[redacted]

Receipt No. 827-06-D-3206

STUDY CODE: B11-0836

FINAL REPORT

TWENTY-EIGHT-DAY REPEATED-DOSE ORAL TOXICITY STUDY OF [redacted] IN RATS

June 2007

[redacted]

STATEMENT

I, the undersigned, hereby declare that this report provides correct English translation of the final report (Study Code B11-0836, issued on June 15, 2007).

[redacted]

October 5, 2009

Date

GLP STATEMENT

[redacted]

Sponsor: [redacted]

Title: Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of [redacted] in Rats

Study Code: B11-0836

I, the undersigned, hereby declare that this study was conducted in compliance with '[redacted]

And, I confirmed that this report accurately reflects the raw data obtained and that data of the study has reliability.

[redacted]

June 15, 2007

QUALITY ASSURANCE STATEMENT

[redacted]

Sponsor: [redacted]

Title: Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of [redacted] in Rats

Study Code: B11-0836

This study was audited and inspected by Quality Assurance Section of [redacted] The dates audited and/or inspected and the dates reported of these results to the study director and management are as follows.

Items of Inspections and Audits	Dates of Inspections and Audits	Dates of Inspections and Audits Reports
Protocol	January 15, 2007	January 15, 2007
Animal receipt	January 16, 2007	January 16, 2007
Amendment to protocol	January 22, 2007	January 24, 2007
Preparation of test substance	January 22, 2007	January 24, 2007
Re-inspection of protocol	January 23, 2007	January 24, 2007
Administration and clinical sign observation	January 24, 2007	January 24, 2007
Amendment to protocol (2nd)	January 27, 2007	January 27, 2007
Amendment to protocol (3rd)	May 9, 2007	May9,2007
Pathological data	May 22, 2007	May22,2007
Animal data	May24,2007	May24,2007
Detailed clinical observation data and sensorimotor function data	May24,2007	May 24, 2007
Documents of test substance and housing conditions	May 24, 2007	May24,2007
Clinical chemistry data	June 1, 2007	June 4, 2007
Re-inspection of animal data	June 6, 2007	June 6, 2007
Documents of accident and deviation	June 12, 2007	June 12, 2007
Draft of final report	June 13, 2007	June 13, 2007
Re-inspection of draft final report	June 15, 2007	June 15, 2007
Draft of final report (2nd)	June 15, 2007	June 15, 2007
Re-inspection of draft final report (2nd)	June 15, 2007	June 15, 2007
Final report	June 15, 2007	June 15, 2007

Following items were reported to the study director and management on the basis of the audit of facility or audit results in other study.

Items of Audits	Dates of Audits	Dates of Audits Reports
Quarantine and acclimatization	December 7, 2006	May 23,2007
Allocation and animal identification	December 7, 2006	May23,2007
Body weight measurements	November 1, 2006	May 23,2007
Food intake measurements	November 1, 2006	May 23, 2007
Detailed clinical observation and sensorimotor function	December 11, 2006	May23,2007
Urine sampling	December 27, 2006	May23,2007
Blood sampling	January 16, 2007	May 23, 2007
Dissection, necropsy and organ weight measurements	January 16, 2007	May23,2007
Hematology	January 16, 2007	May 23,2007
Blood chemistry	January 16, 2007	May23,2007
Urinalysis	January 16, 2007	May23,2007
Pathological preparation	February 6, 9 and 15, 2007	May23,2007

I, the undersigned, hereby declare that this report provides an accurate description of the methods and procedures used in this study and that the reported results accurately reflect the raw data obtained.

Section Chief, Quality Assurance: [redacted] June 15, 2007

TABLE OF CONTENTS

Study Code: B11-0836
Test Substance Code: HR6851
Sponsor Code: D-0060

TITLE

Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of [redacted] in Rats

SPONSOR

[redacted]

TESTING FACILITY

[redacted]

PURPOSE OF STUDY

The purpose of this study is to define the type, severity and reversibility of toxicological signs of the test substance by observing the functional and morphological changes in animals receiving repeated doses orally for 28 days.

TESTING METHOD

This study was conducted in accordance with "28-day Repeated Dose Toxicity Study in Mammalian Species" prescribed in "Concerning Testing Methods Relating to the New Chemical Substances [redacted]

GLP COMPLIANCE

This study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" [redacted]

PERIOD OF STUDY

Commencement of Study:	January 11, 2007
Animal Receipt:	January 16, 2007
Initiation of Examination (Initiation of Dosing):	January 24, 2007
Terminal Necropsy of Dosing Period:	February 21, 2007
Initiation of Recovery Period:	February 21, 2007
Terminal Necropsy of Recovery Period:	March 7, 2007
Termination of Examination (Termination of Histology):	May2,2007
Completion of Study:	June 15, 2007

LOCATION AND PERIOD FOR RETENTION OF RAW DATA AND SPECIMENS

The raw data, protocol and amendment, study contract documents, test substance information, final report, other record documents and specimens will be stored in the archive of [redacted] of our organization, and samples of every lot of the test substance in the test substance storage room, for a period of 10 years from the date of receipt of the notification that they are applicable to Article 4, Paragraphs 1 or 2, Article 4-2, Paragraphs 2,3 or 8,Article5-4,Paragraph 2,Article24,Paragraph2 or Article 25-3, Paragraph 2 of th[redacted]
The sponsor will inform [redacted] of the date of receipt of the notification. After termination of the retention period, any measures taken will be done so with the approval of the sponsor. Samples and specimens that are liable to deteriorate markedly will be retained for 10 years after receipt of the notification or only for as long as the quality of the preparation permits evaluation, and they will be disposed with approval of the sponsor.

RETENTION OF ORIGINAL PROTOCOL AND FINAL REPORT

An original protocol, original protocol amendments and an original final report will be retained at [redacted] The copies of their originals that the study director will have been recognized to be accurate copy will be sent to the sponsor.

AUTHOR AND PERSONNEL CONCERNED WITH STUDY

Study Director: [redacted]

(Planning and management of the study, evaluation of the results, report creation, and over all responsible for the technical conduct of the study)

Study Staff: [redacted]

(Quarantine, acclimation and housing management of animals, preparation and administration of the test substance, clinical observation, detailed clinical observation, sensorimotor function, body weights and food intakes measurements, and responsible for the animal examination)

Person in charge of Pathologic Examination: [redacted]

(Necropsy, collection of tissues, organ weight measurements, histopathological examinations, and responsible for the histopathology)

Person in charge of Clinical Chemistry: [redacted]

(Hematological and blood chemical examinations, urinalysis, and responsible for the biochemistry of the specimens)

AUTHOR APPROVAL

Study Director: Signed in original June 15, 2007

[redacted]

Section 2 (Toxicology area)

[redacted]

SUMMARY

A 28-day repeated-dose oral toxicity study of [redacted] was performed in groups of five male and five female Crl:CD(SD) rats at 5 weeks of age. The high dose was set at 125 mg/kg/day, and altogether three doses including 25 and 5 mg/kg/day were employed. Recovery groups were also set for the 125 mg/kg and vehicle control groups to investigate the reversibility of the effects.

The test substance caused changes suggesting effects on the incisor, liver, and kidney.
As the effects on the incisor, decreased iron pigments and irregular alignment of the ameloblasts at the maturation stage and cyst formation in the papillary layer were observed in both sexes of the 125 mg/kg group. In the necropsy, mottled teeth of the incisor were observed in both sexes.

As the effects on the liver, periportal hypertrophy, periportal prominent nucleoli and single cell necrosis of the hepatocytes in males and diffuse hypertrophy of the hepatocytes in females were observed in the 125 mg/kg group. In the necropsy, enlargement of the liver was observed in both sexes of the 125 mg/kg group. As for the organ weights, relative liver weight in males and absolute and relative liver weights in females were increased in the 125 mg/kg group. In the blood chemical examinations, increased levels of AST, ALT and ALP and decreased level of T-Cho were found as the related changes in males of the 125 mg/kg group. In females of the same group, increased levels of γ-GTP, TG, Albumine, A/G ratio and T-Bil and decreased level of ChE were found.

As the effects on the kidney, dilatation of the tubules in males and ballooning of the tubular epithelium in females were observed in the 125 mg/kg group. Furthermore, relative kidney weight in males given 25 mg/kg or more and absolute and relative kidney weights in females given 125 mg/kg were increased.

The changes found during the dosing period and at the end of the dosing period were considered to be recovered or in a recovery trend.

Based on these results, it was considered that [redacted] had mainly effects on the incisor, liver, and kidney. However, it was also considered that these changes were reversible. The No-Observed-Adverse-Effect Level (NOAEL) of [redacted] was considered to be 5 mg/kg/day based on increased relative kidney weight in males given 25 mg/kg or more.

MATERIALS AND METHODS

1. TEST SUBSTANCE (Information provided by the sponsor)

1.1 Name

[redacted]

Other Name: [redacted]

CASNo.: [redacted]

1.2 Lot No.

6X002

1.3 Supplier

[redacted]

1.4 Structural Formula

[redacted]

1.5 Purity

99.7%

1.6 Names and Concentration of Impurities

Unknown component 0.3%

1.7 Physicochemical Properties

Appearance at Ordinary Temperature: clear colorless liquid

Molecular Weight: [redacted]

Stability: –

Melting Point: –

Boiling Point: 78°C (8 mmHg)

Vapor Presser: –

Partition Coefficient (1-octanol/water partition coefficient): –

Hydrolyzability: Hydrolyzable

[redacted]

Degree of Solubility: Water; insoluble
DMSO; soluble (arbitrary mixable)
Acetone; soluble (arbitrary mixable)
Others; –

1.8 Storage Conditions

The test substance was stored at room temperature under a light shielding condition (desiccator No. 2 in the test substance storage room, permissible temperature range: 10-30°C)

1.9 Handling Precaution

Glove, mask, cap and lab coat were put on.

2. ANIMALS

Crl:CD(SD) rats (SPF) of 33 males and 33 females were obtained from [redacted] at 4 weeks old. Animals were acclimatized for 8 days including 6 days quarantine. No abnormalities were noted in any animals during the quarantine and acclimation periods. All animals were allocated to groups to ensure homogeneity of mean body weights using body weight-stratified randomization on two days before the start of the administration. The animals not treated were excluded from the study and euthanized under ether anesthesia. At the onset of the treatment, the animals were five weeks old with body weight ranges of 135.0-152.5 g and 117.8-134.4 g for males and females, respectively. Animals were identified by means of a marker on the tail before grouping and ear-tags after grouping.

3. HOUSING CONDITIONS

All animals were bred at the barrier-system animal rooms (room No. 4 during the quarantine period, room No. 8 after the quarantine), which were maintained at a stable temperature (21-25°C) and relative humidity (40-70%) with 10-15 air changes per hour and artificial light-dark cycle of 12-12 hours (light on: 7:00 and light off: 19:00), in the biotron (1) throughout the whole feeding period including the quarantine and acclimation periods. The actual temperature and humidity were 22.5-24.0°C and 46.5-58.4%, respectively.

The rats were housed in hanging stainless steel cages with wire-mesh floor at three or five animals/cage (260 W×380 D×180 H mm [redacted] for quarantine and acclimation, and at one animal/cage (165 W×300 D×150 H mm, [redacted] after grouping. Undertrays were changed once a week before grouping, and twice a week after grouping. Feeders, cages and racks were changed once at the grouping, and once at the termination of the dosing period for the recovery group. Racks and cages were identified by individual cards.

The animals had free access to an MF pelleted diet (Lot No. 061004 and 061204[redacted]

[redacted] and chlorinated water from the [redacted] supply via automatic watering system with sipper tubes. The diet and housing materials were autoclaved at 121°C for 30 min prior to use. Analysis of the diet was performed in Japan Food Research laboratories, and the analytical data were provided by the manufacturer. The tested parameters met the requirements in our laboratories according to the "Toxic Substances Control Act of US-EPA". Contaminants in drinking water were analyzed twice yearly in Oita Prefecture Pharmaceutical Association according to the water regulations of the "Notification No. 101 of Environmental Health Bureau, MHLW" except for test of the taste in our laboratory. Contaminants in the water were in the stated ranges in our laboratory.

4. GROUPING

Grouping was as follows.

Group	Dose	Volume	Concentration of dosing formulation	Number of Animals (Animal No.)	
	(mg/kg/day)	(mL/kg)	(w/v%)	Male	Female
Vehicle control	0	10	0	5 (1 - 5)	5 (31 - 35)
Vehicle control (recovery)	0	10	0	5 (6 - 10)	5 (36 - 40)
Low dose	5	10	0.05	5 (11 - 15)	5 (41 - 45)
Intermediate dose	25	10	0.25	5 (16 - 20)	5 (46 - 50)
High dose	125	10	1.25	5 (21 - 25)	5 (51 - 55)
High dose (recovery)	125	10	1.25	5 (26 - 30)	5 (56 - 60)

Rationale for dosage selection: A Range finding study of 7-day repeated oral treatment was performed at 0, 25, 250, 500 and 1,000 mg/kg/day in our Hita labolatory. As a result, death occurred in females of the 1,000 mg/kg group, and effects of test substance on the liver, such as enlargement of the liver and increases in liver weight were noted in both sexes of the groups given 250 mg/kg or more. Accordingly, the high dose was set at 125 mg/kg/day and lower doses of 25 and 5 mg/kg were set for the present study. Recovery groups were also set for the 125 mg/kg and vehicle control groups.

5. STABILITY OF TEST SUBSTANCE

Stability of the test substance during the dosing period was confirmed with infrared (IR) spectrophotometer in our [redacted] (See APPENDIX 1, Study code: X18-0836). IR spectrum of the test substance within 4000 cm^{-1}-400 cm^{-1} was compared with that provided by the sponsor before dosing to determine the identity. The test substance was also analyzed to confirm the stability before and after the dosing period to confirm the stability.

6. PREPARATION OF FORMULATIONS

6.1 Vehicle

The test substance was hydrolysable. Therefore, olive oil (Lot No. 040OHY, [redacted] including 0.5% Tween80 (Lot No. DPK6694, Wako Pure Chemical Industries) was selected as the vehicle.

6.2 Preparation and Storage

The test substance was accurately weighed and mixed with olive oil (including 0.5% Tween80) to prepare the 1.25 w/v% formulation. The lower concentration formulations of 0.05 and 0.25 w/v% were prepared by diluting the 1.25 w/v% formulation with the vehicle. These were stirred with the homogenizer (ULTRA-TURRAX T25 basic、IKA WERKE). The formulations were stored at the dark and cold place (cool box No. 15 in the test substance preparation room).

6.3 Homogeneity and Stability Tests

The homogeneity and stability analyses were performed in our [redacted] (See APPENDIX 1, Study code: X18-0836). In the homogeneity analysis, top, middle and bottom layers of the 1.25 and 0.05 w/v% formulations were taken (n=1) just after preparation, and quantitatively analyzed by Gas chromatography (n=1) after sample pretreatment. In the stability test, the formulations for homogeneity samples were stored at the dark and cold place and analyzed after 5 and 9 days. The test substance in the formulations was confirmed to be stable for 8 days.

6.4 Concentration Conformation

The concentration analysis was performed in our [redacted] (See APPENDIX 1, Study code: X18-0836). The concentrations of the 1.25, 0.25 and 0.05 w/v% formulations were confirmed to be within 100±10% of each nominal concentration at the first preparation of the dosing period.

7. ADMINISTRATION

The formulations were repeatedly administered daily in the morning by oral gavage using a syringe (Terumo) connected to a Nelaton catheter (Terumo) for 28 days. Thereafter, a 14-day recovery period was set.

8. OBSERVATIONS

Concerning the numbering of day and week, the day of initiation of dosing was regarded as day 1, the day before initiation of dosing as day −1 and the week of initiation of dosing as week 1. The day after the last dosing was regarded as day 1 (recovery) and the week of initiation of recovery as week 1 (recovery).

8.1 Clinical Signs

During the dosing period, all animals were observed three times a day, i.e., before dosing, during and just after dosing, and in the afternoon, daily from day 1 to day 28. During the recovery period, observation was performed twice daily i.e., in the morning and in the afternoon.

8.2 Detailed Clinical Observations

The detailed examinations in all animals were performed once before dosing. Thereafter, the examinations were performed once weekly during the dosing and recovery periods on a blind test basis. The blind test was performed using the random numbers and observation labels without identifying the dosing group.

1) Observations at removal from cage

Animal reactions such as excitement from external stimuli (holding animals or bringing a hand close to animals to hold, etc.) were observed.

Observation items: Ease of removal, Vocalization

2) Handling observations

Observation items: Muscle tone, Hypothermia, Piloerection, Hair appearance (staining and unkempt hair), Skin and mucous color (paleness, reddening and cyanosis), Eyes (lacrimation, exophthalmos and pupillary size), Salivation, Secretion

3) Observation in arena

Animals were placed in a standard arena (on an observation platform) and observed for 1 min or more, and the frequencies of defecation (number of feces) and urination (number of pools) were recorded for 1 min.

Observation items: Posture, Motor activity level, Respiration, Lid closure, Gait characteristics, Tremor, Twitch, Convulsion, Stereotypical behavior, Abnormal behavior

8.3 Sensorimotor Function

All animals were examined in week 4 of the dosing period, but not in the recovery period, since no abnormalities were noted in week 4 of the dosing period.

1) Reflex

Reactions of animals were observed and made a score when proper stimuli were given their test subjected sensory organs. The examinations were also performed on a blind test basis.

(1) Approach contact/touch response

The animal's response when a blunt probe was brought approximately 3 cm from the animal's nose for 4 seconds was assessed.

(2) Pinna response

The animal's response when a sudden sound of a finger snap was produced was assessed.

(3) Pain response

The animal's response when the animal's tail was pinched with a clothespin between one-third and base of the tail was assessed.

(4) Pupillary reflex

Following darkness adaptation of the animal's eyes, pupil constriction in response to a bright beam of a light was observed.

(5) Air righting reflex

The animal's response when the animal was held with ventral surface uppermost approx. 30 cm height from the flat surface and released was assessed.

2) Grip strength

The forelimbs and hindlimbs grip strengths were measured with the automated grip strength meter (COLUMBUS) on a blind test basis. Two trials were performed, and the mean values of the forelimbs or hindlimbs were calculated for each animal.

3) Locomotor activity counts

Locomotor activity level of each animal was counted with the activity monitoring system (SCANET: MV-10, MAYTES) by the number of crossing IR beam for 1 hour at 10 min intervals.

8.4 Body Weights

Body weights were measured on day -2 (allocation to groups), and on days 1, 3, 8, 12, 17, 21, 26 and 28 during the dosing period and on days 1, 5, 10 and 14 (recovery) during the recovery period. In addition, immediately before necropsy, body weights were measured for calculation of the relative organ weights.

8.5 Food Intakes

Food intakes were measured at allocation to groups, and on days 1, 3, 8, 15, 22 and 28 during the dosing period and on days 1, 4, 8 and 14 (recovery) during the recovery period. Mean food intakes per day were calculated from their remainders for each period.

8.6 Hematological Examinations

Blood or plasma samples were obtained by blood sampling from the abdominal aorta under ether anesthesia after overnight fasting (16 to 20 hr) at completion of the dosing period (excluding the recovery groups) and at completion of the recovery period. The samples were determined for the following items. In addition, the blood smears were made for unmeasurable cases. As an anticoagulant, 3.2% sodium citrate aqueous solution (Lot No. LTR3558, Wako Pure Chemical Industries) was used for the determination of prothrombin time and activated partial thromboplastin time, and EDTA-2K (Lot No. G5063, Sysmex) for other measurements.

	Parameters		Method
1)	Red blood cell count (RBC)	($\times 10^4/\mu L$)	Electrical resistance detection
2)	White blood cell count (WBC)	($\times 10^2/\mu L$)	Electrical resistance detection
3)	Hemoglobin conc. (Hb)	(g/dL)	Noncyanhemoglobin method
4)	Hematocrit value (Ht)	(%)	$\frac{RBC \times MCV}{10^3}$
5)	Mean corpuscular volume (MCV)	(fL)	Electrical resistance detection
6)	Mean corpuscular hemoglobin (MCH)	(pg)	$\frac{Hb}{RBC} \times 10^3$
7)	Mean corpuscular hemoglobin cone. (MCHC)	(g/dL)	$\frac{Hb}{Ht} \times 10^2$
8)	Platelet count (Platelet)	($\times 10^4/\mu L$)	Electrical resistance detection
9)	Reticulocyte count (Reticulo)	(%)	RNA staining
10)	Prothrombin time (PT)	(sec)	Magnetic sensor
11)	Activated partial thromboplastin time (APTT)	(sec)	Magnetic sensor
12)	Differentiation of leukocytes	(%)	Flow cytometry technique
	Neutrophils (Neutro)		
	Eosinophils (Eosino)		
	Basophils (Baso)		
	Lymphocytes (Lymph)		
	Monocytes (Mono)		
	Large unstained cells (LUC)		

1)-8) CELL-DYN3500, Abbott Laboratories

9), 12) ADVIA 120, Bayer Medical

10), 11) KC-10A, AMELUNG

8.7 Blood Chemical Examinations

Serum samples were separated from blood samples collected at the same times as those described in section 8.6, and the following items were determined in the obtained serum samples.

	Parameters		Method
1)	Aspartate aminotransferase (AST)	(IU/L)	UV method (method based on JSCC)
2)	Alanine aminotransferase (ALT)	(IU/L)	UV method (method based on JSCC)
3)	Alkaline phosphatase (ALP)	(IU/L)	*p*-Nitrophenyl phosphate method
4)	Cholinesterase (ChE)	(IU/L)	Butyrylthiocholine iodide method
5)	γ-Glutamyl transpeptidase (γ-GTP)	(IU/L)	L-γ-glutamyl-3-carboxy-4-nitroanilide method
6)	Total cholesterol (T-Cho)	(mg/dL)	COD-ADPS method
7)	Triglyceride (TG)	(mg/dL)	GPO-ADPS glycerol blocking method
8)	Glucose	(mg/dL)	Hexokinase-G-6-PDH method
9)	Total protein (T-Protein)	(g/dL)	Biuret method
10)	Albumin	(g/dL)	Bromocresol green method
11)	A/Gratio		$\frac{\text{Albumin}}{\text{T-Protein} - \text{Albumin}}$ (calculated value)
12)	Blood urea nitrogen (BUN)	(mg/dL)	Urease-GlDH method
13)	Creatinine	(mg/dL)	Creatininase-F-DAOS method
14)	Total bilirubin (T-Bil)	(mg/dL)	Enzyme method
15)	Calcium (Ca)	(mg/dL)	OCPCmethod
16)	Inorganic phosphorus (IP)	(mg/dL)	Fiske-Subbarow method
17)	Sodium (Na)	(mEq/L)	Crown-Ether membrane electrode method
18)	Potassium (K)	(mEq/L)	Crown-Ether membrane electrode method
19)	Chloride (Cl)	(mEq/L)	Coulometric titration method

1), 2), 4), 9), 10), 14)	7150 Automatic Analyzer, Hitachi
3), 5)-8), 12), 13), 15), 16)	7170 Automatic Analyzer, Hitachi
17)-19)	PVA-αIII, A & T

8.8 Urinalyses

Urinalysis was performed once (day 28) during the dosing period (excluding the recovery groups) and once (day 14) during the recovery period. Urine samples (accumulated for 15-17 hr) collected in individual metabolic cages (150 W×200 D×263 H mm) were determined with drinking water *ad libitum*. The urine sediments were stained and examined in males and females of the vehicle control and 125 mg/kg groups at the end of the dosing period. The urine sediments were not examined at the end of the recovery period since no abnormalities were noted at the end of the dosing period.

	Parameters		Method
1)	Urine volume	(m/L)	Volumetric method
2)	Color		Macroscopy
3)	Turbidity		Macroscopy
4)	Urine specific gravity (Sp.Gr.)		Refractive index
5)	pH		Test paper
6)	Protein		Test paper
7)	Glucose		Test paper
8)	Occult blood		Test paper
9)	Urinary sediments		Sternheimer modified

1) Measuring cylinder

4) SPR-N, ATAGO

5)-8) Hema-Combistix, Bayer Medical

9) Biological microscope, BH2, OLYMPUS

8.9 Pathological Examinations

1) Necropsy

All animals were subjected to the detailed gross necropsy including body surface, all orifices, cranial, thoracic and abdominal cavities, and these contents.

2) Organ weights

The weights of the following organs were measured in all animals. The relative organ weight was calculated based on the body weight at the time of necropsy.

* Left and right organs were measured totally.

Liver(g), heart(g), kidneys*(g), testes*(g), epididymides*(g), ovaries*(mg), brain(g), spleen(g), thymus(mg) and adrenals*(mg)

3) Histopathological examinations

(1) The following organs and tissues were taken in all animals.

Category	Organs and Tissues
Respiratory system	Trachea, lungs
Digestive system	Incisors, Stomach, intestine (duodenum to rectum, with Peyer's patches), liver
Cardiovascular system	Heart
Urinary system	Kidneys, urinary bladder
Reproductive system	Testes, epididymides, prostate, seminal vesicle, ovaries, uterus, vagina
Nervous system	Brain (cerebrum, cerebellum and pons), spinal cord, sciatic nerve
Hematopoietic and lymphatic systems	Bone marrow (femur), axillar and mesenteric lymph nodes, spleen, thymus
Endocrine system	Pituitary gland, thyroid (with parathyroids), adrenals
Special sense organ	Eyeballs

The trachea, lungs and urinary bladder were filled with 10% neutralized buffered formalin before taken. The stomach and intestine were filled and fixed with 10% neutralized buffered formalin and were washed with water. All organs/tissues were preserved in 10% neutralized buffered formalin. However, the testes and epididymides were fixed in Bouin's solution.

(2) Light microscopic examinations were performed for the organs and tissues of the following groups after embedding in paraffin, sectioning and hematoxylin and eosin (HE) staining.

Organ and tissue	Vehicle control group	Vehicle control recovery group	5 mg/kg group	25 mg/kg group	125 mg/kg group	125 mg/kg recovery group
Trachea	♂♀	-	-	-	♂♀	-
Lungs	♂♀	-	-	-	♂♀	-
Incisors[a)]	♂♀	♂♀	♂♀	♂♀	♂♀	♂♀
Forestomach	♂♀	-	-	-	♂♀	-
Glandular stomach	♂♀	-	-	-	♂♀	-
Duodenum-ileum	♂♀	-	-	-	♂♀	-
Cecum- rectum	♂♀	-	-	-	♂♀	-
Liver[a)]	♂♀	♂♀	♂♀	♂♀	♂♀	♂♀
Heart[b)]	♂♀	♂	-	-	♂♀	♂
Kidneys[a)]	♂♀	♂♀	♂♀	♂♀	♂♀	♂♀

Organ and tissue	Vehicle control group	Vehicle control recovery group	5 mg/kg group	25 mg/kg group	125 mg/kg group	125 mg/kg recovery group
Urinary bladder	♂♀	-	-	-	♂♀	-
Testes [b)]	♂	♂	-	-	♂	♂
Epididymides	♂	-	-	-	♂	-
Prostate	♂	-	-	-	♂	-
Seminal vesicles	♂	-	-	-	♂	-
Ovaries	♀	-	-	-	♀	-
Uterus	♀	-	-	-	♀	-
Vagina	♀	-	-	-	♀	-
Cerebrum, cerebellum, pons [b)]	♂♀	♀	-	-	♂♀	♀
Spinal cord	♂♀	-	-	-	♂♀	-
Sciatic nerve	♂♀	-	-	-	♂♀	-
Bone marrow	♂♀	-	-	-	♂♀	-
Axillar lymph nodes	♂♀	-	-	-	♂♀	-
Mesenteric lymph nodes	♂♀	-	-	-	♂♀	-
Spleen	♂♀	-	-	-	♂♀	-
Thymus	♂♀	-	-	-	♂♀	-
Pituitary gland	♂♀	-	-	-	♂♀	-
Thyroid	♂♀	-	-	-	♂♀	-
Parathyroids	♂♀	-	-	-	♂♀	-
Adrenals	♂♀	-	-	-	♂♀	-
Eye balls	♂♀	-	-	-	♂♀	-

a) Since changes suspected to be effects of the test substance were noted in the organ weights or the necropsy in males and females of the 125 mg/kg group, histopathological examinations for both sexes of all groups including the recovery groups were done.

b) Since changes suspected to be effects of the test substance were noted in the organ weights in males or females of the 125 mg/kg recovery group, histopathological examinations for the recovery groups were done.

(3) The following organs/tissues were examined as macroscopic lesions.

Group (Animal No.)	Organs and tissues
25 mg/kg group (No. 20)	Testes
25 mg/kg group (No. 47)	Lungs
125 mg/kg group (No. 22)	Incisors (lower)
125 mg/kg recovery group (No. 57)	Incisors (lower)
125 mg/kg recovery group (No. 59)	Thyroid

(4) The special staining of following organs/tissues was performed.

Group (Animal No.)	Organs and tissues	Method
Vehicle control group (No.31)	Kidneys [c)]	Oil red O staining
125 mg/kg group (No.51)	Kidneys [c)]	Oil redO staining

c) Since vacuolization of the tubular epithelium suspected to be accumulation of fat was noted in the HE specimens of the 125 mg/kg group, Oil red O staining was done.

9. STATISTICAL ANALYSIS

Data regarding body weights (excluding those at the time of necropsy), food intakes, hematological examinations, blood chemical examinations, urine volume, urine specific gravity, organ weights, grip strength and locomotor activity counts were analyzed by using the Bartlett's test for homogeneity of variance. If the variances were homogeneous at a significance level of 5%, one way analysis of variance was performed. If there was a significant difference in this analysis, the difference between the vehicle control group and each of the treatment group was analyzed by the Dunnett's test. If the variances were not homogeneous, the Kruskal-Wallis's test was used. If there was a significant difference in this analysis, the difference between the vehicle control group and each of the treatment group was analyzed by the nonparametric Dunnett's test.

The frequencies of defecation (number of feces) and urination (number of pools) were analyzed by using the Kruskal-Wallis's test. If there was a significant difference in this analysis, the difference between the vehicle control group and each of the treatment group was analyzed by the nonparametric Dunnett's test.

ENVIRONMENTAL FACTORS THAT MIGHT HAVE AFFECTED THE RELIABILITY OF STUDY RESULTS

One female (No.47) of the 25 mg/kg group died from administration malpractice on February 18, 2007. It was considered that the test results would be assessed by using other four survived animal. The evaluation of the test results was considered to be valid by using other four survived animals.

Although the protocol described Lot No. DPP3465 of Tween80 as vehicle, Lot No. DPK6694 was practically used. It was decided that the deviation from the protocol did not have affected the study results.

RESULTS

1. CLINICAL SIGNS (Table 1, Addendum 1)

1.1 During Dosing Period

Males: Salivation in 5-10 min after administration was noted in three animals (Nos. 1, 3 and 10) of the vehicle control group, in two animals (Nos. 13 and 14) of the 5 mg/kg group, in three animals (Nos. 16, 17 and 20) of the 25 mg/kg group and in all animals (Nos. 21-30) of the 125 mg/kg group, respectively. Decreased spontaneous locomotion in 5-10 min after administration was noted in one animal (No. 17) of the 25 mg/kg group and in four animals (Nos. 24, 25, 28 and 29) of the 125 mg/kg group, respectively. White turbid urine in one animal (No. 29) and exudates (neck) in one animal (No. 28) were noted in the 125 mg/kg group.

