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RESEARCH TOXICOLOGY CENTRE - ROMA

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4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FINAL REPORT

VOLUME I OF II

RTC Study no.: 27080

Sponsor

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FINAL REPORT

We, the undersigned, were responsible for the preparation of this report.

C. Longobardi, Biol.D. _____ (Study Director) Date: 21-Oct-2005

I. Andreini, D.V.M. _____ (Study Pathologist) Date: 21 Oct. 05

COMPLIANCE STATEMENT

We, the undersigned, hereby declare that the following report constitutes a true and faithful account of the procedures adopted, and the results obtained in the performance of the study. The aspects of the study conducted by Research Toxicology Centre S.p.A. were performed in accordance with:

A. Decreto Legislativo 27 Gennaio 1992 n. 120, *Adoption of 88/320/EEC and 90/18/EEC Directives on the inspection and verification of good laboratory practice (G.U. 18 Febbraio 1992 n. 40)* and subsequent revisions.

B. Directive 2004/10/EC of European Parliament and of the Council of 11 February 2004. *On the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances.*

C. ENV/MC/CHEM(98)17 *OECD principles on Good Laboratory Practice (as revised in 1997).*

C. Longobardi, Biol.D. Chiara Longobardi (Study Director) Date: 21-Oct-2005

J. Brightwell, Ph.D. J. Brightwell (Scientific Director) Date: 21 Oct 2005

QUALITY ASSURANCE STATEMENT

(Relevant to those aspects of the study conducted by RTC S.p.A.)

Study phases monitored by RTC's QAU According to current relevant Standard Operating Procedures	Quality Assurance Inspections (Day Month Year)		
	Inspection	Report to Study Director	Report to Company Management
PROTOCOL CHECK AND PROTOCOL AMENDMENT (1)	11.06.2004 28.06.2005	11.06.2004 29.06.2005	11.06.2004 29.06.2005
STUDY-BASED INSPECTIONS RELATED TO THIS STUDY			
Allocation	09.06.2004	18.06.2004	22.06.2004
Dose preparation	17.06.2004	18.06.2004	18.06.2004
Dosing (oral)	16.06.2004	18.06.2004	18.06.2004
Pre- and post-dose observations	16.06.2004	18.06.2004	18.06.2004
Body weight	23.06.2004	24.06.2004	24.06.2004
Food consumption	14.07.2004	10.09.2004	17.09.2004
Clinical observations	24.06.2004	30.06.2004	30.06.2004
Motor activity	07.07.2004	10.08.2004	06.09.2004
Sensory reactivity to stimuli	08.07.2004	10.08.2004	23.08.2004
Blood sampling	13.07.2004	09.08.2004	11.08.2004
Urine collection	13.07.2004	09.08.2004	11.08.2004
Timed bleed	08.07.2004	11.08.2004	11.08.2004
Despatch to necropsy	14.07.2004	10.09.2004	17.09.2004
Necropsy	14.07.2004	15.07.2004	15.07.2004
QA inspection regarding Analytical Chemistry, Histology and Clinical Pathology Departments as well as regarding other routine activity not directly related to this study are carried out as process-based inspections. The relevant documentation is kept on file although specific inspection dates are not reported here. Associated laboratories and support functions are subject to regular facility inspections.			
FINAL REPORT Review of this report by RTC's QAU found the reported methods and procedures to describe those used and the results to constitute an accurate representation of the recorded raw data.		Review completed	

M.M. Brunetti, Biol.D.
(Head of Quality Assurance)

Date

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Addenda

1. SUMMARY

1.1 The oral toxicity of [redacted] when given by daily administration to rats, has been investigated over a period of 4 consecutive weeks and recovery from any potential treatment-related effects over a period of 2 consecutive weeks. Three groups, each of 5 male and 5 female Sprague Dawley rats, received the test item by gavage at dosages of 0.5, 2.5 and 8.0 mg/kg/day for 4 consecutive weeks. A fourth similarly constituted group received the vehicle alone (distilled water) and acted as a control. Five additional animals for each sex were included in the high and control groups for recovery assessment. Blood samples were also taken on Day 1 of dosing from a single satellite group of 9 females, dosed at 8.0 mg/kg/day, for toxicokinetic evaluations.

1.2 Mortality

One female animal dosed at 8.0 mg/kg/day was found dead on Day 28 of treatment approximately 2 hours after the bleeding procedure. Clinical signs were seen in this animal on the day of death. On the basis of the findings of microscopic examinations, this death may be considered treatment-related.

1.3 Pre- and post-dose observations and weekly clinical signs

Daily post-dose observations were limited to tremors, noted in a single male animal dosed at 8.0 mg/kg/day for 1 day only.
Detailed clinical signs with neurotoxicity assessment did generally not show any signs which could be correlated to the treatment with the test item. Mobility impairment, slight ataxia and tremors were noted in 1 male animal dosed at 8.0 mg/kg/day on a single occasion.

1.4 Motor activity and sensory reaction to stimuli

Neurotoxicity tests and motor activity measurements taken at the end of treatment did not show changes attributable to the test item.

1.5 Body weight

Body weights were statistically significantly reduced in the high dose animals from Day 15 up to the end of the treatment period when compared to controls. Terminal body weight was also significantly reduced in the high-dose animals. These reductions were still evident up to the end of the recovery period.

1.6 Food consumption

No significant changes were observed in food consumption.

1.7 Haematology

Slight but statistically significant reductions of the white blood cell count and platelets were observed in the high-dose males and high-dose females, respectively, at the end of the treatment period. These parameters were no longer statistically significantly different at the end of recovery. No toxicological importance was attributed to the other statistically significant variations observed at the end of treatment or recovery periods.

1.8 Clinical chemistry

Significant increases of alkaline phosphatase, alanine aminotranferase, aspartate aminotransferase, triglycerides, and urea were observed in the animals dosed at 2.5 and 8.0 mg/kg/day at the end of the treatment period. Total protein and creatinine were also reduced in these animals. In addition, variations of electrolytes were observed in the treated animals when compared to controls. Some of the observed changes (triglycerides and urea increases and electrolyte variations) were also evident in the animals dosed at 0.5 mg/kg/day. Usually, the observed changes showed a dose-related trend. Most of the observed changes were still present at the end of the recovery period.

1.9 Urinalysis

A dose-related increase of urine volume, statistically significant in the mid- and high dose groups, was noted in the treated females at the end of the treatment period. A slight reduction of protein was also observed in the animals dosed at 8.0 mg/kg/day at the end of treatment. These changes were still evident at the end of recovery.

1.10 Toxicokinetic analysis

Detectable plasma levels of the test item were measured between 2 and 168 hours after dosing in the animals dosed at 8.0 mg/kg. The maximum plasma level (C_{max}) was 16050.0 ng/ml. C_{max} was measured 6 hours after dosing (t_{max}). A half-life ($t_{½}$) of approximately 58 hours was estimated. The $AUC_{(6\text{-}168h)}$ was calculated to be 873415 ng/ml·h and the $AUC_{(inf)}$ was calculated to be 1069642 ng/ml·h.

1.11 Organ weights

Dose-related, statistically significant increases in absolute and relative liver weights were noted in all treated males and in mid- and high dose females at the end of the treatment period. This increase was still present at the end of the recovery period. In addition, statistically significant reductions of the absolute and relative weights of the spleen and thymus and increases of the relative weights of the thyroid, kidneys and testes were seen in the high dose animals at the end of treatment. Some of these organs (liver, testes, kidneys and thymus) still showed statistically significant differences from controls at the end of recovery. No other toxicologically significant changes were observed.

1.12 Macroscopic observations

The most relevant changes, observed at necropsy of the early decedent animal, were incomplete collapse of the lungs and pale colour of the liver and pancreas and a scab on the head.
Enlargement of the liver, sometimes accompanied by swollen shape of the organ, was reported in animals (mainly males) from the mid- and high dose groups. Decreased size of the thymus and seminal vesicles were also seen in high dose animals.
The above described changes were generally still evident in the treated males killed after the 2-week recovery period.

1.13 Microscopic observations

Unscheduled death: The most important changes observed in the animal which was found dead on day 28 of the study were observed in the liver where multifocal, moderate haemorrhage, moderate hepatocytic hypertrophy and single cell apoptosis/necrosis were reported; in addition, moderate atrophy of the thymus and mild lymphoid depletion of the the spleen, mineralization in the cortico-medullary junction of the kidney, acinar cell apoptosis in the pancreas, ulceration and presence of scabs from the sample of skin taken from the head were observed in this animal.

Final sacrifice: treatment-related changes were noted in the liver, lungs, thymus, kidneys and seminal vesicles of high and mid- dose group animals, sacrificed after 4 weeks of treatment. These changes were described as follows:
Liver: panlobular hepatocytic hypertrophy, suggestive of an adaptive change, was observed in all high and mid-dose group animals. In the high dose group mainly, this finding was occasionally accompanied by hepatocytic vacuolation, single cell necrosis/apoptosis and increased incidence and severity degree of bile duct proliferation and inflammatory cell foci, when compared to the values reported in the controls. These last changes were considered linked to an inflammatory response to the liver cell damage and regarded as reaction and repair processes.
Lungs: aggregation of alveolar macrophages was seen in the lungs of 4/5 high dose and 1/5 mid-dose males and in 3/5 high dose females. Such a finding could be possible suggestive of a phospholipidosis condition. Only 1 control animal showed this finding, but it was considered part of a chronic inflammatory process, also characterised by bronchial and alveolar haemorrhage, oedema and eosinophilic infiltrates.
Thymus: slight to moderate thymus atrophy was observed in 5/5 males and 3/5 females from the high dose group and 1/5 mid-dose group males. This lesion showed a higher severity degree in the males, when compared to female animals and could be considered a secondary effect due to the poor general condition of the animals.
Seminal vesicles: colloid depletion was described in 5/5 high dose treated males. Also this change could be considered a secondary effect due to the poor condition of the animals. Colloid depletion was also observed in one control animal, but it was associated with unilateral testicular aplasia and it was therefore considered expression of spontaneous pathology.
Kidney: foci of mineralization were observed in the papilla, medulla or cortical-medullary junction of the kidneys from 4/5 high dose and 1/5 mid-dose group females.

Recovery sacrifice: only a partial remission of the changes considered related to the administration of the test item, represented by a reduction in the incidence and/or severity level, was noted in the treated animals, killed after the 2-week recovery period. Some of the treated animals still showed both adaptive and degenerative changes described in the liver, like hepatocytic hypertrophy, hepatocytic vacuolation and single cell apoptosis/necrosis. Aggregations of alveolar macrophages were still visible in the lungs of 2/5 males. Thymic atrophy was again reported in 5/5 males and in 3/5 females. Colloid depletion was described in the seminal vesicles of 2/5 males only. Focal mineralization was still observed in the various zones of the kidneys from 2/5 treated females.
The remaining changes observed in all the tissues/organs examined were considered to be spontaneous or incidental in origin.

1.14 Conclusion

A toxic effect of the test item was seen at the 2 higher dose levels investigated (2.5 and 8.0 mg/kg/day). This effect appeared to be not reversible after the 2 week recovery period. Slight effects were also observed at the low dose level (0.5 mg/kg/day). They were not considered to be adverse, but they were the first step of a dose-related effect which became adverse at the 2 higher dose levels (2.5 and 8.0 mg/kg/day). Therefore, none of the dose levels investigated may be considered the No Observed Effect Level (NOEL) in this 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 4 consecutive weeks, and to investigate possible recovery from any treatment-related effects, during a 2 week recovery period.

The study design was in agreement with the procedures described in OECD Guideline No. 407 adopted on 27 July 1995 and with those described by Japanese METI (Ministry of Economy, Trade and Industry), of 13 July 1974 and subsequent revisions.

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 0.5, 2.5 and 8.0 mg/kg/day were defined in agreement with the Sponsor based on information from preliminary studies.

Each main group comprised 5 male and 5 female rats. Control and high dose groups included 5 additional animals per sex that were killed after 2 weeks of recovery. One satellite group for toxicokinetics comprised 9 female animals.
No treatment was given during the recovery period.

The animals were assigned to treatment groups on 9 June 2004 and dosing began on 16 June 2004. Necropsies of main groups were completed by 15 July 2004 and recovery groups by 28 July 2004. The protocol is presented in Addendum V.

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	: 90156/96-2
Purity	: >85% (referred to dicarboxy chain ends perfluoropolyethers)
Expiry date	: Not applicable for this product
Received from	: SOLVAY SOLEXIS
Date received	: 25th February 2004
Amount received	: Approximately 197 grams
Description	: White granules
Container	: Colourless glass bottle
Storage at RTC	: Ambient conditions
RTC reference number	: 8681

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 0.05, 0.25 and 0.8 mg/ml.

Prior to commencement of treatment the proposed formulation procedure was checked by chemical analysis to confirm that the method was acceptable. Stability over a 24 hour period at room temperature was previously assessed for content check. Samples of the formulations prepared in weeks 1 and 4 were analysed to check the concentration. Results of all the analyses were within the limits of acceptance (95-105%). Results of these analyses, carried out by the Analytical Chemistry Department at RTC, are presented in Addendum III of this report.

4. METHODS

4.1 Test system

4.1.1 Animal supply and acclimatisation

A total of 83 Hsd: Sprague Dawley SD rats (36 males and 47 females, not 80 as indicated in the protocol) 27-29 days old and within a weight range of 92-103 g for males and females, with females nulliparous and non-pregnant, were supplied on 14 May 2004, by Harlan Italy s.r.l., 33049 San Pietro al Natisone (UD), Italy. Animals were ordered in the weight range of 75-80g (and not 75-99g as indicated in the protocol) and therefore, were supplied slighly 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 33 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 (Altromin MT pelleted diet, Altromin, Lange Str. 42, D-3279 Lage, Germany) 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 for main group animals, all animals were weighed.
The rats were then allocated to the 5 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 feet and ear notch. Animals of the main groups were housed 5 of one sex per cage and those of the satellite group 3 per cage. The cages were identified by a label, colour-coded according to group and 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. This resulted in a cage distribution designed to minimise possible environmental effects (Figure 1). Cages of the satellite group animals were arranged in 1 rack, separated from the other dose groups. This was a deviation from the protocol.

4.2 Treatment

4.2.1 Dose levels, group size and identification

Each main group comprised 5 male and 5 female rats. Control and high dose groups included 5 additional animals per sex to be sacrificed after 2 weeks of recovery. One satellite group for toxicokinetics comprised 9 female animals. The group identification and animal numbers assigned to the treatment are summarised below:

MAIN GROUPS

Group Number:	Treatment (mg/kg/day)+	Level	Rat numbers			
			Main phase		Recovery phase	
			M (even)	F (odd)	M (even)	F (odd)
1	0.0	Control	2 - 10	1 - 9	12 - 20	11- 19
2	0.5	Low	22 - 30	21 - 29		
3	2.5	Medium	32 - 40	31 - 39		
4	8.0	High	42 - 50	41 - 49	52 - 60	51 - 59
+: in terms of test item as supplied						

SATELLITE GROUP

Group Number:	Treatment (mg/kg)	Level	Rat numbers Females (odd)
5	8.0	High	61 - 77

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.

4.2.2 Administration of test item

The test item was administered orally by gavage at a dose volume of 10 ml/kg body weight. Control animals received the vehicle alone 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.

4.2.3 Duration of treatment

All animals of the main and recovery groups were dosed once a day for a minimum of 4 consecutive weeks. All animals of the main groups were dosed up until the day before necropsy. No treatment was given during the recovery period. Satellite group animals were dosed once only.

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 to look for dead or moribund animals. 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 (Main groups)

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 up to Day 7 of the study. Since no animals showed any post-dose effects, examinations were reduced to pre-dose, immediately after and approximately 1 hour after dosing until the end of treatment.

4.3.3 Clinical signs and neurotoxicity assessment (Main groups)

All clinical signs were recorded for individual animals. Once before commencement of treatment and once a week thereafter each animal was subjected to a detailed clinical examination, which included an evaluation of neurotoxicity. Animals were examined in an open arena for a period of three minutes. Observed parameters, described by an evaluation scale, are indicated below:

Removal (from cage):	Easy, Difficult, Very difficult
Handling reactivity:	Normal, Slight, Moderate, Marked
Lachrymation:	Absent, Slight, Marked
Palpebral closure:	Absent, Slight, Moderate, Marked
Salivation:	Absent, Slight, Marked
Piloerection:	Absent, Present
Rearing:	Absent, Intervals of number of times (i.e. 1–3, 4-7, 8-10)
Spasms:	Absent, Tonic spasms, Clonic spasms, Tonic-clonic spasms
Myoclonia:	Absent, Present
Mobility impairment:	Absent, Slight, Moderate, Marked
Arousal (animal activity):	Very slow, Slow, Normal, Moderate, Marked
Vocalisation:	Absent, Present
Stereotypies:	Absent, Present
Unusual respiratory pattern:	Absent, Present
Bizarre behaviour:	Absent, Present
Urination:	Absent, Intervals of number of times (i.e. 1–3, 4-6)
Defecation:	Absent, Intervals of number of times (i.e. 1–3, 4-6)
Tremors :	Absent, Present

Gait (one of the following options):	Normal Ataxia (Slight, Moderate, Marked) Hunched (Slight, Moderate, Severely) Pronation Fore limbs drag (Slight, Moderate, Marked) Hind limbs drag (Slight, Moderate, Marked)

All observed parameters, with the exception of the pre-dose, are reported in a group incidence table. Individual data are not included in this report.
Once during week 4 of treatment and once during week 2 of recovery, an evaluation of sensory reactivity to stimuli of different modalities (e.g. auditory, visual and proprioceptive stimuli) and assessment of grip strength were also performed.

4.3.4 Motor activity assessment (MA) (Main groups)

The motor activity of all animals was measured once during week 4 of treatment and week 2 of recovery by an automated activity recording device. Measurements were performed using a computer generated random order.

4.3.5 Body weight

All animals were weighed on the day of allocation to treatment groups, on the day that treatment commenced, weekly thereafter and just prior to necropsy. Satellite group animals were weighed on allocation and on the day of dosing only.

4.3.6 Food consumption (Main groups)

The weight of food consumed by each cage of rats was recorded weekly following allocation and the group mean daily intake per rat calculated.

4.4 Clinical pathology investigations (Main groups)

Once during week 4 of the treatment period and again during week 2 of the recovery period, samples of blood were withdrawn under light ether anaesthesia from the retro-orbital sinus of all male and female animals, under conditions of food and water deprivation. Once during weeks 4 of treatment and 2 of recovery individual overnight urine samples were also collected from the same animals under the same conditions. Before starting urine collection animals were transferred to metabolic cages (with no water bottles or food) and each animal received approximately 10 ml/kg of drinking water by gavage, in order to obtain urine samples suitable for analysis. Blood samples were collected into tubes containing EDTA anticoagulant for haematological investigations, heparin anticoagulant for biochemical tests and citrate anticoagulant for coagulation tests.
Blood samples were collected and analysed in the same order, a computer-generated random cage order being used.
The measurements performed on blood and urine 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
Gamma -Glutamyltransferase
Urea
Creatinine
Glucose
Triglycerides
Phosphorus
Albumin
Globulin
Albumin/globulin ratio
Total bilirubin
Total cholesterol
Total protein
Sodium
Potassium
Calcium
Chloride

4.4.3 Urinalysis

Appearance
Volume
Specific gravity
pH
Protein
Total reducing substances
Glucose
Ketones
Bilirubin
Urobilinogen
Blood

The sediment, obtained from centrifugation at approximately 3000 rpm for 10 minutes, was examined microscopically for:

Epithelial cells
Polymorphonuclear leucocytes
Erythrocytes
Crystals
Spermatozoa and precursors
Other abnormal components

4.5 Toxicokinetics (Satellite group)

Blood samples were collected at 9 points on the day of dosing from all animals of the satellite group as indicated in following scheme:

Group Number:	Treatment (mg/kg)	Animal Number (Males)	Time points (hours)
5	8.0	61, 63, 65 67, 69, 71 73, 75, 77	0, 4, 24 2, 8, 96 6, 48, 168

At each sampling time approximately 0.8 ml blood samples were collected from the tail vein of each animal as indicated above. Samples were transferred into tubes containing heparin anticoagulant, centrifuged and the plasma frozen at –20°C. Analysis of the samples was carried out by the Analytical Chemistry Department of RTC.
Satellite group animals were dosed once only. Satellite group animals were killed at the end of the last bleeding procedure and no necropsy was performed in these animals.

The following parameters were calculated according to standard non-compartmental analysis:

C_{max} : maximum observed plasma concentration
T_{max} : time to C_{max}
$t_{½}$: half life
AUC : area under the concentration-time curve calculated by the linear trapezoidal rule

Means, standard deviations and kinetic parameters were obtained using a suitable Microsoft Excel Worksheet. Values identified in the tables as BLQ were considered as zero in the calculation of means and standard deviations for plasma levels.

4.6 Terminal studies (Main groups)

4.6.1 Euthanasia

All animals were killed by carbon dioxide at the end of the scheduled treatment period and were subjected to necropsy supervised by a pathologist, as detailed below.

4.6.2 Necropsy

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

4.6.3 Organ weights

From all animals, the organs indicated in Section 4.6.6, were dissected free of fat and weighed. The ratios of organ weight to body weight were calculated for each animal.

4.6.4 Tissues fixed and preserved

Samples of all the tissues listed in Section 4.6.6 were fixed and preserved in 10% buffered formol saline (except eyes 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). An extra liver sample was taken from all main group animals and frozen at –80°C (see section 4.6.7).

4.6.5 Histopathological examination

Tissues listed in Section 4.6.6 were fixed and preserved. After dehydration and embedding in paraffin wax, sections of the tissues were cut at 5 micrometre thickness and stained with haematoxylin and eosin. In the first instance, the examination was carried out as detailed below:

a) Tissues specified in Section 4.6.6 from all animals in the control and high dose groups of the main phase.
b) Tissue abnormalities from all main groups.

On the basis of the results obtained, in agreement with the Sponsor, the examination was extended to the liver, seminal vescicles, lungs, thymus and kidneys of low and mid-dose group animals and to the animals which underwent 2 weeks of recovery.

4.6.6 Annex 1 of the Study Protocol

Organs / Tissues	Weight	Fixation Preservation	Microscopic Examination
Abnormalities		✓	✓
Adrenal glands	✓	✓	✓
Bone marrow (from sternum)		✓	✓
Brain	✓	✓	✓
Caecum		✓	✓
Colon		✓	✓
Duodenum		✓	✓
Eyes		✓	*
Epididymides	✓	✓	✓
Heart	✓	✓	✓
Ileum (including Peyer's patches)		✓	✓
Jejunum		✓	✓
Kidneys	✓	✓	✓
Liver	✓	✓	✓
Lungs (including mainstem bronchi)		✓	✓
Lymph nodes - mesenteric		✓	✓
Lymph nodes - cervical		✓	✓
Ovaries	✓	✓	✓
Oviducts[a]		✓	✓
Parathyroid glands[b]		✓	✓
Pituitary gland		✓	✓
Prostate gland		✓	✓
Rectum		✓	✓

*: not examined as no signs of toxicity were observed.
[a]: weighed and preserved with ovaries
[b]: weighed and preserved with thyroid glands

Organs / Tissues	Weight	Fixation Preservation	Microscopic Examination
Sciatic nerve		✓	✓
Seminal vesicles		✓	✓
Spinal column		✓	*
Spinal cord		✓	✓
Spleen	✓	✓	✓
Stomach		✓	✓
Testes	✓	✓	✓
Thymus (where present)	✓	✓	✓
Thyroid	✓	✓	✓
Trachea		✓	✓
Urinary bladder		✓	✓
Uterus - Cervix		✓	✓

*: not examined as no signs of toxicity were observed.

4.6.7 Liver enzymes

Following removal of liver sections for histopathological examination, all remaining tissues (approximately 4 g, taken from the left lateral lobe) were rinsed in ice-cold physiological saline, then placed into individual packages (one per animal) and immediately frozen in liquid nitrogen (–80°C).
No analysis of these samples was carried out as it was not requested by the Sponsor.
This was a deviation from the protocol which indicated to carry out these analyses in the case of treatment-related findings in the liver.

4.7 Statistical analysis

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.

4.8 Deviations from protocol

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

4.9 Archives

Full records were maintained of all aspects of study conduct, together with the results of all measurements and observations.
All specimens, raw data, records and documentation generated during the course of this study will be retained within the archive at RTC. The data will be kept for a period of at least 3 years after which the Sponsor will be contacted for instructions regarding despatch or disposal of the material. Biological samples will be destroyed shortly after the issue of the Final Report.

5. RESULTS

5.1 Mortality (Appendix 1)

One female animal dosed at 8.0 mg/kg/day was found dead on Day 28 of treatment following the bleeding procedure. Clinical signs were seen in this animal on the day of death. The animal was hypoactive, pale, cold to touch and showed breathing difficulties, dark urine and semi-closed eyes following bleed and just prior to death. On the basis of the findings of microscopic examinations, this death may be considered treatment-related.

5.2 Pre- and post-dose observations and weekly clinical signs (Open field measurements) (Tables 1 and 2)

Daily post-dose observations were limited to tremors, noted in a single male animal dosed at 8.0 mg/kg/day for 1 day only.
Detailed clinical signs with neurotoxicity assessment did generally not show any signs which could be correlated to the treatment with the test item. Mobility impairment, slight ataxia and tremors were noted in 1 male animal dosed at 8.0 mg/kg/day on a single occasion.

5.3 Sensory reaction to stimuli and motor activity (Table 3; Appendices 2 and 3)

Neurotoxicity tests and motor activity measurements performed at the end of treatment and recovery periods did not show changes which could be ascribed to treatment.

5.4 Body weight (Figure 2; Tables 4 and 8; Appendix 4)

Body weights were significantly reduced in the high dose animals from Day 15 (7% and 6% less than controls in the males and females, respectively) up to the end of the treatment period, when reductions of 20% (main group animals) and 24% (recovery animals) were noted in the males and 6% (main group animals) and 9% (recovery animals) in the females when compared to controls. Terminal body weight was also statistically significantly reduced in the high-dose animals (21% in the males and 11% in the females). These reductions were still evident until the end of the recovery period (up to 25% in the males and 10% in the females).

5.5 Food consumption (Appendix 5)

No significant variations in food consumption were observed during treatment or recovery periods.

5.6 Haematology (Table 5; Appendix 6)

Statistically significant reductions of the white blood cell count (25% less than controls) were seen in the high-dose males at the end of treatment period. This reduction, though not statistically significant, was still present at the end of recovery. A dose-related decrement trend in the neutrophil, basophil and eosinophil values was observed also in the recovery, even if not statistically significant. A statistically significant reduction in platelets was also observed in the high dose females (20% less than controls). This difference was no longer evident at the end of recovery. No toxicological importance was attributed to this or to the other statistically significant variations observed at the end of treatment or recovery periods, as they were considered to be incidental.

5.7 Clinical chemistry (Table 6; Appendix 7)

Significant increases of alkaline phosphatase (76% and 78% in the mid and high males, 36% and 60% in the mid and high dose females), alanine aminotranferase (58% in the high dose females), aspartate aminotransferase (50% in the high dose males and 42% in the high dose females), triglycerides (35 and 40% in the mid and high dose males, 51%, 75% and 67% in the low, mid and high dose females), urea (30%, 22% and 46% in the low, mid and high dose males, 21% and 24% in the mid and high dose females), and decrease of creatinine (26% and 29% in the mid and high dose males) were observed in the treated animals when compared to controls, at the end of the treatment period. Total protein was statistically significantly reduced in the mid and high dose males (15% and 27% less than controls) and in the high dose females (reduction of 14%). In addition, variations of electrolytes (increase of chloride and potassium and decrease of calcium) were observed in the animals from all treated groups. Most of the values of clinical pathology parameters recorded for animal No. 27080043 were not included in the calculation of the above percentages, as these were so high to upset the means. Usually, the observed changes showed a dose-related trend. The majority of the observed changes were still present at the end of the recovery period. The toxicological significance of the above changes was amply supported by the changes observed in the liver and kidneys at histopathological examination.
Although some of the observed changes (triglycerides and urea increases and electrolyte variations) were also evident in the animals dosed at 0.5 mg/kg/day, they were not considered to be adverse, being of lower severity when compared to those observed at the higher dose levels and within the normal range of historical control data.

5.8 Urinalysis (Table 7; Appendix 8)

A dose-related increase of urine volume, statistically significant in the mid and high-dose groups (35% and 59% greater than controls), was noted in the treated females at the end of the treatment period. A slight reduction of protein was also observed in the high dose animals at the end of treatment. These changes were still evident at the end of recovery.

5.9 Toxicokinetic analysis (Figure 3; Addendum IV)

Detectable plasma levels of the test item were measured between 2 and 168 hours after dosing in the animals dosed at 8.0 mg/kg. The maximum plasma level (C_{max}) was 16050.0 ng/ml. C_{max} was measured 6 hours after dosing (t_{max}). A half-life (t½) of approximately 58 hours was estimated. The $AUC_{(6\text{-}168h)}$ was calculated to be 873415 ng/ml·h and the $AUC_{(inf)}$ was calculated to be 1069642 ng/ml·h.

5.10 Organ weights (Tables 9 and 10; Appendices 9 and 10)

Dose-related, statistically significant increases in absolute and relative liver weights were noted in all treated males (27%, 54% and 34% greater than controls for absolute, 21%, 53% and 70% for relative) and females (21%, 38% and 43% greater than controls for absolute weights, 39% and 62% in mid- and high dose groups for relative weights) at the end of the treatment period. These increases were still present at the end of the recovery period. Statistically significant reductions of the absolute (42% in the high dose males, 21% and 39% in the mid- and high dose females) and relative (27% in the high dose males, 21% and 32% in the mid- and high dose females) weights of the spleen were also observed at termination of the treatment period.

In addition the absolute and/or relative weights of the thymus were reduced in high dose animals (relative showing a reduction of 57% in the males) and the relative weights of the thyroid and testes were significantly increased in the high dose animals at the end of treatment. Also a statistical significant increase in the weight of the kidneys was observed in the high dose males.
Some of these organs (liver, kidneys, testes and thymus) still showed statistically significant differences from controls at the end of recovery.

These changes, supported by findings observed at macroscopic and microscopic examination of these organs, were regarded as an effect of the treatment with the test item, which was not reversible over a 2 week recovery period. No other significant changes were observed.

5.11 Macroscopic observations (Table 11; Appendix 11)

The most relevant changes, observed at necropsy of the early decedent animal, were incomplete collapse of the lungs considered to be an agonal phenomenon, and pale colour of the liver and pancreas and a scab on the head.
Enlargement of the liver, sometimes accompanied by swollen shape of the organ, was reported in 4/5 males and 1/5 females from both groups 3 and 4. Decreased size of the thymus was seen in 4/5 group 4 males and 1/5 group 4 females. Decreased size of the seminal vesicles was reported in 2/5 males from the same group.
The above described changes were still evident in the treated males, killed after the 2-week recovery period, when enlargement of the liver was described in all group 4 males and decreased size of the thymus was reported in 4/5 males. Decreased size of the seminal vesicles was observed in 1 group 4 animal.
The remaining changes reported in the animals sacrificed after completion of the scheduled test periods and in the unscheduled dead animal were considered to be incidental or spontaneous in origin.

5.12 Microscopic observations (Table 12; Appendix 11)

Unscheduled death: The most important changes observed in the animal which was found dead on day 28 of the study were observed in the liver where multifocal, moderate haemorrhage, moderate hepatocytic hypertrophy and single cell apoptosis/necrosis were reported; in addition the following changes were seen, moderate atrophy of the thymus and mild lymphoid depletion of the the spleen; mineralization in the cortico-medullary junction of the kidney; acinar cell apoptosis in the pancreas; ulceration and presence of scabs from the sample of skin taken from the head.

Final sacrifice: treatment-related changes were noted in the liver, lungs, thymus, kidneys and seminal vesicles of high and mid-dose group animals, sacrificed after 4 weeks of treatment. These changes were described as follows:
Liver: panlobular hepatocytic hypertrophy, suggestive of an adaptive change, was observed in all high and mid-dose group animals. In the high dose group mainly, this finding was occasionally accompanied by hepatocytic vacuolation, single cell necrosis/apoptosis and increased incidence and severity degree of bile duct proliferation and inflammatory cell foci, when compared to the values reported in the controls.
These two last changes were considered linked to an inflammatory response to the liver cell damage and regarded as reaction and repair processes.
Lungs: aggregation of alveolar macrophages was seen in the lungs of 4/5 high dose and 1/5 mid-dose males and in 3/5 high dose females. Such a finding could be possible suggestive of a phospholipidosis condition. Only 1 control animal showed this finding, but it was considered part of a chronic inflammatory process, also characterised by bronchial and alveolar haemorrhage, oedema and eosinophilic infiltrates.

Thymus: slight to moderate thymus atrophy was observed in 5/5 males and 3/5 females from the high dose group and 1/5 mid-dose group males. This lesion showed a higher severity degree in the males, when compared to female animals and could be considered a secondary effect due to the poor general condition of the animals.
Seminal vesicles: colloid depletion was described in 5/5 high dose treated males. Also this change could be considered a secondary effect due to the poor general condition of the animals. Colloid depletion was also observed in one control animal, but it was associated with unilateral testicular aplasia and it was therefore considered expression of spontaneous pathology.
Kidney: foci of mineralization were observed in the papilla, medulla or cortical-medullary junction of the kidneys from 4/5 high dose and 1/5 mid-dose group females.
Recovery sacrifice: only a partial remission of the changes considered related to the administration of the test item, represented by a reduction in the incidence and/or severity level, was noted in the treated animals, killed after the 2-week recovery period. Some of the treated animals still showed both adaptive and degenerative changes described in the liver, like hepatocytic hypertrophy, hepatocytic vacuolation and single cell apoptosis/necrosis. Aggregations of alveolar macrophages were still visible in the lungs of 2/5 males. Thymic atrophy was again reported in 5/5 males and in 3/5 females. Colloid depletion was described in the seminal vesicles of 2/5 males only. Focal mineralization was still observed in the various zones of the kidneys from 2/5 treated females.
The remaining changes observed in all the tissues/organs examined were considered to be spontaneous or incidental in origin.

