2.6.7.2 トキシコキネティクス試験の一覧表

Test Article: Lemborexant

Type of Study	Test System	Method of Administration	Dose (mg/kg)	GLP[a]	Study Number	Location
Single-Dose Study	Rat	Oral gavage	0, 100, 300, 1000	Yes	S10120	4.2.3.1.2
Single-Dose Study	Monkey	Oral gavage	0, 100, 300, 1000	Yes	S10118	4.2.3.1.3
7-Day DRF Study	Mouse	Oral gavage	300, 1000, 1500	No	K12075	4.2.3.2.1
7-Day DRF Study	Rat	Oral gavage	100, 300, 1000	No	S10043	4.2.3.2.4
4-Week Toxicity Study	Rat	Oral gavage	0, 30, 100, 1000	Yes	K11004	4.2.3.2.5
13/26-Week Toxicity Study	Rat	Oral gavage	0, 30, 100, 1000	Yes	K12033	4.2.3.2.8
4-Week Toxicity Study	Monkey	Oral gavage	0, 30, 100, 1000	Yes	SBL038-055	4.2.3.2.9
13-Week Toxicity Study	Monkey	Oral gavage	0, 20, 100, 1000	Yes	SBL038-067	4.2.3.2.10
39-Week Toxicity Study	Monkey	Oral gavage	0, 10, 100, 1000	Yes	6700074	4.2.3.2.11
104-Week Carcinogenicity Study	Rat	Oral gavage	0, 10(F), 30, 100, 300(M)	Yes	K13092	4.2.3.4.1.1
4-Week Toxicokinetics Study	Mouse[b]	Oral gavage	100, 300, 1000	Yes No	K14035 DMPKT2014-007[c]	4.2.3.2.3 4.2.3.7.5.1
EFD Study	Rat	Oral gavage	0, 60, 200, 600	Yes	K12010	4.2.3.5.2.2
EFD Study	Rat	Oral gavage	0, 20, 60, 200	Yes	K12080	4.2.3.5.2.3
EFD Study	Rabbit	Oral gavage	0, 10, 30, 100	Yes	K12011	4.2.3.5.2.6
PPND DRF Study	Rat	Oral gavage	200, 400, 600	No	20060759	4.2.3.5.3.1
PPND Study	Rat	Oral gavage	0, 30, 100, 300	Yes	20060760	4.2.3.5.3.2
Mechanistic Study	Rat	Oral gavage	1000/800[d]	Yes	6700122	4.2.3.7.3.1
Mechanistic Study	Rat	Oral gavage	30, 100, 1000	No	K14010	4.2.3.7.3.2
Mechanistic Study	Rat	Oral gavage	100, 1000	No	K14014	4.2.3.7.3.3

Test Article: Lemborexant

Type of Study	Test System	Method of Administration	Dose (mg/kg)	GLP[a]	Study Number	Location
Dependence	Rat	Oral gavage	200 (100×2), 600 (300×2)	Yes	ES13070	4.2.3.7.4.1
Dependence	Monkey	Intravenous	0.04, 0.2, 1	No	ES13261	4.2.3.7.4.2
4-Week Toxicokinetics Study	Rat	Oral gavage	10(F), 30(M), 100, 1000	Yes	ES15364	4.2.3.7.5.2
4-Week Toxicokinetics Study	Monkey	Oral gavage	10, 100, 1000	Yes	ES15365	4.2.3.7.5.3

DRF = dose range-finding, EFD = embryo-fetal development, F = female, GLP = Good Laboratory Practice, M = male, PPND = pre- and postnatal development, Tg = transgenic.

a: Indicates study includes a GLP Compliance statement.
b: Non-transgenic mouse (CB6F1-nonTg rasH2).
c: The TK of lemborexant metabolite M10 is reported in Study No. DMPK2014-007, which was conducted as a non-GLP study.
d: 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.

2.6.7.3 トキシコキネティクス成績の一覧

Test Article:　Lemborexant

	Steady State AUC (ng·h/mL)							
Species	Mouse		Rat		Rabbit	Monkey		Human
Method of Administration	Oral		Oral		Oral	Oral		Oral
Gender (M/F)	M	F	M	F	F	M	F	M and F
Dose (mg/kg)								
0.17[a]	—	—	—	—	—	—	—	441[a]
10	—	—	—	916[b]	2904.2[c]	5510[d]	4970[d]	—
20	—	—	—	2845[c]	—	19,696[e]	12,795[e]	—
30	—	—	3574[b] 2330[f]	7516[b] 6448[g] 5335[f]	10,017[c]	27,335[h]	18,192[h]	—
60	—	—	—	25,529[c]	—	—	—	—
100	8299[h]	18,328[h]	32,185[b] 18,015[f]	48,270[b] 40,833[g] 26,486[f]	61,388[c]	82,900[d]	82,800[d]	—
200	—	—	—	62,870[c] 65,046[g]	—	—	—	—
300	20,692[h]	27,272[h]	36,034[b]	24,255.7[i] 90,718[g]	–	–	–	–
400	—	—	—	107,953[g]	—	—	—	—
600	—	—	—	171,321[c] 131,148[g]	—	—	—	—

Test Article: Lemborexant

	Steady State AUC (ng·h/mL)							
Species	Mouse		Rat		Rabbit	Monkey		Human
1000/800[j]	—	—	—	204,463[j]	—	—	—	—
1000	52,509[h]	55,877[h]	60,697[f]	240,344[f]	—	155,000[d]	98,200[d]	—
1500	106,757[i]	63,686[i]	—	—	—	—	—	—

Note: Values were taken from a longer-term study if the same dose level was used in more than one study.

— = not applicable, DRF = dose range-finding, EFD = embryo-fetal development, F = female, M = male, PPND = pre- and postnatal development.

a: 10 mg/man, Study CPMS-E2006-004R-v1.

b: Carcinogenicity Study (添付資料 4.2.3.4.1.1［ラット，K13092］).

c: EFD Study (添付資料 4.2.3.5.2.2［ラット，K12010］，添付資料 4.2.3.5.2.3［ラット，K12080］，添付資料 4.2.3.5.2.6［ウサギ，K12011］).

d: 39-Week Toxicity Study (添付資料 4.2.3.2.11［サル，6700074］).

e: 13-Week Toxicity Study (添付資料 4.2.3.2.10［サル，SBL038-067］).

f: 13/26-Week Toxicity Study (添付資料 4.2.3.2.8［ラット，K12033］).

g: PPND DRF Study and PPND Study (添付資料 4.2.3.5.3.1 及び 4.2.3.5.3.2［ラット，20060759 及び 20060760］).

h: 4-Week Toxicity/Toxicokinetics Study (添付資料 4.2.3.2.3［マウス，K14035］，添付資料 4.2.3.2.9［サル，SBL038-055］).

i: 7-Day DRF Study (添付資料 4.2.3.2.1［マウス，K12075］，添付資料 4.2.3.2.4［ラット，S10043］).

j: Mechanistic Study (添付資料 4.2.3.7.3.1［ラット，6700122］). 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.

Test Article: Lemborexant

	Steady State C_{max} (ng/mL)							
Species	Mouse		Rat		Rabbit	Monkey		Human
Method of Administration	Oral		Oral		Oral	Oral		Oral
Gender (M/F)	M	F	M	F	F	M	F	M and F
Dose (mg/kg)								
0.17[a]	—	—	—	—	—	—	—	61.6[a]
10	—	—	—	491[b]	528.3[c]	960[d]	1160[d]	—
20	—	—	—	647[c]	–	2655[e]	2171[e]	—
30	—	—	954[b] 690[f]	2159[b] 947[g] 1543[f]	1684[c]	3314[h]	3031[h]	—
60	—	—	—	2006[c]	—	—	—	—
100	1117[h]	1826[h]	4645[b] 2597[f]	6810[b] 3150[g] 5230[f]	5746[c]	6930[d]	8660[d]	—
200	—	—	—	4770[c] 4401[g]	—	—	—	—
300	1460[h]	1946[h]	3355[b]	2670.3[i] 5625[g]	—	—	—	—
400	—	—	—	6859[g]	—	—	—	—
600	—	—	—	10,476[c] 9286[g]	—	—	—	—

Test Article: Lemborexant

	Steady State C_{max} (ng/mL)							
Species	Mouse		Rat		Rabbit	Monkey		Human
1000/800[j]	—	—	—	11,540[j]	—	—	—	—
1000	3628[h]	5026[h]	4798[f]	13,906[f]	—	9620[d]	6930[d]	—
1500	7959[i]	4973[i]	—	—	—	—	—	—

Note: Values were taken from a longer-term study if the same dose level was used in more than one study.

— = not applicable, DRF = dose range-finding, EFD = embryo-fetal development, F = female, M = male, PPND = pre- and postnatal development.

a: 10 mg/man, Study CPMS-E2006-004R-v1.

b: Carcinogenicity Study (添付資料 4.2.3.4.1.1［ラット，K13092］).

c: EFD Study (添付資料 4.2.3.5.2.2［ラット，K12010］，添付資料 4.2.3.5.2.3［ラット，K12080］，添付資料 4.2.3.5.2.6［ウサギ，K12011］).

d: 39-Week Toxicity Study (添付資料 4.2.3.2.11［サル，6700074］).

e: 13-Week Toxicity Study (添付資料 4.2.3.2.10［サル，SBL038-067］).

f: 13/26-Week Toxicity Study (添付資料 4.2.3.2.8［ラット，K12033］).

g: PPND DRF Study and PPND Study (添付資料 4.2.3.5.3.1 及び 4.2.3.5.3.2［ラット，20060759 及び 20060760］).

h: 4-Week Toxicity/Toxicokinetics Study (添付資料 4.2.3.2.3［マウス，K14035］，添付資料 4.2.3.2.9［サル，SBL038-055］).

i: 7-Day DRF Study (添付資料 4.2.3.2.1［マウス，K12075］，添付資料 4.2.3.2.4［ラット，S10043］).

j: Mechanistic Study (添付資料 4.2.3.7.3.1［ラット，6700122］). 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.