In addition, swelling of the third digit in the left forelimb was noted in one animal (No. 29) of the 125 mg/kg group. The digit was considered to be caught in the cage.

Females: Salivation in 5-10 min after administration was noted in two animals (Nos. 41 and 45) of the 5 mg/kg group, in all animals (Nos. 46-50) of the 25 mg/kg group and in all animals (Nos. 51-60) of the 125 mg/kg group, respectively. Decreased spontaneous locomotion in 5-10 min after administration in five animals (Nos. 53, 54, 56, 59 and 60) and staining lower abdomen in two animals (Nos. 58 and 59) were noted in the 125 mg/kg group.

In addition, one animal (No.47) of the 25 mg/kg group was dead on day 26.

1.2 During Recovery Period

Males: Mottled teeth in all animals (Nos. 26-30), discoloration (whitish change) of the teeth in four animals (Nos. 26, 28-30), scab formation (neck) in one animal (No. 28) and exudates (neck) in one animal (No. 28) were noted in the 125 mg/kg recovery group.

In addition, swelling of the third digit in the left forelimb was noted in one animal (No. 29) of the 125 mg/kg group.

Females: Mottled teeth in all animals (Nos. 56-60), discoloration (whitish change) of the teeth in all animals (Nos. 56-60) and surface delamination of the tip of the lower incisors in two animals (Nos. 56 and 57) were noted in the 125 mg/kg recovery group.

2. DETAILED CLINICAL OBSERVATIONS (Table 2, Addendum 2)

2.1 During Dosing Period

Males: A statistically significant increase in frequency of defecation was noted in the 25 mg/kg group in week 3 and week 4.

Females: No abnormalities attributable to the test substance were noted in any treatment groups.

2.2 During Recovery Period

No abnormalities attributable to the test substance were noted in either sex of the 125 mg/kg recovery group.

3. SENSORIMOTOR FUNCTION (Tables 3, 4 and 5, Addenda 3, 4 and 5)

3.1 During Dosing Period

No abnormalities attributable to the test substance were noted in either sex of any treatment groups.

3.2 During Recovery Period

Males or females were not examined since no abnormalities attributable to the test substance were noted during the dosing period.

4. BODY WEIGHTS (Fig.1, Table 6, Addendum 6)

4.1 During Dosing Period

No statistically significant changes attributable to the test substance were noted in either sex of any treatment groups.

4.2 During Recovery Period

No statistically significant changes attributable to the test substance were noted in either sex of the 125 mg/kg recovery group.

5. FOOD INTAKES (Fig.2, Table 7, Addendum 7)

5.1 During Dosing Period

No statistically significant changes attributable to the test substance were noted in either sex of any treatment groups.

5.2 During Recovery Period

No statistically significant changes attributable to the test substance were noted in either sex of the 125 mg/kg recovery group.

6. HEMATOLOGICAL EXAMINATIONS (Table 8, Addendum 8)

6.1 At Termination of Dosing Period

No statistically significant changes attributable to the test substance were noted in either sex of any treatment groups.

6.2 At Termination of Recovery Period

Males: Statistically significant decreases in Hb and Ht were noted in the 125 mg/kg recovery group.

Females: No statistically significant changes attributable to the test substance were noted in the

125 mg/kg recovery group.

7. BLOOD CHEMICAL EXAMINATIONS (Table 9, Addendum 9)

7.1 At Termination of Dosing Period

Males: Statistically significant increases in AST, ALT and ALP and a statistically significant decrease in T-Cho were noted in the 125 mg/kg group.

Females: Statistically significant increases in γ-GTP, TG, albumin, A/G ratio and T-Bil and statistically significant decrease in ChE were noted in the 125 mg/kg group.

7.2 At Termination of Recovery Period

Males: No statistically significant changes attributable to the test substance were noted in the 125 mg/kg recovery group.

Females: A statistically significant decrease in IP was noted in the 125 mg/kg recovery group.

8. URINALYSES (Table 10, Addendum 10)

8.1 At Termination of Dosing Period

No abnormalities attributable to the test substance were noted in either sex of any treatment groups.

8.2 At Termination of Recovery Period

No abnormalities attributable to the test substance were noted in either sex of the 125 mg/kg recovery group.

9. ORGAN WEIGHTS (Tables 11 and 12, Addenda 11 and 12)

9.1 At Termination of Dosing Period

Males: Relative kidney weights were significantly increased in the groups given 25 mg/kg or more. Relative liver weight was significantly increased in the 125 mg/kg group.

Females: Statistically significant increases in absolute and relative weights of the liver and kidney were noted in the 125 mg/kg group.

9.2 At Termination of Recovery Period

Males: Statistically significant increases in absolute heart weight, absolute and relative testis weight were noted in the 125 mg/kg group.

Females: Statistically significant increases in relative liver weight and absolute brain weight were noted in the 125 mg/kg group.

10. NECROPSY (Table 13, Addendum 13)

10.1 Dead animal (No.47, female in the 25 mg/kg group)

Dark reddish change of the lung was noted.

10.2 At Termination of Dosing Period

Males: Small and softening of the testis in one animal (No. 20) of the 25 mg/kg group, mottled teeth in two animals (Nos. 22 and 24) and enlargement of the liver in four animals (Nos. 21, 23-25) of the 125 mg/kg group were noted.

Females: Mottled teeth in two animals (Nos. 51 and 55) and enlargement of the liver in all animals (Nos. 51-55) were noted in the 125 mg/kg group.

10.3 At Termination of Recovery Period

Males: Mottled teeth were noted in all animals (Nos. 26-30) of the 125 mg/kg recovery group.

Females: Mottled teeth in all animals (Nos. 56-60), rough surface of the incisor in one animal (No. 57) and aplasia of the left lobe of the thyroid in one animal (No. 59) were noted in the 125 mg/kg recovery group.

11. HISTOPATHOLOGICAL EXAMINATIONS (Table 14, Addendum 13)

11.1 Dead animal (No.47, female in the 25 mg/kg group)

Congestion and edema of the lung were noted.

11.1 At Termination of Dosing Period

Males: Cyst formation in the papillary layer of the incisor in one animal (No. 22), decreased iron pigments of the ameloblasts at the maturation stage in the incisor in three animals (Nos. 21, 22 and 25), irregular alignment of the ameloblasts at the maturation stage in the incisor in one animal (No. 25), periportal hypertrophy of the hepatocytes in the liver in all animals (Nos. 21-25), periportal prominent nucleoli of the hepatocytes in the liver in three animals (Nos. 21, 22, 24), single cell necrosis of the hapatocytes in the liver in one animal (No. 25), dilatation of the tubules in the kidney in one animal (No. 25), basophilic tubules in the kidney in one animal (No. 22) and focal myocarditis in the heart in one animal (No. 21) were noted in the 125 mg/kg group.

In addition, basophilic tubules in the kidney in two animals (Nos. 2 and 5), focal hyperplasia of the tubular epithelium in the kidney in one animal (No. 3) and focal myocarditis in the heart in one animal (No. 1) and round cell infiltration in the prostate in one animal (No. 3) were noted in the vehicle control group. Diffuse atrophy of the seminiferous tubules and Leydig cell hyperplasia in the testis were noted in one animal (No. 20) of the 25 mg/kg group.

Females: Cyst formation in the papillary layer of the incisor in one animal (No. 54), decreased iron pigments of the ameloblasts at the maturation stage in the incisor in two animals (Nos. 53 and 54), irregular alignment of the ameloblasts at maturation stage in the incisor in one animal (No. 54), diffuse hypertrophy of the hepatocytes in the liver in

two animals (Nos. 53 and 54), ballooning of the tubular epithelium in the kidney in one animal (No. 51), necrosis of the squamaous epithelium in the limiting ridge of the forestomach in one animal (No. 54) were noted in the 25 mg/kg group.

In addition, mineralization in the cortico-medullary junction of the kidney in two animals (Nos. 32 and 33), necrosis of the squamaous epithelium in the limiting ridge of the forestomach in one animal (No. 34), endometrial atrophy of the uterus in one animal (No. 31), mucification of the epithelium in the vagina in one animal (No. 31) and vaginitis of the vagina in one animal (No. 34) were noted in the vehicle control group. Mineralization in the cortico-medullary junction of the kidney was noted in one animal (No. 45) of the 5 mg/kg group.

As the result of the oil red O staining for the kidney in one female (No. 51) of the 125 mg/kg group, no positive substance was found in the vacuolating area of the tubular epithelium. Therefore, this histopathological finding was "ballooning of tubular epithelium" since the vacuolization was not caused by the accumulation of the fat.

11.2 At Termination of Recovery Period

Males: Irregular alignment of the ameloblasts at the maturation stage in the incisor in two animals (No. 28 and 30), basophilic tubules in the kidney in one animal (No. 30) and solitary cyst in the medulla of the kidney in one animal (No. 26) were noted in the 125 mg/kg recovery group.

Females: Irregular alignment of the papillary layer in the incisor in one animal (No. 57), decreased iron pigments of the ameloblasts at the maturation stage in the incisor in one animal (No. 58) and irregular alignment of the ameloblasts at the maturation stage in the incisor in three animals (No. 57, 58 and 60) were noted in the 125 mg/kg recovery group.

In addition, mineralization in the cortico-medullary junction of the kidney in two animals (Nos. 37 and 38) of the vehicle control recovery group and aplasia of the left lobe in the thyroid in one animal (No. 59) of the 125 mg/kg recovery group were noted.

DISCUSSION

A 28-day repeated-dose oral toxicity study of [redacted] with Crl:CD(SD) rats was carried out at doses of 5, 25, and 125 mg/kg/day. A 14-day recovery test was also performed to investigate the reversibility of the effects.

One female in the 25 mg/kg group died during the dosing period. In the histopathological examinations, congestion and edema in the lung were observed. Therefore, it was decided that the

death was due to administration malpractice.

No abnormalities were observed in the sensorimotor function, body weights or food intakes during the dosing period. In addition, no abnormalities were observed in the hematological examinations or the urinalyses at the end of the dosing period.

The test substance caused changes suggesting effects on the incisor, liver, and kidney.
In the histopathological examinations of the incisor, decreased iron pigments and irregular alignment of the ameloblasts at the maturation stage and cyst formation in the papillary layer were observed in both sexes of the 125 mg/kg group. In the necropsy, mottled teeth were observed in both sexes. These changes suggested the effects on the enamel of the incisor due to the test substance. It was also reported that decreased iron pigments, degeneration and necrosis of the ameloblasts were found in the animals including rats with brown enamel surface of the teeth when dosed to fluoride[1)2)]. Therefore, it was suggested that these changes were caused by the fluorine in the test substance.

In the histopathological examinations of the liver, periportal hypertrophy, periportal prominent nucleoli and single cell necrosis of the hepatocytes in males and diffuse hypertrophy of the hepatocytes in females were observed in the 125 mg/kg group. In the necropsy, enlargement of the liver was observed in both sexes of the 125 mg/kg group. These suggest the change of the liver function caused by the test substance. As the related changes, relative liver weight in males and absolute and relative liver weights in females were increased in the 125 mg/kg group. In the blood chemical examinations, increased levels of AST, ALT and ALP and decreased level of T-Cho were found in males of the 125 mg/kg group. In females of the same group, increased levels of γ-GTP, TG, Albumine, A/G ratio and T-Bil and decreased level of ChE were found. In the histopathological examinations of the kidney, dilatation of the tubules in males and ballooning of the tubular epithelium in females were observed in the 125 mg/kg group as a small number of cases. Furthermore, relative kidney weights in the males given 25 mg/kg or more and absolute and relative kidney weights in the females given 125 mg/kg were increased. These suggest the effects of the test substance on the kidney. As for the change of the tubular epithelium, oil red O stain revealed that no positive substance was found in the vacuolating area of the tubular epithelium, indicating that the vacuolization was not caused by the accumulation of the fat.

In the clinical signs, salivation was observed in both sexes given 5 mg/kg or more (5-10 min after administration), indicating transient observation immediately after administration. In the histopathological examinations, no change related to the irritation was observed in the stomach. No change related to the neural system was observed in the detailed clinical observations or the sensorimotor function. Therefore, this change was considered to be no toxicologically significance. In addition, decreased spontaneous locomotion in males given 25 mg/kg or more and in females given

125 mg/kg was observed. However, this was observed during 5-10 min after administration, indicating a transient change. No related change was observed in the detailed clinical observations or the sensorimotor function. Therefore, this change was considered to be no treatment related. Although staining lower abdomen was observed in females of the 125 mg/kg group, this occurred singly in one animal on each day 8 and 22. Therefore, this change was considered to be no treatment related. White turbid urine was observed in one male of the 125 mg/kg group. However, this occurred only on day 15, and no abnormalities in the urinary organs including the kidney were observed in the histopathological examinations. Therefore, this change was considered to be no treatment related. In addition, exudate was observed in male of the 125 mg/kg group. However, this was observed in the neck of one animal. Therefore, it was considered that this change was not caused by the test substance, but handling of the rat. Furthermore, swelling of the digit in the left forelimb was observed in one animal of the 125 mg/kg group because the digit was caught in the cage. Therefore, this change was considered to be no treatment related.

In the detailed clinical observations, the number of the defecation was increased in males of the 25 mg/kg group on week 3 and 4, however, no dose-related change was found. Therefore, this was considered to be no treatment related.

In the histopathological examinations, basophilic tubules of the kidney in males, focal myocarditis of the heart in males, and necrosis of the squamous epithelium in the limiting ridge of the forestomach in females were observed in the 125 mg/kg group. In addition, mineralization in the cortico-medullary junction of the kidney was observed in females of the 5 mg/kg group. However, these changes were also observed in the vehicle control group. Therefore, this change was considered to be no treatment related. In addition, diffuse atrophy of the seminiferous tubules and Leydig cell hyperplasia in the testis were observed in males of the 25 mg/kg group. In the animal, small and softening of the testis were observed in the necropsy. However, this was observed in only one animal and no dose-related change was found. Therefore, this was considered to be no treatment related.

In the recovery group, histopathological changes of the incisor remained in both sexes as the treatment related changes during the recovery period. In the clinical signs, mottled teeth, discoloration (whitish change) of the teeth and surface delamination of the tip of the lower incisors were newly observed during the recovery period. In the necropsy, rough surface of the incisor was observed. It was suggested that these changes were caused by the fluoride as described above. Therefore, it was presumed that these changes would gradationally disappear with elongation of the incisor in the course of the recovery period. Although increased relative liver weight remained in females, the degree diminished. In addition, increased absolute liver weight and histological changes found at the end of the dosing period disappeared at the end of the recovery period. Therefore, these changes were considered to be reversible.

In the hematological examinations, decreased levels of Hb and Ht were found in males of 125 mg/kg recovery group, however, these changes were not found at the end of the dosing period, and these values were also within the range of the historical data[3]. Therefore, these changes were considered to be incidental. In the blood chemical examinations, IP level was newly increased in the females of the 125 mg/kg recovery group, however, this value was also within the range of the historical data[4]. Therefore, this change was considered to be incidental. As for the organ weights, relative heart weight and absolute and relative testes weights were increased in males of the 125 mg/kg recovery group. In addition, increased absolute brain weight was observed in females of the 125 mg/kg recovery group. However, no histological abnormalities in these organs were observed at the end of the recovery period. Furthermore, no changes in these organ weights were observed at the end of dosing period. Therefore, these changes were considered to be no treatment related. In addition, aplasia of the left lobe of the thyroid was found macroscopically and histologically in one female of the 125 mg/kg recovery group. However, it was considered that the change was not treatment-related, but congenital. In the histopathological examinations, solitary cyst in the medulla of the kidney was observed in one male of the 125 mg/kg recovery group. However, this change has been found in historical data[5]. Therefore, this was considered to be an incidental change.

In conclusion, it was considered that [redacted] had mainly effects on the incisor, liver, and kidney. However, it was also considered that these changes were reversible. The No-Observed-Adverse-Effect Level (NOAEL) of [redacted] was considered to be 5 mg/kg/day based on increased relative kidney weights in the male given 25 mg/kg or more.

1) [redacted]

2) [redacted] 1995, Study on Physiology and Pharmacology in Hard Tissue —Effects of chemicals on formation and resorption mechanism of tooth and bone—, [redacted]

3) Historical data of hematological examinations of Crl:CD(SD) rats in [redacted] (11-13 weeks old)

Vehicle: olive oil

Items	Sex	n	Mean	Mean-2S.D.	Mean+2S.D.
Hb (g/dL)	male	186	15.8	14.8	16.8
Ht(%)	male	186	46.8	43.6	50.0

n: number of animals examined.

4) Historical data of blood chemical examinations of Crl:CD(SD) rats in [redacted] (11-13 weeks old)

Vehicle: olive oil

Items	Sex	n	Mean	Mean-2S.D.	Mean+2S.D.
IP (mg/dL)	female	186	6.3	4.9	7.7

n: number of animals examined.

5) Historical data of histopathology of Crl:CD(SD) rats in [redacted] (9-16 weeks old)

Items	Sex	Incidence
Solitary cyst in the medulla of the kidney	male	12/484

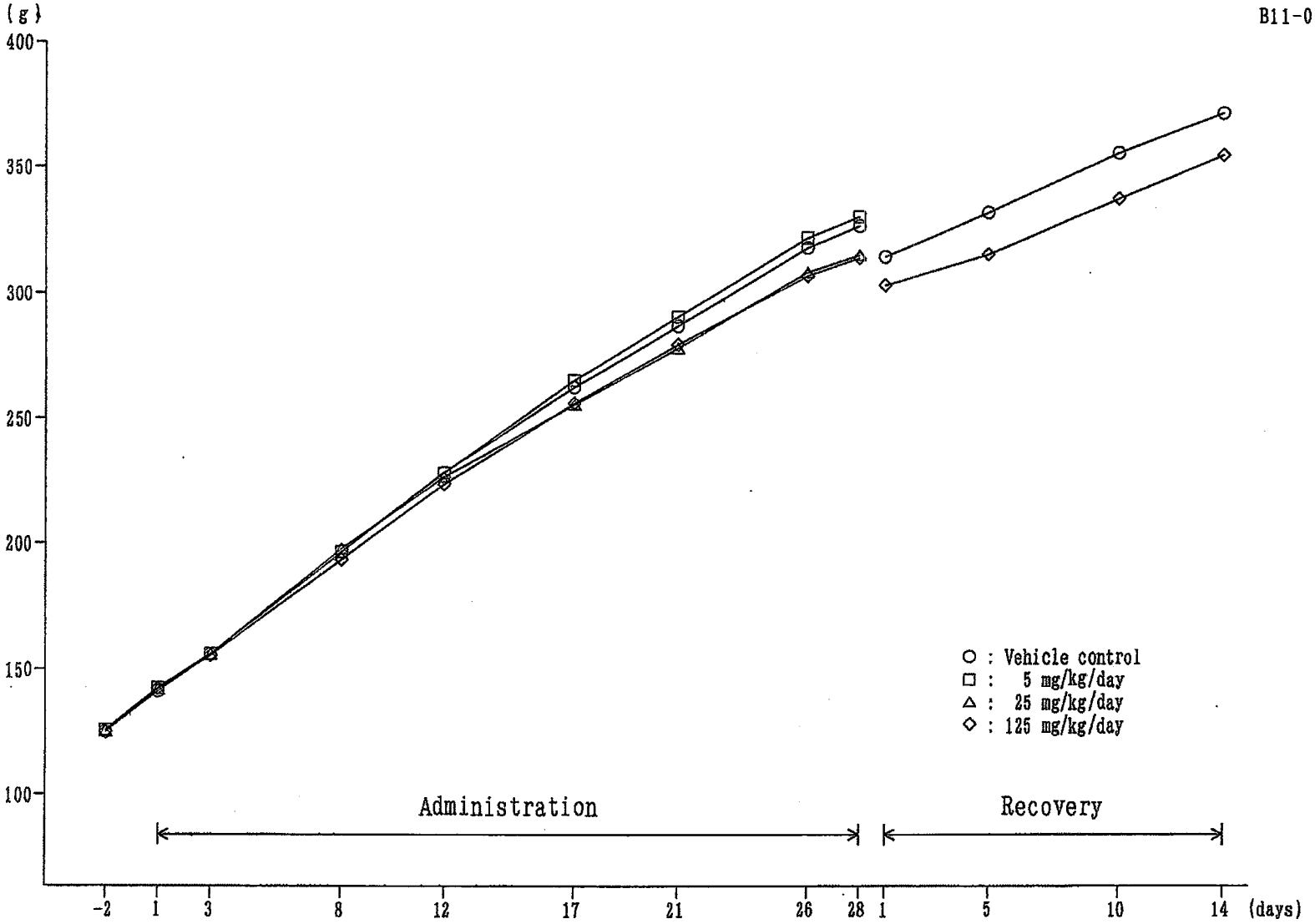


Fig. 1-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights : Male

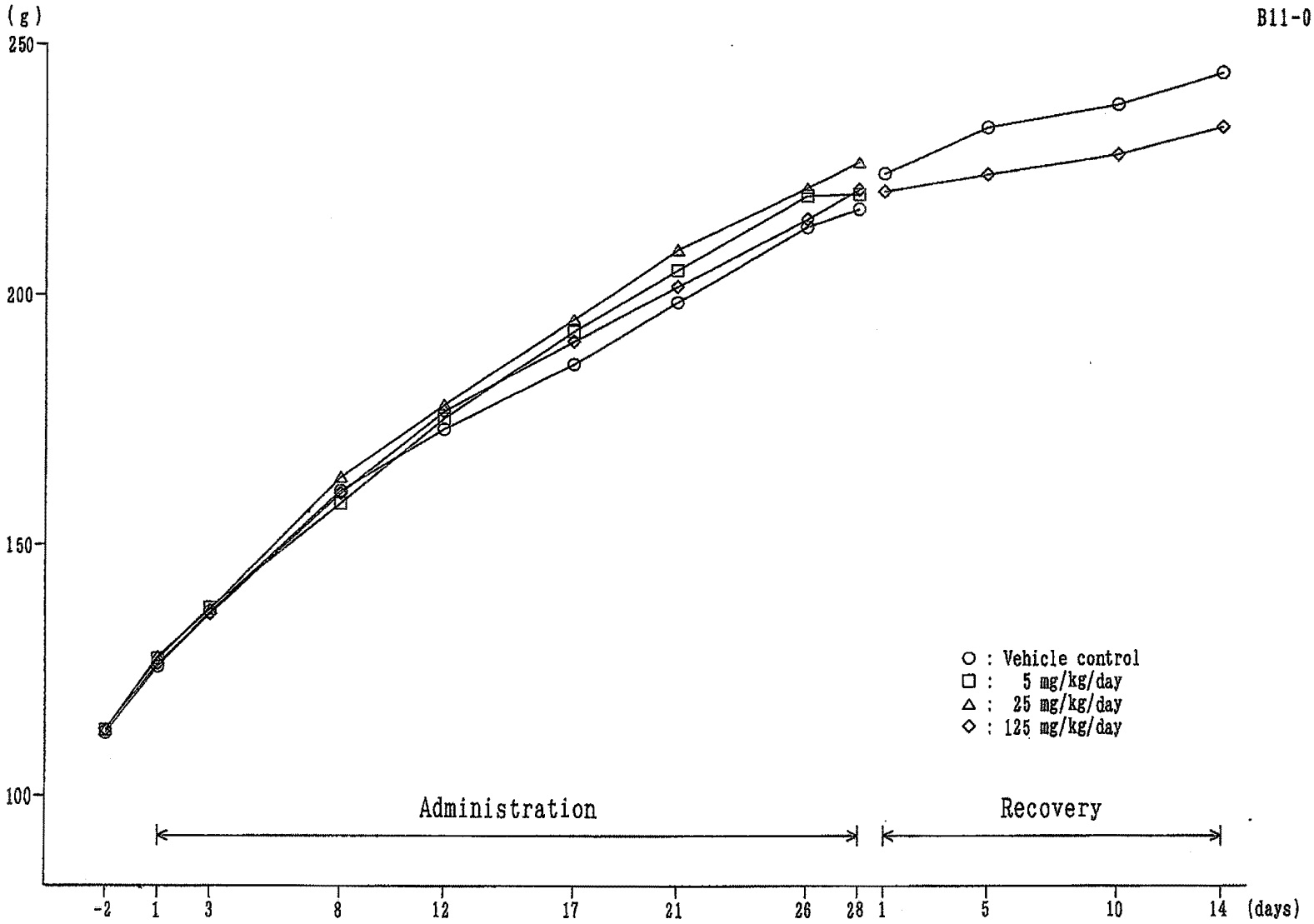


Fig. 1-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights : Female

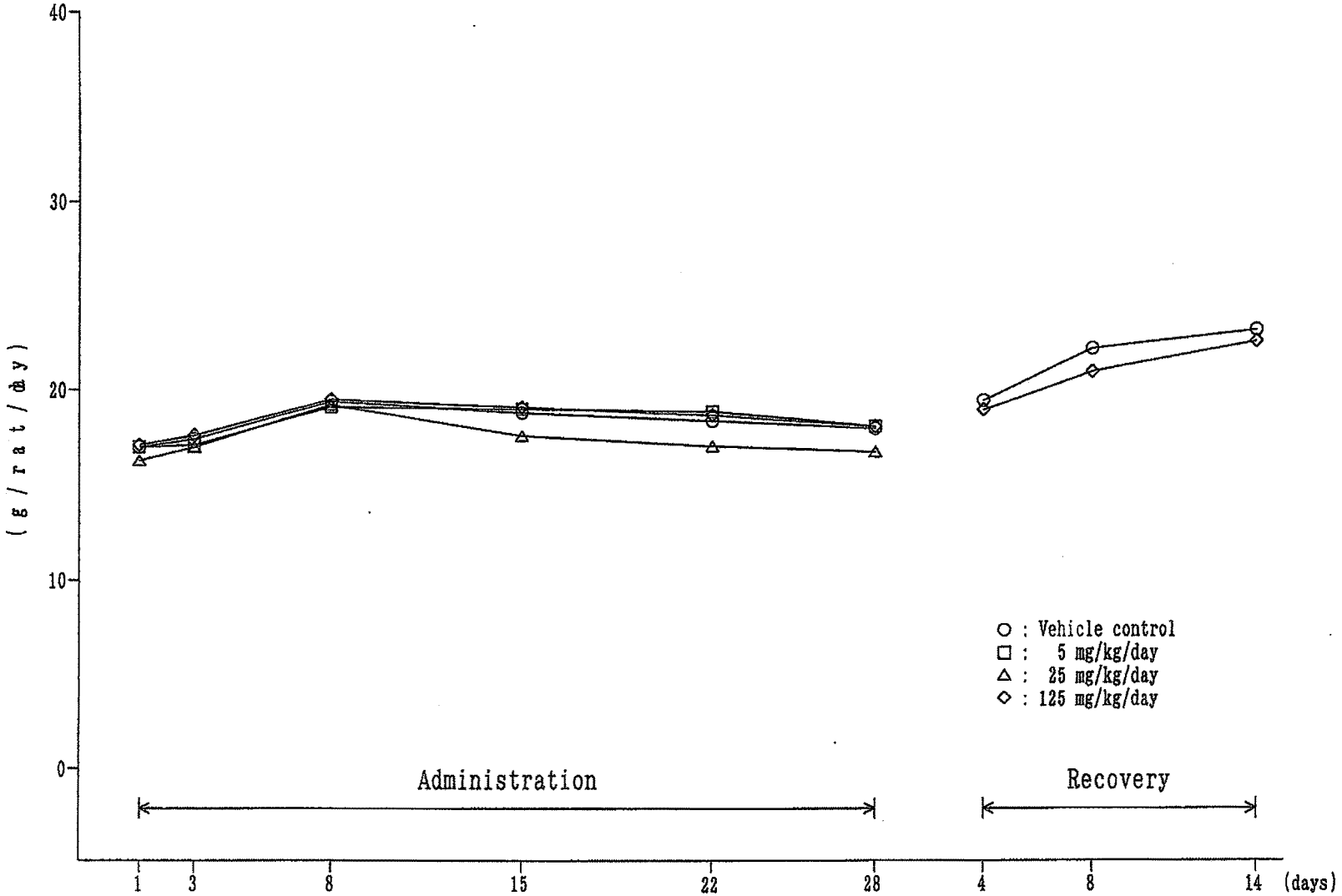


Fig. 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Food intakes : Male

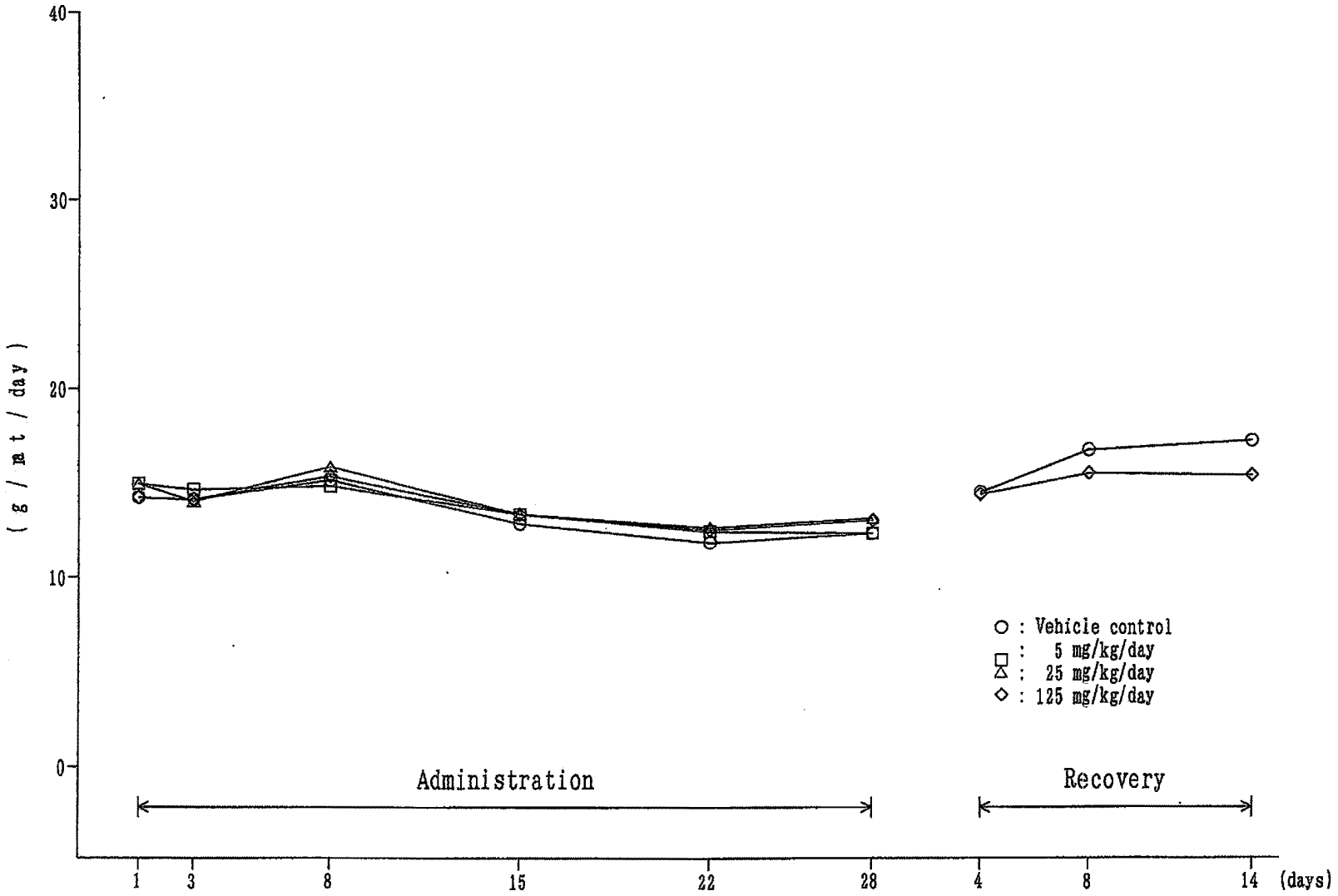


Fig. 2-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Food intakes : Female

Table 1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of clinical signs

Sex	Signs	Administration Period						Recovery Period	
	mg/kg/day	VC	VC (R)	5	25	125	125 (R)	VC	125
Male		ta 5[a)]	ta 5	ta 5	ta 5	ta 5	ta 5	ta 5	ta 5
	No abnormalities detected	3	4	3	2			5	
	Salivation	2	1	2	3	5	5		
	Decreased spontaneous locomotion				1	2	2		
	Swelling of third digit in left forelimb						1		1
	White turbid urine						1		
	Exudate(neck)						1		1
	Scab formation(neck)								1
	Mottled teeth								5
	Whitish change of teeth								4
Female		ta 5	ta 5	ta 5	ta 5	ta 5	ta 5	ta 5	ta 5
	No abnormalities detected	5	5	3				5	
	Salivation			2	5	5	5		
	Decreased spontaneous locomotion					2	3		
	Staining lower abdomen						2		
	Mottled teeth								5
	Whitish change of teeth								5
	Surface delamination of tip lower inisores								2
	Death				1				

a) Number of animals examined.
VC, Vehicle control; (R), Recovery
ta, terminal autopsy.

