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7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

FINAL REPORT

VOLUME I OF I

RTC Study no.: 36700EXT

Sponsor

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7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

RTC Study no.: 36700EXT

FINAL REPORT

We, the undersigned, were responsible for the preparation of the following report, and hereby declare that this report constitutes a true and faithful account of the procedures adopted, and of the results obtained in the performance of this study. This study was exempt from compliance with Good Laboratory Practice regulations of the OECD. However, it was carried out in a GLP compliant facility.

C. Longobardi, Biol.D. Cinzia Longobardi (Study Director) Date: 13-Feb-2007

G. Oberto, D.V.M., Spec. Toxicology (Scientific Director) Date: 13 Febr. 2007

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1. SUMMARY

1.1 The oral toxicity of [redacted] when given by daily administration to rats, has been investigated over a period of 7 consecutive days. Three groups, each of 4 male and 4 female Sprague Dawley rats, received the test item by gavage at dosages of 2.5, 5.0 and 10.0 mg/kg/day for 7 consecutive days. A fourth similarly constituted group received the vehicle alone (distilled water) and acted as a control.

1.2 Mortality, daily pre-post-dose observations and clinical signs

No treatment-related death occurred during the study.
No reaction to treatment was seen at the daily post-dose observations.
No clinical signs were observed at weekly observations.

1.3 Body weight

Body weights measured on Day 8 were statistically significant reduced in the high dose animals when compared to controls. Terminal body weight was also significantly reduced in the high-dose animals.

1.4 Food consumption

Food consumption was reduced in the high dose animals when compared to controls.

1.5 Haematology

Slight but statistically significant increases of the red blood cell count, haemoglobin and haematocrit were observed in the mid and high-dose males and high-dose females. An increased prothrombin time was also observed in the high dose males. No other changes of toxicological significance were observed.

1.6 Clinical chemistry

Statistically significant increases of alanine aminotranferase and aspartate aminotransferase were observed in the high dose males. The urea was increased in the mid and high dose animals and the total bilirubin in the high dose animals. Reduction in cholesterol and total proteins levels were also observed in the mid and high dose animals, while the creatinine was reduced only in the females. In addition, variations of electrolytes were observed at the 2 higher dose levels. Usually, the observed changes showed a dose-related trend.

1.7 Organ weights

Dose-related, statistically significant increases in absolute and relative liver weights were noted in all treated males and in the high dose females. In addition, statistically significant reductions of the absolute and relative weights of the spleen and thymus were seen in the high dose animals. The relative weights of the testes and kidneys were also statistically significantly increased in the high dose males. No other toxicologically significant changes were observed.

1.8 Macroscopic observations

Changes, possibly treatment-related, were observed in the liver and stomach of high dose group animals, when compared with controls. Pale colour of the liver was reported in all high dose group animals. Two males and 1 female from the high dose group also showed single or multiple dark areas in the glandular region of the stomach. An additional female in the same group presented a diffuse dark coloration of the gastric mucosa.
Furthermore, red/dark colour of the lungs was reported in 1 male and 2 females from the high dose group and in 1 female from the intermediate dose group. Dark colour of the pituitary was reported for 3/4 high dose group females.

1.9 Conclusion

A toxic effect of the test item was seen at the 2 higher dose levels investigated (5.0 and 10.0 mg/kg/day). Only a minor effect was observed at the low dose (2.5 mg/kg/day), essentially in the males. Most of the observed changes showed a dose-related trend. The low dose of 2.5 mg/kg/day was reasonably tolerated and, therefore, may potentially be used as a high dose level in a longer duration study.

2. INTRODUCTION

The purpose of this study was to evaluate the toxicity of [redacted] when administered daily to rats by the oral route for 7 consecutive days, to allow selection of dose levels for subsequent studies.

The Sprague Dawley rat was chosen because it is accepted by many regulatory authorities and there is ample experience and background data on this species and strain.

The oral route was selected as it is a possible route of exposure of the test item in man. The dose levels of 2.5, 5.0 and 10.0 mg/kg/day were defined in agreement with the Sponsor.

Each main group comprised 4 male and 4 female rats.

The animals were assigned to treatment groups on 30 December 2004 and dosing began on 28 January 2005. Necropsies were completed by 4 February 2005.
The protocol is presented in Addendum III.

The study was carried out at:

Research Toxicology Centre S.p.A.
Via Tito Speri, 12
00040 Pomezia (Rome)
Italy

The study was conducted on behalf of:

SOLVAY SOLEXIS S.p.A.
Via Lombardia, 20
20121 Bollate (MI)
Italy

3. TEST ITEM

Information received from the Sponsor indicated the following:

Name	: [redacted]
Batch Number	: 90409/86-I
CAS Number	: 330809-92-2
Purity	: 100%
Expiry date	: 1st January 2015
Received from	: SOLVAY SOLEXIS
Date received	: 14th January 2005
Amount received	: Approximately 300 grams
Description	: White solid
Container	: Colourless glass bottle
Storage at RTC	: Ambient conditions
RTC reference number	: 9372

The determination of the identity, strength, purity, composition and stability of the test item was the responsibility of the Sponsor.
A sample of the test item was taken before commencement of treatment and will be stored in the archives at RTC for 10 years prior to disposal.

The test item was dissolved in distilled water to give the required concentrations of 0.25, 0.5 and 1.0 mg/ml.

During handling of the substance, precautions were taken to reduce possible operator exposure. These included, but were not limited to, use of a face mask, eye protection and the wearing of gloves.

4. METHODS

4.1 Test system

4.1.1 Animal supply and acclimatisation

A total of 51 Hsd: Sprague Dawley SD rats (25 males and 26 females, not 50 as indicated in the protocol) 27-29 days old and within a weight range of 106-109 g for males and 87-103 g for females, with females nulliparous and non-pregnant, were supplied on 30 December 2004, by Harlan Italy s.r.l., 33049 San Pietro al Natisone (UD), Italy. Animals were ordered in the weight range of 75-99g and therefore, were supplied slightly outside the range indicated at order.
Following arrival, the animals were temporarily identified within the cage. A health check was performed by a veterinarian. All rats were considered healthy. An overall acclimatisation period of 29 days was allowed before the start of treatment during which time the health status of the rats was assessed by daily observations.

4.1.2 Animal husbandry

The animals were housed in a limited access rodent facility. Animal room controls were set to maintain temperature and relative humidity at 22°C ± 2°C and 55% ± 15% respectively; actual conditions were monitored, recorded and the records retained. There were approximately 15 to 20 air changes per hour and the rooms were lit by artificial light for 12 hours each day.
The animals were housed up to 5 of one sex to a cage, in clear polycarbonate cages measuring 59x38.5x20 cm with a stainless steel mesh lid and floor (Code 1354 G, Techniplast Gazzada S.a.r.l., Buguggiate, Varese). Each cage tray held absorbent paper which was inspected and changed 3 times a week.
Drinking water was supplied *ad libitum* to each cage via water bottles, except as noted in section 4.4.
A commercially available laboratory rodent diet (4 RF 18, Mucedola S.r.l., Via G. Galilei, 4, 20019, Settimo Milanese (MI) Italy) was offered *ad libitum* throughout the study, except as noted in section 4. 4.
There is no information available to indicate that any non-nutrient substance likely to influence the effect of the test item was present in the drinking water or the diet. Records of analyses of water and diet are kept on file at RTC.
Dated and signed records of activities relating to the day to day running and maintenance of the study in the animal house were recorded.

4.1.3 Allocation to groups

On the day of allocation (7 days prior to the start of treatment) all animals were weighed. Animals at the extremes of the weight distribution and/or any animal showing signs of ill health were excluded to leave the required number of animals. The rats were allocated to the 4 groups by computerised stratified randomisation to give approximately equal initial group mean body weights.
Individuals were uniquely identified within the study by sex, tattoo on the hind feet and ear notch and housed 4 of one sex per cage.
The cages were identified by a label recording the study number, animal numbers and details of treatment. The arrangement of cages in batteries was such that cages from each treatment group were evenly distributed across the battery (Figure 1) to minimise possible environmental effects.

4.2 Treatment

4.2.1 Selection of dose levels

Dose levels were selected in consultation with the Sponsor.

4.2.2 Dose levels, group size and identification

Each group comprised 4 male and 4 female rats. The group identification and animal numbers assigned to the treatment are summarised below:

Group Number	Treatment (mg/kg/day)+	Level	Rat Numbers	
			M (even)	F (odd)
1	0	Control	2-8	1-7
2	2.5	Low	10-16	9-15
3	5.0	Medium	18-24	17-23
4	10.0	High	26-32	25-31
+: in terms of test item as supplied				

The rat numbers listed above formed the last digits of a computer generated 8 figure animal number (the remaining digits of the animal number were different for each concurrent study and served to ensure unique animal numbering for any study employing computerised data collection). The software used for data collection in this study was the Xybion Path/Tox System, version 4.2.2.

4.2.3 Administration of test item

The test item was administered orally, by gavage at a dose volume of 10 ml/kg.
Control animals received the vehicle alone, distilled water, at the same dose volume.
The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal.

4.2.4 Duration of treatment

All animals were dosed once a day for 7 consecutive days. All animals were dosed up until the day before necropsy.

4.3 *In vivo* observations

Dated and signed records of all activities relating to the day by day running and maintenance of the study within the animal unit, as well as to the group observations were recorded in the Study Day Book.
Full records were maintained for all measurements and observations.

4.3.1 Mortality

Throughout the study, all animals were checked early in each working day and again in the afternoon. At weekends and Public Holidays a similar procedure was followed except that the final check was carried out at approximately mid-day.

4.3.2 Pre- and post-dose observations

All observations were recorded for individual animals. Examination of individual animals for signs of reaction to treatment was carried out daily before dosing, immediately after, and approximately 1 and 2 hours after dosing.

4.3.3 Clinical signs

All clinical signs were recorded for individual animals.
Once before commencement of treatment, once during treatment period and on termination of the study (Day 8), each animal was observed and any clinical signs were recorded.

4.3.4 Body weight

Each animal was weighed on the day of allocation to treatment group, on the day that treatment commenced and just prior to necropsy.

4.3.5 Food consumption

The weight of food consumed by each cage of rats was recorded on the first day of dosing (Day 1) and on Day 7. This was a deviation from protocol in which was indicated to measure the food consumed at weekly intervals. This deviation allowed a food consumption measurement to be taken prior to the overnight fast for clinical pathology investigations. The group mean daily intake per rat was calculated.

4.4 Clinical pathology investigations

At the end of treatment, on Day 8 of the study, samples of blood were withdrawn under isofluorane anaesthesia from the abdominal vena cava of all animals from each group after overnight fasting.

Blood samples were collected and analysed in the same order.
The blood samples collected were divided into tubes as follows:

EDTA anticoagulant	for haematological investigations
Heparin anticoagulant	for biochemical tests
Citrate anticoagulant	for coagulation test

The measurements performed on blood samples are listed below:

4.4.1 Haematology

Haematocrit
Haemoglobin
Red blood cell count
Reticulocyte count (not performed as no signs of anaemia were present)
Mean red blood cell volume
Mean corpuscular haemoglobin
Mean corpuscular haemoglobin concentration
White blood cell count

Differential leucocyte count
- Neutrophils
- Lymphocytes
- Eosinophils
- Basophils
- Monocytes
- Large unstained cells

Abnormalities of the blood film
Platelets
Prothrombin time

4.4.2 Clinical chemistry

Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Urea
Creatinine
Glucose
Total bilirubin
Total cholesterol
Total protein
Albumin
Sodium
Potassium
Calcium
Chloride

4.5 Terminal studies

4.5.1 Euthanasia

All animals that had completed the scheduled test period were killed by exanguination under isofluorane anaesthesia. All animals were subjected to necropsy, supervised by a pathologist, as detailed below.

4.5.2 Necropsy

The clinical history of the animal was studied and a detailed *post mortem* examination was conducted (including examination of the external surface and orifices).
Changes were noted, the requisite organs weighed and the required tissue samples preserved in fixative and processed for histopathological examination (see sections 4.5.3 to 4.5.5).

4.5.3 Organ weights

From all animals completing the scheduled test period, the organs indicated in Section 4.5.6 were dissected free of fat and weighed.
The ratios of organ weight to body weight were calculated for each animal.

4.5.4 Tissues fixed and preserved

Samples of all the tissues listed in Section 4.5.6 were fixed and preserved in 10% buffered formol saline (except eyes and optic nerves which were fixed in Davidson's fluid; and testes and epididymides which were fixed in Bouin's solution and all preserved in 70% ethyl alcohol).

4.5.5 Histopathological examination

No histopathological examination was performed.

4.5.6 Annex 1 of the Study Protocol

Organs / Tissues	Weight	Fixation Preservation	Microscopic Examination
Abnormalities		✓	
Adrenal glands	✓	✓	
Bone marrow (from sternum)		✓	
Brain	✓	✓	
Caecum		✓	
Colon		✓	
Duodenum		✓	
Epididymides	✓	✓	
Heart	✓	✓	
Ileum (including Peyer's patches)		✓	
Jejunum		✓	
Kidneys	✓	✓	
Liver	✓	✓	
Lungs		✓	
Lymph nodes – mesenteric		✓	
Lymph nodes – cervical		✓	
Ovaries		✓	
Parathyroid glands[a]		✓	
Pituitary gland		✓	
Prostate gland		✓	
Rectum		✓	
Sciatic nerve		✓	
Seminal vesicles		✓	
Spinal column		✓	
Spinal cord		✓	
Spleen	✓	✓	
Stomach		✓	
Testes	✓	✓	
Thymus (where present)	✓	✓	
Thyroid		✓	
Trachea		✓	
Urinary bladder		✓	
Uterus-cervix		✓	

[a] Weighed and preserved with thyroid gland

4.6 Statistical analysis

Standard deviations were calculated as considered appropriate. For continuous variables the significance of the differences amongst groups was assessed by analysis of variance. Differences between each treated group and the control group were assessed by Dunnett's test using a pooled error variance. The homogeneity of the data was verified by Bartlett's test before Dunnett's test. If data were found to be inhomogeneous a Modified t test (Cochran and Cox) was applied. The mean values, standard deviations and statistical analysis were calculated from the actual values in the computer without rounding off.

4.7 Deviations from protocol

Any deviations from protocol are indicated within the text of the report. No deviations occurred which were considered to have affected the integrity of the study.

4.8 Archives

Full records were maintained of all aspects of study conduct, together with the results of all measurements and observations.
All specimens other than the samples described above, raw data, records and documentation generated during the course of this study will be returned to the Sponsor after the issue of the Final Report.

The top copy of the Final Report will be despatched to and archived by the Sponsor.

5. RESULTS

5.1 Mortality, daily pre-post-dose observations and clinical signs (Tables 1 and 2; Appendix 1)

No treatment-related death occurred during the study.
No reaction to treatment was seen at the daily post-dose observations.
No treatment-related clinical signs were observed in treated animals at weekly observations.

