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2.6.3 薬理試験概要表
2.6.3.1 薬理試験：一覧表

Test Article: lemborexant

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Primary Pharmacodynamics						
In Vitro Pharmacodynamics						
Binding affinity to human OX1R and OX2R	No	Recombinant human OX1R and OX2R	in vitro	Tsukuba Research Laboratories, Eisai Co., Ltd.	M10032	4.2.1.1.1
Binding kinetics on human OX1R	No	Recombinant human OX1R	in vitro	[redacted]	100026610	4.2.1.1.2
Binding kinetics on human OX2R	No	Recombinant human OX2R	in vitro	Tsukuba Research Laboratories, Eisai Co., Ltd.	M14007	4.2.1.1.3
Agonist and antagonist effects on human and murine OX1R and OX2R	No	Recombinant human and murine OX1R and OX2R	in vitro	Tsukuba Research Laboratories, Eisai Co., Ltd.	W-20110320	4.2.1.1.4
Agonist and antagonist effects on human, rat, and murine OX1R and OX2R	No	Recombinant human, murine, and rat OX1R and OX2R	in vitro	Tsukuba Research Laboratories, Eisai Co., Ltd.	M16023	4.2.1.1.5
Binding affinity of metabolites to human OX1R and OX2R	No	Recombinant human OX1R and OX2R	in vitro	Tsukuba Research Laboratories, Eisai Co., Ltd.	M13009	4.2.1.1.6
In Vivo Pharmacodynamics						
Effects on sleep time, sleep latency, and REM sleep ratio in mice	No	Mouse/C57BL/6	PO	Tsukuba Research Laboratories, Eisai Co., Ltd.	W-20100965	4.2.1.1.7

Test Article: lemborexant

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Effects on sleep time, sleep latency, and REM sleep ratio in orexin neuron-deficient mice	No	Mouse/C57BL/6 WT, orexin/ataxin-3 Tg/+	PO	Tsukuba Research Laboratories, Eisai Co., Ltd.	M12001	4.2.1.1.8
Effects on sleep time, wake time, and sleep latency in *Hcrt* KO mice	No	Mouse/C57BL/6 WT, *Hcrt* KO	PO	[redacted]	W-20140712	4.2.1.1.9
Effects on sleep time and REM sleep ratio in rats	No	Rat/SD	PO	Tsukuba Research Laboratories, Eisai Co., Ltd.	M10037	4.2.1.1.10
Chronic treatment sleep study in rats to assess tolerance and rebound	No	Rat/SD	PO	Tsukuba Research Laboratories, Eisai Co., Ltd.	M10038	4.2.1.1.11
In vivo functional OX2R assay in rats	No	Rat/Fischer	PO	Tsukuba Research Laboratories, Eisai Co., Ltd.	W-20110223	4.2.1.1.12
Secondary Pharmacodynamics						
Binding panel assay	No	Binding assays to receptors, transporters, and ion channels	in vitro	[redacted]	929062	4.2.1.2.1
Binding panel assay of metabolites	No	Binding assays to receptors, transporters, and ion channels	in vitro	[redacted]	100023762	4.2.1.2.2
Agonist and antagonist effects on human MT1 receptor	No	Recombinant human MT1 receptor	in vitro	Tsukuba Research Laboratories, Eisai Co., Ltd.	M11009	4.2.1.2.3

Test Article: lemborexant

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Effect on human $GABA_A$ Receptor	No	Recombinant human $GABA_A$ receptor with human subunits α1, β3, and γ2	in vitro	Tsukuba Research Laboratories, Eisai Co., Ltd.	W-20110355	4.2.1.2.4
Effect on emotion-induced cataplexy in mice	No	Mouse/C57BL/6 WT, *Hcrt* KO	PO	[redacted]	W-20140712	4.2.1.1.9
Influence on motor coordination and balance in mice	No	Mouse/C57BL/6	PO	Tsukuba Research Laboratories, Eisai Co., Ltd.	W-20110154	4.2.1.2.5
Influence on duration of ethanol-induced anesthesia in mice	No	Mouse/C57BL/6	PO	Tsukuba Research Laboratories, Eisai Co., Ltd.	W-20110180	4.2.1.2.6
Safety Pharmacology						
In vitro effect on hERG potassium current	Yes	CHO cells transfected with hERG	in vitro	[redacted]	SBL038-047	4.2.1.3.1
In vitro effect of metabolites on hERG potassium current	No	CHO cells transfected with hERG	in vitro	Eisai Co., Ltd.	W-20140611	4.2.1.3.2
In vitro effect on slow component of delayed rectifier potassium current	No	CHO cells transfected with KCNQ1/KCNE1	in vitro	Eisai Co., Ltd.	T11038	4.2.1.3.3
In vitro effects on field potential duration in human embryonic stem cell-derived cardiomyocytes	No	Human embryonic stem cell-derived cardiomyocytes	in vitro	Eisai Co., Ltd.	T11031	4.2.1.3.4
Effects on heart rate, aortic pressure, and ECG in anesthetized dogs – an exploratory study	No	Dog/beagle	IV	Eisai Co., Ltd.	W-20110322	4.2.1.3.5

Test Article: lemborexant

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Effects on heart rate, blood pressure, and ECG in conscious dogs – an exploratory study	No	Dog/beagle	PO	Eisai Co., Ltd.	W-20110279	4.2.1.3.6
Effects on heart rate, blood pressure, and the ECG by oral administration in conscious monkeys	Yes	Monkey/cynomolgus	PO	Eisai Co., Ltd.	S10117	4.2.1.3.7
Effects on heart rate, blood pressure, and the ECG by oral administration before habitual sleeping time in conscious monkeys	No	Monkey/cynomolgus	PO	Eisai Co., Ltd.	T11037	4.2.1.3.8
Effects on CNS and respiratory systems in extended single dose toxicology study	Yes	Rat/SD	PO	Eisai Co., Ltd.	S10120	4.2.3.1.2
Pharmacodynamic Drug Interactions						
No studies were conducted						

CHO = Chinese hamster ovary, CNS = central nervous system, CTD = Common Technical Document, ECG = electrocardiogram, GABA = γ-aminobutyric acid, GLP = Good Laboratory Practice, hERG = human ether-à-go-go related gene, KO = knockout, MT1 = melatonin 1, REM = rapid eye movement, SD = Sprague Dawley, Tg = transgenic, WT = wild-type.

a: An entry of "Yes" indicates that the study includes a GLP compliance statement.

