Final Report

Study Title: Compound A: Effects on the Heart Rate, Blood Pressure, and the Electrocardiogram by Oral Administration in Conscious Monkeys

Study Number: CJUGSEND00

Study Director: Taro Sendo

_____ January 30, 2015

Taro Sendo Date

Test Facility: Example Contract Lab Name

This report is 27 pages including cover page

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SUMMARY

The purpose of this study was to investigate the effects of Compound A on the cardiovascular system in 4 conscious, unrestrained male cynomolgus monkeys. The vehicle (0.5 w/v% methylcellulose solution) and Compound A (10, 30 and 100 mg/kg) were dosed orally (dose volume: 5 mL/kg) once a day with a seven-day interval. Blood pressure (systolic, diastolic and mean), heart rate, electrocardiogram (PR interval, QRS duration, QT interval, QTc and RR interval), respiratory rate and intra-abdominal body temperature were measured by telemetry system. Clinical sign was also observed.

There was no test article-related change in any parameter at any dose level. In conclusion, compound A was considered to have no obvious effect on the cardiovascular system.

1. STUDY PURPOSE

The purpose of this study was to examine the effects of compound A on the heart rate, blood pressure, and the electrocardiograms by single oral administration in conscious monkeys.

2. REGULATORY COMPLIANCE

This study was not conducted under regulatory compliance.

3. ANIMAL WELFARE

This study was approved by the Institutional Animal Care and Use Committee (Approved No. IACUC00) and was performed in accordance with the animal welfare bylaws of Example Contract Lab Name, which is accredited by AAALAC International.

4. TEST FACILITY

Example Contract Lab Name
1000 Anywhere Street, Honolulu, HI 11111
USA

5. STUDY SCHEDULE

The day before the first dosing day was designated as Day –1. The first dosing day was designated as Day 1.

Study Initiation:	July 29, 2014
Acclimation Initiation:	July 30, 2014
Acclimation Completion:	August 5, 2014
Surgical Operation:	August 6, 2014 and August 7, 2014
First Dosing (Day 1):	September 3, 2014
Second Dosing (Day 8):	September 10, 2014
Third Dosing (Day 15):	September 17, 2014
Fourth Dosing (Day 22):	September 24, 2014
End of Observation (Day 23):	September 25, 2014
Study Completion:	January 28, 2015

6. MATERIALS AND METHODS

6.1. Test Article

Name:	Compound A
Source:	Example Sponsor Inc.
Lot No.:	123-456

6.2. Control Article / Vehicle

6.2.1. Methylcellulose (MC, Metolose SM-400)

Lot No.: 3075508

Manufacturer: Shin-Etsu Chemical Co., Ltd.

6.2.2. Water for Injection

Lot Nos.: 3L94 and 4B90

Manufacturer: Otsuka Pharmaceutical Factory, Inc.

6.3. Dosing Formulations

6.3.1. Preparation of the Control Article / Vehicle (0.5 w/v% MC solution)

The required amount of MC was weighed, added to hot water for injection equal to 40% of the final volume, and the mixture was stirred until thorough dispersed. Cooled water for injection was then added to dissolve. This preparation was transferred to a measuring cylinder, made up to the final volume with water for injection, and stirred with a magnetic stirrer. This solution was stored in the Refrigeration Room maintained between 2 and 8°C (actual range: 3.4 to 5.3°C, from September 2, 2014 to September 24, 2014) in the Test Article Depository of Example Contract Lab Name and used within 30 days after preparation.

6.3.2. Preparation of the Test Article Formulations

The three test article formulations (2, 6 and 20 mg/mL) were prepared separately. The required amount of test article was weighed and transferred to an agate mortar. Vehicle was gradually added to the agate mortar to prepare a suspension while gently mixing. The suspension was transferred to a measuring cylinder and made up to the final volume of formulation with vehicle. Each test article formulation was prepared just before use on each day of dosing.

6.4. Dosing of the Test and Control Article Formulations

6.4.1. Dosing Route and Dosing Method

The oral route was used in accordance with the intended clinical route. The dosing formulations were administered (between 10:10 and 10:16 a.m.) into the stomach via the nasal cavity using a disposable catheter and syringe. The remaining dosing formulation in the catheter was flushed into the stomach with approximately 5 mL of water. The test article formulations were stirred with a stirrer during collection. This method is commonly used for oral dosing to cynomolgus monkeys.

6.4.2. Dosing Volume

The dosing volume was set at 5 mL/kg. Individual dosing volumes were calculated based on the body weight measured on the day before dosing.

6.4.3. Dosing Period

Four single doses at 7-day intervals

6.5. Test System

Species:	Cynomolgus monkey (purpose-bred)
Gender:	Male
Body Weights:	3.42 to 3.58 kg (on the first day of acclimation) 3.46 to 3.75 kg (on the final day of acclimation)
Age:	3 or 4 years old (on the first day of acclimation)
Origin:	China
CITES Permit/Certificate Nos.:	2013CN/EC0613/GZ, 2014CN/EC0013/GZ, 2014CN/EC0012/GZ and 2014CN/EC0214/GZ
Dates of Arrival:	October 22, 2013, February 18, 2014, March 4, 2014 and April 15, 2014
Date of Receipt:	July 30, 2014
Number of Animals:	Four male cynomolgus monkeys were obtained and four male cynomolgus monkeys were used for this study.
Source:	Example Supplier
Rationale for Selection of the Animal Species:	Cynomolgus monkeys are a commonly used non-rodent species for safety pharmacology studies.

6.6. Husbandry

Animal Room:	Room No. 777
Temperature:	Actual range: 25.5 to 26.6°C (acceptable range: 23 to 29°C)
Relative Humidity:	Actual range: 42 to 59% (acceptable range: 30 to 70%)
Ventilation Rate:	15 times/hour
Illumination:	12 hours/day of artificial light (07:00 a.m. to 7:00 p.m)
Cage Type:	Stainless cages (680 mm (D) × 620 mm (W) × 770 mm (H))
Number of Animals per Cage:	1 animal/cage
Food and Feeding:	Solid food (HF Primate 5K91 12G 5K9J, Purina Mills, LLC) was provided. Approximately 108 g (approximately 12 g × 9 pieces) of solid food was provided to each animal once daily between 2:00 and 4:00 p.m. The remaining food check and removal procedure were performed between 08:00 and 11:00 a.m. on the following day. On the days of surgery, approximately half the amount of solid food (5 pieces) was provided after surgery to each animal that underwent

surgery. On dosing days (except for the sham dosing days), food was provided after 4 hours after dosing, and the remaining food check procedure was performed after 24 hours after dosing (after the telemetry analysis point). On the days before surgery and the days before sham dosing, the remaining food check and removal procedure were performed at approximately 5:00 p.m.

