Daily Dose (mg/kg):	**0 (Control 1)**		**0 (Control 2)**		**10**	**30**		**100**		**300**
Number of Animals:	**M: 60**	**F: 60**	**M: 60**	**F: 60**	**F: 60**	**M: 60**	**F: 60**	**M: 60**	**F: 60**	**M: 60**
Week 1 to Terminal Sacrifice	15	15	18	17	7	13	9	20	9	17
Terminal Sacrifice	45	45	42	43	57	47	41	40	51	43
Survival Rate (%)	75.0	75.0	70.0	71.7	88.3^{+}	78.3	85.0	66.7	85.0	71.7
Cause of Death/Moribundity										
Neoplastic Lesion	11	8	12	11	4	9	6	12	8	9
Non-neoplastic Lesion	0	0	1	0	1	2	0	2	0	3
Humane Reason	1	5	2	6	2	2	2	4	1	5
Accidental/Gavage Error	0	2	1	0	0	0	0	1	0	0
Unclear	3	0	2	0	0	0	1	1	0	0
Body Weight (g)										
Week 1 (Day 1)	168.5	124.8	169.8	123.7	123.1	167.8	122.7	169.1	123.5	169.5
Week 26 (Day 176)	485.3	264.0	473.2	253.2	254.8	476.1	262.3	494.3^{D**}	254.4	474.7
Weeks 53 (Day 365)	520.2	266.9	493.5	255.6	260.1	508.5	262.1	521.5^{S**}	255.9	482.7^{S**}
Weeks 79 (Day 547)	538.6	267.8	506.1	254.9	261.5	526.3	259.4	540.8^{S*}	256.0	484.7^{S**}
Weeks 104 (Day 728)	516.6	271.7	488.2	253.9	263.2	510.4	263.5	506.2	254.4	449.2^{D**}
Food Consumption	—	—	—	—	—	—	—	—	—	—
Tumor incidence										
No. of tumors	51	83	50	75	54	35	36	48	52	50
No. of benign tumors	39	56	40	48	37	27	23	33	34	35
No. of malignant tumors	12	27	10	27	17	8	13	15	18	15
No. of tumor bearing animals	40	47	38	47	40	31	28	40	36	38
Noteworthy Findings:										
Clinical signs (No. of animals observed)										
Discoloration of the teeth	0	0	0	0	11	32	27	60	60	60

Daily Dose (mg/kg):	0 (Control 1)		0 (Control 2)		10	30		100		300
Number of Animals:	**M: 60**	**F: 60**	**M: 60**	**F: 60**	**F: 60**	**M: 60**	**F: 60**	**M: 60**	**F: 60**	**M: 60**
Broken teeth	2	2	2	2	3	6	4	4	2	16
Swelling of limbs	5	0	3	2	1	10	1	8	1	17
Crust on tail	0	7	2	7	19	2	22	1	23	2
Hard thickening of foot pad	14	1	16	1	1	17	1	20	6	28
Clonic convulsion[a]	7	11	13	14	11	27	11	6	5	6
Histopathology										
Number of Animals with Neoplastic Lesions										
Liver										
Hepatocellular adenoma	2	0	0	2	0	0	0	0	1	0
Cholangioma	0	0	0	0	0	0	0	0	0	1
Hepatocellular carcinoma	0	1	0	0	0	0	0	0	0	0
Spleen										
Hemangiosarcoma	0	0	1	0	0	0	0	0	0	1
Heart										
Schwannoma, endocardial	0	0	1	0	1	0	0	0	1	1
Lung										
Adenoma, bronchiolo-alveolar	1	0	0	0	0	0	0	0	0	0
Squamous cell carcinoma	0	0	1	0	0	0	0	0	0	0
Thymus										
Thymoma	0	0	0	0	0	0	0	0	1	0
Malignant thymoma	0	0	1	0	0	0	0	0	0	0
Squamous cell carcinoma	0	0	0	0	0	0	1	0	0	0
Mesenteric lymph node										
Hemangiosarcoma	0	0	0	0	0	0	0	0	0	1

Daily Dose (mg/kg):	0 (Control 1)		0 (Control 2)		10	30		100		300
Number of Animals:	M: 60	F: 60	M: 60	F: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60
Hematopoietic and lymphatic organs										
Malignant lymphoma	3	2	1	2	0	1	0	2	1	1
Histiocytic sarcoma	1	2	0	1	0	1	0	0	2	3
Adrenals										
Pheochromocytoma	6	1	6	1	1	7	1	5	1	2
Cortical adenoma	0	1	1	0	0	1	0	0	1	1
Malignant pheochromocytoma	1	0	0	3	0	1	0	1	0	1
Cortical carcinoma	0	0	0	0	0	0	0	0	0	1
Pituitary										
Adenoma, pars distalis	12	22	13	19	18	14	20	13	7	14
Adenoma, pars intermedia	1	1	0	0	0	0	0	0	0	0
Adenocarcinoma, pars distalis	3	11	4	12	8	4	5	6	4	3
Thyroid										
C-cell adenoma	5	2	5	3	1	0	3	4	3	1
Follicular cell adenoma	0	0	0	1	0	0	0	1	0	1
C-cell carcinoma	0	0	0	1	0	0	0	0	0	0
Parathyroid										
Adenoma	0	0	1	0	0	0	0	0	0	0
Pancreas										
Islet-cell adenoma	4	0	4	1	0	0	0	1	0	4
Stomach										
Squamous cell papilloma	0	0	0	0	0	1	0	0	0	0
Lipoma	0	0	0	0	0	0	0	0	1	0
Leiomyosarcoma	1	0	0	0	0	0	0	0	0	0
Ileum										

Daily Dose (mg/kg):	0 (Control 1)		0 (Control 2)		10	30		100		300
Number of Animals:	M: 60	F: 60	M: 60	F: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60
Adenocarcinoma	0	0	0	0	0	0	0	1	0	0
Rectum										
Adenoma	0	0	0	0	0	0	1	0	0	0
Urinary bladder										
Papilloma	0	0	0	1	0	0	0	0	0	0
Coagulating gland										
Adenocarcinoma	1	NA	0	NA	NA	0	NA	0	NA	0
Prostate										
Adenoma	0	NA	0	NA	NA	0	NA	1	NA	0
Testes										
Hemangioma	1	NA	0	NA	NA	0	NA	0	NA	0
Interstitial cell adenoma	1	NA	1	NA	NA	0	NA	0	NA	1
Malignant seminoma	0	NA	0	NA	NA	0	NA	0	NA	1
Uterus										
Leiomyoma	NA	1	NA	0	0	NA	0	NA	0	NA
Granular cell tumor	NA	1	NA	0	0	NA	0	NA	0	NA
Endometrial stromal polyp	NA	6	NA	2	2	NA	1	NA	4	NA
Endometrial stromal sarcoma	NA	1	NA	0	0	NA	2	NA	0	NA
Endometrial adenocarcinoma	NA	1	NA	1	0	NA	0	NA	0	NA
Vagina										
Vaginal polyp	NA	0	NA	1	2	NA	0	NA	0	NA
Squamous cell carcinoma	NA	0	NA	0	0	NA	1	NA	0	NA
Stromal sarcoma	NA	0	NA	0	0	NA	0	NA	1	NA
Ovaries										
Luteoma	NA	0	NA	0	0	NA	0	NA	1	NA

Daily Dose (mg/kg):	0 (Control 1)		0 (Control 2)		10	30		100		300
Number of Animals:	M: 60	F: 60	M: 60	F: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60
Brain										
Astrocytoma	0	0	2	0	0	1	1	1	0	2
Oligodendroglioma	0	0	0	0	0	0	0	0	0	1
Granular cell tumor	0	0	0	0	0	0	0	1	0	0
Malignant meningioma	0	0	0	0	1	0	0	0	0	0
Spinal cord										
Astrocytoma	0	1	0	0	0	0	0	0	0	0
Skin										
Keratoacanthoma	2	0	4	1	1	0	0	1	0	2
Squamous cell papilloma	0	0	0	1	0	1	0	1	1	1
Basal cell tumor	0	0	0	0	0	0	0	0	0	1
Basal cell carcinoma	0	0	0	0	1	0	0	1	0	0
Squamous cell carcinoma	0	0	0	0	0	0	1	1	0	0
Mammary gland										
Adenoma	0	5	0	2	1	0	1	0	0	0
Fibroadenoma	0	15	0	10	6	1	9	0	2	0
Adenocarcinoma	0	8	0	7	6	0	6	1	3	0
Eyes										
Malignant melanoma	0	0	0	0	0	0	1	0	0	0
Harderian gland										
Adenocarcinoma	1	0	0	0	0	0	0	0	0	0
Tail										
Fibroma	1	0	0	0	0	0	0	0	0	0
Squamous cell papilloma	0	0	0	0	0	0	0	1	0	0
Fibrosarcoma	0	0	0	0	0	0	0	0	0	1

