 1.21]	1.17 [1.05, 1.31]
Fed	12	255 ± 77.7	1.50 [0.50, 2.00]	851 ± 318	1.81 ± 0.336		

Mean ± SD; t_{max}, Median [range]

6.2 Clinical pharmacology

6.2.1 Studies using human biological samples

6.2.1.1 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3-2 to 4.2.2.3-3)

To human plasma specimens, [carbonyl-^{14}C]vornorexant (0.05-20 μg/mL) or its metabolite (M3) (0.05-10 μg/mL) was added, and plasma protein binding was determined by an equilibrium dialysis method. Mean plasma protein binding of vornorexant was 94.5% to 96.3% in a range from 0.05 to 2 μg/mL, but at 20 μg/mL, the protein binding decreased to 89.4% potentially due to saturation of protein binding. Mean plasma protein binding of M3 was 94.7% to 97.3%.

Binding rates of [carbonyl-^{14}C]vornorexant (0.05-20 μg/mL as vornorexant hydrate) to human serum albumin (40 mg/mL), α_1-AGP (1 mg/mL), low-density lipoprotein (LDL) (3 mg/mL), and high density lipoprotein (HDL) (3 mg/mL) were determined by an equilibrium dialysis method. Binding rates of vornorexant to serum albumin, LDL, and HDL were similar across the concentration range tested, with mean values of 56.8% to 62.6%, 42.6% to 50.0%, and 49.8% to 53.7%, respectively, while the binding rate to α_1-AGP was 94.5%, 90.8%, and 56.5% at 0.05, 2.0, and 20 μg/mL, respectively. The applicant explained that the concentration-dependent decrease in plasma protein binding of vornorexant is attributable to saturation of binding to α_1-AGP .

To human blood specimens, [carbonyl-^{14}C]vornorexant (0.05-20 μg/mL as vornorexant hydrate) was added to investigate its distribution in blood cells. Mean blood/plasma radioactivity concentration ratios were 0.568 to 0.587 in the concentration range from 0.05 to 2.0 μg/mL, but the ratio was 0.845 at 20 μg/mL. The applicant explained that the difference is related to the concentration-dependent decrease in plasma protein binding.

6.2.1.2 *In vitro* studies on metabolites (CTD 4.2.2.4-5 to 4.2.2.4-7)

Incubation of [^{14}C]vornorexant with human hepatocytes resulted in the generation of various metabolites, including the primary metabolite M1 formed by hydroxylation of the methyl group of the methylphenyl moiety, and M3 formed by dehydrogenation of the oxazinane ring.

Incubation of [^{14}C]vornorexant or its metabolite M3 (3 μmol/L) with recombinant human CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5) revealed that ≥90% of both vornorexant and M3 were metabolized by CYP3A4.

6.2.1.3 Enzyme inhibition and induction (CTD 4.2.2.6-1 to 4.2.2.6-3, and 4.2.2.6-8)

Inhibition of vornorexant (0-60 μmol/L) and metabolite M3 (0-60 μmol/L) against CYP isoforms[14)] (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) was investigated using human liver microsomes. Vornorexant inhibited CYP2C9 and CYP3A with IC_{50} values of 49.5 and 31.7 μmol/L, respectively, and the inhibitory effect on these isoforms was reversible. IC_{50} values of vornorexant against the other CYP isoforms were >60 μmol/L. Similarly, metabolite M3 inhibited CYP2C9, CYP2C19, and CYP3A with IC_{50} values of 58.6, 53.3 and 55.9 μmol/L, respectively, and the inhibitory effect on these isoforms was reversible. IC_{50} values of M3 against the other CYP isoforms were >60 μmol/L.

Time-dependent inhibitory effect of vornorexant on CYP3A was investigated using human liver microsomes. Vornorexant inhibited CYP3A in a time-dependent manner (inhibition concentration causing half-maximal inactivation [K_I], 30.4-67.9 μmol/L; maximum inactivation rate constant [k_{inact}], 0.0222-0.0302 min^{-1}).

Vornorexant (0.3-100 μmol/L) or metabolite M3 (0.3-100 μmol/L) was incubated with human cryopreserved hepatocytes to investigate changes in mRNA expression of CYP1A2, CYP2B6, and CYP3A4. Vornorexant induced mRNA expression of all CYP isoforms in a concentration-dependent manner. Metabolite M3 induced mRNA expression of CYP2B6 and CYP3A4 in a concentration-dependent manner but did not induce that of CYP1A2. The increase in mRNA expression of CYP1A2 induced by M3 in the concentration range tested was <2-fold and <1% of that induced by the positive control.

6.2.1.4 Transportation by drug transporters (CTD 4.2.2.6-4 to 4.2.2.6-5)

To LLC-PK1 cells expressing P-glycoprotein (P-gp) or MDCKII cells expressing breast cancer resistance protein (BCRP), [carbonyl-^{14}C]vornorexant was added at 1 μmol/L. To HEK293 cells expressing organic anion transporting polypeptide (OATP) 1B1 or OATP1B3, [carbonyl-^{14}C]vornorexant was added at 10 μmol/L. Using these systems, whether vornorexant was a substrate for these transporters was examined. Net efflux ratios for transport via P-gp and BCRP (an efflux ratio is defined as a ratio of apparent permeability in a basolateral-to-brush border direction to that in the brush border-to-basolateral direction, and a net efflux ratio is defined as a ratio of the efflux ratio in transporter-

[14)] Metabolic activities listed below were used as the base.
CYP1A2, Phenacetin *O*-deethylase; CYP2B6, Bupropion hydroxylase; CYP2C8, Amodiaquine *N*-deethylase; CYP2C9, Diclofenac 4'-hydroxylase; CYP2C19, *S*-Mephenytoin 4-hydroxylase; CYP2D6, Bufuralol-hydroxylase; and CYP3A, Testosterone 6β-hydroxylase and Midazolam 1'-hydroxylase

expressing cells to that in control cells) were 2.72 and 1.04, respectively. Ratios of drug uptake in OATP1B1- and OATP1B3-expressing cells to that in control cells were 1.02 to 1.35 and 1.12 to 1.28, respectively. The above results suggested that vornorexant was a weak substrate for P-gp but not a substrate for BCRP, OATP1B1, or OATP1B3. Of note, the applicant explained that vornorexant was unlikely to be affected by drug interactions when coadministered with P-gp inhibitors, for the following reasons: (1) In assays using LLC-PK1 cells expressing P-gp, the efflux ratio for the positive control (digoxin) was 23.4; (2) in a mass balance study, the absorption rate of vornorexant was estimated to be ≥82.4% [see Section 6.2.5], indicating that P-gp is scarcely involved in gastrointestinal absorption of vornorexant; and (3) concomitant use of P-gp inhibitors did not affect safety in Japanese clinical studies.

To LLC-PK1 cells expressing P-gp or BCRP, metabolite M3 was added at 1 μmol/L. To HEK293 cells expressing OATP1B1 or OATP1B3, metabolite M3 was added at 10 μmol/L. Using these systems, whether metabolite M3 was a substrate for these transporters was examined. Net efflux ratios for transport via P-gp and BCRP were 1.31 and 0.99, respectively. Ratios of drug uptake in OATP1B1- and OATP1B3-expressing cells to that in control cells were 0.88 to 1.32 and 0.85 to 1.21, respectively. Based on the above results, metabolite M3 was not considered to be a substrate for P-gp, BCRP, OATP1B1, or OATP1B3.

6.2.1.5 Inhibition against drug transporters (CTD 4.2.2.6-6 to 4.2.2.6-8)

To cells expressing P-gp, BCRP, OATP1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 2, multidrug and toxin extrusion (MATE) 1, or MATE2-K, vornorexant or metabolite M3 was added (concentrations of vornorexant and M3 tested, 0-30 μmol/L for P-gp and BCRP, 0-3 μmol/L for OATP1B1, OATP1B3, MATE1, and MATE2-K, and 0-1 μmol/L for OAT1, OAT3, and OCT2). Vornorexant and M3, at the concentrations tested, did not inhibit any of the transporters.

6.2.2 Phase I study in healthy adults (CTD 5.3.3.1-2, Study TS142-102)

A randomized, double-blind, placebo-controlled study was conducted to investigate the pharmacokinetics and safety of vornorexant in Japanese healthy adults (target sample size, 24 subjects) receiving multiple oral doses of vornorexant.

Placebo or vornorexant at doses of 10, 20, or 30 mg was orally administered once daily (QD) at bedtime for 7 days. All 24 treated subjects (n = 6/group) were included in the safety and pharmacokinetic analysis populations.

Tables 23 and 24 show plasma pharmacokinetic parameters of vornorexant and metabolite M1. No accumulation was observed following once-daily oral administration of vornorexant at doses of 10 to 30 mg.

Table 23. Plasma pharmacokinetic parameters of vornorexant in healthy adults receiving multiple oral doses of vornorexant for 7 days

	Dose of vornorexant (mg)	No. of subjects	C_{max} (ng/mL)	t_{max} (h)	AUC[a)] (ng·h/mL)	$t_{1/2}$ (h)
Day 1	10	6	256 ± 63	1.50 [1.50, 2.00]	1210 ± 420	2.04 ± 0.40
	20	6	358 ± 116	2.00 [1.50, 2.00]	1510 ± 561	1.72 ± 0.29
	30	6	535 ± 83	2.00 [2.00, 3.00]	2740 ± 850	1.93 ± 0.22
Day 7	10	6	265 ± 74	1.75 [0.75, 2.00]	1340 ± 632	2.03 ± 0.40
	20	6	362 ± 100	1.75 [1.50, 3.00]	1640 ± 506	1.82 ± 0.18
	30	6	544 ± 111	2.00 [1.50, 3.00]	2480 ± 964	1.81 ± 0.31

Mean ± SD; t_{max}, Median [range]
a) $AUC_{0-\infty}$ for Day 1, $AUC_{0-\tau}$ for Day 7

Table 24. Plasma pharmacokinetic parameters of metabolite M1 in healthy adults receiving multiple oral doses of vornorexant for 7 days

	Dose of vornorexant (mg)	No. of subjects	C_{max} (ng/mL)	t_{max} (h)	AUC[a)] (ng·h/mL)	$t_{1/2}$ (h)
Day 1	10	6	13.5 ± 1.4	2.50 [1.50, 4.00]	99 ± 18	3.19 ± 0.20
	20	6	23.7 ± 6.0	2.00 [1.50, 3.00]	147 ± 51	2.90 ± 0.44
	30	6	35.4 ± 7.0	3.00 [2.00, 3.00]	260 ± 69	3.08 ± 0.21
Day 7	10	6	13.5 ± 1.7	3.00 [2.00, 4.00]	103 ± 31	3.15 ± 0.27
	20	6	22.6 ± 5.7	2.50 [2.00, 6.00]	152 ± 50	2.91 ± 0.37
	30	6	35.6 ± 5.7	2.00 [2.00, 4.00]	237 ± 70	3.02 ± 0.20

Mean ± SD; t_{max}, Median [range]
a) $AUC_{0-\infty}$ for Day 1, $AUC_{0-\tau}$ for Day 7

For safety, adverse events occurred in 1 subject in the placebo group (somnolence), 2 subjects in the vornorexant 10 mg group (somnolence in 2 subjects), 2 subjects in the vornorexant 20 mg group (creatine phosphokinase increased and somnolence in 1 subject each), and 3 subjects in the vornorexant 30 mg group (somnolence in 2 subjects; somnolence and blood bilirubin increased in 1 subject). A causal relationship to the study drug could not be ruled out for any cases of somnolence. No deaths, serious adverse events other than deaths, or adverse events leading to treatment discontinuation occurred.

6.2.3 Investigation of intrinsic factors

6.2.3.1 Effects of age and sex (CTD 5.3.3.3-1, Study TS142-202)

An open-label (Step 1) or randomized, double-blind, placebo-controlled (Step 2) study was conducted to investigate the pharmacokinetics and safety of vornorexant in Japanese healthy adults (target sample size, 23 subjects, [12 non-elderly subjects (6 males and 6 females) and 11 elderly subjects]) receiving multiple oral doses of vornorexant.

In Step 1, non-elderly subjects received vornorexant 20 mg orally once daily at bedtime for 7 days. In Step 2, elderly subjects received placebo or vornorexant 20 mg orally once daily at bedtime for 7 days. All 23 treated subjects (12 [6 males and 6 females] in Step 1 and 11 in Step 2) were included in the safety and pharmacokinetic analysis populations.

Tables 25 and 26 show plasma pharmacokinetic parameters of vornorexant and metabolite M3. C_{max} and AUC of vornorexant and metabolite M3 did not tend to be higher in elderly subjects than in non-elderly subjects, but tended to be slightly higher in female subjects than in male subjects.