2.6.7.4 毒性試験：被験物質（バッチ毎）一覧

Test Article: Lemborexant

Batch (Lot) No.	Assay (%)	Impurities			Study Number	Type of Study
		Total Impurities (%)	類縁物質A*	Individual Unspecified		
Proposed Commercial Specification:	[redacted]% to [redacted]%	≤[redacted]%	≤[redacted]%	≤[redacted]%, each		
[redacted]	[redacted][a]	[redacted]	Not applicable	Not applicable	S10042	Single-Dose Study in Rats
					S10043	7-Day DRF Study in Rats
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (sum of unspecified impurities)	S10120	Single-Dose Study in Rats
					S10118	Single-Dose Study in Monkeys
					S11002	Ames Assay
[redacted]	[redacted]	≤[redacted]	≤[redacted]	≤[redacted]	K12075	7-Day DRF Study in Mice
					K12033	13/26-Week Toxicity Study in Rats
					6700074	39-Week Toxicity Study in Monkeys
					K13078	FEED Study in Male Rats
					K13063	FEED Study in Female Rats
					20060758	EFD Study in Rats
					20060759	PPND DRF Study in Rats
					20060760	PPND Study in Rats
					6700122	Mechanistic Study in Rats
					K14010	Mechanistic Study in Rats
					K14014	Mechanistic Study in Rats
					ES13070	Dependence Study in Rats

*新薬承認情報提供時に置き換え

Test Article: Lemborexant

Batch (Lot) No.	Assay (%)	Impurities			Study Number	Type of Study
		Total Impurities (%)	類縁物質A*	Individual Unspecified		
Proposed Commercial Specification:	[redacted]% to [redacted]%	≤[redacted]%	≤[redacted]%	≤[redacted]%, each		
					ES13261	Preliminary Intravenous Self-Administration Study in Monkeys
					ES13262	Intravenous Self-Administration Study in Monkeys
					T14019	Phototoxicity Test
					W-20140891	Effect on In Vitro Culture of *Plasmodium falciparum*[a]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (sum of unspecified impurities)	K11004	4-Week Toxicity Study in Rats
					SBL038-055	4-Week Toxicity Study in Monkeys
					K11008	Mouse Lymphoma Assay
					K11011	Micronucleus Assay in Rats
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (sum of unspecified impurities)	K12033	13/26-Week Toxicity Study in Rats
					SBL038-067	13-Week Toxicity Study in Monkeys
					K12001	DRF Study in Pregnant Rats
					K12010	EFD Study in Rats
					K12080	EFD Study in Rats
					K12002	DRF Study in Pregnant Rabbits

*新薬承認情報提供時に置き換え

Test Article: Lemborexant

Batch (Lot) No.	Assay (%)	Impurities			Study Number	Type of Study
		Total Impurities (%)	類縁物質A*	Individual Unspecified		
Proposed Commercial Specification:	[redacted]% to [redacted]%	≤[redacted]%	≤[redacted]%	≤[redacted]%, each		
					K12011	EFD Study in Rabbits
[redacted]	[redacted]	[redacted]	[redacted]	≤[redacted]	K13092	104-Week Carcinogenicity Study in Rats
					K14036	4-Week DRF Study in Mice[b]
					K14035	4-Week Toxicokinetics Study in Mice[c]
					K15016	26-Week Carcinogenicity Study in Mice[d]
					463-058	Drug Discrimination Study in Rats
					T17022	Phototoxicity Test
					ES15364	4-Week Toxicokinetics Study in Rats
					ES15365	4-Week Toxicokinetics Study in Monkeys

DRF = dose range-finding, EFD = embryo-fetal development, FEED = fertility and early embryonic development, PPND = pre- and postnatal development.

a: Assigned purity
b: Lot No. [redacted] was mentioned in the report. This is a typographical error.
c: CB6F1-nonTg rasH2 Mice.
d: CB6F1-Tg rasH2.

*新薬承認情報提供時に置き換え

2.6.7.5 単回投与毒性試験

Test Article: Lemborexant

Species / Strain	Method of Administration (Vehicle / Formulation)	Doses (mg/kg)	Gender and No. per Group	Observed Maximum Nonlethal Dose (mg/kg)	Approximate Lethal Dose	Noteworthy Findings	Study Number
Rat/Sprague Dawley	Oral gavage (0.5% MC solution / suspension)	100, 300, 1000	3M/3F	1000	>1000	100-1000: No toxicity	S10042
Rat/Sprague Dawley	Oral gavage (1 mol/L HCl: 0.5% MC solution [1:4, v/v] / suspension)	0, 100, 300, 1000	10-15M/10-15F	1000	>1000	100: No toxicity 300: No toxicity, ↑Liver weight (F) 1000: NOAEL, ↑Liver weight	S10120
Monkey/ Cynomolgus	Oral gavage (1 mol/L HCl: 0.5% MC solution [1:4, v/v] / suspension)	0, 100, 300, 1000	3-5M/3-5F	1000	>1000	100: No toxicity 300: NOAEL 1000: Vomiting, soft stool, partially closed eyes, ↓ serum chloride	S10118

F = female, M = male, MC = methylcellulose, NOAEL = no observed adverse effect level, ↑ = increased, ↓ = decreased.

2.6.7.6 反復投与毒性試験：重要な試験以外の試験

Test Article: Lemborexant

Species / Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Dose (mg/kg)	Gender and No. per Group	No Observed Adverse Effect Level	Noteworthy Findings	Study Number
Mouse/ICR	Oral gavage (1 mol/L HCl: 0.5% MC solution [1:4, v/v] / suspension)	7 days	300, 1000, 1500	21M/21F	NA	300: No toxicity 1000: No toxicity 1500: ↓Body weights and food consumption, decreased activity, few feces, staining of nose region, enlarged liver	K12075
Mouse/CB6F1 –nonTg rasH2	Oral gavage (1 mol/L HCl: 0.5% MC solution [1:4, v/v] / suspension)	4 weeks	100, 300, 1000	25M/25F	NA	Toxicokinetics study No death.	K14035
Mouse/CB6F1 -nonTg rasH2	Oral gavage (1 mol/L HCl: 0.5% MC solution [1:4, v/v] / suspension)	4 weeks	0, 100, 300, 1000	10M/10F	NA	100: No toxicity 300: ↑Body weights and liver weight (F), ↑ALT (F) 1000: ↑Body weights, liver weight and ALT, centrilobular hypertrophy of hepatocytes	K14036

Test Article: Lemborexant

Species / Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Dose (mg/kg)	Gender and No. per Group	No Observed Adverse Effect Level	Noteworthy Findings	Study Number
Rat/Sprague Dawley	Oral gavage (0.5% MC solution / suspension)	7 days	0, 100, 300, 1000	3M/3F	NA	100: No toxicity 300: No toxicity 1000: ↓Food consumption (F), ↑total cholesterol (F) and liver weight (F)	S10043

ALT = alanine aminotransferase, F = female, M = male, MC = methylcellulose, NA = not applicable, ↑ = increased, ↓ = decreased.

2.6.7.7 反復投与毒性試験：重要な試験

2.6.7.7.A　　**Test Article: Lemborexant**

Report Title: E2006: A 4-Week Oral Toxicity Study in Rats		**Study No.** K11004 (K13044[a], K12012[b])
Species / Strain: Rat / Sprague Dawley	Duration of Dosing: 4 weeks	Location in CTD: 4.2.3.2.5 (4.2.3.2.7, 4.2.3.2.6)
Initial Age: 8 weeks old	Duration of Postdose: Not applicable	GLP Compliance: Yes (except for K12012[b])
Date of First Dose: [redacted] 20[redacted]	Method of Administration: Oral gavage	
Vehicle / Formulation: 1 mol/L HCl: 0.5% MC solution (1:4, v/v) / suspension		
No Observed Adverse Effect Level: 100 (F) and 1000 mg/kg (M)		Special Features: None

Daily Dose (mg/kg):	**0 (Control)**		**30**		**100**		**1000**	
Number of Animals:	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Number of Animals for Toxicokinetics:	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Toxicokinetics: C_{max} (ng/mL)								
Day 1	NA	NA	351	1369	1762	2537	2973	3951
Day 8	NA	NA	380	1409	2235	4119	3727	8018
Day 28	NA	NA	352	1867	1792	4456	4222	7025
Toxicokinetics: $AUC_{(0\text{-}24)}$ (ng·h/mL)								
Day 1	NA	NA	824	3301	11,094	18,058	38,084	62,795
Day 8	NA	NA	1181	3130	11,987	21,333	44,857	128,515
Day 28	NA	NA	1541	3981	13,206	25,873	51,901	88,431
Noteworthy Findings								
Died or sacrificed moribund	0	0	0	0	0	0	0	0
Final Body Weight on Day 28 (g)	349.7	211.5	350.8	211.5	347.5	211.9	344.9	200.8*
Food Consumption on Day 28 (g)	21	14	21	14	21	14	21	14

Daily Dose (mg/kg):	**0 (Control)**		**30**		**100**		**1000**	
Number of Animals:	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Clinical Observations:	–	–	–	–	–	–	–	–
Ophthalmology:	–	–	–	–	–	–	–	–
Hematology:								
Reticulocyte (10^9/L)	158.3	152.7	194.0	149.8	150.1	150.3	153.9	121.5
Serum Chemistry:								
Urea nitrogen (mg/dL)	16.5	17.2	16.9	18.7	17.1	16.4	17.2	24.7##
Total protein (g/dL)	5.0	5.2	5.0	5.5	5.3**	5.5	5.4**	6.1**
Total cholesterol (mg/dL)	62	58	61	66	66	68	73*	147##
Urinalysis:	–	–	–	–	–	–	–	–
Ophthalmology:	–	–	–	–	–	–	–	–
Organ Weights:								
Liver (absolute, g)	11.69	6.36	12.06	6.78	12.49	7.61**	14.52**	12.08**
Liver (relative to BW, g%)	3.26	2.95	3.38	3.13	3.52**	3.52##	4.14**	5.96##
Gross Pathology:								
Number Evaluated:	10	10	10	10	10	10	10	10
Liver, enlarged	0	0	0	0	0	0	0	10
Histopathology:								
Number Evaluated:	10	10	10	10	10	10	10	10
Bone marrow								
Hypocellularity 1+	0	0	0	0	0	0	0	1
Liver								

