was confirmed that they met the acceptance criteria of

Water: Water conforming to the water quality standards required by the Japanese Waterworks Law was available *ad libitum* from an automatic water supply system. The water is analyzed four times a year by Pharmaceutical Association. The analysis results were obtained and it was confirmed that they met the acceptance criteria of .

Environmental Enrichment: Enrichment toys were provided. Treats (apples) were supplied at least twice weekly.

Cleaning: The room and cages were washed daily with water. The cages were exchanged at least once every four weeks for cleaned and disinfected replacements during the dosing period.

Airborne Bacterial Tests: Airborne bacterial tests are conducted four times a year by . The results were obtained, and it was confirmed that they met the acceptance criteria of .

7.6 Identification of Animals and Cages

Animals: During the acclimation period, each animal was identified by an ACN (acclimation number) marked on the chest with . After grouping, each animal was identified by an animal number tattooed on the chest with a tattoo marker (KN-298B Electric Tattoo Marker, Natsume Seisakusho Co., Ltd.).

Cages: During the acclimation period, each cage was identified by cage card bearing the study number, ACN, and sex, and a bar code. After grouping, each cage was identified by a color-coded cage card bearing the study number, group, dose level, sex, and animal number, and a bar code.

7.7 Acclimation

Quarantined cynomolgus monkeys (12 males and 12 females) were received, and acclimated for 3 days. The observations and examinations stated in Section 7.11 "Observations and Examinations" were performed during the acclimation period. Drinking water (10 mL/body) was administered to each animal daily from Day −3 to −1 in the same manner as test article dosing in order to acclimatize the animals to the dosing procedure.

Animals were re-acclimated for 37 days after the end of observation for the single dose study. Animals were restrained for 30 minutes in the same manner as that for electrocardiography and blood pressure measurement once on Days −24, −22, −20, −18, and −16 of repeated dosing. Drinking water (10 mL/body) was administered to each animal once daily from Days −24, −22, −20, −18, −16, −13 to −7, −4, and −2 of repeated dosing in the same manner as that for test article dosing in order to acclimatize the animals to the dosing procedure. Animals were restrained in the same manner as that for blood sampling on the same days.

7.8 Grouping

On the final day of the acclimation period, animals were assigned to groups by stratified randomization (MiTOX System, Ver. 2.0, Mitsui Zosen Systems Research Inc.) according to body weight to minimize bias in body weight among the groups.
On the day before the initiation of repeated dosing, animals were re-assigned based on the results of the examinations prior to the repeated dosing. The detailed re-assignment is described in Section 7.9.

7.9 Study Design

One control group and two test article groups

Group	Test and Control Articles	Dosing Period	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Concentration (mg/mL)	Number of Animals (Animal No.)	
						Males	Females
1	0.5 w/v% MC	single	NA	NA	NA	3 (1 to 3)	3 (4 to 6)
		2 weeks	-	5	-	3 (101 to 103)*	3 (104 to 106)*
2	TAK-070 M-II	single	3	5	0.6	3 (7 to 9)	3 (10 to 12)
		2 weeks	10	5	2	3 (107 to 109)*	3 (110 to 112)*
3	TAK-070 M-II	single	30	5	6	3 (13 to 15)	3 (16 to 18)
		2 weeks	60	5	12	3 (113 to 115)*	3 (116 to 118)*

NA: Not applicable (single dosing was not performed for the control group.)

*: One male (No. 8) and three females (No. 6, 10, and 16) were excluded from the 2-week repeated dose study due to the following reasons: diarrhea, high lymphocyte count (36.29 $\times 10^3/\mu L$), a tendency toward high creatinine kinase (1486 IU/L), and tendencies toward low albumin and high globulin (3.2 and 5.2 g/dL), respectively, and replaced by stock animals. The above-mentioned high or low values were not considered to have been caused by the single dosing of the test article at 3 or 10 mg/kg, because no similar changes were induced by the repeated dosing at higher dose level.

