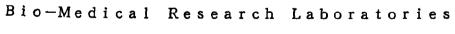
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# REPORT

Twenty-eight-day Repeated Dose Oral Toxicity Study of Sample D-1 in Rats

(BMR143C)



Co., Ltd.

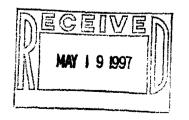


Exhibit 2797 State of Minnesota v. 3M Co., Court File No. 27-CV-10-28862

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# REPORT

Twenty-eight-day Repeated Dose Oral Toxicity Study of Sample D-1 in Rats

(BMR143C)

-TRANSLATION-



February 16, 1993

Bio-Medical Research Laboratories Co., Ltd.

# PREFACE BY TRANSLATOR

This is a total translation of the original report in Japanese language. On this work, I have paid close attention to transfer the real facts and the correct meaning in the text, confirming scientific matters to the original auther, the study director Mr. Michio Otsuka.

April 23, 1997

Translator : M. Termichi

Makoto Tennichi General Manager Bio-Medical Research Laboratories Co., Ltd.

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Title :

Twenty-eight-day Repeated Dose Oral Toxicity Study of Sample D-1 in Rats

Study Number : BMR143C

The said study has been conducted in compliance with the "GLP Standard for Industrial Chemicals" in Japan (1984, amended 1988).

(Signature)

(Date)

Signed

February 16, 1993

(Makoto Tennichi)

General Manager

Bio-Medical Research Laboratories Co., Ltd.

# CERTIFICATION

Title : Twenty-eight-day Repeated Dose Oral Toxicity Study of Sample D-1 in Rats

Study Number : BMR143C

Having audited the final report, I, the undersigned, assure that the study has been conducted in compliance with Japanese "GLP Standard for Industrial Chemicals", and accomplished with the protocol and appropriate standard operating procedures of the testing facility, and the report has been prepared exactly based on the experimental results.

(Signature)

(Date)

February 16, 1993

(Yutaka Kambara)

Signed

Quality Assurance Unit

Bio-Medical Research Laboratories Co., Ltd.

Dates of Inspection

Object I	Dates of Inspectio	on Dates o	f Report
		to Study Director	to Management
Protocol	1992. 6.23	1992. 6.23	1992. 6.23
	1992. 7. <b>3</b>	1992. 7. 3	1992. 7. 3
	1992. 7. 7	1992. 7. 7	1992. 7. 7
Testing Procedure	es 1992. 8. 4	1992. 8. 4	1992. 8. 4
	1992. 8.18	1992. 8.20	1992. 8.20
Records, Raw Data	a 1992.12.17	1992.12.17	1992.12.17
Final Report	1993. 2.16	1993. 2.16	1993. 2.16

(v)

# SIGNATURE

Title:

Twenty-eight-day Repeated Dose Oral Toxicity Study of Sample D-1 in Rats

Study No.:

BMR143C

The said study has been conducted under the responsibility of the undersigned, and this report has been prepared so as to reflect whole study correctly.

(Signature)

(Date)

Signed

February 16, 1993

(Michio Otsuka)

Study Director

Bio-Medical Research Laboratories Co., Ltd.

1. Title

Twenty-eight-day repeated dose oral toxicity study of Sample D-1 in rats

2. Study Number

BMR143C

### 3. Purpose

To investigate toxicological potential of the test substance. Sample D-1, through serial oral administration to rats for 28 days. It was intended to meet Japanese legal regulation for industrial new chemical substances.

### 4. GLP Application

The study was conducted in compliance with the Japanese "GLP Standard for Industrial Chemicals" (1984, ammended 1988).

### 5. Testing Guidelines

The testing methods conformed to the Japanese "Guidelines for Screening Toxicity Testings of Chemicals" (1988).

6. Sponsor

Sumitomo 3M Co., Ltd.

3-8-8, Minami-hashimoto, Sagamihara, Kanagawa, Japan

(Responcible Person)

Manager. Technical Department.

Chemicals Division

Nobushige Murakami

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7. Testing Facilities

Key Facility

① Bio-Medical Research Laboratories Co., Ltd.

3079 Susugaya, Kiyokawa-mura, Aikoh-gun, Kanagawa, Japan Partial Contributor

(Blood Biochemical Examination)

② Kashima Laboratory, Mitsubishi-Kasei Institute of Toxicological and Environmental Sciences (\*)

14, Sunayama, Hasaki-machi, Kashima-gun, Ibaraki, Japan
\*)The company name has altered to Mitsubishi Chemical Safety Institute.

(Histopathological Specimens Preparation)

(3) Nara Pathological Research

Kinomine, Hayama, Tuge~mura, Yamabe~gun, Nara, Japan (Histopathological Examination)

(4) Hatano Research Institute, Food and Drug Safety Center

729-5 Ochiai, Hadano-city, Kanagawa, Japan

8. Responsible Personnel

(Circled figure after the name indicates each belonging facility cited above.)

General Manager	Makoto Tennichi,	
Study Director	Michio Otsuka,	ⓓ
General Participants	Hiroyuki Ishii,	⊕
	Nacto Ichikawa,	ⓓ
	Osamu Tanaka,	ⓓ
	Mikiko Kawanabe,	ⓓ
Quality Assurance	Yutaka Kambara,	1

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Partial Participants

(Responsible to biochemical determination)

Naoto Toyota, 🛛 🖉

(Responsible to histopathological specimens reparation)

Yoshimi Tatsumi, (3)

(Director for histopathological examination)

Shinsuke Yoshimura, (4)

(Participant to histopathological examination)

Fumie Kawashima, 🌰

9. Dates in the Study

(Initiation of the study)	June	23,	1992
(Animals reception)	July	1,	1992

(Administration period)

-Male- July 6 - Aug. 2, 1992

-Female- July 7 - Aug. 3, 1992

(Termination of observation, blood sampling and necropsy)

-Male, main groups-	Aug.	3,	1992
-Female, main groups-	Aug.	4,	1992
-Male, recovery groups-	Aug.	17,	1992
-Female, recovery groups-	Aug.	18,	1992
(Completion of the study)	Feb.	16,	1993 <sup>-</sup>

#### 10. Retention of Records and Samples

All documentation records and samples (including specimens) of the study are retained in the archives of Bio-Medical Research Laboratories Co., Ltd. for 10 years after the completion of the study. As to further retention, it will be decided on consultation with the sponsor and the contractor.

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- Sample D-1 was administered to both sexes of rats with doses of 0.1, 1, 10, and 30 mg/kg for 28 days. A group of rats given the vehicle (olive oil) alone was included as the control. Besides the main groups for nonrecovery study, a satellite group for 14-day recovery study was added to each of the highest dose and the control groups.
- 2. No death occurred throughout the administration period. One male of the 30 mg/kg group, however, died during the recovery period; the death was considered to be caused by the test substance.
- 3. No abnormal clinical signs were found in all rats of the control (including those for the recovery study) and the 10 mg/kg or lower dose groups throughout the whole of the observation period. In the 30 mg/kg group, however, such signs as the followings were observed during the administration and the recovery periods: reduced spontaneous movement, tonicclonic convulsion, lying or crouching, bradypnea or cyanosis, salivation, reddish salivation, brown urine, loss of hair, and coat staining. These were considered to be caused by the test substance.
- 4. Body weight gain was suppressed during the administration period in both males and females of the 30 mg/kg group from the second week and after; the suppression continued throughout the recovery period.
- 5. Food consumption was suppressed during the administration period in both males and females of the 30 mg/kg group from the second week and after; it tended to return during the recovery period, however.
- 6. Hematological examination at the end of the administration period revealed

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decreased hemoglobin concentration in males of the 10 and 30 mg/kg groups, and reduced prothrombin time in females given 30 mg/kg. Moreover, at the end of the recovery period, the followings were still detected in the 30 mg/kg group: decrease of erythrocyte count and hematocrit, shortening of prothrombin time, and increase of leukocyte count, in males; decrease of hemoglobin concentration and mean corpuscular hemoglobin concentration, shortening of activated partial thromboplastin time, and increase of mean corpuscular volume, in females.

7. Biochemical examination revealed the the followings at the end of the administration period: decrease of GOT in females of the 1 mg/kg and higher dose groups; increase of albumin in females of the 10 mg/kg and higher dose groups; increase of GPT and chloride, and decrease of total cholesterol in both sexes, decrease of total protein and increase of alkaline phosphatase and of A/G ratio in males, increase of urea nitrogen in females, all these in the 30 mg/kg group.

At the end of the recovery period, the followings were observed in the 30 mg/kg group: decrease of triglyceride and increase of A/G ratio, in males; increase of urea nitrogen, total protein, albumin, and calcium, and decrease of glucose and triglycerides, in females.

Besides, reddish change of serum was recognized in both sexes with the 10 mg/kg or higher dose main groups, and in the 30 mg/kg recovery group.

- B. By urinalysis, acidic shift in both sexes and decrease of protein in females were noted in the 30 mg/kg group during the administration period. Acidic shift remained in males during the recovery period.
- 9. As for absolute organ weight, the administration resulted in increase of the liver weight in both sexes of the 10 mg/kg or higher dose groups and decrease in the kidneys weight of males given 30 mg/kg. After the recovery

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period, increase in the liver of both sexes and decrease in the kidneys of females were still noted in the 30 mg/kg group.

Relative organ weight increased in the liver of both sexes of the 10 mg/kg or higher dose and increased in the kidneys in females of the 10 mg/kg or higher dose. After the recovery period, increase in the liver of both sexes and increase in the kidneys of females remained in the 30 mg/kg group.

10. Autopsy for the male died during the recovery period revealed atrophy and dark reddish patch in the thymus, hemorrhage and tarry contents in the stomach, tarry contents in the small intestine, and grayish patch in the liver.

In the scheduled necropsy at the end of the administration period, the following findings were detected by macroscopic examination: dark reddish change in the liver of females receiving 30 mg/kg; grayish dot or patch and hypertrophy in the liver and blackish change in the kidneys in males given 30 mg/kg; dark reddish change, yellowish change, grayish patch, and hypertrophy in the liver of females receiving 30 mg/kg.

The examination at the end of the recovery period revealed grayish patch, dark reddish change, and hypertrophy in the liver of both sexes of the 30 mg/kg dose.

11. Histopathological examination at the end of the administration period revealed dose-dependent changes as eosinophilic degeneration in centrilobular hepatocytes and swelling in the liver in males of the 1 mg/kg or higher doses and in females of the 10 mg/kg or higher dose. Other findings: focal necrosis in hepatocytes in both sexes given 30 mg/kg and in males given 10 mg/kg; somewhat remarkable fatty degeneration in peripheral lobule in males receiving 30 mg/kg.

No abnormal change was detected in the heart, kidneys, spleen, adrenals, brain, and testes or ovaries.

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At the end of the recovery period, eosinophilic degeneration in centrilobular hepatocytes turned slighter; swelling in the liver, however, did not recover in both sexes given 30 mg/kg, and focal necrosis also remained. In case of one male given 30 mg/kg and died during the recovery period, in addition to the same changes as found in the liver of the main groups, the followings were detected: hemorrhagic foci in the brain, ulcer and hemorrhage in the glandular stomach, and congestion and hemorrhage in the thymus.

12. Judging from the above, the toxicological no-observed-effect level (NOEL) of the test substance, Sample D-1, was considered to be 0.1 mg/kg for both male and female rats.

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### MTERIALS AND METHODS

### 1. Test Substance

1-1 Name

(Chemical Name)

2-[N-Ethyl-N-perfluoroalkyl(C-1-8)sulfonylamino] ethyl acrylate

(Abbreviation)

Sample D-1

1-2 Structural formula

 $C_2 H_5 O_1 U_1$  $C_n F_{2n+1} SO_2 N - CH_2 CH_2 O - C - CH = CH_2$ 

(n ranges from 1 to 8)

(Composition)	about 78% for $n = 8$ component,
	about 21% for $n = 1-7$ components.
1-3 Molecular weight	625
1-4 Lot number	101 (supplied by the sponsor)
1-5 Appearance	Amber-colored waxy solid
1-6 Purity	99% or above
1-7 Strage conditions	Stored at room temperature

### 2. Preparation of Dosing Solution

2-1 Vehicle Olive oil

- 2-2 Procedure Required amount of the test substance was weighed and suspended homogeneously in the vehicle mentioned above. The dosing solution was divided into daily batches and stored in a refrigerator at 4 °C until just before use.
- 2-3 Frequency of preparation The dosing solution was prepared once a week, because the stability of the test substance in the mixture for eight days was confirmed in Japan Food Research Laboratories (Tokyo) by

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our request.

### 3. Laboratory Animals and Reason for Choice

The animals used were SPF Crj:CD(SD) rats of both sexes. They were purchased from Charles River Japan, Inc. (795 Shimo-furusawa, Atsugi, Kanagawa, Japan) at four weeks of age on July 1, 1992. After five (male) or six (female) days of acclimatization, animals that apparently healthy and showed normal weight gain were selected for the study at five weeks of age. They were grouped to be uniform for the mean body weight based on the last weighing during the acclimatization. The weight ranged from 132 to 151 g for males and 121 to 141 g for females at the initiation of administration.

Reason for choice: Having appropriate nature for laboratory animals and being bred under good genetic and microbial control, this species and strain are widely used in toxicological studies; our testing facility, besides. has accumulated back ground data on this animal.

#### 4. Animal Housing

Five or two (during or after the acclimatization, respectively) animals of the same sex were housed together in a stainless steel wire mesh cage of the hanging type  $(26 \times 38 \times 18 \text{ cm})$ . The animal care room was a barriered facility that was automatically controlled to keep the following conditions:

Temperature	:	22 - 26 °C
Humidity	:	30 - 70% RH
Ventilation	;	13 times/hour (all fresh air)
Lighting	:	Light /dark cycle of 12 hours
		(lights on 6:00 to 18:00)

A little deviation of temperature and humidity occurred during the animal keeping; it was, however, judged not to affect to the reliability of the study.

The diet was MF pelleted food for laboratory animals (Oriental Yeast Co.,

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Ltd.) and drinking water was tap water subjected to filtration and UV irradiation. Animals were allowed access to food and water ad libitum except for fasting from the evening before necropsy. Analysis of the ingredients and microbial contamination of the diet was performed by the manufacturer, and toxic contaminants were examined by Japan Food Research Laboratories (Tokyo) at the manufacturer's responsibility. The quality of the tap water was periodically examined by Atsugi Public Health Center by our request. These data were checked and stored by us.

Cages were replaced with freshly autoclaved ones once a week.

#### 5. Identification of Animals

Each animal was identified by marking a number on the tail with a saturated alcoholic solution of picric acid. To identify the dose group to which each animal belonged, a colored mark was painted on the tail with an oil-based felt-tip pen.

#### 6. Identification of Cages

Each cage was identified with an attached card on which the study number, abbreviated name of the test substance, dosage, and individual animal number were listed.

#### 7. Test Procedures

The testing methods conformed to the Japanese "Guidelines for Screening Toxicity Testing of Chemicals " (amended on December 5, 1986).

### 7-1 Dose levels and reason for selection

Prior to the principal study, preliminary dose-finding studies ranged between 4 and 14 days in administration period was performed with such doses as 20, 40, 50, 100, 200, 500, and 1000 mg/kg, each in a few (three to five) male and female rats. It resulted death of more than half number of rats in

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1000 mg/kg for 14 days repeated administration; suppression of body weight gain was observed in 40 mg/kg dose, though none of changes found in 20 mg/kg dose. Hence, the highest dose was decided at 30 mg/kg in the principal study and the lower doses were set at 10 mg/kg, 1 mg/kg, and 0.1 mg/kg for both sexes. A group of rats given the vehicle alone was included as the control.

#### 7-2 Number of animals

Forty-two rats of each sex were used.

### 7-3 Route, frequency, and duration of administration

Administration was performed via the oral route, once a day for 28 days.

#### 7-4 Method of administration

The dosing mixture was intubated directly into the stomach via a plastic gavage tube. The volume administered was 1 ml per 100 g of body weight based on the most recent weight data.

#### 7-5 Grouping

Four dose groups mentioned above and the control group were set. Besides, to monitor the reversibility of any toxic effects, satellite groups were added to the control and the highest dose groups for a 14-day recovery study.

Grouping by	Dose	Main Groups(*1) Recover	y Groups(*2)
dose levels	(mg/kg)	(Sex and Number of animals)	· · · · · · · · · · · · · · · · · · ·
Control	0	male & female, 6 rats each male & female	, 6 rats each
Lowest dose	0.1	male & female, 6 rats each	
Intermediate-1	1	male & female, 6 rats each	
Intermediate-2	10	male & female, 6 rats each	
Highest dose	30	male & female, 6 rats each male & female	, 6 rats each
Total		male & female, 30 rats each male & female	,12 rats each

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(\*1) Animals were necropsied on the next day of the last administratrion.

(\*2) Animals were necropsied immediately after the recovery period was over.

Note. Individual animal number. Each animal was numbered with four-digit figure.

First digit, Dose groups;	0,	the control group
	1,	the lowest dose group
	2,	the intemediate-1 group
	3,	the intemediate-2 group
	-4,	the highest dose group
Second digit, Sexes;	1,	males
	2,	females
Second digit, Sexes;	3, 4, 1,	the intemediate-2 group the highest dose group males

Third and fourth digits, individual animal of main or recovery groups; 01-06, animals of the main groups

07-12, animals of the recovery groups

#### 8. Parameters Assessed

8-1 General condition

8-1-1 Clinical signs

The appearance, behavior, and excreta of every animal were observed daily throughout the administration and the recovery periods.

8-1-2 Body weight

Every animal was weighed with an electric balance at the commencement of the administration, once a week thereafter.

8-1-3 Food consumption

Leftover food from each cage was weighed on day 0 and once a week thereafter, and the daily average consumption per animal was calculated for each group.

### 8-2 Laboratory tests

8-2-1 Hematology

Blood samples were collected from the inferior vena cava under ether anesthesia just before the scheduled time of sacrifice. Blood sampling was

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done under non-fasting condition. The hematological parameters determined are listed below.

The anticoagulant used was ethylenediaminetetraacetic acid dipotassium salt (EDTA-2K), except that 3.13% sodium citrate was used to determine the prothrombin time and the activated partial thromboplastine time.

	Parameters		Method
(1)	Leukocyte count	(WBC)	Electrical resistance method
(2)	Erythrocyte count	(RBC)	Electrical resistance method
(3)	Platelet count	(PLT)	Electrical resistance method
(4)	Hemoglobin concentration	(Hgb)	Photo-electric colorimetry
(5)	Hematocrit	(Hct)	Pulse detection method
(6)	Mean corpuscular volume	(MCV)	Calculated from (2) and (5)
(7)	Mean corpuscular hemoglobin	(MCH)	Calculated from (2) and (4)
(8)	Mean corpuscular hemoglobin		
	concentration	(MCHC)	Calculated from (4) and (5)
(9)	Differential leukocyte count		Giemsa-stained smear
(10)	Prothrombin time	(PŤ)	Quick's one-stage test
(11)	Activated partial thrombo-		
	plastin time	(APTT)	Activated cefaroplastin method

Insturuments

(1)-(8) : Automatic cell counter, Sysmex model CC-180A, TOA Medical Electronics Co.,Ltd.

(9) : Optical microscopy

(10)-(11) : Blood coagulater, Model KC-1, Amelung Co., Ltd.

Among these data, PT and APTT of one male in the recovery group (animal no. 0111) were missing owing to coagulation at blood sampling. On the other hand, reticulocyte counting was added in the main groups after sequential staining with new methylene blue process and May-Gruenwald-Giemsa process, because anemia was suspected in animals of this group.

#### 8-2-2 Biochemistry

The residual blood sample was let stand at room temperature for 30 min and

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then centrifuged at 3000 rpm for 10 min to separate serum. The serum, being frozen to -20  $\infty$ , was sent to Kashima Laboratory of Mitsubishi-Kasei Institute of Toxicological and Environmental Sciences for biochemical examination. Parameters examined were as follows:

Parameters	Method
(1) Total protein	Biuret's method
(2) Albumin	Bromocresol green method
(3) A/G ratio	Calculated from (1) and (2)
4) Glucose	Enzymatic UV-spectrophotometry (Hexokinase~G6~PDH)
5) Triglycerides	Enzymatic method (LPL-GK-G3PO-POD)
6) Total cholesterol	Enzymatic method (CES-CO-POD)
7) Urea nitrogen	Enzymatic UV-spectrophotometry (Urease-GLDH)
8) Creatinine	Jaffe method
9) Calcium	o-Cresolphthalein complexone method
10) Inorganic phosphoro	us Phosphomolybdate-UV spectrophotometry
11) GOT (AST)	UV spectrophotometry-rate method (Modified SSCC)
12) GPT (ALT)	UV spectrophotometry-rate method (Modified SSCC)
13) γ-GPT	$\gamma$ -Glutamyl-p-nitroanilide substrate method
	(Modified SSCC)
14) Alkaline phosphatas	e (ALP) p-Nitrophenyl phosphate substrate method
15) Sodium	Ion selective electrodes method
16) Potassium	Ion selective electrodes method
17) Chloride	Ion selective electrodes method

Instrument: Automatic analyser (Hitachi 736-10 type)

### 8-2-3 Urinalysis

Fresh urine was collected from all animals at six or seven days before the completion of administration, and four or five days before the end of the recovery period. (In each of two successive days, the former and the latter days were for male and for female respectively.) These were tested for the following parameters.

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Parameter	Method
H, Occult blood, Protein, Glucose,	Paper test, MULTIS
etone bodies, Urobilinogen, Bilirubin	/ (Miles-Sankyo Co.,

#### 8-3 Pathological examination

### 8-3-1 Necropsy and macroscopic examination

On the next day of the last administration, all survived animals except those assigned for the recovery test were sacrificed for necropsy after blood sampling: whereas for animals of the recovery groups, the necropsy was held on the scheduled day just after the recovery period was over. After careful investigation for any macroscopic abnormalities, the following organs were removed and fixed in 10% neutral buffered formalin: brain, pituitary, eye ball, (with Harderian glands), thyloid (with parathyloid), heart, lungs, liver, kidneys, spleen, adrenals, stomach, testes or ovaries, urinary bladder, and right femur (with bone marrow).

#### 8-3-2 Organ weight

The following organs were weighed before fixation, then the relative organ weight (ratio of organ weight to body weight on the day of necropsy) was calculated: brain, liver, kidneys, adrenals, and testes or ovaries.

### 8-4 Histological examination

From the following fixed organs of all rats in the control and the highest dose (30 mg/kg) groups, histological sections of paraffin-embeded specimens were cut and subjected to hematoxylin-eosin staining, then histological changes were surveyed: heart, liver, spleen, kidneys, adrenals, brain, and testes or ovaries. (typical seven organs)

The survey of the liver was expanded to animals of the other dose groups since some chages were found in case of 30 mg/kg dose group.

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Additional histological survey was conducted to the following cases in which any macroscopic changes were observed at the necropsy: lung in one case (animal no. 0105), kidneys in two cases (animal nos. 1103, 2102), and testes in one case (animal no. 0111).

Concerning the dead animal which occurred during the recovery period in one male (animal no. 4109), histological survey was performed in the typical seven organs and in thymus and stomach, the latter two were additional because of the macroscopic changes found at the necropsy. In this animal, tarry intestinal contents were found between duodenum and ileum at autopsy; however, preparation of the specimen and histological examination were not performed because of post-mortem autolysis

All through the histopathology, histological specimens were prepared in Nara Pathological Research, whereas the microscopic examination was carried out in Hatano Research Institute of Food and Drug Research Center, both at our quest.

#### 9. Statistical Analysis

For metrical data, homogeneity of variance among all groups was first tested by Bartlett's method. Then the homogeneity of all group means was tested by one-way layout analysis or Kruskal-Wallis H-test, depending on whether the group variance was homogeneous or not, respectively. When group means were significantly heterogeneous and each group had the same number of data items, differences in mean values between any group and the control were tested by Dunnett's multiple range test or Dunnett's rank sum test, according to whether the group variance was homogeneous or not, respectively. When group means were heterogeneous and the number of data items in each group was unequal, the above-mentioned procedures were replaced by Scheffe's multiple range test or Scheffe's rank sum test, respectively. Armitage's chi-squared test was used to assess discrete data such as urinalysis findings.

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### RESULTS

#### 1. Mortality

All rats survived to the end of administration period; during the recovery period, however, one male given 30 mg/kg died on day 32 (viz. day 4 of recovery \*).

\*) Each day throughout the study is indicated with such way as the day of commencement of the administration is named "day 0 "; and the next day of the last administration (viz. day 28), that is the first day of recovery period, is expressed as "day 0 of recovery ".

### 2. Clinical Signs (Table 1, and Appendix 1)

2-1 During the administration period

No abnormal signs were noted in all rats of the control and the 10 mg/kg or lower dose groups. With rats receiving 30 mg/kg (inclusive of the recovery group), however, the following findings were detected:

Salivation---a considerable number of animals of both sexes, in the latter half of administration period; and in one male on day 0, besides;

Reddish salivation---in a few males and females, occasionally; Tonic-clonic convulsion, lying, bradypnea---in one male on day 26; Reduced spontaneous movement, clonic or tonic-clonic convulsion, lying or crouching, bradypnea or cyanosis----in one and two females on day 20 and from day 25 to 27, respectively;

Loss of hair and coat staining---in three and one females respectively. on day 17 and after.

#### 2-2 During the recovery period

No abnormal signs appeared in both males and females of the control group as well as in the administration period. In case of the male given 30

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mg/kg and died during the recovery period, reduced spontaneous movement,lying, bradypnea, reddish salivation and brownish urine were found on day 31 (viz. day 3 of recovery), then died on the next day. Loss of hair found in females of the 30 mg/kg group during the administration period lasted until the termination of the recovery period, whereas the coat staining in one female disappeared after day 34 (viz. day 6 of recovery).

3. Body Weight (Fig.1, Table 2, Appendix 2)

3-1 During the administration period

Body weight gain in the 10 mg/kg or lower dose groups was similar to that of the control throughout the administration period. Significant suppression of weight gain, however, appeared in both males and females receiving 30 mg/kg (rats of the recovery group inclusive) from week 2 and after.

3-2 During the recovery period

The above-mentioned suppression of weight gain during the administration period lasted until the end of recovery period.

4. Food Consumption (Table 3, Apendix 3)

4-1 During the administration period

Food consumption in the 10 mg/kg or lower dose groups was similar to that of the control throughout the administration period. Significant suppression of the consumption, however, was observed in both sexes receiving 30 mg/kg (rats of the recovery group inclusive) from week 2 and after.

4-2 During the recovery period

The suppression in females of the 30 mg/kg group lasted one more week after the finish of the administration.

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3M\_MN01650013

5. Hematological Findings (Table 4 and 5, Appendix 4 and 5)

5-1 At the end of the administration period

Hematological examination with animals of the main groups performed on the scheduled necropsy-day revealed the following changes: decreased hemoglobin concentration in males of the 10 mg/kg and higher dose groups; reduced prothrombin time in females receiving 30 mg/kg.

#### 5-2 At the end of the recovery period

After-recovery examination with animals of the 30 mg/kg recovery group revealed the following changes: in males, decrease of erythrocyte count, hemoglobin concentration, and hematocrit, shortening of prothrombin time, and increase of leukocyte count; in females, decrease of hemoglobin concentration and mean corpuscular hemoglobin concentration, shortening of activated partial thromboplastin time, and increase of mean corpuscular volume.

6. Biochemical Findings (Table 6, Appendix 6)

6-1 At the end of the administration period

The examination with animals of the main groups resulted in decrease of GOT in females of the 1 mg/kg and higher dose group, and increase of albumin in also females of the 10 mg/kg and higher dose groups. Moreover, in the 30 mg/kg group, the following changes were significant: increase of GPT and of chloride, and decrease of total cholesterol, all these in both sexes; decrease of total protein and increase of alkaline phosphatase and of A/G ratio, all these in males; and increase of urea nitrogen in females.

In addition, reddish change of serum was visually recognized in two males (animal nos. 3102, 3103) and in one female (animal no. 3205) given 10 mg/kg, and in five males (animal nos. 4101, 4102, 4103, 4105, 4106) and in all females given 30 mg/kg.

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#### 6-2 At the end of the recovery period

Significant changes detected in the 30 mg/kg recovery group were as follows: lowering of triglycerides and increase of A/G ratio in males; increase of urea nitrogen, total protein. albumin, calcium, inorganic phosphorous and sodium, and decrease of glucose and triglycerides, all these in females.

And besides, reddish change of serum was recognized in four males (animal nos. 4108, 4110, 4111, 4112) and in three females (animal nos. 4207, 4210, 4211).

#### 7. Urinalysis (Table 7, Appendix 7)

#### 7-1 During the administration period

The examination performed with rats (inclusive of the recovery group) one week before the end of administration period resulted in the following changes: pH shift to alkaline side in males of the 1 mg/kg and 10 mg/kg groups and in females receiving 0.1 mg/kg; pH shift to acidic side in both sexes receiving 30 mg/kg; decrease of occult blood in males receiving 30 mg/kg; decrease of protein in females receiving 30 mg/kg.

#### 7-2 During the recovery period

Shift of pH to acidic side was noted in males of the 30 mg/kg recovery group in the examination conducted one week before the end of the period.

#### 8. Pathological Findings

8-1 Organ weight (Table 8 and 9; Appendix 8 and 9)

8-1-1 Absolute organ weight

1) At the end of the administration period

With the animals of the main groups, liver weight increased in both males

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and females of the 10 mg/kg and higher dose groups: whereas weight decreased in kidneys of males and ovaries of females, both in the 30 mg/kg group.

2) At the end of the recovery period

Changes noted in the 30 mg/kg recovery group were as follows: increase of the liver weight in both sexes; increase in the testes of males; decrease in the kidneys, in the adrenals and in the ovaries, all these of females.