Water: Water conforming to the water quality standards was available *ad libitum* from an automatic water supply system.

Environmental Enrichment: Enrichment toys were provided 24 hours each day. Treats (pieces of apple or sweet potato) were supplied 2 times weekly, but not on the days of surgery or dosing.

Cleaning: The cages and the animal room were washed daily with water. The cages were not exchanged from the initiation of acclimation to the end of observation.

6.7. Identification of the Animals and Cages

Animals: During the study period, each animal was identified by Animal ID tattooed on the leg. For convenience, a correspondence table between an individual Animal ID and an animal number was prepared and recorded as animal number in raw data.

Cage: During the study period, each cage was identified by a cage card listing the study number, Animal ID, sex and animal number.

6.8. Acclimation

Four male cynomolgus monkeys, which had been quarantined, were received, and were then acclimated for 7 days. All animals were weighed using an electronic balance (HP-40K, A&D Co., Ltd.) once on the first and final days of acclimation. During this period, all animals were observed for clinical signs at least once daily. In order to acclimatize the animals to the dosing procedure, 5 mL/kg of water was dosed in the same manner as the control and test article formulations once daily on Days –6, Days –5 and Days –2. The dose volume for each animal was calculated based on the body weight on the day before the first sham dosing.

6.9. Surgical Implantation of the Telemetry Transmitter

6.9.1. Surgical Procedures

Surgery to implant the telemetry transmitter was performed on August 6, 2014 (Nos. M001 and M002) and August 7, 2014 (Nos. M003 and M004). The animals were weighed once before surgery.

Atropine sulfate hydrate (Atropine sulfate injection 0.5 mg, Mitsubishi Tanabe Pharma Corporation, 0.02 mL/kg) was intramuscularly administered to the animals as a pre-anesthetic medication. The animals were sedated by an intramuscular injection of ketamine hydrochloride[a)] (Supriya Lifescience Ltd, 50 mg/mL, 0.2 mL/kg), after which they underwent surgery under isoflurane inhalation anesthesia (Escain, Mylan N.V., 0.5 to 2.0%) and artificial ventilation. Immediately before surgery, buprenorphine hydrochloride (Zalban Injection 0.2 mg, Nissin Pharmaceutical Co., Ltd. 0.05 mL/kg) and antibiotic (Mycillin Sol Meiji[b)], Meiji Seika Pharma Co., Ltd., 0.05 mL/kg) were intramuscularly administered to the animals to alleviate pain and to prevent infection, respectively.

A telemetry transmitter, TL11M2-D70-PCT[c)] (Data Sciences International Inc.), was implanted intraperitoneally and fixed inside the abdominal wall. A catheter for measurement of blood pressure was inserted via the right femoral artery and positioned in the abdominal aorta, and electrodes for recording the electrocardiogram (ECG) were inserted into the thoracic cavity via the bilateral intercostals and fixed in the pericardium near the right atrium and the apex.

a) For Animal No. 1, approximately half of the initial volume was additionally dosed to maintain sedation, before starting inhalation anesthesia.
b) Mycillin Sol Meiji [aqueous suspended injection of dihydrostreptomycin sulfate and benzyl penicillin procaine: dihydrostreptomycin sulfate (250 mg potency/mL), benzyl penicillin procaine (200000 units/mL)]
c) The transmitter contains a pressure catheter filled with a special gel to prevent the entry of blood, two electrodes and a built-in temperature sensor.

6.9.2. Surgical Animal Care

As shown in below table, an antibiotic (Mycillinsol KS, 0.05 mL/kg) and an analgesic (Zalban Injection 0.2 mg, 0.05 mL/kg and Capisten IM 50 mg, 0.1 mL/kg) were intramuscularly administered for 3 days after the surgery, including the day of surgery to prevent infection and to palliate pain, respectively. The animals were allowed 29 or 30 days to recover from surgery, and the telemetry signals (intra-abdominal body temperature, blood pressure patterns and ECG waveforms) were recorded once (at least 26 hours from around 08:00 on Day –6) using the telemetry system. A mild paralysis in the hind limb was observed on 2 to 6 days after surgery in one animal (Animal No. 2) during the recovery period, but it was a temporary symptom. Since there were no abnormalities in clinical signs during the recovery period thereafter, it was judged that there was no influence on the test. All animals including this animal were confirmed to have no abnormality in clinical signs and telemetry signals, and then were subjected to the experiment.

Drugs	Analgesics	Antibiotics
Frequency	Twice a day	Once a day
On the Surgical Day	Immediately before and after surgery	Immediately before surgery

From the day after the surgical day	Morning and afternoon[a)]	Morning

a) The second dosing was conducted approximately 8 hours after dosing in the morning.

6.10. Study Design

Dosing Schedule (Dosing Day)[a)]	Test and Control Articles	Dose Level (mg/kg)	Dosing Volume (mL/kg)	Concentration (mg/mL)	Number of Animals (Animal No.)[b)]
					Males
First (Day 1)	Vehicle	–	5	–	4 (M001 to M004)
Second (Day 8)	Compound A	10	5	2	
Third (Day 15)	Compound A	30	5	6	
Fourth (Day 22)	Compound A	100	5	20	

a) The first day of dosing was designated as Day 1.

b) The same animals were dosed repeatedly.

6.11. Rationale for Selection of the Dose Levels

The toxicity information of Compound A is ... (hereinafter abbreviated because it is not related to data set preparation).

6.12. Observations, Measurements and Examinations

6.12.1. Blood Pressure, Heart Rate, Electrocardiograms, Respiratory Rate and Intra-Abdominal Body Temperature

Telemetry data from each animal were acquired via a receiver, RMC-1 (Data Sciences International Inc.) that was placed on the cage, and the data was analyzed using a telemetry system (Dataquest Open A.R.T. version 4.34 / Ponemah Physiology Platform version 5.20-SP2, Data Sciences International Inc.). The telemetry data were recorded from at least 2 hours before dosing until at least 24 hours after dosing on each dosing day.

Number of Animals: All animals

Analysis Points: Twice before dosing (2 and 1 hours before dosing) and at 9 points after dosing (0.5, 1, 2, 4, 6, 8, 12, 16 and 24 hours after dosing)
The mean of the values at the 2 points before dosing was regarded as the pre-dosing value (baseline).