5.2 Body weight (Figure 2; Tables 3 and 6; Appendix 2)

Body weights at the end of treatment were slightly (15% and 12% in males and females) but statistically significantly reduced in the high dose animals when compared to controls. Terminal body weights were also slightly reduced in the high-dose animals.

5.3 Food consumption (Appendix 3)

A slightly reduced food intake was observed in the high dose animals when compared to controls.

5.4 Haematology (Table 4; Appendix 4)

Slight but statistically significant increases of the red blood cell count, haemoglobin and haematocrit were observed in the mid (6-7%) and high-dose males (17-19%) and high-dose females (7-12%). An increased prothrombin time (31% higher than controls) was also observed in the high dose males. No toxicological importance was attributed to the changes observed in relative values of neutrophils (increment of 19%), monocytes (increment of 2 folds) and lymphocytes (decrement of 14%). No other changes of toxicological significance were observed.

5.5 Clinical chemistry (Table 5; Appendix 5)

Statistically significant increases of alanine aminotranferase (158%) and aspartate aminotransferase (74%), were observed in the high dose males. A marked statistically significant increase in total bilirubin (688% and 369% in males and females, respectively) was also observed in the high dose animals. Statistically significant reductions in cholesterol were seen in mid- and high dose animals in a trend-related manner. The urea was statistically significant increased in the mid and high dose males (53% and 68%) and in the high dose females (32%) with a dose-related significant trend. In addition, a statistically significant reduction in total protein levels was seen in the mid and high dose animals. The creatinine was statistically significant reduced only in the females. Variations of electrolytes were noted at the 2 higher dose levels. Usually, the above observed changes showed a dose-related trend. The observed changes may be considered an effect of the treatment with the test item.

5.6 Organ weights (Tables 7 and 8; Appendices 6 and 7)

Dose-related, statistically significant increases in absolute and relative liver weights were noted in all treated males (43%, 64% and 52% absolute and 43%, 68% and 80% relative) and in the high dose females (27% absolute, although not statistically significant, and 47% relative) at the end of the treatment period. In addition, statistically significant reductions of the absolute and relative weights of the spleen and thymus were seen in the high dose animals at the end of treatment. The relative weights of the testes and kidneys were also statistically significantly increased in the high dose males. All the above changes were regarded as a treatment-related effect.

The major change observed, the increase in liver weight, may be correlated to most of the variations observed in the clinical pathology parameters. No other toxicologically significant changes were observed.

5.7 Macroscopic observations (Table 9; Appendix 8)

Changes, possibly treatment-related, were observed in the liver and stomach of high dose group animals, when compared with controls. Pale colour of the liver was reported in all high dose group animals. Single instances of the same finding were also reported in all the remaining treated and control female groups. Two males and 1 female from the high dose group also showed single or multiple dark areas in the glandular region of the stomach. An additional female in the same group presented a diffuse dark coloration of the gastric mucosa.
Furthermore, red/dark colour of the lungs was reported in 1 male and 2 females from the high dose group and in 1 female from the intermediate dose group. Dark colour of the pituitary was reported for 3/4 high dose group females.

6. CONCLUSION

The oral toxicity of [redacted] when given by daily administration to rats at dosages of 2.5, 5.0 and 10.0 mg/kg/day has been investigated over a period of 7 days.

Reduced body weights and food intake were observed in the high dose animals at the end of the treatment period. No other signs of toxicity were noted during the "in-life" phase. Slight statistically significant variations in some haematological parameters were observed in the mid and high dose animals. The toxicological significance of these variations is unclear, as it may not be correlated to or supported by any macroscopic (or microscopic) change.
Clinical pathology parameters showed a number of statistically significant changes (increased levels of liver enzymes, total bilirubin and urea, decreased levels of total cholesterol and total protein) at the 2 higher dose levels whose toxicological significance was supported by the increases in the weights of the liver (noted in all treated males and in the high dose females) and kidneys in the high dose males. Other treatment-related changes were the decrease in the weights of the spleen and thymus, observed in the high dose animals of both sexes. Slight, even if not statistically significant, changes of most of the above parameters were evident also at the low dose level, particularly in the males.

Macroscopic *post-mortem* examination revealed changes in the liver and stomach of high dose group animals.

On the basis of these results, some toxic effect of the test item was demonstrated at the 2 higher dose levels investigated (5.0 and 10.0 mg/kg/day). Most of the observed changes showed a dose-related trend. Only a minor effect was observed at the low dose (2.5 mg/kg/day), essentially in the males. The low dose of 2.5 mg/kg/day was reasonably tolerated and, therefore, may potentially be used as a high dose level in a study of longer duration study.

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

FIGURE 1 - Group and cage arrangement on battery

STUDY NO.: 36700EXT

Group Number	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
1	0	Control	2-8	1-7	1	5
2	2.5	Low	10-16	9-15	2	6
3	5.0	Medium	18-24	17-23	3	7
4	10.0	High	26-32	25-31	4	8
+: in terms of test item as supplied						

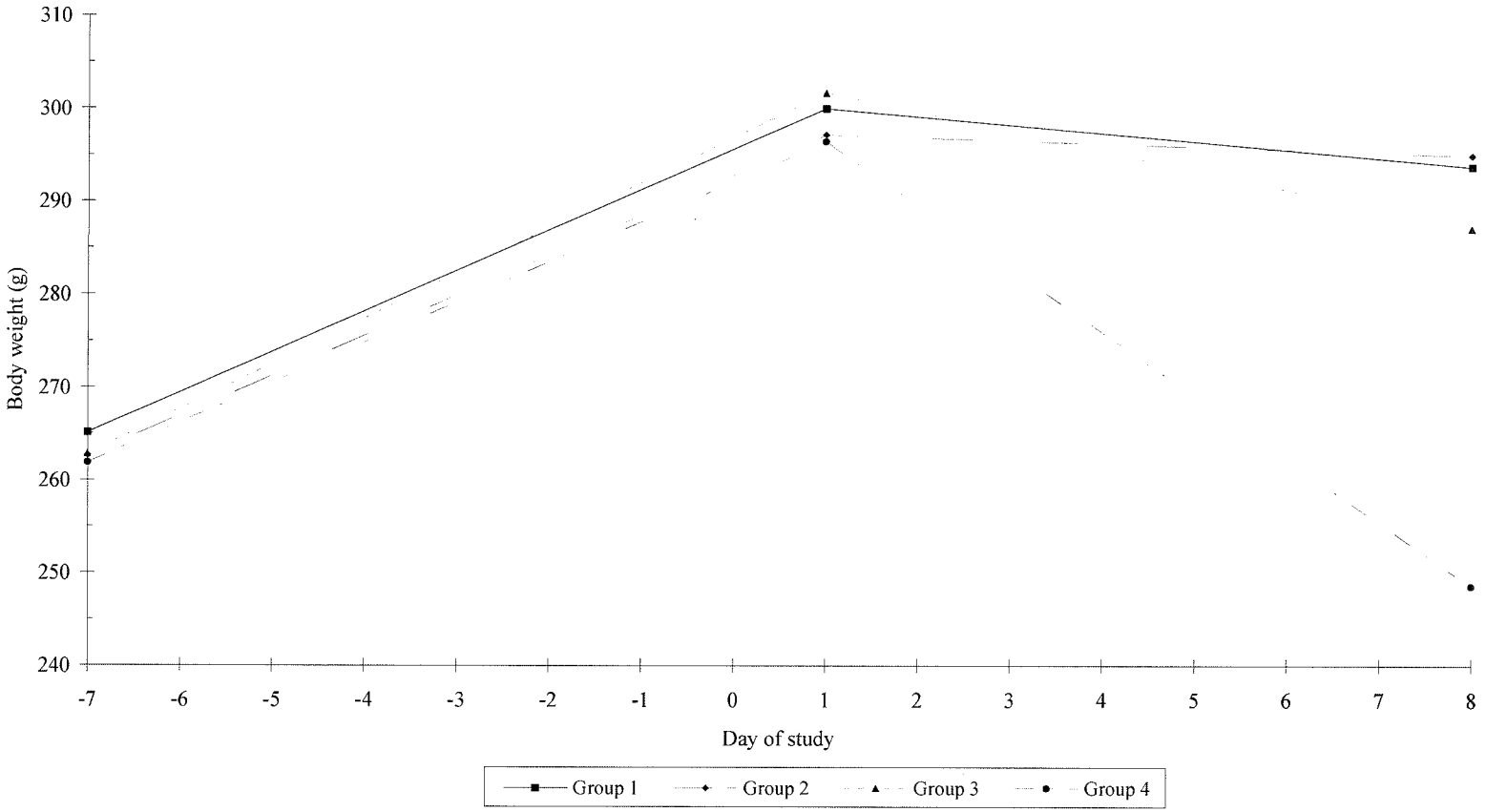
Group/Sex
Cage no.

Males		Females	
1M	1	4F	8
2M	2	3F	7
3M	3	2F	6
4M	4	1F	5

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

FIGURE 2.1 - Body weight versus day of study - Males

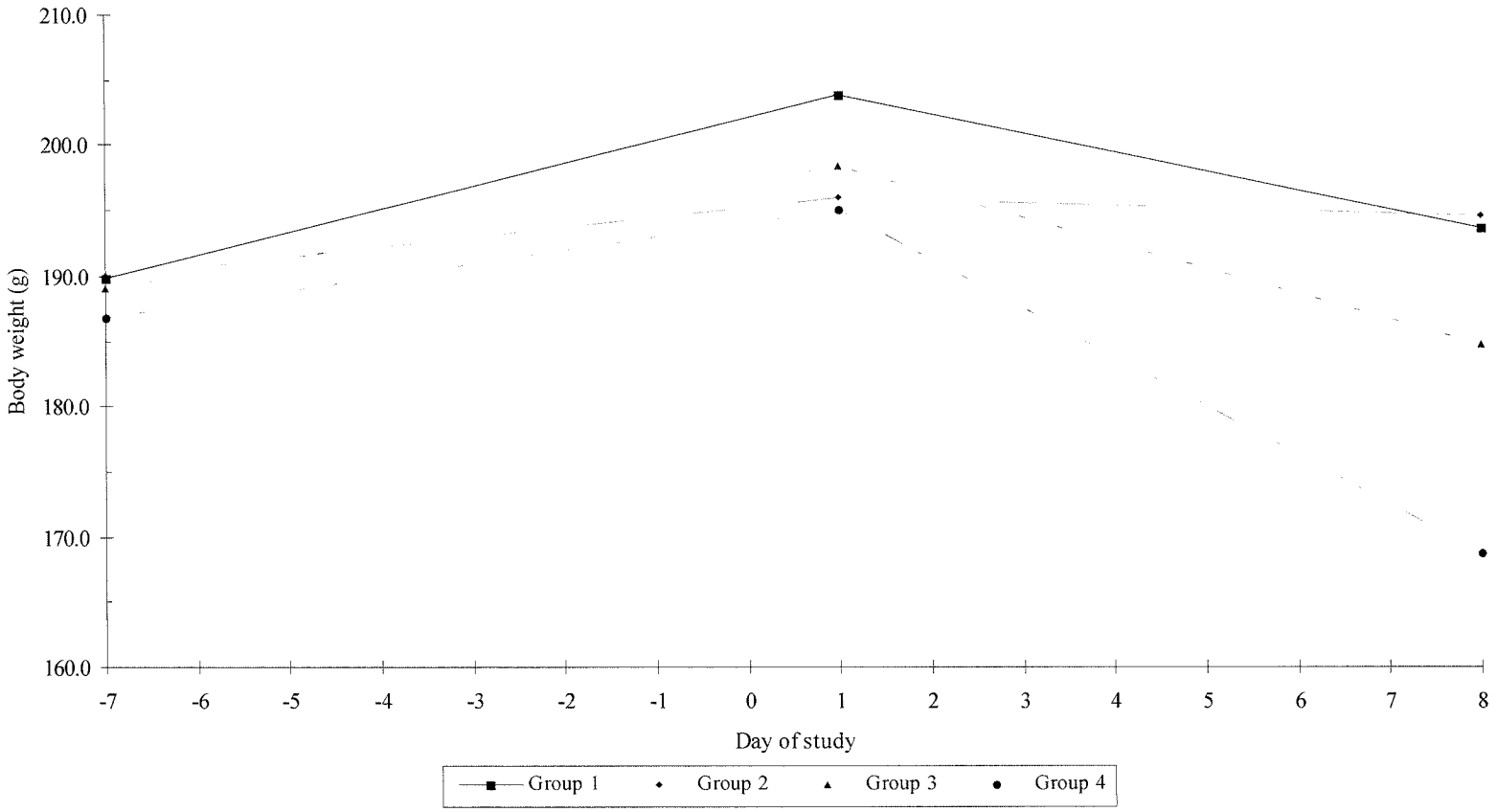
STUDY NO.: 36700EXT



[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

FIGURE 2.2 - Body weight versus day of study - Females

STUDY NO.: 36700EXT



[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 1 - Clinical signs - Group incidence

STUDY NO.: 36700EXT

MALES

Interval: 1 - 2 Weeks Group Observation	1 (4)		2 (4)		3 (4)		4 (4)	
	a	b	a	b	a	b	a	b
No significant signs	4	1.8	4	2.0	4	2.0	4	2.0
APPEARANCE								
Staining	1	1.0	0	0.0	0	0.0	0	0.0
Hairloss	1	1.0	0	0.0	0	0.0	0	0.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 1 - Clinical signs - Group incidence

STUDY NO.: 36700EXT

FEMALES

Interval: 1 - 2 Weeks Group Observation	1 (4)		2 (4)		3 (4)		4 (4)	
	a	b	a	b	a	b	a	b
No significant signs	4	2.0	4	2.0	4	2.0	4	2.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 2 - Pre and post-dose observations - Group incidence

STUDY NO.: 36700EXT

Group	Sex	Observation	Day --->	1	1	1	1	2	2	2	2	3	3	3	3	4	4
			Session --->	1	2	3	4	1	2	3	4	1	2	3	4	1	2
		NO ABNORMALITY DETECTED															
1	M			4	4	4	4	4	4	4	4	4	4	4	4	4	4
2				4	4	4	4	4	4	4	4	4	4	4	4	4	4
3				4	4	4	4	4	4	4	4	4	4	4	4	4	4
4				4	4	4	4	4	4	4	4	4	4	4	4	4	4
1	F			4	4	4	4	4	4	4	4	4	4	4	4	4	4
2				4	4	4	4	4	4	4	4	4	4	4	4	4	4
3				4	4	4	4	4	4	4	4	4	4	4	4	4	4
4				4	4	4	4	4	4	4	4	4	4	4	4	4	4

Note: Data for Dosing phase
Key: Number of animals with sign during session

Session: 1: Pre- dose
2: At dosing
3: Approximately 1 hour after dosing
4: Approximately 2 hours after dosing

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 2 - Pre and post-dose observations - Group incidence