Daily Dose (mg/kg):		**0 (Control)**		**30**		**100**		**1000**	
Number of Animals:		**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Hypertrophy, hepatocytes	1+	0	0	0	0	0	0	0	6
Thymus									
Lymphoid depletion	1+	0	0	0	0	0	0	0	1
Femur[a]									
Pigmentation	MIN	0	0	0	0	0	0	1	5
Immunohistochemistry[b]:									
Number Evaluated:		0	3	0	0	0	0	0	3
CYP1A2	1+	NA	3	NA	NA	NA	NA	NA	0
	2+	NA	0	NA	NA	NA	NA	NA	3
CYP3A1	1+	NA	3	NA	NA	NA	NA	NA	0
	3+	NA	0	NA	NA	NA	NA	NA	3
CYP3A4	1+	NA	3	NA	NA	NA	NA	NA	0
	3+	NA	0	NA	NA	NA	NA	NA	3

–: No noteworthy findings, GRADE; MIN: minimal, 1+: slight, 2+: moderate, 3+: marked.

$AUC_{(0\text{-}24)}$ = AUC from zero time to 24 hours, BW = body weight, CTD = Common Technical Document, CYP = cytochrome P450, F = female, GLP =Good Laboratory Practice, M = male, MC = methylcellulose, NA = not applicable.

a: Histopathologic reevaluation of bone tissue (femur and sternum) from Study No. K11004 was performed in a separate study (添付資料 4.2.3.2.7 ［K13044］).

b: CYP induction in rat liver from Study No. K11004 was evaluated immunohistochemically in a separate study (添付資料 4.2.3.2.6［K12012］).

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

2.6.7.7.B　　**Test Article: Lemborexant**

Report Title: E2006: 13-Week and 26-Week Oral Toxicity Study in Rats		**Study No.** K12033
Species / Strain: Rat / Sprague Dawley	Duration of Dosing: 13/26 weeks	Location in CTD: 4.2.3.2.8
Initial Age: 8 weeks old	Duration of Postdose: Not applicable	GLP Compliance: Yes
Date of First Dose: [redacted] 20[redacted]	Method of Administration: Oral gavage	
Vehicle / Formulation: 1 mol/L HCl: 0.5% MC solution (1:4, v/v) / suspension		
No Observed Adverse Effect Level: 30 (F) and 100 mg/kg (M)		Special Features: None

Daily Dose (mg/kg):	**0 (Control)**		**30**		**100**		**1000**	
Number of Animals[a]:	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**
Number of Animals for Toxicokinetics:	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Toxicokinetics: C_{max} (ng/mL)								
Day 1	NA	NA	371	955	1816	2711	4151	7461
Day 92	NA	NA	662	1829	2650	3667	4819	10,811
Day 183	NA	NA	690	1543	2597	5230	4798	13,906
Toxicokinetics: $AUC_{(0\text{-}24)}$ (ng·h/mL)								
Day 1	NA	NA	609	1886	10,233	16,661	67,457	115,969
Day 92	NA	NA	2195	5207	21,470	21,971	56,749	168,962
Day 183	NA	NA	2330	5335	18,015	26,486	60,697	240,344
Noteworthy Findings								
Died or sacrificed moribund	0	0	0	0	0	0	2[b]	4[c]
Final Body Weight on Day 92 (g)	457.1	241.6	459.2	244.3	451.4	251.0[#]	442.2	221.9[##]
Final Body Weight on Day 183 (g)	524.9	249.1	518.7	264.3*	519.1	272.4**	493.1*	242.4
Food Consumption on Day 50 (g)	21	14	21	14	21	14	20	13
Food Consumption on Day 92 (g)	21	14	21	14	21	14	21	13
Food Consumption on Day 141 (g)	21	14	21	14	21	14	19	12
Food Consumption on Day 183 (g)	21	14	21	14	21	14	21	13

Daily Dose (mg/kg):		**0 (Control)**		**30**		**100**		**1000**	
Number of Animals[a]:		**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**
Clinical Observations:									
Emaciation		0	0	0	0	0	0	1	2
Food left		2[k]	1[j]	2[k]	0[j]	2[k]	2[j]	14[k]	20[j]
Decreased activity		0	0	0	0	0	0	1[b]	3
Staining, oral region		0	0	0	0	0	0	1	1
Discoloration of teeth		0	0	1	0	13	10	21	22
Few feces		0	0	0	0	0	0	1	2
Ophthalmology:		—	—	—	—	—	—	—	—
Hematology:									
RBC (10^6/μL)	Day 93/94	8.12	7.34	8.03	7.47	7.97	7.38	7.52**	7.03
	Day 184/185	8.33	7.33	8.33	7.64*	8.31	7.44	8.04	7.62
Hemoglobin (g/dL)	Day 93/94	14.9	13.8	14.6	13.7	13.9**	13.6	13.4**	12.2**
	Day 184/185	14.8	13.9	14.7	14.2	14.6	13.8	13.9**	13.3*
Hematocrit (%)	Day 93/94	42.8	39.2	42.0	39.4	40.6	38.9	38.9	35.6
	Day 184/185	43.8	40.2	43.5	41.1	43.2	40.3	41.3	39.4
MCV (fL)	Day 93/94	52.8	53.4	52.3	52.8	51.0	52.7	51.7	50.7**
	Day 184/185	52.7	54.8	52.3	53.8	52.0	54.2	51.5	51.8**
MCH (pg)	Day 93/94	18.4	18.8	18.1	18.4	17.5*	18.5	17.8	17.3**
	Day 184/185	17.8	19.0	17.7	18.6	17.6	18.5	17.3	17.5**
Reticulocyte (10^9/L)	Day 93/94	137.3	124.3	132.3	118.8	147.7	139.1	147.1	123.0
	Day 184/185	139.9	127.0	145.4	124.7	165.2	132.8	158.4	174.0
WBC (10^3/μL)	Day 93/94	7.03	3.31	7.51	4.33	8.05	3.64	8.17	5.45*
	Day 184/185	7.91	2.95	6.60	3.84	7.93	4.83[#]	7.77	7.02[##]
APTT (sec.)	Day 93/94	24.1	20.0	25.4	20.2	26.0	21.6	28.2**	21.0
	Day 184/185	22.4	19.9	22.9	19.1	23.6	19.8	24.8[#]	19.3
Lymphocyte Subset analysis[d]:		—	—	—	—	—	—	—	—

Daily Dose (mg/kg):		**0 (Control)**		**30**		**100**		**1000**	
Number of Animals[a]:		**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**
Serum Chemistry:									
Urea nitrogen (mg/dL)	Day 93/94	17.4	21.5	15.8	19.2	15.3	18.4	18.7	30.5
	Day 184/185	15.7	19.6	16.7	20.0	16.0	19.2	18.2*	29.2$^{\#}$
Total protein (g/dL)	Day 93/94	5.0	5.6	5.1	5.6	5.3**	5.9	5.6**	5.9
	Day 184/185	5.3	5.8	5.5	5.9	5.6*	6.3*	5.8**	6.5**
Albumin (g/dL)	Day 93/94	2.3	2.7	2.3	2.7	2.4	2.8	2.5**	2.5
	Day 184/185	2.2	2.9	2.4*	2.8	2.4**	3.0	2.5**	2.9
Globulin (g/dL)	Day 93/94	2.7	2.9	2.8	2.9	3.0**	3.1	3.2**	3.4$^{\#\#}$
	Day 184/185	3.1	3.0	3.1	3.1	3.2	3.3**	3.3*	3.7**
Total cholesterol (mg/dL)	Day 93/94	63	74	71	76	71	92	86**	180$^{\#\#}$
	Day 184/185	71	85	71	84	71	114$^{\#}$	95$^{\#}$	176$^{\#\#}$
Ca (mg/dL)	Day 93/94	9.5	9.5	9.6	9.8	9.9**	10.0*	10.1**	10.2**
	Day 184/185	9.4	9.5	9.5	9.5	9.6	10.1**	10.0**	10.3**
K (mEq/L)	Day 93/94	4.9	4.1	4.9	4.3	4.9	4.1	4.9	4.9$^{\#\#}$
	Day 184/185	4.8	3.9	4.7	4.1	4.8	4.1	4.8	4.5**
Fe (μg/dL)	Day 184/185	188.3	387.6	188.0	343.6	198.4	303.6*	191.0	220.4**
Bone Metabolism Markers[e]		—	—	—	—	—	—	—	—
Urinalysis:		—	—	—	—	—	—	—	—
Ophthalmology:		—	—	—	—	—	—	—	—
Organ Weights:									
Liver (absolute, g)	Day 93/94	12.83	6.51	13.58	7.05	15.02$^{\#}$	8.75$^{\#\#}$	18.84$^{\#\#}$	12.61$^{\#\#}$
	Day 184/185	14.27	6.78	14.97	7.27	16.43**	9.47**	19.60**	13.27**
Liver (relative to BW, g%)	Day 93/94	2.83	2.60	2.90	2.86	3.30$^{\#\#}$	3.47$^{\#\#}$	4.21$^{\#\#}$	5.75$^{\#\#}$
	Day 184/185	2.69	2.70	2.85	2.73	3.13$^{\#\#}$	3.45$^{\#\#}$	3.95$^{\#\#}$	5.45$^{\#\#}$
Adrenals (absolute, mg) Day93/94		56	61	59	60	52	62	60	50