Analysis Methods: Systolic, diastolic and mean blood pressure (mmHg), heart rate (beats/min) derived from the blood pressure waveform, respiratory rate (breaths/min) derived from the blood pressure waveform and intra-abdominal body temperature (°C) were averaged over a 60-second period. ECG parameters (PR interval (ms), QRS duration

(ms), RR interval (ms), QT interval (ms) and QTc (corrected QT interval by Bazett formula, ms)) were averaged for 10 consecutive waveforms. The electrocardiogram waveform to be analyzed was set within the range of 60-second in which the blood pressure was analyzed.

6.12.2. Clinical Signs

Number of Animals: All animals

Observation Point and Methods

During the Telemetry Recording Period:

Each animal was observed via cage-side observation at each observation point; immediately before and after dosing, 4 and 24 hours after dosing, on each dosing day.

Other Period: Each animal was observed directly more than once daily.

6.13. Treatment of Animals after the End of Experiments

The animals were excluded from the study on Day 23 after observation on the final observation day.

6.14. Statistical Analyses

Data on blood pressure, heart rate, ECG parameters, respiratory rate and intra-abdominal body temperature at each analysis point were expressed as the mean value ± standard deviation (SD).
Analysis of covariance (ANCOVA) was performed using a model including PRE, DOSE and ANIMAL. Multiple comparisons between the control article and the test article at each analysis point (sampling point) were performed by ANCOVA with Dunnett's multiplicity adjustment. These statistical analyses were performed at a two-sided significance level of 5% using SAS System for Windows, Release 9.2 (SAS Institute Inc.). Statistical analysis was not performed for clinical signs.

7. DEVIATIONS

None

8. RESULTS AND DISCUSSIONS

8.1. Blood Pressure

(Tables 1-1 to 1-3)
There was no test article-related change in blood pressure (systolic, diastolic or mean) at any dose level. There were statistically significant decreases as shown below in comparison with vehicle, but the change was less than 10 mmHg in either case.
Systolic: 12 hours after dosing of 100 mg/kg (−7.5 mmHg on average, −10 mmHg for individual

values)

Diastolic: 12 hours after dosing of 100 mg/kg (−5.2 mmHg on average, −8 mmHg for individual values)

Mean: 1 hour after dosing of 30 mg/kg (−5.5 mmHg on average, −7 mmHg for individual values) and 12 hours after dosing of 30 mg/kg (−5.5 mmHg on average, −10 mmHg for individual values), and 12 hours after dosing of 100 mg/kg (−6.5 mmHg on average, −10 mmHg for individual values)

8.2. Heart Rate

(Table 2)

There was no test article-related change in heart rate at any dose level.

There were statistically significant decreases at 12 hours after dosing of 30 and 100 mg/kg, the changes were less than 20 bpm in either group. The changes at 30 and 100 mg/kg were −13.5 bpm on average and −20 bpm for individual values, −15.0 bpm on average and −19 bpm for individual values, respectively.

8.3. Electrocardiograms

(Tables 3-1 to 3-5)

There were no test article-related changes in any ECG parameters (PR interval, QRS duration, QT interval or QTc) at any dose level.

There was no statistically significant change in QTc compared with vehicle, and the following parameters were also changed with less than 10 ms (PR interval), 2 ms or less (QRS duration), about 30 ms (QT interval).

PR interval: 6 hours after dosing of 100 mg/kg (+4.8 ms on average, +9 ms for individual value)

QRS duration: 1 hour after dosing of 100 mg/kg (−0.3 ms on average, −2 ms for individual value)

QT interval: 12 hours after dosing of 30 mg/kg and 100 mg/kg (+22.0 ms and +28.0 ms on average, +32 ms and +38 ms for individual value, respectively)

RR interval: 8 hours after dosing of 100 mg/kg (−19.5 ms on average, −203 ms for individual value)

8.4. Respiratory Rate

(Table 4)

There were no significant changes in respiratory rate at any dose level.

8.5. Intra-abdominal Body Temperature

(Table 5)

There was no test article-related change in intra-abdominal body temperature at any dose level.

There were statistically significant increases 2 hours after dosing of 100 mg/kg in comparison with

vehicle, and any individual value was less than 0.1°C.

8.6. Clinical Signs

(Table 6)
Vomiting (feed-like substance) was observed in 1 animal (Animal No. 4) before dosing of 10 mg/kg, but it was considered to be incidental because it was not found on other dosing days.
No abnormality was found in clinical signs at any dose level.

9. CONCLUSION

There was no test article-related change in any parameter at any dose level. Statistically significant changes were sporadically observed in blood pressure, heart rate, electrocardiogram (PR interval, QRS duration, RR interval, QT interval) and intra-abdominal body temperature compared with the vehicle. However, since they were slight variations, it was considered to be the variation range of each parameter in this study design.
From the above, compound A was considered to have no obvious effect on the cardiovascular system.

10. PERSONNEL INVOLVED IN THE STUDY

Study Director:	Taro Sendo
Statistical analysis Supervisor:	Hanako Sendo
Dosing:	Jiro Sendo
Telemetry Analysis:	Saburo Sendo
Observation of Clinical Signs:	Shiro Sendo

11. ARCHIVE OF RECORDS, DATA AND SAMPLE

The records, data and samples generated at the Test Facility will be archived in the Archives of Example Contract Lab Name for a period of 5 years after preparation of the Final Report.

Protocol
Records and data on test and control articles
Records and data on test system
Records and data on husbandry
Acclimation records
Surgery records
Dosing records
Records and data on telemetry (including a DVD-R)

Records on clinical sign observations

Statistical analysis records

Final Report

All other data related to the study

Attachment 1

Tables

Table 1-1 Systolic blood pressure (mmHg)