STUDY NO.: 36700EXT

Group	Sex	Observation	Day --->	4	4	5	5	5	5	6	6	6	6	7	7	7	7
			Session --->	3	4	1	2	3	4	1	2	3	4	1	2	3	4
		NO ABNORMALITY DETECTED															
1	M			4	4	4	4	4	4	4	4	4	4	4	4	4	4
2				4	4	4	4	4	4	4	4	4	4	4	4	4	4
3				4	4	4	4	4	4	4	4	4	4	4	4	4	4
4				4	4	4	4	4	4	4	4	4	4	4	4	4	4
1	F			4	4	4	4	4	4	4	4	4	4	4	4	4	4
2				4	4	4	4	4	4	4	4	4	4	4	4	4	4
3				4	4	4	4	4	4	4	4	4	4	4	4	4	4
4				4	4	4	4	4	4	4	4	4	4	4	4	4	4

Note: Data for Dosing phase
Key: Number of animals with sign during session

Session: 1: Pre- dose
2: At dosing
3: Approximately 1 hour after dosing
4: Approximately 2 hours after dosing

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 3 - Body weight (g) - Individual data

STUDY NO.: 36700EXT

MALES

Group(s)		Day of Phase 1!	Day of Phase 1"	Day of Phase 8
1	(n)	4	4	4
	Mean	265.10	300.05	293.84
	SD	6.16	7.57	12.53
2	(n)	4	4	4
	Mean	262.65	297.18	295.02
	SD	3.42	5.22	5.08
3	(n)	4	4	4
	Mean	262.81	301.79	287.12
	SD	3.38	4.86	5.28
4	(n)	4	4	4
	Mean	261.90	296.49	248.59**
	SD	3.56	7.67	11.21

Note: ! = Pretest phase; " = Dosing phase
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 3 - Body weight (g) - Individual data

STUDY NO.: 36700EXT

FEMALES

		Day of Phase		
Group(s)		1!	1"	8
1	(n)	4	4	4
	Mean	189.85	203.73	193.53
	SD	7.83	10.75	11.33
2	(n)	4	4	4
	Mean	190.02	195.95	194.49
	SD	9.44	8.24	11.74
3	(n)	4	4	4
	Mean	188.98	198.31	184.63
	SD	7.41	19.14	15.98
4	(n)	4	4	4
	Mean	186.84	195.07	168.75*
	SD	6.96	8.35	12.13

Note: ! = Pretest phase; " = Dosing phase
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 4 - Haematology - At the end of treatment - Group mean data

STUDY NO.: 36700EXT

MALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
RED BLOOD CELL COUNT 10^12/l	7.750	0.191	4	7.648	0.081	4	8.180*	0.191	3	9.170**	0.142	3
HAEMOGLOBIN g/dl	15.30	0.20	4	15.35	0.37	4	16.27**	0.35	3	17.83**	0.40	3
HAEMATOCRIT %	44.48	0.76	4	44.88	0.95	4	47.60**	0.87	3	53.03**	0.90	3
MEAN RED BLOOD CELL VOLUME fl	57.40	0.83	4	58.65	0.84	4	58.23	0.32	3	57.83	0.15	3
MEAN CORPUSCULAR Hb pg	19.75	0.37	4	20.05	0.31	4	19.87	0.23	3	19.43	0.15	3
MEAN CORPUSCULAR Hb CONC. g/dl	34.43	0.21	4	34.20	0.14	4	34.13	0.40	3	33.60**	0.26	3

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 4 - Haematology - At the end of treatment - Group mean data

STUDY NO.: 36700EXT

MALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
PLATELETS 10^9/l	940.5	94.8	4	918.3	58.0	4	770.3	169.3	3	855.3	89.5	3
PROTHROMBIN TIME sec	16.28	0.88	4	16.05	1.10	4	16.90	1.41	4	21.35**	0.78	2

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 4 - Haematology - At the end of treatment - Group mean data

STUDY NO.: 36700EXT

MALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
WHITE BLOOD CELL COUNT 10^9/l	10.475	1.326	4	8.883	2.454	4	8.567	0.915	3	9.190	1.227	3
NEUTROPHILS %	7.55	1.91	4	10.53	4.66	4	11.73	2.61	3	15.77*	3.13	3
LYMPHOCYTES %	86.00	1.84	4	81.93	5.68	4	80.37	4.38	3	73.83*	5.00	3
MONOCYTES %	3.23	0.50	4	3.80	1.12	4	4.23	1.14	3	6.47**	1.23	3
EOSINOPHILS %	1.00	0.48	4	1.08	0.10	4	1.33	0.50	3	0.57	0.12	3
BASOPHILS %	0.20	0.00	4	0.25	0.10	4	0.17	0.06	3	0.17	0.06	3
LARGE UNSTAINED CELLS %	2.05	0.31	4	2.43	0.39	4	2.13	0.49	3	3.10*	0.61	3

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 4 - Haematology - At the end of treatment - Group mean data

STUDY NO.: 36700EXT

FEMALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
RED BLOOD CELL COUNT 10^12/l		7.820	0.400	4	7.455	0.179	4	7.788	0.355	4	8.543*	0.377	4
HAEMOGLOBIN g/dl		15.33	0.71	4	14.95	0.59	4	15.38	0.98	4	17.13*	0.50	4
HAEMATOCRIT %	($)	45.15	3.50	4	41.40	0.51	4	43.68	2.81	4	48.20	0.94	4
MEAN RED BLOOD CELL VOLUME fl		57.68	1.49	4	55.58	0.74	4	56.08	1.14	4	56.48	1.54	4
MEAN CORPUSCULAR Hb pg		19.63	0.21	4	20.10	0.58	4	19.73	0.43	4	20.05	0.69	4
MEAN CORPUSCULAR Hb CONC. g/dl		33.98	1.07	4	36.15**	1.14	4	35.23	0.32	4	35.55	0.57	4

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 4 - Haematology - At the end of treatment - Group mean data

STUDY NO.: 36700EXT

FEMALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
PLATELETS 10^9/l		962.0	113.8	4	1027.8	126.1	4	1009.0	24.6	3	1058.5	47.1	4
PROTHROMBIN TIME sec	($)	18.23	0.35	3	16.33*	0.17	4	17.58	1.33	4	18.68	0.57	4

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 4 - Haematology - At the end of treatment - Group mean data

STUDY NO.: 36700EXT

FEMALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
WHITE BLOOD CELL COUNT 10^9/l		8.040	2.033	4	6.700	1.748	4	8.115	2.364	4	5.868	1.607	4
NEUTROPHILS %		8.73	2.12	4	10.53	1.97	4	4.58*	2.17	4	5.03	2.24	4
LYMPHOCYTES %		84.15	2.48	4	83.98	2.17	4	89.65*	2.85	4	88.88	2.58	4
MONOCYTES %		3.30	0.41	4	2.40	0.18	4	2.60	0.68	4	3.60	0.67	4
EOSINOPHILS %		1.38	0.31	4	1.35	0.29	4	1.38	0.82	4	0.73	0.17	4
BASOPHILS %	($)	0.23	0.05	4	0.20	0.27	4	0.20	0.08	4	0.18	0.10	4
LARGE UNSTAINED CELLS %		2.23	0.44	4	1.53	0.38	4	1.60	0.57	4	1.58	0.38	4

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 5 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: 36700EXT

MALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
ALKALINE PHOSPHATASE U/l	($)	339.83	32.88	4	310.80	45.59	4	379.63	51.09	4	291.88	5.42	4
ALANINE AMINO-TRANSFERASE U/l		37.03	5.51	4	39.88	4.67	4	43.98	5.12	4	95.45**	14.15	4
ASPARTATE AMINO-TRANSFERASE U/l		69.63	6.36	4	74.93	7.77	4	79.95	8.14	4	121.23**	14.81	4
TOTAL BILIRUBIN mg/dl	($)	0.048	0.010	4	0.063	0.062	4	0.038	0.022	4	0.378**	0.054	4
TOTAL CHOLESTEROL mg/dl		83.93	12.32	4	68.68	7.45	4	59.20*	11.12	4	51.15**	7.21	4
GLUCOSE mg/dl		131.08	28.68	4	102.00	11.32	4	112.78	11.80	4	121.13	4.98	4

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 5 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: 36700EXT

MALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
UREA mg/dl	42.65	7.51	4	44.70	5.59	4	65.25*	12.72	4	71.45**	8.58	4
CREATININE mg/dl	0.380	0.024	4	0.385	0.044	4	0.380	0.064	4	0.333	0.053	4
CHLORIDE mmol/l	99.65	0.96	4	101.15	0.58	4	100.03	1.88	4	102.13*	1.41	4
CALCIUM mmol/l	2.650	0.050	4	2.615	0.110	4	2.610	0.088	4	2.423**	0.074	4
SODIUM mmol/l	138.58	0.79	4	139.68	0.99	4	137.75	0.95	4	133.30**	2.46	4
POTASSIUM mmol/l	3.910	0.133	4	4.020	0.262	4	3.903	0.235	4	4.223	0.070	4

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 5 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: 36700EXT

MALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
TOTAL PROTEIN g/dl		6.20	0.12	4	6.28	0.21	4	6.03	0.25	4	4.90**	0.29	4
ALBUMIN g/dl	($)	3.90	0.12	4	4.10	0.08	4	4.10	0.18	4	3.28	0.53	4
GLOBULIN g/dl		2.30	0.00	4	2.18	0.17	4	1.93	0.10	4	1.63**	0.44	4
ALBUMIN/GLOBULIN RATIO	($)	1.70	0.05	4	1.89	0.14	4	2.13**	0.09	4	2.19	0.86	4

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 5 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: 36700EXT

FEMALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
ALKALINE PHOSPHATASE U/l		219.43	26.99	4	225.43	27.73	4	205.45	24.49	4	187.55	27.20	4
ALANINE AMINO-TRANSFERASE U/l		34.95	4.16	4	27.90	3.88	4	30.95	4.71	4	34.05	13.31	4
ASPARTATE AMINO-TRANSFERASE U/l	($)	85.00	8.97	4	73.03	5.49	4	78.18	2.15	4	91.85	16.18	4
TOTAL BILIRUBIN mg/dl		0.048	0.010	4	0.080	0.042	4	0.090	0.027	4	0.225**	0.037	4
TOTAL CHOLESTEROL mg/dl		84.45	12.26	4	75.95	14.61	4	45.48**	10.67	4	45.65**	7.90	4
GLUCOSE mg/dl		103.15	15.79	4	94.43	26.62	4	116.73	7.04	4	118.75	7.58	4

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 5 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: 36700EXT

FEMALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
UREA mg/dl		52.88	10.05	4	53.08	5.27	4	61.75	7.54	4	69.88*	5.77	4
CREATININE mg/dl		0.423	0.068	4	0.400	0.045	4	0.325*	0.017	4	0.318*	0.029	4
CHLORIDE mmol/l		99.03	1.65	4	100.80	2.94	4	99.95	0.91	4	101.43	1.41	4
CALCIUM mmol/l		2.605	0.047	4	2.613	0.075	4	2.675	0.087	4	2.585	0.065	4
SODIUM mmol/l		136.13	1.85	4	137.43	1.90	4	135.00	2.05	4	135.18	0.30	4
POTASSIUM mmol/l	($)	4.948	2.200	4	3.615	0.108	4	3.533	0.491	4	3.713	0.164	4

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett's test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 5 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: 36700EXT

FEMALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
TOTAL PROTEIN g/dl	6.28	0.41	4	6.23	0.24	4	5.90	0.20	4	5.33**	0.10	4
ALBUMIN g/dl	4.20	0.22	4	4.25	0.24	4	4.13	0.05	4	3.88	0.17	4
GLOBULIN g/dl	2.08	0.22	4	1.98	0.13	4	1.78*	0.15	4	1.45**	0.10	4
ALBUMIN/GLOBULIN RATIO	2.04	0.17	4	2.16	0.22	4	2.33	0.16	4	2.69**	0.31	4

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 6 - Terminal body weight (g) - Group mean data

STUDY NO.: 36700EXT

MALES

Controls from group(s): 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	292.20	291.85	284.98	246.43
Standard deviation	12.92	4.96	5.75	10.01
Group diff. at p < 0.05		17.10	17.10	17.10*
Group diff. at p < 0.01		22.82	22.82	22.82*

Analysis of variance: F ratio = 23.58 Df = 3/ 12 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 6 - Terminal body weight (g) - Group mean data

STUDY NO.: 36700EXT

FEMALES

Controls from group(s): 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	191.05	190.60	184.33	166.08
Standard deviation	11.27	10.92	15.34	12.23
Group diff. at p < 0.05		23.83	23.83	23.83*
Group diff. at p < 0.01		31.81	31.81	31.81

Analysis of variance: F ratio = 3.47 Df = 3/ 12 F probability = 0.050
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 7 - Absolute organ weights (g) - Group mean data

STUDY NO.: 36700EXT

MALES

Organ: Adrenals Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.0460	0.0440	0.0405	0.0445
Standard deviation	0.0029	0.0066	0.0026	0.0047
Group diff. at p < 0.05		0.0086	0.0086	0.0086
Group diff. at p < 0.01		0.0114	0.0114	0.0114

Analysis of variance: F ratio = 1.07 Df = 3/ 12 F probability = 0.401
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Brain Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	1.779	1.790	1.764	1.670
Standard deviation	0.056	0.050	0.032	0.011
Group diff. at p < 0.05		0.078	0.078	0.078*
Group diff. at p < 0.01		0.104	0.104	0.104*

Analysis of variance: F ratio = 7.23 Df = 3/ 12 F probability = 0.005
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 7 - Absolute organ weights (g) - Group mean data

STUDY NO.: 36700EXT

MALES

Organ: Epididymides Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.9028	0.9275	0.8283	0.8105
Standard deviation	0.0330	0.0419	0.0637	0.0606
Group diff. at p < 0.05		0.0975	0.0975	0.0975
Group diff. at p < 0.01		0.1302	0.1302	0.1302

Analysis of variance: F ratio = 4.86 Df = 3/ 12 F probability = 0.019
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Heart Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	1.094	1.018	1.012	0.850
Standard deviation	0.039	0.062	0.026	0.078
Group diff. at p < 0.05		0.104	0.104	0.104*
Group diff. at p < 0.01		0.139	0.139	0.139*

Analysis of variance: F ratio = 14.05 Df = 3/ 12 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 7 - Absolute organ weights (g) - Group mean data

STUDY NO.: 36700EXT

MALES

Organ: Kidneys Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	1.959	2.032	1.915	1.923
Standard deviation	0.098	0.148	0.060	0.182
Group diff. at p < 0.05		0.248	0.248	0.248
Group diff. at p < 0.01		0.332	0.332	0.332

Analysis of variance: F ratio = 0.67 Df = 3/ 12 F probability = 0.591
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Liver Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	8.375	11.991	13.709	12.759
Standard deviation	0.182	0.241	0.935	1.154
Group diff. at p < 0.05		0.481*	1.520*	1.865*
Group diff. at p < 0.01		0.892*	2.817*	3.457*

Analysis of variance: F ratio = 37.83 Df = 3/ 12 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 7 - Absolute organ weights (g) - Group mean data