8-1-2 Relative organ weight

1) At the end of the administration period

Increase of liver weight found in the absolute weight with the 10 mg/kg and higher dose groups was also detected in the relative weight in both males and females. In addition, the followings were observed: increase in the brain of both sexes receiving 30 mg/kg; increase in the adrenals and the testes of males receiving 30 mg/kg; increase in the kidneys of females given 10 mg/kg and higher dose.

2) At the end of the recovery period

Changes detected in the 30 mg/kg recovery group were as follows: increase in the liver and the brain of both sexes; increase in the testes of males; increase in the kidneys of females.

8-2 Macroscopic findings at necropsy (Table 10; Appendix 10 and 12)

8-2-1 Macroscopic findings in the dead animal

Autopsy on the male died during the recovery period (animal no. 4109) revealed the following changes: atrophy and dark reddish patch in the thymus; hemorrhage and tarry contents in the stomach; tarry contents in the small intestine; grayish patch in the liver.

8-2-2 Macroscopic findings at scheduled necropsy

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Gross pathological findings observed were listed below.

1) At the end of the administration period

Males of the 30 mg/kg group---greyish dot or patch in the liver and hypertrophy of the liver, in all six rats; blackish change in the kidneys and dark reddish change in the adrenals, in one rat.

Females of the 30 mg/kg group---dark reddish change. yellowish change and grayish patch in the liver, in four, one and one rats respectively; hypertrophy of the liver, in all six rats; pyelectasis in the kidneys of one rat.

- Females of the 10 mg/kg group---dark reddish change in the liver in one rat.
- Others---graysh patch in the kidneys of one male of the 1 mg/kg group; pyelectasis in the kidneys of one male of the 0.1 mg/kg group; cyst in the kidneys and dark reddish patch in the lung, each in one male of the control group.

2) At the end of the recovery period

Males of the 30 mg/kg group---grayish patch and dark reddish change, and hypertrophy in the liver, all these in two rats.

Females of the 30 mg/kg group---dark reddish change and grayish patch, and hypertrophy in the liver, in five, one, and one rat respectively.

Others---atrophy of the testes in one male of the control.

8-3 Histological findings (Table 11; Appendix 11 and 12)

8-3-1 Histological findings in the dead animal

Histopathological examination with the male died during the recovery period (animal no.4109) revealed the following findings: eosinophilic degeneration in centrilobular hepatocytes, focal necrosis and peripheral fatty change in the liver; dilated tubules in restricted part of the

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8-3-2 Histological findings at scheduled necropsy

Histological findings observed were listed below.

1) At the end of the administration period

① Liver

In centrilobular hepatocytes, cytoplasm appeared to be granular and eosinophilic, and swelling was recognized in all males and females of the 30 mg/kg group; in the 10 mg/kg group, the similar changes, though slightly, were found in all males; and in females, either the swelling or eosinophilic change was observed in four rats even slighter in incidence and intensity than in male; in the 1 mg /kg group, the similar change was slighter in intensity and incidence than in 10 mg/kg group. (Photo 1 and 2).

Focal necrosis in hepatocytes was found in five males and two females of the 30 mg/kg group, and in two males of the 10 mg/kg group. The necrosis was found also in one male of the control.

Fatty change in peripheral lobule was remarkable in males of the 30 mg/kg group (Photo 4); in females, however, the incidence and intensity was similar to that in the control. Localized fatty change was also observed in one male of the control.

Microglanuloma was found in a few males and females of all groups, though clear difference in incidence and intensity was not noticed between each dose group and the control group.

(2) Heart

No abnormalities were found except extremely localized myocardinal degeneration in two male of the control group.

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③ Spleen

No abnormalities were found except extramedullary hematopoiesis in three male of the control group.

(4) Kidneys

Regenerated tubules were found in both males and females of the 30 mg/kg and the control groups though no difference in incidence and intensity between two groups was noted. Other findings: dilated tubules in one male of the control; infiltration of lymphocytes in the interstitial tissue in one male of the 30 mg/kg group and three male and female of the control; dilation of pelvis in two males and in one female of the 30 mg/kg group. (5) Adrenals, brain and testes or ovaries No abnormalities were observed.

2) At the end of the recovery period

### (1) Liver

Centrilobular hepatocytes were eosinophilic and showed swelling in all males and females given 30 mg/kg. As compared to the main group animals, eosinophilic intensity turned slighter in both sexes; however, the intensity of swelling was similar to that in the main group.

Focal necrosis in hepatocytes was found in three males and two females of the 30 mg/kg group, though none in the control.

Other findings: fatty change in peripheral lobule and microglanuloma were observed, the former was somewhat definite in males given 30 mg/kg, the latter, however, no difference was found with the control.

(2) Heart

Very slight myocardial fibrosis was found in one male of each of the 30 mg/kg and the control group, and myocardial degeneration was found in one female of the cotrol. No other abnormal findings were noted.

③ Spleen

No abnormal findings were found except extramedullary hematopoiesis in one

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male of each of the 30 mg/kg and control groups.

# ④ Kidneys

Regenerated tubules were found in both sexes of every group; infiltration of lymphocytes in interstitial tissue was observerd in one male and in two female of the 30 mg/kg and the control group, respectively; very slight chronic nephropathy was found in one male given 30 mg/kg. No other abnornmalities was found.

(5) Testes

No abnormal findings were noticed except atrophy in one male of the control group.

(6) Adrenals, brain and ovaries

No abnormalities were observed.

3) Histological findings for gross pathological abnormalities Swelling of cytoplasm of centrilobular hepatocytes and focal necrosis were found corresponding to the macroscopic findings of hypertrophy and grayish patch, respectively.

# DISCUSSION AND CONCLUSION

Major findings obtained through repeated oral administration of the test substance to rats for 28 days were summarized below. Those changes were considered to be affected by the test substance.

m: male, f: female
--------------------

	Period	Administration				Recovery
Examination Findings	Dose					1
· · · · · · · · · · · · · · · · · · ·	(mg/kg)	0.1	1	10	30	30
Clinical signs (*1)reduced spontaneous	movement,					
bradypnea, anemia, salivation, convulsion; sup-					m	m
pression of body weight gain and food consump-					f	f
tion						
death occurred (number of the animal)					•••••	m (1)
Hematological findingsinclination to an	nemia,			m	m	m
abnormal change of blood coagulation					f	f
Biochemical findingsAbnormal changes in	lipids,				m	m
protein, and in enzymes or in electolyte	s		£	f	f	f
Jrinalysis (*2)acidic urine .					m	m
		_		f		
Organ weight change in absolute weight o	f the			m	m	. m
liver;				f	f	f
change in relative weight of the liver a	nd kid-			n	m	m
neys				f	f	f
facroscopic findingsgreyish dot or patc	h and				m	m
hypertrophy in the liver					f	f
listological findingssuch changes as eo	sinophil-		m	щ	jiti	m
ic swelling and focal necrosis in the li	ver,			f	f	f
fatty change in peripheral lobule					m	

- (\*1) Observation during each of the administration and the recovery period.
- (\*2) Examination one week before each end of the administration and the recovery period.
- The other examination was practised at each end of the administration and the recovery period.

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[Changes suggesting relation with the liver]

Among the changes detected, decrease of serum cholesterol was remarkable. Though the mechanism of the reaction is not clear, it is generally accepted that cholesterol is produced through synthesis in the liver and absorption of lipid in the intestine and is controlled through accumulation in tissues, conversion into energy and excretion from the body. As decrease of total protein and increase of A/G ratio in males or increase of albumin in females were found, considering the connection among protein and lipoprotein and cholesterol, influence of the test substance on globulin or effect to decrease lipoprotein was suggested; hence, for the reduction of serum cholesterol, concern of the liver was suspected.

Lowering of triglyceride found in both males and females of the 30 mg/kg recovery group was also considered to be affected by the test substance; because the same tendency was observed in the main group though statistically insignificant and the facts that the test substance was suspected to affect to lipids as mentioned above.

Moreover, changes in enzymes relating to the liver, increase of the liver weight such macroscopic findings in the necropsy as grayish dot/patch and hypertrophy, and histopathological pictures such as eosinophilic swelling and focal necrosis in centrilobular hepatocytes which were considered to be connected with the macroscopic findings, all these changes suggested that the test substance affected to the liver parenchyma.

Additional changes suggesting relation with the liver were shortened prothrombin time in females of the 30 mg/kg main group and in males of the same dose of the recovery group, shortened activated partial thromboplastine time in females of the 30 mg/kg recovery group. Changes of calcium and glucose observed in females of the 30 mg/kg recovery group, though not found in the main group, were a little remarkable comparing with level of physiological variation, and connection with the administ-

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3M MN01650022

## [Changes suggesting relation with other organs]

As to the increase of leukocyte count observed in the 30 mg/kg recovery group, the mechanism was unclear; the same tendency, however, was noticed in the main group though statistically insignificant. Therefore the connection with the test substance was suspected.

For the increase of urea nitrogen found in females given 30 mg/kg in both the main and the recovery groups. it was not clear whether the change was caused by degradation of protein or by excretion disturbance in the kidneys; however, considering such facts as the increase of chloride in both sexes of the 30 mg/kg main group and the increase of the kidneys weight in females of the 10 mg/kg or higher dose main groups and of the 30 mg/kg recovery group, effect of the test substance to the kidneys was suspected, though no histological changes were found.

As to reddish change of serum recognized visually in both sexes of the 10 and 30 mg/kg groups, sometimes  $\gamma$ -GTP activity does not change apparently when reddish serum was caused by hemolysis. In this case of the study, however, the relation among the reddish serum and hemolysis and  $\gamma$ -GTP was unclear.

[Changes considered not to be related to the test substance]

The following changes were considered not to be related to the effect of the test substance.

Changes of inorganic phosphorous and sodium observed in females of the 30 mg/kg recovery group were unconnected to the test substance, because the magnitude of the changes was within limit of physiological variation and the changes were not found in the main group.

In urinalysis, significant decrease of occult blood was recorded in males of the 30 mg/kg main group; it was, however, considered to be apparent.

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because one case of occult blood occurred in the control accidentally, hence the change was detected statistically.

Urine pH shifted to alkaline side with the administration in males receiving 1 and 10 mg/kg and in females receiving 0.1 mg/kg; the change, however, was not dose-dependent, and the change was considered not to be related to the test substance, therefore.

Weight increase of the brain and the testes and decrease of the ovaries were observed in males or females given 30 mg/kg in both the main and the recovery groups; no histological findings, however, were detected. Therefore, the changes were considered to be apparent caused by decrease of the body weight and to have no toxicological significance.

As for the macroscopic changes in the adrenals found in males or females given 30 mg/kg, no histological findings were detected; they were judged to have little toxicological significance, therefore.

Concerning any other changes such as gross pathological findings having no dose dependency and no histologocal findings except above-mentioned incidents, they were judged to be unconnected with the test substance.

### [Conclusion]

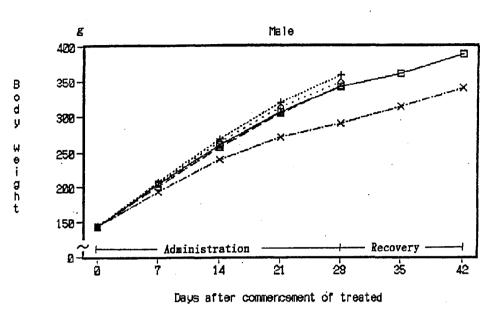
As mentioned above, significant response was found in the liver by administering the test substance to both sexes of rats with 1 mg/kg or higher dose. Whereas none of response was observed in the 0.1 mg/kg group with both male and female.

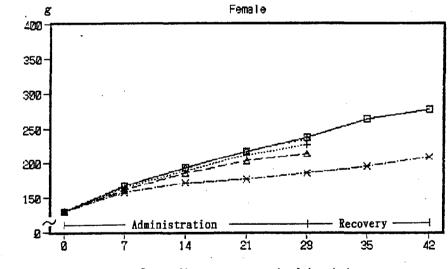
Therefore the toxicological no-observed-effect level (NOEL) of the test substance, Sample D-1, was concluded to be 0.1 mg/kg for both male and female of rats.

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## FIGURES AND TABLES (Group Mean Data)

3M\_MN01650025



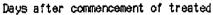


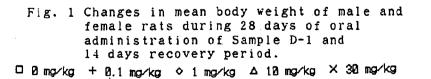
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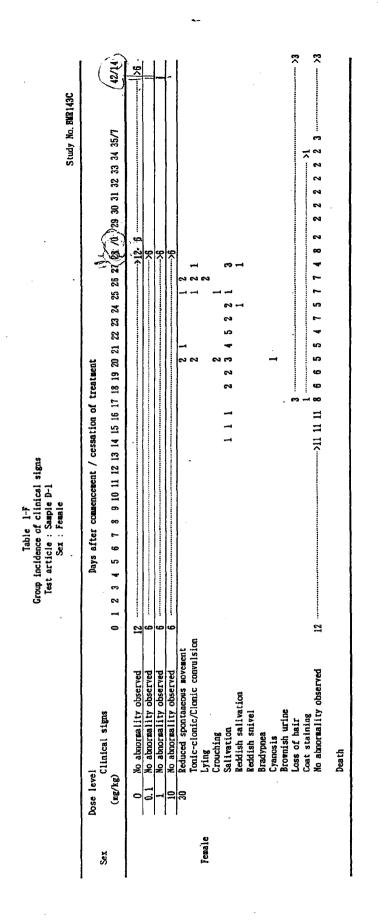
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## 2797.0040

	signs	
<u>e</u>	<pre>6roup incidence of clinical Test article : Sample D-1 Sex : Male</pre>	

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Car	Dose level Clinical nime	Days after commencement / cessation of treatment	
430	ug/kg)	0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 /0 29 30 31 32 33 34 35/7	42/14
	0 No abnormality observed	. 12	, s
	0.1 No abnormality observed	9.	
	1 No abnormality observed	9	
		2	
	30 Reduced spontaneous movement		
	Tonic-clonic/Clonic convulsion		
Kalc	Lying	4	
	Crouching		
	Salivation	2 2 2 2 5 5 5 3 2 3 4 3	
	Reddish salivation		
	Reddish snivel		
	Bradypnea		
	Cyanosis		
	Brownish urine	-	
	Loss of hair		
	Coat staining		
	No abnormality observed	11 12	×
	Death	-	



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Table 2 - M

Body weight - Group mean values Sex : Male Test article : Sample D-1

Dose level			Veeks afte	Veeks after commencement/	it/ cessatio	cessation of treatment	nt	
		Ō		2	ന	4	5/1	6/2
0 mg/kg	Mean	143	204	260	307	342	361	389
	S.D.	5.6	8.8	12.2	15.4	21.8	26.8	34.4
	z	12	71	12	12	12	9	9
0.1 mg/kg	Mean	143	207	269	320	359		
	S.D.	4.6	6.6	16.7	24.7	31.8		
	z	9	9	9	9	9		
mg/kg	Mean	144	206	265	314	349		
	S.D.	4.2	7.1	9.9	13.2	17.7		
	Z	9	9	9	9	ġ		
10 mg/kg	Mean	143	201	257	305	343		
	S.D.	5.8	8.8	14.2	19.6	24.5		
	z	9	9	9	9	9		
30 mg/kg	Mean	143	193	239 #*	272 **	290 **	315 ±	341
	S.D.	3.7	7.0	10.2	14.5		13.4	18 5
	z	12.	12 12 13	12	12	12		200

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No.	
Study	

Body weight – Group mean values Sex : Female Test article : Sample D-1

2 - F

Table

Dose level			Weeks aft	Weeks after commencement/ cessation of treatment	it/ cessation	l of treatmen	nt	
		0	1	7	ო	<b>t</b>	5/1	6/2
0 mg/kg	Mean	130	166	193	217	237	264	277
	s.D. N	5.4 12	8.1 12	13.1 12	16.5 12	18.6 12	20.7 6	24.8 6
0.1 mg/kg	Mean	129	164	189	212	227		
	N N	÷ 9	99	0.0 9	0°9	6.01 6		
mg/kg	Mean	131	167	192	217	235		
	5.D.	6.6 A	13.7 6	14.2 E	15.2	15.9		
	5	5	5	5	Ð	٥		
10 mg/kg	Mean	130	161	185	203	214		
	S.D.	5.9	7.9	9.8	13.4	14.4		
	z	9	9	9	9	g		
30 mg/kg	Mean	130	158	171 **	176 **	185 **	195 **	208 ±±
	S.D.	3.9	7.0	7.2		10.9		14.5
	Z	N 12 12 1	12	12	12	12	9	9

. Jampie Commencement/ o 5 6 18.9 19.5 19.5 19.5 19.5 19.5 19.5 19.5 19	·			Food consumption Sex :	tion - :	Ĕ	es	rid .on yours	DI1K 1 4 3 C
I       Weeks after commencement/ cessation of treatment         1       2       3       4 $5/1$ 1       2       3       4 $5/1$ Mean       16.8       19.1       18.9       16.8 $21.8$ Mean       16.8       19.1       18.9       16.8 $21.8$ Mean       16.8       0.92 $0.77$ $1.27$ $1.26$ Mean       18.0 $20.6$ $6.6$ $6.6$ $6.3$ Mean       18.0 $20.6$ $2.52$ $11.26$ $1.28$ Nean       17.0       19.3 $18.1$ $17.3$ $2.52$ N $3.3$ $3.3$ $3.3$ $3.5$ $3.5$ N $0.57$ $1.00$ $0.65$ $2.52$ $17.3$ $2.52$ N $3.3$ $3.3$ $3.3$ $3.3$ $3.5$ $3.5$ Mean       16.6 $18.3$ $18.1$ $17.8$ $17.8$ N $3.3$ $3.3$ $3.3$ $3.3$ $3.5$ $3.6$ N $3.3$ $3.3$				1001 41 610	•			Unit : g/Anima	l/Day
1234 $5/1$ Mean16.819.118.916.821.8Nean16.819.118.916.821.8S.D.0.850.920.771.271.26N666665Nean18.020.620.218.82.55N1.261.882.962.5218.8Nean17.019.318.117.3Nean17.019.318.117.3Nean16.618.319.517.8Nean15.415.815.12.77N.0.720.680.360.64S.D.0.720.680.360.64	Dose level			Weeks afte	r commenceme	nt/ cessatio	n of treatm	ent	
Mean16.819.118.916.821.8S.D. $0.85$ $0.92$ $0.77$ $1.27$ $1.26$ N $6$ $6$ $6$ $6$ $5$ Nean $18.0$ $20.6$ $20.2$ $18.8$ Mean $11.26$ $1.88$ $2.96$ $2.52$ S.D. $1.26$ $1.88$ $2.96$ $2.52$ S.D. $1.26$ $1.88$ $2.96$ $2.52$ S.D. $0.77$ $19.3$ $18.1$ $17.3$ Mean $17.0$ $19.3$ $18.1$ $17.3$ Nean $17.0$ $19.3$ $18.1$ $17.3$ Nean $17.0$ $19.3$ $18.1$ $17.3$ S.D. $0.75$ $0.57$ $1.00$ $0.65$ N $3$ $3$ $3$ $3$ Mean $16.6$ $18.3$ $19.5$ $17.8$ Mean $15.4$ $15.8$ $19.5$ $17.8$ N $3.0$ $3$ $3$ $3$ S.D. $0.72$ $0.68$ $0.36$ $0.64$ S.D. $0.72$ $0.68$ $0.36$ $0.64$ S.D. $0.72$ $0.68$ $0.36$ $0.64$			1	. 2	ຕ	Ŧ	5/1	6/2	
Mean18.020.620.218.8S.D.1.261.882.962.52N33333Mean17.019.318.117.3Nean17.019.318.117.3S.D.0.750.571.000.65N3333S.D.1.251.612.772.63N1.251.612.772.63N33333N0.720.680.360.642.46N0.720.680.360.642.46S.D.0.720.680.360.642.46	0 Eg/kg	Mean S.D. N	16.8 0.85 6	19.1 0.92 6	18.9 0.77 6	16.8 1.27 6	21.8 1.26 3	23.0 0.75 3	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	0.1 mg/kg	Mean S.D. N	18.0 1.26 3	20.6 1.88 3	20.2 2.96 3	18.8 2.52 3	·		
Mean         16.6         18.3         19.5         17.8           S.D.         1.25         1.61         2.77         2.63           N         3         3         3         3         3           Mean         15.4         15.8 <b>**</b> 15.3 <b>*</b> 12.7 <b>*</b> 20.4           No         6         6         6         6         6         3	1 mg/kg	Mean S.D. N	17.0 0.75 3	19.3 0.57 3	18.1 1.00 3.	17.3 0.65 3			
Mean         15.4         15.8 **         15.3 *         12.7 *         20.4           S.D.         0.72         0.68         0.36         0.64         2.46           N         6         6         6         6         3	10 mg/kg	Mean S.D. N	16.6 1.25 3	18.3 1.61 3	19.5 2.77 3	17.8 2.63 3			
	30 mg/kg	Mean S.D. N	15.4 0.72 6	15.8 <b>*</b> 0.68 6			20.4 2.46 3	21.2 2.12 3	

3 - M

Table

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Table

							Unit : g/Animal/Day
Dose level			Weeks afte	r commenceme	Veeks after commencement/ cessation of treatment	of treatme	nt
		1	₽.	m	4	5/1	6/2
0 mg/kg	Mean S.D. N	13.8 1.15 6	13.1 1.36 6	13.9 1.50 6	12.7 1.42 6	19.4 0.20 3	20.0 0.35 3
0.1 mg/kg	Mean S.D. N	13.7 0.40 3	12.6 0.80 3	13.4 1.42 3	12.4 1.12 3	·	
l mg/kg	Mean S.D. N	14.0 2.35 3	12.3 1.55 3	12.9 1.07 3	11.9 0.79 3		
10 mg/kg	Mean S.D. N	12.7 1.10 3	11.5 0.81 3	11.2 0.75 3	9.7 0.36 3		
30 mg/kg	Mean S.D. N	12.9 0.78 6	10.3 <b>*</b> 0.72 6	8.1 ** 0.82 6	8.0 <b>**</b> 1.09 6	14.3 <b>*</b> 1.51 3	15.4 1.97 3

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Table 4 - M - 1

Hematology - Group mean values Sex : Male Testarticle : Sample D-1 Animals killed on schedule (4 weeks)

(Jace		RBC	8	Ht	MCV	MCH	MCHC	Platelet	ΡT	APTT	Reticulo-
level		$(x10^4/mm^3)$	(g/d1)	(%)	( <sub>E</sub> u <i>ti</i> )	(bg)	(%)	count (x10 <sup>4</sup> /mm <sup>3</sup> )	(sec)	(sec)	cyte count (%)1
0 mg/kg	Mean	735	14.2	47.3	65	19.3	30.0	96.6	14.3	16.4	26
	S.D.	46.0	0.39	2.66	2.9	1.02	1.66	12.88	0.59	1.16	3.9
	N	6	6	6	6	6	6	6	6	6	6
0.1 mg/kg	Mean S.D. N	698 33.7 6	14.0 0.18 6	46.7 2.74 6	67 1.0 6	20.1 0.91 6	30.1 1.54 6	93.8 10.51 6	14.0 0.44 6	16.7 1.57 6	23 29 5.3
1 mg/kg	Mean	737	14.0	47.2	64	19.0	29.7	103.7	14.0	15.5	28
	S.D.	38.8	0.43	3.21	1.9	0.69	1.34	18.92	0.31	1.60	2.1
	N	6	6	6	6	6	6	6	6	6	6
10 mg/kg	Mean	728	13.4 <b>*</b>	46.2	64	18.4	28.9	103.7	13.9	15.6	27
	S.D.	31.4	0.33	2.15	2.4	0.80	1.20	11.79	0.30	1.26	5.6
	N	6	6	6	6	6	6	6	6	6	6
30 mg/kg	Mean	700	13.3 *	46.1	66	19.1	29.0	89.9	14.4	18.1	20
	S.D.	53.3	0.85	3.30	1.5	1.01	1.63	6.76	0.29	2.29	5.0
	N	6	6	6	6	6	6	6	6	6	6

3M\_MN01650033

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Table 4 - M - 2

Hematology - Group mean values Sex : Male Test article : Sample D-1

Jose		RBC HB count conc.	HB	Ht	MCV	MCH	MCHC	Platelet count	<b>1</b> 4	APTT	Reticulo- rute count
level	-	$(c_{mm}/b_{0}/x)$	(lþ/g)	(%)	(/////	(bg)	(%)	(x10 <sup>4</sup> /mm <sup>3</sup> )	(sec)	(sec)	( %)
0 mg/kg	Mean	798	14.1	45.5	57	17.7	31.0	88.4	13.8	16.0	25
1	5.0. K	54.4 6	0.39 6	$\begin{array}{c} 2.82 \\ 6 \end{array}$	2.2 6	0.88 6	1.44	16.90 6.	0.11 5	0.79 5	4.9 6
30 mg/kg	Mean	717 <b>*</b> 718 <b>*</b>	12.7 ** 0 50	41.6 <b>*</b> 1 68	58 33	17.7	30.4	95.5 11 28	13.4 *	15.2	31 6 )
		24	5 0	2	י זי	200	2 1 1	2.11	- <u>-</u>	0 1 1	<u>م</u> ہ

\* : Significantly different from control value , \* ; p<0.05 , \*\* ; p<0.01.</pre>

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Table 4 - F - 1

Hematology - Group mean values Sex : Female Test article : Sample D-1 Animals killed on schedule (4 w

Doce		RBC Count	8	Ht	MCV	MCH	MCHC	Platelet	PT	APTT	Reticulo-
level		(x10 <sup>4</sup> / mm <sup>3</sup> ) (g/d1)	(g/d1)	(%)	( // III )	(gd)	(%)	count (x10 <sup>4</sup> /mm <sup>3</sup> )	(sec)	(sec)	cyte count (% )
0 mg/kg	Mean S.D.	705 51.2	13.3 0.43	42.8 3.36	61 2.5	18.9 1.00	31.3 1.70	115.7	14.3	14.0 1 64	22
	Z	9	9	9	9	9	9	9	9	9	9.0
0.1 mg/kg	Mean	169	13.6	42.0	61	19.7	32.4	103.1	14.3	14.8	22
	5.U.S N	25.2 6	0.18 6	1.40 6	3.4 6	0.66 6	1.24 6	12.27 6	0.46 6	1.19 6	2.9 6
1 mg/kg	Mean	101	13.3	41.3	8	19.4	32.2	107.9	14.2	15.7	22
	s.0.	52.0	0.29	1.79	2.3	1.09	1.19	6.81	0.57	1.66	2.5
	z	9	9	9	9	9	<b>9</b>	9	9	9	9
10 mg/kg	Mean	716	13.7	43.8	61	19.2	31.4	105.9	14.0	15.2	21
	S.D.	35.6	0.30	2.06	2.7	0.96	1.00	13.81	0.42	0.99	2.1
	z	9	Ģ	9	Ð	9	9	9	9	9	9
30 mg/kg	Mean	722	13.0	43.1	09	18.0	30.1	103.2	13.4 **	14.6	20
	s.D.	54.6	0.49	2.95	1.5	1.16	1.92	11.39	0.21	2.12	2.8
	z	9	9	9	9	9	9	9	9	9	9

3M\_MN01650035

Table 4-F-2

Hematology – Group mean values Sex : Female Test article : Sample D-1 Animals killed on schedule (Recovery)

		RBC	HB	Ht	MCV	MCH	MCHC	Platelet	РТ	APTT	Reticulo-
Dose level		count conc. (x10 <sup>4</sup> /mm <sup>5</sup> ) (g/d1)	conc. (g/dl)	(%)	( £¤ 17 )	(bg)	<ul><li>%</li></ul>	count (x10 <sup>4</sup> /mm <sup>3</sup> )	(sec)	(sec)	cyte count (%) <sup>1</sup>
0 mg/kg	Mean	715	13.7	43.1	60	19.2	31.8	93.8	13.5	15.5	24
	S.D.	24.6 6	0.28 6	1.68 6	2.3 6	0.38 6	1.12 6	13.44 6	0.37 6	1.62 6	3.3 6
30 mg/kg	Mean	678	12.6 **	42.7	63 <b>*</b>	18.7	29.6 #	110.3	13.1	12.3 ##	25
)	S.D. N	33.3 6	0.29 6	1.62 6	1.3 6	0.61 6	0.80 6	17.87 6	0.46 6	1.35 6	2.6 6

BMR143C Study No.