Daily Dose (mg/kg):	**0 (Control)**		**30**		**100**		**1000**	
Number of Animals[a]:	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**
Day 184/185	62	70	57	67	59	61	54	50##
Adrenals (relative to BW, mg%) Day 93/94	13	24	12	25	12	25	13	23
Day 184/185	12	28	11	25	11	22**	11	21**
Gross Pathology[f]:								
Day 93/94								
Number Evaluated:	10	10	10	10	10	10	10	10
Incisor, discoloration	0	0	0	0	5	2	10	10
Liver, enlarged	0	0	0	0	0	0	4	9
Day 184/185								
Number Evaluated:	12	12	12	12	12	12	10(2)[g]	8(4)[g]
Incisor, discoloration	0	0	1	0	8	8	10(1)	8(4)
Liver, enlarged	0	0	0	0	0	0	2(2)	8(0)
Tibia, fracture	0	0	0	0	0	0	0(1)	0(2)
Fibula, fracture	0	0	0	0	0	0	0(1)	0(1)
Histoathology[h]:								
Day 93/94								
Number Evaluated:	10	10	10	10	10	10	10	10
Femur								
Decreased trabecular bone 1+	0	0	0	0	0	0	0	3
2+	0	0	0	0	0	0	0	3
Decreased mature lamellar bone 1+	0	0	0	0	0	0	2	7
2+	0	0	0	0	0	0	1	2
Pigmentation MIN	0	0	1	0	1	2	0	0
1+	0	0	1	0	4	2	2	2
2+	0	0	0	0	3	3	5	5

Daily Dose (mg/kg):		**0 (Control)**		**30**		**100**		**1000**	
Number of Animals[a]:		**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**
	3+	0	0	0	0	0	0	0	3
Tibia									
Decreased trabecular bone	1+	0	0	0	0	0	0	0	3
	2+	0	0	0	0	0	0	0	3
Decreased mature lamellar bone	1+	0	0	0	0	0	0	3	6
	2+	0	0	0	0	0	0	0	1
Pigmentation	MIN	0	0	0	0	0	1	0	0
	1+	0	0	0	0	2	6	5	6
	2+	0	0	0	0	0	0	4	3
	3+	0	0	0	0	0	0	0	1
Sternum									
Pigmentation	1+	0	0	0	0	0	0	0	2
	2+	0	0	0	0	0	0	0	1
Alveolar bone									
Pigmentation	1+	0	0	0	0	1	0	6	2
	2+	0	0	0	0	0	0	4	8
Incisor									
Decreased iron contents, ameloblasts	1+	0	0	0	0	0	0	5	0
	2+	0	0	0	0	0	0	4	10
Degeneration, ameloblasts	1+	0	0	0	0	0	0	1	1
	2+	0	0	0	0	0	0	0	6
Pigmentation, dentin	1+	0	0	0	0	1	0	8	5
	2+	0	0	0	0	0	0	1	5
Molar									
Pigmentation, dentin	1+	0	0	0	0	0	0	1	3

Daily Dose (mg/kg):		**0 (Control)**		**30**		**100**		**1000**	
Number of Animals[a]:		**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**
Liver									
Hypertrophy, hepatocytes	1+	0	0	0	0	0	0	2	4
	2+	0	0	0	0	0	0	0	6
Thyroids									
Follicular cell hypertrophy	1+	0	0	0	0	0	0	0	2
Day 184/185									
Number Evaluated:		12	12	12	12	12	12	10(2)[f]	8(4)[f]
Femur									
Decreased trabecular bone	1+	0	0	0	0	0	0	2(0)	4(2)
	2+	0	0	0	0	0	0	0(0)	1(0)
Decreased mature lamellar bone	1+	0	0	0	0	0	0	2(0)	2(0)
	2+	0	0	0	0	0	0	6(1)	4(1)
Pigmentation	MIN	0	0	5	0	0	1	0(0)	0(0)
	1+	0	0	5	4	3	3	4(0)	1(0)
	2+	0	0	1	0	8	7	5(1)	6(4)
	3+	0	0	0	0	0	0	0(0)	1(0)
Tibia									
Decreased trabecular bone	1+	0	0	0	0	0	0	0(0)	3(2)
	2+	0	0	0	0	0	0	0(0)	2(0)
Decreased mature lamellar bone	1+	0	0	0	0	0	0	1(0)	0(0)
	2+	0	0	0	0	0	0	3(0)	1(0)
Fracture		0	0	0	0	0	0	0(1)	0(2)
Pigmentation	MIN	0	0	0	0	1	2	0(0)	0(0)
	1+	0	0	0	0	7	9	9(1)	5(3)
	2+	0	0	0	0	3	1	1(0)	3(1)

Daily Dose (mg/kg):		**0 (Control)**		**30**		**100**		**1000**	
Number of Animals[a]:		**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**
Sternum									
Pigmentation	1+	0	0	0	0	1	1	4(1)	3(1)
	2+	0	0	0	0	0	0	3(0)	5(0)
Fibula									
Fracture		0	0	0	0	0	0	0(1)	0(1)
Alveolar bone									
Pigmentation	1+	0	0	0	0	0	0	2(0)	2(0)
	2+	0	0	0	0	0	0	7(1)	6(3)
	3+	0	0	0	0	0	0	1(0)	0(1)
Incisor									
Decreased iron contents, ameloblasts	1+	0	0	0	0	0	1	6(1)	2(0)
	2+	0	0	0	0	0	0	3(0)	6(4)
Degeneration, ameloblasts	1+	0	0	0	0	0	0	3(1)	2(0)
	2+	0	0	0	0	0	0	1(0)	6(3)
Pigmentation, dentin	1+	0	0	0	0	1	1	10(1)	4(3)
	2+	0	0	0	0	0	0	0(0)	4(1)
Molar									
Pigmentation, dentin	1+	0	0	0	0	0	0	0(0)	6(2)
Liver									
Hypertrophy, hepatocytes	1+	0	0	0	0	0	0	2(1)	4(3)
	2+	0	0	0	0	0	0	0(0)	4(1)
Thyroids									
Follicular cell hypertrophy	1+	0	0	0	0	0	0	0(0)	2(0)
Bone densitometry[i]:									
Femur									

Daily Dose (mg/kg):		**0 (Control)**		**30**		**100**		**1000**	
Number of Animals[a]:		**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**	**M: 10+12**	**F: 10+12**
Area (Whole, cm^2)	Day 93/94	2.487	1.900	2.472	1.889	2.415	1.925	2.414	1.852
	Day 184/185	2.498	1.866	2.501	1.893	2.395	1.916	2.509	1.770
BMC (Whole, mg)	Day 93/94	389.4	273.6	396.5	271.9	380.3	283.5	380.1	240.4
	Day 184/185	427.9	290.0	429.8	295.4	403.9	287.8	423.2	252.0
BMD (Whole, mg/cm^2)	Day 93/94	156.4	144.0	160.4	143.8	157.5	147.2	157.3	129.8**
	Day 184/185	171.0	155.3	171.6	156.0	168.7	150.1	168.7	142.2**
Tibia									
Area (Whole, cm^2)	Day 93/94	1.945	1.511	2.007	1.489	1.902	1.506	1.942	1.452
	Day 184/185	2.057	1.536	2.079	1.540	1.950	1.483	1.880	1.469
BMC (Whole, mg)	Day 93/94	234.5	170.2	251.2	165.4	234.8	173.3	236.9	148.7
	Day 184/185	275.0	183.9	282.5	182.4	263.1	169.3	254.5	165.4

Daily Dose (mg/kg):		0 (Control)		30		100		1000	
Number of Animals[a]:		M: 10+12	F: 10+12	M: 10+12	F: 10+12	M: 10+12	F: 10+12	M: 10+12	F: 10+12
BMD (Whole, mg/cm^2)	Day 93/94	120.5	112.8	125.2	111.1	123.4	115.0	122.0	102.3**
	Day 184/185	133.4	119.7	135.8	118.3	135.0	113.9*	135.4	112.6**

—: No noteworthy findings. GRADE; MIN: minimal (for pigmentation only), 1+: slight, 2+: moderate, 3+: marked.

APTT = activated partial thromboplastin time, $AUC_{(0\text{-}24)}$ = AUC from zero time to 24 hours, BMC = bone mineral content, BMD = bone mineral density, BW = body weight, CTD = Common Technical Document, F = female, GLP =Good Laboratory Practice, M = male, MC = methylcellulose, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, NA = not applicable, RBC = red blood cells, WBC = white blood cells.

a: 10 animals for 13-week and 12 animals for 26-week treatment.

b: One mortality was considered related to test article (One male [Animal No. 03M09] exhibited abnormal gait because of bone fractures of hindlimbs, and euthanized because of humane reason on Day 153. Another male [Animal No. 03M07] showed decreased activity and was found dead approximately 1 hour after dosing on Day 16. Necropsy findings of this animal revealed intubation error.

c: Three mortalities were considered related to test article (One female was euthanized because of moribund condition on Day 142 [Animal No. 03F01]. The cause of moribundity in this animal was not identified by postmortem examinations. Two females [Animal Nos. 03F10, and 03F12] exhibited abnormal gait because of bone fractures of hindlimbs, and were euthanized for humane reasons on Days 134 and 127, respectively. One female [Animal No. 03F04] was euthanized because of moribund condition on Day 115. However, the moribundity was considered due to accidental injuries of the mandibular and hindlimb claw).

d: Lymphocytes were stained by CD3, CD4, CD8, CD161a, CD45RA or CD45.

e: Inorganic phosphorus, osteocalcin [active type], collagen type I cross-linked C-teropeptide, tartrate-resistant acid phosphatase, total ALP and bone-type ALP.

f: Macroscopic findings of animals that were found dead or moribund sacrifice at 1000 mg/kg (related to test article) include: bone fracture in the hindlimb (unilateral or bilateral tibia or fibula) in 1 male and 2 females; hemorrhage related to bone fracture in 1 female; discoloration of the incisor teeth in these animals; enlarged liver in 2 males; emaciation and intestinal changes including small and firm feces in large intestine in 1 female.

g: Numbers in parenthesis mean number of animals that were found dead or moribund.

h: In 5 moribund sacrificed animals, changes similar to those in the terminally sacrificed animals were observed in the bones, teeth and liver. Fracture of the tibia or fibula occurred in 3 animals and included: right tibia and fibula (Animal No. 03M09), left tibia (Animal No. 03F12), and right and left tibia and left fibula (Animal No. 03F10), and was accompanied by either callus formation or hemorrhage depending on the timing of the bone fracture. There were various secondary changes related to severe stress or poor physical condition in the moribund animals.

i: Bone density of the femur and tibia fixed by 10% neutral buffered formalin was determined by dual-energy X-ray absorptiometry (DXA).

j: Numbers of animals which showed food left on Day 36 or later were 0, 0, 2, and 19 (control, 30, 100, and 1000 mg/kg, respectively).

k: Numbers of animals which showed food left on Day 106 or later were 1, 0, 2, and 10 (control, 30, 100, and 1000 mg/kg, respectively).