STUDY NO.: 36700EXT

MALES

Organ: Spleen Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.7860	0.7458	0.6395	0.5200
Standard deviation	0.1095	0.0858	0.0664	0.0581
Group diff. at p < 0.05		0.1562	0.1562	0.1562*
Group diff. at p < 0.01		0.2086	0.2086	0.2086*

Analysis of variance: F ratio = 8.38 Df = 3/ 12 F probability = 0.003
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Testes Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	3.4658	3.4675	3.5170	3.4680
Standard deviation	0.1908	0.0501	0.0593	0.2382
Group diff. at p < 0.05		0.3147	0.3188	0.4869
Group diff. at p < 0.01		0.5835	0.5910	0.9027

Analysis of variance: F ratio = 0.10 Df = 3/ 12 F probability = 0.953
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 7 - Absolute organ weights (g) - Group mean data

STUDY NO.: 36700EXT

MALES

Organ: Thymus Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.6405	0.5223	0.5235	0.3673
Standard deviation	0.0634	0.0462	0.0667	0.0927
Group diff. at p < 0.05		0.1315	0.1315	0.1315*
Group diff. at p < 0.01		0.1755	0.1755	0.1755*

Analysis of variance: F ratio = 10.47 Df = 3/ 12 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 7 - Absolute organ weights (g) - Group mean data

STUDY NO.: 36700EXT

FEMALES

Organ: Adrenals Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.0600	0.0635	0.0553	0.0495
Standard deviation	0.0035	0.0019	0.0050	0.0070
Group diff. at p < 0.05		0.0090	0.0090	0.0090*
Group diff. at p < 0.01		0.0120	0.0120	0.0120

Analysis of variance: F ratio = 6.53 Df = 3/ 12 F probability = 0.007
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Brain Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	1.651	1.661	1.627	1.644
Standard deviation	0.047	0.048	0.075	0.083
Group diff. at p < 0.05		0.123	0.123	0.123
Group diff. at p < 0.01		0.165	0.165	0.165

Analysis of variance: F ratio = 0.20 Df = 3/ 12 F probability = 0.895
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 7 - Absolute organ weights (g) - Group mean data

STUDY NO.: 36700EXT

FEMALES

Organ: Heart Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.800	0.787	0.706	0.606
Standard deviation	0.049	0.053	0.094	0.020
Group diff. at p < 0.05		0.114	0.114	0.114*
Group diff. at p < 0.01		0.152	0.152	0.152*

Analysis of variance: F ratio = 8.86 Df = 3/ 12 F probability = 0.002
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Kidneys Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	1.368	1.351	1.377	1.208
Standard deviation	0.201	0.120	0.143	0.079
Group diff. at p < 0.05		0.271	0.271	0.271
Group diff. at p < 0.01		0.362	0.362	0.362

Analysis of variance: F ratio = 1.23 Df = 3/ 12 F probability = 0.341
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 7 - Absolute organ weights (g) - Group mean data

STUDY NO.: 36700EXT

FEMALES

Organ: Liver Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	5.808	6.389	6.552	7.403
Standard deviation	1.178	0.491	0.937	1.032
Group diff. at p < 0.05		1.794	1.794	1.794
Group diff. at p < 0.01		2.394	2.394	2.394

Analysis of variance: F ratio = 1.95 Df = 3/ 12 F probability = 0.175
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Spleen Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.5608	0.5660	0.4863	0.3688
Standard deviation	0.0219	0.0793	0.0669	0.0225
Group diff. at p < 0.05		0.1029	0.1029	0.1029*
Group diff. at p < 0.01		0.1373	0.1373	0.1373*

Analysis of variance: F ratio = 11.51 Df = 3/ 12 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 7 - Absolute organ weights (g) - Group mean data

STUDY NO.: 36700EXT

FEMALES

Organ: Thymus Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.4120	0.3653	0.4043	0.2878
Standard deviation	0.0291	0.0758	0.0875	0.0823
Group diff. at p < 0.05		0.1380	0.1380	0.1380
Group diff. at p < 0.01		0.1843	0.1843	0.1843

Analysis of variance: F ratio = 2.44 Df = 3/ 12 F probability = 0.114
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 8 - Relative organ weights° - Group mean data

STUDY NO.: 36700EXT

MALES

Organ: Adrenals Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.0157	0.0151	0.0142	0.0180
Standard deviation	0.0006	0.0024	0.0009	0.0014
Group diff. at p < 0.05		0.0028	0.0028	0.0028
Group diff. at p < 0.01		0.0038	0.0038	0.0038

Analysis of variance: F ratio = 4.80 Df = 3/ 12 F probability = 0.020
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Brain Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.610	0.614	0.619	0.678
Standard deviation	0.039	0.027	0.024	0.027
Group diff. at p < 0.05		0.057	0.057	0.057*
Group diff. at p < 0.01		0.076	0.076	0.076

Analysis of variance: F ratio = 4.67 Df = 3/ 12 F probability = 0.022
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 8 - Relative organ weights° - Group mean data

STUDY NO.: 36700EXT

MALES

Organ: Epididymides Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.3092	0.3179	0.2904	0.3298
Standard deviation	0.0123	0.0161	0.0169	0.0356
Group diff. at p < 0.05		0.0420	0.0420	0.0420
Group diff. at p < 0.01		0.0561	0.0561	0.0561

Analysis of variance: F ratio = 2.24 Df = 3/ 12 F probability = 0.135
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Heart Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.375	0.349	0.355	0.344
Standard deviation	0.017	0.019	0.007	0.018
Group diff. at p < 0.05		0.030	0.030	0.030*
Group diff. at p < 0.01		0.040	0.040	0.040

Analysis of variance: F ratio = 2.83 Df = 3/ 12 F probability = 0.083
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 8 - Relative organ weights° - Group mean data

STUDY NO.: 36700EXT

MALES

Organ: Kidneys Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.670	0.696	0.672	0.779
Standard deviation	0.019	0.049	0.020	0.044
Group diff. at p < 0.05		0.068	0.068	0.068*
Group diff. at p < 0.01		0.091	0.091	0.091*

Analysis of variance: F ratio = 8.18 Df = 3/ 12 F probability = 0.003
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Liver Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	2.869	4.108	4.808	5.171
Standard deviation	0.107	0.032	0.263	0.297
Group diff. at p < 0.05		0.178*	0.453*	0.504*
Group diff. at p < 0.01		0.331*	0.839*	0.934*

Analysis of variance: F ratio = 97.02 Df = 3/ 12 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 8 - Relative organ weights° - Group mean data

STUDY NO.: 36700EXT

MALES

Organ: Spleen Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.2687	0.2554	0.2241	0.2109
Standard deviation	0.0328	0.0275	0.0195	0.0201
Group diff. at p < 0.05		0.0485	0.0485	0.0485*
Group diff. at p < 0.01		0.0648	0.0648	0.0648

Analysis of variance: F ratio = 4.40 Df = 3/ 12 F probability = 0.026
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Testes Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	1.1875	1.1882	1.2344	1.4074
Standard deviation	0.0787	0.0171	0.0276	0.0797
Group diff. at p < 0.05		0.1106	0.1106	0.1106*
Group diff. at p < 0.01		0.1477	0.1477	0.1477*

Analysis of variance: F ratio = 12.82 Df = 3/ 12 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 8 - Relative organ weights° - Group mean data

STUDY NO.: 36700EXT

MALES

Organ: Thymus Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.2189	0.1789	0.1837	0.1483
Standard deviation	0.0150	0.0140	0.0225	0.0317
Group diff. at p < 0.05		0.0417	0.0417	0.0417*
Group diff. at p < 0.01		0.0557	0.0557	0.0557*

Analysis of variance: F ratio = 6.93 Df = 3/ 12 F probability = 0.006
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 8 - Relative organ weights° - Group mean data

STUDY NO.: 36700EXT

FEMALES

Organ: Adrenals Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.0315	0.0334	0.0302	0.0297
Standard deviation	0.0023	0.0021	0.0041	0.0023
Group diff. at p < 0.05		0.0051	0.0051	0.0051
Group diff. at p < 0.01		0.0068	0.0068	0.0068

Analysis of variance: F ratio = 1.50 Df = 3/ 12 F probability = 0.264
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Brain Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.865	0.873	0.888	0.995
Standard deviation	0.033	0.045	0.093	0.106
Group diff. at p < 0.05		0.144	0.144	0.144
Group diff. at p < 0.01		0.192	0.192	0.192

Analysis of variance: F ratio = 2.55 Df = 3/ 12 F probability = 0.104
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 8 - Relative organ weights° - Group mean data

STUDY NO.: 36700EXT

FEMALES

Organ: Heart Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.419	0.413	0.382	0.366
Standard deviation	0.012	0.022	0.024	0.027
Group diff. at p < 0.05		0.041	0.041	0.041*
Group diff. at p < 0.01		0.055	0.055	0.055

Analysis of variance: F ratio = 5.29 Df = 3/ 12 F probability = 0.015
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Kidneys Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.714	0.708	0.748	0.728
Standard deviation	0.072	0.027	0.056	0.015
Group diff. at p < 0.05		0.091	0.091	0.091
Group diff. at p < 0.01		0.122	0.122	0.122

Analysis of variance: F ratio = 0.54 Df = 3/ 12 F probability = 0.669
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 8 - Relative organ weights° - Group mean data

STUDY NO.: 36700EXT

FEMALES

Organ: Liver Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	3.029	3.349	3.547	4.458
Standard deviation	0.499	0.067	0.340	0.539
Group diff. at p < 0.05		0.803	0.963	1.171*
Group diff. at p < 0.01		1.488	1.785	2.171

Analysis of variance: F ratio = 9.13 Df = 3/ 12 F probability = 0.002
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Spleen Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.2941	0.2964	0.2630	0.2222
Standard deviation	0.0180	0.0331	0.0183	0.0039
Group diff. at p < 0.05		0.0601	0.0410	0.0294*
Group diff. at p < 0.01		0.1114	0.0760	0.0545*

Analysis of variance: F ratio = 10.88 Df = 3/ 12 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 8 - Relative organ weights° - Group mean data

STUDY NO.: 36700EXT

FEMALES

Organ: Thymus Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	4	4	4	4
Mean	0.2156	0.1913	0.2177	0.1714
Standard deviation	0.0053	0.0321	0.0289	0.0360
Group diff. at p < 0.05		0.0536	0.0536	0.0536
Group diff. at p < 0.01		0.0715	0.0715	0.0715

Analysis of variance: F ratio = 2.41 Df = 3/ 12 F probability = 0.117
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

TABLE 9 - Macroscopic observations - Group incidence

STUDY NO.: 36700EXT

	-- Males --				-- Females --			
Group:	1	2	3	4	1	2	3	4
Number in group:	4	4	4	4	4	4	4	4
Adrenals								
Abnormal size	0	0	1	0	0	0	0	0
Cervical nodes								
Abnormal size	0	0	1	0	0	0	0	0
Kidneys								
Abnormal area(s)	0	0	0	1	0	0	0	0
Abnormal size	0	0	1	0	0	0	0	0
Liver								
Abnormal colour	0	0	0	4	1	1	1	4
Abnormal shape	0	0	0	1	0	0	0	0
Lungs								
Abnormal colour	0	0	0	1	0	0	1	2
Ovaries								
Cyst(s)					1	0	0	0
Pituitary								
Abnormal colour	0	0	0	0	0	0	0	3
Stomach								
Abnormal area(s)	0	0	0	2	0	0	0	1
Abnormal colour	0	0	0	0	0	0	0	1
Abnormal contents	0	0	0	1	0	1	0	0
Thymus								
Abnormal colour	0	0	1	0	0	0	0	0
Uterus								
Abnormal size					1	0	0	0
Abnormal contents					1	0	0	0
Whole animal								
No abnormalities detected	4	4	1	0	2	2	2	0

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 1 - Clinical signs - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group: 1 Dosage: 0.0 mg/kg/day	Week of Study First Seen	Week of Study Last Seen	Weeks Present
36700002	No significant signs	1	2	2
36700004	No significant signs	2	2	1
	Staining, Both eyelids	1	1	1
	Hairloss, Head	1	1	1
36700006	No significant signs	1	2	2
36700008	No significant signs	1	2	2

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 1 - Clinical signs - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group: 2 Dosage: 2.5 mg/kg/day	Week of Study First Seen	Week of Study Last Seen	Weeks Present
36700010	No significant signs	1	2	2
36700012	No significant signs	1	2	2
36700014	No significant signs	1	2	2
36700016	No significant signs	1	2	2

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 1 - Clinical signs - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group: 3 Dosage: 5.0 mg/kg/day	Week of Study First Seen	Week of Study Last Seen	Weeks Present
36700018	No significant signs	1	2	2
36700020	No significant signs	1	2	2
36700022	No significant signs	1	2	2
36700024	No significant signs	1	2	2

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 1 - Clinical signs - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group: 4 Dosage: 10.0 mg/kg/day	Week of Study First Seen	Week of Study Last Seen	Weeks Present
36700026	No significant signs	1	2	2
36700028	No significant signs	1	2	2
36700030	No significant signs	1	2	2
36700032	No significant signs	1	2	2

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 1 - Clinical signs - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group: 1 Dosage: 0.0 mg/kg/day	Week of Study First Seen	Week of Study Last Seen	Weeks Present
36700001	No significant signs	1	2	2
36700003	No significant signs	1	2	2
36700005	No significant signs	1	2	2
36700007	No significant signs	1	2	2

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 1 - Clinical signs - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group: 2 Dosage: 2.5 mg/kg/day	Week of Study First Seen	Week of Study Last Seen	Weeks Present
36700009	No significant signs	1	2	2
36700011	No significant signs	1	2	2
36700013	No significant signs	1	2	2
36700015	No significant signs	1	2	2

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 1 - Clinical signs - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group: 3 Dosage: 5.0 mg/kg/day	Week of Study First Seen	Week of Study Last Seen	Weeks Present
36700017	No significant signs	1	2	2
36700019	No significant signs	1	2	2
36700021	No significant signs	1	2	2
36700023	No significant signs	1	2	2

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 1 - Clinical signs - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group: 4 Dosage: 10.0 mg/kg/day	Week of Study First Seen	Week of Study Last Seen	Weeks Present
36700025	No significant signs	1	2	2
36700027	No significant signs	1	2	2
36700029	No significant signs	1	2	2
36700031	No significant signs	1	2	2

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 2 - Body weight (g) - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group		Day of Phase 1!	Day of Phase 1"	Day of Phase 8
36700002	1		262.1	292.5	283.6
36700004			259.3	296.3	287.2
36700006			273.6	310.0	311.8
36700008			265.4	301.5	292.8
		(n)	4	4	4
		Mean	265.10	300.05	293.84
		SD	6.16	7.57	12.53
36700010	2		258.9	294.5	295.9
36700012			263.3	292.0	288.7
36700014			267.0	304.0	294.5
36700016			261.4	298.3	301.0
		(n)	4	4	4
		Mean	262.65	297.18	295.02
		SD	3.42	5.22	5.08
36700018	3		265.5	304.4	293.1
36700020			260.6	304.5	289.4
36700022			265.9	303.8	285.1
36700024			259.2	294.5	280.9
		(n)	4	4	4
		Mean	262.81	301.79	287.12
		SD	3.38	4.86	5.28
36700026	4		260.6	298.3	242.5
36700028			257.5	285.2	236.5
36700030			265.5	301.2	253.7
36700032			263.9	301.3	261.6
		(n)	4	4	4
		Mean	261.90	296.49	248.59
		SD	3.56	7.67	11.21