Table 2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations (scoring scale for detailed clinical observations)

REMOVAL FROM CAGE	
Ease of removal	
-2	No reaction
-1	Very easy
0	Easy (slight resistance)
+1	Difficult
+2	Very difficult
Vocalizati on	
0	None
+1	Vocalization during handling
+2	Continuous vocalization
HANDLING OBSERVATIONS	
Muscle tone	
-1	Decreased
0	Normal
+1	Increased
Subnormal temperature	
-	Absent
+	Present
Piloerection	
-	Absent
+	Present
Staining hair	
-	Absent
+	Present
Unkempt hair	
-	Absent
+	Present
Paleness	
-	Absent
+	Present
Reddening	
-	Absent
+	Present
Cyanosis	
-	Absent
+	Present
Lacrimation	
-	Absent
+	Present

Table 2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations (scoring scale for detailed clinical observations)

HANDLING OBSERVATIONS-continued		
	Exophthalmos	
	-	Absent
	+	Present
	Pupillary size	
	-1	Miosis
	0	Normal
	+1	Mydriasis
	Salivation	
	-	Absent
	+	Present
	Secretion	
	-	Absent
	+	Present
OBSERVATIONS IN ARENA		
	Posture	
	0	Normal
	+1	Crouching position or hunchback position
	+2	Prone position or lateral position
	Motor activity	
	-2	Significantly decreased
	-1	Decreased
	0	Normal
	+1	Increased
	+2	Significantly increased
	Respiration	
	0	Normal
	+1	Slightly insufficiency
	+2	Moderately insufficiency
	+3	Severely insufficiency
	Lid closure	
	-	Absent
	+	Present
	Gait	
	-	Normal
	S	Staggering gait
	T	Tiptoe gait
	P	Shuffling (paralytic) gait
	GD	Gait disturbance

Table 2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations (scoring scale for detailed clinical observations)

OBSERVATIONS IN ARENA-continued	
Tremor/twitch/convulsion	
0	None
+1	Tremor
+2	Twitch or convulsion
+3	Systematic tonic convulsion (opisthotonus or episthotonus etc.)
Stereotypic behavior	
-	None
C	Circling
G	Grooming
S	Sniffing
H	Head bobbing
Abnormal behavior	
-	None
S	Self-biting
B	Backing
C	Circling
R	Rolling
W	Writhing
V	Vocalization
ST	Straub tail
T	Tail lashing behavior

Table 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Removal from cage							
				Ease of removal					Vocalization		
				-2	-1	0	+1	+2	0	+1	+2
Male	Predosing	Vehicle control	10	0	0	10	0	0	8	2	0
		5	5	0	0	5	0	0	4	1	0
		25	5	0	0	5	0	0	5	0	0
		125	10	0	0	9	1	0	10	0	0
	week 1	Vehicle control	10	0	0	10	0	0	7	3	0
		5	5	0	0	5	0	0	4	1	0
		25	5	0	0	5	0	0	4	1	0
		125	10	0	0	10	0	0	10	0	0
	week 2	Vehicle control	10	0	0	10	0	0	9	1	0
		5	5	0	0	5	0	0	4	1	0
		25	5	0	0	5	0	0	5	0	0
		125	10	0	0	10	0	0	10	0	0
	week 3	Vehicle control	10	0	0	10	0	0	8	2	0
		5	5	0	0	5	0	0	5	0	0
		25	5	0	0	5	0	0	5	0	0
		125	10	0	0	10	0	0	10	0	0
	week 4	Vehicle control	10	0	0	10	0	0	8	2	0
		5	5	0	0	5	0	0	4	1	0
		25	5	0	0	5	0	0	5	0	0
		125	10	0	0	10	0	0	10	0	0
	Recovery week 1	Vehicle control	5	0	0	5	0	0	5	0	0
		125	5	0	0	5	0	0	5	0	0
	Recovery week 2	Vehicle control	5	0	0	5	0	0	4	1	0
		125	5	0	0	5	0	0	5	0	0

Table 2-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Removal from cage							
				Ease of removal					Vocalization		
				-2	-1	0	+1	+2	0	+1	+2
Female	Predosing	Vehicle control	10	0	0	10	0	0	9	1	0
		5	5	0	0	4	1	0	3	2	0
		25	5	0	0	5	0	0	3	2	0
		125	10	0	0	10	0	0	10	0	0
	week 1	Vehicle control	10	0	0	10	0	0	8	2	0
		5	5	0	0	5	0	0	3	2	0
		25	5	0	0	5	0	0	4	1	0
		125	10	0	1	8	1	0	9	1	0
	week 2	Vehicle control	10	0	0	10	0	0	6	4	0
		5	5	0	0	5	0	0	5	0	0
		25	5	0	0	5	0	0	2	3	0
		125	10	0	0	10	0	0	9	1	0
	week 3	Vehicle control	10	0	0	10	0	0	7	3	0
		5	5	0	0	5	0	0	3	2	0
		25	5	0	0	5	0	0	5	0	0
		125	10	0	0	10	0	0	10	0	0
	week 4	Vehicle control	10	0	0	10	0	0	7	3	0
		5	5	0	0	5	0	0	4	1	0
		25	4	0	0	4	0	0	3	1	0
		125	10	0	0	10	0	0	10	0	0
	Recovery week 1	Vehicle control	5	0	0	5	0	0	4	1	0
		125	5	0	0	5	0	0	5	0	0
	Recovery week2	Vehicle control	5	0	0	5	0	0	3	2	0
		125	5	0	0	5	0	0	4	1	0

Table 2-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations						
				Muscle tone			Subnormal temperature		Piloerection	
				-1	0	+1	-	+	-	+
Male	Predosing	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	0	5	0	5	0	5	0
		125	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	0	5	0	5	0	5	0
		125	5	0	5	0	5	0	5	0

Table 2-4 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations						
				Muscle tone			Subnormal temperature		Piloerection	
				-1	0	+I	-	+	-	+
Female	Predosing	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week4	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	4	0	4	0	4	0	4	0
		125	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	0	5	0	5	0	5	0
		125	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	0	5	0	5	0	5	0
		125	5	0	5	0	5	0	5	0

Table 2-5 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations							
				Staining hair		Unkempt hair		Paleness		Reddening	
				-	+	-	+	-	+	-	+
Male	Predosing	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		125	10	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		125	10	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		125	10	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		125	10	10	0	10	0	10	0	10	0
	week4	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		125	10	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	5	0	5	0	5	0	5	0
		125	5	5	0	5	0	5	0	5	0
	Recovery week2	Vehicle control	5	5	0	5	0	5	0	5	0
		125	5	5	0	5	0	5	0	5	0

Table 2-6 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations							
				Staining hair		Unkempt hair		Paleness		Reddening	
				-	+	-	+	-	+	-	+
Female	Predosing	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		125	10	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		125	10	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		125	10	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		125	10	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	4	4	0	4	0	4	0	4	0
		125	10	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	5	0	5	0	5	0	5	0
		125	5	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	5	0	5	0	5	0	5	0
		125	5	5	0	5	0	5	0	5	0

Table 2-7 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations					
				Cyanosis		Lacrimation		Exophthalmos	
				-	+	-	+	-	+
Male	Predosing	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		125	10	10	0	10	0	10	0
	week 1	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		125	10	10	0	10	0	10	0
	week 2	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		125	10	10	0	10	0	10	0
	week 3	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		125	10	10	0	10	0	10	0
	week 4	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		125	10	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	5	0	5	0	5	0
		125	5	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	5	0	5	0	5	0
		125	5	5	0	5	0	5	0

Table 2-8 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations					
				Cyanosis		Lacrimation		Exophthalmos	
				-	+	-	+	-	+
Female	Predosing	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		125	10	10	0	10	0	10	0
	week 1	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		125	10	10	0	10	0	10	0
	week 2	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		125	10	10	0	10	0	10	0
	week3	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		125	10	10	0	10	0	10	0
	week 4	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	4	4	0	4	0	4	0
		125	10	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	5	0	5	0	5	0
		125	5	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	5	0	5	0	5	0
		125	5	5	0	5	0	5	0

Table 2-9 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations						
				Pupillary size			Salivation		Secretion	
				-1	0	+1	-	+	-	+
Male	Predosing	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week3	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	0	5	0	5	0	5	0
		125	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	0	5	0	5	0	5	0
		125	5	0	5	0	5	0	5	0

Table 2-10 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations						
				Pupillary size			Salivation		Secretion	
				-1	0	+1	-	+	-	+
Female	Predosing	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	4	0	4	0	4	0	4	0
		125	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	0	5	0	5	0	5	0
		125	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	0	5	0	5	0	5	0
		125	5	0	5	0	5	0	5	0

Table 2-11 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena							
				Posture			Motor activity				
				0	+1	+2	-2	-1	0	+1	+2
Male	Predosing	Vehicle control	10	10	0	0	0	0	10	0	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	0	5	0	0
		125	10	10	0	0	0	0	8	2	0
	week 1	Vehicle control	10	10	0	0	0	0	10	0	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	0	4	1	0
		125	10	10	0	0	0	0	10	0	0
	week 2	Vehicle control	10	10	0	0	0	0	10	0	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	0	4	1	0
		125	10	10	0	0	0	0	9	1	0
	week 3	Vehicle control	10	10	0	0	0	0	9	1	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	1	4	0	0
		125	10	10	0	0	0	0	10	0	0
	week4	Vehicle control	10	10	0	0	0	0	10	0	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	0	5	0	0
		125	10	10	0	0	0	0	10	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0	5	0	0
		125	5	5	0	0	0	0	5	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0	3	2	0
		125	5	5	0	0	0	0	4	1	0

Table 2-12 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena							
				Posture			Motor activity				
				0	+1	+2	-2	-1	0	+1	+2
Female	Predosing	Vehicle control	10	10	0	0	0	0	10	0	0
		5	5	5	0	0	0	0	4	1	0
		25	5	5	0	0	0	0	4	1	0
		125	10	10	0	0	0	0	9	1	0
	week 1	Vehicle control	10	10	0	0	0	0	8	2	0
		5	5	5	0	0	0	0	4	1	0
		25	5	5	0	0	0	0	5	0	0
		125	10	10	0	0	0	0	10	0	0
	week2	Vehicle control	10	10	0	0	0	0	9	1	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	0	5	0	0
		125	10	10	0	0	0	0	10	0	0
	week 3	Vehicle control	10	10	0	0	0	0	10	0	0
		5	5	5	0	0	0	0	4	1	0
		25	5	5	0	0	0	0	5	0	0
		125	10	10	0	0	0	0	10	0	0
	week 4	Vehicle control	10	10	0	0	0	0	10	0	0
		5	5	5	0	0	0	0	5	0	0
		25	4	4	0	0	0	0	4	0	0
		125	10	10	0	0	0	0	10	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0	5	0	0
		125	5	5	0	0	0	0	5	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0	5	0	0
		125	5	5	0	0	0	0	4	1	0

Table 2-13 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena					
				Respiration				Lid closure	
				0	+1	+2	+3	-	+
Male	Predosing	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		125	10	10	0	0	0	10	0
	week 1	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		125	10	10	0	0	0	10	0
	week 2	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		125	10	10	0	0	0	10	0
	week 3	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		125	10	10	0	0	0	10	0
	week 4	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		125	10	10	0	0	0	10	0
	Recovery week 1	Vehicle control	5	5	0	0	0	5	0
		125	5	5	0	0	0	5	0
	Recovery week 2	Vehicle control	5	5	0	0	0	5	0
		125	5	5	0	0	0	5	0

Table 2-14 Twenty-eight-day repeated-dose oral toxicity study in rats BII-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena					
				Respiration				Lid closure	
				0	+1	+2	+3	-	+
Female	Predosing	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		125	10	10	0	0	0	10	0
	week 1	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		125	10	10	0	0	0	10	0
	week 2	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		125	10	10	0	0	0	10	0
	week 3	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		125	10	10	0	0	0	10	0
	week 4	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	4	4	0	0	0	4	0
		125	10	10	0	0	0	10	0
	Recovery week 1	Vehicle control	5	5	0	0	0	5	0
		125	5	5	0	0	0	5	0
	Recovery week 2	Vehicle control	5	5	0	0	0	5	0
		125	5	5	0	0	0	5	0

Table 2-15 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena				
				Gait				
				-	S	T	P	GD
Male	Predosing	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0
		125	5	5	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0
		125	5	5	0	0	0	0

Table 2-16 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena				
				Gait				
				-	S	T	P	GD
Female	Predosing	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week4	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	4	4	0	0	0	0
		125	10	10	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0
		125	5	5	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0
		125	5	5	0	0	0	0

Table 2-17 Twenty-eight-day repeated-dose oral toxicity study in rats BII-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Tremor/twitch/convulsion 0	+1	+2	+3	Defecation (count/min)[a]	Urination (count/min)[a]
Male	Predosing	Vehicle control	10	10	0	0	0	0.2 ±0.42	1.1 ±1.45
		5	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		25	5	5	0	0	0	0.0 ±0.00	2.8 ±3.63
		125	10	10	0	0	0	0.6 ±1.07	1.1 ±1.45
	week 1	Vehicle control	10	10	0	0	0	0.4 ±0.97	0.4 ±0.70
		5	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		25	5	5	0	0	0	0.6 ±0.89	1.4 ±1.67
		125	10	10	0	0	0	1.1 ±1.66	0.2 ±0.42
	week 2	Vehicle control	10	10	0	0	0	0.7 ±1.06	0.7 ±0.82
		5	5	5	0	0	0	0.4 ±0.89	0.0 ±0.00
		25	5	5	0	0	0	0.6 ±0.89	1.6 ±1.52
		125	10	10	0	0	0	0.7 ±1.34	1.1 ±1.66
	week 3	Vehicle control	10	10	0	0	0	0.5 ±1.27	1.3 ±1.70
		5	5	5	0	0	0	0.2 ±0.45	0.0 ±0.00
		25	5	5	0	0	0	1.4 ±1.14 *	3.2 ±3.35
		125	10	10	0	0	0	0.0 ±0.00	0.5 ±1.08
	week 4	Vehicle control	10	10	0	0	0	0.3 ±0.67	0.7 ±1.34
		5	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		25	5	5	0	0	0	1.6 ±1.14 *	1.2 ±1.30
		125	10	10	0	0	0	0.3 ±0.67	0.4 ±0.70
	Recovery week 1	Vehicle control	5	5	0	0	0	0.2 ±0.45	0.2 ±0.45
		125	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
	Recovery week 2	Vehicle control	5	5	0	0	0	0.0 ±0.00	0.2 ±0.45
		125	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00

a) Mean ±S.D.

* Significantly different from vehicle control at P<0.05.

** Significantly different from vehicle control at P<0.01.

Table 2-18 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Tremor/twitch/convulsion 0	+1	+2	+3	Defecation (count/min)[a]	Urination (count/min)[a]
Female	Predosing	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.8 ±0.92
		5	5	5	0	0	0	0.0 ±0.00	1.4 ±2.61
		25	5	5	0	0	0	0.0 ±0.00	1.8 ±2.95
		125	10	10	0	0	0	0.0 ±0.00	0.3 ±0.48
	week 1	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.5 ±0.71
		5	5	5	0	0	0	0.0 ±0.00	0.6 ±0.89
		25	5	5	0	0	0	0.0 ±0.00	0.4 ±0.89
		125	10	10	0	0	0	0.0 ±0.00	1.0 ±1.41
	week 2	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.3 ±0.95
		5	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		25	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		125	10	10	0	0	0	0.0 ±0.00	0.5 ±1.08
	week 3	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.0 ±0.00
		5	5	5	0	0	0	0.0 ±0.00	0.4 ±0.89
		25	5	5	0	0	0	0.0 ±0.00	0.2 ±0.45
		125	10	10	0	0	0	0.0 ±0.00	0.0 ±0.00
	week 4	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.4 ±0.97
		5	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		25	4	4	0	0	0	0.0 ±0.00	0.0 ±0.00
		125	10	10	0	0	0	0.0 ±0.00	0.3 ±0.48
	Recovery week 1	Vehicle control	5	5	0	0	0	0.0 ±0.00	0.2 ±0.45
		125	5	5	0	0	0	0.0 ±0.00	1.0 ±2.24
	Recovery week 2	Vehicle control	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		125	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00

a) Mean ±S.D.

* Significantly different from vehicle control at $P<0.05$.

** Significantly different from vehicle control at $P<0.01$.

Table 2-19 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena				
				Stereotypic behavior				
				-	C	G	S	H
Male	Predosing	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0
		125	5	5	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0
		125	5	5	0	0	0	0

Table 2-20 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Stereotypic behavior -	C	G	S	H
Female	Predosing	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		125	10	10	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	4	4	0	0	0	0
		125	10	10	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0
		125	5	5	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0
		125	5	5	0	0	0	0

Table 2-21 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Abnormal behavior: -	S	B	C	R	W	V	ST	T
Male	Predosing	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		125	10	10	0	0	0	0	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		125	10	10	0	0	0	0	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		125	10	10	0	0	0	0	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		125	10	10	0	0	0	0	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		125	10	10	0	0	0	0	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0	0	0	0	0
		125	5	5	0	0	0	0	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0	0	0	0	0
		125	5	5	0	0	0	0	0	0	0	0

Table 2-22 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Abnormal behavior								
				-	S	B	C	R	W	V	ST	T
Female	Predosing	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		125	10	10	0	0	0	0	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		125	10	10	0	0	0	0	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		125	10	10	0	0	0	0	0	0	0	0
	week3	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		125	10	10	0	0	0	0	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	4	4	0	0	0	0	0	0	0	0
		125	10	10	0	0	0	0	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0	0	0	0	0
		125	5	5	0	0	0	0	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0	0	0	0	0
		125	5	5	0	0	0	0	0	0	0	0

Table 3 Twenty-eight-day repeated-dose oral toxicity study in rats BII-0836
Summary of reflex (scoring scale for reflex)

SENSORIMOTOR FUNCTION	
Approach contact/touch response	
-1	No reaction
0	Normal
+1	Hyper reaction
Pinna response	
-1	No reaction
0	Normal
+1	Hyper reaction
Pain response (tail pinch)	
-1	No reaction
0	Normal
+1	Hyper reaction
Pupillary reflex	
+	Normal
-	Abnormal reaction
Air righting reflex	
+	Normal
-	Abnormal reaction

Table 3-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836
Summary of reflex

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Sensorimotor function					
				Approach contact/ touch response			Pinna response		
				-1	0	+1	-1	0	+1
Male	week 4	Vehicle control	10	0	10	0	0	10	0
		5	5	0	5	0	0	5	0
		25	5	0	5	0	0	5	0
		125	10	0	10	0	0	10	0
Female	week 4	Vehicle control	10	0	10	0	0	10	0
		5	5	0	5	0	0	5	0
		25	4	0	4	0	0	4	0
		125	10	0	10	0	0	10	0

Table 3-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836
Summary of reflex

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Sensorimotor function						
				Pain response (tail pinch)			Pupillary reflex		Air righting reflex	
				-1	0	+1	+	-	+	-
Male	week 4	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		125	10	0	10	0	10	0	10	0
Female	week 4	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	4	0	4	0	4	0	4	0
		125	10	0	10	0	10	0	10	0

Table4 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of grip strength

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Forelimb (g)	Hindlimb (g)
Male	week4	Vehicle control	10	834 ±153	509 ±103
		5	5	821 ±62	499 ±113
		25	5	987 ±123	474 ±119
		125	10	914 ±90	450 ±144
Female	week 4	Vehicle control	10	689 ±218	478 ±122
		5	5	810 ±136	400 ±112
		25	4	717 ±125	408 ±153
		125	10	735 ±156	430 ±100

Mean ±S.D.

* Significantly different from vehicle control at P<0.05.

** Significantly different from vehicle control at P<0.01.

Table 5 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Summary of motor activity

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Motor activity (count) 0-10	10-20	20-30	30-40	40-50	50-60	0-60 (min)
Male	week 4	Vehicle control	10	2688 ±1519	2983 ±1313	2295 ±1341	2110 ±1162	1411 ±1185	1245 ±1471	12731 ±6139
		5	5	2609 ±1837	4079 ±1320	2130 ±963	1746 ±1097	967 ±787	838 ±846	12370 ±4524
		25	5	4003 ±638	2640 ±978	1629 ±719	916 ±872	979 ±1018	623 ±764	10791 ±3870
		125	10	3517 ±1693	3276 ±760	2505 ±862	1865 ±1216	1321 ±1199	1050 ±818	13534 ±4877
Female	week4	Vehicle control	10	4536 ±886	3766 ±1162	3313 ±1456	2161 ±1422	2290 ±1701	794 ±1019	16860 ±6470
		5	5	6179 ±1589	4556 ±1157	4115 ±1550	2803 ±1411	1750 ±680	1613 ±1720	21014 ±5331
		25	4	5759 ±1663	4899 ±1783	3912 ±2046	2266 ±1700	2957 ±1564	1419 ±1643	21211 ±7891
		125	10	4874 ±1101	4116 ±1180	3834 ±1375	2806 ±1908	1943 ±1721	1369 ±1670	18942 ±7426

Mean ±S.D.

* Significantly different from vehicle control at $P<0.05$.

** Significantly different from vehicle control at $P<0.01$.

Table 6-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of body weights(g)

B11-0836

Sex	Exp.group (mg/kg/day)	Number of animals	Administration period								
			-2	1	3	8	12	17	21	26	28 (days)
Male	Vehicle control	10	125.3 ± 4.1	141.2 ± 5.1	155.9 ± 7.0	196.5 ± 13.9	228.6 ± 18.0	262.5 ± 22.9	287.0 ± 25.4	318.0 ± 31.1	326.6 ± 31.8
	5	5	125.9 ± 4.3	142.5 ± 6.0	156.1 ± 7.0	196.4 ± 10.4	228.3 ± 10.7	265.3 ± 12.1	290.7 ± 14.2	321.9 ± 18.7	330.1 ± 20.8
	25	5	125.5 ± 4.5	142.0 ± 4.8	155.9 ± 7.1	197.6 ± 11.2	226.7 ± 15.8	255.6 ± 20.2	278.3 ± 24.9	308.4 ± 28.3	315.2 ± 31.2
	125	10	125.2 ± 3.2	142.3 ± 3.2	155.5 ± 4.5	193.4 ± 10.8	223.8 ± 14.6	256.1 ± 17.5	279.7 ± 18.1	307.0 ± 20.5	314.1 ± 20.1
Female	Vehicle control	10	112.7 ± 3.6	125.9 ± 2.4	136.7 ± 3.5	160.7 ± 5.5	173.2 ± 6.4	186.1 ± 8.1	198.6 ± 11.0	213.6 ± 12.1	217.1 ± 13.2
	5	5	113.2 ± 3.0	127.5 ± 3.9	137.6 ± 6.8	158.2 ± 14.7	175.3 ± 19.6	192.7 ± 21.2	205.1 ± 23.5	219.7 ± 21.8	220.0 ± 25.3
	25	5	113.2 ± 3.6	127.9 ± 3.6	137.2 ± 4.4	163.4 ± 9.5	178.0 ± 10.5	195.1 ± 10.8	209.1 ± 9.3	221.2 ± 12.8(4)	226.4 ± 13.8(4)
	125	10	113.3 ± 3.8	126.4 ± 5.0	136.3 ± 8.5	160.2 ± 14.1	176.7 ± 18.9	190.7 ± 20.7	201.8 ± 21.6	215.1 ± 22.5	220.9 ± 23.6

Mean ±S.D.
Figure(s) in parentheses indicate number of animals used for mean calculation.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 6-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of body weights(g)

B11-0836

Sex	Exp.group (mg/kg/day)	Number of animals	Recovery period 1	5	10	14 (days)
Male	Vehicle control	5	314.7 ± 28.3	332.0 ± 28.0	355.9 ± 31.6	371.7 ± 33.0
	125	5	303.4 ± 12.0	315.7 ± 10.9	337.6 ± 10.4	355.1 ± 10.0
Female	Vehicle control	5	224.2 ± 13.8	233.4 ± 13.2	238.0 ± 16.4	244.4 ± 18.4
	125	5	220.8 ± 27.2	224.1 ± 27.2	228.1 ± 27.6	233.6 ± 31.3

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 7-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836
Summary of food intakes(g/rat/day)

Sex	Exp.group (mg/kg/day)	Number of animals	Administration period 1	3	8	15	22	28 (days)
Male	Vehicle control	10	17.0 ± 1.1	17.4 ± 1.6	19.4 ± 2.2	18.8 ± 2.4	18.4 ± .5	18.0 ± 2.6
	5	5	17.0 ± 0.9	17.1 ± 1.2	19.1 ± 1.4	19.0 ± 0.7	.9 ± 18.8	18.1 ± 1.7
	25	5	16.3 ± 0.9	17.0 ± 0.9	19.2 ± 1.3	17.6 ± 1.2	0 .1 ± 17.3	16.8 ± 1.3
	125	10	17.1 ± 0.8	17.6 ± 1.2	19.5 ± 1.9	19.1 ± 2.0	1.7 ± 18.7	18.1 ± 1.2
Female	Vehicle control	10	14.3 ± 0.5	14.2 ± 1.0	15.2 ± 1.0	12.9 ± 1.4	11.9 ± 1.1	12.4 ± 1.3
	5	5	15.0 ± 1.5	14.7 ± 2.5	14.9 ± 2.9	13.4 ± 2.3	12 .5 ± 2.3	12.4 ± 2.3
	25	5	15.0 ± 0.6	14.1 ± 1.2	15.9 ± 0.8	13.4 ± 0.8	12.7 ± 0.7	13.2 ± 1.5(4)
	125	10	14.3 ± 0.9	14.2 ± 1.8	15.4 ± 2.1	13.4 ± 1.9	12.6 ± 1.6	13.1 ± 1.5

Mean ±S.D.
Figure(s) in parentheses indicate number of animals used for mean calculation.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 7-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836
Summary of food intakes(g/rat/day)

Sex	Exp.group (mg/kg/day)	Number of animals	Recovery period 4	8	14 (days)
Male	Vehicle control	5	19.5 ± 2.0	22.2 ± 2.0	23.2 ± 2.2
	125	5	19.0 ± 1.5	21.0 ± 0.1	22.6 ± 0.4
Female	Vehicle control	5	14.6 ± 2.2	16.8 ± 2.1	17.3 ± 1.8
	125	5	14.5 ± 1.8	15.6 ± 1.5	15.5 ± 1.9

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 8-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of hematological examinations

B11-0836

Sex	Exp.group (mg/kg/day)	Number of animals	RBC ($\times 10^4/\mu L$)	WBC ($\times 10^2/\mu L$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet ($\times 10^4/\mu L$)	Reticulo (%)	P T (sec)	APTT (sec)
Male	Vehicle control	5	782 ± 20	122 ± 15	15.4 ± 0.3	45.9 ± 0.8	58.7 ± 1.6	19.8 ± 0.6	33.7 ± 0.3	99.3 ± 8.5	2.4 ±0.5	14.3 ± 1.1	25.2 ± 2.2
	5	5	782 ± 23	119 ± 23	15.5 ± 0.5	45.8 ± 1.6	58.7 ± 1.2	19.9 ± 0.5	33.9 ± 0.4	99.7 ± 7.8	2.4 ±0.4	14.7 ± 1.5	+26.5 - 3.7
	25	5	756 ± 53	115 ± 18	15.1 ± 0.9	44.7 ± 3.0	59.2 ± 1.2	20.0 ± 0.4	33.8 ± 0.2	94.8 ± 5.4	2.8 ±0.5	+15.5 - 1.4	26.6 ± 0.8
	125	5	784 ± 43	108 ± 27	15.4 ± 0.6	45.8 ± 2.4	58.4 ± 1.2	19.7 ± 0.5	33.7 ± 0.5	97.5 ± 10.9	2.2 ±0.3	15.1 ± 0.7	-26.2 ± 1.3
	Recovery												
	Vehicle control	5	847 ± 17	108 ± 19	16.1 ± 0.4	47.7 ± 1.0	56.3 ± 0.2	19.0 ± 0.3	33.7 ± 0.3	103.7 ± 8.5	1.7 ±0.3	18.6 ± 4.2	31.4 ± 1.0
	125	5	798 ± 55	111 ± 9	15.0** ± 0.5	43.8** ± 1.2	55.0 ± 2.6	18.8 ± 0.9	34.2 ± 0.4	103.4 ± 14.0	2.2 ±0.6	18.0 ± 5.3	28.2 ± 3.1
Female	Vehicle control	5	777 ± 32	+ 80 - 5	15.4 ± 0.4	44.7 ± 0.9	57.6 ± 1.7	19.8 ± 0.5	34.3 ± 0.4	109.2 ± 14.3	1.8 ±0.5	13.3 ± 0.5	22.4 ± 1.9
	5	5	760 ± 27	88 ± 16	15.2 ± 0.4	44.9 ± 1.4	59.1 ± 0.5	20.0 ± 0.3	33.8 ± 0.3	-102.9 ± 8.2	1.8 ±0.2	13.0 ± 0.8	23.4 ± 2.0
	25	4	778 ± 26	109 ± 37	15.2 ± 0.4	45.0 ± 1.6	57.8 ± 1.4	19.5 ± 0.4	33.8 ± 0.3	106.1 ± 6.4	1.9 ±0.5	13.4 ± 0.7	24.0 ± 1.1
	125	5	763 ± 21	94 ± 21	15.3 ± 0.5	45.1 ± 1.8	59.1 ± 2.1	20.1 ± 0.7	34.0 ± 0.2	105.3 ± 7.3	1.7 ±0.3	12.8 ± 0.5	23.3 ± 2.5
	Recovery												
	Vehicle control	5	777 ± 47	67 ± 17	15.0 ± 0.7	42.8 ± 1.9	55.1 ± 1.8	19.4 ± 0.7	35.2 ± 0.3	123.8 ± 10.7	1.5 ±0.3	13.6 ± 0.8	21.1 ± 1.5
	125	5	798 ± 26	81 ± 12	14.7 ± 0.5	42.3 ± 1.3	53.0 ± 1.5	18.5 ± 0.6	34.9 ± 0.2	127.2 ± 5.4	1.3 ±0.2	13.7 ± 0.4	21.9 ± 2.7