6. CONCLUSION

The oral toxicity of [redacted] when given by daily administration to rats at dosages of 0.5, 2.5 and 8.0 mg/kg/day has been investigated over a period of 4 weeks and possible recovery from any treatment-related changes over a 2 week recovery period.

No significant clinical signs or post-dose reactions were observed during the "in-life" phase of the study. Slight reductions in body weight gain were noted in the high dose animals, mainly in the males. These resulted in a reduced body weight of the high dose animals when compared to controls. Body weights were statically significantly reduced also at the end of the recovery period.
A reduction in white blood cell count was observed in the high dose males at the end of treatment and recovery periods. This reduction was slight and limited to one sex. However, it was considered a treatment-related change, as it could be correlated to the thymus atrophy observed in all male animals from the high-dose group.

A number of clinical chemistry parameters showed changes at the end of treatment, mainly in the mid- and high dose animals (total cholesterol and creatinine decreases were evident only in the males). Most of the observed variations were still evident at the end of recovery. Some of the observed variations were still present only in the males at the end of recovery. These changes were a clear indication of a toxic effect of the test item to the liver, supported by the *post-mortem* findings reported for this organ.
The absolute and relative weights of the liver were significantly increased in animals of both sexes from all treated groups at the end of treatment and recovery periods. The increase of the liver weights noted in the low-dose group animals (0.5 mg/kg/day), although not supported by any significant microscopic change, was an indication of some treatment-related effect. Weights of the thymus and spleen were significantly reduced in males and females from mid and/or high-dose groups. In addition, weight of thyroid was increased in high dose animals, while those of the kidneys and testes were increased in high-dose males. These changes were not reversible at the end of the 2 week recovery period.
The toxicological significance of the above quoted changes was definitely supported by the changes observed at *post mortem* examination. Enlargement of the liver, sometimes accompanied by swollen shape of the organ, was reported in the majority of the mid and high-dose males and in individual females of the 2 higher dose groups. Decreased size of the thymus was also seen in the high dose animals (mainly in the males).
Treatment-related changes were noted microscopically in the liver, lungs, thymus, kidneys and seminal vesicles of high and mid-dose dose group animals. The liver was the most affected organ.
Panlobular hepatocytic hypertrophy suggestive of an adaptive change, was observed in all high and mid-dose group animals. In the high dose group mainly, this finding was occasionally accompanied by hepatocytic vacuolation, single cell necrosis/apoptosis and increased incidence and severity degree of inflammatory cell foci and bile duct proliferation, when compared to the values reported in the controls. These two last changes were considered linked to an inflammatory response to the liver cell damage and regarded as reaction and repair processes. The observed findings were of lower severity and incidence in female animals.
Thymus atrophy was observed in the high dose animals and in the mid-dose males. This lesion showed a higher severity degree in the males, when compared to female animals and could be considered a secondary effect due to the poor general conditions of the animals, as well as the colloid depletion of seminal vesicles, noted in all the high dose males.
Foci of mineralization were observed in the kidneys from the mid and high-dose females.

Aggregation of alveolar macrophages was seen in the lungs of the high dose animals and in the mid-dose females. Such a finding could be possibly suggestive of a phospholipidosis condition.
Only a partial remission of these changes, represented by a reduction in incidence and/or severity, was noted at the end of recovery.

On the basis of these results, signs of an evident toxic effect of the test item were seen at the 2 higher dose levels (2.5 and 8.0 mg/kg/day). Most of the observed effects were not reversible over a 2 week recovery period in the high dose animals. The males appeared to be more sensitive than females to the test item. Slight effects, although less severe when compared to those observed at the higher dose levels and generally within the normal range of historical control data, were also observed at the low dose level (0.5 mg/kg/day). These were not considered adverse, but they were the first step of a dose-related effect which became adverse at the 2 higher dose levels investigated (2.5 and 8.0 mg/kg/day). Therefore, none of the dose levels investigated may be considered a No Observed Effect Level (NOEL) in this study.

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FIGURE 1 - Group and cage arrangement on battery

STUDY NO.: 27080

MAIN PHASE

Group Number:	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
1	0.0	Control	2 - 10	1 - 9	1	7
2	0.5	Low	22 - 30	21 - 29	3	9
3	2.5	Medium	32 - 40	31 - 39	4	10
4	8.0	High	42 - 50	41 - 49	5	11

RECOVERY PHASE

Group Number:	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
1	0.0	Control	12 - 20	11 - 19	2	8
4	8.0	High	52 - 60	51 - 59	6	12

+: in terms of test item as supplied
No treatment was given during the recovery period.

SATELLITE GROUP

Group Number:	Treatment (mg/kg)+	Level	Rat numbers Females (odd)	Cage numbers
5	8.0	High	61 - 77	13-15

+: in terms of test item as supplied

MAIN PHASE

Group/Sex
Cage no.

Males	Females
1M 4M^{R} 1 6	1F 4F^{R} 7 12
2M 3	2F 9
3M 4	3F 10
4M 5	4F 11
1M^{R} 2	1F^{R} 8

^{R} = Recovery

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FIGURE 1 - Group and cage arrangement on battery

STUDY NO.: 27080

RECOVERY PHASE

Group/Sex	Cage no.
	Males Females
$1M^R$ $1F^R$	2 8
$4M^R$ $4F^R$	6 12

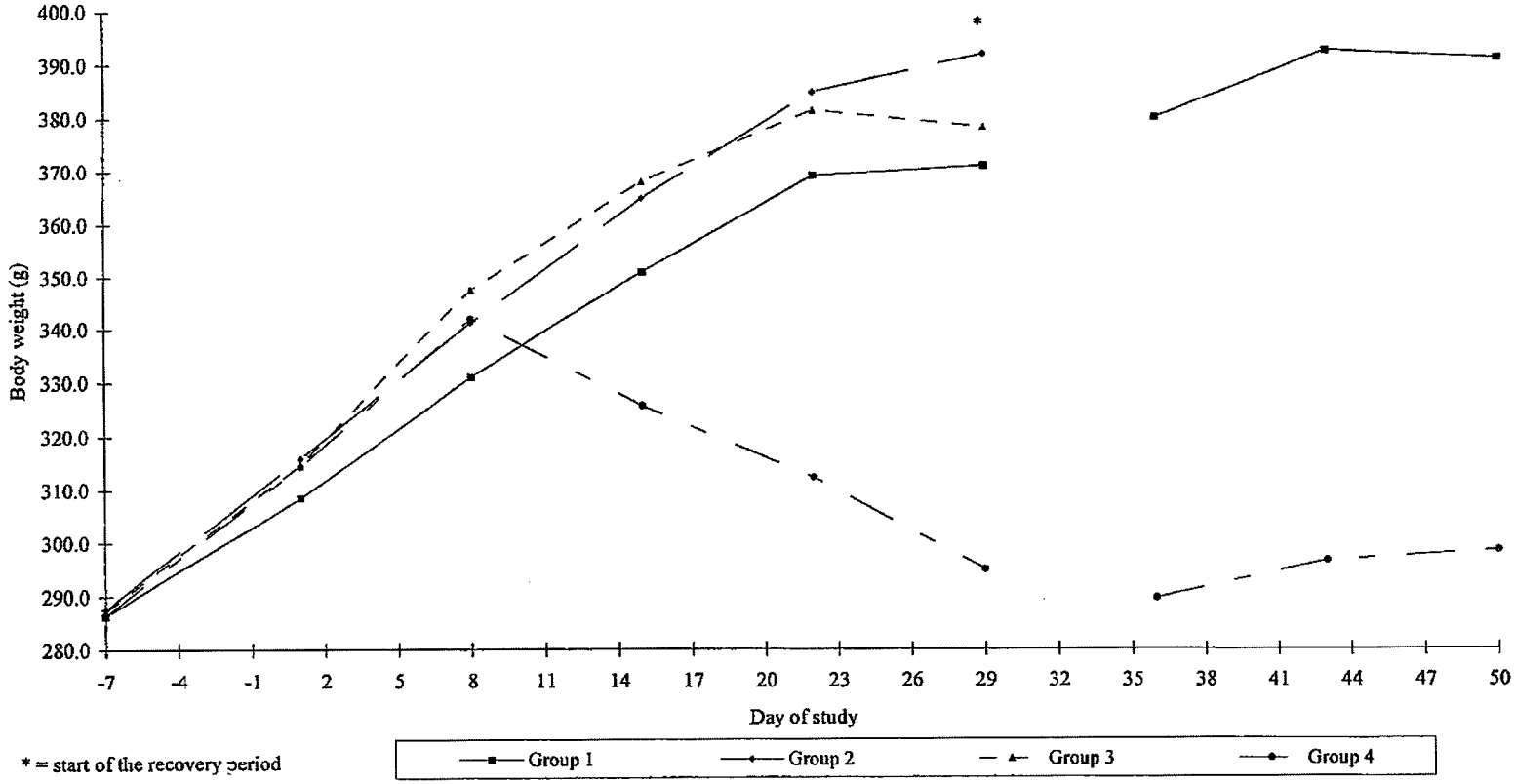
SATELLITE GROUP

Group/Sex	Cage no.
	Females
5F	13
5F	14
5F	15

[redacted]4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FIGURE 2.1 - Body weight versus day of study - Males

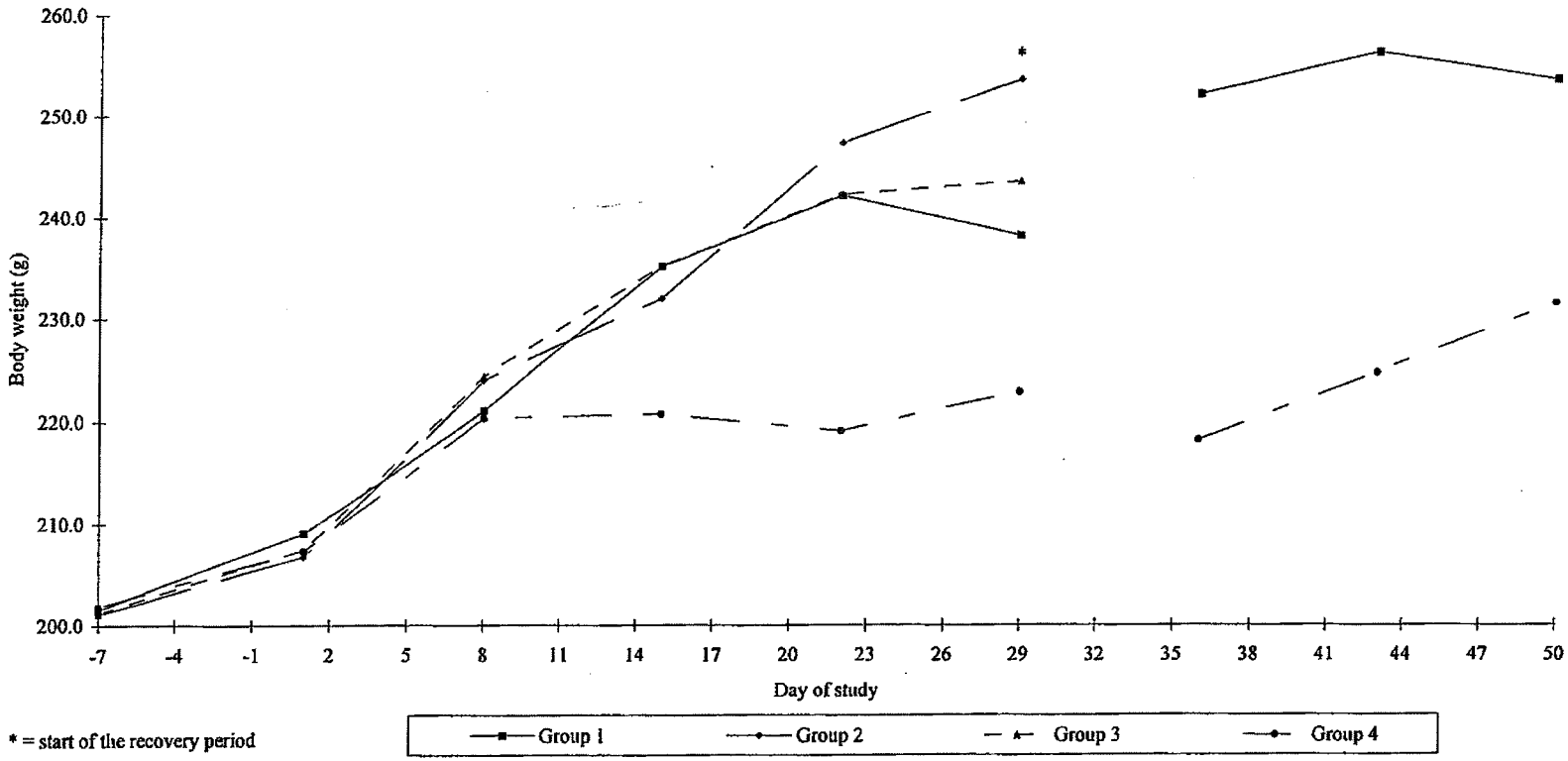
STUDY NO.: 27080



[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FIGURE 2.2 - Body weight versus day of study - Females

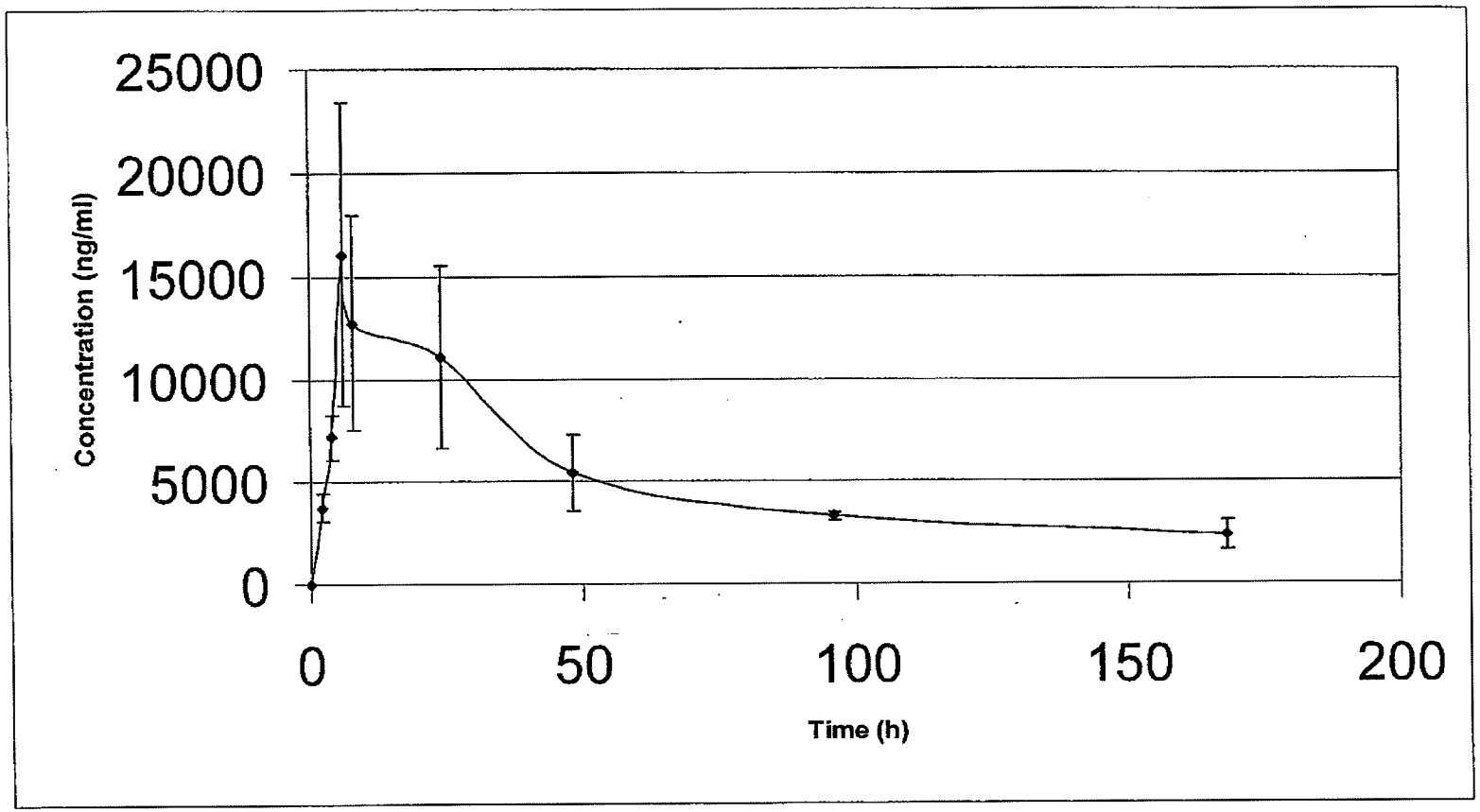
STUDY NO.: 27080



[redacted]4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FIGURE 3 - Plasma levels of [redacted]

STUDY NO.: 27080



[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: 27080

MALES

Interval: 1 - 4 Weeks

Group	1 (10)		2 (5)		3 (5)		4 (10)	
Observation	a	b	a	b	a	b	a	b
BEHAVIOUR - ACTIVITY								
Leaning to one side	1	4.0	0	0.0	0	0.0	0	0.0
APPEARANCE								
Scab(s)	0	0.0	0	0.0	0	0.0	1	1.0
Staining	1	1.0	0	0.0	0	0.0	0	0.0
Hairloss	1	2.0	0	0.0	0	0.0	0	0.0
EYE - EAR - MOUTH								
Ocular discharge	1	1.0	0	0.0	0	0.0	0	0.0
REMOVAL								
Removal easy	10	4.0	5	4.0	5	4.0	10	4.0
HANDLING REACTIVITY								
Handling reactivity slow	1	2.0	0	0.0	0	0.0	0	0.0
Handling reactivity normal	10	3.8	5	4.0	5	4.0	10	4.0
LACHRYMATION								
Lachrymation absent	10	4.0	5	4.0	5	4.0	10	4.0
PALPEBRAL CLOSURE								
Palpebral closure absent	10	4.0	5	4.0	5	4.0	10	4.0
SALIVATION								
Salivation absent	10	4.0	5	4.0	5	4.0	10	4.0

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

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: 27080

MALES

Interval: 1 - 4 Weeks Group Observation	1 (10)		2 (5)		3 (5)		4 (10)	
	a	b	a	b	a	b	a	b
PILOERECTION								
Piloerection absent	10	4.0	5	4.0	5	4.0	10	4.0
REARING								
Rearing absent	2	1.0	1	2.0	2	1.0	5	1.4
Rearing 1 - 3	2	2.5	2	1.0	1	1.0	6	1.3
Rearing 4 - 7	5	2.0	2	1.5	3	1.3	7	1.3
Rearing 8 - 10	5	1.0	2	2.0	4	1.3	6	1.0
Rearing 11 - 14	4	1.0	2	1.0	4	1.5	2	1.5
Rearing 15 - 20	6	1.5	3	1.7	2	1.0	4	1.3
Rearing 21 - 30	4	1.3	1	2.0	0	0.0	3	1.0
SPASMS								
Spasms absent	10	4.0	5	4.0	5	4.0	10	4.0
MYOCLONIA								
Myoclonia absent	10	4.0	5	4.0	5	4.0	10	4.0
GAIT								
Normal gait	10	4.0	5	4.0	5	4.0	10	4.0
Slight ataxia	0	0.0	0	0.0	0	0.0	1	1.0
MOTILITY IMPAIRMENT								
motility impairment absent	10	4.0	5	4.0	5	4.0	10	4.0
motility impairment slight	0	0.0	0	0.0	0	0.0	1	1.0
AROUSAL								
Arousal normal	10	3.5	5	3.4	5	4.0	10	3.3
Arousal very slow	1	1.0	1	2.0	0	0.0	1	2.0
Arousal slow	2	1.5	0	0.0	0	0.0	4	1.5
Arousal moderate	1	1.0	1	1.0	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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: 27080

MALES

Interval: 1 - 4 Weeks Group	1 (10)		2 (5)		3 (5)		4 (10)	
Observation	a	b	a	b	a	b	a	b
VOCALISATION								
Vocalisation absent	10	4.0	5	4.0	5	4.0	10	4.0
STEREOTYPIES								
Stereotypies absent	10	4.0	5	4.0	5	4.0	10	4.0
UNUSUAL RESPIRATION								
Unusual respiration absent	10	4.0	5	4.0	5	4.0	10	4.0
BIZARRE BEHAVIOUR								
Bizarre behaviour absent	10	4.0	5	4.0	5	4.0	10	4.0
URINATION								
Urination absent	8	1.5	4	2.3	4	1.5	10	2.3
Urination 1 - 3	3	2.0	3	1.3	4	1.5	8	1.8
Urination 4 - 6	5	1.2	0	0.0	4	1.3	3	1.0
Urination 7 - 9	5	1.8	1	1.0	1	1.0	0	0.0
Urination more than 10	5	1.4	3	2.0	2	1.0	1	1.0
DEFECATION								
Defecation absent	10	4.0	5	3.8	5	4.0	10	4.0
Defecation 1 - 3	0	0.0	1	1.0	0	0.0	0	0.0
TREMORS								
Tremors absent	10	4.0	5	4.0	5	4.0	10	4.0
Tremors present	0	0.0	0	0.0	0	0.0	1	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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: 27080

FEMALES

Interval: 1 - 4 Weeks Group Observation	1 (10)		2 (5)		3 (5)		4 (10)	
	a	b	a	b	a	b	a	b
BEHAVIOUR - ACTIVITY								
Aggressive	1	4.0	0	0.0	0	0.0	0	0.0
APPEARANCE								
Abrasion	0	0.0	0	0.0	0	0.0	1	2.0
Scab(s)	0	0.0	0	0.0	0	0.0	1	2.0
Hairloss	1	1.0	0	0.0	0	0.0	0	0.0
REMOVAL								
Removal easy	10	4.0	5	4.0	5	4.0	10	4.0
HANDLING REACTIVITY								
Handling reactivity normal	*9	4.0	5	4.0	5	4.0	10	4.0
LACHRYMATION								
Lachrymation absent	10	4.0	5	4.0	5	4.0	10	4.0
PALPEBRAL CLOSURE								
Palpebral closure absent	10	4.0	5	4.0	5	4.0	10	4.0
SALIVATION								
Salivation absent	10	4.0	5	4.0	5	4.0	10	4.0
PILOERECTION								
Piloerection absent	10	4.0	5	4.0	5	4.0	10	4.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal
* = Sign inadvertently not recorded for 1 animal

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: 27080

FEMALES

Interval: 1 - 4 Weeks Group	1 (10)		2 (5)		3 (5)		4 (10)	
Observation	a	b	a	b	a	b	a	b
REARING								
Rearing 1 - 3	0	0.0	1	1.0	0	0.0	0	0.0
Rearing 4 - 7	4	1.3	1	1.0	1	1.0	4	1.3
Rearing 8 - 10	6	1.3	2	1.0	2	1.0	4	1.8
Rearing 11 - 14	6	1.3	3	2.3	4	1.8	6	1.3
Rearing 15 - 20	6	2.0	4	1.3	4	1.8	7	1.9
Rearing 21 - 30	5	1.2	2	2.0	2	1.0	5	1.0
Rearing more than 30	1	1.0	0	0.0	1	1.0	2	1.0
SPASMS								
Spasms absent	10	4.0	5	4.0	5	4.0	10	4.0
MYOCLONIA								
Myoclonia absent	10	4.0	5	4.0	5	4.0	10	4.0
GAIT								
Normal gait	10	4.0	5	4.0	5	4.0	10	4.0
MOTILITY IMPAIRMENT								
Motility impairment absent	10	4.0	5	4.0	5	4.0	10	4.0
AROUSAL								
Arousal normal	10	3.7	5	3.6	5	3.8	10	4.0
Arousal moderate	1	3.0	1	2.0	1	1.0	0	0.0
VOCALISATION								
Vocalisation absent	10	4.0	5	4.0	5	4.0	10	4.0

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

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: 27080

MALES

Interval: 1 - 4 Weeks Group Observation	1 (10)		2 (5)		3 (5)		4 (10)	
	a	b	a	b	a	b	a	b
STEREOTYPIES								
Stereotypies absent	*9	4.0	5	4.0	5	4.0	10	4.0
UNUSUAL RESPIRATION								
Unusual respiration absent	10	4.0	5	4.0	5	4.0	*9	4.0
BIZARRE BEHAVIOUR								
Bizarre behaviour absent	10	4.0	5	4.0	5	4.0	10	4.0
URINATION								
Urination absent	10	3.5	5	3.4	5	2.6	10	3.2
Urination 1 - 3	3	1.0	3	1.0	2	1.5	3	1.3
Urination 4 - 6	0	0.0	0	0.0	2	1.0	2	1.0
Urination 7 - 9	1	2.0	0	0.0	1	1.0	2	1.0
Urination more than 10	0	0.0	0	0.0	1	1.0	0	0.0
DEFECATION								
Defecation absent	10	4.0	5	4.0	5	4.0	10	4.0
TREMORS								
Tremors absent	10	4.0	5	4.0	5	4.0	10	4.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal
* = Sign inadvertently not recorded for 1 animal

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: 27080

MALES

Interval: 1 - 2 Weeks Group Observation	1 (5)		4 (5)	
	a	b	a	b
BEHAVIOUR - ACTIVITY				
Leaning to one side	0	0.0	1	1.0
APPEARANCE				
Scab(s)	0	0.0	2	2.0
Hairloss	1	2.0	0	0.0
EYE - EAR - MOUTH				
Ocular discharge	1	1.0	0	0.0
REMOVAL				
Removal easy	5	2.0	5	2.0
HANDLING REACTIVITY				
Handling reactivity normal	5	2.0	5	2.0
LACHRYMATION				
Lachrymation absent	5	2.0	5	2.0
PALPEBRAL CLOSURE				
Palpebral closure absent	5	2.0	5	2.0
SALIVATION				
Salivation absent	5	2.0	5	2.0
PILOERECTION				
Piloerection absent	5	2.0	5	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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: 27080

MALES

Interval: 1 - 2 Weeks Group Observation	1 (5)		4 (5)	
	a	b	a	b
REARING				
Rearing absent	0	0.0	1	1.0
Rearing 4 - 7	0	0.0	1	1.0
Rearing 8 - 10	1	2.0	1	1.0
Rearing 11 - 14	2	2.0	5	1.2
Rearing 15 - 20	2	2.0	1	1.0
SPASMS				
Spasms absent	5	2.0	5	2.0
MYOCLONIA				
Myoclonia absent	5	2.0	5	2.0
GAIT				
Normal gait	5	2.0	5	2.0
MOTILITY IMPAIRMENT				
motility impairment absent	5	2.0	5	2.0
AROUSAL				
Arousal normal	5	2.0	5	1.8
Arousal slow	0	0.0	1	1.0
VOCALISATION				
Vocalisation absent	5	2.0	5	2.0
STEREOTYPIES				
Stereotypies absent	5	2.0	5	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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: 27080

MALES

Interval: 1 - 2 Weeks Group Observation	1 (5)		4 (5)	
	a	b	a	b
UNUSUAL RESPIRATION				
Unusual respiration absent	5	2.0	5	2.0
BIZARRE BEHAVIOUR				
Bizarre behaviour absent	5	2.0	5	2.0
URINATION				
Urination absent	0	0.0	4	1.8
Urination 1 - 3	2	1.5	1	1.0
Urination 4 - 6	2	1.0	2	1.0
Urination 7 - 9	1	1.0	0	0.0
Urination more than 10	2	2.0	0	0.0
DEFECATION				
Defecation absent	5	2.0	5	2.0
TREMORS				
Tremors absent	5	2.0	5	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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: 27080

FEMALES

Interval: 1 - 2 Weeks Group Observation	1 (5)		4 (5)	
	a	b	a	b
BEHAVIOUR - ACTIVITY				
Aggressive	1	2.0	0	0.0
REMOVAL				
Removal easy	5	2.0	5	2.0
HANDLING REACTIVITY				
Handling reactivity normal	*4	2.0	5	2.0
LACHRYMATION				
Lachrymation absent	5	2.0	5	2.0
PALPEBRAL CLOSURE				
Palpebral closure absent	5	2.0	5	2.0
SALIVATION				
Salivation absent	5	2.0	5	2.0
PILOERECTION				
Piloerection absent	5	2.0	5	2.0
REARING				
Rearing 8 - 10	0	0.0	2	1.0
Rearing 11 - 14	0	0.0	2	1.0
Rearing 15 - 20	2	2.0	3	1.7
Rearing 21 - 30	3	2.0	1	1.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal
* = Sign inadvertently not recorded for 1 animal

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: 27080

FEMALES

Interval: 1 - 2 Weeks Group	1 (5)		4 (5)	
Observation	a	b	a	b
SPASMS				
Spasms absent	5	2.0	5	2.0
MYOCLONIA				
Myoclonia absent	5	2.0	5	2.0
GAIT				
Normal gait	5	2.0	5	2.0
MOTILITY IMPAIRMENT				
MOTILITY impairment absent	5	2.0	5	2.0
AROUSAL				
Arousal normal	4	2.0	5	2.0
Arousal moderate	1	2.0	0	0.0
VOCALISATION				
Vocalisation absent	5	2.0	5	2.0
STEREOTYPIES				
Stereotypies absent	*4	2.0	5	2.0
UNUSUAL RESPIRATION				
Unusual respiration absent	5	2.0	4	2.0
BIZARRE BEHAVIOUR				
Bizarre behaviour absent	5	2.0	5	2.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal
* = Sign inadvertently not recorded for 1 animal

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: 27080

FEMALES

Interval: 1 - 2 Weeks Group Observation	1 (5)		4 (5)	
	a	b	a	b
URINATION				
Urination absent	4	2.0	4	2.0
Urination 1 - 3	0	0.0	1	2.0
Urination 4 - 6	1	2.0	0	0.0
DEFECATION				
Defecation absent	5	2.0	5	2.0
TREMORS				
Tremors absent	5	2.0	5	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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

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

STUDY NO.: 27080

Group	Sex	Observation	Observation Day --->	1	1	1	1	2	2	2	2	3	3	3	3
			Session --->	1	2	3	4	1	2	3	4	1	2	3	4
		No abnormalities detected													
1	M			10	10	10	10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10	10	10	10
1	F			10	10	10	10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10	10	10	10

Note: Data for Dosing phase
Key: Number of animals with sign at least once during session
Session: 1: Pre-dose
2: At dosing
3: Approximately 1 hour after dosing
4: Approximately 2 hours after dosing

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

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

STUDY NO.: 27080

Group	Sex	Observation	Observation Day ---> / Session --->	4 1	4 2	4 3	4 4	5 1	5 2	5 3	5 4	6 1	6 2	6 3	6 4
		No abnormalities detected													
1	M			10	10	10	10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10	10	10	10
1	F			10	10	10	10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10	10	10	10

Note: Data for Dosing phase
Key: Number of animals with sign at least once during session
Session: 1: Pre-dose
2: At dosing
3: Approximately 1 hour after dosing
4: Approximately 2 hours after dosing

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

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

STUDY NO.: 27080

Group	Sex	Observation	Observation Day ---> / Session --->	7 1	7 2	7 3	7 4	8 1	8 2	8 3	9 1	9 2	9 3
		No abnormalities detected											
1	M			10	10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10	10
1	F			10	10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10	10

Note: Data for Dosing phase
Key: Number of animals with sign at least once during session
Session: 1: Pre-dose
2: At dosing
3: Approximately 1 hour after dosing
4: Approximately 2 hours after dosing

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

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

STUDY NO.: 27080

Group	Sex	Observation	Observation Day ---> / Session --->	10 1	10 2	10 3	11 1	11 2	11 3	12 1	12 2	12 3
		No abnormalities detected										
1	M			10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10
1	F			10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10

Note: Data for Dosing phase
Key: Number of animals with sign at least once during session
Session: 1: Pre-dose
2: At dosing
3: Approximately 1 hour after dosing

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

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

STUDY NO.: 27080

Group	Sex	Observation	Observation Day ---> / Session --->	13 1	13 2	13 3	14 1	14 2	14 3	15 1	15 2	15 3
		No abnormalities detected										
1	M			10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10
1	F			10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10

Note: Data for Dosing phase
Key: Number of animals with sign at least once during session
Session: 1: Pre-dose
2: At dosing
3: Approximately 1 hour after dosing

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

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

STUDY NO.: 27080

Group	Sex	Observation	Observation Day ---> / Session --->	16 1	16 2	16 3	17 1	17 2	17 3	18 1	18 2	18 3
		No abnormalities detected										
1	M			10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5
4				10	10	10	9	9	9	10	10	10
1	F			10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10
		Tremors										
1	M			-	-	-	-	-	-	-	-	-
2				-	-	-	-	-	-	-	-	-
3				-	-	-	-	-	-	-	-	-
4				-	-	-	1	1	1	-	-	-
1	F			-	-	-	-	-	-	-	-	-
2				-	-	-	-	-	-	-	-	-
3				-	-	-	-	-	-	-	-	-
4				-	-	-	-	-	-	-	-	-

Note: Data for Dosing phase
Key: Number of animals with sign at least once during session
Session: 1: Pre-dose
2: At dosing
3: Approximately 1 hour after dosing

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

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

STUDY NO.: 27080

Group	Sex	Observation	Observation Day ---> / Session --->	19 1	19 2	19 3	20 1	20 2	20 3	21 1	21 2	21 3
		No abnormalities detected										
1	M			10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10
1	F			10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10

Note: Data for Dosing phase
Key: Number of animals with sign at least once during session
Session: 1: Pre-dose
2: At dosing
3: Approximately 1 hour after dosing

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

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

STUDY NO.: 27080

Group	Sex	Observation	Observation Day ---> / Session --->	22 1	22 2	22 3	23 1	23 2	23 3	24 1	24 2	24 3	25 1	25 2	25 3
		No abnormalities detected													
1	M			10	10	10	10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10	10	10	10
1	F			10	10	10	10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10	10	10	10

Note: Data for Dosing phase
Key: Number of animals with sign at least once during session
Session: 1: Pre-dose
2: At dosing
3: Approximately 1 hour after dosing

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

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

STUDY NO.: 27080

Group	Sex	Observation	Observation Day ---> / Session --->	26 1	26 2	26 3	27 1	27 2	27 3	28 1	28 2	28 3
		No abnormalities detected										
1	M			10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	10	10	10
1	F			10	10	10	10	10	10	10	10	10
2				5	5	5	5	5	5	5	5	5
3				5	5	5	5	5	5	5	5	5
4				10	10	10	10	10	10	a9	9	9

Note: Data for Dosing phase
Key: Number of animals with sign at least once during session
Session: 1: Pre-dose
2: At dosing
3: Approximately 1 hour after dosing
a = Animal no. 43 showed hunched posture, decreased activity, ataxia, tremors, yellow staining around uro-genital region, semi-closed eyes, breathing difficulty, pallor and cold to touch at pre-dose observation. The animal died before dosing.

