第 2 部（モジュール 2）
CTD の概要

2.6.7 毒性試験概要表

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略語

略語	略さない用語	日本語訳
abs.	Absolute	絶対の
ALP	Alkaline phosphatase	アルカリホスファターゼ
ALT	Alanine aminotransferase	アラニンアミノトランスフェラーゼ
AST	Aspartate aminotransferase	アスパラギン酸アミノトランスフェラーゼ
AUC	Area under the plasma concentration vs time curve	血漿中濃度－時間曲線下面積
AUC_{last}	Area under the plasma concentration vs time curve from 0 h to the last available measurement	0 時間から最終測定可能時間までの血漿中濃度－時間曲線下面積
b.i.d	Twice daily	1 日 2 回
BLQ	Below the limit of quantification	定量限界未満
bpm	Beats per minute	－
b.w.	Body weight	体重
C_{max}	Maximum plasma concentration	最高血漿中濃度
CTD	Common Technical Document	コモン・テクニカル・ドキュメント
CPA	Cyclophosphamid	シクロホスファミド
DDT	Drug discrimination training	薬物弁別訓練
DMSO	Dimethylsulfoxide	ジメチルスルホキシド
DRF	Dose-range finding	用量設定
ECG	Electrocardiogram	心電図
EMS	Ethylmethane sulfonate	エチルメタンスルホン酸
F	Female	雌
GD ××	Gestation day ××	妊娠××日
GGT	Gamma glutamyl transferase	γ-グルタミルトランスフェラーゼ
GLDH	Glutamate dehydrogenase	グルタミン酸脱水素酵素
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
HEK	Human embryonic kidney	ヒト胎児腎臓
hERG	Human ether-à-go-go-related gene	ヒト ether-a-go-go 関連遺伝子
HPLC	High-performance liquid chromatography	高速液体クロマトグラフィー
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	医薬品規制調和国際会議
i.p.	Intra peritoneal	腹腔内
i.v.	Intravenous	静脈内

略語	略さない用語	日本語訳
LC-MS	Liquid chromatography coupled to mass spectrometry	液体クロマトグラフィー質量分析
LD ××	Lactation day ××	授乳××日
M	Male	雄
MTD	Maximum tolerated dose	最大耐量
n.a.	not applicable	該当なし
NMR	Nuclear magnetic resonance	核磁気共鳴分析
NMT	Not more than ××	××以下
NMU	N-nitroso-N-methylurea	N-メチルニトロソウレア
NOAEL	No-observed-adverse-effect level	無毒性量
NOEL	No-observed-effect level	無作用量
p.c.	Post coitum	交尾後
PCE	Polychromatic erythrocyte	正染性赤血球
PND ××	Post natal day ××	出生後××日
PCV	Packed cell volume	ヘマトクリット
p.o.	Oral(ly)	経口
pos.	Positive	陽性
p.p.	Post partum	分娩後
RBC	Red blood cell count	赤血球
rel.	Relative	相対の
s.c.	Subcutaneous(ly)	皮下
T4	Thyroxine	サイロキシン
TK	Toxicokinetics	トキシコキネティクス
t_{max}	Time to reach maximum plasma concentration	最高血漿中濃度到達時間
TRPV1	Transient receptor potential cation channel subfamily V member 1	―
TSH	Thyroid-stimulating hormone	甲状腺刺激ホルモン

1. 毒性試験：一覧表

Test Article: ダリドレキサント

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg) [1)]	GLP Compliance	Testing Facility	Report No.	Location in CTD
Single-Dose Toxicity	Single-dose toxicity studies were not performed							
Repeat-Dose Toxicity								
2-week DRF study	Mouse CByB6F1	Oral (gavage)	2 weeks	0, 1000, 2000 (as 1000 mg/kg b.i.d)	no	Idorsia Pharmaceuticals Ltd	T-16.061	モジュール 4.2.3.2.1
4-week DRF study	Mouse CByB6F1	Oral (gavage)	4 weeks (DRF for carcinogenicity study)	0, 100, 300, 1500	yes	[redacted]	T-17.009	モジュール 4.2.3.2.2
Determination of the MTD	Rat RccHan: WIST	Oral (gavage)	3 days	1000	no	Actelion Pharmaceuticals Ltd	T-13.144	モジュール 4.2.3.2.3
2-week DRF study	Rat RccHan: WIST	Oral (gavage)	2 weeks	0, 100, 300, 600 (F only), 1000	no	Actelion Pharmaceuticals Ltd	T-13.163	モジュール 4.2.3.2.4
4-week toxicity study with 4-week recovery	Rat RccHan: WIST	Oral (gavage)	4 weeks	0, 100, 300, 1000	yes	[redacted]	T-13.221	モジュール 4.2.3.2.5
13-week toxicity study with 4-week recovery	Rat RccHan: WIST	Oral (gavage)	13 weeks	0, 50, 150, 450	yes	[redacted]	T-14.068	モジュール 4.2.3.2.6
26-week toxicity study with 8-week recovery	Rat RccHan: WIST	Oral (gavage)	26 weeks	0, 50, 150, 450	yes	[redacted]	T-15.076	モジュール 4.2.3.2.7

Test Article: ダリドレキサント

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg) [1)]	GLP Compliance	Testing Facility	Report No.	Location in CTD
Determination of the MTD	Dog Beagle	Oral (gavage)	MTD: 3 days each dose 14 days	30, 100, 300, 1000 0, 600	no	[redacted]	T-13.172	モジュール 4.2.3.2.8
4-week toxicity study with 4-week recovery	Dog Beagle	Oral (gavage)	4 weeks	0, 30, 100, 300/200	yes	[redacted]	T-13.220	モジュール 4.2.3.2.9
13-week toxicity study with 4-week recovery	Dog Beagle	Oral (gavage)	13 weeks	0, 20 [2)], 50, 150	yes	[redacted]	T-14.067	モジュール 4.2.3.2.10
39-week toxicity study with 8-week recovery	Dog Beagle	Oral (gavage)	39 weeks	0, 10 [2)], 30, 100	yes	[redacted]	T-16.017	モジュール 4.2.3.2.11
Genotoxicity								
Ames test	*S. typhimurium*	*In vitro*	n.a.	≤ 5000 µg/plate	yes	[redacted]	T-14.007	モジュール 4.2.3.3.1.1
Chromosome aberration test	Human lymphocytes	*In vitro*	4 and 22 h (without S9) 4 h (with S9)	≤ 490 µg/mL	yes	[redacted]	T-14.008	モジュール 4.2.3.3.1.2
Micronucleus assay in bone marrow cells	Rat RccHan: WIST	Oral (gavage)	twice at 24 h intervals (48 h)	0, 125, 500, 2000 pos. control: cyclophos-phamide (dosed once orally)	yes	[redacted]	T-14.010	モジュール 4.2.3.3.2.1

Test Article: ダリドレキサント

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg) [1)]	GLP Compliance	Testing Facility	Report No.	Location in CTD
Carcinogenicity	Rat RccHan: WIST	Oral (gavage)	104 weeks	0, 15, 50, 150 0 (water control)	yes	[redacted]	T-16.060	モジュール 4.2.3.4.1.1
	Mouse CByB6F1-Tg(HRAS)2Jic (hemizygous)	Oral (gavage)	26 weeks	0, pos. control (NMU), 100, 200 (F only), 300 (M only), 1000	yes	[redacted]	T-18.041	モジュール 4.2.3.4.2.1
Reproductive and Developmental Toxicity								
Male fertility (Segment I)	Rat Wistar Crl: WI (Han)	Oral (gavage)	M: 7 weeks (incl. pre-mating, mating, gestation)	0, 50, 150, 450	yes	[redacted]	T-16.003	モジュール 4.2.3.5.1.1
Female fertility (Segment I)	Rat Wistar Crl: WI (Han)	Oral (gavage)	F: 14 days before mating, throughout mating and until GD7	0, 30, 100, 300	yes	[redacted]	T-16.004	モジュール 4.2.3.5.1.2
DRF study for Segment II	Rat Wistar Crl: WI (Han)	Oral (gavage)	F: Day 6 p.c. to Day 17 p.c.	0, 100, 300, 1000	no	[redacted]	T-14.016	モジュール 4.2.3.5.2.1
Embryo-fetal development (Segment II)	Rat Wistar Crl: WI (Han)	Oral (gavage)	F: Day 6 p.c. to Day 17 p.c.	0, 30, 100, 300 [3)]	yes	[redacted]	T-14.017	モジュール 4.2.3.5.2.2
Pre and postnatal development (Segment III)	Rat Wistar Crl: WI (Han)	Oral (gavage)	F_0 F: from GD6 to Day 20 of lactation	0, 50, 100, 300	yes	[redacted]	T-19.005	モジュール 4.2.3.5.3.1

Test Article: ダリドレキサント

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg) [1)]	GLP Compliance	Testing Facility	Report No.	Location in CTD
Determination of the MTD	Rabbit New Zealand White	Oral (gavage)	F: MTD; 3 days each dose 7 days	30, 100, 200, 300 200	no	[redacted]	T-14.013	モジュール 4.2.3.5.2.4
DRF study for Segment II	Rabbit New Zealand White	Oral (gavage)	F: Day 6 p.c. to Day 19 p.c.	0, 30, 60, 120	no	[redacted]	T-14.014	モジュール 4.2.3.5.2.5
Embryo-fetal development (Segment II)	Rabbit New Zealand White	Oral (gavage)	F: Day 6 p.c. to Day 19 p.c.	0, 30, 60, 120 [3)]	yes	[redacted]	T-14.015	モジュール 4.2.3.5.2.6
Juvenile Toxicity								
Juvenile DRF study	Rat RccHan: WIST	Oral (gavage)	2 weeks, starting on Day 21 p.p.	0, 50, 150, 450	no	[redacted]	T-18.097	モジュール 4.2.3.5.4.1
Juvenile toxicity study	Rat RccHan: WIST	Oral (gavage)	9 weeks (Day 21 p.p. to pairing on Day 84 p.p.)	0, 50, 150, 450	yes	[redacted]	T-19.049	モジュール 4.2.3.5.4.2
Local Tolerance	Local tolerance toxicity studies were not performed.							
Other Toxicity Studies								
In vitro cytotoxicity	Primary cultured human and murine hepatocytes	*In vitro*	24 h	≤ 300 µM	no	Actelion Pharmaceuticals Ltd	T-16.030	モジュール 4.2.3.7.7.4

Test Article: ダリドレキサント

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg) [1)]	GLP Compliance	Testing Facility	Report No.	Location in CTD
Photoxicity	Balb/c 3T3 fibroblasts	*In vitro*	n.a.	0.49, 0.98, 1.95, 3.91, 7.81, 15.63, 31.25, 62.50 µg/mL (with and without irradiation)	yes	[redacted]	T-14.009	モジュール 4.2.3.7.7.5
Mechanistic studies	Recombinant CHO cells expressing TRPV1	*In vitro*	n.a.	3.0–60 µM	no	[redacted]	T-14.052	モジュール 4.2.3.7.3.1
	Rat RccHan: WIST	Oral (gavage)	1 day	0, 100, 300, 1000	no	Actelion Pharmaceuticals Ltd.	T-14.060	モジュール 4.2.3.7.3.2
	Rat RccHan: WIST	Oral (gavage)	4 weeks	0, 1000	no	Actelion Pharmaceuticals Ltd.	T-14.064	モジュール 4.2.3.7.3.3
	Rat RccHan: WIST	Oral (gavage)	1 day	0, 1000	no	Actelion Pharmaceuticals Ltd.	B-14.060	モジュール 4.2.3.7.3.4
	Morphometry of hepatocytes from 39-week study in Beagle dogs (モジュール 4.2.3.2.11)	n.a.	n.a.	n.a.	no	Idorsia Pharmaceuticals Ltd	T-17.043	モジュール 4.2.3.7.3.5

Test Article: ダリドレキサント

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg) [1)]	GLP Compliance	Testing Facility	Report No.	Location in CTD
Exploratory tolerability studies	Mouse Crl:CD1 (ICR)	Oral (gavage)	2 weeks	0, 100, 300, 1000	no	[redacted]	T-15.074	モジュール 4.2.3.7.7.1
	Mouse Crl:CD1 (ICR)	Oral (gavage)	2 weeks	0, 1000, 2000 (as 1000 mg/kg b.i.d)	no	Actelion Pharmaceuticals Ltd	T-16.054	モジュール 4.2.3.7.7.2
	Mouse B6C3F1CrlBR	Oral (gavage)	2 weeks	0, 100, 300, 1000 (Day 1 only)/600 (from Day 2 on)	no	[redacted]	T-16.019	モジュール 4.2.3.7.7.3
Dependency - Drug Abuse Liability Testing Studies								
Drug discrimination training with suvorexant	Rat Crl:CD(SD) Sprague Dawley (F only)	Oral (gavage)	Food shaping: up to 2 sessions (days) DDT phase 1: 23 sessions (days) DDT phase 2: 29 sessions (days) DDT phase 3: 29 sessions (days)	n.a. Suvorexant: 0, 30 Suvorexant: 0, 100 Suvorexant: 0, 100	no	[redacted]	T-18.033	モジュール 4.2.3.7.4.1

Test Article: ダリドレキサント

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg) [1)]	GLP Compliance	Testing Facility	Report No.	Location in CTD
Drug discrimination training with zolpidem	Rat Crl:CD(SD) Sprague Dawley (F only)	Oral (gavage)	up to 48 sessions (days)	Zolpidem: 0, 3	no	[redacted]	T-18.035	モジュール 4.2.3.7.4.2
Assessment of stimulus generalization to zolpidem in a two-choice drug discrimination paradigm	Rat Crl:CD(SD) Sprague Dawley (F only)	Oral (gavage)	Daridorexant generalization phase (daridorexant dosing): 1 day per dose level in a cross-over design (4 treatment days in total)	Daridorexant: 0, 15, 30, 60 [2)] Zolpidem: 0, 3 (maintenance training); 0.3, 0.56, 1, 1.8 (generalization testing)	yes	[redacted]	T-18.065	モジュール 4.2.3.7.4.3
Assessment of reinforcing properties in a cocaine self-administration substitution procedure	Rat Crl:CD(SD) Sprague Dawley (F only)	i.v. (catheter implant)	Max. 2 h (with up to 25 infusions) in 6 substitution test sessions (1 per day) per animal	Daridorexant: 0, 0.1, 0.3, 1 [2)] Cocaine: 0.8	yes	[redacted]	T-17.046	モジュール 4.2.3.7.4.4
Pharmacokinetics study for study T-17.046	Rat Crl:CD(SD) Sprague Dawley (F only)	i.v. (catheter implant)	2.2 sec (occasion 1)-2 h (in 1, 5 or 25 infusions on Day 1, 15 and 22, respectively)	0.4, 1, 2	no	[redacted]	T-18.066	モジュール 4.2.3.7.4.5

Test Article: ダリドレキサント

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg) [1)]	GLP Compliance	Testing Facility	Report No.	Location in CTD
Assessment of spontaneous withdrawal	Rat Crl:CD(SD) Sprague Dawley (F, only)	Oral (gavage)	4 weeks	Daridorexant: 0, 20, 200 Chlor-diazepoxide (pos. control): 10-200	yes	[redacted]	T-17.048	モジュール 4.2.3.7.4.6
In vitro genotoxicity studies of impurities	*S. typhimurium* (Ames test of 不純物1*)	*In vitro*	-	≤ 5000 µg/plate	yes	[redacted]	T-13.155	モジュール 4.2.3.7.6.1
	S. typhimurium (Ames test of 不純物5*)	*In vitro*	-	≤ 5000 µg/plate	yes	[redacted]	T-13.156	モジュール 4.2.3.7.6.2
	S. typhimurium (Ames test of 不純物4*)	*In vitro*	-	≤ 5000 µg/plate	yes	[redacted]	T-13.157	モジュール 4.2.3.7.6.3
	S. typhimurium (Ames test of 不純物3*)	*In vitro*	-	≤ 5000 µg/plate	yes	[redacted]	T-13.158	モジュール 4.2.3.7.6.4
	S. typhimurium (Ames test of 不純物6*)	*In vitro*	-	≤ 5000 µg/plate	yes	[redacted]	T-13.159	モジュール 4.2.3.7.6.5
	S. typhimurium (Ames test of 不純物2*)	*In vitro*	-	≤ 5000 µg/plate	yes	[redacted]	T-13.160	モジュール 4.2.3.7.6.6

＊新薬承認情報提供時に置き換え

Test Article: ダリドレキサント

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg) [1)]	GLP Compliance	Testing Facility	Report No.	Location in CTD
In vitro genotoxicity studies of impurities (cont.)	*S. typhimurium* (Ames test of 不純物7*)	*In vitro*	-	≤ 5000 µg/plate	yes	[redacted]	T-15.065	モジュール 4.2.3.7.6.7
	S. typhimurium (Ames test of ACT-699581A)	*In vitro*	-	≤ 5000 µg/plate	yes	[redacted]	T-18.087	モジュール 4.2.3.7.6.8
	S. typhimurium (Ames test of 不純物8*)	*In vitro*	-	≤ 5000 µg/plate	yes	[redacted]	T-20.004	モジュール 4.2.3.7.6.9
Qualification of impurity ACT-699581A	Human lymphocytes (chromosome aberration test)	*In vitro*	4 and 22 h (without S9) 4 h (with S9)	≤ 530 µg/mL	yes	[redacted]	T-18.088	モジュール 4.2.3.7.6.10
	Rat Wistar Han: Crl:WI	Oral (gavage)	4 weeks	0, 0.01, 0.05, 0.15	yes	[redacted]	T-18.085	モジュール 4.2.3.7.6.11

1) Unless otherwise specified, the NOAEL for repeat-dose toxicity is underlined
2) NOEL
3) NOEL for litter

b.i.d = twice daily; CTD = common technical document; DDT = drug discrimination training; DRF = dose-range finding; F = female; GD = gestation day; GLP = Good Laboratory Practice; i.v. = intravenous; M = male; MTD = maximum tolerated dose; n.a. = not applicable; NMU = N-nitroso-N-methylurea; NOAEL = no-observed-adverse-effect level; NOEL = no-observed-effect level; p.c. = post coitum; pos. = positive; p.p. = post partum

＊新薬承認情報提供時に置き換え

2. トキシコキネティクス：トキシコキネティクス試験の一覧表

Test Article: ダリドレキサント

Type of Study	Test System	Method of Administration	Doses (mg/kg/day)	GLP Compliance	Testing Facility	Report No.	Location in CTD
2-week DRF study	Crl:CD1 (ICR) Mouse	Oral (gavage)	0, 100, 300, 1000	no	[redacted]	T-15.074	モジュール 4.2.3.7.7.1
2-week DRF study	Crl:CD1 (ICR) Mouse	Oral (gavage)	0, 1000, 2000 (1000 b.i.d.)	no	Actelion Pharmaceuticals Ltd	T-16.054	モジュール 4.2.3.7.7.2
2-week DRF study	B6C3F1crlBR Mouse	Oral (gavage)	0, 100, 300, 1000 (day1) /600	no	[redacted]	T-16.019	モジュール 4.2.3.7.7.3
2-week DRF study	CByB6F1 Mouse	Oral (gavage)	0, 1000, 2000 (1000 b.i.d.)	no	Idorsia Pharmaceuticals Ltd	T-16.061	モジュール 4.2.3.2.1
4-week DRF study for carcinogenicity study	CByB6F1 Mouse	Oral (gavage)	0, 100, 300, 1500 (Days 1–2: 500, Days 3–4: 1000, Days 5–28: 1500)	yes	[redacted]	T-17.009	モジュール 4.2.3.2.2
Determination of the MTD	RccHan:WIST Rat	Oral (gavage)	1000	no	Actelion Pharmaceuticals Ltd.	T-13.144	モジュール 4.2.3.2.3
2-week DRF study	RccHan:WIST Rat	Oral (gavage)	0, 100, 300, 600 (F only), 1000	no	Actelion Pharmaceuticals Ltd.	T-13.163	モジュール 4.2.3.2.4
4-week mechanistic study	RccHan:WIST Rat	Oral (gavage)	0, 1000	no	Actelion Pharmaceuticals Ltd.	T-14.064	モジュール 4.2.3.7.3.3

Test Article: ダリドレキサント

Type of Study	Test System	Method of Administration	Doses (mg/kg/day)	GLP Compliance	Testing Facility	Report No.	Location in CTD
4-week toxicity study with 4-week recovery	RccHan:WIST Rat	Oral (gavage)	0, 100, 300, 1000	yes	[redacted]	T-13.221	モジュール 4.2.3.2.5
13-week toxicity study with 4-week recovery	RccHan:WIST Rat	Oral (gavage)	0, 50, 150, 450	yes	[redacted]	T-14.068	モジュール 4.2.3.2.6
26-week toxicity study with 8-week recovery	RccHan:WIST Rat	Oral (gavage)	0, 50, 150, 450	yes	[redacted]	T-15.076	モジュール 4.2.3.2.7
Determination of the MTD	Beagle Dog	Oral (gavage)	30, 100, 300, 1000 (3 days each dose) 0, 600 (14 days)	no	[redacted]	T-13.172	モジュール 4.2.3.2.8
4-week toxicity study with 4-week recovery	Beagle Dog	Oral (gavage)	0, 30, 100, 300/200	yes	[redacted]	T-13.220	モジュール 4.2.3.2.9
13-week toxicity study with 4-week recovery	Beagle Dog	Oral (gavage)	0, 20, 50, 150	yes	[redacted]	T-14.067	モジュール 4.2.3.2.10
39-week toxicity study with 8-week recovery	Beagle Dog	Oral (gavage)	0, 10, 30, 100	yes	[redacted]	T-16.017	モジュール 4.2.3.2.11
Micronucleus assay	RccHan: WIST Rat	Oral (gavage)	0, 125, 500, 2000, pos. control cyclophosphamide	yes	[redacted]	T-14.010	モジュール 4.2.3.3.2.1
Carcinogenicity study	RccHan:WIST Rat	Oral (gavage)	0, 15, 50, 150, 0 (water control)	yes	[redacted]	T-16.060	モジュール 4.2.3.4.1.1

