第 2 部（モジュール 2）
CTD の概要

2.6.3 薬理試験概要表

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略語

略語	略さない用語	日本語訳
bpm	Beats per minute	心拍数/分
CHO	Chinese hamster ovary	チャイニーズハムスター卵巣
C_{max}	Maximum plasma concentration	最高血漿中濃度
CSF	Cerebrospinal fluid	脳脊髄液
F	Female	雌
GLP	Good Laboratory Practice	医薬品の安全性に関する非臨床試験の実施の基準
HEK293	Human embryonic kidney 293 (cell line)	ヒト胎児腎 293（株化細胞）
hERG	Human ether-à-go-go-related gene	ヒト ether-à-go-go 関連遺伝子
IC_{20}	Concentration that causes 20% inhibition	20%阻害濃度
IC_{50}	Concentration that causes 50% inhibition	50%阻害濃度
M	Male	雄
M	Metabolite	代謝物
N/A	Not applicable	適用外
NOAEL	No-observed-adverse-effect level	無毒性量
NOEL	No-observed-effect level	無影響量
OX1R	Orexin receptor type 1	オレキシン 1 受容体
OX2R	Orexin receptor type 2	オレキシン 2 受容体
QTc	Corrected QT interval	補正 QT 間隔
SHR	Spontaneously hypertensive rat	自然発症高血圧ラット
WIST	Wistar rat	Wistar ラット

1. 薬理試験：一覧表

Test article: ダリドレキサント

Type of study	Test system	Method of administration	Testing facility	Report no.	Location in CTD
Primary Pharmacodynamics					
Functional inhibition of orexin receptors and evaluation of receptor binding mode and kinetics	Recombinant CHO cells expressing OX1R and OX2R from various species	*In vitro*	Actelion	B-14.010	モジュール 4.2.1.1.1
Human orexin receptor occupancy half-life at 37°C	Recombinant CHO cells expressing human OX1R and OX2R	*In vitro*	Idorsia	B-20.019	モジュール 4.2.1.1.2
Effect on sleep-wake cycle (including brain, CSF and plasma concentrations)	Healthy male Wistar rats	Oral	Actelion	B-14.036	モジュール 4.2.1.1.4
Effect on motor function	Healthy male Wistar rats	Oral	Idorsia	B-20.029	モジュール 4.2.1.1.5
Effect on vigilance and sleep	Healthy male Beagle dog	Oral	Actelion	B-14.056	モジュール 4.2.1.1.6
Secondary Pharmacodynamics					
Selectivity for orexin receptors (off-target screen)	Panel of enzyme and radioligand binding assays	*In vitro*	[redacted]	B-14.063	モジュール 4.2.1.2.1
Selectivity for orexin receptors (off-target screen)	Cellular and nuclear receptor functional assays	*In vitro*	[redacted]	B-14.069	モジュール 4.2.1.2.2
Activity on β_3-adrenergic receptors	Cellular, radioligand binding, and tissue assays	*In vitro*	[redacted]	B-14.068	モジュール 4.2.1.2.3
Activity on dopamine uptake, opiate κ (OP2, KOP) receptor, and phosphodiesterase PDE4B1	Cellular receptor functional assays	*In vitro*	[redacted]	B-20.057	モジュール 4.2.1.2.4

CHO, Chinese hamster ovary; CSF, cerebrospinal fluid; OX1R, orexin receptor type 1; OX2R, orexin receptor type 2

1. 薬理試験：一覧表（2/2）

Test article: ダリドレキサント

Type of study	Test system	Method of administration	Testing facility	Report no.	Location in CTD
Safety Pharmacology					
Effect on body temperature	Rat / RccHan:WIST	Oral (gavage)	Actelion	B-14.036	モジュール 4.2.1.1.4
Irwin profile test (effect on central nervous system) [1)]	Rat / RccHan:WIST	Oral (gavage)	[redacted]	T-13.223	モジュール 4.2.1.3.1
Effect on hERG tail currents [1)]	Recombinant HEK293 cells expressing hERG	*In vitro*	[redacted]	T-14.012	モジュール 4.2.1.3.2
Telemetry (effect on cardiovascular and locomotor systems, body temperature)	Conscious rat / RccHan:WIST	Oral (gavage)	Actelion	B-14.057	モジュール 4.2.1.3.3
Telemetry (effect on cardiovascular and locomotor systems, body temperature)	Conscious rat / SHR	Oral (gavage)	Actelion	B-14.058	モジュール 4.2.1.3.4
Telemetry (effect on cardiovascular systems)	Anesthetized guinea pig / Dunkin Hartley	Intravenous infusion	Actelion	B-14.059	モジュール 4.2.1.3.5
Telemetry (effect on cardiovascular function, body temperature) [1)]	Conscious dog / Beagle	Oral (gavage)	[redacted]	T-13.252	モジュール 4.2.1.3.6
Whole-body plethysmography (effect on respiratory system) [1)]	Conscious, freely moving rat / RccHan:WIST	Oral (gavage)	[redacted]	T-13.222	モジュール 4.2.1.3.7
Pharmacodynamic drug interactions					
N/A					