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

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

STUDY NO.: 27080

Group	Sex	Observation	Observation Day ---> / Session --->	29 / 1	29 / 2	29 / 3
		No abnormalities detected				
1	F			5	5	5
2				5	5	5
3				5	5	5
4				4	4	4

Note: Data for Dosing phase
Key: Number of animals with sign at least once during session
Session: 1: Pre-dose
2: At dosing
3: Approximately 1 hour after dosing

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 3.1 - Motor activity - At the end of treatment - Group mean data

STUDY NO.: 27080

MALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
Counter display	1188.4	205.6	10	1195.8	229.7	5	947.2	212.4	5	1006.4	213.3	10

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

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 3.1 - Motor activity - At the end of treatment - Group mean data

STUDY NO.: 27080

FEMALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
Counter display	1352.0	126.4	10	1232.8	175.7	5	1309.4	289.6	5	1244.7	247.3	10

Controls from group(s): 1 Subgroup(s): 1
Data homogeneous by Bartlett's test Test of significance is Dunnett's test
($) Data inhomogeneous by Bartlett's test Modified t test of significance
* = 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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 3.2 - Motor activity - At the end of recovery - Group mean data

STUDY NO.: 27080

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
Counter display	930.4	225.0	5	762.0	413.8	5

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

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 3.2 - Motor activity - At the end of recovery - Group mean data

STUDY NO.: 27080

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
Counter display	1427.4	151.1	5	1134.6	292.1	5

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

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 4.1 - Body weight (g) - During treatment - Group mean data

STUDY NO.: 27080

MALES

Group(s)		Day of Phase 1!	1"	8	15	22	29
1	(n)	10	10	10	10	10	5
	Mean	286.36	308.50	331.08	351.17	369.32	371.21
	SD	9.00	13.23	13.91	15.29	15.58	18.09
2	(n)	5	5	5	5	5	5
	Mean	287.60	315.97	341.34	365.13	385.06	392.14
	SD	8.95	11.92	16.74	16.87	16.92	19.01
3	(n)	5	5	5	5	5	5
	Mean	287.26	314.80	347.72	368.21	381.64	378.50
	SD	9.87	14.46	18.93	22.00	27.46	23.60
4	(n)	10	10	10	10	10	5
	Mean	286.52	314.49	342.02	325.90**	312.41**	295.67**
	SD	8.98	13.24	11.17	11.97	14.20	14.98

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 4.1 - Body weight (g) - During treatment - Group mean data

STUDY NO.: 27080

FEMALES

Group(s)		Day of Phase 1!	1"	8	15	22	29
1	(n)	10	10	10	10	10	5
	Mean	201.49	209.09	221.08	235.24	242.29	238.41
	SD	6.97	9.10	15.36	12.12	7.85	9.48
2	(n)	5	5	5	5	5	5
	Mean	201.03	206.73	224.02	232.12	247.49	253.85
	SD	7.27	10.50	10.38	4.17	7.86	11.00
3	(n)	5	5	5	5	5	5
	Mean	201.17	207.42	224.39	235.33	242.43	243.66
	SD	8.19	5.98	10.37	10.11	12.56	11.33
4	(n)	10	10	10	10	10	4
	Mean	201.82	207.31	220.39	220.79**	219.20**	223.00
	SD	6.56	8.79	9.26	7.99	9.07	6.73

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 4.2 - Body weight (g) - During recovery - Group mean data

STUDY NO.: 27080

MALES

Group(s)		Day of Phase 1"	8	15
1	(n)	5	5	5
	Mean	380.29	392.93	391.53
	SD	13.16	11.83	15.10
4	(n)	5	5	5
	Mean	289.63**	296.66**	298.66**
	SD	18.53	24.11	22.75

Note: " = Recovery 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]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 4.2 - Body weight (g) - During recovery - Group mean data

STUDY NO.: 27080

FEMALES

Group(s)		Day of Phase 1"	8	15
1	(n)	5	5	5
	Mean	252.41	256.66	254.00
	SD	5.82	8.36	10.60
4	(n)	5	5	5
	Mean	218.37**	224.85**	231.79**
	SD	3.46	2.85	5.72

Note: " = Recovery 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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.1 - Haematology - Week 4 of treatment - Group mean data

STUDY NO.: 27080

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	8.663	0.331	10	8.218	0.612	5	8.500	0.243	5	8.523	0.279	9
HAEMOGLOBIN g/dl	15.94	0.38	10	14.94*	1.22	5	15.64	0.50	5	15.41	0.56	9
HAEMATOCRIT %	47.45	1.39	10	44.40*	3.32	5	46.54	1.76	5	45.67	1.96	9
MEAN RED BLOOD CELL VOLUME fl	54.81	1.48	10	53.98	0.90	5	54.76	0.83	5	53.57	1.33	9
MEAN CORPUSCULAR Hb pg	18.42	0.39	10	18.20	0.21	5	18.42	0.13	5	18.09	0.38	9
MEAN CORPUSCULAR Hb CONC. g/dl	33.61	0.55	10	33.88	0.53	5	33.66	0.25	5	33.76	0.56	9

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]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.1 - Haematology - Week 4 of treatment - Group mean data

STUDY NO.: 27080

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	844.3	141.7	10	865.2	89.9	5	828.8	52.5	5	746.9	100.8	9
PROTHROMBIN TIME sec	29.84	8.72	7	NT	NT	-	25.23	4.74	4	33.60	N/C	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

NT = Data not taken for technical problems
N/C = Not calculable due to low sample size

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.1 - Haematology - Week 4 of treatment - Group mean data

STUDY NO.: 27080

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		13.425	2.582	10	12.302	0.918	5	10.886	1.447	5	10.053*	3.213	9
NEUTROPHILS %	($)	12.22	7.73	10	10.04	1.56	5	10.28	2.20	5	7.12	3.51	9
LYMPHOCYTES %	($)	81.24	8.46	10	85.04	1.70	5	83.70	1.99	5	88.13*	3.92	9
MONOCYTES %		2.99	0.85	10	2.56	0.21	5	3.28	0.58	5	2.72	0.76	9
EOSINOPHILS %	($)	2.11	1.41	10	1.04*	0.29	5	1.38	0.23	5	0.64*	0.27	9
BASOPHILS %		0.31	0.07	10	0.28	0.08	5	0.24	0.05	5	0.23	0.11	9
LARGE UNSTAINED CELLS %		1.17	0.26	10	1.06	0.28	5	1.14	0.17	5	1.18	0.38	9

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.1 - Haematology - Week 4 of treatment - Group mean data

STUDY NO.: 27080

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	8.186	0.507	10	7.900	0.315	5	7.882	0.269	5	8.248	0.475	10
HAEMOGLOBIN g/dl	15.08	1.01	10	14.76	0.36	5	14.62	0.51	5	15.21	1.06	10
HAEMATOCRIT %	44.76	2.96	10	43.38	1.68	5	43.12	1.66	5	45.29	3.62	10
MEAN RED BLOOD CELL VOLUME fl	54.70	1.44	10	54.88	0.58	5	54.68	0.99	5	54.88	1.89	10
MEAN CORPUSCULAR Hb pg	18.43	0.46	10	18.68	0.37	5	18.56	0.27	5	18.44	0.53	10
MEAN CORPUSCULAR Hb CONC. g/dl	33.67	0.32	10	34.06	0.53	5	33.94	0.37	5	33.60	0.74	10

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.1 - Haematology - Week 4 of treatment - Group mean data

STUDY NO.: 27080

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	996.2	73.3	10	1072.8	89.5	5	941.0	66.3	5	796.3**	139.6	10
PROTHROMBIN TIME sec	25.60	3.65	8	28.04	6.15	5	25.44	2.69	5	32.08*	4.68	6

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.1 - Haematology - Week 4 of treatment - Group mean data

STUDY NO.: 27080

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		9.708	2.839	10	7.012	1.215	5	7.848	2.230	5	7.824	2.085	10
NEUTROPHILS %	($)	11.41	2.96	10	11.14	2.34	5	9.26	1.74	5	16.82	21.17	10
LYMPHOCYTES %	($)	83.36	2.85	10	82.34	2.27	5	86.04	2.07	5	78.57	19.80	10
MONOCYTES %		2.75	0.45	10	3.10	0.79	5	2.24	0.48	5	2.39	0.80	10
EOSINOPHILS %		1.44	0.40	10	2.22*	0.62	5	1.52	0.55	5	1.09	0.63	10
BASOPHILS %		0.22	0.09	10	0.16	0.05	5	0.12	0.08	5	0.19	0.10	10
LARGE UNSTAINED CELLS %		0.83	0.16	10	1.08	0.33	5	0.84	0.31	5	0.93	0.37	10

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.2 - Haematology - Week 2 of recovery - Group mean data

STUDY NO.: 27080

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
RED BLOOD CELL COUNT 10^12/l	9.022	0.366	5	8.074**	0.306	5
HAEMOGLOBIN g/dl	16.18	0.41	5	13.86**	0.56	5
HAEMATOCRIT %	49.18	1.49	5	41.72**	1.90	5
MEAN RED BLOOD CELL VOLUME fl	54.56	1.56	5	51.68*	1.58	5
MEAN CORPUSCULAR Hb pg	17.94	0.32	5	17.14**	0.19	5
MEAN CORPUSCULAR Hb CONC. g/dl	32.94	0.60	5	33.20	0.75	5

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 Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.2 - Haematology - Week 2 of recovery - Group mean data

STUDY NO.: 27080

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
PLATELETS 10^9/l	815.6	245.3	5	781.2	223.8	5
PROTHROMBIN TIME sec	28.62	7.06	5	31.06	2.99	5

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 Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.2 - Haematology - Week 2 of recovery - Group mean data

STUDY NO.: 27080

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
WHITE BLOOD CELL COUNT 10^9/l	11.288	1.209	5	8.074	3.115	5
NEUTROPHILS %	10.72	4.35	5	7.50	1.57	5
LYMPHOCYTES %	84.40	4.81	5	87.60	2.50	5
MONOCYTES %	2.74	0.40	5	2.78	0.88	5
EOSINOPHILS %	0.86	0.11	5	1.02	0.61	5
BASOPHILS %	0.18	0.04	5	0.16	0.09	5
LARGE UNSTAINED CELLS %	1.08	0.19	5	0.94	0.30	5

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 Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.2 - Haematology - Week 2 of recovery - Group mean data

STUDY NO.: 27080

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
RED BLOOD CELL COUNT 10^12/l	8.166	0.227	5	8.038	0.153	5
HAEMOGLOBIN g/dl	15.54	0.78	5	14.72	0.44	5
HAEMATOCRIT %	45.34	2.26	5	43.72	1.28	5
MEAN RED BLOOD CELL VOLUME fl	55.50	1.55	5	54.44	2.18	5
MEAN CORPUSCULAR Hb pg	19.02	0.54	5	18.32	0.64	5
MEAN CORPUSCULAR Hb CONC. g/dl	34.28	0.19	5	33.64*	0.47	5

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 Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.2 - Haematology - Week 2 of recovery - Group mean data

STUDY NO.: 27080

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
PLATELETS 10^9/l	1003.4	114.5	5	974.4	42.2	5
PROTHROMBIN TIME sec	29.88	11.69	5	34.26	8.12	5

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 Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.2 - Haematology - Week 2 of recovery - Group mean data

STUDY NO.: 27080

FEMALES

Parameter/units		Control Mean	SD	n	Group 4 Mean	SD	n
WHITE BLOOD CELL COUNT 10^9/l	($)	8.194	5.534	5	5.468	0.752	5
NEUTROPHILS %		14.76	3.95	5	8.66**	0.86	5
LYMPHOCYTES %		79.98	4.30	5	85.68*	1.35	5
MONOCYTES %		2.54	0.49	5	2.82	1.30	5
EOSINOPHILS %		1.68	0.53	5	1.76	0.34	5
BASOPHILS %		0.14	0.11	5	0.16	0.05	5
LARGE UNSTAINED CELLS %		0.90	0.37	5	0.96	0.15	5

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 Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.1 - Clinical Chemistry - Week 4 of treatment - Group mean data

STUDY NO.: 27080

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		280.57	33.03	10	320.44	72.19	5	494.12**	30.36	5	499.89**	85.14	10
ALANINE AMINO-TRANSFERASE U/l		56.98	9.10	10	54.96	11.24	5	70.94	7.75	5	63.54	11.76	10
ASPARTATE AMINO-TRANSFERASE U/l		100.91	17.18	10	110.10	20.25	5	121.56	16.55	5	150.95**	37.34	10
GAMMA-GLUTAMYL TRANSFERASE U/l	($)	0.980	0.377	10	0.600	0.406	5	1.740	2.685	5	3.470*	3.148	10
TOTAL BILIRUBIN mg/dl		0.068	0.021	10	0.032*	0.013	5	0.024**	0.015	5	0.065	0.026	10
TOTAL CHOLESTEROL mg/dl	($)	82.07	3.68	10	45.98**	5.19	5	64.06*	9.30	5	86.68	14.32	10
TRIGLYCERIDES mg/dl		36.62	8.96	10	43.28	7.63	5	49.38	13.13	5	51.10*	11.59	10
GLUCOSE mg/dl		111.67	6.61	10	174.18**	7.70	5	137.02**	6.95	5	116.01	10.75	10

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.1 - Clinical Chemistry - Week 4 of treatment - Group mean data

STUDY NO.: 27080

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		45.15	5.96	10	58.52**	3.82	5	55.12**	4.00	5	65.89**	3.91	10
CREATININE mg/dl		0.537	0.057	10	0.478	0.031	5	0.396**	0.049	5	0.383**	0.041	10
CHLORIDE mmol/l		98.81	0.91	10	99.66	1.35	5	101.32**	1.49	5	102.50**	1.24	10
INORGANIC PHOSPHORUS mg/dl		7.47	0.65	10	7.37	0.33	5	7.56	0.55	5	7.29	0.46	10
CALCIUM mmol/l		2.698	0.060	10	2.608*	0.044	5	2.520**	0.043	5	2.400**	0.049	10
SODIUM mmol/l	($)	156.97	3.99	9	152.64*	2.05	5	156.28	1.14	5	155.66	1.15	10
POTASSIUM mmol/l		3.932	0.175	9	4.406*	0.427	5	4.372*	0.332	5	4.508**	0.310	10

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.1 - Clinical Chemistry - Week 4 of treatment - Group mean data

STUDY NO.: 27080

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		6.93	0.30	10	6.80	0.24	5	5.88**	0.19	5	5.07**	0.28	10
ALBUMIN g/dl		4.16	0.13	10	4.32	0.04	5	4.20	0.19	5	3.48**	0.20	10
GLOBULIN g/dl		2.77	0.24	10	2.48	0.20	5	1.68**	0.26	5	1.59**	0.21	10
ALBUMIN/GLOBULIN RATIO	($)	1.51	0.13	10	1.75*	0.12	5	2.56**	0.45	5	2.23**	0.33	10

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.1 - Clinical Chemistry - Week 4 of treatment - Group mean data

STUDY NO.: 27080

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	($)	225.71	20.34	10	252.94	45.96	5	308.06**	30.00	5	434.93*	250.20	10
ALANINE AMINO-TRANSFERASE U/l	($)	41.37	2.78	10	39.08	3.99	5	41.34	3.73	5	575.19	1612.90	10
ASPARTATE AMINO-TRANSFERASE U/l	($)	95.03	7.51	10	86.84	9.02	5	89.30	9.63	5	146.31**	46.10	10
GAMMA-GLUTAMYL TRANSFERASE U/l	($)	0.720	0.494	10	1.440**	0.251	5	0.320	0.239	5	4.910	13.668	10
TOTAL BILIRUBIN mg/dl	($)	0.086	0.013	10	0.066	0.036	5	0.032**	0.020	5	0.713	2.002	10
TOTAL CHOLESTEROL mg/dl	($)	87.52	10.19	10	82.22	10.34	5	78.36	16.45	5	70.27	40.45	10
TRIGLYCERIDES mg/dl		22.11	5.32	10	33.46*	8.31	5	38.80**	5.40	5	39.44**	9.82	10
GLUCOSE mg/dl		109.47	22.19	10	118.82	11.53	5	148.16*	10.06	5	120.41	28.67	10

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.1 - Clinical Chemistry - Week 4 of treatment - Group mean data

STUDY NO.: 27080

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	($)	61.66	3.90	10	57.38	10.51	5	74.62	11.28	5	84.07*	25.98	10
CREATININE mg/dl		0.519	0.080	10	0.526	0.066	5	0.464	0.057	5	0.439	0.106	10
CHLORIDE mmol/l	($)	98.34	1.25	10	100.84**	0.84	5	102.54**	0.36	5	100.45*	2.13	10
INORGANIC PHOSPHORUS mg/dl	($)	6.72	0.36	10	6.27	0.70	5	6.55	0.59	5	7.35	1.28	10
CALCIUM mmol/l	($)	2.777	0.040	10	2.770	0.046	5	2.670**	0.047	5	2.612*	0.165	10
SODIUM mmol/l		144.74	2.58	10	149.68**	0.97	5	148.16*	1.72	5	145.91	2.16	10
POTASSIUM mmol/l		3.551	0.200	10	3.216	0.148	5	3.804	0.272	5	3.939*	0.372	10

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.1 - Clinical Chemistry - Week 4 of treatment - Group mean data

STUDY NO.: 27080

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	($)	6.90	0.15	10	7.00	0.21	5	6.84	0.15	5	5.91**	0.73	10
ALBUMIN g/dl	($)	4.46	0.14	10	4.78*	0.22	5	4.94**	0.21	5	4.28	0.67	10
GLOBULIN g/dl		2.44	0.13	10	2.22	0.13	5	1.90**	0.10	5	1.63**	0.23	10
ALBUMIN/GLOBULIN RATIO	($)	1.83	0.13	10	2.16*	0.18	5	2.61**	0.23	5	2.66**	0.49	10

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.2 - Clinical Chemistry - Week 2 of recovery - Group mean data

STUDY NO.: 27080

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
ALKALINE PHOSPHATASE U/l	259.18	41.05	5	465.92**	68.29	5
ALANINE AMINO-TRANSFERASE U/l	53.28	7.99	5	55.30	4.76	5
ASPARTATE AMINO-TRANSFERASE U/l	83.18	9.84	5	114.06*	21.29	5
GAMMA-GLUTAMYL TRANSFERASE U/l	2.260	0.658	5	3.980	1.757	5
TOTAL BILIRUBIN mg/dl	0.066	0.011	5	0.050	0.019	5
TOTAL CHOLESTEROL mg/dl	83.44	6.00	5	63.82**	11.04	5
TRIGLYCERIDES mg/dl	32.30	3.34	5	41.44*	6.47	5
GLUCOSE mg/dl	116.46	13.80	5	118.70	6.29	5

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 Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.2 - Clinical Chemistry - Week 2 of recovery - Group mean data

STUDY NO.: 27080

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
UREA mg/dl	36.64	4.29	5	54.34**	4.03	5
CREATININE mg/dl	0.404	0.055	5	0.250**	0.016	5
CHLORIDE mmol/l	96.38	1.57	5	101.06**	1.01	5
INORGANIC PHOSPHORUS mg/dl	7.72	0.50	5	7.94	0.76	5
CALCIUM mmol/l	2.724	0.072	5	2.534*	0.146	5
SODIUM mmol/l	147.38	1.43	5	145.84	1.63	5
POTASSIUM mmol/l	3.692	0.356	5	4.744**	0.514	5

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 Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.2 - Clinical Chemistry - Week 2 of recovery - Group mean data

STUDY NO.: 27080

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
TOTAL PROTEIN g/dl	6.80	0.24	5	5.34**	0.21	5
ALBUMIN g/dl	4.16	0.05	5	3.60**	0.12	5
GLOBULIN g/dl	2.64	0.23	5	1.74**	0.26	5
ALBUMIN/GLOBULIN RATIO	1.59	0.14	5	2.11*	0.36	5

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 (S)
Note: Data for Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.2 - Clinical Chemistry - Week 2 of recovery - Group mean data

STUDY NO.: 27080

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
ALKALINE PHOSPHATASE U/l	196.80	15.03	5	286.56**	42.17	5
ALANINE AMINO-TRANSFERASE U/l	35.44	4.94	5	44.92**	2.48	5
ASPARTATE AMINO-TRANSFERASE U/l	100.76	34.91	5	86.40	7.89	5
GAMMA-GLUTAMYL TRANSFERASE U/l	1.200	1.091	5	2.680*	0.606	5
TOTAL BILIRUBIN mg/dl	0.086	0.030	5	0.050*	0.012	5
TOTAL CHOLESTEROL mg/dl	88.24	14.44	5	73.74	14.66	5
TRIGLYCERIDES mg/dl	30.80	5.59	5	34.34	1.93	5
GLUCOSE mg/dl	126.72	12.30	5	138.02	10.36	5

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 Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.2 - Clinical Chemistry - Week 2 of recovery - Group mean data

STUDY NO.: 27080

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
UREA mg/dl	52.86	7.90	5	52.80	5.33	5
CREATININE mg/dl	0.522	0.035	5	0.428**	0.035	5
CHLORIDE mmol/l	98.34	1.16	5	99.40	0.91	5
INORGANIC PHOSPHORUS mg/dl	6.04	0.35	5	5.96	0.71	5
CALCIUM mmol/l	2.694	0.041	5	2.610*	0.063	5
SODIUM mmol/l	145.88	1.11	5	145.32	1.49	5
POTASSIUM mmol/l	3.706	0.488	5	3.860	0.277	5

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 Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.2 - Clinical Chemistry - Week 2 of recovery - Group mean data

STUDY NO.: 27080

FEMALES

Parameter/units		Control Mean	SD	n	Group 4 Mean	SD	n
TOTAL PROTEIN g/dl	($)	6.98	0.04	5	6.60	0.35	5
ALBUMIN g/dl		4.52	0.13	5	4.82	0.33	5
GLOBULIN g/dl		2.46	0.13	5	1.78**	0.15	5
ALBUMIN/GLOBULIN RATIO		1.84	0.15	5	2.72**	0.29	5

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 Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 7.1 - Urinalysis - Week 4 of treatment - Group mean data

STUDY NO.: 27080

MALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
URINE VOLUME (OVERNIGHT) ml	8.35	2.67	10	9.50	1.50	5	10.70	2.11	5	9.05	2.74	10
SPECIFIC GRAVITY	1.0145	0.0050	10	1.0160	0.0055	5	1.0180	0.0027	5	1.0165	0.0058	10

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 7.1 - Urinalysis - Week 4 of treatment - Group mean data

STUDY NO.: 27080

FEMALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
URINE VOLUME (OVERNIGHT) ml	5.35	2.17	10	5.30	0.67	5	7.20	1.79	5	8.50*	3.07	10
SPECIFIC GRAVITY	1.0255	0.0050	10	1.0200	0.0061	5	1.0170*	0.0045	5	1.0225	0.0059	10

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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 7.2 - Urinalysis - Week 2 of recovery - Group mean data

STUDY NO.: 27080

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
URINE VOLUME (OVERNIGHT) ml	6.70	1.04	5	7.10	1.19	5
SPECIFIC GRAVITY	1.0210	0.0065	5	1.0200	0.0035	5

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 Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 7.2 - Urinalysis - Week 2 of recovery - Group mean data

STUDY NO.: 27080

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
URINE VOLUME (OVERNIGHT) ml	3.00	1.22	5	5.50*	2.03	5
SPECIFIC GRAVITY	1.0250	0.0071	5	1.0220	0.0067	5

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 Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 8.1 - Terminal body weight (g) - Final sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	369.16	387.28	372.76	291.48
Standard deviation	19.37	16.29	24.96	14.27
Group diff. at p < 0.05		31.39	31.39	31.39*
Group diff. at p < 0.01		41.06	41.06	41.06*

Analysis of variance: F ratio = 25.42 Df = 3/ 16 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 8.1 - Terminal body weight (g) - Final sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	242.94	253.78	242.86	216.45
Standard deviation	11.17	9.65	11.80	6.13
Group diff. at p < 0.05		16.73	16.73	17.74*
Group diff. at p < 0.01		21.96	21.96	23.30*

Analysis of variance: F ratio = 10.55 Df = 3/ 15 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 8.2 - Terminal body weight (g) - Recovery sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	4
Number/group	5	5
Mean	390.42	294.60
Standard deviation	14.21	22.42
Group diff. at p < 0.05		27.45*
Group diff. at p < 0.01		39.95*

Analysis of variance: F ratio = 65.18 Df = 1/ 8 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 8.2 - Terminal body weight (g) - Recovery sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	4
Number/group	5	5
Mean	252.04	228.04
Standard deviation	9.85	5.92
Group diff. at p < 0.05		11.89*
Group diff. at p < 0.01		17.30*

Analysis of variance: F ratio = 21.80 Df = 1/ 8 F probability = 0.002
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.0528	0.0518	0.0502	0.0464
Standard deviation	0.0086	0.0028	0.0059	0.0029
Group diff. at p < 0.05		0.0091	0.0091	0.0091
Group diff. at p < 0.01		0.0120	0.0120	0.0120

Analysis of variance: F ratio = 1.27 Df = 3/ 16 F probability = 0.318
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	5	5	5	5
Mean	1.770	1.728	1.767	1.701
Standard deviation	0.085	0.041	0.077	0.117
Group diff. at p < 0.05		0.138	0.138	0.138
Group diff. at p < 0.01		0.181	0.181	0.181

Analysis of variance: F ratio = 0.77 Df = 3/ 16 F probability = 0.529
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	1.1292	1.1190	1.1826	1.0130
Standard deviation	0.1680	0.0564	0.0598	0.0606
Group diff. at p < 0.05		0.1611	0.1611	0.1611
Group diff. at p < 0.01		0.2107	0.2107	0.2107

Analysis of variance: F ratio = 2.61 Df = 3/ 16 F probability = 0.087
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	5	5	5	5
Mean	1.389	1.343	1.342	1.148
Standard deviation	0.054	0.096	0.084	0.070
Group diff. at p < 0.05		0.127	0.127	0.127*
Group diff. at p < 0.01		0.167	0.167	0.167*

Analysis of variance: F ratio = 9.59 Df = 3/ 16 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	2.804	2.913	3.144	2.812
Standard deviation	0.226	0.235	0.304	0.169
Group diff. at p < 0.05		0.391	0.391	0.391
Group diff. at p < 0.01		0.511	0.511	0.511

Analysis of variance: F ratio = 2.21 Df = 3/ 16 F probability = 0.125
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	16.031	20.382	24.720	21.489
Standard deviation	1.687	0.557	2.528	2.461
Group diff. at p < 0.05		3.238*	3.238*	3.238*
Group diff. at p < 0.01		4.234*	4.234*	4.234*

Analysis of variance: F ratio = 16.53 Df = 3/ 16 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.9406	0.9646	0.8304	0.5412
Standard deviation	0.0753	0.0958	0.1341	0.0411
Group diff. at p < 0.05		0.1523	0.1523	0.1523*
Group diff. at p < 0.01		0.1991	0.1991	0.1991*

Analysis of variance: F ratio = 21.89 Df = 3/ 16 F probability = 0.000
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	5	5	5	5
Mean	3.5676	3.5114	3.8236	3.5834
Standard deviation	0.7091	0.1622	0.1970	0.2462
Group diff. at p < 0.05		0.9045	0.9151	0.9333
Group diff. at p < 0.01		1.5068	1.5245	1.5549

Analysis of variance: F ratio = 0.61 Df = 3/ 16 F probability = 0.623
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.4478	0.4320	0.3886	0.1536
Standard deviation	0.0761	0.0772	0.0546	0.0390
Group diff. at p < 0.05		0.1045	0.1045	0.1045*
Group diff. at p < 0.01		0.1367	0.1367	0.1367*

Analysis of variance: F ratio = 23.05 Df = 3/ 16 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.0196	0.0222	0.0212	0.0218
Standard deviation	0.0039	0.0027	0.0013	0.0019
Group diff. at p < 0.05		0.0043	0.0043	0.0043
Group diff. at p < 0.01		0.0057	0.0057	0.0057

Analysis of variance: F ratio = 0.94 Df = 3/ 16 F probability = 0.448
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	0.0718	0.0674	0.0616	0.0553
Standard deviation	0.0068	0.0024	0.0067	0.0081
Group diff. at p < 0.05		0.0103	0.0103	0.0109*
Group diff. at p < 0.01		0.0135	0.0135	0.0143*

Analysis of variance: F ratio = 5.93 Df = 3/ 15 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	5	5	5	4
Mean	1.678	1.643	1.641	1.596
Standard deviation	0.033	0.044	0.072	0.112
Group diff. at p < 0.05		0.113	0.113	0.120
Group diff. at p < 0.01		0.149	0.149	0.158

Analysis of variance: F ratio = 1.07 Df = 3/ 15 F probability = 0.394
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	0.945	0.956	0.906	0.850
Standard deviation	0.073	0.052	0.060	0.033
Group diff. at p < 0.05		0.095	0.095	0.101
Group diff. at p < 0.01		0.125	0.125	0.132

Analysis of variance: F ratio = 3.05 Df = 3/ 15 F probability = 0.060
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	5	5	5	4
Mean	1.902	1.980	1.917	1.792
Standard deviation	0.188	0.073	0.086	0.071
Group diff. at p < 0.05		0.194	0.194	0.206
Group diff. at p < 0.01		0.255	0.255	0.270

Analysis of variance: F ratio = 1.92 Df = 3/ 15 F probability = 0.168
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	9.972	12.038	13.796	14.294
Standard deviation	1.364	1.026	0.584	1.245
Group diff. at p < 0.05		1.791*	1.791*	1.900*
Group diff. at p < 0.01		2.352	2.352*	2.495*

Analysis of variance: F ratio = 15.34 Df = 3/ 15 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	0.1272	0.1208	0.1130	0.0945
Standard deviation	0.0154	0.0270	0.0091	0.0104
Group diff. at p < 0.05		0.0287	0.0287	0.0304*
Group diff. at p < 0.01		0.0377	0.0377	0.0399

Analysis of variance: F ratio = 2.89 Df = 3/ 15 F probability = 0.070
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	0.8146	0.7554	0.6426	0.4933
Standard deviation	0.1124	0.0709	0.0455	0.0448
Group diff. at p < 0.05		0.1242	0.1242*	0.1318*
Group diff. at p < 0.01		0.1631	0.1631*	0.1730*

Analysis of variance: F ratio = 15.58 Df = 3/ 15 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	0.3406	0.3034	0.3760	0.2533
Standard deviation	0.0642	0.0495	0.0740	0.0419
Group diff. at p < 0.05		0.0985	0.0985	0.1045
Group diff. at p < 0.01		0.1294	0.1294	0.1372

Analysis of variance: F ratio = 3.46 Df = 3/ 15 F probability = 0.043
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	0.0202	0.0228	0.0184	0.0190
Standard deviation	0.0044	0.0004	0.0017	0.0032
Group diff. at p < 0.05		0.0055	0.0059	0.0075
Group diff. at p < 0.01		0.0092	0.0098	0.0130

Analysis of variance: F ratio = 2.31 Df = 3/ 15 F probability = 0.117
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	4
Number/group	5	5
Mean	0.0528	0.0544
Standard deviation	0.0054	0.0109
Group diff. at p < 0.05		0.0125
Group diff. at p < 0.01		0.0183

Analysis of variance: F ratio = 0.09 Df = 1/ 8 F probability = 0.766
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	4
Number/group	5	5
Mean	1.845	1.807
Standard deviation	0.113	0.093
Group diff. at p < 0.05		0.151
Group diff. at p < 0.01		0.220

Analysis of variance: F ratio = 0.34 Df = 1/ 8 F probability = 0.583
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	4
Number/group	5	5
Mean	1.2452	1.0250
Standard deviation	0.1071	0.0907
Group diff. at p < 0.05		0.1452*
Group diff. at p < 0.01		0.2113*

Analysis of variance: F ratio = 12.31 Df = 1/ 8 F probability = 0.008
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	4
Number/group	5	5
Mean	1.387	1.161
Standard deviation	0.101	0.208
Group diff. at p < 0.05		0.239
Group diff. at p < 0.01		0.349

Analysis of variance: F ratio = 4.80 Df = 1/ 8 F probability = 0.058
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	4
Number/group	5	5
Mean	2.859	2.822
Standard deviation	0.120	0.171
Group diff. at p < 0.05		0.216
Group diff. at p < 0.01		0.314

Analysis of variance: F ratio = 0.15 Df = 1/ 8 F probability = 0.707
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	4
Number/group	5	5
Mean	16.013	22.828
Standard deviation	1.073	2.785
Group diff. at p < 0.05		3.087*
Group diff. at p < 0.01		4.492*

Analysis of variance: F ratio = 26.08 Df = 1/ 8 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	4
Number/group	5	5
Mean	0.9310	0.6268
Standard deviation	0.1128	0.1321
Group diff. at p < 0.05		0.1797*
Group diff. at p < 0.01		0.2616*

Analysis of variance: F ratio = 15.33 Df = 1/ 8 F probability = 0.005
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	4
Number/group	5	5
Mean	3.7868	3.4260
Standard deviation	0.2610	0.1397
Group diff. at p < 0.05		0.3063*
Group diff. at p < 0.01		0.4457