In order to comply with the online data system, Animal No. 101 to 118, except the replacement animals mentioned above, were successfully used for the 2-week repeated dose study. Animal No. 1 to 5, and 7, 9, 11 to 15, 17, and 18 were expressed as Animal No. 101 to 105, and 107, 109, 111 to 115, 117, and 118, respectively.

7.10 Justification for Selection of the Dose Levels

In a 4-week repeated dose study in rats, dose levels of TAK-070 M-II at 3 and 30 mg/kg yielded AUC values of TAK-070 M-II [redacted] respectively, the estimated AUC of TAK-070 M-II [redacted] μg·h/mL) following administration of TAK-070 to humans at 100 mg/body, the intended highest dose level in clinical use. Therefore, dose levels of TAK-070 M-II for the single dose study were set at 3 and 30 mg/kg to determine AUC after single administration to monkeys.

In the single dose study, AUC at 30 mg/kg was lower than expected (around [redacted] μg·h/mL). Therefore, the high dose level of TAK-070 M-II for the 2-week repeated dose study was set at 60 mg/kg. A low dose level of 10 mg/kg was set to evaluate toxicokinetic and toxic profiles of TAK-070 M-II in more detail.

7.11 Observations and Examinations

7.11.1 Single Dose Study

The animals in the control group and stock animals were observed for clinical signs once daily.

7.11.1.1 Clinical Signs

Number of Animals:	All
Frequency	
Acclimation Period:	Once daily
Dosing Day and Observation Period:	At each sampling point
Method:	All animals were observed for clinical signs and mortality.

7.11.1.2 Body Weight

Number of Animals:	All
Frequency	
Acclimation Period:	Once on the first and final days of acclimation
Dosing Day:	Before dosing
Observation Period:	Day 2
Method:	All animals were weighed using an electronic balance (HP-40K, A&D Co., Ltd.).

7.11.1.3 Toxicokinetics

Number of Animals:	All
Sampling Points:	1, 2, 4, 8, 24, and 48 hours after dosing (total: 6 points)
Sampling Volume:	Approximately 0.3 mL (approximately 100 µL as plasma) at each sampling point
Sampling Method:	Blood was drawn from the femoral vein with a syringe containing heparin sodium. The blood was centrifuged (4°C, 1710×*g*, 3000 rpm, 15 minutes, Inverter Refrigerated Centrifuge Model 5910 and 5922, and High Speed Refrigerated Centrifuge Model 6930, Kubota Manufacturing Corporation). The obtained plasma was stored in a freezer [actual range from the day of sampling to the day of

shipment (November 30, 2012 to December 3, 2012): −27.6°C to −20.0°C, acceptable range: −15°C or below].

Shipping method: Frozen plasma samples were sent to , Inc. on dry ice.

Destination: , Inc.
Pharmacokinetic Research Laboratory
, Japan
TEL 81 (0) FAX 81 (0)

Analyte: TAK-070 M-II

Stability: The analyte was confirmed stable in frozen cynomolgus monkey plasma (−15°C or below) for 31 days[1)].
It was judged that TAK-070 M-II was stable in the analysis samples during the analysis period, since the samples were stored within the acceptable temperature range and analyzed within the period for which stability had been confirmed.

Analysis: Analysis was performed by LC/MS/MS at , Inc. The results of analysis (concentrations of TAK-070 M-II and the following parameters) were obtained and are reflected in the Final Report.

Parameters: WinNonlin (Ver.6.3, Pharsight Corporation) was used for calculation. AUC was calculated using the trapezoidal formula. Plasma concentrations pre-dosing and below the lower limit of quantification (5.00 ng/mL) were regarded as 0 ng/mL.
Maximum plasma drug concentration (C_{max})
Time to reach maximum plasma drug concentration (T_{max})
Half-life period ($t_{1/2}$)
Area under the plasma drug concentration-time curve ($AUC_{0\text{-}24h}$, AUC_{inf})

7.11.2 2-Week Repeated Dose Study

The observations and examinations during the non-dosing period were also performed for the stock animals.