Test/control article	Animal	Dosing	Pre	Pre	Pre	Time after dosing (h)								
(Oral, 5 mL/kg)	No.	Day	-2	-1	0	0.5	1	2	4	6	8	12	16	24
0.5 w/v%	M001	1	108	102	105	146	115	110	109	127	98	92	90	101
methylcellulose	M002	1	97	107	102	106	110	108	107	104	93	100	105	102
solution	M003	1	115	111	113	115	111	112	113	104	100	93	88	115
	M004	1	97	98	98	107	106	105	101	101	104	88	90	99
		Mean	104.3	104.5	104.5	118.5	110.5	108.8	107.5	109.0	98.8	93.3	93.3	104.3
		SD	8.8	5.7	6.4	18.8	3.7	3.0	5.0	12.1	4.6	5.0	7.9	7.3
Compound A	M001	8	105	102	104	109	108	113	108	137	94	95	93	104
10 mg/kg	M002	8	104	104	104	104	106	100	103	108	100	96	89	99
	M003	8	110	112	111	105	107	106	112	104	89	87	90	107
	M004	8	91	98	95	106	101	101	86	94	102	81	86	97
		Mean	102.5	104.0	103.5	106.0	105.5	105.0	102.3	110.8	96.3	89.8	89.5	101.8
		SD	8.1	5.9	6.6	2.2	3.1	5.9	11.4	18.5	5.9	7.1	2.9	4.6
Compound A	M001	15	99	105	102	124	108	101	107	128	104	93	92	100
30 mg/kg	M002	15	103	102	103	106	106	107	104	107	100	94	105	105
	M003	15	106	119	113	114	106	112	116	101	93	84	94	109
	M004	15	91	85	88	99	95	95	92	91	90	78	85	90
		Mean	99.8	102.8	101.5	110.8	103.8	103.8	104.8	106.8	96.8	87.3	94.0	101.0
		SD	6.5	14.0	10.3	10.8	5.9	7.4	9.9	15.6	6.4	7.6	8.3	8.2
Compound A	M001	22	94	100	97	139	119	114	116	140	105	89	99	103
100 mg/kg	M002	22	98	103	101	102	104	99	101	108	104	90	101	103
	M003	22	110	102	106	117	108	105	110	99	94	86	84	111
	M004	22	94	94	94	97	97	90	95	84	89	78	79	94
		Mean	99.0	99.8	99.5	113.8	107.0	102.0	105.5	107.8	98.0	85.8*	90.8	102.8
		SD	7.6	4.0	5.2	18.9	9.2	10.1	9.3	23.7	7.8	5.4	10.9	6.9

Notes) Pre 0: Mean of the values at 2 hours and 1 hour before dosing

*: Significantly different from the values on Day 1 at $p<0.05$

Table 1-2 Diastolic blood pressure (mmHg)

Test/control article	Animal	Dosing	Pre	Pre	Pre	Time after dosing (h)								
(Oral, 5 mL/kg)	No.	Day	-2	-1	0	0.5	1	2	4	6	8	12	16	24
0.5 w/v%	M001	1	72	67	70	101	77	73	71	86	63	57	55	65
methylcellulose	M002	1	60	66	63	66	71	69	68	66	57	59	63	64
solution	M003	1	79	76	78	76	75	77	79	69	62	52	49	79
	M004	1	65	66	66	65	68	71	68	69	72	58	59	66
		Mean	69.0	68.8	69.3	77.0	72.8	72.5	71.5	72.5	63.5	56.5	56.5	68.5
		SD	8.3	4.9	6.5	16.8	4.0	3.4	5.2	9.1	6.2	3.1	6.0	7.0
Compound A	M001	8	70	65	68	71	71	76	71	99	62	61	58	69
10 mg/kg	M002	8	65	65	65	64	66	63	66	72	68	58	53	62
	M003	8	78	79	79	71	74	73	78	72	51	49	51	73
	M004	8	62	69	66	70	70	69	56	66	71	54	59	69
		Mean	68.8	69.5	69.5	69.0	70.3	70.3	67.8	77.3	63.0	55.5	55.3	68.3
		SD	7.0	6.6	6.5	3.4	3.3	5.6	9.3	14.8	8.8	5.2	3.9	4.6
Compound A	M001	15	62	70	66	83	71	66	70	88	71	57	57	64
30 mg/kg	M002	15	61	61	61	69	64	68	67	69	66	53	64	65
	M003	15	72	80	76	77	71	76	78	68	54	44	54	74
	M004	15	64	59	62	71	67	69	65	67	67	54	59	66
		Mean	64.8	67.5	66.3	75.0	68.3	69.8	70.0	73.0	64.5	52.0	58.5	67.3
		SD	5.0	9.6	6.8	6.3	3.4	4.3	5.7	10.0	7.3	5.6	4.2	4.6
Compound A	M001	22	60	69	65	103	78	75	76	101	69	54	66	67
100 mg/kg	M002	22	59	66	63	63	64	60	64	71	70	51	59	64
	M003	22	74	67	71	79	74	70	74	65	55	45	47	74
	M004	22	70	70	70	70	70	66	70	62	67	55	56	71
		Mean	65.8	68.0	67.3	78.8	71.5	67.8	71.0	74.8	65.3	51.3*	57.0	69.0
		SD	7.4	1.8	3.9	17.4	6.0	6.3	5.3	17.9	6.9	4.5	7.9	4.4

Notes) Pre 0: Mean of the values at 2 hours and 1 hour before dosing

*: Significantly different from the values on Day 1 at $p<0.05$

Table 1-3 Mean blood pressure (mmHg)

Test/control article	Animal	Dosing	Pre	Pre	Pre	Time after dosing (h)								
(Oral, 5 mL/kg)	No.	Day	-2	-1	0	0.5	1	2	4	6	8	12	16	24
0.5 w/v%	M001	1	90	85	88	125	97	92	91	107	80	74	72	82
methylcellulose	M002	1	79	86	83	86	91	89	88	85	76	80	84	83
solution	M003	1	97	94	96	96	93	95	97	87	81	72	68	97
	M004	1	82	83	83	87	88	89	85	85	90	73	76	83
		Mean	87.0	87.0	87.5	98.5	92.3	91.3	90.3	91.0	81.8	74.8	75.0	86.3
		SD	8.1	4.8	6.1	18.2	3.8	2.9	5.1	10.7	5.9	3.6	6.8	7.2
Compound A	M001	8	88	83	86	91	90	95	90	120	77	78	76	87
10 mg/kg	M002	8	85	85	85	84	86	82	85	90	84	78	71	81
	M003	8	95	95	95	88	91	90	95	88	69	67	70	91
	M004	8	77	84	81	89	86	86	71	80	87	68	74	84
		Mean	86.3	86.8	86.8	88.0	88.3	88.3	85.3	94.5	79.3	72.8	72.8	85.8
		SD	7.5	5.6	5.9	2.9	2.6	5.6	10.3	17.5	8.0	6.1	2.8	4.3
Compound A	M001	15	81	88	85	104	90	83	89	109	87	75	75	81
30 mg/kg	M002	15	82	82	82	88	86	88	85	89	84	74	85	85
	M003	15	90	100	95	95	89	94	97	85	73	62	74	92
	M004	15	78	73	76	86	82	83	79	79	79	66	72	79
		Mean	82.8	85.8	84.5	93.3	86.8*	87.0	87.5	90.5	80.8	69.3*	76.5	84.3
		SD	5.1	11.3	7.9	8.1	3.6	5.2	7.5	13.0	6.1	6.3	5.8	5.7
Compound A	M001	22	77	85	81	122	99	95	96	121	87	71	83	85
100 mg/kg	M002	22	79	85	82	83	84	80	82	89	88	70	80	84
	M003	22	92	85	89	98	91	88	93	82	74	65	66	93
	M004	22	83	82	83	84	84	78	83	73	79	67	68	83
		Mean	82.8	84.3	83.8	96.8	89.5	85.3	88.5	91.3	82.0	68.3*	74.3	86.3
		SD	6.7	1.5	3.6	18.2	7.1	7.8	7.0	20.9	6.7	2.8	8.5	4.6