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 8-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836
Summary of hematological examinations

Sex	Exp.group (mg/kg/day)	Number of animals	Differentiation of leukocyte (%) Neutro	Eosino	Baso	Lymph	Mono	LUC
Male	Vehicle control	5	18.0 ± 6.3	0.6 ±0.2	0.1 ±0.0	78.1 ± 6.6	2.5 ±0.6	0.7 ±0.2
	5	5	15.9 ± 4.6	0.8 ±0.3	0.1 ±0.0	80.5 ± 4.8	2.1 ±0.2	0.6 ±0.1
	25	5	19.5 ± 4.5	0.8 ±0.3	0.1 ±0.1	76.5 ± 4.9	2.6 ±1.0	0.6 ±0.3
	125	5	21.2 ± 5.0	0.6 ±0.4	0.1 ±0.0	75.0 ± 5.1	2.5 ±0.5	0.6 ±0.1
	Recovery							
	Vehicle control	5	14.6 ± 5.4	0.9 ±0.4	1.6 ±0.7	80.4 ± 5.0	1.9 ±0.4	0.7 ±0.2
	125	5	20.1 ± 5.9	0.8 ±0.4	0.8 ±0.5	75.8 ± 6.3	2.0 ±0.6	0.6 ±0.2
Female	Vehicle control	5	16.5 ± 9.3	0.7 ±0.3	0.1 ±0.0	79.8 ±11.4	2.4 ±2.1	0.6 ±0.1
	5	5	13.8 ± 6.2	0.8 ±0.2	0.1 ±0.1	82.7 ± 6.8	1.7 ±0.7	0.9 ±0.2
	25	4	15.7 ± 4.9	1.0 ±0.5	0.1 ±0.0	80.7 ± 4.3	1.9 ±0.7	0.8 ±0.2
	125	5	15.7 ± 4.7	0.7 ±0.3	0.1 ±0.0	81.5 ± 4.8	1.4 ±0.4	0.7 ±0.1
	Recovery							
	Vehicle control	5	16.3 ± 6.7	1.3 ±0.4	0.3 ±0.1	79.4 ± 6.6	2.1 ±0.7	0.7 ±0.3
	125	5	16.8 ± 4.9	1.5 ±0.6	0.4 ±0.2	78.4 ± 4.8	2.1 ±0.5	0.8 ±0.4

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 9-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of blood chemical examinations

B11-0836

Sex	Exp.group (mg/kg/day)	Number of animals	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	ChE (IU/L)	γ-GTP (IU/L)	T-Cho (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	T-Protein (g/dL)	Albumin (g/dL)	A/G ratio
Male	Vehicle control	5	61 ± 4	20 ± 3	463 ± 96	53 ± 16	0.5 ±0.3	70 ±18	86 ±26	154 ± 15	5.6 ±0.3	2.9 ±0.0	1.08 ±0.10
	5	5	63 ± 5	21 ± 2	505 ± 92	43 ± 12	0.5 ±0.1	60 ±13	79 ±21	157 ± 9	5.5 ±0.2	2.9 ±0.1	1.09 ±0.06
	25	5	70 ±11	24 ± 8	559 ± 90	42 ± 7	0.6 ±0.2	50 ± 6	60 ±21	164 ± 18	5.5 ±0.3	2.9 ±0.3	1.07 ±0.14
	125	5	79* ±15	33** ± 7	727** ± 99	44 ± 5	0.6 ±0.2	44* ± 4	87 ±29	176 ± 15	5.7 ±0.4	2.9 ±0.2	1.07 ±0.08
	Recovery Vehicle control	5	67 ± 3	23 ± 2	321 ± 43	45 ± 5	0.6 ±0.3	62 ±11	76 ±34	143 ± 25	5.8 ±0.1	2.8 ±0.0	0.95 ±0.04
	125	5	67 ± 7	23 ± 2	357 ± 45	35 ± 12	0.6 ±0.3	54 ±12	74 ±25	129 ± 6	5.7 ±0.2	2.7 ±0.1	0.94 ±0.09
Female	Vehicle control	5	71 ±12	18 ± 4	313 ± 76	184 ± 53	0.7 ±0.3	62 ±12	21 ±11	135 ± 15	5.7 ±0.1	3.1 ±0.1	1.15 ±0.04
	5	5	64 ± 6	16 ± 3	260 ± 53	199 ± 35	0.7 ±0.3	67 ±10	26 ± 7	131 ± 24	5.7 ±0.2	3.0 ±0.1	1.14 ±0.02
	25	4	65 ± 8	17 ± 2	246 ± 86	194 ± 49	0.7 ±0.3	69 ±11	38 ±15	156 ± 25	5.8 ±0.2	3.1 ±0.1	1.18 ±0.04
	125	5	62 ± 5	21 ± 2	317 ±114	100* ± 19	1.4* ±0.5	79 ±15	40* ±12	129 ± 17	6.0 ±0.3	3.3** ±0.2	1.25* ±0.09
	Recovery Vehicle control	5	69 ± 7	20 ± 5	169 ± 44	333 ±132	0.9 ±0.1	66 ±11	20 ± 5	130 ± 17	6.2 ±0.3	3.1 ±0.2	1.04 ±0.08
	125	5	71 ± 7	19 ± 1	172 ± 26	230 ± 55	1.0 ±0.2	70 ±13	32 ±15	137 ± 26	6.4 ±0.2	3.3 ±0.1	1.07 ±0.07

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 9-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of blood chemical examinations

B11-0836

Sex	Exp.group (mg/kg/day)	Number of animals	BUN (mg/dL)	Creatinine (mg/dL)	T-Bil (mg/dL)	Ca (mg/dL)	IP (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Male	Vehicle control	5	9.0 ± 2.7	0.25 ±0.02	0.06 ±0.01	9.8 ±0.4	7.6 ±0.6	143 ± 1	4.5 ±0.4	105.4 ± 1.1
	5	5	9.0 ± 1.1	0.22 ±0.02	0.07 ±0.01	9.7 ±0.1	7.8 ±0.1	142 ± 1	4.3 ±0.2	103.6 ± 1.5
	25	5	9.8 ± 1.6	0.22 ±0.03	0.07 ±0.02	9.5 ±0.4	8.4 ±1.2	142 ± 1	4.4 ±0.1	105.0 ± 1.2
	125	5	9.6 ± 0.9	0.24 ±0.03	+0.09 -0.03	9.6 ±0.6	8.2 ±1.0	142 ± 1	4.5 ±0.4	104.5 ± 1.7
	Recovery									
	Vehicle control	5	14.1 ± 1.9	0.26 +0.03	0.07 ±0.01	9.7 ±0.4	7.1 ±0.6	144 ± 1	4.2 ±0.3	106.7 ± 1.1
	125	5	15.1 ± 1.3	-0.25 ±0.02	0.06 ±0.01	9.2 ±0.3	7.1 ±0.4	144 ± 0	4.4 ±0.3	107.4 ± 1.2
Female	Vehicle control	5	10.1 ± 1.9	0.25 ±0.01	0.05 ±0.01	9.6 ±0.2	7.8 ±0.8	142 ± 1	4.4 ±0.2	105.5 ± 0.7
	5	5	9.4 ± 1.0	0.24 ±0.04	0.05 ±0.01	9.9 ±0.1	8.0 ±0.4	143 ± 1	4.3 +0.1	105.9 ± 1.1
	25	4	9.3 ± 0.8	0.24 ±0.01	0.05 ±0.01	9.8 ±0.2	7.9 ±0.6	142 ± 1	-4.3 ±0.2	106.2 ± 0.7
	125	5	9.1 ± 1.5	0.23 ±0.04	0.07* ±0.02	9.9 ±0.4	7.9 ±0.4	142 ± 1	4.4 ±0.2	106.5 ± 0.9
	Recovery									
	Vehicle control	5	15.8 ± 1.3	0.29 ±0.04	0.06 ±0.01	9.3 ±0.2	5.8 ±0.3	143 ± 1	4.0 ±0.2	109.2 ± 0.8
	125	5	17.8 ± 2.8	0.29 ±0.05	0.07 ±0.02	9.7 ±0.3	6.8** ±0.6	143 ± 1	4.3 ±0.5	108.9 ± 1.7

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 10-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836
Summary of urinalyses

Sex	Exp.group (mg/kg/day)	Number of animals	Urine volume (mL)	Sp.Gr.
Male	Vehicle control	5	7 ± 3	1.042 ±0.026
	5	5	4 ± 1	1.057 ±0.024
	25	5	6 ± 3	1.041 ±0.023
	125	5	11 ± 5	1.027 ±0.013
	Recovery			
	Vehicle control	5	14 ± 6	1.027 ±0.013
	125	5	+15 −9	1.030 ±0.012
Female	Vehicle control	5	8 ± 6	1.026 ±0.023
	5	5	+6 −3	1.025 ±0.009
	25	4	4 ± 1	1.040 ±0.010
	125	5	8 ± 3	1.024 ±0.012
	Recovery			
	Vehicle control	5	9 ± 5	1.029 ±0.014
	125	5	+8 −3	1.027 ±0.008

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 10-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of urinalyses

B11-0836

Sex	Exp.group (mg/kg/day)	Number of animals	Color SY	Color Y	Turbidity NT	pH 6.0	pH 6.5	pH 7.0	Protein ±	Protein 1+	Protein 2+	Glucose −	Occult blood −	Occult blood ±
Male	Vehicle control	5	0	5	5	1	4	0	0	3	2	5	5	0
	5	5	0	5	5	2	3	0	0	2	3	5	5	0
	25	5	0	5	5	1	4	0	0	3	2	5	4	1
	125	5	1	4	5	1	4	0	1	4	0	5	5	0
	Recovery													
	Vehicle control	5	3	2	5	0	2	3	2	3	0	5	5	0
	125	5	2	3	5	0	2	3	2	3	0	5	5	0
Female	Vehicle control	5	2	3	5	1	3	1	2	2	1	5	4	1
	5	5	1	4	5	1	3	1	1	3	1	5	5	0
	25	4	0	4	4	2	2	0	0	2	2	4	4	0
	125	5	2	3	5	1	3	1	2	2	1	5	5	0
	Recovery													
	Vehicle control	5	3	2	5	1	3	1	3	2	0	5	5	0
	125	5	2	3	5	1	3	1	3	2	0	5	5	0

SY, Slightly yellow.
Y, Yellow.
NT, Not turbid.

Table 10-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of urinalyses (Urinary sediment)

B11-0836

Sex	Exp.group (mg/kg/day)	Number of animals	Red blood cells[a]	White blood cells[a]		Epithelial cells[a]		Casts[b]	Crystals[c]			
			0	0	1-5	0	1-5	0	−	±	+	++
Male	Vehicle control	5	5	4	1	0	5	5	1	1	1	2
	5	0	-	-	-	-	-	-	-	-	-	-
	25	0	-	-	-	-	-	-	-	-	-	-
	125	5	5	5	0	0	5	5	2	2	1	0
	Recovery											
	Vehicle control	0	-	-	-	-	-	-	-	-	-	-
	125	0	-	-	-	-	-	-	-	-	-	-
Female	Vehicle control	5	5	3	2	1	4	5	3	2	0	0
	5	0	-	-	-	-	-	-	-	-	-	-
	25	0	-	-	-	-	-	-	-	-	-	-
	125	5	5	4	1	2	3	5	4	1	0	0
	Recovery											
	Vehicle control	0	-	-	-	-	-	-	-	-	-	-
	125	0	-	-	-	-	-	-	-	-	-	-

a) Number of cells/10 views (×400).
b) Number of casts/18×18 mm^2.
c) Incidence of crystals/18×18 mm^2.

Table 11 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of absolute organ weights

B11-0836

Sex	Exp.group (mg/kg/day)	Number of animals	Liver (g)	Heart (g)	Kidney (g)	Testis (g)	Epididymis (g)	Ovary (mg)	Brain (g)	Spleen (g)	Thymus (mg)	Adrenal (mg)	Body weight a) (g)
Male	Vehicle control	5	10.80 ± 2.27	1.03 ± 0.08	2.17 ± 0.17	2.77 ± 0.24	0.66 ± 0.06	- -	1.88 ± 0.06	0.55 ± 0.15	485.9 ± 99.2	52.3 ± 5.5	319.3 ± 33.4
	5	5	10.36 ± 1.00	1.05 ± 0.07	2.31 ± 0.21	2.67 ± 0.10	0.66 ± 0.04	- -	2.00 ± 0.13	0.52 ± 0.07	493.1 ± 47.2	48.9 ± 5.3	314.2 ± 20.3
	25	5	10.37 ± 1.57	1.06 ± 0.10	2.35 ± 0.38	2.50 ± 0.82	0.66 ± 0.11	- -	1.92 ± 0.06	0.58 ± 0.06	454.0 ± 97.9	43.4 ± 6.1	297.3 ± 30.6
	125	5	12.22 ± 0.91	1.03 ± 0.07	2.44 ± 0.16	2.85 ± 0.27	0.65 ± 0.03	- -	1.94 ± 0.03	0.49 ± 0.13	464.4 ± 128.1	45.6 ± 10.5	301.1 ± 20.8
	Recovery												
	Vehicle control	5	9.66 ± 2.19	1.06 ± 0.06	2.39 ± 0.19	2.89 ± 0.21	0.98 ± 0.03	- -	2.02 ± 0.05	0.57 ± 0.08	405.4 ± 75.8	45.6 ± 3.8	348.5 ± 30.3
	125	5	8.76 ± 0.22	1.07 ± 0.03	2.45 ± 0.20	3.20* ± 0.15	0.99 ± 0.03	- -	1.97 ± 0.05	0.58 ± 0.07	451.8 ± 99.4	46.9 ± 8.5	334.6 ± 8.5
Female	Vehicle control	5	6.27 ± 0.65	0.76 ± 0.03	1.44 ± 0.10	- -	- -	73.9 ± 8.2	1.83 ± 0.02	0.37 ± 0.05	396.6 ± 78.5	53.8 ± 4.8	202.8 ± 10.5
	5	5	6.48 ± 1.04	0.83 ± 0.09	1.59 ± 0.15	- -	- -	70.8 ± 20.5	1.81 ± 0.03	0.38 ± 0.04	434.8 ± 80.4	56.8 ± 7.5	211.8 ± 22.0
	25	4	7.31 ± 0.73	0.76 ± 0.02	1.56 ± 0.07	- -	- -	72.2 ± 1.4	1.88 ± 0.07	0.44 ± 0.07	435.5 ± 25.3	57.0 ± 5.4	214.0 ± 11.4
	125	5	8.35** ± 0.94	0.78 ± 0.06	1.72* ± 0.17	- -	- -	73.8 ± 7.7	1.85 ± 0.05	0.38 ± 0.04	464.4 ± 74.7	56.1 ± 9.8	209.3 ± 21.0
	Recovery												
	Vehicle control	5	6.11 ± 0.73	0.82 + 0.09	1.60 ± 0.13	- -	- -	74.6 ± 16.4	1.85 ± 0.04	0.45 ± 0.03	364.6 ± 59.3	56.8 ± 10.5	229.5 ± 16.8
	125	5	6.59 ± 0.66	- 0.82 ± 0.07	1.58 ± 0.11	- -	- -	71.5 ± 8.3	1.92* ± 0.04	0.43 ± 0.02	401.6 ± 82.1	62.9 ± 8.8	221.9 ± 30.7

Mean ±S.D.
a) Statistical analysis was not applied.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 12 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of relative organ weights

B11-0836

Sex	Exp. group (mg/kg/day)	Number of animals	Liver (g/100g)	Heart (g/100g)	Kidney (g/100g)	Testis (g/100g)	Epididymis (g/100g)	Ovary (mg/100g)	Brain (g/100g)	Spleen (g/100g)	Thymus (mg/100g)	Adrenal (mg/100g)	Body weight [a] (g)
Male	Vehicle control	5	3·36 ±0·34	0·32 ±0·01	0·68 ±0·05	0·88 ±0·12	0·21 ±0·03	- -	0·60 ±0·06	0·17 ±0·03	152.6 ± 29.4	16.5 ± 2.3	319.3 ± 33.4
	5	5	3·29 ±0·20	0·34 ±0·03	0·74 ±0·05	0·85 ±0·05	0·21 ±0·02	- -	0·64 ±0·05	0·17 ±0·02	157.3 ± 15.4	15.6 ± 1.3	314.2 ± 20.3
	25	5	3·47 ±0·20	0·36 ±0·02	0·79* ±0·05	0·83 ±0·25	0·22 ±0·03	- -	0·65 ±0·05	0·20 ±0·04	151.4 ± 21.5	14.6 ± 1.6	297.3 ± 30.6
	125	5	4·06** ±0·25	0·34 ±0·01	0·81** ±0·07	0·95 ±0·09	0·22 ±0·03	- -	0·65 ±0·04	0·16 ±0·04	153.5 ± 34.9	15.3 ± 4.4	301.1 ± 20.8
	Recovery Vehicle control	5	2·75 ±0·41	0·30 ±0·01	0·69 ±0·07	0·83 ±0·06	0·28 ±0·02	- -	0·58 ±0·04	0·16 ±0·02	115.8 ± 14.9	13.2 ± 1.2	348.5 ± 30.3
	125	5	2·62 ±0·08	0·32* ±0·01	0·73 ±0·07	0·96** ±0·05	0·30 ±0·01	- -	0·59 ±0·01	0·18 ±0·03	134.8 ± 28.7	14.0 ± 2.4	334.6 ± 8.5
Female	Vehicle control	5	3·09 ±0·25	0·38 ±0·03	0·71 ±0·04	- -	- -	36·6 ± 5.2	0·90 ±0·04	0·18 ±0·01	194.9 ± 32.1	26.6 ± 2.9	202.8 ± 10.5
	5	5	3·05 ±0·18	0·39 ±0·02	0·75 ±0·05	- -	- -	33·0 ± 6.2	0·86 ±0·08	0·18 ±0·01	205.3 ± 34.5	26.8 ± 2.6	211.8 ± 22.0
	25	4	3·42 ±0·29	0·35 ±0·01	0·73 ±0·03	- -	- -	33·8 ± 1.6	0·88 ±0·02	0·21 ±0·03	204.5 ± 23.1	26.7 ± 3.0	214.0 ± 11.4
	125	5	3·98** ±0·10	0·38 ±0·01	0·82** ±0·04	- -	- -	35·4 ± 4.6	0·89 ±0·10	0·18 ±0·00	222.1 ± 30.2	26.8 ± 3.7	209.3 ± 21.0
	Recovery Vehicle control	5	2·66 ±0·13	0·36 ±0·03	0·70 ±0·06	- -	- -	32·3 ± 5.4	0·81 ±0·05	0·20 ±0·02	158.4 ± 17.8	24.7 ± 3.3	229.5 ± 16.8
	125	5	2·99* ±0·26	0·38 ±0·04	0·72 ±0·09	- -	- -	32·8 ± 6.1	0·88 ±0·13	0·20 ±0·03	181.7 ± 29.8	28.7 ± 5.4	221.9 ± 30.7

Mean ±S.D.
a) Statistical analysis was not applied.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 13 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of macroscopic examinations

Findings	Male						Female							
	Vehicle control	Vehicle control (Recovery)	5	25	125	125 (Recovery)	Vehicle control	Vehicle control (Recovery)	5	25		125	125 (Recovery)	(mg/kg/day)
	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	fd	ta	ta	
	5[a)]	5	5	5	5	5	5	5	5	4	1	5	5	
No abnormalities detected	5	5	5	4	0	0	5	5	5	4	0	0	0	
Lung														
Dark reddish change	0	0	0	0	0	0	0	0	0	0	1	0	0	
Oral cavity														
Mottled teeth	0	0	0	0	2	5	0	0	0	0	0	2	5	
Rough surface of incisor	0	0	0	0	0	0	0	0	0	0	0	0	1	
Liver														
Enlargement	0	0	0	0	4	0	0	0	0	0	0	5	0	
Testis														
Small	0	0	0	1	0	0								
Softening	0	0	0	1	0	0								
Thyroid														
Aplasia of left lobe	0	0	0	0	0	0	0	0	0	0	0	0	1	

ta, terminal autopsy; fd, found dead.

a) Number of animals examined.

Table 14-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female							(mg/kg/day)
		Vehicle control	Vehicle control (Recovery)	5	25	125	125 (Recovery)	Vehicle control	Vehicle control (Recovery)	5	25		125	125 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	fd	ta	ta	
		5[a]	5	5	5	5	5	5	5	5	4	1	5	5	
Trachea															
No abnormalities detected		5/5[b]	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Lung															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	0/1	5/5	—	
Congestion	++	0/5	—	—	—	0/5	—	0/5	—	—	—	1/1	0/5	—	
Edema	+	0/5	—	—	—	0/5	—	0/5	—	—	—	1/1	0/5	—	
Incisor															
No abnormalities detected		5/5	5/5	5/5	5/5	2/5	3/5	5/5	5/5	5/5	4/4	1/1	3/5	2/5	
Cyst formation in papillary layer	+	0/5	0/5	0/5	0/5	1/5	0/5	0/5	0/5	0/5	0/4	0/1	1/5	0/5	
Decreased iron pigments of ameloblasts at maturation stage	+	0/5	0/5	0/5	0/5	3/5	0/5	0/5	0/5	0/5	0/4	0/1	2/5	1/5	
Irregular alignment of ameloblasts at maturation stage	+	0/5	0/5	0/5	0/5	1/5	2/5	0/5	0/5	0/5	0/4	0/1	1/5	3/5	
Irregular alignment of papillary layer	+	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/4	0/1	0/5	1/5	
Forestomach															
No abnormalities detected		5/5	—	—	—	5/5	—	4/5	—	—	—	—	4/5	—	
Necrosis of squamous epithelium in limiting ridge	±	0/5	—	—	—	0/5	—	1/5	—	—	—	—	0/5	—	
	+	0/5	—	—	—	0/5	—	0/5	—	—	—	—	1/5	—	
Glandular stomach															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	

ta, terminal autopsy; fd, found dead.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.
±, very slight; +, slight; ++, moderate.

Table 14-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female							(mg/kg/day)
		Vehicle control	Vehicle control (Recovery)	5	25	125	125 (Recovery)	Vehicle control	Vehicle control (Recovery)	5	25		125	125 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	fd	ta	ta	
		5[a)]	5	5	5	5	5	5	5	5	4	1	5	5	
Duodenum															
No abnormalities detected		5/5[b)]	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Jejunum															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Ileum															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Cecum															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Colon															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Rectum															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Liver															
No abnormalities detected		5/5	5/5	5/5	5/5	0/5	5/5	5/5	5/5	5/5	4/4	1/1	3/5	5/5	
Diffuse hypertrophy of hepatocytes	+	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/4	0/1	2/5	0/5	
Periportal hypertrophy of hepatocytes	+	0/5	0/5	0/5	0/5	5/5	0/5	0/5	0/5	0/5	0/4	0/1	0/5	0/5	
Periportal prominent nucleoli of hepatocytes	+	0/5	0/5	0/5	0/5	3/5	0/5	0/5	0/5	0/5	0/4	0/1	0/5	0/5	
Single cell necrosis of hepatocytes	+	0/5	0/5	0/5	0/5	1/5	0/5	0/5	0/5	0/5	0/4	0/1	0/5	0/5	

ta, terminal autopsy; fd, found dead.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.
+, slight.

Table 14-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female							(mg/kg/day)
		Vehicle control	Vehicle control (Recovery)	5	25	125	125 (Recovery)	Vehicle control	Vehicle control (Recovery)	5	25		125	125 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	fd	ta	ta	
		5[a)]	5	5	5	5	5	5	5	5	4	1	5	5	
Heart															
No abnormalities detected		4/5[b)]	5/5	—	—	4/5	5/5	5/5	—	—	—	—	5/5	—	
Focal myocarditis	+	1/5	0/5	—	—	1/5	0/5	0/5	—	—	—	—	0/5	—	
Kidney															
No abnormalities detected		2/5	5/5	5/5	5/5	3/5	3/5	3/5	3/5	4/5	4/4	1/1	4/5	5/5	
Ballooning of tubular epithelium	+	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/4	0/1	1/5	0/5	
Basophilic tubules	+	2/5	0/5	0/5	0/5	1/5	1/5	0/5	0/5	0/5	0/4	0/1	0/5	0/5	
Dilatation of tubules	+	0/5	0/5	0/5	0/5	1/5	0/5	0/5	0/5	0/5	0/4	0/1	0/5	0/5	
Focal hyperplasia of tubular epithelium	+	1/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/4	0/1	0/5	0/5	
Mineralization in cortico-medullary junction	+	0/5	0/5	0/5	0/5	0/5	0/5	2/5	2/5	1/5	0/4	0/1	0/5	0/5	
Solitary cyst in medulla	+	0/5	0/5	0/5	0/5	0/5	1/5	0/5	0/5	0/5	0/4	0/1	0/5	0/5	
Urinary bladder															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Testis															
No abnormalities detected		5/5	5/5	—	0/1	5/5	5/5								
Diffuse atrophy of seminiferous tubules	+++	0/5	0/5	—	1/1	0/5	0/5								
Leydig cell hyperplasia	++	0/5	0/5	—	1/1	0/5	0/5								
Epididymis															
No abnormalities detected		5/5	—	—	—	5/5	—								

ta, terminal autopsy; fd, found dead.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.
+, slight; ++, moderate; +++, severe.

Table 14-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female							(mg/kg/day)
		Vehicle control	Vehicle control (Recovery)	5	25	125	125 (Recovery)	Vehicle control	Vehicle control (Recovery)	5	25		125	125 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	fd	ta	ta	
		5[a)]	5	5	5	5	5	5	5	5	4	1	5	5	
Prostate															
No abnormalities detected		4/5[b)]	—	—	—	5/5	—								
Round cell infiltration	+	1/5	—	—	—	0/5	—								
Seminal vesicle															
No abnormalities detected		5/5	—	—	—	5/5	—								
Ovary															
No abnormalities detected								5/5	—	—	—	—	5/5	—	
Uterus															
No abnormalities detected								4/5	—	—	—	—	5/5	—	
Endometrial atrophy	+							1/5	—	—	—	—	0/5	—	
Vagina															
No abnormalities detected								3/5	—	—	—	—	5/5	—	
Mucification of epithelium	++							1/5	—	—	—	—	0/5	—	
Vaginitis	+							1/5	—	—	—	—	0/5	—	
Cerebrum															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	5/5	—	—	—	5/5	5/5	
Cerebellum															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	5/5	—	—	—	5/5	5/5	
Pons															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	5/5	—	—	—	5/5	5/5	
Spinal cord															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Sciatic nerve															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	

ta, terminal autopsy; fd, found dead.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.
+, slight; ++, moderate.

Table 14-5 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female							
		Vehicle control	Vehicle control (Recovery)	5	25	125	125 (Recovery)	Vehicle control	Vehicle control (Recovery)	5	25		125	125 (Recovery)	(mg/kg/day)
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	fd	ta	ta	
		5[a]	5	5	5	5	5	5	5	5	4	1	5	5	
Bone marrow															
No abnormalities detected		5/5[b]	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Axillar lymph node															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Mesenteric lymph node															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Spleen															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Thymus															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Pituitary gland															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Thyroid															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	0/1	
Aplasia of left lobe		0/5	—	—	—	0/5	—	0/5	—	—	—	—	0/5	1/1	
Parathyroid															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Adrenal															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	
Eye ball															
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	—	5/5	—	

ta, terminal autopsy; fd, found dead.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.

Addendum I-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Clinical signs of individual animals
Vehicle control

Signs	Sex	Administration Period 1	2	3	4	Recovery Period 1	2	(week)
No abnormalities detected	Male	2,[a] 4, 5, 6, 7, 8, 9	1, 2, 3, 4, 5, 6, 7, 8, 9, 10	1, 2, 3, 4, 5, 6, 7, 8, 9	1, 2, 3, 4, 5, 6, 7, 8, 9, 10	6, 7, 8, 9, 10	6, 7, 8, 9, 10	
	Female	31, 32, 33, 34, 35, 36, 37, 38, 39, 40	31, 32, 33, 34, 35, 36, 37, 38, 39, 40	31, 32, 33, 34, 35, 36, 37, 38, 39, 40	31, 32, 33, 34, 35, 36, 37, 38, 39, 40	36, 37, 38, 39, 40	36, 37, 38, 39, 40	
Salivation	Male	1, 3, 10		10				
	Female							

a) Animal number.

Addendum 1-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Clinical signs of individual animals
5 mg/kg/day

Signs	Sex	Administration Period				Recovery Period		
		1	2	3	4	1	2	(week)
No abnormalities detected	Male	11,[a] 12, 15	11,12, 13, 14, 15	11,12, 13, 14, 15	11,12, 13, 14, 15			
	Female	42,43, 44	41, 42, 43, 44, 45	42,43, 44, 45	42,43, 44,45			
Salivation	Male	13, 14						
	Female	41, 45		41	41			

a) Animal number.

Addendum 1-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Clinical signs of individual animals
25 mg/kg/day

Signs	Sex	Administration Period 1	2	3	4	Recovery Period 1	2	(week)
No abnormalities detected	Male	16,[a] 17, 18, 19, 20	16, 17, 18, 19	18, 19	16, 18, 19, 20			
	Female	47		48, 50	48			
Salivation	Male		20	16, 17, 20	17			
	Female	46, 48, 49, 50	46, 47, 48, 49, 50	46, 47, 49	46, 47, 49, 50			
Decreased spontaneous locomotion	Male				17			
	Female							
Death	Male							
	Female				47			

a) Animal number.