7.11.2.1 Clinical Signs

Number of Animals:	All
Frequency	
Acclimation Period:	Once daily
Dosing Period:	Twice daily [before dosing and approximately 4 hours after dosing (around T_{max})]
Day of Necropsy:	Once
Method:	All animals were observed for clinical signs and mortality.

7.11.2.2 Body Weight

Number of Animals:	All
Frequency	
Non-dosing Period:	Day −37 and −1 of repeated dosing
Dosing Period:	Days 3, 7, 10, and 14 of dosing (before dosing)
Day of Necropsy:	Once (for calculation of relative organ weights)
Method:	All animals were weighed using an electronic balance (HP-40K, A&D Co., Ltd.).

7.11.2.3 Food Consumption

Number of Animals:	All
Frequency:	Daily from Day −7 of repeated dosing
Method:	The number of pieces provided to animals and the number remaining were recorded daily, and food consumption per day (g) was calculated.

7.11.2.4 Electrocardiography

Number of Animals:	All
Frequency	
Non-dosing Period:	Day −14 of repeated dosing At a time corresponding to that during the dosing period [before dosing and approximately 4 hours after dosing (around T_{max})]

Dosing Period:	Day 10 (Week 2) of dosing Before dosing and approximately 4 hours after dosing (around T_{max})
Method:	The animals were restrained unanesthetized in the sitting position using a procedure cage. Electrocardiograms (leads I, II, III and aVR, aVL, and aVF) were recorded with an ECG processor (SP-2000, Softron Co., Ltd.) via an electrocardiograph for animals (Cardisuny α6000AX-D or Cardisuny D500, Fukuda M·E Kogyo Co., Ltd.), and the following parameters were analyzed using averaged continuous waveforms in lead II for 8 seconds.
Parameters:	Heart rate (beats/min), PR interval (ms), QRS duration (ms), QT interval (ms), and QTc (Bazett's formula)

7.11.2.5 Blood Pressure

Number of Animals:	All
Frequency	
Non-dosing Period:	Day −14 of repeated dosing At a time corresponding to that during the dosing period [before dosing and approximately 4 hours after dosing (around T_{max})]
Dosing Period:	Day 10 (Week 2) of dosing Before dosing and approximately 4 hours after dosing (around T_{max})
Method:	After electrocardiography, blood pressure was measured non-invasively at the upper arm using an automatic blood pressure manometer (BP-8800NC, Omron Colin Co., Ltd.). The animals were restrained unanesthetized in the sitting position using a procedure cage.
Parameters Evaluated:	Diastolic pressure, systolic pressure, and mean pressure

7.11.2.6 Respiration Rate

Number of Animals:	All
Frequency	
Non-dosing Period:	Day −14 of repeated dosing At a time corresponding to that during the dosing period [before dosing and approximately 4 hours after dosing (around T_{max})]
Dosing Period:	Day 10 (Week 2) of dosing Before dosing and approximately 4 hours after dosing (around T_{max})
Method:	After blood pressure measurement, the number of respirations in 15 seconds was counted by gently placing a hand on the animal's abdomen and the respiration rate per minute was calculated. The animals were restrained unanesthetized in the sitting position using a procedure cage.