Analysis of variance: F ratio = 7.43 Df = 1/ 8 F probability = 0.025
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	4
Number/group	5	5
Mean	0.3596	0.1594
Standard deviation	0.0702	0.0398
Group diff. at p < 0.05		0.0835*
Group diff. at p < 0.01		0.1216*

Analysis of variance: F ratio = 30.73 Df = 1/ 8 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	4
Number/group	5	5
Mean	0.0232	0.0194
Standard deviation	0.0022	0.0019
Group diff. at p < 0.05		0.0030*
Group diff. at p < 0.01		0.0044

Analysis of variance: F ratio = 8.49 Df = 1/ 8 F probability = 0.019
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	4
Number/group	5	5
Mean	0.0686	0.0632
Standard deviation	0.0087	0.0047
Group diff. at p < 0.05		0.0102
Group diff. at p < 0.01		0.0149

Analysis of variance: F ratio = 1.50 Df = 1/ 8 F probability = 0.256
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	4
Number/group	5	5
Mean	1.727	1.647
Standard deviation	0.069	0.084
Group diff. at p < 0.05		0.112
Group diff. at p < 0.01		0.164

Analysis of variance: F ratio = 2.71 Df = 1/ 8 F probability = 0.136
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	4
Number/group	5	5
Mean	0.979	0.957
Standard deviation	0.071	0.070
Group diff. at p < 0.05		0.103
Group diff. at p < 0.01		0.150

Analysis of variance: F ratio = 0.25 Df = 1/ 8 F probability = 0.633
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	4
Number/group	5	5
Mean	1.837	1.943
Standard deviation	0.102	0.129
Group diff. at p < 0.05		0.171
Group diff. at p < 0.01		0.248

Analysis of variance: F ratio = 2.07 Df = 1/ 8 F probability = 0.186
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	4
Number/group	5	5
Mean	9.042	13.099
Standard deviation	0.747	0.592
Group diff. at p < 0.05		0.985*
Group diff. at p < 0.01		1.434*

Analysis of variance: F ratio = 90.69 Df = 1/ 8 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	4
Number/group	5	5
Mean	0.1318	0.1158
Standard deviation	0.0172	0.0145
Group diff. at p < 0.05		0.0233
Group diff. at p < 0.01		0.0339

Analysis of variance: F ratio = 2.52 Df = 1/ 8 F probability = 0.149
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	4
Number/group	5	5
Mean	0.6744	0.5616
Standard deviation	0.0775	0.0504
Group diff. at p < 0.05		0.0959*
Group diff. at p < 0.01		0.1396

Analysis of variance: F ratio = 7.40 Df = 1/ 8 F probability = 0.026
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	4
Number/group	5	5
Mean	0.3032	0.3138
Standard deviation	0.0469	0.0810
Group diff. at p < 0.05		0.0968
Group diff. at p < 0.01		0.1409

Analysis of variance: F ratio = 0.06 Df = 1/ 8 F probability = 0.793
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	4
Number/group	5	5
Mean	0.0170	0.0180
Standard deviation	0.0037	0.0041
Group diff. at p < 0.05		0.0057
Group diff. at p < 0.01		0.0083

Analysis of variance: F ratio = 0.16 Df = 1/ 8 F probability = 0.696
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.0143	0.0134	0.0135	0.0160
Standard deviation	0.0022	0.0007	0.0021	0.0015
Group diff. at p < 0.05		0.0028	0.0028	0.0028
Group diff. at p < 0.01		0.0037	0.0037	0.0037

Analysis of variance: F ratio = 2.36 Df = 3/ 16 F probability = 0.109
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	5	5	5	5
Mean	0.480	0.447	0.476	0.586
Standard deviation	0.021	0.028	0.045	0.063
Group diff. at p < 0.05		0.070	0.070	0.070*
Group diff. at p < 0.01		0.091	0.091	0.091*

Analysis of variance: F ratio = 10.27 Df = 3/ 16 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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.3059	0.2891	0.3186	0.3481
Standard deviation	0.0444	0.0123	0.0295	0.0242
Group diff. at p < 0.05		0.0490	0.0490	0.0490
Group diff. at p < 0.01		0.0641	0.0641	0.0641

Analysis of variance: F ratio = 3.47 Df = 3/ 16 F probability = 0.041
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	5	5	5	5
Mean	0.377	0.347	0.360	0.394
Standard deviation	0.021	0.012	0.009	0.022
Group diff. at p < 0.05		0.028*	0.028	0.028
Group diff. at p < 0.01		0.036	0.036	0.036

Analysis of variance: F ratio = 7.49 Df = 3/ 16 F probability = 0.002
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.759	0.752	0.842	0.965
Standard deviation	0.032	0.042	0.038	0.044
Group diff. at p < 0.05		0.064	0.064*	0.064*
Group diff. at p < 0.01		0.084	0.084	0.084*

Analysis of variance: F ratio = 32.37 Df = 3/ 16 F probability = 0.000
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	5	5	5	5
Mean	4.336	5.267	6.623	7.372
Standard deviation	0.298	0.163	0.317	0.743
Group diff. at p < 0.05		0.422*	0.541*	0.996*
Group diff. at p < 0.01		0.703*	0.902*	1.659*

Analysis of variance: F ratio = 48.02 Df = 3/ 16 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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.2550	0.2489	0.2223	0.1856
Standard deviation	0.0201	0.0203	0.0290	0.0097
Group diff. at p < 0.05		0.0342	0.0342	0.0342*
Group diff. at p < 0.01		0.0448	0.0448	0.0448*

Analysis of variance: F ratio = 11.45 Df = 3/ 16 F probability = 0.000
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	5	5	5	5
Mean	0.9652	0.9073	1.0309	1.2299
Standard deviation	0.1846	0.0413	0.1068	0.0696
Group diff. at p < 0.05		0.2352	0.2652	0.2453*
Group diff. at p < 0.01		0.3919	0.4418	0.4087

Analysis of variance: F ratio = 7.58 Df = 3/ 16 F probability = 0.002
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.1218	0.1111	0.1042	0.0523
Standard deviation	0.0236	0.0160	0.0118	0.0110
Group diff. at p < 0.05		0.0269	0.0269	0.0269*
Group diff. at p < 0.01		0.0351	0.0351	0.0351*

Analysis of variance: F ratio = 17.79 Df = 3/ 16 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.0053	0.0057	0.0057	0.0075
Standard deviation	0.0011	0.0008	0.0002	0.0007
Group diff. at p < 0.05		0.0017	0.0014	0.0016*
Group diff. at p < 0.01		0.0028	0.0023	0.0027

Analysis of variance: F ratio = 7.99 Df = 3/ 16 F probability = 0.002
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	0.0295	0.0266	0.0254	0.0256
Standard deviation	0.0020	0.0018	0.0024	0.0045
Group diff. at p < 0.05		0.0046	0.0046	0.0048
Group diff. at p < 0.01		0.0060	0.0060	0.0063

Analysis of variance: F ratio = 2.33 Df = 3/ 15 F probability = 0.114
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	5	5	5	4
Mean	0.692	0.648	0.678	0.738
Standard deviation	0.045	0.027	0.053	0.050
Group diff. at p < 0.05		0.073	0.073	0.078
Group diff. at p < 0.01		0.096	0.096	0.102

Analysis of variance: F ratio = 3.10 Df = 3/ 15 F probability = 0.058
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	0.389	0.377	0.373	0.393
Standard deviation	0.016	0.016	0.013	0.019
Group diff. at p < 0.05		0.026	0.026	0.028
Group diff. at p < 0.01		0.034	0.034	0.036

Analysis of variance: F ratio = 1.67 Df = 3/ 15 F probability = 0.215
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	5	5	5	4
Mean	0.782	0.781	0.790	0.829
Standard deviation	0.052	0.029	0.040	0.056
Group diff. at p < 0.05		0.074	0.074	0.079
Group diff. at p < 0.01		0.097	0.097	0.103

Analysis of variance: F ratio = 1.10 Df = 3/ 15 F probability = 0.382
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	4.093	4.737	5.692	6.617
Standard deviation	0.386	0.237	0.382	0.723
Group diff. at p < 0.05		0.735	0.735*	0.780*
Group diff. at p < 0.01		0.965	0.965*	1.024*

Analysis of variance: F ratio = 27.63 Df = 3/ 15 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	0.0523	0.0476	0.0467	0.0437
Standard deviation	0.0044	0.0109	0.0051	0.0050
Group diff. at p < 0.05		0.0115	0.0115	0.0122
Group diff. at p < 0.01		0.0151	0.0151	0.0161

Analysis of variance: F ratio = 1.18 Df = 3/ 15 F probability = 0.350
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	0.3348	0.2976	0.2649	0.2276
Standard deviation	0.0374	0.0250	0.0192	0.0158
Group diff. at p < 0.05		0.0432	0.0432*	0.0459*
Group diff. at p < 0.01		0.0568	0.0568*	0.0602*

Analysis of variance: F ratio = 13.77 Df = 3/ 15 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	0.1402	0.1195	0.1545	0.1170
Standard deviation	0.0259	0.0187	0.0274	0.0184
Group diff. at p < 0.05		0.0383	0.0383	0.0407
Group diff. at p < 0.01		0.0503	0.0503	0.0534

Analysis of variance: F ratio = 2.79 Df = 3/ 15 F probability = 0.076
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	2	3	4
Number/group	5	5	5	4
Mean	0.0083	0.0090	0.0076	0.0088
Standard deviation	0.0016	0.0003	0.0008	0.0017
Group diff. at p < 0.05		0.0020	0.0022	0.0033
Group diff. at p < 0.01		0.0034	0.0037	0.0059

Analysis of variance: F ratio = 1.33 Df = 3/ 15 F probability = 0.301
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	4
Number/group	5	5
Mean	0.0135	0.0185
Standard deviation	0.0012	0.0036
Group diff. at p < 0.05		0.0039*
Group diff. at p < 0.01		0.0057

Analysis of variance: F ratio = 8.78 Df = 1/ 8 F probability = 0.018
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	4
Number/group	5	5
Mean	0.473	0.614
Standard deviation	0.026	0.017
Group diff. at p < 0.05		0.033*
Group diff. at p < 0.01		0.047*

Analysis of variance: F ratio = 101.54 Df = 1/ 8 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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	4
Number/group	5	5
Mean	0.3186	0.3481
Standard deviation	0.0182	0.0200
Group diff. at p < 0.05		0.0280*
Group diff. at p < 0.01		0.0407

Analysis of variance: F ratio = 5.92 Df = 1/ 8 F probability = 0.040
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	4
Number/group	5	5
Mean	0.355	0.392
Standard deviation	0.024	0.040
Group diff. at p < 0.05		0.048
Group diff. at p < 0.01		0.070

Analysis of variance: F ratio = 3.05 Df = 1/ 8 F probability = 0.116
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	4
Number/group	5	5
Mean	0.732	0.959
Standard deviation	0.029	0.028
Group diff. at p < 0.05		0.042*
Group diff. at p < 0.01		0.061*

Analysis of variance: F ratio = 158.02 Df = 1/ 8 F probability = 0.000
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	4
Number/group	5	5
Mean	4.100	7.740
Standard deviation	0.187	0.632
Group diff. at p < 0.05		0.820*
Group diff. at p < 0.01		1.366*

Analysis of variance: F ratio = 152.45 Df = 1/ 8 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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	4
Number/group	5	5
Mean	0.2380	0.2119
Standard deviation	0.0222	0.0356
Group diff. at p < 0.05		0.0434
Group diff. at p < 0.01		0.0631

Analysis of variance: F ratio = 1.94 Df = 1/ 8 F probability = 0.200
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	4
Number/group	5	5
Mean	0.9692	1.1702
Standard deviation	0.0378	0.1215
Group diff. at p < 0.05		0.1582*
Group diff. at p < 0.01		0.2636

Analysis of variance: F ratio = 12.48 Df = 1/ 8 F probability = 0.008
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: 27080

MALES

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

Group	Control	4
Number/group	5	5
Mean	0.0919	0.0544
Standard deviation	0.0162	0.0152
Group diff. at p < 0.05		0.0230*
Group diff. at p < 0.01		0.0334*

Analysis of variance: F ratio = 14.27 Df = 1/ 8 F probability = 0.005
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	4
Number/group	5	5
Mean	0.0059	0.0067
Standard deviation	0.0004	0.0011
Group diff. at p < 0.05		0.0012
Group diff. at p < 0.01		0.0018

Analysis of variance: F ratio = 1.83 Df = 1/ 8 F probability = 0.211
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	4
Number/group	5	5
Mean	0.0273	0.0277
Standard deviation	0.0039	0.0022
Group diff. at p < 0.05		0.0047
Group diff. at p < 0.01		0.0068

Analysis of variance: F ratio = 0.05 Df = 1/ 8 F probability = 0.810
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	4
Number/group	5	5
Mean	0.686	0.722
Standard deviation	0.036	0.029
Group diff. at p < 0.05		0.047
Group diff. at p < 0.01		0.069

Analysis of variance: F ratio = 3.12 Df = 1/ 8 F probability = 0.113
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	4
Number/group	5	5
Mean	0.389	0.420
Standard deviation	0.028	0.037
Group diff. at p < 0.05		0.048
Group diff. at p < 0.01		0.070

Analysis of variance: F ratio = 2.25 Df = 1/ 8 F probability = 0.169
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	4
Number/group	5	5
Mean	0.729	0.852
Standard deviation	0.020	0.041
Group diff. at p < 0.05		0.047*
Group diff. at p < 0.01		0.069*

Analysis of variance: F ratio = 36.48 Df = 1/ 8 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] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	4
Number/group	5	5
Mean	3.584	5.745
Standard deviation	0.188	0.240
Group diff. at p < 0.05		0.316*
Group diff. at p < 0.01		0.459*

Analysis of variance: F ratio = 250.96 Df = 1/ 8 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	4
Number/group	5	5
Mean	0.0523	0.0507
Standard deviation	0.0062	0.0055
Group diff. at p < 0.05		0.0086
Group diff. at p < 0.01		0.0125

Analysis of variance: F ratio = 0.18 Df = 1/ 8 F probability = 0.686
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	4
Number/group	5	5
Mean	0.2676	0.2461
Standard deviation	0.0305	0.0188
Group diff. at p < 0.05		0.0371
Group diff. at p < 0.01		0.0540

Analysis of variance: F ratio = 1.80 Df = 1/ 8 F probability = 0.214
Note: a * indicates group mean is significantly different from control at level of significance shown.

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

Group	Control	4
Number/group	5	5
Mean	0.1207	0.1377
Standard deviation	0.0207	0.0360
Group diff. at p < 0.05		0.0430
Group diff. at p < 0.01		0.0625

Analysis of variance: F ratio = 0.84 Df = 1/ 8 F probability = 0.390
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: 27080

FEMALES

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

Group	Control	4
Number/group	5	5
Mean	0.0068	0.0079
Standard deviation	0.0016	0.0019
Group diff. at p < 0.05		0.0026
Group diff. at p < 0.01		0.0038

Analysis of variance: F ratio = 1.02 Df = 1/ 8 F probability = 0.343
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 11.1 - Macroscopic observations - Unscheduled deaths - Group incidence

STUDY NO.: 27080

	-- Females --
Group:	4
Number in group:	1
Liver	
Abnormal colour	1
Lungs	
Incomplete collapse	1
Head	
Abnormal area(s)	1
Pancreas	
Abnormal colour	1

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 11.2 - Macroscopic observations - Final sacrifice - Group incidence

STUDY NO.: 27080

	-- Males --				-- Females --			
Group:	1	2	3	4	1	2	3	4
Number in group:	5	5	5	5	5	5	5	4
Cervical nodes								
Abnormal colour	0	1	1	1	1	1	0	0
Epididymides								
Abnormal size	1	0	0	0				
Kidneys								
Abnormal colour	0	0	1	0	0	0	0	1
Liver								
Abnormal area(s)	0	0	0	1	0	0	0	0
Abnormal shape	0	0	2	1	0	0	0	0
Abnormal size	0	1	4	4	0	0	1	1
Lungs								
Abnormal area(s)	1	1	0	1	0	0	0	0
Abnormal colour	0	0	0	0	0	0	2	0
Ovaries								
Abnormal size					2	0	0	0
Seminal vesicles								
Abnormal size	0	0	0	2				
Spleen								
Abnormal shape	1	1	0	0	1	0	0	0
Abnormal size	1	0	0	1	0	0	0	0
Testes								
Abnormal size	1	0	0	0				

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 11.2 - Macroscopic observations - Final sacrifice - Group incidence

STUDY NO.: 27080

	-- Males --				-- Females --			
Group:	1	2	3	4	1	2	3	4
Number in group:	5	5	5	5	5	5	5	4
Thymus								
Abnormal area(s)	1	1	0	0	0	0	1	0
Abnormal colour	0	0	0	0	0	0	2	1
Abnormal size	0	0	0	4	0	0	0	1
Uterus								
Abnormal size					1	0	0	0
Abnormal contents					1	0	0	0
Whole animal								
No abnormalities detected	1	1	0	1	1	4	1	2

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 11.3 - Macroscopic observations - Recovery sacrifice - Group incidence

STUDY NO.: 27080

	-- Males --		-- Females --	
Group:	1	4	1	4
Number in group:	5	5	5	5
Cervical nodes				
Abnormal colour	2	1	2	3
Eyes				
Abnormal area(s)	0	1	0	0
Heart				
Abnormal colour	0	1	0	0
Ileum				
Abnormal contents	0	0	0	1
Liver				
Abnormal area(s)	0	1	0	0
Abnormal colour	0	1	0	0
Abnormal shape	0	2	0	0
Abnormal size	0	5	0	0
Abnormal consistency	0	1	0	0
Lungs				
Abnormal area(s)	0	1	0	0
Abnormal colour	1	0	1	0
Seminal vesicles				
Abnormal size	0	1		
Spleen				
Abnormal shape	2	2	0	1

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 11.3 - Macroscopic observations - Recovery sacrifice - Group incidence

STUDY NO.: 27080

	-- Males --		-- Females --	
Group:	1	4	1	4
Number in group:	5	5	5	5
Stomach				
Abnormal colour	0	1	0	0
Abnormal contents	0	1	0	1
Thymus				
Abnormal area(s)	1	3	0	1
Abnormal size	0	4	0	0
Uterus				
Abnormal size			0	2
Abnormal contents			0	2
Head				
Staining	1	0	0	0
Skin				
Not confirmed mass(es)	0	2	0	0
Whole animal				
No abnormalities detected	1	0	2	0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 12.1 - Microscopic observations - Final sacrifice - Group incidence

STUDY NO.: 27080

Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --				-- Animals Affected -- Females --			
Tissues With Diagnoses	Dosage group:	Ctls	2	3	4	Ctls	2	3	4
	No. in group:	5	5	5	5	5	5	5	5*
Cervical nodes	Number examined:	5	1	1	5	5	1	0	5*
CONGESTION/HAEMORRHAGE		0	1	1	1	3	1	0	2
Epididymides	Number examined:	5	0	0	5				
ABSENCE OF SPERM		1	0	0	0				
Kidneys	Number examined:	5	5	5	5	5	5	5	5*
NEPHROPATHY		4	5	3	4	1	3	1	2*
CORTICAL TUBULAR DILATATION		0	0	0	0	0	0	0	1*
MEDULLARY MINERALIZATION		0	0	0	0	0	0	1	4*
PAPILLARY MINERALIZATION		0	0	0	0	0	0	0	1
INFLAMMATORY CELL INFILTRATION		0	0	0	0	0	0	1	1
Liver	Number examined:	5	5	5	5	5	5	5	5*
INFLAMMATORY CELL FOCI		5	4	5	5	4	4	5	5*
EXTRAMEDULLARY HAEMOPOIESIS		0	0	0	0	0	2	0	0
BILE DUCT PROLIFERATION		2	5	4	5	1	4	5	4*
HEPATOCYTIC HYPERTROPHY		0	0	5	5	0	0	5	5*
HEPATOCYTIC NECROSIS		0	0	0	2	0	0	0	0
SINGLE CELL APOPTOSIS/NECROSIS		0	0	0	5	0	0	0	3*
HEPATOCYTIC VACUOLATION		0	0	3	2	0	0	0	1
HAEMORRHAGE		0	0	0	0	0	0	0	1*

* = Includes one found dead animal

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 12.1 - Microscopic observations - Final sacrifice - Group incidence

STUDY NO.: 27080

Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --				-- Animals Affected -- Females --			
Tissues With Diagnoses	Dosage group:	Ctls	2	3	4	Ctls	2	3	4
	No. in group:	5	5	5	5	5	5	5	5
Lungs ..... Number examined:		5	5	5	5	5	5	5	5*
INFLAMMATORY CELL FOCI		2	2	4	3	2	4	1	1
AGGREGATIONS OF ALVEOLAR MACROPHAGES		1	0	1	4	0	0	0	3
ALVEOLAR HAEMORRHAGE		2	3	0	0	3	0	1	1
VASCULAR MINERALIZATION		1	3	3	3	1	0	0	0
CHRONIC INFLAMMATION		1	0	0	0	0	0	0	0
BRONCHIAL HAEMORRHAGE		1	0	0	0	0	0	0	0
EOSINOPHILIC INFILTRATION		1	1	0	0	0	0	0	0
Ovaries ..... Number examined:						5	0	0	5*
LUTEIN CYST						1	0	0	0
Prostate ..... Number examined:		5	0	0	5				
INFLAMMATORY CELL INFILTRATION		5	0	0	2				
Seminal vesicles ..... Number examined:		5	5	5	5				
COLLOID DEPLETION		1	0	0	5				
Spleen ..... Number examined:		5	1	0	5	5	0	0	5*
LYMPHOID DEPLETION		0	0	0	0	0	0	0	1*
EXTRAMEDULLARY HAEMOPOIESIS		0	1	0	0	0	0	0	0
Stomach ..... Number examined:		5	0	0	5	5	0	0	5*
GLANDULAR DILATATION		2	0	0	0	0	0	0	0
OEDEMA		0	0	0	0	0	0	0	1
MUCOSAL ULCERATION		0	0	0	0	0	0	0	1
EPITHELIAL HYPERPLASIA		0	0	0	0	0	0	0	1
INFLAMMATORY CELL INFILTRATION		0	0	0	0	0	0	0	1
Testes ..... Number examined:		5	0	0	5				
UNILATERAL CONGENITAL APLASIA		1	0	0	0				

* = Includes one found dead animal

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 12.1 - Microscopic observations - Final sacrifice - Group incidence

STUDY NO.: 27080

Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Dosage group:	Ctls	2	3	4	Ctls	2	3	4
Tissues With Diagnoses	No. in group:	5	5	5	5	5	5	5	5
Thymus	Number examined:	5	5	5	5	5	5	5	5*
ATROPHY		0	0	1	5	0	0	0	3*
CONGESTION/HAEMORRHAGE		2	0	1	1	1	1	1	1
Thyroid	Number examined:	5	0	0	5	5	0	0	5*
ECTOPIC THYMIC TISSUE		2	0	0	0	1	0	0	0
DEVELOPMENTAL CYST(S)		0	0	0	0	0	0	0	1
Urinary bladder	Number examined:	5	0	0	5	5	0	0	5*
PROTEINACEOUS PLUG		2	0	0	1	0	0	0	0
Uterus	Number examined:					5	0	0	5*
HYDROMETRA						2	0	0	0
GLANDULAR DILATATION						1	0	0	0
Pancreas	Number examined:	0	0	0	0	0	0	0	1*
ACINAR CELL APOPTOSIS		0	0	0	0	0	0	0	1*
Head	Number examined:	0	0	0	0	0	0	0	1*
ULCERATION		0	0	0	0	0	0	0	1*
SCAB		0	0	0	0	0	0	0	1*

* = Includes one found dead animal

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 12.2 - Microscopic observations - Recovery sacrifice - Group incidence

STUDY NO.: 27080

Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --		-- Females --	
Tissues With Diagnoses	Dosage group:	Ctls	4	Ctls	4
	No. in group:	5	5	5	5
Kidneys	Number examined:	5	5	5	5
NEPHROPATHY		5	4	4	1
CORTICAL TUBULAR DILATATION		0	0	0	0
MEDULLARY MINERALIZATION		0	0	0	2
PAPILLARY MINERALIZATION		0	0	0	0
INFLAMMATORY CELL INFILTRATION		0	0	0	0
Liver	Number examined:	5	5	5	5
INFLAMMATORY CELL FOCI		4	5	5	5
EXTRAMEDULLARY HAEMOPOIESIS		0	0	0	0
BILE DUCT PROLIFERATION		3	5	4	4
HEPATOCYTIC HYPERTROPHY		0	4	0	3
HEPATOCYTIC NECROSIS		0	2	0	0
SINGLE CELL APOPTOSIS/NECROSIS		0	2	0	1
HEPATOCYTIC VACUOLATION		0	5	0	0
HAEMORRHAGE		0	0	0	0
Lungs	Number examined:	5	5	5	5
INFLAMMATORY CELL FOCI		3	3	2	3
AGGREGATIONS OF ALVEOLAR MACROPHAGES		0	2	0	0
ALVEOLAR HAEMORRHAGE		1	0	2	0
VASCULAR MINERALIZATION		2	2	1	0
CHRONIC INFLAMMATION		0	0	0	0
BRONCHIAL HAEMORRHAGE		0	0	0	0
EOSINOPHILIC INFILTRATION		0	0	0	0
Seminal vesicles	Number examined:	5	5		
COLLOID DEPLETION		0	2		
Thymus	Number examined:	5	5	5	5
ATROPHY		0	5	0	1
CONGESTION/HAEMORRHAGE		1	2	0	0

REDACTED AS TO TRADE NAMES

RESEARCH TOXICOLOGY CENTRE - ROMA

[redacted]

4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FINAL REPORT

VOLUME II OF II

RTC Study no.: 27080

Sponsor

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Appendices

Addenda

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 1 - Mortality - Individual data

STUDY NO.: 27080

Animal Number	Group	Sex	Study Phase	Description of death	Date of Death	Day of Death	Terminal body Weight (g)
27080043	4	F	Dosing phase	Found dead	13.Jul.04	28	183.3

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUPI	RIGH
27080002	1	2	1	2	4	+	1
27080004	1	1	1	2	4	-	1
27080006	1	1	1	2	1	+	1
27080008	1	2	1	2	2	+	1
27080010	1	1	1	2	4	+	1
27080012	1	1	1	2	2	+	1
27080014	1	2	1	2	4	+	1
27080016	1	1	2	2	1	+	1
27080018	1	2	1	2	2	+	1
27080020	1	2	1	2	2	+	1
27080022	2	2	1	2	2	+	1
27080024	2	2	2	2	4	+	1
27080026	2	2	1	1	2	+	1
27080028	2	2	1	2	4	+	1
27080030	2	1	1	2	2	+	1
27080032	3	2	1	1	2	+	1
27080034	3	2	2	2	2	+	1
27080036	3	1	1	1	1	+	1
27080038	3	2	2	2	1	+	1
27080040	3	1	1	1	2	+	1
27080042	4	1	1	2	2	+	1
27080044	4	1	1	2	2	+	1
27080046	4	1	1	1	2	+	1
27080048	4	1	1	2	2	+	1
27080050	4	1	1	2	1	+	1
27080052	4	1	2	2	4	+	1
27080054	4	1	1	1	1	+	2
27080056	4	1	1	2	2	+	1
27080058	4	1	2	1	2	+	1
27080060	4	1	2	1	2	+	1

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	GRI1 s	GRI2 s	GRIM s	BW g	LAN1 cm	LAN2 cm	LANM cm
27080002	1	6	4	5.0	364.2	7.5	7.5	7.50
27080004	1	7	2	4.5	348.0	7.0	6.5	6.75
27080006	1	2	10	6.0	358.1	6.0	5.5	5.75
27080008	1	3	18	10.5	361.0	5.0	5.0	5.00
27080010	1	2	2	2.0	400.2	7.0	10.0	8.50
27080012	1	6	3	4.5	373.9	4.5	5.5	4.75
27080014	1	2	2	2.0	381.2	5.5	5.5	5.50
27080016	1	2	2	2.0	366.3	4.0	6.0	5.00
27080018	1	5	3	4.0	386.2	3.5	4.0	3.75
27080020	1	3	2	2.5	366.3	4.5	4.5	4.50
	Mean	3.8	4.8	4.30	370.54	5.45	6.00	5.700
	SD	2.0	5.2	2.61	15.20	1.38	1.70	1.466
27080022	2	5	4	4.5	388.0	9.5	5.5	7.50
27080024	2	2	2	2.0	395.7	7.5	7.0	7.25
27080026	2	6	4	5.0	410.3	4.5	5.0	4.75
27080028	2	3	4	3.5	365.0	5.0	5.5	5.25
27080030	2	5	3	4.0	375.1	8.5	8.5	8.50
	Mean	4.2	3.4	3.80	389.82	7.00	6.30	6.650
	SD	1.6	0.9	1.15	17.64	2.18	1.44	1.587
27080032	3	4	8	6.0	354.7	7.5	7.0	7.25
27080034	3	29	6	17.5	412.2	8.0	10.0	9.00
27080036	3	2	2	2.0	365.5	7.5	7.5	7.50
27080038	3	8	2	5.0	372.4	7.5	7.0	7.25
27080040	3	24	13	18.5	385.9	7.0	8.5	7.75
	Mean	13.4	6.2	9.80	378.14	7.50	8.00	7.700
	SD	12.3	4.6	7.64	22.15	0.35	1.27	0.779
27080042	4	13	12	12.5	320.2	5.5	5.5	5.50
27080044	4	16	9	12.5	322.2	6.5	5.5	6.00
27080046	4	8	6	7.0	321.1	6.0	5.0	5.50
27080048	4	3	10	6.5	300.9	5.0	6.5	5.75
27080050	4	3	5	4.0	308.5	6.0	6.5	6.25
27080052	4	4	3	3.5	327.3	6.0	6.5	6.25
27080054	4	21	11	16.0	302.9	6.5	6.5	6.50
27080056	4	6	5	5.5	294.2	5.0	7.0	6.00
27080058	4	8	4	6.0	288.1	7.5	7.5	7.50
27080060	4	3	8	5.5	290.2	6.5	6.0	6.25
	Mean	8.5	7.3	7.90	307.56	6.05	6.25	6.150
	SD	6.2	3.1	4.22	14.42	0.76	0.75	0.580

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUPI	RIGH
27080001	1	1	1	2	2	+	1
27080003	1	1	1	2	2	-a	1
27080005	1	1	2	2	4	+	1
27080007	1	2	2	2	2	+	1
27080009	1	1	1	2	2	+	1
27080011	1	1	2	2	2	+	1
27080013	1	2	2	2	2	+	1
27080015	1	2	1	2	2	+	1
27080017	1	2	1	2	2	+	1
27080019	1	1	1	2	4	+	1
27080021	2	1	1	2	1	+	1
27080023	2	2	1	2	2	+	1
27080025	2	1	1	2	2	+	1
27080027	2	2	2	2	3	+	1
27080029	2	1	1	2	2	+	1
27080031	3	1	1	1	2	+	1
27080033	3	2	2	3	2	+	1
27080035	3	2	2	2	2	+	1
27080037	3	2	1	2	2	+	1
27080039	3	2	3	2	2	+	1
27080041	4	1	1	2	1	+	1
27080043	4	2	2	2	2	+	1
27080045	4	1	2	2	1	+	1
27080047	4	1	2	2	4	+	1
27080049	4	1	1	2	2	+	1
27080051	4	2	1	2	1	+	1
27080053	4	1	1	2	2	+	1
27080055	4	1	3	2	2	+	1
27080057	4	2	2	2	4	+	1
27080059	4	1	1	1	2	+	1

a = Pupil reflex missing in left eye

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	GRI1 s	GRI2 s	GRIM s	BW g	LAN1 cm	LAN2 cm	LANM cm
27080001	1	29	13	21.0	231.7	5.0	5.0	5.00
27080003	1	31	22	26.5	246.1	8.5	8.5	8.50
27080005	1	30	28	29.0	250.2	7.5	6.0	6.75
27080007	1	26	12	19.0	235.5	6.0	6.0	6.00
27080009	1	24	20	22.0	237.7	5.0	7.0	6.00
27080011	1	12	15	13.5	268.2	8.0	6.0	7.00
27080013	1	30	6	18.0	247.3	6.0	6.0	6.00
27080015	1	19	8	13.5	246.7	7.0	7.0	7.00
27080017	1	7	5	6.0	249.2	7.5	8.5	8.00
27080019	1	8	6	7.0	251.4	6.0	8.0	7.00
	Mean	21.6	13.5	17.55	246.54	6.65	6.80	6.725
	SD	9.5	7.8	7.62	10.19	1.23	1.21	1.030
27080021	2	7	3	5.0	257.1	6.0	7.0	6.50
27080023	2	24	37	30.5	238.5	6.5	8.0	7.25
27080025	2	24	4	14.0	261.8	9.0	7.0	8.00
27080027	2	55	7	31.0	249.3	6.0	6.0	6.00
27080029	2	63	11	37.0	239.2	7.0	6.0	6.50
	Mean	34.6	12.4	23.50	249.18	6.90	6.80	6.850
	SD	23.5	14.1	13.42	10.44	1.24	0.84	0.783
27080031	3	33	9	21.0	259.4	8.0	7.0	7.50
27080033	3	48	8	28.0	248.4	7.5	6.5	7.00
27080035	3	18	8	13.0	249.1	6.0	6.0	6.00
27080037	3	6	9	7.5	245.7	7.0	6.5	6.75
27080039	3	40	35	37.5	220.2	7.0	7.0	7.00
	Mean	29.0	13.8	21.40	244.56	7.10	6.60	6.850
	SD	16.9	11.9	11.90	14.58	0.74	0.42	0.548
27080041	4	24	40	32.0	230.6	7.0	6.0	6.50
27080043	4	58	18	38.0	207.4	6.5	6.0	6.25
27080045	4	15	20	17.5	228.5	7.0	6.5	6.75
27080047	4	45	3	24.0	219.1	5.0	7.0	6.00
27080049	4	15	25	20.0	240.9	7.0	7.5	7.25
27080051	4	25	35	30.0	225.3	6.0	5.0	5.50
27080053	4	20	31	25.5	222.3	5.0	7.0	6.00
27080055	4	56	8	32.0	231.8	6.0	6.0	6.00
27080057	4	34	13	23.5	221.5	7.0	7.0	7.00
27080059	4	15	11	13.0	220.6	8.0	5.0	6.50
	Mean	30.7	20.4	25.55	224.80	6.45	6.30	6.375
	SD	16.8	12.2	7.58	8.98	0.96	0.86	0.530