Addendum I-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Clinical signs of individual animals
125 mg/kg/day

Signs	Sex	Administration Period 1	2	3	4	Recovery Period 1	2 (week)
No abnormalities detected	Male	23[a)]		22			
	Female	59, 60	58			59	
Salivation	Male	21, 22, 24, 25, 26, 27, 28, 29, 30	21,22, 23,24, 25,26, 27, 28, 29,30	21,23, 24,25, 26,27, 28,29, 30	21,22, 23,24, 25, 26, 27, 28, 29,30		
	Female	51, 52, 53, 54, 55, 56, 57, 58	51, 52, 53, 54, 55, 56, 57, 60	51, 52, 53, 54, 55, 56, 57, 58, 59, 60	51,52, 53, 54, 55, 56, 57, 58, 59, 60		
Decreased spontaneous locomotion	Male				24,25, 28,29		
	Female		53, 54, 56	56, 59, 60	53, 54, 56		
Staining lower abdomen	Male						
	Female		59		58		
Swelling of third digit in left forelimb	Male		29	29	29	29	
	Female						
White turbid urine	Male			29			
	Female						
Exudate(neck)	Male		28	28	28	28	
	Female						
Scab formation(neck)	Male					28	
	Female						
Mottled teeth	Male					26, 27, 28,29, 30	26,27, 28, 29, 30
	Female					56, 57, 58,60	56, 57, 58,59, 60
Whitish change of teeth	Male					26,28, 29, 30	26, 28, 29, 30
	Female					56, 57, 60	56, 57, 58,59, 60
Surface delamination of tip lower inisores	Male						
	Female						56, 57

a) Animal number.

Addendum 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	+1
		2	0	0
		3	0	0
		4	0	0
		5	0	0
		6	0	0
		7	0	0
		8	0	0
		9	0	0
		10	0	+1
	5	11	0	0
		12	0	+1
		13	0	0
		14	0	0
		15	0	0
	25	16	0	0
		17	0	0
		18	0	0
		19	0	0
		20	0	0
	125	21	0	0
		22	0	0
		23	0	0
		24	0	0
		25	0	0
		26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	+1	0

Addendum 2-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	0
		33	0	0
		34	0	+1
		35	0	0
		36	0	0
		37	0	0
		38	0	0
		39	0	0
		40	0	0
	5	41	0	+1
		42	0	0
		43	0	0
		44	0	0
		45	+1	+1
	25	46	0	0
		47	0	+1
		48	0	+1
		49	0	0
		50	0	0
	125	51	0	0
		52	0	0
		53	0	0
		54	0	0
		55	0	0
		56	0	0
		57	0	0
		58	0	0
		59	0	0
		60	0	0

Addendum 2-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	0
		2	0	0
		3	0	+1
		4	0	0
		5	0	0
		6	0	0
		7	0	+1
		8	0	0
		9	0	0
		10	0	+1
	5	11	0	0
		12	0	0
		13	0	0
		14	0	0
		15	0	+1
	25	16	0	0
		17	0	0
		18	0	0
		19	0	0
		20	0	+1
	125	21	0	0
		22	0	0
		23	0	0
		24	0	0
		25	0	0
		26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-4 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	+1
		33	0	0
		34	0	0
		35	0	0
		36	0	0
		37	0	0
		38	0	0
		39	0	+1
		40	0	0
	5	41	0	+1
		42	0	0
		43	0	0
		44	0	0
		45	0	+1
	25	46	0	0
		47	0	0
		48	0	+1
		49	0	0
		50	0	0
	125	51	0	0
		52	0	0
		53	-1	0
		54	0	+1
		55	0	0
		56	0	0
		57	0	0
		58	+1	0
		59	0	0
		60	0	0

Addendum 2-5 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	0
		2	0	0
		3	0	0
		4	0	0
		5	0	+1
		6	0	0
		7	0	0
		8	0	0
		9	0	0
		10	0	0
	5	11	0	+1
		12	0	0
		13	0	0
		14	0	0
		15	0	0
	25	16	0	0
		17	0	0
		18	0	0
		19	0	0
		20	0	0
	125	21	0	0
		22	0	0
		23	0	0
		24	0	0
		25	0	0
		26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-6 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	+1
		33	0	0
		34	0	+1
		35	0	+1
		36	0	0
		37	0	0
		38	0	0
		39	0	+1
		40	0	0
	5	41	0	0
		42	0	0
		43	0	0
		44	0	0
		45	0	0
	25	46	0	0
		47	0	+1
		48	0	+1
		49	0	0
		50	0	+1
	125	51	0	0
		52	0	0
		53	0	0
		54	0	+1
		55	0	0
		56	0	0
		57	0	0
		58	0	0
		59	0	0
		60	0	0

Addendum 2-7 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 3)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	+1
		2	0	0
		3	0	0
		4	0	0
		5	0	+1
		6	0	0
		7	0	0
		8	0	0
		9	0	0
		10	0	0
	5	11	0	0
		12	0	0
		13	0	0
		14	0	0
		15	0	0
	25	16	0	0
		17	0	0
		18	0	0
		19	0	0
		20	0	0
	125	21	0	0
		22	0	0
		23	0	0
		24	0	0
		25	0	0
		26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-8 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 3)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	0
		33	0	0
		34	0	+1
		35	0	0
		36	0	0
		37	0	+1
		38	0	0
		39	0	+1
		40	0	0
	5	41	0	+1
		42	0	0
		43	0	+1
		44	0	0
		45	0	0
	25	46	0	0
		47	0	0
		48	0	0
		49	0	0
		50	0	0
	125	51	0	0
		52	0	0
		53	0	0
		54	0	0
		55	0	0
		56	0	0
		57	0	0
		58	0	0
		59	0	0
		60	0	0

Addendum 2-9 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 4)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	0
		2	0	0
		3	0	+1
		4	0	+1
		5	0	0
		6	0	0
		7	0	0
		8	0	0
		9	0	0
		10	0	0
	5	11	0	0
		12	0	0
		13	0	0
		14	0	0
		15	0	+1
	25	16	0	0
		17	0	0
		18	0	0
		19	0	0
		20	0	0
	125	21	0	0
		22	0	0
		23	0	0
		24	0	0
		25	0	0
		26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-10 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 4)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	0
		33	0	0
		34	0	+1
		35	0	0
		36	0	0
		37	0	+1
		38	0	0
		39	0	+1
		40	0	0
	5	41	0	0
		42	0	0
		43	0	+1
		44	0	0
		45	0	0
	25	46	0	0
		47[a)]	—	—
		48	0	+1
		49	0	0
		50	0	0
	125	51	0	0
		52	0	0
		53	0	0
		54	0	0
		55	0	0
		56	0	0
		57	0	0
		58	0	0
		59	0	0
		60	0	0

a) Dead animal

Addendum 2-11 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	6	0	0
		7	0	0
		8	0	0
		9	0	0
		10	0	0
	125	26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-12 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	36	0	0
		37	0	0
		38	0	0
		39	0	+1
		40	0	0
	125	56	0	0
		57	0	0
		58	0	0
		59	0	0
		60	0	0

Addendum 2-13 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	6	0	0
		7	0	0
		8	0	0
		9	0	0
		10	0	+1
	125	26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-14 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	36	0	0
		37	0	+1
		38	0	0
		39	0	+1
		40	0	0
	125	56	0	0
		57	0	+1
		58	0	0
		59	0	0
		60	0	0

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	5	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	25	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	125	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Detailed clinical observations of individual animals (Predosing)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	5	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	25	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	125	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-17 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	5	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	25	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	125	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-18 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	5	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	25	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	125	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-19 Twenty-eight-day repeated-dose oral toxicity study in rats BII-0836

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	5	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	25	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	125	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-20 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	5	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	25	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	125	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-21 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	5	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	25	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	125	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-22 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	5	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	25	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	125	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-23 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	5	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	25	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	125	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	5	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	25	46	0	-	-	-	-	-	-
		47[a)]	—	—	—	—	—	—	—
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	125	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

a) Dead animal.

Addendum 2-25 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	125	26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-26 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	125	56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-27 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	125	26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	125	56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-29 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	5	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	25	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	125	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-30 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Predosing)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	5	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	25	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	125	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-31 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	5	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	25	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	125	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-32 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	5	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	25	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	125	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-33 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	5	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	25	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	125	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-34 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 2)

Sex	Exp.group (mg/kg/day)	AnimalNo.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	5	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	25	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	125	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-35 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	5	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	25	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	125	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-36 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	5	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	25	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	125	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-37 Twenty-eight-day repeated-dose oral toxicity study in rats BII-0836

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	5	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	25	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	125	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-38 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	5	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	25	46	-	-	-	0	-	-
		47[a)]	—	—	—	—	—	—
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	125	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

a) Dead animal.

Addendum 2-39 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	125	26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-40 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	125	56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-41 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	125	26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-42 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	125	56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-43 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	AnimalNo.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	0	0	-	-
	125	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	+1	0	-	-
		25	0	0	0	-	-
		26	0	+1	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-44 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Predosing)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	+1	0	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	+1	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	125	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	+1	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-45 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	0	-	-
		17	0	+1	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	0	0	-	-
	125	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-46 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	+1	0	-	-
		39	0	+1	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	+1	0	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	125	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-47 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	+1	0	-	-
	125	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	+1	0	-	-
		30	0	0	0	-	-

Addendum 2-48 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	+1	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	125	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-49 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	+1	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	0	-	-
		17	0	-1	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	0	0	-	-
	125	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-50 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	+1	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	125	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-51 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	0	0	-	-
	125	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-52 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	25	46	0	0	0	-	-
		47[a)]	—	—	—	—	—
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	125	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

a) Dead animal.

Addendum 2-53 Twenty-eight-day repeated-dose oral toxicity study in rats BI1-0836

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	125	26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-54 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	125	56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-55 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	6	0	+1	0	-	-
		7	0	+1	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	125	26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	+1	0	-	-
		30	0	0	0	-	-

Addendum 2-56 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	125	56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	+1	0	-	-
		60	0	0	0	-	-

Addendum 2-57 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	4	-	-
		3	0	1	0	-	-
		4	0	0	1	-	-
		5	0	1	3	-	-
		6	0	0	0	-	-
		7	0	0	1	-	-
		8	0	0	2	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	1	-	-
		17	0	0	3	-	-
		18	0	0	0	-	-
		19	0	0	9	-	-
		20	0	0	1	-	-
	125	21	0	0	2	-	-
		22	0	0	0	-	-
		23	0	3	0	-	-
		24	0	2	3	-	-
		25	0	1	1	-	-
		26	0	0	1	-	-
		27	0	0	4	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-58 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Predosing)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	1	-	-
		32	0	0	2	-	-
		33	0	0	2	-	-
		34	0	0	1	-	-
		35	0	0	0	-	-
		36	0	0	2	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	6	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	1	-	-
		45	0	0	0	-	-
	25	46	0	0	7	-	-
		47	0	0	1	-	-
		48	0	0	1	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	125	51	0	0	0	-	-
		52	0	0	1	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	1	-	-
		59	0	0	0	-	-
		60	0	0	1	-	-

Addendum 2-59 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	1	-	-
		5	0	3	2	-	-
		6	0	0	1	-	-
		7	0	1	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	1	0	-	-
		17	0	0	0	-	-
		18	0	0	2	-	-
		19	0	0	1	-	-
		20	0	2	4	-	-
	125	21	0	0	1	-	-
		22	0	2	0	-	-
		23	0	2	0	-	-
		24	0	0	0	-	-
		25	0	5	1	-	-
		26	0	2	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-60 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	2	-	-
		33	0	0	0	-	-
		34	0	0	1	-	-
		35	0	0	0	-	-
		36	0	0	1	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	1	-	-
	5	41	0	0	2	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	1	-	-
		45	0	0	0	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	2	-	-
	125	51	0	0	4	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	1	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	3	-	-
		59	0	0	1	-	-
		60	0	0	1	-	-

Addendum 2-61 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	0	0	-	-
		2	0	1	1	-	-
		3	0	0	2	-	-
		4	0	2	1	-	-
		5	0	3	1	-	-
		6	0	0	0	-	-
		7	0	1	0	-	-
		8	0	0	2	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	2	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	2	2	-	-
		17	0	0	0	-	-
		18	0	0	1	-	-
		19	0	0	4	-	-
		20	0	1	1	-	-
	125	21	0	4	1	-	-
		22	0	0	0	-	-
		23	0	1	5	-	-
		24	0	0	1	-	-
		25	0	0	1	-	-
		26	0	2	3	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-62 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	3	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	125	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	2	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	3	-	-

Addendum 2-63 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	0	1	-	-
		2	0	0	5	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	4	2	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	1	2	-	-
		9	0	0	3	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	1	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	1	1	-	-
		17	0	0	1	-	-
		18	0	1	2	-	-
		19	0	3	9	-	-
		20	0	2	3	-	-
	125	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	3	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	2	-	-

Addendum 2-64 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	2	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	1	-	-
	125	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-65 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	0	0	-	-
		2	0	1	4	-	-
		3	0	2	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	1	-	-
		7	0	0	0	-	-
		8	0	0	2	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	2	0	-	-
		17	0	0	0	-	-
		18	0	3	3	-	-
		19	0	1	1	-	-
		20	0	2	2	-	-
	125	21	0	1	1	-	-
		22	0	0	0	-	-
		23	0	0	1	-	-
		24	0	0	0	-	-
		25	0	0	2	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	2	0	-	-

Addendum 2-66 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	3	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	1	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	25	46	0	0	0	-	-
		47[a)]	—	—	—	—	—
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	125	51	0	0	1	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	1	-	-
		59	0	0	0	-	-
		60	0	0	1	-	-

a) Dead animal.

Addendum 2-67 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	6	0	0	0	-	-
		7	0	1	0	-	-
		8	0	0	1	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	125	26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-68 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	1	-	-
		40	0	0	0	-	-
	125	56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	5	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-69 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	6	0	0	1	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	125	26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-70 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	125	56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 3-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Reflex of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Sensorimotor function				
			Approach contact/ touch response	Pinna response	Pain response (tail pinch)	Pupillary reflex	Air righting reflex
Male	Vehicle control	1	0	0	0	+	+
		2	0	0	0	+	+
		3	0	0	0	+	+
		4	0	0	0	+	+
		5	0	0	0	+	+
		6	0	0	0	+	+
		7	0	0	0	+	+
		8	0	0	0	+	+
		9	0	0	0	+	+
		10	0	0	0	+	+
	5	11	0	0	0	+	+
		12	0	0	0	+	+
		13	0	0	0	+	+
		14	0	0	0	+	+
		15	0	0	0	+	+
	25	16	0	0	0	+	+
		17	0	0	0	+	+
		18	0	0	0	+	+
		19	0	0	0	+	+
		20	0	0	0	+	+
	125	21	0	0	0	+	+
		22	0	0	0	+	+
		23	0	0	0	+	+
		24	0	0	0	+	+
		25	0	0	0	+	+
		26	0	0	0	+	+
		27	0	0	0	+	+
		28	0	0	0	+	+
		29	0	0	0	+	+
		30	0	0	0	+	+

Addendum 3-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Reflex of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Sensorimotor function				
			Approach contact/ touch response	Pinna response	Pain response (tail pinch)	Pupillary reflex	Air righting reflex
Female	Vehicle control	31	0	0	0	+	+
		32	0	0	0	+	+
		33	0	0	0	+	+
		34	0	0	0	+	+
		35	0	0	0	+	+
		36	0	0	0	+	+
		37	0	0	0	+	+
		38	0	0	0	+	+
		39	0	0	0	+	+
		40	0	0	0	+	+
	5	41	0	0	0	+	+
		42	0	0	0	+	+
		43	0	0	0	+	+
		44	0	0	0	+	+
		45	0	0	0	+	+
	25	46	0	0	0	+	+
		47[a)]	—	—	—	—	—
		48	0	0	0	+	+
		49	0	0	0	+	+
		50	0	0	0	+	+
	125	51	0	0	0	+	+
		52	0	0	0	+	+
		53	0	0	0	+	+
		54	0	0	0	+	+
		55	0	0	0	+	+
		56	0	0	0	+	+
		57	0	0	0	+	+
		58	0	0	0	+	+
		59	0	0	0	+	+
		60	0	0	0	+	+

a) Dead animal.

Addendum 4-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Grip strength of individual animals (week 4)

Sex	Exp.group (mg/kg/day)	Animal No.	Forelimb (g)			Hindlimb (g)		
			Trial 1	Trial 2	Mean	Trial 1	Trial 2	Mean
Male	Vehicle control	1	644	863	754	415	570	493
		2	1179	990	1085	299	338	319
		3	1161	957	1059	444	385	415
		4	944	588	766	410	601	506
		5	919	805	862	536	629	583
		6	665	649	657	529	637	583
		7	738	1054	896	494	415	455
		8	516	985	751	658	625	642
		9	643	617	630	585	687	636
		10	794	969	882	428	492	460
	5	11	889	785	837	491	359	425
		12	1033	761	897	323	448	386
		13	635	891	763	492	400	446
		14	748	757	753	353	858	606
		15	847	863	855	636	631	634
	25	16	771	901	836	390	328	359
		17	881	889	885	504	837	671
		18	1036	1089	1063	372	449	411
		19	1173	1084	1129	527	398	463
		20	980	1060	1020	440	494	467
	125	21	613	1127	870	468	430	449
		22	1069	939	1004	322	431	377
		23	906	839	873	598	602	600
		24	948	809	879	546	511	529
		25	1060	740	900	266	399	333
		26	829	1116	973	274	347	311
		27	1065	515	790	316	297	307
		28	1164	1012	1088	720	766	743
		29	951	940	946	385	313	349
		30	804	825	815	544	451	498

Addendum 4-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836

Grip strength of individual animals (week 4)

Sex	Exp.group (mg/kg/day)	Animal No.	Forelimb (g)			Hindlimb (g)		
			Trial 1	Trial 2	Mean	Trial 1	Trial 2	Mean
Female	Vehicle control	31	1045	817	931	318	636	477
		32	415	661	538	354	443	399
		33	795	946	871	310	536	423
		34	515	346	431	584	671	628
		35	506	406	456	394	350	372
		36	889	984	937	452	302	377
		37	858	924	891	360	273	317
		38	418	415	417	619	634	627
		39	623	618	621	486	503	495
		40	924	662	793	645	674	660
	5	41	909	810	860	379	556	468
		42	1021	676	849	368	413	391
		43	738	545	642	293	281	287
		44	1149	826	988	220	386	303
		45	627	791	709	554	552	553
	25	46	514	609	562	348	311	330
		47[a)]	—	—	—	—	—	—
		48	555	848	702	417	565	491
		49	1058	671	865	583	567	575
		50	728	751	740	265	207	236
	125	51	785	780	783	390	339	365
		52	839	1022	931	392	483	438
		53	494	605	550	532	647	590
		54	566	1054	810	364	304	334
		55	504	538	521	224	339	282
		56	830	1005	918	549	485	517
		57	728	869	799	364	357	361
		58	855	834	845	307	498	403
		59	425	666	546	502	606	554
		60	670	627	649	311	591	451

a) Dead animal

Addendum 5-1 :ated-dose oral toxicity study in rats B11-0836

Motor activity of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Motor activity (count)						
			0-10	10-20	20-30	30-40	40-50	50-60	0-60 (min)
Male	Vehicle control	1	5391	5127	3180	4159	3876	1994	23727
		2	3014	3430	2104	2513	892	2460	14413
		3	3185	1605	189	37	3	2	5021
		4	22	2043	2831	2283	2260	72	9511
		5	797	2245	4523	1830	130	29	9554
		6	2798	1596	332	959	851	462	6998
		7	2010	3180	2543	1995	1722	1158	12608
		8	3867	4942	3478	3288	2468	4540	22583
		9	3379	3704	1786	2590	981	70	12510
		10	2412	1953	1981	1448	924	1665	10383
	5	11	5206	4676	2662	2481	1950	2066	19041
		12	885	6029	3458	2597	447	1200	14616
		13	790	2578	2024	2433	1551	89	9465
		14	3181	3614	1495	1106	865	807	11068
		15	2984	3497	1013	114	24	26	7658
	25	16	4169	1724	1107	1534	282	592	9408
		17	4504	3846	1977	2114	2097	1950	16488
		18	2957	1545	661	260	436	254	6113
		19	4497	2974	1994	582	2067	199	12313
		20	3890	3110	2407	90	15	119	9631
	125	21	1138	2174	890	396	45	286	4929
		22	2358	3939	3133	3901	2180	1974	17485
		23	2082	3661	1863	209	3054	800	11669
		24	3460	2635	2828	1995	1243	5	12166
		25	1974	3545	3228	1459	370	695	11271
		26	3108	2350	1388	1494	282	887	9509
		27	5523	4318	2516	1483	4	1101	14945
		28	6287	4055	3406	3581	2641	2372	22342
		29	4478	3390	2527	2688	2652	2053	17788
		30	4763	2690	3272	1446	741	325	13237

Motor activity of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Motor activity (count)						
			0-10	10-20	20-30	30-40	40-50	50-60	0-60 (min)
Female	Vehicle control	31	3655	4833	2754	1482	3667	2365	18756
		32	3105	1738	1353	0	2	22	6220
		33	3949	3384	1840	2327	1683	234	13417
		34	5934	5338	5033	3352	3650	323	23630
		35	5337	4212	3584	2627	3153	1968	20881
		36	3799	2056	1298	26	10	1	7190
		37	4675	3709	3325	1160	2	10	12881
		38	5307	3783	4789	3669	3757	276	21581
		39	4852	4837	4956	3285	3004	318	21252
		40	4751	3770	4197	3683	3975	2418	22794
	5	41	4674	4527	2689	294	1789	188	14161
		42	6663	4300	3331	3375	583	3017	21269
		43	4586	2779	3725	3228	2328	695	17341
		44	8394	5508	6724	3660	2038	273	26597
		45	6578	5664	4104	3456	2011	3891	25704
	25	46	5562	4569	4133	2919	4074	3494	24751
		47[a)]	—	—	—	—	—	—	—
		48	5654	3730	3471	1646	926	30	15457
		49	7935	7511	6501	4231	4294	174	30646
		50	3885	3786	1542	266	2533	1977	13989
	125	51	4864	3477	3225	6	4	7	11583
		52	4354	4276	4649	1675	0	0	14954
		53	4343	4165	4902	2977	4484	2365	23236
		54	4252	3769	3340	3299	3289	35	17984
		55	4281	4864	4092	3992	2555	2129	21913
		56	4215	3959	4056	648	2	32	12912
		57	7338	6320	5377	6079	3567	5306	33987
		58	5396	4873	4698	4245	2629	1825	23666
		59	6039	3751	3523	4059	2698	652	20722
		60	3660	1703	479	1083	201	1334	8460

a) Dead animal

Addendum 6-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights of individual animals(g)

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period								
			-2	1	8	12	17	21	26	28 (days)	
Male	Vehicle control	1	118.1	135.6	147.1	191.1	221.0	256.9	280.3	309.7	317.5
		2	125.5	142.8	159.7	206.9	244.6	273.2	301.7	328.6	334.7
		3	125.0	142.5	152.8	188.7	218.5	250.9	270.2	301.8	313.4
		4	124.6	138.5	156.5	196.8	231.8	269.1	294.8	321.1	328.1
		5	133.3	150.1	169.2	224.8	265.6	312.8	339.8	387.2	398.9
		6	123.8	139.8	154.4	196.5	226.7	255.3	282.3	315.7	321.1
		7	122.0	135.0	149.8	181.3	210.0	244.6	277.4	310.0	321.0
		8	124.7	146.5	161.0	196.9	227.8	255.4	276.0	299.7	307.0
		9	125.6	138.4	147.6	175.1	202.1	228.2	243.5	267.2	275.2
		10	130.0	142.1	161.2	206.3	237.8	278.6	303.5	339.4	348.7
	5	11	123.7	140.0	157.6	197.1	230.4	264.8	290.7	327.9	335.4
		12	126.0	142.7	152.2	192.7	220.8	263.5	289.7	318.1	329.2
		13	133.1	150.5	167.6	213.7	245.9	285.5	313.4	346.3	354.1
		14	124.6	146.9	153.3	192.3	224.1	258.4	285.1	322.5	334.7
		15	122.0	136.4	149.8	186.0	220.1	254.2	274.6	294.5	296.9
	25	16	120.1	130.9	152.3	195.3	225.4	254.0	275.1	308.8	315.7
		17	132.5	151.1	168.3	216.9	253.1	288.6	315.0	348.5	361.2
		18	126.1	148.2	154.2	197.2	225.9	256.9	287.2	319.7	324.1
		19	124.7	131.2	150.8	187.2	213.3	242.0	265.4	290.4	296.2
		20	123.9	141.6	153.9	191.4	215.7	236.6	248.7	274.6	278.8
	125	21	128.3	143.7	160.1	207.9	239.6	281.7	306.6	344.1	353.7
		22	125.4	144.6	154.8	196.3	225.6	258.5	277.1	301.3	306.5
		23	121.7	141.4	158.1	201.9	228.0	256.8	277.5	303.7	308.1
		24	128.0	146.0	158.5	202.9	241.0	277.1	305.5	336.4	342.6
		25	123.2	142.6	156.0	197.6	234.1	264.3	288.3	306.9	312.9
		26	125.1	141.5	153.9	183.4	209.9	241.7	265.5	284.7	293.7
		27	122.7	139.4	149.7	180.0	204.2	236.6	261.4	290.1	300.7
		28	120.8	135.7	147.1	175.3	199.3	228.1	249.8	281.1	290.8
		29	126.2	141.7	155.2	189.9	223.6	248.3	279.2	310.8	316.8
		30	130.7	146.8	161.5	198.8	232.2	268.2	285.8	310.7	315.3

Addendum 6-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights of individual animals(g)

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period								
			-2	1	3	8	12	17	21	26	28 (days)
Female	Vehicle control	31	116.5	130.3	136.6	161.6	173.2	181.8	184.9	217.9	226.5
		32	107.1	122.4	132.1	156.6	170.0	180.5	193.4	207.5	209.1
		33	114.8	127.2	140.3	156.6	165.4	171.5	183.6	196.1	198.7
		34	113.4	125.9	132.6	152.1	167.8	183.5	197.0	207.4	205.9
		35	111.0	124.6	136.3	166.6	183.2	194.7	205.0	220.1	222.0
		36	111.6	124.4	137.0	159.9	172.4	188.9	198.9	210.2	208.4
		37	114.3	127.7	142.0	169.2	176.8	193.9	213.6	234.7	234.8
		38	112.6	127.1	135.3	155.7	165.9	185.5	198.2	212.0	219.1
		39	118.4	126.1	140.9	162.1	173.6	182.6	193.6	198.2	208.4
		40	107.3	122.8	133.6	166.3	183.5	199.3	217.3	231.1	238.5
	5	41	112.9	126.1	134.6	144.1	153.7	173.6	184.8	196.7	200.9
		42	109.7	126.6	137.8	155.1	175.0	181.2	191.2	210.2	202.6
		43	114.6	127.9	145.3	172.1	188.2	208.2	224.4	239.1	233.2
		44	117.5	133.8	142.6	174.9	200.5	222.1	236.1	246.5	258.6
		45	111.2	123.1	127.9	144.6	159.1	178.6	188.9	206.0	204.8
	25	46	118.0	132.0	139.8	168.7	185.5	200.5	211.9	219.1	223.3
		47	116.0	131.6	141.9	170.3	188.1	205.7	218.8	- a)	-
		48	109.6	126.0	130.2	146.9	162.5	177.2	194.0	205.1	209.0
		49	110.3	125.6	136.8	165.4	172.5	196.8	213.1	235.9	241.6
		50	112.3	124.4	137.2	165.8	181.5	195.2	207.7	224.6	231.5
	125	51	108.9	120.5	131.4	147.7	156.3	173.2	181.7	194.1	196.4
		52	110.6	123.7	125.4	151.8	164.5	176.2	185.8	200.1	204.4
		53	118.9	134.4	147.0	171.7	189.1	207.6	219.7	222.9	231.7
		54	115.9	130.1	144.0	177.6	201.1	219.8	230.4	242.4	251.6
		55	113.3	126.8	134.8	161.8	179.6	194.9	207.3	222.2	222.1
		56	107.5	117.8	128.4	144.2	155.5	167.8	176.6	181.2	192.0
		57	110.7	126.0	128.9	144.7	158.8	169.4	181.9	193.5	197.9
		58	113.9	126.4	137.2	168.1	191.5	204.8	215.7	239.6	239.3
		59	117.9	132.0	150.7	182.1	204.8	218.5	231.9	243.3	256.0
		60	115.0	125.9	135.5	152.2	165.4	175.2	186.9	211.8	217.2

a) Dead animal.

Addendum 6-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836
Body weights of individual animals(g)

Sex	Exp.group (mg/kg/day)	Animal No.	Recovery period 1	5	10	14 (days)
Male	Vehicle control	6	320.1	339.7	361.7	376.7
		7	319.9	337.0	365.4	381.3
		8	308.1	322.4	342.4	356.7
		9	273.2	292.0	312.0	316.0
		10	352.0	368.9	397.8	447.7
	125	26	292.5	305.7	328.9	349.3
		27	301.3	313.2	336.7	353.2
		28	291.5	306.4	328.6	372.5
		29	314.7	331.0	354.1	353.4
		30	317.1	322.4	339.5	333.2
Female	Vehicle control	36	212.8	222.7	226.8	262.4
		37	238.0	238.3	248.9	262.2
		38	218.8	235.6	235.9	243.0
		39	211.5	218.5	219.0	220.5
		40	239.9	251.7	259.5	262.9
	125	56	192.3	193.8	190.2	192.8
		57	202.2	205.2	211.0	210.2
		58	242.9	243.1	242.1	248.1
		59	255.5	260.1	260.5	269.9
		60	209.9	218.3	236.8	247.0

Addendum 7-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Food intakes of individual animals(g/rat/day)

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period 1	3	8	15	22	28 (days)
Male	Vehicle control	1	16.3	16.4	19.6	18.6	18.4	17.4
		2	17.8	18.1	20.8	21.0	19.0	16.7
		3	17.2	16.0	17.9	16.3	16.0	17.4
		4	16.0	17.0	19.2	18.7	18.3	16.5
		5	18.1	20.5	23.7	23.9	23.5	24.2
		6	17.0	17.4	18.9	17.9	17.3	16.9
		7	15.4	16.3	19.3	17.2	18.1	18.4
		8	18.2	18.5	16.2	17.7	17.2	17.5
		9	15.4	14.8	11.1	16.0	15.0	14.9
		10	18.2	18.7	28.2	20.6	21.3	20.3
	5	11	16.4	16.9	18.9	17.9	17.8	17.8
		12	17.5	15.8	11.1	18.7	19.8	18.6
		13	18.3	19.0	29.4	19.5	19.1	18.7
		14	16.3	16.9	17.3	19.8	19.2	20.1
		15	16.6	17.1	17.7	19.0	18.5	15.4
	25	16	16.5	16.4	19.1	17.7	16.4	16.8
		17	15.3	18.6	21.5	19.4	16.0	18.7
		18	17.2	16.3	18.8	16.7	19.3	16.9
		19	16.5	17.2	18.3	17.7	17.5	16.5
		20	15.1	16.6	18.4	16.4	15.5	15.0
	125	21	17.8	18.8	20.9	20.9	20.2	20.2
		22	16.8	17.2	29.4	18.6	18.2	16.7
		23	17.8	18.5	10.8	17.8	16.4	16.5
		24	17.2	17.9	22.0	22.0	11.0	18.4
		25	17.0	18.4	21.2	21.3	29.9	18.9
		26	18.5	17.4	17.5	16.8	17.2	16.7
		27	16.3	16.7	17.6	18.3	18.8	19.0
		28	15.6	15.4	18.3	16.0	16.0	17.6
		29	16.5	16.4	18.3	18.7	18.9	18.4
		30	17.8	19.0	20.6	20.1	19.9	18.2

Addendum 7-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836
Food intakes of individual animals(g/rat/day)

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period 1	3	8	15	22	28 (days)
Female	Vehicle control	31	14.6	13.3	14.8	11.8	10.2	13.6
		32	13.5	13.2	14.2	12.2	11.9	11.8
		33	14.3	15.2	14.0	11.8	12.0	12.9
		34	13.8	12.6	14.4	12.8	11.5	10.9
		35	15.2	15.0	16.6	14.4	12.7	13.2
		36	14.0	15.4	15.4	13.4	11.6	10.7
		37	14.9	15.3	15.9	13.9	11.3	12.7
		38	14.3	13.3	14.2	11.9	12.6	12.3
		39	14.4	14.6	15.3	11.0	10.5	10.9
		40	14.1	14.0	16.9	15.4	14.2	14.7
	5	41	14.1	13.8	12.4	11.7	11.6	10.2
		42	14.2	14.4	13.3	11.5	10.0	12.3
		43	14.9	16.8	17.8	15.0	12.8	12.5
		44	17.7	17.3	18.4	16.6	16.2	16.3
		45	14.1	11.0	12.8	12.2	12.0	11.8
	25	46	15.6	14.5	16.5	13.9	12.6	11.6
		47	15.7	14.8	16.0	12.7	12.1	- a)
		48	14.4	12.2	14.5	12.4	12.2	12.8
		49	14.8	13.6	16.3	14.2	13.9	15.2
		50	14.6	15.2	16.3	14.6	12.8	13.1
	125	51	13.2	14.0	13.2	13.0	10.8	10.8
		52	13.6	11.3	13.9	11.9	11.8	12.5
		53	15.2	15.0	15.4	11.9	13.8	13.7
		54	15.8	17.6	19.4	13.1	15.4	15.1
		55	14.5	14.3	16.8	16.4	13.7	14.0
		56	13.2	13.0	13.7	15.9	11.1	11.8
		57	14.1	12.6	13.4	11.5	10.4	11.2
		58	13.3	13.3	16.4	15.1	13.4	13.0
		59	15.2	16.4	17.4	15.2	13.2	14.8
		60	14.5	14.4	14.4	12.0	12.2	13.7

a) Dead animal.