Daily Dose (mg/kg):	0 (Control 1)		0 (Control 2)		10	30		100		300
Number of Animals:	M: 60	F: 60	M: 60	F: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60
Subcutis										
Fibroma	2	0	3	2	0	0	0	3	0	2
Lipoma	0	0	0	1	1	1	0	0	0	0
Leiomyoma	0	0	0	0	1	0	0	0	0	0
Rhabdomyosarcoma	0	1	0	0	0	0	0	0	0	0
Liposarcoma	0	0	0	0	0	0	0	0	1	0
Fibrosarcoma	0	0	0	0	0	0	0	2	0	0
Abdominal cavity										
Liposarcoma	0	0	0	0	0	1	0	0	0	0
Malignant mesothelioma	0	0	0	0	1	0	0	0	0	0
Ears										
Squamous cell papilloma	1	0	0	0	0	0	0	0	0	1
Skeletal muscle										
Rhabdomyosarcoma	1	0	0	0	0	0	0	0	0	0
Trigeminal ganglion										
Malignant schwannoma	0	0	0	0	0	0	0	0	0	1
Other bone										
Osteosarcoma	0	0	1	0	0	0	0	0	0	0
Number of Animals with Non-Neoplastic Lesions										
Liver										
Hypertrophy, hepatocytes, centrilobular	0	0	0	0	0	0	2	12	11	38
Altered cell foci, tigroid, basophilic	12	18	9	11	14	6	19	13	13	24
Angiectasis	2	3	2	2	5	2	1	4	4	5
Cystic degeneration, focal	0	0	1	0	0	2	0	4	0	9

Daily Dose (mg/kg):	0 (Control 1)		0 (Control 2)		10	30		100		300
Number of Animals:	M: 60	F: 60	M: 60	F: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60
Seminal vesicles										
Atrophy	0	NA	3	NA	NA	2	NA	6	NA	16
Coagulating glands										
Atrophy	0	NA	2	NA	NA	0	NA	5	NA	10
Prostate										
Atrophy	11	NA	15	NA	NA	6	NA	11	NA	15
Mammary gland										
Atrophy, lobule	44	0	38	0	0	39	0	42	0	49
Sternum										
Pigmentation	0	0	0	0	8	50	24	51	54	48
Femur										
Pigmentation	0	0	0	0	50	30	58	51	53	52
Osteofluorosis	0	0	0	0	0	0	0	0	0	1
Paw										
Pigmentation	0	0	0	0	0	0	0	0	0	7
Osteofluorosis	0	0	0	0	0	0	0	0	0	10
Tail										
Osteofluorosis	0	0	0	0	0	0	0	0	0	2
Abscess/folliculitis	9	9	9	4	2	7	6	9	4	19
Necrosis	0	6	2	10	15	2	19	1	20	2
Limb										
Ulcer, plantar	14	1	17	2	1	18	1	19	6	28
Incisor										
Degeneration, ameloblasts	0	0	0	0	0	0	0	2	5	38
Pigmentation, dentin	0	0	0	0	0	2	0	17	5	49

Daily Dose (mg/kg):	0 (Control 1)		0 (Control 2)		10	30		100		300
Number of Animals:	M: 60	F: 60	M: 60	F: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60
Alveolar bone										
Pigmentation	0	0	0	0	0	3	1	14	2	49
Eye										
Retinal atrophy	42	53	36	48	54	41	54	39	46	44

—: No noteworthy findings.

$AUC_{(0\text{-}24)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, F = female, GLP =Good Laboratory Practice, M = male, MC = methylcellulose, NA = not applicable.

a: Clonic convulsions were observed in rats of all dose groups including controls starting from Day 113, although similar findings were not observed in the chronic 26-week rat study in which rats were observed up to Day 185. The frequency at 30 mg/kg in males, but not females, was higher than other groups. The convulsion usually ceased within 30 seconds and was often triggered by some external stimuli, eg, when the cage was moved or the animal was held for a procedure such as dosing or general observation. There was no dose-dependency in the incidence, and the nature of the findings was similar between all groups including controls. The clonic convulsions observed in this study were consistent with spontaneous convulsions known to occur in long-term studies in rats (Satomoto, 2012).

$^{+}P<0.05$ (log-rank test), $^{D}*P<0.05$, $^{D}**P<0.01$ (Dunnett's test), $^{S}*P<0.05$, $^{S}**P<0.01$ (Steel's test).

2.6.7.10.B　　**Test Article: lemborexant**

Report Title: **E2006: A 26-Week Oral Carcinogenicity Study in CB6F1-Tg rasH2 Mice**		Study No. K15016
Species / Strain: Mouse / CB6F1-Tg rasH2	Duration of Dosing: 26-week	Location in CTD: 4.2.3.4.2.1
Initial Age: 8 weeks old	Method of Administration: Oral gavage	GLP Compliance: Yes
Date of First Dose: [redacted] 20[redacted]	Treatment of Controls: Vehicle	
Vehicle / Formulation: 1 mol/L HCl: 0.5% MC solution (1:4, v/v) / suspension		
Basis for High Dose Selection: Toxicity-based endpoint		
Special Features: This study included a positive control group (15 mice / sex). The animals in the positive control group received a single intraperitoneal injection of *N*-nitroso-*N*-methylurea (MNU) at 75 mg/kg on Day 1 and were subjected to necropsy on Day 134 (males) or Day 154 (females) when more than half of animals died or became moribund. Histopathology findings related to death or moribundity included high incidences of malignant lymphoma and squamous cell carcinoma/papilloma in the forestomach or skin; these are typical neoplasms induced by MNU or commonly seen in Tg rasH2 mice.		

Daily Dose (mg/kg):	**0 (Control)**		**50**		**150**		**500**	
Number of Animals:	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**
Died/Sacrificed Moribund	1	0	0	2	0	2	2	0
Terminal sacrifice	24	25	25	23	25	23	23	25
Survival Rate (%)	96	100	100	92	100	92	92	100
Body weight (g) Day 182	29.0	23.5	30.7*	24.3	31.0**	24.3	30.9**	25.1##
Food consumption	—	—	—	—	—	—	—	—
Clinical sign (No. of animals observed)								
Discoloration of teeth	0	0	0	0	23	22	23	25
Number of Animals with Neoplasmic Lesions								
Spleen								

Daily Dose (mg/kg):	0 (Control)		50		150		500	
Number of Animals:	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**
Hemangiosarcoma	0	1	0	1	0	0	3^{+}	2
Testes								
Hemangiosarcoma	0	NA	0	NA	0	NA	1	NA
Subcutis								
Hemangiosarcoma	NA	NA	NA	NA	NA	1	NA	NA
Vertebra								
Hemangiosarcoma	NA	NA	NA	NA	NA	1	NA	NA
Adipose tissue								
HemangiomaNA	NA	NA	NA	NA	NA	1	NA	NA
Ileum								
Hemangioma	0	0	1	0	0	0	0	0
Submaxillary lymph node								
Hemangioma	0	0	1	0	0	0	0	0
Combined all examined tissue/organs								
Hemangiosarcoma	0	1	0	1	0	2	4^{+}	2
Hemangioma	0	0	2	0	0	1	0	0
Lung								
Bronchiolo-alveolar adenoma	1	0	0	0	0	0	0	0
Bronchiolo-alveolar carcinoma	1	0	1	0	0	0	0	0
Hematopoietic/lymphatic organs								
Malignant lymphoma	0	0	0	0	0	0	0	1

Daily Dose (mg/kg):	0 (Control)		50		150		500	
Number of Animals:	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**
Skin								
Papilloma	0	0	1	0	0	0	0	0
Stomach								
Papilloma	0	0	0	0	0	0	1	0
Thymus								
Thymoma	0	1	0	0	0	0	0	0
Number of Animals with Non-neoplastic Lesions								
Liver								
Hypertrophy, hepatocytes, centrilobular	0	0	0	0	0	0	8	10
Subcapsular degeneration/necrosis, hepatocytes	0	0	0	0	0	0	1	1
Femur								
Pigmentation	0	0	0	0	0	4	0	3

—: No noteworthy findings.

CTD = Common Technical Document, F = female, GLP =Good Laboratory Practice, M = male, MC = methylcellulose, MNU = *N*-nitroso-*N*-methylurea , NA = not applicable, Tg = transgenic.