Test Article: ダリドレキサント

Type of Study	Test System	Method of Administration	Doses (mg/kg/day)	GLP Compliance	Testing Facility	Report No.	Location in CTD
Carcinogenicity study	CByB6F1-Tg (HRAS)2Jic Mouse	Oral (gavage)	0, pos. control (NMU), 100, 200 (F, only), 300 (M, only), 1000	yes	[redacted]	T-18.041	モジュール 4.2.3.4.2.1
DRF study for Segment II	New Zealand White Rabbit, pregnant F	Oral (gavage)	0, 30, 60, 120	no	[redacted]	T-14.014	モジュール 4.2.3.5.2.5
Embryo-fetal development (Segment II)	New Zealand White Rabbit, pregnant F	Oral (gavage)	0, 30, 60, 120	yes	[redacted]	T-14.015 T-18.073	モジュール 4.2.3.5.2.6 モジュール 4.2.3.5.2.7
DRF study for Segment II	Wistar Han: Crl: WI Rat	Oral (gavage)	0, 100, 300, 1000	no	[redacted]	T-14.016	モジュール 4.2.3.5.2.1
Embryo-fetal development (Segment II)	Wistar Han: Crl: WI Rat (pregnant F)	Oral (gavage)	0, 30, 100, 300	yes	[redacted]	T-14.017 T-17.042	モジュール 4.2.3.5.2.2 モジュール 4.2.3.5.2.3
Male fertility (Segment I)	Wistar Han: Crl: WI Rat	Oral (gavage)	0, 50, 150, 450	yes	[redacted]	T-16.003	モジュール 4.2.3.5.1.1
Female fertility (Segment I)	Wistar Han: Crl: WI Rat	Oral (gavage)	0, 30, 100, 300	yes	[redacted]	T-16.004	モジュール 4.2.3.5.1.2
Pre- and postnatal development (Segment III)	Wistar Han: Crl: WI Rat	Oral (gavage)	0, 50, 100, 300	yes	[redacted]	T-19.005	モジュール 4.2.3.5.3.1

Test Article: ダリドレキサント

Type of Study	Test System	Method of Administration	Doses (mg/kg/day)	GLP Compliance	Testing Facility	Report No.	Location in CTD
Juvenile DRF study	RccHan: WIST Rat	Oral (gavage)	0, 50, 150, 450	no	[redacted]	T-18.097	モジュール 4.2.3.5.4.1
Juvenile toxicity study	RccHan: WIST Rat	Oral (gavage)	0, 50, 150, 450	yes	[redacted]	T-19.049	モジュール 4.2.3.5.4.2
4-weeks toxicity study (qualification of impurity ACT-699581A)	Wistar Han: Crl: WI Rat	Oral (gavage)	0, 0.01, 0.05, 0.15	yes	[redacted]	T-18.085	モジュール 4.2.3.7.6.11
Assessment of stimulus generalization to zolpidem in a two-choice drug discrimination paradigm	Rat Crl:CD(SD) Sprague Dawley (F only)	Oral (gavage)	Daridorexant: 0, 15, 30, 60 Zolpidem: 0, 3 (maintenance training); 0.3, 0.56, 1, 1.8 (generalization testing)	yes	[redacted]	T-18.065	モジュール 4.2.3.7.4.3
Assessment of reinforcing properties in a cocaine self-administration substitution procedure	Rat Crl:CD(SD) Sprague Dawley (F only)	i.v. (catheter implant)	Daridorexant: 0, 0.1, 0.3, 1 Cocaine: 0.8	yes	[redacted]	T-17.046	モジュール 4.2.3.7.4.4
Pharmacokinetics study for study T-17.046	Rat Crl:CD(SD) Sprague Dawley (F only)	i.v. (catheter implant)	0.4, 1, 2	no	[redacted]	T-18.066	モジュール 4.2.3.7.4.5

Test Article: ダリドレキサント

Type of Study	Test System	Method of Administration	Doses (mg/kg/day)	GLP Compliance	Testing Facility	Report No.	Location in CTD
Assessment of spontaneous withdrawal	Rat Crl:CD(SD) Sprague Dawley (F only)	Oral (gavage)	0, 20, 200 Chlordiazepoxide (pos. control): 200	yes	[redacted]	T-17.048	モジュール 4.2.3.7.4.6

b.i.d = twice daily; CTD = common technical document; DRF = dose-range finding; F = female; GLP = Good Laboratory Practice; i.v. = intravenous; M = male; MTD = maximum tolerated dose; NMU = N-nitroso-N-methylurea; pos. = positive

3. トキシコキネティクス：トキシコキネティクス試験成績（AUC_{0-24}）の一覧

Test Article: ダリドレキサント

ダリドレキサント: steady state AUC_{0-24} (μg·h/mL) at the end of treatment

Daily Dose (mg/kg)	Mice		Rats		Dogs		Juvenile Rats		Pregnant rats	Pregnant rabbits	Humans
	male	female	male	female	male	female	male	female			
0.83											6.31
10					9.10 [3)]	17.5 [3)]					
15			0.743 [4)]	1.45 [4)]							
20					34.1 [1)]	19.7 [1)]					
30					70.6 [3)]	58.7 [3)]			5.46	20.9	
50			4.59 [1)]	7.41 [1)]	126 [1)]	65.4 [1)]	2.95 [5)]	4.64 [5)]			
			4.76 [2)]	7.69 [2)]							
			4.20 [4)]	7.82 [4)]							
60										24.5	
100	0.403 [4)]	0.245 [4)]			269 [3)]	238 [3)]			19.6		
120										62.0	
150			18.2 [1)]	26.5 [1)]	304 [1)]	245 [1)]	16.7 [5)]	15.3 [5)]			
			16.8 [2)]	26.5 [2)]							
			16.8 [4)]	35.0 [4)]							
200		0.668 [4)]									
300	2.17 [4)]								51.6		
450			34.5 [1)]	52.1 [1)]			49.0 [5)]	57.3 [5)]			
			41.2 [2)]	54.5 [2)]							

ダリドレキサント: steady state AUC_{0-24} (µg·h/mL) at the end of treatment

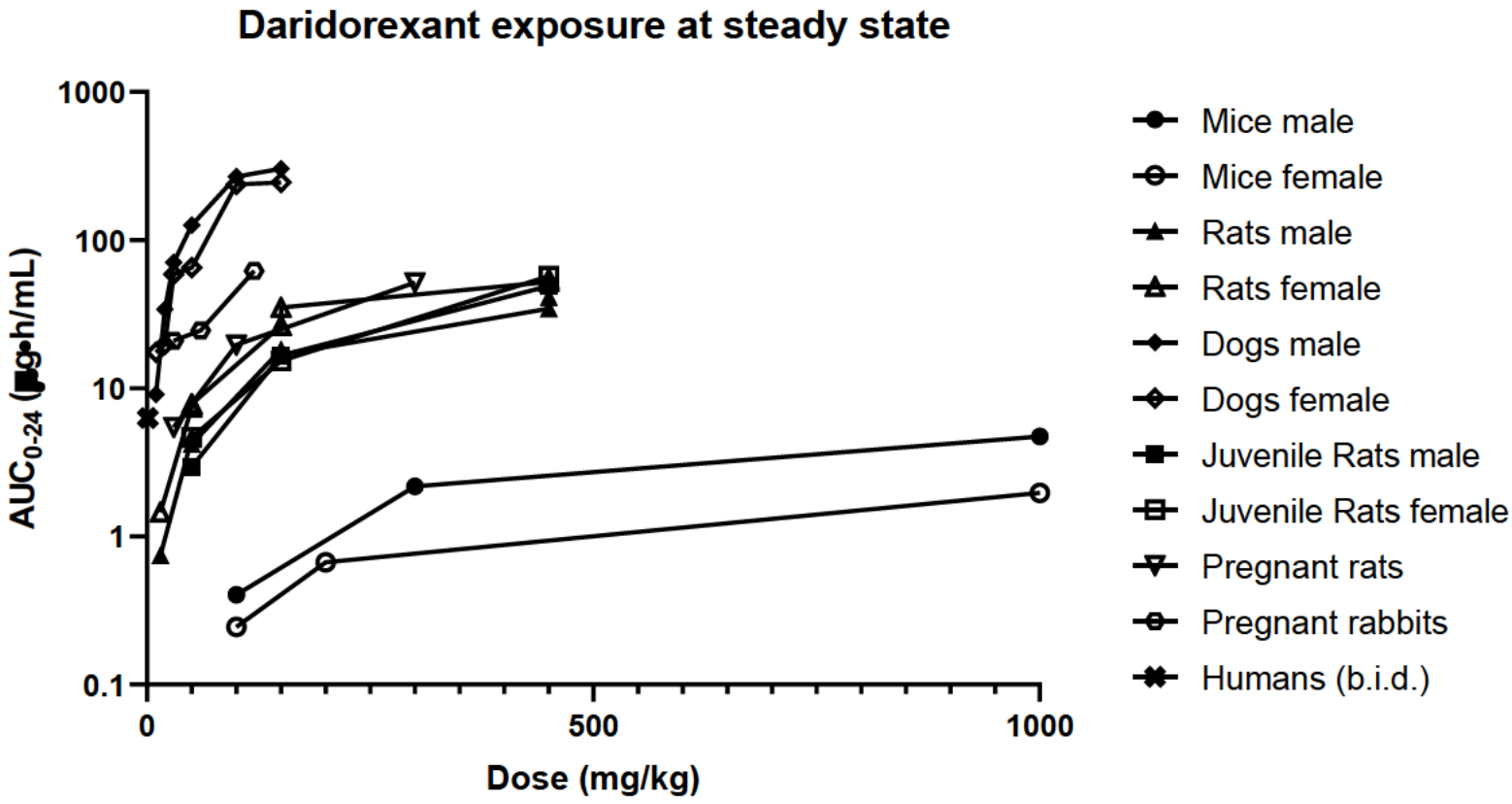
Daily Dose (mg/kg)	Mice		Rats		Dogs		Juvenile Rats		Pregnant rats	Pregnant rabbits	Humans
	male	female	male	female	male	female	male	female			
1000	4.73 [4)]	1.97 [4)]									

1) 13-week study [モジュール 4.2.3.2.6] (rat) or [モジュール 4.2.3.2.10] (dog)
2) 26-week study [モジュール 4.2.3.2.7]
3) 39-week study [モジュール 4.2.3.2.11]
4) carcinogenicity study [モジュール 4.2.3.4.2.1] (mouse) or [モジュール 4.2.3.4.1.1] (rat), Week 26
5) AUC_{last}

AUC_{0-24} = area under the plasma concentration vs time curve from 0 to 24 h after dosing; AUC_{last} = area under the plasma concentration vs time curve from 0 h to the last available measurement.

3. トキシコキネティクス：トキシコキネティクス試験成績（AUC_{0-24}）の一覧

Test Article: ダリドレキサント



3. トキシコキネティクス：トキシコキネティクス試験成績（AUC_{0-24}）の一覧

Test Article: ACT-776537

ACT-776537 (M1): steady state AUC_{0-24} (µg·h/mL) at the end of treatment

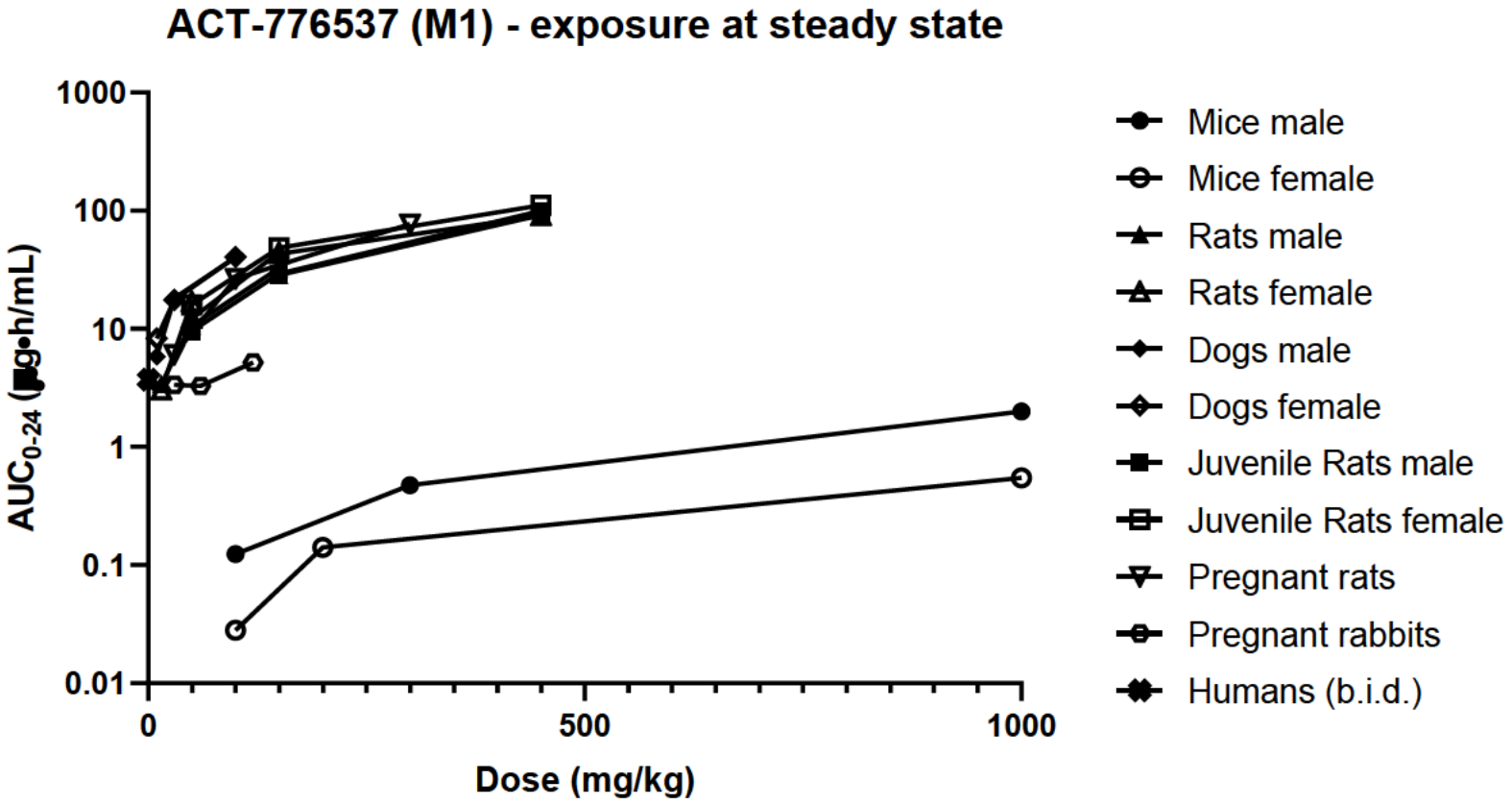
Daily Dose (mg/kg)	Mice male	Mice female	Rats male	Rats female	Dogs male	Dogs female	Juvenile Rats male	Juvenile Rats female	Pregnant rats	Pregnant rabbits	Humans
0.83											3.71
10					5.82 [2)]	8.3 [2)]					
15			3.40 [3)]	3.04 [3)]							
30					18.2 [2)]	17.6 [2)]			6.05	3.34	
50			11.2 [1)]	16.9 [1)]			9.59 [4)]	15.9 [4)]			
			10.6 [3)]	12.2 [3)]							
60										3.28	
100	0.124 [3)]	0.0281 [3)]			40.3 [2)]	40.6 [2)]			26.6		
120										5.17	
150			32.7 [1)]	44.2 [1)]			29.3 [4)]	48.5 [4)]			
			28.4 [3)]	43.2 [3)]							
200		0.141 [3)]									
300	0.474 [3)]								77.1		
450			92.0 [1)]	90.8 [1)]			99.5 [4)]	111 [4)]			
1000	2.0 [3)]	0.547 [3)]									

1) 26-week study [モジュール 4.2.3.2.7]
2) 39-week study [モジュール 4.2.3.2.11]
3) carcinogenicity study [モジュール 4.2.3.4.2.1] (mouse) or [モジュール 4.2.3.4.1.1] (rat), Week 26
4) AUC_{last}

AUC_{0-24} = area under the plasma concentration vs time curve from 0 to 24 h after dosing; AUC_{last} = area under the plasma concentration vs time curve from 0 h to the last available measurement

3. トキシコキネティクス：トキシコキネティクス試験成績（AUC_{0-24}）の一覧

Test Article: ACT-776537



3. トキシコキネティクス：トキシコキネティクス試験成績（AUC_{0-24}）の一覧

Test Article: ACT-776063

ACT-776063 (M3): steady state AUC_{0-24} (µg·h/mL) at the end of treatment

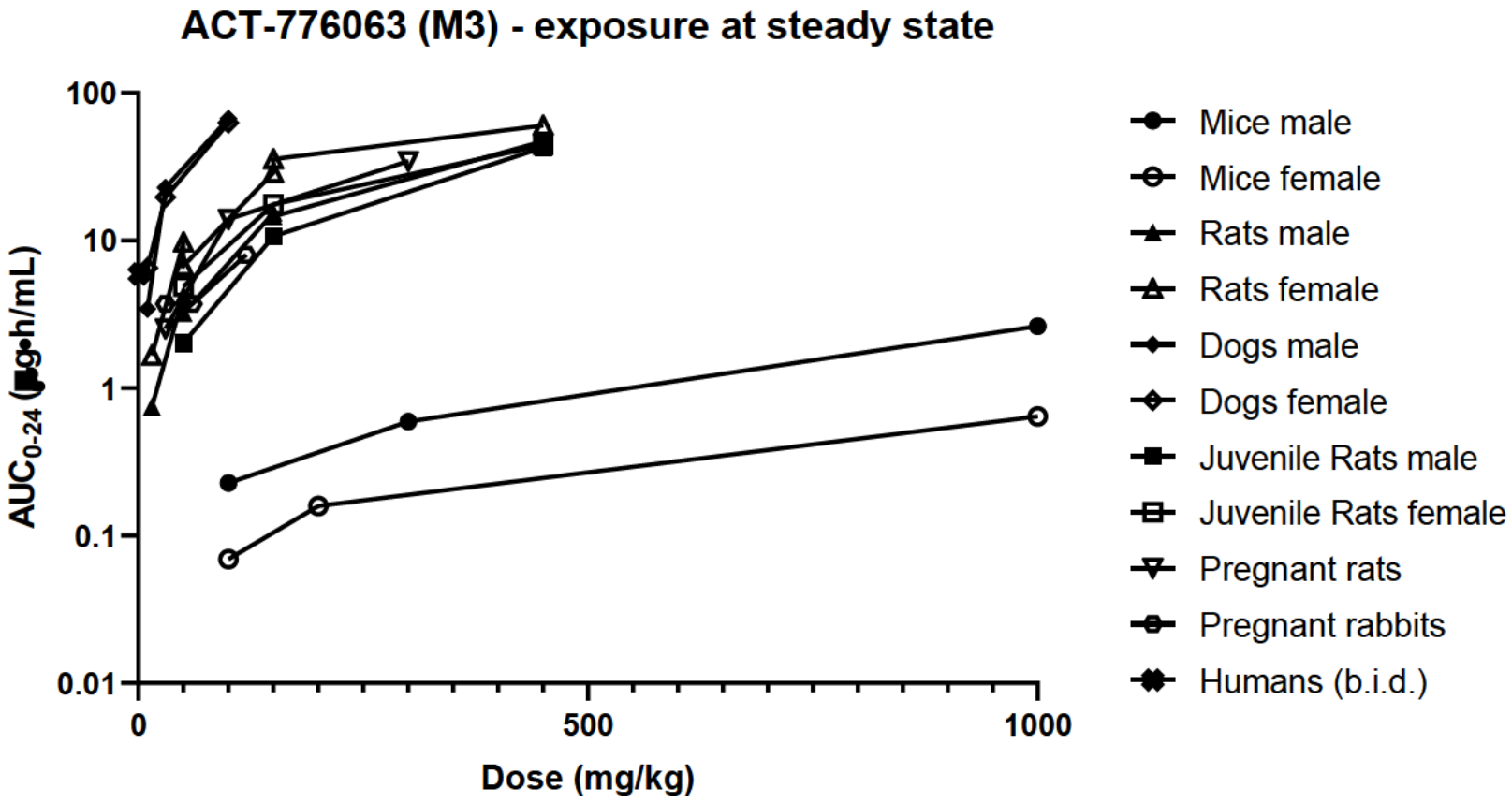
Daily Dose (mg/kg)	Mice male	Mice female	Rats male	Rats female	Dogs male	Dogs female	Juvenile Rats male	Juvenile Rats female	Pregnant rats	Pregnant rabbits	Humans
0.83											5.92
10					3.44 [2)]	6.54 [2)]					
15			0.743 [3)]	1.67 [3)]							
30					22.9 [2)]	19.7 [2)]			2.53	3.73	
50			4.26 [1)]	9.78 [1)]			2.02 [4)]	4.89 [4)]			
			3.22 [3)]	6.74 [3)]							
60										3.73	
100	0.227 [3)]	0.0694 [3)]			67.1 [2)]	62.9 [2)]			14.0		
120										8.00	
150			15.4 [1)]	28.9 [1)]			10.7 [4)]	17.6 [4)]			
			14.6 [3)]	35.6 [3)]							
200		0.159 [3)]									
300	0.592 [3)]								34.5		
450			47.0 [1)]	60.3 [1)]			42.9 [4)]	44.4 [4)]			
1000	2.63 [3)]	0.644 [3)]									

1) 26-week study [モジュール 4.2.3.2.7]
2) 39-week study [モジュール 4.2.3.2.11]
3) carcinogenicity study [モジュール 4.2.3.4.2.1] (mouse) or [モジュール 4.2.3.4.1.1] (rat), Week 26
4) AUC_{last}

AUC_{0-24} = area under the plasma concentration vs time curve from 0 to 24 h after dosing; AUC_{last} = area under the plasma concentration vs time curve from 0 h to the last available measurement

3. トキシコキネティクス：トキシコキネティクス試験成績（AUC_{0-24}）の一覧

Test Article: ACT-776063



3. トキシコキネティクス：トキシコキネティクス試験成績（AUC_{0-24}）の一覧

Test Article: ACT-1016-3307

ACT-1016-3307 (M10): steady state AUC_{0-24} (µg·h/mL) at the end of treatment

Daily Dose (mg/kg)	Mice male	Mice female	Rats male	Rats female	Dogs male	Dogs female	Juvenile Rats male	Juvenile Rats female	Pregnant rats	Pregnant rabbits	Humans
0.83											1.09
10					9.912 [2)]	25.9 [2)]					
15			0.328 [3)]	0.304 [3)]							
30					60.8 [2)]	63.9 [2)]			0.314	0.812	
50			1.39 [1)] 1.20 [3)]	1.42 [1)] 1.06 [3)]			1.03 [4)]	1.07 [4)]			
60										0.517	
100	0.0502 [3)]	0.00686 [3)]			205 [2)]	221 [2)]			1.54		
120										0.591	
150			4.01 [1)] 3.57 [3)]	4.98 [1)] 3.88 [3)]			4.30 [4)]	3.49 [4)]			
200		0.101 [3)]									
300	0.209 [3)]								7.88		
450			13.5 [1)]	10.3 [1)]			12.4 [4)]	10.9 [4)]			
1000	1.09 [3)]	0.268 [3)]									