* $P<0.05$, ** $P<0.01$ (Dunnett's test); # $P<0.05$, ## $P<0.01$ (Dunnett's rank test).

2.6.7.7.C　　**Test Article: Lemborexant**

Report Title: E2006: A 4-Week Oral Toxicity Study in Monkeys		**Study No.** SBL038-055
Species / Strain: Monkey / Cynomolgus	Duration of Dosing: 4 weeks	Location in CTD: 4.2.3.2.9
Initial Age: 3-6 years old (M) / 3-5 years old (F)	Duration of Postdose: Not applicable	GLP Compliance: Yes
Date of First Dose: [redacted] 20[redacted] (M) / [redacted] 20[redacted] (F)	Method of Administration: Oral gavage	
Vehicle / Formulation: 1 mol/L HCl: 0.5% MC solution (1:4, v/v) / suspension		
No Observed Adverse Effect Level: 30 mg/kg		Special Features: None

Daily Dose (mg/kg):		**0 (Control)**		**30**		**100**		**1000**	
Number of Animals:		**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4[a]**	**F: 4**
Toxicokinetics: C_{max} (ng/mL)									
	Day 1	NA	NA	2249	1995	3312	3878	3362	3226
	Day 7	NA	NA	3635	2774	6289	4849	6590	7737
	Day 28	NA	NA	3314	3031	7165	8500	5611	3945
Toxicokinetics: $AUC_{(0\text{-}24)}$ (ng·h/mL)									
	Day 1	NA	NA	17,627	10,537	43,734	44,880	64,655	48,143
	Day 7	NA	NA	29,735	19,230	85,738	55,867	106,448	125,210
	Day 28	NA	NA	27,335	18,192	70,446	80,856	88,409	39,299
Noteworthy Findings									
Died or sacrificed moribund		0	0	0	0	0	0	0	0
Body Weight (kg)	Day –1	4.605	2.660	4.733	2.838	4.538	2.658	4.433	2.713
	Day 28	4.548	2.673	4.835	2.853	4.570	2.533	4.363	2.620
Food Consumption (g/day)	Day –1	108.0	97.5	108.0	84.0	108.0	82.5	108.0	105.0
	Day 28	108.0	93.0	108.0	87.0	108.0	79.5	99.0	81.0

Daily Dose (mg/kg):		**0 (Control)**		**30**		**100**		**1000**	
Number of Animals:		**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4[a]**	**F: 4**
Clinical Observations:									
Vomiting		0	0	0	0	4	3	4	3
Salivation		0	0	0	0	4	0	3	2
Sedation		0	0	0	0	0	0	2	0
Sitting position		0	0	0	0	0	0	2	0
Incomplete eyelid opening		0	0	0	0	0	0	1	0
Somnolence		0	0	0	0	0	0	1	0
Lateral position		0	0	1	0	0	0	0	0
Hematology:									
RBC (10^6/mm^3)	Predose	5.650	5.475	5.705	5.233	5.815	5.445	5.750	5.183
	Day 28	5.505	5.318	5.325	5.083	5.178	4.923	4.883	4.578
Hematocrit (%)	Predose	46.83	43.98	44.23	41.88	45.58	40.98	46.20	41.48
	Day 28	44.95	43.00	41.80	40.85	41.48	37.63	39.18	38.10
Hemoglobin (g/dL)	Predose	14.38	13.63	13.90	12.88	14.50	12.73	14.15	12.90
	Day 28	13.98	13.33	12.88	12.53	12.78	11.40	11.63	11.13
Reticulocytes (10^9/L)	Predose	1.05	1.33	1.13	1.48	1.48	1.23	1.00	1.65
	Day 28	1.13	1.08	1.93	1.80	1.70	1.38	2.13	3.28
Serum Chemistry:		—	—	—	—	—	—	—	—
Urinalysis:		—	—	—	—	—	—	—	—
Ophthalmology:		—	—	—	—	—	—	—	—
Electrocardiography:		—	—	—	—	—	—	—	—

Daily Dose (mg/kg):	**0 (Control)**		**30**		**100**		**1000**	
Number of Animals:	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4[a]**	**F: 4**
Organ Weights:	—	—	—	—	—	—	—	—
Gross Pathology:	—	—	—	—	—	—	—	—
Histopathology:	—	—	—	—	—	—	—	—

—: 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, RBC = red blood cells.

a: In one male at 1000 mg/kg, there was a complex clinical syndrome including renal glomerulonephropathy, pulmonary thrombosis, edema in subcutis, and inflammation in the large intestine with correlated clinical pathology changes. Since similar findings were not observed in other studies including 39-week study with up to 1000 mg/kg, the findings were considered incidental.

2.6.7.7.D　　**Test Article: Lemborexant**

Report Title: E2006: A 13-Week Oral Toxicity Study in Monkeys		**Study No.** SBL038-067
Species / Strain: Monkey / Cynomolgus	Duration of Dosing: 13 weeks	Location in CTD: 4.2.3.2.10
Initial Age: 3-6 years old (at the initiation of acclimation)	Duration of Postdose: Not applicable	GLP Compliance: Yes
Date of First Dose: [redacted] 20[redacted] (M) / [redacted] 20[redacted] (F)	Method of Administration: Oral gavage	
Vehicle / Formulation: 1 mol/L HCl: 0.5% MC solution (1:4, v/v) / suspension		
No Observed Adverse Effect Level: 20 mg/kg		
Special Features: Animals in this cohort were subclinically infected by *Plasmodium spp.* and *Plasmodium* recrudescence was observed in one male at 1000 mg/kg.		

Daily Dose (mg/kg):		**0 (Control)**		**20**		**100**		**1000**	
Number of Animals:		**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Toxicokinetics: C_{max} (ng/mL)									
	Day 1	NA	NA	1185	1070	3354	2745	5906	3842
	Day 28	NA	NA	2246	1761	6444	8438	7223	6050
	Day 56	NA	NA	2459	2476	6268[a]	9978	9473	4756
	Day 91	NA	NA	2655	2171	6680[a]	6871	8660	4887
Toxicokinetics: $AUC_{(0\text{-}24)}$ (ng·h/mL)									
	Day 1	NA	NA	7805	5299	56,623	20,705	103,650	72,601
	Day 28	NA	NA	15,524	11,628	74,099	68,539	111,759	94,490
	Day 56	NA	NA	17,355	14,667	69,769[a]	80,375	165,788	58,294
	Day 91	NA	NA	19,696	12,795	72,183[a]	56,480	132,720	70,875
Noteworthy Findings									
Died or sacrificed moribund		0	0	0	0	1[a]	0	0	0
Body Weight (kg)	Day –1	4.960	2.820	4.820	2.715	4.658	2.643	4.925	2.680
	Week 4	4.973	2.858	4.908	2.733	4.715	2.560	4.833	2.605

Daily Dose (mg/kg):		**0 (Control)**		**20**		**100**		**1000**	
Number of Animals:		**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
	Week 13	5.070	2.945	5.190	2.800	4.767[a]	2.698	4.793	2.790
Food Consumption (g/day)	Week –1	108.00	96.43	106.93	91.08	108.00	100.30	108.00	101.58
	Week 4	108.00	105.43	104.58	103.93	108.00	103.93	107.15	96.20
	Week13	108.00	93.23	107.15	94.08	107.43[a]	103.50	100.73	99.20
Clinical Observations:									
Decrease in spontaneous activity		0	0	0	0	0	0	1	0
Sedation		0	0	0	0	0	0	1	1
Sitting position		0	0	0	0	0	0	1	1
Lateral position		0	0	0	0	1	0	0	0
Gasping		0	0	0	0	1	0	0	0
Vomiting		0	0	0	0	4	4	4	4
Salivation		0	0	0	1	4	4	4	4
Hematology:									
RBC (10^6/μL)	Predose	5.573	5.323	6.103	5.233	5.820	5.428	5.728	5.228
	Week 4	5.615	5.243	5.828	5.128	5.043	4.725	4.380	4.658
	Week 8	5.730	5.340	5.783	5.250	5.593[a]	5.008	5.190	4.748
	Week 13	5.645	5.248	5.908	5.208	5.357[a]	4.858	3.753	4.370
Hematocrit (%)	Predose	44.48	44.20	47.03	41.93	45.63	43.70	46.13	42.48
	Week 4	45.10	43.38	44.08	41.48	41.48	38.35	37.95	39.73
	Week 8	44.85	43.70	43.53	41.50	42.87[a]	39.90	41.70	38.75
	Week 13	43.58	41.53	44.15	40.10	41.07[a]	38.65	31.38	36.20
Hemoglobin (g/dL)	Predose	13.78	13.23	14.15	12.30	14.03	12.90	14.03	12.45
	Week 4	14.13	13.23	13.25	12.20	11.78	11.60	10.60	11.03
	Week 8	13.98	13.30	13.15	12.15	12.40[a]	11.75	11.73	10.68
	Week 13	14.20	13.10	13.68	12.13	12.27[a]	11.55	9.10	10.23
Reticulocytes (10^9/L)	Predose	81.00	75.28	63.80	68.25	88.13	55.98	97.20	83.58