7.11.2.7 Hematology

Number of Animals:	All
Frequency	
Non-dosing Period:	Day −6 of repeated dosing (at a time corresponding to that during the dosing period)
Dosing Period:	Day 14 (Week 2) of dosing (before dosing)
Sampling Volume:	Approximately 1 mL
Sampling Method:	Blood was drawn from the femoral vein with a syringe and treated with an anticoagulant, EDTA-2K.
Blood Smears:	Wright-stained blood smears were prepared from remaining blood samples. The blood smears were not examined because no changes which would have necessitated examination were noted, and accordingly they were discarded.
Parameters and Method:	As shown in the following table:

Parameters	Unit	Method	Apparatus
Erythrocyte count	$10^6/\mu L$	Dual angle laser flow-cytometric measurement	ADVIA120[a)]
Leukocyte count	$10^3/\mu L$	Dual angle laser flow-cytometric measurement	
Hematocrit value	%	Calculation: (mean corpuscular volume × erythrocyte count) / 10	
Hemoglobin concentration	g/dL	Modified cyanmethemoglobin method	
Platelet count	$10^3/\mu L$	Dual angle laser flow-cytometric measurement	
Mean corpuscular volume	fL	Dual angle laser flow-cytometric measurement	
Mean corpuscular hemoglobin	pg	Calculation: (hemoglobin concentration / erythrocyte count) × 10	
Mean corpuscular hemoglobin concentration	g/dL	Calculation: [hemoglobin concentration / (erythrocyte count × mean corpuscular volume)] × 1000	
Reticulocyte ratio	%	Laser flow-cytometric measurement with RNA stain	
Differential leukocytes[b)]	$10^3/\mu L$, %[c)]	Flow-cytometric measurement with peroxidase stain and dual angle laser flow-cytometric measurement	

a) Hematology system (Siemens Healthcare Diagnostics Manufacturing Ltd.)
b) Parameters: eosinophils, basophils, monocytes, lymphocytes, neutrophils, and large unstained cells
c) Only differential leukocyte counts were evaluated.

7.11.2.8 Blood Chemistry

Number of Animals: All

Frequency

Non-dosing Period: Day −6 of repeated dosing (at a time corresponding to that during the dosing period)

Dosing Period: Day 14 (Week 2) of dosing (before dosing)

Sampling Volume: Approximately 2 mL

Sampling Method: Blood was drawn from the femoral vein. The samples were left at room temperature for 20 to 60 minutes, and serum was obtained by centrifugation (room temperature, 1710×g, 3000 rpm, 10 minutes, Refrigerated Centrifuge Model 5800, Kubota Manufacturing Corporation).

Parameters and Method: As shown in the following table:

Parameters	Unit	Method	Apparatus
Aspartate transaminase	IU/L	JSCC transferable method	JCA-BM6070[a)]
Alanine transaminase	IU/L	JSCC transferable method	
Alkaline phosphatase	IU/L	JSCC transferable method	
Creatinine kinase	IU/L	JSCC transferable method	
Total bilirubin	mg/dL	Vanadate oxidation method	
Total protein	g/dL	Biuret method	
Albumin	g/dL	BCG method	
Globulin	g/dL	Calculation: total protein − albumin	-
A/G ratio	-	Calculation: albumin / globulin	
Total cholesterol	mg/dL	COD ·HMMPS method	JCA-BM6070[a)]
Triglycerides	mg/dL	GPO · HMMPS method, glycerol blanking method	
Glucose	mg/dL	Hexokinase · G-6-PDH method	
Urea nitrogen	mg/dL	Urease-GlDH method	
Creatinine	mg/dL	Creatininase · HMMPS method	
Inorganic phosphorus	mg/dL	PNP · XDH method	
Calcium	mg/dL	MXB method	
Sodium	mEq/L	Electrode method	
Potassium	mEq/L	Electrode method	
Chloride	mEq/L	Electrode method	

a) Automatic analyzer (JEOL Co., Ltd.)