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.2 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUPI	RIGH
27080012	1	1	1	2	2	+	1
27080014		1	1	2	1	+	1
27080016		1	1	2	1	+	1
27080018		1	1	2	1	+	1
27080020		1	1	2	1	+	1
27080052	4	1	1	2	2	+	1
27080054		1	1	1	2	+	1
27080056		2	1	2	1	+	1
27080058		2	1	1	1	+	1
27080060		2	1	1	1	+	1

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.2 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		GRI1 s	GRI2 s	GRIM s	BW g	LAN1 cm	LAN2 cm	LANM cm
27080012	1		2	3	2.5	383.0	4.5	5.0	4.75
27080014			3	14	8.5	406.9	8.0	6.0	7.00
27080016			4	4	4.0	374.1	9.0	8.0	8.50
27080018			6	4	5.0	404.3	8.0	7.5	7.75
27080020			4	4	4.0	390.3	7.5	6.5	7.00
		Mean	3.8	5.8	4.80	391.72	7.40	6.60	7.000
		SD	1.5	4.6	2.25	13.94	1.71	1.19	1.403
27080052	4		6	3	4.5	337.5	6.0	5.5	5.75
27080054			14	6	10.0	315.0	6.5	5.5	6.00
27080056			30	6	18.0	280.9	5.0	4.5	4.75
27080058			3	13	8.0	286.9	5.0	5.0	5.00
27080060			20	9	14.5	276.8	6.0	4.5	5.25
		Mean	14.6	7.4	11.00	299.42	5.70	5.00	5.350
		SD	10.9	3.8	5.33	26.00	0.67	0.50	0.518

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.2 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUPI	RIGH
27080011	1	1	1	2	1	+	1
27080013		1	1	2	2	+	1
27080015		1	1	2	2	+	1
27080017		1	1	2	2	+	1
27080019		1	1	2	2	+	1
27080051	4	1	1	2	1	+	1
27080053		1	1	1	2	+	1
27080055		1	1	2	2	+	1
27080057		1	1	1	1	+	1
27080059		1	1	2	2	+	1

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.2 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		GRI1 s	GRI2 s	GRIM s	BW g	LAN1 cm	LAN2 cm	LANM cm
27080011	1		5	7	6.0	264.5	5.5	5.5	5.50
27080013			6	6	6.0	255.9	4.5	4.5	4.50
27080015			6	3	4.5	256.8	6.5	6.5	6.50
27080017			9	3	6.0	250.0	5.0	5.0	5.00
27080019			5	7	6.0	268.8	5.5	5.5	5.50
		Mean	6.2	5.2	5.70	259.20	5.40	5.40	5.400
		SD	1.6	2.0	0.67	7.44	0.74	0.74	0.742
27080051	4		40	4	4.0	239.4	6.0	5.5	5.75
27080053			15	13	14.0	232.5	5.5	5.0	5.25
27080055			22	15	18.5	234.3	6.0	6.0	6.00
27080057			20	10	15.0	230.1	5.5	6.0	5.75
27080059			21	13	17.0	232.0	6.0	6.0	6.00
		Mean	20.9	11.8	13.70	233.66	5.80	5.70	5.750
		SD	13.6	4.3	5.70	3.54	0.27	0.45	0.306

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 3.1 - Motor activity - At the end of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		COUN
27080002	1		1048
27080004			1420
27080006			1078
27080008			1469
27080010			1184
27080012			747
27080014			1190
27080016			1323
27080018			1243
27080020			1182
		Mean	1188.4
		SD	205.6
27080022	2		944
27080024			975
27080026			1267
27080028			1478
27080030			1315
		Mean	1195.8
		SD	229.7
27080032	3		1276
27080034			968
27080036			726
27080038			797
27080040			969
		Mean	947.2
		SD	212.4
27080042	4		1068
27080044			946
27080046			997
27080048			730
27080050			898
27080052			786
27080054			1325
27080056			1222
27080058			1285
27080060			807
		Mean	1006.4
		SD	213.3

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 3.1 - Motor activity - At the end of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		COUN
27080001	1		1308
27080003			1312
27080005			1532
27080007			1280
27080009			1283
27080011			1166
27080013			1270
27080015			1363
27080017			1429
27080019			1577
		Mean	1352.0
		SD	126.4
27080021	2		1403
27080023			1306
27080025			1075
27080027			1016
27080029			1364
		Mean	1232.8
		SD	175.7
27080031	3		1214
27080033			996
27080035			1727
27080037			1469
27080039			1141
		Mean	1309.4
		SD	289.6
27080041	4		677
27080043			1268
27080045			1398
27080047			943
27080049			1487
27080051			1433
27080053			1302
27080055			1338
27080057			1285
27080059			1316
		Mean	1244.7
		SD	247.3

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 3.2 - Motor activity - At the end of recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		COUN
27080012	1		679
27080014			710
27080016			1020
27080018			1052
27080020			1191
		Mean	930.4
		SD	225.0
27080052	4		1236
27080054			398
27080056			261
27080058			948
27080060			967
		Mean	762.0
		SD	413.8

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 3.2 - Motor activity - At the end of recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		COUN
27080011	1		1218
27080013			1389
27080015			1514
27080017			1621
27080019			1395
		Mean	1427.4
		SD	151.1
27080051	4		1367
27080053			1144
27080055			645
27080057			1350
27080059			1167
		Mean	1134.6
		SD	292.1

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 4.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		Day of Phase 1!	1"	8	15	22	29
27080002	1		297.5	319.4	336.7	350.3	363.6	372.1
27080004			274.5	283.1	301.3	326.6	345.9	353.5
27080006			279.2	299.8	321.9	340.6	358.2	365.4
27080008			284.4	302.6	325.8	341.3	361.8	363.8
27080010			297.0	327.2	350.7	379.1	398.4	401.3
27080012			280.8	306.3	333.1	350.2	370.9	
27080014			290.9	315.6	338.3	359.4	380.3	
27080016			275.3	303.8	330.3	347.8	362.0	
27080018			286.7	324.2	346.7	371.0	388.5	
27080020			297.4	303.0	326.1	345.4	363.7	
		(n)	10	10	10	10	10	5
		Mean	286.36	308.50	331.08	351.17	369.32	371.21
		SD	9.00	13.23	13.91	15.29	15.58	18.09
27080022	2		299.0	327.6	350.1	369.8	386.0	397.1
27080024			293.6	319.2	352.2	377.4	395.6	399.5
27080026			287.3	326.3	357.5	383.4	406.4	417.6
27080028			281.3	303.5	319.5	344.8	364.2	372.3
27080030			276.9	303.3	327.6	350.3	373.1	374.2
		(n)	5	5	5	5	5	5
		Mean	287.60	315.97	341.34	365.13	385.06	392.14
		SD	8.95	11.92	16.74	16.87	16.92	19.01

Note: ! = Pretest phase; " = Dosing phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 4.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		Day of Phase 1!	1"	8	15	22	29
27080032	3		281.9	302.7	330.9	349.9	356.4	362.8
27080034			300.9	335.7	376.5	399.5	423.8	415.7
27080036			281.7	301.3	330.2	344.8	358.3	355.7
27080038			294.3	322.6	351.2	370.3	380.6	373.0
27080040			277.5	311.7	349.8	376.6	389.1	385.3
		(n)	5	5	5	5	5	5
		Mean	287.26	314.80	347.72	368.21	381.64	378.50
		SD	9.87	14.46	18.93	22.00	27.46	23.60
27080042	4		286.4	324.7	353.7	333.8	318.5	303.1
27080044			298.9	331.9	357.4	347.7	329.4	313.8
27080046			286.2	306.1	335.6	327.4	325.2	300.7
27080048			273.2	296.8	323.3	326.9	306.9	277.0
27080050			280.6	299.2	330.6	327.3	316.2	283.8
27080052			297.3	334.0	350.1	335.2	333.0	
27080054			295.6	321.8	351.0	319.1	307.8	
27080056			275.6	304.7	333.2	303.9	296.4	
27080058			281.3	310.3	341.5	322.9	294.2	
27080060			290.2	315.4	344.0	314.9	296.6	
		(n)	10	10	10	10	10	5
		Mean	286.52	314.49	342.02	325.90	312.41	295.67
		SD	8.98	13.24	11.17	11.97	14.20	14.98

Note: ! = Pretest phase; " = Dosing phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 4.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		Day of Phase 1!	1"	8	15	22	29
27080001	1		192.3	192.4	198.5	216.3	227.7	225.2
27080003			199.7	202.7	222.8	243.1	248.0	237.1
27080005			212.5	216.1	232.3	256.3	241.4	250.0
27080007			198.0	208.9	220.0	222.9	240.4	235.1
27080009			202.8	208.7	214.9	228.6	238.1	244.6
27080011			208.3	227.0	252.5	249.9	254.3	
27080013			198.3	213.2	225.8	238.4	242.4	
27080015			191.0	204.0	204.2	230.3	242.3	
27080017			203.9	211.5	213.0	231.7	235.9	
27080019			208.1	206.5	225.7	234.8	252.4	
		(n)	10	10	10	10	10	5
		Mean	201.49	209.09	221.08	235.24	242.29	238.41
		SD	6.97	9.10	15.36	12.12	7.85	9.48
27080021	2		209.5	215.5	236.1	238.6	253.6	269.0
27080023			203.4	205.3	217.9	232.6	244.0	244.9
27080025			201.0	208.6	221.3	231.1	254.5	256.7
27080027			201.8	214.7	233.3	231.3	249.9	257.2
27080029			189.5	189.6	211.6	227.0	235.5	241.5
		(n)	5	5	5	5	5	5
		Mean	201.03	206.73	224.02	232.12	247.49	253.85
		SD	7.27	10.50	10.38	4.17	7.86	11.00

Note: ! = Pretest phase; " = Dosing phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 4.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		Day of Phase 1!	1"	8	15	22	29
27080031	3		203.2	210.2	232.1	243.5	256.1	253.4
27080033			208.5	210.8	231.0	240.6	244.1	247.8
27080035			205.9	210.3	224.1	240.2	247.9	249.4
27080037			200.9	209.0	228.1	234.1	242.0	243.1
27080039			187.4	196.8	206.7	218.3	222.1	224.5
		(n)	5	5	5	5	5	5
		Mean	201.17	207.42	224.39	235.33	242.43	243.66
		SD	8.19	5.98	10.37	10.11	12.56	11.33
27080041	4		202.4	204.8	223.0	225.7	223.7	224.5
27080043			211.1	209.8	210.0	201.9	206.9	
27080045			208.2	225.1	232.9	226.5	220.3	219.8
27080047			207.8	214.2	226.0	221.3	221.1	216.0
27080049			204.8	213.0	228.1	232.0	237.7	231.6
27080051			192.1	193.7	206.6	217.0	216.4	
27080053			199.7	199.6	214.9	223.3	227.7	
27080055			203.3	206.8	220.6	222.5	216.2	
27080057			195.9	201.4	230.7	219.5	212.1	
27080059			192.9	204.7	211.2	218.2	210.1	
		(n)	10	10	10	10	10	4
		Mean	201.82	207.31	220.39	220.79	219.20	223.00
		SD	6.56	8.79	9.26	7.99	9.07	6.73

Note: ! = Pretest phase; " = Dosing phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 4.2 - Body weight (g) - During recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	Day of Phase 1"	8	15
27080012	1	374.0	386.5	380.2
27080014		387.6	400.4	406.2
27080016		364.2	379.1	374.7
27080018		398.5	409.0	408.1
27080020		377.1	389.6	388.5
	(n)	5	5	5
	Mean	380.29	392.93	391.53
	SD	13.16	11.83	15.10
27080052		317.2	331.7	332.5
27080054	4	299.6	312.2	310.6
27080056		277.0	278.4	276.2
27080058		282.1	281.9	284.9
27080060		272.3	279.2	289.1
	(n)	5	5	5
	Mean	289.63	296.66	298.66
	SD	18.53	24.11	22.75

Note: " = Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 4.2 - Body weight (g) - During recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		Day of Phase 1"	8	15
27080011	1		260.2	249.3	260.4
27080013			250.2	264.1	251.8
27080015			246.1	255.6	255.9
27080017			249.0	248.0	237.2
27080019			256.6	266.4	264.8
		(n)	5	5	5
		Mean	252.41	256.66	254.00
		SD	5.82	8.36	10.60
27080051	4		219.3	226.2	236.4
27080053			219.6	226.0	227.6
27080055			221.7	227.2	238.3
27080057			218.7	224.9	231.8
27080059			212.5	220.0	224.7
		(n)	5	5	5
		Mean	218.37	224.85	231.79
		SD	3.46	2.85	5.72

Note: " = Recovery phase

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 5.1 - Food consumption° (g/animal/day) - During treatment - Cage data

STUDY NO.: 27080

MALES

Cage	Group		Day of Phase 1!	1"	15	22	29
1	1		26.3	25.7	26.8	25.8	23.1
2			29.1	27.9	28.5	27.2	
		(n)	2	2	2	2	
		Mean	27.71	26.81	27.65	26.49	
3	2		26.7	27.5	27.0	26.8	23.4
4	3		27.8	28.7	29.1	30.4	26.1
5	4		28.8	29.5	31.1	28.9	21.8
6			29.2	29.5	29.5	26.3	
		(n)	2	2	2	2	
		Mean	29.01	29.48	30.31	27.59	

Note: ! = Pretest phase; " = Dosing phase
° = food consumed over the previous period

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 5.1 - Food consumption° (g/animal/day) - During treatment - Cage data

STUDY NO.: 27080

FEMALES

Cage	Group		Day of Phase 1!	1"	15	22	29
7	1		22.2	19.7	21.6	19.0	16.9
8			24.6	20.2	21.3	20.4	
		(n)	2	2	2	2	
		Mean	23.38	19.95	21.47	19.68	
9	2		19.6	20.8	22.3	20.5	18.9
10	3		19.2	20.1	21.8	20.8	18.8
11	4		20.0	19.8	21.1	22.8	20.0
12			19.8	19.8	21.7	24.3	
		(n)	2	2	2	2	
		Mean	19.90	19.82	21.42	23.55	

Note: ! = Pretest phase; " = Dosing phase
° = food consumed over the previous period

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 5.2 - Food consumption° (g/animal/day) - During recovery - Cage data

STUDY NO.: 27080

MALES

Cage	Group	Day of Phase 1	8	15
2	1	23.6	28.6	22.0
6	4	22.0	27.5	23.3

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

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 5.2 - Food consumption° (g/animal/day) - During recovery - Cage data

STUDY NO.: 27080

FEMALES

Cage	Group	Day of Phase 1	Day of Phase 8	Day of Phase 15
8	1	18.2	20.1	16.2
12	4	22.1	23.7	19.4

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

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		RBC 10^12/l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
27080002	1		8.60	15.9	48.0	55.8	18.5	33.1
27080004	1		8.49	15.9	47.7	56.2	18.8	33.4
27080006	1		9.02	16.6	49.2	54.5	18.4	33.8
27080008	1		8.08	15.4	45.4	56.2	19.0	33.9
27080010	1		8.95	16.2	47.1	52.6	18.1	34.5
27080012	1		8.79	16.2	48.5	55.2	18.4	33.4
27080014	1		8.32	15.7	46.6	56.1	18.9	33.6
27080016	1		8.87	15.9	46.1	52.0	17.9	34.4
27080018	1		9.08	16.2	49.6	54.6	17.9	32.8
27080020	1		8.43	15.4	46.3	54.9	18.3	33.2
		Mean	8.663	15.94	47.45	54.81	18.42	33.61
		SD	0.331	0.38	1.39	1.48	0.39	0.55
27080022	2		8.95	16.2	48.2	53.8	18.1	33.7
27080024	2		7.38	13.2	39.5	53.4	17.9	33.6
27080026	2		7.84	14.2	43.1	55.0	18.2	33.8
27080028	2		8.44	15.5	46.3	54.8	18.4	33.5
27080030	2		8.48	15.6	44.9	52.9	18.4	34.8
		Mean	8.218	14.94	44.40	53.98	18.20	33.88
		SD	0.612	1.22	3.32	0.90	0.21	0.53

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		RBC 10^12/l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
27080032	3		8.25	15.1	44.7	54.2	18.3	33.9
27080034	3		8.83	16.4	49.4	56.0	18.6	33.3
27080036	3		8.60	15.7	46.5	54.0	18.3	33.8
27080038	3		8.55	15.7	46.5	54.4	18.4	33.8
27080040	3		8.27	15.3	45.6	55.2	18.5	33.5
		Mean	8.500	15.64	46.54	54.76	18.42	33.66
		SD	0.243	0.50	1.76	0.83	0.13	0.25
27080042	4		8.59	15.9	46.6	54.3	18.5	34.1
27080044	4		8.54	14.9	45.6	53.3	17.5	32.8
27080046	4		8.06	14.5	42.2	52.4	18.0	34.4
27080048	4		8.64	15.7	46.2	53.5	18.2	34.0
27080050	4		8.68	15.9	46.9	54.0	18.3	33.9
27080052	4		8.48	15.8	48.0	56.6	18.7	33.0
27080054	4		8.14	14.7	43.1	52.9	18.0	34.0
27080056	4		8.98	15.9	47.5	52.9	17.7	33.4
27080060	4		8.60	15.4	44.9	52.2	17.9	34.2
		Mean	8.523	15.41	45.67	53.57	18.09	33.76
		SD	0.279	0.56	1.96	1.33	0.38	0.56

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		PLT 10^9/l	PT sec
27080002	1		768	22.4
27080004	1		767	47.3
27080006	1		902	30.8
27080008	1		527	NT
27080010	1		899	30.4
27080012	1		993	NT
27080014	1		793	29.1
27080016	1		1027	NT
27080018	1		863	28.7
27080020	1		904	20.2
		Mean	844.3	29.84
		SD	141.7	8.72
27080022	2		905	NT
27080024	2		960	NT
27080026	2		750	NT
27080028	2		791	NT
27080030	2		920	NT
		Mean	865.2	-
		SD	89.9	-

NT = NOT TAKEN

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		PLT 10^9/l	PT sec
27080032	3		872	21.0
27080034	3		888	28.1
27080036	3		770	30.4
27080038	3		782	NT
27080040	3		832	21.4
		Mean	828.8	25.23
		SD	52.5	4.74
27080042	4		626	NT
27080044	4		649	49.4
27080046	4		778	NT
27080048	4		878	NT
27080050	4		704	NT
27080052	4		863	NT
27080054	4		802	17.8
27080056	4		806	NT
27080060	4		616	NT
		Mean	746.9	N/C
		SD	100.8	N/C

NT = NOT TAKEN
N/C = Not calculable due to low sample size

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		WBC 10^9/l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
27080002	1		14.02	7.4	85.5	2.3	3.3	0.3	1.2
27080004	1		13.73	10.5	81.8	4.7	1.2	0.3	1.5
27080006	1		16.73	11.5	82.3	3.1	1.3	0.3	1.6
27080008	1		12.89	10.5	79.0	4.1	4.8	0.3	1.4
27080010	1		16.30	33.5	58.6	2.6	4.0	0.3	0.9
27080012	1		17.08	6.8	89.1	1.9	0.9	0.5	0.9
27080014	1		11.29	11.7	83.5	2.3	1.1	0.3	1.1
27080016	1		11.20	12.4	81.8	3.2	1.5	0.3	0.9
27080018	1		10.22	10.4	83.7	2.8	2.0	0.2	1.0
27080020	1		10.79	7.5	87.1	2.9	1.0	0.3	1.2
		Mean	13.425	12.22	81.24	2.99	2.11	0.31	1.17
		SD	2.582	7.73	8.46	0.85	1.41	0.07	0.26
27080022	2		12.71	11.1	83.7	2.6	1.4	0.4	0.8
27080024	2		12.03	9.9	84.8	2.8	0.8	0.3	1.4
27080026	2		12.38	10.6	84.3	2.7	1.2	0.3	1.0
27080028	2		13.44	7.4	88.0	2.3	0.7	0.2	1.3
27080030	2		10.95	11.2	84.4	2.4	1.1	0.2	0.8
		Mean	12.302	10.04	85.04	2.56	1.04	0.28	1.06
		SD	0.918	1.56	1.70	0.21	0.29	0.08	0.28

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		WBC 10^9/l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
27080032	3		12.78	7.5	86.7	2.8	1.7	0.2	1.2
27080034	3		11.88	13.4	81.2	2.8	1.3	0.3	1.0
27080036	3		10.06	9.6	83.3	4.0	1.5	0.2	1.4
27080038	3		10.56	9.6	84.1	3.8	1.3	0.2	1.0
27080040	3		9.15	11.3	83.2	3.0	1.1	0.3	1.1
		Mean	10.886	10.28	83.70	3.28	1.38	0.24	1.14
		SD	1.447	2.20	1.99	0.58	0.23	0.05	0.17
27080042	4		5.66	12.3	83.3	2.3	1.1	0.2	0.9
27080044	4		8.19	10.4	85.1	2.3	0.7	0.2	1.2
27080046	4		10.68	3.8	92.4	2.2	0.7	0.2	0.8
27080048	4		13.71	4.9	89.4	3.2	0.5	0.3	1.8
27080050	4		5.74	4.1	91.9	2.3	1.0	0.0	0.7
27080052	4		14.64	10.8	83.9	3.2	0.3	0.4	1.4
27080054	4		12.41	4.4	92.4	1.6	0.4	0.3	0.9
27080056	4		9.15	9.4	84.3	4.0	0.7	0.3	1.3
27080060	4		10.30	4.0	90.5	3.4	0.4	0.2	1.6
		Mean	10.053	7.12	88.13	2.72	0.64	0.23	1.18
		SD	3.213	3.51	3.92	0.76	0.27	0.11	0.38

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		RBC 10^12/l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
27080001	1		7.10	12.6	37.5	52.7	17.8	33.8
27080003	1		8.77	15.9	47.6	54.3	18.1	33.3
27080005	1		8.57	15.9	47.4	55.4	18.6	33.5
27080007	1		8.10	14.8	43.9	54.2	18.3	33.7
27080009	1		8.18	15.4	46.3	56.6	18.8	33.3
27080011	1		8.24	14.7	43.8	53.2	17.8	33.5
27080013	1		8.90	16.2	47.2	53.1	18.2	34.3
27080015	1		7.92	14.9	43.9	55.5	18.9	34.0
27080017	1		8.12	15.2	44.8	55.2	18.7	33.8
27080019	1		7.96	15.2	45.2	56.8	19.1	33.5
		Mean	8.186	15.08	44.76	54.70	18.43	33.67
		SD	0.507	1.01	2.96	1.44	0.46	0.32
27080021	2		8.32	15.2	45.3	54.4	18.2	33.5
27080023	2		7.98	14.8	43.8	54.8	18.5	33.8
27080025	2		7.99	15.0	44.5	55.7	18.8	33.8
27080027	2		7.73	14.4	42.0	54.3	18.7	34.4
27080029	2		7.48	14.4	41.3	55.2	19.2	34.8
		Mean	7.900	14.76	43.38	54.88	18.68	34.06
		SD	0.315	0.36	1.68	0.58	0.37	0.53

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		RBC 10^12/l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
27080031	3		8.26	15.2	44.6	54.0	18.4	34.2
27080033	3		7.96	14.8	43.6	54.8	18.6	34.0
27080035	3		7.73	14.7	43.2	55.8	19.0	34.0
27080037	3		7.54	13.8	40.3	53.4	18.3	34.2
27080039	3		7.92	14.6	43.9	55.4	18.5	33.3
		Mean	7.882	14.62	43.12	54.68	18.56	33.94
		SD	0.269	0.51	1.66	0.99	0.27	0.37
27080041	4		7.99	15.2	43.2	54.2	19.0	35.1
27080043	4		9.44	17.9	54.9	58.2	19.0	32.6
27080045	4		8.44	15.4	46.1	54.6	18.2	33.4
27080047	4		7.99	14.5	43.8	54.9	18.1	33.0
27080049	4		8.25	15.5	45.2	54.7	18.8	34.3
27080051	4		8.00	14.0	41.5	51.9	17.6	33.8
27080053	4		8.43	14.8	44.1	52.3	17.6	33.7
27080055	4		8.13	15.2	45.3	55.7	18.7	33.5
27080057	4		8.12	15.2	45.0	55.4	18.7	33.8
27080059	4		7.69	14.4	43.8	56.9	18.7	32.8
		Mean	8.248	15.21	45.29	54.88	18.44	33.60
		SD	0.475	1.06	3.62	1.89	0.53	0.74

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		PLT 10^9/l	PT sec
27080001	1		946	23.4
27080003	1		997	23.0
27080005	1		1035	33.0
27080007	1		1090	26.0
27080009	1		956	28.4
27080011	1		940	21.5
27080013	1		1097	25.4
27080015	1		961	NT
27080017	1		1065	24.1
27080019	1		875	NT
		Mean	996.2	25.60
		SD	73.3	3.65
27080021	2		1189	23.8
27080023	2		1110	32.7
27080025	2		943	26.7
27080027	2		1064	21.1
27080029	2		1058	35.9
		Mean	1072.8	28.04
		SD	89.5	6.15

NT = NOT TAKEN

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		PLT 10^9/l	PT sec
27080031	3		1021	24.4
27080033	3		916	28.2
27080035	3		918	28.1
27080037	3		994	24.6
27080039	3		856	21.9
		Mean	941.0	25.44
		SD	66.3	2.69
27080041	4		808	27.7
27080043	4		469	NT
27080045	4		798	41.0
27080047	4		670	33.0
27080049	4		927	30.1
27080051	4		940	30.5
27080053	4		816	NT
27080055	4		900	NT
27080057	4		852	NT
27080059	4		783	30.2
		Mean	796.3	32.08
		SD	139.6	4.68

NT = NOT TAKEN

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		WBC 10^9/l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
27080001	1		10.66	13.9	81.0	2.4	1.4	0.2	1.0
27080003	1		13.52	12.7	82.3	2.4	1.3	0.3	1.0
27080005	1		11.91	9.0	86.2	2.3	1.4	0.3	0.7
27080007	1		9.89	9.8	84.5	3.2	1.3	0.3	0.9
27080009	1		11.21	7.9	85.6	3.2	2.2	0.3	0.9
27080011	1		7.92	18.0	76.8	2.8	1.5	0.1	0.9
27080013	1		12.70	9.2	86.1	2.2	1.2	0.3	1.0
27080015	1		8.32	10.1	83.5	3.5	2.0	0.2	0.7
27080017	1		5.63	12.1	83.0	3.0	1.3	0.1	0.6
27080019	1		5.32	11.4	84.6	2.5	0.8	0.1	0.6
		Mean	9.708	11.41	83.36	2.75	1.44	0.22	0.83
		SD	2.839	2.96	2.85	0.45	0.40	0.09	0.16
27080021	2		6.87	14.5	78.5	3.8	1.7	0.2	1.3
27080023	2		7.72	10.1	82.1	3.5	2.9	0.2	1.3
27080025	2		6.97	10.9	83.3	2.7	1.8	0.2	1.1
27080027	2		8.37	8.2	84.0	3.6	2.9	0.1	1.2
27080029	2		5.13	12.0	83.8	1.9	1.8	0.1	0.5
		Mean	7.012	11.14	82.34	3.10	2.22	0.16	1.08
		SD	1.215	2.34	2.27	0.79	0.62	0.05	0.33

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		WBC 10^9/l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
27080031	3		5.44	7.8	88.0	2.0	1.5	0.0	0.7
27080033	3		8.34	11.4	83.6	1.8	2.4	0.1	0.7
27080035	3		11.21	7.3	88.3	2.0	1.1	0.2	1.0
27080037	3		6.26	10.5	85.7	2.4	1.0	0.1	0.5
27080039	3		7.99	9.3	84.6	3.0	1.6	0.2	1.3
		Mean	7.848	9.26	86.04	2.24	1.52	0.12	0.84
		SD	2.230	1.74	2.07	0.48	0.55	0.08	0.31
27080041	4		7.67	12.7	82.6	2.4	1.2	0.2	0.8
27080043	4		4.17	76.0	23.0	1.0	0.0	0.0	0.0
27080045	4		6.77	19.9	77.2	1.5	0.3	0.2	0.9
27080047	4		7.01	8.7	85.2	2.5	2.3	0.2	1.1
27080049	4		8.35	10.3	85.7	1.7	1.3	0.2	0.8
27080051	4		5.93	8.3	85.2	3.5	1.5	0.2	1.3
27080053	4		11.61	10.9	83.4	3.1	1.2	0.2	1.2
27080055	4		9.79	5.2	89.8	2.2	1.3	0.4	1.1
27080057	4		9.21	7.8	87.1	2.8	0.9	0.2	1.2
27080059	4		7.73	8.4	86.5	3.2	0.9	0.1	0.9
		Mean	7.824	16.82	78.57	2.39	1.09	0.19	0.93
		SD	2.085	21.17	19.80	0.80	0.63	0.10	0.37

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Haematology - Week 2 of recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		RBC 10^12/l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
27080012	1		8.94	16.3	49.2	55.0	18.2	33.1
27080014	1		8.69	15.7	48.3	55.6	18.1	32.6
27080016	1		9.43	16.5	48.8	51.8	17.5	33.8
27080018	1		9.38	16.6	51.7	55.1	17.7	32.2
27080020	1		8.67	15.8	47.9	55.3	18.2	33.0
		Mean	9.022	16.18	49.18	54.56	17.94	32.94
		SD	0.366	0.41	1.49	1.56	0.32	0.60
27080052	4		8.23	14.3	44.4	54.0	17.4	32.2
27080054	4		8.03	13.9	41.7	51.9	17.3	33.3
27080056	4		8.51	14.5	42.6	50.1	17.0	34.0
27080058	4		7.86	13.4	39.6	50.3	17.0	33.8
27080060	4		7.74	13.2	40.3	52.1	17.0	32.7
		Mean	8.074	13.86	41.72	51.68	17.14	33.20
		SD	0.306	0.56	1.90	1.58	0.19	0.75

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Haematology - Week 2 of recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		PLT 10^9/l	PT sec
27080012	1		999	21.1
27080014	1		842	27.8
27080016	1		955	23.5
27080018	1		390	31.8
27080020	1		892	38.9
		Mean	815.6	28.62
		SD	245.3	7.06
27080052	4		464	35.6
27080054	4		655	31.0
27080056	4		939	27.5
27080058	4		1019	29.6
27080060	4		829	31.6
		Mean	781.2	31.06
		SD	223.8	2.99

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Haematology - Week 2 of recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		WBC 10^9/l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
27080012	1		11.65	8.0	87.6	2.2	1.0	0.2	1.0
27080014	1		12.23	14.0	80.7	2.8	0.9	0.2	1.4
27080016	1		10.86	9.3	85.8	3.0	0.7	0.2	1.0
27080018	1		12.31	16.4	78.2	3.2	0.9	0.2	1.1
27080020	1		9.39	5.9	89.7	2.5	0.8	0.1	0.9
		Mean	11.288	10.72	84.40	2.74	0.86	0.18	1.08
		SD	1.209	4.35	4.81	0.40	0.11	0.04	0.19
27080052	4		13.36	7.2	86.6	3.1	1.5	0.3	1.2
27080054	4		8.29	5.6	92.0	1.4	0.3	0.2	0.6
27080056	4		5.72	7.8	86.4	3.2	1.8	0.1	0.7
27080058	4		6.09	9.9	85.9	2.5	0.7	0.1	0.9
27080060	4		6.91	7.0	87.1	3.7	0.8	0.1	1.3
		Mean	8.074	7.50	87.60	2.78	1.02	0.16	0.94
		SD	3.115	1.57	2.50	0.88	0.61	0.09	0.30

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Haematology - Week 2 of recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		RBC 10^12/l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
27080011	1		8.29	15.4	45.0	54.3	18.6	34.2
27080013	1		7.83	14.3	41.8	53.4	18.3	34.3
27080015	1		8.14	15.9	45.9	56.4	19.5	34.6
27080017	1		8.13	15.7	46.0	56.5	19.3	34.2
27080019	1		8.44	16.4	48.0	56.9	19.4	34.1
		Mean	8.166	15.54	45.34	55.50	19.02	34.28
		SD	0.227	0.78	2.26	1.55	0.54	0.19
27080051	4		7.92	14.1	42.4	53.6	17.8	33.1
27080053	4		8.22	14.4	42.3	51.5	17.5	33.9
27080055	4		7.93	15.0	44.9	56.6	18.9	33.4
27080057	4		8.19	15.1	44.2	53.9	18.5	34.3
27080059	4		7.93	15.0	44.8	56.6	18.9	33.5
		Mean	8.038	14.72	43.72	54.44	18.32	33.64
		SD	0.153	0.44	1.28	2.18	0.64	0.47

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Haematology - Week 2 of recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		PLT 10^9/l	PT sec
27080011	1		1030	15.2
27080013	1		1181	23.2
27080015	1		993	28.8
27080017	1		932	37.0
27080019	1		881	45.2
		Mean	1003.4	29.88
		SD	114.5	11.69
27080051	4		1035	26.8
27080053	4		928	32.5
27080055	4		997	28.8
27080057	4		949	35.8
27080059	4		963	47.4
		Mean	974.4	34.26
		SD	42.2	8.12