Daily Dose (mg/kg):		**0 (Control)**		**20**		**100**		**1000**	
Number of Animals:		**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
	Week 4	75.70	68.50	63.53	60.93	140.10	64.43	245.00	160.05
	Week 8	69.75	73.25	77.58	58.35	91.33[a]	50.30	93.38	104.25
	Week 13	60.75	63.70	66.38	51.40	145.07[a]	71.65	181.70	170.95
Serum Chemistry:									
AST (IU/L)	Predose	31.3	27.8	24.0	32.3	36.5	31.5	30.3	37.0
	Week 4	26.8	30.3	23.8	29.8	24.5	27.0	21.8	28.5
	Week 8	30.5	27.5	23.8	30.3	27.7[a]	26.8	19.5	30.3
	Week 13	26.3	35.5	24.8	29.3	46.3[a]	30.5	77.5	41.0
Total bilirubin (mg/dL)	Predose	0.103	0.158	0.135	0.113	0.098	0.168	0.140	0.138
	Week 4	0.098	0.170	0.103	0.125	0.090	0.168	0.158	0.190
	Week 8	0.103	0.160	0.128	0.130	0.087 [a]	0.150	0.215	0.128
	Week 13	0.113	0.175	0.120	0.128	0.127 [a]	0.140	0.300	0.148
Total protein (g/dL)	Predose	7.50	7.30	7.48	7.33	7.58	7.18	7.73	7.15
	Week 4	7.45	7.03	7.23	7.28	7.48	7.08	7.58	7.40
	Week 8	7.40	7.25	7.25	7.35	7.27[a]	7.05	7.55	7.18
	Week 13	7.35	6.95	7.30	7.28	7.13[a]	6.93	7.15	7.10
Albumin (g/dL)	Predose	3.95	4.10	4.18	4.03	4.05	4.05	4.13	4.00
	Week 4	3.93	3.98	3.85	3.90	3.68	3.90	3.63	3.83
	Week 8	3.93	4.10	3.98	3.90	3.50[a]	3.90	3.83	3.78
	Week 13	3.95	3.95	3.98	3.83	3.50[a]	3.85	3.65	3.73
Triglyceride (mg/dL)	Predose	40.5	46.8	32.3	36.3	27.0	36.5	30.8	37.3
	Week 4	35.8	51.5	33.5	32.5	52.8	40.3	90.0	71.8
	Week 8	36.0	36.8	32.5	26.5	59.0[a]	43.0	163.3	77.5
	Week 13	53.3	37.0	54.8	39.0	70.0[a]	60.5	180.3	62.0
Ca (mg/dL)	Predose	10.05	10.33	10.65	10.35	10.28	10.10	10.33	10.30
	Week 4	10.03	9.68	10.05	9.85	10.00	9.68	9.83	9.18

Daily Dose (mg/kg):	**0 (Control)**		**20**		**100**		**1000**	
Number of Animals:	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Week 8	10.05	10.10	10.03	9.75	10.07[a]	9.73	9.88	9.58
Week 13	10.28	9.78	10.13	10.03	9.93[a]	9.88	9.75	9.78
Urinalysis:	—	—	—	—	—	—	—	—
Ophthalmology:	—	—	—	—	—	—	—	—
Electrocardiography:	—	—	—	—	—	—	—	—
Organ Weights:								
Number Evaluated:	4	4	4	4	3	4	4	4
Adrenal (absolute, g)	0.535	0.488	0.630	0.555	0.463	0.493	0.648	0.488
Adrenal (relative to BW, g/kg)	0.1070	0.1710	0.1240	0.2048	0.0973	0.1845	0.1390	0.1773
Liver (absolute, g)	78.15	57.95	81.08	53.80	98.10	63.33	134.23	73.45
Liver (relative to BW, g/kg)	15.673	20.010	15.900	19.390	20.833	23.673	28.973	26.653
Kidney (absolute, g)	15.40	12.53	16.68	11.33	15.60	11.65	18.65	12.20
Kidney (relative to BW, g/kg)	3.085	4.323	3.280	4.145	3.273	4.355	4.003	4.420
Gross Pathology:								
Number Evaluated:	4	4	4	4	3	4	4	4
Spleen, enlargement	0	0	0	0	0	0	2	0
Spleen, dark discoloration	0	0	0	0	0	0	2	0
Lung, white discoloration	0	0	0	0	0	0	1	0
Liver, enlargement	0	0	0	0	0	0	2	0
Liver, dark discoloration	0	0	0	0	0	0	2	0
Liver, accentuated lobular pattern	0	0	0	0	0	0	2	0
Histopathology:								
Number Evaluated:	4	4	4	4	4[b]	4	4	4
Spleen								
Hemozoin pigments 1+	1	1	4	4	0	3	0	0
2+	0	0	0	0	3	0	2	4

Daily Dose (mg/kg):		0 (Control)		20		100		1000	
Number of Animals:		**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
	3+	0	0	0	0	0	0	2	0
Congestion	1+	0	0	0	0	1	1	2	2
	2+	0	0	0	0	0	0	2	0
Lymphoid hyperplasia	1+	1	0	0	0	2	1	2	3
Liver									
Hemozoin pigments	1+	0	0	0	0	1	0	1	3
	2+	0	0	0	0	0	0	2	0
Hypertrophy, Kupffer cells	1+	0	0	0	0	0	0	1	0
	2+	0	0	0	0	0	0	1	0
Bone marrow									
Increased hematopoiesis	1+	0	0	0	0	1	0	2	0
Hemozoin pigments	1+	0	0	0	0	0	0	1	0
	2+	0	0	0	0	0	0	1	0

—: No noteworthy findings. GRADE; 1+: slight, 2+: moderate, 3+: marked.

AST = aspartate aminotransferase, $AUC_{(0\text{-}24)}$ = AUC from zero time to 24 hours BW = body weight, , CTD = Common Technical Document, F = female, GLP = Good Laboratory Practice, M = male, MC = methylcellulose, NA = not applicable, RBC = red blood cells.

a: For 100 mg/kg males, n=3 as a result of the accidental death (intubation error) of 1 animal on Day 41.
b: Includes the animal that died due to intubation error on Day 41.

2.6.7.7.E　　**Test Article: Lemborexant**

Report Title: E2006: A 39-Week Oral Toxicity Study in Monkeys		**Study No.** 6700074
Species / Strain: Monkey / Cynomolgus	Duration of Dosing: 39 weeks	Location in CTD: 4.2.3.2.11
Initial Age: 2 - 4 years old	Duration of Postdose: Not applicable	GLP Compliance: Yes
Date of First Dose: [redacted] 20[redacted] (M) / [redacted] 20[redacted] (F)	Method of Administration: Oral gavage	
Vehicle / Formulation: 1 mol/L HCl: 0.5% MC solution (1:4, v/v) / suspension		
No Observed Adverse Effect Level: 10 mg/kg		Special Features: None

Daily Dose (mg/kg):		**0 (Control)**		**10**		**100**		**1000**	
Number of Animals:		**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Toxicokinetics: C_{max} (ng/mL)									
	Day 1	NA	NA	584	506	1880	3780	4250	3640
	Day 85	NA	NA	1280	763	5580	6600	5480	4590
	Day 269	NA	NA	960	1160	6930	8660	9620	6930
Toxicokinetics: $AUC_{(0\text{-}24)}$ (ng·h/mL)									
	Day 1	NA	NA	2850	2650	28,000	34,600	70,700	53,500
	Day 85	NA	NA	6670	4370	48,000	54,800	75,900	56,500
	Day 269	NA	NA	5510	4970	82,900	82,800	155,000	98,200
Noteworthy Findings									
Died or sacrificed moribund		0	0	0	0	0	0	0	0
Body Weight (kg)	Day 1	2.80	2.83	2.88	2.78	2.95	2.85	2.93	2.73
	Day 92	3.08	2.93	3.35	3.00	3.35	3.13	3.03	2.83
	Day 183	3.43	3.13	3.95	3.38	3.93	3.53	3.40	2.88
	Day 267	3.88	3.38	4.45	3.75	4.35	4.10	3.88	3.03
Clinical Observations[a]:									
Decreased activity / Somnolence[b]		1	0	4	4	4	4	4	4
Feces soft		0	2	0	1	3	1	3	2