1) Study was GLP compliant.
GLP, good laboratory practice; hERG, human ether-à-go-go-related gene; N/A, not applicable; SHR, spontaneously hypertensive rat

1. 薬理試験：一覧表（ACT-776537）

Test article: ACT-776537

Type of study	Test system	Method of administration	Testing facility	Report no.	Location in CTD
Primary Pharmacodynamics					
Characterization of functional inhibition of human orexin receptors by daridorexant metabolites	Recombinant CHO cells expressing human OX1R and OX2R	*In vitro*	Idorsia	B-17.052	モジュール 4.2.1.1.3
Secondary Pharmacodynamics					
Selectivity for orexin receptors (off-target screen)	Cellular and nuclear receptor functional assays	*In vitro*	[redacted]	B-17.064	モジュール 4.2.1.2.5
Activity on angiotensin receptor (AT_1) and neurokinin receptor (NK_3)	Cellular receptor functional assays	*In vitro*	[redacted]	B-20.056	モジュール 4.2.1.2.6
Activity on opiate κ (OP2, KOP) receptor	Cellular receptor functional assays	*In vitro*	[redacted]	B-20.057	モジュール 4.2.1.2.4
Safety Pharmacology					
N/A					
Pharmacodynamic drug interactions					
N/A					

CHO, Chinese hamster ovary; N/A, not applicable; OX1R, orexin receptor type 1; OX2R, orexin receptor type 2

1. 薬理試験：一覧表（ACT-776063）

Test article: ACT-776063

Type of study	Test system	Method of administration	Testing facility	Report no.	Location in CTD
Primary Pharmacodynamics					
Characterization of functional inhibition of human orexin receptors by daridorexant metabolites	Recombinant CHO cells expressing human OX1R and OX2R	*In vitro*	Idorsia	B-17.052	モジュール 4.2.1.1.3
Secondary Pharmacodynamics					
Selectivity for orexin receptors (off-target screen)	Cellular and nuclear receptor functional assays	*In vitro*	[redacted]	B-17.065	モジュール 4.2.1.2.7
Activity on dopamine uptake	Cellular receptor functional assays	*In vitro*	[redacted]	B-20.057	モジュール 4.2.1.2.4
Safety Pharmacology					
N/A					
Pharmacodynamic drug interactions					
N/A					

CHO, Chinese hamster ovary; N/A, not applicable; OX1R, orexin receptor type 1; OX2R, orexin receptor type 2

1. 薬理試験：一覧表（ACT-1016-3307）

Test article: ACT-1016-3307

Type of study	Test system	Method of administration	Testing facility	Report no.	Location in CTD
Primary Pharmacodynamics					
Characterization of functional inhibition of human orexin receptors by daridorexant metabolites	Recombinant CHO cells expressing human OX1R and OX2R	*In vitro*	Idorsia	B-17.052	モジュール 4.2.1.1.3
Secondary Pharmacodynamics					
Selectivity for orexin receptors (off-target screen)	Cellular and nuclear receptor functional assays	*In vitro*	[redacted]	B-17.066	モジュール 4.2.1.2.8
Safety Pharmacology					
N/A					
Pharmacodynamic drug interactions					
N/A					

CHO, Chinese hamster ovary; N/A, not applicable; OX1R, orexin receptor type 1; OX2R, orexin receptor type 2