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Haematology - Week 2 of recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		WBC 10^9/l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
27080011	1		6.25	13.8	81.3	2.2	1.5	0.1	1.0
27080013	1		17.94	20.8	73.2	2.9	1.3	0.3	1.5
27080015	1		6.91	13.5	80.1	3.1	2.6	0.2	0.6
27080017	1		4.29	15.7	80.2	1.9	1.4	0.0	0.8
27080019	1		5.58	10.0	85.1	2.6	1.6	0.1	0.6
		Mean	8.194	14.76	79.98	2.54	1.68	0.14	0.90
		SD	5.534	3.95	4.30	0.49	0.53	0.11	0.37
27080051	4		4.90	9.1	85.9	2.1	1.9	0.1	0.9
27080053	4		5.43	7.3	87.6	1.8	2.3	0.1	1.0
27080055	4		6.09	9.6	85.9	1.9	1.6	0.2	0.8
27080057	4		4.58	8.5	83.9	4.8	1.5	0.2	1.2
27080059	4		6.34	8.8	85.1	3.5	1.5	0.2	0.9
		Mean	5.468	8.66	85.68	2.82	1.76	0.16	0.96
		SD	0.752	0.86	1.35	1.30	0.34	0.05	0.15

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		AP U/l	ALT U/l	AST U/l	GGT U/l	BILT mg/dl	CHOL mg/dl	TRI mg/dl	GLU mg/dl
27080002	1		284.5	52.5	99.7	0.70	0.08	85.9	38.6	112.6
27080004	1		330.9	64.6	126.9	1.50	0.10	82.1	37.3	113.7
27080006	1		258.2	48.4	94.5	1.40	0.06	89.9	58.7	118.1
27080008	1		257.0	55.8	94.0	1.20	0.09	78.6	32.2	111.9
27080010	1		310.9	77.9	134.9	0.50	0.08	82.6	34.8	119.3
27080012	1		230.5	48.9	92.8	1.20	0.08	82.4	25.9	102.8
27080014	1		305.2	60.2	99.1	1.30	0.03	79.3	29.5	102.2
27080016	1		313.5	58.5	101.8	0.60	0.06	77.1	31.1	105.1
27080018	1		261.5	48.6	83.5	0.80	0.05	80.9	39.3	110.6
27080020	1		253.5	54.4	81.9	0.60	0.05	81.9	38.8	120.4
		Mean	280.57	56.98	100.91	0.980	0.068	82.07	36.62	111.67
		SD	33.03	9.10	17.18	0.377	0.021	3.68	8.96	6.61
27080022	2		292.5	51.9	97.1	0.10	0.03	49.5	49.9	185.3
27080024	2		268.3	58.4	103.6	0.40	0.05	38.9	38.8	163.8
27080026	2		304.0	45.9	98.6	1.20	0.02	52.3	47.7	172.0
27080028	2		289.9	72.8	145.8	0.60	0.04	43.8	48.0	175.0
27080030	2		447.5	45.8	105.4	0.70	0.02	45.4	32.0	174.8
		Mean	320.44	54.96	110.10	0.600	0.032	45.98	43.28	174.18
		SD	72.19	11.24	20.25	0.406	0.013	5.19	7.63	7.70

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		AP U/l	ALT U/l	AST U/l	GGT U/l	BILT mg/dl	CHOL mg/dl	TRI mg/dl	GLU mg/dl
27080032	3		514.9	68.1	129.3	6.50	0.02	57.3	40.6	136.7
27080034	3		469.5	82.1	123.2	0.20	0.01	75.5	69.9	145.8
27080036	3		533.8	66.9	130.2	1.00	0.04	53.5	40.5	141.7
27080038	3		490.9	75.2	132.5	0.20	0.04	71.5	55.3	132.4
27080040	3		461.5	62.4	92.6	0.80	0.01	62.5	40.6	128.5
		Mean	494.12	70.94	121.56	1.740	0.024	64.06	49.38	137.02
		SD	30.36	7.75	16.55	2.685	0.015	9.30	13.13	6.95
27080042	4		636.0	61.7	131.8	10.80	0.03	115.4	60.6	108.1
27080044	4		440.4	65.1	130.9	6.30	0.06	84.1	62.2	104.0
27080046	4		426.0	51.7	117.9	0.50	0.03	74.6	42.1	121.6
27080048	4		562.4	89.5	245.3	4.80	0.05	99.3	45.5	130.5
27080050	4		477.5	53.2	157.1	1.40	0.06	73.8	38.5	116.6
27080052	4		609.3	63.9	154.9	2.00	0.11	66.6	60.6	97.2
27080054	4		455.2	59.5	118.0	3.30	0.10	83.5	48.4	123.2
27080056	4		381.8	50.2	131.1	1.20	0.07	92.0	61.2	128.2
27080058	4		556.8	74.3	156.9	3.20	0.08	95.6	61.3	111.1
27080060	4		453.5	66.3	165.6	1.20	0.06	81.9	30.6	119.6
		Mean	499.89	63.54	150.95	3.470	0.065	86.68	51.10	116.01
		SD	85.14	11.76	37.34	3.148	0.026	14.32	11.59	10.75

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		UREA mg/dl	CREA mg/dl	CL mmol/l	PHOS mg/dl	CA mmol/l	Na mmol/l	K mmol/l
27080002	1		42.7	0.59	99.2	8.1	2.71	NT	NT
27080004	1		49.2	0.65	98.8	7.8	2.74	158.5	4.09
27080006	1		57.6	0.58	97.6	7.7	2.80	151.0	3.83
27080008	1		47.7	0.54	98.9	8.7	2.65	164.2	4.17
27080010	1		42.3	0.49	97.3	7.2	2.68	152.0	3.60
27080012	1		46.0	0.55	99.1	7.4	2.71	159.9	4.06
27080014	1		36.2	0.48	98.8	6.8	2.59	155.4	3.97
27080016	1		46.8	0.50	98.3	6.6	2.72	158.1	3.81
27080018	1		44.5	0.52	99.8	7.1	2.74	156.9	4.00
27080020	1		38.5	0.47	100.3	7.2	2.64	156.7	3.86
		Mean	45.15	0.537	98.81	7.47	2.698	156.97	3.932
		SD	5.96	0.057	0.91	0.65	0.060	3.99	0.175
27080022	2		55.5	0.50	97.9	7.3	2.63	151.6	4.06
27080024	2		56.0	0.45	99.3	7.0	2.62	150.0	4.16
27080026	2		61.8	0.52	100.7	7.9	2.62	154.9	4.47
27080028	2		63.5	0.45	101.3	7.5	2.53	154.5	5.12
27080030	2		55.8	0.47	99.1	7.2	2.64	152.2	4.22
		Mean	58.52	0.478	99.66	7.37	2.608	152.64	4.406
		SD	3.82	0.031	1.35	0.33	0.044	2.05	0.427

NT = NOT TAKEN

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		UREA mg/dl	CREA mg/dl	CL mmol/l	PHOS mg/dl	CA mmol/l	Na mmol/l	K mmol/l
27080032	3		48.5	0.32	101.6	7.9	2.49	155.1	4.41
27080034	3		55.8	0.41	99.4	6.9	2.54	155.6	4.06
27080036	3		59.0	0.38	102.9	7.8	2.56	156.2	4.37
27080038	3		57.3	0.45	102.5	7.0	2.46	158.1	4.90
27080040	3		55.0	0.42	100.2	8.2	2.55	156.4	4.12
		Mean	55.12	0.396	101.32	7.56	2.520	156.28	4.372
		SD	4.00	0.049	1.49	0.55	0.043	1.14	0.332
27080042	4		63.5	0.32	103.6	7.6	2.35	154.3	4.77
27080044	4		70.5	0.42	104.8	7.0	2.37	158.4	5.03
27080046	4		64.3	0.39	100.7	7.2	2.39	156.0	4.51
27080048	4		61.1	0.37	102.9	6.9	2.42	156.0	3.99
27080050	4		61.0	0.33	101.8	6.6	2.32	155.5	4.57
27080052	4		68.6	0.37	101.4	7.9	2.42	155.8	4.71
27080054	4		70.0	0.37	103.2	8.0	2.48	155.1	4.28
27080056	4		61.8	0.38	101.8	7.3	2.37	154.6	4.59
27080058	4		69.6	0.43	101.6	7.6	2.46	154.8	4.12
27080060	4		68.5	0.45	103.2	6.9	2.42	156.1	4.51
		Mean	65.89	0.383	102.50	7.29	2.400	155.66	4.508
		SD	3.91	0.041	1.24	0.46	0.049	1.15	0.310

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		PROT g/dl	ALB g/dl	GLO g/dl	AGR
27080002	1		7.2	4.3	2.9	1.5
27080004	1		6.7	3.9	2.8	1.4
27080006	1		7.3	4.2	3.1	1.4
27080008	1		6.4	4.0	2.4	1.7
27080010	1		7.2	4.2	3.0	1.4
27080012	1		6.9	4.2	2.7	1.6
27080014	1		6.6	4.1	2.5	1.6
27080016	1		7.2	4.2	3.0	1.4
27080018	1		7.0	4.2	2.8	1.5
27080020	1		6.8	4.3	2.5	1.7
		Mean	6.93	4.16	2.77	1.51
		SD	0.30	0.13	0.24	0.13
27080022	2		6.6	4.3	2.3	1.9
27080024	2		6.8	4.3	2.5	1.7
27080026	2		6.6	4.3	2.3	1.9
27080028	2		6.8	4.3	2.5	1.7
27080030	2		7.2	4.4	2.8	1.6
		Mean	6.80	4.32	2.48	1.75
		SD	0.24	0.04	0.20	0.12

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		PROT g/dl	ALB g/dl	GLO g/dl	AGR
27080032	3		5.8	4.3	1.5	2.9
27080034	3		5.9	3.9	2.0	2.0
27080036	3		5.6	4.2	1.4	3.0
27080038	3		6.0	4.4	1.6	2.8
27080040	3		6.1	4.2	1.9	2.2
		Mean	5.88	4.20	1.68	2.56
		SD	0.19	0.19	0.26	0.45
27080042	4		5.1	3.2	1.9	1.7
27080044	4		5.3	3.6	1.7	2.1
27080046	4		5.3	3.8	1.5	2.5
27080048	4		5.1	3.5	1.6	2.2
27080050	4		4.7	3.4	1.3	2.6
27080052	4		5.0	3.4	1.6	2.1
27080054	4		5.1	3.7	1.4	2.6
27080056	4		5.4	3.6	1.8	2.0
27080058	4		5.2	3.4	1.8	1.9
27080060	4		4.5	3.2	1.3	2.5
		Mean	5.07	3.48	1.59	2.23
		SD	0.28	0.20	0.21	0.33

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		AP U/l	ALT U/l	AST U/l	GGT U/l	BILT mg/dl	CHOL mg/dl	TRI mg/dl	GLU mg/dl
27080001	1		227.2	40.6	96.4	1.40	0.07	71.0	12.4	102.3
27080003	1		269.3	38.8	94.9	0.20	0.08	83.4	18.0	121.7
27080005	1		202.2	43.3	85.6	0.40	0.09	87.2	22.4	124.0
27080007	1		214.6	38.0	97.8	0.20	0.11	92.2	21.4	142.6
27080009	1		213.7	44.8	88.0	0.50	0.07	83.7	19.6	145.1
27080011	1		223.6	42.0	94.6	1.30	0.09	82.0	24.0	88.5
27080013	1		212.6	40.5	84.3	1.10	0.08	104.1	23.7	90.9
27080015	1		253.3	46.0	96.9	0.30	0.10	104.0	25.9	99.5
27080017	1		218.9	37.8	104.5	0.50	0.09	85.0	32.8	92.8
27080019	1		221.7	41.9	107.3	1.30	0.08	82.6	20.9	87.3
		Mean	225.71	41.37	95.03	0.720	0.086	87.52	22.11	109.47
		SD	20.34	2.78	7.51	0.494	0.013	10.19	5.32	22.19
27080021	2		250.7	39.5	81.3	1.80	0.05	97.5	40.6	131.4
27080023	2		220.2	34.0	77.5	1.20	0.04	77.9	40.1	126.7
27080025	2		313.6	45.1	98.5	1.60	0.13	72.8	20.5	101.4
27080027	2		199.1	37.9	82.7	1.30	0.06	74.9	30.5	118.6
27080029	2		281.1	38.9	94.2	1.30	0.05	88.0	35.6	116.0
		Mean	252.94	39.08	86.84	1.440	0.066	82.22	33.46	118.82
		SD	45.96	3.99	9.02	0.251	0.036	10.34	8.31	11.53

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		AP U/l	ALT U/l	AST U/l	GGT U/l	BILT mg/dl	CHOL mg/dl	TRI mg/dl	GLU mg/dl
27080031	3		320.0	46.6	104.7	0.20	0.05	83.2	44.6	138.0
27080033	3		274.3	41.8	85.2	0.30	0.01	98.0	38.4	154.8
27080035	3		279.9	42.0	88.8	0.00	0.01	82.0	43.9	146.6
27080037	3		321.3	36.3	78.5	0.50	0.05	52.8	32.6	161.7
27080039	3		344.8	40.0	89.3	0.60	0.04	75.8	34.5	139.7
		Mean	308.06	41.34	89.30	0.320	0.032	78.36	38.80	148.16
		SD	30.00	3.73	9.63	0.239	0.020	16.45	5.40	10.06
27080041	4		400.9	49.9	105.2	0.50	0.07	54.8	37.6	121.7
27080043	4		1107.1	5165.0	230.2	43.80	6.41	183.5	62.4	42.5
27080045	4		162.1	129.8	211.2	0.30	0.05	49.4	42.6	129.9
27080047	4		423.4	83.0	179.2	0.40	0.07	62.7	46.1	130.2
27080049	4		411.7	63.0	157.8	1.00	0.09	50.0	39.2	124.3
27080051	4		415.0	53.7	127.7	0.70	0.09	53.8	33.1	117.9
27080053	4		401.1	47.8	119.1	0.50	0.13	54.9	39.9	123.0
27080055	4		347.3	51.4	119.9	0.90	0.05	74.6	26.9	129.6
27080057	4		404.4	43.9	104.9	0.90	0.09	60.2	35.6	137.4
27080059	4		276.3	64.4	107.9	0.10	0.08	58.8	31.0	147.6
		Mean	434.93	575.19	146.31	4.910	0.713	70.27	39.44	120.41
		SD	250.20	1612.90	46.10	13.668	2.002	40.45	9.82	28.67

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		UREA mg/dl	CREA mg/dl	CL mmol/l	PHOS mg/dl	CA mmol/l	Na mmol/l	K mmol/l
27080001	1		66.0	0.50	98.6	6.5	2.79	146.5	3.77
27080003	1		57.8	0.44	99.4	7.2	2.80	147.8	3.40
27080005	1		61.3	0.46	99.2	7.1	2.84	147.5	3.52
27080007	1		59.9	0.43	98.1	6.5	2.76	146.0	3.58
27080009	1		66.6	0.44	100.1	6.7	2.80	146.1	3.70
27080011	1		64.5	0.54	96.7	6.4	2.78	144.8	3.91
27080013	1		65.8	0.58	96.7	6.2	2.79	143.8	3.54
27080015	1		56.3	0.55	98.0	6.6	2.78	142.3	3.37
27080017	1		57.0	0.57	97.0	7.0	2.69	139.6	3.24
27080019	1		61.4	0.68	99.6	7.0	2.74	143.0	3.48
		Mean	61.66	0.519	98.34	6.72	2.777	144.74	3.551
		SD	3.90	0.080	1.25	0.36	0.040	2.58	0.200
27080021	2		51.8	0.54	99.8	6.8	2.83	149.3	3.03
27080023	2		52.7	0.47	101.3	5.7	2.70	150.0	3.24
27080025	2		74.2	0.63	100.6	7.2	2.77	149.2	3.44
27080027	2		60.6	0.52	102.0	5.9	2.78	148.7	3.18
27080029	2		47.6	0.47	100.5	5.7	2.77	151.2	3.19
		Mean	57.38	0.526	100.84	6.27	2.770	149.68	3.216
		SD	10.51	0.066	0.84	0.70	0.046	0.97	0.148

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		UREA mg/dl	CREA mg/dl	CL mmol/l	PHOS mg/dl	CA mmol/l	Na mmol/l	K mmol/l
27080031	3		71.8	0.47	102.8	6.6	2.71	149.6	3.92
27080033	3		86.5	0.54	102.8	7.4	2.69	149.8	3.96
27080035	3		57.1	0.39	102.8	6.4	2.71	148.3	4.01
27080037	3		81.8	0.49	102.2	6.7	2.61	147.5	3.79
27080039	3		75.9	0.43	102.1	5.7	2.63	145.6	3.34
		Mean	74.62	0.464	102.54	6.55	2.670	148.16	3.804
		SD	11.28	0.057	0.36	0.59	0.047	1.72	0.272
27080041	4		62.8	0.39	99.5	6.1	2.48	146.5	3.55
27080043	4		152.1	0.72	95.3	10.7	2.91	141.9	4.43
27080045	4		86.5	0.39	102.5	6.4	2.33	143.1	3.78
27080047	4		66.2	0.44	101.8	6.4	2.50	147.7	3.66
27080049	4		84.9	0.50	102.2	7.8	2.49	148.5	4.43
27080051	4		90.4	0.41	100.5	7.2	2.63	145.3	4.12
27080053	4		75.0	0.37	99.8	7.5	2.67	144.6	4.27
27080055	4		83.3	0.41	102.1	7.0	2.68	147.4	4.09
27080057	4		61.6	0.37	99.6	7.3	2.68	146.4	3.59
27080059	4		77.9	0.39	101.2	7.2	2.75	147.7	3.47
		Mean	84.07	0.439	100.45	7.35	2.612	145.91	3.939
		SD	25.98	0.106	2.13	1.28	0.165	2.16	0.372

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		PROT g/dl	ALB g/dl	GLO g/dl	AGR
27080001	1		6.8	4.4	2.4	1.8
27080003	1		6.9	4.6	2.3	2.0
27080005	1		6.9	4.4	2.5	1.8
27080007	1		7.0	4.7	2.3	2.0
27080009	1		6.7	4.3	2.4	1.8
27080011	1		6.9	4.3	2.6	1.7
27080013	1		7.2	4.5	2.7	1.7
27080015	1		7.0	4.6	2.4	1.9
27080017	1		6.7	4.3	2.4	1.8
27080019	1		6.9	4.5	2.4	1.9
		Mean	6.90	4.46	2.44	1.83
		SD	0.15	0.14	0.13	0.13
27080021	2		7.2	4.9	2.3	2.1
27080023	2		6.7	4.6	2.1	2.2
27080025	2		7.0	4.6	2.4	1.9
27080027	2		6.9	4.7	2.2	2.1
27080029	2		7.2	5.1	2.1	2.4
		Mean	7.00	4.78	2.22	2.16
		SD	0.21	0.22	0.13	0.18

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		PROT g/dl	ALB g/dl	GLO g/dl	AGR
27080031	3		7.0	5.1	1.9	2.7
27080033	3		6.9	4.9	2.0	2.5
27080035	3		6.9	5.1	1.8	2.8
27080037	3		6.6	4.6	2.0	2.3
27080039	3		6.8	5.0	1.8	2.8
		Mean	6.84	4.94	1.90	2.61
		SD	0.15	0.21	0.10	0.23
27080041	4		6.2	4.4	1.8	2.4
27080043	4		4.8	3.0	1.8	1.7
27080045	4		4.4	3.2	1.2	2.7
27080047	4		5.7	4.2	1.5	2.8
27080049	4		6.4	4.4	2.0	2.2
27080051	4		6.3	4.8	1.5	3.2
27080053	4		6.1	4.5	1.6	2.8
27080055	4		6.3	4.5	1.8	2.5
27080057	4		6.4	4.8	1.6	3.0
27080059	4		6.5	5.0	1.5	3.3
		Mean	5.91	4.28	1.63	2.66
		SD	0.73	0.67	0.23	0.49

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Clinical chemistry - Week 2 of recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		AP U/l	ALT U/l	AST U/l	GGT U/l	BILT mg/dl	CHOL mg/dl	TRI mg/dl	GLU mg/dl
27080012	1		203.6	44.0	81.4	2.90	0.07	77.7	27.4	106.9
27080014	1		278.1	59.9	83.5	1.60	0.08	77.1	36.3	132.7
27080016	1		314.5	62.7	86.3	2.70	0.06	90.5	31.1	109.4
27080018	1		255.3	52.5	96.0	2.60	0.05	88.0	32.7	130.0
27080020	1		244.4	47.3	68.7	1.50	0.07	83.9	34.0	103.3
		Mean	259.18	53.28	83.18	2.260	0.066	83.44	32.30	116.46
		SD	41.05	7.99	9.84	0.658	0.011	6.00	3.34	13.80
27080052	4		497.0	61.2	144.5	4.10	0.07	49.3	39.3	109.4
27080054	4		411.2	48.2	88.2	4.50	0.02	59.0	35.1	122.6
27080056	4		376.4	54.3	119.9	6.50	0.05	70.8	37.6	115.6
27080058	4		534.3	55.4	100.8	3.00	0.05	78.0	51.6	125.3
27080060	4		510.7	57.4	116.9	1.80	0.06	62.0	43.6	120.6
		Mean	465.92	55.30	114.06	3.980	0.050	63.82	41.44	118.70
		SD	68.29	4.76	21.29	1.757	0.019	11.04	6.47	6.29

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Clinical chemistry - Week 2 of recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		UREA mg/dl	CREA mg/dl	CL mmol/l	PHOS mg/dl	CA mmol/l	Na mmol/l	K mmol/l
27080012	1		42.8	0.39	96.5	8.1	2.69	149.3	3.73
27080014	1		34.0	0.45	97.8	7.3	2.62	146.3	3.50
27080016	1		35.4	0.37	94.5	7.1	2.81	145.7	3.19
27080018	1		39.0	0.47	95.1	7.8	2.74	147.5	4.04
27080020	1		32.0	0.34	98.0	8.3	2.76	148.1	4.00
		Mean	36.64	0.404	96.38	7.72	2.724	147.38	3.692
		SD	4.29	0.055	1.57	0.50	0.072	1.43	0.356
27080052	4		52.1	0.27	101.5	9.0	2.67	147.5	5.49
27080054	4		53.6	0.24	102.4	8.3	2.63	147.7	4.07
27080056	4		49.8	0.23	100.1	7.7	2.37	145.1	4.89
27080058	4		55.8	0.26	101.3	7.0	2.38	144.4	4.65
27080060	4		60.4	0.25	100.0	7.7	2.62	144.5	4.62
		Mean	54.34	0.250	101.06	7.94	2.534	145.84	4.744
		SD	4.03	0.016	1.01	0.76	0.146	1.63	0.514

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Clinical chemistry - Week 2 of recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		PROT g/dl	ALB g/dl	GLO g/dl	AGR
27080012	1		6.9	4.1	2.8	1.5
27080014	1		6.5	4.1	2.4	1.7
27080016	1		7.1	4.2	2.9	1.4
27080018	1		6.9	4.2	2.7	1.6
27080020	1		6.6	4.2	2.4	1.8
		Mean	6.80	4.16	2.64	1.59
		SD	0.24	0.05	0.23	0.14
27080052	4		5.1	3.6	1.5	2.4
27080054	4		5.3	3.8	1.5	2.5
27080056	4		5.5	3.6	1.9	1.9
27080058	4		5.6	3.5	2.1	1.7
27080060	4		5.2	3.5	1.7	2.1
		Mean	5.34	3.60	1.74	2.11
		SD	0.21	0.12	0.26	0.36

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Clinical chemistry - Week 2 of recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		AP U/l	ALT U/l	AST U/l	GGT U/l	BILT mg/dl	CHOL mg/dl	TRI mg/dl	GLU mg/dl
27080011	1		209.6	30.6	79.6	0.80	0.06	78.8	29.0	144.7
27080013	1		197.4	41.0	162.6	3.10	0.11	111.9	40.6	111.7
27080015	1		211.3	40.5	82.1	0.90	0.09	92.1	26.7	121.6
27080017	1		191.2	31.8	92.3	0.90	0.05	81.0	29.7	131.5
27080019	1		174.5	33.3	87.2	0.30	0.12	77.4	28.0	124.1
		Mean	196.80	35.44	100.76	1.200	0.086	88.24	30.80	126.72
		SD	15.03	4.94	34.91	1.091	0.030	14.44	5.59	12.30
27080051	4		339.5	44.6	97.9	2.80	0.03	65.2	32.6	130.8
27080053	4		308.1	41.4	83.8	3.00	0.05	58.1	35.6	131.1
27080055	4		249.6	45.2	83.8	3.30	0.05	90.0	37.0	131.1
27080057	4		297.6	45.0	89.7	1.70	0.06	66.6	33.9	143.1
27080059	4		238.0	48.4	76.8	2.60	0.06	88.8	32.6	154.0
		Mean	286.56	44.92	86.40	2.680	0.050	73.74	34.34	138.02
		SD	42.17	2.48	7.89	0.606	0.012	14.66	1.93	10.36

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Clinical chemistry - Week 2 of recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		UREA mg/dl	CREA mg/dl	CL mmol/l	PHOS mg/dl	CA mmol/l	Na mmol/l	K mmol/l
27080011	1		52.8	0.54	98.3	6.2	2.72	144.1	3.81
27080013	1		64.5	0.56	99.4	6.3	2.64	146.0	4.48
27080015	1		45.6	0.48	97.0	5.7	2.73	145.7	3.64
27080017	1		45.6	0.49	99.6	5.6	2.66	146.7	3.37
27080019	1		55.8	0.54	97.4	6.4	2.72	146.9	3.23
		Mean	52.86	0.522	98.34	6.04	2.694	145.88	3.706
		SD	7.90	0.035	1.16	0.35	0.041	1.11	0.488
27080051	4		61.7	0.41	99.5	7.1	2.57	144.3	4.30
27080053	4		53.8	0.42	98.8	5.7	2.57	145.1	3.82
27080055	4		48.9	0.41	100.1	5.5	2.59	145.6	3.90
27080057	4		50.1	0.41	98.2	6.1	2.60	143.9	3.72
27080059	4		49.5	0.49	100.4	5.4	2.72	147.7	3.56
		Mean	52.80	0.428	99.40	5.96	2.610	145.32	3.860
		SD	5.33	0.035	0.91	0.71	0.063	1.49	0.277

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Clinical chemistry - Week 2 of recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		PROT g/dl	ALB g/dl	GLO g/dl	AGR
27080011	1		7.0	4.4	2.6	1.7
27080013	1		7.0	4.4	2.6	1.7
27080015	1		7.0	4.6	2.4	1.9
27080017	1		6.9	4.5	2.4	1.9
27080019	1		7.0	4.7	2.3	2.0
		Mean	6.98	4.52	2.46	1.84
		SD	0.04	0.13	0.13	0.15
27080051	4		6.3	4.6	1.7	2.7
27080053	4		6.5	4.7	1.8	2.6
27080055	4		6.6	4.6	2.0	2.3
27080057	4		6.4	4.8	1.6	3.0
27080059	4		7.2	5.4	1.8	3.0
		Mean	6.60	4.82	1.78	2.72
		SD	0.35	0.33	0.15	0.29

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		VOL ml	SG
27080002	1		9.0	1.010
27080004	1		10.5	1.010
27080006	1		8.0	1.020
27080008	1		7.0	1.015
27080010	1		13.0	1.010
27080012	1		9.0	1.010
27080014	1		3.0	1.015
27080016	1		6.0	1.025
27080018	1		9.0	1.015
27080020	1		9.0	1.015
		Mean	8.35	1.0145
		SD	2.67	0.0050
27080022	2		12.0	1.010
27080024	2		9.5	1.015
27080026	2		9.0	1.015
27080028	2		9.0	1.025
27080030	2		8.0	1.015
		Mean	9.50	1.0160
		SD	1.50	0.0055

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		VOL ml	SG
27080032	3		9.0	1.020
27080034	3		14.0	1.015
27080036	3		9.0	1.015
27080038	3		10.0	1.020
27080040	3		11.5	1.020
		Mean	10.70	1.0180
		SD	2.11	0.0027
27080042	4		12.0	1.015
27080044	4		9.0	1.020
27080046	4		11.0	1.015
27080048	4		10.0	1.015
27080050	4		9.0	1.015
27080052	4		8.5	1.015
27080054	4		9.5	1.025
27080056	4		2.0	1.015
27080058	4		11.0	1.025
27080060	4		8.5	1.005
		Mean	9.05	1.0165
		SD	2.74	0.0058

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
27080002	1	0	0	7.5	0	100	0.00	0	0.0
27080004	1	0	0	7.5	0	100	0.00	0	0.0
27080006	1	0	0	7.0	0	300	0.00	0	0.0
27080008	1	0	0	7.0	0	30	0.00	0	0.0
27080010	1	1	0	7.5	0	30	0.00	0	0.5
27080012	1	1	0	7.5	0	100	0.00	0	0.0
27080014	1	0	0	7.0	0	30	0.00	0	0.0
27080016	1	0	0	7.0	0	100	0.00	0	0.0
27080018	1	0	0	7.5	1000	100	0.00	0	0.0
27080020	1	0	0	7.5	0	30	0.00	0	0.0
27080022	2	1	0	7.5	0	100	0.00	0	0.0
27080024	2	1	0	7.5	0	30	0.00	0	0.0
27080026	2	1	0	7.5	0	100	0.00	0	0.0
27080028	2	0	0	7.0	0	30	0.00	0	0.0
27080030	2	0	0	7.5	0	100	0.00	0	0.0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
27080032	3	0	0	7.0	0	30	0.20	0	0.0
27080034	3	0	0	7.0	0	300	0.00	0	0.0
27080036	3	0	0	7.5	0	30	0.00	0	0.0
27080038	3	0	0	7.0	0	30	0.00	0	0.0
27080040	3	0	0	7.0	0	15	0.06	0	0.0
27080042	4	0	0	6.5	0	100	0.00	0	0.0
27080044	4	0	0	7.0	0	30	0.00	0	0.0
27080046	4	0	0	7.5	0	15	0.00	0	0.0
27080048	4	0	0	7.0	0	30	0.00	0	0.0
27080050	4	0	0	7.0	0	0	0.00	0	0.0
27080052	4	0	0	7.0	0	15	0.00	0	0.0
27080054	4	0	0	6.5	0	30	0.00	0	0.0
27080056	4	0	0	7.5	0	100	0.00	0	0.0
27080058	4	0	0	6.5	0	15	0.00	0	0.0
27080060	4	0	0	7.0	0	15	0.00	0	0.0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	URO mg/dl
27080002	1	1.0
27080004	1	1.0
27080006	1	1.0
27080008	1	1.0
27080010	1	1.0
27080012	1	1.0
27080014	1	1.0
27080016	1	1.0
27080018	1	1.0
27080020	1	1.0
27080022	2	1.0
27080024	2	1.0
27080026	2	1.0
27080028	2	1.0
27080030	2	1.0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	URO mg/dl
27080032	3	1.0
27080034	3	1.0
27080036	3	1.0
27080038	3	1.0
27080040	3	1.0
27080042	4	1.0
27080044	4	1.0
27080046	4	1.0
27080048	4	1.0
27080050	4	1.0
27080052	4	1.0
27080054	4	1.0
27080056	4	1.0
27080058	4	1.0
27080060	4	1.0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	EPI	LEU	[illegible]RY	CRY	SPE	ABN
27080002	1	2	2	0	2	1	0
27080004	1	2	2	0	1	1	0
27080006	1	1	2	0	1	1	0
27080008	1	2	2	0	2	1	0
27080010	1	1	1	0	1	0	0
27080012	1	2	1	0	1	0	0
27080014	1	1	2	0	1	0	0
27080016	1	2	2	0	1	2	0
27080018	1	1	2	0	1	2	0
27080020	1	1	2	0	1	0	0
27080022	2	1	0	0	2	1	0
27080024	2	2	2	0	2	1	0
27080026	2	1	1	0	1	1	0
27080028	2	1	1	0	1	1	0
27080030	2	1	1	0	0	0	0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
27080032	3	1	1	0	2	2	0
27080034	3	2	2	0	2	1	0
27080036	3	2	2	0	1	1	0
27080038	3	1	1	0	1	1	0
27080040	3	2	2	0	0	0	0
27080042	4	2	1	0	1	1	0
27080044	4	2	2	0	1	0	0
27080046	4	2	1	0	1	0	0
27080048	4	2	2	0	1	0	0
27080050	4	1	1	0	1	0	0
27080052	4	2	2	0	2	0	0
27080054	4	2	1	0	1	0	0
27080056	4	1	1	0	1	0	0
27080058	4	2	1	0	1	0	0
27080060	4	2	1	0	1	0	0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		VOL ml	SG
27080001	1		3.5	1.025
27080003	1		2.0	1.020
27080005	1		6.5	1.025
27080007	1		6.0	1.030
27080009	1		5.0	1.015
27080011	1		10.0	1.030
27080013	1		6.0	1.025
27080015	1		6.0	1.025
27080017	1		3.5	1.030
27080019	1		5.0	1.030
		Mean	5.35	1.0255
		SD	2.17	0.0050
27080021	2		6.0	1.030
27080023	2		4.5	1.020
27080025	2		5.0	1.015
27080027	2		6.0	1.015
27080029	2		5.0	1.020
		Mean	5.30	1.0200
		SD	0.67	0.0061

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		VOL ml	SG
27080031	3		7.0	1.020
27080033	3		7.0	1.020
27080035	3		5.0	1.015
27080037	3		10.0	1.010
27080039	3		7.0	1.020
		Mean	7.20	1.0170
		SD	1.79	0.0045
27080041	4		8.0	1.020
27080043	4		2.0	1.030
27080045	4		7.0	1.035
27080047	4		9.0	1.020
27080049	4		14.0	1.020
27080051	4		10.0	1.020
27080053	4		9.0	1.015
27080055	4		9.5	1.025
27080057	4		6.5	1.020
27080059	4		10.0	1.020
		Mean	8.50	1.0225
		SD	3.07	0.0059