Daily Dose (mg/kg):		**0 (Control)**		**10**		**100**		**1000**	
Number of Animals:		**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Feces liquid		0	0	1	0	4	2	3	4
Material in cage or tray		1	0	0	1	4	3	4	3
Vomitus in cage tray		0	0	1	1	4	1	2	3
Reduced appetite		1	2	1	2	3	1	4	4
Ophthalmology:		—	—	—	—	—	—	—	—
Hematology:									
RBC (10^6/μL)	Week –1	5.343	5.208	5.578	5.223	5.373	5.378	5.723	5.033
	Week 13	5.905	5.210	5.380	5.098	4.860	5.308	5.040	4.828
	Week 26	6.263	5.610	5.693	5.525	5.213	5.403	5.413	5.198
	Week 39	5.713	5.415	5.555	5.383	4.948	5.223	5.073	4.785
Hemoglobin (g/dL)	Week –1	12.03	12.78	13.65	12.90	13.10	13.23	13.68	12.48
	Week 13	13.40	12.73	13.40	12.65	12.20	12.88	12.20	11.80
	Week 26	13.73	13.28	13.63	13.15	12.43	12.83	12.53	12.18
	Week 39	12.68	12.73	13.40	12.68	12.10	12.28	11.70	11.38
Hematocrit (%)	Week –1	38.48	40.30	43.38	40.95	41.90	42.63	43.43	39.28
	Week 13	42.38	39.13	41.50	39.03	40.00	42.05	40.28	38.33
	Week 26	45.18	41.95	43.38	42.20	41.73	42.65	42.23	40.40
	Week 39	41.03	41.43	42.08	41.60	39.50	42.63	30.68	38.65
Reticulocytes (10^9/μL)	Week –1	54.33	46.80	58.78	50.63	51.75	67.03	63.48	63.33
	Week 13	45.53	55.93	64.18	68.08	61.65	92.50	124.48	116.15
	Week 26	37.68	32.65	41.88	49.48	42.40	78.48	67.07	85.05
	Week 39	49.48	55.03	61.83	63.80	76.33	106.18	128.70	115.10
Serum Chemistry:									
Triglyceride (mg/dL)	Week –3	41.8	35.8	46.5	29.0	44.8	40.5	71.0	41.5
	Week 13	29.5	45.3	45.8	30.8	159.8	107.0	106.8	100.3
	Week 26	45.5	36.3	44.3	35.5	191.5	228.5	223.0	144.8

Daily Dose (mg/kg):		**0 (Control)**		**10**		**100**		**1000**	
Number of Animals:		**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
	Week 39	39.5	41.8	53.0	37.3	189.8	231.5	183.0	67.8
Phosphorus (mg/dL)	Week –3	6.10	7.35	6.10	6.38	6.60	6.00	5.90	6.53
	Week 13	6.10	6.45	6.85	6.25	7.35	6.10	7.40	6.83
	Week 26	6.08	5.60	6.23	6.08	6.48	5.53	7.15	5.93
	Week 39	6.35	6.00	6.45	6.05	7.35	5.78	8.35	6.28
Iron Metabolism									
Fe (μg/dL)	Week –3	113.8	150.8	121.3	167.3	117.8	160.0	117.3	163.3
	Week 13	90.5	111.0	96.0	145.5	123.3	161.5	139.3	147.0
	Week 26	129.0	161.8	138.5	197.0	168.5	206.0	187.5	165.8
	Week 39	110.5	138.0	145.5	161.8	150.3	174.0	114.8	161.5
TIBC (μg/dL)	Week –3	372.0	435.5	369.8	385.3	376.0	379.5	334.0	362.8
	Week 13	359.8	352.0	365.8	371.5	440.8	452.5	444.5	462.8
	Week 26	378.5	357.3	377.5	390.5	448.0	513.8	433.0	477.0
	Week 39	438.5	351.8	364.8	374.0	458.5	480.8	469.3	446.0
UIBC (μg/dL)	Week –3	258.3	284.8	248.5	218.0	258.3	219.5	216.8	199.5
	Week 13	269.3	241.0	269.8	226.0	317.5	291.0	305.3	315.8
	Week 26	249.5	195.5	239.0	193.5	279.5	307.8	245.5	311.3
	Week 39	328.0	213.8	219.3	212.3	308.3	306.8	354.5	284.5
Bone Metabolism Markers[c]		—	—	—	—	—	—	—	—
Urinalysis		—	—	—	—	—	—	—	—
Urinary Fluoride:									
Total F excretion to BW (mg/day/kg)									
	Day 180	0.040	0.038	0.070	0.080	0.175	0.323	0.283	0.450
	Day 240	0.030	0.040	0.055	0.058	0.215	0.200	0.310	0.320
	Day 271	0.023	0.028	0.020	0.043	0.043	0.238	0.208	0.245
Ophthalmology:		—	—	—	—	—	—	—	—

Daily Dose (mg/kg):		**0 (Control)**		**10**		**100**		**1000**	
Number of Animals:		**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Electrocardiography:		—	—	—	—	—	—	—	—
Immunotoxicology[d]:		—	—	—	—	—	—	—	—
Bone Densitometry[e]:		—	—	—	—	—	—	—	—
Organ Weights:									
Liver (absolute, g)		61.8973	61.4388	71.2593	65.5848	91.5305*	88.9113*	78.1868	74.9513
Liver (relative to BW, %)		1.6823	1.9025	1.6603	1.7835	2.1660*	2.2320	2.1930*	2.6335***
Gross Pathology:									
Number Evaluated:		4	4	4	4	4	4	4	4
Spleen, discoloration dark		0	0	0	0	0	0	0	1
Spleen, enlargement		0	0	0	0	0	1	0	0
Liver, discoloration dark		0	0	0	0	0	0	0	1
Liver, enlargement		0	0	0	0	0	0	0	1
Adrenal, focus dark		0	0	0	0	0	0	0	1
Adrenal, discoloration dark		0	0	0	0	0	0	1	0
Histopathology:									
Number Evaluated:		4	4	4	4	4	4	4	4
Femur									
Pigmentation	1+	0	0	0	0	0	0	1	2
Spleen									
Increased hemosiderin	1+	0	0	0	0	4	2	3	3
Congestion	1+	0	1	1	0	4	2	4	2
Bone marrow									
Increased hemosiderin	1+	0	0	0	0	1	1	1	2
Increased hematopoiesis	1+	0	0	0	0	1	1	2	2
Liver									
Hypertrophy, hepatocytes	1+	0	0	0	0	3	3	4	2

Daily Dose (mg/kg):	**0 (Control)**		**10**		**100**		**1000**	
Number of Animals:	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Adrenals								
Decreased lipid droplets 1+	0	0	0	0	0	0	3	1

—: No noteworthy findings. GRADE; 1+: slight.

$AUC_{(0\text{-}24)}$ = AUC from zero time to 24 hours, BW = body weight, CTD = Common Technical Document, F = female, G-CSF = granulocyte-colony stimulating factor, GLP =Good Laboratory Practice, GM-CSF = granulocyte macrophage colony-stimulating factor, M = male, MC = methylcellulose, NA = not applicable, PBMC = peripheral blood mononuclear cell, RBC = red blood cells, TIBC = total iron binding capacity, UIBC = unsaturated iron binding capacity.

a: Including qualitative evaluation of food consumption.

b: Due to a specific, pharmacologically-mediated clinical sign, somnolence (the animal's activity is decreased but upon external stimuli, the animal reacts normally) was used as of Day 14/13 instead of decreased activity.

c: C-telopeptides of type I collagen, active isoform 5b of the tartrate-resistant acid phosphatase, osteocalcin, and bone specific alkaline phosphatase.

d: Immunophenotyping (B lymphocytes, T lymphocytres, T-helper lymphocytes, T- cytotoxic lymphocytes and Natural-killer [NK) lymphocytes), NK activity, peripheral blood granulocyte functions, and cytokine (IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12/23 (p40), IL-13, IL-17, IFN-γ, TNF-α, G-CSF and GM-CSF) release following PBMC stimulation.

e: Dual Energy X-Ray Absorptiometry and Peripheral Quantitative Computed Tomography.

* $P \leq 0.05$, *** $P \leq 0.001$ (Dunnett's test).

2.6.7.8 In vitro 遺伝毒性試験

2.6.7.8.A　　**Test Article: Lemborexant**

Report Title: E2006: Reverse Mutation Assay in Bacteria		Study No. S11002
Test for Induction of: Reverse mutation in bacterial cells	No. of Independent Assays: 2	Location in CTD: 4.2.3.3.1.1
Strains: *S. typhimurium* and *E. coli*	No. of Replicate Cultures: 3	GLP Compliance: Yes
Metabolizing System: PB/BF-induced male rat liver S9	No. of Cells Analyzed/Cultured: NA	
Vehicles: for Test Article: DMSO; for Positive Controls: DMSO (AF2, 9AA, and 2AA) or WFI (SA)		
Treatment: Pre- and main incubation at 37 ℃ for 20 minutes and 48 hours, respectively, with or without S9 mix		Date of Treatment: [redacted] 20[redacted] and [redacted] 20[redacted]
Cytotoxic Effects: Not observed at doses up to 5000 µg/plate in all of bacterial strains with or without S9 mix.		
Genotoxic Effects: None		

Metabolic Activation	**Test Article**	**Dose Level (µg/plate)**	**Range-finding test Revertant Colony Counts (Mean ±SD)**				
			TA100	**TA1535**	**TA98**	**TA1537**	**WP2 *uvrA* (pKM101)**
Without Activation	DMSO	0	120±6.4	8±2.1	17±1.5	9±1.2	115±8.5
	Lemborexant	39	121±1.2	8±3.0	17±4.4	11±1.5	109±12.5
		78	118±7.4	7±1.2	18±2.1	6±1.5	100±6.6
		156	119±9.0	6±1.5	16±3.0	8±3.5	102±8.3
		313	97±6.0	4±2.3	14±0.6	10±4.6	99±4.0
		625	117±7.8[P]	6±0.6[P]	24±3.1[P]	8±4.0[P]	82±1.5[P]
		1250	109±15.1[P]	10±1.7[P]	20±2.6[P]	4±1.2[P]	74±12.2[P]
		2500	110±10.6[P]	5±2.0[P]	22±1.5[P]	5±1.5[P]	60±4.7[P]
		5000	103±6.2[P]	5±2.1[P]	22±3.1[P]	6±2.3[P]	67±5.1[P]
	AF2	0.005	NT	NT	NT	NT	921±20.0