* $P<0.05$, ** $P<0.01$ (Dunnett's rank test), $^{\#\#}$ $P<0.01$ (Dunnett's test), $^{+}$ $P<0.01$ (trend test)

2.6.7.11 生殖発生毒性試験：重要な試験以外の試験

Test Article: Lemborexant

Species / Strain	Method of Administration (Vehicle / Formulation)	Dosing Period	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Rat / Sprague Dawley	Oral gavage (1 mol/L HCl: 0.5% MC solution [1:4, v/v] / suspension)	GD6 – 17	0 100 300 1000	7F (pregnant)	Dams: 100 mg/kg: No effects 300 mg/kg: ↓ Transient food consumption 1000 mg/kg: Euthanized on GD15 (1F) due to severe toxicity, ↓ body weight, body weight gain and food consumption, decreased activity, few feces, higher postimplantation loss (20%, 1F) Offspring: ≤300 mg/kg: No fetal morphology 1000 mg/kg: ↓ mean fetal body weights, cleft palate (8.3%) in fetus in 2 litters	K12001

Test Article: Lemborexant

Species / Strain	Method of Administration (Vehicle / Formulation)	Dosing Period	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Rat / Sprague Dawley	Oral gavage (1 mol/L HCl: 0.5% MC solution [1:4, v/v] / suspension)	GD6 – LD6	0 200 400 600	8F (Pregnant)	Dams: 200 mg/kg: ↓ body weight gain and food consumption 400 mg/kg: ↓ body weight and food consumption 600 mg/kg: Hunched posture, ↓ body weight and food consumption Offspring: 600 mg/kg: ↑ percentage of stillborn pups, ↓ pup body weight and viability index	20060759
Rabbit / NZW	Oral gavage (1 mol/L HCl: 0.5% MC solution [1:4, v/v] / suspension)	GD7 – 20	0 100 300 1000	3 – 5F (Pregnant)	Dams: 100 mg/kg: ↓ food consumption, ↓ body weight and abortion in 1 F 300 mg/kg: Death, ↓ body weight and food consumption 1000 mg/kg: Death, ↓ body weight and food consumption, prostration, tonic convulsion, or lateral position Offspring: 100 mg/kg: ↓ fetal body weight in 1 litter	K12002

F = female, GD = gestation day, LD= lactation day, MC = methylcellulose, NZW = New Zealand White, ↑ = increased, ↓ = decreased.

2.6.7.12 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

2.6.7.12.A　　**Test Article: Lemborexant**

Report Title: E2006: An Oral Fertility and Early Embryonic Development Study in Male Rats			Study No. K13078
Species / Strain: Rat / Sprague Dawley	Duration of Dosing:	M: 28 days before mating, throughout the mating period (for a maximum of 13 days)	Location in CTD: 4.2.3.5.1.1
Initial Age: 10 weeks old (male)		F: NA	
Date of First Dose: [redacted] 20[redacted]	Day of Mating (presence of vaginal plug or sperm in the vaginal smear): GD0		GLP Compliance: Yes
Special Features: None	Day of C-Section: GD14		
Basis for High Dose Selection: 添付資料 4.2.3.2.5［K11004］	Method of Administration: Oral gavage		Design compliant with ICH S5(R2)? Yes
No Observed Adverse Effect Level	Vehicle/Formulation: 1 mol/L HCl: 0.5% MC solution (1:4, v/v) / suspension		
F0 Males: 1000 mg/kg			
F1 Litters: 1000 mg/kg			

Daily Dose (mg/kg):		**0 (Control)**	**30**	**100**	**1000**
Males	Number of Animals Evaluated	20	20	20	20
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	–	–	–	–
	Necropsy Observations	–	–	–	–
	Body Weight (g) Day 28 of Premating period	452.6 g	452.4	461.6	455.5
	Food Consumption (g) Day 28 of Premating period	27 g	27	28	28
	Mean Mating Period	1.8	3.6	3.1	2.8
	No. of Males that Mated	20	20	20	20

Daily Dose (mg/kg):		0 (Control)	30	100	1000
	No. of Fertile Males	12	18	17	19
Females	No. Evaluated	12	18	17	19
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	—	—	—	—
	Necropsy Observations	—	—	—	—
	Mean No. Days Prior to Mating	1.8	3.6	3.1	2.8
	No. of Females Sperm-Positive	20	20	20	20
	No. of Pregnant Females	12	18	17	19
	No. Aborted or with Total Resorption of Litter	0	0	0	0
	Mean No. Corpora Lutea	14.2	14.8	15.2	14.8
	Mean No. Implantations	11.8	14.4	14.8	14.4
	Mean % Preimplantation Loss	19.0	2.0	2.5	2.2
	Mean No. Live Conceptuses	10.6	13.2	13.9	13.5
	Mean No. Resorptions	1.3	1.2	0.8	0.9
	Mean % Postimplantation Loss	12.2	8.5	5.8	6.6

—: No noteworthy findings.

CTD = Common Technical Document, F = female, F0 = parental generation, F1 = first filial generation, GD = gestation day, GLP =Good Laboratory Practice, M = male, MC = methylcellulose, NA = not applicable.

2.6.7.12.B　　**Test Article: Lemborexant**

Report Title: E2006: An Oral Fertility and Early Embryonic Development Study in Female Rats			Study No. K13063
Species / Strain: Rat / Sprague Dawley	Duration of Dosing:	M: NA	Location in CTD: 4.2.3.5.1.2
Initial Age: 11 – 12 weeks old		F: 14 days prior to mating, mating period (maximum 13 days), and through GD6	
Date of First Dose: [redacted] 20[redacted]	Day of Mating (presence of vaginal plug or sperm in the vaginal smear): GD0		GLP Compliance: Yes
Special Features: None	Day of C-Section: GD14		
Basis for High Dose Selection: 添付資料 4.2.3.2.5［K11004］	Method of Administration: Oral gavage		Design compliant with ICH S5(R2)? Yes
No Observed Adverse Effect Level	Vehicle/Formulation: 1 mol/L HCl: 0.5% MC solution (1:4, v/v) / suspension		
F0 Females: 100 mg/kg (general toxicity), 30 mg/kg (fertility)			
F1 Litters: 100 mg/kg			

Daily Dose (mg/kg):		**0 (Control)**	**30**	**100**	**1000**
Females	Number of Animals Evaluated	20	20	20	22[a]
	No. Died or Sacrificed Moribund	0	0	0	4[b]
	Clinical Observations				
	Abnormal respiratory sounds	0	0	0	2
	Decreased activity	0	0	0	1[c]
	Irregular respiration	0	0	0	2[c]
	Lateral position	0	0	0	1[c]

Daily Dose (mg/kg):		0 (Control)	30	100	1000
	Prostration	0	0	0	2[c]
	Staining, abdomen	0	0	0	1[c]
	Staining, genital region	0	0	0	2[c]
	Staining, nose	0	0	0	2
	Few/No faces	0	0	0	2[c]
	Premating Body Weight (g)[d] PMD13	257.6 g	258.2	259.7	233.3**
	Gestation Body Weight (g) GD14	333.2 g	328.1	328.8	292.1**
	Premating Food Consumption (g) PMD12	20 g	19	18	14**
	Gestation Food Consumption (g) GD13	24 g	24	23	25
	Mean No. Estrous Cycles/14 days	3.4	3.3	2.9	3.2
	No. of Females with Irregular Estrous Cycle	1	1	4	7
	Mean Mating Period	2.7	1.8	2.2	2.6
	No. of Females Sperm-Positive	20	20	19	19
	No. of Pregnant Females	17	17	14	11
	No. Aborted or with Total Resorption of Litter	0	0	0	0
	Mean No. Corpora Lutea	14.8	14.2	14.6	12.3**
	Mean No. Implantations	13.9	14.2	13.0	11.6**
	Mean % Preimplantation Loss	8.4	0.5[#]	10.8	5.1
	Mean No. Live Conceptuses	13.0	13.4	12.5	10.3**

Daily Dose (mg/kg):		0 (Control)	30	100	1000
	Mean No. Resorptions	0.9	0.8	0.5	1.4
	Mean % Postimplantation Loss	6.1	5.5	3.7	12.1

CTD = Common Technical Document, F = female, F0 = parental generation, F1 = first filial generation, GD = gestation day, GLP =Good Laboratory Practice, M = male, MC = methylcellulose, NA = not applicable, PMD = premating day.

a: Two females (Animal Nos.3F09 and 3F12) died on PMD7 due to gavage error and additional 2 females (Animal Nos. 3F21 and 3F22) were added.
b: Deaths were due to gavage error. One female at 1000 mg/kg (Animal No. 3F22) was sacrificed moribund on GD10. Two females at 1000 mg/kg (Animal Nos. 3F09 and 3F12) were found dead after dosing on PMD7. One female at 1000 mg/kg (Animal No. 3F13) was found dead before dosing on GD4. Histopathologic examination was performed for these females, and the death of 3 females found dead was due to gavage error. One moribund sacrificed female showed advance clinical signs including decreased activity, abnormal respiratory sounds, few/no feces, staining, and decreases in body weight and food consumption. The cause of moribundity was not fully defined, but changes were suggestive of gavage error.
c: Limited to animals that died or were sacrificed moribund.
**$P<0.01$ (Dunnett's rank test), $^{\#}P<0.05$ (Wilcoxon's rank test).