1) 26-week study [モジュール 4.2.3.2.7]
2) 39-week study [モジュール 4.2.3.2.11]
3) carcinogenicity study [モジュール 4.2.3.4.2.1] (mouse) or [モジュール 4.2.3.4.1.1] (rat), Week 26
4) AUC_{last}

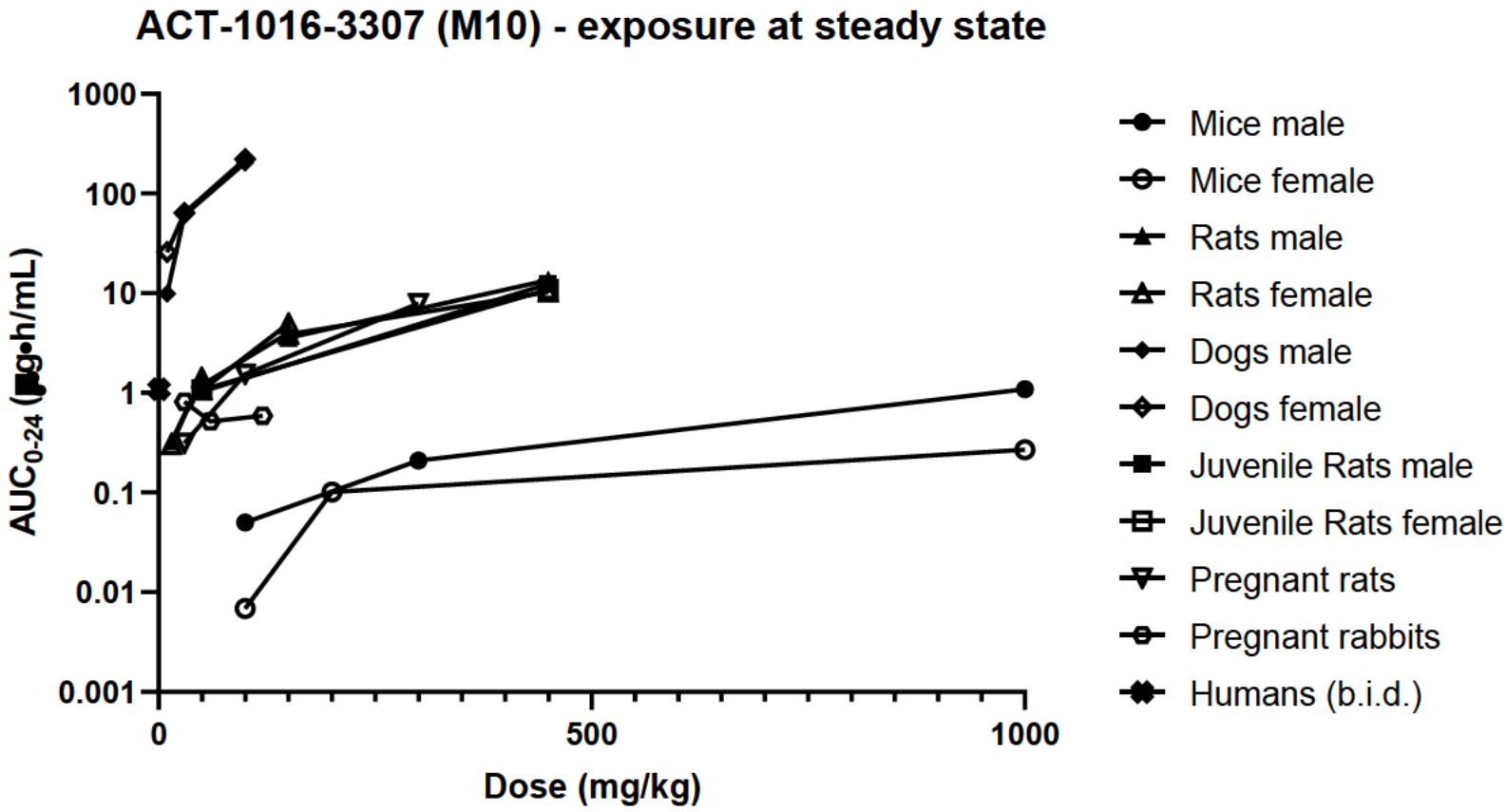
ACT-1016-3307 (M10): steady state AUC_{0-24} (μg·h/mL) at the end of treatment

Daily Dose (mg/kg)	Mice		Rats		Dogs		Juvenile Rats		Pregnant rats	Pregnant rabbits	Humans
	male	female	male	female	male	female	male	female			

AUC_{0-24} = area under the plasma concentration vs time curve from 0 to 24 h after dosing; AUC_{last} = area under the plasma concentration vs time curve from 0 h to the last available measurement

3. トキシコキネティクス：トキシコキネティクス試験成績（AUC_{0-24}）の一覧

Test Article: ACT-1016-3307



4. 毒性試験：被験物質（バッチ毎）一覧

Test Article: ダリドレキサント

Batch No.	**Purity (%)**	**Specified Impurities (%)** [1)]		**Report No./ Location in CTD**	**Type of Study**
Proposed specification	n.a.	不純物9*	NMT [redacted]%	n.a.	n.a
		不純物10*	NMT [redacted]%		
		不純物11*	NMT [redacted]%		
		ACT-699581 [2)]	NMT 1% area		
ELN023-1806.3 VV-ANAY-002878 V1.0 SEP 2013	98.2% Assay (NMR)	n.a.		T-13.144/ モジュール 4.2.3.2.3 T-13.163/ モジュール 4.2.3.2.4	3-day range finding study in Wistar rat (gavage) 2-week range finding study in Wistar rat (gavage)
ELN096-1661.1	99.65% (LC-MS)	n.a.		T-13.172/ モジュール 4.2.3.2.8	Determination of the maximum tolerated dose in Beagle dog (gavage)

＊新薬承認情報提供時に置き換え

Test Article: ダリドレキサント

Batch No.	Purity (%)	Specified Impurities (%) [1)]	Report No./ Location in CTD	Type of Study
RH01L117A0 VV-MANU-002836 V1.0 JAN 2014	98.9% (HPLC)	-不純物9(塩酸塩)*: [redacted]% -不純物10*: [redacted]%	T-13.220/ モジュール 4.2.3.2.9	4-week toxicity study with 4-week recovery in Beagle dog (gavage)
			T-13.221/ モジュール 4.2.3.2.5	4-week toxicity study with 4-week recovery in Wistar rat (gavage)
			T-13.252/ モジュール 4.2.1.3.6	Cardiovascular telemetry study in Beagle dog (gavage)
			T-13.222/ モジュール 4.2.1.3.7	Respiratory function evaluation (whole body plethysmography) in Wistar rat (gavage)
			T-13.223/ モジュール 4.2.1.3.1	Irwin profile test in Wistar rat (gavage)
			T-14.012/ モジュール 4.2.1.3.2	Effect on hERG tail currents recorded from stably transfected HEK293 cells
			T-14.007/ モジュール 4.2.3.3.1.1	Ames test
			T-14.008/ モジュール 4.2.3.3.1.2	Chromosome Aberration in human lymphocytes
			T-14.009/ モジュール 4.2.3.7.7.5	Phototoxicity in Balb/c 3T3 fibroblasts
			T-14.010/ モジュール 4.2.3.3.2.1	Micronucleus assay in bone marrow cells of Wistar rat (gavage)
			T-14.060/ モジュール 4.2.3.7.3.2	Telemetry study in female Wistar rat (gavage)
			B-14.060/ モジュール 4.2.3.7.3.4	Gastro-intestinal motility in female Wistar rat (gavage)
			T-14.064/ モジュール 4.2.3.7.3.3	Telemetry study in female Wistar rat (gavage) Dose Response (in-house)
			T-14.052/ モジュール 4.2.3.7.3.1	Effect on TRPV1 currents recorded from stably transfected Chinese Hamster Ovary Cells

＊新薬承認情報提供時に置き換え

Test Article: ダリドレキサント

Batch No.	Purity (%)	Specified Impurities (%) [1)]	Report No./ Location in CTD	Type of Study
RH01L117A1 VV-MANU-002840 V1.0 MAR 2014	98.9% (HPLC)	-不純物9(塩酸塩)*: [redacted]% -不純物10*: [redacted]%	T-14.068/ モジュール 4.2.3.2.6	13-week toxicity study with 4-week recovery in Wistar rat (gavage)
			T-14.067/ モジュール 4.2.3.2.10	13-week toxicity study with 4-week recovery in Beagle dog
			T-14.016/ モジュール 4.2.3.5.2.1	Dose-range-finding study for Segment II in pregnant female Wistar rat (gavage)
			T-14.017/ モジュール 4.2.3.5.2.2	Embryo-fetal development (Segment II) in Wistar rat (gavage)
			T-14.013/ モジュール 4.2.3.5.2.4	Determination of the maximum tolerated dose for Segment II in non-pregnant female New Zealand White rabbit (gavage)
			T-14.014/ モジュール 4.2.3.5.2.5	Dose-range-finding study for Segment II in pregnant female New Zealand White rabbit (gavage)
			T-14.015/ モジュール 4.2.3.5.2.6	Embryo-fetal development (Segment II) in New Zealand White rabbit (gavage)
			T-15.074/ モジュール 4.2.3.7.7.1	2-week range finding study in Crl:CD1 (ICR) mouse (gavage)
			T-16.019/ モジュール 4.2.3.7.7.3	2-week range finding study in B6C3F1/CrlBR mouse (gavage)
			T-16.061/ モジュール 4.2.3.2.1	2-week range finding study in CByB6F1 mouse (gavage)
			T-16.030/ モジュール 4.2.3.7.7.4	*In vitro* cytotoxicity, primary human and murine hepatocytes
			T-16.054/ モジュール 4.2.3.7.7.2	2-week range finding study in Crl:CD1 (ICR) mouse (gavage)

＊新薬承認情報提供時に置き換え

Test Article: ダリドレキサント

Batch No.	Purity (%)	Specified Impurities (%) [1)]		Report No./ Location in CTD	Type of Study
RH02L117A1 VV-MANU-002874 V1.0 Nov 2015	99.6% (HPLC)	-不純物9(塩酸塩)* -不純物10* -不純物11*	[redacted]% [redacted]% [redacted]%	T-15.076/ モジュール 4.2.3.2.7 T-16.017/ モジュール 4.2.3.2.11 T-16.003/ モジュール 4.2.3.5.1.1 T-16.004/ モジュール 4.2.3.5.1.2	26-week toxicity study with 8-week recovery in Wistar rat (gavage) 39-week toxicity study with 8-week recovery in Beagle dog (gavage) Male fertility (Segment I) in Wistar rat (gavage) Female fertility (Segment I) in Wistar rat (gavage)

＊新薬承認情報提供時に置き換え

Test Article: ダリドレキサント

Batch No.	Purity (%)	Specified Impurities (%) [1)]	Report No./ Location in CTD	Type of Study
RH03L117A1 VV-MANU-002902 V1.0 MAY 2017	99.6% (HPLC)	-不純物9(塩酸塩)*: [redacted]% -不純物10*: [redacted]% -不純物11*: [redacted]%	T-16.060/ モジュール 4.2.3.4.1.1	Carcinogenicity study in Wistar rat (gavage)
			T-17.009/ モジュール 4.2.3.2.2	4-week range finding study for carc study in CByB6F1 mouse (gavage)
			T-18.041/ モジュール 4.2.3.4.2.1	Carcinogenicity study in CByB6F1-Tg(HRAS)2Jic Mouse (gavage)
			T-18.065/ モジュール 4.2.3.7.4.3	Assessment of stimulus generalization to Zolpidem in a two-choice drug discrimination paradigm in female Sprague Dawley rat (gavage)
			T-17.046/ モジュール 4.2.3.7.4.4	Assessment of reinforcing properties in a cocaine self-administration substitution procedure in female Sprague Dawley rat (i.v.)
			T-18.066/ モジュール 4.2.3.7.4.5	Pharmacokinetics in female Sprague Dawley rat (i.v.)
			T-17.048/ モジュール 4.2.3.7.4.6	Assessment of spontaneous withdrawal following 28 days oral dosing in female Sprague Dawley rat (gavage)
			T-18.097/ モジュール 4.2.3.5.4.1	Juvenile dose-range-finding study in Wistar rat (gavage)
			T-19.049/ モジュール 4.2.3.5.4.2	Juvenile toxicity study in Wistar rat (gavage)
			T-19.005/ モジュール 4.2.3.5.3.1	Pre and postnatal development (Segment III) in the Wistar rat (gavage)

1) area percent
2) extra studies were done for the qualification of ACT-699581 [モジュール 4.2.3.7.6.11; モジュール 4.2.3.7.6.8; モジュール 4.2.3.7.6.10]

HEK = human embryonic kidney; hERG = human ether-à-go-go-related gene; HPLC = high-performance liquid chromatography; i.v. = intravenous; LC-MS = liquid chromatography coupled to mass spectrometry; n.a. = not applicable; NMR = nuclear magnetic resonance; NMT = not more than; TRPV1 = transient receptor potential cation channel subfamily V member 1.

＊新薬承認情報提供時に置き換え

5. 単回投与毒性試験

Test Article: ダリドレキサント

単回投与毒性試験は実施しなかった

6. 反復投与毒性試験：重要な試験以外の試験

Test Article: ダリドレキサント

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Report No./ Location in CTD
Mouse/ CByB6F1	Oral (gavage) aqueous suspension containing 0.5% (w/v) methyl-cellulose	2 weeks	0, 1000, 2000 (as 1000 b.i.d) [1)]	0: 5M/5F 1000: 7M/7F 2000: 7M/7F	2000	1000: • decreased activity and hunched posture (single occasions) • single-dose: decrease in rectal temperature (F only) ≥ 1000: • increased body weight gain (F only) • decreased bilirubin and increased cholesterol • increased liver weight (abs. and rel.) • hepatocellular hypertrophy 2000: • salivation (single occasions)	T-16.061/ モジュール 4.2.3.2.1
Mouse/ CByB6F1	Oral (gavage) aqueous suspension containing 0.5% (w/v) methyl-cellulose	4 weeks	0, 100, 300, 1500 [2)]	Main: 10M/10F TK: 5M/5F (vehicle) 20M/20F (dose groups)	300	≥ 300: • increased liver weights (abs. and rel.) • centrilobular hypertrophy 1500: • enlargement of the liver • minimal to mild focal liver necrosis and minimal to mild single cell necrosis in liver • exudative inflammation in nasal cavity	T-17.009/ モジュール 4.2.3.2.2
Rat/RccHan: WIST	Oral (gavage) aqueous suspension containing 0.5% (w/v) methyl-cellulose	3 days	1000	Main: 3M/3F TK: 2M/2F	Not defined	1000: • salivation, reduced cage activity • decreased food consumption and body weight loss in females, transient in males on Day 1 • increased cholesterol, increased activity of GGT, ALT (females) and ALP (males) • cytoplasmatic vacuolation in liver, in some instances associated with glycogen depletion	T-13.144/ モジュール 4.2.3.2.3

Test Article: ダリドレキサント

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Report No./ Location in CTD
Rat/RccHan: WIST	Oral (gavage) aqueous suspension containing 0.5% (w/v) methyl-cellulose	2 weeks	0, 100, 300, 600 (F, only), 1000	Main: 5M/5F (vehicle, 100, 300, 1000); 5F (600) TK: 1M/1F (vehicle); 3M/3F (100, 300, 1000); 3F (600)	Not defined	≥ 100: • reduced cage activity ≥ 300: • increased thyroid (F) and liver weights ≥ 600: • transiently decreased body weight development and food consumption • increased GGT activity (F) • increased cholesterol (F) 1000: • increased GGT activity (M) • increased thyroid weights (M)	T-13.163/ モジュール 4.2.3.2.4

Test Article: ダリドレキサント

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Report No./ Location in CTD
Rat/RccHan: WIST	Oral (gavage) aqueous suspension containing 0.5% (w/v) methyl-cellulose	4 weeks	0, 100, 300, 1000	Main: 10M/10F Recovery: 5M/5F (0, 100, 300) 5M/6F (1000) [3)] TK: 6M/6F (0, 100, 300) 6M/5F (1000) [3)]	300	≥ 100: • hypersalivation and associated signs related (abnormal foraging, pedaling) • elevated triglyceride, cholesterol, and protein (globulin) concentrations • increased mean liver weight ≥ 300: • distended abdomen noted sporadically • enlargement of the liver • follicular cell hypertrophy in the thyroid gland • increased hematopoiesis in the spleen 1000: • 6F found dead between Day 12 and Day 26, with 'distended abdomen' being the only relevant observation before their demise • reduced cage activity, distended abdomen, and piloerection • slightly lower hemoglobin concentration and PCV, and slightly higher reticulocyte counts in females • slightly elevated GGT and ALT activity • centrilobular hepatocellular hypertrophy in the liver • cell hypertrophy of the pars distalis in the anterior pituitary gland of males • increased presence of adipocytes in the sternum bone marrow with the highest severity noted in four decedent females from the main study group. Exposure at the NOAEL: mean $AUC_{0\text{-}24}$ was 54.6 µg·h/mL (F) and 32.1 µg·h/mL (M); C_{max} was 7.86 µg/mL (F) and 4.56 µg/mL (M)	T-13.221/ モジュール 4.2.3.2.5

Test Article: ダリドレキサント

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Report No./ Location in CTD
Rat/RccHan: WIST	Oral (gavage) aqueous suspension containing 0.5% (w/v) methyl-cellulose	13 weeks	0, 50, 150, 450	Main: 10M/10F Recovery: 5M/5F TK: 6M/6F	450	≥ 50: • reduced cage activity and subdued/sluggish behavior ≥ 150: • salivation with related mouth rubbing and paddling were observed • increase in TSH levels (M) • slightly increased cholesterol (F only) and globulin concentrations • increased organ weight was noted for the liver and thyroid gland • centrilobular hepatocellular hypertrophy in the liver • follicular cell hypertrophy in the thyroid gland (M) 450: • slightly lower hemoglobin concentration and PCV, minor increase in mean reticulocyte count • increase in TSH levels (F) • enlargement of liver and thyroid • follicular cell hypertrophy in the thyroid gland (F) Histological findings were adaptive and non-adverse. Exposure at the NOAEL: mean AUC_{0-24} was 52.1 µg·h/mL (F) and 34.5 µg·h/mL (M) and mean C_{max} was 8.06 µg/mL (F) and 5.06 µg/mL (M).	T-14.068/ モジュール 4.2.3.2.6

Test Article: ダリドレキサント

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Report No./ Location in CTD
Dog/ Beagle	Oral (gavage) aqueous suspension containing 0.5% (w/v) methyl-cellulose	MTD: 3 days each dose	30, 100, 300, 1000	1M/1F	Not defined	≥ 300: • vomiting, loss of appetite, hypersalivation (M) • body weight loss	T-13.172/ モジュール 4.2.3.2.8
		2 weeks	0, 600	1M/1F (vehicle) 2M/2F (dose group)		600: • vomiting, loss of appetite, hypersalivation, red ocular and/or buccal mucous membranes • body weight loss • decreased food consumption • increased activity of ALT AST, ALP, GLDH (1M) • increased inflammatory cell infiltrate and/or accumulation of secretory material in the gall bladder • increased bile duct hyperplasia and/or inflammatory cell infiltration in the liver Based on the body weight loss and reduced food consumption, the dose level of 600 mg/kg/day was considered to be above the MTD.	

Test Article: ダリドレキサント

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Report No./ Location in CTD
Dog/ Beagle	Oral (gavage) aqueous suspension containing 0.5% (w/v) methyl-cellulose	4 weeks	0, 30, 100, 300/200 [4)]	Main: 3M/3F Recovery: 2M/2F (0, 300/200)	100	≥ 30: • increases in liver weight (M) ≥ 100: • a slight increase in ALP levels • increases in liver weight (F) • centrilobular hepatocellular hypertrophy in the liver and follicular cell hypertrophy in the thyroid gland 300/200: • marked vomiting, reduced food consumption, body weight loss, and decreased activity or slow movements. In addition, intermittent tremors were observed in the first days of treatment. Treatment was stopped on Day 6 and resumed at a reduced dose of 200 mg/kg/day from Day 12 onward. At this dose level, clinical signs included vomiting, hypersalivation, and intermittent tremors and/or head shaking were observed. Food consumption and weight gain improved in males, whereas females continued to lose weight due to reduced food consumption. • a slight reduction in RBC count, hemoglobin level and PCV. • An increased amount of luminal secretory material in the gallbladder (F) and increased number of adipocytes in the sternal bone marrow. Based on the severity of clinical signs at 200 mg/kg/day, the NOAEL was established at 100 mg/kg/day. Exposure at the NOAEL: mean $AUC_{0\text{-}24}$ was 83.5 µg·h/mL (F) and 184 µg·h/mL (M), and mean C_{max} was 13.7 µg/mL (F) and 22.6 µg/mL (M).	T-13.220/ モジュール 4.2.3.2.9

Test Article: ダリドレキサント

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Report No./ Location in CTD

1) 1000 mg/kg on Days 1–4, 2000 mg/kg from Day 5 on
2) 500 mg/kg on Days 1–2, 1000 mg/kg on Days 3–4, 1500 mg/kg from Day 5 on
3) one female was transferred from TK to recovery group
4) 300 mg/kg on Days 1–5; 0 mg/kg on Days 6–11, 200 mg/kg from Day 12 on

abs. = absolute; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; $AUC_{0\text{-}24}$ = area under the plasma concentration vs time curve from 0 to 24 h after dosing; b.i.d = twice daily; C_{max} = maximum plasma concentration; F = female(s); GGT = gamma glutamyl transferase; GLDH = glutamate dehydrogenase; M = male(s); MTD = maximum tolerated dose; NOAEL = no-observed-adverse-effect level; rel. = relative; PCV = packed cell volume; RBC = red blood cell count; TK = toxicokinetics; TSH = thyroid-stimulating hormone.