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
27080001	1	1	0	7.0	0	15	0.00	0	0.0
27080003	1	1	0	8.5	0	30	0.00	0	0.0
27080005	1	0	0	7.0	0	100	0.00	0	0.0
27080007	1	0	0	6.0	0	15	0.00	0	0.0
27080009	1	0	0	7.0	0	0	0.00	0	0.0
27080011	1	1	0	9.0	0	30	0.00	0	0.0
27080013	1	0	0	7.0	0	>400	0.00	0	0.0
27080015	1	0	0	7.0	0	30	0.00	0	0.0
27080017	1	0	0	6.5	0	100	0.00	0	0.0
27080019	1	0	0	6.5	0	15	0.00	0	0.0
27080021	2	0	0	6.5	0	300	0.00	0	0.0
27080023	2	0	0	7.0	0	0	0.00	0	0.0
27080025	2	0	0	7.5	0	15	0.00	0	0.0
27080027	2	0	0	7.5	0	30	0.00	0	0.0
27080029	2	0	0	7.0	0	15	0.00	0	0.0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
27080031	3	0	0	7.5	0	15	0.00	0	0.0
27080033	3	0	0	7.0	0	30	0.00	0	0.0
27080035	3	0	0	7.5	0	15	0.00	0	0.0
27080037	3	0	0	7.5	0	15	0.00	0	0.0
27080039	3	0	0	7.0	0	0	0.00	0	0.0
27080041	4	0	0	7.0	0	0	0.00	0	0.0
27080043	4	0	0	7.0	0	300	0.20	0	2.0
27080045	4	1	0	8.5	0	15	0.00	0	0.0
27080047	4	0	0	7.5	0	0	0.00	0	0.0
27080049	4	0	0	7.0	0	30	0.00	0	0.0
27080051	4	0	0	7.0	0	0	0.00	0	0.0
27080053	4	0	0	7.0	0	15	0.00	0	0.0
27080055	4	0	0	7.0	0	15	0.00	0	0.0
27080057	4	0	0	7.0	0	0	0.00	0	0.0
27080059	4	0	0	7.0	0	15	0.00	0	0.0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	URO mg/dl
27080001	1	1.0
27080003	1	1.0
27080005	1	1.0
27080007	1	1.0
27080009	1	1.0
27080011	1	1.0
27080013	1	1.0
27080015	1	1.0
27080017	1	1.0
27080019	1	1.0
27080021	2	1.0
27080023	2	1.0
27080025	2	1.0
27080027	2	1.0
27080029	2	1.0

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	URO mg/dl
27080031	3	1.0
27080033	3	1.0
27080035	3	1.0
27080037	3	1.0
27080039	3	1.0
27080041	4	1.0
27080043	4	1.0
27080045	4	1.0
27080047	4	1.0
27080049	4	1.0
27080051	4	1.0
27080053	4	1.0
27080055	4	1.0
27080057	4	1.0
27080059	4	1.0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
27080001	1	1	1	0	1	0	0
27080003	1	1	1	0	1	0	0
27080005	1	1	2	0	1	0	0
27080007	1	1	1	0	0	0	0
27080009	1	2	2	0	1	0	0
27080011	1	1	2	0	2	0	0
27080013	1	1	2	0	1	0	0
27080015	1	1	2	0	2	0	0
27080017	1	1	0	0	1	0	0
27080019	1	2	0	0	2	0	0
27080021	2	0	1	0	1	0	0
27080023	2	1	1	0	1	0	0
27080025	2	2	2	0	2	0	0
27080027	2	2	1	0	1	0	0
27080029	2	1	1	0	1	0	0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - Week 4 of treatment - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
27080031	3	2	1	0	0	0	0
27080033	3	1	1	0	0	0	0
27080035	3	1	1	0	0	0	0
27080037	3	1	1	0	1	0	0
27080039	3	1	2	0	1	0	0
27080041	4	1	2	0	1	0	0
27080043	4	2	2	0	1	0	0
27080045	4	2	2	0	2	0	0
27080047	4	1	2	0	1	0	0
27080049	4	2	2	0	1	0	0
27080051	4	1	1	0	1	0	0
27080053	4	2	1	0	1	0	0
27080055	4	1	1	0	1	0	0
27080057	4	2	2	0	1	0	0
27080059	4	2	1	0	1	0	0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - Week 2 of recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group		VOL ml	SG
27080012	1		6.5	1.015
27080014	1		5.5	1.025
27080016	1		6.0	1.030
27080018	1		7.5	1.015
27080020	1		8.0	1.020
		Mean	6.70	1.0210
		SD	1.04	0.0065
27080052	4		8.5	1.020
27080054	4		8.0	1.025
27080056	4		5.5	1.015
27080058	4		6.5	1.020
27080060	4		7.0	1.020
		Mean	7.10	1.0200
		SD	1.19	0.0035

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - Week 2 of recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
27080012	1	1	0	7.0	0	100	0.00	0	0.0
27080014	1	1	0	7.0	0	100	0.00	0	0.0
27080016	1	1	0	7.0	0	300	0.00	0	0.0
27080018	1	1	0	7.5	0	100	0.00	0	0.0
27080020	1	1	0	7.0	0	100	0.00	0	0.0
27080052	4	0	0	7.0	0	30	0.00	0	0.0
27080054	4	0	0	6.5	0	15	0.00	0	0.0
27080056	4	0	0	7.0	0	30	0.00	0	0.0
27080058	4	0	0	7.0	0	30	0.00	0	0.0
27080060	4	0	0	7.0	0	100	0.00	0	0.0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - Week 2 of recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	URO mg/dl
27080012	1	1.0
27080014	1	1.0
27080016	1	1.0
27080018	1	1.0
27080020	1	1.0
27080052	4	1.0
27080054	4	1.0
27080056	4	1.0
27080058	4	1.0
27080060	4	1.0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - Week 2 of recovery - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
27080012	1	1	1	0	1	1	0
27080014	1	1	2	0	1	1	0
27080016	1	1	1	0	1	1	0
27080018	1	2	1	0	1	1	0
27080020	1	2	1	0	1	1	0
27080052	4	1	1	0	1	1	0
27080054	4	1	1	0	0	0	0
27080056	4	1	0	0	1	0	0
27080058	4	1	0	0	1	0	0
27080060	4	2	1	0	1	0	0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - Week 2 of recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group		VOL ml	SG
27080011	1		3.0	1.015
27080013	1		3.0	1.020
27080015	1		4.0	1.030
27080017	1		1.0	1.030
27080019	1		4.0	1.030
		Mean	3.00	1.0250
		SD	1.22	0.0071
27080051	4		4.5	1.025
27080053	4		4.0	1.015
27080055	4		4.5	1.025
27080057	4		9.0	1.015
27080059	4		5.5	1.030
		Mean	5.50	1.0220
		SD	2.03	0.0067

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - Week 2 of recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
27080011	1	0	0	7.0	0	30	0.00	0	0.0
27080013	1	0	0	7.0	0	300	0.00	0	0.0
27080015	1	0	0	6.5	0	30	0.00	0	0.0
27080017	1	0	0	7.0	0	100	0.00	0	0.5
27080019	1	0	0	6.5	0	15	0.00	0	0.0
27080051	4	0	0	7.0	0	15	0.00	0	0.0
27080053	4	0	0	7.5	0	30	0.00	0	0.0
27080055	4	0	0	7.0	0	30	0.00	0	0.0
27080057	4	0	0	7.0	0	0	0.00	0	0.0
27080059	4	0	0	6.5	0	15	0.00	0	0.0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - Week 2 of recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	URO mg/dl
27080011	1	1.0
27080013	1	1.0
27080015	1	1.0
27080017	1	1.0
27080019	1	1.0
27080051	4	1.0
27080053	4	1.0
27080055	4	1.0
27080057	4	1.0
27080059	4	1.0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - Week 2 of recovery - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
27080011	1	1	1	0	1	0	0
27080013	1	1	1	0	1	0	0
27080015	1	1	0	0	1	0	0
27080017	1	2	1	0	1	0	0
27080019	1	2	1	0	0	0	0
27080051	4	2	1	0	0	0	0
27080053	4	1	1	0	0	0	0
27080055	4	2	1	0	0	0	0
27080057	4	1	2	0	0	0	0
27080059	4	1	1	0	1	0	0

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
27080002	1	368.8	0.053	1.79	1.204	1.45	2.68	15.54
27080004	1	352.0	0.039	1.77	0.839	1.41	2.63	14.90
27080006	1	365.2	0.053	1.64	1.168	1.36	2.93	17.24
27080008	1	358.0	0.062	1.77	1.272	1.31	2.64	14.20
27080010	1	401.8	0.057	1.88	1.163	1.41	3.14	18.28
	Mean	369.16	0.0528	1.770	1.1292	1.389	2.804	16.031
	SD	19.37	0.0086	0.085	0.1680	0.054	0.226	1.687
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080022	2	389.8	0.055	1.73	1.203	1.40	2.69	19.84
27080024	2	394.6	0.054	1.70	1.092	1.37	3.02	20.61
27080026	2	409.4	0.051	1.69	1.150	1.46	3.26	21.16
27080028	2	370.6	0.051	1.79	1.068	1.26	2.71	19.85
27080030	2	372.0	0.048	1.74	1.082	1.23	2.89	20.46
	Mean	387.28	0.0518	1.728	1.1190	1.343	2.913	20.382
	SD	16.29	0.0028	0.041	0.0564	0.096	0.235	0.557
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080032	3	354.0	0.056	1.80	1.152	1.25	3.07	24.40
27080034	3	414.1	0.046	1.69	1.175	1.48	3.58	29.12
27080036	3	353.5	0.044	1.75	1.253	1.33	2.78	22.77
27080038	3	365.9	0.057	1.88	1.229	1.32	3.00	23.55
27080040	3	376.3	0.048	1.71	1.104	1.33	3.29	23.76
	Mean	372.76	0.0502	1.767	1.1826	1.342	3.144	24.720
	SD	24.96	0.0059	0.077	0.0598	0.084	0.304	2.528
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080042	4	299.8	0.044	1.58	0.961	1.15	3.07	24.81
27080044	4	307.1	0.048	1.76	1.099	1.25	2.87	23.06
27080046	4	296.8	0.043	1.58	0.962	1.07	2.79	18.86
27080048	4	272.1	0.047	1.83	0.991	1.10	2.73	21.15
27080050	4	281.6	0.050	1.77	1.052	1.17	2.61	19.56
	Mean	291.48	0.0464	1.701	1.0130	1.148	2.812	21.489
	SD	14.27	0.0029	0.117	0.0606	0.070	0.169	2.461
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus	Thyroid
27080002	1	368.8	1.018	4.111	0.365	0.018
27080004	1	352.0	0.945	2.377	0.517	0.025
27080006	1	365.2	0.822	3.504	0.539	0.015
27080008	1	358.0	0.928	4.068	0.399	0.018
27080010	1	401.8	0.990	3.778	0.419	0.022
	Mean	369.16	0.9406	3.5676	0.4478	0.0196
	SD	19.37	0.0753	0.7091	0.0761	0.0039
	(n)	(5)	(5)	(5)	(5)	(5)
27080022	2	389.8	1.026	3.696	0.495	0.018
27080024	2	394.6	1.095	3.323	0.402	0.021
27080026	2	409.4	0.950	3.663	0.532	0.024
27080028	2	370.6	0.874	3.408	0.357	0.024
27080030	2	372.0	0.878	3.467	0.374	0.024
	Mean	387.28	0.9646	3.5114	0.4320	0.0222
	SD	16.29	0.0958	0.1622	0.0772	0.0027
	(n)	(5)	(5)	(5)	(5)	(5)
27080032	3	354.0	0.912	3.977	0.426	0.021
27080034	3	414.1	0.999	3.727	0.464	0.023
27080036	3	353.5	0.644	4.089	0.352	0.020
27080038	3	365.9	0.803	3.657	0.333	0.020
27080040	3	376.3	0.794	3.668	0.368	0.022
	Mean	372.76	0.8304	3.8236	0.3886	0.0212
	SD	24.96	0.1341	0.1970	0.0546	0.0013
	(n)	(5)	(5)	(5)	(5)	(5)
27080042	4	299.8	0.539	3.829	0.154	0.025
27080044	4	307.1	0.566	3.798	0.208	0.021
27080046	4	296.8	0.596	3.309	0.173	0.021
27080048	4	272.1	0.511	3.343	0.115	0.022
27080050	4	281.6	0.494	3.638	0.118	0.020
	Mean	291.48	0.5412	3.5834	0.1536	0.0218
	SD	14.27	0.0411	0.2462	0.0390	0.0019
	(n)	(5)	(5)	(5)	(5)	(5)

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
27080001	1	227.4	0.067	1.73	0.88	1.73	8.80	0.114
27080003	1	251.0	0.073	1.67	0.97	1.83	10.94	0.129
27080005	1	256.0	0.080	1.65	1.06	2.22	11.87	0.150
27080007	1	241.9	0.076	1.65	0.92	1.87	9.36	0.131
27080009	1	238.4	0.063	1.69	0.89	1.86	8.89	0.112
	Mean	242.94	0.0718	1.678	0.945	1.902	9.972	0.1272
	SD	11.17	0.0068	0.033	0.073	0.188	1.364	0.0154
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080021	2	268.6	0.064	1.62	1.04	2.00	13.49	0.112
27080023	2	247.6	0.069	1.61	0.94	1.97	11.82	0.157
27080025	2	258.0	0.068	1.71	0.92	2.09	12.46	0.140
27080027	2	250.0	0.066	1.67	0.92	1.89	11.71	0.104
27080029	2	244.7	0.070	1.61	0.96	1.95	10.71	0.091
	Mean	253.78	0.0674	1.643	0.956	1.980	12.038	0.1208
	SD	9.65	0.0024	0.044	0.052	0.073	1.026	0.0270
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080031	3	255.3	0.064	1.58	1.00	1.90	13.76	0.112
27080033	3	247.1	0.072	1.56	0.89	2.06	14.14	0.110
27080035	3	247.3	0.059	1.74	0.94	1.86	14.22	0.101
27080037	3	240.7	0.055	1.65	0.87	1.93	12.80	0.126
27080039	3	223.9	0.058	1.67	0.85	1.84	14.06	0.116
	Mean	242.86	0.0616	1.641	0.906	1.917	13.796	0.1130
	SD	11.80	0.0067	0.072	0.060	0.086	0.584	0.0091
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080041	4	216.4	0.051	1.45	0.89	1.76	14.96	0.079
27080045	4	220.8	0.049	1.61	0.82	1.78	14.36	0.101
27080047	4	207.8	0.067	1.60	0.84	1.90	15.33	0.100
27080049	4	220.8	0.054	1.72	0.85	1.74	12.52	0.098
	Mean	216.45	0.0553	1.596	0.850	1.792	14.294	0.0945
	SD	6.13	0.0081	0.112	0.033	0.071	1.245	0.0104
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Thyroid
27080001	1	227.4	0.784	0.362	0.016
27080003	1	251.0	0.960	0.400	0.025
27080005	1	256.0	0.903	0.371	0.023
27080007	1	241.9	0.711	0.233	0.015
27080009	1	238.4	0.715	0.337	0.022
	Mean	242.94	0.8146	0.3406	0.0202
	SD	11.17	0.1124	0.0642	0.0044
	(n)	(5)	(5)	(5)	(5)
27080021	2	268.6	0.750	0.346	0.023
27080023	2	247.6	0.763	0.318	0.023
27080025	2	258.0	0.857	0.248	0.023
27080027	2	250.0	0.750	0.351	0.022
27080029	2	244.7	0.657	0.254	0.023
	Mean	253.78	0.7554	0.3034	0.0228
	SD	9.65	0.0709	0.0495	0.0004
	(n)	(5)	(5)	(5)	(5)
27080031	3	255.3	0.646	0.380	0.018
27080033	3	247.1	0.692	0.498	0.020
27080035	3	247.3	0.670	0.367	0.016
27080037	3	240.7	0.572	0.312	0.020
27080039	3	223.9	0.633	0.323	0.018
	Mean	242.86	0.6426	0.3760	0.0184
	SD	11.80	0.0455	0.0740	0.0017
	(n)	(5)	(5)	(5)	(5)
27080041	4	216.4	0.525	0.239	0.017
27080045	4	220.8	0.506	0.218	0.020
27080047	4	207.8	0.427	0.242	0.023
27080049	4	220.8	0.515	0.314	0.016
	Mean	216.45	0.4933	0.2533	0.0190
	SD	6.13	0.0448	0.0419	0.0032
	(n)	(4)	(4)	(4)	(4)

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Absolute organ weights (g) - Recovery sacrifice - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
27080012	1	378.7	0.057	1.87	1.214	1.35	2.88	14.37
27080014	1	404.6	0.054	1.81	1.293	1.51	2.95	17.07
27080016	1	375.3	0.045	1.67	1.150	1.30	2.66	15.53
27080018	1	405.7	0.058	1.93	1.408	1.30	2.84	16.52
27080020	1	387.8	0.050	1.94	1.161	1.48	2.96	16.58
	Mean	390.42	0.0528	1.845	1.2452	1.387	2.859	16.013
	SD	14.21	0.0054	0.113	0.1071	0.101	0.120	1.073
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080052	4	329.4	0.050	1.95	1.136	1.52	3.01	24.65
27080054	4	302.9	0.073	1.86	1.051	1.17	2.98	26.33
27080056	4	272.4	0.050	1.72	0.917	1.04	2.59	19.10
27080058	4	281.1	0.054	1.77	1.073	1.01	2.75	22.42
27080060	4	287.2	0.045	1.74	0.948	1.07	2.79	21.64
	Mean	294.60	0.0544	1.807	1.0250	1.161	2.822	22.828
	SD	22.42	0.0109	0.093	0.0907	0.208	0.171	2.785
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Absolute organ weights (g) - Recovery sacrifice - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus	Thyroid
27080012	1	378.7	0.860	3.754	0.370	0.022
27080014	1	404.6	0.977	4.048	0.477	0.025
27080016	1	375.3	0.772	3.427	0.302	0.020
27080018	1	405.7	1.051	4.033	0.330	0.025
27080020	1	387.8	0.995	3.672	0.319	0.024
	Mean	390.42	0.9310	3.7868	0.3596	0.0232
	SD	14.21	0.1128	0.2610	0.0702	0.0022
	(n)	(5)	(5)	(5)	(5)	(5)
27080052	4	329.4	0.793	3.193	0.174	0.017
27080054	4	302.9	0.561	3.477	0.133	0.018
27080056	4	272.4	0.520	3.418	0.211	0.022
27080058	4	281.1	0.515	3.560	0.108	0.020
27080060	4	287.2	0.745	3.482	0.171	0.020
	Mean	294.60	0.6268	3.4260	0.1594	0.0194
	SD	22.42	0.1321	0.1397	0.0398	0.0019
	(n)	(5)	(5)	(5)	(5)	(5)

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Absolute organ weights (g) - Recovery sacrifice - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
27080011	1	262.0	0.068	1.74	0.90	1.95	10.03	0.157
27080013	1	247.9	0.056	1.81	1.02	1.83	9.11	0.109
27080015	1	249.5	0.067	1.62	0.96	1.73	8.94	0.127
27080017	1	239.0	0.080	1.72	0.94	1.74	7.94	0.135
27080019	1	261.8	0.072	1.75	1.08	1.94	9.20	0.131
	Mean	252.04	0.0686	1.727	0.979	1.837	9.042	0.1318
	SD	9.85	0.0087	0.069	0.071	0.102	0.747	0.0172
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080051	4	232.0	0.066	1.70	0.97	2.00	12.43	0.128
27080053	4	224.0	0.064	1.51	0.87	1.81	12.89	0.122
27080055	4	235.2	0.065	1.71	0.92	2.03	14.05	0.128
27080057	4	228.5	0.055	1.67	0.97	2.08	13.09	0.105
27080059	4	220.5	0.066	1.64	1.06	1.80	13.04	0.096
	Mean	228.04	0.0632	1.647	0.957	1.943	13.099	0.1158
	SD	5.92	0.0047	0.084	0.070	0.129	0.592	0.0145
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Absolute organ weights (g) - Recovery sacrifice - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Thyroid
27080011	1	262.0	0.640	0.248	0.017
27080013	1	247.9	0.782	0.312	0.015
27080015	1	249.5	0.683	0.376	0.021
27080017	1	239.0	0.570	0.292	0.020
27080019	1	261.8	0.697	0.288	0.012
	Mean	252.04	0.6744	0.3032	0.0170
	SD	9.85	0.0779	0.0469	0.0037
	(n)	(5)	(5)	(5)	(5)
27080051	4	232.0	0.551	0.398	0.013
27080053	4	224.0	0.552	0.253	0.021
27080055	4	235.2	0.590	0.316	0.015
27080057	4	228.5	0.625	0.214	0.023
27080059	4	220.5	0.490	0.388	0.018
	Mean	228.04	0.5616	0.3138	0.0180
	SD	5.92	0.0504	0.0810	0.0041
	(n)	(5)	(5)	(5)	(5)

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Relative organ weights° - Final sacrifice - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
27080002	1	368.8	0.014	0.48	0.326	0.39	0.73	4.21
27080004	1	352.0	0.011	0.50	0.238	0.40	0.75	4.23
27080006	1	365.2	0.015	0.45	0.320	0.37	0.80	4.72
27080008	1	358.0	0.017	0.49	0.355	0.37	0.74	3.97
27080010	1	401.8	0.014	0.47	0.289	0.35	0.78	4.55
	Mean	369.16	0.0143	0.480	0.3059	0.377	0.759	4.336
	SD	19.37	0.0022	0.021	0.0444	0.021	0.032	0.298
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080022	2	389.8	0.014	0.44	0.309	0.36	0.69	5.09
27080024	2	394.6	0.014	0.43	0.277	0.35	0.76	5.22
27080026	2	409.4	0.012	0.41	0.281	0.36	0.80	5.17
27080028	2	370.6	0.014	0.48	0.288	0.34	0.73	5.36
27080030	2	372.0	0.013	0.47	0.291	0.33	0.78	5.50
	Mean	387.28	0.0134	0.447	0.2891	0.347	0.752	5.267
	SD	16.29	0.0007	0.028	0.0123	0.012	0.042	0.163
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080032	3	354.0	0.016	0.51	0.325	0.35	0.87	6.89
27080034	3	414.1	0.011	0.41	0.284	0.36	0.86	7.03
27080036	3	353.5	0.012	0.50	0.354	0.38	0.79	6.44
27080038	3	365.9	0.016	0.51	0.336	0.36	0.82	6.44
27080040	3	376.3	0.013	0.46	0.293	0.35	0.87	6.31
	Mean	372.76	0.0135	0.476	0.3186	0.360	0.842	6.623
	SD	24.96	0.0021	0.045	0.0295	0.009	0.038	0.317
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080042	4	299.8	0.015	0.53	0.321	0.38	1.02	8.28
27080044	4	307.1	0.016	0.57	0.358	0.41	0.93	7.51
27080046	4	296.8	0.014	0.53	0.324	0.36	0.94	6.36
27080048	4	272.1	0.017	0.67	0.364	0.40	1.00	7.77
27080050	4	281.6	0.018	0.63	0.374	0.41	0.93	6.95
	Mean	291.48	0.0160	0.586	0.3481	0.394	0.965	7.372
	SD	14.27	0.0015	0.063	0.0242	0.022	0.044	0.743
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Relative organ weights° - Final sacrifice - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus	Thyroid
27080002	1	368.8	0.276	1.115	0.099	0.005
27080004	1	352.0	0.268	0.675	0.147	0.007
27080006	1	365.2	0.225	0.959	0.148	0.004
27080008	1	358.0	0.259	1.136	0.111	0.005
27080010	1	401.8	0.246	0.940	0.104	0.005
	Mean	369.16	0.2550	0.9652	0.1218	0.0053
	SD	19.37	0.0201	0.1846	0.0236	0.0011
	(n)	(5)	(5)	(5)	(5)	(5)
27080022	2	389.8	0.263	0.948	0.127	0.005
27080024	2	394.6	0.277	0.842	0.102	0.005
27080026	2	409.4	0.232	0.895	0.130	0.006
27080028	2	370.6	0.236	0.920	0.096	0.006
27080030	2	372.0	0.236	0.932	0.101	0.006
	Mean	387.28	0.2489	0.9073	0.1111	0.0057
	SD	16.29	0.0203	0.0413	0.0160	0.0008
	(n)	(5)	(5)	(5)	(5)	(5)
27080032	3	354.0	0.258	1.123	0.120	0.006
27080034	3	414.1	0.241	0.900	0.112	0.006
27080036	3	353.5	0.182	1.157	0.100	0.006
27080038	3	365.9	0.219	0.999	0.091	0.005
27080040	3	376.3	0.211	0.975	0.098	0.006
	Mean	372.76	0.2223	1.0309	0.1042	0.0057
	SD	24.96	0.0290	0.1068	0.0118	0.0002
	(n)	(5)	(5)	(5)	(5)	(5)
27080042	4	299.8	0.180	1.277	0.051	0.008
27080044	4	307.1	0.184	1.237	0.068	0.007
27080046	4	296.8	0.201	1.115	0.058	0.007
27080048	4	272.1	0.188	1.229	0.042	0.008
27080050	4	281.6	0.175	1.292	0.042	0.007
	Mean	291.48	0.1856	1.2299	0.0523	0.0075
	SD	14.27	0.0097	0.0696	0.0110	0.0007
	(n)	(5)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Relative organ weights° - Final sacrifice - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
27080001	1	227.4	0.029	0.76	0.39	0.76	3.87	0.050
27080003	1	251.0	0.029	0.67	0.39	0.73	4.36	0.051
27080005	1	256.0	0.031	0.64	0.41	0.87	4.64	0.059
27080007	1	241.9	0.031	0.68	0.38	0.77	3.87	0.054
27080009	1	238.4	0.026	0.71	0.37	0.78	3.73	0.047
	Mean	242.94	0.0295	0.692	0.389	0.782	4.093	0.0523
	SD	11.17	0.0020	0.045	0.016	0.052	0.386	0.0044
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080021	2	268.6	0.024	0.60	0.39	0.74	5.02	0.042
27080023	2	247.6	0.028	0.65	0.38	0.80	4.77	0.063
27080025	2	258.0	0.026	0.66	0.36	0.81	4.83	0.054
27080027	2	250.0	0.026	0.67	0.37	0.76	4.68	0.042
27080029	2	244.7	0.029	0.66	0.39	0.80	4.38	0.037
	Mean	253.78	0.0266	0.648	0.377	0.781	4.737	0.0476
	SD	9.65	0.0018	0.027	0.016	0.029	0.237	0.0109
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080031	3	255.3	0.025	0.62	0.39	0.74	5.39	0.044
27080033	3	247.1	0.029	0.63	0.36	0.83	5.72	0.045
27080035	3	247.3	0.024	0.70	0.38	0.75	5.75	0.041
27080037	3	240.7	0.023	0.69	0.36	0.80	5.32	0.052
27080039	3	223.9	0.026	0.75	0.38	0.82	6.28	0.052
	Mean	242.86	0.0254	0.678	0.373	0.790	5.692	0.0467
	SD	11.80	0.0024	0.053	0.013	0.040	0.382	0.0051
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080041	4	216.4	0.024	0.67	0.41	0.81	6.91	0.037
27080045	4	220.8	0.022	0.73	0.37	0.81	6.51	0.046
27080047	4	207.8	0.032	0.77	0.40	0.91	7.38	0.048
27080049	4	220.8	0.024	0.78	0.39	0.79	5.67	0.044
	Mean	216.45	0.0256	0.738	0.393	0.829	6.617	0.0437
	SD	6.13	0.0045	0.050	0.019	0.056	0.723	0.0050
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)

° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Relative organ weights° - Final sacrifice - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Thyroid
27080001	1	227.4	0.345	0.159	0.007
27080003	1	251.0	0.382	0.159	0.010
27080005	1	256.0	0.353	0.145	0.009
27080007	1	241.9	0.294	0.096	0.006
27080009	1	238.4	0.300	0.141	0.009
	Mean	242.94	0.3348	0.1402	0.0083
	SD	11.17	0.0374	0.0259	0.0016
	(n)	(5)	(5)	(5)	(5)
27080021	2	268.6	0.279	0.129	0.009
27080023	2	247.6	0.308	0.128	0.009
27080025	2	258.0	0.332	0.096	0.009
27080027	2	250.0	0.300	0.140	0.009
27080029	2	244.7	0.268	0.104	0.009
	Mean	253.78	0.2976	0.1195	0.0090
	SD	9.65	0.0250	0.0187	0.0003
	(n)	(5)	(5)	(5)	(5)
27080031	3	255.3	0.253	0.149	0.007
27080033	3	247.1	0.280	0.202	0.008
27080035	3	247.3	0.271	0.148	0.006
27080037	3	240.7	0.238	0.130	0.008
27080039	3	223.9	0.283	0.144	0.008
	Mean	242.86	0.2649	0.1545	0.0076
	SD	11.80	0.0192	0.0274	0.0008
	(n)	(5)	(5)	(5)	(5)
27080041	4	216.4	0.243	0.110	0.008
27080045	4	220.8	0.229	0.099	0.009
27080047	4	207.8	0.205	0.11[illegible]	0.011
27080049	4	220.8	0.233	0.142	0.007
	Mean	216.45	0.2276	0.1170	0.0088
	SD	6.13	0.0158	0.0184	0.0017
	(n)	(4)	(4)	(4)	(4)

° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.2 - Relative organ weights° - Recovery sacrifice - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
27080012	1	378.7	0.015	0.49	0.321	0.36	0.76	3.80
27080014	1	404.6	0.013	0.45	0.320	0.37	0.73	4.22
27080016	1	375.3	0.012	0.44	0.306	0.35	0.71	4.14
27080018	1	405.7	0.014	0.48	0.347	0.32	0.70	4.07
27080020	1	387.8	0.013	0.50	0.299	0.38	0.76	4.27
	Mean	390.42	0.0135	0.473	0.3186	0.355	0.732	4.100
	SD	14.21	0.0012	0.026	0.0182	0.024	0.029	0.187
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080052	4	329.4	0.015	0.59	0.345	0.46	0.91	7.48
27080054	4	302.9	0.024	0.61	0.347	0.39	0.98	8.69
27080056	4	272.4	0.018	0.63	0.337	0.38	0.95	7.01
27080058	4	281.1	0.019	0.63	0.382	0.36	0.98	7.98
27080060	4	287.2	0.016	0.61	0.330	0.37	0.97	7.54
	Mean	294.60	0.0185	0.614	0.3481	0.392	0.959	7.740
	SD	22.42	0.0036	0.017	0.0200	0.040	0.028	0.632
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.2 - Relative organ weights° - Recovery sacrifice - Individual data

STUDY NO.: 27080

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus	Thyroid
27080012	1	378.7	0.227	0.991	0.098	0.006
27080014	1	404.6	0.241	1.000	0.118	0.006
27080016	1	375.3	0.206	0.913	0.080	0.005
27080018	1	405.7	0.259	0.994	0.081	0.006
27080020	1	387.8	0.257	0.947	0.082	0.006
	Mean	390.42	0.2380	0.9692	0.0919	0.0059
	SD	14.21	0.0222	0.0378	0.0162	0.0004
	(n)	(5)	(5)	(5)	(5)	(5)
27080052	4	329.4	0.241	0.969	0.053	0.005
27080054	4	302.9	0.185	1.148	0.044	0.006
27080056	4	272.4	0.191	1.255	0.077	0.008
27080058	4	281.1	0.183	1.266	0.038	0.007
27080060	4	287.2	0.259	1.212	0.060	0.007
	Mean	294.60	0.2119	1.1702	0.0544	0.0067
	SD	22.42	0.0356	0.1215	0.0152	0.0011
	(n)	(5)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.2 - Relative organ weights° - Recovery sacrifice - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
27080011	1	262.0	0.026	0.66	0.34	0.74	3.83	0.060
27080013	1	247.9	0.023	0.73	0.41	0.74	3.67	0.044
27080015	1	249.5	0.027	0.65	0.38	0.69	3.58	0.051
27080017	1	239.0	0.033	0.72	0.39	0.73	3.32	0.056
27080019	1	261.8	0.028	0.67	0.41	0.74	3.51	0.050
	Mean	252.04	0.0273	0.686	0.389	0.729	3.584	0.0523
	SD	9.85	0.0039	0.036	0.028	0.020	0.188	0.0062
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
27080051	4	232.0	0.028	0.73	0.42	0.86	5.36	0.055
27080053	4	224.0	0.029	0.67	0.39	0.81	5.75	0.054
27080055	4	235.2	0.028	0.73	0.39	0.86	5.97	0.054
27080057	4	228.5	0.024	0.73	0.42	0.91	5.73	0.046
27080059	4	220.5	0.030	0.75	0.48	0.82	5.91	0.044
	Mean	228.04	0.0277	0.722	0.420	0.852	5.745	0.0507
	SD	5.92	0.0022	0.029	0.037	0.041	0.240	0.0055
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.2 - Relative organ weights° - Recovery sacrifice - Individual data

STUDY NO.: 27080

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Thyroid
27080011	1	262.0	0.244	0.095	0.006
27080013	1	247.9	0.315	0.126	0.006
27080015	1	249.5	0.274	0.151	0.008
27080017	1	239.0	0.238	0.122	0.008
27080019	1	261.8	0.266	0.110	0.005
	Mean	252.04	0.2676	0.1207	0.0068
	SD	9.85	0.0305	0.0207	0.0016
	(n)	(5)	(5)	(5)	(5)
27080051	4	232.0	0.238	0.172	0.006
27080053	4	224.0	0.246	0.113	0.009
27080055	4	235.2	0.251	0.13[illegible]	0.006
27080057	4	228.5	0.274	0.094	0.010
27080059	4	220.5	0.222	0.176	0.008
	Mean	228.04	0.2461	0.1377	0.0079
	SD	5.92	0.0188	0.0360	0.0019
	(n)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080002 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Prostate		INFLAMMATORY CELL INFILTRATION, Multifocal, Slight.
Spleen	Abnormal size, Enlarged/ 40x10x6mm Abnormal shape, Swollen	Tissue is unremarkable.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Eyes	Heart	Ileum
Jejunum	Mesenteric nodes	Parathyroid gl.	Pituitary
Rectum	Sciatic nerve	Seminal vesicles	Spinal column
Spinal cord	Stomach	Testes	Thymus
Thyroid	Trachea	Urinary bladder	

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080004 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Epididymides	Abnormal size, Small/ left	ABSENCE OF SPERM, Unilateral, Present.
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		VASCULAR MINERALIZATION, Multifocal, Slight.
Prostate		INFLAMMATORY CELL INFILTRATION, Focal, Slight.
Seminal vesicles		COLLOID DEPLETION, Slight.
Testes	Abnormal size, Small/ left, 7x5x4mm	UNILATERAL CONGENITAL APLASIA, Present.
Thyroid		ECTOPIC THYMIC TISSUE, Unilateral, Present.
Urinary bladder		PROTEINACEOUS PLUG, Present.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Eyes	Heart	Ileum	Jejunum
Mesenteric nodes	Parathyroid gl.	Pituitary	Rectum
Sciatic nerve	Spinal column	Spinal cord	Spleen
Stomach	Thymus	Trachea	

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080006 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Mild.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
Lungs		ALVEOLAR HAEMORRHAGE, Focal, Slight.
Prostate		INFLAMMATORY CELL INFILTRATION, Multifocal, Mild.
Thymus		CONGESTION/HAEMORRHAGE, Focal, Slight.
Thyroid		ECTOPIC THYMIC TISSUE, Present.
Whole animal	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Eyes	Heart	Ileum
Jejunum	Mesenteric nodes	Parathyroid gl.	Pituitary
Rectum	Sciatic nerve	Seminal vesicles	Spinal column
Spinal cord	Spleen	Stomach	Testes
Trachea	Urinary bladder		

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080008 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
Prostate		INFLAMMATORY CELL INFILTRATION, Multifocal, Slight.
Stomach		GLANDULAR DILATATION, Multifocal, Slight.
Thymus	Abnormal area(s), Multiple, Red/ up to 2x2mm, left lobe	Tissue is unremarkable.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Eyes	Heart	Ileum
Jejunum	Lungs	Mesenteric nodes	Parathyroid gl.
Pituitary	Rectum	Sciatic nerve	Seminal vesicles
Spinal column	Spinal cord	Spleen	Testes
Thyroid	Trachea	Urinary bladder	

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080010 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
Lungs	Abnormal area(s), Multiple, Dark/ up to 9x9mm	AGGREGATIONS OF ALVEOLAR MACROPHAGES, Multifocal, Slight.
		ALVEOLAR HAEMORRHAGE, Multifocal, Mild.
		CHRONIC INFLAMMATION, Multifocal, Moderate.
		BRONCHIAL HAEMORRHAGE, Multifocal, Mild.
		EOSINOPHILIC INFILTRATION, Multifocal, Mild, Peribronchial.
Parathyroid gl.		Tissue is missing.
Prostate		INFLAMMATORY CELL INFILTRATION, Multifocal, Slight.
Stomach		GLANDULAR DILATATION, Focal, Slight.
Thymus		CONGESTION/HAEMORRHAGE, Focal, Slight.
Urinary bladder		PROTEINACEOUS PLUG, Present.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Eyes	Heart	Ileum
Jejunum	Kidneys	Mesenteric nodes	Pituitary
Rectum	Sciatic nerve	Seminal vesicles	Spinal column
Spinal cord	Spleen	Testes	Thyroid
Trachea			

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080012 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		VASCULAR MINERALIZATION, Focal, Slight.
Whole animal	No abnormalities detected	

The following tissues are normal microscopically: Seminal vesicles Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080014 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes	Abnormal colour, Red	Tissue not examined microscopically.
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		VASCULAR MINERALIZATION, Focal, Slight.
Spleen	Abnormal shape, Swollen	Tissue not examined microscopically.
Thymus		CONGESTION/HAEMORRHAGE, Focal, Slight.
Head	Staining, Brown/ left periorbital region	Miscellaneous tissue not examined.