Table 25. Plasma pharmacokinetic parameters of vornorexant in healthy adults receiving multiple oral doses of vornorexant for 7 days

		Sex	Dose of vornorexant (mg)	No. of subjects	C_{max} (ng/mL)	t_{max} (h)	AUC[a)] (ng·h/mL)	$t_{1/2}$ (h)
Day 1	Non-elderly	Male	20	6	271 ± 101	2.50 [1.00, 5.00]	1260 ± 415	1.68 ± 0.26
		Female	20	6	442 ± 39.4	2.50 [1.50, 3.00]	2310 ± 817	1.98 ± 0.29
	Elderly	Male	20	8	345 ± 109	3.50 [1.00, 4.00]	1750 ± 674	1.95 ± 0.33
		Female	20	0	-	-	-	-
Day 7	Non-elderly	Male	20	6	305 ± 114	3.00 [1.50, 3.00]	1450 ± 389	1.61 ± 0.24
		Female	20	6	487 ± 120	2.00 [1.50, 4.00]	2500 ± 929	2.01 ± 0.29
	Elderly	Male	20	8	332 ± 124	3.00 [2.00, 4.00]	1860 ± 866	1.90 ± 0.33
		Female	20	0	-	-	-	-

Mean ± SD; t_{max}, Median [range]
a) $AUC_{0-\infty}$ for Day 1, $AUC_{0-\tau}$ for Day 7

Table 26. Plasma pharmacokinetic parameters of metabolite M3 in healthy adults receiving multiple oral doses of vornorexant for 7 days

		Sex	Dose of vornorexant (mg)	No. of subjects	C_{max} (ng/mL)	t_{max} (h)	AUC[a)] (ng·h/mL)	$t_{1/2}$ (h)
Day 1	Non-elderly	Male	20	6	66.0 ± 16.2	3.50 [2.00, 6.00]	673 ± 186	4.40 ± 0.97
		Female	20	6	74.0 ± 6.2	5.00 [2.00, 9.00]	1200 ± 310	6.96 ± 1.06
	Elderly	Male	20	8	70.0 ± 16.0	4.00 [2.00, 5.00]	850 ± 298	4.95 ± 1.35
		Female	20	0	-	-	-	-
Day 7	Non-elderly	Male	20	6	74.6 ± 22.4	4.00 [2.00, 5.00]	774 ± 210	4.25 ± 1.19
		Female	20	6	88.6 ± 16.5	3.00 [3.00, 9.00]	1310 ± 354	6.96 ± 1.43
	Elderly	Male	20	8	74.4 ± 22.0	4.00 [2.00, 9.00]	905 ± 384	5.29 ± 1.50
		Female	20	0	-	-	-	-

Mean ± SD; t_{max}, Median [range]
a) $AUC_{0-\infty}$ for Day 1, $AUC_{0-\tau}$ for Day 7

For safety, adverse events occurred only in 4 female subjects in Step 1 (somnolence in all cases), and a causal relationship to the study drug could not be ruled out for any of these events. No deaths, serious adverse events other than deaths, or adverse events leading to treatment discontinuation occurred.

Concerning a trend toward slightly higher C_{max} and AUC of vornorexant and metabolite M3 observed in female subjects compared with male subjects, the applicant explained that an effect of sex on the pharmacokinetics of vornorexant was limited for the following considerations: (1) Body weight of subjects was considered to have affected the pharmacokinetics of vornorexant; however, in a QT/QTc evaluation study (Study TS142-209), although a sex-related difference in body weight was observed, no sex-related differences in pharmacokinetics were observed [see Section 6.2.6]; (2) in a population pharmacokinetic (PPK) analysis, sex was not identified as a covariate [see Section 6.2.7]; and (3) in Japanese clinical studies in patients with insomnia, no differences in safety profiles, including incidence of adverse events, were observed between sexes.

6.2.3.2 Effects of hepatic function (CTD 5.3.3.3-2, Study TS142-303)

An open-label, parallel-group study was conducted to investigate the effect of hepatic impairment on the pharmacokinetics of vornorexant in Japanese subjects with normal hepatic function and those with mild or moderate hepatic impairment (Child-Pugh classification A or B) (target sample size, 24 subjects, 8 per group).

A single oral dose of vornorexant 5 mg was administered. All 26 subjects enrolled in the study and treated with the study drug (10 subjects with normal hepatic function, 8 subjects with mild hepatic impairment, and 8 subjects with moderate hepatic impairment) were included in the pharmacokinetic analysis population.

For pharmacokinetics, the geometric mean ratios [90% confidence interval (CI)] of plasma pharmacokinetic parameters of plasma protein-unbound vornorexant in subjects with mild and moderate hepatic impairment to those in subjects with normal hepatic function were 1.07 [0.88, 1.30] and 1.42 [1.05, 1.93], respectively, for C_{max}, and 1.37 [1.06, 1.77] and 3.06 [1.89, 4.96], respectively, for $AUC_{0-\infty}$. In subjects with moderate hepatic impairment, both C_{max} and $AUC_{0-\infty}$ were increased.

Adverse events occurred in 4 subjects with normal hepatic function (somnolence in all cases), 3 subjects with mild hepatic impairment (somnolence in 2 subjects and somnolence and diarrhoea in 1 subject), and 6 subjects with moderate hepatic impairment (somnolence in 5 subjects, and somnolence and thirst in 1 subject). A causal relationship to the study drug could not be ruled out for any of these events. No deaths, serious adverse events other than deaths, or adverse events leading to treatment discontinuation occurred.

6.2.4 Drug-drug interaction study (CTD 5.3.3.4-1, Study TS142-205-01)

In vitro studies showed that vornorexant is metabolized by CYP3A [see Section 6.2.1.2]. An open-label study was conducted to investigate the effect of itraconazole (a potent CYP3A inhibitor) on the pharmacokinetics of vornorexant in Japanese healthy adults.

A single oral dose of vornorexant 5 mg was administered in the fasted state on Day 1, and then a single oral dose of vornorexant 1 mg was administered on Day 6, while itraconazole 200 mg was orally administered twice daily on Day 3 and then once daily on Days 4 to 7.

Table 27 shows geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of vornorexant and metabolite M3 after coadministration with itraconazole to those without itraconazole.

Table 27. Geometric mean ratios of plasma pharmacokinetic parameters of vornorexant and metabolite M3 after coadministration with itraconazole to those without itraconazole[a)]

Dose of vornorexant (mg)	No. of subjects	Vornorexant		M3	
		C_{max}	$AUC_{0-\infty}$	C_{max}	$AUC_{0-\infty}$
1	10	2.24 [2.05, 2.45]	12.2 [11.2, 13.4]	0.50 [0.46, 0.54]	3.15 [2.06, 4.83] [b)]

Geometric mean ratio [90% CI]
a) Coadministration with itraconazole/administration without itraconazole
b) n = 3

6.2.5 Mass balance study (CTD 5.3.3.1-3, Study TS142-206)

An open-label study was conducted to investigate the mass balance in Japanese healthy adults (target sample size, 6 subjects) who orally received a single dose of ^{14}C-vornorexant.

A single oral dose of ^{14}C-vornorexant 7.5 mg was administered after at least 10 hours of fasting. All 6 subjects enrolled in this study were included in the pharmacokinetic analysis population.

In plasma up to 96 hours after administration of ^{14}C-vornorexant, vornorexant was mainly detected (18.9% of total plasma radioactivity), followed by metabolite M3 (8.6% of total plasma radioactivity). Table 28 shows the pharmacokinetic parameters of vornorexant and its metabolites (M1 and M3).

Table 28. Plasma pharmacokinetic parameters in Japanese healthy adults who orally received a single dose of ^{14}C-vornorexant in the fasted state

Dose of vornorexant (mg)	Analyte	No. of subjects	C_{max} (nmol/L)	t_{max} (h)	AUC_{last} (nmol·h/L)	$t_{1/2}$ (h)
7.5	Vornorexant	6	731 ± 157	0.50 [0.25, 0.50]	1540 ± 458	1.42 ± 0.27
	metabolite M1	6	30 ± 6	1.00 [0.50, 2.00]	124 ± 31	2.24 ± 0.24
	metabolite M3	6	110 ± 19	0.50 [0.25, 4.00]	693 ± 190	4.39 ± 0.85

Mean ± SD; t_{max}, Median [range]

Up to 168 hours after administration of ^{14}C-vornorexant, 82.4% ± 2.7% and 21.8% ± 3.5% (mean ± standard deviation [SD]) of the administered radioactivity were excreted in urine and feces, respectively. In urine, metabolite M5 was detected (6.2% of the administered radioactivity), but vornorexant was not. In feces up to 72 hours after administration of ^{14}C-vornorexant, metabolite M5 was mainly detected (10.7% of the administered radioactivity), but vornorexant was not.

6.2.6 QT/QTc evaluation study (CTD 5.3.4.1-2, Study TS142-209)

A randomized, placebo- and active-controlled, partial double-blind (open-label for moxifloxacin), 4-treatment, 4-period crossover study was conducted to investigate the effect of a single oral dose of vornorexant on QT/QTc interval in Japanese healthy adults (target sample size, 48 subjects).

A single oral dose of placebo, vornorexant 10 or 30 mg, or the positive control moxifloxacin 400 mg was administered in the fasted state.

All 59 subjects treated with the study drug (25 males and 34 females)[15)] were included in the QT/QTc analysis and pharmacokinetic analysis populations.

The maximum (upper limit of 90% CI) of the differences in change from baseline in QT interval corrected using Fridericia's formula (QTcF) between the active treatment period and placebo treatment period (ΔΔQTcF) was 2.4 (4.9) ms during the vornorexant 10 mg treatment period and 4.8 (7.2) ms during the vornorexant 30 mg treatment period. The upper limits of 90% CI were both below 10 ms. On the other hand, during the moxifloxacin treatment period, lower limits of 90% CI for ΔΔQTcF exceeded 5 ms at all sampling points except 24 hours post-dose, indicating that assay sensitivity was considered to be demonstrated.

Table 29 shows the plasma pharmacokinetic parameters of vornorexant and metabolite M3.

15) Body weight (mean ± SD) of subjects was 56.2 ± 7.4 kg (62.2 ± 5.4 kg for males and 51.9 ± 5.5 kg for females).

Table 29. Plasma pharmacokinetic parameters of vornorexant and metabolite M3 in healthy adults who orally received a single dose of vornorexant

Analyte	Dose of vornorexant (mg)	Sex	No. of subjects	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)
Vornorexant	10	Overall population	55	225 ± 66	946 ± 390
		Male	23	205 ± 75	863 ± 441
		Female	32	239 ± 56	1010 ± 343
	30	Overall population	56	474 ± 143	2440 ± 981
		Male	24	449 ± 157	2310 ± 1160
		Female	32	493 ± 132	2530 ± 825
Metabolite M3	10	Overall population	55	43 ± 7	436 ± 140
		Male	23	40 ± 7	389 ± 142
		Female	32	45 ± 6	471 ± 130
	30	Overall population	56	106 ± 19	1180 ± 370
		Male	24	101 ± 18	1090 ± 358
		Female	32	111 ± 19	1240 ± 370

Mean ± SD

6.2.7 PPK analysis

A PPK analysis (software used, NONMEM Version 7.5.1) was performed based on plasma pharmacokinetic data on vornorexant (5181 sampling points in 1081 subjects) obtained from Japanese phase I studies (Studies TS142-101, TS142-102, TS142-202, TS142-205-01, TS142-207, TS142-208, TS142-209, TS142-303, TS142-304, and TS142-305), Japanese phase II studies (Studies TS142-201 [Study 201] and TS142-203 [Study 203]), and a Japanese phase III study (Study TS142-301 [Study 301]) and a Japanese long-term treatment study (Study 302). Pharmacokinetics of vornorexant were described as a 1-compartment model with first-order absorption.

For the absorption rate constant (K_a) of vornorexant, formulation and meal condition were subjected to covariate search, and meal condition was selected as a covariate. For CL/F, age, body weight, sex, alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, total protein, and estimated glomerular filtration rate (eGFR) were subjected to covariate search, and the age, body weight, ALT, and ALP were selected as covariates.

For the covariates in the final model, their effects on various pharmacokinetic parameters (C_{max}, AUC) were investigated. The ratios of C_{max} and AUC in subjects with the value of each covariate falling at the 5th and 95th percentiles of the measured data to those in subjects with a representative value of the corresponding covariate were 0.940 to 1.20 and 0.795 to 1.20, respectively. The applicant explained that the effects on exposure were limited.

6.R Outline of the review conducted by PMDA

6.R.1 Use of vornorexant in patients with hepatic impairment

The applicant's explanation about the use of vornorexant in patients with hepatic impairment:

In the phase I study to investigate the effects of hepatic impairment on the pharmacokinetics of vornorexant (Study TS142-303), a single dose of vornorexant 5 mg was orally administered, and C_{max} and $AUC_{0-\infty}$ of plasma protein-unbound vornorexant were 1.07 and 1.37 times higher, respectively, in

subjects with mild hepatic impairment, and 1.42 and 3.06 times higher, respectively, in subjects with moderate hepatic impairment, than those in subjects with normal hepatic function [see Section 6.2.3.2].

In the Japanese phase II studies (Studies 201 and 203) and Japanese phase III studies (Studies 301 and 302), subjects with severe hepatic impairment were excluded, and vornorexant was administered to subjects with mild or moderate hepatic impairment without dose adjustment based on hepatic function. Table 30 shows the safety profiles by hepatic function level in Studies 201, 203, 301, and 302. The above clinical studies included only 1 subject with moderate hepatic impairment. For safety, incidences of adverse events did not clearly differ between subjects with mild hepatic impairment and those with normal hepatic function, and no increasing trend in specific adverse events was observed in subjects with mild hepatic impairment.