5 - M - 1 Table Hematology - Group mean values

1-0	(4 weeks)
Male Sample D-1	scilennie
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$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Dose Level		WBC count (x10 <sup>2</sup> /mm <sup>3</sup> )	Differential Lympho- cytes Seg		count of leukocytes Neutrophils mented Band		( % of total counted cells ) Eosino- Baso- Mono- Phils phils cytes	cells ) Mono- cytes
8       Mean       106       87       5.7       3.9       0.5         8       5.10.       24.8       5.7       3.9       0.5       0.5         8       8       5.7       3.9       6       6       0.5         8       8       5.7       3.9       0.5       0.5         8       8       5.6       3.1       0.4       0.4         8       8.8       3.1       0.4       0.4       0.4         8       8.5       3.1       0.4       0.4       0.4         8       8.5       3.1       0.4       0.4       0.4         8       5.6       3.10       0.4       0.0       0         8       5.6       3.5       0.0       0       0       0         8       5.6       3.5       0.0       0       0       0       0       0         8       8       5.6       3.5       0.0       0       0       0       0       0       0         8       8       5.4       5.4       5.4       5.4       5.4       5.4       5.4       5.4       5.4       5.4       5.4       5.4	mg/kg	Mean S.D.	88 22.6 6	86 5.7 6	3.2 6	1 0.5 6	0.5	\$ 00 0	2.9 6 6
Mean       118       85       10       0.4 <th< td=""><td>.l mg/kg</td><td>Mean S.D. N</td><td>106 24.8 6</td><td>87 5.7 6</td><td></td><td>0.5 0</td><td>1.2 6</td><td>0.0</td><td>2.2 6</td></th<>	.l mg/kg	Mean S.D. N	106 24.8 6	87 5.7 6		0.5 0	1.2 6	0.0	2.2 6
Nean         97         85         10         0           S.D.         17.4         5.6         3.5         0.0           N         6         6         6         6           N         6         6         3.5         0.0           Nean         137         86         9         6           S.D.         65.5         2.8         2.4         0.0	mg/kg	Mean S.D. N	118 23.3 6	88 4.3 6	3.1 6	0 0 0 6 0	$\begin{array}{c} 1\\ 0.5\\ 6\end{array}$	0.0	1.3 6
Mean 137 86 9 1 S.D. 65.5 2.8 2.4 0.8	0 mg/kg	Mean S.D. N	97 17.4 6	85 5.6 6	10 3.5 6	0.0	1.0 6	0.0	2.8 6
0 6 6	0 mg/kg	Mean S.D. N	137 65.5 6	86 2.8 6	9 2.4 6	1 0.8 6	0.0	0.0	302 302

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BMR143C Study No.

llematology - Group mean values
 Sex : Male
 Test article : Sample D-1
Animals killed on schedule (Recovery) Table

5 - M - 2

		WBC	-	ential count o	of leukocytes		total counted	cells)
level		(x10 <sup>2</sup> /mm <sup>3</sup> )	C L	Segmented	Band	phils	tes Segmented Band phils phils cytes	cytes
0 mg/kg	Mean	97.	85	11	0	\$	<b>\$</b> 0	2
)	S.D.	13.9	6.5	6.1	0.5	0.0	0.0	1.6
	Z	9	9	9	ຍ	9	9	9
30 mg/kg	Mean	126 **	87	8	1	0	0	<b>.</b>
1	s.D.	11.6	4.6	1.8	0.5	0.0	0.0	3.2
	Z	2	വ	ഹ	പ	ഹ	പ	ς,

5 Statistical analysis impossible.

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ر د د 00 Hematology - Group mean values Sex : Female Test article : Sample D-1 Animals killed on schedule (4 k Table

5 - F - 1

Dose level		WBC count (x10 <sup>2</sup> /mm <sup>3</sup> )	Differ Lympho- cytes	Differential count of leukocytes ( X of total counted cells ) npho- Baso- Mono- tes Segmented Band phils phils cytes	f leukocytes phils Band	( % of Eosino- phils	total counted Baso- phils	cells ) Mono- cytes
0 mg/kg	Mean	75	ßß	- -	-	c	<b>6</b> 2	
	S.D.	10.8	3.0	2.1	0.8	0.0	0.0	2 0 2
	N	9	9	9	9	9	9	9
0.1 mg/kg	Mean	101	88	. 2	0	0	0	Þ
	S.D.	30.7	4.7	4.0	0.5	0.4	0.0	2.5
	Z	9	9	9	9	9	9	9
mg/kg	Mean	86	88	10	0	0	<b>C</b>	~
	S.D.	21.9	4.4	3.7	0.5	0.5	0.0	
	z	9	9	9	9	9	9	9
10 mg/kg	Mean	85	89	ŝ	0	0	0	<i>с</i> ,
	s.D.	22.3	3.1	2.1	0.4	0.5	0.0	-
	z	Ð	9	9	9	9	5	9
30 mg/kg	Mean	77	87	8	0	C	C	LC.
	S.D.	15.6	4.4	4.8	0.4	0.4	0.0	2.4
	z	9	9	Ľ				

BMR143C
Study No.
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Hematology - Group mean values Sex : Female Test article : Sample D-1 Animals killed on schedule (Recovery)

Dose		WBC count	2	Differential count of leukocytes ( % of total counted cells ) mpho- Baso- Mono-	f leukocytes phils	( % of Eosino-	total counted Baso-	cells ) Mono-
level		(x10 <sup>2</sup> /mm <sup>3</sup> )	3	Segmented	Band	phi ls	phils *	cytes
0 mg/kg	Mean	85	86	6	0	1	•	5
)	S.D.	23.9	6.3	5.3	0.4	1.3	0.0	3.1
	N	9	9	9	9	9	9	9
30 mg/kg	Mean	86	91		0	0	0	4
)	S.D.	18.1	2.3	2.2	0.4	0.4	0.0	1.9
	X	9	9	9	9	9	9	9

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BMR143C Study No. ~

6 - M - 1	
Table	

Clinical chemistry – Group mean values Sex : Male Test article : Sample D-1

aad		GOT	GPT	r -GTP	ALP	Urea	Creatinin	Glucose	Total	Trigly
level		(1/01)	(1/11)	(1/11)	(1/11)	mitrogen (mg/di)	(mg/dl)	(mg/dl)	cnol. (mg/dl)	ceride (mg/dl)
0 me/ke	Mean	89	30	\$ C	711	A C1	30	140	G	Ę
0	S.D.	7.0	4.6	0.0	129.3	1.62	0.00	9.4	00 0 0	18.2
÷	z	9	9	9	9	9	9	9	e G	9
0.1 mg/kg	Mean	65	30	0	677	10.6	0.5	150	57	55
	S.D.	9.0	5.1	0.0	84.9	2.18	0.05	10.5	3.5	11.8
	z	9	9	9	9	9	9	9	9	9
mg/kg	Mean	11	31	0	734	13.3	0.5	140	61	. 09
	S.D.	8.1	·4.5	0.0	127.7	2.34	0.04	6.9	4.3	28.6
	z	9	9	9	9	9	9	9	9	9
10 mg/kg	Mean	65	34	0	780	12.4	0.5	142	38	48
	s.0.	3.9	3.2	0.0	130.2	2.56	0.05	0.6	1.1	28.0
	X	9	9	9	9	9	9	9	9	9
30 mg/kg	Mean	73	53 #		1191 **	14.1	0.6	142	47 0	10
	S.D.	9.5	13.2	0.0		1.93	0.12	11.5	2.0	9.6
	Z	9	ġ		9	9	9	9	9	9

Study No. BMR143C

- M - 2	
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Table	

Clinical chemistry - Group mean values Sex : Male Test article : Sample D-1 Animals killed on schedule (4 weeks)

6.51       3.98       1.58       9.8         0.212       0.125       0.110       0.46         6       6       6       6       6         6.38       3.96       1.63       9.8         6.38       3.96       1.63       9.8         6.38       3.96       1.63       9.8         6.38       3.96       1.63       9.8         6.103       0.103       0.076       0.28         6.190       0.103       0.076       0.28         6.22       3.84       1.63       9.8         6.22       3.84       1.63       9.8         6.190       0.079       0.149       0.31         6       6       6       6         6.20       3.93       1.74       9.8         0.099       0.146       0.141       0.30         6       6       6       6         6.01       4.01       2.04       9.4	Dose Level		Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/d!)	Inorganic phos. (mg/dl)	Na (mEq/1)	K (mEq/1)	CI (mEq/1)
Mean         6.38         3.96         1.63         9.8           S.D.         0.166         0.103         0.076         0.28           N         6         6         6         6         0           Mean         6.22         3.84         1.63         9.8           Mean         6.22         3.84         1.63         9.8           S.D.         0.190         0.079         0.149         0.31           Mean         6.20         3.93         1.74         9.8           Mean         6.01 ##         4.01         2.04 ##         9.4	0 mg/kg	Mean S.D. N	6.51 0.212 6	3.98 0.125 6	1.58 0.110 6	9.8 0.46 6	10.2 0.70 6	142 0.5 6	4.1 0.08 6	102 2.2 6
Mean         6.22         3.84         1.63         9.8           S.D.         0.190         0.079         0.149         0.31           N         6         6         6         6           Mean         6.20         3.93         1.74         9.8           Mean         6.20         3.93         1.74         9.8           S.D.         0.099         0.146         0.141         0.30           Mean         6.20         3.93         1.74         9.8           Mean         6.20         3.93         1.74         9.8           N         6         6         6         6         6           Mean         6.01 ##         4.01         2.04 ##         9.4	0.1 mg/kg	Mean S.D. N	6.38 0.166 6	3.96 0.103 6	1.63 0.076 6	9.8 0.28 6	9.5 0.98 6	142 0.4 6	4.0 0.08 6	102 0.8 6
Mean         6.20         3.93         1.74         9.8           S.D.         0.099         0.146         0.141         0.30           N         6         6         6         6           Mean         6.01 <b>**</b> 4.01         2.04 <b>**</b> 9.4	1 mg/kg	Mean S.D. N	6.22 0.190 6	3.84 0.079 6	1.63 0.149 6	9.8 0.31 6	9.5 0.72 6	142 0.8 6	4.2 0.20 6	103 1.2 6
Mean 6.01 ** 4.01 2.04 ** 9.4	10 mg/kg	Mean S.D. N	6.20 0.099 6	3.93 0.146 6	1.74 0.141 6	9.8 0.30 6	9.3 0.82 6	142 0.9 6	4.3 0.33 6	104 1.4 6
0.368 0.166 0.264 0.54 6 6 6 6	30 mg/kg	Mean S.D. N	6.01 ## 0.368 6	4.01 0.166 6	2.04 ** 0.264 6	9.4 0.54 6	10.0 3.06 6	144 1.9 6	4.2 0.35 6	106 # 1.3 6

3M\_MN01650042

Table 6 - M - 3

Clinical chemistry - Group mean values Sex : Male Testarticle : Sample D-1 Animals killed on schedule (Recovery)

		F	GPT	r -GTP	ALP	Urea	Creatinin	Glucose	Total	Trigly-
level	(1/11)	(1/	(1/1)	(1/11)	(1/1)	m trogen (mg/dl)	(Ib/gm)	(Ib/gm)	cnol. (mg/dl)	ceriue (mg/dl)
		ŀ	5	<del>به</del> م	c c				L L	ŀ
U mg/kg riean S.D.		85 12.7	34 4.5	0.0	613 65,2	18. ( 2.42	6.05 0.05	148 5.9	00 14.1	85 45.0
		9	9	9	9	9	9	9	9	9
30 mg/kg Mea		76	44	0	716	21.8	0.5	152	29	10 #
S.D.		6.5 5	10.1 5	0.0	105.4 5	3.61 5	0.08	12.8 5	11.3 5	4.2 5

\* : Significantly different from control value , \*\* : p<0
\$ : Statistical analysis impossible.</pre>

3M\_MN01650043

6 - M - 4 Table

Study No. BMR143C

mean values	D-1 (Recovery)
v - Group m Male	sclo
Clinical chemistry	Test article : nimals killed on
Clinic	Test

		Total	Albumin	A/G	Calcium	Inorganic	Na	¥	C
Jose level		protein (g/dl)	(lþ/g)	ratio	(mg/dl)	pnos. (mg/dl)	(mEq/1)	(mEq/1)	(mEq/1)
0 mg/kg M	ean	6.42	3.85	1.50	9.6	8.7	141	4.2	104
	S.D.	0.167	0.056	0.072	0.28	0.18	1.5	0.28	1.5
	z	9	9	9	9	Ð	9	9	9
30 mg/kg M	ean	6.57	4.14	1.70 \$	9.7	8.9	142	4.2	106
	S.D.	0.288	0:195	0.109	0.08	0.63	1.1	0.20	2.5
	z	ស	5	5	ຄ	പ	5 2	9	പ

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Tab

Clinical chemistry - Group mean values Sex : Female Test article : Sample D-1 Animals killed on schedule (4 veeks)

Jose		GOT	GPT	r -GTP	ALP	Urea	Creatinin	Glucose	Total	Trigly-
level		(1/1)	(1/1)	(1/1)	(1/1)	murogen (mg/di)	(Ib/gm)	(lb/gm)	chol. (mg/dl)	ceride (mg/dl)
0 mg/kg	Mean	80	23	0	472	11.9	0.5	133	28	24
	S.U. N	8°0	3.5 G	0.4 6	65.2 6	1.33 6	0.04 6	7.6 6	10.5 6	4.9
0.1 mg/kg	Mean	20	25	0	419	13.2	0.6	140	57	28
	s.D. N	5.0 6	4.8 6	0.0 8	84.6 6	3.41 6	0.08 6	22.0 6	6.2 6	9.4 9
mg/kg	Mean	<b>##</b> 09	20	0	437	13.1	0.5	143	59	05
	s.D. N	7.4 6	2.9 fi	0.4 6	82.1 6	2.89 6	0 <b>.</b> 0		5.1	9.7 9
	:	)		>	5	5	D	<b>.</b>	٥	ġ
10 mg/kg	Mean	<b>**</b> 09		0	451	13.5	0.5	135	48	21
	5.U.S	12.5 6	0.7 0	0.0	81.8 6	2.59 6	0.04 6	11.7 6	8.1 6	2.9 6
30 mg/kg	Mean	56 #	36 #	0	590	18.0 **	0.5	126	95 44	UC UC
	s.D. N	4.1 6	7.2 6	0.0 6	170.9 6	3.43	0.05 6	15.0	5.1	4.7 6

3M\_MN01650045

Table 6 - F - 2

Clinical chemistry - Group mean values Sex : Female Testarticle : Sample D-1 Animals killerd on schedule (4 weeks)

Dose level		Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	lnorganic phos. (mg/dl)	Na (mEq/1)	K (mEq/1)	CI (mEa/1)
) mg/kg	Mean S.D. N	6.63 0.173 6	4.18 0.060 6	1.72 0.099 6	9.4 0.15 6	8.4 1.09 6	1	4.1 0.27 6	104 0.5
0.1 mg/kg	Mean	6.61	4.19	1.74	9.8	9.7	141	4.5	02
	S.D.	0.320	0.154	0.095	0.59	1.01	0.9	0.58	1.4
	N	6	6	6	6	6	6	6	6
l mg/kg	Mean	6.45	4.15	1.82	9.6	8.7	141	4.4	104
	S.D.	0.335	0.125	0.191	0.18	0.31	1.2	0.48	1.9
	N	6	6	6	6	6	6	6	6
10 mg/kg	Mean	6.91	.4.42 <b>*</b>	1.77	9.7	7.9	142	4.1	106
	S.D.	0.255	0.143	0.072	0.35	0.73	1.5	0.45	1.2
	N	6	6	6	6	6	6	6	6
30 mg/kg	Mean	7.01	4.59 **	1.90	9.9	8.6	142	4.9	106 ##
	S.D.	0.327	0.140	0.143	0.49	0.93	1.1	0.72	1.5
	N	6	6	6	6	6	6	6	6

3M\_MN01650046

\* : Significantly different from control value , \* : p<0.05 , \*\* ; p<0.01.
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Table 6 - F - 3

BNR143C

Study No.

Clinical chemistry - Group mean values Sex : Female Testarticle : Sample D-1 Animals killed on schedule (Recovery)

hoea		100	CPT	r -GIP	ALP	Urea	Creatinin	Glucose	Total	Trigly-
level		(I/II)	(1/11)	(1/1)	(I/Nİ)	ni trogen (mg/dl)	(Up/gm)	(lb/gm)	chol. (mg/dl)	ceride (mg/dl)
	•			\$						
0 mg/kg	Mean	11	30	0	323	17.3	0.6	150	61	48
	S.D.	8.8	7.7	0.0	63.4	2.55	0.05	6.9	10.1	31.1
	Z	9	9	9	9	9	9	9	9	9
30 mg/kg	Mean	61	30	0	387	24.1 **	0.6	126 ±±	15	18 44
	S.D.	10.6	5.9	0.0	52.4	2.99	0.04	9.6	7.3	2.4
	z	9	9	9	9	9	9	9	9	9

\* • >1811111Callul and value \$ : Statistical analysis impossible.

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6 - F - 4 Table Clinical chemistry - Group mean values Sex : Female Test article : Sample D-1 Animals killed on schedule (Recovery)

Study No. BMR143C

		Total	Albumin	A/G	Calcium	Inorganic	Na	⊻	ပ
level		g/dl)	(1p/8)	ratio	(mg/di)	pnos. (mg/dl)	(mEq/1)	(mEq/1)	(mEq/1)
0 mg/kg	Mean	7.02	4.34	1.62	9.6	7.3	140	4.1	105
	S.D.	0.286	0.142	0.064	0.16	· 0•54	0.6	0.12	1.2
	z		٥	٥	٥	D	_ م	۵	٥
30 mg/kg	Mean		4.72 **	1.70	10.2 **	8.1 *	141 ##	4.3	105
	S.U.	0.379 e	0.204	0.123 f	0.19 E	0.31 E	0.4 6	0.39 6	1.0 e

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3M\_MN01650048

. Table 7 - M - 1

Urinalysis - Group mean values Sex : Male Test article : Sample D-1 3 weeks after commencement of treatment

Dose level	z	<b>J E</b>	vrobiii- nogen (EU/dl)					Occul t Blood			12	Bilirubin	i an		- - 	× BV	Ketone bodies (mg/dl)					Glucose (g/dl)	e U		-		Protein (mg/dl)	<u> </u>	• .			Hđ		<b>4</b>
(mg/kg)		0.1		2	4 2	8	F	H ~	5	3		<b>±</b>	24	3	1	2	15	40	8		0.1 (	.25 0	5	<b>N</b>	1	TR	30 1(	<u>0.1 1 2 4 ≧8 - TR 1+ 2+ 3+ - 1+ 2+ 3+ - 5 15 40 ≧80 - 0.1 0.25 0.5 ≧1 - TR 30 100 ≧300 6.0 6.5 7.0 7.5 8.0 8.5</u>	00	0 6.	5 7.1	0 7.1	5 8.0	ŝ
6	12	12	0	0	0	\$	6	2		12 12 0 0 0 0 9 2 0 0 1 12 0	12	0	ł	0	0 0 1 10 1 0 0	10	-	0	. 0	12	0	0	•	<b>\$</b> 0	0	6	10	0	0 1 0		0	et	9	
0.1	9	9	0	0	60000	~	2	1	0	5100	9	0	0	0	0	4	1	-	0	9	0	0	0	0	0	0	വ	ц	0	0	-		2	
1	ŋ	9	0	0	0000		2	0	0	000	ຍ	0	0	0	0	ŝ	1	0	0	9	0	0	0	0	0	0	4	5	0	0	0	-	4	
10	9	9	0	0	60000		9	0 0 9	0	01	9	0	0	0	0	9	0 0	0	0	9	0	0	0	Q	0	0	4	5	0	0	0	0	5	<b>~</b> •
30	12	12	0	0	0	1.	5	5	0	12 12 0 0 0 0 12 0 0 0 0	12	0		00		8	7	0 8 2 2	0	12	0	0	0	0	0	-	6	5	0	2	_	et		<del>~</del> 0

\* : Startsucar analysis impossible. \*: Significantly different from control value , \*; p<0.05 , \*\* ; p<0.01.

Table · 7 - M - 2

Urinalysis - Group mean values Sex : Male Test article : Sample D-1 5 weeks after commencement of treatment (Recovery)

Study No. BMR143C

$\frac{28}{3} - 781 + 2 + 3 + - 1 + 2 + 3 + - 5$ $\frac{5}{0}$ $\frac{5}{0}$ $\frac{5}{0}$ $\frac{5}{0}$ $\frac{5}{0}$ $\frac{15}{0}$ $\frac{5}{0}$ $\frac{5}{0}$ $\frac{5}{0}$ $\frac{5}{0}$ $\frac{5}{0}$ $\frac{5}{0}$	noge	Urobili- nogen	Occult Blood	Bilirubin	Ketone bodies	Glucose	Se			Protein	E		ЪH		٠.
$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$		•			(mg/d1)	(g/d)	$\sim$			(mg/d)	~				
0 0 0 1 5 0 0 0 6 0 0 0 0 2 4 0 0 0 1 2 3 0 0 0 0 5 0 0 0 5 0 0 0 0 0 0 5 0 0 0 2 3 0 0	2	<b>₩</b>	<u>8 - TR 1+ 2+ 3</u>	- <u>+ 2+ 3+</u>	<u>- 5 15 40 ≥8</u>	0 - 0.1 0.25	0.5		X	30 100	<u>≧300 6.</u>	0 6.5	7.0.7.	5 8.0	8.5
500005000 5000 500000000000000000000000	0	0 0	\$ 2400(	0	<b>\$</b> 15000	Ġ	0	<b>↔</b> 0	3	4 0		0	-	3	0
	0	0	4 0 0 1 (	5 0	0 2 0 0 0	5 0	0	0	0	5	0	0	ಣ	0	<b>#</b> 0

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Table 7-F-1

Urinalysis - Group mean values Sex : Female Test article : Sample D-1 3 weeks after commencement of treatment

	Dose Ievel	z		Urobili- nogen (EU/di)	lrobili- logen (EU/dl)	. ~			0cc Bla	Occult Blood		Bi	Bilin	rubin	c			Ketone bodies (mg/d1)	ketone bodies (mg/dl)			0 0	Glucose (g/d1)	8				Protein (mg/dl)	ein JI)				둽		•
12       12       10       0       0       12       10       0       0       12       10       0       0       11       3       3       4         12       12       0       0       0       0       0       0       0       0       0       0       1       3       3       4         12       12       0       0       6       0       0       0       0       0       0       0       1       3       3       4         6       6       0       0       0       0       0       0       0       0       0       0       1       3       3       4         6       6       0       0       6       0       0       0       0       0       0       1       3       3       4         6       6       0       0       0       6       0       0       0       0       0       0       1       1       3       3       4         12       1       0       0       0       0       0       0       0       0       0       0       1       1	(mg/kg)		0.1	-	2	4	8	Ē	±	5	*		<b>±</b>	5	5 5	1		15	40	≥80	<b> </b>	0.1.0	.25 (	.5	N	1	TR	30 1	00 ≥3	00 6	.0 6.	57.	0 7.5	5 8.0	8.5
1       6       6       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       1       3         6       6       0       0       0       0       0       0       0       0       0       0       0       0       1       3       2         6       6       0       0       0       0       0       0       0       0       0       0       0       1       3       2         6       6       0       0       0       0       0       0       0       0       0       0       0       1       3       2         12       12       0       0       0       0       0       0       0       0       0       1       1       1       1       2       0       1       1       1       1       2       1       1       1       1       1       2       1       1       1       1       1       2       1       1       1       1       1       1       1       1       1 <td< th=""><th>0</th><th>12</th><th>12</th><th>0</th><th>0</th><th>0</th><th>*</th><th></th><th>2</th><th></th><th>0</th><th>12</th><th>-</th><th></th><th>0</th><th>69</th><th>3</th><th>0</th><th>0</th><th>0</th><th>12</th><th>0</th><th>0</th><th>0</th><th>•</th><th>0</th><th>~</th><th>10</th><th>0</th><th>0</th><th>0</th><th>-</th><th>, m</th><th>3</th><th></th></td<>	0	12	12	0	0	0	*		2		0	12	-		0	69	3	0	0	0	12	0	0	0	•	0	~	10	0	0	0	-	, m	3	
6       6       0	0.1	9	9	0	0	0		4	2	0	0		-	0	0		-	0	0	0	9	0	0	0	0	0	2	Ч	0	0	0	0	0	.,	~
6 6 0 0 0 0 5 1 0 0 0 6 0 0 0 3 3 0 0 0 6 0 0 0 0 0 2 4 0 0 0 1 1 1 2 12 12 0 0 0 0 7 3 2 0 0 12 0 0 10 2 0 0 0 12 0 0 0 0 3 5 4 0 0 3 1 6 2 0	1	9	9	0	0	0			2	~	0	9	0	0	0	* 1	4	0	0	0	9	0	0	0	0	0	-	പ	0	0	0	0		 ന	~
12120000732001200012000120001200012000035400**	10	9	9	0	0	0		S	1	0	0		0	0.	0	6.3		0	0	0	9	0	0	0	0	0	3	Ъ	0	0	0	1	-		~
	30	12	12	0	0	0	0	~	с. С	2	0	12		0	0	Η	2	0	0	0	12		0	0	0	e S	ß	4	0	** 0	S	1	9	5	

\*: Significantly different from control value , # ; p<0.05 . ## ; p<0.01.

Table 7 - F - 2

Urinalysis - Group mean values Sex : Female Test article : Sample D-1 5 weeks after commencement of treatment (Recovery)

Study No. BMR143C

Dose		Urol	Urobili- nogen			0 C C C C	Occu1t Blood		Bil	Bilirubin	'n			Keto	Ketone bodies			611	Glucose	-			2	Protein	_			<u>a</u>	Ħ	
level N	z	E)											-	(mg/	(Ip			<u>8</u>	(lþ/ĝ)				5	(lp/gm)	_					
(mg/kg) <u>0.1 1 2 4 ≧8 — TR 1+ 2+ 3+ —</u>	ol		24	200 NI	1	<u>R 1-</u>	1 24	34		1+ 2	+ 3		ณ	15	40	<u>1+ 2+ 3+ - 5 15 40 ≧80 - 0.1 0.25 0.5 ≧1 - TR 30 100 ≧300 6.0 6.5 7.0 7.5 8.0 8.5</u>	-0 -	1 0.	<u>25 0.</u>	2		Ē	<u>بر</u>	100	<u>≩ 300</u>	6.0	6.5	7.0	7.5	8.0
	9 9	0	6 6 0 0 0 3 2 0 1 0	0	3	2	-	0	9	0 0 0 9 0 0 0 <b>3</b>	0	*	0	0	0	•	9	0	0	0	<b>*</b> 0		~	0 0 0 1 3 2 0		0	0	-	0 0 1 2	~ ~
30	99	0	66000024000	0	7	4 (	0 (	Ò	.0	0	0	0 0 0 9 0 0 0	0	0	0	0	9	0	0	0	0 0 0 4	, (	~	2 0	0			~	0 1 3 1 1	-

\$ : Statistical analysis impossible.

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BMR143C Study No.

Table

8 - M - 1

Organ weight (Absolute) - Group mean values Sex : Male Test article : Sample D-1 Animals killed on schedule (4 weeks)

		(8)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (8)
0 mg/kg	Mean	351	1.96	13.60	2.43	50.5	2.99
	S.D.	22.0	0.117	1.180	0.156	3.19	0.265
	N	6	6	6	6	6	6
0.1 mg/kg	Mean S.D. N	359 31.8 6	$1.98 \\ 0.094 \\ 6$	14.50 1.194 6	2.55 0.257 6	54.3 4.90 6	3.14 0.196 6
1 mg/kg	Mean	349	1.94	13.88	2.26	52.9	3.14
	S.D.	17.7	0.045	1.459	0.170	3.71	0.194
	N	6	6	6	6	6	6
10 mg/kg	Mean	343	1.94	16.93 <b>**</b>	2.39	49.5	3.01
	S.D.	24.5	0.078	1.179	0.101	5.14	0.189
	N	6	6	6	6	6	6
30 mg/kg	Mean	292 <b>*</b>	1.97	20.36 **	2.11 <b>*</b>	50.4	3.08
	S.D.	17.6	0.072	2.228	0.084	4.15	0.250
	N	6	6	6	6	6	6

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Table 8 - M - 2

Organ weight (Absolute) – Group mean values Sex : Male Test article : Sample D–1 Animals killed on schedule (Recovery)

	-	-						
Dose level		F.B.V (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)	
0 mg/kg	Mean S.D.	389 34.4 6	2.05 0.051 6	13.57 1.768 1.768	2.47 0.151 6	53.1 6.85 6	2.74 0.942 6	
30 mg/kg	Mean S.D. N	341 * 18.5 5	2.02 0.058 5	20.66°‡ <b>‡</b> 1.693 5	2.40 0.157 5	51.5 7.31 5	3.38 <b>*</b> 0.117 5	
	F.B.V :	: Final body weight	ight	-				

\* : Significantly different from control value . \* ; p<0.05 , \*\* ; p<0.01.

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Table	Orgon

BMR143C

Study No.

Organ weight (Absolute) - Group mean values Sex : Female Test article : Sample D-1

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nose level		F.B.V (8)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Ovaries (mg)
0 mg/kg	Mean S.D. N	230 17.4 6	1.85 0.067 6	8.76 8.76 0.471 6	1.62 0.177 6	60.1 5.46 6	83.7 10.13 6
0.1 mg/kg	Mean S.D. N	227 10.5 6	$\begin{array}{c}1.79\\0.054\\6\end{array}$	8.65 0.679 6	1.61 0.162 6	59.8 6.93 6	83.7 7.86 6
mg/kg	Mean S.D.	235 15.9 6	$\begin{array}{c}1.91\\0.069\\6\end{array}$	9.07 0.852 6	1.67 0.081 6	62.6 7.79 6	92.0 15.11 6
10 mg/kg	Mean S.D. N	214 14.4 6	1.85 0.063 6	10.58 <b>**</b> 0.973 6	1.70 0.109 6	60.8 8.01 6	75.8 8.53 6
30 mg/kg	Mean S.D. N	190 <b>**</b> 9.5 6	1.83 0.064 6	13.78 <b>*</b> * 0.816 6	1.50 0.126 6	55.6 6.28 6	62.6 <b>*</b> 1.57 6

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BMR143C Study No.