Notes) Pre 0: Mean of the values at 2 hours and 1 hour before dosing

*: Significantly different from the values on Day 1 at $p<0.05$

Table 2 Heart rate (beats/min)

Test/control article	Animal	Dosing	Pre	Pre	Pre	Time after dosing (h)								
(Oral, 5 mL/kg)	No.	Day	-2	-1	0	0.5	1	2	4	6	8	12	16	24
0.5 w/v%	M001	1	134	111	123	209	118	98	100	155	108	102	95	104
methylcellulose	M002	1	93	94	94	113	120	127	129	121	88	103	93	104
solution	M003	1	86	76	81	82	75	79	83	72	66	56	55	83
	M004	1	101	97	99	136	135	127	112	112	115	105	103	103
		Mean	103.5	94.5	99.3	135.0	112.0	107.8	106.0	115.0	94.3	91.5	86.5	98.5
		SD	21.2	14.4	17.6	54.1	25.8	23.5	19.4	34.1	22.0	23.7	21.4	10.3
Compound A	M001	8	98	83	91	122	93	82	97	143	104	91	90	92
10 mg/kg	M002	8	105	117	111	127	126	111	110	136	112	98	91	111
	M003	8	78	77	78	76	72	72	79	70	63	56	54	78
	M004	8	93	110	102	121	97	116	121	103	108	95	99	101
		Mean	93.5	96.8	95.5	111.5	97.0	95.3	101.8	113.0	96.8	85.0	83.5	95.5
		SD	11.4	19.7	14.2	23.8	22.2	21.6	18.1	33.6	22.7	19.5	20.1	14.0
Compound A	M001	15	132	108	120	149	109	96	111	142	107	82	84	80
30 mg/kg	M002	15	99	96	98	143	128	122	121	114	107	88	95	105
	M003	15	84	74	79	79	73	75	78	70	60	52	52	74
	M004	15	128	123	126	144	114	108	126	112	118	90	86	96
		Mean	110.8	100.3	105.8	128.8	106.0	100.3	109.0	109.5	98.0	78.0**	79.3	88.8
		SD	23.1	20.7	21.5	33.3	23.4	19.9	21.6	29.7	25.9	17.7	18.8	14.3
Compound A	M001	22	89	96	93	167	152	103	102	131	139	83	91	110
100 mg/kg	M002	22	93	107	100	114	114	108	115	113	119	86	89	100
	M003	22	85	69	77	87	73	75	80	72	62	51	52	74
	M004	22	90	86	88	140	109	103	105	104	100	86	95	97
		Mean	89.3	89.5	89.5	127.0	112.0	97.3	100.5	105.0	105.0	76.5**	81.8	95.3
		SD	3.3	16.1	9.7	34.3	32.3	15.0	14.8	24.7	32.8	17.1	20.0	15.2

Notes) Pre 0: Mean of the values at 2 hours and 1 hour before dosing

**: Significantly different from the values on Day 1 at $p<0.01$

Table 3-1 PR interval (ms)

Test/control article	Animal	Dosing	Pre	Pre	Pre	Time after dosing (h)								
(Oral, 5 mL/kg)	No.	Day	-2	-1	0	0.5	1	2	4	6	8	12	16	24
0.5 w/v%	M001	1	88	92	90	75	97	95	94	92	99	101	93	94
methylcellulose	M002	1	75	79	77	74	73	71	74	69	76	72	80	74
solution	M003	1	76	80	78	78	80	83	80	73	72	69	69	78
	M004	1	94	94	94	89	89	91	92	90	90	91	91	89
		Mean	83.3	86.3	84.8	79.0	84.8	85.0	85.0	81.0	84.3	83.3	83.3	83.8
		SD	9.3	7.8	8.5	6.9	10.5	10.6	9.6	11.7	12.5	15.3	11.1	9.3
Compound A	M001	8	93	94	94	92	96	94	94	94	99	100	94	97
10 mg/kg	M002	8	80	78	79	74	72	71	77	78	72	78	82	79
	M003	8	82	78	80	70	79	79	79	75	69	79	77	79
	M004	8	91	89	90	89	91	91	86	91	90	93	94	91
		Mean	86.5	84.8	85.8	81.3	84.5	83.8	84.0	84.5	82.5	87.5	86.8	86.5
		SD	6.5	8.1	7.4	10.9	11.0	10.7	7.7	9.4	14.4	10.8	8.6	9.0
Compound A	M001	15	90	89	90	88	93	93	98	104	94	89	100	92
30 mg/kg	M002	15	75	79	77	75	75	74	75	78	84	74	78	72
	M003	15	78	77	78	76	78	79	78	78	66	70	72	78
	M004	15	89	90	90	89	90	91	89	90	89	94	95	86
		Mean	83.0	83.8	83.8	82.0	84.0	84.3	85.0	87.5	83.3	81.8	86.3	82.0
		SD	7.6	6.7	7.2	7.5	8.8	9.2	10.6	12.4	12.2	11.6	13.4	8.8
Compound A	M001	22	88	82	85	79	87	85	88	101	90	90	87	89
100 mg/kg	M002	22	75	78	77	70	71	74	72	77	78	76	78	75
	M003	22	80	69	75	79	80	79	77	73	64	66	73	79
	M004	22	88	86	87	88	92	87	88	92	86	87	87	89
		Mean	82.8	78.8	81.0	79.0	82.5	81.3	81.3	85.8 *	79.5	79.8	81.3	83.0
		SD	6.4	7.3	5.9	7.3	9.1	5.9	8.1	13.0	11.5	11.0	6.9	7.1

Notes) Pre 0: Mean of the values at 2 hours and 1 hour before dosing

*: Significantly different from the values on Day 1 at $p<0.05$

Table 3-2 QRS duration (ms)