Table 30. Incidence of adverse events by hepatic function level (safety analysis population)

Study	Group	Hepatic function		
		Normal	Mildly impaired	Moderately impaired
201	Placebo	1/22 (4.5)	0/1 (0)	-
	5 mg	1/22 (4.5)	1/1 (100)	-
	10 mg	3/22 (13.6)	1/1 (100)	-
	30 mg	8/23 (34.8)	1/1 (100)	-
203	Placebo	8/44 (18.2)	0/1 (0)	-
	2.5 mg	5/43 (11.6)	0/1 (0)	-
	5 mg	11/45 (24.4)	-	-
	10 mg	11/42 (26.2)	0/1 (0)	1/1 (100)
301	Placebo	25/195 (12.8)	0/1 (0)	-
	5 mg	28/188 (14.9)	1/8 (12.5)	-
	10 mg	32/194 (16.5)	0/2 (0)	-
302	5 mg	91/177 (51.4)	2/7 (28.6)	-
	10 mg	90/175 (51.4)	5/8 (62.5)	-

Number of subjects with adverse events/Number of subjects evaluated (incidence)
-, Of subjects treated with the study drug in the clinical study, none were applicable.

In view of the above results, vornorexant should be contraindicated in patients with severe hepatic impairment. For the following considerations, the dosage for patients with insomnia who have moderate hepatic impairment should not exceed 5 mg once daily: (1) C_{max} and $AUC_{0-\infty}$ of plasma protein-unbound vornorexant in subjects with moderate hepatic impairment were 1.42 and 3.06 times higher, respectively, than those in subjects with normal hepatic function; and (2) in clinical studies in patients with insomnia, only 1 patient with moderate hepatic impairment received vornorexant, and safety information on the use of vornorexant in this population is extremely limited. For patients with mild hepatic impairment, dose adjustment of vornorexant is considered unnecessary.

PMDA's view:
Although the extent to which plasma concentrations of unbound vornorexant increase in patients with severe hepatic impairment remains unclear, increased exposure was observed in subjects with moderate hepatic impairment, and clinical studies in patients with insomnia (Studies 201, 203, 301, and 302) excluded those with severe hepatic impairment. Therefore, the applicant's policy to contraindicate vornorexant in patients with severe hepatic impairment is acceptable.

For patients with moderate hepatic impairment, in a clinical study where vornorexant 5 mg was administered to investigate the effects of hepatic impairment on the pharmacokinetics of vornorexant,

C_{max} and $AUC_{0-\infty}$ of plasma protein-unbound vornorexant in subjects with moderate hepatic impairment were 1.42 and 3.06 times higher than those in subjects with normal hepatic function [see Section 6.2.3.2], and in clinical studies in patients with insomnia, only 1 subject with moderate hepatic impairment received vornorexant, and the safety information on the use of vornorexant in this population is limited. Based on the above, the applicant's policy that the dosage for patients with moderate hepatic impairment should not exceed 5 mg once daily is acceptable.

In patients with mild hepatic impairment, concentrations of unbound vornorexant did not greatly differ from those in subjects with normal hepatic function. In Studies 201, 203, 301, no safety concerns were identified, including the incidence of adverse events. Therefore, the applicant's view that dose adjustment of vornorexant is not necessary is acceptable.

6.R.2 Use of vornorexant in patients with renal impairment

The applicant's explanation about the use of vornorexant in patients with renal impairment:

No clinical studies have been conducted to investigate the effects of renal impairment on the pharmacokinetics of vornorexant in patients with renal impairment. In view of the following points, dose adjustment of vornorexant is not necessary for patients with renal impairment:

- Based on the results from the Japanese phase I study (Study TS142-206) to investigate the mass balance of vornorexant, the contribution of the renal excretion to the elimination of vornorexant is considered small [see Section 6.2.5].
- In the PPK analysis, a potential effect of renal function was investigated (1081 subjects; eGFR, 30.14-142.45 mL/min/1.73 m^2), but eGFR was not a significant covariate for CL/F [see Section 6.2.7].
- Table 31 shows the safety profiles by renal function level in Studies 201, 203, 301, and 302. Although there were no subjects with severe renal impairment who received vornorexant, the incidence of adverse events did not clearly differ depending on renal function level, and no increasing trend in specific adverse events was observed in subjects with renal impairment.

Table 31. Incidence of adverse events by renal function level (safety analysis population)

Study	Group	Renal function			
		Normal	Mildly impaired	Moderately impaired	Severely impaired
201	Placebo	0/2 (0)	1/21 (4.8)	-	-
	5 mg	0/2 (0)	2/19 (10.5)	0/2 (0)	-
	10 mg	1/4 (25.0)	3/18 (16.7)	0/1 (0)	-
	30 mg	2/4 (50.0)	6/18 (33.3)	1/2 (50.0)	-
203	Placebo	3/15 (20.0)	4/26 (15.4)	1/4 (25.0)	-
	2.5 mg	1/14 (7.1)	4/26 (15.4)	0/4 (0)	-
	5 mg	4/14 (28.6)	7/29 (24.1)	0/2 (0)	-
	10 mg	3/9 (33.3)	8/32 (25.0)	1/3 (33.3)	-
301	Placebo	5/32 (15.6)	16/142 (11.3)	4/21 (19.0)	0/1 (0)
	5 mg	6/33 (18.2)	18/145 (12.4)	5/18 (27.8)	-
	10 mg	7/25 (28.0)	23/147 (15.6)	2/24 (8.3)	-
302	5 mg	14/27 (51.9)	72/130 (55.4)	7/27 (25.9)	-
	10 mg	17/31 (54.8)	69/133 (51.9)	9/19 (47.4)	-

Number of subjects with adverse events/Number of subjects evaluated (incidence)
-, Of subjects treated with the study drug in the clinical study, none were applicable.

PMDA accepted the applicant's explanation.

6.R.3 CYP3A-mediated pharmacokinetic interactions

The applicant's explanation about the coadministration of vornorexant with CYP3A inhibitors and inducers:

In the drug-drug interaction study (Study TS142-205-01), coadministration with itraconazole (a potent CYP3A inhibitor) affected exposure to vornorexant [see Section 6.2.4]. The Effects of CYP3A inhibitors and inducers on the pharmacokinetics of vornorexant were investigated using a PBPK model.

In the PBPK model analysis, Simcyp version 23 was used to evaluate the effects of CYP3A inhibitors on the pharmacokinetics of vornorexant. Verification of the formulated model for predictive performance was conducted using data from Japanese phase I studies (Studies TS142-101, TS142-102, TS142-202, TS142-209, and TS142-304). Comparison of the estimated and measured values of exposure following coadministration with itraconazole (a potent CYP3A inhibitor) supported the validity of the formulated model. Simcyp version 23 was used to evaluate the effects of CYP3A inducers on the pharmacokinetics of vornorexant. Verification of the formulated model for predictive performance was conducted using data from Japanese phase I studies (Studies TS142-101, TS142-102, TS142-202, TS142-209, and TS142-304). Comparison of the estimated and measured values of exposure following single and multiple dosing supported the validity of the formulated model.

In Study 205, the effects of coadministration with a potent CYP3A inhibitor (itraconazole) were investigated. Geometric mean ratios of C_{max} and $AUC_{0-\infty}$ of vornorexant following coadministration with the potent CYP3A inhibitor to those without coadministration (coadministration/administration of vornorexant alone) were 2.24 and 12.2, respectively. Thus, coadministration of vornorexant with potent CYP3A inhibitors should be contraindicated.

For effects of coadministration with moderate CYP3A inhibitors (fluconazole, erythromycin, and verapamil), geometric mean ratios of C_{max} and $AUC_{0-\infty}$ of vornorexant following coadministration with moderate CYP3A inhibitors to those without coadministration (coadministration/administration of vornorexant alone) were predicted to be 1.59 to 1.85 and 2.67 to 4.00, respectively. In Studies 201, 203, and 301, coadministration with moderate CYP3A inhibitors was prohibited. In Study 302, coadministration with moderate CYP3A inhibitors was allowed with the condition that the dose of vornorexant should be reduced to 2.5 mg once daily. In Study 302, of 2 subjects who concomitantly received a moderate CYP3A inhibitor, 1 subject experienced an adverse event (tonsillitis); however, the event was moderate and the outcome was reported as "resolved." Although it should be noted that coadministration with moderate CYP3A inhibitors in clinical studies was limited to a very small number of subjects, no safety concerns were observed. Therefore, in the case of coadministration with moderate CYP3A inhibitors, the dose of vornorexant should be 2.5 mg once daily, as done in Study 302.

For effects of coadministration with weak CYP3A inhibitors, the geometric mean ratios of C_{max} and $AUC_{0-\infty}$ of vornorexant after coadministration with a weak CYP3A inhibitor (cimetidine) to those without coadministration (coadministration/administration of vornorexant alone) were predicted to be 1.25 and 1.31, respectively. In Studies 201 and 203, coadministration with weak CYP3A inhibitors was prohibited. In Study 301, coadministration with weak CYP3A inhibitors was allowed, but no subjects received such concomitant treatment. In Study 302, weak CYP3A inhibitors were used in 1 subject in

the vornorexant 5 mg group and 4 subjects in the vornorexant 10 mg group. Adverse events (dental caries, nasopharyngitis, and C-reactive protein [CRP] increased; abnormal dreams, somnolence, tonsillitis) occurred in 2 subjects in the vornorexant 10 mg group; however, all events were mild, and all resolved except CRP increased. Therefore, dose adjustment of vornorexant is not considered necessary when coadministered with weak CYP3A inhibitors.

For effects of coadministration with CYP3A inducers, C_{max} and $AUC_{0-\infty}$ of vornorexant after coadministration with a CYP3A inducer (rifampicin) were predicted to be decreased to 31% and 18%, respectively, of those without coadministration. Thus, CYP3A inducers will be included in the Precautions for Co-administration section with the cautionary statement that the coadministration may decrease exposure to vornorexant, thereby weakening the therapeutic effect.

PMDA accepted the applicant's explanation.

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

The applicant submitted the results of the clinical studies shown in Table 32 as the main efficacy and safety data. The main study results are described below.

Table 32. List of clinical studies for efficacy and safety

Data category	Region	Study CTD	Phase	Population	No. of subjects treated	Dosage regimen	Main endpoints
Evaluation	Japan	TS142-201 5.3.5.1-1	II	Patients with insomnia	24	Vornorexant (capsule) 5, 10, 30 mg, or placebo; orally administered QD before bedtime	Efficacy Safety
		TS142-203 5.3.5.1-2	II	Patients with insomnia	178	Vornorexant 2.5, 5, 10 mg, or placebo; orally administered QD before bedtime for 2 weeks	Efficacy Safety
		TS142-301 5.3.5.1-3	III	Patients with insomnia	589	Vornorexant 5, 10 mg, or placebo; orally administered QD before bedtime for 2 weeks	Efficacy Safety
		TS142-302 5.3.5.2-1, 5.3.5.2-2	III	Patients with insomnia	367	Vornorexant 5 or 10 mg; orally administered QD before bedtime for up to 52 weeks	Safety

7.1 Phase II studies

7.1.1 Japanese phase II study (CTD 5.3.5.1-1, Study TS142-201, July 2017 to February 2019)

A randomized, placebo-controlled, double-blind, 4-treatment, 4-period crossover study was conducted to investigate the efficacy and safety of vornorexant in patients with insomnia (target sample size, 32 subjects) in an exploratory manner.

The main inclusion criteria were as follows: (1) a diagnosis of insomnia disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (2) sleep latency of ≥30 minutes and wake time after sleep onset of ≥30 minutes occurring on at least 3 days per week; (3) usual time in bed of ≥6.5 hours and ≤9 hours with the bedtime between 21:00 and 24:00; and (4) an Insomnia Severity Index score of ≥15.

This study consisted of a run-in placebo treatment period[16] and a double-blind period.

During the run-in placebo treatment period, a single dose of placebo was orally administered before bedtime, and during the double-blind period, a single dose of placebo or vornorexant[17] 5, 10, or 30 mg was orally administered before bedtime. These treatment periods were separated by a washout period of 7 days.

All 24 subjects treated with the study drug during the double-blind period were included in the full analysis set (FAS) and the safety analysis population. The FAS was used for the efficacy analysis population. Because of protocol deviation (violation of the inclusion or exclusion criteria), 1 subject discontinued the study after the study treatment during the vornorexant 30 mg treatment period.

The co-primary endpoints were latency to persistent sleep (LPS) and wake after sleep onset (WASO) measured by polysomnography (PSG) on Day 1 of each treatment period. As shown in Table 33, results on both parameters tended to be more favorable in the vornorexant treatment periods at all doses than in the placebo treatment period.

Table 33. Co-primary endpoints (FAS)

Item	Treatment period	Day 1[a]	Difference from placebo treatment period [95% CI][b]
LPS	Placebo	53.57 ± 59.30	
	Vornorexant 5 mg	12.37 ± 14.56	-42.38 [-60.13, -24.63]
	Vornorexant 10 mg	10.72 ± 8.72	-42.10 [-60.02, -24.17]
	Vornorexant 30 mg	7.83 ± 10.32	-44.68 [-62.41, -26.95]
WASO	Placebo	83.11 ± 67.50	
	Vornorexant 5 mg	54.91 ± 40.53	-27.52 [-46.90, -8.14]
	Vornorexant 10 mg	47.61 ± 32.26	-35.44 [-55.02, -15.87]
	Vornorexant 30 mg	30.38 ± 21.32	-54.69 [-74.16, -35.23]

Unit, minutes
a) Mean ± SD
b) Analysis in a mixed-effects model formulated using group, drug, and treatment period as fixed effects and subject as a random effect. The Kenward-Roger method was applied to adjust the degree of freedom.

Table 34 shows the incidence of all adverse events during the double-blind period and those occurring in ≥2 subjects during any treatment period. No deaths, serious adverse events other than deaths, or adverse events leading to treatment discontinuation occurred.