8 - F - 2 Table

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Organ weight (Absolute) - Group mean values Sex : Female Test article : Sample D-1 Animals killed on schedule (Recovery)

lose level		F.B.V (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Ovaries (mg)
0 mg/kg	Mean	277	1.93	9.09	1.78	70.8	89.7
	S.D.	24.8	0.074	1.122	0.100	12.55	9.96
	N	6	6	6	6	6	6
30 mg/kg	Mean	208 **	1.86	12.46 **	1.59 <b>*</b>	54.0 <b>*</b>	68.5 <b>*</b>
	S.D.	14.5	0.131	0.574	0.146	7.39	6.22
	N	6	.6	6	6	6	6

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Table 9 - M - 1

Crown weight (Relative : percentage of body weight) - Group mean values - Sex : Male Test article : Samule D.1 •-

		r.6.W (8)	Brain	Liver	Kidneys	Adrenals (x10 <sup>-3</sup> )	` Testes
0 mg/kg	Mean	351	0.56	3.88	0.69	14.5	0.86
	S.D.	22.0	0.037	0.197	0.026	1.55	0.094
	N	6	6	6	6	6	6
0.1 mg/kg	Mean S.D.	359 31.8 6	0.55 0.066 6	4.04 0.210 6	0.71 0.018 6	15.3 2.70 6	0.88 0.071 6
1 mg/kg	Mean	349	0.56	3.97	0.65	15.2	0.90
	S.D.	17.7	0.037	0.272	0.060	1.03	0.057
	N	6	6	6	6	6	6
10 mg/kg	Mean	343	0.57	4.98 **	0.70	14.5	0.88
	S.D.	24.5	0.043	0.611	0.060	1.10	0.075
	N	6	6	6	6	6	6
30 mg/kg	Mean	292. <b>**</b>	0.68 <b>*</b> *	6.97 <b>*</b>	0.72	17.3 <b>*</b>	1.06 **
	S.D.	• 17.6	0.048	0.475	0.035	1.54	0.112
	N	6	6	6	6	6	6

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BMR143C

9 - M - 2 Table

Study No. Organ weight (Relative : percentage of body weight) - Group mean values Sex : Male Test article : C----

			Animals k	Animals killed on schedule (Recovery)	dule (Recover	.v)	-	
Dose level		F.B.W (g)	Brain	Liver .	Kidneys	Adrenals (x10 <sup>-3</sup> )	Testes	
0 mg/kg	Mean S.D. N	389 34.4 6	0.53 0.044 6	3.48 0.160 6	0.64 0.058 6	13.7 1.82 6	0.70 0.231 6	
30 mg/kg	Mean S.D. N	341 * 18.5 5	0.59 <b>*</b> 0.030 5	6.06 ** 0.482 5	0.70 0.029 5	15.2 2.67 5	0.99 ## 0.069 5	
	F.B.V :		ight farant from	final body veight ificantly different from control volue - + +		•		

\* : Significantly different from control value , \* ; p<0.05 , ‡\* ; p<0.01.

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BMR143C

Study No.

9 - F - I Table

Organ weight (Relative : percentage of body weight) - Group mean values Sex : Female

$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Dose level		F.B.W (g)	Brain	Liver	Kidneys	Adrenals (x10 <sup>-3</sup> )	0varies (x10 <sup>-3</sup> )
Mean $227$ 8.0. $0.79$ 6 $3.81$ 6 $0.71$ 6 $26.4$ 6S.D. N $6$ 6 $0.053$ 6 $0.148$ 6 $0.042$ 	0 mg/kg	Mean S.D.	230 17.4 6	0.80 0.037 6	3.81 0.198 6	0.70 0.043 6	26.2 2.76 6	36.4 4.28 6
Mean235 $0.81$ $3.85$ $0.71$ $26.6$ S.D. $15.9$ $0.047$ $0.237$ $0.71$ $26.6$ N66666Mean $214$ $0.87$ $4.95$ $*$ $0.79$ $*$ Nean $214$ $0.87$ $4.95$ $*$ $0.79$ $*$ $28.4$ Mean $214$ $0.87$ $4.95$ $*$ $0.79$ $*$ $28.4$ Mean $214$ $0.055$ $0.255$ $0.015$ $2.54$ $6$ N66666 $6$ N9.5 $0.034$ $0.321$ $0.053$ $*$ $29.2$ S.D. $9.5$ $0.034$ $0.321$ $0.053$ $*$ $250$	0.1 mg/kg	Mean S.D. N	227 10.5 6	0.79 0.053 6	3.81 0.148 6	0.71 0.042 6	26.4 2.89 6	36.9 2.90 6
Mean         214         0.87         4.95         **         0.79         **         28.4           S.D.         14.4         0.055         0.255         0.015         2.54           N         6         6         6         6         6         6           Mean         190         **         0.96         **         7.24         **         0.79         **         29.2           Mean         190         **         0.96         **         7.24         **         0.79         **         29.2           N         6 </td <td>1 mg/kg</td> <td>Mean S.D. N</td> <td>235 15.9 6</td> <td>0.81 0.047 6</td> <td>3.85 0.237 6</td> <td>0.71 0.043 6</td> <td>26.6 2.73 6</td> <td>39.3 6.90 6</td>	1 mg/kg	Mean S.D. N	235 15.9 6	0.81 0.047 6	3.85 0.237 6	0.71 0.043 6	26.6 2.73 6	39.3 6.90 6
Mean 190 ## 0.96 ## 7.24 ## 0.79 ## 29.2 S.D. 9.5 0.034 0.321 0.053 2.50 N 6 6 6 6 6	10 mg/kg	Mean S.D. N	214 14.4 6	0.87 0.055 6			28.4 2.54 6	35.4 3.23 6
	30 mg/kg	Mean S.D. N	190 ** 9.5 6	0.96 <b>*</b> 0.034 6	7.24 ** 0.321 6	0.79 ** 0.053 6	29.2 2.50 6	33.0 4.37 6

BMR143C

9 - F - 2 Table

. Study No.

Organ weight (Relative : percentage of body weight) - Group mean values Sex : Female Test article : Sample D-1

		-	Animals ki	Animals killed on schedule (Recovery)	dule (Recove	۲y		
Dose level		F.B.W (g)	Brain	Liver	Kidneys	Adrenals (x10 <sup>-3</sup> )	0varies (x10 <sup>-3</sup> )	
0 mg/kg	Mean S.D. N	277 24.8 6	0.70 0.059 6	3.28 0.157 6	0.64 0.035 6	25.6 4.10 6	32.5 2.25 6	
30 mg/kg	Mean S.D. N	208 ## 14.5 6	0.90 <b>**</b> 0.047 6	6.00 <b>**</b> 0.358 6	0.76 ## 0.033 6	25.9 2.43 6	33.0 3.18 6	
	F.B.V : F * : Signi	Final body weight ificantly different from control value , ** ; p<0.01.	ght erent from c	control value	, ** ; p<0.	01.		

		ů	oup lin	c I dence Tes	Table ID-N.F e of macrosc st article :	D-N.F croscop cle : S	Table 10-K.F Group Incidence of macroscopic findings Test article : Sample D-I	lings L								Study	Study No.BMR143C
Organ	Perlod :					28 da	days							Recovery	Bry		Dead an al sal
P I nd i ngs	sex : Dose level(mg/kg) : Number of animals :	0	0 <sup>.1</sup>	<u>Male</u> 6	0.0	<u>30</u>	0	0.1 6	Female 1 6	o <u>ت</u>	80		Male 5	1 12 10	Fenal 0	30	Hale 30
Thymus Dark reddish patch Atrophy	-	00	00	00	00	00	00	00	00	00	00				00		
Lungs Dark reddish patch	£		0	0	0	0	0	0.	0	0	0				. 0	) CO	. 0
Liver Scatterring of greyish dot/patch liypertrophy Greyish patch Dark reddish change Yeilovish change	eyish Ge	00000	00000		00000	၀၀မစာ	00000	00000	00000	00000	00444		00000	0000	00000	04450	
kidneys Cyst Pyelectasis Greyish patch Blackish change		-000	0-00	00-00	0000	000-	0000	0000	0000	0000	0-00		0000	0000	0000	0000	0000
Adrenals Dark reddish change	93	0	0	0	0	1	0	0	0	0	0		0	. 0	0	0	0
Stomach Tarry contents/llemorrhage	lot rhage	0	0	0	0	0	0	0	0	0	0	• -	. 0	0	0	0	L
Testes Atrophy		0	0	0	0	0							-	0			0

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					les	lest article				Sample U-L											Stud	iy Ko	Study No.BMR143C	1430	
Dose level :		0 mg	g/kg		(9-U)	0.1	i ng	ng/kg	(9-V)	()			ag/kg	(9-U)	()		10 mg/kg	c/kg	(9-U)	<b>_</b>		30	30 mg/kg	1	(9-U)
Findings Grade :	1	++	+	#	Ξ	ŀ	4	+	#	ŧ	1	++	+	≠	Ξ	1	+	+	#	∃ ≖	'	+	+	*	₿
Liver																			·						
elcrogranuloma	01	40	01	0		Ö	9	0	0	0	0	4	~	0	0	0	m	ო	0	0	0		m	0	0
local necrosis focal fatty change	ու			00	00	v م	00	00	00	00	94	00	00	00	00	4,	00	00	0,0	0			4	•	0
peripheral fatty change	υ Ο	00	10	0		ഹ	<b>~</b>	0	00	00	04	5 M	00	00	00	001	201	201	00	00	0-1	00	00	0	00
hepalocytes	9	0	0	0	0	9	0	0	0	0	'n	ę	0	0	0	0	1	ŝ	0	С	C	C	~	P	C
cosinophific change in centrilobular hepatocytes	9	0	0	0	0	9	0	0	0	0	3	4	0	0	0				, u			_		r (	
neart ryocardial degeneration	4	~			C									•	1	1	1	,	١	,	) (		> (		5 (
ayocardial fibrosis Soleen	0		0	0	0																00	00	00	00	00
extramedullary hematopofesis	m	3 2	٦	0	0							•									9	0	0	0	0
regenerated tubules	m	-	0	0	0																'n		ç	C	C
dilated tubules fafiitration of ivenhorvies	un (f	00		00																	اف		101	00	00
dilation of pelvis	ישע	100	+00	000																	ru 4.	HO:	00	00	00
Adrenals	5	>																			9		0	0	0
abnormaiity Rrain	9	0	0	0	0							•									9	0	0	0	0
abnormal i Ly Testas	9	0	0	0	0																9	0	0	0	0
atrophy	9	0	0	0	0																`	0	¢	(	1

— : Negative. ± : Yery slight. + : Silght. H : Moderate. H : Severe

#### 3M\_MN01650062

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30 sg/kg (n-6)

(g-0) #

10 mg/kg +

(g-E) \*

sa/kg +

F 1

(g-e) ≠

0.1 mg/kg

(9-u) #

O ag/kg ÷

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Dose level

Table LI-F Group Incidence of alcroscopic findings (23days) Sex : Female Test article : Sample D-1

Study No.BMR143C

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Focal mecrosis focal fatty change peripheral fatty change sveiling of centrilobular hepatocytes cosinophilic change in centrilobular hepatocytes

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extramedullary hematopolesis Kidneys

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dilated tubules infiltration of iymphocytes dilation of pelvis chronic nephropathy Adremais abnormality Brain Brain Ovaries abnormality

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#### 3M\_MN01650063

#### 2797.0077

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Table II-R-I Group incidence of microscopic findings (Recovery) Test article : Sample D-I

Ser						Male												Fom to				
Dose level	•••	þ	#g/kg	1 1	(u-e)		6	30 mg	ag/kg	(9-8)	2)	_		0	ng/kg	( <b>0-</b> 0)	I		30	ag/kg	K 8	(9-11)
Findings Grade	••	1	+1	‡ +	ŧ		Ŧ	+i	+	ŧ	≖		1	+	+	=	≢	1	1	++	+	=
lver			ĺ										.									l
+ crogranu osa [ocal_necros s			nc	20			00		40	00	οc		04	90	00	00	00			ma	20	00
focal fatty change							<mark>ما</mark> ا	00	10	00	00		00	00	50	50	50		4 C			
peripheral fatty change sveliing of centrilobular							2		2	0	0		4	-		0	0		പ	0	) <b></b> 1	0
hepatocytes		9	0	00	0		0	0	0	Ŋ	0		9	0	0	0	0		0	0	3	4
contrupting change in centrilobular hepatocytes		9	0	00	0		0	0	Ś	2	0		9	0	0	0	0		0	0	9	0
ncart nyocardiai degeneration							ſ	C	C	C	C		Ľ	-	C	C	c		y	c	c	c
ayocardial fibrosis		ŝ	, <b>–</b>	0	0		4	) <del></del> 1	0	0	0		9	•0	0	0	0		ور	0	0	0
extramedullary hematopolesis		ŝ	-	00	0		4	1	0	0	0		9	.0	0	0	0		9	0	0	0
regenerated tubules							4	-	0	0	0		2	4	0	0	0		ŝ	-	C	C
dilated tubules							<u>س</u>	00	0,	0	0		9	0	0	0	0		ە	0	0	0
dilation of pelvis		مە		00 00	00		4 W	00	~0	00	00		40	00	00	00	00		90	00	00	00
chronic nephropathy Adrenais							4	Ч	0	0	0		9	0	0	0	0		9	0	0	0
abnormal i ty		9	0	0	0		ŋ	0	0	0	0		9	0	0	0	0		9	0	0	0
abnormality		9	0	0	0		ŋ	0	0	0	0		9	0	0	0	0		9	0	0	0
atrophy			0	0	0		ŝ	0	0	0	0			•								
abnormality													9	0	Ō	0	0		9	0	0	0

Study No. BMR143C

بيد

Set Dose level:Male (n=1)FindlagsGrade: $\overline{30 \text{ eg}/kg}$ (n=1)FindlagsGrade: $\overline{-\pm + H}$ Liver: $\overline{-\pm + H}$ HLosinophile change in costnophiler hepatocytes001Coston lecrosis:001Sveilling of centrilobular hepatocytes001Nepatocytes0010Peribheral fatty change0010Peribheral fatty change0010Nidneys00100Iladotar stoaach00100Stoaach:0100Nidneys::010Stoaach:::010Uler and hemorrhage in glandular stoaach::::No ahnoreality::::::No ahnoreality::::::No ahnoreality::::::No ahnoreality::::::No ahnoreality::::::No ahnoreality::::::No ahnoreality::::::No ahnoreality::::::No ahnoreality <t< th=""><th></th><th></th><th></th><th></th><th></th><th></th><th>ĺ</th><th></th><th></th></t<>							ĺ		
Dose level: $3U \text{ g}/kg$ $(n-1)$ isGrade: $- \pm + H$ if lobular hepatocytes001ig of centrilobular001ig of centrilobular001ig of centrilobular001ig of centrilobular001ig of centrilobular001ig of centrilobular001if ubules001if ubules001orytes001if ubules001if ubules001old hemorrhage001if ubules001of all a stomach001if of001if ubules001of all a stomach001of all0000if ubules0000if ubules000 <t< th=""><th>Sex</th><th>••</th><th></th><th>1</th><th></th><th>Mal</th><th></th><th>ł</th><th></th></t<>	Sex	••		1		Mal		ł	
isGrade: $\pm$ $\pm$ $+$ $+$ illic change in ig of centrilobular ig of centrilobular is of centrilobular <b< th=""><th>Dose level</th><th>••</th><th></th><th></th><th>0 mg</th><th>/kg</th><th>Ę</th><th>=  </th><th></th></b<>	Dose level	••			0 mg	/kg	Ę	=	
bhlile change in g fo centrilobular       0       0       1         if lobular hepatocytes       0       0       0       1         if of centrilobular       0       0       0       1       0         icrosis       0       0       0       1       0       1       0         icrosis       0       0       1       0       0       1       0         arai fatty change       0       0       1       0       0       1       0         arait fatty change       0       0       1       0       0       1       0         arait fatty change       0       0       1       0       0       1       0         arait foor       1       0       0       1       0       0       1       0         arait foor       1       0       0       1       0       0       0       0       0       0       0       0         arait foor       1       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       <		••		I	+i	+	#	≣	
hills change in clobelar hepatocytes       0       0       1         centrilobular locytes       0       0       0       1         no cortes       0       0       1       0       1         no cortes       0       0       1       0       0       1       0         recrosis       0       0       1       0       0       1       0       1       0         recrosis       0       1       0       0       1       0       1       0         agic foci       1       0       0       1       0       1       0       1       0         agic foci       1       0       0       1       0       0       1       0       0       1       0	, l ver								
Inoutiar heratocytes     0     0     0     1       Ig of centrilobular     0     0     0     1       Icytes     0     0     1     0     0     1       real faity change     0     0     1     0     0     1     0       recrosis     0     0     1     0     0     1     0       recrosis     0     0     1     0     0     1     0       recrosis     0     0     1     0     1     0       recrosis     0     0     1     0     1     0       radiar stomach     0     0     1     0     0     1       fular stomach     0     0     1     0     0     0       rion     1     0     0     1     0     0       ormality     1     0     0     0     0     0	Eosinophilic change in			ľ		1			
Be of centritouular       0       0       1         Be of centritouular       0       0       1       0         crosts       0       0       1       0       1       0         icrosts       0       0       1       0       0       1       0         i tubules       0       0       1       0       0       1       0         nagic foci       1       0       0       1       0       1       0         nud hemorrhage in       1       0       0       1       0       1       0         fular stomach       1       0       0       1       0       0       1       0         ride       1       0       0       1       0       0       0       0       0       0         ride       1       0       0       1       0	centrifobular hepatocytes			0	0	0	-	0	
correctes       0       0       0       0       0       1         recrosis       0       0       0       0       0       0       1       0         attry change       0       0       0       0       0       1       0       0       1       0         agic foci       0       0       0       1       0       0       1       0         und hemorrhage in       0       0       1       0       0       1       0         und hemorrhage in       0       0       1       0       0       1       0         und hemorrhage in       0       0       1       0       0       1       0         und hemorrhage in       0       0       1       0       0       0       0       0         und hemorrhage in       0       0       1       0       0       0       0       0       0       0         iage       0       0       1       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0	SVELLING OL CENTRIODULAR			¢	¢	Ċ	•	Ċ	
at if if y change       0       0       1       0         i tubules       0       0       1       0       1       0         nagic foci       0       0       1       0       1       0         nagic foci       0       0       1       0       1       0         nad hemorrhage in       0       0       1       0       1       0         und hemorrhage in       0       0       1       0       0       1       0         und hemorrhage in       0       0       1       0       0       1       0         und hemorrhage in       0       0       1       0       0       0       0         und hemorrhage in       0       0       1       0       0       0       0       0         und hemorrhage in       0       0       1       0	nepatocytes Pocal necrosis			- C		-	-	50	
I tubules       0       1       0       1       0         nagic foct       0       0       1       0       1       0         and hemorrhage in dular stomach       0       0       1       0       1       0         fular stomach       0       0       1       0       0       1       0         ade       1       0       0       1       0       0       0       0         reality       1       0       0       1       0       0       0       0         reality       1       0       0       0       0       0       0       0       0       0         reality       1       0	Peripheral fatty change			0	0	> <del></del> 1	•0	00	
I tubules       0       0       1       0         nagic foci       0       0       1       0         and hemorrhage in       0       0       1       0         und hemorrhage in       0       0       1       0       0         inge       0       0       1       0       0       0       0         ormality       1       0       0       1       0       0       0       0         inge       0       1       0       0       0       0       0       0         ormality       1       0       0       0       0       0       0       0	ldneys								
nagic foci       0       1       0         ind hemorrhage in       0       0       1       0         iular stomach       0       0       1       0         ion       1       0       0       1       0         ion       1       0       0       1       0         inage       0       1       0       0       0         ormality       1       0       0       0       0         imality       1       0       0       0       0         imality       1       0       0       0       0       0	Dilated tubules			0	0		0	0	
Ind hemorrhage in     0     0     1     0       Idea     stomach     0     0     1     0       Idea     0     0     1     0     1     0       Idea     0     0     1     0     0     1     0       Inde     0     0     1     0     0     0     0       Inde     0     1     0     0     0     0       Inde     0     1     0     0     0       Inde     0     1     0     0     0       Inde     0     1     0     0     0       Inde     0     0     1     0     0	llenorrhagic foel		•	C	C	-	C	<b>_</b>	
and hemorrhage in     0     1     0       dular stomach     0     1     0       dular stomach     0     1     0       lon     0     1     0     0       nage     1     0     0     0       ormality     1     0     0     0	Stomach			)	>	4	)	>	
Idular stomach     0     1     0       stion     0     0     1     0       chage     0     0     1     0     0       inormality     1     0     0     0       inormality     1     0     0     0	Ulcer and hemorrhage in								-
tion 0 0 1 0 1 0 1 0 1 1 0 1 1 0 1 1 0 1 0	glandular stomach			0	0	-	0	0	
stion 0 0 1 0 chage 0 0 1 0 normality 1 0 0 0 normality 1 0 0 0 is 1 0 0 0 normality 1 0 0 0	hyeus								
chage     0     1     0       normality     1     0     0     0       normality     1     0     0     0       is     1     0     0     0       normality     1     0     0     0       is     1     0     0     0       normality     1     0     0     0	Congestion			0	0	-	0	0	
Intradity         1         0	lienorrhage Leart			0	0	-	0	0	
Intradict         1         0	No abnormality			-	C	0	0	C	
Ormality         1         0<	spleen			1	,	)	•	,	
mailty 1 0 0 0 1 mailty 1 0 0 0	No abnormality			-	0	0	0	0	
iormaticy I 0 0 0 1 0 0 0	ldrenals			•	¢	(	(	c	
iormality 1 0 0	NO ADNOTMALILY Pestes				∍	∍	⊃	D	
	No abnormality			H	0	0	0	0	

- : Negative.  $\pm$  : Yery slight. + : Slight. H : Moderato. H : Severe

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## APPENDICES (Individual Data)

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Appendix 1-H-1 Test article : Sample D-1 Sax : kale D-1         Study No. Birl 43C           Clinical signs - Individual Test article : Sample D-1 Sax : kale D-1         Study No. Birl 43C           Sex         Dose level         Animal         Study No. Birl 43C           O         1101         23.4         5         6         7         8         10.112         13         14         Study No. Birl 43C           O         101         101         1.01         0.1         2.3         4.5         6.7         8         9         10.112         13         14         Study No. Birl 43C           0         11         1.01         0.1         2.3         4.5         6.7         8         9         10.112         13         14         50         21         23         24         55         7         8         10.1	4112
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Dose level (ag/kg) 0 30	
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Appendix 1-F-1 Clinical signs - Individual Test article : Sample D-1 Sey : Famale	Days after commencement Days after commencement Days after 7 19 10 10 00 00 00 00 00 00 00 00 00 00 00	27 17 07 07 67 67 77 17 07 61 01 11 01 11 01 01 01 01 01 01 0 0 0 0				
) T	Animal number		1201 ↓	2201 4 2206	3201 ↓	ity observed
	Sex Dose level (mg/kg)	0	0.1 Fenale	1	10	- : No abnormality observed

No abnormality observed.

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KM : Keduced spontaneous movement, TC : Tonic-clonic/Clonic convulsion, LY : Lying, CR : Crouching, SA : Salivation, RS : Reddish salivation, CY : Cyanosis, LU : Loss of hair, CS : Coat staining, - : No abnormality observed,

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			Appendix 1-F-2 Clinical signs - Individual Test article · Samole D-1
Sex	Dose level	Animal	Sex : Fenale Days after commencement
	(Bg/kg)	number 4201 4909	0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
		4204	
Female	30	4205 4206 4207	
	•	4208	SA SA SA Lu La Lu La La La La La
		4209 4210	
		4211	
		4212	

-

LH : Loss of hair, CS : Coat staining, - : No abnormality observed.

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**BMR143C** 

Study No.

0 mg/kg

Body weight - Individual values Sex : Male Dose level : Sample D-1

2 - M - 1

Appendix

		Weeks after	commencement/	cessation of	n of treatment		
Number	0	1	2	ę	۲ ۲	5/1	6/2
0101	139	213	9	313	≍		
0102	4	196	249	291	318 KS		
0103	က	196	ŝ	301	X		
0104	4	207	G	318	Я		
0105	4	208	~	329	×		
0106	4	215	~	327	X		
0107	4	210	9	300		345	65 K
0108	4	207	ŝ	299	331	363	05 K
0109	ŝ	206	9	319	361	401	38 K
0110	149	211	9	306	327	352	74 K
0111	က	185	က	275	304	324	44 K
0112	143	198	ß	308	346	378	410 KS
Mean	143	204	9	307	4	് ഗ	600
5.D.	5.6	8.8	12.2	15.4	21.8	26.8	34.4
z	. 12	. 12	12	12	-		

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Unit : g

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BMR143C

Study No.

	0.1 mg/kg
values	l.e D-1
ndividual : Male	: Sampl
Body weight - I Sex	Dose level

2 - M - 2

Appendix

treatme	
of	
cessation	
commencement/	
after	
Weeks	

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		Weeks after	Weeks after commencement/		cessation of treatment	nt	
Number	0	I	2	e	4	5/1	6/2
1101	137	206	277	333			
1102	140	200	244	288			
1103	141	210	268	318			
1104	146	199	254	293			
1105	148	214	284	340			
1106	148	214	285	347	399 KS		
Mean	143	207		320	359		
S.D.	4.6	6.6	16.7	24.7	31.8		
z	9	9 -		9	9		

KS : Killed on schedule

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1 Σ 1 2 Appendix

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	BMR143C			Unit : g
	Study No. BMR143C			
			1 mg/kg	
- W - 3	Body weight - Individual values	: Male	: Sample D-1	
Appendix 2 - M - 3	Body weight -	Sex	Dose level	

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Animal		Weeks after	Weeks after commencement/	cessation	cessation of treatment		
Number	0	1	2	ю	4	5/1	6/2
2101	136	197	255	308			
2102	143	206	265	315			
2103	142	202	264	296			
2104	146	203	254	311			
2105	147	213	278	336			
2106	147	216	275	318	350 KS		
Mean	- 144	206		314	349		
S.D.	4.2	7.1	6.6	13.2	17.7		
z	9	9		9	9		

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KS : Killed on schedule

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Unit : g

**BMR143C** 

Study No.

- M - 4

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Appendix

Body weight - Individual values Sex : Male Dose level : Sample D-1 10 mg/kg

	5/1
treatment	4
of	•
cessation	3
commencement/	2
after	
Weeks	1

0

Animal Number

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6/2

326 KS						343 24.5 6
293	298	289	301	343	308	305 19.6 6
245	252	245	253	282	264	257 14.2 6
196	193	195	198	214	210	201 8.8 6
135	137	143	145	150	147	143 5.8 6
3101	3102	3103	3104	3105	3106	Mean S.D. N

KS : Killed on schedule

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Unit : g

**30 mg/kg** 

Body weight - Individual values Sex : Male Dose level : Sample D-I

2 - M - 5

Appendix

BMR143C

Study No.

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Animal		Weeks after	commencement/	cessation	of treatment	
Number	0	1	5	'n	- ₽	5/1
4101	140	6	( c	1	00	
4102	139	8	2	ഴ	286 KS	
4103	144	0	മ	0	21	
4104	147	9	-7	9	83	
4105	143	6	3	ŝ	69	
4106	146	6	4	8	63	
4107	147	6	ŝ	9	84	304
4108	136	œ	ŝ	9	162	311
4109	145	6	က	5	261	
4110	138	œ	2	9	284	a
4111	142	194	238	271	292	315
4112	146	0	9	297	310	338
Mean	143	193	3	272	6	315
S.D.	3.7	7.0	10.2	14.5	16.2	•
Z	12	12	12	12	12	

326 KS 336 KS 331 KS 340 KS 373 KS

341 18.5 5

20 - | - |

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6/2

KS : Killed on schedule<sup>.</sup> D : Dead.

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Unit : K

0 mg/kg

Body weight - Individual values Sex : Female Dose level : Sample D-1

- F - 1

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Appendix

BMR143C

Study No.

		Weeks after	commencement/	cessation of	of treatment		
Animal Number	0		2	3	4	5/1	6/2
0201	N 2	9	റ		28		
0202	123	151	177	193	214 KS		
0203	3	9	æ	0	21	÷	
0204	-7	1-	0	ĉ	64		
0205	2	164	æ	0	27		
0206	က	9	æ		27		
0207	e	5	~	ഹ	~	0	25
0208	3	9	-	2	ဗ	à	65
0209	2	9	æ	-	က	â	64.
0210	10	-	$\sim$	2	4	9	70
0211	1.63	· [-	Ċ,	2	4	262	278 KS
0212	121	156	179	201	2	4	57
Mean	0130	9	6			9	5
S.D.	5 4 4	8.1	13.1	16.5	18.6	20.7	24.8
,	12			12		9	9

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2 - F - 2 Appendix

**BMR143C** Study No. Body weight - Individual values Sex : Female Dose level : Sample D-1

0.1 mg/kg

		Weeks aft	Weeks after commencement/		cessation of treatment	nt	
Animal Number	0	1	0	e	4	5/1	6/2
1201	124	159	188	210			
1202	125	ø	180	196			
1203	132	165	192	219			
1204	130	9	192	222			
1205	128	165	194	217	227 KS		
1206	132	163	189	207	-		
Mean	129	164	189	212	227		
S.D.	3.4	2.3	5.0	9.6	10.5		
Z	و	9	9	9	9		

KS : Killed on schedule

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3M\_MN01650078

#### 2797.0092

12

Unit : g

Unit : g

1 mg/kg

Body weight - Individual values Sex : Female Dose level : Sample D-1

2 - F - 3

Appendix

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BMR143C

Study No.

		MCCAS S	Aceva arter commencement	כבוובויר כבו	1011000	CESSALIUM UL LICALMENT	۰.	
Animai Number	0	1	2	<b>m</b>		4	5/1	6/2
2201	121	152	177	20	4	1		
2202	128	157	184	205	5	226 KS		
2203	130	157	180	20	1			
2204	132	171	202	. 22	8			
2205	134	185	213	23	7			
2206	141	180	198	22	5			
Mean	-131	167	192	21	2	235		
S.D.	6.6	13.7	14.2	15.2	5	15.9		
Z	ĝ	<b>9</b>	9		9	6		

KS : Killed on schedule

3M\_MN01650079

13

Unit : g

10 mg/kg

Body weight - Individual values Sex : Female Dose level : Sample D-1

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2 - F - 4

Appendix

BMR143C

Study No.