Test/control article	Animal	Dosing	Pre	Pre	Pre	Time after dosing (h)								
(Oral, 5 mL/kg)	No.	Day	-2	-1	0	0.5	1	2	4	6	8	12	16	24
0.5 w/v%	M001	1	36	37	37	37	36	36	37	38	36	38	40	38
methylcellulose	M002	1	36	38	37	36	38	40	37	39	36	38	38	38
solution	M003	1	40	40	40	40	40	41	41	40	40	40	40	40
	M004	1	41	42	42	43	43	41	40	43	43	42	42	41
		Mean	38.3	39.3	39.0	39.0	39.3	39.5	38.8	40.0	38.8	39.5	40.0	39.3
		SD	2.6	2.2	2.4	3.2	3.0	2.4	2.1	2.2	3.4	1.9	1.6	1.5
Compound A	M001	8	39	37	38	38	36	38	38	39	38	41	41	37
10 mg/kg	M002	8	41	39	40	35	38	40	38	38	39	38	39	38
	M003	8	42	40	41	40	40	41	40	41	40	40	41	40
	M004	8	42	42	42	41	42	41	42	41	43	42	42	42
		Mean	41.0	39.5	40.3	38.5	39.0	40.0	39.5	39.8	40.0	40.3	40.8	39.3
		SD	1.4	2.1	1.7	2.6	2.6	1.4	1.9	1.5	2.2	1.7	1.3	2.2
Compound A	M001	15	40	36	38	34	36	37	36	35	41	40	38	37
30 mg/kg	M002	15	38	45	42	40	41	44	40	43	39	38	38	39
	M003	15	41	41	41	40	41	41	41	42	40	40	41	41
	M004	15	42	41	42	40	40	41	41	41	44	43	43	41
		Mean	40.3	40.8	40.8	38.5	39.5	40.8	39.5	40.3	41.0	40.3	40.0	39.5
		SD	1.7	3.7	1.9	3.0	2.4	2.9	2.4	3.6	2.2	2.1	2.4	1.9
Compound A	M001	22	36	39	38	35	36	38	36	37	38	39	41	37
100 mg/kg	M002	22	40	42	41	42	38	41	40	38	39	38	38	42
	M003	22	42	40	41	39	41	41	40	41	40	40	41	38
	M004	22	42	42	42	42	41	42	42	41	42	39	37	42
		Mean	40.0	40.8	40.5	39.5	39.0*	40.5	39.5	39.3	39.8	39.0	39.3	39.8
		SD	2.8	1.5	1.7	3.3	2.4	1.7	2.5	2.1	1.7	0.8	2.1	2.6

Notes) Pre 0: Mean of the values at 2 hours and 1 hour before dosing

*: Significantly different from the values on Day 1 at $p<0.05$

Table 3-3 QT interval (ms)

Test/control article	Animal	Dosing	Pre	Pre	Pre	Time after dosing (h)								
(Oral, 5 mL/kg)	No.	Day	-2	-1	0	0.5	1	2	4	6	8	12	16	24
0.5 w/v%	M001	1	226	240	233	177	237	258	244	206	248	266	281	249
methylcellulose	M002	1	311	288	300	253	248	242	231	242	310	296	324	278
solution	M003	1	287	308	298	299	326	330	304	338	364	464	489	296
	M004	1	279	283	281	239	238	250	261	255	254	281	285	290
		Mean	275.8	279.8	278.0	242.0	262.3	270.0	260.0	260.3	294.0	326.8	344.8	278.3
		SD	35.8	28.6	31.2	50.3	42.8	40.5	31.8	55.8	54.4	92.3	98.1	20.9
Compound A	M001	8	251	268	260	228	254	266	248	206	248	273	279	259
10 mg/kg	M002	8	284	251	268	241	233	259	253	230	276	313	327	267
	M003	8	306	295	301	321	326	320	297	333	371	463	466	314
	M004	8	298	266	282	246	281	259	253	263	257	302	291	292
		Mean	284.8	270.0	277.8	259.0	273.5	276.0	262.8	258.0	288.0	337.8	340.8	283.0
		SD	24.3	18.3	18.0	42.0	40.1	29.5	23.0	55.2	56.6	85.2	86.0	25.0
Compound A	M001	15	227	235	231	207	238	254	240	209	243	286	291	276
30 mg/kg	M002	15	291	285	288	234	236	241	240	248	277	326	313	268
	M003	15	304	306	305	301	320	315	308	337	369	470	448	317
	M004	15	256	270	263	237	263	272	257	257	259	313	318	305
		Mean	269.5	274.0	271.8	244.8	264.3	270.5	261.3	262.8	287.0	348.8**	342.5	291.5
		SD	34.8	29.9	32.2	39.9	39.1	32.3	32.2	53.7	56.4	82.5	71.3	23.3
Compound A	M001	22	262	252	257	192	205	235	237	216	220	286	281	233
100 mg/kg	M002	22	301	273	287	253	252	252	247	246	255	334	335	283
	M003	22	276	330	303	297	329	323	305	337	367	485	471	322
	M004	22	301	312	307	241	270	271	280	260	277	314	299	293
		Mean	285.0	291.8	288.5	245.8	264.0	270.3	267.3	264.8	279.8	354.8**	346.5	282.8
		SD	19.3	35.6	22.7	43.2	51.3	38.1	31.2	51.5	62.7	89.0	86.0	37.1

Notes) Pre 0: Mean of the values at 2 hours and 1 hour before dosing

**: Significantly different from the values on Day 1 at $p<0.01$

Table 3-4 QTc (Bazett's formula, ms)

Test/control article	Animal	Dosing	Pre	Pre	Pre	Time after dosing (h)								
(Oral, 5 mL/kg)	No.	Day	-2	-1	0	0.5	1	2	4	6	8	12	16	24
0.5 w/v%	M001	1	326	327	327	331	340	329	311	326	330	351	351	335
methylcellulose	M002	1	383	371	377	364	352	346	344	338	374	382	408	350
solution	M003	1	339	347	343	344	368	372	358	378	377	443	464	353
	M004	1	358	375	367	352	349	355	355	352	359	372	369	373
		Mean	351.5	355.0	353.5	347.8	352.3	350.5	342.0	348.5	360.0	387.0	398.0	352.8
		SD	24.8	22.4	22.7	13.9	11.7	17.9	21.5	22.4	21.5	39.5	50.0	15.6
Compound A	M001	8	319	313	316	320	326	308	318	323	323	337	342	332
10 mg/kg	M002	8	371	338	355	336	337	347	331	344	375	404	406	359
	M003	8	342	328	335	356	352	347	340	358	385	449	443	356
	M004	8	376	361	369	354	355	355	352	341	348	382	389	374
		Mean	352.0	335.0	343.8	341.5	342.5	339.3	335.3	341.5	357.8	393.0	395.0	355.3
		SD	26.6	20.1	23.2	16.9	13.5	21.2	14.4	14.4	27.9	46.6	41.9	17.4
Compound A	M001	15	302	301	302	326	317	318	314	313	311	338	343	311
30 mg/kg	M002	15	366	397	382	345	328	332	342	332	379	396	390	348
	M003	15	354	338	346	337	348	349	354	367	367	431	423	348
	M004	15	353	387	370	361	361	357	342	346	346	380	382	361
		Mean	343.8	355.8	350.0	342.3	338.5	339.0	338.0	339.5	350.8	386.3	384.5	342.0
		SD	28.5	44.7	35.3	14.7	19.7	17.5	17.0	22.8	29.8	38.6	32.9	21.6
Compound A	M001	22	315	309	312	332	304	306	324	318	312	341	345	310
100 mg/kg	M002	22	358	371	365	332	345	337	338	342	366	401	413	338
	M003	22	307	351	329	339	369	359	356	379	374	448	440	356
	M004	22	377	355	366	363	357	342	349	329	341	379	380	356
		Mean	339.3	346.5	343.0	341.5	343.8	336.0	341.8	342.0	348.3	392.3	394.5	340.0
		SD	33.7	26.5	26.9	14.7	28.3	22.1	14.0	26.5	28.0	44.7	41.1	21.7