Table 34. All adverse events and adverse events reported by ≥2 subjects during any treatment period (double-blind period, safety analysis population)

	Placebo (n = 23)	Vornorexant 5 mg (n = 23)	Vornorexant 10 mg (n = 23)	Vornorexant 30 mg (n = 24)
All adverse events	1 (4.3)	2 (8.7)	4 (17.4)	9 (37.5)
Events reported by ≥2 subjects during any treatment period				
Somnolence	0	0	1 (4.3)	2 (8.3)
Nightmare	0	0	0	2 (8.3)

Number of subjects with event (incidence, %)

16) It was established to perform sleep assessment for determination of eligibility.
17) Capsules were used.

7.1.2 Japanese phase II study (CTD 5.3.5.1-2, Study TS142-203, September 2020 to November 2021)

A randomized, placebo-controlled, double-blind, parallel-group study was conducted to investigate efficacy and safety of vornorexant in patients with insomnia (target sample size, 160 subjects, 40 per group) in an exploratory manner.

The main inclusion criteria were as follows: (1) a diagnosis of insomnia disorder based on the DSM-5; (2) sleep latency of ≥30 minutes and wake time after sleep onset of ≥30 minutes occurring on at least 3 days per week; (3) usual time in bed of ≥6.5 hours and ≤9 hours with the bedtime between 21:00 and 25:00; and (4) an Insomnia Severity Index score of ≥15.

This study consisted of a run-in placebo treatment period,[18)] a double-blind period, and a follow-up placebo treatment period.[19)]

During the run-in placebo treatment period, placebo was orally administered once daily before bedtime for 2 weeks; during the double-blind period, placebo, or vornorexant 2.5, 5, or 10 mg was orally administered once daily before bedtime for 2 weeks; and during the follow-up placebo treatment period, placebo was orally administered once daily before bedtime for 1 week.

A total of 178 subjects who were randomized and treated with the study drug during the double-blind period (45 in the placebo group, 44 in the vornorexant 2.5 mg group, 45 in the vornorexant 5 mg group, and 44 in the vornorexant 10 mg group, the same order applies hereinafter) were included in the FAS and the safety analysis population. The FAS was used as the main efficacy analysis population. Four subjects (0, 2, 1, and 1) discontinued the study because of protocol deviation in 1 subject (vornorexant 2.5 mg group), lost to follow-up in 1 subject (vornorexant 2.5 mg group), consent withdrawal in 1 subject (vornorexant 10 mg group), and other reasons in 1 subject (vornorexant 5 mg group).

The primary endpoint was a “change in subjective sleep latency (sSL) from baseline to end of study treatment,” and results for this endpoint in each vornorexant group were compared with those in the placebo group. As shown in Table 35, vornorexant tended to shorten sSL, and results in the vornorexant 10 mg group tended to be more favorable than those in the placebo group.

[18)] It was established to perform sleep assessment for determination of eligibility.
[19)] It was established to monitor dependence risk, rebound insomnia, and withdrawal symptoms.

Table 35. Change in sSL from baseline to end of study treatment (FAS)

	Baseline	Week 1	Week 2	End of treatment	Change from baseline to end of treatment[a)] [95% CI]	Difference from placebo [95% CI][b)]
Placebo	63.8 ± 33.3 (45)	52.6 ± 25.5 (45)	52.5 ± 32.5 (45)	52.5 ± 32.5 (45)	-8.4 [-13.4, -3.4]	
Vornorexant 2.5 mg	50.5 ± 20.5 (44)	41.0 ± 15.3 (44)	41.1 ± 18.3 (43)	41.3 ± 18.2 (44)	-11.9 [-16.9, -6.9]	-3.5 [-10.6, 3.7]
Vornorexant 5 mg	48.0 ± 19.0 (45)	39.0 ± 15.8 (45)	37.5 ± 14.0 (44)	37.6 ± 13.9 (45)	-14.1 [-19.1, -9.1]	-5.6 [-12.8, 1.5]
Vornorexant 10 mg	65.1 ± 29.9 (44)	43.6 ± 21.9 (44)	43.9 ± 21.9 (44)	43.9 ± 21.9 (44)	-17.7 [-22.8, -12.7]	-9.3 [-16.3, -2.3]

Unit, minutes; mean ± SD (number of subjects evaluated)

a) Least squares mean

b) Analysis of covariance model formulated using baseline as a covariate. Missing data at the end of treatment, where applicable, were imputed by a last observation carried forward (LOCF) approach.

Table 36 shows the incidence of all adverse events during the double-blind period and that of adverse events reported by ≥2 subjects in any group. No deaths, serious adverse events other than deaths, or adverse events leading to treatment discontinuation occurred.

Table 36. All adverse events and adverse events reported by ≥2 subjects in any group (double-blind period, safety analysis population)

	Placebo (n = 45)	Vornorexant 2.5 mg (n = 44)	Vornorexant 5 mg (n = 45)	Vornorexant 10 mg (n = 44)
All adverse events	8 (17.8)	5 (11.4)	11 (24.4)	12 (27.3)
Events reported by ≥2 subjects in any group				
Somnolence	1 (2.2)	0	4 (8.9)	5 (11.4)
Headache	0	0	0	4 (9.1)
Vaccination site pain	2 (4.4)	0	0	1 (2.3)
Glucose urine present	1 (2.2)	0	2 (4.4)	0

Number of subjects with event (incidence, %)

7.2 Phase III studies

7.2.1 Japanese phase III study (CTD 5.3.5.1-3, Study TS142-301, August 2022 to December 2023)

A randomized, placebo-controlled, double-blind, parallel-group study was conducted to investigate the efficacy and safety of vornorexant in patients with insomnia (target sample size, 540 subjects, 180 per group[20)]).

The main inclusion criteria were as follows: (1) a diagnosis of insomnia disorder based on the DSM-5; (2) sleep latency of ≥30 minutes and wake time after sleep onset of≥30 minutes occurring on at least 3 days per week; (3) usual time in bed of ≥6.5 hours and ≤9 hours with the bedtime between 21:00 and 25:00; and (4) an Insomnia Severity Index score of ≥15.

This study consisted of a run-in placebo treatment period,[18)] a double-blind period, and a follow-up placebo treatment period.[19)]

20) Based on the results from the Japanese phase II study (Study TS142-203), the following assumption was made: Mean changes in sSL from baseline in the vornorexant 5 mg and 10 mg groups differ from that in the placebo group by -6.1 and -9.3 minutes with the common SD of 16.8 minutes; mean changes in subjective sleep efficiency (sSE) from baseline in the 5 mg and 10 mg groups differ from that in the placebo group by 2.32% and 2.99% with the common SD of 7.63%; and a two-sided significance level is 5%. To detect a significant difference in either endpoint between both vornorexant groups and the placebo group with ≥80% of probability on the above assumption, 171 subjects per group was estimated to be needed. With dropout taken into account, 180 subjects per group or a total of 540 subjects with 3 groups was established.

During the run-in placebo treatment period, placebo was orally administered once daily before bedtime for 2 weeks; during the double-blind period, placebo or vornorexant 5 or 10 mg was orally administered once daily before bedtime for 2 weeks; and during the follow-up placebo treatment period, placebo was orally administered once daily before bedtime for 1 week.

Of 590 randomized subjects (197 in the placebo group, 196 in the vornorexant 5 mg group, and 197 in the vornorexant 10 mg group, the same order applies hereinafter), 589 subjects were included in the FAS and safety analysis population, excluding 1 subject in the placebo group who did not receive the study drug. The FAS was used as the main efficacy analysis population. Six subjects (3, 1, and 2) discontinued the study because of adverse events in 1 subject (placebo group), consent withdrawal in 1 subject (placebo group), lost to follow-up in 1 subject (vornorexant 5 mg group), and other reasons in 3 subjects (1 in the placebo group and 2 in the vornorexant 10 mg group).

The primary endpoint was the "change in sSL from baseline to Week 2," and results for this endpoint in each vornorexant group were compared with those in the placebo group. As shown in Table 37, vornorexant 5 and 10 mg groups were demonstrated to be superior to the placebo group.

Table 37. Change in sSL from baseline to Week 2 (FAS)

Group	Baseline	Week 2	Change from baseline to Week 2 [95% CI][a)]	Difference from placebo [95% CI][a) b)]	*P* value[c)]
Placebo	58.9 ± 28.8 (196)	50.2 ± 27.0 (194)	-8.6 [-11.1, -6.0]		
Vornorexant 5 mg	57.0 ± 26.4 (196)	38.4 ± 19.4 (196)	-19.2 [-21.7, -16.6]	-10.6 [-14.2, -7.0]	<0.001
Vornorexant 10 mg	58.6 ± 28.0 (197)	39.7 ± 20.6 (197)	-18.7 [-21.3, -16.2]	-10.1 [-13.8, -6.5]	<0.001

Unit, minutes; mean ± SD (number of subjects evaluated)

a) Least squares mean

b) It was calculated by a mixed-effects model for repeated measures (MMRM) where dose group, evaluation time point, and interaction between dose group and evaluation time point were handled as fixed effects; baseline was handled as a covariate; the covariance structure was deemed to be unstructured (UN); and degree of freedom was adjusted by the Kenward-Roger method.

c) A two-sided significance level was 5%. Multiplicity of the test was adjusted by a fixed sequence procedure in which comparison between placebo and vornorexant 5 mg was performed only when comparison between placebo and vornorexant 10 mg provided a significant difference.

Table 38 shows the incidence of all adverse events during the double-blind period and adverse events reported by ≥2% of subjects in any group.

Table 38. All adverse events and adverse events reported by ≥2% of subjects in any group (double-blind period, safety analysis population)

	Placebo (n = 196)	Vornorexant 5 mg (n = 196)	Vornorexant 10 mg (n = 197)
All adverse events	25 (12.8)	29 (14.8)	32 (16.2)
Events reported by ≥2% of subjects in any group			
Somnolence	3 (1.5)	6 (3.1)	7 (3.6)
Nasopharyngitis	3 (1.5)	1 (0.5)	6 (3.0)
Blood creatine phosphokinase increased	1 (0.5)	2 (1.0)	4 (2.0)
Headache	2 (1.0)	4 (2.0)	2 (1.0)

Number of subjects with event (incidence, %)

Neither deaths nor serious adverse events other than deaths occurred. An adverse event leading to treatment discontinuation occurred in 1 subject in the placebo group (pyrexia). A causal relationship to the study drug was ruled out for the event.

7.2.2 Japanese long-term treatment study (CTD 5.3.5.2-1 and 5.3.5.2-2, Study TS142-302, October 2022 to March 2024)

An open-label study was conducted to investigate the long-term safety of vornorexant in patients with insomnia (target sample size, 300 subjects,[21] 150 per group).

The main inclusion criteria were as follows: (1) a diagnosis of insomnia disorder based on the DSM-5; (2) sleep latency of ≥30 minutes and wake time after sleep onset of≥30 minutes occurring on at least 3 days per week; (3) usual time in bed of ≥6.5 hours and ≤9 hours with the bedtime between 21:00 and 25:00; and (4) an Insomnia Severity Index score of ≥15.

This study consisted of a study treatment period and a follow-up placebo treatment period.[19]

During the study treatment period, vornorexant 5 or 10 mg was orally administered once daily before bedtime for up to 52 weeks,[22] and during the follow-up placebo treatment period, placebo was orally administered once daily before bedtime for 1 week.

A total of 367 subjects who were randomized and treated with the study drug (184 in the vornorexant 5 mg group and 183 in the vornorexant 10 mg group, the same order applies hereinafter) were included in the safety analysis population. Of the 367 subjects treated with the study drug, 329 subjects completed the 26 weeks of treatment. Of them, 131 subjects continued the treatment at Week 26 and thereafter and 123 subjects completed the 52 weeks of treatment. A total of 46 subjects (24 and 22) discontinued the study mainly because of consent withdrawal in 19 subjects (9 and 10), adverse events in 9 subjects (5 and 4), protocol deviations in 6 subjects (5 and 1), and other reasons in 12 subjects (5 and 7).

Table 39 shows the incidence of all adverse events during the study treatment period and adverse events reported by ≥2% of subjects in either group.

---

[21] Subjects aged ≥65 years were enrolled to account for 20% of the overall population.
[22] At Week-26 visit, consent to enter the 52-week study treatment was obtained.

Table 39. All adverse events and adverse events reported by ≥2% of subjects in either group (study treatment period, safety analysis population)

	Vornorexant 5 mg (n = 184)	Vornorexant 10 mg (n = 183)
All adverse events	93 (50.5)	95 (51.9)
Events reported by ≥2% of subjects in either group		
Somnolence	10 (5.4)	22 (12.0)
Nasopharyngitis	20 (10.9)	15 (8.2)
COVID-19	4 (2.2)	8 (4.4)
Nightmare	2 (1.1)	6 (3.3)
Contusion	1 (0.5)	6 (3.3)
Cystitis	2 (1.1)	5 (2.7)
Coronavirus infection	1 (0.5)	5 (2.7)
Vaccination site pain	0	5 (2.7)
Headache	11 (6.0)	4 (2.2)
Malaise	5 (2.7)	3 (1.6)
Immunisation reaction	8 (4.3)	1 (0.5)
Influenza	5 (2.7)	1 (0.5)
Dental caries	4 (2.2)	1 (0.5)

Number of subjects with event (incidence, %)

No deaths occurred. Serious adverse events other than deaths occurred in 5 subjects in the vornorexant 5 mg group (intestinal obstruction, ankle fracture, lumbar spinal stenosis, oropharyngeal cancer, and subarachnoid haemorrhage) and 2 subjects in the vornorexant 10 mg group (haemorrhoids and central nervous system lesion). A causal relationship to the study drug was ruled out for any of the above events.