7.11.2.9 Plasma Cortisol Measurement

Number of Animals: All

Frequency

Non-dosing Period: Day −6 of repeated dosing (at a time corresponding to that during the dosing period)

Dosing Period: Day 14 (Week 2) of dosing (before dosing)

Sampling Volume: Approximately 0.5 mL (approximately 0.2 mL as plasma) at each sampling point

Sampling Method: Blood was drawn from the femoral vein with a syringe containing heparin sodium, and plasma was obtained immediately by centrifugation (4°C, 1710×g, 3000 rpm, 15 minutes, Inverter Refrigerated Centrifuge Model 5910 and 5922, and High Speed Refrigerated Centrifuge Model 6930, Kubota Manufacturing Corporation). The plasma samples were stored in a deep freezer [actual range from the day of sampling to the day of analysis (January 3, 2013 to January 25, 2013): −87.8°C to −75.8°C, acceptable range: −70°C or below]

Analysis: Plasma cortisol (unit: ng/mL) was measured by LC/MS/MS.

7.11.2.10 Pathological Examinations

Organs and tissues for pathological examinations

Organs and tissues		Organ weight	Fixation	Histopathology (specimen preparation and examination)
Trachea		–	Y	Y
Lungs (including bronchi)	Left	Y	Y	Y
	Right			Y
Tongue		–	Y	Y
Submandibular glands	Left	Y	Y	Y
	Right	Y	Y	Y
Esophagus	Thoracic	–	Y	Y
Stomach	Body	–	Y	Y
	Pylorus	–		Y
Small intestine	Duodenum	–	Y	Y
	Jejunum	–		Y
	Ileum	–		Y
Peyer's patches (ileum)		–		Y
Large intestine	Cecum	–	Y	Y
	Colon	–		Y
	Rectum	–		Y
Pancreas		–	Y	Y
Liver		Y[a)]	Y	Y
Gallbladder		–	Y	Y

Organs and tissues		Organ weight	Fixation	Histopathology (specimen preparation and examination)
Aorta	Thoracic	–	Y	Y
Heart		Y	Y	Y
Kidneys	Left	Y	Y	Y
	Right	Y	Y	Y
Urinary bladder		–	Y	Y
Testes	Left	Y	Y	Y
	Right	Y	Y	Y
Epididymides	Left	Y	Y	Y
	Right	Y	Y	Y
Prostate		Y	Y	Y
Seminal vesicles	Left	Y	Y	Y
	Right			–
Ovaries	Left	Y	Y	Y
	Right	Y	Y	Y
Uterus		Y	Y	Y
Vagina		–	Y	Y
Brain	Cerebrum[b)]	Y	Y	Y
	Cerebellum			Y
	Pons			Y
	Medulla oblongata			Y
Spinal cord	Thoracic	–	Y	Y
Sciatic nerves	Left	–	Y	Y
	Right	–	Y	–
Sternum/Sternal bone marrow		–	Y	Y
Femur /Femoral bone marrow	Left	–	Y	Y
	Right	–	Y	–
Submandibular lymph nodes	Left	–	Y	Y
	Right	–	Y	–
Mesenteric lymph nodes		–	Y	Y
Spleen		Y	Y	Y
Thymus		Y	Y	Y
Pituitary		Y	Y	Y
Thyroids/Parathyroids	Left	Y	Y	Y
	Right	Y	Y	Y
Adrenals	Left	Y	Y	Y
	Right	Y	Y	Y
Eyeballs/Optic nerves	Left	–	Y	Y
	Right	–	Y	Y

Organs and tissues		Organ weight	Fixation	Histopathology (specimen preparation and examination)
Lacrimal glands	Left	–	Y	Y
	Right	–	Y	Y
Skeletal muscles (gastrocnemius)	Left	–	Y	Y
	Right	–	Y	–
Mammary glands /Skin (thoracic)	Left	–	Y	Y[c]
	Right	–	Y	–
Skin (region of back)[d]		–	Y	Y

Y: Examined, –: Not examined

a) Including gallbladder

b) Parietal lobe, temporal lobe, and diencephalon

c) Mammary glands: only females

d) Interscapular

7.11.2.10.1 Necropsy

Number of Animals: All

Frequency: On the day following the end of the dosing period

Method: The animals were anesthetized by an intravenous injection of sodium pentobarbital (Tokyo Chemical Industry Co., Ltd.) solution (64.8 mg/mL, 0.4 mL/kg) into the cephalic vein, and weighed, and euthanized by exsanguination. External appearance, and internal organs and tissues were examined macroscopically.