Note: ! = Pretest phase; " = Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 2 - Body weight (g) - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group		Day of Phase 1!	Day of Phase 1"	Day of Phase 8
36700001	1		192.1	212.0	204.2
36700003			183.2	196.7	185.0
36700005			200.0	213.8	202.4
36700007			184.2	192.4	182.6
		(n)	4	4	4
		Mean	189.85	203.73	193.53
		SD	7.83	10.75	11.33
36700009	2		203.5	208.3	204.8
36700011			189.7	191.8	203.6
36700013			182.6	191.3	180.4
36700015			184.4	192.5	189.2
		(n)	4	4	4
		Mean	190.02	195.95	194.49
		SD	9.44	8.24	11.74
36700017	3		198.0	226.2	204.9
36700019			183.2	182.5	166.2
36700021			192.1	191.7	180.9
36700023			182.6	192.8	186.5
		(n)	4	4	4
		Mean	188.98	198.31	184.63
		SD	7.41	19.14	15.98
36700025	4		185.8	200.0	166.7
36700027			194.1	204.3	186.4
36700029			189.7	188.3	159.1
36700031			177.7	187.7	162.9
		(n)	4	4	4
		Mean	186.84	195.07	168.75
		SD	6.96	8.35	12.13

Note: ! = Pretest phase; " = Dosing phase

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 3 - Food consumption° (g/animal/day) - Cage data

STUDY NO.: 36700EXT

MALES

Cage	Group	Day of Phase 1	7
1	1	25.9	25.6
2	2	25.5	26.0
3	3	27.0	26.1
4	4	26.9	20.0

Note: Data for Dosing phase
° = food consumed over the previous period

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 3 – Food consumption° (g/animal/day) – Cage data

STUDY NO.: 36700EXT

FEMALES

Cage	Group	Day of Phase 1	Day of Phase 7
5	1	18.6	19.7
6	2	17.0	18.9
7	3	18.6	18.6
8	4	16.4	15.7

Note: Data for Dosing phase
° = food consumed over the previous period

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 4 - Haematology - At the end of treatment - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group		RBC 10^12/l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
36700002	1		7.97	15.6	45.5	57.1	19.6	34.3
36700004	1		7.72	15.2	43.8	56.7	19.6	34.6
36700006	1		7.80	15.2	44.6	57.2	19.5	34.2
36700008	1		7.51	15.2	44.0	58.6	20.3	34.6
		Mean	7.750	15.30	44.48	57.40	19.75	34.43
		SD	0.191	0.20	0.76	0.83	0.37	0.21
36700010	2		7.64	15.2	44.4	58.1	19.9	34.3
36700012	2		7.62	15.6	45.4	59.6	20.4	34.3
36700014	2		7.76	15.7	45.9	59.1	20.2	34.2
36700016	2		7.57	14.9	43.8	57.8	19.7	34.0
		Mean	7.648	15.35	44.88	58.65	20.05	34.20
		SD	0.081	0.37	0.95	0.84	0.31	0.14
36700020	3		7.96	15.9	46.6	58.6	20.0	34.2
36700022	3		8.28	16.6	48.0	58.0	20.0	34.5
36700024	3		8.30	16.3	48.2	58.1	19.6	33.7
		Mean	8.180	16.27	47.60	58.23	19.87	34.13
		SD	0.191	0.35	0.87	0.32	0.23	0.40
36700026	4		9.28	18.2	53.6	57.7	19.6	33.9
36700030	4		9.22	17.9	53.5	58.0	19.4	33.5
36700032	4		9.01	17.4	52.0	57.8	19.3	33.4
		Mean	9.170	17.83	53.03	57.83	19.43	33.60
		SD	0.142	0.40	0.90	0.15	0.15	0.26

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 4 - Haematology - At the end of treatment - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group		PLT 10^9/l	PT sec
36700002	1		900	16.1
36700004	1		880	17.5
36700006	1		1082	15.4
36700008	1		900	16.1
		Mean	940.5	16.28
		SD	94.8	0.88
36700010	2		936	14.6
36700012	2		908	16.5
36700014	2		845	17.2
36700016	2		984	15.9
		Mean	918.3	16.05
		SD	58.0	1.10
36700018	3		NT	16.0
36700020	3		586	15.4
36700022	3		919	18.1
36700024	3		806	18.1
		Mean	770.3	16.90
		SD	169.3	1.41
36700026	4		945	21.9
36700028	4		NT	NT
36700030	4		766	NT
36700032	4		855	20.8
		Mean	855.3	21.35
		SD	89.5	0.78

NT = NOT TAKEN

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 4 - Haematology - At the end of treatment - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group		WBC 10^9/l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
36700002	1		10.51	7.2	87.0	2.8	0.9	0.2	2.0
36700004	1		9.31	8.8	85.6	2.9	0.8	0.2	1.8
36700006	1		12.32	5.0	87.8	3.9	0.6	0.2	2.5
36700008	1		9.76	9.2	83.6	3.3	1.7	0.2	1.9
		Mean	10.475	7.55	86.00	3.23	1.00	0.20	2.05
		SD	1.326	1.91	1.84	0.50	0.48	0.00	0.31
36700010	2		9.34	7.9	85.9	2.6	1.2	0.3	2.2
36700012	2		8.50	15.7	75.4	4.8	1.0	0.3	2.8
36700014	2		11.82	5.5	87.4	3.1	1.0	0.3	2.7
36700016	2		5.87	13.0	79.0	4.7	1.1	0.1	2.0
		Mean	8.883	10.53	81.93	3.80	1.08	0.25	2.43
		SD	2.454	4.66	5.68	1.12	0.10	0.10	0.39
36700020	3		9.48	14.2	75.6	5.5	1.8	0.1	2.7
36700022	3		8.57	9.0	84.2	3.9	0.8	0.2	1.9
36700024	3		7.65	12.0	81.3	3.3	1.4	0.2	1.8
		Mean	8.567	11.73	80.37	4.23	1.33	0.17	2.13
		SD	0.915	2.61	4.38	1.14	0.50	0.06	0.49
36700026	4		7.78	16.3	72.7	6.8	0.5	0.2	3.5
36700030	4		10.02	18.6	69.5	7.5	0.7	0.2	3.4
36700032	4		9.77	12.4	79.3	5.1	0.5	0.1	2.4
		Mean	9.190	15.77	73.83	6.47	0.57	0.17	3.10
		SD	1.227	3.13	5.00	1.23	0.12	0.06	0.61

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 4 - Haematology - At the end of treatment - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group		RBC 10^12/l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
36700001	1		7.45	14.7	42.3	56.8	19.8	34.8
36700003	1		7.87	15.6	45.4	57.6	19.8	34.3
36700005	1		8.36	16.2	50.0	59.8	19.4	32.4
36700007	1		7.60	14.8	42.9	56.5	19.5	34.4
		Mean	7.820	15.33	45.15	57.68	19.63	33.98
		SD	0.400	0.71	3.50	1.49	0.21	1.07
36700009	2		7.50	14.6	41.2	55.0	19.5	35.4
36700011	2		7.38	14.5	41.4	56.0	19.7	35.1
36700013	2		7.68	15.8	42.1	54.9	20.6	37.6
36700015	2		7.26	14.9	40.9	56.4	20.6	36.5
		Mean	7.455	14.95	41.40	55.58	20.10	36.15
		SD	0.179	0.59	0.51	0.74	0.58	1.14
36700017	3		7.99	15.8	45.2	56.6	19.8	35.0
36700019	3		8.00	15.9	45.5	56.9	19.9	35.1
36700021	3		7.90	15.9	44.5	56.4	20.1	35.7
36700023	3		7.26	13.9	39.5	54.4	19.1	35.1
		Mean	7.788	15.38	43.68	56.08	19.73	35.23
		SD	0.355	0.98	2.81	1.14	0.43	0.32
36700025	4		8.14	16.4	46.9	57.6	20.1	34.9
36700027	4		8.31	17.5	48.2	58.0	21.0	36.3
36700029	4		8.93	17.4	49.1	55.0	19.5	35.5
36700031	4		8.79	17.2	48.6	55.3	19.6	35.5
		Mean	8.543	17.13	48.20	56.48	20.05	35.55
		SD	0.377	0.50	0.94	1.54	0.69	0.57

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 4 - Haematology - At the end of treatment - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group		PLT 10^9/l	PT sec
36700001	1		993	18.6
36700003	1		1018	NT
36700005	1		794	18.2
36700007	1		1043	17.9
		Mean	962.0	18.23
		SD	113.8	0.35
36700009	2		1039	16.3
36700011	2		988	16.5
36700013	2		1193	16.4
36700015	2		891	16.1
		Mean	1027.8	16.33
		SD	126.1	0.17
36700017	3		1019	16.8
36700019	3		981	19.3
36700021	3		1027	16.3
36700023	3		NT	17.9
		Mean	1009.0	17.58
		SD	24.6	1.33
36700025	4		1048	19.1
36700027	4		1118	19.1
36700029	4		1004	17.9
36700031	4		1064	18.6
		Mean	1058.5	18.68
		SD	47.1	0.57

NT = NOT TAKEN

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 4 - Haematology - At the end of treatment - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group		WBC 10^9/l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
36700001	1		7.05	10.9	82.7	3.0	1.4	0.2	1.8
36700003	1		10.75	6.4	87.4	2.9	1.1	0.3	1.9
36700005	1		6.04	10.1	81.8	3.6	1.8	0.2	2.5
36700007	1		8.32	7.5	84.7	3.7	1.2	0.2	2.7
		Mean	8.040	8.73	84.15	3.30	1.38	0.23	2.23
		SD	2.033	2.12	2.48	0.41	0.31	0.05	0.44
36700009	2		8.04	7.8	87.2	2.3	1.0	0.1	1.6
36700011	2		4.79	10.7	83.3	2.6	1.3	0.1	2.0
36700013	2		8.32	11.1	82.7	2.5	1.7	0.6	1.4
36700015	2		5.65	12.5	82.7	2.2	1.4	0.0	1.1
		Mean	6.700	10.53	83.98	2.40	1.35	0.20	1.53
		SD	1.748	1.97	2.17	0.18	0.29	0.27	0.38
36700017	3		10.65	4.7	88.4	3.5	1.0	0.2	2.3
36700019	3		7.41	2.4	93.1	1.9	0.9	0.3	1.3
36700021	3		9.22	3.7	90.6	2.7	1.0	0.2	1.8
36700023	3		5.18	7.5	86.5	2.3	2.6	0.1	1.0
		Mean	8.115	4.58	89.65	2.60	1.38	0.20	1.60
		SD	2.364	2.17	2.85	0.68	0.82	0.08	0.57
36700025	4		5.90	7.9	85.2	3.7	0.8	0.2	2.1
36700027	4		7.63	3.8	90.9	3.2	0.5	0.3	1.3
36700029	4		6.20	5.6	89.0	3.0	0.7	0.1	1.6
36700031	4		3.74	2.8	90.4	4.5	0.9	0.1	1.3
		Mean	5.868	5.03	88.88	3.60	0.73	0.18	1.58
		SD	1.607	2.24	2.58	0.67	0.17	0.10	0.38

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 5 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group		AP U/l	ALT U/l	AST U/l	BILT mg/dl	CHOL mg/dl	GLU mg/dl
36700002	1		305.3	33.9	62.4	0.06	82.7	173.8
36700004	1		332.1	39.0	72.8	0.05	76.4	117.5
36700006	1		384.4	31.4	66.6	0.04	74.9	120.6
36700008	1		337.5	43.8	76.7	0.04	101.7	112.4
		Mean	339.83	37.03	69.63	0.048	83.93	131.08
		SD	32.88	5.51	6.36	0.010	12.32	28.68
36700010	2		338.2	43.7	82.5	0.01	73.2	88.4
36700012	2		300.5	41.9	77.4	0.15	69.9	103.1
36700014	2		251.1	33.1	64.1	0.06	57.8	116.0
36700016	2		353.4	40.8	75.7	0.03	73.8	100.5
		Mean	310.80	39.88	74.93	0.063	68.68	102.00
		SD	45.59	4.67	7.77	0.062	7.45	11.32
36700018	3		398.2	39.3	73.4	0.02	55.1	119.0
36700020	3		372.1	50.8	91.8	0.03	75.0	114.8
36700022	3		313.4	44.9	76.5	0.07	49.1	95.6
36700024	3		434.8	40.9	78.1	0.03	57.6	121.7
		Mean	379.63	43.98	79.95	0.038	59.20	112.78
		SD	51.09	5.12	8.14	0.022	11.12	11.80
36700026	4		288.8	92.4	136.6	0.32	41.2	118.5
36700028	4		298.6	78.0	101.4	0.36	54.1	128.6
36700030	4		293.7	111.9	126.5	0.45	51.2	118.8
36700032	4		286.4	99.5	120.4	0.38	58.1	118.6
		Mean	291.88	95.45	121.23	0.378	51.15	121.13
		SD	5.42	14.15	14.81	0.054	7.21	4.98

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 5 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group		UREA mg/dl	CREA mg/dl	CL mmol/l	CA mmol/l	Na mmol/l	K mmol/l
36700002	1		50.6	0.36	100.0	2.62	137.6	4.10
36700004	1		47.2	0.39	99.2	2.72	139.0	3.89
36700006	1		38.3	0.36	98.6	2.65	138.3	3.86
36700008	1		34.5	0.41	100.8	2.61	139.4	3.79
		Mean	42.65	0.380	99.65	2.650	138.58	3.910
		SD	7.51	0.024	0.96	0.050	0.79	0.133
36700010	2		52.7	0.44	100.4	2.50	138.8	4.35
36700012	2		39.7	0.34	101.7	2.74	141.1	4.06
36700014	2		43.5	0.36	101.5	2.55	139.4	3.72
36700016	2		42.9	0.40	101.0	2.67	139.4	3.95
		Mean	44.70	0.385	101.15	2.615	139.68	4.020
		SD	5.59	0.044	0.58	0.110	0.99	0.262
36700018	3		57.7	0.32	102.4	2.55	136.7	3.78
36700020	3		83.7	0.47	97.8	2.64	137.2	4.00
36700022	3		63.6	0.36	100.0	2.72	138.4	4.18
36700024	3		56.0	0.37	99.9	2.53	138.7	3.65
		Mean	65.25	0.380	100.03	2.610	137.75	3.903
		SD	12.72	0.064	1.88	0.088	0.95	0.235
36700026	4		63.3	0.33	102.1	2.33	134.5	4.23
36700028	4		71.0	0.33	100.9	2.46	135.4	4.14
36700030	4		83.4	0.40	101.4	2.50	129.8	4.21
36700032	4		68.1	0.27	104.1	2.40	133.5	4.31
		Mean	71.45	0.333	102.13	2.423	133.30	4.223
		SD	8.58	0.053	1.41	0.074	2.46	0.070