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	5/1
treatment	4
0 f	
cessation	3
commencement/	2
after	
Weeks	1
	0

Number         0         1         2         3         4         5/1         6/2           3201         125         156         185         203         216 KS         5/1         6/2           3201         125         156         185         203         216 KS         218         225 KS           3203         125         149         166         178         186 KS         221 KS           3204         130         159         187         203         221 KS         221 KS           3205         136         169         187         203         223 KS         233 KS           3206         138         169         187         203         223 KS         233 KS           3206         138         169         191         208         223 KS         233 KS           3205         130         161         186         203         214         14.4           6         6         6         7.9         9.8         13.4         14.4         6	Number							
$ \begin{bmatrix} 125 & 156 & 185 & 203 & 216 \\ 125 & 164 & 193 & 218 & 225 \\ 125 & 149 & 166 & 178 & 186 \\ 130 & 159 & 189 & 208 & 221 \\ 136 & 169 & 187 & 203 & 221 \\ 138 & 169 & 191 & 208 & 221 \\ 130 & 161 & 187 & 203 & 212 \\ 130 & 161 & 186 & 203 & 214 \\ 5 \cdot 9 & 7 \cdot 9 & 9 \cdot 8 & 13 \cdot 4 & 14 \cdot 4 \\ 6 & 6 & 6 & 6 \\ \end{bmatrix} $		0	1	2	ß	4	5/1	6/2
$ \begin{bmatrix} 125 & 164 & 193 & 218 & 225 \\ 125 & 149 & 166 & 178 & 186 \\ 130 & 159 & 189 & 208 & 221 \\ 136 & 169 & 187 & 203 & 221 \\ 138 & 169 & 191 & 208 & 221 \\ 130 & 161 & 185 & 203 & 212 \\ 130 & 161 & 186 & 203 & 214 \\ 5 \cdot 9 & 7 \cdot 9 & 9 \cdot 8 & 13 \cdot 4 & 14 \cdot 4 \\ 6 & 6 & 6 & 6 \\ 6 & 6 & 6 & 6 \\ 6 & 6 &$	3201	125	156	185	203	1		
$ \begin{bmatrix} 125 & 149 & 166 & 178 & 186 \\ 130 & 159 & 189 & 208 & 221 \\ 136 & 169 & 187 & 203 & 221 \\ 138 & 169 & 191 & 208 & 223 \\ 130 & 161 & 185 & 203 & 213 \\ 5 \cdot 9 & 7 \cdot 9 & 9 \cdot 8 & 13 \cdot 4 & 14 \cdot 4 \\ 6 & 6 & 6 & 6 & 6 \end{bmatrix} $	3202	125	164	193	218			
$ \begin{bmatrix} 130 & 159 & 189 & 208 & 212 \\ 136 & 169 & 187 & 203 & 212 \\ 138 & 169 & 191 & 208 & 223 \\ 130 & 161 & 191 & 208 & 223 \\ 5.9 & 7.9 & 9.8 & 13.4 & 14.4 \\ 6 & 6 & 6 & 6 \\ 6 & 6 & 6 & 6 \end{bmatrix} $	3203	125	149	166	178			
136     169     187     203     212       138     169     191     208     223       130     161     185     203     214       5.9     7.9     9.8     13.4     14.4       6     6     6     6     6	3204	130	159	189	208			
138     169     191     208     223       130     161     185     203     214       5.9     7.9     9.8     13.4     14.4       6     6     6     6     6	32.05	136	169	187	203			
130 161 185 203 5.9 7.9 9.8 13.4 6 6 6 6	3206	138	169	191	208			
· 5.9 7.9 9.8 13.4 V 6 6 6 6 6 6	Mean	130	161	185	203	214		
6 6 6	S.D.	•	7.9	9.8	13.4	14.4		
	Z	9	9	9	9	9		·

KS : Killed on schedule

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3M\_MN01650080

14

Unit

BMR143C

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Appendix

Study No. 30 mg/kg , weight - Individual values Sex : Female Dose level : Body weight

3M\_MN01650081

15

		Food consum	consumption - Indivi see - Moio	Individual values	10	Study No. BMR143C
		Dose level	• ••	mare Sample D-1	0 mg/kg	Unit : g/Animal/Day
		Weeks after	Weeks after commencement/ cessation of treatment	cessation	of treatment	
Lage Number	1	2	e	4	5/1	6/2
1	17.8	20.4	18.6	16.3	NA	
2	17.0	19.2	19.6	18.8	NA	
ന്	16.9	19.6	19.6	17.4	NA	
ন	17.4	19.1	17.6	15.0	20.6	22.3
£	16.1	18.5	19.2	17.1	23.1	23.8
9	15.5	17.7	18.5	16.4	21.6	23.0
Mean	16.8	19.1	18.9	16.8	21.8	23.0
S.D.	0.85	0.92	0.77	1.27	1.26	0.75
Z	9	9	9	9	co	5
NA : No a	animal existe	ted.				

NA : NO ANIMAL EXISTED.

16

3M\_MN01650082

2797.0096

Study No. BMR143C

3 - M - 1

Appendix.

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دی ۱ 9 - M Appendix

Study No.

Unit : g/Animal/Day 0.1 mg/kg Food consumption - Individual values Sex : Male Dose level : Sample D-1 (

BMR143C

6/2 Weeks after commencement/ cessation of treatment A A A N N N 5/1 18.8 2.52 3 18.1 16.7 21.6 4 20.2 2.96 3 19.5 17.6 23.4 ი 20.6 1.88 3 20.218.9 22.6 2 17.8 16.8 19.3 18.0 1.26 3 -Cage Number - 2 C

NA : No animal existed.

Mean S.D. Z

17

3M\_MN01650083

			1	ulan landust	es	or uay No.		DMA143C
	·	Food consumption		גועושגו עמוש פוס				
		. Dose	• ••	Sample D-1	1 mg/kg	Unit : g/Animal/Day	g/Anlm.	al/Day
		Weeks aft	er commenceme	Weeks after commencement/ cessation of treatment	n of treatme	nt		
vage Number	-	2	e	4	5/1	6/2	<b>.</b>	
1	16.3	18.8	18.1	17.3	NA			
2	16.9	19.1	17.1	16.6	NA			
ຕ່	17.8	19.9	19.1	17.9	NA			
Mean	17.0	19.3	18.1	17.3				
S.D.	0.75	0.57	1.00	0.65				
z	n	n	с	ന				

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BMR143C		
Study No.		
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	value	
•	I - Individual values	2 · · · · · · · · · · · · · · · · · · ·
:	- uo	
2	umption	έ

	mg/kg
	10
values	
la l	D1
Individua	Male Sample
I	
umption	Sex level
CONS	Dose
Food	•

Unit : g/Animal/Day

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treatment
οf
cessation
commencement/
after
Weeks

1     15.7     17.1     16.9     15.9     NA       2     16.0     17.6     19.1     16.7     NA       3     18.0     20.1     22.4     20.8     NA       ean     16.6     18.3     19.5     17.8       D.     1.25     1.8.3     19.5     17.8       N     3     3     3     2.77       D.     1.55     1.61     2.77     2.63	Number	1	0	က	4	5/1	6/2	
16.0       17.6       19.1       16.7         18.0       20.1       22.4       20.8         18.0       20.1       22.4       20.8         16.6       18.3       19.5       17.8         1.25       1.61       2.77       2.63         3       3       3       3	1	15.7	17.1	16.9	15.9	NA		
18.0         20.1         22.4         20.8           16.6         18.3         19.5         17.8           1.25         1.61         2.77         2.63           3         3         3         3         3	67	16.0	17.6	19.1	16.7	NA		•
18.3 19.5 1.61 2.77 3	3	18.0	20.1	22.4	20.8	NA		
1.25 1.61 2.77 3 3 3 3	ean	16.6	18.3	19.5	17.8	•		
	Z	1.25 3	1.61 3	2.77	2.63 3			

NA : No animal existed.

19

# 2797.0099

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BMR143C	
Study No.	
Food consumption - Individual values	Sex : Male Dose level : Sample D-1 30 mg/kg

Unit : g/Animal/Day

0 20 C						•
Number	1	. 2	n	4	5/1	6/2
1	14.8	14.9	14.7	12.8	NA	
2	15.8	16.3	15.6	12.8	NA	
n	15.8	16.4	15.3	11.7	NA	
4	15.1	15.2	15.6	13.7	17.8	20.2
ഖ	14.5	15.4	15.0	12.5	22.7	19.7
9	16.4	16.4	15.4	12.8	20.6	23.6
Mean	15.4	15.8	15.3	12.7	20.4	21.2
s.D.	0.72	0.68	0.36	0.64	2.46	2.12
z	9	9	9	. 9	n	6

NA : No animal existed.

20

---Ľ. ו ר Appendix

BMR143C Study No. 0 mg/kg - Individual values Female Sample D-1 Sex : Dose level : Food consumption

Unit : g/Animal/Day 20.0 0.35 3 20.4 20.0 19.7 6/2 Weeks after commencement/ cessation of treatment 19.4 0.20 3 NA NA NA 19.6 19.2 5/1 11.2 13.8 10.8 14.3 13.3 12.7 1.42 6 4 13.9 1.50 6 15.1 12.4 15.6 15.1 13.1 ŝ က 2 12.1 13.6 11.4 14.9 14.3 12.4 13.1 9 2 13.8 1.15 6 12.4 14.7 12.6 14.8 14.9 13.4 -Cage Number Mean S.D. N 00430 ----.

NA : No animal existed.

21

I		Weeks aft	Weeks after commencement/ cessation of treatment	ent/ cessari	on of treatme	nt	
Cage Number	1	2	3	4	5/1	6/2	
1	13.3	11.8	12.1	11.4	NA		
2	14.1	13.4	14.9	13.6	NA		-
Ċ,	13.6	12.7	13.1	12.1	NA		
Mean	13.7	12.6	13.4	12.4			
S.D.	0.40	0.80	1.42	1.12	-		
Z	e	ę	c	n			

Appendix 3 - F - 2 Frond ronsumption - Ind

BMR143C

Study No.

3M\_MN01650088

22

		Weeks afte	er commencen	ient/ cessati	Weeks after commencement/ cessation of treatment	nt
Cage Number	1	ດ	က	4	5/1	6/2
-	11.6	10.5	11.7	11.0	NA	
5	14.1	12.9	13.1	12.2	NA	
ന്	16.3	13.4	13.8	12.5	NA	-
Mean	14.0	.12.3	12.9	11.9	- - - - - - -	
s.D. N	2.35 3	1.55 3	1.07 3	0.79 3		

3 - F - 3 Appendix

3M\_MN01650089

#### 2797.0103

23

Food consumption - Individual values Sex : Female

BMR143C Study No.

3 - F - 4

BMR143C . Study No. Food consumption - Individual values Sex : Female Dose level : Sample D-1 Appendix

**10 mg/kg** 

6/2 Weeks after commencement/ cessation of treatment A A A N Z Z 5/1 9.7 0.36 3  $9.6 \\ 9.4 \\ 10.1$ 4 - $11.2 \\ 0.75 \\ 3$ 11.2 10.4 11.9 ŝ 11.5 0.81 3 11.9 10.6 12.1 2 12.6 11.6 13.8 12.7 1.10 3 -Cage Number Mean s.b. 

NA : No animal existed.

3M\_MN01650090

#### 2797.0104

24

Unit : g/Animal/Day

ы 1 Е Appendix

BMR143C Study No. 30 mg/kg Food consumption - Individual values Sex : Female Dose level : Sample D-1 3 ى ۱

Unit : g/Animal/Day 6/2 Weeks after commencement/ cessation of treatment 5/1 7 ო 2 F

**.**...

				9 13.9			l 1.97	
				6.8 12.9			1.09 1.51	
7.9	8.5	9.0	6.6	7.9	8.4	8.1	0.82	9
9.6	11.3	10.6	9.8	10.7	9 • 8	1,0.3	0.72	9
12.0	13.4	13.4	11.9	13.7	13.2	12.9	0.78	9
<b>1</b>	2	ຕ່	4	വ	9	Mean	s.D.	z

NA : No animal existed

3M\_MN01650091

25

Cage Number

Study No. BNR143C

Appendix 4 - M - 1

Hematology - Individual values
 Sex : Male
 Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (4 weeks)

Study No. BMR143C

Appendix 4 - M - 2

llematology - Individual values
 Sex : Male
 Dose level : Sample D-1 0.1 mg/kg
Animals killed on schedule (4 weeks)

Animal	RBC count	HB conc.	Ht.	MCV	MCH	MCHC	Platelet count	РТ	APTT	Reticulo- cyte count
lumber	(x10 <sup>4</sup> /mu <sup>3</sup> )	(lþ/g)	( % )	( 11 m3)	(bg)	~ % )	(x10 <sup>4</sup> /mm <sup>3</sup> )	(sec)	(sec)	(%)
101	765	14.1	52.2	68	18.4	27.0	106.1	14.9	15.5	26
1102	683	13.9	46.0	67	20.4	30.2	78.2	13.9	15.7	26
1103	689	13.9	45.4	99	20.2	30.6	88.3	13.9	15.4	21
1104	675	13.8	44.8	66	20.4	30.8	91.0	14.0	16.4	33
1105	679	14.3	46.1	68	21.1	31.0	94.7	13.8	19.4	32
1106	696	14.1	45.6	99	20.3	30.9	104.7	13.7	17.6	35
Mean	698	14.0	46.7	67	20.1	30.1	93.8	14.0	16.7	59
S.D.	33.7	0.18	2.74	1.0	0.91	1.54	10.51	0.44	1.57	5.3
z	ĝ	9	9	g	9	5	9	G	Ľ	5

27

Study No. BMR143C

Appendix 4 - M - 3

Hematology - Individual values Sex : Male Bose level : Sample D-1 1 mg/kg Animals killed on schedule (4 weeks)

Reticulo- cyte count (960)	27 25 26 30 26 27 27	28 2.1 2.1
APTT (sec)	13.0 14.7 15.8 15.8 17.6 15.4	15.5 1.60
PT (sec)	13.9 14.1 14.1 14.1 14.4 13.5	14.0 0.31
Platelet count (x10 <sup>4</sup> /mm <sup>3</sup> )	97.4 92.1 134.7 112.7 105.4 79.8	103.7 18.92 6
MCHC ( % )	31.2 30.2 30.0 29.9 29.4	29.7 1.34
MCH (pg)	19.4 19.1 17.8 19.2 19.8	19.0 0.69
МСV (д ш <sup>э</sup> )	<b>61 85 83 87</b>	64 1.9 8
Ht ( % )	42.3 46.3 51.9 47.7 46.2 49.0	47.2 3.21
HB conc. (g/dl)	13.2 14.1 14.3 13.8 14.4	14.0 0.43
RBC count (x10 <sup>4</sup> /mm <sup>3</sup> )	681 733 794 719 719 728	737 38.8 5
An i ma l Number	2101 2103 2104 2105 2105 2106	Mean S.D.

.78

Appendix 4 - M. - 4

Hematology - Individual values Sex : Male Dose level : Sample D-1 10 mg/kg Animals killed on schedule (4 veeks)

Reticulo- cyte count (9‰)	19 31 32 33 33 34 34 35 35 35 35 35 35 35 35 35 35 35 35 35	27 5.6 6
APTT (sec)	14.8 14.4 14.7 17.2 17.1 15.1	15.6 1.26 6
PT (sec)	14.4 13.9 13.6 13.8 14.0 13.6	13.9 0.30 6
Platelet count (x10 <sup>4</sup> /mm <sup>3</sup> )	97.5 111.8 84.3 115.5 115.5 111.9	103.7 11.79 6
MCHC	29.5 29.3 29.3 29.3 29.3 29.3 29.3	28.9 1.20 6
MCH (pg)	18.8 19.0 18.3 17.6 17.2	18.4 0.80 6
MCV ( <i>L</i> m <sup>3</sup> )	65 65 65 65 65 65	64 2.4 6
lit (%)	43.4 45.1 49.6 45.4 47.6	46.2 2.15 6
HB conc. (g/d1)	12.8 13.6 13.3 13.2	13.4 0.33 6
RBC count (x10 <sup>4</sup> /mm <sup>3</sup> )	681 714 737 713 713 713 766	728 31.4 6
Animal Number	3101 3102 3103 3104 3105 3106	Mean S.D. N

Appendix 4 - M - 5

Hematology - Individual values Sex : Male Dose level : Sample D-1 30 mg/kg Animals killed on schedule (4 weeks)

	RBC Count	HB	Ht	MCV	MCH	MCHC	Platelet	РТ	APTT	Reticulo-
Number	(x10 <sup>4</sup> /mm <sup>3</sup> )	(g/d1)	(%)	(η <sub>113</sub> )	(bg)	(%)	count (x10 <sup>4</sup> /mm <sup>3</sup> )	(sec)	(sec)	cyte count (%)
4101	647	13.1	44.1	89	20.2	29.7	92.1	14.4	15.0	14
4102	665	12.5	43.8	99	18.8	28.5	88.1	14.8	20.4	21
4103	702	13.0	45.9	65	18.5	28.3	96.0	14.6	15.7	12
4104	725	12.9	48.4	67	17.8	26.7	96.3	14.2	18.4	14
4105	209	13.6	43.0	64	20.4	31.6	78.0	14.0	20.2	12
4106	792	14.9	51.6	65	18.8	28.9	89.1	14.2	19.1	27
Mean	200	13.3	46.1	99	19.1	29.0	6.68	14.4	18.1	30
S.D.	53.3	0.85	3.30	1.5	1.01	1.63	6.76	0.29	2.29	5.0
z	9	9	9	9	ų	5	Ľ	5		

Appendix 4 - M - 6

Hematology - Individual values Sex : Male Dose level : Sample D-1 0 mg/kg Animals killed on schedule (Recovery)

l cui a	RBC Callet	HB	lt	MCV	MCII	NCHC	Platelet	ЪТ	APTT	Reticulo-
Number	(x10 <sup>4</sup> /mm <sup>3</sup> ) (g/d1)	(g/dl)	<ul><li>% )</li></ul>	( m <sup>3</sup> )	(8d)	( % )	(x10 <sup>4</sup> /mm <sup>3</sup> )	(sec)	(sec)	(%) (%)
0107	062	14.5	45.0	57	18.4	32.2	71.4	13.8	17.3	
0108	728	13.4	40.4	55	18.4	33.2	97.0	14.0	16.2	
0109	798	14.2	46.6	58	17.8	30.5	71.0	13.8	15.3	
0110	896	14.3	48.2	54	16.0	29.7	97.6	13.8	15.9	
0111	784	13.8	45.2	58	17.6	30.5	80.2	ರ	ਹੋ	
0112	162	14.1	47.7	60	17.8	29.6	113.1	13.7	15.5	32
Mean	798	14.1	45.5	57	17.7	31.0	88.4	13.8	16.0	25
S.D.	54.4	0.39	2.82	2.2	0.88	1.44	16.90	0.11	0.79	4.9
z	9	9	9	9	9	9	9	വ	ŝ	9

Appendix 4 - M - 7

Hematology - Individual values
 Sex : Male
 Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (Recovery)

•	RBC.		11	MCV	NCH	MCHC	Platelet		APTT	Reticulo-
Animal Number	count (x10 <sup>4</sup> /mm <sup>3</sup> )	conc. (g/d1)	<pre>     % &gt; </pre>	(	(8d)	(%)	count (x10 <sup>4</sup> /mm <sup>3</sup> )	(sec)	(sec)	(%)
4107	743	12.7	43.8	28	17.1	29.0	82.8	13.3	14.2	31
4108 4109	688	11.9	39.6	28	17.3	30.1	112.7	13.7	14.3	34
4110	718	12.5	41.5	58	17.4	30.1	96.0	13.7	15.8	22
4111	703	13.2	42.7	61	18.8	30.9	88.6	12.6	14.6	31
4112	735	13.0	40.5	55	17.7	32.1	97.4	13.6	17.2	33
Mean	717	12.7	41.6	28	17.7	30.4	95.5	13.4	15.2	31
s.0. N	22.6 5	0.50 5	1.68 5	.2 <b>.</b> 2	0.67 5	1.15	11.28 5	0.47 5	1.28 5	6.2 5

Appendix 4 - F - 1

Hematology - Individual values
 Sex : Female
 Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (4 weeks)

-	RBC		Ht	MCV	MCH	MCHC		ΡT	APTT	Reticulo-
vumber Vumber	count (x10 <sup>4</sup> /mm <sup>3</sup> )	conc. (g/d1)	(%)	( <sub>E</sub> III 7/ )	(bg)	(※)	$(x10^4/mm^3)$	(sec)	(sec)	cyte count (% )
0201	720	13.2	44.5	62	18.3	29.7	117.7	14.3	15.9	22
0202	777	13.7	46.3	09	17.6	29.6	142.0	14.4	13.6	24
0203	658	13.3	40.6	62	20.2	32.8	95.2	14.6	11.8	26
0204	635	12.6	37.6	29	19.8	33.5	107.5	14.2	12.9	18
0205	727	13.4	41.8	57	18.4	32.1	120.4	14.0	15.9	19
0206	714	13.8	45.7	64	19.3	30.2	111.4	<b>i4.</b> 3	14.1	24
Mean	705	13.3	42.8	19	18.9	31.3	115.7	14.3	14.0	22
S.D.	51.2	0.43	3.36	2.5	1.00	1.70	15.64	0.20	1.64	3.1
X	9	9	9	9	9	-	£	5	2	~

Appendix 4 - F - 2

Reticulo-cyte count (‰)  $2.9^{2.9}$ 22228<sup>18</sup>2 (sec) 14.8 1.19 6 17.0 14.5 15.1 14.0 14.4 13.7 APTT (sec) 14.7 14.5 14.5 13.4 14.2 14.2 14.3 0.46 6 ΡT Platelet count (x10<sup>4</sup>/mm<sup>3</sup>) 103.1 12.27 6 101.4 97.6 124.0 87.7 99.1 108.6 Hematology - Individual values Sex : Female Dose level : Sample D-1 mg/kg Animals killed on schedule (4 weeks)  $\langle % \rangle$ 33.2 33.1 31.5 31.5 33.7 32.4 30.4 32.4 1.24 6 MCIIC 19.7 0.66 6 18.8 19.5 19.9 19.6 19.6 MCH (gd) ( €<sup>m</sup> 7 )  $\begin{array}{c} 61\\ 3.4\\ 6\end{array}$ 520 520 520 520 520 КŅ ( % ) 42.0 1.40 6 40.7 40.8 42.6 41.3 44.4 Ħt HB conc. (g/d1) 13.5 13.5 13.4 13.4 13.5 13.5 13.6 0.18 6 RBC count (x10<sup>4</sup>/mm<sup>3</sup>) 720 693 699 699 693 693 691 25.2 6 Animal Number 1201 1202 1203 1204 1205 1206 Mean S.D. z

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3M\_MN01650100

Appendix 4 - F - 3

Hematology - Individual values Sex : Female Dose level : Sample D-1 Animals killed on schedule (4 weeks)

mg/kg

Animal Number	RBC count (x10 <sup>4</sup> /mm <sup>3</sup> )	HB conc. (g/d1)	王 《 % )	НСУ ( д. m <sup>3</sup> )	MCH (pg)	MCHC % >	Platelet count (x10 <sup>4</sup> /mm <sup>3</sup> )	PT (sec)	APTT (sec)	Reticulo- cyte count (%)
2201 2203 2205 2206 2206	726 708 724 634 643	13.7 13.5 13.5 13.1 13.3	842.0 84.0 84.0 88.8 88.8 88.8	8 E E E Z 2	18.9 18.6 19.3 20.8 20.8	32.2 31.8 30.7 32.4 31.7 34.3	106.3 115.6 113.6 111.1 102.7 97.9	13.9 14.2 14.8 14.4 14.6	13.1 16.8 15.1 14.7 17.1	822828
Mean S.D. N	701 52.0 6	13.3 0.29 6	41.3 1.79 6	60 60 6	19.4 1.09 6	32.2 1.19 6	107.9 6.81 6	14.2 0.57 6	15.7 1.66 1.66	22 2.5 6

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3M\_MN01650101

Appendix 4 - F - 4

Hematology - Individual values
 Sex : Female
 bose level : Sample D-1 10 mg/kg
Animals killed on schedule (4 weeks)

$ \begin{array}{c} \text{Im}^{3} \ (g/\text{ull}) \ (g/\text{um}^{3}) \ (g/\text{um}^{3}) \ (g/\text{um}^{3}) \ (g/\text{um}^{3}) \ (g/\text{um}^{3}) \ (g/\text{um}^{3}) \ (gc) \ (gc) \ (g/\text{um}^{3}) \ (gc) \ (g$	RBC		Ht	NCV	NCH	MCHC	Platelet	Ы	APTT	<b>Reticulo</b> -
14.0     44.0     64     20.4     31.8     88.0     14.3       13.5     43.4     57     17.8     31.1     111.0     14.3       13.5     43.4     57     17.8     31.1     111.0     14.2       14.1     47.4     62     18.5     29.7     123.3     14.1       13.4     41.0     59     19.1     32.7     93.7     13.5       13.5     43.4     63     19.5     31.1     117.7     13.5       13.5     43.8     63     20.0     31.7     101.9     14.5       13.7     43.8     61     19.2     31.7     101.9     14.5       0.30     2.06     2.7     0.96     1.00     13.81     0.42	(x10 <sup>4</sup> /mm <sup>3</sup> )		<ul><li>% )</li></ul>	( <sub>6</sub> m 7/ )	(bg)	( % )	count (x10 <sup>4</sup> /mm <sup>3</sup> )	(sec)	(sec)	cyte count · (%o)
13.5       43.4       57       17.8       31.1       111.0       14.2         14.1       47.4       62       18.5       29.7       123.3       14.1         13.4       41.0       59       19.1       32.7       93.7       13.5         13.5       43.4       63       19.1       32.7       93.7       13.5         13.5       43.4       63       19.5       31.1       117.7       13.5         13.9       43.8       63       20.0       31.7       101.9       14.5         13.7       43.8       61       19.2       31.7       101.9       14.5         13.7       20.0       31.7       101.9       14.5       14.5         0.30       2.06       2.7       0.96       1.00       13.81       0.42	685	14.0	44.0	64	20.4	31.8	88.0	14.3	15.3	6
14.1     47.4     62     18.5     29.7     123.3     14.1       13.4     41.0     59     19.1     32.7     93.7     13.5       13.5     43.4     63     19.1     32.7     93.7     13.5       13.5     43.4     63     19.1     32.7     93.7     13.5       13.9     43.8     63     20.0     31.7     101.9     14.5       13.7     43.8     61     19.2     31.4     105.9     14.0       0.30     2.06     2.7     0.96     1.00     13.81     0.42	759	13.5	43.4	57	17.8	31.1	111.0	14.2	14.0	35
13.4     41.0     59     19.1     32.7     93.7     13.5       13.5     43.4     63     19.1     32.7     93.7     13.5       13.5     43.4     63     19.5     31.1     117.7     13.5       13.9     43.8     63     20.0     31.7     101.9     14.5       13.7     43.8     61     19.2     31.4     105.9     14.0       030     2.06     2.7     0.96     1.00     13.81     0.42	764	14.1	47.4	62	18.5	29.7	123.3	14.1	15.0	1 K
13.5     43.4     63     19.5     31.1     117.7     13.5       13.9     43.8     63     20.0     31.7     101.9     14.5       13.7     43.8     61     19.2     31.4     105.9     14.0       030     2.06     2.7     0.96     1.00     13.81     0.42	200	13.4	41.0	59	19.1	32.7	93.7	13.5	14.3	20
13.9         43.8         63         20.0         31.7         101.9         14.5           13.7         43.8         61         19.2         31.4         105.9         14.0           0.30         2.06         2.7         0.96         1.00         13.81         0.42	683	13.5	43.4	3	19.5	31.1	117.7	13.5	15.4	
13.7 43.8 61 19.2 31.4 105.9 14.0 0.30 2.06 2.7 0.96 1.00 13.81 0.42	695	13.9	.43.8	63	20.0	31.7	6.101	14.5	16.8	20
	716 35.6	13.7 0.30	43.8 2.06	61 2.7	19.2 0.96	31.4 1.00	105.9 13.81	14.0 0.42	15.2 0.99	21

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Appendix 5 - F - 3

Hematology - Individual values Sex. : Female Dose level : Sample D-1 1 mg/kg Animals killed on schedule (4 weeks)

Animal Number	WBC count (x10 <sup>2</sup> /mm <sup>3</sup> )	Differ Lympho- cytes	ential count c Neutro Segmented	of leukocytes ophils Band	(% of Eosino- phils	Differential count of leukocytes (% of total counted cells) mpho- Neutrophils Eosino- Baso- Mono- tes Segmented Band phils phils cytes	cells ) Mono- cytes
2201	57	. 86	6		c	0	
2202	94	92	-	· C			ť <del>-</del>
2203	108	87	10	00		> c	- C
2204	112	81	15	0		• <b>-</b>	16
2205	77	86	13	. 0	• C	• c	· - (
2206	70	6	2		0	0	
Mean	86	88	10	0	0	c	6
s.D.	21.9	म - म	3.7	0.5	0.5	0.0	1.3
z	Ō	Û	<b>ب</b>	Ľ	u	U	Ľ

Appendix 5 - F - 4

Hematology - Individual values Sex : Female Dose level : Sample D-1 10 mg/kg Animals killed on schedule (4 weeks)

3201 3202	117		Segmented	hils Band	(% of Eosino- phils	Dirferential count of jeukocytes (% of total counted cells ) 1Pho- Neutrophils Eosino- Baso- Mono- ces Segmented Band phils phils cytes	cells) Mono- cytes
3202		92	4	-	c		
	103	87	. 6	• C			זכ
3203	61	06	9	, c			• •
3204	67	89	9	0	C		1 ~
3205	89	92	2	. 0	• 0		г u
3206	70	84	80	0	<b>,</b> –		
Mean	85	89	- -	0	c	c	1
S.D. R	22.3 6	3.1 6	2.1 6	0.4	0.5	0.0	1.7

Appendix 5 - F - 5

Study No. BMR143C

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Hematology - Individual values Sex : Female Dose level : Sample D-1 30 mg/kg Animals killed on schedule (4 weeks)