Addendum 7-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836
Food intakes of individual animals(g/rat/day)

Sex	Exp.group (mg/kg/day)	Animal No.	Recovery period 4	8	14 (days)
Male	Vehicle control	6	19.4	22.0	22.1
		7	18.8	21.9	21.9
		8	19.0	21.6	23.1
		9	17.5	19.9	22.1
		10	22.9	25.4	27.0
	125	26	20.3	21.2	22.3
		27	20.5	21.1	23.2
		28	17.2	20.9	22.6
		29	19.3	20.9	22.9
		30	17.8	20.9	22.1
Female	Vehicle control	36	14.0	15.0	15.4
		37	11.9	15.8	17.6
		38	16.5	18.8	18.3
		39	13.4	15.1	15.4
		40	17.1	19.3	19.6
	125	56	12.5	13.4	14.0
		57	14.3	15.9	13.9
		58	13.3	14.0	14.7
		59	15.8	17.4	17.9
		60	16.8	16.3	17.1

Addendum 8-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Hematological data of individual animals

B11-0838

Sex	Exp.group (mg/kg/day)	Animal No.	RBC ($\times 10^4/\mu L$)	WBC ($\times 10^2/\mu L$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet ($\times 10^4/\mu L$)	Reticulo (%)	P T (sec)	APTT (sec)
Male	Vehicle control	1	774	110	15.4	45.1	58.3	19.9	34.1	104.5	2.5	14.1	28.4
		2	806	116	15.8	46.8	58.1	19.7	33.9	98.6	2.0	16.1	24.8
		3	775	141	15.1	45.1	58.2	19.5	33.5	93.4	2.8	13.6	23.1
		4	798	108	15.3	45.8	57.3	19.2	33.5	110.6	1.7	14.5	23.5
		5	755	136	15.6	46.5	61.5	20.7	33.6	89.2	3.0	13.4	26.3
		Recovery											
		6	847	111	16.0	47.6	56.2	18.9	33.7	109.9	1.7	17.6	30.2
		7	864	89	16.3	48.5	56.1	18.8	33.6	92.6	1.4	19.0	30.6
		8	856	89	16.4	48.5	56.6	19.2	33.8	108.4	1.6	15.0	32.2
		9	820	121	15.4	46.1	56.1	18.7	33.3	96.7	2.0	15.9	31.3
		10	849	131	16.4	48.0	56.5	19.3	34.2	111.2	2.0	25.6	32.6
	5	11	757	158	15.0	43.7	57.8	19.8	34.3	91.4	2.7	12.9	22.0
		12	764	123	15.8	46.2	60.4	20.7	34.3	104.8	2.4	13.5	24.5
		13	792	105	15.2	45.3	57.2	19.2	33.6	104.9	2.5	15.4	29.9
		14	781	101	15.5	46.0	59.0	19.8	33.6	106.5	2.5	14.8	25.6
		15	815	110	16.2	48.0	58.9	19.8	33.7	91.1	1.7	16.7	30.7
	25	16	672	140	13.9	40.8	60.7	20.7	34.1	95.3	3.6	14.8	26.3
		17	784	113	15.6	46.3	59.1	19.9	33.7	102.3	3.0	14.3	25.3
		18	730	88	14.4	44.3	57.4	19.5	34.0	97.2	2.7	14.3	27.5
		19	790	117	15.8	46.6	59.1	20.0	33.8	88.4	2.4	16.9	26.9
		20	798	116	16.0	47.6	59.7	20.0	33.6	91.0	2.3	17.2	27.0
	125	21	762	133	14.8	43.6	57.2	19.4	33.9	110.0	2.4	16.1	25.4
		22	770	136	15.6	45.3	58.8	20.2	34.4	86.7	1.7	14.7	26.0
		23	775	99	15.2	44.7	57.7	19.5	33.9	91.7	2.3	15.9	24.6
		24	753	72	15.2	45.4	60.3	20.2	33.5	90.5	2.6	14.3	27.0
		25	859	100	16.4	49.9	58.1	19.1	33.0	108.6	2.1	15.2	28.0
		Recovery											
		26	850	114	15.5	45.4	53.4	18.2	34.1	112.5	1.8	22.9	28.5
		27	788	112	14.9	43.5	55.3	18.9	34.2	106.7	2.2	24.7	32.8
		28	733	120	14.2	42.2	57.5	19.3	33.6	99.4	3.2	13.6	25.1
		29	762	114	15.2	43.7	57.4	20.0	34.8	81.3	1.9	14.3	29.0
		30	858	95	15.2	44.1	51.4	17.7	34.3	116.9	2.0	14.7	25.6

Addendum 8-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Hematological data of individual animals

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	RBC (x10⁴/μL)	WBC (x10²/μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet (x10⁴/μL)	Reticulo (%)	P T (sec)	APTT (sec)
Female	Vehicle control	31	752	74	14.7	43.3	57.5	19.5	33.9	102.8	2.3	13.0	20.4
		32	780	77	15.5	44.9	57.6	19.9	34.5	128.2	1.6	13.1	22.0
		33	784	81	15.4	45.4	58.0	19.7	33.9	89.6	2.0	13.6	21.1
		34	826	88	15.9	45.5	55.2	19.2	34.9	114.9	1.0	14.0	23.9
		35	745	78	15.3	44.6	59.9	20.5	34.2	110.4	1.9	12.7	24.8
		Recovery											
		36	808	56	15.6	44.0	54.4	19.3	35.6	125.0	1.3	13.9	19.5
		37	727	73	13.9	39.8	54.8	19.1	34.9	137.7	2.0	14.5	23.6
		38	726	44	14.8	42.2	58.1	20.4	35.1	119.7	1.6	12.7	21.4
		39	820	73	15.2	43.8	53.4	18.6	34.8	128.1	1.4	13.9	20.7
		40	806	87	15.6	44.2	54.8	19.4	35.4	108.6	1.1	12.9	20.5
	5	41	727	103	14.8	43.3	59.6	20.4	34.3	96.5	1.6	14.2	20.5
		42	755	81	15.2	44.6	59.0	20.1	34.0	107.8	1.4	13.3	25.7
		43	766	105	15.4	45.8	59.7	20.1	33.6	92.7	1.3	12.3	22.3
		44	750	67	14.8	44.1	58.9	19.7	33.6	104.6	1.8	12.8	24.5
		45	802	86	15.8	46.8	58.4	19.7	33.7	112.9	1.8	12.2	24.0
	25	46	745	73	14.7	43.0	57.7	19.7	34.1	104.4	1.2	14.1	24.0
		47 a)	–	–	–	–	–	–	–	–	–	–	–
		48	804	82	15.2	45.0	55.9	19.0	33.9	115.3	1.8	13.9	24.3
		49	791	148	15.7	46.8	59.2	19.8	33.5	104.6	2.4	12.7	25.0
		50	771	131	15.1	45.0	58.4	19.6	33.5	100.2	2.1	12.8	22.5
	125	51	727	99	14.8	43.1	59.3	20.3	34.2	97.3	1.3	12.9	19.0
		52	772	61	15.4	45.3	58.6	19.9	34.0	108.6	1.6	12.9	24.1
		53	770	96	14.8	43.7	56.7	19.2	33.9	113.3	1.8	13.4	25.4
		54	764	94	16.0	47.7	62.4	21.0	33.6	97.7	2.0	13.0	24.5
		55	780	120	15.6	45.8	58.7	20.0	34.1	109.4	1.7	12.0	23.3
		Recovery											
		56	769	83	14.7	41.9	54.5	19.1	35.1	123.1	1.4	13.9	22.6
		57	839	63	15.3	43.9	52.3	18.2	34.8	132.8	1.2	13.5	24.3
		58	789	92	15.0	43.1	54.7	19.0	34.8	120.6	1.2	14.2	24.5
		59	797	92	14.1	40.7	51.1	17.7	34.6	132.2	1.2	13.5	20.0
		60	794	75	14.6	41.7	52.5	18.4	35.1	127.2	1.6	13.3	18.3

a) Dead animal.

Addendum 8-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836
Hematological data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Differentiation of leukocyte (%) Neutro	Eosino	Baso	Lymph	Mono	LUC
Male	Vehicle control	1	14.0	0.4	0.1	82.5	2.4	0.6
		2	17.4	0.7	0.2	77.7	3.2	0.8
		3	19.5	0.6	0.1	78.8	2.3	0.6
		4	11.2	0.7	0.1	85.4	1.7	1.0
		5	27.8	0.8	0.1	68.2	2.7	0.4
		Recovery						
		6	12.0	0.7	2.0	83.0	1.5	0.9
		7	9.2	0.7	2.7	85.0	1.9	0.6
		8	17.9	1.3	0.9	76.9	2.5	0.5
		9	22.3	0.3	1.3	73.4	1.8	0.8
		10	11.5	1.3	1.1	83.8	1.7	0.6
	5	11	10.3	0.4	0.1	86.7	2.0	0.5
		12	19.7	0.9	0.1	77.0	1.7	0.6
		13	11.8	1.1	0.1	84.1	2.3	0.6
		14	16.8	0.7	0.1	79.7	2.2	0.5
		15	20.7	1.1	0.1	75.2	2.2	0.6
	25	16	16.9	1.0	0.0	79.7	2.1	0.4
		17	14.1	0.8	0.1	81.6	2.8	0.6
		18	18.2	1.1	0.1	78.1	2.1	0.5
		19	23.8	1.0	0.1	69.7	4.2	1.1
		20	24.4	0.3	0.0	73.3	1.7	0.3
	125	21	15.9	0.3	0.1	80.9	2.1	0.7
		22	18.4	0.5	0.1	77.4	3.1	0.6
		23	19.2	0.7	0.0	76.6	2.7	0.7
		24	23.9	1.2	0.1	72.3	2.0	0.5
		25	28.6	0.4	0.1	67.7	2.6	0.6
		Recovery						
		26	21.5	0.4	1.6	73.4	2.6	0.5
		27	29.3	0.6	0.6	66.1	2.8	0.6
		28	17.8	0.7	0.3	78.9	1.6	0.7
		29	18.5	0.7	0.9	77.7	1.7	0.4
		30	13.3	1.4	0.4	82.7	1.4	0.8

Addendum 8-4 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836
Hematological data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Differentiation of leukocyte (%) Neutro	Eosino	Baso	Lymph	Mono	LUC
Female	Vehicle control	31	7.7	0.4	0.1	89.9	1.3	0.7
		32	30.2	0.8	0.0	62.2	6.0	0.8
		33	20.9	1.0	0.1	76.7	1.8	0.4
		34	16.1	0.9	0.1	80.3	2.0	0.6
		35	8.3	0.4	0.1	89.7	0.8	0.6
		Recovery						
		36	8.7	1.2	0.4	86.7	2.4	0.6
		37	20.3	1.0	0.2	76.9	1.2	0.3
		38	20.6	1.8	0.4	73.6	3.0	0.5
		39	9.4	1.5	0.2	86.2	1.8	0.9
		40	22.4	0.8	0.2	73.6	2.1	1.0
	5	41	10.2	0.7	0.1	86.7	1.3	1.0
		42	24.4	1.0	0.1	71.1	2.2	1.1
		43	13.3	0.7	0.0	82.4	2.8	0.8
		44	12.3	0.6	0.0	85.0	1.4	0.7
		45	8.7	1.0	0.1	88.3	1.0	1.0
	25	46	19.7	0.9	0.1	76.4	2.2	0.7
		47 a)	–	–	–	–	–	–
		48	20.0	0.6	0.1	77.7	0.9	0.7
		49	11.6	0.7	0.1	85.0	1.7	1.0
		50	11.3	1.6	0.1	83.7	2.6	0.7
	125	51	14.7	0.4	0.1	83.2	1.0	0.6
		52	12.8	0.9	0.1	83.6	1.9	0.7
		53	10.3	0.5	0.1	87.2	1.2	0.7
		54	18.3	1.2	0.1	78.2	1.5	0.6
		55	22.3	0.5	0.0	75.2	1.2	0.9
		Recovery						
		56	16.1	1.2	0.3	78.6	2.9	0.8
		57	17.1	2.4	0.3	78.0	1.7	0.5
		58	11.9	1.0	0.4	83.3	2.0	1.4
		59	13.9	1.8	0.2	81.4	1.9	0.7
		60	24.8	1.3	0.7	70.8	1.8	0.6

a) Dead animal.

Addendum 9-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	ChE (IU/L)	γ-GTP (IU/L)	T-Cho (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	T-Protein (g/dL)	Albumin (g/dL)	A/G ratio
Male	Vehicle control	1	67	23	413	49	0.2	96	106	146	5.4	2.9	1.16
		2	57	15	439	61	0.5	57	66	176	5.6	3.0	1.15
		3	60	21	572	55	1.1	80	62	162	5.4	2.9	1.16
		4	63	18	549	30	0.5	52	74	144	5.8	2.9	1.00
		5	57	21	341	72	0.4	64	120	142	6.0	2.9	0.94
		Recovery											
		6	63	20	373	43	0.3	65	65	129	5.7	2.8	0.97
		7	69	25	350	41	0.7	81	59	121	5.8	2.9	1.00
		8	64	25	273	42	0.2	74	41	135	5.8	2.8	0.93
		9	69	23	328	48	0.8	66	84	146	5.8	2.8	0.93
		10	71	24	283	53	0.8	72	129	185	5.9	2.8	0.90
	5	11	65	20	549	64	0.4	76	91	152	5.4	2.8	1.08
		12	58	18	438	34	0.7	57	66	153	5.7	3.0	1.11
		13	71	24	476	38	0.5	67	108	170	5.6	2.8	1.00
		14	59	22	644	38	0.5	59	72	161	5.2	2.8	1.17
		15	60	22	420	41	0.3	42	57	147	5.8	3.0	1.07
	25	16	71	31	500	45	0.6	46	48	153	5.4	2.6	0.93
		17	65	27	483	48	0.4	54	75	156	5.7	2.8	0.97
		18	69	22	551	46	0.5	45	70	152	5.1	2.6	1.04
		19	87	26	710	42	0.9	58	78	161	5.5	3.1	1.29
		20	58	15	552	30	0.5	45	28	196	6.0	3.2	1.14
	125	21	71	31	672	45	0.6	47	109	159	5.8	2.8	0.93
		22	62	24	621	43	0.9	45	86	173	5.5	2.9	1.12
		23	74	28	756	50	0.6	47	119	184	5.8	2.7	1.08
		24	94	39	703	46	0.7	43	45	197	5.5	2.9	1.12
		25	95	41	881	36	0.4	37	76	169	6.3	3.3	1.10
		Recovery											
		26	72	26	386	29	0.6	62	95	135	5.3	2.6	0.96
		27	73	24	331	25	0.2	39	35	127	5.6	2.9	1.07
		28	64	21	379	29	0.5	62	95	133	5.8	2.6	0.81
		29	55	23	290	54	0.7	65	82	121	5.8	2.8	0.93
		30	70	22	399	36	0.9	42	63	127	5.8	2.8	0.93

Addendum 9-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	ChE (IU/L)	γ-GTP (IU/L)	T-Cho (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	T-Protein (g/dL)	Albumin (g/dL)	A/G ratio
Female	Vehicle control	31	57	15	422	242	0.7	54	12	129	5.7	3.1	1.19
		32	86	24	354	215	0.2	59	39	123	5.8	3.1	1.15
		33	78	16	248	120	0.8	83	17	148	5.7	3.1	1.19
		34	70	20	296	209	1.0	56	17	121	5.9	3.1	1.11
		35	62	15	243	135	0.6	60	18	155	5.5	2.9	1.12
		Recovery											
		36	78	23	133	203	1.0	58	24	141	5.9	3.1	1.11
		37	59	15	181	474	0.9	50	16	129	6.0	3.2	1.14
		38	70	20	237	396	0.8	72	20	103	6.2	3.0	0.94
		39	65	15	168	181	1.0	77	15	131	6.0	3.0	1.00
		40	74	25	126	412	0.8	73	25	148	6.7	3.4	1.03
	5	41	62	14	286	237	0.7	52	25	122	5.4	2.9	1.16
		42	63	14	336	229	0.8	63	17	115	5.8	3.1	1.15
		43	69	18	229	156	1.0	79	29	148	5.6	3.0	1.15
		44	62	15	201	189	0.9	67	26	165	5.9	3.1	1.11
		45	74	20	247	175	0.3	74	35	107	5.9	3.1	1.11
	25	46	62	15	177	158	0.4	57	24	135	5.8	3.2	1.23
		47 a)	–	–	–	–	–	–	–	–	–	–	–
		48	66	17	321	263	0.7	81	58	142	6.0	3.2	1.14
		49	75	19	167	162	1.0	64	29	154	5.6	3.0	1.15
		50	56	15	320	194	0.8	75	41	192	5.7	3.1	1.19
	125	51	56	22	346	95	1.2	101	40	155	5.8	3.3	1.32
		52	63	23	229	108	1.2	71	26	111	5.9	3.3	1.27
		53	68	19	496	87	1.1	60	35	130	5.8	3.2	1.23
		54	58	19	212	83	2.4	80	59	134	6.3	3.3	1.10
		55	65	22	304	129	1.3	82	42	116	6.3	3.6	1.33
		Recovery											
		56	59	17	189	249	0.8	61	21	166	6.2	3.3	1.14
		57	70	21	192	187	1.3	73	20	118	6.4	3.4	1.13
		58	78	19	156	164	0.9	62	44	163	6.2	3.2	1.07
		59	74	19	134	304	1.0	91	22	123	6.7	3.3	0.97
		60	75	19	188	245	1.0	63	53	114	6.6	3.4	1.06

a) Dead animal.

Addendum 9-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	BUN (mg/dL)	Creatinine (mg/dL)	T-Bil (mg/dL)	Ca (mg/dL)	IP (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Male	Vehicle control	1	7.6	0.28	0.05	9.3	7.2	144	4.4	106.5
		2	9.5	0.25	0.06	9.8	7.3	141	4.6	106.0
		3	7.7	0.22	0.06	9.7	8.1	143	4.8	106.0
		4	6.9	0.24	0.07	9.6	7.6	143	4.7	103.7
		5	13.5	0.24	0.06	10.5	8.4	142	3.8	104.9
		Recovery								
		6	13.6	0.29	0.08	9.4	7.0	143	4.6	106.8
		7	13.7	0.25	0.08	9.5	6.7	145	4.3	106.6
		8	11.7	0.21	0.07	9.4	6.5	145	4.1	106.9
		9	14.8	0.26	0.07	9.7	7.3	145	3.9	108.3
		10	16.8	0.27	0.06	10.3	8.1	144	4.2	105.1
	5	11	10.5	0.21	0.06	9.5	7.6	140	4.3	102.1
		12	9.4	0.21	0.07	9.6	7.8	142	4.2	106.0
		13	8.8	0.25	0.06	9.8	7.8	143	4.1	103.8
		14	7.5	0.21	0.08	9.8	7.9	143	4.4	103.4
		15	8.6	0.21	0.07	9.8	7.9	142	4.5	102.6
	25	16	11.3	0.25	0.08	9.2	7.6	141	4.5	104.1
		17	9.1	0.19	0.07	9.4	7.5	143	4.3	106.7
		18	7.4	0.22	0.08	9.3	8.7	143	4.3	105.3
		19	9.9	0.21	0.09	9.6	7.9	143	4.2	103.6
		20	11.1	0.25	0.05	10.1	10.4	142	4.5	105.3
	125	21	8.5	0.23	0.07	9.4	7.7	143	4.7	105.6
		22	9.2	0.26	0.06	9.5	7.0	142	3.8	105.7
		23	10.0	0.23	0.09	9.3	8.5	141	4.6	102.2
		24	9.4	0.28	0.14	9.1	8.2	142	4.4	103.2
		25	10.8	0.20	0.09	10.7	9.6	143	4.9	105.9
		Recovery								
		26	15.7	0.24	0.06	9.0	7.1	144	4.4	106.5
		27	13.0	0.25	0.05	8.9	6.5	144	4.4	107.6
		28	16.1	0.23	0.06	9.1	7.1	144	4.2	108.6
		29	14.5	0.28	0.07	9.8	7.6	144	4.0	105.8
		30	16.0	0.26	0.07	9.4	7.1	143	4.8	108.4

Addendum 9-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	BUN (mg/dL)	Creatinine (mg/dL)	T-Bil (mg/dL)	Ca (mg/dL)	IP (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Female	Vehicle control	31	10.7	0.26	0.05	9.5	6.8	142	4.1	105.7
		32	11.0	0.27	0.05	9.5	7.4	142	4.3	105.1
		33	9.9	0.25	0.04	9.6	8.0	142	4.5	106.1
		34	7.0	0.24	0.06	9.8	7.7	143	4.5	104.5
		35	11.9	0.24	0.03	9.8	8.9	143	4.4	106.1
		Recovery								
		36	16.1	0.26	0.07	9.2	5.9	143	4.2	109.9
		37	13.9	0.29	0.05	9.4	5.2	143	4.0	108.4
		38	17.5	0.35	0.06	9.4	5.8	143	3.8	108.4
		39	16.4	0.27	0.07	9.0	5.6	143	4.1	110.1
		40	15.3	0.28	0.07	9.5	5.6	145	4.1	109.1
	5	41	8.3	0.22	0.05	9.7	8.3	143	4.4	106.9
		42	10.2	0.30	0.04	9.9	7.7	142	4.3	105.2
		43	9.3	0.26	0.04	9.9	8.7	142	4.3	105.9
		44	8.5	0.22	0.06	9.9	7.8	143	4.5	105.2
		45	10.7	0.21	0.04	10.0	7.7	143	4.1	107.2
	25	46	10.0	0.24	0.04	9.6	7.9	143	4.2	107.2
		47 a)	–	–	–	–	–	–	–	–
		48	8.1	0.24	0.05	9.7	7.2	142	4.2	106.0
		49	9.3	0.25	0.05	9.6	7.8	141	4.6	106.1
		50	9.6	0.24	0.05	10.1	8.6	142	4.3	105.4
	125	51	9.7	0.26	0.10	10.1	8.5	143	4.5	106.7
		52	11.4	0.27	0.07	9.5	7.9	142	4.4	106.8
		53	7.7	0.22	0.06	9.5	7.9	142	4.7	106.3
		54	8.0	0.19	0.06	10.4	7.5	142	4.2	107.7
		55	8.9	0.20	0.05	10.2	7.8	141	4.2	105.1
		Recovery								
		56	17.8	0.27	0.08	9.2	6.8	143	3.7	110.0
		57	21.8	0.37	0.06	9.5	6.2	144	4.0	109.9
		58	14.4	0.27	0.05	9.7	7.6	143	4.7	109.9
		59	16.0	0.26	0.06	9.8	6.1	142	4.5	106.0
		60	18.9	0.28	0.11	10.1	7.1	144	4.8	108.9

a) Dead animal.

Addendum 10-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836
Urinalytic data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Urine volume (mL)	Sp.Gr.
Male	Vehicle control	1	10	1.022
		2	5	1.050
		3	9	1.024
		4	6	1.030
		5	3	1.084
		Recovery		
		6	21	1.013
		7	18	1.020
		8	12	1.029
		9	6	1.048
		10	14	1.027
	5	11	5	1.038
		12	2	1.090
		13	4	1.052
		14	3	1.070
		15	5	1.033
	25	16	2	1.081
		17	10	1.033
		18	8	1.026
		19	7	1.027
		20	5	1.038
	125	21	7	1.040
		22	9	1.023
		23	7	1.040
		24	19	1.013
		25	15	1.018
		Recovery		
		26	16	1.034
		27	10	1.010
		28	30	1.040
		29	10	1.038
		30	9	1.029

Addendum 10-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0836
Urinalytic data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Urine volume (mL)	Sp.Gr.
Female	Vehicle control	31	6	1.021
		32	18	1.007
		33	7	1.024
		34	8	1.012
		35	3	1.064
		Recovery		
		36	11	1.021
		37	1	1.026
		38	6	1.035
		39	13	1.050
		40	6	1.014
	5	41	10	1.014
		42	2	1.038
		43	7	1.020
		44	6	1.030
		45	5	1.021
	25	46	4	1.034
		47 a)	-	-
		48	3	1.036
		49	5	1.034
		50	3	1.054
	125	51	7	1.010
		52	8	1.024
		53	11	1.017
		54	9	1.031
		55	4	1.040
		Recovery		
		56	4	1.038
		57	8	1.026
		58	9	1.024
		59	12	1.016
		60	7	1.030

a) Dead animal.

Addendum 10-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	Color	Turbidity	pH	Protein	Glucose	Occult blood
Male	Vehicle control	1	Y	NT	6.5	1+	−	−
		2	Y	NT	6.5	2+	−	−
		3	Y	NT	6.5	1+	−	−
		4	Y	NT	6.5	1+	−	−
		5	Y	NT	6.0	2+	−	−
		Recovery						
		6	SY	NT	7.0	±	−	−
		7	SY	NT	6.0	±	−	−
		8	Y	NT	6.5	1+	−	−
		9	Y	NT	7.0	1+	−	−
		10	SY	NT	7.0	1+	−	−
	5	11	Y	NT	6.5	1+	−	−
		12	Y	NT	6.0	2+	−	−
		13	Y	NT	6.5	2+	−	−
		14	Y	NT	6.0	2+	−	−
		15	Y	NT	6.5	1+	−	−
	25	16	Y	NT	6.0	2+	−	±
		17	Y	NT	6.5	1+	−	−
		18	Y	NT	6.5	1+	−	−
		19	Y	NT	6.5	1+	−	−
		20	Y	NT	6.5	2+	−	−
	125	21	Y	NT	6.0	1+	−	−
		22	Y	NT	6.5	1+	−	−
		23	Y	NT	6.5	1+	−	−
		24	SY	NT	6.5	±	−	−
		25	Y	NT	6.5	1+	−	−
		Recovery						
		26	SY	NT	7.0	±	−	−
		27	Y	NT	6.5	1+	−	−
		28	SY	NT	7.0	±	−	−
		29	Y	NT	7.0	1+	−	−
		30	Y	NT	6.5	1+	−	−

SY, Slightly yellow.
Y, Yellow.
NT, Not turbid.

Addendum 10-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	Color	Turbidity	pH	Protein	Glucose	Occult blood
Female	Vehicle control	31	Y	NT	6.5	±	−	−
		32	SY	NT	7.0	±	−	−
		33	Y	NT	6.5	1+	−	±
		34	SY	NT	6.0	1+	−	−
		35	Y	NT	6.5	2+	−	−
		Recovery						
		36	SY	NT	6.5	±	−	−
		37	SY	NT	6.5	±	−	−
		38	Y	NT	6.5	1+	−	−
		39	Y	NT	6.0	1+	−	−
		30	SY	NT	7.0	±	−	−
	5	41	SY	NT	7.0	±	−	−
		42	Y	NT	6.0	2+	−	−
		43	Y	NT	6.5	1+	−	−
		44	Y	NT	6.5	1+	−	−
		45	Y	NT	6.5	1+	−	−
	25	46	Y	NT	6.5	1+	−	−
		47 a)	-	-	-	-	-	-
		48	Y	NT	6.0	2+	−	−
		49	Y	NT	6.5	1+	−	−
		50	Y	NT	6.0	2+	−	−
	125	51	SY	NT	6.5	±	−	−
		52	Y	NT	6.5	1+	−	−
		53	SY	NT	7.0	±	−	−
		54	Y	NT	6.5	1+	−	−
		55	Y	NT	6.0	2+	−	−
		Recovery						
		56	Y	NT	6.0	1+	−	−
		57	Y	NT	6.5	±	−	−
		58	SY	NT	6.5	±	−	−
		59	SY	NT	7.0	±	−	−
		60	Y	NT	6.5	1+	−	−

SY, Slightly yellow.
Y, Yellow.
NT, Not turbid.
a) Dead animal.

Addendum 10-5 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals (Urinary sediment)

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	Red blood cells[a]	White blood cells[a]	Epithelial cells[a]	Casts[b]	Crystals[c]
Male	Vehicle control	1	0	0	2	0	+
		2	0	1	2	0	++
		3	0	0	4	0	±
		4	0	0	1	0	+
		5	0	0	1	0	++
		Recovery					
		6 [d]	-	-	-	-	-
		7 [d]	-	-	-	-	-
		8 [d]	-	-	-	-	-
		9 [d]	-	-	-	-	-
		10 [d]	-	-	-	-	-
	5	11 [d]	-	-	-	-	-
		12 [d]	-	-	-	-	-
		13 [d]	-	-	-	-	-
		14 [d]	-	-	-	-	-
		15 [d]	-	-	-	-	-
	25	16 [d]	-	-	-	-	-
		17 [d]	-	-	-	-	-
		18 [d]	-	-	-	-	-
		19 [d]	-	-	-	-	-
		20 [d]	-	-	-	-	-
	125	21	0	0	3	0	+
		22	0	0	1	0	±
		23	0		4	0	±
		24	0	0	1	0	±
		25	0	0	1	0	±
		Recovery					
		26 [d]	-	-	-	-	-
		27 [d]	-	-	-	-	-
		28 [d]	-	-	-	-	-
		29 [d]	-	-	-	-	-
		30 [d]	-	-	-	-	-

a) Number of cells/10 views (×400).
b) Number of casts/18×18 mm^2.
c) Incidence of crystals/18×18 mm^2.
d) Not examined.