7. 反復投与毒性試験：重要な試験

7. A 反復投与毒性試験

Report No. T-15.076

Report Title:	ACT-541468A - 26-week oral (gavage) toxicity study in the rat followed by a 8-week treatment-free period			**Test Article:**	ダリドレキサント
Species/Strain:	Rat/RCCHan: WIST	**Duration of Dosing:**	26 weeks	**Report No.**	T-15.076
Initial Age:	6 weeks	**Duration of Postdose:**	8 weeks	**Testing Facility Study No.**	AB21150
Date of First Dose:	[redacted] 20[redacted]	**Method of Administration:**	oral (gavage)	**Location in CTD:**	モジュール 4.2.3.2.7
Special Features:	none	**Vehicle/Formulation:**	aqueous suspension containing 0.5% (w/v) methylcellulose	**GLP Compliance:**	yes
No-observed-adverse-effect Level:	450 mg/kg/day (kidney findings were not considered, as they represent an early manifestation of chronic progressive nephropathy, which is a rodent-specific disease without human relevance)				

Report No. T-15.076 (continued)

Daily Dose (mg/kg)		**0 (Control)**		**50**		**150**		**450**	
Number of Animals	**[Main]**	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20	M: 20 (19) [3)]	F: 20 (18) [3)]
	[Recovery]	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5 (4) [3)]	F: 5
	[TK satellites]	M: 6	F: 6 (5) [3)]	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6 (5)[3)]
Toxicokinetics:									
ダリドレキサント									
AUC_{0-24} [µg·h/mL]									
Day 1		n.a.	n.a.	3.270 [4)]	5.430	25.400	54.400	84.100	97.700
Week 13		n.a.	n.a.	4.060 [4)]	6.230 [4)]	17.400 [4)]	21.100 [4)]	54.300	80.500
Week 27		n.a.	n.a.	4.760 [4)]	7.690	16.800	26.500 [4)]	41.200	54.500 [4)]
C_{max} [µg/mL]									
Day 1		n.a.	n.a.	1.020	2.040	5.570	9.760	9.010	11.300
Week 13		n.a.	n.a.	1.510	1.730	5.190	5.560	9.530	13.500
Week 27		n.a.	n.a.	2.050	1.740	5.750	6.600	7.270	10.900
ACT-776063									
AUC_{0-24} [µg·h/mL]									
Day 1		n.a.	n.a.	2.740	4.220 [4)]	12.300 [4)]	32.800 [4)]	43.200	62.600
Week 13		n.a.	n.a.	2.750 [4)]	5.350 [4)]	11.600 [4)]	23.400 [4)]	45.400	60.300
Week 27		n.a.	n.a.	4.260 [4)]	9.780	15.400	28.900 [4)]	47.000	60.300
C_{max} [µg/mL]									
Day 1		n.a.	n.a.	0.668	1.220	2.340	6.490	4.520	5.990
Week 13		n.a.	n.a.	0.898	1.200	2.940	5.340	6.100	7.630
Week 27		n.a.	n.a.	1.540	1.630	3.290	5.790	5.800	7.280

Report No. T-15.076 (continued)

Daily Dose (mg/kg)		**0 (Control)**		**50**		**150**		**450**	
Number of Animals	**[Main]**	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20	M: 20 (19) [3)]	F: 20 (18) [3)]
	[Recovery]	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5 (4) [3)]	F: 5
	[TK satellites]	M: 6	F: 6 (5) [3)]	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6 (5)[3)]
ACT-776537									
AUC_{0-24} [µg·h/mL]									
Day 1		n.a.	n.a.	6.350	6.830	12.800 [4)]	11.500 [4)]	53.100	65.200
Week 13		n.a.	n.a.	9.860	13.300	34.000	43.700	91.800	99.400
Week 27		n.a.	n.a.	11.200	16.900	32.700	44.200	92.000	90.800
C_{max} [µg/mL]									
Day 1		n.a.	n.a.	0.849	0.557	2.070	3.190	4.940	3.860
Week 13		n.a.	n.a.	1.070	1.090	2.760	4.570	7.510	8.610
Week 27		n.a.	n.a.	1.190	1.110	2.940	4.020	6.960	7.730
ACT-1016-3307									
AUC_{0-24} [µg·h/mL]									
Day 1		n.a.	n.a.	0.779 [4)]	0.365 [4)]	3.500 [4)]	1.550 [4)]	13.200	6.670
Week 13		n.a.	n.a.	1.270 [4)]	1.180 [4)]	4.620 [4)]	4.840 [4)]	11.700 [4)]	17.300
Week 27		n.a.	n.a.	1.390 [4)]	1.420 [4)]	4.010 [4)]	4.980 [4)]	13.500	10.300 [4)]
C_{max} [µg/mL]									
Day 1		n.a.	n.a.	0.201	0.073	0.533	0.444	1.800	0.688
Week 13		n.a.	n.a.	0.367	0.179	0.937	0.746	1.810	1.650
Week 27		n.a.	n.a.	0.389	0.244	0.940	0.713	1.490	1.640

Report No. T-15.076 (continued)

Daily Dose (mg/kg)		**0 (Control)**		**50**		**150**		**450**	
Number of Animals	**[Main]**	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20	M: 20 (19) [3]	F: 20 (18) [3]
	[Recovery]	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5 (4) [3]	F: 5
	[TK satellites]	M: 6	F: 6 (5) [3]	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6 (5)[3]
Noteworthy Findings:									
Died or Sacrificed Moribund		0	1	0	0	0	0	**2**	**3**
Body Weight, Day 182 (%) [1]		456.48 g	262.97 g	-	-	-	-	+5	+8**
Food Consumption		-	-	-	-	-	-	-	-
Clinical Observations (no of animals concerned)									
Slow breathing		-	-	25	25	25	25	24	24
Rapid breathing		-	-	-	-	5	10	5	11
Decreased activity		-	-	-	-	1	2	4	6
Lying down		-	-	25	25	25	25	24	24
Partly closed eyes		-	-	25	25	25	25	24	24
Pedalling		-	-	2	2	16	14	16	20
Abnormal foraging		-	-	7	11	18	21	24	25
Hypersalivation		1	1	19	16	25	25	25	25
Piloerection		-	-	-	-	3	3	10	8
Raised tail		-	-	-	1	-	19	14	24
Ophthalmoscopy		-	-	-	-	-	-	-	-
Hematology, Week 27 (%) [1]									
Hemoglobin (g/L)		159.4	151.6	-	-	-	-	−6.7**	−13.9**
Packed cell volume (%)		46.84	45.36	-	-	-	-	−3.7*	−10.7**
Mean corpuscular volume (fL)		54.54	57.06	-	-	-	-	−8.4**	−7.9**
Mean corpuscular hemoglobin (pg)		18.59	19.08	-	-	-	-	−11.4**	−11.1**
Mean corpuscular hemoglobin concentration (g/L)		340.8	334.3	-	-	-	-	−3.2**	−3.5**
Coagulation		-	-	-	-	-	-	-	-

Report No. T-15.076 (continued)

Daily Dose (mg/kg)		**0 (Control)**		**50**		**150**		**450**	
Number of Animals	**[Main]**	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20	M: 20 (19) [3)]	F: 20 (18) [3)]
	[Recovery]	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5 (4) [3)]	F: 5
	[TK satellites]	M: 6	F: 6 (5) [3)]	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6 (5)[3)]
Clinical Chemistry, Week 27 (%) [1)]									
Gamma-glutamyl transferase (IU/L)		1.8	2.1	-	-	-	-	+383**	+186**
Triglycerides (mmol/L)		1.040	0.493	-	-	-	-	+29*	+91**
Cholesterol (mmol/L)		1.961	2.206	-	-	−23**	+34**	−37**	+86**
Globulin (g/L)		33.59	32.66	-	-	-	+13**	+10**	+25**
Urinalysis, Week 27									
Leucocytes (Leuco/µL)									
Negative (0)		-	20	-	-	-	15	-	4
Traces (15)		-	0	-	-	-	3	-	7
+ (70)		-	0	-	-	-	2	-	4
++ (125)		-	0	-	-	-	0	-	0
+++ (500)		-	0	-	-	-	0	-	3
Protein (g/L)									
Negative		-	19	-	-	-	15	-	7
Traces		-	1	-	-	-	4	-	7
+ (0.3)		-	0	-	-	-	1	-	0
++ (1)		-	0	-	-	-	0	-	3
+++ (>3)		-	0	-	-	-	0	-	1
Thyroid hormone analysis, Week 27 (%) [1)]									
T4 (nmol/L)		44	35	-	-	-	-	–18	-
TSH (ng/mL)		7.6	6.7	-	-	+61	+42	+99	+118

Report No. T-15.076 (continued)

Daily Dose (mg/kg)		**0 (Control)**		**50**		**150**		**450**	
Number of Animals	**[Main]**	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20	M: 20 (19) [3)]	F: 20 (18) [3)]
	[Recovery]	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5 (4) [3)]	F: 5
	[TK satellites]	M: 6	F: 6 (5) [3)]	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6 (5)[3)]
Organ Weights [1), 2)]									
Liver		10.96 g	6.80 g	+12**	+11 **	+22 **	+45**	+59 **	+121**
Kidneys		2.32 g	1.50 g	-	-	-	-	-	+20 **
Thyroid/parathyroid gland		19.41 mg	17.78 mg	-	-	+24**	-	+41**	+31**
Macroscopic Examination									
Liver									
Enlarged, all lobes		0	0	0	0	0	0	0	9
Microscopic Examination									
[No. examined, incl. deaths]		20	20	20	20	20	20	20	20
Kidneys									
Tubular hyaline casts									
Minimal		0	1	1	1	2	2	2	**7**
Slight		0	0	0	0	0	0	0	**3**
Moderate		0	0	0	0	0	0	0	**1**
Liver									
Centrilobular hepatocellular hypertrophy									
Minimal		7	3	**15**	3	**16**	**11**	**14**	**16**
Slight		0	0	**0**	0	**0**	**0**	**5**	**1**
Thyroid gland									
Follicular cell hypertrophy									
Minimal		2	1	**10**	0	**13**	**6**	**5**	**9**
Slight		0	0	**3**	0	**4**	**0**	**5**	**6**
Moderate		0	0	**0**	0	**0**	**0**	**9**	**3**

Report No. T-15.076 (continued)

Daily Dose (mg/kg)		**0 (Control)**		**50**		**150**		**450**	
Number of Animals	**[Main]**	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20	M: 20 (19) [3)]	F: 20 (18) [3)]
	[Recovery]	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5 (4) [3)]	F: 5
	[TK satellites]	M: 6	F: 6 (5) [3)]	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6 (5)[3)]
Postdose Evaluation D56:									
[No. examined]		5	5	5	5	5	5	4	5
Urinalysis									
Leucocytes (Leuco/µL)									
Negative (0)		-	5	-	-	-	-	-	1
Traces (15)		-	0	-	-	-	-	-	0
+ (70)		-	0	-	-	-	-	-	3
++ (125)		-	0	-	-	-	-	-	0
+++ (500)		-	0	-	-	-	-	-	1
Protein (g/L)									
Negative		-	4	-	-	-	-	-	1
Traces		-	1	-	-	-	-	-	0
+ (0.3)		-	0	-	-	-	-	-	1
++ (1)		-	0	-	-	-	-	-	2
+++ (≥3)		-	0	-	-	-	-	-	1
Organ Weights [1), 2)]									
Liver		-	7.21 g	-	-	-	-	-	+30**
Kidney		-	1.58 g	-	-	-	-	-	+22**

Report No. T-15.076 (continued)

Daily Dose (mg/kg)		**0 (Control)**		**50**		**150**		**450**	
Number of Animals	**[Main]**	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20	M: 20 (19) [3]	F: 20 (18) [3]
	[Recovery]	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5 (4) [3]	F: 5
	[TK satellites]	M: 6	F: 6 (5) [3]	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6 (5)[3]
Microscopic Examination									
Kidneys									
Tubular hyaline casts									
Minimal		0	0	0	2	0	0	0	**2**
Slight		0	0	0	0	1	0	1	**1**
Moderate		0	0	0	0	0	0	0	**1**
Liver		-	-	-	-	-	-	-	-
Thyroid gland									
Follicular cell hypertrophy									
Minimal		0	1	0	0	**3**	**2**	**1**	**3**
Slight		0	0	1	0	**0**	**0**	**2**	**0**

1) For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)
2) Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights
3) The six deaths (or unscheduled termination which occurred during the study) were considered a consequence of blood sampling, misgavage, or head trauma, or did not indicate any clear/consistent toxicity induced by the test item
4) AUC_{0-8}

- No noteworthy findings; Drug related values are shown in **bold;** * = $p \leq 0.05$; ** = $p \leq 0.01$ (see モジュール 4.2.3.2.7 for applied statistical analysis methods)
$AUC_{(0-8)0-24}$ = area under the plasma concentration vs time curve from 0 to (8)24 h after dosing; C_{max} = maximum plasma concentration; CTD = Common Technical Document; F = female(s); GLP = Good Laboratory Practice; M = male(s); n.a. = not applicable; T4 = thyroxine; TK = toxicokinetics; TSH = thyroid-stimulating hormone.

7. B 反復投与毒性試験

Report No. T-14.067

Report Title:	ACT-541468A: 13-week oral (gavage) administration toxicity study in the dog followed by a 4-week treatment-free period			**Test Article:**	ダリドレキサント
Species/Strain:	Dog/Beagle	**Duration of Dosing:**	13 weeks	**Report No.**	T-14.067
Initial Age:	Approx. 7 months	**Duration of Postdose:**	4 weeks	**Testing Facility Study No.**	8311200
Date of First Dose:	[redacted] 20[redacted]	**Method of Administration:**	oral (gavage)	**Location in CTD:**	モジュール 4.2.3.2.10
Special Features:	none	**Vehicle/Formulation:**	aqueous suspension containing 0.5% (w/v) methylcellulose	**GLP Compliance:**	yes
No-observed-effect Level		20 mg/kg/day			

Daily Dose (mg/kg)		**0 (Control)**		**20**		**50**		**150**	
Number of Animals	**[Main]**	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
	[Recovery]	M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2
Toxicokinetics:									
ダリドレキサント									
AUC_{0-24} [µg·h/mL]									
Day 1		BLQ	BLQ	17.6	10.50	34.50	22.40	144	122
Week 4		0.152	BLQ	26.5	17.40	62.10	39.30	234	220
Week 13		3.85	BLQ	34.1	19.70	126	65.40	304	245
C_{max} [µg/mL]									
Day 1		BLQ	BLQ	3.03	2.02	4.66	3.90	14.50	14.10
Week 4		0.029	BLQ	4.35	3.41	9.06	6.98	22.80	29.60
Week 13		0.321	BLQ	4.49	3.51	14.60	8.31	27.50	29.00

Report No. T-14.067 (continued)

Daily Dose (mg/kg)		**0 (Control)**		**20**		**50**		**150**	
Number of Animals	**[Main]**	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
	[Recovery]	M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2
Noteworthy Findings:									
Died or Sacrificed Moribund		0	0	0	0	0	0	0	0
Body Weight Gain (%) [1)]									
Day 1 to Day 92		1.76 kg	1.30 kg	-	-	-	-	−44	−92
Food Consumption (%) [1)]									
Day 1 to Day 91		258.6 g/day	204.8 g/day	−10	−5	−8	4	−4	4
Clinical Observations (no of animals concerned)									
Thin, minimal		-	-	-	-	-	-	-	2
Subdued/sluggish behavior									
Minimal		-	-	-	-	-	-	-	2
Moderate		-	-	-	-	-	-	-	1
Fainting (when stimulated at play)		-	-	-	-	-	2	3	1
Salivation, post dosing		-	1	-	-	1	1	5	5
Vomit									
Brown, diet		-	-	-	-	-	-	6	4
White, frothy		-	-	-	-	-	-	3	2
White, liquid		-	-	-	-	-	-	2	2
Neurological evaluation		-	-	-	-	-	-	-	-
Ophthalmoscopy		-	-	-	-	-	-	-	-
Cardiac examinations (Electrocardiography)		-	-	-	-	-	-	-	-

Report No. T-14.067 (continued)

Daily Dose (mg/kg)		**0 (Control)**		**20**		**50**		**150**	
Number of Animals	**[Main]**	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
	[Recovery]	M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2
Hematology									
Red blood cells (10^{12}/L)		7.26	-	-	-	-	-	6.00	-
Packed cell volume (%)		49.5	-	-	-	-	-	42.5	-
Reticulocytes (%)		0.8	-	-	-	-	-	0.7	-
Coagulation		-	-	-	-	-	-	-	-
Clinical Chemistry									
Alkaline phosphatase (IU/L)		60	65	101	74	97	94	161	129
Globulin (g/L)		22	19	24	23	23	22	25	23
Albumin/globulin ratio		1.7	2.0	1.6	1.6	1.6	1.7	1.2	1.4
Urinalysis		-	-	-	-	-	-	-	-
Thyroid hormone analysis		-	-	-	-	-	-	-	-
Organ Weights [1), 2)]									
Liver		256.2 g	202.2 g	+10	+30	+30	+50	+35	+29
Thyroid/parathyroid gland		0.645 g	0.450 g	-	+38	-	+68	-	+36
Macroscopic Examination									
Gallbladder									
Abnormal contents		0	0	0	0	0	0	1	1
Microscopic Examination									
[No. examined]		4	4	4	4	4	4	4	4
Gallbladder									
Secretory material									
Minimal		0	0	0	1	0	0	0	1
Slight		0	0	0	0	0	0	1	2
Moderate		0	0	0	0	0	0	2	1

Report No. T-14.067 (continued)

Daily Dose (mg/kg)		**0 (Control)**		**20**		**50**		**150**	
Number of Animals	**[Main]**	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
	[Recovery]	M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2
Postdose Evaluation:									
[No. examined]		2	2	n.a.	n.a.	n.a.	n.a.	2	2
All parameters		-	-	n.a.	n.a.	n.a.	n.a.	-	-

1) For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical analyses were not performed
2) Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights

- No noteworthy findings; AUC_{0-24} = area under the plasma concentration vs time curve from 0 to 24 h after dosing; BLQ = Below the limit of quantification; C_{max} = maximum plasma concentration; CTD = Common Technical Document; F = female(s); GLP = Good Laboratory Practice; M = male(s); n.a. = not applicable.

7. C 反復投与毒性試験

Report No. T-16.017

Report Title:	ACT-541468A - 39-week toxicity study by the oral (gavage) route in the beagle dog followed by an 8-week treatment-free period			**Test Article:**	ダリドレキサント
Species/Strain:	Dog/Beagle	**Duration of Dosing:**	39 weeks	**Report No.**	T-16.017
Initial Age:	10–11 months	**Duration of Postdose:**	8 weeks	**Testing Facility Study No.**	AB21316
Date of First Dose:	[redacted] 20[redacted]	**Method of Administration:**	oral (gavage)	**Location in CTD:**	モジュール 4.2.3.2.11
Special Features:	none	**Vehicle/Formulation:**	aqueous suspension containing 0.5% (w/v) methylcellulose	**GLP Compliance:**	yes
No-observed-effect Level:		10 mg/kg/day			

Dose (mg/kg/day)		**0 (Control)**		**10**		**30**		**100**	
Number of Animals	**[Main]**	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
	[Recovery]	M: 3	F: 3	M: 0	F: 0	M: 0	F: 0	M: 3 (2) [1)]	F: 3
Toxicokinetics:									
ダリドレキサント									
AUC_{0-24} [µg·h/mL]									
Day 1		n.a.	n.a.	5.18	6.41	28.5	24.8	85.2	120
Week 39		n.a.	n.a.	9.10	17.5	70.6	58.7	269	238
C_{max} [µg/mL]									
Day 1		n.a.	n.a.	1.43	1.98	4.87	5.63	8.27	11.2
Week 39		n.a.	n.a.	1.83	3.53	10.6	9.31	23.7	26.6

Report No. T-16.017 (continued)

Dose (mg/kg/day)		**0 (Control)**		**10**		**30**		**100**	
Number of Animals	**[Main]**	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
	[Recovery]	M: 3	F: 3	M: 0	F: 0	M: 0	F: 0	M: 3 (2) [1)]	F: 3
Toxicokinetics (cont.):									
ACT-776063									
AUC_{0-24} [µg·h/mL]									
Day 1		n.a.	n.a.	2.170	2.56	10.2	9.80	25.4	35.5
Week 39		n.a.	n.a.	3.440	6.54	22.9	19.7	67.1	62.9
C_{max} [µg/mL]									
Day 1		n.a.	n.a.	0.484	0.721	1.14	1.47	1.95	2.75
Week 39		n.a.	n.a.	0.556	1.06	2.31	2.32	4.62	5.40
ACT-776537									
AUC_{0-24} [µg·h/mL]									
Day 1		n.a.	n.a.	4.270	4.02 [2)]	12.9	13.1	29.2	41.1
Week 39		n.a.	n.a.	5.820	8.30	18.2	17.6	40.3	40.6
C_{max} [µg/mL]									
Day 1		n.a.	n.a.	0.421	0.607	0.863	1.15	1.61	2.39
Week 39		n.a.	n.a.	0.464	0.692	1.28	1.30	2.27	2.43
ACT-1016-3307									
AUC_{0-24} [µg·h/mL]									
Day 1		n.a.	n.a.	5.660	10.1	17.5	21.9	29.9	42.6
Week 39		n.a.	n.a.	9.910	25.9	60.8	63.9	205	221
C_{max} [µg/mL]									
Day 1		n.a.	n.a.	0.462	0.994	0.985	1.300	1.750	2.580
Week 39		n.a.	n.a.	0.842	1.610	3.620	3.730	9.960	11.700

Report No. T-16.017 (continued)

Dose (mg/kg/day)		**0 (Control)**		**10**		**30**		**100**	
Number of Animals	**[Main]**	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
	[Recovery]	M: 3	F: 3	M: 0	F: 0	M: 0	F: 0	M: 3 (2) [1)]	F: 3
Noteworthy Findings:									
Died or Sacrificed Moribund		0	0	0	0	0	0	1 [1)]	0
Body Weight, End of Treatment		-	-	-	-	-	-	-	-
Food Consumption, Day 1-274 (%) [3)]		75955.46 g/ animal	-	-	-	-	-	−17	-
Clinical Observations (no of animals concerned)									
Lateral or ventral decubitus		-	-	-	-	-	-	4	2
Lying down		-	-	-	-	1	-	3	-
Loss of balance		-	-	-	-	-	-	2	1
Unsteady gait		-	-	-	-	-	2	6	4
Clumsy movements		-	-	-	-	-	-	1	-
Unable to stand		-	-	-	-	-	-	1	-
Immobility		-	-	-	-	-	-	1	-
Subdued behaviour		-	-	-	-	-	-	1	-
Vomiting (dose)		-	1	-	-	-	-	4	1
Vomiting (food)		-	-	-	1	-	3	5	6
Regurgitation		-	1	-	-	-	-	3	2
Hypersalivation, slight		2	1	2	1	1	2	6	5
Hypersalivation, abundant		-	-	-	-	-	-	3	2
Neurological evaluation		-	-	-	-	-	-	-	-
Ophthalmoscopy		-	-	-	-	-	-	-	-
Cardiac examinations (Electrocardiography)		-	-	-	-	-	-	-	-
Hematology		-	-	-	-	-	-	-	-
Coagulation		-R	-	-	-	-	-	-	-