Animal Number	WBC count (X10 <sup>2</sup> /mm <sup>3</sup> )	Differe Lympho- cytes	ntial count of Neutrop Segmented	f leukocytes phils Band	( % of Eosino- phils	Differential count of leukocytes (% of total counted cells) mpho- Neutrophils Eosino- Baso- Mono- tes Segmented Band phils phils cytes	cells ) Mono- cytes
42.01	78	89	ġ.	0	-	0	Ľ
4202	66	83	-	)		> <	
4203	83	- 68 -	-	0		~ ~	n -
4204	104	87	. <b>(</b>	• C	- ، م		t, n
4205	60	92	ŝ	- 0	• •		ה נ
4206	71	80	18	0	0	00	0 0
Mean	77	87	8	0	C	c	Ľ
5.D.	15.6	<del>ا</del> . د	4.8	0.4	0.4	0.0	, ,
z	9	9	9	ų	Ľ	, ,	

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Appendix

Study No. BMR143C

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: :

Hematology - Individual values Sex : Female Dose level : Sample D-1 O mg/kg Animals killed on schedule (Recovery)

$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Animal Number	WBC count (x10 <sup>2</sup> /mm <sup>3</sup> )	Differe Lympho- cytes	ntial count of Neutrop Segmented	f leukocytes phils Band	(% of Eosino- phils	Differential count of leukocytes (% of total counted cells) mpho- Neutrophils Eosino- Baso- Mono- tes Segmented Band phils phils cytes	cells ) Mono- cytes
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	02.07		82	4	-	6		11
$ \begin{bmatrix} 54 & 87 \\ 72 & 91 \\ 72 & 91 \\ 77 & 7 \\ 109 & 77 \\ 77 & 16 \\ 77 & 16 \\ 77 & 0 & 0 \\ 77 & 16 \\ 6 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 &$	0208		94	' ev	• O •	1 C		+ <sup>-</sup>
$ \begin{bmatrix} 114 & 82 & 13 \\ 72 & 91 & 7 \\ 77 & 7 & 0 & 0 \\ 109 & 77 & 16 & 0 & 3 \\ 77 & 16 & 0 & 0 \\ 77 & 16 & 0 & 0 \\ 77 & 16 & 0 & 0 \\ 6 & 5.3 & 0.4 & 1.3 \\ 6 & 6 & 6 & 6 \end{bmatrix} $	0209	54	87	5	0			* ¬
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	<b>0210</b>	114	82	13	0	ò	• c	° LС
109 77 16 0 3 85 86 9 0.4 1.3 6 6 6 6 6 6 6 0.4 0.4 0.4 0.4 0.4	0211	72	91		0		• c	
85 86 9 0 1 23.9 6.3 5.3 0.4 1.3 6 6 6 6	0212	109	11	16	0		0	1 -7
23.9 6.3 5.3 0.4 1.3 6 6 6 6 6 6	Mean		86	6	0	-	0	LC.
	s.D. N	•	6.3 6	5.3 6	0•4 6	1 • 3 6	0.0	3.1 6

Hematology - Individual values Sex : Female Dose level : Sample D-1 30 mg/kg Animals killed on schedule (Recovery)

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Appendix

Animal Number	WBC count (x10 <sup>2</sup> /mm <sup>3</sup> )	Differe Lympho- cytes	ential count o Neutro Segmented	f leukocytes phils Band	(%of Eosino- Phils	Differential count of leukocytes (% of total counted cells) mpho- Neutrophils Eosino- Baso- Mono- tes Segmented Band phils phils cytes	cells ) Mono- cytes
4207	105	92	3	1	0	0	4
208	104	88	9	0.	0	c	' <b>'</b>
209	84	88	പ	0	-	ò	
210	76	63	-7	0			
211.	88	91	80	0	c		• <del>-</del>
212	57	93	N	0	0	0	a no
Mean	86	91	ى م	0	c	c	
5.D.	18.1 6	2.3	2.2	0.4	0.4	0.0	1.9
2	D	0	0	Ð	9	ſ	5

Appendix 6 - M - 1

	Trigly-t ceride (mg/dl)	59 37 81 41 43	49 18.2 6
	Total chol. (mg/d!)	52 63 48 63 48	58 6.9 6
	Glucose (mg/dl)	134 129 153 150 150	140 9.4 6
ues 0 mg/kg s)	Creatinin (mg/dl)	ດດດດດດ ດີດດວດດີດ	0.5 0.00 6
Clinical chemistry - Individual values Sex : Nale Dose level : Sample D-1 0 m Animals killed on schedule (4 weeks)	Urea nitrogen (mg/dl)	11.2 13.4 12.2 12.6 10.2	12.4 1.62 6
chemistry - I Sex : Na Svel : Sa svel : Sa illed on sche	ALP (11/1)	739 667 859 642 518 518	711 129.3 6
Clinical c bose le Animals ki	r -GTP (1U/1)	000000	0.0
	GPT (1U/1)	37 26 33 33 26 31 26	30 4.6 6
	60T (1U/1)	80 70 60 64 65 71	68 7.0 8
	Anima I Number	0101 0102 0103 0104 0105 0105 0106	Mean S.D. N

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Appendix G - M - 2

Clinical chemistry - Individual values Sex : Male Dose level : Sample D-1 0 mg/kg Animals killed on schedule (4 weeks)

	Total	Albumain	A/G	Calcium	lnorganic	Na	¥	CI
Number	(1) (8/d1)	(8/41)	rat 10	(mg/dl)	phos. (mg/d1)	(mEq/1)	(mEq/1)	(mEq/1)
0101	6.36	4.07	1.78	9.5	9.4	142	4.0	103
0102	6.34	3.92	1.62	9.3	8.6	143	1 1	105
0103	6.63	4.00	1.52	10.6	10.8	143	1.1	101
0104	6.68	4.04	1.53	9.6	10.0	142	4.2	00
0105	6.27	3.75	1.49	9.9	11.2	142	1.0	001
0106	6.78	4.08	1.51	9.9	9.7	142	4.1	101
Mean	6.51	3.98	1.58	9.8	10.2	142	4.1	102
S.D. N	0.212 6	0.125 6	0.110 6	0.46 6	0.70	0.5	0.08	2.2

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Appendis 6 - N - 3

Clinical chemistry - Individual values Sex : Male Dose level : Sample D-1 0.1 mg/kg Animals killed on schedule (4 weeks)

-	G0T	GPT	7 -GTP	ALP	Urea	Creatinin	Glucose	Total	Trigly-
unber	(1/11)	(1711)	(1/11)	(1/11)	nıtrogen (mg/dl)	(mg/dl)	(mg/dl)	chol. (mg/dl)	ceride (mg/dl)
1101	65	29	0	822	11.8	0.4	136	62	71
1102	17	31	0	666	13.2	0.5	138	58	59
1103	69	38	0	713	10.1	0.4	157	59	41
1104	61	26	0	577	11.5	. 0.4	149	57	61
1105	66	30	0	618	10.4	0.5	159	53	56
1106	20	23	0	666	6.8	0.5	159	53	41
Mean	65	30	0	677 <sup>°</sup>	10.6	0.5	150	57	55
S.D.	9.0	5.1	0.0	84.9	2.18	0.05	10.5	3.5	11.8
z	<b>.9</b>	9	5	c	c	а	ಶ	U U	د.

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Append i x

Study No. BMR143C

Clinical chemistry - Individual values Sex : Male Dose level : Sample D-1 0.1 mg/kg Animals killed on schedule (4 weeks) •

Anima! Vumber	Total protein (g/d1)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	lnorganic phos. (mg/d1)	Na (mEq/l)	K (mEa/1)	C1 (mEn/1)
1101	6.29	3.95	1.69	9.6	9.3	142	3.9	102
1102	6.67	4.16	1.66	9.9	<b>0°</b> 6	142	4.1	103
1103	6.21	3.93	1.72	10.1	10.4	142	4.1	101
1104	6.31	3.90	1.62	9.8	8.8	142	4.0	101
1105	6.48	3.90	1.51	9.9	10.9	142	4.0	101
1106	6.33	3.89	1.59	ŋ.3	8.4	141	4.0	101
'lean	6.38	3.96	1.63	9.8	9.5	142	4.0	102
s.b.	0.166	0.103	0.076	0.28	0.98	0.4	0.08	0.8
z	9	9	9	9	÷	Ľ	<u>د</u>	c

Study No. BMR143C

Clinical chemistry - Individual values Sex : Male Dose level : Sample D-1 mg/kg Animals killed on schedule (4 weeks)

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Appendix

l Trigly- ceride	6 41 2 54 39 113 72	9 3 5 60 60 60 60
Total chol. (mg/dl)	46 44 49 49 49 49 49 49 49 49 49 49 49 49	49 4.3 6
Glucose (mg/dl)	145 145 129 136 136 139	140 6.9 6
Creatinin (mg/dl)	000000 • • • • • • • •	0.5 0.04 6
Urea nitrogen (mg/dl)	11.3 11.1 12.3 16.8 16.8 16.8	13.3 2.34 6
ALP (IU/I)	705 923 537 806 727 703	734 127.7 6
- <b>7 - GTP</b> (1U/1)	000000	0.0
GPT (1U/1)	25 33 33 3 3 3 3 3 3 3 3 3 5 6 3 3 3 5 6 3 3 5 6 3 3 5 6 3 3 5 6 3 3 5 6 3 3 5 6 3 5 6 3 5 6 3 5 6 5 5 5 5	31 4.5 6
60T (1V/1)	66 67 70 66	71 8.1 6
Animal Number	2101 2102 2103 2104 2105 2106	Mean S.D. N

BMR143C Study No.

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Appendix

i mg/kg (Tinical chemistry - Individual values Sex : Male Uose level : Sample U-1 1 m Animals killed on schedule (4 weeks)

	Total	Albumin	A/G	Calcium	Inorganic	Na	<b>بر</b>	CI
Number	(g/d1)	(11))	Latio	(mg/dl)	phos. (mg/di)	(mEq/1)	(mEq/1)	(mEq/1)
2101		3.88	1.70	9.4	8.7	142	6.1	104
2102		3.92	1.61	9.8	0.6	141	4.4	103
2103		3.82	1.51	9.9	10.1	141	4.0	101
2104	6.07	3.93	1.84	9.8	10.3	142	4.0	103
2105		3.77	1.42	10.2	10.1	143	4	
2106		3.74	1.69	9.4	8.9	141	4.2	103
Mean '	6.22	3.84	1.63	9.8	9.5	142	4.2	103
S.D. N	0.190 6	0.079 6	0.149 6	0.31 6	0.72	8.0	0.20	1.2

.

Clinical chemistry - Individual values Sex : Male Dose level : Sample D-1 10 mg/kg Animals killed on schedule (4 weeks)

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Appendix

Animal Number	60T (1U/1)	GPT (1U/1)	r -GTP (10/1)	ALP (11/1)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Trigly- <sup>f</sup> ceride (mg/dl)
3101 3102 3103 3104 3105 3105	65 66 63 63 63 63	40 33 34 33 34 33 34 31	000000	988 755 682 615 615 841	12.8 14.8 11.0 11.0 8.1 8.1	000000 0000404	131 142 145 145 155 132	26 35 29 49	65 30 17 89 25
Mean S.D. N	65 3.9 6	34 3.2 6	0.0	780 130.2 6	12.4 2.56 6	0.5 0.05 6	142 9.0 6	38 11.1 6	48 28.0 6

Study No.

BMR143C

Appendix 6 - M - 8

Clinical chemistry - Individual values Sex : Male Dose level : Sample D-1 10 mg/kg Animals killed on schedule (4 weeks)

lnima l	Total	Albumin	A/6	Calcium	Inorganic	Na	×	CI
Number	(g/dl)	(8/d1)	1 4 1 1 0	(mg/dl)	puos. (mg/dl)	(mEq/1)	(mEq/l)	(mEq/1)
3101	6.29	4.15	1.94	10.2	9.2	143	4.1	100
3102	6.05	3.84	1.74	6.6	10.8	143	4.8	
3103	6.28	4.05	1.82	9.9	8.8	141	0.5	501
3104	6.16	3.94	1.77	9.7	5.000	142.	4.2	105
3105	6.15	3.75	1.56	9.8	9.6	142	0 ° C	105
3106	6.29	3.87	1.60	9.3	8.5	141	4.3	105
Hean	6.20	3.93	1.74	9.8	9.3	142	4.3	104
5.U. N	0.099 6	0.146 6	0.141 6	0.30 6	0.82 6	0.9 6	0.33	1.4 6

Clinical chemistry - Individual values Sex : Male Dose level : Sample D-1 30 mg/kg Animals killed on schedule (4 weeks)

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Append i x

	G0T	GPT	r -6TP	ALP	Urea	Creatinin	Glucose	Total	Trigly
vumber	(1/01)	(1711)	(IZAL)	(1/01)	nitrogen (mg/dl)	(ng/dl)	( p/gm)	chol. (mg/dl)	ceride (mg/dl)
4101	81	46	0	1639	15.1	0.6	139	0	
4102	22	57	0	1243	15.8	0.5	144	5	200
4103	76	46	0	1036	13.7	0.5	127	15	5.0
4104	61	47	0	1179	10.4	0.5	140		4 L 4 -
4105	62	43	0	940	14.9	0.5	137	01	06
4106	83	78	0	1111	14.5	. 0.8	162	6	36
Mean	73	53	0	191	14.1	0.6	142		16
s.b.	9.5	13.2	0.0	243.7	1.93	0.12	11.5	2.0	17
z	9	9	9	9	9	9	9	9	9

Appendix 6 - M - 10

Study No. BMR143C

Clinical chemistry - Individual values Sex : Male Dose level : Sample D-1 30 mg/kg Animals killed on schedule (4 weeks)

	Total	Albumrin	A/G	Calcium	Inorganic	Na	Ķ	CI
Number	(1p/8)	(8/d1)	rati o	(lþ/gm)	phos. (mg/dl)	(mEq/l)	(mEq/1)	(mEq/1)
4101	6.06	3.94	1.86	9.3	8.8	142	1 1	107
4102	5.87	3.97	2.09	9.1		142		
4103	6.28	4.06	1.83	9.9	6.0	143	1.1	104
4104	5.45	3.91	2.54	8.8	0.6	144		107
4105	5.87	. 3.86	1.92	9.1	8.7	143		201
4106	6.51	4.32	1.97	10.2	16.2	147	4.5	105
Mean	6.01	4.01	2.04	9.4	10.0	144	6 1	106
S.D.	0.368 6	0.166 6	0.264 6	0.54 6	3.06	0.1 0.9	0.35	1.3

Appendix 6 - M - 11

Clinical chemistry - Individual values Sex : Male Dose level : Sample D-1 0 mg/kg Animals killed on schedule (Recovery)

6PT (1U/1)	т ()
28 0	28 0
30	30 0
37 0	37 0
36 0	36 0
40 0	40 0
33 0	33 0
34 0	
4.5 0.0	
U B	

Appendix 6 - M - 12

Study No. BMR143C

# Clinical chemistry - Individual values Sex : Male Dose level : Sample D-1 0 mg/kg Animals kitled on schedule (Recovery)

CI (mEq/1)	105 104 104 104 101	104 1.5 6
K (mEq/1)	444664 0.000.000 0.000.000	4.2 0.28 6
Na (mEq/1)	143 142 142 133	- 141 1.5 6
lnorganic phos. (mg/dl)	88988 88988 9	8.7 0.18 6
Calcium (mg/dl)	10.0 9.9 9.9 9.9 9.4	9.6 0.28 6
A/G ratio	1.46 1.53 1.44 1.42 1.61 1.54	1.50 0.072 6
Albumin (g/dl)	3.82 3.77 3.89 3.90 3.91 3.82	3.85 0.056 6
Total protein (g/dl)	6.43 6.23 6.59 6.34 6.34 6.30	6.42 0.167 6
Anjma   Number	0107 0108 0109 0110 0111 0111	Mean S.D. N

Appendix 6 - M - 13

Clinical chemistry - Individual valuesSexNaleSexNaleSexSample D-1Bose levelSample D-1Animals killed on schedule (Recovery)Animals killed on schedule (Recovery)GPTr-GTPALPUreaCIVI)(1U/1)(1U/1)(1U/1)(mg/d1)(mg/d1)

Trigly-f ceride (mg/dl)  $10^{10}$ ດສຸດ 22 Total chol. (mg/dl) 29 11.3 5 19 48 27 22 (Ib/gm) 152 12.8 5 159 141 150 ·141 171 (Ib/gm) 0.6 0.5 0.08 5 0.5 Urea nitrogen (mg/dl) 24.4 21.7 26.1 19.6 17.1 21.8 3.61 5 (1/1) 716 105.4 5 792 852 681 671 586 (1/11) 0.0 5 00 000 (1/1) 44 10.1 5 3642 37 44 61 (1/1) 74 71 70 78 86 76 6.5 5 <u>60</u> D : Dead. Animal Number 4107 4108 4109 4110 4111 4111 Mean S.b. z

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Study No.

BMR143C

Appendix 6 - M - 14

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	mg/kg	
- Individual values Male	e U-1 30 e (Recovery)	-
	Sample U-1 schedule (Re	
chemistr Sex :	no	
Clinical chemistry Sex :	Dose level Animals killed	

\nima	Total nrotein	Albumin	A/6	Calcium		· Na	Х	C
Number	(1p/g)	(1p/g)	14110	(mg/dl)	pnos. (mg/dl)	(mEy/1)	(mEq/1)	(mEq/1)
4107	6.08	3.80	1.67	9.7	8.3	143		001
4108 4109	6.81 D	4.13	1.54	9.8	9.4	141	4.5	108
4110	6.70	4.24	1.72	9.8	9.4	140	4.1	103
4111	6.70	4.25	1.73	9.7	9.4	142	6	
4112	6.57	4.26	1.84	9.6	8.2	142	4.0	106
Mean C n	6.57 0 290	4.14 0.105	1.70	9.7	8.9	142	4.2	106
. <b>x</b>	51 51 51	2	2 2 0	0.00	U.03 5	1.I 5	0.20	2.5 2

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Appendix 6 - F - 1

Clinical chemistry - Individual values Sex : Female Dose level : Sample D-1 0 mg/kg Animals killed on schedule (4 weeks)

----

Animal Number	G0T (1U/1)	GPT (1U/1)	r -GTP (11/1)	ALP (11/1)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Trigly- ceride (mg/dl)
0201 0202 0203 0204 0206	75 67 88 88 83	138888	000-00	364 534 525 507	11.3 10.7 14.2 12.4 10.7		137 130 143 131 137 121	48 74 53 69 69	22 22 22 22 23 22 23 23 23 23 23 23 23 2
Mean S.D. N	80 8.0 6	23 3.5 6	0.4	472 65.2 6	11.9 1.33 6	0.5 0.04 6	133 7.6 6	58 10.5 6	24 4.9 6

6 - F - 2 Appendix

	C1 (mEq/1)	104 104 104 103 103	104 0.5 6
	K (mEq/1)	4 8 8 9 4 4 8 4 8 4 8 4	4.1 0.27 6
ues 0 mg/kg .)	Na (mEq/1)	141 143 141 141 141 141	141 0.8 6
ndividual val male mple D-1 Jule (4 weeks	lnorganic phos. (mg/dl)	7.4 9.2 9.2	8.4 1.09 6
Clinical chemistry - Individual values Sex : Female Dose level : Sample D-1 0 n Animals hilled on schedule (4 weeks)	Calcium (mg/dl)	9999999 9.59999 9.5	9.4 0.15 6
Clinical c bose le Animals ki	A/G ratio	1.85 1.61 1.73 1.77 1.59 1.74	$1.72 \\ 0.099 \\ 6$
	Ałbumin (g/dl)	4.23 4.24 4.20 4.15 4.15	4.18 0.060 6
	Total protein (g/d1)	6.52 6.87 6.63 6.38 6.76 6.62	6.63 0.173 6
	Animal Number	0201 0202 0203 0204 0205 0206	Mean S.D. N

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Appendix 6 - F - 3

Clinical chemistry - Individual values Sex : Female Dose level : Sample D-1 0.1 mg/kg Animals killed on schedule (4 weeks)

	G0T	GPT	7 -GTP	ALP	Urea	Creatinin	Glucose	Total	Trigly
Number	(1711)	(1/1)	(1/1)	(1/11)	nıtrogen (mg/dl)	(ID/gm)	(mg/dl)	chol. (mg/dl)	ceride (mg/dl)
1201	74	32	0	409	17.0	0.7	126	55	24
1202	64	23	0	504	10.6	0.5	140	56	24
1203	64	25	0	362	16.7	0.5	136	58	
1204	76	29	0	540	14.9	0.5	182	59	43
1205	71	19	0	366	9.9	0.5	120	67	17
1206	68	22	0	331	9.9	0.6	134	48	26
Mean	70	25	0	419	13.2	0.6	140	57	28
с. р. к	0.0 0.0	4.8 6	0.0	8 <b>4.6</b> 6	3.41 6	0.08 6	22.0 6	6.2 ƙ	9.4

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Appendix 6 - F - 4

Clinical chemistry – Individual values Sex : Female Dose level : Sample D–1 0.1 mg/kg Animals killed on schedule (4 weeks)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	lnorganic phos. (mg/dl)	Na (mEq/1)	K (mEq/1)	C1 (mEq/1)
1201 1202 1203 1204 1205 1206	6.85 6.08 6.61 6.61 6.63 7.00	4.39 4.19 4.16 4.16 4.16 4.16 7.30	1.78 1.84 1.73 1.81 1.81 1.66 1.59	9.68 9.8 9.8 9.8 9.8	909-99 999-99	141 142 142 140 140	8.84.8 9.9 9.9 9.9 9.9 9.9 9.9 9.9 9.9 9.9 9	102 105 102 102 101
Mean S.D. N	6.61 0.320 6	4.19 0.154 6	1.74 0.095 6	9.8 0.59 6	9.7 1.01 6	141 0.9 6	4.5 0.58 6	102 1.4 6

Appendix 6 - F - 5

Clinical chemistry - Individual values Sex : Female Dose level : Sample D-1 1 mg/kg Animals killed on schedule (4 weeks)

Total Trigly- chol. ceride (mg/dl) (mg/dl)	69 57 59 32 58 33 35 33 35 33 58 18	59 30 5.1 6.2 6 6
Glucose Tota chol (mg/dl) (mg/	156 133 142 142	143 8.3 6
Creatinin (mg/dl)	00.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	0.5 0.06 6
Urea nitrogen (mg/dl)	17.7 14:1 13.0 13.6 10.6 9.5	13.1 2.89 6
ALP (11/1)	491 504 377 372 372	437 82.1 6
7 - GTP (11/1)	0-0000	0 4 6
GPT (1U/1)	20 20 23 23 23 20 20 20 20 20 20 20 20 20 20 20 20 20	20 2.9 6
GOT (1U/1)	62 51 51 51 51 52 52 52 52 52 52 52 52 52 52 52 52 52	60 7.4 6
, Animal Number	2201 2202 2203 2204 2205 2205 2205	Mean S.D. N

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Appendix 6 - F - 6

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Study No. BMR143C

Clinical chemistry - Individual values Sex : Female Dose level : Sample D-1 1 mg/kg Animals killed on schedule (4 weeks)

.

	Total	Albumin	A/G	Calcium	Inorganic	Na	¥	CI
Anımal Number	protein (g/dl)	(11/8)	ratio	(mg/dl)	phos. (mg/dl)	(mEq/1)	(mEq/1)	(mEq/l)
2201	6.48	4.17	1.81	9.6	8.5	140	4.4	102
2202	6.08	4.11	2.09	6°6 .	8:8	143	5.2	106
2203	6.02	4.01	2.00	9.5	9.3	141	4.4	104
2204	6.86	4.38	1.77	9.8	8.7	140	4.0	103
2205	6.68	4.11	1.60	9.5	8.4	142	3.8	103
2206	6.58	4.11	1.66	9.5	8.7	142	4.4	107
Mean	6.45	4.15	1.82	9.6	8.7	141	4.4	104
5.U. N	0.335 6	0.125 8	0.191 6	0.18 6	0.31 6	2.1	0.48 6	ກຸ ປ

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Appendix 6 - F - 7

Clinical chemistry - Individual values Sex : Female Dose level : Sample D-1 10 mg/kg Animals killed on schedule (4 weeks)

	C0T	GPT	r -GTP	ALP	Urea	Crèatinin	Glucose	Total	Trigly-
Vumber	(1/11)	(1/11)	(1711)	(1/11)	nitrogen (mg/dl)	(mg/dl)	(mg/dl)	chol. (mg/dl)	ceride (mg/dl)
3201	65	24	0	567	17.4	0.6	122	36	10
3202	52	21	0	361	11.1	0.5	149	200	101
3203	99	27	0	531	13.7	0.5	148	46	25
3204	50	28	0	429	14.0	0.5	136	04	17
3205	50	24		382	14.7	0.5	126	48	- 66
3206	46	20	0	436	10.2	0.5	127	56	23
Mean	60	24	0	451	13.5	0.5	135	48	16
S.D.	12.5	3.2	0.0	81.8	2.59	0.04	11.7	8.1	2.9
z	9	9	9	0	5	ŝ	ď	. 2	

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BMR143C Study No.

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Append i x

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Clinical chemistry - Individual values Sex : Female Dose level : Sample D-1 10 Animals killed on schedule (4 weeks)

10 mg/kg

, Animal	Total protein	Albumin	A/G ratio	Calcium	lnorganic phos.		×.	cı
Number	( [])	(g/dl)		(mg/dl)	(mg/dl)	(mEq/l)	(mEq/1)	(mEq/1)
3201	6.68	4.35	1.87	9.6	7.0	141	3.7	105
3202	6.84	4.34	1.74	9.2	7.6	140	- 0	106
3203	7.14	4.52	1.73	10.2	6.7	143	4.8	201
3204	6.58	4.24	1.81	9.5	8.0	141	4.5	101
3205	7.21	4.64	1.81	9.9	9.2	144		104
3206	7.03	4.40	1.67	9.5	7.6	142	4.2	107
Mean	6.91	4.42	1.77	9.7	7.9	142	4.1	106
s.b.	0.255	0.143	0.072	0.35	0.73	· I • 5	0.45	1.2
Z	50	9	9	9	9	9	9	9

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	Trigly- <sup>t</sup> ceride (mg/dl)	23 15 15 27 20	20 4.7 6
	Total chol. (mg/dl)	24 23 23 23 20 20 20 27	25 5.1 6
-	Glucose (mg/dl)	152 125 111 119 116 116 135	126 15.0 6
ues 30 mg/kg	Creatinin (mg/dl)	00000 0.55 0.55	0.5 6.05
Clinical chemistry - Individual values Sex : Female Dose level : Sample D-1 30 Animals killed on schedule (4 weeks)	Urea nitrogen (mg/dl)	14.3 20.9 19.8 13.7 21.8 17.3	18.0 3.43 6
chemistry - Sex : Fr svel : S( illed on sch	ALP (11/1)	826 609 717 392 392	590 170.9 6
Clinical c Dose le Animals k	r - GTP (1U/1)	000000	0.0 8
	GPT (1U/1)	40 31 38 38 48 48	36 7.2 6
	G0T (1U/1)	62 55 55 59 59	56 4.1 6
	Anima   Number	4201 4202 4203 4203 4205 4205	Mean S.D. N

Appendix 6 - F -

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	C1 (mEq/1)	108 107 105 107 107	106 1.5 6
	K (mEq/1)	4.4 6.9 6.9 6.9	4.9 0.72 6
ues 30 mg/kg 5)	Na (mEq/l)	143 142 142 143 143	142 ·1.1 6
ndividual val male mple D-1 dule (4 weeks	lnorganic phos. (mg/dl)	7.0 8.9 9.3 9.3 9.3	8.6 0.93 6
<pre>Clinical chemistry - Individual values     Sex : Female     Dose level : Sample D-1 30 Animals killed on schedule (4 weeks)</pre>	Calcium (mg/dl)	9.5 9.9 9.9 9.5 10.8	9.9 0.49 6
Clinical c Dose le Animals ki	4/G ratio	1.80 1.77 1.93 1.91 2.16 1.82	1.90 0.143 6
	Albumin (g/dl)	4.61 4.68 4.53 4.56 4.77	4.59 0.140 6
	Total protein (g/dl)	7.17 7.32 6.88 6.64 7.39	7.01 0.327 6
	Animal Number	4201 4203 4203 4204 4205 4205	Nean S.D. N

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Appendix

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			Clinical c bose le Animals k	chemistry - Sex : Fr evel : Si illed on sch	<pre>Clinical chemistry - Individual values     Sex : Female     Dose level : Sample D-1 0 mg/kg Animals killed on schedule (Recovery)</pre>	lues 0 mg/kg ry)			
Anima i Number	60T (1V/1)	GPT (1U/1)	r -GTP (1U/1)	4LP (1U/1)	Urea ni trogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Trigly- <sup>1</sup> ceride (mg/dl)
0207 0208 0209 0210 0211 0212	57 75 71 71 86 81 81	24 30 28 29 44	000000	266 273 411 393 313	18.0 19.9 15.0 14.9 14.9	000000 000000 000000	152 154 149 141 160	76 65 68 48	104 65 35 26 28 28 28
Mean S.D. N	7] 8.8 6	30 7.7 6	0.0	323 63.4 6	17.3 2.55 6	0.6 0.05 6	150 6.9 6	61 10.1 6	48 31.1 6

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Study No.