Adverse events leading to treatment discontinuation occurred in 5 subjects in the vornorexant 5 mg group (atrial fibrillation; lumbar spinal stenosis; oropharyngeal cancer; subarachnoid haemorrhage; and blood uric acid increased and renal dysfunction) and 4 subjects in the vornorexant 10 mg group (palpitations; vertigo; nausea and malaise; and central nervous system lesion). A causal relationship to the study drug could not be ruled out for palpitations, vertigo, and nausea and malaise in the vornorexant 10 mg group, but these events resolved after treatment discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Results on primary endpoints

The applicant's explanation of efficacy of vornorexant:

The "Guideline for Clinical Evaluation of Hypnotics (in Japanese)" (PFSB/ELD Notification No. 1213-1, dated December 13, 2011) states that in clinical development of hypnotics, efficacy evaluation should be designed to ensure assessment of insomniac symptoms and next-day mental and physical impairment, covering key endpoints such as sleep latency, wake after sleep onset, total sleep time, sleep quality, and freshness of sleep as well as next-day mental and physical functions, and thus confirmatory studies need to include subjective assessment using sleep questionnaires, etc. In clinical studies of vornorexant, efficacy endpoints were specified with reference to the guideline for clinical evaluation of hypnotics, etc.

In Study 301, results for the primary endpoint, "change in sSL from baseline to Week 2," demonstrated the superiority of both vornorexant 5 and 10 mg over placebo (Table 37). Table 40 provides results for the main secondary endpoints. For all endpoints, the vornorexant 5 mg and 10 mg groups show an improving trend compared with the placebo group.

Table 40. Results on main secondary endpoints (Study 301, FAS)

Item	Group	Baseline[a)]	Week 2[a)]	Change from baseline to Week 2[b)c)]	Difference from placebo [95% CI][c)]
Subjective sleep efficiency (sSE)	Placebo	73.0 ± 11.1 (196)	77.1 ± 11.7 (194)	4.1 [3.0, 5.2]	
	Vornorexant 5 mg	74.2 ± 9.2 (196)	81.6 ± 9.5 (196)	7.6 [6.5, 8.6]	3.4 [1.9, 5.0]
	Vornorexant 10 mg	73.3 ± 9.8 (197)	80.4 ± 11.3 (197)	7.1 [6.0, 8.2]	2.9 [1.4, 4.5]
Subjective total sleep time (sTST)	Placebo	325.1 ± 49.5 (196)	345.9 ± 54.7 (194)	20.4 [14.7, 26.1]	
	Vornorexant 5 mg	332.9 ± 41.0 (196)	366.5 ± 48.7 (196)	34.5 [28.9, 40.2]	14.1 [6.1, 22.2]
	Vornorexant 10 mg	328.4 ± 42.6 (197)	359.5 ± 54.8 (197)	31.0 [25.4, 36.6]	10.6 [2.6, 18.6]
Subjective wake after sleep onset (sWASO)	Placebo	62.9 ± 40.0 (196)	53.1 ± 39.3 (194)	-9.9 [-13.4, -6.3]	
	Vornorexant 5 mg	60.0 ± 34.5 (196)	44.3 ± 31.8 (196)	-16.2 [-19.8, -12.6]	-6.3 [-11.4, -1.3]
	Vornorexant 10 mg	62.4 ± 36.4 (197)	48.3 ± 39.4 (197)	-14.0 [-17.5, -10.4]	-4.1 [-9.2, 0.9]
Sheehan disability Scale[d)] (SDS)	Placebo	10.9 ± 6.7 (181)	9.9 ± 6.8 (175)	-0.8 [-1.6, -0.1]	
	Vornorexant 5 mg	9.8 ± 7.0 (178)	7.5 ± 6.8 (177)	-2.7 [-3.4, -2.0]	-1.9 [-2.9, -0.8]
	Vornorexant 10 mg	11.8 ± 7.0 (183)	9.0 ± 7.3 (183)	-2.3 [-3.1, -1.6]	-1.5 [-2.5, -0.4]

Unit, % (sSE), minutes (sTST, sWASO)

a) Mean ± SD (number of subjects evaluated)

b) Least squares mean [95% CI]

c) It was calculated by an MMRM where dose group, evaluation time point, and interaction between dose group and evaluation time point were handled as fixed effects; baseline was handled as a covariate; the covariance structure was deemed to be UN; and degree of freedom was adjusted by the Kenward-Roger method.

d) Daytime function impairment

Figures 1 and 2 show time-course profiles of changes in sSL and subjective sleep efficiency (sSE) from baseline through Week 52 in Study 302. Reductions in sSL and increases in sSE were observed from Week 1 and were maintained throughout the evaluation period.

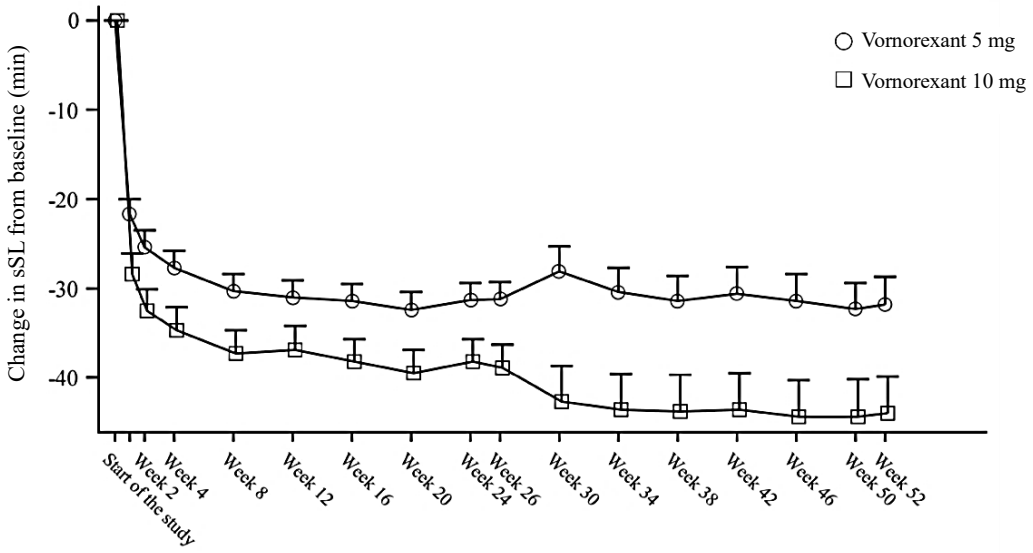


Figure 1. Time-course profile of changes in sSL from baseline (mean ± standard error [SE]) in Study 302

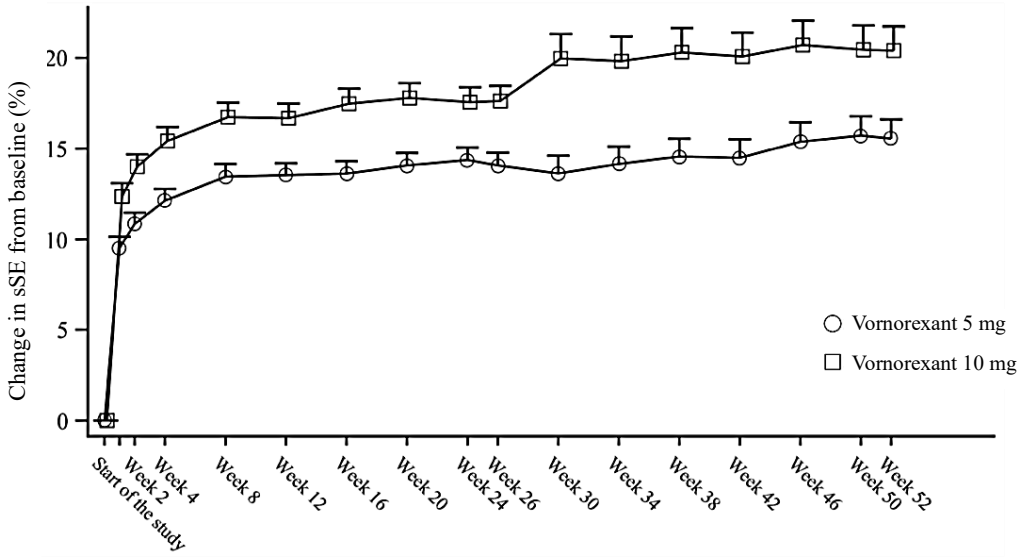


Figure 2. Time-course profile of changes in sSE from baseline (mean ± SE) in Study 302

Based on the above results, the applicant considers that the efficacy of vornorexant in the treatment of insomnia was demonstrated.

PMDA's view:
In Study 301, results for the primary endpoint, "change in sSL from baseline to Week 2," demonstrated the superiority of both vornorexant 5 and 10 mg over placebo (Table 37), and thus efficacy of vornorexant in the treatment of difficulty initiating sleep was confirmed. In addition, for sSE, subjective total sleep time (sTST), subjective wake time after sleep onset (sWASO), and Sheehan disability scale (SDS), the vornorexant 5 mg and 10 mg groups showed an improving trend compared with the placebo group (Table 40), and thus efficacy of vornorexant in the treatment of difficulty maintaining sleep and improvement of daytime function can be expected.

For long-term efficacy of vornorexant, reductions in sSL and increases in sSE were maintained throughout the evaluation period of 52 weeks without any weakening trend of efficacy in Study 302 (Figures 1 and 2).

Based on the above review, PMDA has concluded that efficacy of vornorexant in the treatment of insomnia is demonstrated.

7.R.1.2 Effects on sleep architecture

The applicant's explanation of the effects of vornorexant on sleep architecture:
The "Guideline for Clinical Evaluation of Hypnotics" (PFSB/ELD Notification No. 1213-1, dated December 13, 2011) states that investigation of the effects of study drugs on sleep architecture is required not only for efficacy evaluation but also from the viewpoint of safety evaluation.

In Study 201, total sleep time (TST) (mean ± SD) measured by PSG was 347.4 ± 101.3 minutes in the placebo treatment period, 415.5 ± 42.4 minutes in the vornorexant 5 mg treatment period, 423.7 ± 35.3

minutes in the vornorexant 10 mg treatment period, and 444.8 ± 23.3 minutes in the vornorexant 30 mg treatment period.

Table 41 shows the percentage of each sleep stage (REM sleep, non-REM sleep Stage 1-3) compared to TST in Study 201. The Percentage of REM sleep time compared to TST tended to be greater in each vornorexant treatment period than in the placebo treatment period but did not deviate from the normal range of sleep in healthy adults (*Sleep.* 2007;30:829-36).

Table 41. Percentage of each sleep stage compared to TST (Study 201, FAS)

Item	Treatment period	No. of subjects	Measured value[a)]	Difference from placebo[b)]
REM sleep	Placebo	23	20.8 ± 7.8	
	Vornorexant 5 mg	23	23.6 ± 6.9	2.8 [-0.4, 6.0]
	Vornorexant 10 mg	23	26.0 ± 6.7	5.1 [1.9, 8.4]
	Vornorexant 30 mg	24	26.4 ± 8.2	6.0 [2.8, 9.2]
Non-REM sleep Stage 1	Placebo	23	19.2 ± 9.5	
	Vornorexant 5 mg	23	18.0 ± 10.1	-1.3 [-4.4, 1.9]
	Vornorexant 10 mg	23	16.6 ± 8.8	-2.7 [-5.9, 0.5]
	Vornorexant 30 mg	24	14.8 ± 6.3	-4.8 [-8.0, -1.7]
Non-REM sleep Stage 2	Placebo	23	49.5 ± 7.9	
	Vornorexant 5 mg	23	47.1 ± 7.6	-2.3 [-5.1, 0.6]
	Vornorexant 10 mg	23	45.7 ± 6.7	-3.5 [-6.3, -0.6]
	Vornorexant 30 mg	24	47.9 ± 8.0	-1.7 [-4.5, 1.2]
Non-REM sleep Stage 3	Placebo	23	10.6 ± 6.4	
	Vornorexant 5 mg	23	11.3 ± 6.4	0.8 [-1.2, 2.8]
	Vornorexant 10 mg	23	11.7 ± 5.8	1.0 [-1.0, 3.1]
	Vornorexant 30 mg	24	11.0 ± 5.8	0.5 [-1.6, 2.5]

Unit, %

a) Mean ± SD

b) Difference in least squares mean between the vornorexant treatment period and placebo treatment period [95% CI]. It was calculated by a mixed-effects model where dose group, drug, and treatment period were handled as fixed effects; subject was handled as a covariate; and degree of freedom was adjusted by the Kenward-Roger method.

As shown in Table 42, results for REM sleep latency measured by PSG in Study 201 showed a trend toward a dose-dependent decrease.

Table 42. Results on REM sleep latency (Study 201, FAS)

Treatment period	No. of subjects	Measured value[a)]	Difference from placebo[b)]
Placebo	22	122.0 ± 54.7	
Vornorexant 5 mg	23	72.8 ± 74.6	-47.8 [-78.6, -17.0]
Vornorexant 10 mg	23	48.5 ± 39.9	-74.0 [-105.0, -43.0]
Vornorexant 30 mg	24	39.4 ± 45.4	-82.3 [-113.0, -51.6]

Unit, minutes

a) Mean ± SD

b) Difference in least squares mean between the vornorexant treatment period and placebo treatment period [95% CI]. It was calculated by a mixed-effects model where dose group, drug, and treatment period were handled as fixed effects; subject was handled as a covariate; and degree of freedom was adjusted by the Kenward-Roger method.