2.6.3.2 効力を裏付ける試験

効力を裏付ける試験結果は 2.6.2.2 項に記載した。

2.6.3.3 副次的薬理試験

副次的薬理試験結果は 2.6.2.3 項に記載した。

2.6.3.4 安全性薬理試験

Test Article: lemborexant

Organ Systems Evaluated	Species / Strain	Method of Administration	Dose (mg/kg)	Gender and n per Group	Noteworthy Findings	GLP[a]	Study Number	CTD Location
Cardiovascular (hERG)	CHO cells stably transfected with hERG cDNA	in vitro	Lemborexant: 0, 1, 3, 10 µmol/L	5 cells/group	Concentration-dependent inhibition of hERG tail current; IC_{50} = 6.1 µmol/L.	Yes	SBL038-047	4.2.1.3.1
Cardiovascular (hERG)	CHO cells stably transfected with hERG cDNA	in vitro	M4, M9, M10: 0, 1, 3, 10, 30 µmol/L	5 − 6 cells/ group	Concentration-dependent inhibition of hERG tail current; M4, M9, M10; IC_{50} = 5.2, 11.2, 9.0 µmol/L, respectively	No	W-20140611	4.2.1.3.2
Cardiovascular (IKs)	CHO cells stably transfected with KCNQ1/KCNE1	in vitro	Lemborexant: 0, 1, 3, 10, 30 µmol/L	6 data/ concentration	Partial inhibition without concentration dependence; 24.3% reduction of IKs at 10 µmol/L	No	T11038	4.2.1.3.3
Cardiovascular (FPD)	Human embryonic stem cell-derived cardiomyocytes	in vitro	Lemborexant: 0, 1, 3, 10, 30 µmol/L	3 clusters/ group	Concentration-dependent prolongation of FPD; about 10% FPD prolongation at 10 µmol/L.	No	T11031	4.2.1.3.4
Cardiovascular (heart rate, aortic pressure, ECG)	Anesthetized dog/beagle	IV infusion (0.3% DMSO in 0.012 mol/L HCL, 0.9% DMSO in 0.036 mol/L HCL, 3% DMSO in 0.12 mol/L HCL)	Lemborexant: 0.36, 1.08, 3.6 mg/kg	3 males	1.08 and 3.6 mg/kg: Shortening of PQ interval (4.7% to 15.0% versus predose) 3.6 mg/kg: Increase in heart rate (13.8% versus predose) Decreased mean aortic pressure (7.8% versus predose).	No	W-20110322	4.2.1.3.5
Cardiovascular (heart rate, blood pressure, ECG)	Conscious dog/beagle	PO (gavage) (0.2 mol/L HCl)	Lemborexant: 0, 10, 30 mg/kg	2 males, 1 female	None except vomiting, muddy stool, mucous stool, and salivation at ≥ 10 mg/kg.	No	W-20110279	4.2.1.3.6

Test Article: lemborexant

Organ Systems Evaluated	Species / Strain	Method of Administration	Dose (mg/kg)	Gender and n per Group	Noteworthy Findings	GLP[a]	Study Number	CTD Location
Cardiovascular (heart rate, blood pressure, ECG)	Monkey/ cynomolgus	PO (gavage) (1 mol/L HCl/ 0.5% MC solution, 1:4 [v/v])	Lemborexant: 0, 10, 30, 100 mg/kg	4 males	30 and 100 mg/kg: significant prolongation of QTc (up to 6.3% and 4.2% versus predose) 10, 30 and 100 mg/kg: drowsiness and sleep	Yes	S10117	4.2.1.3.7
Cardiovascular (heart rate, blood pressure, ECG)	Monkey/ cynomolgus	PO (gavage) (1 mol/L HCl/ 0.5% MC solution, 1:4 [v/v])	Lemborexant: 0, 30, 100 mg/kg	4 males	100 mg/kg: significant prolongation of QTc (up to 11.0% versus predose)	No	T11037	4.2.1.3.8
Respiratory System (respiratory rate, tidal volume, minute volume); CNS (FOB)	Rat/SD	PO (gavage) (1 mol/L HCl : 0.5 % MC [1:4]/suspension)	Lemborexant: 0, 100, 300, 1000 mg/kg	6 males	Respiratory system No changes CNS (FOB) No changes	Yes	S10120	4.2.3.1.2

CHO = Chinese hamster ovary, CNS = central nervous system, DMSO = dimethyl sulfoxide, ECG = electrocardiogram, FOB = functional observational battery, FPD = field potential duration, GLP = Good Laboratory Practice, hERG = human ether-à-go-go-related gene, IC_{50} = 50% inhibitory concentration, IKs = slow component of delayed rectifier potassium current, MC = methylcellulose, QTc = corrected QT, SD = Sprague Dawley.

a: An entry of "Yes" indicates that the study includes a GLP compliance statement.