Metabolic Activation	Test Article	Dose Level (µg/plate)	Range-finding test Revertant Colony Counts (Mean ±SD)				
			TA100	TA1535	TA98	TA1537	WP2 *uvrA* (pKM101)
		0.01	471±13.4	NT	NT	NT	NT
		0.1	NT	NT	708±40.8	NT	NT
	9AA	80	NT	NT	NT	754±30.7	NT
	SA	0.5	NT	568±81.4	NT	NT	NT
With Activation	DMSO	0	125±4.0	9±1.5	24±4.0	9±1.5	109±3.1
	Lemborexant	39	109±18.2	10±2.1	24±1.5	8±1.0	99±15.1
		78	107±8.7	6±2.3	23±1.0	8±1.5	90±11.0
		156	98±2.5	6±1.2	22±3.2	9±1.7	79±5.3
		313	104±8.1	6±1.5	15±1.0	6±3.1	88±2.0
		625	113±9.1	8±1.5	21±1.5	8±1.7	101±9.6
		1250	106±4.0[P]	6±3.1[P]	20±2.6[P]	8±2.0[P]	96±10.4[P]
		2500	92±17.4[P]	5±1.5[P]	19±2.5[P]	5±0.6[P]	81±17.2[P]
		5000	106±6.1[P]	6±3.6[P]	18±2.1[P]	4±1.2[P]	72±14.0[P]
	2AA	0.5	NT	NT	453±40.5	NT	NT
		1	1189±30.3	NT	NT	NT	NT
		2	NT	215±8.1	NT	162±11.6	1243±62.6

Metabolic Activation	Test Article	Dose Level (µg/plate)	Main test Revertant Colony Counts (Mean ±SD)				
			TA100	TA1535	TA98	TA1537	WP2 *uvrA* (pKM101)
Without Activation	DMSO	0	131±4.2	7±0.0	18±3.2	7±1.0	122±11.9
	Lemborexant	313	119±6.1	7±1.5	20±1.5	6±2.5	114±10.5
		625	105±6.7[P]	6±1.0[P]	19±3.5[P]	7±1.7[P]	116±11.6[P]
		1250	111±1.7[P]	8±1.0[P]	18±0.6[P]	7±1.5[P]	119±4.7[P]
		2500	99±6.7[P]	7±2.5[P]	19±1.5[P]	5±1.0[P]	111±2.1[P]
		5000	95±6.1[P]	6±0.6[P]	18±4.0[P]	6±2.5[P]	105±8.1[P]
	AF2	0.005	NT	NT	NT	NT	897±93.1
		0.01	538±45.5	NT	NT	NT	NT
		0.1	NT	NT	656±37.3	NT	NT
	9AA	80	NT	NT	NT	643±91.7	NT
	SA	0.5	NT	557±27.5	NT	NT	NT
With Activation	DMSO	0	127±11.0	10±2.3	24±3.2	9±2.5	132±12.9
	Lemborexant	313	124±10.1	5±2.3	24±4.0	6±1.7	137±3.1
		625	109±10.3	8±1.2	23±4.5	7±2.1	130±6.5
		1250	104±4.4[P]	7±2.1[P]	16±1.2[P]	7±1.0[P]	124±14.8[P]
		2500	101±11.4[P]	7±2.1[P]	17±5.6[P]	6±1.5[P]	104±9.2[P]
		5000	105±10.4[P]	7±2.6[P]	16±4.0[P]	5±2.0[P]	101±14.7[P]
	2AA	0.5	NT	NT	481±51.0	NT	NT
		1	1316±35.7	NT	NT	NT	NT
		2	NT	245±3.1	NT	150±14.0	1247±71.4

AF2 = 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, 2AA = 2-aminoanthracene, 9AA = 9-aminoacridine hydrochloride, CTD = Common Technical Document,

Metabolic Activation	Test Article	Dose Level (µg/plate)	Main test Revertant Colony Counts (Mean ±SD)				
			TA100	TA1535	TA98	TA1537	WP2 *uvrA* (pKM101)

DMSO = dimethyl sulfoxide, GLP = Good Laboratory Practice, NA = not applicable, NT = not tested, P = precipitate, PB/BF = phenobarbital and 5,6-benzoflavone, SA = sodium azide, WFI = water for injection.

2.6.7.8.B　　**Test Article: Lemborexant**

Report Title: E2006: Mouse Lymphoma *tk* Assay		Study No. K11008
Test for Induction of: Gene mutation in mammalian cells	No. of Independent Assays: 1	Location in CTD: 4.2.3.3.1.2
Strains: Mouse lymphoma L5178Y $tk^{+/-}$ cells	No. of Replicate Cultures: 2	GLP Compliance: Yes
Metabolizing System: PB/BF-induced male rat liver S9	No. of Cells Analyzed/Cultured: NA	
Vehicles: for Test Article: DMSO; for Positive Controls: DMSO		
Treatment: Short treatment method for 3 hours with or without S9 mix Continuous treatment method for 24 hours without S9 mix		Date of Treatment: [redacted] 20[redacted] to [redacted] 20[redacted]
Cytotoxic Effects: In the range-finding cytotoxicity test using the short, 3-hour treatment method in the presence or absence of S9 mix, no marked cytotoxicity was observed at concentrations up to 400 µg/mL. In the continuous, 24-hour treatment method in the absence of S9 mix, a marked decrease (more than 80%) in relative survival was observed at 100 µg/mL.		
Genotoxic Effects: None		

Short treatment method for 3 hours

Metabolic Activation	**Test Article**	**Concentration (µg/mL)**	**Cytotoxicity (% of Control)**		**Mutant Frequency ($\times 10^{-6}$ cells)**	**% of Small Colony**
			Relative Survival	**Relative Total Growth**		
Without Activation	DMSO	0	100	100	92	32
	Lemborexant	25	105	101	84	30
		50	91	107	72	30
		100	60	64	76	38
		200 [P]	71	48	66	36
	MMS	20	80	39	1055	46

With Activation	DMSO	0	100	100	78	34
	Lemborexant	25	112	92	99	28
		50	100	70	136*	25
		100	93	73	109	26
		200[P]	66	47	109	39
	CP	2	68	39	822	52

Continuous treatment method for 24 hours

Metabolic Activation	Test Article	Concentration (μg/mL)	Cytotoxicity (% of Control)		Mutant Frequency ($\times 10^{-6}$ cells)	% of Small Colony
			Relative Survival	Relative Total Growth		
Without Activation	DMSO	0	100	100	79	36
	Lemborexant	10	86	77	87	25
		20	70	66	73	26
		40	61	44	97	29
		50	50	40	84	22
		60	36	26	96	34
		70	22	15	106	39
		80	13	7	NM	NM
	MMS	5	68	51	498	40

CTD = Common Technical Document , CP = cyclophosphamide monohydrate, DMSO = dimethyl sulfoxide, GLP = Good Laboratory Practice, MMS = methyl methanesulfonate, NA = not applicable, NM = not measured, PB/BF = phenobarbital and 5,6-benzoflavone, P = precipitate.

*$P<0.05$ (Dunnett's test, one-sided).

2.6.7.9 In vivo 遺伝毒性試験

Test Article: Lemborexant

Report Title: E2006: Micronucleus Assay in Rats after Oral Administration		Study No. K11011
Test for Induction of: Micronuclei in bone marrow cells	Treatment Schedule: Once	Location in CTD: 4.2.3.3.2.1
Species / Strain: Rat/Sprague Dawley	Sampling Time: 24 and 48 hours after administration	GLP Compliance: Yes
Initial Age: 8 weeks old	Method of Administration: Oral gavage	
No. of Cells Evaluated / Animal: 2000		Date of Treatment: [redacted] 20[redacted]
Special Features: None		
Toxic / Cytotoxic Effects: A slight decrease in food consumption was observed in one animal at 2000 mg/kg on 2 days after administration.		
Genotoxic Effects: None		
Evidence of Exposure: Toxicokinetics in a separate extended single-dose oral toxicity study (添付資料 4.2.3.1.2［S10120］).		

Test Article	Dose Level or Concentration (mg/kg)	Sampling time (hours)	Number of Animals	MNPCEs (%) (Mean)	PCEs (%) (Mean)
Vehicle (1 mol/L HCl:0.5% MC solution [1:4, v/v] / suspension)	0	24	5M	0.15	44.3
		48	5M	0.08	44.3
Lemborexant	500	24	5M	0.11	41.2
		48	5M	0.05	42.4
	1000	24	5M	0.11	47.1
		48	5M	0.06	36.2
	2000	24	5M	0.12	41.5
		48	5M	0.10	34.1

Test Article	Dose Level or Concentration (mg/kg)	Sampling time (hours)	Number of Animals	MNPCEs (%) (Mean)	PCEs (%) (Mean)
Cyclophosphamide	10	24	5M	0.98	33.0

CTD = Common Technical Document, GLP = Good Laboratory Practice, M = males, MNPCEs = micronucleated polychromatic erythrocytes, PCEs = polychromatic erythrocytes.

2.6.7.10 がん原性試験

2.6.7.10.A　　**Test Article: Lemborexant**

Report Title: E2006: An Oral Carcinogenicity study in Rats		Study No. K13092
Species / Strain: Rat / Sprague Dawley	Duration of Dosing: 104-week	Location in CTD: 4.2.3.4.1.1
Initial Age: 6 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: Study includes 2 vehicle control groups. Four additional males and 4 additional females per drug-treated group were bled at 6 months for toxicokinetic monitoring and then removed from the study.		

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**
Number of Animals for Toxicokinetics:	**M: 4**	**F: 4**	**NA**	**NA**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**
Toxicokinetics:										
C_{max} (ng/mL)										
Day 93	NA	NA	NA	NA	529	536	1566	2628	3887	3147
Day 178	NA	NA	NA	NA	491	954	2159	4645	6810	3355
$AUC_{(0\text{-}24)}$ (ng·h/mL)										
Day 93	NA	NA	NA	NA	836	2307	5350	17,041	36,956	38,346
Day 178	NA	NA	NA	NA	916	3574	7516	32,185	48,270	36,034
Died/Sacrificed Moribund										
Week 1 to 26	0	1	2	0	0	0	0	0	0	0
Week 1 to 52	0	1	3	2	0	1	0	0	1	2
Week 1 to 78	2	1	5	4	1	2	2	7	2	7