Table 43 shows the incidence of adverse events in subjects with REM sleep latency <15 minutes and those with REM sleep latency ≥15 minutes. The incidence tended to increase in a dose-dependent manner.

Table 43. Incidence of adverse events in subjects with REM sleep latency <15 minutes and those with REM sleep latency ≥15 minutes (Study 201, safety analysis population)

	Subjects with REM sleep latency <15 minutes				Subjects with REM sleep latency ≥15 minutes			
Treatment period	Placebo (n = 0)	Vornorexant 5 mg (n = 5)	Vornorexant 10 mg (n = 7)	Vornorexant 30 mg (n = 11)	Placebo (n = 22)	Vornorexant 5 mg (n = 18)	Vornorexant 10 mg (n = 16)	Vornorexant 30 mg (n = 13)
All adverse events	0	0	2 (28.6)	6 (54.5)	1 (4.5)	2 (11.1)	2 (12.5)	3 (23.1)
Main adverse events[a)]								
Nightmare	0	0	0	2 (18.2)	0	0	0	0
Somnolence	0	0	1 (14.3)	1 (9.1)	0	0	0	1 (7.7)
Hypnagogic hallucination	0	0	1 (14.3)	1 (9.1)	0	0	0	0
Muscular weakness	0	0	0	0	0	1 (5.6)	1 (6.3)	0
Nasopharyngitis	0	0	0	0	1 (4.5)	1 (5.6)	0	0

Number of subjects with event (incidence, %)
a) Adverse events reported by more than 1 subject

PMDA's view:
In Study 201, the percentage of REM sleep relative to TST tended to be slightly greater than those reported in healthy adults (18.2% ± 5.2% to 21.0% ± 3.9%, mean ± SD) (*Sleep.* 2009;32:139-49); however, this finding is understandable in view of its pharmacological effect of vornorexant. In addition, in Study 201, nightmare, REM sleep parasomnia, and hypnagogic hallucination (narcolepsy-related symptom) occurred only during the vornorexant treatment period, and their incidence tended to be higher in subjects with shorter REM sleep latency than in those with longer REM sleep latency. Although interpretation of the results has limitations due to the limited sample size in Study 201, in view of the pharmacological effect of vornorexant, which shortens REM sleep latency (*Neuropsychopharmacology.* 2012;37:1224-33), PMDA continues to assess the risks of parasomnia and related symptoms as well as narcolepsy-related symptoms associated with vornorexant in Sections 7.R.2.2 and 7.R.2.3.

7.R.2 Safety

7.R.2.1 Safety profile of vornorexant

The applicant's explanation of the safety profile of vornorexant:
Table 38 shows the incidence of adverse events during the double-blind period (2 weeks) in Study 301. The incidence of all adverse events and the types of events did not differ between the placebo group and each vornorexant group. A relatively commonly observed event in the vornorexant groups was "somnolence," the incidence of which tended to be slightly higher in each vornorexant group than in the placebo group. No deaths, serious adverse events other than deaths, or adverse events leading to treatment discontinuation occurred in the vornorexant groups [see Section 7.2.1]. Subjects aged ≥65 years accounting for 21.9% of the study population (129 of 589 subjects; 44 in the placebo group, 42 in the vornorexant 5 mg group, and 43 in the vornorexant 10 mg group). No trend toward a higher incidence of adverse events or any specific adverse events was observed in subjects aged ≥65 years compared to those aged <65 years.

Table 39 shows the incidence of adverse events during the study treatment period (up to 52 weeks) in Study 302. The incidence of all adverse events and the types of events did not differ between the vornorexant groups, but the incidence of the relatively commonly observed event "somnolence" tended to be higher in the vornorexant 10 mg group than in the vornorexant 5 mg group. No deaths occurred. Serious adverse events other than deaths occurred in 5 subjects in the vornorexant 5 mg group and 2 subjects in the vornorexant 10 mg group. A causal relationship to the study drug was ruled out for any

of the events. Adverse events leading to treatment discontinuation occurred in 5 subjects in the vornorexant 5 mg group and 4 subjects in the vornorexant 10 mg group. The adverse events in 3 subjects in the vornorexant 10 mg group for which a causal relationship to vornorexant could not be ruled out (palpitations; vertigo; and nausea and malaise) were all mild or moderate and non-serious, and these events resolved after treatment discontinuation [see Section 7.2.2]. Subjects aged ≥65 years were enrolled, accounting for 33.0% of the study population (121 of 367 subjects; 61 in the vornorexant 5 mg group and 60 in the vornorexant 10 mg group). No trend toward a higher incidence of adverse events or specific adverse events was observed in subjects aged ≥65 years compared to those aged <65 years.

Table 44 shows the incidence of somnolence by duration of treatment in Studies 301 and 302. The incidence was high during the first dose to <1 week of treatment and did not increase over time with extending duration of treatment. The events reported as somnolence were all mild or moderate and non-serious. Extending duration of treatment did not tend to increase the severity, and no events led to treatment discontinuation.

Table 44. Incidence of somnolence by duration of treatment (safety analysis population)

	Study 301 (double-blind period)			Study 302 (study treatment period)	
	Treatment period: 2 weeks			Treatment period: Up to 52 weeks	
	Placebo (n = 196)	Vornorexant 5 mg (n = 196)	Vornorexant 10 mg (n = 197)	Vornorexant 5 mg (n = 184)	Vornorexant 10 mg (n = 183)
Entire period	3/196 (1.5)	6/196 (3.1)	7/197 (3.6)	10/184 (5.4)	22/183 (12.0)
First dose to <1 week	3/196 (1.5)	6/196 (3.1)	4/197 (2.0)	4/184 (2.2)	16/183 (8.7)
1 to <2 weeks	0/196 (0)	0/196 (0)	2/197 (1.0)	1/183 (0.5)	1/180 (0.6)
2 to <12 weeks[a)]	0/161 (0)	0/161 (0)	1/175 (0.6)	2/183 (1.1)	7/179 (3.9)
12 to <26 weeks				2/175 (1.1)	2/172 (1.2)
26 to <38 weeks				1/149 (0.7)	0/145 (0)
38 to <52 weeks				0/61 (0)	0/68 (0)
52 weeks				0/50 (0)	0/54 (0)

Number of subjects with adverse events/Number of subjects evaluated (incidence)
a) 2 weeks for Study 301

PMDA's view:
In Studies 301 and 302, the incidence of somnolence was slightly higher with vornorexant. In Study 302, the incidence of somnolence tended to be higher in the vornorexant 10 mg group than in the vornorexant 5 mg group. Based on these findings, attention should be paid to the occurrence of somnolence associated with vornorexant; however, all reported events were all mild or moderate and non-serious, and none led to treatment discontinuation. In view of these findings, no clinically relevant difference has been observed between the dose groups.

For adverse events of special interest specified based on the mechanism of action of vornorexant and events reported with the other drugs in the same class, PMDA continues to discuss details of incidences in Sections 7.R.2.2 to 7.R.2.8.

7.R.2.2 Adverse events related to parasomnia

The applicant's explanation about the risk of parasomnia-related adverse events[23)] associated with vornorexant:

In Studies 301 and 302, parasomnia-related adverse events reported were "nightmare," "abnormal dreams," and "exploding head syndrome." The incidence of "nightmare" was 0% (0 of 196 subjects) in the placebo group, 0% (0 of 196 subjects) in the vornorexant 5 mg group, and 0.5% (1 of 197 subjects) in the vornorexant 10 mg group in Study 301, and 1.1% (2 of 184 subjects) in the vornorexant 5 mg group and 3.3% (6 of 183 subjects) in the vornorexant 10 mg group in Study 302. In Study 301, nightmare occurred only in the vornorexant groups. In Study 302, nightmare tended to occur more frequently in the vornorexant 10 mg group than in the vornorexant 5 mg group; however, all events were mild and non-serious and did not lead to treatment discontinuation. Nightmare in Study 302 was mostly reported in the early phase of treatment, and the incidence did not increase with extending duration of treatment with vornorexant. "Abnormal dreams" and "exploding head syndrome" each occurred only in 0.5% (1 of 183) of subjects in the vornorexant 10 mg group in Study 302, and both events were mild and non-serious, and neither lead to treatment discontinuation.

As described above, parasomnia-related adverse events occurred only in the vornorexant groups; however, the reported events were all mild and non-serious and did not lead to treatment discontinuation. Based on the information available to date, parasomnia-related adverse events associated with vornorexant are considered unlikely to raise a clinically relevant problem.

PMDA's view:

Parasomnia-related adverse events associated with vornorexant occurred in Studies 301 and 302; however, in view of the incidence and severity, PMDA confirmed that these events did not tend to raise a clinically relevant problem.

7.R.2.3 Narcolepsy-related adverse events

The applicant's explanation about a risk of narcolepsy-related adverse events[24)] associated with vornorexant:

In Study 301, no narcolepsy-related adverse events occurred. In Study 302, "sleep paralysis" and "hypnagogic hallucination" occurred as narcolepsy-related adverse events. "Sleep paralysis" occurred in 1.1% (2 of 184) of subjects in the vornorexant 5 mg group and 0.5% (1 of 183) of subjects in the vornorexant 10 mg group, and "hypnagogic hallucination" occurred in 0.5% (1 of 184) of subjects in the vornorexant 5 mg group and 1.1% (2 of 183) of subjects in the vornorexant 10 mg group. The reported events were all mild and non-serious and did not lead to treatment discontinuation. During use of vornorexant, narcolepsy-related adverse events are considered unlikely to raise a clinically relevant problem.

However, in view of the mechanism of action of vornorexant, the possibility that administration of vornorexant may worsen symptoms in patients with narcolepsy or cataplexy cannot be ruled out; therefore, precautions will be included in the package insert.

---

23) Events coded to Medical Dictionary for Regulatory Activities Japanese version (MedDRA) HLT "Parasomnia"
24) Events coded to MedDRA HLT "Narcolepsy and associated conditions"

PMDA's view:
In Study 302, narcolepsy-related adverse events occurred; however, no serious events or events leading to treatment discontinuation were reported. PMDA thus confirmed that no clinically relevant effects were observed. In view of the exclusion criteria in clinical studies of vornorexant, which excluded patients with narcolepsy, and the mechanism of action of vornorexant, the applicant's opinion that the package insert will include precautions in the package insert regarding the use of vornorexant in patients with narcolepsy or cataplexy is acceptable.

7.R.2.4 Suicide-related adverse events

Insomnia is known to coexist with mental disorders. Their relationship is not a one-way causal one but is rather a two-way interactive one (*Curr Psychiatr Rep.* 2017;19:44). In patients, mainly with depression, treated with hypnotics, worsening of depression as well as suicidal ideation and suicidal behavior (including completed suicide) have been reported (*BMC Geriatr.* 2009;9:20). In view of these findings, PMDA asked the applicant to explain the risk of suicide-related adverse events[25)] associated with vornorexant.

The applicant's explanation:
In clinical studies of vornorexant, suicide-related effects associated with vornorexant were assessed using Columbia-Suicide Severity Rating Scale (C-SSRS). In clinical studies in healthy adults, no suicide-related adverse events occurred. In clinical studies in patients with insomnia, Study 302 had 1 subject who reported suicidal ideation. However, it was not classified as an adverse event by the investigator who interviewed the subject, based on the subject's background leading to the suicidal ideation and the fact that the event was temporary and not associated with urgency and seriousness. In the other clinical studies in patients with insomnia, no suicide-related adverse events occurred.

Based on the information available to date, the risk of suicidal ideation and suicide attempt potentially associated with vornorexant is unlikely to become a clinically relevant problem.

PMDA's view:
Suicidal ideation occurred in 1 subject in Study 302, the clinical study of vornorexant, but in view of the applicant's explanation, PMDA confirmed that currently available information regarding the risk of suicidal ideation and suicide attempt potentially associated with vornorexant does not raise any particular concerns.

7.R.2.5 Carryover effect

The applicant's explanation about a risk of carryover effect associated with vornorexant:
(a) Assessment using Karolinska sleepiness scale (KSS)[26)]
In Study 301, the Japanese Version of Karolinska Sleepiness Scale (KSS-J) was used as a measure to assess the carryover effect. Table 45 shows changes in KSS-J score from baseline to Week 2, and no carryover effect of vornorexant was observed.

[25)] Events coded to MedDRA SMQ "Suicide/self-injury"
[26)] Subjects rated their sleepiness on a 1-to-9 scale on the day after vornorexant treatment. Greater scores indicate greater carryover effects.

Table 45. Changes in KSS-J score from baseline to Week 2 (Study 301, safety analysis population)

	Baseline	Change from baseline
Placebo	5.2 ± 2.2 (196)	-0.4 ± 1.9 (191)
Vornorexant 5 mg	4.9 ± 2.1 (196)	-0.8 ± 1.8 (195)
Vornorexant 10 mg	5.1 ± 2.2 (197)	-0.4 ± 1.9 (196)

Mean ± SD (number of subjects evaluated)

(b) Assessment using Digit Symbol Substitution Test

In Study 301, the effect on cognitive function was evaluated using the number of correct responses and the correct response rate in Digit Symbol Substitution Test (DSST).[27] Table 46 shows changes in DSST scores from baseline to Week 2 of study treatment, and neither the number of correct responses nor the correct response rate was affected by vornorexant.