7.11.2.10.2 Organ Weights (absolute and relative)

Number of Animals: All

Method: The organs listed in the above table were weighed using an electronic balance (HR-200 and HF-3000, A&D Co., Ltd.). Relative organ weight per kg was calculated from body weight on the day of necropsy. In the case of bilateral organs weighed separately, the total bilateral weight was calculated.

7.11.2.10.3 Histopathology

Organs and Tissues:	Listed in the above table
Fixation	
Number of Animals:	All
Method:	The eyeballs and optic nerves were fixed in a mixture of 3% glutaraldehyde and 2.5% formalin, and the testes were fixed in formalin-sucrose-acetic acid (FSA) solution. The other organs and tissues were fixed in 10% neutral buffered formalin. The trachea, sternum, and femur were decalcified with Kalkitox (Wako Pure Chemical Industries, Ltd.).
Specimen Preparation	
Number of Animals:	All
Method:	The fixed organs and tissues were embedded in paraffin, sectioned, and stained with hematoxylin-eosin (HE) stain.
Examination	
Number of Animals:	All
Method:	The slide specimens were examined histopathologically.

7.11.2.11 Toxicokinetics

Number of Animals:	All animals in the test article groups Blood was drawn from animals in the control group in the same manner as in the test article groups, and discarded.
Sampling Points	
Day 1 of Dosing:	Before dosing, and 1, 2, 4, 8, and 24 hours after dosing (total: 6 points)
Day 14 of Dosing:	Before dosing, and 1, 2, 4, 8, and 24 hours after dosing (total: 6 points)
Sampling Volume:	Approximately 0.3 mL (approximately 100 µL as plasma) at each sampling point
Sampling Method:	Blood was drawn from the femoral vein with a syringe containing heparin sodium. The blood was centrifuged (4°C, 1710×g, 3000 rpm, 15 minutes, Inverter Refrigerated Centrifuge Model 5910 and 5922, and High Speed Refrigerated Centrifuge Model 6930, Kubota Manufacturing

Corporation). The obtained plasma was stored in a freezer (acceptable range: –15°C or below).

Sample Storage temperature

Day of sampling to day of shipment	Actual range
January 9, 2013 to January 10, 2013	–27.2°C to –20.4°C
January 22, 2013 to January 23, 2013	–28.1°C to –21.3°C

Shipping method: Frozen plasma samples were sent to Inc. on dry ice.

Destination: Inc.
Pharmacokinetic Research Laboratory
, Japan
TEL 81 (0) FAX 81 (0)

Analyte: TAK-070 M-II

Stability: The analyte was confirmed stable in frozen cynomolgus monkey plasma (–15°C or below) for 31 days[1)].
It was judged that TAK-070 M-II was stable in the analysis samples during the analysis period, since the samples were stored within the acceptable temperature range and analyzed within the period for which stability had been confirmed.

Analysis: Analysis was performed by LC/MS/MS at Inc. The results of analysis (concentrations of TAK-070 M-II and the following parameters) were obtained and are reflected in the Final Report.

Parameters: WinNonlin (Ver.6.3, Pharsight Corporation) was used for calculation. AUC was calculated using the trapezoidal formula. Plasma concentrations below the lower limit of quantification (5.00 ng/mL) were regarded as 0 ng/mL.
Maximum plasma drug concentration (C_{max})
Time to reach maximum plasma drug concentration (T_{max})
Half-life period ($t_{1/2}$)
Area under the plasma drug concentration-time curve ($AUC_{0\text{-}24h}$, $AUC_{0\text{-}inf}$)

7.12 Statistical Analysis

7.12.1 Single Dose Study

Statistical analysis was not conducted.