2.6.7.13 生殖発生毒性試験：胚・胎児発生に関する試験

2.6.7.13.A　　**Test Article: Lemborexant**

Report Title: E2006: An Oral Embryo-Fetal Development Study in Rats		Study No. K12010
Species / Strain: Rat / Sprague Dawley	Duration of Dosing: GD6 to 17	Location in CTD: 4.2.3.5.2.2
Initial Age: 10 or 11 weeks old at GD0	Day of Mating (vaginal plug observation): GD0	
Date of First Dose: [redacted] 20[redacted]	Day of C-Section: GD20	GLP Compliance: Yes
Special Features: None	Method of Administration: Oral gavage	
Basis for High Dose Selection: 添付資料 4.2.3.5.2.1 ［K12001］	Vehicle/Formulation: 1 mol/L HCl: 0.5% MC solution (1:4, v/v) / suspension	Design compliant with ICH S5(R2)? Yes
No Observed Adverse Effect Level: See 2.6.7.13.B		

Daily Dose (mg/kg):		**0 (Control)**	**60**	**200**	**600**
Dams:	Toxicokinetics: C_{max} (ng/mL) on GD17	NA	2006	4770	10,476
	Toxicokinetics: $AUC_{(0\text{-}24)}$ (ng·h/mL) on GD17	NA	25,529	62,870	171,321
	No. Pregnant	18	20	20	22
	No. Died or Sacrificed Moribund	0	0	0	0
	No. Aborted or with Total Resorption of Litter	0	0	0	0
	Clinical Observations (No. of females)				
	Decreased activity	0	0	0	3
	Few feces	0	0	0	3
	Staining Anogenital region	0	0	0	2
	Necropsy Observations				

Daily Dose (mg/kg):		0 (Control)	60	200	600
	Distension with gas, Gastrointestinal	1	0	0	2
	Body Weights (g) on GD6	282.9	289.6	284.9	284.3
	Body Weights (g) on GD18	365.5	385.2	370.5	315.1**
	Body Weights (g) on GD20	396.6	418.5	407.4	359.0**
	Body Weights gain from GD6 to 18 (g)	82.6	95.6	85.6	30.8##
	Body Weights gain from GD18 to 20 (g)	31.1	33.3	36.9	43.9##
	Food Consumption (g) on GD6	25	25	18 **	17**
	Food Consumption (g) on GD17	29	29	28	20##
	Food Consumption (g) on GD19	27	29#	29 #	30##
	Placenta and Amniotic Fluid	—	—	—	—
	Mean No. Corpora Lutea	14.7	15.4	15.5	15.3
	Mean No. Implantations	13.6	14.8	14.7	14.9
	Mean % Preimplantation Loss	8.8	4.1	5.2	2.4
Litters:	No. Litters Evaluated	18	20	20	22
	No. Live Fetuses	234	283	279	308
	No. Live Fetuses/Litter	13.0	14.2	14.0	14.0
	Postimplantation Loss (Mean %)	10 (4.0)	12(4.1)	14 (4.9)	20 (5.8)
	Early Resorptions (Mean %)	9 (3.4)	12(4.1)	14 (4.9)	17 (5.0)
	Late Resorptions (Mean %)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Daily Dose (mg/kg):		0 (Control)	60	200	600
	Dead (Mean%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)
	Mean Fetal Body Weight (g)	3.72	3.76	3.79	3.45
	Fetal Sex Ratios (males ratio %)	48.3	45.4	55.5	55.4
	Fetal Anomalies:				
	External Anomalies (No. fetuses [Litter incidence %])				
	No. Fetuses Examined	234	283	279	308
	Cleft palate (Mean %)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
	Ectrodactyly (Mean %)	0 (0.0)	0 (0.0)	1 (0.3)[a]	0 (0.0)
	Anal atresia (Mean %)	0 (0.0)	0 (0.0)	1 (0.3)[a]	0 (0.0)
	Omphalocele (Mean %)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)
	Visceral Anomalies (No. fetuses [Litter incidence %])				
	No. Fetuses Examined	111	136	135	149
	Membranous VSD (Mean %)	0 (0.0)	1 (0.8)	1 (1.0)	5 (3.6)
	Retroesophageal subclavian artery (Mean %)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Supernumerary lung lobe (Mean %)	15 (13.1)	31 (23.5)	32 (24.1)	21 (14.5)
	Skeletal Anomalies (No. fetuses [Litter incidence %])				
	No. Fetuses Examined	123	147	144	159
	Multiple defects	0 (0.0)	0 (0.0)	1 (0.6)[a]	0 (0.0)

Daily Dose (mg/kg):			0 (Control)	60	200	600
	Skeletal Variation (No. fetuses [Litter incidence %])					
	Rib	14th	16 (13.0)	21 (14.3)	25 (16.7)	91 (56.8)$^{\#\#W}$
	Vertebra	27 Presacral vertebrae	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
	Cervical arch	Incomplete ossification	1 (0.8)	4 (2.9)	1 (1.0)	24 (15.7)
	Thoracic arch	Incomplete ossification	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)
	Thoracic centrum	Incomplete ossification	1 (0.7)	0 (0.0)	2 (1.5)	15 (9.7)
	Lumbar centrum	Incomplete ossification	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
	No. Sacro-caudal vertebrae		8.1	8.0	8.0	7.6

—: No noteworthy findings.
CTD = Common Technical Document, GD = gestation day, GLP =Good Laboratory Practice, MC = methylcellulose, NA= not applicable, VSD = ventricular septal defect.
a: Multiple defects were observed in one fetus at 200 mg/kg (Animal No. 2F18, L06), and included ectrodactyly, anal atresia, skeletal fusion (rib, cervical vertebrae, lumber vertebrae), absence of lumber vertebrae, absent metacarpal and incomplete ossification of various bones.
$^{\#}P<0.05$, $^{\#\#}P<0.01$ (Dunnett's rank test), ** $P<0.01$ (Dunnett's test), $^{\#\#W}P<0.01$ (Wilcoxon's rank test).

2.6.7.13.B　　**Test Article: Lemborexant**

Report Title: E2006: An Oral Embryo-Fetal Development Study in Rats (Additional Study)		Study No. K12080
Species / Strain: Rat / Sprague Dawley	Duration of Dosing: GD6 to 17	Location in CTD: 4.2.3.5.2.3
Initial Age: 10 or 11 weeks old at GD0	Day of Mating (vaginal plug observation): GD0	
Date of First Dose: [redacted] 20[redacted]	Day of C-Section: GD20	GLP Compliance: Yes
Special Features: All live fetuses were examined for external or visceral anomalies.	Method of Administration: Oral gavage	
Basis for High Dose Selection: 添付資料 4.2.3.5.2.1 及び 4.2.3.5.2.2［K12001 及び K12010］	Vehicle/Formulation: 1 mol/L HCl: 0.5% MC solution (1:4, v/v) / suspension	Design compliant with ICH S5(R2)? No
No Observed Adverse Effect Level		
F0 Females: 60 mg/kg		
F1 Litters: 200 mg/kg		

Daily Dose (mg/kg):		**0 (Control)**	**20**	**60**	**200**
Dams:	Toxicokinetics: C_{max} (ng/mL) on GD17	BQL	647	NA[a]	NA[a]
	Toxicokinetics: $AUC_{(0\text{-}24)}$ (ng·h/mL) on GD17	NA	2845	NA[a]	NA[a]
	No. Pregnant	20	17	19	19
	No. Died or Sacrificed Moribund	0	0	0	0
	No. Aborted or with Total Resorption of Litter	0	0	0	0
	Clinical Observations (No. of females)				
	Alopecia forelimb	0	0	1 (GD13-20)	0
	Necropsy Observations	—	—	—	—

Daily Dose (mg/kg):		0 (Control)	20	60	200
	Body Weights (g) on GD6	292.6	289.4	288.5	293.1
	Body Weights (g) on GD18	377.6	379.4	380.4	381.6
	Body Weights (g) on GD20	409.1	409.5	408.7	415.8
	Body Weights gain from GD6 to 18 (g)	85.0	90.0	91.9	88.5
	Body Weights gain from GD18 to 20 (g)	31.5	30.1	28.3	34.2
	Food Consumption (g) on GD6	25	26	25	20**
	Food Consumption (g) on GD17	29	29	29	29
	Food Consumption (g) on GD19	27	28	28	29
	Placenta and Amniotic Fluid	—	—	—	—
	Mean No. Corpora Lutea	15.2	15.5	14.9	15.1
	Mean No. Implantations	14.1	13.8	13.9	14.4
	Mean % Preimplantation Loss	7.6	9.9	6.8	4.8
Litters:	No. Litters Evaluated	20	17	19	19
	No. Live Fetuses	272	226	244	258
	No. Live Fetuses/Litter	13.6	13.3	12.8	13.6
	Postimplantation Loss (Mean %)	10 (3.4)	8 (3.7)	20 (7.3)	15 (5.4)
	Early Resorptions (Mean %)	9 (3.1)	8 (3.7)	20 (7.3)	15 (5.4)
	Late Resorptions (Mean %)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
	Dead (Mean%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Daily Dose (mg/kg):		0 (Control)	20	60	200
	Mean Fetal Body Weight (g)	3.72	3.71	3.71	3.77
	Fetal Sex Ratios (males ratio %)	45.6	46.7	44.1	42.0
	Fetal Anomalies:				
	Gross External Anomalies (No. fetuses [Litter incidence%])				
	No. Fetuses Examined	272	226	244	258
	Conjoined twins (Mean %)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
	Visceral Anomalies (No. fetuses [Litter incidence %])				
	No. Fetuses Examined	271	226	244	258
	Membranous VSD (Mean %)	0 (0.0)	1 (0.4)	2 (0.7)	0 (0.0)
	Supernumerary lung lobe (Mean %)	55 (19.3)	42 (18.0)	57 (23.2)	47 (17.5)
	Dilated renal pelvis (Mean %)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

—: No noteworthy findings.
BQL = below quantifiable limit, CTD = Common Technical Document, F0 = parental generation, F1 = first filial generation, GD = gestation day, GLP =Good Laboratory Practice, MC = methylcellulose, NA = not applicable, VSD = ventricular septal defect.

a: Not applicable because toxicokinetics at these doses were evaluated in previous study conducted (添付資料 4.2.3.5.2.2［K12010］) in same facility.
$^{**}P<0.01$ (Dunnett's test), $^{\#\#}P<0.01$ (Dunnett's rank test).