Report No. T-16.017 (continued)

Dose (mg/kg/day)		**0 (Control)**		**10**		**30**		**100**	
Number of Animals	**[Main]**	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
	[Recovery]	M: 3	F: 3	M: 0	F: 0	M: 0	F: 0	M: 3 (2) [1)]	F: 3
Clinical Chemistry, Day 268									
Albumin (g/L or %) [3)]		32.31	33.56	-	-	-	-	−16*	−16**
A/G ratio (%) [3)]		1.27	1.34	-	-	-	-	−25**	−17*
ALP (IU/L or %) [3)]		177.6	163.6	-	-	+69*	+132**	+305**	+320**
Female no. 402, Week 39 (fold vs pretest)									
ALT (IU/L)		n.a.	50 [5)]	n.a.	n.a.	n.a.	n.a.	n.a.	× 10
GLDH (IU/L)		n.a.	9 [5)]	n.a.	n.a.	n.a.	n.a.	n.a.	× 19
AST (IU/L)		n.a.	29 [5)]	n.a.	n.a.	n.a.	n.a.	n.a.	× 3
GGT (IU/L)		n.a.	6 [5)]	n.a.	n.a.	n.a.	n.a.	n.a.	× 2.5
Urinalysis		-	-	-	-	-	-	-	-
Thyroid hormone analysis		-	-	-	-	-	-	-	-
Organ Weights (%) [3), 4)]									
Liver		256.44 g	208.77 g	-	-	+29**	+31	+34**	+34
Macroscopic Examination									
Liver									
Enlarged, all lobes		0	0	0	0	0	0	(1) killed in extremis	1
Gallbladder									
Increased consistency of bile		0	0	0	0	0	0	0	1

Report No. T-16.017 (continued)

Dose (mg/kg/day)		**0 (Control)**		**10**		**30**		**100**	
Number of Animals	**[Main]**	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
	[Recovery]	M: 3	F: 3	M: 0	F: 0	M: 0	F: 0	M: 3 (2) [1)]	F: 3
Microscopic Examination									
[No. examined]		4	4	4	4	4	4	4	4
Bone marrow									
Adipocytes									
Minimal		0	0	0	0	1	1	**0**	**0**
Slight		1	3	2	2	2	1	**0**	**1**
Moderate		3	1	2	2	1	2	**3**	**2**
Marked		0	0	0	0	0	0	**1**	**1**
Gallbladder									
Secretory material									
Minimal		0	2	0	2	1	2	**0**	**1**
Slight		0	0	0	0	0	1	**2**	**0**
Moderate		0	0	0	0	0	0	**1**	**1**
Marked		0	0	0	0	0	0	**0**	**1**

Report No. T-16.017 (continued)

Dose (mg/kg/day)		**0 (Control)**		**10**		**30**		**100**	
Number of Animals	**[Main]**	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
	[Recovery]	M: 3	F: 3	M: 0	F: 0	M: 0	F: 0	M: 3 (2) [1)]	F: 3
Postdose Evaluation:									
[No. examined]		3	3	n.a.	n.a.	n.a.	n.a.	2	3
Food Consumption, D274-330 (%) [3)]		15259.73 g/ animal	-	n.a.	n.a.	n.a.	n.a.	−15	-

1) Male no. 395 treated at 100 mg/kg/day was prematurely sacrificed on Day 39. Misgavage was considered to be the cause of death
2) AUC_{0-10} for animal no. 380
3) For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)
4) Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights
5) Pretest value

- No noteworthy findings; Drug related values are shown in **bold**; * = $p < 0.05$; ** = $p < 0.01$ (see モジュール 4.2.3.2.11 for applied statistical analysis methods)
ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC_{0-10} = area under the plasma concentration vs time curve from 0 to 10 h after dosing; AUC_{0-24} = area under the plasma concentration vs time curve from 0 to 24 h after dosing; C_{max} = maximum plasma concentration; CTD = Common Technical Document; F = female(s); GGT = gamma glutamyl transferase; GLDH = glutamate dehydrogenase; GLP = Good Laboratory Practice; M = male(s); n.a. = not applicable.

8. *In Vitro* 遺伝毒性試験

8. A *In Vitro* 遺伝毒性試験

Report No. T-14.007

Report Title: ACT-541468A*: Salmonella typhimurium* reverse mutation assay

Test Article: ダリドレキサント

Test for Induction of: reverse mutation in bacterial cells

No. of Independent Assays: 2

Report No.: T-14.007

Strains: *Salmonella typhimurium*

No. of Replicate Cultures: 3

Testing Facility Study No. 1613901

Metabolizing System: Phenobarbital/β-Naphthoflavone induced rat liver S9 mix

No. of Cells Analyzed/Culture: –

Location in CTD: モジュール 4.2.3.3.1.1

Vehicles: **For Test Article:** Dimethylsulfoxide (DMSO)

For Positive Controls: DMSO [1)] or water [2)]

GLP Compliance: yes

Treatment: Plate incorporation for at least 3 days

Date of Treatment: [redacted] 20[redacted]

Cytotoxic Effects: none

Genotoxic Effects: none

Report No. T-14.007

Metabolic Activation	Test Article	Dose Level (µg/plate)	Assay # 1 (Plate Incorporation method); Revertant Colony Counts				
			TA 98	TA 100	TA 1535	TA 1537	TA 102
Without	Vehicle	0	29 ± 7	91 ± 8	18 ± 4	7 ± 1	473 ± 18
	Negative control	0	22 ± 7	107 ± 12	12 ± 4	8 ± 2	476 ± 19
	ACT-541468A [3)]	3	23 ± 1	83 ± 15	14 ± 3	13 ± 3	461 ± 14
		10	17 ± 6	89 ± 4	16 ± 3	8 ± 2	487 ± 29
		33	23 ± 5	100 ± 9	21 ± 1	10 ± 3	502 ± 9
		100	25 ± 9	94 ± 4	17 ± 7	12 ± 4	496 ± 9
		333	23 ± 9	77 ± 11	10 ± 2	9 ± 1	436 ± 23
		1000	21 ± 3	89 ± 5	14 ± 3	7 ± 2	458 ± 23
		2500	26 ± 2 [p m]	95 ± 6 [p m]	12 ± 2 [p m]	7 ± 1 [p m]	487 ± 20 [p m]
		5000	29 ± 3 [p m]	96 ± 2 [p m]	17 ± 2 [p m]	6 ± 1 [p m]	453 ± 32 [p m]
	4-Nitro-o-phenylene-diamine	10	306 ± 7				
		50				61 ± 1	
	Sodium azide	10		2386 ± 66	3134 ± 178		
	Methyl methane sulfonate	2					5578 ± 235

Report No. T-14.007 (continued)

Metabolic Activation	Test Article	Dose Level (µg/plate)	Assay # 1 (Plate Incorporation method); Revertant Colony Counts				
			TA 98	TA 100	TA 1535	TA 1537	TA 102
With	Vehicle	0	46 ± 4	105 ± 18	12 ± 4	17 ± 2	615 ± 34
	Negative control	0	39 ± 6	108 ± 9	18 ± 5	24 ± 4	573 ± 34
	ACT-541468A [3)]	3	39 ± 8	95 ± 16	16 ± 3	19 ± 6	561 ± 13
		10	38 ± 9	110 ± 3	11 ± 2	16 ± 4	569 ± 22
		33	37 ± 7	101 ± 3	18 ± 2	18 ± 3	611 ± 85
		100	37 ± 4	101 ± 7	17 ± 5	16 ± 4	645 ± 32
		333	38 ± 6	83 ± 7	17 ± 3	22 ± 6	550 ± 36
		1000	40 ± 7	97 ± 11	15 ± 4	19 ± 3	577 ± 7
		2500	37 ± 5 p m	95 ± 10 p m	11 ± 3 p m	12 ± 2 p m	581 ± 20 p m
		5000	26 ± 9 p m	97 ± 5 p m	10 ± 2 p m	11 ± 1 p m	563 ± 25 p m
	2 aminoanthracene	2.5	3436 ± 254	3500 ± 125	437 ± 30	414 ± 34	
		10					2062 ± 372

1) Vehicle for 2-aminoanthracene, 4-nitro-o-phenylene-diamine
2) Vehicle for sodium azide, methyl methane sulfonate
3) ACT-541468A = HCl salt of daridorexant

CTD = common technical document; GLP = Good Laboratory Practice; m = manual count; p = precipitate.

8. B *In Vitro* 遺伝毒性試験

Report No. T-14.008

Report Title: ACT-541468A: *In vitro* chromosome aberration test in human lymphocytes

Test for Induction of: chromosome aberrations (structural and numerical aberrations)

Cell Type: Peripheral Human Blood Lymphocytes

Metabolizing System: Phenobarbital/β-Naphthoflavone-induced rat liver S9

Vehicles: **For Test Article:** DMSO **For Positive Controls:** Nutrient medium (EMS)/Saline (CPA)

Treatment: Exp. I: 4 h +/− S9; Preparation interval: 22 h
Exp. II: 22 h –S9; Preparation interval: 22 h

Cytotoxic Effects: yes

Genotoxic Effects: none

No. of Independent Assays: 2

No. of Replicate Cultures: 2

No. of Cells Analyzed/Culture: 100

Test Article: ダリドレキサント

Report No.: T-14.008

Testing Facility Study No.: 1614101

Location in CTD: モジュール 4.2.3.3.1.2

GLP Compliance: yes

Date of Treatment: Exp. I: [redacted] 20[redacted], Exp. II: [redacted] 20[redacted]

Report No. T-14.008 (continued)

Metabolic Activation	Test Article	Concentration (µg/mL)	Polyploid cells (%)	Mitotic indices (% of control)	Aberrant cells including gaps (%)	Aberrant cells excluding gaps (%)	Aberrant cells with exchanges (%)
Exp. I	DMSO	0.5%	-	100.0	0.5	0.5	0.0
Without	EMS	770.0	-	97.1	9.5	9.5 S	2.0
Activation	ACT-541468A 1)	17.1	-	92.3	3.0	3.0 S	0.0
(4 h treatment)		29.9	-	99.4	0.0	0.0	0.0
		52.2 P	-	93.6	0.5	0.5	0.0
Exp. II	DMSO	0.5%	-	100.0	2.0	2.0	0.5
Without	EMS	660.0	-	31.5	46.0	46.0 S	14.0
Activation	ACT-541468A 1)	29.9	-	77.5	3.0	2.5	0.0
(22 h treatment)		52.2	-	94.9	0.0	0.0	0.0
		91.4 P	-	53.9	1.5	1.5	0.5
Exp. I	DMSO	0.5%	-	100.0	1.0	1.0	0.0
With	CPA	2.5	-	87.3	10.5	10.5 S	1.0
Activation	ACT-541468A 1)	17.1	-	100.6	1.0	1.0	0.0
(22 h treatment)		29.9	-	97.8	1.0	1.0	0.5
		52.2 P	-	105.4	1.0	1.0	0.0

1) ACT-541468A = HCl salt of daridorexant.

CTD = Common Technical Document; CPA = cyclophosphamide; DMSO = Dimethylsulfoxide; EMS = ethylmethane sulfonate; GLP = Good Laboratory Practice; P = precipitation was observed at the end of treatment; S = statistically significant ($p < 0.05$) compared to the solvent control value (Fisher's Exact Test).

9. *In Vivo* 遺伝毒性試験

9. A *In Vivo* 遺伝毒性試験

Report No. T-14.010

Report Title: ACT-541468A: Micronucleus Assay in Bone Marrow Cells of the Rat

Test Article: ダリドレキサント

Test for Induction of: micronuclei in rat bone marrow

Treatment Schedule: once daily for 2 days

Report No.: T-14.010

Species/Strain: Rat/RccHan: WIST

Sampling Time: 24 h after final administration

Testing Facility Study No. 1614201

Age: 8–12 weeks

Method of Administration: oral (gavage)

Location in CTD: モジュール 4.2.3.3.2.1

Cells Evaluated: polychromatic erythrocytes (PCEs)

Vehicle/Formulation: aqueous suspension containing 0.5% (w/v) methylcellulose

GLP Compliance: yes

No. of Cells Analyzed/Animal: at least 2000 PCEs

Positive control: cyclophosphamide (once orally)

Date of Dosing: [redacted] 20[redacted]

Special Features: none

Toxic/Cytotoxic Effects: yes. At 2000 mg/kg/day, the mean decrease in PCEs per 2000 erythrocytes was 19.3% in male and 26.3% in female animals, respectively, compared to vehicle controls.

Genotoxic Effects: none. ACT-541468A is considered to be non-mutagenic. No-observed-adverse-effect level (NOAEL): 2000 mg/kg body weight

Evidence of Exposure: yes. Daridorexant concentrations in animals dosed with ACT-541468A at 2000 mg/kg body weight (free base dose) ranged from 4.70 to 12.5 µg/mL

Number and sex of animals		**6 males**			**6 females**		
Test Group	**Dose (mg/kg b.w.)**	**PCEs with Micronuclei (%)**	**Range**	**PCE per 2000 Erythrocytes**	**PCEs with Micronuclei (%)**	**Range**	**PCE per 2000 Erythrocytes**
Vehicle control	0	0.217	1–10	1219	0.258	2–11	1015 [1)]
ACT-541468A [2)]	125	0.217	2–6	1154	0.125	1–4	948
	500	0.267	2–11	1142	0.133	1–6	944
	2000	0.192	1–7	984	0.108	1–4	748
Positive control	20	1.267	18–41	1003	0.575	7–14	956 [1)]

Report No. T-14.010 and BA-18.046 (continued)

Number and sex of animals	**6 males**				**6 females**			
Clinical Observations	**Time post 1st application (h)**				**Time post 2nd application (h)**			
	0–1	2–4	5–6	24	0–1	2–4	5–6	24
	High dose 2000 mg/kg b.w.; males/females							
Reduction of spontaneous activity	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
	Mid dose 500 mg/kg b.w.; males/females							
Reduction of spontaneous activity	6/6	6/6	6/6	0/0	6/6	6/6	6/6	0/0
	Low dose 125 mg/kg b.w.; males/females							
Reduction of spontaneous activity	6/6	6/6	6/6	0/0	6/6	6/6	6/6	0/0
Body Weight	-							
Determination of Daridorexant, M1, M3, and M10 in Plasma Samples	Daridorexant concentrations in plasma of animals dosed with ACT-541468A at 2000 mg/kg b.w. ranged from 4.70 to 12.5 µg/mL, confirming bioavailability of the test item. Plasma concentrations of major metabolites ranged from 8.66 to 18.2 µg/mL for M1 (ACT-776537), from 4.29 to 9.63 µg/mL for M3 (ACT-776063), and from 1.13 to 2.67 µg/mL for M10 (ACT-1016-3307). Daridorexant was not detected in any control group samples.							
Died or Sacrificed Moribund	none							

1) In order to confirm the data, a total of 6000 PCEs were evaluated. The value shown is adjusted to 2000 PCEs for better comparison
2) ACT-541468A – HCl salt of daridorexant

- = no noteworthy findings; b.w. = body weight; PCE = polychromatic erythrocyte; CTD = common technical document; GLP = Good Laboratory Practice; PCE = polychromatic erythrocyte

10. がん原性試験

10. A がん原性試験

Report No. T-16.060

Report Title: ACT-541468A - 104-week carcinogenicity study by the oral (gavage) route in the rat

Test Article: ダリドレキサント

Species/Strain: Rat/Wistar (RccHan:Wist)

Duration of Dosing: at least 104 weeks

Report No. T-16.060

Initial Age: 5 weeks at initiation of dosing

Method of Administration: Oral (gavage)

Testing Facility Study No. AB21679

Date of First Dose: main study animals: [redacted] 20[redacted] (males/females), satellite animals: [redacted] 20[redacted]

Vehicle/Formulation: Aqueous suspension containing 0.5% (w/v) methylcellulose

Location in CTD: モジュール 4.2.3.4.1.1

Treatment of Controls: Control I: oral (gavage) vehicle
Control II: oral (gavage) sterile water

GLP Compliance: yes

Basis for High Dose Selection: Toxicity-based endpoint

Special Features: 2 control groups

Daily Dose (mg/kg)	**0 (Control I)**		**0 (Control II)**		**15**		**50**		**150**	
No. of animals										
Main groups (allocation A)	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50
Toxicokinetics (allocation B)	M: 6	F: 6	M: 0	F: 0	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6
Toxicokinetics:										
ダリドレキサント										
Week 1 (Day 1)										
AUC_{0-24} [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.366	0.693	3.26	5.28	19.1	31.3
C_{max} [µg/mL]	BLQ	BLQ	BLQ	BLQ	0.150	0.294	1.39	2.15	3.77	5.78
Week 26 (Day 176)										
AUC_{0-24} [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.743	1.45	4.20	7.82	16.8	35.0
C_{max} [µg/mL]	BLQ	BLQ	BLQ	BLQ	0.338	0.748	1.55	3.26	3.91	8.46

Report No. T-16.060 (continued)

Daily Dose (mg/kg)	**0 (Control I)**		**0 (Control II)**		**15**		**50**		**150**	
No. of animals										
Main groups (allocation A)	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50
Toxicokinetics (allocation B)	M: 6	F: 6	M: 0	F: 0	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6
ACT-776063										
Week 1 (Day 1)										
AUC_{0-24} [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.300	0.667	2.31	3.81	12.0	19.1
C_{max} [µg/mL]	BLQ	BLQ	BLQ	BLQ	0.115	0.236	0.939	1.11	1.95	2.88
Week 26 (Day 176)										
AUC_{0-24} [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.743	1.67	3.22	6.74	14.6	35.6
C_{max} [µg/mL]	BLQ	BLQ	BLQ	BLQ	0.326	0.595	1.01	1.70	2.69	5.10
ACT-776537										
Week 1 (Day 1)										
AUC_{0-24} [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	1.42	1.71	8.37	9.62	40.5	40.4
C_{max} [µg/mL]	BLQ	BLQ	BLQ	BLQ	0.356	0.322	1.33	1.08	5.10	6.02
Week 26 (Day 176)										
AUC_{0-24} [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	3.40	3.04	10.6	12.2	28.4	43.2
C_{max} [µg/mL]	BLQ	BLQ	BLQ	BLQ	0.434	0.302	0.997	0.930	2.26	4.18
ACT-1016-3307										
Week 1 (Day 1)										
AUC_{0-24} [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.0828	0.0771	0.467	0.410	2.65	1.81
C_{max} [µg/mL]	BLQ	BLQ	BLQ	BLQ	0.0406	0.0239	0.160	0.0803	0.544	0.536
Week 26 (Day 176)										
AUC_{0-24} [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.328	0.304	1.20	1.06	3.57	3.88
C_{max} [µg/mL]	BLQ	BLQ	BLQ	BLQ	0.115	0.0644	0.303	0.179	0.702	0.546

Report No. T-16.060 (continued)

Daily Dose (mg/kg)	**0 (Control I)**		**0 (Control II)**		**15**		**50**		**150**	
No. of animals										
Main groups (allocation A)	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50
Toxicokinetics (allocation B)	M: 6	F: 6	M: 0	F: 0	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6
Mortality/Survival										
Died or Sacrificed Moribund										
Allocation A	10	28	17	21	17	17	17	19	17	22
Allocation B	0	0	0	0	0	0	0	0	0	0
Terminal Sacrifice										
Allocation A	40	22	33	29	33	33	33	31	33	28
Survival (%)- Day 734										
Allocation A	80	44	66	58	66	66	66	62	66	56
Clinical Observations	-	-	-	-	-	-	-	-	-	-
Body Weight and Food Consumption										
Body Weight, Week 105 (%) [1)]	609 g	413 g	602 g	407 g	-	-	-	-	+7*	-
Body Weight Gain, Day 1 to Week 105 (%) [1)]	447 g	281 g	442 g	276 g	-	-	-	-	+11**	-
Food Consumption	-	-	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	-	-
Palpable mass observation	-	-	-	-	-	-	-	-	-	-
Organ weights [2)]										
Body weight at necropsy (%) [1)]	575.8 g	383.6 g	566.4 g	384.0 g	-	-	-	-	+9**	-
Liver (%) [1)]	15.51 g	10.29 g	15.81 g	10.34 g	-	-	-	-	+26**	+42**
Thyroid glands (%) [1)]	0.0353 g	0.0264 g	0.0341 g	0.0274 g	-	-	-	-	+38**	+23**

Report No. T-16.060 (continued)

Daily Dose (mg/kg)	**0 (Control I)**		**0 (Control II)**		**15**		**50**		**150**	
No. of animals										
Main groups (allocation A)	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50
Toxicokinetics (allocation B)	M: 6	F: 6	M: 0	F: 0	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6
Macroscopic examination										
Kidneys										
Irregular surface	4	-	3	-	2	-	**10**	-	**14**	-
Enlarged	5	-	4	-	1	-	**9**	-	**12**	-
Pale, pale/raised focus	2	-	5	-	2	-	**8**	-	**6**	-
Neoplastic lesions	-	-	-	-	-	-	-	-	-	-
Non-neoplastic lesions										
Liver										
Bile duct hyperplasia	4	6	3	14	3	13	4	14	0	**25**
minimal	2	6	3	9	3	6	4	10	0	**21**
slight	1	0	0	4	0	7	0	4	0	**3**
moderate	0	0	0	1	0	0	0	0	0	**0**
marked	1	0	0	0	0	0	0	0	0	**1**
Increased karyocytomegaly/ multinucleated hepatocytes	0	0	0	1	0	1	0	4	0	**25**
minimal	0	0	0	1	0	1	0	4	0	**22**
slight	0	0	0	0	0	0	0	0	0	**3**
Hepatocellular hypertrophy, centrilobular	1	1	0	0	0	0	1	2	1	**9**
minimal	0	1	0	0	0	0	1	2	0	**9**
slight	1	0	0	0	0	0	0	0	1	**0**
Sinusoidal angiectasis	3	2	7	0	5	1	1	3	6	**10**
minimal	3	2	7	0	5	1	1	3	5	**10**
slight	0	0	0	0	0	0	0	0	1	**0**