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 5 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group		PROT g/dl	ALB g/dl	GLO g/dl	AGR
36700002	1		6.1	3.8	2.3	1.7
36700004	1		6.1	3.8	2.3	1.7
36700006	1		6.3	4.0	2.3	1.7
36700008	1		6.3	4.0	2.3	1.7
		Mean	6.20	3.90	2.30	1.70
		SD	0.12	0.12	0.00	0.05
36700010	2		6.5	4.1	2.4	1.7
36700012	2		6.3	4.1	2.2	1.9
36700014	2		6.0	4.0	2.0	2.0
36700016	2		6.3	4.2	2.1	2.0
		Mean	6.28	4.10	2.18	1.89
		SD	0.21	0.08	0.17	0.14
36700018	3		5.7	3.9	1.8	2.2
36700020	3		6.3	4.3	2.0	2.2
36700022	3		6.0	4.0	2.0	2.0
36700024	3		6.1	4.2	1.9	2.2
		Mean	6.03	4.10	1.93	2.13
		SD	0.25	0.18	0.10	0.09
36700026	4		4.6	2.5	2.1	1.2
36700028	4		4.8	3.5	1.3	2.7
36700030	4		5.3	3.4	1.9	1.8
36700032	4		4.9	3.7	1.2	3.1
		Mean	4.90	3.28	1.63	2.19
		SD	0.29	0.53	0.44	0.86

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 5 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group		AP U/l	ALT U/l	AST U/l	BILT mg/dl	CHOL mg/dl	GLU mg/dl
36700001	1		233.9	33.9	86.2	0.05	88.3	103.0
36700003	1		179.8	32.2	80.5	0.04	72.4	100.1
36700005	1		238.7	41.1	97.0	0.04	99.9	85.6
36700007	1		225.3	32.6	76.3	0.06	77.2	123.9
		Mean	219.43	34.95	85.00	0.048	84.45	103.15
		SD	26.99	4.16	8.97	0.010	12.26	15.79
36700009	2		212.0	22.3	65.1	0.05	85.9	121.5
36700011	2		262.2	30.2	77.1	0.08	68.6	112.8
36700013	2		229.6	30.8	73.6	0.05	90.2	75.1
36700015	2		197.9	28.3	76.3	0.14	59.1	68.3
		Mean	225.43	27.90	73.03	0.080	75.95	94.43
		SD	27.73	3.88	5.49	0.042	14.61	26.62
36700017	3		195.3	24.6	75.0	0.07	57.1	113.6
36700019	3		207.5	30.2	78.8	0.08	32.2	119.5
36700021	3		180.7	34.0	79.7	0.08	50.1	125.0
36700023	3		238.3	35.0	79.2	0.13	42.5	108.8
		Mean	205.45	30.95	78.18	0.090	45.48	116.73
		SD	24.49	4.71	2.15	0.027	10.67	7.04
36700025	4		190.6	31.3	81.4	0.23	35.7	114.4
36700027	4		174.9	18.7	75.2	0.18	52.2	123.3
36700029	4		160.7	51.0	109.4	0.27	42.9	110.5
36700031	4		224.0	35.2	101.4	0.22	51.8	126.8
		Mean	187.55	34.05	91.85	0.225	45.65	118.75
		SD	27.20	13.31	16.18	0.037	7.90	7.58

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 5 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group		UREA mg/dl	CREA mg/dl	CL mmol/l	CA mmol/l	Na mmol/l	K mmol/l
36700001	1		41.4	0.34	98.2	2.56	134.8	4.05
36700003	1		61.6	0.45	100.5	2.60	138.3	3.74
36700005	1		47.5	0.50	97.1	2.67	134.4	8.24
36700007	1		61.0	0.40	100.3	2.59	137.0	3.76
		Mean	52.88	0.423	99.03	2.605	136.13	4.948
		SD	10.05	0.068	1.65	0.047	1.85	2.200
36700009	2		58.2	0.44	104.5	2.62	139.6	3.76
36700011	2		45.7	0.34	101.2	2.53	138.3	3.61
36700013	2		54.0	0.43	97.4	2.71	135.3	3.59
36700015	2		54.4	0.39	100.1	2.59	136.5	3.50
		Mean	53.08	0.400	100.80	2.613	137.43	3.615
		SD	5.27	0.045	2.94	0.075	1.90	0.108
36700017	3		53.2	0.32	98.8	2.69	134.4	3.86
36700019	3		70.7	0.32	100.2	2.59	134.2	3.19
36700021	3		64.5	0.31	101.0	2.79	138.0	3.04
36700023	3		58.6	0.35	99.8	2.63	133.4	4.04
		Mean	61.75	0.325	99.95	2.675	135.00	3.533
		SD	7.54	0.017	0.91	0.087	2.05	0.491
36700025	4		69.0	0.28	103.2	2.57	134.9	3.50
36700027	4		71.4	0.32	100.1	2.63	135.1	3.69
36700029	4		76.5	0.32	101.9	2.64	135.6	3.89
36700031	4		62.6	0.35	100.5	2.50	135.1	3.77
		Mean	69.88	0.318	101.43	2.585	135.18	3.713
		SD	5.77	0.029	1.41	0.065	0.30	0.164

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 5 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group		PROT g/dl	ALB g/dl	GLO g/dl	AGR
36700001	1		6.4	4.2	2.2	1.9
36700003	1		5.9	4.1	1.8	2.3
36700005	1		6.8	4.5	2.3	2.0
36700007	1		6.0	4.0	2.0	2.0
		Mean	6.28	4.20	2.08	2.04
		SD	0.41	0.22	0.22	0.17
36700009	2		6.4	4.4	2.0	2.2
36700011	2		6.2	4.4	1.8	2.4
36700013	2		6.4	4.3	2.1	2.0
36700015	2		5.9	3.9	2.0	2.0
		Mean	6.23	4.25	1.98	2.16
		SD	0.24	0.24	0.13	0.22
36700017	3		6.2	4.2	2.0	2.1
36700019	3		5.8	4.1	1.7	2.4
36700021	3		5.8	4.1	1.7	2.4
36700023	3		5.8	4.1	1.7	2.4
		Mean	5.90	4.13	1.78	2.33
		SD	0.20	0.05	0.15	0.16
36700025	4		5.2	3.7	1.5	2.5
36700027	4		5.4	4.1	1.3	3.2
36700029	4		5.4	3.9	1.5	2.6
36700031	4		5.3	3.8	1.5	2.5
		Mean	5.33	3.88	1.45	2.69
		SD	0.10	0.17	0.10	0.31

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 6 - Absolute organ weights (g) - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
36700002	1	281.1	0.043	1.76	0.907	1.12	1.95	8.48
36700004	1	284.3	0.044	1.86	0.896	1.06	1.87	8.14
36700006	1	309.9	0.048	1.75	0.944	1.13	2.10	8.55
36700008	1	293.5	0.049	1.74	0.864	1.06	1.92	8.33
	Mean	292.20	0.0460	1.779	0.9028	1.094	1.959	8.375
	SD	12.92	0.0029	0.056	0.0330	0.039	0.098	0.182
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36700010	2	292.3	0.043	1.77	0.947	0.95	1.90	12.15
36700012	2	284.7	0.049	1.86	0.934	1.00	2.02	11.63
36700014	2	295.0	0.049	1.79	0.867	1.10	2.24	12.08
36700016	2	295.4	0.035	1.75	0.962	1.02	1.97	12.11
	Mean	291.85	0.0440	1.790	0.9275	1.018	2.032	11.991
	SD	4.96	0.0066	0.050	0.0419	0.062	0.148	0.241
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36700018	3	289.6	0.039	1.73	0.880	1.03	1.99	13.60
36700020	3	288.9	0.041	1.75	0.884	1.04	1.85	15.01
36700022	3	284.3	0.044	1.78	0.792	0.98	1.93	13.42
36700024	3	277.1	0.038	1.80	0.757	1.00	1.88	12.80
	Mean	284.98	0.0405	1.764	0.8283	1.012	1.915	13.709
	SD	5.75	0.0026	0.032	0.0637	0.026	0.060	0.935
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36700026	4	241.4	0.046	1.65	0.767	0.82	1.78	11.73
36700028	4	235.4	0.038	1.68	0.900	0.76	1.76	11.80
36700030	4	250.9	0.045	1.67	0.792	0.88	2.03	13.87
36700032	4	258.0	0.049	1.68	0.783	0.94	2.12	13.64
	Mean	246.43	0.0445	1.670	0.8105	0.850	1.923	12.759
	SD	10.01	0.0047	0.011	0.0606	0.078	0.182	1.154
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 6 - Absolute organ weights (g) - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus
36700002	1	281.1	0.685	3.643	0.632
36700004	1	284.3	0.718	3.195	0.559
36700006	1	309.9	0.812	3.519	0.711
36700008	1	293.5	0.929	3.506	0.660
	Mean	292.20	0.7860	3.4658	0.6405
	SD	12.92	0.1095	0.1908	0.0634
	(n)	(4)	(4)	(4)	(4)
36700010	2	292.3	0.694	3.527	0.476
36700012	2	284.7	0.704	3.410	0.492
36700014	2	295.0	0.874	3.448	0.575
36700016	2	295.4	0.711	3.485	0.546
	Mean	291.85	0.7458	3.4675	0.5223
	SD	4.96	0.0858	0.0501	0.0462
	(n)	(4)	(4)	(4)	(4)
36700018	3	289.6	0.673	3.582	0.618
36700020	3	288.9	0.676	3.523	0.475
36700022	3	284.3	0.669	3.438	0.478
36700024	3	277.1	0.540	3.525	0.523
	Mean	284.98	0.6395	3.5170	0.5235
	SD	5.75	0.0664	0.0593	0.0667
	(n)	(4)	(4)	(4)	(4)
36700026	4	241.4	0.481	3.214	0.326
36700028	4	235.4	0.523	3.500	0.304
36700030	4	250.9	0.475	3.379	0.334
36700032	4	258.0	0.601	3.779	0.505
	Mean	246.43	0.5200	3.4680	0.3673
	SD	10.01	0.0581	0.2382	0.0927
	(n)	(4)	(4)	(4)	(4)

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 6 - Absolute organ weights (g) - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Spleen
36700001	1	202.4	0.063	1.67	0.82	1.43	5.70	0.588
36700003	1	183.7	0.063	1.65	0.78	1.23	5.08	0.542
36700005	1	198.8	0.057	1.70	0.86	1.63	7.51	0.544
36700007	1	179.3	0.057	1.59	0.75	1.19	4.95	0.569
	Mean	191.05	0.0600	1.651	0.800	1.368	5.808	0.5608
	SD	11.27	0.0035	0.047	0.049	0.201	1.178	0.0219
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36700009	2	201.0	0.064	1.66	0.86	1.46	6.85	0.633
36700011	2	199.0	0.066	1.71	0.76	1.45	6.77	0.588
36700013	2	180.2	0.062	1.68	0.74	1.28	5.90	0.451
36700015	2	182.2	0.062	1.60	0.78	1.22	6.03	0.592
	Mean	190.60	0.0635	1.661	0.787	1.351	6.389	0.5660
	SD	10.92	0.0019	0.048	0.053	0.120	0.491	0.0793
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36700017	3	204.0	0.056	1.61	0.84	1.44	7.36	0.556
36700019	3	166.7	0.059	1.65	0.64	1.21	5.38	0.396
36700021	3	181.5	0.048	1.71	0.68	1.33	7.26	0.507
36700023	3	185.1	0.058	1.53	0.66	1.54	6.22	0.486
	Mean	184.33	0.0553	1.627	0.706	1.377	6.552	0.4863
	SD	15.34	0.0050	0.075	0.094	0.143	0.937	0.0669
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36700025	4	165.8	0.045	1.59	0.58	1.20	6.80	0.370
36700027	4	183.4	0.060	1.59	0.62	1.32	8.49	0.400
36700029	4	156.3	0.046	1.63	0.62	1.17	8.03	0.355
36700031	4	158.8	0.047	1.76	0.60	1.14	6.28	0.350
	Mean	166.08	0.0495	1.644	0.606	1.208	7.403	0.3688
	SD	12.23	0.0070	0.083	0.020	0.079	1.032	0.0225
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 6 - Absolute organ weights (g) - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group	Terminal B.W. (g)	Thymus
36700001	1	202.4	0.448
36700003	1	183.7	0.402
36700005	1	198.8	0.419
36700007	1	179.3	0.379
	Mean	191.05	0.4120
	SD	11.27	0.0291
	(n)	(4)	(4)
36700009	2	201.0	0.472
36700011	2	199.0	0.353
36700013	2	180.2	0.288
36700015	2	182.2	0.352
	Mean	190.60	0.3663
	SD	10.92	0.0768
	(n)	(4)	(4)
36700017	3	204.0	0.529
36700019	3	166.7	0.325
36700021	3	181.5	0.389
36700023	3	185.1	0.374
	Mean	184.33	0.4043
	SD	15.34	0.0875
	(n)	(4)	(4)
36700025	4	165.8	0.295
36700027	4	183.4	0.400
36700029	4	156.3	0.244
36700031	4	158.8	0.212
	Mean	166.08	0.2878
	SD	12.23	0.0823
	(n)	(4)	(4)

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 7 - Relative organ weights° - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
36700002	1	281.1	0.015	0.63	0.323	0.40	0.69	3.02
36700004	1	284.3	0.015	0.65	0.315	0.37	0.66	2.86
36700006	1	309.9	0.015	0.57	0.305	0.37	0.68	2.76
36700008	1	293.5	0.017	0.59	0.294	0.36	0.65	2.84
	Mean	292.20	0.0157	0.610	0.3092	0.375	0.670	2.869
	SD	12.92	0.0006	0.039	0.0123	0.017	0.019	0.107
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36700010	2	292.3	0.015	0.60	0.324	0.33	0.65	4.16
36700012	2	284.7	0.017	0.65	0.328	0.35	0.71	4.09
36700014	2	295.0	0.017	0.61	0.294	0.37	0.76	4.09
36700016	2	295.4	0.012	0.59	0.326	0.35	0.67	4.10
	Mean	291.85	0.0151	0.614	0.3179	0.349	0.696	4.108
	SD	4.96	0.0024	0.027	0.0161	0.019	0.049	0.032
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36700018	3	289.6	0.013	0.60	0.304	0.35	0.69	4.70
36700020	3	288.9	0.014	0.61	0.306	0.36	0.64	5.20
36700022	3	284.3	0.015	0.63	0.279	0.35	0.68	4.72
36700024	3	277.1	0.014	0.65	0.273	0.36	0.68	4.62
	Mean	284.98	0.0142	0.619	0.2904	0.355	0.672	4.808
	SD	5.75	0.0009	0.024	0.0169	0.007	0.020	0.263
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36700026	4	241.4	0.019	0.69	0.318	0.34	0.74	4.86
36700028	4	235.4	0.016	0.71	0.382	0.32	0.75	5.01
36700030	4	250.9	0.018	0.67	0.316	0.35	0.81	5.53
36700032	4	258.0	0.019	0.65	0.303	0.36	0.82	5.29
	Mean	246.43	0.0180	0.678	0.3298	0.344	0.779	5.171
	SD	10.01	0.0014	0.027	0.0356	0.018	0.044	0.297
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)