Addendum 10-6 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals (Urinary sediment)

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	Red blood cells[a]	White blood cells[a]	Epithelial cells[a]	Casts[b]	Crystals[c]
Female	Vehicle control	31	0	1	1	0	−
		32	0	0	3	0	±
		33	0	2	4	0	−
		34	0	0	0	0	±
		35	0	0	1	0	−
		Recovery					
		36 d)	-	-	-	-	-
		37 d)	-	-	-	-	-
		38 d)	-	-	-	-	-
		39 d)	-	-	-	-	-
		40 d)	-	-	-	-	-
	5	41 d)	-	-	-	-	-
		42 d)	-	-	-	-	-
		43 d)	-	-	-	-	-
		44 d)	-	-	-	-	-
		45 d)	-	-	-	-	-
	25	46 d)	-	-	-	-	-
		47 e)	-	-	-	-	-
		48 d)	-	-	-	-	-
		49 d)	-	-	-	-	-
		50 d)	-	-	-	-	-
	125	51	0	2	4	0	−
		52	0	0	1	0	±
		53	0	0	0	0	−
		54	0	0	0	0	−
		55	0	0	2	0	−
		Recovery					
		56 d)	-	-	-	-	-
		57 d)	-	-	-	-	-
		58 d)	-	-	-	-	-
		59 d)	-	-	-	-	-
		60 d)	-	-	-	-	-

a) Number of cells/10 views (×400).
b) Number of casts/18×18 mm^2.
c) Incidence of crystals/18×18 mm^2.
d) Not examined.
e) Dead animal.

Addendum 11-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Absolute organ weights of individual animals

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g)	Heart (g)	Kidney (g)	Testis (g)	Epididymis (g)	Ovary (mg)	Brain (g)	Spleen (g)	Thymus (mg)	Adrenal (mg)	Body weight (g)
Male	Vehicle control	1	8.92	0.96	1.94	3.19	0.75	-	1.91	0.41	488.8	55.2	299.7
		2	10.55	1.04	2.16	2.63	0.62	-	1.86	0.59	329.1	50.5	316.9
		3	9.36	0.96	2.27	2.65	0.64	-	1.79	0.51	540.2	44.4	295.7
		4	10.49	1.05	2.07	2.65	0.61	-	1.95	0.47	478.4	59.1	306.7
		5	14.66	1.15	2.39	2.75	0.68	-	1.90	0.79	593.0	52.5	377.3
		Recovery											
		6	8.83	1.07	2.17	3.16	1.00	-	1.95	0.61	355.7	51.6	354.1
		7	9.02	1.09	2.47	2.73	1.00	-	2.07	0.49	433.9	47.0	357.3
		8	8.74	1.00	2.61	2.83	0.93	-	2.04	0.49	435.9	43.6	335.4
		9	8.18	0.99	2.22	2.67	0.96	-	1.97	0.58	304.0	42.0	306.6
		10	13.53	1.13	2.49	3.04	1.01	-	2.05	0.67	497.6	43.8	388.9
	5	11	9.92	0.92	2.42	2.59	0.60	-	1.87	0.63	569.4	49.9	321.7
		12	11.11	1.16	2.37	2.59	0.68	-	1.90	0.49	499.2	48.1	314.4
		13	11.12	1.11	2.29	2.84	0.67	-	2.16	0.49	482.9	49.4	337.7
		14	10.05	1.01	2.51	2.70	0.70	-	2.10	0.54	444.1	56.0	315.2
		15	8.98	1.03	1.97	2.65	0.64	-	1.95	0.46	469.7	41.2	282.0
	25	16	9.72	1.11	2.44	2.92	0.75	-	1.92	0.54	508.1	39.4	295.6
		17	12.89	1.19	2.90	2.92	0.74	-	2.01	0.61	552.9	54.1	340.2
		18	10.45	1.07	2.42	2.86	0.66	-	1.93	0.53	486.9	39.3	311.5
		19	9.60	0.98	2.09	2.77	0.68	-	1.88	0.57	421.3	42.1	279.4
		20	18.90	0.93	1.91	1.03	0.48	-	1.86	0.67	300.8	42.1	260.0
	125	21	13.78	1.10	2.46	2.82	0.70	-	1.93	0.69	688.3	35.2	327.7
		22	10.11	0.93	2.18	2.80	0.66	-	1.92	0.37	441.2	40.8	288.4
		23	11.89	1.01	2.57	2.92	0.68	-	1.92	0.51	397.4	50.9	288.0
		24	12.72	1.09	2.46	3.28	0.85	-	1.99	0.38	369.5	40.0	319.4
		25	12.59	1.01	2.55	2.65	0.65	-	1.98	0.48	425.5	61.3	282.1
		Recovery											
		26	8.68	1.03	2.29	3.22	0.94	-	1.97	0.59	517.5	32.8	328.4
		27	8.46	1.08	2.53	3.08	1.02	-	1.90	0.58	294.8	53.4	327.8
		28	8.97	1.10	2.29	3.21	0.99	-	1.96	0.69	526.4	50.6	334.4
		29	8.70	1.10	2.38	3.07	1.01	-	2.03	0.49	509.3	52.3	348.9
		30	8.98	1.05	2.75	3.44	0.97	-	1.99	0.55	410.9	45.4	333.3

Addendum 11-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Absolute organ weights of individual animals

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g)	Heart (g)	Kidney (g)	Testis (g)	Epididymis (g)	Ovary (mg)	Brain (g)	Spleen (g)	Thymus (mg)	Adrenal (mg)	Body weight (g)
Female	Vehicle control	31	6.67	0.75	1.46	-	-	74.9	1.84	0.44	489.5	57.5	217.1
		32	6.07	0.81	1.52	-	-	69.2	1.85	0.37	429.3	46.8	200.6
		33	6.14	0.77	1.29	-	-	77.7	1.82	0.34	363.4	58.8	189.7
		34	5.38	0.73	1.41	-	-	84.7	1.80	0.31	281.1	53.7	197.7
		35	7.09	0.73	1.52	-	-	63.2	1.84	0.39	419.7	52.0	208.7
		Recovery											
		36	5.25	0.74	1.46	-	-	54.8	1.81	0.43	334.8	44.2	211.7
		37	6.74	0.98	1.76	-	-	84.3	1.90	0.49	346.2	72.5	243.1
		38	6.08	0.83	1.46	-	-	63.9	1.89	0.43	388.0	58.4	231.6
		39	5.56	0.77	1.65	-	-	73.5	1.83	0.46	299.7	51.1	212.9
		40	6.64	0.79	1.65	-	-	96.4	1.84	0.42	454.5	58.0	248.1
	5	41	7.70	0.80	1.60	-	-	56.0	1.79	0.32	318.3	49.6	194.5
		42	5.09	0.80	1.48	-	-	52.6	1.85	0.35	384.5	62.0	199.2
		43	5.90	0.90	1.55	-	-	79.2	1.79	0.41	472.3	57.0	229.8
		44	7.05	0.92	1.84	-	-	102.5	1.85	0.42	495.2	66.2	240.9
		45	8.94	0.71	1.50	-	-	63.6	1.78	0.38	503.5	49.1	194.5
	25	46	6.51	0.75	1.59	-	-	70.4	1.88	0.34	432.9	58.6	212.4
		47 a)	12.24	1.11	2.36	-	-	70.0	1.93	0.43	618.0	50.7	224.1
		48	7.93	0.73	1.50	-	-	72.8	1.79	0.43	469.8	55.4	299.2
		49	8.56	0.77	1.64	-	-	73.7	1.97	0.49	408.8	50.6	126.5
		50	8.24	0.77	1.49	-	-	72.5	1.89	0.49	430.6	53.4	217.7
	125	51	7.21	0.72	1.53	-	-	77.5	1.81	0.35	399.0	46.3	186.1
		52	7.57	0.73	1.54	-	-	68.9	1.88	0.34	397.1	58.9	193.0
		53	9.06	0.80	1.82	-	-	82.7	1.88	0.39	564.1	65.2	218.5
		54	9.40	0.85	1.85	-	-	76.6	1.78	0.43	441.9	65.0	239.0
		55	8.37	0.81	1.85	-	-	63.1	1.91	0.38	519.7	45.3	210.1
		Recovery											
		56	6.21	0.81	1.59	-	-	74.2	1.89	0.44	386.8	68.4	182.9
		57	6.19	0.76	1.39	-	-	62.8	1.97	0.42	359.7	54.1	201.4
		58	6.41	0.81	1.58	-	-	73.7	1.92	0.43	316.7	68.5	234.0
		59	7.75	0.94	1.70	-	-	64.1	1.87	0.46	534.7	70.8	262.2
		60	6.39	0.80	1.62	-	-	82.9	1.94	0.40	409.9	52.5	228.9

a) Dead animal.

Addendum 12-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Relative organ weights of individual animals

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g/100g)	Heart (g/100g)	Kidney (g/100g)	Testis (g/100g)	Epididymis (g/100g)	Ovary (mg/100g)	Brain (g/100g)	Spleen (g/100g)	Thymus (mg/100g)	Adrenal (mg/100g)	Body weight (g)
Male	Vehicle control	1	2.98	0.32	0.65	1.06	0.25	-	0.64	0.14	163.1	18.4	299.7
		2	3.33	0.33	0.68	0.83	0.20	-	0.59	0.19	103.8	15.9	316.9
		3	3.17	0.32	0.77	0.90	0.22	-	0.61	0.17	183.4	15.0	295.7
		4	3.42	0.34	0.67	0.86	0.20	-	0.64	0.15	155.3	19.3	306.7
		5	3.89	0.30	0.63	0.73	0.18	-	0.50	0.21	157.2	13.9	377.3
		Recovery											
		6	2.49	0.30	0.61	0.89	0.28	-	0.55	0.17	100.5	14.6	354.1
		7	2.52	0.31	0.69	0.76	0.28	-	0.58	0.14	121.4	13.2	357.3
		8	2.61	0.30	0.78	0.84	0.28	-	0.61	0.15	130.0	13.0	335.4
		9	2.67	0.32	0.72	0.87	0.31	-	0.54	0.19	99.2	13.7	366.6
		10	3.48	0.29	0.64	0.78	0.26	-	0.52	0.17	128.0	11.3	328.9
	5	11	3.08	0.30	0.75	0.81	0.19	-	0.68	0.20	117.0	15.5	311.7
		12	3.53	0.36	0.75	0.82	0.22	-	0.60	0.16	158.8	15.6	314.4
		13	3.26	0.31	0.68	0.84	0.20	-	0.64	0.15	143.0	14.8	337.7
		14	3.47	0.35	0.80	0.86	0.22	-	0.67	0.17	140.9	17.6	315.2
		15	3.11	0.37	0.70	0.94	0.23	-	0.69	0.16	166.6	14.3	282.0
	25	16	3.32	0.38	0.83	0.99	0.25	-	0.55	0.18	171.9	13.3	295.6
		17	3.82	0.35	0.85	0.86	0.22	-	0.69	0.18	162.5	15.9	340.2
		18	3.35	0.34	0.78	0.92	0.21	-	0.62	0.17	156.3	12.6	311.5
		19	3.46	0.35	0.75	0.99	0.24	-	0.77	0.20	110.8	15.1	279.4
		20	3.42	0.36	0.73	0.40	0.18	-	0.72	0.26	115.7	16.2	260.0
	125	21	4.02	0.34	0.75	0.80	0.18	-	0.59	0.21	140.0	10.7	327.7
		22	3.78	0.32	0.76	0.97	0.23	-	0.67	0.13	153.0	12.1	288.4
		23	4.06	0.35	0.89	1.01	0.24	-	0.67	0.18	138.0	17.7	288.0
		24	3.98	0.34	0.77	1.03	0.20	-	0.62	0.12	115.7	12.5	319.4
		25	4.46	0.36	0.90	0.94	0.23	-	0.69	0.17	150.8	21.7	282.1
		Recovery											
		26	2.64	0.31	0.70	0.98	0.29	-	0.60	0.18	157.6	10.0	328.4
		27	2.58	0.33	0.77	0.94	0.31	-	0.58	0.18	89.9	16.3	327.8
		28	2.68	0.33	0.68	0.96	0.30	-	0.59	0.21	157.4	15.1	334.4
		29	2.49	0.32	0.68	0.88	0.29	-	0.58	0.14	146.0	15.0	348.9
		30	2.69	0.32	0.83	1.03	0.29	-	0.60	0.17	123.3	13.6	333.3

Addendum 12-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Relative organ weights of individual animals

B11-0836

Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g/100g)	Heart (g/100g)	Kidney (g/100g)	Testis (g/100g)	Epididymis (g/100g)	Ovary (mg/100g)	Brain (g/100g)	Spleen (g/100g)	Thymus (mg/100g)	Adrenal (mg/100g)	Body weight (g)
Female	Vehicle control	31	3.07	0.35	0.67	–	–	34.5	0.85	0.20	225.5	26.5	217.1
		32	3.03	0.40	0.76	–	–	34.5	0.92	0.18	214.0	23.3	200.8
		33	3.24	0.41	0.68	–	–	41.0	0.96	0.18	191.6	31.0	189.7
		34	2.72	0.37	0.71	–	–	42.8	0.91	0.16	142.2	27.2	197.7
		35	3.40	0.35	0.73	–	–	30.3	0.88	0.19	201.1	24.9	208.7
		Recovery											
		36	2.48	0.35	0.69	–	–	25.9	0.85	0.20	158.1	20.9	211.7
		37	2.77	0.40	0.72	–	–	34.7	0.78	0.20	142.4	29.8	243.1
		38	2.63	0.36	0.63	–	–	27.6	0.82	0.19	167.5	25.2	231.6
		39	2.61	0.36	0.78	–	–	34.5	0.86	0.22	148.8	24.0	212.9
		40	2.80	0.32	0.67	–	–	38.3	0.74	0.17	183.2	23.4	248.1
	5	41	2.88	0.41	0.82	–	–	28.8	0.92	0.16	163.7	25.5	194.5
		42	2.91	0.40	0.74	–	–	26.4	0.93	0.18	195.0	31.1	199.2
		43	3.07	0.39	0.67	–	–	34.5	0.78	0.18	205.5	24.8	229.8
		44	3.34	0.38	0.76	–	–	42.5	0.77	0.17	205.6	27.5	240.9
		45	3.04	0.37	0.77	–	–	32.7	0.92	0.20	208.9	25.2	194.5
	25	46	3.08	0.35	0.75	–	–	33.1	0.89	0.16	253.8	27.6	294.4
		47 a)	5.46	0.50	2.05	–	–	31.2	0.86	0.19	205.8	22.6	214.1
		48	3.49	0.37	0.75	–	–	36.1	0.90	0.22	275.8	27.8	129.2
		49	3.33	0.34	0.72	–	–	32.6	0.87	0.22	130.5	22.3	296.5
		50	3.77	0.35	0.68	–	–	33.4	0.87	0.23	187.8	29.1	227.7
	125	51	3.91	0.39	0.82	–	–	41.6	0.97	0.19	294.4	24.9	186.1
		52	3.92	0.38	0.80	–	–	35.7	0.97	0.18	215.8	30.5	193.0
		53	4.15	0.37	0.83	–	–	37.8	0.86	0.18	208.2	29.8	218.5
		54	3.96	0.36	0.77	–	–	32.1	0.74	0.18	164.9	27.2	239.0
		55	3.98	0.39	0.88	–	–	30.0	0.91	0.18	247.4	21.6	210.1
		Recovery											
		56	3.40	0.44	0.87	–	–	40.6	1.03	0.24	211.5	37.4	182.9
		57	3.07	0.38	0.69	–	–	31.2	0.98	0.21	178.6	26.9	201.4
		58	2.74	0.35	0.68	–	–	31.5	0.82	0.18	135.3	29.3	234.0
		59	2.96	0.36	0.65	–	–	24.4	0.71	0.18	203.9	27.0	262.2
		60	2.79	0.35	0.71	–	–	36.2	0.85	0.17	179.1	22.9	228.9

a) Dead animal.

Addendum 13-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	Vehicle control	1	ta	No abnormalities detected	Heart Focal myocarditis +
		2	ta	No abnormalities detected	Kidney Basophilic tubules+
		3	ta	No abnormalities detected	Kidney Focal hyperplasia of tubular epithelium+ Prostate Round cell infiltration +
		4	ta	No abnormalities detected	No abnormalities detected
		5	ta	No abnormalities detected	Kidney Basophilic tubules +

a) Organs/tissues examined as follows: trachea, lungs, incisor, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, urinary bladder, testes, epididymides, prostate, seminal vesicle, cerebrum, cerebellum, pons, spinal cord, sciatic nerve, bone marrow, axillar lymph node, mesenteric lymph node, spleen, thymus, pituitary gland, thyroid, parathyroid, adrenals and eye ball.

ta, terminal autopsy.

+, slight.

Addendum 13-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	Vehicle control (Recovery)	6	ta	No abnormalities detected	No abnormalities detected
		7	ta	No abnormalities detected	No abnormalities detected
		8	ta	No abnormalities detected	No abnormalities detected
		9	ta	No abnormalities detected	No abnormalities detected
		10	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: incisor, liver, heart, kidneys and testes.
ta, terminal autopsy.

Addendum 13-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	5	11	ta	No abnormalities detected	No abnormalities detected
		12	ta	No abnormalities detected	No abnormalities detected
		13	ta	No abnormalities detected	No abnormalities detected
		14	ta	No abnormalities detected	No abnormalities detected
		15	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: incisor, liver and kidneys.
ta, terminal autopsy.

Addendum 13-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	25	16	ta	No abnormalities detected	No abnormalities detected
		17	ta	No abnormalities detected	No abnormalities detected
		18	ta	No abnormalities detected	No abnormalities detected
		19	ta	No abnormalities detected	No abnormalities detected
		20	ta	Testis Small (bilateral) Softening (bilateral)	Testis Diffuse atrophy of seminiferous tubules +++ Leydig cell hyperplasia ++

a) Organs/tissues examined as follows: incisor, liver, kidneys and macroscopic lesion.
ta, terminal autopsy.
++, moderate; +++, severe.

Addendum 13-5 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	125	21	ta	Liver Enlargement	Incisor Decreased iron pigments of ameloblasts at maturation stage + Liver Periportal hypertrophy of hepatocytes + Periportal prominent nucleoli of hepatocytes + Heart Focal myocarditis +
		22	ta	Oral cavity Mottled teeth (lower incisors)	Incisor Cyst formation in papillary layer + Decreased iron pigments of ameloblasts at maturation stage + Liver Periportal hypertrophy of hepatocytes + Periportal prominent nucleoli of hepatocytes + Kidney Basophilic tubules +
		23	ta	Liver Enlargement	Liver Periportal hypertrophy of hepatocytes +
		24	ta	Oral cavity Mottled teeth (upper incisors) Liver Enlargement	Incisor No abnormalities detected Liver Periportal hypertrophy of hepatocytes + Periportal prominent nucleoli of hepatocytes +

a) Organs/tissues examined as follows: trachea, lungs, incisor, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, urinary bladder, testes, epididymides, prostate, seminal vesicle, cerebrum, cerebellum, pons, spinal cord, sciatic nerve, bone marrow, axillar lymph node, mesenteric lymph node, spleen, thymus, pituitary gland, thyroid, parathyroid, adrenals and eye ball.

ta, terminal autopsy.

+, slight.

Addendum 13-6 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	125	25	ta	Liver Enlargement	Incisor Decreased iron pigments of ameloblasts at maturation stage + Irregular alignment of ameloblasts at maturation stage + Liver Periportal hypertrophy of hepatocytes + Single cell necrosis of hepatocytes + Kidney Dilatation of tubules +

a) Organs/tissues examined as follows: trachea, lungs, incisor, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, urinary bladder, testes, epididymides, prostate, seminal vesicle, cerebrum, cerebellum, pons, spinal cord, sciatic nerve, bone marrow, axillar lymph node, mesenteric lymph node, spleen, thymus, pituitary gland, thyroid, parathyroid, adrenals and eye ball.

ta, terminal autopsy.

+, slight.

Addendum 13-7 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	125 (Recovery)	26	ta	Oral cavity Mottled teeth (upper and lower incisors)	Incisor No abnormalities detected Kidney Solitary cyst in medulla+
		27	ta	Oral cavity Mottled teeth (upper and lower incosors)	No abnormalities detected Incisor No abnormalities detected
		28	ta	Oral cavity Mottled teeth (upper incisors)	Incisor Irregular alignment of ameloblasts at maturation stage +
		29	ta	Oral cavity Mottled teeth (upper and lower incisors)	No abnormalities detected Incisor No abnormalities detected
		30	ta	Oral cavity Mottled teeth (upper and lower incisors)	Incisor Irregular alignment of ameloblasts at maturation stage + Kidney Basophilic tubules +

a) Organs/tissues examined as follows: incisor, liver, heart, kidney and testes.
ta, terminal autopsy.
+, slight.

Addendum 13-8 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	Vehicle control	31	ta	No abnormalities detected	Uterus Endometrial atrophy + Vagina Mucification of epithelium ++
		32	ta	No abnormalities detected	Kidney Mineralization in cortico-medullary junction +
		33	ta	No abnormalities detected	Kidney Mineralization in cortico-medullary junction+
		34	ta	No abnormalities detected	Forestomach Necrosis of squamous epithelium in limiting ridge ± Vagina Vaginitis +
		35	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: trachea, lungs, incisor, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, urinary bladder, ovaries, uterus, vagina, cerebrum, cerebellum, pons, spinal cord, sciatic nerve, bone marrow, axillar lymph node, mesenteric lymph node, spleen, thymus, pituitary gland, thyroid, parathyroid, adrenals and eye ball.

ta, terminal autopsy.

±, very slight; +, slight; ++, moderate.

Addendum 13-9 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	Vehicle control (Recovery)	36	ta	No abnormalities detected	No abnormalities detected
		37	ta	No abnormalities detected	Kidney Mineralization in cortico-medullary junction +
		38	ta	No abnormalities detected	Kidney Mineralization in cortico-medullary junction +
		39	ta	No abnormalities detected	No abnormalities detected
		40	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: incisor, liver, kidneys, cerebrum, cerebellum and pons.
ta, terminal autopsy.
+, slight.

Addendum 13-10 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	5	41	ta	No abnormalities detected	No abnormalities detected
		42	ta	No abnormalities detected	No abnormalities detected
		43	ta	No abnormalities detected	No abnormalities detected
		44	ta	No abnormalities detected	No abnormalities detected
		45	ta	No abnormalities detected	Kidney Mineralization in cortico-medullary junction +

a) Organs/tissues examined as follows: incisor, liver and kidneys.
ta, terminal autopsy.
+, slight.

Addendum 13-11 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	25	46	ta	No abnormalities detected	No abnormalities detected
		47	fd	Lung Dark reddish change	Lung. Congestion ++ Edema+
		48	ta	No abnormalities detected	No abnormalities detected
		49	ta	No abnormalities detected	No abnormalities detected
		50	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: incisor, liver, kidneys and macroscopic lesion.
ta, terminal autopsy; fd, found dead.
+, slight; ++, moderate.

Addendum 13-12 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	125	51	ta	Oral cavity Mottled teeth (upper incisors) Liver Enlargement	Incisor No abnormalities detected Liver No abnormalities detected Kidney Ballooning of tubular epithelium +
		52	ta	Liver Enlargement	No abnormalities detected Liver No abnormalities detected
		53	ta	Liver Enlargement	Incisor Decreased iron pigments of ameloblasts at maturation stage + Liver Diffuse hypertrophy of hepatocytes +
		54	ta	Liver Enlargement	Incisor Cyst formation in papillary layer + Decreased iron pigments of ameloblasts at maturation stage + Irregular alignment of ameloblasts at maturation stage + Forestomach Necrosis of squamous epithelium in limiting ridge + Liver Diffuse hypertrophy of hepatocytes +
		55	ta	Oral cavity Mottled teeth (upper incisors) Liver Enlargement	No abnormalities detected Incisor No abnormalities detected Liver No abnormalities detected

a) Organs/tissues examined as follows: trachea, lungs, incisor, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, urinary bladder, ovaries, uterus, vagina, cerebrum, cerebellum, pons, spinal cord, sciatic nerve, bone marrow, axillar lymph node, mesenteric lymph node, spleen, thymus, pituitary gland, thyroid, parathyroid, adrenals and eye ball.

ta, terminal autopsy.

+, slight.

Addendum 13-13 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	125 (Recovery)	56	ta	Oral cavity Mottled teeth (upper and lower incisors)	No abnormalities detected Incisor No abnormalities detected
		57	ta	Oral cavity Mottled teeth (upper and lower incisors) Rough surface of incisor (lower incisors)	Incisor Irregular alignment of ameloblasts at maturation stage + Irregular alignment of papillary layer+
		58	ta	Oral cavity Mottled teeth (upper and lower incisors)	Incisor Decreased iron pigments of ameloblasts at maturation stage + Irregular alignment of ameloblasts at maturation stage+
		59	ta	Oral cavity Mottled teeth (upper and lower incisors) Thyroid Aplasia of left lobe	Incisor No abnormalities detected Thyroid Aplasia of left lobe
		60	ta	Oral cavity Mottled teeth (upper and lower incisors)	Incisor Irregular alignment of ameloblasts at maturation stage +

a) Organs/tissues examined as follows: incisor, liver, kidneys, cerebrum, cerebellum, pons and macroscopic lesion.
ta, terminal autopsy.
+, slight.

APPENDIX 1

"STABILITY ANALYSIS OF [redacted] HOMOGENEITY, STABILITY AND CONCENTRATION ANALYSES OF THE TEST SUBSTANCE FORMULATION (Study code: X18-0836)"

[redacted]

Receipt No. 827-06-D-3206

STUDY CODE: X18-0836

FINAL REPORT

STABILITY ANALYSIS OF [redacted] HOMOGENEITY, STABILITY AND CONCENTRATION ANALYSES OF THE TEST SUBSTANCE FORMULATION

May 2007

[redacted]

STATEMENT

I, the undersigned, hereby declare that this report provides a correct English translation of the final report (Study Code: X18-0836, issued on May 23, 2007).

[redacted]

September 6, 2009

Date

GLP STATEMENT

[redacted]

Sponsor: [redacted]

Title: Stability Analysis of [redacted] Homogeneity, Stability and Concentration Analyses of the Test Substance Formulation

Study Code: X18-0836

I, the undersigned, hereby declare that this study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" on [redacted]

I also confirmed that this report accurately reflected the raw data and the test data were valid.

Study Director: Signed in original [redacted] May 23, 2007

QUALITY ASSURANCE STATEMENT

[redacted]

Sponsor: [redacted]

Title: Stability Analysis of [redacted] Homogeneity, Stability and Concentration Analyses of the Test Substance Formulation

Study Code: X18-0836

This study was inspected by Quality Assurance Unit of [redacted] The dates inspected and the dates reported these results to the study director and management are as follows

Item of Inspections/Audits	Dates of Inspections/Audits	Dates of Report of Inspections/Audits
Protocol	December 26, 2006	December 26, 2006
IR spectrum of test substance	December 27, 2006	December 27, 2006
Amendment to protocol	January 10, 2007	January 11, 2007
Homogeneity and stability analyses of test substance formulation	January 10, 2007	January 11, 2007
Concentration analysis of test substance formulation	January 22, 2007	January 22, 2007
Reinspection of amendment to protocol	March 8, 2007	March 8, 2007
Raw data and draft final report	May 11, 2007	May 11, 2007
Reinspection of raw data and draft final report	May 18, 2007	May 18, 2007
Draft final report (2nd)	May 23, 2007	May 23, 2007
Final report	May 23, 2007	May 23, 2007

I, the undersigned, hereby declare that this report provides an accurate description of the methods and procedures used in this study, and that the reported results accurately reflect obtained raw data.

Head, Quality Assurance Unit: Signed in original [redacted] May 23, 2007

TABLE OF CONTENTS

TABLES

FIGURES

REFERENCE

Study Code: X18-0836
Test Substance Code: HR6851
Sponsor Code: D-0060

TITLE

Stability Analysis of [redacted] Homogeneity, Stability and Concentration Analyses of the Test Substance Formulation

SPONSOR

[redacted]

TESTING FACILITY

[redacted]

PURPOSE OF STUDY

The purpose of this study is to determine the stability of the test substance during the dosing period, and homogeneity, stability and concentration of the test substance in formulation in "Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of [redacted] in Rats" (Study Code: B11-0836).

GLP COMPLIANCE

This study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" on [redacted]

Health Department, MOE (November 21, 2003)].

PERIOD OF STUDY

Commencement of Study:	December 25, 2006
Initiation of Examination (Initiation of Analysis):	December 27, 2006
Termination of Examination (Termination of Analysis):	March 5, 2007
Completion of Study:	May 23, 2007

STORAGE AND RETENTION PERIOD OF DATA

The raw data, protocol, amendment to protocol, study contract documents, test substance information, final report and other record documents will be retained in the archive of the Hita Laboratory of our organization for the same period of B11-0836 paper data. After termination of the retention period, any measures taken will be done so with the approval of the sponsor.

RETENTION OF ORIGINAL DOCUMENTS

An original protocol, an original amendment to protocol and an original final report will be retained at [redacted] The copies of their original that the study director will be recognized to be accurate copy will be sent to the sponsor.

STUDY DIRECTOR AND PERSONS CONCERNED WITH THE STUDY AND THE OPERATION

Study director: [redacted]

Study staff: [redacted]

(Analysis of the test substance)

[redacted]

(Preparation of the test substance formulation)

APPROVAL BY AUTHOR

Study director: Signed in original May 23, 2007

[redacted]

Analytical Chemistry Section

[redacted]

SUMMARY

The test substance [redacted] was stable during the dosing period of subject study (Study Code: B11-0836).

The test substance in 1.25 and 0.05 w/v% formulations was stable for 8 days after preparation at cold and dark place and showed good homogeneity. The concentration of test substance in 1.25, 0.25 and 0.05 w/v% dose formulations for subject study was acceptable level.

MATERIALS

1. TEST SUBSTANCE (INFORMATION PROVIDED BY THE SPONSOR)

1.1 Name

[redacted]

Other Name: [redacted]

CASNo.:

1.2 LotNo.

6X002

1.3 Supplier

[redacted]

1.4 Structural Formula

[redacted]

(Molecular formula: [redacted]

1.5 Purity

99.7%

1.6 Names and Concentration of Impurities

Unknown 0.3%

1.7 Physicochemical Properties

Appearance at ordinary temperature:	clear colorless liquid
Molecular weight:	[redacted]
Stability:	—
Melting point:	—
Boiling point:	78°C (8 mmHg)
Vapor pressure:	—
Density:	1.554 g/cm^3 (25°C)
Partition coefficient:	—
Hydrolyzability:	hydrolyzable
[redacted]	
Solubility:	—
Degree of solubility	
Water:	insoluble

DMSO:	soluble (arbitrary mixable)
Acetone:	soluble (arbitrary mixable)
Others:	—

1.8 Storage Conditions

The test substance was stored at room temperature under a light shielding condition (desiccator No. 2 in the test substance storage room, tolerance temperature: 10-30°C).