2.6.7.13.C　　**Test Article: Lemborexant**

Report Title: E2006: An Oral Study in Pregnant Rats for Reversibility of Fetal Membranous Ventricular Septal Defect (mVSD)		Study No. 20060758
Species / Strain: Rat / Sprague Dawley	Duration of Dosing: GD6 to 17	Location in CTD: 4.2.3.5.2.4
Initial Age: 12 weeks old	Day of Mating (vaginal plug observation): GD0	
Date of First Dose: [redacted] 20[redacted]	Day of C-Section: GD21	GLP Compliance: Yes
Special Features: Conducted at different location/lab with previous EFD studies. There were no test article-related fetal cardiac findings in cesarean-sectioned fetus in the lemborexant dose groups, all remaining dams and pups were euthanized on PND4–14 postpartum without further examination.		Method of Administration: Oral gavage
Basis for High Dose Selection: 添付資料 4.2.3.5.2.2 及び 4.2.3.5.2.3［K12010 及び K12080］	Vehicle/Formulation: 1 mol/L HCl: 0.5% MC solution (1:4, v/v) / suspension	Design compliant with ICH S5(R2)? No
No Observed Adverse Effect Level		
F0 Females: 60 mg/kg		
F1 Litters: 200 mg/kg		

Daily Dose (mg/kg):		**Lemborexant**							**Positive control (TMD[b])**
		0 (Control)					**600**		
Subgroup		**A[a]**	**B/C[a]**	**20**	**60**	**200**	**A**	**B/C**	
Dams:	No of animals	20	35	20	20	20	20	35	10
	No. Pregnant	20	34	20	18	20	18	32	8
	No. Died or Sacrificed Moribund	0	0	0	0	0	0	2[c]	0
	Dams with any resorption, N (%)	9 (45.0)	NA	10 (50.0)	5 (27.8)	12 (60.0)	7 (38.9)	NA	5 (62.5)
	Clinical Observations (No. of females)								
	Dehydration	0	0	0	0	3	15	20	8

Daily Dose (mg/kg):		Lemborexant							Positive control (TMD[b])
		0 (Control)		20	60	200	600		
	Subgroup	A[a]	B/C[a]				A	B/C	
	Hunched posture	0	0	0	0	0	7	7	2
	Ungroomed coat	0	0	0	0	1	0	2	1
	Light brown feces	0	0	0	0	0	5	3	0
	Thin body condition	0	0	0	0	0	4	3	0
	Piloerection	0	0	0	0	0	2	0	0
	Left inguinal area: mass	0	0	0	0	0	1	0	0
	Pale extremities	0	0	0	0	0	1	3	0
	Hyperpnea	0	0	0	0	0	1	0	0
	Decreased motor activity	0	0	0	0	0	1	2	0
	Ptosis	0	0	0	0	0	1	3	0
	Rales	0	0	0	0	0	1	1	0
	Body Weights (g) on GD6	276.1	279.2	272.7	272.7	272.2	272.2	277.4	266.4
	Body Weights (g) on GD18	365.2	369.9	367.6	364.9	350.9	288.4**	315.8**	335.4**
	Body Weights (g) on GD21	416.6	410.8	418.9	416.7	405.3	364.4**	368.8**	383.5*
	Body Weights gain from GD6 to 18 (g)	89.0	90.7	94.8	92.2	78.7	16.3**	37.1**	69.0**
	Body Weights gain from GD18 to 21 (g)	51.5	46.4	51.4	51.8	54.4	75.9**	66.7**	48.1
	Food Consumption (g/day) on GD6–9	20.5	20.2	21.5	19.8	17.3**	10.2**	11.4**	20.0
	Food Consumption (g/day) on GD15–18	25.8	25.0	26.7	25.6	23.4*	13.9**	17.4**	27.6
	Food Consumption (g/day) on GD18–21	25.5	24.5	25.5	25.2	26.2	26.6	28.4 **	26.6

Daily Dose (mg/kg):		Lemborexant							Positive control (TMD[b])
		0 (Control)		20	60	200	600		
	Subgroup	A[a]	B/C[a]				A	B/C	
	Placenta	—	NA	—	—	—	—	NA	—
	Mean No. Corpora Lutea	15.5	NA	15.4	15.6	15.0	15.8	NA	14.5
	Mean No. Implantations	14.8	NA	15.0	15.0	14.0	14.8	NA	13.4
	Mean % Preimplantation Loss	4.7	NA	2.6	3.5	6.6	6.5	NA	7.4
Litters (F1):	No. Litters Evaluated	20	NA	20	18	20	17	NA	8
	No. Live Fetuses	275	NA	281	262	258	244	NA	96
	No. Live Fetuses/Litter	13.8	NA	14.0	14.6	12.9	14.4	NA	12.0
	Postimplantation Loss (Mean %)	20 (7.2)	NA	18 (6.7)	8 (2.8)	21 (8.1)	22 (8.5)	NA	11(12.4)
	Early Resorptions (Mean %)	20 (1.0)	NA	18 (0.9)	8 (0.4)	21 (1.0)	22 (1.2)	NA	5 (0.6)
	Late Resorptions (Mean %)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	6 (0.8)**
	No. Dead (Mean %)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)
	Mean Fetal Body Weight (g)	5.70	NA	5.64	5.60	5.78	5.12**	NA	4.58**
	Fetal Sex Ratios (males ratio %)	53.4	NA	54.4	44.3	47.6	40.9**	NA	54.0
	Fetal Anomalies:								
	Gross External Anomalies (No. fetuses [Litter incidence %])								
	No. Fetuses Examined	275	NA	281	262	258	244	NA	96
	Tail: curled (Mean %)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	5 (62.5)**
	Tail: short (Mean %)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	3 (37.5)**

Daily Dose (mg/kg):		Lemborexant							Positive control (TMD[b])
		0 (Control)		20	60	200	600		
Subgroup		A[a]	B/C[a]				A	B/C	
	Visceral Anomalies (No. fetuses [Litter incidence %])[d, e]								
	No. Fetuses Examined	275	NA	280	262	258	244	NA	96
	Muscular VSD (Mean %)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	6 (75.0)**
	Membranous VSD (Mean %)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	6 (75.0)**
F1 Litters:	No. Delivered Litters	NA	34	NA	NA	NA	NA	31	NA
	Mean No. Pups/Litter	NA	15.1	NA	NA	NA	NA	14.0	NA
	Mean No. Liveborn Pups/Litter	NA	14.9	NA	NA	NA	NA	13.6	NA
	Mean No Stillborn Pups/Litter	NA	0.1	NA	NA	NA	NA	0.4	NA
	Mean No. Surviving Pups on PND4 / Litter	NA	14.8	NA	NA	NA	NA	11.1**	NA
	Percent male pups per number of pups sexed	NA	52.0	NA	NA	NA	NA	48.7	NA
	Pup weight / Litter (g) on PND1	NA	6.6	NA	NA	NA	NA	6.7	NA
	Pup weight / Litter (g) on PND7 (postculling on PND4)	NA	15.7	NA	NA	NA	NA	15.2	NA
F1 pups	Litters examined	NA	34	NA	NA	NA	NA	31	NA
	Pup Clinical Signs from birth to PND13								
	Whole body, purple or pale	NA	0	NA	NA	NA	NA	2	NA
	Cold to touch	NA	1	NA	NA	NA	NA	1	NA
	Dehydration, severe	NA	1	NA	NA	NA	NA	0	NA

Daily Dose (mg/kg):		Lemborexant							Positive control (TMD[b])
		0 (Control)		20	60	200	600		
Subgroup		A[a]	B/C[a]				A	B/C	
	Necropsy observation								
	No. pups stillborn / found dead[f]	NA	4 / 1	NA	NA	NA	NA	11 / 4	NA
	No milk in stomach	NA	0	NA	NA	NA	NA	1	NA
	Appeared normal	NA	5	NA	NA	NA	NA	11	NA

Daily Dose (mg/kg):		Lemborexant							Positive control (TMD[b])
		0 (Control)		20	60	200	600		
Subgroup		A[a]	B/C[a]				A	B/C	
	No. Pups euthanized and necropsied on PND4	NA	193	NA	NA	NA	NA	121	NA
	Appeared normal	NA	193	NA	NA	NA	NA	121	NA

—: No noteworthy findings.