BMR143C

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Clinical chemistry - Individual values Sex : Female bose level : Sample D-1 0 mg/kg Animals killed on schedule (Recovery)

	Total	Albumrin	A/G	Calcium	Inorganic	Na	.:×	C
Vumber	(10/8)	(8/41)	1 4 (1 0	(mg/dl)	pnos. (mg/dl)	(mEq/1)	(mEq/l)	(mEq/1)
0207	7.00	4.35	1.64	9.8	7.1	140	4.1	104
0208	7.26	4.41	1.55	9.7	6.7	140	4.0	107
0209	7.01	4.42	1.71	9.5	7.9	141	4.2	101
0210	7.18	4.38	1.56	9.6	6.8	140	4.2	105
0211	6.47	4.05	1.67	9.4	7.9	140	4.0	106
0212	7.17	4.40	1.59	9.8	7.6	139	3.9	104
Mean	7.02	4.34	1.62	9.6	7.3	. 140	4.1	105
S.D.	0.286	0.142	0.064	0.16	0.54	0.6	0.12	1.2
z	9	9	9	9	9	9	9	5

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Appendiv 6 - F - 13

Clinical chemistry - Individual values Sex : Female Dose level : Sample D-1 30 mg/kg Animals killed on schedule (Recovery)

Animal Number	60T (1971)	GPT (11/1)	7 -GTP (11/1)	4LP (11/1)	Urea nitrogen (mg/dl)	Creatinin (mg/df)	(lucose	Total chol. (mg/dl)	Trigly- ceride (me/dl))
100	. (1.13.)								
4207	. 62	41	0	404	29.2	0.6	132	47	15
208	53	29	0	347	22.5	0.6	141	46	22
209	47	25	0	363	22.6	0.5	123	53	18
210	78	25	0	486	26.2	0.6	117	62	17
211	64	28	0	353	22.2	0.6	116	42	17
212	62	31	0	369	21.7	0.6	129	55	16
ean	61	30	0	387	24.1	0.6	126	51	18
S.D.	10.6	5.9	0.0	52.4	2.99	0.04	9.6	7.3	2.4
2	c	2	c	ಷ	2	2	2	c	c

Appendix 6 - F - 14

**BMR143C** 

Study No.

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# Clinical chemistry - Individual values Sex : Female Dose level : Sample D-1 30 mg/kg Animals killed on schedule (Recovery)

	Total	A I bum i n	A/6	Calcium	lnorganic	Na	. ¥	CI
Number	( [] ( [] ( [] ( [] ( [] ( [] ( [] ( []	(11/8)	1910	(mg/dl)	pnos. (mg/dl)	(mEq/!)	(mEq/1)	(mEq/1)
4207	7.63	4.72	1.62	10.2	8.2	141	4.7	105
4208	7.51	4.85	1.82	10.4	7.9	141	3.9	107
4209	7.24	4.55	1.69	10.4	7.7	141	4.1	105
4210	8.18	4.99	1.56	10.3	8.1	141		104
4211	7.12	4.43	1.65	9.9	8.6	141	4.2	106
4212	7.34	4.79	1.88	10.1	8.2	142	4.8	105
Mean	7.50	4.72	1.70	10.2	8.1	141	4.3	105
S.D. N	0.379	0.204	0.123 6	0.19 6	0.31	0.4	0.39	0.1

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Appendix 7 - M - 1

Urinalysis - Individual values Sex : Male Dose level : Sample D-1 0 mg/kg 3 weeks after commencement of treatment

Animal Number	Urobili- nogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/d1)	Ηđ
					r D		
0101	0.1	. 1	ı	Ľ	ı	06	C I
102	0.1	ı	I	) U	I		) · ·
103		I		о I т	1	30	8.0
		•	1	- 61	1	30	7.5
104	1.0	1	1	<u>م</u>	ı	30	8.0
105	0.1	ı	1	ഹ		30	7.0
106	0.1	t	I	ഹ	5	Trace	8.0
107	0.1	ł	I	10	I	30	0 C
108	0.1	+++	I	10	1	30	
109	0.1	Trace	ı	• •	1		
110	0.1	Trace	I	Ľ	1		<b>.</b>
				יכ	1	30	6.0
	0.1	1	1	ഹ	1	Trace	7.0
717	1.0	1	I		ı	30	8.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

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Appendix	

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Study No.				
			0.1 mg/kg	
			0.1	3 weeks after commencement of treatment
	ues		D-1	oft
I	Urinalysis - Individual values	Male	Sample D-	encement
:	ndiv	••	••	comm
	iis - I	Sex	Dose level	after
	inalys.		Dose	weeks
	5			ന

Animal Number	Urobili- nogen (EU/dl)	Occul t Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	Ηđ
101	0.1	ľ	1	2	1	30	7.5
102	0.1		ł	വ	1	30	8.0
103	0.1	ı	ŀ	15	ı	30	8.0
104	0.1	Trace		aı	ı	30	7.5
105	0.1		•	40		30	8.0
1106	0.1	ı	ı	ស	1	100	8.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

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Appendix 7 - M - 3

Urinalysis - Individual values Sex : Male Dose level : Sample D-1 1 mg/kg 3 weeks after commencement of treatment

Animal	Urobili-	Occult Blood	Bilirubin	Ketone	Glucose	Protein	Hđ
Taolin	(EU/d1)	00010		(mg/dl)	(g/dl)	(mg/d1)	
101	0.1	J		15	8	30	8.0
102	0.1	ı	1	Ω	I	30	8.5
2103	0.1	ı	ı	ເວ	١	30	8.0
2104	0.1	I	I	ю	۱.	100	8.5
2105	0.1	Trace	I	£	1	100	8.0
2106	0.1	ı	1	ى د		30	8.0

: Negative, + : Slight, ++ : Moderate, +++ : Severe

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1 - W - 4 Appendix Urinalysis - Individual values Sex : Male Dose level : Sample D-1 10 mg/kg 3 weeks after commencement of treatment

Animal Number	Urobili- nogen	Occul t Blood	Bilirubin	Ketone	Glucose	Protein	Ηđ
	(EU/d1)			(mg/dl)	(g/d1)	(mg/dl)	
3101	0.1	1		л	ſ	06	0
3102	0.1	ı	ſ	) I.C.	ı		5 r
103		1		<b>.</b>		Or .	<b>c</b> ••
		, . I	ł	Q	I	100	8.0
104	0.1	1	ł	a	I	30	8.0
105	0.1	1		ъ С		100	8.0
106	0.1	I	I	വ	ı	30	8.0

: Negative, + : Slight, ++ : Moderate, +++ ; Severe

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BMR143C Study No.

- M --Appendix

Urinalysis - Individual values Sex Dose level

Sex : Male Dose level : Sample D-1 30 mg/kg 3 weeks after commencement of treatment

	ł	1 1	
ນ C ຍ ຢ ຍ ຍ ະ ະ	111111	1 1 1 1 1 1 1	1.1.1.1.1.1

Negative, + : Slight, ++ : Moderate, +++ : Severe

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AppendiX

Urinalysis - Individual values Sex : Male Dose level : Sample D-1 0 mg/kg 5 weeks after commencement of treatment (Recovery)

Hd			8.0 7.5	8.0	7.0	8.0			
Protein	(mg/dl)		Trace	0.6	Trace	000	20		
		(g/a1/	ı	ı	-\$	1			clight ++ : Moderate, +++ : Severe
		(mg/dl)	u	<u>م</u> و	, I	<sup>ی</sup> م	ດ ເດ		Moderate, +
	Bilirubin			1	1 1	. 1	<b>s</b> 1		
-	occul t	Blood	-	1	Trace	Trace -	Trace	Trace	
	IIrobili-	nogen rell/dl)		-	1.0	0.1	0.1	0.1	
		Animal Number			0107	0109	0110	0111 0112	

: Negative, + : Slight, <sup>+ .</sup>

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7 - M - 7 Appendix

Urinalysis - Individual values Urinalysis - Individual values Sex : Male D-1 30 mg/Kg Dose level : Sample D-1 30 mg/Kg b weeks after commencement of treatment (Recovery)

μd		7.0	6.5	6.5 7.0		-	
Protein	(mg/dl)	30	30	30			
Glucose	(g/dl)	1	۱	1 i		++ : Severe	
	Ketone bodies (mg/dl)	20	נע	<u>ى</u> ي	ها	Moderate, ++	
	Bilirubin		1 1	ı	1 1	Severe to the severe the severe	light,
	occul t Blood		, + , +	. 1	- 1 1		ative, + : 5
	Urobili-	(EU/dl)	0.1	0.1 D	1.0		· Nag
	Animal	Number	4107	4108	4110	4112	

: Negative, : Dead. 10

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Appendix 7 - F - 1

Urinalysis - Individual values Sex : Female Dose level : Sample D-1 0 mg/kg 3 weeks after commencement of treatment

Animal Number	Urabili- nasen	Occul t Blood	Billrubin	Ketone	Glucose	Protein	Ηđ
	(EU/d])			(mg/dl)	([g/d])	(mg/dl)	
0201	0.1	1	ľ		5	30	
0202	0.1	ł		• 1		00	
0203	0.1	,	ł	-	ı	30	2
0204	0.1	,	1	ł	ı	30	8.0
0205	0.1	1	,	1	1	30	8.0
0206	0.1	1	1	ى م	1	30	8.0
0207	0.1	1	1	ß	ı	30	7.0
0208	0.1	J	,	ł	Ę	30	7.5
0209	0.1	Trace	ł	ł	1	Trace	7.5
0210	0.1	1	ı	ł	ł	30	7.0
0211	0.1	ı,	ł	,	<b>J</b>	30	7.5
0212	0.1	Trace	1		5	Trace	7.0

: Negative, + : Slight, ++ : Moderate, +++ : Severe

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Appendix 7.-F-2

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Urinalysis - Individual values Sex : Female Dose level : Sample D-1 0.1 mg/kg 3 weeks after commencement of treatment

Animal	Urobili-	Occul t Blood	Bilirubin	Ketone Podior	Gl ucose	Protein	μd
	(EU/dl)	na010		(mg/dl)	(g/d])	(mg/d])	
1201	0, 1	Trace	• •	I	8	30	8.5
1202	0.1	ı	ı	•	1	Trace	8.5
1203	0.1	s	ι	I	1	30	7.5
1204	0.1	Trace	ŧ	ı	ı	30	8.0
1205	0.1	ı	1	1	1	Trace	8.0
1206	0.1	<b>I</b>	ſ	പ	• 1	30	8.0

: Negative, + : Slight, ++ : Moderate, +++ : Severe

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BMR143C

Study No.

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Appendix 7 - F - 3

Urinalysis - Individual values Sex : Female Dose level : Sample D-1 1 mg/Kg 3 weeks after commencement of treatment

Hď		8.0	8.0	7.5 7	7.5	7.0			
Protein	(mg/dl)	08	30	Trace	06	000			
Glucose	(g/d1)		I T	1 1	I	11			++ : Severe
1	bodies (mg/dl)		1	ເວີ	1 10	ភេ រ	a		William to the tet : Severe
			1	1	١	1 1	ł		
	Occult Blood			Trace	Trace	14	+ +		
	Urobili- nogen	(EU/d1)		0.1	0.1	0.1	0.1	1.0	
	Animal			2201	2202	2203 2204	2205	2206	

- : Negative, + : Slight, ++ : Moderate, +++ : S

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- H - L Appendix

Sex : Female Dose level : Sample D-1 10 mg/kg weeks after commencement of treatment Urinalysis - Individual values

Hq		8.8 8.0 8.0 7.0 7.0	
Protein	(mg/dl)	30 Trace 70 30 30 30	
Glucose	(g/dl)	11111	
Ketone	bodies (mg/dl)	ស សេ ស រ រ	
Bilirubin			
	Blood	e suce titti	
	Urobili- nogen (FU/AI)	0.1	
	Animal Number	3201 3201 3203 3204 3205 3205	

Negative, + : Slight, ++ : Moderate. +++ : Severe .. ł

BMR143C

Study No.

7 - F - 5 Appendix Urinalysis - Individual values Sex : Female Dose level : Sample D-1 30 mg/kg 3 weeks after commencement of treatment

	والمتعادين والمتعادين والمتعادين والمتعادين والمتعادين والمتعادين والمتعادين والمتعادين والمتعادين						
Animal Number	Urobili- nogen	Occult Blood	Billrubin	Ketone bodies	Glucose	Protein	Ηđ
	(EU/d1)			(mg/d1)	(g/d1)	(mg/dl)	
4201	0.1	•	1	1	ł	Trace	7.0
4202	0.1	۱	1	1		Trace	7.0
4203	0.1	1	1	ŝ	ı	30	6.5
4204	0.1	۱		1.	ı	,	7.0
4205	0.1	ı	1	3	1	30	7.5
4206	0.1	Trace	ł	ł	ı	30	6.0
4207	0.1	Trace	ł	ı	١	1	6.0
4208	0.1	+		ı	1	Trace	6.0
4209	0,1	t	1	2	1	Trace	7.0
4210	0.1	٢	1	1	1	30	7.0
4211	0.1	ſ	ł	5	٩.	I	7.5
4212	0.1	Trace	<b>)</b>	I	í	Trace	7.0

: Negative, + : Slight, ++ : Moderate, +++ : Severe i

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Appendix 7 - F - 6

Urinalysis - Individual values Sex : Female Dose level : Sample D-1 0 mg/kg

c/kg	(Recovery)	
0 mg	treatment	
D-1	of	
Sample	encement	
••	comm	
ose level	after	
Dose	weeks	

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Animal Number	Urobili- nagen	Occult Blood	Bilirubin	Ketone	Glucose	Protein	Hđ
	(EU/dl)			(mg/d])	(g/d])	(mg/d])	
0207	0.1	Trace	1		1	Trace	C R
0208	0.1	ł	ı	ł	5	30	
0209	0.1	+ +	5	1	1	, <b>1</b> ,	7.5
0210	0.1	ł	I	1	1	Trace	
0211	0.1			ł	1	Trace	8,0
0212	0.1	Trace		1	ı	30	7.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Study No.

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SexFemaleDose level:SampleD-1Weeks after commencement of treatment (Recovery) Urinalysis - Individual values

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Appendix

BMR143C

(mg/dl) Protein 30 Trace 30 Trace Trace Glucose ([p/g) t Ketone bodies (mg/dl) ı 1 Bilirubin \$ 1 Occul t Blood Trace Trace Trace nogen (EU/dl) Urobili-0.1 0.1 0.1 Animal Number

6.5 7.0 7.0 8.0 7.5

t 1 1

t

ı 1 J ł

> ł 1.1

Trace-1

0.1

4210 4211 4212

0.1

4207 4208 4209

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Negative, + : Slight, ++ : Moderate, +++ : Severe .. ł

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Organ weight (Absolute) - Individual values Sex : Male Dose level : Sample D-1 0 mg/kg Animals killed on schedule (4 weeks)

8 - M - 1

Appendíx

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
0101	354	1.90	13.07	85 6	-	
0102	318	2.00	12.17	9.16	7.10	10.0
0103	. 334	1.77	13.50	2.45		
0104	352	1.95	12.92	2.45	P 73	* 0 ° 6
0105	377	2.03	14.52	2.50	1.44	
0106	370	2.11	15.42	2.63	50.4	2.84
Mean	351	1.96	13.60	2.43	50.5	2.90
s.d. N	22.0 6	0.117 6	1.180 6	0.156 6	3.19	0.265

F.B.W : Final body weight

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# 2797.0164

- M - 2 œ Appendix

BMR143C Study No.

> 0.1 mg/kg Organ weight (Absolute) - Individual values Sex : Male Dose level : Sample D-1 0.1 mg/K Animals killed on schedule (4 weeks)

Anímal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)	
1101	375	2.06	16.05	2.75	62.2	2.92	
1102	321	2.13	13.25	2.19	55.6	2.92	
1103	362	1.90	13.55	2,60	50.4	3.20	
1104	321	1.94	13.52	2.27	63.4	3.18	
1105	376	1.92	15.24	2.71	53.9	3.17	
1106	366	1.92	15.37	2.78	50.3	3.44	
Mean	359	1.98	14.50	2.55	54.3	3.14	
s.D.	31.8	0.094	1.194	0.257	4.90	0.196	
z	9	9	9	9	9	9	

F.B.W : Final body weight

3M\_MN01650151

Appendix 8 - M - 3

Organ weight (Absolute) - Individual values Sex : Male Dose level : Sample D-1 1 mg/kg Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
2101	.346	1,99	14.63	2.42	50.6	2.85
2102	345	1.89	12.98	2.24	47.1	3.10
2103	354	1.95	14.84	2.46	57.4	3.04
2104	321	2.00	12.15	2.25	52.4	3.15
2105	376	1.91	15.90	2.18	55.3	3.40
2106	350	1.92	12.75	1.99	54.8	3,30
Mean	349	1.94	13.88	2.26	52.9	3.14
s.D.	17.7	0.045	1.459	0.170	3.71	0.194
z	6	9	9	9	9	9

F.B.W : Final body weight

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8 i M

Appendix

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Study No. BMR143C

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values	0 mg/kg	
Organ weight (Absolute) - Individual	Sex : Male Dose level : Sample D-1 1 Animals killed on schedule (4 weeks)	

Animal Number	F.В.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
3101	326	1,83	17.23	2.46	6.97	9 7 8
3102	341	1.92	18.33	2.28	46.6	2.84
3103	320	1.96	17.38	2.35	52.2	50.5
3104	335	2.07	17.50	2.56	9 L P	
3105	389	1.95	15.01	2.33	28° 89	2 T 2
3106	345	1.92	16.10	2.37	45.5	2.91
Mean	343	1.94	16.93	2.39	49.5	3.01
s.D. N	24.5 6	0.078 6	1.179 6	0.101 6	5.14	.0.189 6

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study No.

Appendix 8 - M - 5.

Organ weight (Absolute) - Individual values Sex : Male Dose level : Sample D-1 30 mg/kg Animals killed on schedule (4 weeks)

	•		•				
Testes (g)	2.62	3.26	3.21		3.08 0.250	ម	
Adrenals (mg)	44.3	48.5 54.0	50.3	56.0	50.4	9 9	
Kidneys (g)	°0 °	2.21	2.04	2.17	2.11	0.084 6	
Liver (g)		19.22 20.73	18.08	21.22	96 00	2.228 6	
Brain (g)	2	1.92	1.97	1.93		1.97	ם
F.B.W	( g )	300	321	2695	067	292 17.6	9
Animal	Number	4101	$\frac{4}{4103}$	4104	4106	Mean	 

F.B.W : Final body weight

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Appendix 8 - M - 6

weight (Absolute) - Individua

Organ weight (Absolute) - Individual values Sex : Male Dose level : Sample D-1 0 mg/kg Animals killed on schedule (Recovery)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
0107	365	2.07	12.43	2.29	48.5	3.00
0108	405	1.98	13.98	2.35	54.0	3.36
0109	438	2.10	15.91	2.50	46.9	2.89
0110	374	2.01	12.82	2.62	59.0	3.24
0111	344	2.04	11.18	2.41	46.8	0.85
0112	410	2.11	15.12	2.67	63.1	3.12
Mean	389	2.05	13.57	2.47	53.1	2.74
s.D.	34.4	0.051	1.768	0.151	6.85	0.942
z	9		9	9	9	9

F.B.W : Final body weight

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Appendix 8 - M - 7

Organ weight (Absolute) - Individual values Sex : Male Dose level : Sample D-1 30 mg/kg Animals killed on schedule (Recovery)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
4107	326	1.96	17.69	2.23	53.4	3 0 5
4108	336 D	2.09	21.36	2.30	61.5	3.40
4110	331	2.05	21,91	2.33	53.0	5 7 7
4111	340	1.96	20.99	2.56	45.0	5 V 3
4112	373	2.04	21.35	2.57	43.6	3.27
Mean	341	2.02	20.66	2.40	51.5	3.38
s.d. N	18.5 5	0.058 5	1.693 5	0.157	7.31	0.117

F.B.W : Final body weigh D.: Dead.

Study No.

BMR143C

Appendix 8 - F - 1

Organ weight (Absolute) - Individual values Sex : Female Dose level : Sample D-1 0 mg/kg Animals killed on schedule (4 weeks)

F.B.WBrainLiverKidneysAdrenals(g)(g)(g)(g)(mg)(g)(g)(g)(g)(mg) $228$ 1.878.531.5950.8 $214$ 1.788.751.3658.4 $221$ 1.788.931.6266.6 $221$ 1.969.601.7269.1 $227$ 1.848.321.5260.1 $227$ 1.788.321.5260.1 $227$ 1.788.761.6260.1 $230$ 1.850.0670.4710.177660.0670.4710.1775.46						,		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	An i ma l Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	UVALIES (mg)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$					1 50	50.8	95.2	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	01	01	1.87	8.75	1.36	58.4	89.2	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	02	214	1.86	8.93	1.62	00.00 63.4	93.7	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	803	s co	1.96	9.60	1 72	59.1	72.7	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	05	0	1.84 . 78	8.32 8.32	1.52	62.5		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	:06	2	1.10					
	ean .D.	230 17.4 6	1.85 0.067 6	8.76 0.471 6	$\begin{array}{c}1.62\\0.177\\6\end{array}$	60.1 5.46 6	83.7 10.13 6	

F.B.W : Final body weight

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Appendix	

Organ weight (Absolute) - Individual values Sex : Female Dose level : Sample D-1 0.1 mg/kg Animals killed on schedule (4 weeks)

אח i	3	(g) (g)
-	8.	1.83 8.
	.0	
	9.41	
	8.	
	8	
	8.	
•	0.679	0.054 0.6

F.B.W : Final body weight

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Organ weight (Absolute) - Individual values Sex : Female Dose level : Sample D-1 1 mg/kg Animals killed on schedule (4 weeks)	Brain Liver Kidneys Adrenals Ovaries (g) (g) (mg) (mg)	9.55 1.72 48.1	1.92 8.39 1.71 66.5 93.7	7.95 1.57 59.1	9.33 1.62 66.8	10.32 1.79 68.3	8.85 1.63 66.5	9.07 1.67 .62.6	0.081	
Organ weight Sex Dose level Animals kille		1.87	1.92	1.81				1.91		
	F.B.W (g)	225	226	216	240	259	246	235	15.9	
	· Animal Number		2202	2		2	2	Mean	S.D.	

Appendix 8 - F -

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F.B.W : Final body weight

Appendix 8 - F - 4

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**F** 

Organ weight (Absolute) - Individual values Sex : Female Dose level : Sample D-1 10 mg/kg Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Ovaries (mg)
3201	216	1.96	10.04	1.69	62.6	90.1
3202	225	1.83	11.96	1.81	71.4	72.6
3203	186	1.77	9.06	1.51	48.4	63.7
3204	221	1.86	10.75	1.76	55.0	76.8
3205	212	1.84	11.01	1.64	63.9	74.7
3206	223	1,82	10.68	1.76	63.7	76.7
Mean	214	1.85	10.58	1.70	60.8	75.8
S.D.	14.4	0.063	0.973	0.109	8.01	8.53
z	9	9	9	Ð	9	9

F.B.W : Final body weight

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Appendix 8 - F - 5

Organ weight (Absolute) - Individual values Sex : Female Dose level : Sample D-1 30 mg/kg Animals killed on schedule (4 weeks)

	, 1		
I	Ovaries (mg)	66.0 61.6 76.2 56.4 56.7 58.6	62.6 7.57 6
	Adrenals (mg)	55.9 60.0 64.6 47.0 50.8	55.6 6.28 6
	Kidneys (g)	1.28 1.46 1.51 1.62 1.53 1.62	1.50 0.126 6
	Liver (g)	12.25 14.65 14.18 14.18 14.04 13.81 13.73	13.78 0.816 6
	Brain (g)	1.79 1.80 1.80 1.96 1.81 1.81	1.83 0.064 6
	F.B.W (g)	178 194 194 181 191	190 9.5
	Animal Mumber	4201 4202 4203 4204 4205	Mean S.D.

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F.B.W : Final body weight

3M\_MN01650161

Appendix 8 - F - 6

Organ weight (Absolute) - Individual values Sex : Female Dose level : Sample D-1 0 mg/kg Animals killed on schedule (Recovery)

						20120	
Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	(mg)	
0207 0208 0209 0210 0211 0212	325 265 264 270 278 278	1.91 1.85 1.93 2.04 1.99 1.86	11.30 8.12 8.55 8.97 8.81 8.81 8.80	1.92 1.63 1.72 1.78 1.78	80.7 51.1 60.3 82.7 72.0 72.0	106.4 86.3 78.3 95.7 83.6 88.1	
Mean S.D. N	277 24.8 6	1.93 0.074 6	9.09 1.122 6	1.78 0.100 6	70.8 12.55 6	89.7 9.96 6	

F.B.W : Final body weight

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3M\_MN01650162

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Appendix 8 - F - 7

Organ weight (Absolute) - Individual values Sex : Female Dose level : Sample D-1 30 mg/kg Animals killed on schedule (Recovery)

Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Ovaries (mg)
4207	- 201	1.71	11 02			
4208	199	1.72	13.04	1.44	1.00	51.8
42.09	208	1.90	12.90			יים מיים
4210	193	1.90	11.64	1 27	40.7	1.27
4211	213	1.89	12.40		0.00	0.67
4212	234	2.06	12.85	1.85	67.7	72.1
Mean	208	1.86	12.46	1.59	54.0	68.5
s.D.	14.5 6	0.131 6	0.574 6	0.146 6	7.39	6.22

. Testes 0.094 0.85 1.02 0.76 0.87 0.87 0.87 g Organ weight (Relative : percentage of body weight) - Individual values Adrenals (x10<sup>-3</sup>) 0 mg/kg 14.5 1.55 6 14.5 16.7 14.2 15.5 12.2 13.6 Sex : Male Dose level : Sample D-1 ( Animals killed on schedule (4 weeks) Kidneys 0.69 0.026 6 0.67 0.68 0.73 0.70 0.66 3.88 0.197 3.69 3.83 4.04 3.67 3.85 4.17 9 Liver 0.56 0.54 0.63 0.53 0.55 0.54 Brain 9 . F.B.W (g) 351 22.0 354 318 334 352 377 370 9 . Number Animal 0102 0103 0104 0105 0105 Mean S.D. Z 0101

Appendix 9 - M - 1

Study No. BMR143C

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F.B.W : Final body weight

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BMR143C study No.

Organ weight (Relative : percentage of body weight) - Individual values Sex : Male D-1 0.1 mg/kg Dose level : Sample D-1 0.1 mg/kg Animals killed on schedule (4 weeks)

			·								
Testes		. 0.78	0.91	0.88	56°0	40°0		0	0.071		
	(x10 <sup>-3</sup> )	0 61	17.3	13.9	19.8	14.3	12.6		15.3 2.70 6	5	
	Kidneys		0.73	0.72	0.71	0.72	0.70		0.71 0.018	Q	
	Liver		4.28	4.13	3.74	4.61 4 05	3.85		4.04	9	
	Brain		0.55	0.66	0.52	0.60	0.51	<b>5F</b> • <b>5</b>	0.55	0.000	
	F.B.W (g)		276	100	362	321	376	399	359	31.8	•
	Animal	Number		1011	1102	1103	1105	1106	Mean	s.D.	z

F.B.W : Final body weight

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Appendix 9 – M – 3

Organ weight (Relative : percentage of body weight) - Individual values Sex : Male Dose level : Sample D-1 1 mg/kg Animals killed on schedule (4 weeks)

Adrenals Testes (x10 <sup>-3</sup> )	14.6 0.82 13.7 0.90 16.2 0.96 16.3 0.98 16.3 0.98 14.7 0.94 15.7 0.94	15.2 0.90 1.03 0.057 6 6
Kidneys Adre (X10	0.70 0.65 0.65 0.69 0.70 0.58 0.58 114 0.58	0.65 15 0.060 1.
Liver	4.23 3.76 3.79 3.79 4.23 3.64	3.97 0.272 6
Brain	0.55 0.55 0.65 0.62 0.51 0.55	0.56
al F.B.W er (g)	1 2 3 4 5 4 5 3 4 5 3 5 0 5 0 5 0 5 0 5 0 5 0 5 0 1 1 3 4 5 1 3 4 5 1 3 4 5 4 5 3 4 5 4 5 4 5 4 5 4 5 4 5 4 5	17.7 0. 17.7 6
Animal Number	2101 2102 2103 2104 2105 2105	Mean S.D. N

F.B.W : Final body weight

Appendix 9 - M - 4

Stud Organ weight (Relative : percentage of body weight) - Individual values Sex : Male

	υ υ	55	33	11	13	32	34	88	75	6
	Testes	0.0	0.83	1.0	5·0	0.8	0.8	0.6	0.075	
10 mg/kg ks)	Adrenals (x10 <sup>-3</sup> )	14.2	13.7	16.3	14.2	15.1	13.2	14.5	1.10	9
Sample D-1 schedule (4 weeks)	Kidneys	0.75	0.67	0.73	0.76	0.60	0.69	0.70	0.060	9
Dose level : Animals killed on scl	Liver	5.29	5.38	5.43	5.22	3.86	4.67	4.98	0.611	9
Dose   Animals	Brain	0.56	0.56	0.61	0.62	0.50	0.56	0.57	0.043	9
	F, B, W (g)	326	341	320	335	389	345	343	24.5	9
	Animal Number	3101	3102	3103	3104	3105	3106	Mean	S.D.	z

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F.B.W : Final body weight

BMR143C Study No.

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9 - W - 6 Appendix

Organ weight (Relative : percentage of body weight) - Individual values 30 mg/kg Sex : Male Dose level : Sample D-1 3 Animals killed on schedule (4 weeks)

rain Liver Kidneys Adrenals Testes (x10 <sup>-3</sup> )	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
Brain Liv	0.64 0.74 0.74 0.70 0.71 0.71 0.66	0.68 0.048 6
F.B.W (g)	300 286 283 283 293 293	292 17.6
Animal Number	4101 4102 4103 4103 4105	Mean S.D.