Table 46. Changes in DSST scores from baseline to Week 2 of study treatment (Study 301, safety analysis population)

Group	Baseline	Change from baseline
Number of correct responses		
Placebo	57.4 ± 10.8 (196)	3.4 ± 5.8 (191)
Vornorexant 5 mg	56.1 ± 10.5 (196)	2.9 ± 6.3 (195)
Vornorexant 10 mg	57.7 ± 9.5 (196)	3.0 ± 5.1 (195)
Correct response rate (%)		
Placebo	99.5 ± 1.8 (196)	0.0 ± 2.1 (191)
Vornorexant 5 mg	99.6 ± 1.3 (196)	0.0 ± 1.7 (195)
Vornorexant 10 mg	99.4 ± 1.7 (196)	0.2 ± 1.8 (195)

Mean ± SD (number of subjects evaluated)

(c) Effects on driving performance

In the driving performance evaluation study (Study TS142-207) (Study 207), placebo, vornorexant 10, 20 mg, or positive control zopiclone 7.5 mg was orally administered once daily at bedtime for 8 days to healthy adults including elderly , and the effect on driving performance was investigated. The primary measure of driving performance was standard deviation of the vehicle's distance from the lane line (center line), measured while a subject drove in a driving simulator at 100 km per hour for 60 minutes the next morning (at 9 hours post-dose) after study treatment, trying to keep the distance from the center line constant wherever possible (standard deviation of lateral position [SDLP]).[28]

Differences from placebo in SDLP in a 60-minute test performed the next morning (at 9 hours post-dose) after single-dose and 8-day multiple-dose administrations were determined. The lower limit of 90% CI of the difference after single-dose administration of vornorexant 20 mg exceeded zero (0), but the upper limit of 90% CI of the differences after single-dose and multiple-dose administrations of vornorexant 10 mg and 20 mg was all below the pre-determined clinically meaningful threshold (9.229 cm). No clinically meaningful effect of vornorexant on driving performance was observed.

---

[27] After confirmation of digit-symbol pairs (1-9), subjects are asked to write the corresponding digit to each of the symbols presented (in 90 seconds). Number of correct responses and correct response rate (number of correct responses/total number of responses attempted ×100) are calculated.

[28] SD of distance between the center line on the road and the right edge of the vehicle's body. In a clinical study of vornorexant conducted to establish an assessment system before implementation of the Study 207, a clinically meaningful effect of vornorexant on driving performance was ruled out when the upper limit of two-sided 90% CI of difference from placebo in SDLP in a 60-minute test was <9.229 cm based on the SDLP value representing the impaired driving performance with a blood alcohol level of 0.05%. The SDLP value associated with a blood alcohol level of 0.05% used as the threshold for a difference between the study drug and placebo was supported by literature (*Neuropsychopharmacol Rep.* 2024;44:308-13).

As shown above, the effect on driving performance was not observed; however, driving performance during a period from administration to 9 hours post-dose was not assessed. Based on the study conditions, the applicant will include a precaution in the package insert of vornorexant, instructing that patients taking vornorexant should not engage in operating hazardous machinery such as driving a motor vehicle until 9 hours post-dose.

PMDA's view:
In Study 301, a carryover effect of vornorexant was evaluated based on assessment results of subjective daytime sleepiness and cognitive function, and no worsening trend was observed in the vornorexant group compared with the placebo group.

In Study 207, no clinically meaningful effect on driving performance the next morning (at 9 hours post-dose) was observed after single-dose and multiple-dose administrations of vornorexant. In view of assessment results of subjective daytime sleepiness and cognitive function, PMDA considers it unnecessary, as a blanket measure, to caution against engaging in operating hazardous machinery such as driving a motor vehicle, on the assumption that appropriate sleep hygiene instructions for insomnia are provided, and vornorexant is taken before bedtime to ensure adequate sleep time. However, in Studies 301 and 302 in patients with insomnia, somnolence was reported, and therefore, cautionary instruction should be provided that patients exercise sufficient caution when engaging in operating hazardous machinery such as driving a motor vehicle the next morning after taking vornorexant and thereafter, irrespective of time after dosing.

7.R.2.6 Effects on respiratory function

The applicant's explanation about effects of vornorexant on respiratory function:
Respiratory-related adverse events[29)] occurred in 0.5% (1 of 196) of subjects in the placebo group (oropharyngeal pain), 0% (0 of 196) of subjects in the vornorexant 5 mg group, and 0.5% (1 of 197) of subjects in the vornorexant 10 mg group (cough) in Study 301, and 2.2% (4 of 184) of subjects in the vornorexant 5 mg group (cough in 2 subjects, and rhinitis allergic and oropharyngeal pain in 1 subject each) and 3.3% (6 of 183) of subjects in the vornorexant 10 mg group (cough and oropharyngeal pain in 2 subjects each, and asthma and obstructive sleep apnoea syndrome in 1 subject each) in Study 302. All reported events were mild and non-serious, and a causal relationship to the study drug was ruled out. Studies 301 and 302 included 173 and 116 patients with mild obstructive sleep apnea (OSA), respectively.

In a Japanese phase I study in patients with mild OSA (Study TS142-208) (Study 208), a single dose of vornorexant 10 mg was administered to evaluate the effect on nocturnal respiratory function. Vornorexant was not confirmed to reduce nocturnal respiratory function.

Based on the results from the above clinical study, no clinically relevant effects of vornorexant on respiratory function have been observed. The applicant, however, considers that a precaution should be included stating that vornorexant has not been used in patients with moderate or severe respiratory impairment.

[29)] Events coded to MedDRA SOC "Respiratory, thoracic and mediastinal disorders"

PMDA's view:
Based on the information available to date, no clinically relevant effects of vornorexant on respiratory function have been observed. However, a precaution should be included stating that vornorexant has not been used in patients with respiratory impairment except those with mild OSA.

7.R.2.7 Rebound insomnia and withdrawal syndrome

The applicant's explanation about the risk of rebound insomnia and withdrawal syndrome associated with discontinuation of vornorexant:

(a) Rebound insomnia

Table 47 shows changes in mean values of sSL, sSE, sTST, and sWASO from baseline during the first 3 days of the follow-up placebo treatment period in Study 301. No worsening trend was observed for any item in the placebo group or any vornorexant group.

During the follow-up placebo treatment period in Studies 301 and 302, no adverse events related to rebound insomnia occurred.

As described above, rebound insomnia associated with discontinuation of vornorexant did not occur and is considered unlikely to become a clinically relevant problem.

Table 47. Changes in each endpoint from baseline during the follow-up placebo treatment period (Study 301, safety analysis population)

Item	Group	Baseline	Change from baseline
Subjective sleep latency (sSL)	Placebo	58.9 ± 28.8 (196)	-10.2 ± 25.1 (193)
	Vornorexant 5 mg	57.0 ± 26.4 (196)	-9.0 ± 27.1 (195)
	Vornorexant 10 mg	58.6 ± 28.0 (197)	-7.9 ± 27.4 (196)
Subjective sleep efficiency (sSE)	Placebo	73.0 ± 11.1 (196)	4.7 ± 9.2 (193)
	Vornorexant 5 mg	74.2 ± 9.2 (196)	4.4 ± 10.0 (195)
	Vornorexant 10 mg	73.3 ± 9.8 (197)	3.2 ± 9.4 (196)
Subjective total sleep time (sTST)	Placebo	325.1 ± 49.5 (196)	23.7 ± 44.4 (193)
	Vornorexant 5 mg	332.9 ± 41.0 (196)	21.8 ± 53.1 (195)
	Vornorexant 10 mg	328.4 ± 42.6 (197)	13.3 ± 46.8 (196)
Subjective wake after sleep onset (sWASO)	Placebo	62.9 ± 40.0 (196)	-10.6 ± 28.2 (193)
	Vornorexant 5 mg	60.0 ± 34.5 (196)	-11.1 ± 30.6 (195)
	Vornorexant 10 mg	62.4 ± 36.4 (197)	-8.2 ± 30.2 (196)

Unit, minutes (sSL, sTST, and sWASO), % (sSE)
Mean ± SD (number of subjects evaluated)

(b) Withdrawal syndrome

During the follow-up placebo treatment period in Studies 301 and 302, no adverse events related to withdrawal syndrome occurred. Changes (mean ± SD) in total score [30)] of the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) from baseline to the end of the follow-up placebo treatment period in Study 301 were -0.4 ± 1.7 in the placebo group, -0.5 ± 2.5 in the vornorexant 5 mg group, and -0.4 ± 2.1 in the vornorexant 10 mg group, and no worsening of the total BWSQ score was observed in any group.

30) Subjects are asked to respond to 20 questions about withdrawal syndrome by rating their state in the past 2 weeks on a 3-point scale, consisting of "No symptom," "Moderate symptom," and "Severe symptom." Greater scores indicate severer withdrawal syndrome.

As described above, withdrawal syndrome associated with discontinuation of vornorexant did not occur and is considered unlikely to become a clinically relevant problem.

PMDA accepted the applicant's explanation.

7.R.2.8 Abuse and dependence

The applicant's explanation about the risk of abuse and dependence associated with vornorexant:
In a non-clinical dependence study, neither physical nor psychic dependence developed [see Section 5.6.1].

In Studies 203 and 302 in patients with insomnia, effects of vornorexant on dependence development were evaluated using a dependence questionnaire.[31)] In Study 203, 1 subject in the vornorexant 10 mg group had a rating of "Substantial" dependence based on the dependence questionnaire at the end of the double-blind period, but only 1 item was applicable. A rating of "Slight" dependence based on the dependence questionnaire was given to 4.4% (2 of 45) of subjects in the placebo group, 2.2% (1 of 44) of subjects in the vornorexant 2.5 mg group, and 2.2% (1 of 44) of subjects in the vornorexant 10 mg group at the end of the double-blind period and 4.5% (2 of 44) of subjects in the vornorexant 2.5 mg group, 2.2% (1 of 45) of subjects in the vornorexant 5 mg group, and 2.2% (1 of 44) of subjects in the vornorexant 10 mg group at the end of the follow-up placebo treatment period. In Study 302, a rating of "Slight" dependence based on the dependence questionnaire was given to 1.6% (3 of 183) of subjects in the vornorexant 10 mg group at the end of the open-label period and 0.5% (1 of 184) of subjects in the vornorexant 5 mg group and 0.5% (1 of 183) of subjects in the vornorexant 10 mg group at the end of the follow-up placebo treatment period, but at either time point, a rating of "Very" or "Substantial" dependence was not given to any subject.

In Studies 203 and 302, no adverse events related to abuse and dependence[32)] occurred.

As described above, vornorexant is considered unlikely to lead to the development of abuse and dependence.

PMDA's view:
Based on the results from non-clinical studies and Japanese clinical studies, the risk of abuse and dependence associated with vornorexant has not been clearly identified. However, information on the potential for abuse and dependence should be provided through materials such as a guide for proper use and a brochure for the following reasons: (1) Drugs with the same mechanism of action as that of vornorexant have been characterized by increased drug preference and abuse potential in drug abuse studies according to reports; and (2) in clinical practice, vornorexant is expected to be administered to patients with various characteristics, including those at risk of dependence on or abuse of hypnotics.

---

31) Subjects are asked to respond to 10 questions, and to the response for each question, a physician gives a rating on a 5-point scale, consisting of "Very," "Substantial," "Slight," "No," and "Unknown" dependences.
32) Events coded to MedDRA SMQ "Drug abuse and dependence"

7.R.3 Clinical positioning and indication

The applicant's explanation about clinical positioning and indication of vornorexant:

The "Clinical Practice Guideline for the Proper Use and Cessation of Hypnotics (in Japanese) (research group for clinical practice guideline for proper use and withdrawal/discontinuation of hypnotics and working group of the Japanese Society of Sleep Research, 2023) proposes a treatment algorithm for insomnia in patients deemed to require treatment, which is comprised of sleep hygiene instructions (including regular exercise, consumption of regular meals, and avoiding worries at bedtime) and drug therapy. In Japan, drug therapies currently available for insomnia include benzodiazepines, non-benzodiazepines, melatonin receptor agonists, and orexin receptor antagonists. Physicians are instructed to select drugs from them carefully based on the type of the insomnia symptoms and clinical characteristics of the patient. All drugs for the treatment of insomnia currently approved in Japan include a precaution in their package insert that patients should not engage in operating hazardous machinery such as driving a motor vehicle, while taking these drugs.

Results from Studies 301 and 302 and other data showed that vornorexant improved difficulty initiating sleep, difficulty maintaining sleep, and daytime functioning [see Section 7.R.1], and has acceptable safety [see Section 7.R.2]. Thus, considering that vornorexant could offer a new treatment option for patients with insomnia, "insomnia" was specified as the proposed indication. In addition, results from Study 207 showed that vornorexant did not have any clinically meaningful effect on driving performance the next morning after administration of vornorexant [see Section 7.R.2.5], further indicating that vornorexant could offer a new treatment option for patients with insomnia.

PMDA's view:

Since Studies 301 and 302 demonstrated efficacy of vornorexant [see Section 7.R.1], and it has acceptable safety [see Section 7.R.2], vornorexant offers another treatment option for insomnia, and the proposed indication of "insomnia" is acceptable. Vornorexant does not require a general precaution to preclude patients from engaging in operating hazardous machinery such as driving a motor vehicle, on the assumption that sleep hygiene instructions to address insomnia be appropriately provided, and vornorexant be taken before bedtime to ensure adequate sleep time. However, in clinical studies of vornorexant in patients with insomnia, somnolence was reported, and thus it is important to advise patients to exercise caution when engaging in operating hazardous machinery such as driving a motor vehicle the next morning and thereafter, irrespective of time elapsed since dosing [see Section 7.R.2.5]. Choice of vornorexant from drugs for treatment of insomnia is considered to be determined in clinical practice on an individual patient basis in view of status of engagement in operating hazardous machinery such as driving a motor vehicle and the presence or absence of hepatic impairment.