CTD = Common Technical Document, F0 = parental generation, F1 = first filial generation, GD = gestation day, GLP =Good Laboratory Practice, MC = methylcellulose, NA = not applicable, PND = postnatal day, TMD = trimethadione, VSD = ventricular septal defect.

a: Rats assigned to Subgroup A were dosed daily on GD6–17 and Caesarean-sectioned on GD21. Rats assigned to Subgroup B/C were dosed daily on GD6-17. The study was terminated early and all surviving dams and litters in Subgroup B/C were euthanized on PND4-14.

b: A positive control group was administered TMD, twice daily (12 hours apart, 300 mg/kg at 10 mL/kg), for a total dose of 600 mg/kg/day on GD9 and 10.

c: Two rats (Animal No. 1747 and 1756) were euthanized on GD16 and 17, respectively, due to adverse clinical observation. Animal No. 1747 showed mild to dehydration, hunched posture, ptosis, thin body condition, decreased motor activity, bradypnea, and scant feces. Animal No. 1756 showed dehydration, hunched posture, ptosis, thin body condition, pale extremities, decreased motor activity, bradypnea, chromorhinorrhea, ungroomed coat, ataxia, convulsion (tonic flexor), and head tilt to the right.

d: The following spontaneous malformations were also noted in the lemborexant-treated groups (No. of fetus [Litter incidence, %]) and were not considered related to treatment with lemborexant because: 1) they were not dose dependent; 2) they occurred in single fetuses; or 3) the incidences were within the ranges observed historically at the testing facility.

- 20 mg/kg: Small ventricles (1, [5.0%]) in heart, absent innominate artery (1, [5.0]), right subclavian artery arises from pulmonary artery (1, [5.0]), pulmonary artery descends to the right (1, [5.0]) in vessels, and absent lobes (1, [5.0]) in lungs.
- 600 mg/kg: Absent innominate artery (1, [5.9]), right subclavian arises to the left of the left subclavian (1, [5.9]), and right subclavian passes dorsal to the trachea and esophagus (1, [5.9]) in vessels.

e: The following malformations were observed in TMD group (No. of fetus [Litter incidence, %]).
Small ventricles (1 [12.5]) in heart, and persistent truncus arteriosis (3, [37.5]), ductus arteriosis patent (2, [25.0]), pulmonary arteries arise from ductus arteriosis (1 [12.5]), interrupted aortic arch (2, [25.0]), Innominate artery absent (4, [50.0]), right subclavian arises to the left of the left subclavian (2, [25.0]), right subclavian passes dorsal to the trachea and esophagus (3, [37.5]), aorta descends to the right (2, [25.0]), arises in the incorrect order (1, [12.5]), left subclavian artery arises from left carotid artery (1, [12.5]), constricted pulmonary artery, distended aorta (1, [12.5]), left carotid arises from innominate artery (3, [37.5]) in vessels.

f: Restricted to pups in which complete necropsies were performed. Complete necropsies were not performed to pups in which autolysis or cannibalization precluded full evaluation.

*$P \leq 0.05$, **$P \leq 0.01$ (Dunnett's test).

2.6.7.13.D　　**Test Article: Lemborexant**

Report Title: E2006: An Oral Embryo-Fetal Development Study in Rabbits		Study No. K12011
Species / Strain: Rabbit / Kbl:NZW	Duration of Dosing: GD7 to 20	Location in CTD: 4.2.3.5.2.6
Initial Age: 22 or 25 weeks	Day of Mating (insemination): Day 0	
Date of First Dose: [redacted] 20[redacted]	Day of C-Section: GD29	GLP Compliance: Yes
Special Features: None	Method of Administration: Oral gavage	
Basis for High Dose Selection: 添付資料 4.2.3.5.2.5 ［K12002］	Vehicle/Formulation: 1 mol/L HCl: 0.5% MC solution (1:4, v/v) / suspension	Design compliant with ICH S5(R2)? Yes
No Observed Adverse Effect Level		
F0 Females: 30 mg/kg		
F1 Litters: 30 mg/kg		

Daily Dose (mg/kg):		**0 (Control)**	**10**	**30**	**100**
Dams:	Toxicokinetics: C_{max} (ng/mL) on GD20	NA	528.3	1684	5746
	Toxicokinetics: $AUC_{(0\text{-}24)}$ (ng·h/mL) on GD20	NA	2904.2	10017	61388
	No. Pregnant	20	19	20	20
	No. Died or Sacrificed Moribund	0	0	0	0
	No. Aborted or with Total Resorption of Litter	1[a]	0	0	2[a]
	Clinical Observations (No. of females)				
	Partially closed eyes	0	10	4	6
	Few feces	0	1	0	4
	Vaginal hemorrhage	0	1	0	0

Daily Dose (mg/kg):		0 (Control)	10	30	100
	Necropsy Observations				
	Kidney: Absent	0	1	0	0
	Intragastric hairball	0	0	0	1
	Body Weights (kg) on GD7	3.57	3.53	3.55	3.55
	Body Weights (kg) on GD21	3.66	3.67	3.67	3.56
	Body Weights (kg) on GD29	3.88	3.87	3.82	3.85
	Body Weights gain (kg) from GD7–21	0.08	0.13	0.12	0.01
	Body Weights gain (kg) from GD21–-29	0.22	0.20	0.15	0.25
	Food Consumption (g) on GD7	148	161	152	130*
	Food Consumption (g) on GD20	125	133	121	110
	Food Consumption (g) on GD28	137	132	133	136
	Placenta and Amniotic Fluid (No. of females)	—	1 [b]	—	—
	Mean No. Corpora Lutea	9.2	9.6	9.1	8.9
	Mean No. Implantations	8.1	8.8	7.4	7.8
	Mean % Preimplantation Loss	14.7	9.6	18.8	14.5
Litters:	No. Litters Evaluated	19	19	20	18
	No. Live Fetuses	152	157	141	140
	No. Live Fetuses/Litter	7.6	8.3	7.1	7.4

Daily Dose (mg/kg):		0 (Control)	10	30	100
	Postimplantation Loss (Mean %)	9 (10.2)	11 (5.9)	6 (4.8)	9 (10.7)
	Early Resorptions (Mean %)	7 (9.3)	6 (3.2)	5 (3.9)	6 (8.7)
	Late Resorptions (Mean %)	2 (0.9)	4 (2.1)	0 (0.0)	2 (1.2)
	Dead (Mean %)	0 (0.0)	1 (0.7)	1 (0.8)	1 (0.8)
	Mean Fetal Body Weight (g)	41.75	41.32	42.24	41.25
	Fetal Sex Ratios (males ratio %)	52.2	41.8	60.7	47.4
	Fetal Anomalies:				
	No. Fetuses Examined	152	157	141	140
	Gross External Anomalies				
	No. Fetuses with Anomalies (Litter incidence %)	1 (0.7)	0 (0.0)	1 (1.0)	1 (0.6)
	Multiple defects	1[c] (0.7)	0 (0.0)	1[d] (1.0)	0 (0.0)
	Malroated paw	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
	Visceral Anomalies				
	No. Fetuses with Anomalies (Litter incidence %)	8 (5.6)	10 (5.8)	12 (6.7)	15 (10.1)
	Retroesophageal subclavian artery	1 (0.5)	2 (1.5)	2 (1.1)	4 (2.4)
	Abnormal lung lobation	5 (2.8)	7 (3.8)	8 (4.2)	10 (7.0)
	Absent gallbladder	1 (0.6)	0 (0.0)	1 (0.5)	1 (0.6)
	Small gallbladder	1 (1.8)	0 (0.0)	2 (1.0)	0 (0.0)
	Small spleen	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
	Malpositioned kidney	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)

Daily Dose (mg/kg):		0 (Control)	10	30	100
	Skeletal Anomaly				
	No. Litters with Skeletal Anomalies (Litter incidence %)	4 (21.1)	2 (10.5)	2 (10.0)	2 (11.1)
	No. Fetuses with Anomalies (Litter incidence %)	4 (2.7)	2 (1.1)	2 (2.7)	2 (1.7)
	General: Multiple defects	1 (0.7)[e]	0 (0.0)	0 (0.0)	0 (0.0)
	Sternebra: Fused	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
	Rib: Absent	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
	Rib: Fused	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
	Rib: Branched	2 (1.4)	0 (0.0)	2 (2.7)	0 (0.0)
	Costal cartilage: Fused	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
	Costal cartilage: Branched	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
	Thoracic vertebra: Hemivertebra	3 (2.1)	1 (0.5)	2 (2.7)	1 (1.1)
	Lamber vertebra: Absent	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
	Sacral vertebra: Absent	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
	Caudal centrum: Fused	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.6)
	Caudal vertebra: Absent	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
	Skeletal Variation				
	No. Litters with Skeletal Variations (Litter incidence %)	19 (100.0)	19 (100.0)	18 (90.0)	18 (100.0)
	No. Fetuses with Variations (Litter incidence %)	89 (57.7)	94 (59.7)	86 (66.8)	91 (64.0)
	Frontal: Incomplete ossification	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
	Parietal: Incomplete ossification	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)