7.12.2 2-Week Repeated Dose Study

Data obtained during the acclimation and dosing periods on body weight, food consumption, electrocardiography, blood pressure, respiration rate, hematology (except for ratios of differential leukocytes), blood chemistry, plasma cortisol concentration, and organ weights (absolute and relative) were analyzed for homogeneity of variance by Bartlett's test. When the variance was homogeneous, Dunnett's test was performed for multiple comparison between the control group and each test article group. When the variance was heterogeneous by Bartlett's test, a Dunnett-type test (Miller's test) was performed for multiple comparison between the control group and each test article group. MUSCOT statistical analysis software (Yukms Co., Ltd.) was used for these statistical analyses at a significance level of 5% for Bartlett's test or at a two-sided significance level of 5% for other tests. Data on clinical signs, necropsy, histopathology, and toxicokinetics were not analyzed statistically.

8. Unexpected Conditions which May Have Affected the Reliability of the Study and Deviations from the Approved Protocol

There were no unexpected conditions that might have affected the reliability of the study and no deviations from the approved protocol.

9. Results

9.1 Single Dose Study

9.1.1 Clinical Signs

(Appendices 1-1 and 1-2)

No abnormalities were observed at any dose level.

9.1.2 Body Weight

(Appendices 2-1 and 2-2)

No test article-related changes were noted at any dose level.

9.1.3 Toxicokinetics

(Appendix 3)

The mean values of the toxicokinetic parameters at 3 and 30 mg/kg were as follows: T_{max} of 1.67 and 2.00 hours in males and 1.00 and 2.00 hours in females, C_{max} of and ng/mL in males and and ng/mL in females, $AUC_{0\text{-}24h}$ of and ng·h/mL in males and and ng·h/mL in females, $AUC_{0\text{-}inf}$ of and ng·h/mL in males and and ng·h/mL in females, and $t_{1/2}$ of 10.72 and 10.43 hours in males and 7.70 and 9.49 hours in females.

There were no sex differences in these parameters, and the total mean values for males and females at 3 and 30 mg/kg were: T_{max} of 1.33 and 2.00 hours, C_{max} of and ng/mL, $AUC_{0\text{-}24h}$ of and ng·h/mL, $AUC_{0\text{-}inf}$ of and ng·h/mL, and $t_{1/2}$ of 9.21 and 9.96 hours.

C_{max} and AUCs increased with dose level, but less than dose proportionally.

9.2 2-Week Repeated Dose Study

9.2.1 Clinical Signs

(Tables 1-1 and 1-2)

No abnormalities were observed at any dose level.

9.2.2 Body Weight

(Tables 2-1 and 2-2)

No test article-related changes were noted at any dose level.

Body weight tended to be decreased in 1 male (No. 115) in the 60 mg/kg group on Day 14; however, this change was not considered toxicologically significant because it

was slight (10% loss of the pre-dosing value) and no change was noted in food consumption.

9.2.3 Food Consumption

(Tables 3-1 to 3-4)

No test article-related changes were noted at any dose level.

Statistically significantly low food consumption was noted in females in the 60 mg/kg group on Day 14 compared with the control group; however, this change was considered incidental because the individual values did not differ from the pre-dosing values.

9.2.4 Electrocardiography

(Tables 4-1 to 4-4)

No test article-related changes were noted at any dose level.

Statistically significantly high heart rate and QT interval were noted in males in the 10 mg/kg group at Week 2 compared with the control group; however, these changes were considered incidental because there was no dose dependency.

9.2.5 Blood Pressure

(Tables 5-1 and 5-2)

No test article-related changes were noted at any dose level.

9.2.6 Respiratory Rate

(Tables 6-1 and 6-2)

No test article-related changes were noted at any dose level.

9.2.7 Hematology

(Tables 7-1 to 7-8)

No test article-related changes were noted at any dose level.

Statistically significantly high monocyte count was noted in males in the 60 mg/kg group at Week 2 compared with the control group; however, these changes were considered incidental because the individual values did not differ from the pre-dosing values and were within the range of the control background data[2)].