7.R.4 Dosage and administration

The applicant's explanation about the appropriateness of dosage regimen of vornorexant:

In Studies 301 and 302 in patients with insomnia, vornorexant 5 or 10 mg was orally administered once daily before bedtime based on the following results: Studies 201 and 203 in patients with insomnia provided favorable results on efficacy and safety of vornorexant; and in Study 207 in healthy adults where single-dose and multiple-dose of vornorexant 10 or 20 mg were administered to evaluate the effect on driving performance, no clinically meaningful effect on driving performance was observed.

In Study 301, results on the primary endpoint "change in sSL from baseline to Week 2" demonstrated superiority of vornorexant 5 and 10 mg over placebo (Table 37). In Study 302, both vornorexant 5 and 10 mg also tended to remain effective throughout the evaluation period (Figures 1 and 2).

For efficacy of vornorexant 5 and 10 mg, Table 48 shows proportions of responders[33)] at Week 2 for each of sSL, sSE, sTST, and sWASO in Study 301. The proportion of responders for each endpoint tended to be higher in the vornorexant 10 mg group than in the vornorexant 5 mg group.

Table 48. Proportions of responders at Week 2 for sSL, sSE, sTST, and sWASO (Study 301, FAS)

Item	Group	No. of subjects	Proportion of responders[a)]	Difference from placebo [95% CI][b)]
sSL	Placebo	196	20.9 (41)	
	Vornorexant 5 mg	196	32.1 (63)	11.2 [2.6, 19.9]
	Vornorexant 10 mg	197	38.1 (75)	17.2 [8.3, 26.0]
sSE	Placebo	196	17.9 (35)	
	Vornorexant 5 mg	196	31.1 (61)	13.3 [4.9, 21.7]
	Vornorexant 10 mg	197	30.5 (60)	12.6 [4.2, 21.0]
sTST	Placebo	196	36.7 (72)	
	Vornorexant 5 mg	196	46.9 (92)	10.2 [0.5, 19.9]
	Vornorexant 10 mg	197	53.3 (105)	16.6 [6.9, 26.3]
sWASO	Placebo	196	15.3 (30)	
	Vornorexant 5 mg	196	23.0 (45)	7.7 [-0.1, 15.4]
	Vornorexant 10 mg	197	25.4 (50)	10.1 [2.2, 18.0]

a) Unit, % (number of responders)
b) Unit, %, calculated by normal approximation to the binomial distribution

In clinical studies of vornorexant, the safety of vornorexant 5 and 10 mg was acceptable [see Section 7.R.2].

Based on the above, the applicant considered that the usual dose should be 5 mg, with the dose allowed to increase to 10 mg according to the patient's condition. In addition, based on the following instruction in the guideline, the proposed dosage and administration included the statement that the dose may be adjusted according to the symptom within a range not exceeding 10 mg once daily: The "Clinical Practice Guideline for the Proper Use and Cessation of Hypnotics, Revised Version 2013" ("research group for clinical practice guideline for proper use and withdrawal/discontinuation of hypnotics," the project of Comprehensive Research on Disability Health and Welfare, supported by the Health and Labour Sciences Research Grants and working group for preparation of guideline for proper use of hypnotics under the Japanese Society of Sleep Research) recommends that efforts to reduce the dose should be made according to the situation when symptoms improve, aiming at withdrawal, wherever possible.

PMDA's view:
In view of the dosage regimen in Study 301, as well as the efficacy and safety results obtained, there are no issues with setting the usual dose at 5 mg. However, in Study 302, the incidence of somnolence tended to be higher in the vornorexant 10 mg group than in the vornorexant 5 mg group [see Section

33) A clinically meaningful threshold (change from baseline to the post-dose time point) was defined as 20 minutes for sSL, 10% for sSE, 30 minutes for sTST, and 30 minutes for sWASO (*J Clin Sleep Med.* 2017;13:307-49), and subjects who achieved the threshold were counted as responders.

7.R.2], and shortened REM sleep latency was observed in the vornorexant 10 mg group [see Section 7.R.1.2]. In view of these findings, the dose should not be increased without caution. Thus, caution should be exercised when the dose is increased to 10 mg. Only if the patient has an inadequate response to vornorexant 5 mg, and the increased dose of 10 mg is considered to cause no safety problems, the dose may be increased to 10 mg once daily.

Cautionary instructions to the following effects should be included in the package inserts: (1) If the dose is increased, vornorexant should be used carefully by closely monitoring the patient's condition because of an increased risk of adverse drug reactions such as somnolence; and (2) efforts to reduce the dose should be made if symptoms improve. Furthermore, efficacy and safety of vornorexant coadministered with the other drugs for treatment of insomnia have not been investigated in clinical studies, and this information should also be included in the package inserts to advise caution.

7.R.5 Post-marketing investigations

In view of the clinical study results available to date and pharmacological action of vornorexant, the applicant plans a general use-results survey with the main objective to monitor incidences of parasomnia, narcolepsy symptoms, sleep paralysis, suicidal ideation and suicidal behavior, and drug abuse in routine clinical practice.

PMDA considers the applicant's action acceptable; however, the details of the risk management plan, including the post-marketing surveillance plan, will be finalized, taking account 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 inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. 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.

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

The new drug application data (CTD 5.3.5.1-3, CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that vornorexant has efficacy in the treatment of insomnia, and that vornorexant has acceptable safety in view of its benefits. Neither the drug product

nor its drug substance is classified as a poisonous drug or a powerful drug. Vornorexant is clinically meaningful because it offers a new treatment option for patients with insomnia.
PMDA has concluded that vornorexant may be approved if vornorexant is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

July 4, 2025

Product Submitted for Approval

Brand Name	Vorzzz Tablets 2.5 mg Vorzzz Tablets 5 mg Vorzzz Tablets 10 mg
Non-proprietary Name	Vornorexant Hydrate
Applicant	Taisho Pharmaceutical Co., Ltd.
Date of Application	September 12, 2024

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 conclusion on efficacy, clinical positioning, and indication presented in the Review Report (1).

1.1 Safety

The expert advisors supported PMDA's conclusion presented in Section "7.R.2 Safety" of the Review Report (1) and also made the following comment.

- The Committee has no objections to the PMDA's approach to precautionary measures regarding the operation of hazardous machinery such as driving a motor vehicle. Although Study 207, which evaluated the effects of vornorexant on driving performance, assessed performance only at 9 hours post-dose, there are no clear grounds to justify specifying to "9 hours post-dose" as the time period during which patients should be advised not to drive. Therefore, it is appropriate to advise patients to exercise caution when operating hazardous machinery such as driving a motor vehicle irrespective of the time elapsed since dosing. However, the package inserts of drugs in the same class include precautionary statements advising against engaging in operating hazardous machinery such as driving a motor vehicle. The precautionary statements on this issue was made based on (a) the assumption that sleep hygiene instructions to address insomnia be appropriately provided, and vornorexant be taken before bedtime to ensure adequate sleep time; and (b) the key principle that patients should not engage in operating hazardous machinery such as driving a motor vehicle if

feeling sleepiness, established in view of occurrence of somnolence in Studies 301 and 302 where patients with insomnia received vornorexant. The above information should be provided to physicians and patients adequately. Physicians must thoroughly ensure that patients take vornorexant after fully understanding details of precautionary statements.

Based on the above comment at the Expert Discussion, PMDA requested the applicant to include appropriate precautionary statements in the package insert of vornorexant and to provide appropriate information through materials. The applicant responded to both requests appropriately, and PMDA accepted these measures.

1.2 Dosage and administration

For the dosage regimen of vornorexant, the expert advisors supported the PMDA's conclusion presented in Section "7.R.4 Dosage and administration" of the Review Report (1) and also made the following comment.

- The increase in plasma vornorexant concentration in patients with moderate hepatic impairment is comparable to that observed with coadministration of a moderate CYP3A inhibitor. Although the safety of vornorexant 10 mg was confirmed in Studies 203, 301, and 302 in patients with insomnia, only 1 subject with moderate hepatic impairment received vornorexant 10 mg in these studies. In view of these findings, it is desirable to reconsider whether dose reduction to 2.5 mg once daily should be recommended for patients with moderate hepatic impairment, as is done for coadministration with moderate CYP3A inhibitors.

Based on the above comment at the Expert Discussion, PMDA requested the applicant to explain again the dosage for patients with moderate hepatic impairment in view of the extent of increased exposure in patients with hepatic impairment and the adverse events of concern associated with the increased exposure. The applicant responded as follows, and PMDA accepted the response.

- The applicant initially considered it appropriate to include the precautionary statement that the dosage in patients with moderate hepatic impairment should not exceed 5 mg, for the following reasons: (1) In Studies 203, 301, and 302, 1 patient with moderate hepatic impairment received vornorexant 10 mg, and no major safety concerns were identified; and (2) in a phase I study that investigated the effects of hepatic impairment on the pharmacokinetics of vornorexant (Study TS142-303), no significant safety issues were observed when vornorexant 5 mg was administered to patients with moderate hepatic impairment. However, considering that clinical studies in patients with insomnia provide limited safety information in patients with hepatic impairment, and that increased exposure to vornorexant may increase the risk of somnolence, the applicant will include the precautionary statement in the package insert that the dosage for patients with moderate hepatic impairment should be 2.5 mg once daily.

1.3 Risk management plan (draft)

At the Expert Discussion, expert advisors supported the PMDA's conclusion on post-marketing investigations presented in Section "7.R.5 Post-marketing investigations" of the Review Report (1) and expressed the view that information, including somnolence should be collected in the post-marketing surveillance.

In view of the discussion at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for vornorexant should include the safety specification presented in Table 49, and that the applicant should conduct the additional pharmacovigilance activities and additional risk minimization activities presented in Table 50 and that the general use-results survey presented in Table 51 should be conducted.

Table 49. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Somnolence	• Narcolepsy symptoms • Sleep paralysis • Parasomnia • Suicidal ideation and suicidal behavior • Abuse potential	None
Efficacy specification		
None		

Table 50. Summary of additional pharmacovigilance activities and additional 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	• Organize and disseminate information materials for healthcare professionals • Organize and disseminate information materials for patients • Disseminate data gathered during early post-marketing phase vigilance

Table 51. Outline of general use-results survey (draft)

Objective	To investigate the safety of vornorexant in clinical use
Survey method	Central registry system
Population	Patients with insomnia
Observation period	Up to 24 weeks
Planned sample size	450 patients
Main survey items	• Patient characteristics (birth date, sex, body weight, treatment category [inpatient or outpatient], duration of insomnia, etc.) • Prior drugs for treatment of insomnia • Use status of vornorexant (daily dose, duration of treatment, reasons for change or discontinuation, etc.) • Presence or absence of concomitant drugs, reason for the coadministration, etc. • Sleep status during treatment with vornorexant • Adverse events (name of adverse event, date of onset, seriousness, actions taken, outcome, causal relationship to vornorexant, etc.)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and the proposed dosage and administration as shown below, with the following condition. Since the product is a drug with a new active ingredient, 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 dosage is 5 mg of vornorexant orally administered once daily just before bedtime.

The dose may be adjusted according to the patient's symptoms. The dose should not exceed 10 mg once daily.

Approval Condition

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

Appendix

List of Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BCRP	Breast cancer resistance protein
BMI	Body mass index
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum plasma concentration
CPP	Critical process parameter
CQA	Critical quality attribute
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
DSST	Digit Symbol Substitution Test
DTA	Differential thermal analysis
FAS	Full analysis set
HDL	High density lipoprotein
HPLC	High performance liquid chromatography
IC_{50}	Concentration which results in 50% inhibition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ICH S1 guideline	"Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals" (PAB/ELD Notification No. 315 dated April 14, 1997)
K_a	Absorption rate constant
K_I	Inhibition concentration causing half-maximal inactivation
k_{inact}	Maximum inactivation rate constant
KSS	Karolinska sleepiness scale
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
LPS	Latency to persistent sleep
MATE	Multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities Japanese version
MMRM	Mixed-effects model for repeated measures
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
OSA	Obstructive sleep apnea
OX1R	Orexin receptor type 1
OX2R	Orexin receptor type 2
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PSG	Polysomnography
PTP	Press Through Packaging
QbD	Quality by Design
QTc	Corrected QT
QTcF	QT interval corrected using Fridericia formula
ROS	Reactive oxygen species

SBEβCD	Sulfobutyl ether β-cyclodextrin
SDS	Sheehan disability scale
sSE	Subjective sleep efficiency
sSL	Subjective sleep latency
sTST	Subjective total sleep time
Study 201	Japanese phase II study (Study TS142-201)
Study 203	Japanese phase II study (Study TS142-203)
Study 207	Driving performance evaluation study (Study TS142-207)
Study 208	Japanese phase I study (Study TS142-208)
Study 301	Japanese phase III study (Study TS142-301)
Study 302	Japanese phase III study (Study TS142-302)
sWASO	Subjective wake time after sleep onset
$t_{1/2}$	Half life
t_{max}	Time to reach maximum concentration
Vorzzz	Vorzzz Tablets
Vornorexant	Vornorexant Hydrate
WASO	Wake after sleep onset