Report No. T-16.060 (continued)

Daily Dose (mg/kg)	**0 (Control I)**		**0 (Control II)**		**15**		**50**		**150**	
No. of animals										
Main groups (allocation A)	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50	M: 50	F: 50
Toxicokinetics (allocation B)	M: 6	F: 6	M: 0	F: 0	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6
Kidneys										
Chronic progressive										
nephropathy	42	15	42	6	35	14	33	11	48	**35**
minimal	25	13	17	4	18	11	13	9	17	**25**
slight	8	1	13	0	10	1	5	1	8	**9**
moderate	4	0	6	0	4	0	6	0	12	**1**
marked	3	1	1	1	0	2	2	0	6	**0**
severe	2	0	5	1	3	0	7	1	5	0

1) For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)
2) Both absolute and relative weights differed from control I in the direction indicated. Number indicates percent difference for the absolute organ weights

- No noteworthy findings; Drug related values are shown in **bold;** n.a. = not applicable; * = p<0.05; ** = p<0.01 (see モジュール 4.2.3.4.1.1 for applied statistical analysis methods); AUC_{0-24} = area under the plasma concentration vs time curve from 0 to 24 h after dosing; BLQ = below the limit of quantification; C_{max} = maximum plasma concentration; CTD = common technical document; F = female(s); GLP = Good Laboratory Practice; M = male(s)

10. B がん原性試験

Report No. T-18.041

Report Title: ACT-541468A: A 26-Week Oral Oncogenicity Study in CByB6F1-Tg(HRAS)2Jic Mice
Test Article: ダリドレキサント
Species/Strain: Mouse/CByB6F1-Tg(HRAS)2Jic
Duration of Dosing: 26 weeks
Report No. T-18.041
Initial Age: 6.5 weeks
Method of Administration: Oral (gavage)
Testing Facility Study No. 2762-001
Date of First Dose: [redacted] 20[redacted]
Vehicle/Formulation: Aqueous suspension containing 0.5 % (w/v) methylcellulose
Location in CTD: モジュール 4.2.3.4.2.1
Treatment of Controls: Oral (gavage) vehicle
GLP Compliance: yes
Basis for High-Dose Selection: Toxicity-based endpoint
Special Features: Two control groups (including positive control group treated with a single i.p. injection of 75 mg/kg NMU)

Daily Dose (mg/kg)	**0 (Control)**		**0 (Positive control)**		**100**		**300**	**200**	**1000**	
No. of animals										
Main groups (allocation A)	M: 25	F: 25	M: 10	F: 10	M: 25	F: 25	M: 25	F: 25	M: 25	F: 25
Toxicokinetics (allocation B)	M: 8	F: 8	M: 0	F: 0	M: 38	F: 38	M: 38	F: 38	M: 38	F: 38
Toxicokinetics:										
ダリドレキサント										
Week 1 (Day 1)										
$AUC_{0\text{-}24}$ [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.765	1.47	5.84	3.27	31.8	38.5
C_{max} [µg/mL]	n.a.	n.a.	n.a.	n.a.	0.517	0.516	3.89	1.60	9.61	13.9
Week 26 (Day 182)										
$AUC_{0\text{-}24}$ [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.403	0.245	2.17	0.668	4.73	1.97
C_{max} [µg/mL]	n.a.	n.a.	n.a.	n.a.	0.184	0.152	1.01	0.244	0.832	0.559

Report No. T-18.041 (continued)

Daily Dose (mg/kg)	**0 (Control)**		**0 (Positive control)**		**100**		**300**	**200**	**1000**	
No. of animals										
Main groups (allocation A)	M: 25	F: 25	M: 10	F: 10	M: 25	F: 25	M: 25	F: 25	M: 25	F: 25
Toxicokinetics (allocation B)	M: 8	F: 8	M: 0	F: 0	M: 38	F: 38	M: 38	F: 38	M: 38	F: 38
Toxicokinetics (cont.):										
ACT-776063										
Week 1 (Day 1)										
$AUC_{0\text{-}24}$ [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.311	0.323	2.44	1.53	13.8	13.3
C_{max} [µg/mL]	n.a.	n.a.	n.a.	n.a.	0.219	0.206	1.65	0.636	3.68	4.00
Week 26 (Day 182)										
$AUC_{0\text{-}24}$ [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.227	0.0694	0.592	0.159	2.63	0.644
C_{max} [µg/mL]	n.a.	n.a.	n.a.	n.a.	0.0803	0.0295	0.142	0.0433	0.532	0.185
ACT-776537										
Week 1 (Day 1)										
$AUC_{0\text{-}24}$ [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.584	0.663	2.79	2.18	17.7	17.3
C_{max} [µg/mL]	n.a.	n.a.	n.a.	n.a.	0.263	0.240	0.755	0.646	3.10	2.79
Week 26 (Day 182)										
$AUC_{0\text{-}24}$ [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.124	0.0281	0.474	0.141	2.00	0.547
C_{max} [µg/mL]	n.a.	n.a.	n.a.	n.a.	0.0675	0.0198	0.204	0.0390	0.419	0.190
ACT-1016-3307										
Week 1 (Day 1)										
$AUC_{0\text{-}24}$ [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.149	0.186	0.870	0.668	4.86	4.55
C_{max} [µg/mL]	n.a.	n.a.	n.a.	n.a.	0.109	0.134	0.528	0.283	1.10	1.17
Week 26 (Day 182)										
$AUC_{0\text{-}24}$ [µg·h/mL]	n.a.	n.a.	n.a.	n.a.	0.0502	0.00686	0.209	0.101	1.09	0.268
C_{max} [µg/mL]	n.a.	n.a.	n.a.	n.a.	0.0345	0.0137	0.0868	0.0320	0.219	0.106

Report No. T-18.041 (continued)

Daily Dose (mg/kg)	**0 (Control)**		**0 (Positive control)**		**100**		**300**	**200**	**1000**	
No. of animals										
Main groups (allocation A)	M: 25	F: 25	M: 10	F: 10	M: 25	F: 25	M: 25	F: 25	M: 25	F: 25
Toxicokinetics (allocation B)	M: 8	F: 8	M: 0	F: 0	M: 38	F: 38	M: 38	F: 38	M: 38	F: 38
Mortality/Survival										
Died or Sacrificed Moribund										
Allocation A	2	2	1	3	0	0	2	0	1	3
Allocation B	0	0	0	0	0	0	0	0	0	0
Terminal Sacrifice										
Allocation A	23	23	9	7	25	25	23	25	24	22
Survival (%)										
Allocation A	92	92	90	70	100	100	92	100	96	88
Clinical Observations	-	-	-	-	-	-	-	-	-	-
Masses	-	-	-	-	-	-	-	-	-	-
Body Weight and Food Consumption										
Body Weight (%) [1)]										
Day 182	33.03 g	23.74 g	33.36 g	26.53 g**	-	-	−3	-	−9**	-
Body Weight Gain (%) [1)]										
Days 77–84	1.16 g	0.52 g	1.97 g	1.5 g	-	-	−47*	-	−84**	-
Days 168–182	0.45 g	0.2 g	0.31g	0.54 g	−49	-	−44	-	−131	-
Food Consumption	-	-	-	-	-	-	-	-	-	-
Organ weights [1), 2)]										
Liver	1.68 g	1.25 g	1.79 g	1.59 g**	+5.8	+4.6	**+15.6***	+7.6	**+39.1****	**+48.5****
Macroscopic examination	-	-	-	-	-	-	-	-	-	-
Neoplastic Lesions	-	-	-	-	-	-	-	-	-	-

Report No. T-18.041 (continued)

Daily Dose (mg/kg)	**0 (Control)**		**0 (Positive control)**		**100**		**300**	**200**	**1000**	
No. of animals										
Main groups (allocation A)	M: 25	F: 25	M: 10	F: 10	M: 25	F: 25	M: 25	F: 25	M: 25	F: 25
Toxicokinetics (allocation B)	M: 8	F: 8	M: 0	F: 0	M: 38	F: 38	M: 38	F: 38	M: 38	F: 38
Non-Neoplastic Lesions										
Liver										
Hypertrophy, hepatocellular, centrilobular	0/25	0/25	0/10	0/10	**15/25**	0/25	**21/25**	0/25	**24/25**	**11/25**
Minimal	0	0	0	0	**14**	0	**7**	0	**0**	**5**
Mild	0	0	0	0	**1**	0	**13**	0	**7**	**6**
Moderate	0	0	0	0	**0**	0	**1**	0	**16**	**0**
Marked	0	0	0	0	**0**	0	**0**	0	**1**	**0**

1) For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)
2) Both absolute and relative weights differed from control in the direction indicated. Number indicates percent difference for the absolute organ weights

- = No noteworthy findings; Drug related values are shown in **bold**; * = p<0.05, ** = p<0.01 (see モジュール 4.2.3.4.2.1 for applied statistical analysis methods)
AUC_{0-24} = area under the plasma concentration vs time curve from 0 to 24 h after dosing; C_{max} = maximum plasma concentration; CTD = common technical document; F = female(s); GLP = Good Laboratory Practice; i.p. = intra peritoneal; M = male(s); n.a. not applicable; NMU = N-Nitroso-N-methylurea.

11. 生殖発生毒性試験：重要な試験以外の試験

Test Article: ダリドレキサント

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Dosing Period	Doses (mg/kg)	No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Report No./ Location in CTD
Rat/ Wistar Han: Crl: WI	Oral (gavage) aqueous suspension containing 0.5% methylcellulose	GD6–GD17	0, 100, 300, 1000	Main: 6F TK: 3F (vehicle), 6F (dose groups)	n.a.	≤ 300 • no embryo-fetal toxicity (no effect on embryo-fetal survival and mean live litter size, no effect on gravid uterus weight, no test item-related effect on fetal sex ratio, no fetal external malformation) ≥ 100: • decreased mean food consumption 300: • irregular breathing • piloerection and/or decreased • activity • marginally lower mean fetal weight 1000: • all high-dose group females found dead or were sacrificed after 9, 10 or 11 days of dosing (macroscopical examination: cause of death or morbidity could not be determined) • body weight loss • decreased food consumption • decreased activity, subdued behavior, slow and irregular breathing, piloerection, abnormal vocalization	T-14.016/ モジュール 4.2.3.5.2.1

Test Article: ダリドレキサント

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Dosing Period	Doses (mg/kg)	No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Report No./ Location in CTD
Rabbit/ New Zealand White	Oral (gavage) aqueous suspension containing 0.5% (w/v) methyl-cellulose	MTD: 3 days each dose	30, 100, 200, 300	3F	n.a.	≥ 200: • decreased mean food consumption • body weight loss 300: • marked clinical signs including rapid breathing and recumbency	T-14.013/ モジュール 4.2.3.5.2.4
		Repeat-dose phase: 7 days	200	3F	n.a.	200: • decreased mean food consumption • body weight loss • decreased activity	
Rabbit/ New Zealand White	Oral (gavage) aqueous suspension containing 0.5% methylcellulose	GD6–GD19	0, 30, 60, 120	6F	n.a.	≤ 120: • no embryo-fetal toxicity (no findings on embryo-fetal survival, no fetal external and visceral malformation, no test item-related effect on fetal sex ratio, no findings on mean gravid uterus and fetal weights) 30: • 1F found dead on Day 16 p.c. (misgavage) 120: • slightly reduced food consumption	T-14.014/ モジュール 4.2.3.5.2.5

F = female; GD = gestation day; n.a. = not applicable; MTD = maximum tolerated dose; NOAEL = no-observed-adverse-effect level; p.c. = post coitum; TK = toxicokinetic satellite animals.

12. 生殖発生毒性試験：受胎能及び着床までの初期胚発生に関する試験

12. A 生殖発生毒性試験：受胎能及び着床までの初期胚発生に関する試験

Report No. T-16.003

Report Title: ACT-541468A - Fertility toxicity study by the oral route (gavage) in the male rat (Segment I).

Test Article: ダリドレキサント

Design similar to ICH 4.1.1? yes

Duration of Dosing: 14 days before mating, throughout mating and up to the day before necropsy (Day 43), i.e., up to 43 days of treatment in total

Report No. T-16.003

Species/Strain: Rat/Wistar Crl: WI (Han)

Day of Mating: Day 0 of gestation

Testing Facility Study No.: AB21305

Initial Age: Males: approx. 10 weeks (start of treatment); females: approx. 11 weeks (start of pairing)

Day of C-Section: Day 13 of gestation

Location in CTD: モジュール 4.2.3.5.1.1

Special Features: none

Method of Administration: oral (gavage)

GLP Compliance: yes

Date of First Dose: [redacted] 20[redacted] (males only)

Vehicle/Formulation: aqueous suspension containing 0.5% (w/v) methylcellulose

No-observed-adverse-effect level:

Males (gonadal function, mating behaviour and reproductive performance)

Not determined (no-observed-effect level [NOEL]: 450 mg/kg/day)

Dose (mg/kg/day)	**0 (Control)**	**50**	**150**	**450**
No. of animals evaluated	M: 22/F: 22	M: 22/F: 22	M: 22/F: 22	M: 22/F: 22
Toxicokinetics: ダリドレキサント (males):				
$AUC_{0\text{-}24}$ [µg·h/mL]				
Day1	n.a.	4.03	28.6	66.8
Week 6	n.a.	4.58	18.2	46.7
C_{max} [µg/mL]				
Day 1	n.a.	1.15	3.94	7.21
Week 6	n.a.	1.43	4.42	7.60

Report No. T-16.003 (continued)

Dose (mg/kg/day)	**0 (Control)**	**50**	**150**	**450**
No. of animals evaluated	M: 22/F: 22	M: 22/F: 22	M: 22/F: 22	M: 22/F: 22
Died or Sacrificed Moribund	0	0	0	0
Clinical Observations (affected males)				
Hypersalivation (Day 19 to Day 40)	-	12	22	22
Abnormal foraging (Day 26 to Day 33)	-	3 (Day 26)	12	20
Partly closed eyes (Day 26 to Day 43)	-	12	22	21
Animal lying down (Day 26 to Day 43)	-	21	22	22
Slow breathing (Day 26 to Day 43)	-	20 (Day 26)	22	21
Pedalling (Day 33)	-	-	4	7
Body Weight Gain (%) [1)]				
Males (Day 11-16)	12.37 g	+8	+24*	+32**
Females	-	-	-	-
Food Consumption (%) [1)]				
Males (Day 8-16)	24.79 g/day	-	-	+5***
Females	-	-	-	-
Mating performance and fertility (pre-coital interval, copulation index, fertility index)	-	-	-	-
Sperm analysis (motility, count, morphology)	-	n.a.	n.a.	-
Paternal macroscopy observations	-	-	-	-
Organ weights				
Epididymides	-	-	-	-
Testes	-	-	-	-

Report No. T-16.003 (continued)

Dose (mg/kg/day)	**0 (Control)**	**50**	**150**	**450**
No. of animals evaluated	M: 22/F: 22	M: 22/F: 22	M: 22/F: 22	M: 22/F: 22
Maternal macroscopy observations	-	-	-	-
No. of pregnant females	18	18	20	22
Dams with viable fetuses	18	18	20	22
Pre-implantation parameters (mean numbers of corpora lutea, implantation sites and percentage pre-implantation loss)	-	-	-	-
Post implantation parameters (percentage post-implantation loss, mean live litter size)	-	-	-	-

1) Group means are provided for controls and percent difference from controls are provided for treated groups. Statistical significance is based on raw data, not percent difference.

- = No noteworthy findings; * = $p < 0.05$ (Williams 2-sided test), ** = $p < 0.01$ (Williams 2-sided test), *** = $p < 0.001$ (Shirley 2-sided test)
$AUC_{0\text{-}24}$ = Area under the plasma concentration vs time curve from 0 to 24 h after dosing, C_{max} = Maximum plasma concentration; CTD = Common Technical Document; F = Female; GLP = Good Laboratory Practice; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; M = Male; n.a. = not applicable; NOEL = no-observed-effect level.

12. B 生殖発生毒性試験：受胎能及び着床までの初期胚発生に関する試験

Report No. T-16.004

Report Title: ACT-541468A - Fertility toxicity study by the oral route (gavage) administration in the female rat (Segment I)

Test Article: ダリドレキサント

Design similar to ICH 4.1.1? yes

Duration of Dosing: 14 days before mating, throughout mating and until day 7 of gestation (inclusive)

Report No. T-16.004

Species/Strain: Rat/Wistar Crl: WI (Han)

Day of Mating: Day 0 of gestation

Testing Facility Study No. AB21306

Initial Age: Females: approx. 9 weeks (start of treatment); males: approx. 13 weeks (start of pairing)

Day of C-Section: Day 13 of gestation

Location in CTD: モジュール 4.2.3.5.1.2

Special Features: none

Method of Administration: oral (gavage)

GLP Compliance: yes

Date of First Dose: [redacted] 20[redacted] (females only)

Vehicle/Formulation: aqueous suspension containing 0.5% (w/v) methylcellulose

No-observed-adverse-effect level:
Females (gonadal function, mating behaviour and reproductive performance)

300 mg/kg/day

Dose (mg/kg/day)		**0 (Control)**	**30**	**100**	**300**
No. of animals evaluated	Main	F: 22/M: 22	F: 22/M: 22	F: 22/M: 22	F: 22/M: 22
	TK satellite	F: 3 (M: 3)	F: 6 (M: 6)	F: 6 (M: 6)	F: 6 (M: 6)
Toxicokinetics: ダリドレキサント (females):					
AUC_{0-24} [µg·h/mL]					
Day 1		n.a.	3.21	27.9	75.3
GD7		n.a.	3.44 [1)]	17.8	57.9
C_{max} [µg/mL]					
Day 1		n.a.	1.18	4.85	8.01
GD7		n.a.	1.23	4.10	7.66

Report No. T-16.004 (continued)

Dose (mg/kg/day)		**0 (Control)**	**30**	**100**	**300**
No. of animals evaluated	Main	F: 22/M: 22	F: 22/M: 22	F: 22/M: 22	F: 22/M: 22
	TK satellite	F: 3 (M: 3)	F: 6 (M: 6)	F: 6 (M: 6)	F: 6 (M: 6)
Died or Sacrificed Moribund		0	0	0	0
Clinical Observations (affected females)					
Hypersalivation					
Pre-mating period		-	-	18	22
Gestation period		-	8	20	20
Abnormal foraging					
Pre-mating period		-	-	4	13
Gestation period		-	1	13	14
Partly closed eyes					
Pre-mating period		-	-	9	14
Gestation period		-	-	-	-
Animal lying down					
Pre-mating period		-	-	9	14
Gestation period		-	-	-	-
Slow breathing					
Pre-mating period		-	-	9	14
Gestation period		-	-	-	-
Pedalling					
Pre-mating period		-	-	-	4
Gestation period		-	1	3	8
Body temperature (females GD0 to GD7)		-	-	-	-
Body Weight					
Pre-mating and gestation Body Weight [2)]		-	-	-	-
Food Consumption (%) [2)]					
Females (pre-mating period Day 1 to Day 15)		16.81 g/day	-5*	-4**	-4***
Females (gestation period GD0 to GD13)		-	-	-	-

Report No. T-16.004 (continued)

Dose (mg/kg/day)		0 (Control)	30	100	300
No. of animals evaluated	Main	F: 22/M: 22	F: 22/M: 22	F: 22/M: 22	F: 22/M: 22
	TK satellite	F: 3 (M: 3)	F: 6 (M: 6)	F: 6 (M: 6)	F: 6 (M: 6)
Estrus cycle (cycle length, irregularity index, percentage of estrus days, percentage of females acyclic or with acyclic period)		-	-	-	-
Mating performance and fertility (pre-coital interval, copulation index, fertility index)		-	-	-	-
Gravid uterus weight (main group) (%) [2)]		6.52 g	+18	−13	−13
Maternal macroscopy observations		-	-	-	-
Organ weights		-	-	-	-
No. of pregnant females (main group)		19	21	20	20
Dams with viable fetuses (main group)		18	21	20	20
Pre-implantation parameters					
Mean numbers of corpora lutea		-	-	-	-
Mean numbers of implantation sites		11.8	-	-	10.7
Percentage of pre-implantation loss		13.34	-	-	19.21
Post-implantation parameters					
Live litter size		11.0	-	-	10.2
Percentage post-implantation loss		-	-	-	-

1) AUC_{0-8}
2) Group means are provided for controls and percent difference from controls are provided for treated groups. Statistical significance is based on raw data, not percent difference

- = No noteworthy findings; * = $p<0.05$, ** = $p<0.01$, *** = $p < 0.001$ (Shirley 2-sided test)
AUC_{0-8}/AUC_{0-24} = area under the plasma concentration vs time curve from 0 to 8/24 h after dosing; C_{max} = maximum plasma concentration; CTD = common technical document; F = female; GD = gestation day; GLP = Good Laboratory Practice; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; M = male; n.a. = not applicable; TK = toxicokinetic(s).