F.B.W : Final body weight

#### 2797.0182

9 - W -6 Appendix

Study No. BMR143C

Organ weight (Relative : percentage of body weight) - Individual values Sex : Male Dose level : Sample D-1 0 mg/kg Animals killed on schedule (Recovery)

8	667.632	31 6
Testes	0.82 0.83 0.86 0.87 0.25 0.76	0.70 0.231 6
Adrenals (x10 <sup>-3</sup> )	13.3 13.3 10.7 15.8 15.4	13.7 1.82 6
Kidneys	0.63 0.58 0.70 0.70 0.70	0.64 0.056 6
Liver	3.41 3.45 3.63 3.63 3.45 3.63 3.25 3.69	3.48 0.160 6
Brain	0.57 0.49 0.48 0.54 0.55 0.51	0.53 0.044 6
F.B.W (g)	365 405 438 344 410	389 34•4 6
Animal Number	0107 0108 0109 0110 0111	S.D.

F.B.W : Final body weight

		Organ we - Indivi	ight (Relati dual values	Organ weight (Relative : percentage of body weight) - Individual values	ge af body we	ight)	-
		Dose Animals	sex : level : killed on	male Sample D-1 30 schedule (Recovery)	30 mg/kg ery)		
Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals (x10 <sup>-3</sup> )	Testes	
4107	326	0.60	5.43	0.68	16.4	1,00	
4108	336	0.62	6.36	0.68	18.3	1.01	
4110	331	0,62	6.62	0.70	16_3	1 07	
4111	340	0.58	6.17	0.75	13.2	1.01	
4112	373	0.55	5.72	0.69	11.7	0.88	
Mean	341	0.59	6.06	0.70	15.2	0.99	
s.D.	18.5	0.030	0.482	0.029	2.67	0,069	
z	£	വ	വ	3	ц.	6	
F.B.W : F	Final body we	weight					

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Appendix

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D : Dead.

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BMR143C Study No.

9 - F - 1 Appendix

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Ovaries Organ weight (Relative : percentage of body weight) - Individual values Sex : Female Dose level : Sample D-1 0 mg/kg Animals killed on schedule (4 weeks) Adrenals Kidneys Liver Brain Э Ц ۲.

Ovaries (x10 <sup>-3</sup> )	41.8	41.7	34.3	35.5	32.0	33.3		4.26	6
Adrenals (x10 <sup>-3</sup> )	22.3	27.3	30.1	24.0	26.0	27.5	26.2	2.76	9
Kidneys	0.70	0.64	0.73	0.71	0.76	0.67	0.70	0.043	9
Li ver	3.74	4.09	4.04	3.64	3.70	3.67	3.81	0.198	9
Brain	0.82	0.83	0.84	F7.0	0.81	0.78	0.80	0.037	9
F.B.W (g)	228	214	221	264	227	227	230	17.4	9
Animal Number	0201	0202.	0203	0204	0205	0206	Mean	S.D.	z

F.B.W : Final body weight

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Appendix 9 - F - 2

Study No. BMR143C

Organ weight (Relative : percentage of body weight) - Individual values Sex : Female Dose level : Sample D-1 0.1 mg/kg Animals killed on schedule (4 weeks)

					( ex		
Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Ádrenals (x10 <sup>-3</sup> )	Ovaries (x10 <sup>-3</sup> )	
	1						
1021	ດາ	0.82	3,83	0.67	27 O	0 7 6	
1202	<b>,</b>	0.87	3.69	0.67			
1203	235	0.77	A 05		1.02	31.0	
1204					23.1	39.6	
1905	۴c	1	0.00	0.18	25.2	35.3	
0077	v	0.80	3,69	0.73	21.4	AO 6	
1206	2	0.78	3.68	0.72	27.1	33.2	
Mean	200		- c	1			
s.D.	10.5	0.053	0,148	0.042	26.4	36,8	
Z	Q	9	9	5	9 9	0 9 9	
	. Rinel hod w	110 i mh t					

F.B.W : Final body weight

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Appendix 9 - F - 3

Organ weight (Relative : percentage of body weight) - Individual values Sex : Female Dose level : Sample D-1 1 mg/kg Animals killed on schedule (4 weeks)

(x10 <sup>-3</sup> )	7.85	41.5	43.4	29.2	39.3		39.3 6.90	9	
Adrenals (x10 <sup>-3</sup> )		21.4	27.4	27.8	27.0		26.6 273	9 9 1 1	
Kidneys		0.76	0.73	0.68	0.69		0.71	0.043 6	
Liver		4.24	3.71	3.80 3.80	3,98	3.60	3.85	0.237 6	
Brain		0.83	0.85	0.84	0.73	0.78		0.047	o
F.B.W	(g)	2 <b>2</b> E	226	216	240	246		235 15.9	9
Animal	Number		2201	2203	2204	2205 2206		Mean	Z

F.B.W : Final body weight

Appendix 9 - F - 4

Study No. BMR143C

		Dose level Animals killed	sex : I level : S killed on sch	Dose level : Female Dose level : Sample D-1 10 mg/kg Animals killed on schedule (4 weeks)	10 mg/kg s)		
Animal F. Number (	F.B.W (g)	Brain	Liver	Kidneys	Adrenals (x10 <sup>-3</sup> )	Ovaries (x10 <sup>-3</sup> )	
3201	216	0.91	4.65	0.78	29_0	41.7	
3202	225	0.81	5.32	0.80	31.7	32.3	
3203	186	0.95	4.87	0.81	26.0	34.2	
3204	221	0.84	4.86	0.80	24.9	34.8	
20	212	0.87	5.19	0.77	30.1	35.2	
3206	223	0.82	4.79	0.79	28.6	34.4	
Mean	214	0.87	4.95	0.79	28.4	35.4	
	14.4	0.055	0.255	0.015	2.54	3.23	
z	9	9	9	9	9	9	

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ight)	Ovaries (X10 <sup>-3</sup> )	37.1 31.8 39.3 39.3 31.3 31.3 30.7 30.7 4.37 6
e of body we 30 mg/kg s)	Adrenals (x10 <sup>-3</sup> )	31.4 30.9 28.6 26.0 26.6 26.6 2.50 2.50 2.50
Organ weight (Relative : percentage of body weight) - Individual values Sex : Female Dose level : Sample D-1 30 mg/kg Animals killed on schedule (4 weeks)	Kidneys	0.72 0.75 0.75 0.79 0.85 0.85 0.85 0.79 0.79 0.053
Organ weight (Relativ - Individual values Sex : F Dose level : S Animals killed on sch	Liver	6.88 7.55 7.31 6.88 6.88 7.53 7.19 7.24 0.321 6
Organ weight - Individual Sex Dose level Animals kille	Brain	1.01 0.93 0.93 1.00 1.00 0.95 0.95 0.034 6
	F.B.W (g)	178 194 194 181 181 191 192 0.5 0.5
-	An i ma l Number	4201 4202 4203 4203 4205 4205 8205 8205 N N

Appendix 9 - F - 5

Study No. BMR143C

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F.B.W : Final body weight

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Organ weight (Relative : percentage of body weight) - Individual values - Sex : Female Dose level : Sample D-1 0 mg/kg Animals killed on schedule (Recovery)

Animal Number	F.В.W (g)	Brain	Liver	Kidneys	Adrenals (x10 <sup>-3</sup> )	Ovaries (x10 <sup>-3</sup> )	
0207	325	0.59	3.48	0.59	B F C	202	
0208	265	0.70	3.06	0.62		37.6	
0209	264	0.73	3.24	0.65	22.8	20.7	
0210	270	0.76	3.32	0.68	30.6	35.4	
0211	278	0.72	3.17	0.64	27.9		
0212	257	0.72	3.42	0.68	28.0	34.3	
Mean	51	0.70	3.28	0.64	25.6	32.5	
. D. D.	24.8 6	0.059	0.157	0.035 6	4.10 6	2.27 6	

F.B.W : Final body weight

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Appendix 9 - F - 7

Study No. BMR143C

F.B.W (g) 201 199 193 234 234		Liver 5.93 5.49 5.49 5.49	Animals killed on schedule (Recovery)         Brain       Liver         Brain       Liver         0.85       5.93         0.86       6.55         0.91       6.20         0.98       6.03         0.98       5.49	30 mg/kg ry) Adrenals (X10 <sup>-3</sup> ) 24.9 27.0 22.0 27.5 28.9 28.9	Ovaries (X10 <sup>-3</sup> ) 30.7 29.8 35.0 38.1 33.4 30.8
208	0.90	6.00	0.76	26.0	0 0 0
14.5	0.047	0.358	0.033	2.43	33.0 3.18
9	9	9	Ľ		

F.B.W : Final body weight

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Findings       Animal number       :       01       02       03       04       05       06       01       05       06       01       05       06       01       05       06       01       0       01       0       01       0       01       0       01       0       01       0       05       06       01       05       06       01       01       0       01       01       0       01       0       01       0       01       0       01       0       0	1 mg/kg (21-) 10 mg/kg (31-) 30 mg/kg (41-)
r r r r r r r r r r r r r r r r r r r	14 05 06 01 02 03 04
erring of greylsh patch	
Rypertrophy	
kidneys Cyst Cyst P	
Adrenals Dark reddish change	2 2 2 2 2 3 2 3 3 3 3 3 3 3 3 3 3 3 3 3
Testes	. 1 3 3 3 3 4 3 4 3 4 3 4 3 4 4 1 1 1 1

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Appendix 10-F Individual macroscopic findings (26days) Sex : Female Test article : Sampic D-I

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DC	Dose level			•	∎g/kg (02-)	ື	(-2-)		0	0.1 mg/kg (12-)	:/kg	Ξ	1			1 #g/kg (22-)	t/kg	3	ĩ				10 mg/kg (32-)	(32	I			30 mg/kg (42-)	g/kg	3	5-)	1
findings An	Findings Animal number :	••	01 02		03	10	03 04 05 06	90	10	01 02 03	33	04 05		8	10	02	33	03 04 05 08	15		10	02 0	03 0	94 0	05 0	8	10	02 03 04	03	3	05	8
Lungs Dark reddish patch	patch		1	1	1		1	l .	,						,	1	.	1									,	1	1	.	1	1 1
Liver •Scatterring of greyish dot/patch	of greyish		I	i	I	1	ł	ł	I	1	,	. 1	1	1	ł	ı	I	1	1	,					ſ	ſ	ſ	t	. 1	· •	1	,
llypertrophy Grevish natch	~		11	1.1	1 1	1.1	1.1	11	11	1 1	1 1	1 1	11	1 1	1.1	í.	11	1	5		1	4	· ·	1	1	1	Ч	۵.	а	4	4 ہو	۵.
Dark reddish change Yellovish change	change unge		11	1.1	1 1	11	11		11	. 1 1	11	11		F F F					5 1 L						111	1 4.1	1 -	1 1 0	( <u>p.</u> 1	، <u>م</u> ا	<u>، م ا</u>	
k idneys Cyst			I	1	ł	1	I	ł	i	1	1	1	1	1	1	i	1	(	1	,		· ·			i	i	1	. 1	I	1	1	1
yelectasis Trevish nairt	_		11	11		+ 1	11	11	[]	11	11	11	11	11	11		r i	11	£ 1	1	1					1	1	1	1	1	4	• •
Blackish char	ığe		i	1	1	1	ł	ł	•1	1	1	1	1	- 1	1	1	1	1	i 1	11	i k						11	11	1 1	11	11	
Adrenais Dark reddish change	change		í	ł	1	ł	ł	1	I	1	1	1		ł	ł	t	1	1	1	1		ł	1			ł	1	ł	I	ł	i i	1

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	Sex	••	k	ľ	Ĩ		Ма	Kale										Fe	Fease				
	UOSe tevel		∍│	∎g/kg	2	<u>-</u> ]			30	30 mg/kg	<u>ي</u>	(11-)	ł	0	0 mg/kg		(-20)			30	30 #g/kg		(-21)
Findings	Animal number	: 07	80	60	10 11		12	10	08	0]	10 11	12	10	08		01 60	11 12	12	5	8	5	2	=
Lungs Dark reddish patch	patch	1	1	1	1	1	,	'	'	1			1	1	1	1	1	1	1	1	1	1	1
Liver - Scatterring of greyish dot/patch Nypertrophy Greyish patch Dark reddish change Yeilovish change	of greyish h change ange	* * * i *	11.111					11441	<b>AA</b>	14111	11141	11211	* * * * *	11111	1 4 1 1 1	a a ka k		1 1 1 1 1	11141	1 - 1 - 1	11141	11141	11161
kidneys Cyst Pyelectasis Greyish palch Blackish change	ຊີຍ 2	1111	111		1111	FFFF		111	1 1 1 1	1111	1 5 1 1	1111		1111			1111	1111	1111	1111		1111	1111
Adrenals Dark reddish change	change	ł	ł	ł	1	1	t	I	1	ł	j	ł	• 1	1	I	1	ł	t	1	1	ł	I	ť
Testes Atrophy		I	1	ſ	1	<u>م</u>	I	I	1	. 1	. 1	1											

Appendix [0-R-i individual macroscopic findings (Reco

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Study No. BWR143C						
Individual Macroscopic findings in died male rat (32 days) Sex : Male Test article : Sample D-L	Macroscopic findings	Dark reddish patch	Atrophy	Tarry contents	llesorrhage	Scatterring of greyish dot/patch
ndividual Macr	Organ	Thyeus		Stonach		Ll ver
	Asias number	4109				
	Dose level (ag/kg) Animal number Organ	30				

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Appendix 11-M Individuai microscopic findings (28days) Sex : Mate

								Tes	t ar	tleit	s	amp!	Test articie : Sample D-1	-											Stu	dy N	o.BM	Study No. BMR143C		•	
	Dose level	••		0		ıg/kg (01-)	(-10			0.1 1	0.1 mg/kg (11-)	E	<u>:</u>			1 8	■g/kg (21-)	(21	<b> </b> <u>-</u>		19	10 sg/kg	8	(31-)			8	30 ng/kg		(-1)	
Findings	Findings Animal number	••	10	02	03	04	02	99	10	02	03	10	05 (	18	0 10	02 0	03 04	1	05 06	5	1 02	03	5	05	8	5	02	03	3	05	80
Liver																															
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peripheral	peripheral fatty change		ł	1	ł	ł	1	ł	I	I	1	ł	i	+	,	· •	- T	<del>ر</del> ا	، ، د ا		-	( <sup>-</sup>	-	\$	ł	1	1.	1.	1.	i -	::
sveiling of	svelling of centrilobular													ł			•	-		4	F	+	н	j	ł	\$	ł	H	H	ł	ŧ
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lleart		}																			<b>‡</b>	<b>‡</b>	ł	H	+	ŧ	ŧ	ŧ	\$	ŧ	ŧ
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wyocardia! fibrosis	fibrosis		ł	i	t	ł	ł	}																		ł	1	ł	ţ	ł	ſ
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- : Negative. ± : Yery slight. + : Slight. H : Moderate.

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Appendix 11-F Individual alcroscopic findings (28days) Sex : Fewale Test article : Sample D-1

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Study No. BMR143C

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Findings Animal number Liver Liver aicrogranuioma focal necrosis focal necrosis focal fatty change peripheral fatty change sveiling of centrilobular ensinophilic change in centrilobular hepatorytes	number : hange lobular e In patocytes atlon		8 +111 + 1	<b>8</b> +111 + 1 1	3 +11+	02	8	5	02	63	3	50	8	10	6	2	1		1					1						1
Liver aicrogranufowa focai metrosis focai fatty change peripherai fatty ch sveiilng of centril hepatorytes eosinophilic change centrilobular hej	hange Iobular e in patocytes ation	+++++++++++++++++++++++++++++++++++++++	+1111111	+111+11	+1 1 1 4													05 0	10 90	1 02	2 03	10	05	90	ī	02	63	5	65	90
<pre>elcrogranufows focal metrosis focal fatty change peripheral fatty ch sveliing of centril hepatoryies eosinophilic change centrilobular hej centrilobular hej</pre>	hange lobular e In patocytes ation	++ + + + + + + + + + + + + + + + + + +	+1111 1 1	+111+11	+1 1 1 +																									
focal necrosis focal fatty change peripheral fatty ch sveling of centril hepatocytes eosinophilic change centrilobular hel	hange lobular e in patocytes ation			11+11	114	+1	1	+1	+	Ŧ	ŧ	ŧ	+	ł	1	+	+	+	+	+	+	4	+	+	T	4	ł	4	ļ	4
focal faity change peripheral faity ch svelling of centril hepatocytes eosinophilic change centrilobular hep	hange lobular e in patocytes ation			1 + 1 1	14	1	ł	1	1	1	ł	1		۱	1							+ 1	1 1	1	⊧ -	+ +	1	H		н
peripheral fatty ch sveiiing of centril hepatocytes eosinophilic change centrilobuiar hej	hange Iobular e In patocytes ation	1 1 1		+ 1 1	+	ł	ł	1	ł	1	1	1	ł	1	ł	1	,	1	•			1	1	1	+ 1	+ 1	1		1	1
svelling of centril hepatocytes cosinophilic change centrilobuiar hel	lobular e In patocytes atlon	1 1	1	11	H	+	H	+	-++	+	+1	+	+	1	1	1	+	4	4	-	• +	+	1	•	1	1 4	1 4		1	1 -
hepatocytes eosinophilic change centrilobular hei	e in patocytes ation	1 3	1 1	11					!		1		-				1	-	4	F	4	ł	i	I	I	ł	۲	ł	1	F
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Brain																														
abnormailty		ł	1	ł	1	1	ł								•										i	1	I	1	1	1
Ovaries																													t	I
abnormality		I	1	I	ł	i	1																		I	1	1	1	i	1

- : Negative. ± : Yery slight. + : Slight. H : Hoderate.

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					-	est	Test article : Sample D-1	<u>_</u>	Sam		<u>-</u>									5	Study No. BMR143C	8.0		ي ا ي
Sex							Male					-					•	Fenale	1		1	•	•	
Dose level			0	0 mg/kg (01-	10)	h-			0	30 mg/kg	(-11)	1		0	0 #g/kg	-20)	-			30 #g/kg	g/kg	2	(12-)	1
Findings Animal number	••	07	80	1 60	1 01	11 12		0 L D	08 [	1 01	1	12	07	80	60	10	=	12	07	80	09	10	Π	≌
Liver																								
sicrogranulona		+)	+1	+	1	++	نى.	+	+	+i	+	+	H	+i	+1		+	+I	+ı	++	+	H	+	i
focal necrosis		1	5	ī	1	1	1	+	+	•	1	+	ł	ł	1	1	ł	1	ſ	+	1	ŧ	1	+
focal fatty change		1	1	1	•	,	1	ı	i	, 1	1	1	1	1	1	1	1	1	١	1	1	ł	ı	t
· peripheral faily change		ł	1	ł	,	1	,	1	+	+	;	+1	+	,	H	ŧ	ł	1	ļ	1	ł	,	i	+
svelling of centrilobular																								
hepatocytes		ł	1	1	• •	, ,	,	÷	÷	+ ≠	ŧ	<b>#</b>	1	ı	I	1	I	1	#	+	+	¥	#	#
eosinophilic change in														·										
centrilobular hepatocytes	20	3	ſ	I	•	,	,	+	+	+	<b>‡</b>	<b>#</b>	1	1	1	ł	1	ł	+	+	+	+	+	+
lleart																								
ayocardial degeneration		3	ſ	ı			3	1		ì	1	f	ł	1	H	ł	F	1	i	ł	ł	ł	ſ	ł
myocardial fibrosis		1	1	ł	н	ì	1	t	+1	ì	ł	I	ł	t	1	ł	ł	1	ſ	ł	ŧ	1	t	ł
Spieen			,																					
extramedullary hematopolesis	ls	ī	ſ	+1	• •	1	;	1	1	;	#1	I	1	J	ţ	ł	1	ţ	ţ	1	1	1	ł	ł
Kldneys																								
regenerated tubules		H	I	<del>I</del>	,	1	+	1	1	1	+1	ſ	ł.	+1	+I	+ł	ł	+1	+ł	ł	I	1	1	ł
dilated tubules		1	I	ł	1	1	1	1	ı	ł	,	1	1	1	I	ł	ł	ł	1	ł	1	ı	t	ł
infiltration of lymphocytes	50	1	۱	1	1		1	1	1	+	1	1	ł	I	+	1	ł	+	l	1	ì	1	t	I
dilation of pelvis		I	ſ	ł	1	1	,	{	ł	1	,	1	1	1	t	t	1	ł	t	1	1	1	ſ	ł
chronic nephropathy		١	ŧ	ł	1	1	1	1	1	,	1	+1	1	1	ı	ł	1	1	t	ł	ł	1	1	ł
Adrenals			-																					
abnormality		1	1	4	ì	1	1	4	ł	;	,	1	ł	I	ŧ	ł	1	1	t	ł	1	ŧ	t	ł
Brain																								
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atrophy		1	ŧ	ī	1	≠	1	1	1	i.	1	ſ												
Ovaries																								
abnormai i ty													1	I	1	ł	1	1	ł	ł	1	ſ	ı	ł
- : Negative, ± : Very slight, + : Silght, H : Moderate.	. + : Silght.	 #	Mode	rate	.														.					1

Appendix L1-R-1 individual ∎icroscople findings (Recovery) Test maricle : Samble D-1

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Study No.BWR143C		•	
	+ + + + + +	+ + + +	
Appendix 11-R-2 Appendix 11-R-2 Individual Microscopic findings in dicd male Sex : Male Test article : Sample D-1	Microscopic findings Eosinophilic change in centrilobular hepatocytes Svelling of centrilobular hepatocytes Focal necrosis Peripheral fatty change	Dilated tubules Hemorrhagic foci Ulcor and hemorrhage in glandular stomach Congestion Hemorrhage	No abnormailty No abnormailty No abnormailty No abnormailty
subivibni	Dose ievel (sg/kg) Anlsal number Organ 30 4109 Liver	Kldneys Brain Stomach Thymus	fleart Spieen Adrenals Testes

+ : Silght, + + : Woderate

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Dose level (mg/kg)	Anisal number	Urgan	Maeroscopic findings	Nicroscopic findings
0	0102	Kidneys	Cyst	Dilated tubules(+)
	0105	Lungs	Dark reddlsh patch	Nemorrhage(+)
0.1	1103	Kidneys	Pyclectasis	Dilation of beivis (+)
	2102	Kidneys	Grayish patch	Focal degeneration and calcification in tubutes(+).
				regeneraled tubules (+) and inflitration of ventorvies(+)
30	4101	Liver	Scattering of grayish dot	Focal necros(s(+)
			liyper trophy	Svellag of centrilobular hepatocytes(++)
	4102	Liver	Scattering of gravish dol/patch	No abnormality except for microgranuloms (±)
				peripheral fatty change (+).eosinophilic change in
			:	centrilobuiar hepatocytes (++)
			llyper trophy	Sveitlag of centrilobular hepatocytes(++)
	4103	Liver	Scattering of gravish dot	Focal necrosis(+)
			liyper trophy	Svelling of centrilohular hepatocytes(+)
	4104	Liver	Scattering of grayish dot/patch	Focal necrosis(+)
			liyper (rophy	Sveliing of centrilobular hepatocytes(++)
	4105	Liver	Grayish patch	focal necrosis(+)
			llyper t rophy	Svelling of contrilobular hepatocytes(++)
	4106	Liver	Scattering of grayish dot	Focal necrosis(++)
			llypertrophy	Swelling of contrilobular hepatocytes(+)
		Kidneys	Dark reddish/Blackish dot	No abnormality
		Adrenals	Dark reddish/Blackish dot	No abnormality

Appendix 12-W Microscopic findings of the organs showed gross lesion (28 days) Sex : Male Test article : Sample D-i

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с с Appendix 12-F Microscopic findings of the organs showed gross lesion (28 days) Ser : Female

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Dose level (mg/kg)	Animal number	Urgan	Macroscopic findings	Microscopie findings
10	3206	Liver	Dark reddish change	No abnorgality except for microgranuloms ( $\pm$ ) . Svelling of centrilobular hepatocytes( $\pm$ ) and eosimonial the change in centrilobular hematorytes(+)
30	4201	Liver	Dark reddish change	No abnorte change in controvers increase of the second for microgramuloma(++). eosi- nophilic change in centrilobular hepatocytes (++) and forsi nerrots(+)
	4202	Liver	Nypertrophy Yellovish change	Svelling of centrilobular hepatocytes (++) Periohensi fatty change (+)
			liyper trophy	Svelling of centrilobular hepatocytes (++)
	4 2 0 3	LIVET	Uark reddish chango	.No abnormaiity except for microgranuloma (⊥) eosinophilic change in centrilobular hepatocytes(++)
			livbert rophy	and peripheral faity change(+) Sveliing of centrilobular henatorytes(++)
	4204	Llver	Dark reddish change	No abnorgality except for microgranuloma (±) and
			lly per trophy	eosinophilic change in centrilobular hepalocytes(++) Swelling of centrilobular hepatocytes(+)
	4205	Liver	Dark reddish change	No abnormality except for eostnophilic change in centrijobular hepatocytes(++)
-			Grayish patch	No abnormality except for eosinophilic change
			llyper t rophy	Swelling of centrilobular hepatocytes (++)
		Kidneys	Pyelectasis	Dilation of peivis(+)
	4206	Liver	liyper t rophy	Swelling of centrilobular hepatocytes (++)

± : Yery slight, + : Slight, ++ : Moderate

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		MIC	Microscopic findings of the organs showed gross lesion (Recovery) Test article : Sample D-i	s lesion (Recovery) Study No.BMR143C
Dose level (mg/kg)	Animai number	Organ	Macroscopic findings	Microscopic findings
. Male 0	0111	Testes Liver	Atrophy Dark reddish change	Atrophy(++) No abnormality except for svelling of centrilobular heartowise(++) and contromities shore 1-
	4108 4180 ÷	Liver	Grayish patch Nypertrophy	Contributation and costrophilic change in Contributation beatocytes(+) and microgranuioma(+) Focal mecrosis(+) Sveiling of centrilobular hepatocytes(++)
			uark reggisn patcn Atrophy	Congestion(+) and hemorrhage(+) No abnormality
		Stonach	Tarry contents/llemorrhage	Ulter and hemorrhage in glandular storach(+)
	1110	Liver	Scattering of grayish dot/patch	Focal necrosis(++)
	1111	Liver	bark reddish change	SVBIIING OI CENTIIODUIAT NEPATOCYTES(++) No abnormality except for microgranuloma(+).
	4112	Liver	Grayish patch	sveiiing of centrilobular hepatocytes(++) and eosinophilic change in centrilobular hepatocytes(++) Focal necrosis(+)
Female 30	4207	Liver	Dark reddish change	No abnormality except for elerogranuloma ( $\pm$ ).sveliing
	4208	Liver	Dark reddish change	of centrilobular hepatocytes(++) and eosinophilic change in centrilobular hepatocytes(+) No abnormaality except for microgranuloma (±), focal mecrosis(+) and eosimophilic change in cent-
	4209	Liver	llypertrophy Dark reddish change	<pre>-rilobular hepatocytes(+) Sveiling of centrilobular hepatocytes(+) No abnormality except for microgranuloma(+).sveiling</pre>
	4210	Liver	Dark reddish change	U CENTRI DEPARTORISTING AND ENTRINGED IN CONTRICT CHANGE IN CENTRICOULAR hepatocytes (+) No abnormality steept for microgranuloma ( $\pm$ ). Swelling of centrichty steept for microgranuloma ( $\pm$ ).
	4211	Liver	Dark reddish change	change in contributiar newatores(res)(r) and eosinophilic change in contribubliar hepatocytes(+) No abnormality ercept for microgramuloma(+).sveliling of centrilobular hepatocytes(++) and eosinophilic
	4212	Liver	Grayish patch	<ul> <li>change in centrilobular hepatocytes(+)</li> <li>Focal necrosis(+)</li> </ul>

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#### 2797.0203

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# PHOTOGRAPHS (Hisopathological Pictures)

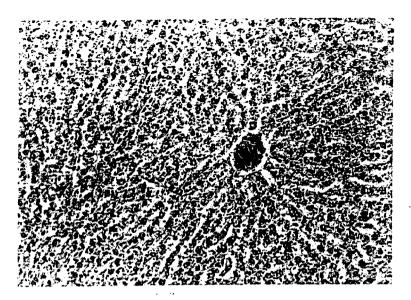


Photo.1 Liver of a male rat of control. (Animal No. 0103) Showing normal centrilobular region. H.E.stain  $\times 180$ 

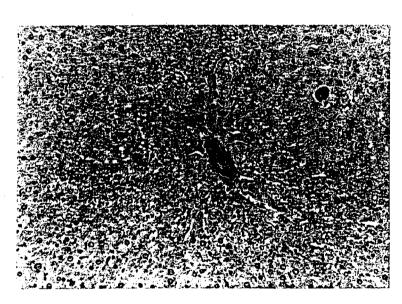


Photo.2 Liver of a male rat given 30 mg/kg. (Animal No. 4105) Eosinophilic change and swelling of centrilobular hepatocytes are noted.

H.E.stain  $\times$  180

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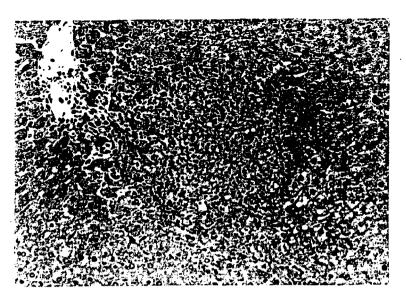


Photo.3 Liver of a male rat given 30 mg/kg. (Animal No. 4105)

Focal necrosis is noted.

H.E.stain  $\times$  180

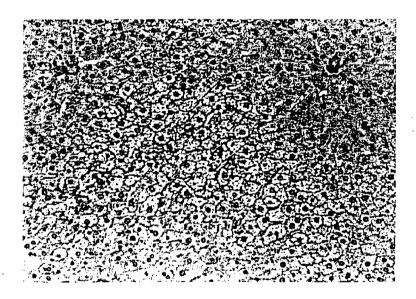


Photo.4 Liver of a male rat given 30 mg/kg. (Animal No. 4106) Peripheral fatty change is found.

H.E.stain  $\times$  180

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