Daily Dose (mg/kg):		0 (Control)	10	30	100
	Sternabra: Extra ossification site	1 (0.6)	0 (0.0)	1 (0.6)	3 (1.9)
	Rib: Cervical rib	1 (0.7)	4 (2.4)	3 (2.7)	13 (9.3)$^{\#w}$
	Rib: 13th	86 (55.6)	90 (57.3)	83 (64.0)	81 (56.0)
	Rib: Knobby	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
	Rib: Intercostal	1 (0.7)	0 (0.0)	0 (0.0)	1 (1.1)
	Vertebra: 25 Presacral vertebrae	2 (1.4)	1 (0.5)	1 (0.6)	2 (2.5)
	Vertebra: 27 Presacral vertebrae	7 (6.5)	1 (0.7)$^{\#w}$	9 (7.3)	4 (2.6)
	Cervical centrum: Incomplete ossification	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)

$AUC_{(0\text{-}24)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, F0 = parental generation, F1 = first filial generation, GD = gestation day, GLP =Good Laboratory Practice, MC = methylcellulose, NC= not calculated, NZW = New Zealand White.

a: Animal No. 3F09 aborted on GD23, Animal Nos. 0F03 and 3F12 had total resorption.

b: Yellowish amniotic fluid.

c: Animal No. 0F16 Fetus No. L03, Anomalies included cranioschisis, spina bifida, malrotated paw, brachydactyly, ectrodactyly, gastroschisis, micromelia, and kinked tail.

d: Animal No. 2F19 Fetus No. L04, Anomalies included short trunk, acaudate and malrotated limb.

e: Animal No.0F16 Fetus No. L03, Anomalies included absent of frontal bone, parietal bones, vertebral arches and metacarpus, and deformed radius, ulna and ribs.

*P<0.05, **P<0.01 (Dunnett's test), $^{\#W}P$<0.05 (Wilcoxon's rank test).

2.6.7.14 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

Test Article: Lemborexant

Report Title: An Oral Toxicity Study of Effects on Pre- and Postnatal Development, Including Maternal Function in Rats		Study No. 20060760
Species / Strain: Rat / Sprague Dawley	Duration of Dosing: GD6 to LD20	Location in CTD: 4.2.3.5.3.2
Initial Age: 9 weeks old	Day of Mating: GD0	Day of Birth: LD/PND 1
Date of First Dose: [redacted] 20[redacted]	Day of C-Section: None	GLP Compliance: yes
Special Features: Bone fluoride measurement, histopathology of the femur, serum bone biomarkers	Method of Administration: Oral gavage	
Basis for High Dose Selection: 添付資料 4.2.3.5.3.1 ［20060759］	Vehicle / Formulation: 1 mol/L HCl: 0.5% MC solution (1:4, v/v) / suspension	Design compliant with ICH S5(R2)? Yes
No Observed Adverse Effect Level	Litters Culled / Not Culled: Culled	
F0 Females: 100 mg/kg (maternal general toxicity), 300 mg/kg: (maternal reproductive function)		
F1 Males/Females: 100 mg/kg (offspring growth), 300 mg/kg (other parameters)		

Daily Dose (mg/kg):		**0 (Control)**	**30**	**100**	**300**
F0 Females:	Toxicokinetics: C_{max} (ng/mL) on GD17	NA	947	3150	5625
	Toxicokinetics: $AUC_{(0-24)}$ (ng·h/mL) on GD17	NA	6448	40833	90718
	No. Pregnant	22	22	22	22
	No. Died or Sacrificed Moribund	0	0	0	0
	No. Aborted or with Total Resorption of Litter	0	0	0	0

Daily Dose (mg/kg):		0 (Control)	30	100	300
	Clinical Observations	—	—	—	—
	Necropsy Observations	—	—	—	—
	Gestation Body Weight (g) GD20	349.1	350.9	353.1	331.4*
	Gestation Body Weight Changes (g) GD6—20	119.5	121.9	122.9	102.0**
	Lactation Body Weight (g) LD21	307.4	309.3	319.5	306.3
	Lactation Body Weight Change (g) LD1—21	41.7	38.2	47.5	49.3
	Gestation Food Consumption (g/day) GD6—20	21.6	21.8	21.6	18.5**
	Lactation Food Consumption (g/day) LD1—14[a]	46.0	45.5	45.3	38.6**
	Mean Duration of Gestation	22.4	22.0*	22.3	22.3
	Abnormal Parturition	—	—	—	—
F1 Litters:	No. Litters Evaluated	22	22	22	22
(preweaning)	Mean No. Pups/Litter	12.2	12.0	11.9	11.9
	Mean No. Liveborn Pups/Litter	12.1	12.0	11.9	11.9
	Mean No Stillborn Pups/Litter	0.0	0.0	0.0	0.0
	Postnatal Survival to PND4 (% to PND1)	99.6	98.9	99.2	99.6
	Postnatal Survival to Weaning (% to PND4)	100.0	100.0	100.0	100.0
	Pup Body Weights (g) PND 1	6.9	6.7	6.7	6.4**
	Pup Body Weights (g) PND 21	49.4	48.5	48.8	41.0**

Daily Dose (mg/kg):		0 (Control)	30	100	300
	Pup Clinical Signs	—	—	—	—
	Pup Necropsy Observations	—	—	—	—
	Femur Length (mm) on PND21 - Male	17.2	17.0	17.0	16.6**
	Femur Length (mm) on PND 21- Female	17.2	16.8*	17.0	16.4**
	No. Evaluated (Bone Fluoride) [d]	10	10	10	10
	Concentration (ppm) of Fluoride in Bone (Tibia) on PND 21, [Mean±SD] - Male	0	0	0 [e]	24±2
	Concentration (ppm) of Fluoride in Bone (Tibia) on PND 21, [Mean±SD] - Female	0	0	0 [e]	22±4
F1 Males	No. Evaluated Postweaning	22	22	22	22
(postweaning)	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	—	—	—	—
	Necropsy Observations	—	—	—	—
	Body Weight (g)[b] PND36	153.0	155.5	158.8	142.3*
	Body Weight (g)[b] PND92	502.8	504.2	501.2	484.7
	Body Weight Change (g) [b] PND22–29	44.0	43.5	44.9	40.5*
	Body Weight Change (g)[b] PND22–92	448.9	450.7	447.6	440.2
	Food Consumption (g/day/cage) [b] PND29–92	51.7	52.2	49.7	51.7
	Mean Age of Preputial Separation (PND)	44.5	44.4	44.2	45.5
	Acoustic Startle Response and Habituation				
	Average Response Amplitude	—	—	—	↓*
	Maximum Response Amplitude	—	—	—	↓*
	Latency to Maximum Response Amplitude	—	—	—	↑*

Daily Dose (mg/kg):		0 (Control)	30	100	300
	Motor Activity	—	—	—	—
	Learning and Memory (M-Shaped Water Maze)	—	—	—	—
	Mean No. Days Prior to Mating	2.4	2.9	2.8	2.5
	No. of Males that Mated	21	22	21	22
	No. of Fertile Males	21	22	21	22
	Epididymal weight	—	—	—	—
	Testicular weight	—	—	—	—
F1 Females	No. Evaluated Postweaning	22	22	22	22
(postweaning)	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	—	—	—	—
	Necropsy Observations	—	—	—	—
	Body Weight (g)[b] PND 36	128.1	128.3	131.8	122.8*
	Body Weight (g)[b] PND 92	266.0	272.7	275.4	265.3
	Body Weight Change (g)[b] PND22-29	35.9	35.9	37.4	36.0
	Body Weight Change (g)[b] PND22-92	214.8	221.5	224.3	221.1
	Gestation Body Weight Change (g)[b] GD0-13	62.4	65.0	62.0	68.0
	Premating Food Consumption (g/day/cage)[b, c] PND29-92	34.1	35.3	35.0	34.3
	Gestation Food Consumption (g/day/cage)[b, c] GD0-13	22.7	23.3	22.9	23.0

Daily Dose (mg/kg):		0 (Control)	30	100	300
	Mean Age of Vaginal Patency (PND)	33.0	33.0	33.1	33.7
	Acoustic Startle Response and Habituation				
	Average Response Amplitude	—	—	—	↓*
	Maximum Response Amplitude	—	—	—	↓**
	Latency to Maximum Response Amplitude	—	—	—	↑**
	Motor Activity	—	—	—	—
	Learning and Memory (M-Shaped Watermaze)	—	—	—	—
	Estrus Cycle	—	—	—	—
	Mean No. Days Prior to Mating	2.4	2.9	2.9	2.5
	No. of Females Sperm Positive	22	22	21	22
	No. of Pregnant Females	22	22	21	21
	Mean No. Corpora Lutea	15.9	16.8	16.8	16.7
	Mean No. Implantations	15.2	16.4	15.8	16.1
	Mean % Preimplantation Loss	5.2	2.0	7.8	4.2
F2 Litters	Mean No. Live Conceptuses/Litter	14.4	15.4	14.8	15.4
	Mean No. Nonviable Embryos	0.8	1.0	0.9	0.7
	Mean % Postimplantation Loss	5.9	6.0	10.0	5.5

—: No noteworthy findings.
$AUC_{(0\text{-}24)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, F0 = parental generation, F1 = first filial generation, GD = gestation day, GLP =Good Laboratory Practice, LD = lactation day, MC = methylcellulose, NA = not applicable, PND = postnatal day, ↑ = increased, ↓ = decreased.
a: Because it is presumed that the pups begin to consume maternal food after LD14, maternal food consumption values were not tabulated on LD14-21.
b: Data from Subset A (Subset A: Animals euthanized after completion of cohabituation period or on GD13 [Subset B: euthanized on PND 70])
c: Excludes values for cages with 1 or 3 rats per cage.