13. 生殖発生毒性試験：胚・胎児発生に関する試験

13. A 生殖発生毒性試験：胚・胎児発生に関する試験

Report No. T-14.017, T-17.042 and BA-17.048

Report Title: ACT-541468A – Embryo-fetal toxicity study by the oral route (gavage) in the rat (Segment II)

Test Article: ダリドレキサント

Design similar to ICH 4.1.3? yes	**Duration of Dosing:**	From GD6 to GD17	**Report No.**	T-14.017, T-17.042
Species/Strain: rat/Wistar:Crl:WI	**Day of Mating:**	Day 0 of gestation	**Testing Facility Study No.**	AB20518
Initial Age: females: 10 to 13 weeks (at mating)	**Day of C-Section:**	Day 20 of gestation	**Location in CTD:**	モジュール 4.2.3.5.2.2, モジュール 4.2.3.5.2.3
Special Features: none	**Method of Administration:**	oral (gavage)	**GLP Compliance:**	yes
Date of First Dose: [redacted] to [redacted] 20[redacted] (main); [redacted] 20[redacted] (TK satellites)	**Vehicle/Formulation:**	aqueous suspension containing 0.5% (w/v) methylcellulose		

No-observed-adverse-effect level:

F_0 Females (dams): 100 mg/kg/day

F_1 Litters: n.a. (no-observed-effect level [NOEL]: 300 mg/kg/day)

Daily Dose (mg/kg/day)		**0 (Control)**	**30**	**100**	**300**
No. Animals (Dams)	Main	22	22	22	22
	TK satellites	3	6	6	6
Toxicokinetics:					
ダリドレキサント					
$AUC_{0\text{-}24}$ [µg·h/mL]					
GD6		n.a.	3.93	32.2	98.4
GD17		n.a.	5.46	19.6	51.6
C_{max} [µg/mL]					
GD6		n.a.	1.46	6.33	9.54
GD17		n.a.	1.65	3.70	7.94

Report No. T-14.017, T-17.042 and BA-17.048 (continued)

Daily Dose (mg/kg/day)		**0 (Control)**	**30**	**100**	**300**
No. Animals (Dams)	Main	22	22	22	22
	TK satellites	3	6	6	6
Toxicokinetics (cont.):					
ACT-776063					
AUC_{0-24} [µg·h/mL]					
GD6		n.a.	2.9	19.9	54.9
GD17		n.a.	2.53	14.0	34.5
C_{max} [µg/mL]					
GD6		n.a.	0.71	2.45	4.17
GD17		n.a.	0.6	1.99	3.58
ACT-776537					
AUC_{0-24} [µg·h/mL]					
GD6		n.a.	4.48	17.5	56.1
GD17		n.a.	6.05	26.6	77.1
C_{max} [µg/mL]					
GD6		n.a.	0.345	1.39	4.70
GD17		n.a.	0.419	2.29	6.25
ACT-1016-3307					
AUC_{0-24} [µg·h/mL]					
GD6		n.a.	0.226	1.32	4.68
GD17		n.a.	0.314	1.54	7.88
C_{max} [µg/mL]					
GD6		n.a.	0.0408	0.132	0.324
GD17		n.a.	0.0470	0.224	0.797

Report No. T-14.017, T-17.042 and BA-17.048 (continued)

Daily Dose (mg/kg/day)		**0 (Control)**	**30**	**100**	**300**
No. Animals (Dams)	Main	22	22	22	22
	TK satellites	3	6	6	6
Died or Sacrificed Moribund		0	0	0	0
Clinical Observations					
Hypersalivation		0	0	17	22
Body Weight		-	-	-	-
Food Consumption					
Gestation Food Consumption, GD6–GD18 (%) [1)]		24.03 g/day	-	-	−7*
Gestation Food Consumption, GD6–GD9 (%) [1)]		22.19 g/day	-	-	−20***
Necropsy observations (dams)		-	-	-	-
Gravid uterus weight		-	-	-	-
No. of pregnant females		22	20	18	21
Dams with viable fetuses		21	20	18	21
Pre-implantation parameters (mean numbers of corpora lutea, implantation sites and percentage pre-implantation loss)		-	-	-	-
Post-implantation parameters (embryo-fetal survival and mean live litter size)		-	-	-	-
Fetal parameters (fetal weight, sex ratio, external examination, internal [visceral] body and head examination, skeletal body and head examination)		-	-	-	-

1) Group means are provided for controls and percent difference from controls are provided for treated groups. Statistical significance is based on raw data, not percent difference

- = No noteworthy findings; * = p<0.05 (Williams 2 sided), *** = p < 0.001 (Shirley 2-sided)
$AUC_{0\text{-}24}$ = area under the plasma concentration vs time curve from 0 to 24 h after dosing; C_{max} = maximum plasma concentration; CTD = Common Technical Document; GD = gestation day; GLP = Good Laboratory Practice; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; n.a. = not applicable; NOEL = No-observed-effect level; TK = toxicokinetic(s).

13. B 生殖発生毒性試験：胚・胎児発生に関する試験

Report No. T-14.015, T-18.073 and BA-18.034

Report Title: ACT-541468A – Embryo-fetal toxicity study by the oral route (gavage) in the rabbit (Segment II)

Test Article: ダリドレキサント

Design similar to ICH 4.1.3? yes

Duration of Dosing: From GD6 to GD19

Report No. T-14.015, T-18.073

Species/Strain: rabbit/New Zealand White

Day of Mating: Day 0 of gestation

Testing Facility Study No. AB20516

Initial Age: Females: 17 to 19 weeks (at mating)

Day of C-Section: Day 29 of gestation

Location in CTD: モジュール 4.2.3.5.2.6, モジュール 4.2.3.5.2.7

Special Features: none

Method of Administration: oral (gavage)

GLP Compliance: yes

Date of First Dose: [redacted], [redacted], [redacted] and [redacted] 20[redacted]

Vehicle/Formulation: aqueous suspension containing 0.5% (w/v) methylcellulose

No-observed-adverse-effect level:

F_0 Females (dams): 60 mg/kg/day

F_1 Litters: 120 mg/kg/day

Daily Dose (mg/kg/day)	**0 (Control)**	**30**	**60**	**120**
No. Animals (Dams)	22	22	22	22
Toxicokinetics				
ダリドレキサント				
$AUC_{0\text{-}24}$ [µg·h/mL]				
GD6	n.a.	2.93	8.99	30.0
GD19	n.a.	20.9	24.5	62.0
C_{max} [µg/mL]				
GD6	n.a.	0.568	1.42	2.93
GD19	n.a.	2.06	2.53	5.06

Report No. T-14.015, T-18.073 and BA-18.034 (continued)

Daily Dose (mg/kg/day)	**0 (Control)**	**30**	**60**	**120**
No. Animals (Dams)	22	22	22	22
Toxicokinetics (cont.)				
ACT-776063				
AUC_{0-24} [µg·h/mL]				
GD6	n.a.	0.650 [1)]	1.68 [1)]	6.83
GD19	n.a.	3.73	3.73	8.00
C_{max} [µg/mL]				
GD6	n.a.	0.182	0.414	0.863
GD19	n.a.	0.445	0.417	0.656
ACT-776537				
AUC_{0-24} [µg·h/mL]				
GD6	n.a.	2.68	4.78	8.67
GD19	n.a.	3.34	3.28	5.17
C_{max} [µg/mL]				
GD6	n.a.	0.338	0.499	0.749
GD19	n.a.	0.244	0.280	0.306
ACT-1016-3307				
AUC_{0-24} [µg·h/mL]				
GD6	n.a.	0.114 [2)]	0.134 [2)]	0.250 [1)]
GD19	n.a.	0.812	0.517	0.591
C_{max} [µg/mL]				
GD6	n.a.	0.0389	0.0466	0.0615
GD19	n.a.	0.0681	0.0345	0.0454
No. Died or Sacrificed Moribund	1	0	1	0
Clinical Observations				
Persistent reduced fecal output	0	0	1	2

Report No. T-14.015, T-18.073 and BA-18.034 (continued)

Daily Dose (mg/kg/day)	**0 (Control)**	**30**	**60**	**120**
No. Animals (Dams)	22	22	22	22
Body Weight and Food Consumption				
Gestation body weight gain, GD6–GD9 (%) [3)]	34.8 g	-	-	−73
Gestation body weight gain, GD9–GD13 (%) [3)]	62.1 g	-	-	−17
Gestation food consumption, GD6–GD20 (%) [3)]	164.04 g/day	-	-	−15**
Necropsy Observations (dams)	-	-	-	-
Gravid uterus weight	-	-	-	-
No. of pregnant females	18	21	19	21
Dams with viable fetuses	18	21	18	21
Pre-implantation parameters (mean numbers of corpora lutea, implantation sites and percentage pre-implantation loss)	-	-	-	-
Post-implantation parameters (embryo-fetal survival and mean live litter size)	-	-	-	-
Fetal parameters				
Mean fetal weight	-	-	-	-
Other fetal parameters (sex ratio, external examination, internal (visceral) body and head examination, skeletal body and head examination)	-	-	-	-

1) $AUC_{0\text{-}8}$
2) $AUC_{0\text{-}5}$
3) Group means are provided for controls and percent difference from controls are provided for treated groups. Statistical significance is based on raw data, not percent difference

- = No noteworthy findings; * = $p<0.05$ (Shirley 2-sided)
$AUC_{0\text{-}5}$/$AUC_{0\text{-}8}$/$AUC_{0\text{-}24}$ = area under the plasma concentration vs time curve from 0 to 5/8/24 h after dosing; C_{max} = maximum plasma concentration; CTD = common technical document; GD = gestation day; GLP = Good Laboratory Practice; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; n.a. = not applicable.

14. 生殖発生毒性試験：出生前及び出生後の発生並びに母体の機能に関する試験

Report No. T-19.005

Report Title: Pre- and postnatal development study of ACT-541468A by the oral (gavage) route in the rat (Segment III) **Test Article:** ダリドレキサント

Design similar to ICH 4.1.2?	yes	**Duration of Dosing:**	From Day 6 of gestation to Day 20 of lactation	**Report No.:**	T-19.005
Species/Strain:	Rat/Wistar: Crl; WI (Han)	**Day of Mating:**	Day 0	**Testing Facility Study No:**	20179169
Initial Age (at mating):	Approx. 9 to 12 weeks	**Method of Administration:**	oral (gavage)	**Location in CTD:**	モジュール 4.2.3.5.3.1
Date of First Dose:	[redacted] 20[redacted]	**Vehicle/Formulation:**	aqueous suspension containing 0.5% (w/v) methylcellulose	**GLP Compliance:**	yes
		Litters Culled:	culled to 4/sex/litter		

Special Features: none

No-observed-adverse-effect Level:

F_0 Females:	300 mg/kg/day
F_1 Males:	300 mg/kg/day
F_1 Females:	300 mg/kg/day

Dose (mg/kg/day)		**0**	**50**	**100**	**300**
F_0 Females:	No. of dams mated	20	20	20	20
	No. pregnant	18	20	18	20
Toxicokinetics: ダリドレキサント					
Dams (F_0)					
Lactation Day 4					
AUC_{0-24} [µg·h/mL]		n.a.	6.68	20.4	60.9
C_{max} [µg/mL]		n.a.	2.30	5.25	8.36
Lactation Day 20					
AUC_{0-24} [µg·h/mL]		n.a.	8.49	21.1	55.6
C_{max} [µg/mL]		n.a.	3.01	5.79	11.2

Report No. T-19.005 (continued)

Dose (mg/kg/day)		**0**	**50**	**100**	**300**
F_0 Females:	No. of dams mated	20	20	20	20
	No. pregnant	18	20	18	20
Toxicokinetics of daridorexant (cont.)					
Pups (F_1)					
Postnatal Day 4					
Geometric mean plasma concentration [µg/mL]		n.a.	0.019	0.049	0.058
Postnatal Day 20					
Geometric mean plasma concentration [µg/mL], M/F		n.a.	0.009/0.012	0.016/0.021	0.028/0.029
No. Died or Sacrificed Moribund (F0 females)		0	0	1	1
No. Aborted or with Total Resorption of Litter		0	0	1 (total resorption of litter)	0
Clinical Observations		-	-	-	-
Clinical Signs					
Hypersalivation, associated on occasions with abnormal foraging and/or pedaling (starting from 2nd week of treatment)		-	+	+	+
Piloerection (occasional)		-	-	-	8/20
Necropsy Observations		-	-	-	-
Body Weight and Food Consumption					
Gestation body weight, GD20		335.42 g	-	-	-
Lactation body weight, LD21		286.28 g	-	-	-
Gestation food consumption, GD6–GD20 (%) [1)]		23.62 g/day	−0.61	5.06	−6.78*
Lactation food consumption, LD1–LD21		53.19 g/day	-	-	-
Mean Duration of Gestation (days)		22.5	-	-	-
Abnormal Parturition		0	0	0	0

Report No. T-19.005 (continued)

Dose (mg/kg/day)		**0**	**50**	**100**	**300**
F_0 Females:	No. of dams mated	20	20	20	20
	No. pregnant	18	20	18	20
Birth index (%)		100	100	99.5	98.5
Viability index (%, PND 0–4)		99.5	96.5	98.5	95.0
Weaning index (%, PND 4–21)		98.6	99.3	100	100
Litters (pre-weaning)					
No. Litters Evaluated		18	20	18	20
Mean No. of Implantations		11.9	11.4	12.1	11.4
Mean No. Pups/Litter		10.9	10.1	11.2	10.2
Mean No. Liveborn Pups/Litter		10.9	10.1	11.2	10.1
No. of Litters with Stillborn Pups		0	0	1	3
Total Postnatal Survival to Day 4		196	194	198	191
Total Postnatal Loss to Day 4		1	7	3	10
Mean Postnatal Survival to Weaning		7.8	7.6	7.8	7.7
No. of Total Litter Losses		0	0	0	1
Pup weight (%) [1)]					
PND1, M		7.34 g	-	-	−4.60
PND1, F		7.08 g	-	-	+0.75
PND21, M		55.89 g	-	-	−7.50**
PND21, F		54.11 g	-	-	−6.54*
Change in pup body weights, PND 1–21, M (g)		48.54	-	-	44.69**
Change in pup body weights, PND 1–21, F (g)		47.04	-	-	43.80*
Pup Sex Ratios (% males, PND 21)		48.4	49.3	52.6	47.7
Pup Clinical Signs		-	-	-	-
Pup Reflexes and Physical Development		-	-	-	-
Pup Necropsy		-	-	-	-

Report No. T-19.005 (continued)

Dose (mg/kg/day)		**0**	**50**	**100**	**300**
F_0 Females:	No. of dams mated	20	20	20	20
	No. pregnant	18	20	18	20
F_1 males (post-weaning)					
Dose (mg/kg)		**0**	**0**	**0**	**0**
No. Evaluated Post-weaning Per Litter		20	20	20	20
No. Died or Sacrificed Moribund		0	0	0	0
Clinical Observations		-	-	-	-
Body Weight (BW) (%) [1)]					
BW at sexual maturation		248.57 g	−3.12	+4.91	−2.81
BW at start of pre-pairing, Day 2		55.42 g	-	-	−4.29
BW at end of pre-pairing, Day 56		353.45 g	-	-	−3.78
BW at end of after-pairing, Day 77		400.54 g	-	-	−4.49
Necropsy Observations		1 M (No. 209): small seminal vesicles, left testes, epididymides, prostate, and granular appearance of liver	-	-	-
Developmental variables					
Balano-preputial Skinfold Cleavage		-	-	-	-
Learning and Memory (Water Maze)		-	-	-	-
Motor Activity		-	-	-	-
Sensory Function (Auditory Startle Function)		-	-	-	-
Mating Performance					
Copulation Index (%)		-	-	-	-

Report No. T-19.005 (continued)

Dose (mg/kg/day)		**0**	**50**	**100**	**300**
F_0 Females:	No. of dams mated	20	20	20	20
	No. pregnant	18	20	18	20
F_1 females (post-weaning)					
Dose (mg/kg)		**0**	**0**	**0**	**0**
No. Evaluated Post-weaning		20	20	20	20
No. Died or Sacrificed Moribund		0	0	0	0
Clinical Observations		-	-	-	-
Body weight (BW) (%) [1)]					
BW at sexual maturation		117.86 g	-	-	−7.25
BW at start of pre-pairing, Day 2		54.83 g	-	-	−9.75***
BW at end of pre-pairing, Day 56		220.99 g	-	-	-
BW at GD13		285.99 g	-	-	-
Developmental Variables					
Vaginal Opening		-	-	-	-
Learning and Memory (Water Maze)		-	-	-	-
Motor Activity		-	-	-	-
Sensory Function (Auditory Startle Function)		-	-	-	-
Mating Performance and Fertility					
Mean No. Days Prior to Mating		-	-	-	-
No. of Females Sperm or Plug-Positive		-	-	-	-
No. of Pregnant Females		-	-	-	-
No. of not Pregnant Females		-	-	-	-
No. of Females failed to Mate		-	-	-	-
Mean No. Corpora Lutea		-	-	-	-
Mean No. Implantations		-	-	-	-
Mean No. Post-implantation Loss		-	-	-	-
Mean % Pre-implantation Loss		-	-	-	-
Mean % Post-implantation Loss		-	-	-	-

Report No. T-19.005 (continued)

Dose (mg/kg/day)		**0**	**50**	**100**	**300**
F_0 Females:	No. of dams mated	20	20	20	20
	No. pregnant	18	20	18	20
F_1 females (post-weaning) (cont.)					
Mating Performance and Fertility (cont.)					
No. of Live Embryos		-	-	-	-
Fertility Index (%)		-	-	-	-
Necropsy Observations		-	-	-	-

1) For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

- = no noteworthy findings; * = p<0.05, ** = p<0.01, *** = p<0.001 (see モジュール 4.2.3.5.3.1 for statistical methods applied)
AUC_{0-24} = area under the plasma concentration vs time curve from 0 to 24 h after dosing; C_{max} = maximum plasma concentration; CTD = common technical document; F = female; GD = gestation day; GLP = Good Laboratory Practice; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; LD = lactation day; M = male; n.a. = not applicable; PND = post natal day.

15. 新生児を用いた試験

15. A 新生児を用いた試験

Test Article: ダリドレキサント

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Report No./ Location in CTD
Rat/Han Wistar	Oral (gavage) aqueous suspension containing 0.5% methylcellulose	2 weeks, starting day 21 postpartum	0, 50, 150, 450	5M/5F (main) 4M/4F (TK satellite)	450	≥ 50: • decreased activity on Day 1 and 2 • increased urea and phosphate, decreased potassium (M) 450: • erected fur in females on Day 1 • increased GGT level • increased liver weight (abs. and rel.) • minimal diffuse follicular cell hypertrophy in thyroid gland (one male)	T-18.097/ モジュール 4.2.3.5.4.1

abs. = absolute; F = female(s); GGT = gamma glutamyl transferase; M = male(s); NOAEL = no-observed-adverse-effect level; rel. = relative; TK = toxicokinetic(s)

15. B 新生児を用いた試験

Report No. T-19.049

Report Title: ACT-541468A: A 9 week juvenile toxicity study by oral (gavage) in rats with a 4 week recovery period **Test Article:** ダリドレキサント

Species/Strain: rat/Han Wistar

Initial Age: PND 21

Date of First Dose:
Main study animals: [redacted] 20[redacted]
Recovery animals: [redacted] and [redacted] 20[redacted]
Toxicokinetic (TK) animals: [redacted] 20[redacted]
Reproductive animals: [redacted], [redacted] and [redacted] 20[redacted]

Special Features: 4 key phases:
(1) Main study,
(2) Recovery phase,
(3) Toxicokinetic Phase,
(4) Reproductive Phase

No-observed-adverse-effect Level:

Duration of Dosing: 9 weeks

Duration of Post dose: 4 weeks

Method of Administration: oral (gavage)

Vehicle/Formulation: aqueous suspension containing 0.5% (w/v) methylcellulose

Day of Mating: Day 0

450 mg/kg/day

Report No. T-19.049

Testing Facility Study No. 490314

Location in CTD: モジュール 4.2.3.5.4.2

GLP Compliance: yes

Day of C-section: GD13–GD15

Report No. T-19.049 (continued)

Daily Dose (mg/kg)	**0 (Control)**		**50**		**150**		**450**	
Number of Animals	M	F	M	F	M	F	M	F
TK animals	9	9	9	9	9	9	9	9
Toxicokinetics								
ダリドレキサント								
AUC_{last} [µg·h/mL]								
Day 1	n.a.	n.a.	10.0	10.7	65.5	47.9	132	142
Week 4 (Day 22)	n.a.	n.a.	1.87	3.69	10.8	14.7	40.2	49.0
Week 9 (Day 57)	n.a.	n.a.	2.95	4.64	16.7	15.3	49.0	57.3
C_{max} [µg/mL]								
Day 1	n.a.	n.a.	2.23	2.58	7.74	7.97	14.1	16.7
Week 4 (Day 22)	n.a.	n.a.	1.07	1.69	2.90	3.42	5.76	8.76
Week 9 (Day 57)	n.a.	n.a.	1.17	1.20	3.41	3.82	7.83	9.12
ACT-776063								
AUC_{last} [µg·h/mL]								
Week 4 (Day 22)	n.a.	n.a.	1.37	3.50	7.13	12.0	30.1	32.6
Week 9 (Day 57)	n.a.	n.a.	2.02	4.89	10.7	17.6	42.9	44.4
C_{max} [µg/mL]								
Week 4 (Day 22)	n.a.	n.a.	0.870	1.50	2.00	2.65	4.25	4.63
Week 9 (Day 57)	n.a.	n.a.	0.865	1.28	2.61	3.18	5.49	7.09
ACT-776537								
AUC_{last} [µg·h/mL]								
Week 4 (Day 22)	n.a.	n.a.	3.94	7.42	20.8	29.5	69.9	71.9
Week 9 (Day 57)	n.a.	n.a.	9.59	15.9	29.3	48.5	99.5	111
C_{max} [µg/mL]								
Week 4 (Day 22)	n.a.	n.a.	1.11	0.860	2.74	2.68	6.44	6.34
Week 9 (Day 57)	n.a.	n.a.	1.14	1.47	3.03	4.19	7.87	8.54

Report No. T-19.049 (continued)

Daily Dose (mg/kg)	**0 (Control)**		**50**		**150**		**450**	
Number of Animals	M	F	M	F	M	F	M	F
TK animals	9	9	9	9	9	9	9	9
Toxicokinetics (cont.)								
ACT-1016-3307								
AUC_{last} [µg·h/mL]								
Week 4 (Day 22)	n.a.	n.a.	0.613	0.444	2.61	2.20	9.43	7.45
Week 9 (Day 57)	n.a.	n.a.	1.03	1.07	4.30	3.49	12.4	10.9
C_{max} [µg/mL]								
Week 4 (Day 22)	n.a.	n.a.	0.256	0.0936	0.655	0.369	1.26	0.942
Week 9 (Day 57)	n.a.	n.a.	0.313	0.225	0.813	0.566	1.53	1.17

Report No. T-19.049 (continued)

Main study Recovery and Reproductive Phase – Noteworthy Findings

Daily Dose (mg/kg)	**0 (Control)**		**50**		**150**		**450**	
Number of Animals	M	F	M	F	M	F	M	F
Main animals	10	10	10	10	10	10	10	10
Recovery animals	6	6	6	6	6	6	6	6
Reproductive animals [1)]	20	20	20	20	20	20	20	20
Died or Sacrificed Moribund	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(1)[-]	-(-)[-]	-(-)[-]
Body Weight (%)	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]
Food Consumption (%)	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]
Clinical Observations	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]	-(-)[-]
Ophthalmoscopy [2)]	-(-)	-(-)	n.a.	n.a.	n.a.	n.a.	-(-)	-(-)
Detailed Functional Observations [3), 4), 7)]								
Arena Rearing (Week 8-10, dosing period)	6.2	7.9	−16.3	3.8	−18.7	−17.8	−39.0	−32.5
Functional Tests [3), 4), 7)]								
Basic Movement (overall) (Week 8-10, dosing period)	3127.3	3807.6	22.8	14.0	32.3**	29.3	44.9**	20.4
Fine Movement (overall) (Week 8-10, dosing period)	2519.6	2906.2	22.6	15.9	30.3*	29.4	45.2**	24.3
X-ambulation (overall) (Week 8-10, dosing period)	181.3	291.2	22.5	9.7	41.9**	29.9	38.7*	5.3
Y-ambulation (overall) (Week 8-10, dosing period)	441.9	642.3	26.6	7.1	43.2**	29.1	48.1**	9.4