9.2.8 Blood Chemistry

(Tables 8-1 to 8-8)

No test article-related changes were noted in the 10 mg/kg group.

In the 60 mg/kg group, alanine transaminase activity was increased in 2 males and 2 females (No. 113, 115, 116, and 118) at Week 2. Aspartate transaminase activity was also increased in 1 male and 1 female (No. 113 and 118).

Statistically significantly low total bilirubin was noted in females in the 10 mg/kg group at Week 2 compared with the control group; however, this change was considered incidental because there was no dose dependency. Statistically significantly low total protein and globulin and/or high albumin/globulin were noted in females in the 10 and 60 mg/kg groups at Week 2; however, these changes were considered incidental because the individual values did not differ from the pre-dosing values and were within the range of the control background data[2)].

9.2.9 Plasma Cortisol Measurement

(Tables 9-1 and 9-2)

No test article-related changes were noted at any dose level.

9.2.10 Necropsy

(Tables 10-1 and 10-2)

No abnormalities were observed at any dose level.

Small testis was observed in 1 male (No. 108) and red focus in the lungs in 1 female (No. 112) was observed in the 10 mg/kg group; however, these changes were considered incidental because there was no dose dependency.

9.2.11 Organ Weights (absolute and relative)

(Tables 11-1 to 11-10)

No test article-related changes were noted at any dose level.

Statistically significantly low absolute submandibular gland weight was noted in males in the 60 mg/kg group; however, this change was considered incidental because the individual values were within the range of the control background data[2)] and no relevant histopathological changes were observed.

9.2.12 Histopathology

(Tables 12-1 to 12-18)

No test article-related changes were observed at any dose level.

Changes observed in the present study were not concluded test article related because similar findings are seen in the control background data[2)] and/or there was no dose dependency.

9.2.13 Toxicokinetics

(Tables 13-1 and 13-2)

Day 1

The mean values of the toxicokinetic parameters at 10 and 60 mg/kg were as follows: T_{max} of 2.33 and 2.67 hours in males and 1.67 and 2.67 hours in females, C_{max} of and ng/mL in males and and ng/mL in females, $AUC_{0\text{-}24h}$ of and ng·h/mL in males and and ng·h/mL in females, $AUC_{0\text{-}inf}$ of and ng·h/mL in males and and ng·h/mL in females, and $t_{1/2}$ of 8.42 and 14.06 hours in males and 6.98 and 10.15 hours in females.

There were no sex differences in these parameters, and the total mean values for males and females at 10 and 60 mg/kg were: T_{max} of 2.00 and 2.67 hours, C_{max} of and ng/mL, $AUC_{0\text{-}24h}$ of and ng·h/mL, $AUC_{0\text{-}inf}$ of and ng·h/mL, and $t_{1/2}$ of 7.70 and 12.11 hours.

C_{max} and AUCs increased with dose level, but less than dose proportionally. The pre-dosing values ranged from 0 (below the lower limit of quantification) to 88.6 ng/mL, and were substantially lower than the C_{max} values.

Day 14

The mean values of toxicokinetic parameters at 10 and 60 mg/kg were as follows: T_{max} of 2.33 and 2.00 hours in males and 2.67 and 1.67 hours in females, C_{max} of and ng/mL in males and and ng/mL in females, $AUC_{0\text{-}24h}$ of and ng·h/mL in males and and ng·h/mL in females, $AUC_{0\text{-}inf}$ of and ng·h/mL in males and and ng·h/mL in females, and $t_{1/2}$ of 9.47 and 12.82 hours in males and 10.59 and 13.41 hours in females.

There were no sex differences in these parameters, and the total mean values for males and females at 10 and 60 mg/kg were: T_{max} of 2.50 and 1.83 hours, C_{max} of and ng/mL, $AUC_{0\text{-}24h}$ of and ng·h/mL, $AUC_{0\text{-}inf}$ of and