° = expressed as % organ to body weight ratio

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 7 - Relative organ weights° - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus
36700002	1	281.1	0.244	1.296	0.225
36700004	1	284.3	0.253	1.124	0.197
36700006	1	309.9	0.262	1.136	0.229
36700008	1	293.5	0.317	1.195	0.225
	Mean	292.20	0.2687	1.1875	0.2189
	SD	12.92	0.0328	0.0787	0.0150
	(n)	(4)	(4)	(4)	(4)
36700010	2	292.3	0.237	1.207	0.163
36700012	2	284.7	0.247	1.198	0.173
36700014	2	295.0	0.296	1.169	0.195
36700016	2	295.4	0.241	1.180	0.185
	Mean	291.85	0.2554	1.1882	0.1789
	SD	4.96	0.0275	0.0171	0.0140
	(n)	(4)	(4)	(4)	(4)
36700018	3	289.6	0.232	1.237	0.213
36700020	3	288.9	0.234	1.219	0.164
36700022	3	284.3	0.235	1.209	0.168
36700024	3	277.1	0.195	1.272	0.189
	Mean	284.98	0.2241	1.2344	0.1837
	SD	5.75	0.0195	0.0276	0.0225
	(n)	(4)	(4)	(4)	(4)
36700026	4	241.4	0.199	1.331	0.135
36700028	4	235.4	0.222	1.487	0.129
36700030	4	250.9	0.189	1.347	0.133
36700032	4	258.0	0.233	1.465	0.196
	Mean	246.43	0.2109	1.4074	0.1483
	SD	10.01	0.0201	0.0797	0.0317
	(n)	(4)	(4)	(4)	(4)

° = expressed as % organ to body weight ratio

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 7 - Relative organ weights° - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Spleen
36700001	1	202.4	0.031	0.82	0.40	0.71	2.81	0.291
36700003	1	183.7	0.034	0.90	0.42	0.67	2.76	0.295
36700005	1	198.8	0.029	0.85	0.43	0.82	3.78	0.274
36700007	1	179.3	0.032	0.89	0.42	0.66	2.76	0.317
	Mean	191.05	0.0315	0.865	0.419	0.714	3.029	0.2941
	SD	11.27	0.0023	0.033	0.012	0.072	0.499	0.0180
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36700009	2	201.0	0.032	0.82	0.43	0.72	3.41	0.315
36700011	2	199.0	0.033	0.86	0.38	0.73	3.40	0.295
36700013	2	180.2	0.034	0.93	0.41	0.71	3.27	0.250
36700015	2	182.2	0.034	0.88	0.43	0.67	3.31	0.325
	Mean	190.60	0.0334	0.873	0.413	0.708	3.349	0.2964
	SD	10.92	0.0011	0.045	0.022	0.027	0.067	0.0331
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36700017	3	204.0	0.027	0.79	0.41	0.71	3.61	0.273
36700019	3	166.7	0.035	0.99	0.38	0.72	3.23	0.238
36700021	3	181.5	0.026	0.94	0.37	0.73	4.00	0.279
36700023	3	185.1	0.031	0.83	0.36	0.83	3.36	0.263
	Mean	184.33	0.0302	0.888	0.382	0.748	3.547	0.2630
	SD	15.34	0.0041	0.093	0.024	0.056	0.340	0.0183
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36700025	4	165.8	0.027	0.96	0.35	0.72	4.10	0.223
36700027	4	183.4	0.033	0.87	0.34	0.72	4.63	0.218
36700029	4	156.3	0.029	1.05	0.40	0.75	5.14	0.227
36700031	4	158.8	0.030	1.11	0.38	0.72	3.96	0.220
	Mean	166.08	0.0297	0.995	0.366	0.728	4.458	0.2222
	SD	12.23	0.0023	0.106	0.027	0.015	0.539	0.0039
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)

° = expressed as % organ to body weight ratio

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 7 - Relative organ weights° - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group	Terminal B.W. (g)	Thymus
36700001	1	202.4	0.221
36700003	1	183.7	0.219
36700005	1	198.8	0.211
36700007	1	179.3	0.211
	Mean	191.05	0.2156
	SD	11.27	0.0053
	(n)	(4)	(4)
36700009	2	201.0	0.235
36700011	2	199.0	0.177
36700013	2	180.2	0.160
36700015	2	182.2	0.193
	Mean	190.60	0.1913
	SD	10.92	0.0321
	(n)	(4)	(4)
36700017	3	204.0	0.259
36700019	3	166.7	0.195
36700021	3	181.5	0.214
36700023	3	185.1	0.202
	Mean	184.33	0.2177
	SD	15.34	0.0289
	(n)	(4)	(4)
36700025	4	165.8	0.178
36700027	4	183.4	0.218
36700029	4	156.3	0.156
36700031	4	158.8	0.134
	Mean	166.08	0.1714
	SD	12.23	0.0360
	(n)	(4)	(4)

° = expressed as % organ to body weight ratio

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 8 - Macroscopic observations - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group	Tissue / Observation(s)
36700002	1	Whole animal No abnormalities detected
36700004		Whole animal No abnormalities detected
36700006		Whole animal No abnormalities detected
36700008		Whole animal No abnormalities detected

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 8 - Macroscopic observations - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group	Tissue / Observation(s)
36700010	2	Whole animal No abnormalities detected
36700012		Whole animal No abnormalities detected
36700014		Whole animal No abnormalities detected
36700016		Whole animal No abnormalities detected

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 8 - Macroscopic observations - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group	Tissue / Observation(s)
36700018	3	Adrenals Abnormal size, Small 2mm diam left Cervical nodes Abnormal size, Single, Enlarged 10x6x3mm
36700020		Kidneys Abnormal size, Small 11x8x5mm, right
36700022		Thymus Abnormal colour, Dark right lobe
36700024		Whole animal No abnormalities detected

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 8 - Macroscopic observations - Individual data

STUDY NO.: 36700EXT

MALES

Animal Number	Group	Tissue / Observation(s)
36700026	4	Liver Abnormal colour, Pale Stomach Abnormal area(s), Single, Dark 2x2mm, glandular region
36700028		Kidneys Abnormal area(s), Single, Pale 5x3mm, left Liver Abnormal colour, Pale Lungs Abnormal colour, Dark Stomach Abnormal contents, Dark, Granular
36700030		Liver Abnormal colour, Pale Abnormal shape, Irregular surface
36700032		Liver Abnormal colour, Pale Stomach Abnormal area(s), Multiple, Dark up to 2x2mm, glandular region

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 8 - Macroscopic observations - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group	Tissue / Observation(s)
36700001	1	Ovaries Cyst(s), Single, Clear, Fluid filled 3mm diam, left Uterus Abnormal contents, Clear, Fluid Abnormal size, Distended 7mm diam
36700003		Liver Abnormal colour, Pale
36700005		Whole animal No abnormalities detected
36700007		Whole animal No abnormalities detected

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 8 - Macroscopic observations - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group	Tissue / Observation(s)
36700009	2	Liver Abnormal colour, Pale
36700011		Stomach Abnormal contents, Yellow, Mucoid
36700013		Whole animal No abnormalities detected
36700015		Whole animal No abnormalities detected

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 8 - Macroscopic observations - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group	Tissue / Observation(s)
36700017	3	Whole animal No abnormalities detected
36700019		Liver Abnormal colour, Pale
36700021		Lungs Abnormal colour, Dark
36700023		Whole animal No abnormalities detected

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

APPENDIX 8 - Macroscopic observations - Individual data

STUDY NO.: 36700EXT

FEMALES

Animal Number	Group	Tissue / Observation(s)
36700025	4	Liver Abnormal colour, Pale
36700027		Liver Abnormal colour, Pale Lungs Abnormal colour, Red Pituitary Abnormal colour, Red
36700029		Liver Abnormal colour, Pale Lungs Abnormal colour, Red Pituitary Abnormal colour, Dark red Stomach Abnormal area(s), Multiple, Dark, Pinpoint glandular region
36700031		Liver Abnormal colour, Pale Pituitary Abnormal colour, Dark Stomach Abnormal colour, Dark glandular region

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

ADDENDUM I - Computer abbreviations and symbols

STUDY NO.: 36700EXT

Abbreviations	Parameters names	Units
HCT	HAEMATOCRIT	%
RBC	RED BLOOD CELL COUNT	10^12/l
HGB	HAEMOGLOBIN	g/dl
MCV	MEAN RED BLOOD CELL VOLUME	fl
MCH	MEAN CORPUSCULAR HAEMOGLOBIN	pg
MCHC	MEAN CORPUSCULAR HAEMOGLOBIN CONCENTRATION	g/dl
PLT	PLATELETS	10^9/l
WBC	WHITE BLOOD CELL COUNT	10^9/l
NEU	NEUTROPHILS	%
LYM	LYMPHOCYTES	%
MON	MONOCYTES	%
EOS	EOSINOPHILS	%
BAS	BASOPHILS	%
LUC	LARGE UNSTAINED CELLS	%
PT	PROTHROMBIN TIME	sec
AP	ALKALINE PHOSPHATASE	U/l
ALT	ALANINE AMINOTRANSFERASE	U/l
AST	ASPARTATE AMINOTRANSFERASE	U/l
GLU	GLUCOSE	mg/dl
BILT	TOTAL BILIRUBIN	mg/dl
CHOL	TOTAL CHOLESTEROL	mg/dl
PROT	TOTAL PROTEIN	g/dl
NA	SODIUM	mmol/l
K	POTASSIUM	mmol/l
CA	CALCIUM	mmol/l
CL	CHLORIDE	mmol/l
UREA	UREA	mg/dl
CREA	CREATININE	mg/dl
ALB	ALBUMIN	mg/dl
GLO	GLOBULIN	g/dl
AGR	ALBUMIN/GLOBULIN RATIO	g/dl

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

ADDENDUM I - Computer abbreviations and symbols

STUDY NO.: 36700EXT

Abbreviations	Parameters names	Units/Key
Ctls	Control	
SD	Standard deviation	
Cervical nodes	Cervical lymph nodes	
Mesenteric nodes	Mesenteric lymph nodes	
gl	Glands	

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

ADDENDUM II - Certificate of analysis

STUDY NO.: 36700EXT

SOLVAY SOLEXIS

Bollate 23 dicembre, 2004

[redacted] : 7 gg e 28 gg + 14 gg rec. orale

Il prodotto [redacted] è un perfluoropolietere monofunzionale salificato con NH4+ e ha la seguente formula:

$$Cl - (C_3F_6O)_n - CF_2 - COO^- NH4^+ \quad (M.W. = circa\ 600)$$

Sulla soluzione al 5% in acqua del prodotto in esame sono state eseguite al laboratorio RTC le prove di tossicità acuta orale (Report no. 9563-003), dermale, (Report no. 8833-006) e irritazione dermale (Report no. 8835-006).
LD50 acuta orale è risultata essere compresa tra 200 mg/kg e 2000 mg/kg.
Il prodotto su cui si effettuerà la 7 gg e la 28 gg orale è il sale secco, quindi i dati dell'acuta orale riferiti alla soluzione al 5%, al fine di stabilire le dosi per i nuovi studi, dovrebbero essere ricalcolati per riferirsi al prodotto secco e non in soluzione. Così facendo otterremmo una LD50 compresa tra 10 e 100 mg/kg.

Per maggiori informazioni vengono riportati di seguito i risultati della acuta orale effettuata sul prodotto acido con struttura analoga ma con composizione leggermente differente. La formula è la seguente:

$$Cl - (C_3F_6O)_n - CF_2 - COO\ H$$

Si consiglia di tenere in cosiderazione anche questi risultati al fine di una corretta valutazione delle dosi per i nuovi studi.
5 maschi per gruppo sono stati trattati con 200, 100, 75, 50 e 25 mg/kg. Si è osservata 100% di mortalità fino alla dose di 50 mg/kg in cui un solo animale è rimasto vivo. Questi animali, a necroscopia, hanno mostrato congestione gastrica, erosione e ulcerazione delle pareti intestinali con contenuto emorragico. Congestione di polmoni, timo e rene, pallore del fegato e diminuzione della dimensione della milza.

Alla dose più bassa (25 mg/kg) sono stati trattati oltre ai 5 maschi anche 5 femmine, sono morte solo 2 femmine.
La tossicità acuta orale del suddetto prodotto ha dato un valore di LD50 = 38 mg/kg con livelli di confidenza compresi tra 27.4 – 56.7 mg/kg. Il prodotto è stato somministrato allo stato puro non diluito (100%).

Si ricorda inoltra che il laboratorio RTC ha eseguito anche un test di acuta orale sul prodotto 7800 S-W (Report no. 9563-002), sale di Na+ in soluzione al 20%. Questo prodotto ha struttura analoga al prodotto da testare ma è caratterizzato da un peso molecolare leggermente inferiore ed è, come già specificato, sale di Sodio.

$$Cl - (C_3F_6O)_n - CF_2 - COO^- Na^+$$

LD50 risultata dal testi di acuta orale è compresa tra 200 e 2000 mg/kg. Calcolando il valore di LD50 riferito al sale secco (100%) anziché alla soluzione, risulta un LD50 compreso tra 40 e 400 mg/kg.
Si consiglia di tenere in considerazione anche i risultati del suddetto test per stabilire le dosi dei nuovi studi.

[redacted] 7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

ADDENDUM III - Study protocol

STUDY NO.: 36700EXT

[redacted]

7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS

Final Protocol
prepared for

SOLVAY SOLEXIS S.p.A.
Via Lombardia, 20
20121 Bollate (MI)
Italy

by

RESEARCH TOXICOLOGY CENTRE S.p.A.
Via Tiburtina 12
00040 Pomezia (Rome)
Italy

RTC Enquiry Number: 36700EXT

January 2005

Commercial Office

Head Office and Administration

1. INTRODUCTION

1.1 Objective

The purpose of this study is to investigate the toxicity of [redacted] in rats after daily oral administration for 7 days. The data generated will allow selection of dose levels for subsequent toxicological studies.

1.2 Species

The Sprague Dawley SD rat is the species and strain of choice because it is accepted by many regulatory authorities and there is ample experience and background data on this species and strain.

1.3 Route of administration

The test item will be administered orally, by gavage. The oral route has been selected as it is a possible route of exposure of the test item in man.