Report No. T-19.049 (continued)

Daily Dose (mg/kg)	**0 (Control)**		**50**		**150**		**450**	
Number of Animals	M	F	M	F	M	F	M	F
Main animals	10	10	10	10	10	10	10	10
Recovery animals [5]	6	6	6	6	6	6	6	6
Hematology	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)
Coagulation	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)
Clinical Chemistry								
Gamma-glutamyl Transferase (U/L) [6]	1.5(-)	1.5(-)	-(-)	-(-)	-(-)	-(-)	4.5**(-)	12.2** (-)
Urea (mmol/L) [7]	7.40(-)	7.86(-)	-(-)	-(-)	8.02 (-)	-(-)	8.59(-)	9.70** (-)
Triglycerides (mmol/L) [6]	1.110(-)	0.507(-)	-(-)	-(-)	-(-)	0.769(-)	1.801(-)	0.899** (-)
Cholesterol (mmol/L) [7]	-(-)	2.027(-)	-(-)	-(-)	-(-)	3.031** (-)	-(-)	3.947** (-)
Total Protein (g/L) [7]	68.18(-)	69.90(-)	-(-)	-(-)	71.54*(-)	73.85** (-)	72.52** (-)	76.27** (-)
Globulin (g/L) [7]	24.75(-)	20.64(-)	-(-)	-(-)	25.95 (-)	23.40** (-)	27.68** (-)	27.48** (-)
Albumin/Globulin Ratio [7]	1.76(-)	2.40(-)	-(-)	-(-)	-(-)	-(-)	1.64 (-)	1.79** (-)
Glucose (mmol/L) [7]	9.432	-(-)	-(-)	-(-)	-(-)	-(-)	7.394** (-)	-(-)
Urinalysis	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)
Organ Weights (%) [8]								
Liver	12.6934 g (-)	6.7167 g (-)	-(-)	-(-)	6(-)	33* [6] (-)	31** [7] (-)	101** [6] (-)
Thyroid	-(-)	0.01620 g (-)	-(-)	-(-)	-(-)	-(-)	-(-)	36** [7] (-)
Gross Pathology	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	Liver: Prominent lobular architecture (1 animal) +

Report No. T-19.049 (continued)

Daily Dose (mg/kg)	**0 (Control)**		**50**		**150**		**450**	
Number of Animals	M	F	M	F	M	F	M	F
Main animals	10	10	10	10	10	10	10	10
Recovery animals [5)]	6	6	6	6	6	6	6	6
Histopathology								
Liver: Hypertrophy, Hepatocellular	0(-)	0(0)	-(-)	-(-)	-(-)	-(-)	7(-)	10(1)
Minimal	0(-)	0(0)	-(-)	-(-)	-(-)	-(-)	7(-)	8(1)
Mild	0(-)	0(0)	-(-)	-(-)	-(-)	-(-)	0(-)	2(0)
Thyroid Gland: Hypertrophy Follicular cell, Diffuse	0(0)	0(-)	-(-)	-(-)	2(-)	1(-)	5(2)	8(-)
Minimal	0(0)	0(-)	-(-)	-(-)	2(-)	1(-)	2(2)	8(-)
Mild	0(0)	0(-)	-(-)	-(-)	0(-)	0(-)	3(0)	0(-)
Bone Measurement								
Tibia	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)
Femur	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)
Bone Densitometry								
Femur Metaphysis	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)
Femur Diaphysis	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)	-(-)

Report No. T-19.049 (continued)

Reproductive Phase

Dose (mg/kg/day)	**0 (Control)**		**50**		**150**		**450**	
Number of Animals	M	F	M	F	M	F	M	F
Reproductive animals	20	20	20	20	20	20	20	20
Sexual Maturation								
Vaginal openings	n.a.	-	n.a.	-	n.a.	-	n.a.	-
Preputial Separation	-	n.a.	-	n.a.	-	n.a.	-	n.a.
Mating Performance and Fertility								
Mean No. Days Prior to Mating	-	-	-	-	-	-	-	-
No. of Males that Mated	-	n.a.	-	n.a.	-	n.a.	-	n.a.
No. of Fertile Males	-	n.a.	-	n.a.	-	n.a.	-	n.a.
Mean No. Estrous Cycles	n.a.	-	n.a.	-	n.a.	-	n.a.	-
No. of Females Sperm Positive	n.a.	-	n.a.	-	n.a.	-	n.a.	-
No. of Pregnant Females	n.a.	-	n.a.	-	n.a.	-	n.a.	-
Ovarian and Uterine Examinations								
No. Aborted or with Total Resorption of Litter	n.a.	-	n.a.	-	n.a.	-	n.a.	-
Mean No. Corpora Lutea	n.a.	-	n.a.	-	n.a.	-	n.a.	-
Mean No. Implantations	n.a.	-	n.a.	-	n.a.	-	n.a.	-
Mean % Pre-implantation Loss	n.a.	-	n.a.	-	n.a.	-	n.a.	-
Mean No. Live Conceptuses	n.a.	-	n.a.	-	n.a.	-	n.a.	-
Mean No. Resorptions	n.a.	-	n.a.	-	n.a.	-	n.a.	-
No. Dead Conceptuses	n.a.	-	n.a.	-	n.a.	-	n.a.	-
Mean % Post implantation Loss	n.a.	-	n.a.	-	n.a.	-	n.a.	-
Gravid Uterus Weights	n.a.	-	n.a.	-	n.a.	-	n.a.	-

Report No. T-19.049 (continued)

Reproductive Phase

Dose (mg/kg/day)	**0 (Control)**		**50**		**150**		**450**	
Number of Animals	M	F	M	F	M	F	M	F
Reproductive animals	20	20	20	20	20	20	20	20
Computer Aided Sperm Assessment (CASA)								
CASA: Cauda Epididymis	-	n.a.	-	n.a.	-	n.a.	-	n.a.
Spermatid Counts: Testis	-	n.a.	-	n.a.	-	n.a.	-	n.a.
Sperm Counts: Cauda Epididymis	-	n.a.	-	n.a.	-	n.a.	-	n.a.
Sperm Morphology: Cauda Epididymis	-	n.a.	-	n.a.	-	n.a.	-	n.a.

1) Animal 5001M replaced reproductive animal 4316M (Group 4, 450 mg/kg/day) and was dosed from PND 23. Animal 4316M was found dead on Day 2
2) Parameter not assessed in reproductive phase animals
3) Main study and reproductive phase animals (first 10 of 20 reproductive animals per sex per group selected)
4) For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
5) Clinical pathology samples collected at the end of treatment period for main study group and at the end of recovery period for the recovery group
6) Kruskal-Walis and Dunn tests
7) Anova & Dunnett tests
8) Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights.

- = No noteworthy findings; ( ) = recovery animals; [ ] = reproductive animals; * = $p \leq 0.05$; ** = $p \leq 0.01$
AUC_{last} = area under the plasma concentration vs time curve from 0 to the last available measurement; C_{max} = maximum plasma concentration; CTD = common technical document; F = female; GD = gestation day; GLP = Good Laboratory Practice; M = male; n.a. = not applicable; PND = post natal day; TK = toxicokinetic(s).

16. 局所刺激性試験

Test Article: ダリドレキサント

局所刺激性試験は実施しなかった

17. その他の毒性試験

Test Article: ダリドレキサント

Test System or Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
***In vitro* cytotoxicity**						
Primary cultured human and murine hepatocytes	*In vitro*	n.a.	3, 10, 30, 50, 100, 300 µM	n.a.	Not cytotoxic ≤ 50 µM Cytotoxic ≥ 100 µM	T-16.030/ モジュール 4.2.3.7.7.4
***In vitro* phototoxicity**						
Mouse/ Balb/c 3T3 fibroblasts	*In vitro*	n.a.	≤ 62.50 µg/mL with and without irradiation	n.a.	Photo-irritancy factor of 1.21	T-14.009/ モジュール 4.2.3.7.7.5
Mechanistic Studies						
Recombinant CHO cells expressing TRPV1	*In vitro*	n.a.	3.0–60 µM	n.a.	Weak agonistic activity on TRPV1 receptor, which cannot account for the decrease of body temperature observed at high doses of daridorexant in rats	T-14.052/ モジュール 4.2.3.7.3.1

Test Article: ダリドレキサント

Test System or Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
Rat RccHan: WIST (F only)	Oral (gavage)	1 day	Phase 1 0, 100, 300, 1000 Phase 2 0, 1000 + 3 mg/kg s.c. atropine	Phase 1 10F (dose groups), 5F (vehicle) Phase 2 5F	≥ 100: • Decreased body core temperature, heart rate, and respiratory rate ≥ 300: • Increased mean arterial pressure and decreased locomotor activity 1000: • ECG: increased number of pauses • Response to atropine.: increased heart rate and mortality (2/5 sacrificed in moribund condition) NOAEL: 300 mg/kg	T-14.060/ モジュール 4.2.3.7.3.2

Test Article: ダリドレキサント

Test System or Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
Rat RccHan: WIST (F only)	Oral (gavage)	4 weeks	0, 1000	10F (dose group), 5F (vehicle)	1000: • Mortality: 2F: 3 and 18 h after 2nd administration. Body weight loss, severe hypoactivity, ruffled fur. Core body temperature down to ≈ 32°C (approx. –5°C), heart rate down to ≈ 230 bpm (–170 bpm), ↑ number of pauses (1/2F), respiration rate transiently increased. • Clinical signs: Reduced cage activity, distended abdomen, ruffled fur (slight), increased salivation and rooting. • Body weight: ↓ after 1st administration; ↑ subsequently (+9% on Day 27) • Food consumption: ↓ Days 1–4 (–30%); ↑ from Day 5 onwards (+12% in average) • Blood pressure: ↑ on Days 1–2 (max +13 mmHg on Day 1), slight ↓ on Days 2–19 (max −13 mmHg), normalized subsequently • ECG: increased number of pauses • Decreased heart rate, respiratory rate and body core temperature • Increased relative weight of liver (+107%) and thyroid (+57%) • Stomach enlarged by material and liver enlarged • Liver: periportal tinctorial change, hepatocyte hypertrophy • Thyroid: colloid depletion with follicular hypertrophy	T-14.064/ モジュール 4.2.3.7.3.3

Test Article: ダリドレキサント

Test System or Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
Rat RccHan: WIST (F only)	Oral (gavage)	1 day	0, 1000 (pos. controls atropine: 3 mg/kg i.p.; neostigmine, 30 mg/kg p.o.)	8F	1000: • increased stomach content (+111%) and slightly decreased small intestinal transit (−6%) compared to vehicle Positive controls showed changes in small intestinal transit as expected (–17% for atropine and +31% for neostigmine compared to vehicle).	B-14.060/ モジュール 4.2.3.7.3.4
Morphometry of hepatocytes from study (モジュール 4.2.3.2.11)		n.a.	n.a.	n.a.	A moderate enlargement of hepatocytes is the cause for the increased liver weight recorded in the 39-week repeat-dose toxicity study in Beagle dogs.	T-17.043/ モジュール 4.2.3.7.3.5

Test Article: ダリドレキサント

Test System or Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
Exploratory tolerability studies						
Mouse/ Crl:CD1 (ICR)	Oral (gavage)	2 weeks	0, 100, 300, 1000	9M/9F (main) 18M/18F (TK)	≥ 100: • up to moderate hepatocellular necrosis, frequently accompanied by granulocytic inflammatory cell infiltrates • hepatocellular hypertrophy (M) ≥ 300: • increase in triglyceride, AST and ALT, and decrease in total bilirubin • increased liver weight • hepatocellular hypertrophy (F) 1000: • found dead on Day 13 (1M) • increased body weight gain • increased food intake (M) • increased cholesterol, plasma protein and globulin concentrations • mottled liver surface NOAEL: not defined	T-15.074/ モジュール 4.2.3.7.7.1

Test Article: ダリドレキサント

Test System or Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
Mouse/ Crl:CD1 (ICR)	Oral (gavage)	2 weeks	0, 1000, 2000 (as 1000 b.i.d; 1000 on Days 1–4, 2000 from Day 5 on)	7M/7F (1000) 3M/3F (2000) 5M/5F (vehicle)	≥ 1000: • increased body weight gain • decreased bilirubin and increased cholesterol • hepatocellular hypertrophy 2000: • increased ALT, AST, and GLDH activities • focal liver necrosis NOAEL: 1000 mg/kg	T-16.054/ モジュール 4.2.3.7.7.2

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Test System or Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
Mouse/ B6C3F1 CrlBR	Oral (gavage)	2 weeks	0, 100, 300, 1000 (Day 1)/ 600 (from Day 2 on)	9M/9F (main) 12M/12F (TK)	≥ 100: • dose-dependent increase in liver weight (absolute and relative) • centrilobular to diffuse hepatocellular hypertrophy ≥ 300: • increased globulin, cholesterol, triglyceride levels and decreased total bilirubin levels 600: • transient clinical signs (decreased activity, partly closed eyes, cold to touch) after the first administration (F) 1000 (actual dose based on formulation analysis: 1200) • Day 1: decreased activity, partly closed eyes, low body temperature (TK animals); one TK female sacrificed in extremis on Day 1 due to convulsions and a body temperature at 29.4°C. NOAEL: 600 mg/kg AUC_{last} was 9490 ng·h/mL (males) and 2920 ng·h/mL (females) on Day 14 at the NOAEL	T-16.019/ モジュール 4.2.3.7.7.3
Rat/ Crl:CD(SD) Sprague	Oral (gavage)	Food shaping: up to 2 sessions (days)	n.a.	12F	Drug discrimination training (DDT) with suvorexant Interoceptive stimulus induced by suvorexant in rats at the tested doses and pre-treatment times was not sufficiently strong to be clearly discriminated from the vehicle.	T-18.033/ モジュール 4.2.3.7.4.1

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Test System or Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
Dawley (F only)		DDT phase 1: 23 sessions (days) DDT phase 2: 29 sessions (days) DDT phase 3: 29 sessions (days)	Suvorexant: 0, 30 Suvorexant: 0, 100 Suvorexant: 0, 100		Plasma concentrations provided robust pharmacological effects in animals and were in the range of 0.5- to 3.5-fold of the human C_{max} at an efficacious dose.	
Rat/ Crl:CD(SD) Sprague Dawley (F only)	Oral (gavage)	up to 48 sessions (days)	Zolpidem: 0, 3	12F	Drug discrimination training with zolpidem 11/12 rats were successfully trained to discriminate zolpidem from vehicle and were then transferred to study T-18.065 for generalization testing of daridorexant	T-18.035/ モジュール 4.2.3.7.4.2

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Test System or Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
Rat/ Crl:CD(SD) Sprague Dawley (F only)	Oral (gavage)	Daridorexant generalization phase (daridorexant dosing): 1 day per dose level in a cross-over design (4 treatment days in total)	Daridorexant: 0, 15, 30, 60 Zolpidem: 0, 3 (maintenance training); 0.3, 0.56, 1, 1.8 (generalization testing)	11F	Assessment of stimulus generalization to zolpidem in a two-choice drug discrimination paradigm In rats trained to discriminate 3 mg/kg zolpidem from vehicle, there was no similarity between the discriminative cue of zolpidem and the potential discriminative cue induced by daridorexant at any tested dose level. Thus, daridorexant did not generalize to zolpidem. Rats were tested at daridorexant plasma concentrations, which were around the C_{max} (653, 1750, and 1990 ng/mL at 15, 30, 60 mg/kg, respectively), which was 0.65-, 1.74-, 1.98-fold the human C_{max}, respectively.	T-18.065/ モジュール 4.2.3.7.4.3
Rat/ Crl:CD(SD) Sprague Dawley (F only)	i.v. (catheter implant)	Max. 2 h (with up to 25 infusions) in 6 substitution test sessions (1 per day) per animal	Daridorexant: 0, 0.1, 0.3, 1 Cocaine: 0.8	68F (at study start) 38F (used for substitution phase)	Assessment of reinforcing properties in a cocaine self-administration substitution procedure Daridorexant at all tested dose levels did not support self-administration in rats trained to self-administer cocaine (0.8 mg/kg). Daridorexant plasma ranged 33.2–2660 ng/mL after the first substitution session and ranged 18.2–1010 ng/mL after the last substitution session.	T-17.046/ モジュール 4.2.3.7.4.4

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Test System or Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
Rat/ Crl:CD(SD) Sprague Dawley (F only)	i.v. (catheter implant)	2.2 sec (occasion 1)-2 h (in one, 5 or 25 infusions on day 1, 15, and 22, respectively)	0.4, 1, 2	3F	Pharmacokinetics study to T-17.046 The average C_{max} values (geometric mean) at 0.4, 1 and 2 mg/kg per infusion were: • 353, 910, and 738 ng/mL on dosing occasion 1, • 219, 637, and 1210 ng/mL on dosing occasion 2 and • 711, 4000, and 7940 ng/mL on dosing occasion 3, respectively. The average AUC_{last} values at 0.4, 1 and 2 mg/kg/infusion were: • 136, 393, and 296 ng·h/mL on dosing occasion 1, • 124, 384, and 637 ng·h/mL on dosing occasion 2, • 484, 3950, and 11,600 ng·h/mL on dosing occasion 3, respectively. Although a t_{max} of 0.20 h was observed in some animals, t_{max} median values were calculated at 0.03 h after the last infusion in all occasions, regardless of the number of infusions given.	T-18.066/ モジュール 4.2.3.7.4.5

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Test System or Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
Rat/ Crl:CD(SD) Sprague Dawley (F only)	Oral (gavage)	4 weeks	Daridorexant: 0, 20, 200 Chlordiaz-epoxide (positive control): 10-200	10F	Assessment of spontaneous withdrawal ≥ 20: • slight reduction in body temperature, rearing time, total distance travelled and vertical activity, as well as an increase of time spent in the margin area 200: • slight decrease in body weight upon discontinuation of treatment The abrupt discontinuation of daridorexant treatment at all doses tested did not induce any changes of physiological, neurobehavioral, or locomotor activity parameters consistent with the development of a withdrawal syndrome. C_{max} values of ~499 ng/mL and ~2920 ng/mL were achieved at the end of the treatment phase, which is approximately 0.5-fold and 2.9-fold above the human efficacious C_{max} of 1006 ng/mL after a 50 mg dose (4.65-fold and 27-fold above the human efficacious C_{max} when considering the free fractions), respectively.	T-17.048/ モジュール 4.2.3.7.4.6

Test article: 不純物1*

Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)/ Concentration	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
S. typhimurium	*In vitro*	n.a.	≤5000 µg/plate	n.a.	Mutagenic	T-13.155/ モジュール 4.2.3.7.6.1

Test article: 不純物5*

Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)/ Concentration	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
S. typhimurium	*In vitro*	n.a.	≤5000 µg/plate	n.a.	Not mutagenic	T-13.156/ モジュール 4.2.3.7.6.2

Test article: 不純物4*

Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)/ Concentration	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
S. typhimurium	*In vitro*	n.a.	≤5000 µg/plate	n.a.	Not mutagenic	T-13.157/ モジュール 4.2.3.7.6.3

Test article: 不純物3*

Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)/ Concentration	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
S. typhimurium	*In vitro*	n.a.	≤ 5000 µg/plate	n.a.	Mutagenic	T-13.158/ モジュール 4.2.3.7.6.4

＊新薬承認情報提供時に置き換え

Test article: 不純物6*

Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)/ Concentration	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
S. typhimurium	*In vitro*	n.a.	≤ 5000 µg/plate	n.a.	Not mutagenic	T-13.159/ モジュール 4.2.3.7.6.5

Test article: 不純物2*

Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)/ Concentration	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
S. typhimurium	*In vitro*	n.a.	≤ 5000 µg/plate	n.a.	Mutagenic	T-13.160/ モジュール 4.2.3.7.6.6

Test article: 不純物7*

Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)/ Concentration	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
S. typhimurium	*In vitro*	n.a.	≤5000 µg/plate	n.a.	Not mutagenic	T-15.065/ モジュール 4.2.3.7.6.7

Test article: 不純物8*

Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)/ Concentration	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
S. typhimurium	*In vitro*	n.a.	≤ 5000 µg/plate	n.a.	Not mutagenic	T-20.004/ モジュール 4.2.3.7.6.9

＊新薬承認情報提供時に置き換え

Test article: ACT-699581A

Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)/ Concentration	Sex and No. per Group	Noteworthy Findings	Report No./ Location in CTD
Genotoxicity - Ames test						
S. typhimurium	*In vitro*	n.a.	≤ 5000 µg/plate	n.a.	Not mutagenic	T-18.087/ モジュール 4.2.3.7.6.8
Genotoxicity - Chromosome aberration test						
Human lymphocytes	*In vitro*	n.a.	≤ 530 µg/mL	4 and 22 h (without S9) 4 h (with S9)	Not clastogenic	T-18.088/ モジュール 4.2.3.7.6.10
Repeat-dose toxicity study						
Rat/ Wistar Han: Crl:WI	Oral (gavage)	4 weeks	0, 0.01, 0.05, 0.15	Main: 10M/10F TK: 6M/6F (0, 0.15), 3M/3F (0.01, 0.05)	NOEL: 0.15 mg/kg/day	T-18.085/ モジュール 4.2.3.7.6.11

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC_{last} = area under the plasma concentration vs time curve from 0 to the last available measurement; b.i.d = twice daily; bpm = beats per minute; C_{max} = maximum plasma concentration; DDT = drug discrimination training; ECG = electrocardiogram; F = female; GLDH = glutamate dehydrogenase; i.p. = intra peritoneal; i.v. = intravenous; M = male; n.a. = not applicable; NOAEL = no-observed-adverse-effect level; NOEL = no-observed-effect level; p.o. = oral(ly); s.c. = subcutaneous(ly); TK = toxicokinetic(s); t_{max} = time to reach maximum plasma concentration; TRPV1 = transient receptor potential cation channel subfamily V member 1.