1.9 Handling Precaution

Gloves, mask, cap and lab coat were worn.

METHODS

1. SUBJECT STUDY

Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of [redacted] in Rats (Study Code: B11-0836)

2. STABILITY ANALYSIS OF THE TEST SUBSTANCE

The infrared (IR) spectrum was measured by IR spectrophotometer before and after the dosing period of subject study. Test substance was used under light shield.

2.1 Measurement of IR

1) Instrument

IR spectrophotometer: FT-720 (HORIBA, Ltd.)

2) Condition

Wave number: 4000 cm^{-1} - 400 cm^{-1}

3) Pre-Treatment

Potassium bromide neat

2.2 Criteria for Judgment

IR spectrum of the test substance that measured prior to dosing in our laboratory should be identical with provided from the sponsor. The test substance was judged to be stable when there are no differences in the IR spectrums at before and after dosing period.

3. HOMOGENEITY, STABILITY AND CONCENTRATION ANALYSES OF THE TEST SUBSTANCE FORMULATION

In the homogeneity analysis, the samples were taken (n=1) from the upper, middle and lower layers of formulations immediately after preparation, respectively. These samples were pretreated and measured (n=1) with gas chromatography (GC).

In the stability analysis, the formulations were stored at cold and dark place for 8 days, and the sample was taken (n=1) from the middle layer of the formulations at point of

measurement (5 days and 9 days after preparation). These samples were pretreated and measured (n=1) with GC.

In the concentration analysis, the samples were taken (n=1) from the middle layer of dose formulations immediately after preparation for subject study. These samples were pretreated and measured (n=1) with GC.

Test substance and formulations were used under light shield.

3.1 The Test Substance Formulation

1) Homogeneity and Stability Analyses

(1) Concentration

1.25 and 0.05 w/v%

(2) Preparation Method

Weighed accurately 1.88 g of the test substance, added olive oil (including 0.5% Tween80) to make 150 mL, and used as 1.25 w/v% formulation. After stirred with homogenizer, accurate 4 mL of 1.25 w/v% formulation was diluted with olive oil (including 0.5% Tween80) to make 100 mL, and used as 0.05 w/v% formulation.

Vehicle: olive oil (Fujimi Pharmaceutical)
Polyoxyethylene (20) sorbitan mono-oleate (Tween80, Wako Pure Chemical Industries)

2) Concentration Analysis

The 1.25, 0.25 and 0.05 w/v% dose formulations at first administration for subject study were used.

3.2 Outline of Analytical Method

The analytical method was decided, according to results of validation of the analytical method on non-GLP at the test facility.

1) Validation of the Analytical Method

(1) Preparation for Measurement Sample

a) Standard Stock Solution for Validation of the Analytical Method

Weighed 0.1000 g of the test substance, dissolved in ethyl acetate to make 100 mL, and used this solution as 1000 μg/mL standard stock solution for validation of the analytical method.

b) Sample for Specificity

The standard stock solution for validation of the analytical method was diluted with ethyl acetate to make 10.0 μg/mL standard solution and 10.0 μg/mL vehicle-containing standard solution (containing 10 v/v% vehicle (olive oil including 0.5% Tween80)). Ethyl acetate was used as solvent blank, and vehicle blank (containing 10 v/v% vehicle) was prepared.

c) Sample for Linearity

The standard stock solution for validation of the analytical method was diluted with ethyl acetate to make 5.00, 10.0[*1] and 20.0 μg/mL standard solutions.

*1: It was used 10.0 μg/mL standard solution which prepared in section 3.2.1) (1) b).

d) Sample for Accuracy and Repeatability

Standard solutions (concentration: 5.00, 10.0 and 20.0 μg/mL, each concentration: n=3) were prepared in the same way of sample for linearity.

(2) Specificity

Samples for specificity were measured with GC. The variation of detection value (peak area) of the test substance between standard solution with and without vehicle was 0.9%. Therefore, it was confirmed that the result of variation satisfied criteria for judgment (within ±5%). In the results of GC analysis of solvent blank and vehicle blank, it was confirmed there were no background and interfering peaks at the elution peak position of test substance.

(3) Linearity

Samples for linearity were measured with GC. The calibration curve was made by the concentration of the test substance in the horizontal line and the detection value of test substance in the vertical line. The regression formula passed through the origin of the coordinates, and the coefficient of correlation of calibration curve which was obtained from least square was R=0.999. Therefore, it was confirmed that the result of linearity satisfied criteria for judgment (more than 0.999).

(4) Accuracy and Repeatability

Samples for accuracy and repeatability were measured with GC. The concentrations of the test substance were calculated with regression formula that was obtained at linearity. Accuracy and repeatability were calculated with these values.

Accuracy of 5.00 μg/mL standard solution was 0.3,-1.1 and 2.6%.

Accuracy of 10.0 μg/mL standard solution was -1.5, -1.7 and 0.1%.

Accuracy of 20.0 μg/mL standard solution was 0.1, -1.4 and -0.1%.

Repeatability of 5.00, 10.0 and 20.0 μg/mL standard solution was 1.9, 1.0 and 0.8%, respectively.

It was confirmed that the result of accuracy and repeatability satisfied criteria for judgment (accuracy: within ±10%, repeatability: less than 5%).

2) Preparation for Standard Solution

Weighed 0.1001 g of the test substance dissolved in ethyl acetate to make 100 mL, and used this solution as 1001 μg/mL standard stock solution. Accurate 2 mL of

standard stock solution diluted with ethyl acetate to make 20 mL, and 100 μg/mL standard solution was prepared. Accurate 2 mL of 100 μg/mL standard solution diluted with ethyl acetate to make 20 mL, and 10.0 μg/mL standard solution was prepared.

3) Pre-Treatment

Formulations were mixed well using a magnetic stirrer.

(1) Homogeneity and Stability Analyses

a) 1.25 w/v% Formulation

Accurate 0.5 mL of formulation was dissolved in ethyl acetate to make 25 mL. Accurate 1 mL of this solution was diluted with ethyl acetate to make 25 mL, and served as a GC sample (dilution rate: 1250).

b) 0.05 w/v% Formulation

Accurate 0.5 mL of formulation was dissolved in ethyl acetate to make 25 mL, and served as a GC sample (dilution rate: 50).

(2) Concentration Analysis

a) 1.25 w/v% Formulation

Accurate 0.5 mL of formulation was dissolved in ethyl acetate to make 25 mL. Accurate 1 mL of this solution was diluted with ethyl acetate to make 25 mL, and served as a GC sample (dilution rate: 1250).

b) 0.25 w/v% Formulation

Accurate 0.5 mL of formulation was dissolved in ethyl acetate to make 25 mL. Accurate 2 mL of this solution was diluted with ethyl acetate to make 10 mL, and served as a GC sample (dilution rate: 250).

c) 0.05 w/v% Formulation

Accurate 0.5 mL of formulation was dissolved in ethyl acetate to make 25 mL, and served as a GC sample (dilution rate: 50).

4) Conditions of GC Analysis

(1) Instruments (HP6890)

Gas chromatograph:	HP6890 Series [redacted]
Controller:	G1512A [redacted]
Auto sampler:	18596C [redacted]
Injector:	18593B [redacted]
Data processor:	GC-Chemstation [redacted]

(2) Conditions

Column:	HP-1MS (F.T. 0.25 μm) 0.25 mm I.D. × 30 m
Column oven temperature:	100°C
Temperature of injection port:	250°C
Detector:	FID

Detector temperature:	250°C
Injection volume:	2μL
Injection method:	split (split ratio 10:1)
Carrier gas:	helium
Carrier gas flow rate:	1.0 mL/min

3.3 Data Processing

1) Detection Value

A peak area was used as the detection value.

2) Quantitative Analytical Method

In validation of the analytical method, the result of linearity was a straight line range of 5.00, 10.0 and 20.0 μg/mL standard solutions, and it passed through the origin of the coordinates. Therefore, the concentrations of analytical samples were determined by single level calibration.

3) Calculation of the Test Substance Concentration in Formulation

Concentration of test substance in each sample (C: w/v%) was calculated with the equation shown below and rounded off to three significant figures.

$$C = \frac{Cs \times A \times D}{As \times 10000}$$

Cs: Test substance concentration in standard solution (μg/mL)

As: Detection value of test substance in standard solution

A: Detection value of test substance in each GC sample

D: Dilution rate in each GC sample

3.4 Criteria for Judgment

1) Homogeneity Analysis

The test substance was judged as homogeneous dispersion in vehicle if a coefficient of variation (CV) was within 5%. The CV was calculated using the following equation:

$$CV(\%) = \frac{\text{Standard deviation for concentration of test substance in each layer}}{\text{Mean concentration of test substance in each layer}} \times 100$$

2) Stability Analysis

The test substance was judged as stable state in vehicle if a rate to the nominal concentration for the actual concentration (R.N.) and a rate to the mean concentration immediately after preparation for the actual concentration (R.P.) were within the range of 100±10%. The R.N. and R.P. were calculated using the following equation:

$$R.N.(\%) = \frac{\text{Actual concentration}}{\text{Nominal concentration}} \times 100$$

$$R.P.(\%) = \frac{\text{Actual concentration}}{\text{Mean concentration immediately after preparation}} \times 100$$

3) Concentration Analysis

It was confirmed that R.N. was within the range of 100±10%. The R.N. was calculated using the following equation:

$$R.N.(\%) = \frac{\text{Actual concentration}}{\text{Nominal concentration}} \times 100$$

ENVIRONMENTAL FACTORS THAT MIGHT HAVE AFFECTED RELIABILITY OF STUDY RESULTS

There were no factors that might have affected the reliability of the study data.

RESULTS AND DISCUSSION

1. RESULTS

1.1 Stability Analysis of the Test Substance

IR spectrum of test substance provided by the sponsor (Reference 1) was identical with that measured before dosing period for subject study (Figure 1).

There were no differences in the IR spectra between before and after dosing period (Figures 1, 2).

1.2 Homogeneity, Stability and Concentration Analyses of the Test Substance Formulation

1) Homogeneity and Stability Analyses

The results of homogeneity and stability analyses of the test substance formulation are shown in Table 1.

(1) Homogeneity Analysis

CV of 1.25 and 0.05 w/v% formulations were 0.8 and 1.4%, respectively. The results satisfied criteria for judgment.

(2) Stability Analysis

a) 1.25 w/v% Formulation

At immediately after preparation, R.N. were 96.0 to 97.6%.

At 5 days after preparation, R.N. was 99.2%, and R.P. was 102%.

At 9 days after preparation, R.N. was 97.6%, and R.P. was 101%.

All the results of R.N. and R.P. satisfied criteria for judgment.

b) 0.05 w/v% Formulation

At immediately after preparation, R.N. were 95.6 to 98.2%.

At 5 days after preparation, R.N. was 99.4%, and R.P. was 102%.

At 9 days after preparation, R.N. was 98.0%, and R.P. was 101%.

All the results of R.N. and R.P. satisfied criteria for judgment.

2) Concentration Analysis

The results of concentration analysis of the test substance formulation are shown in Table 2.

R.N. of 1.25, 0.25 and 0.05 w/v% dose formulations were 98.4 to 99.2%. All the results satisfied criteria for judgment.

2. DISCUSSION

The test substance was stable during the dosing period of subject study.

The test substance in 1.25 and 0.05 w/v% formulations was stable for 8 days after preparation at cold and dark place and showed good homogeneity. The concentration of test substance in 1.25, 0.25 and 0.05 w/v% dose formulations for subject study was acceptable level.

Table 1 Homogeneity and stability analyses of the test substance formulation

Nominal cone. (w/v%)	Time point of measurement	Layer of measurement	Actual cone. (w/v%)	R.N. (%)	Mean conc. (w/v%)	R.P. (%)	CV (%)
1.25	Immediately after preparation	Upper	1.21	96.8	1.21	-	0.8
		Middle	1.22	97.6			
		Lower	1.20	96.0			
	5 days after preparation	Middle	1.24	99.2	-	102	-
	9 days after preparation	Middle	1.22	97.6	-	101	-
0.05	Immediately after preparation	Upper	0.0489	97.8	0.0486	-	1.4
		Middle	0.0478	95.6			
		Lower	0.0491	98.2			
	5 days after preparation	Middle	0.0497	99.4	-	102	-
	9 days after preparation	Middle	0.0490	98.0	-	101	-

R.N.: Rate to the nominal concentration

R.P.: Rate to the concentration measured immediately after preparation

CV: Coefficient of variation

Table 2 Concentration analysis of the dose formulation

Date of analysis	Nominal cone. (w/v%)	Actual cone. (w/v%)	R.N. (%)
January 22, 2007	1.25	1.23	98.4
	0.25	0.247	98.8
	0.05	0.0496	99.2

R.N.: Rate to the nominal concentration

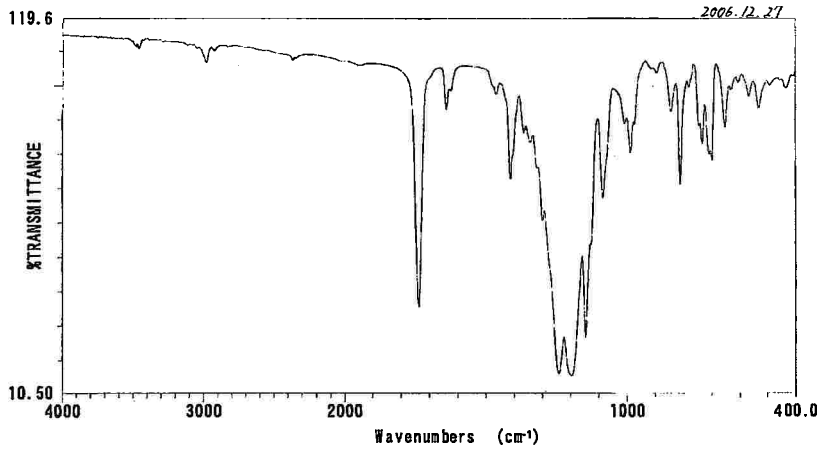


Figure 1 IR spectrum measured prior to the administration period

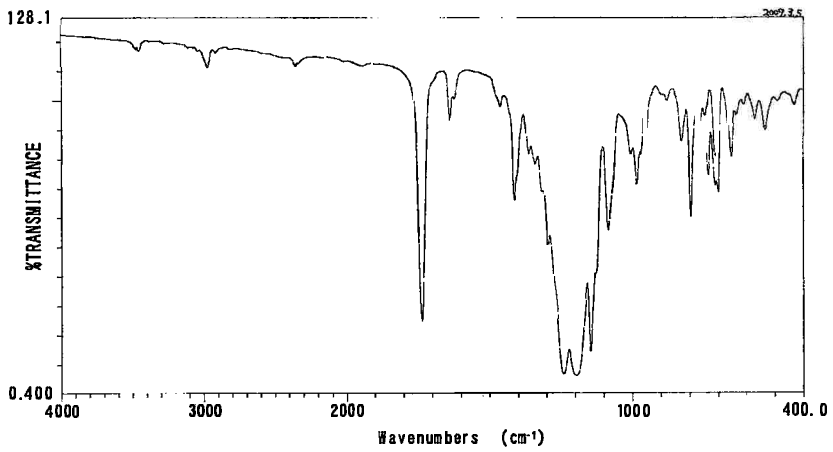
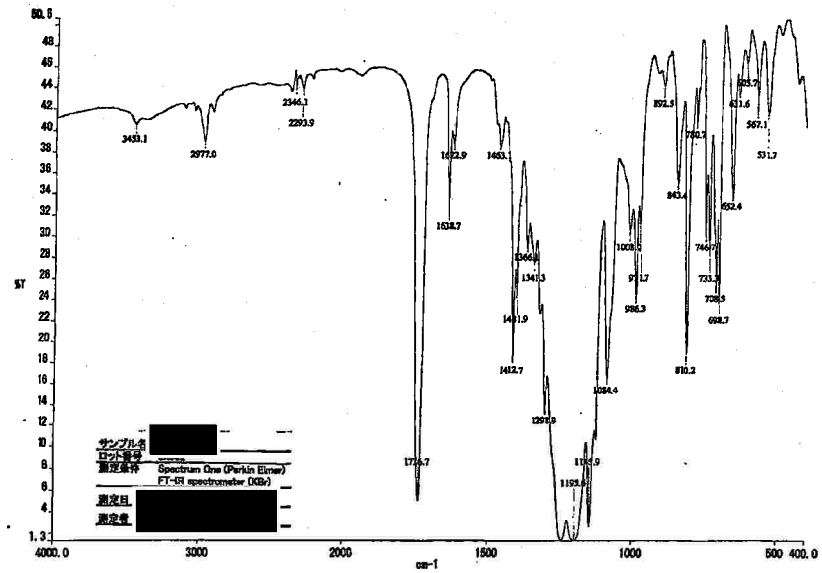


Figure 2 IR spectrum measured after the end of the administration period



Reference 1 IR spectrum provided by the sponsor

APPENDIX2

"HISTOPATHOLOGICAL PHOTOS"

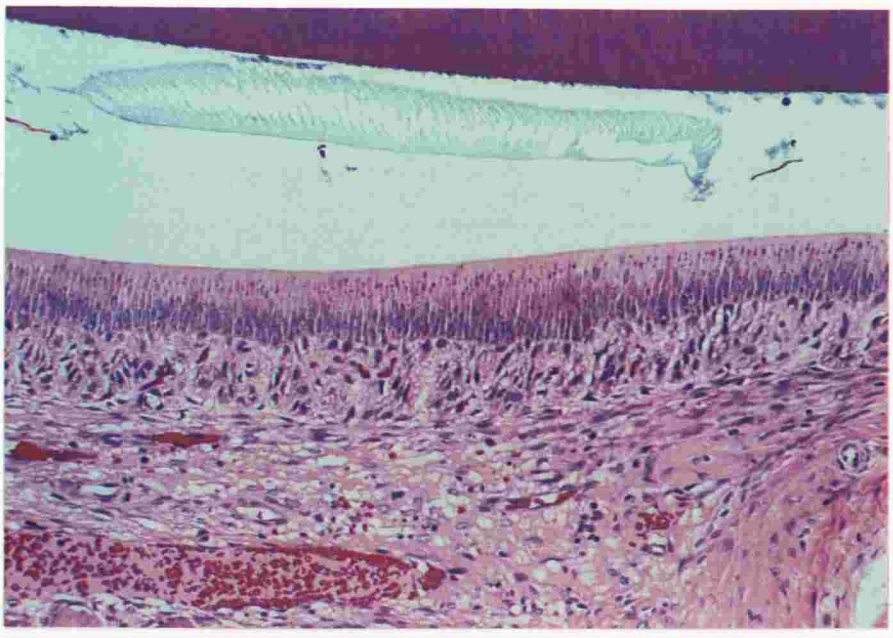


Photo. 1 Incisor of a female rat from vehicle control group.
Normal.
No. 31 animal. HE. ×180.

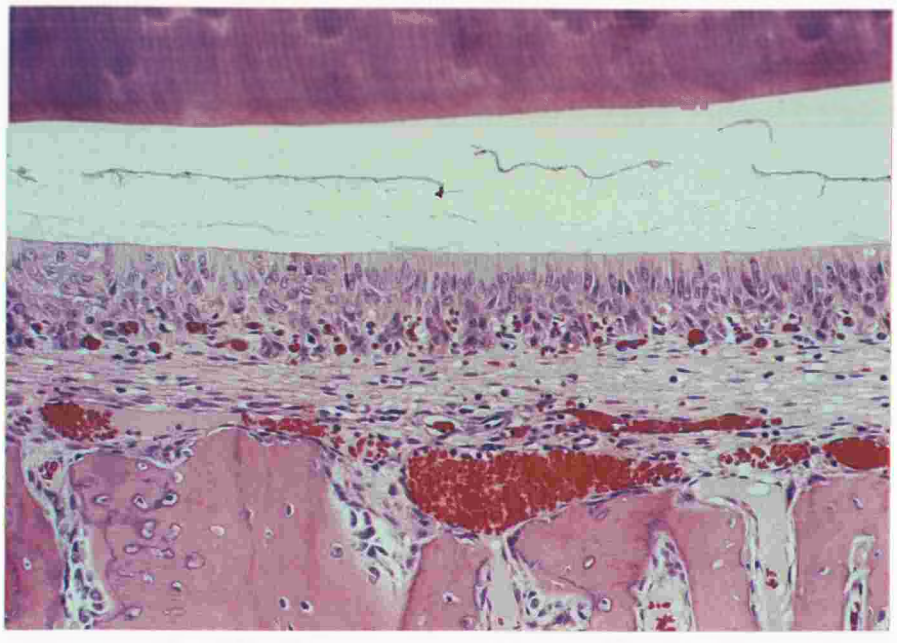


Photo. 2 Incisor of a female rat from 125 mg/kg/day group.
Decreased iron pigments and irregular alignment of ameloblasts at maturation stage.
No. 54 animal. HE. ×180.

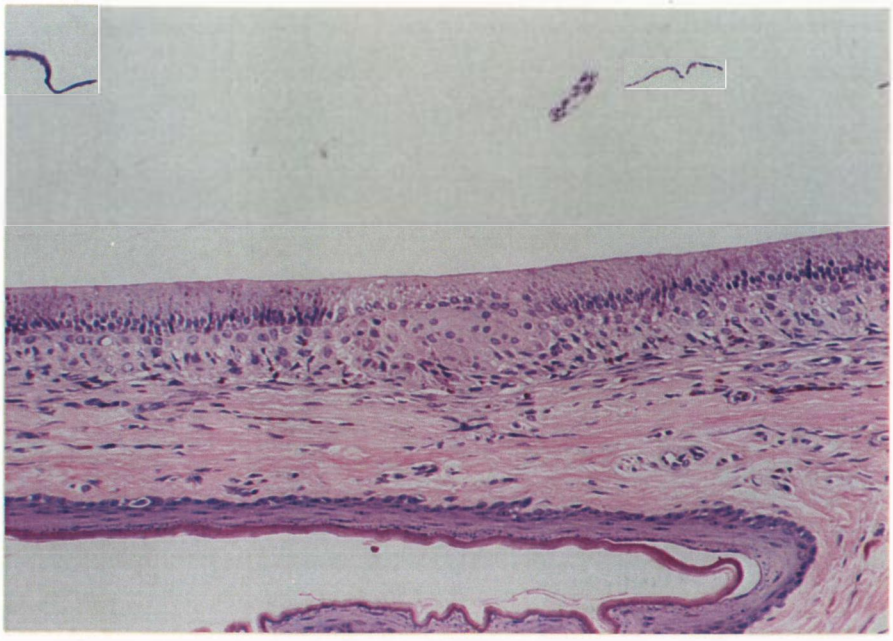


Photo. 3 Incisor of a female rat from 125 mg/kg/day group (recovery).
Irregular alignment of papillary layer.
No. 57 animal. HE. ×180.

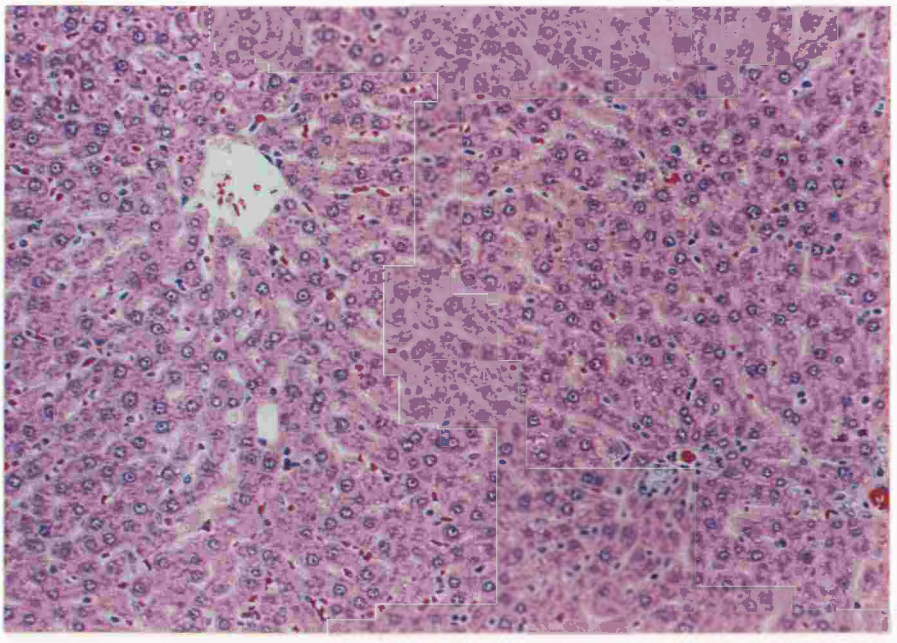


Photo. 4 Liver of a female rat from vehicle control group.
Normal.
No. 33 animal. HE. ×180.

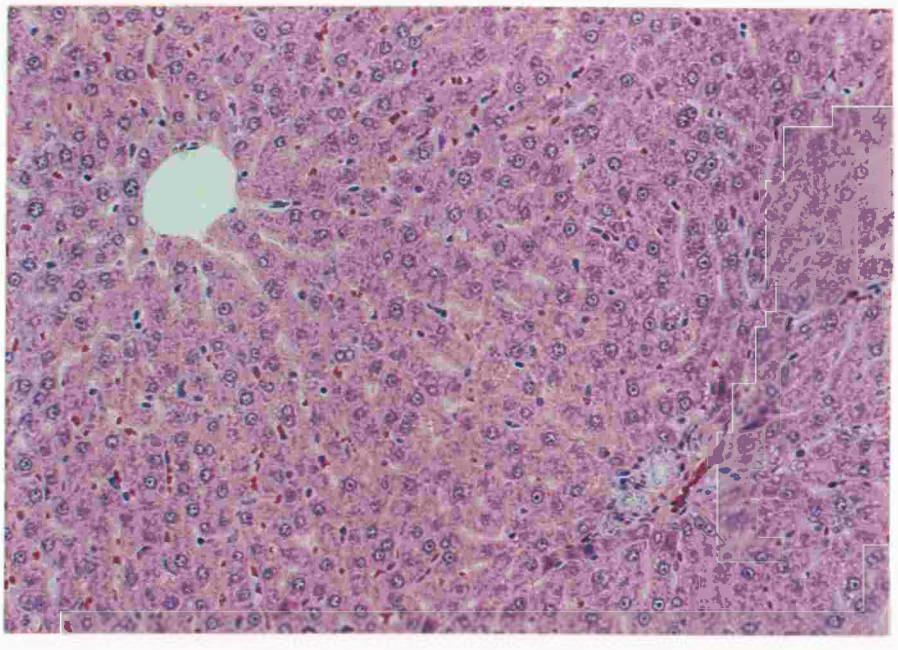


Photo. 5 Liver of a female rat from 125 mg/kg/day group.
Diffuse hypertrophy of hepatocytes.
No. 53 animal. HE. ×180.

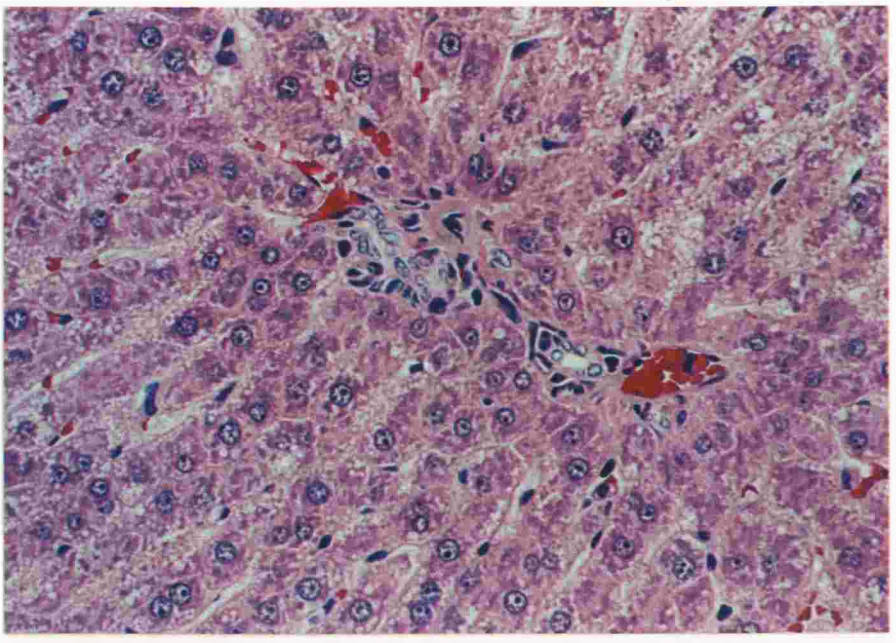


Photo. 6 Liver of a male rat from vehicle control group.
Normal.
No. 2 animal. HE. ×360.

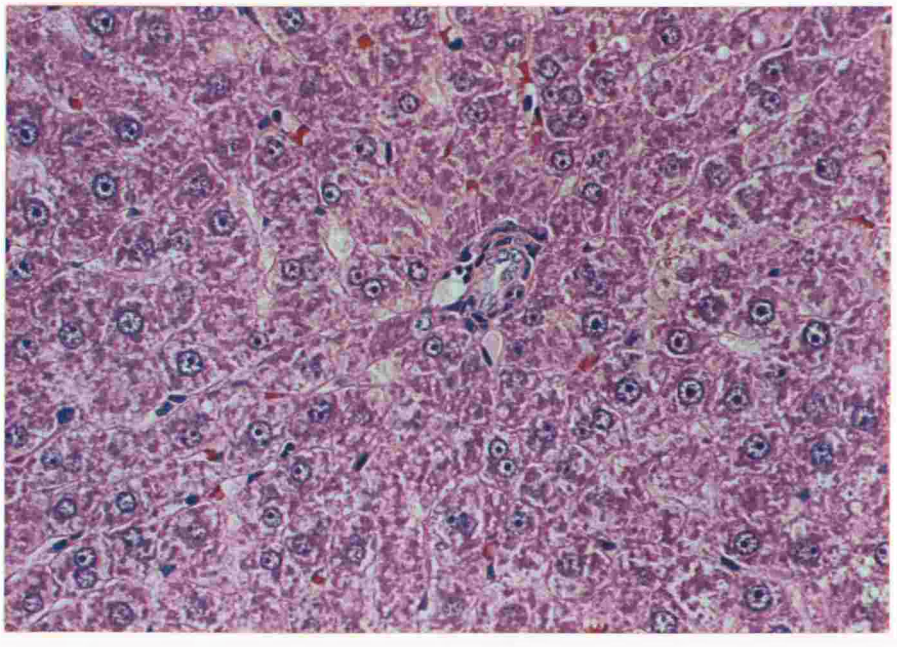


Photo. 7 Liver of a male rat from 125 mg/kg/day group.
Periportal hypertrophy and prominent nucleoli of hepatocytes.
No. 22 animal. HE. ×360.