Daily Dose (mg/kg):	0 (Control)	30	100	300

d: Tibias from 10 litters with 2 pups/sex were evaluated. The tibias of 2 pups of the same sex were pooled for evaluation.
e: Low level of fluoride were detected in pooled tibias of 5 male and 2 female pup pairs in the 100 mg/kg/day maternal dose group but the group average was 0 ppm.
*P<0.05, **P<0.01 (Dunnett's test).

2.6.7.15 その他の毒性試験

Test Article: Lemborexant

Species / Strain	Method of Administration	Dose (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Mechanistic Studies for Bone Toxicity					
Rat / Sprague Dawley	Oral gavage (14 weeks with a 12-week recovery periods)	0 1000/800[a]	Week 9: 16F Week 14: 15F Week 26: 15F	Exposure to fluoride and its accumulation with changes consistent with fluorosis: ● Increases in fluoride in urine, serum, and bone ● Bone: decreased trabecular bone and mature lamellar bone associated with imbalance in turnover markers and decreases in mass, strength, mineral density, and geometry. ● Teeth: degeneration and decreased iron contents of ameloblast. ● All changes reversible	6700122
Rat / Sprague Dawley	Oral gavage (4 weeks)	0 30 100 1000	10F	≥100 mg/kg: Dose-dependent increases in urinary fluoride excretion and bone fluoride concentration. 1000 mg/kg: Increased serum fluoride concentrations	K14010
Rat / Sprague Dawley	Oral gavage (single dose)	Lemborexant/1-ABT 0/100 100/100 1000/100	5M/5F	1-ABT (CYP inhibitor) pretreatment: Marked increase in lemborexant plasma exposure with complete inhibition of increases in urinary fluoride excretion.	K14014

Test Article: Lemborexant

Species / Strain	Method of Administration	Dose (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Dependence					
Rat / Sprague Dawley	Oral gavage (4 weeks with a 1-week withdrawal period)	0 200 (100, BID) 600 (300, BID)	10M	No physical dependence.	ES13070
Monkey / Rhesus	Intravenous (single dose)	0.04, 0.2, or 1	1M/1F	No clinical signs were observed.	ES13261
Monkey / Rhesus	Self-administration (venous infusion of a specified volume)	0.3, 0.1, 0.03, 0.01, and 0.003 mg/kg / infusion, 2 hours/day, for 4 to 7 days/dose Doses were administered in a descending manner	3M/1F	No reinforcing effect.	ES13262
Rat / Sprague Dawley	Oral gavage (single dose[b])	Lemborexant: 0, 10, 30, 100, or 1000 mg/kg Comparator: (suvorexant): 0,30, 100, 300, or 1000 mg/kg	6F	● Lemborexant did not generalize to the imidazopyridine, zolpidem, in rats. ● In cross-generalization tests, the comparator, suvorexant (a marketed dual orexin receptor antagonist), did engender partial generalization to the zolpidem.	463-058

Test Article: Lemborexant

Species / Strain	Method of Administration	Dose (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Metabolites					
Mouse / CB6F1-nonTg rasH2	Oral gavage (4 weeks, Samples from Study No. K14035)	100 300 1000	4M/4F for each time point	● The C_{max} and $AUC_{(0-24)}$ values of metabolite M10 increased less than dose-proportionally from 100 to 1000 mg/kg in both male and female mice. ● The C_{max} and $AUC_{(0-24)}$ values of M10 in females were higher than in males.	DMPKT2014 -007[c]
Rat / Sprague Dawley	Oral gavage (4 weeks)	10 (F) 30 (M) 100 1000	4M/4F	● The C_{max} or $AUC_{(0-24)}$ values of lemborexant increased more than dose-proportionally up to 100 mg/kg and less than dose-proportionally between 100 and 1000 mg/kg. ● The PK parameters of the metabolites (M4, M9, and M10) increased with dose escalation up to 1000 mg/kg. ● The C_{max} or $AUC_{(0-24)}$ values of lemborexant and its metabolites were higher in females than males at 100 and 1000 mg/kg.	ES15364
Monkey / cynomolgus	Oral gavage (4 weeks)	10 100 1000	3M/3F	● The mean C_{max} or $AUC_{(0-24)}$ of lemborexant and its metabolites increased in a dose-proportional manner in both sexes between 10 and 100 mg/kg, and were comparable between 100 and 1000 mg/kg. ● There was no clear sex difference in the mean C_{max} and $AUC_{(0-24)}$ values of lemborexant, M4, M9, and M10.	ES15365
Impurities					
Bacteria[d] (不純物A*)	In vitro, incubation (±S9 mix)	156 to 5000 µg/plate	NA	Negative	14K5368G

*新薬承認情報提供時に置き換え

Test Article: Lemborexant

Species / Strain	Method of Administration	Dose (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Bacteria[d] (不純物B*)	In vitro, incubation (±S9 mix)	313 to 5000 µg/plate	NA	Negative	14K5358G
Bacteria[d] (不純物C*)	In vitro, incubation (±S9 mix)	19.5 to 5000 µg/plate	NA	Positive	15K2008G
Bacteria[d] (不純物D*)	In vitro, incubation (±S9 mix)	19.5 to 5000 µg/plate	NA	Positive	15K1998G
Bacteria[d] (不純物E*)	In vitro, incubation (±S9 mix)	156 to 5000 µg/plate	NA	Positive	15K2018G
Bacteria[d] (不純物F*)	In vitro, incubation (±S9 mix)	313 to 5000 µg/plate	NA	Negative	14K5348G
Bacteria[d] (不純物G*)	In vitro, incubation (±S9 mix)	6.86 to 5000 µg/plate	NA	Positive	16K8568G
Bacteria[d] (不純物H*)	In vitro, incubation (±S9 mix)	19.5 to 5000 µg/plate	NA	Positive	14K3348G
Bacteria[d] (不純物I*)	In vitro, incubation (±S9 mix)	1.58 to 5000 µg/plate	NA	Negative	964018
Bacteria[d] (不純物J*)	In vitro, incubation (±S9 mix)	6.86 to 5000 µg/plate	NA	Negative	15K1538G
Photosafety					
Mouse BALB/c 3T3 cells	In vitro, incubation, ±light irradiation (UV-A; ca. 7.4 J/cm^2)	0.78 to 100 µg/mL	NA	Negative	T14019

*新薬承認情報提供時に置き換え

Test Article: Lemborexant

Species / Strain	Method of Administration	Dose (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Mouse BALB/c 3T3 cells	In vitro, incubation, ±light irradiation (UV-A; ca. 6 J/cm^2)	0.78 to 100 µg/mL	NA	Negative	T17022
Other Studies					
Plasmodium falciparum	In vitro, incubation for 3 days	0.1 to 100 µg/mL	NA	Lemborexant did not accelerate parasite growth and inhibited it at higher concentrations.	W-20140891

The impurity profile is summarized in Section 3.2.S.3.2.4 in Module 3.2.S.3.2 (Study Nos. 14K5368G, 14K5358G, 15K2008G, 15K1998G, 15K2018G, 14K5348G, 16K8568G, 14K3348G, 964018, 15K1538G).

1-ABT = 1-aminobenzotriazole, $AUC_{(0-24)}$ = AUC from zero time to 24 hours, BID = twice daily, CYP = cytochrome P450, F = female, M = male, NA = not applicable, PK = pharmacokinetic, SD = Sprague Dawley, Tg = transgenic.

a: Due to marked body weight loss during the first 2 weeks of the study, animals were given a 7-day dosing holiday starting on Day 15. Dosing was resumed on Day 22 with a reduced dose level of 800 mg/kg.

b: Animals were trained to differentiate between oral gavage administrations of zolpidem (3 mg/kg) and vehicle using a 2-choice drug versus vehicle 2-lever operant discrimination task under a fixed-ratio 10 (FR10) schedule of reinforcement. Once the training criteria were met, testing sessions were initiated and animals were administered vehicles, zolpidem, comparator article (suvorexant), and/or lemborexant.

c: This study was considered exploratory (non-GLP) and the methods used for the measurement of M10 in mice were qualified but not fully validated.

d: *Salmonella typhimurium* TA100, TA1535, TA98, TA1537, and *Escherichia coli* WP2 *uvrA*..