Notes) Pre 0: Mean of the values at 2 hours and 1 hour before dosing

Not significantly different from the values on Day 1

Table 3-5 RR interval (ms)

Test/control article	Animal	Dosing	Pre	Pre	Pre	Time after dosing (h)								
(Oral, 5 mL/kg)	No.	Day	-2	-1	0	0.5	1	2	4	6	8	12	16	24
0.5 w/v%	M001	1	481	537	509	285	488	614	614	398	563	575	639	550
methylcellulose	M002	1	658	601	630	483	496	489	452	515	688	600	629	632
solution	M003	1	717	790	754	754	785	790	720	799	930	1099	1113	702
	M004	1	605	569	587	462	466	499	543	522	501	571	595	607
		Mean	615.3	624.3	620.0	496.0	558.8	598.0	582.3	558.5	670.5	711.3	744.0	622.8
		SD	100.5	113.5	102.4	193.6	151.4	140.0	113.3	170.1	189.7	258.8	246.7	63.0
Compound A	M001	8	621	733	677	506	605	742	612	407	590	655	668	610
10 mg/kg	M002	8	588	551	570	513	478	557	584	446	542	602	648	552
	M003	8	799	808	804	812	859	852	762	864	928	1062	1104	777
	M004	8	627	544	586	484	626	531	514	596	547	625	558	608
		Mean	658.8	659.0	659.3	578.8	642.0	670.5	618.0	578.3	651.8	736.0	744.5	636.8
		SD	95.1	132.4	107.4	156.0	158.8	153.2	104.5	207.2	185.4	218.4	244.4	97.3
Compound A	M001	15	568	613	591	402	564	640	585	444	610	717	718	785
30 mg/kg	M002	15	632	514	573	458	515	530	493	556	537	678	645	593
	M003	15	735	816	776	794	846	815	758	840	1013	1188	1121	827
	M004	15	526	487	507	430	533	581	568	551	561	676	691	716
		Mean	615.3	607.5	611.8	521.0	614.5	641.5	601.0	597.8	680.3	814.8	793.8	730.3
		SD	91.0	149.2	115.3	183.4	155.7	124.1	112.0	169.6	223.9	249.5	220.2	102.3
Compound A	M001	22	695	662	679	334	454	589	534	464	495	706	664	564
100 mg/kg	M002	22	705	542	624	578	533	560	535	518	485	696	658	701
	M003	22	808	885	847	770	795	811	733	794	963	1172	1149	817
	M004	22	635	772	704	439	570	625	645	625	661	690	620	678
		Mean	710.8	715.3	713.5	530.3	588.0	646.3	611.8	600.3	651.0 *	816.0	772.8	690.0
		SD	71.8	147.1	95.1	188.5	146.2	113.0	96.2	145.5	223.1	237.4	251.6	103.7

Notes) Pre 0: Mean of the values at 2 hours and 1 hour before dosing

*: Significantly different from the values on Day 1 at $p<0.05$

Table 4 Respiratory rate (breaths/min)

Test/control article	Animal	Dosing	Pre	Pre	Pre	Time after dosing (h)								
(Oral, 5 mL/kg)	No.	Day	-2	-1	0	0.5	1	2	4	6	8	12	16	24
0.5 w/v%	M001	1	25	34	30	39	22	24	21	40	31	29	28	26
methylcellulose	M002	1	29	23	26	33	31	35	35	28	30	28	25	29
solution	M003	1	27	20	24	16	22	20	19	24	20	17	14	21
	M004	1	29	30	30	26	25	34	32	31	32	26	29	32
		Mean	27.5	26.8	27.5	28.5	25.0	28.3	26.8	30.8	28.3	25.0	24.0	27.0
		SD	1.9	6.4	3.0	9.9	4.2	7.4	7.9	6.8	5.6	5.5	6.9	4.7
Compound A	M001	8	25	26	26	29	22	25	26	20	35	32	30	19
10 mg/kg	M002	8	27	31	29	38	36	30	33	36	34	25	27	31
	M003	8	23	8	16	20	22	22	20	18	22	19	16	14
	M004	8	26	24	25	28	22	24	30	30	26	23	24	24
		Mean	25.3	22.3	24.0	28.8	25.5	25.3	27.3	26.0	29.3	24.8	24.3	22.0
		SD	1.7	9.9	5.6	7.4	7.0	3.4	5.6	8.5	6.3	5.4	6.0	7.3
Compound A	M001	15	39	26	33	26	23	29	31	39	30	27	24	23
30 mg/kg	M002	15	29	28	29	29	35	29	37	34	28	28	28	28
	M003	15	17	24	21	20	20	27	22	21	17	19	8	19
	M004	15	31	37	34	32	22	25	30	30	24	25	22	24
		Mean	29.0	28.8	29.3	26.8	25.0	27.5	30.0	31.0	24.8	24.8	20.5	23.5
		SD	9.1	5.7	5.9	5.1	6.8	1.9	6.2	7.6	5.7	4.0	8.7	3.7
Compound A	M001	22	26	26	26	35	36	28	25	26	38	27	28	21
100 mg/kg	M002	22	26	27	27	31	37	28	34	30	29	29	30	25
	M003	22	19	18	19	22	25	21	18	17	12	11	11	19
	M004	22	23	23	23	30	22	22	23	24	25	27	28	20
		Mean	23.5	23.5	23.8	29.5	30.0	24.8	25.0	24.3	26.0	23.5	24.3	21.3
		SD	3.3	4.0	3.6	5.4	7.6	3.8	6.7	5.4	10.8	8.4	8.9	2.6

Notes) Pre 0: Mean of the values at 2 hours and 1 hour before dosing

Not significantly different from the values on Day 1

Table 5 Intra-abdominal body temperature (°C)