2. 効力を裏付ける試験

モジュール 2.6.2 薬理試験の概要文参照

3. 副次的薬理試験

モジュール 2.6.2 薬理試験の概要文参照

4. 安全性薬理試験

Test Article: ダリドレキサント

Organ Systems Evaluated (Location in CTD)	Species/ Strain	Method of Admin. (Vehicle/Formulation)	Doses (mg/kg) [1)]	Sex and No. per Group	Noteworthy Findings	GLP Compli-ance	Report Number
Body temperature (モジュール 4.2.1.1.4)	Rat / RccHan: WIST	Oral (gavage); aqueous suspension containing 0.5% methylcellulose	0, 10, 30, 100, 300 (single dose)	8M/ group	↓ body temperature during the first 6 h post dose at 30 and 300 mg/kg vs vehicle (remained within the normal physiological range) Exposure assessment: C_{max} = 1468 ng/mL [2)]	no	B-14.036
Central nervous system (Irwin profile test) (モジュール 4.2.1.3.1)	Rat / RccHan: WIST	Oral (gavage); aqueous suspension containing 0.5% methylcellulose	0, 100, 300, 1000 (single dose)	6M/ group	Body temperature slightly decreased at all doses. Reduced activity, decreased exploratory activity, and decreased postural and arousal scores were observed at all dose levels. NOAEL: 300 mg/kg. Exposure assessment: C_{max} = 8030 ng/mL [3)]	yes	T-13.223
hERG (human- ether-à-go-go-related gene) potassium channels (モジュール 4.2.1.3.2)	Stably trans-fected HEK293 cells	*In vitro*	3.0, 10, 30, 60 µM	N/A	Concentration-dependent reduction in inward and outward K^+ current with an IC_{20} of 7.4 µM and an IC_{50} of 25 µM	yes	T-14.012
Cardiovascular and locomotor system, body temperature (telemetry in conscious animals) (モジュール 4.2.1.3.3)	Rat / RccHan: WIST	Oral (gavage); aqueous suspension containing 0.5% methylcellulose	0, 300 (single dose)	5M/ group	↓ in heart rate (max. −42 bpm), body temperature (max. −0.3°C), and locomotor activity (max. −55%). Exposure assessment: C_{max} = 4757 ng/mL	no	B-14.057

4. 安全性薬理試験（2/3）

Test Article: ダリドレキサント

Organ Systems Evaluated (Location in CTD)	**Species/ Strain**	**Method of Admin. (Vehicle/ Formulation)**	**Doses (mg/kg) [1)]**	**Sex and No. per Group**	**Noteworthy Findings**	**GLP Compli-ance**	**Report Number**
Cardiovascular and locomotor system, body temperature (telemetry in conscious animals) (モジュール 4.2.1.3.4)	Rat / SHR	Oral (gavage); aqueous suspension containing 0.5% methylcellulose	0, 300 (single dose)	6M/group	↓ in mean arterial pressure (max. −8 mmHg), heart rate (max. −40 bpm), body temperature (max. −0.5°C) and locomotor activity (max. −63%)	no	B-14.058
Cardiovascular system (telemetry in anesthetized animals) (モジュール 4.2.1.3.5)	Guinea pig / Dunkin Hartley	Intravenous infusion; 20% solutol	0, 3, 10, 30 mg/kg/ 20 min (3 consecutive infusions)	6M/dose group, 5M/control group	No noteworthy findings. NOEL: 30 mg/kg. Exposure assessment: C_{max} = 23265 ng/mL	no	B-14.059
Cardiovascular system and body temperature (telemetry in conscious animals) (モジュール 4.2.1.3.6)	Dog / Beagle	Oral (gavage); aqueous suspension containing 0.5% methylcellulose	0, 10, 30, 100 (single dose; × 4 in a crossover design)	3M/3F	↓ in heart rate (max. –23 bpm at 10 mg/kg) and related ↑ in RR, PR and QT durations at 4 h (all doses) and 7 h (≥ 30 mg/kg) post dose. No effect on QTc. NOAEL: 100 mg/kg Exposure assessment: C_{max} = 8900 ng/mL (M) and 9550 ng/mL(F)	yes	T-13.252

4. 安全性薬理試験（3/3）

Test Article: ダリドレキサント

Organ Systems Evaluated (Location in CTD)	Species/ Strain	Method of Admin. (Vehicle/ Formulation)	Doses (mg/kg) [1)]	Sex and No. per Group	Noteworthy Findings	GLP Compli-ance	Report Number
Respiratory system (whole-body plethysmography in conscious, freely moving animals) (モジュール 4.2.1.3.7)	Rat / RccHan: WIST	Oral (gavage); aqueous suspension containing 0.5% methylcellulose	0, 100, 300, 1000 (single dose)	8M/group	No noteworthy findings. NOEL: 1000 mg/kg	yes	T-13.222

1) Doses are calculated for the free base.
2) Mean (n = 4) exposure at 30 mg/kg at 1 h post dose.
3) Based on exposure in males in a 4-week toxicity study (see section Module 2.6.6.9.4)

Decrease: ↓ slight; increase: ↑ slight; bpm, beats per minute; C_{max}, maximum observed plasma concentration; F, female; GLP, Good Laboratory Practice; HEK293, human embryonic kidney 293 (cell line); hERG, human ether-à-go-go-related gene; IC_{20}, concentration that causes 20% inhibition; IC_{50}, concentration that causes 50% inhibition; M, male; max., maximum; N/A, not applicable; NOAEL, no observed-adverse-effect level; NOEL, no-observed-effect level; QTc, calculated QT interval; SHR, spontaneously hypertensive rat; WIST, Wistar rat

5. 薬力学的薬物相互作用試験

ダリドレキサントを用いた非臨床薬力学的薬物相互作用試験は実施しなかった