1.4 Regulatory compliance

This study is a preliminary dose range finding study and is exempt from compliance with the Good Laboratory Practice regulations of the OECD Guidelines for testing of Chemicals. The RTC Quality Assurance Unit will not review the protocol or the final report and will not monitor any phase of the in-life procedures. However, the principles and the procedures of the GLP regulations will be followed in all other respects.
Procedures and facilities will comply with the requirements of Commission Directive 86/609/EEC concerning the protection of animals used for experimental and other scientific purposes. National legislation, harmonising with this Directive, is defined in Decreto Legislative no. 116 of 27 January 1992. Aspects of the protocol concerning animal welfare have been approved by the RTC's Ethical Committee.

2. TEST ITEM

2.1 Characterisation

It will be the responsibility of the Sponsor to determine, for each batch of test item, the identity, strength, purity and composition, or other characteristics which appropriately define the test item, before its use in the study. The determination of the stability of the test item will also be the Sponsor's responsibility.
A certificate of analysis for the test item should also be supplied.

2.2 Identity

The test item will be [redacted]

The following information refers to the original batch of test item received for the study:

Batch Number	:	90409-86-1
Date of expiry	:	01 January 2015
Appearance	:	White solid
Storage conditions	:	Ambient

Should further batches be required to complete the study, full details of batch usage will be maintained in the formulation records but protocol amendments will not be issued.
The amount of test item received and used at RTC will be recorded according to RTC standard procedures.

2.3 Safety precautions

The precautions necessary when handling either the test item or prepared formulations of the test item are based on information supplied by the Sponsor. The minimum safety precautions necessary are detailed under the RTC Hazard Classification System, according to RTC standard procedures.

2.4 Vehicle

The vehicle will be distilled water.

2.5 Formulation procedure

The required amount of [redacted] will be dissolved/suspended in the vehicle. The formulation will be prepared daily (concentrations of 0.25, 0.50 and 1.00 mg/ml). Concentrations will be calculated and expressed in terms of test item as supplied.

2.6 Disposal

Approximately 1 year after the final report has been issued, remaining amounts of the test item, with the exception of the reserve samples taken for archival purposes, will be destroyed by incineration.

3. TEST SYSTEM

3.1 Animal supply and acclimatisation

A total of 50 Hsd: Sprague Dawley SD rats (25 males and 25 females), 27-29 days old and within a weight range of approximately 75-99 g, will be obtained from Harlan Italy s.r.l., San Pietro al Natisone (UD), Italy.
After arrival the weight range for each sex will be determined and the animals will be temporarily identified within the cage by means of a coloured mark on the tail. A health check will then be performed by a veterinarian.
An acclimatisation period of approximately 2 weeks will be allowed before the start of treatment, during which time the health status of the animals will be assessed by thorough observations.
Rats considered unsatisfactory will be killed and where appropriate subjected to pathological examination. Unsatisfactory batches of animals will be rejected before the start of treatment.

3.2 Animal husbandry

The animals will be housed in a limited access rodent facility. Animal room controls will be set to maintain temperature and relative humidity at 22°C ± 2°C and 55% ± 15% respectively; actual conditions will be monitored, recorded and the records retained. There will be approximately 15 to 20 air changes per hour and the rooms will be lit by artificial light for 12 hours each day.
The animals will be housed 4 of one sex to a cage, in clear polycarbonate cages measuring 59x38.5x20 cm with a stainless steel mesh lid and floor (Code 1354 G, Techniplast Gazzada S.r.l., Buguggiate, Varese). Each cage tray will hold absorbent paper which will be inspected and changed at least 3 times a week.
Drinking water will be supplied *ad libitum* to each cage via water bottles.
A commercially available laboratory rodent diet (4 RF 18, Mucedola S.r.l., Via G. Galilei, 4, 20019, Settimo Milanese (MI), Italy) will be offered *ad libitum* throughout the study, except as indicated in section 4.3.
There is no information available to indicate that any non-nutrient substance likely to influence the effect of the test item is present in the drinking water or the diet. Records of analyses of water and diet are kept on file at RTC.
Dated and signed records of activities relating to the day to day running and maintenance of the study in the animal house will be recorded in a Study Day Book.

3.3 Allocation to groups

On the day of allocation (about 7 days prior to the start of treatment) all animals will be weighed. Animals at the extremes of the weight distribution and/or any animal showing signs of ill health will be excluded to leave the required number of animals. The rats will be allocated to the 4 groups by computerised stratified randomisation to give approximately equal initial group mean body weights.
Individuals will be uniquely identified within the study by sex, tattoo on the hind feet and ear notch and housed 4 of one sex per cage.
The cages will be identified by a label recording the study number, animal numbers and details of treatment. The arrangement of cages on batteries will be such that cages from each treatment group will be evenly distributed across the battery (Annex 2) to minimise possible environmental effects.

Any animal showing signs of ill health during the period between allocation and the start of treatment will be subjected to pathological examination as considered appropriate, and replaced with a surplus animal selected from the same batch.

4. EXPERIMENTAL PROCEDURE

4.1 Treatment

4.1.1 Selection of dose levels

Dose levels have been selected in consultation with the Sponsor.

4.1.2 Dose levels, group size and identification

Each group will comprise 4 male and 4 female rats. The group identification and animal numbers assigned to the treatment are summarised below:

Group Number:	Treatment (mg/kg/day)+	Level	Rat Numbers	
			M (even)	F (odd)
1	0	Control	2-8	1-7
2	2.5	Low	10-16	9-15
3	5.0	Medium	18-24	17-23
4	10.0	High	26-32	25-31

+: in terms of test item as supplied

The rat numbers listed above will form the last digits of a computer generated 8 figure animal number (the remaining digits of the animal number will be different for each concurrent study and will serve to ensure unique animal numbering for any study employing computerised data collection). The computerised system used in this study will be the Xybion Path/Tox System, Version 4.2.2.

4.1.3 Administration of test item

The test item will be administered orally, by gavage at a dose volume of 10 ml/kg.
Control animals will receive the vehicle alone at the same dose volume.
The dose will be administered to each animal on the basis of the most recently recorded body weight and the volume administered will be recorded for each animal.

4.1.4 Duration of treatment

All animals will be dosed once a day for a minimum of 7 consecutive days. All animals will be dosed up until the day before necropsy.

4.2 *In vivo* observations

Full records will be maintained for all measurements and observations.

4.2.1 Mortality

Throughout the study, all animals will be checked early in each working day and again in the afternoon. At weekends and Public Holidays a similar procedure will be followed except that the final check will be carried out at approximately mid-day. This will allow *post mortem* examinations to be carried out during the working period of that day. Severely debilitated animals will be observed carefully. Animals judged to be *in extremis* will be killed. A complete necropsy will be performed on all cases as detailed in section 4.4.2 below.

4.2.2 Pre- and post-dose observations

All observations will be recorded for individual animals. Examination of individual animals for signs of reaction to treatment will be carried out daily prior to dosing, immediately after and approximately 1 and 2 hours after dosing.

4.2.3 Clinical signs

All clinical signs will be recorded for individual animals.
Once before commencement of treatment, once during treatment period, and on day 8 of the study, each animal will be observed and any clinical signs will be recorded.

4.2.4 Body weight

Each animal will be weighed on the day of allocation to treatment group, on the day that treatment commences and just prior to necropsy.

4.2.5 Food consumption

The weight of food consumed by each cage of rats will be recorded at weekly intervals following allocation. The group mean daily intake per rat will be calculated.

4.3 Clinical pathology investigations

At the end of treatment, or day 8 of the study, samples of blood will be withdrawn prior to necropsy under isoflurane anaesthesia from the abdominal vena cava of all surviving male and female rats from each group, after overnight fasting.

Blood samples will be collected and analysed in the same order.
The blood samples collected will be divided into tubes as follows:

EDTA anticoagulant	for haematological investigations
Heparin anticoagulant	for biochemical tests
Citrate anticoagulant	for coagulation test

The measurements to be performed on blood samples are listed below:

4.3.1 Haematology

Haematocrit
Haemoglobin
Red blood cell count
Reticulocyte count (if there are signs of anaemia)
Mean red blood cell volume
Mean corpuscular haemoglobin
Mean corpuscular haemoglobin concentration
White blood cell count
Differential leucocyte count - Neutrophils
- Lymphocytes
- Eosinophils
- Basophils
- Monocytes
- Large unstained cells
Abnormalities of the blood film
Platelets
Prothrombin time

4.3.2 Clinical chemistry

Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Urea
Creatinine
Glucose
Total bilirubin
Total cholesterol
Total protein
Albumin
Sodium
Potassium
Calcium
Chloride

4.4 Terminal studies

4.4.1 Euthanasia

Animals in extremis or killed for humane reasons and those that have completed the scheduled test period will be killed by exsanguination under isoflurane anaesthesia. All animals, including those found dead, will be subjected to necropsy, supervised by a pathologist, as detailed below.

4.4.2 Necropsy

The clinical history of the animal will be studied and a detailed *post mortem* examination will be conducted (including examination of the external surface and orifices).
Changes will be noted, the requisite organs weighed and the required tissue samples preserved in fixative and processed for histopathological examination (see sections 4.4.3 to 4.4.5).
Representative photographs will be taken of any significant findings, if considered appropriate.

4.4.3 Organ weights

From all animals completing the scheduled test period, the organs indicated in Annex I will be dissected free of fat and weighed.
The ratios of organ weight to body weight will be calculated for each animal.
At the discretion of the pathologist, organs may be weighed from animals dying or killed prior to terminal kill.

4.4.4 Tissues fixed and preserved

Samples of all the tissues listed in Annex I will be fixed and preserved in 10% buffered formal saline (except testes and epididymides which will be fixed in Bouin's solution and preserved in 70% ethyl alcohol).

4.4.5 Histopathological examination (if required)

Histopathological examination will be undertaken only if toxicity to the test item is evident during the treatment period, following consultation with and approval of the Sponsor (additional cost). If performed, the tissues to be examined will be discussed and agreed with the Sponsor.

4.4.6 Photomicrographs

Representative photomicrographs may be taken of any treatment-related lesions. Other photomicrographs may be taken as required by the Sponsor.

5. ANALYSIS OF DATA

5.1 Presentation of data

The data will be summarised and presented in the form of tables or figures. Individual observations and findings for each animal will also be tabulated.

5.2 Statistics

For continuous variables the significance of the differences amongst group means will be assessed by Dunnett's test or a modified t test, depending on the homogeneity of data.

6. AMENDMENTS TO THE PROTOCOL

It is not intended to make any amendment to this protocol without authorisation by the Sponsor. However, in the event of difficulty in contacting the Sponsor and/or for humane reasons and/or for the protection of scientific integrity, the testing laboratory retains the right to take independent action.

7. REPORTING

7.1 Interim report

Any unexpected findings during the course of the study will be reported to the Sponsor's Monitoring Scientist immediately.

7.2 Final report

A draft report will be sent to the Sponsor. With the exception of the dated signature of scientists and other professional personnel, the draft report will contain all information and data included in the final report.
Comments made by the Sponsor may be incorporated into the draft, after which it will be issued as the final report.
The final report will include the information and data required by current internationally recognised regulations. One original unbound, one copy bound and a PDF version will be supplied.

7.3 Corrections or additions to the final report

Corrections or additions to the approved (i.e. signed) version of the final report will be in the form of an amendment by the Study Director.

8. RECORDS AND ARCHIVES

Full records will be maintained of all aspects of study conduct, together with results of all measurements and observations.
RTC will retain all relevant computer stored data generated by electronic on-line capture in a manner fully compliant with Good Laboratory Practice. At the end of the specified period, these data will be despatched to the Sponsor in the original format. If requested, reformatting of these data on alternative media may be carried out and will incur an additional cost.
Prior to commencement of treatment and at each batch change a reserve sample of the test item will be taken and kept under the storage conditions of the bulk supply at RTC.
The reserve sample(s) of the test item will be retained within the RTC archives for a period of 10 years and then destroyed.
All specimens other than the samples described above, raw data, records and documentation generated during the course of this study will be returned to the Sponsor after the issue of the Final Report.

The signed Final Protocol and the top copy of the Final Report will be despatched to and archived by the Sponsor.

9. LOCATION OF THE STUDY

Research Toxicology Center S.p.A.
Via Tito Speri, 12
00040 Pomezia (Rome)
Italy

10. PROJECTED TIME PLAN

			Date
1.	Animal arrival	:	End of December 2004
2.	Start of treatment	:	Mid January 2005
3.	End of in vivo phase	:	Second half of January 2005
4.	Draft Report to Sponsor	:	6 Weeks from the start of treatment

ANNEX 1. TISSUE PROCESSING

Organs / Tissues	Weight	Fixation Preservation	Microscopic Examination
Abnormalities		✓	
Adrenal glands	✓	✓	
Bone marrow (from sternum)		✓	
Brain	✓	✓	
Caecum		✓	
Colon		✓	
Duodenum		✓	
Epididymides	✓	✓	
Heart	✓	✓	
Ileum (including Peyer's patches)		✓	
Jejunum		✓	
Kidneys	✓	✓	
Liver	✓	✓	
Lungs		✓	
Lymph nodes – mesenteric		✓	
Lymph nodes – cervical		✓	
Ovaries		✓	
Parathyroid glands[a]		✓	
Pituitary gland		✓	
Prostate gland		✓	
Rectum		✓	
Sciatic nerve		✓	
Seminal vesicles		✓	
Spinal column		✓	
Spinal cord		✓	
Spleen	✓	✓	
Stomach		✓	
Testes	✓	✓	
Thymus (where present)	✓	✓	
Thyroid		✓	
Trachea		✓	
Urinary bladder		✓	
Uterus-cervix		✓	

[a] Weighed and preserved with thyroid gland

ANNEX 2. GROUP AND CAGE ARRANGEMENT ON BATTERY

Group Number:	Treatment (mg/kg/day)1+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
1	0	Control	2-8	1-7	1	5
2	2.5	Low	10-16	9-15	2	6
3	5.0	Medium	18-24	17-23	3	7
4	10.0	High	26-32	25-31	4	8

1+ in terms of test item as supplied

Group/Sex
Cage no.

Males		Females	
1M	1	4F	8
2M	2	3F	7
3M	3	2F	6
4M	4	1F	5

PROTOCOL APPROVAL PAGE

STUDY TITLE	:	7-DAY PRELIMINARY ORAL TOXICITY STUDY IN RATS
TEST FACILITY	:	RESEARCH TOXICOLOGY CENTRE S.p.A. Via Tito Speri, 12 00040 Pomezia (Roma) Italy
RTC ENQUIRY NO.	:	36700EXT
TEST ITEM	:	[redacted]
APPROVED BY	:	C. Longobardi, Biol.D. Study Director — Date: 10 Jan 2005
APPROVED BY	:	L. Luperi, D.V.M. Responsible for Animal Welfare — Date: 10 Jan 2005
RELEASED BY	:	J. Brightwell, Ph.D. Scientific Director — Date: 10 Jan 2005
SPONSOR	:	SOLVAY SOLEXIS S.p.A. Via Lombardia, 20 20121 Bollate (MI) Italy
AUTHORISED BY SPONSOR*	:	Date: 10/Jan/2005
Name and Address	:	MARIA COLOMBO INDUSTRIAL TOXICOLOGY

* Please print or type your name and company status below your signature.