Test/control article	Animal	Dosing	Pre	Pre	Pre	Time after dosing (h)								
(Oral, 5 mL/kg)	No.	Day	-2	-1	0	0.5	1	2	4	6	8	12	16	24
0.5 w/v%	M001	1	38.2	38.0	38.1	38.8	38.5	38.3	38.5	38.8	38.3	37.1	37.1	38.4
methylcellulose	M002	1	37.9	38.1	38.0	38.7	38.5	38.6	38.9	38.5	38.1	37.2	37.1	38.3
solution	M003	1	38.2	38.2	38.2	38.4	38.4	38.5	38.7	38.4	38.6	37.2	37.0	38.4
	M004	1	38.2	38.1	38.2	38.4	38.4	38.3	38.4	38.2	38.3	37.5	37.3	38.3
		Mean	38.13	38.10	38.13	38.58	38.45	38.43	38.63	38.48	38.33	37.25	37.13	38.35
		SD	0.15	0.08	0.10	0.21	0.06	0.15	0.22	0.25	0.21	0.17	0.13	0.06
Compound A	M001	8	38.1	38.0	38.1	38.7	38.4	38.2	38.6	38.5	38.2	37.1	36.9	38.4
10 mg/kg	M002	8	37.7	38.2	38.0	38.7	38.6	38.7	38.7	38.4	38.1	37.2	36.9	38.3
	M003	8	38.1	38.2	38.2	38.4	38.3	38.4	38.7	38.2	38.4	37.2	36.7	38.4
	M004	8	38.0	38.2	38.1	38.4	38.3	38.2	38.4	38.2	38.3	37.4	37.3	38.2
		Mean	37.98	38.15	38.10	38.55	38.40	38.38	38.60	38.33	38.25	37.23	36.95	38.33
		SD	0.19	0.10	0.08	0.17	0.14	0.24	0.14	0.15	0.13	0.13	0.25	0.10
Compound A	M001	15	38.2	38.2	38.2	38.7	38.5	38.4	38.4	38.1	38.0	37.1	37.0	38.1
30 mg/kg	M002	15	37.8	38.0	37.9	38.6	38.6	38.6	38.7	38.4	38.1	37.4	37.2	38.5
	M003	15	38.0	38.1	38.1	38.2	38.3	38.4	38.6	37.9	38.4	37.1	37.1	38.4
	M004	15	38.3	38.3	38.3	38.5	38.5	38.4	38.5	38.3	38.4	37.4	37.1	38.3
		Mean	38.08	38.15	38.13	38.50	38.48	38.45	38.55	38.18	38.23	37.25	37.10	38.33
		SD	0.22	0.13	0.17	0.22	0.13	0.10	0.13	0.22	0.21	0.17	0.08	0.17
Compound A	M001	22	38.0	38.0	38.0	38.9	38.3	38.4	38.5	38.1	38.0	37.2	37.0	38.5
100 mg/kg	M002	22	37.6	38.0	37.8	38.6	38.6	38.7	38.8	38.5	38.2	37.0	36.6	38.2
	M003	22	38.1	38.2	38.2	38.5	38.5	38.6	38.9	37.9	38.2	37.0	36.6	38.4
	M004	22	38.1	38.2	38.2	38.4	38.4	38.4	38.5	38.3	38.3	37.5	37.5	38.4
		Mean	37.95	38.10	38.05	38.60	38.45	38.53 *	38.68	38.20	38.18	37.18	36.93	38.38
		SD	0.24	0.12	0.19	0.22	0.13	0.15	0.21	0.26	0.13	0.24	0.43	0.13

Notes) Pre 0: Mean of the values at 2 hours and 1 hour before dosing

*: Significantly different from the values on Day 1 at $p<0.05$

Table 6 Clinical signs (cage-side observation)

Animal	Acclimation period							Recovery period						
No.	Day -35	Day -34	Day -33	Day -32	Day -31	Day -30	Day -29	Day -28	Day -27	Day -26	Day -25	Day -24	Day -23	Day -22
M001	-	-	-	-	-	-	-	- *1 (4.0)	- (5.5)	- (2.0)	- (2.5)	-	-	-
M002	-	-	-	-	-	-	-	- *1 (5.0)	- (8.0)	dC+ (8.0)	dC+ (2.5)	dC+ (5.0)	dC+ (5.0)	dC+ (4.0)
M003	-	-	-	-	-	-	-	-	- *1 (3.0)	- (7.0)	-	-	-	-
M004	-	-	-	-	-	-	-	-	- *1 (1.5)	- (5.0)	- (2.0)	- (1.0)	-	-

Animal	Recovery period													
No.	Day -21	Day -20	Day -19	Day -18	Day -17	Day -16	Day -15	Day -14	Day -13	Day -12	Day -11	Day -10	Day -9	Day -8
M001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M002	- (1.5)	-	-	-	-	-	-	-	-	-	-	-	-	-
M003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M004	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Animal	Recovery period						
No.	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1
M001	-	-	-	-	-	-	-
M002	-	-	-	-	-	-	-
M003	-	-	-	-	-	-	-
M004	-	-	-	-	-	-	-

Notes) *1: day of surgery, -: No abnormal signs, dC+: Paralysis of hindleg (Right)
"()" states the number of pieses of remaining food.
Approximately 108 g (approximately 12 g × 9 pieces) of solid food was provided to each animal once daily, and remaining food check was performed on the following day.
On the day of surgery, approximately 60 g (5 pieces) of solid food was provided to each animal that had undergone surgery.

Table 6 Clinical signs (cage-side observation, continued)

Control article (Oral, 5 mL/kg)	Dosing Day	Animal No.	Pre	Time after dosing (h)			Day after dosing[*1]
				0	4	24	
0.5 w/v% methylcellulose solution	1	M001	-	-	-	-	-
		M002	-	-	-	-	-
		M003	-	-	-	-	-
		M004	-	-	-	-	-
Compound A 10 mg/kg	8	M001	-	-	-	-	-
		M002	-	-	-	-	-
		M003	-	-	-	-	-
		M004	Vomitus	-	-	-	-
Compound A 30 mg/kg	15	M001	-	-	-	-	-
		M002	-	-	-	-	-
		M003	-	-	-	-	-
		M004	-	-	-	-	-
Compound A 100 mg/kg	22	M001	-	-	-	-	
		M002	-	-	-	-	
		M003	-	-	-	-	
		M004	-	-	-	-	

Notes) Pre: Before dosing, 0: Immediately after dosing

*1: Corresponding to Days 3 to 7, Days 10 to 14, and Days 17 to 21 (depending on dosing day)

-: No abnormal signs

Vomitus: food like, Could not be measured due to dry