The following tissues are normal microscopically: Seminal vesicles

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080016 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Reccvery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
Lungs	Abnormal colour, Red	INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		ALVEOLAR HAEMORRHAGE, Focal, Slight.

The following tissues are normal microscopically: Seminal vesicles Thymus

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080018 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPAROPATHY, Bilateral, Slight
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
Spleen	Abnormal shape/ and irregular surface; and swollen	Tissue not examined microscopically.
Thymus	Abnormal area(s), Multiple, Red/ up to 2x2mm left lobe	Tissue is unremarkable.

The following tissues are normal microscopically: Lungs Seminal vesicles

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080020 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes . .	Abnormal colour, Single, Red	Tissue not examined microscopically.
Kidneys		NEPHROPATHY, Unilateral, Slight.

The following tissues are normal microscopically: Liver Lungs Seminal vesicles Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080022 Sex: Male Group: 2 Dose level: 0.5 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
Lungs	Abnormal area(s), Multiple, Dark, Pinpoint	INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		ALVEOLAR HAEMORRHAGE, Focal, Slight.
		VASCULAR MINERALIZATION, Focal, Slight.

The following tissues are normal microscopically: Seminal vesicles Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080024 Sex: Male Group: 2 Dose level: 0.5 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver		BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		ALVEOLAR HAEMORRHAGE, Focal, Slight.
Spleen	Abnormal shape, Swollen	EXTRAMEDULLARY HAEMOPOIESIS, Mild.

The following tissues are normal microscopically: Seminal vesicles Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080026 Sex: Male Group: 2 Dose level: 0.5 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		ALVEOLAR HAEMORRHAGE, Focal, Slight.
		VASCULAR MINERALIZATION, Focal, Slight.
Thymus	Abnormal area(s), Multiple, Dark, Pinpoint/ right lobe	Tissue is unremarkable.

The following tissues are normal microscopically: Seminal vesicles

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080028 Sex: Male Group: 2 Dose level: 0.5 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes . .	Abnormal colour, Single, Dark	CONGESTION/HAEMORRHAGE, Multifocal, Slight.
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		EOSINOPHILIC INFILTRATION, Focal, Slight, Peribronchial.

The following tissues are normal microscopically: Seminal vesicles Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080030 Sex: Male Group: 2 Dose level: 0.5 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		VASCULAR MINERALIZATION, Focal, Slight.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Seminal vesicles Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080032 Sex: Male Group: 3 Dose level: 2.5 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys	Abnormal colour, Pale	Tissue is unremarkable.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
	Abnormal shape, Swollen	BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Slight.
		HEPATOCYTIC VACUOLATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		VASCULAR MINERALIZATION, Focal, Slight.

The following tissues are normal microscopically: Seminal vesicles Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080034 Sex: Male Group: 3 Dose level: 2.5 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver	Abnormal shape, Swollen	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		HEPATOCYTIC HYPERTROPHY, Slight.
		HEPATOCYTIC VACUOLATION, Multifocal, Slight.
Lungs		VASCULAR MINERALIZATION, Focal, Slight.
Thymus		CONGESTION/HAEMORRHAGE, Focal, Slight.

The following tissues are normal microscopically: Seminal vesicles

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080036 Sex: Male Group: 3 Dose level: 2.5 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes	Abnormal colour, Single, Red	CONGESTION/HAEMORRHAGE, Multifocal, Slight.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Mild.
Lungs		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Interstitial.

The following tissues are normal microscopically: Kidneys Seminal vesicles Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080038 Sex: Male Group: 3 Dose level: 2.5 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Slight.
		HEPATOCYTIC VACUOLATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight.
		VASCULAR MINERALIZATION, Focal, Slight, Perivascular, Interstitial.
Thymus		ATROPHY, Slight.

The following tissues are normal microscopically: Seminal vesicles

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080040 Sex: Male Group: 3 Dose level: 2.5 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.

The following tissues are normal microscopically: Seminal vesicles Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080042 Sex: Male Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Mild.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
	Abnormal shape, Swollen	BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Moderate.
		SINGLE CELL APOPTOSIS/NECROSIS, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Multifocal, Slight.
Seminal vesicles	Abnormal size, Small	COLLOID DEPLETION, Moderate.
Thymus	Abnormal size, Small	ATROPHY, Mild.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Eyes	Heart	Ileum
Jejunum	Mesenteric nodes	Parathyroid gl.	Pituitary
Prostate	Rectum	Sciatic nerve	Spinal column
Spinal cord	Spleen	Stomach	Testes
Thyroid	Trachea	Urinary bladder	

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080044 Sex: Male Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Mild, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
		HEPATOCYTIC HYPERTROPHY, Mild.
		SINGLE CELL APOPTOSIS/NECROSIS, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
		VASCULAR MINERALIZATION, Focal, Slight.
Seminal vesicles		COLLOID DEPLETION, Slight.
Thymus	Abnormal size, Small	ATROPHY, Mild.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Eyes	Heart	Ileum
Jejunum	Mesenteric nodes	Parathyroid gl.	Pituitary
Prostate	Rectum	Sciatic nerve	Spinal column
Spinal cord	Spleen	Stomach	Testes
Thyroid	Trachea	Urinary bladder	

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080046 Sex: Male Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Moderate, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Mild.
		HEPATOCYTIC HYPERTROPHY, Moderate.
		SINGLE CELL APOPTOSIS/NECROSIS, Multifocal, Moderate.
		HEPATOCYTIC VACUOLATION, Multifocal, Mild.
Lungs		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
		VASCULAR MINERALIZATION, Focal, Slight.
Seminal vesicles		COLLOID DEPLETION, Mild.
Thymus		ATROPHY, Moderate.
Urinary bladder		PROTEINACEOUS PLUG, Present.
Whole animal	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Eyes	Heart	Ileum
Jejunum	Mesenteric nodes	Parathyroid gl.	Pituitary
Prostate	Rectum	Sciatic nerve	Spinal column
Spinal cord	Spleen	Stomach	Testes
Thyroid	Trachea		

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080048 Sex: Male Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver	Abnormal area(s), Single, Pale/ 3x1mm, left lobe	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
	Abnormal size, Enlarged	BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Moderate.
		HEPATOCYTIC NECROSIS, Focal, Mild.
		SINGLE CELL APOPTOSIS/NECROSIS, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Interstitial.
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
		VASCULAR MINERALIZATION, Focal, Slight.
Prostate		INFLAMMATORY CELL INFILTRATION, Focal, Slight.
Seminal vesicles		COLLOID DEPLETION, Slight.
Spleen	Abnormal size, Small/ 31x8x4mm	Tissue is unremarkable.
Thymus	Abnormal size, Small	ATROPHY, Mild.

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080048 Sex: Male Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments			
The following tissues are normal microscopically:		Adrenals	Bronchi	Bone marrow	Brain
		Caecum	Cervical nodes	Colon	Duodenum
		Epididymides	Eyes	Heart	Ileum
		Jejunum	Mesenteric nodes	Parathyroid gl.	Pituitary
		Rectum	Sciatic nerve	Spinal column	Spinal cord
		Stomach	Testes	Thyroid	Trachea
		Urinary bladder			

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080050 Sex: Male Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes	Abnormal colour, Single, Red	CONGESTION/HAEMORRHAGE, Multifocal, Slight.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
		HEPATOCYTIC HYPERTROPHY, Moderate.
		HEPATOCYTIC NECROSIS, Focal, Slight.
		SINGLE CELL APOPTOSIS/NECROSIS, Multifocal, Slight.
		HEPATOCYTIC VACUOLATION, Focal, Slight.
Lungs	Abnormal area(s), Single, Dark/ 2x2mm left lobe	Tissue is unremarkable.
Prostate		INFLAMMATORY CELL INFILTRATION, Focal, Slight.
Seminal vesicles	Abnormal size, Small	COLLOID DEPLETION, Mild.
Thymus	Abnormal size, Small	ATROPHY, Moderate.
		CONGESTION/HAEMORRHAGE, Focal, Slight.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Colon	Duodenum	Epididymides
Eyes	Heart	Ileum	Jejunum
Kidneys	Mesenteric nodes	Parathyroid gl.	Pituitary
Rectum	Sciatic nerve	Spinal column	Spinal cord
Spleen	Stomach	Testes	Thyroid
Trachea	Urinary bladder		

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080052 Sex: Male Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Heart	Abnormal colour, Pale	Tissue not examined microscopically
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver	Abnormal shape, Irregular surface	INFLAMMATORY CELL FOCI, Multifocal, Mild, Perivascular, Intralobular.
	Abnormal size, Enlarged	BILE DUCT PROLIFERATION, Multifocal, Mild.
	Abnormal consistency, Firm	HEPATOCYTIC HYPERTROPHY, Moderate.
		SINGLE CELL APOPTOSIS/NECROSIS, Multifocal, Mild.
		HEPATOCYTIC VACUOLATION, Focal, Slight.
Lungs		VASCULAR MINERALIZATION, Focal, Slight.
Spleen	Abnormal shape, Swollen	Tissue not examined microscopically.
Thymus	Abnormal size, Small	ATROPHY, Mild.
Skin	Not confirmed mass(es), Mass 1, No abnormalities detected	
	Not confirmed mass(es), Mass 2, No abnormalities detected	

The following tissues are normal microscopically: Seminal vesicles

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080054 Sex: Male Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Eyes	Abnormal area(s), Ruptured/ right	Tissue not examined microscopically.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
		HEPATOCYTIC HYPERTROPHY, Mild.
		HEPATOCYTIC VACUOLATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Thymus	Abnormal size, Small	ATROPHY, Moderate.

The following tissues are normal microscopically: Kidneys Seminal vesicles

[redacted]: 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080056 Sex: Male Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Mild.
		HEPATOCYTIC NECROSIS, Focal, Mild.
		HEPATOCYTIC VACUOLATION, Multifocal, Mild.
Lungs		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
Seminal vesicles .	Abnormal size, Small	COLLOID DEPLETION, Slight.
Thymus	Abnormal area(s), Multiple, Red, Pinpoint	ATROPHY, Mild.
		CONGESTION/HAEMORRHAGE, Multifocal, Slight.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080058 Sex: Male Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Mild.
		SINGLE CELL APOPTOSIS/NECROSIS, Multifocal, Slight.
		HEPATOCYTIC VACUOLATION, Multifocal, Mild.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
Spleen	Abnormal shape, Swollen	Tissue not examined microscopically.
Thymus	Abnormal size, Small	ATROPHY, Moderate.
	Abnormal area(s), Multiple, Red, Pinpoint	CONGESTION/HAEMORRHAGE, Multifocal, Slight.

The following tissues are normal microscopically: Seminal vesicles

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080060 Sex: Male Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes	Abnormal colour, Single, Red	Tissue not examined microscopically.
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
	Abnormal shape, Swollen	BILE DUCT PROLIFERATION, Multifocal, Slight.
	Abnormal colour, Pale	HEPATOCYTIC NECROSIS, Multifocal, Moderate, Lobar.
	Abnormal area(s)/ single, dark, firm, raised, 7x6x3mm, right, left median lobes; multiple, pale, up to 3x1mm, caudal right lateral lobe	HEPATOCYTIC VACUOLATION, Multifocal, Mild.
Lungs	Abnormal area(s), Multiple, Pale, Pinpoint	INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		VASCULAR MINERALIZATION, Focal, Slight.
Seminal vesicles		COLLOID DEPLETION, Slight.
Stomach	Abnormal contents, White, Mucoid	Tissue not examined microscopically.
	Abnormal colour, Red/ glandular region	
Thymus	Abnormal size, Small	ATROPHY, Mild.
	Abnormal area(s), Multiple, Red/ up to 2x2mm	

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080001 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes . .	Abnormal colour, Single, Dark	CONGESTION/HAEMORRHAGE, Multifocal, Slight.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
Uterus	Abnormal size, Distended/ 5mm diam	HYDROMETRA, Bilateral, Mild.
	Abnormal contents, Clear, Fluid	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervix	Colon	Duodenum
Eyes	Heart	Ileum	Jejunum
Kidneys	Lungs	Mesenteric nodes	Ovaries
Oviducts	Parathyroid gl.	Pituitary	Rectum
Sciatic nerve	Spinal column	Spinal cord	Spleen
Stomach	Thymus	Thyroid	Trachea
Urinary bladder			

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080003 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes		CONGESTION/HAEMORRHAGE, Focal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		ALVEOLAR HAEMORRHAGE, Multifocal, Slight.
Thymus		CONGESTION/HAEMORRHAGE, Focal, Slight.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervix	Colon	Duodenum
Eyes	Heart	Ileum	Jejunum
Kidneys	Liver	Mesenteric nodes	Ovaries
Oviducts	Parathyroid gl.	Pituitary	Rectum
Sciatic nerve	Spinal column	Spinal cord	Spleen
Stomach	Thyroid	Trachea	Urinary bladder
Uterus			

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080005 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
Lungs		ALVEOLAR HAEMORRHAGE, Focal, Slight.
Ovaries	Abnormal size, Enlarged/ up to 5x4x3mm	LUTEIN CYST, Bilateral, Present.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Eyes	Heart	Ileum
Jejunum	Mesenteric nodes	Oviducts	Parathyroid gl.
Pituitary	Rectum	Sciatic nerve	Spinal column
Spinal cord	Spleen	Stomach	Thymus
Thyroid	Trachea	Urinary bladder	Uterus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080007 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
Lungs		ALVEOLAR HAEMORRHAGE, Focal, Slight.
Ovaries	Abnormal size, Enlarged/ up to 6mm diam	Tissue is unremarkable.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Eyes	Heart	Ileum
Jejunum	Kidneys	Mesenteric nodes	Oviducts
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
Spinal column	Spinal cord	Spleen	Stomach
Thymus	Thyroid	Trachea	Urinary bladder
Uterus			

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080009 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes		CONGESTION/HAEMORRHAGE, Focal, Slight.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		VASCULAR MINERALIZATION, Focal, Slight.
Spleen	Abnormal shape, Swollen	Tissue is unremarkable.
Thyroid		ECTOPIC THYMIC TISSUE, Present.
Uterus		HYDROMETRA, Bilateral, Mild.
		GLANDULAR DILATATION, Focal, Slight.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervix	Colon	Duodenum
Eyes	Heart	Ileum	Jejunum
Kidneys	Mesenteric nodes	Ovaries	Oviducts
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
Spinal column	Spinal cord	Stomach	Thymus
Trachea	Urinary bladder		

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080011 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes	Abnormal colour, Red	Tissue not examined microscopically.
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.

The following tissues are normal microscopically: Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080013 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes . .	Abnormal colour, Two, Red	Tissue not examined microscopically.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		ALVEOLAR HAEMORRHAGE, Focal, Slight.
		VASCULAR MINERALIZATION, Focal, Slight.

The following tissues are normal microscopically: Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080015 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
Lungs	Abnormal colour, Red	ALVEOLAR HAEMORRHAGE, Focal, Slight.

The following tissues are normal microscopically: Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080017 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Lungs Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080019 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

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Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Kidneys Lungs Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080021 Sex: Female Group: 2 Dose level: 0.5 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver		EXTRAMEDULLARY HAEMOPOIESIS, Focal, Slight.
		BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080023 Sex: Female Group: 2 Dose level: 0.5 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Kidneys Lungs Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080025 Sex: Female Group: 2 Dose level: 0.5 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080027 Sex: Female Group: 2 Dose level: 0.5 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080029 Sex: Female Group: 2 Dose level: 0.5 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes	Abnormal colour, Single, Red	CONGESTION/HAEMORRHAGE, Focal, Slight.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
		EXTRAMEDULLARY HAEMOPOIESIS, Focal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Thymus		CONGESTION/HAEMORRHAGE, Focal, Slight.

The following tissues are normal microscopically: Kidneys

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080031 Sex: Female Group: 3 Dose level: 2.5 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Mild.
Lungs	Abnormal colour, Dark/pale	ALVEOLAR HAEMORRHAGE, Multifocal, Moderate, Lobar.
Thymus	Abnormal area(s), Multiple, Red, Pinpoint	CONGESTION/HAEMORRHAGE, Focal, Slight.

The following tissues are normal microscopically: Kidneys

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080033 Sex: Female Group: 3 Dose level: 2.5 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Unilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Mild.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080035 Sex: Female Group: 3 Dose level: 2.5 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		INFLAMMATORY CELL INFILTRATION, Unilateral, Slight.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight. HEPATOCYTIC HYPERTROPHY, Mild.

The following tissues are normal microscopically: Lungs Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080037 Sex: Female Group: 3 Dose level: 2.5 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		MEDULLARY MINERALIZATION, Unilateral, Slight, Cortico-medullary junction.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Slight.
Lungs	Abnormal colour, Dark	Tissue is unremarkable.
Thymus	Abnormal colour, Red/ right lobe	Tissue is unremarkable.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080039 Sex: Female Group: 3 Dose level: 2.5 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Mild.
Thymus	Abnormal colour, Red/ right lobe	Tissue is unremarkable.

The following tissues are normal microscopically: Kidneys Lungs

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080041 Sex: Female Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes		CONGESTION/HAEMORRHAGE, Multifocal, Slight.
Kidneys	Abnormal colour, Dark	MEDULLARY MINERALIZATION, Unilateral, Slight, Pelvic urothelium.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		HEPATOCYTIC HYPERTROPHY, Mild.
Stomach		OEDEMA, Multifocal, Mild, non-glandular region.
		MUCOSAL ULCERATION, Focal, Mild, non-glandular region.
		EPITHELIAL HYPERPLASIA, Multifocal, Mild.
		INFLAMMATORY CELL INFILTRATION, Multifocal, Mild, non-glandular region.
Thymus		ATROPHY, Slight.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervix	Colon	Duodenum
Eyes	Heart	Ileum	Jejunum
Lungs	Mesenteric nodes	Ovaries	Oviducts
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
Spinal column	Spinal cord	Spleen	Thyroid
Trachea	Urinary bladder	Uterus	

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080043 Sex: Female Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 28 Dosing phase Status: Found dead

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Slight.
		CORTICAL TUBULAR DILATATION, Diffuse, Mild.
		MEDULLARY MINERALIZATION, Unilateral, Slight, Cortico-medullary junction.
Liver	Abnormal colour, Pale	INFLAMMATORY CELL FOCI, Multifocal, Mild, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
		HEPATOCYTIC HYPERTROPHY, Moderate.
		SINGLE CELL APOPTOSIS/NECROSIS, Multifocal, Moderate.
		HAEMORRHAGE, Multifocal, Moderate.
Lungs	Incomplete collapse	Tissue is unremarkable.
Parathyroid gl.		Tissue is missing.
Spleen		LYMPHOID DEPLETION, Mild.
Thymus		ATROPHY, Moderate.
Pancreas	Abnormal colour, Pale	ACINAR CELL APOPTOSIS, Focal, Mild.
Head	Abnormal area(s), Single, Scab(s)/ 6x3mm, (ABN SKIN 1)	ULCERATION, Focal, Moderate.
		SCAB, Focal, Present.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080043 Sex: Female Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 28 Dosing phase Status: Found dead

Tissue	Gross observations / Comments	Microscopic observations / Comments			
The following tissues are normal microscopically:		Adrenals	Bronchi	Bone marrow	Brain
		Caecum	Cervical nodes	Cervix	Colon
		Duodenum	Eyes	Heart	Ileum
		Jejunum	Mesenteric nodes	Ovaries	Oviducts
		Pituitary	Rectum	Sciatic nerve	Spinal column
		Spinal cord	Stomach	Thyroid	Trachea
		Urinary bladder	Uterus		

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080045 Sex: Female Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		MEDULLARY MINERALIZATION, Unilateral, Slight, Cortico-medullary junction.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
		HEPATOCYTIC HYPERTROPHY, Moderate.
		SINGLE CELL APOPTOSIS/NECROSIS, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
Thymus	Abnormal colour, Red/ right lobe	ATROPHY, Slight.
	Abnormal size, Small	CONGESTION/HAEMORRHAGE, Multifocal, Slight.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Eyes	Heart	Ileum
Jejunum	Mesenteric nodes	Ovaries	Oviducts
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
Spinal column	Spinal cord	Spleen	Stomach
Thyroid	Trachea	Urinary bladder	Uterus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080047 Sex: Female Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes		CONGESTION/HAEMORRHAGE, Multifocal, Slight.
Kidneys		MEDULLARY MINERALIZATION, Unilateral, Slight, Cortico-medullary junction.
		PAPILLARY MINERALIZATION, Unilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Moderate.
		SINGLE CELL APOPTOSIS/NECROSIS, Focal, Slight.
		HEPATOCYTIC VACUOLATION, Multifocal, Slight.
Lungs		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
		ALVEOLAR HAEMORRHAGE, Focal, Slight.
Whole animal	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervix	Colon	Duodenum
Eyes	Heart	Ileum	Jejunum
Mesenteric nodes	Ovaries	Oviducts	Parathyroid gl.
Pituitary	Rectum	Sciatic nerve	Spinal column
Spinal cord	Spleen	Stomach	Thymus
Thyroid	Trachea	Urinary bladder	Uterus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080049 Sex: Female Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Unilateral, Slight.
		INFLAMMATORY CELL INFILTRATION, Unilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
		HEPATOCYTIC HYPERTROPHY, Moderate.
Lungs		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
Thyroid		DEVELOPMENTAL CYST(S), Focal, Present.
Whole animal	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain	
Caecum	Cervical nodes	Cervix	Colon	
Duodenum	Eyes	Heart	Ileum	
Jejunum	Mesenteric nodes	Ovaries	Oviducts	
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve	
Spinal column	Spinal cord	Spleen	Stomach	
Thymus	Trachea	Urinary bladder	Uterus	

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080051 Sex: Female Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes . .	Abnormal colour, Dark red	Tissue not examined microscopically.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Uterus	Abnormal size, Distended/ 5mm diam	Tissue not examined microscopically.
	Abnormal contents, Clear, Fluid	

The following tissues are normal microscopically: Kidneys Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080053 Sex: Female Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Ileum	Abnormal contents, Yellow, Mucoid	Tissue not examined microscopically.
Kidneys		MEDULLARY MINERALIZATION, Bilateral, Slight, Cortico-medullary junction.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Mild, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Slight.
		SINGLE CELL APOPTOSIS/NECROSIS, Multifocal, Slight.
Stomach	Abnormal contents, Yellow, Mucoid	Tissue not examined microscopically.
Thymus	Abnormal area(s), Multiple, Red/ up to 3x2mm	Tissue is unremarkable.

The following tissues are normal microscopically: Lungs

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080055 Sex: Female Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes . .	Abnormal colour, Single, Red	Tissue not examined microscopically.
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Slight.
Lungs		INFLAMMATORY CELL FOCI, Multifocal, Mild, Perivascular, Interstitial.

The following tissues are normal microscopically: Thymus

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080057 Sex: Female Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes	Abnormal colour, Two, Red	Tissue not examined microscopically.
Kidneys		MEDULLARY MINERALIZATION, Bilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Multifocal, Mild, Perivascular, Interstitial.
Spleen	Abnormal shape, Swollen	Tissue not examined microscopically.
Thymus		ATROPHY, Slight.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 27080

Animal: 27080059 Sex: Female Group: 4 Dose level: 8.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

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Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		HEPATOCYTIC HYPERTROPHY, Slight.
Uterus	Abnormal size, Enlarged/ 5mm diam	Tissue not examined microscopically.
	Abnormal contents, Clear, Fluid	

The following tissues are normal microscopically: Kidneys Lungs Thymus

[redacted] WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM I - Computer abbreviations and symbols

STUDY NO.: 27080

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
GGT	GAMMAGLUTAMYLTRANSFERASE	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
VOL	URINE VOLUME (OVERNIGHT)	ml
SG	SPECIFIC GRAVITY	
PRO	PROTEIN	mg/dl
BLD	HAEMOGLOBIN	mg/dl
KET	KETONES	mg/dl
BIL	BILIRUBIN	mg/dl
URO	UROBILINOGEN	mg/dl
TRI	TRIGLYCERIDES	mg/dl
ALB	ALBUMIN	g/dl
GLO	GLOBULIN	g/dl
AGR	ALBUMIN/GLOBULIN RATIO	

[redacted] WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM I - Computer abbreviations and symbols

STUDY NO.: 27080

Abbreviations	Parameters names	Units/Key
EPI	EPITHELIAL CELLS	0 = no cells or crystals 1 = few cells or crystals in some fields 2 = few cells or crystals in all fields 3 = many cells or crystals in all fields
LEU	LEUCOCYTES	
ERY	ERYTHROCYTES	
CRY	CRYSTALS	
SPE	SPERMATOZOA	
ABN	ABNORMAL COMPONENTS	
APP	URINE APPEARANCE	0 = normal 1 = turbid
RED	REDUCING SUBSTANCES	0 = 0.0 - 2.5 g/l 1 = 2.5 - 7.5 g/l 2 = 7.5 - 10.0 g/l 3 = 10.0 - 20.0 g/l
Ctls	Control	
SD	Standard deviation	
Cervical nodes	Cervical lymph nodes	
Mesenteric nodes	Mesenteric lymph nodes	
gl	Glands	

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM II - Abbreviations of neurotoxicity tests

STUDY NO.: 27080

STIMULUS REACTIVITY		
APPR	APPROACH RESPONSE	1) no reaction 2) rat slowly approaches and sniffs or turns away 3) rat freezes, actual muscle contractions 4) more energetic response than 2) or 3) 5) exaggerated reaction - jumps, bites, or attacks
TOUC	TOUCH RESPONSE	1) no response 2) rat may slowly turn or walk away, or vocalizations with little or no movement 3) rat freezes, actual muscle contractions 4) more energetic response than 2) or 3) 5) exaggerated reaction - jumps, bites, or attacks
CLIK	CLIKER RESPONSE	1) no reaction 2) slight reaction, some evidence that noise was heard 3) rat freezes, actual muscle contractions 4) more energetic response than 2) or 3) 5) exaggerated reaction - jumps, bites, or attacks
TAIL	TAIL PINCH RESPONSE	1) no reaction 2) rat may turn or walk forward, or vocalizations with little or no movement 3) rat freezes, actual muscle contractions 4) more energetic response than 2) or 3) 5) exaggerated response - jumps, bites, or attacks
COUN	COUNT	The number of times the animal crosses the beam of the photoelectric cell.
BW		Body weight

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM II - Abbreviations of neurotoxicity tests

STUDY NO.: 27080

Abbreviations	Parameter names	Key
PUPI	PUPIL RESPONSE	constriction of the pupil is noted with "+" and "-" indicates lack of response
RIGH	RIGHTING REFLEX	1) normal, rat lands on feet 2) slightly uncoordinated 3) lands on side 4) lands on back
GRI1/2/M	GRIP STRENGTH 1/2/MEAN	two readings (GRI 1 and GRI 2) are taken and averaged. Forelimb strength is evaluated by assessing the time (seconds) the animal grips on a horizontal bar
LAN1/2/M	LANDING FOOT SPLAY 1/2/MEAN	two readings are taken and averaged. Measurements of distance between ink blots (cm)

[redacted]4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM III - Analytical method and validation report for formulation analysis and formulation analysis

STUDY NO.: 27080

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Analytical method and validation report for formulation analysis
[redacted] Determination in water with LC-MS/MS detection

STUDY NO.: 27080

WARNING AND SAFETY PRECAUTIONS

SAFETY

Organic solvents - all organic solvents must be treated as potentially hazardous and all procedures using them must be performed in a fume cupboard.

[redacted]
Appropriate eye protection, impervious gloves and lab coat should be worn.
This method requires the use of corrosive and toxic reagents. It is the responsibility of the analyst to perform the method consistent with safe laboratory practices. The analyst should wear eye protection, impervious gloves, and a lab coat when preparing standards and processing samples. Caution statements have been included in the method giving specific guidance to certain procedural steps. Detailed hazard information should be obtained from the current MSDS available from the manufacturer of the solvent or reagent.

FIRST AID

Solvents, acids and alkalis in contact with skin - wash with copious amounts of cold water. Splashes in the eye - irrigate with water and seek medical attention immediately.

Cuts - seek assistance of first aider immediately.

Burns and frostbite - run affected part under cold water (burns) or tepid water (frostbite) for 10 minutes and seek medical attention.

INTRODUCTION

[redacted] is a product developed by the Sponsor.

1. SCOPE

This method of analysis describes the analysis of [redacted] in water.

2. FIELD OF APPLICATION

The method is described to be used for formulated product in water. The range of application is from 0.05 mg/ml to 0.8 mg/ml.

3. REFERENCES

ISO Standard 78/2-1982 Layout for standards - Part 2: Standard for Chemical Analysis.

4. DEFINITIONS

[redacted] content is taken to mean the amount of [redacted] in the formulation determined according to the described method and expressed as mg of analyte per ml test sample.

5. PRINCIPLE

The method essentially consists of three steps:
- Sampling
- Dilution
- LC-MS/MS

6. REACTIONS

Not Applicable

7. REAGENTS AND MATERIALS

Note: The reagents (and equipment) for which examples of their sources are quoted are known to be satisfactory, nevertheless reagents and equipment from other sources may be equally suitable. All the reagents must be of analytical grade or better.

7.1 Chemicals

7.1.1 Methanol HPLC grade (Baker 8402)

7.1.2 Water HPLC grade (produced by EASYPURE)

7.2 Solutions

7.2.1 Mobile phase A: Methanol

7.3 Standard solutions

7.3.1 [redacted] STOCK A/B (for formulations):
About 10 mg are transferred into a 250 ml volumetric flask and dissolved with distilled water obtaining a 0.04 mg/ml solution. This solution needs to be mixed with a magnetic stirrer for 5 minutes.

7.3.2 [redacted] STD A/B:
0.5 ml of STOCK A is transferred into a 200 ml volumetric flask and dissolved with water obtaining a 0.1 µg/ml solution equivalent to 100 ng/ml (working concentration).

8. APPARATUS

8.1	Analytical balance	Mettler AT 261 Delta range or equivalent
8.2	HPLC system	Agilent 1100 series
8.3	Detector	LC-MS/MS
8.4	Software	Analyst

8.5	Printer	HP Laser Jet 4050 Series PCL6
8.6	Precolumn	Phenomenex C18 ODS 4 mm x 2 mm ID
8.7	HPLC microvials	
8.8	Pasteur pipettes	
8.9	Volumetric pipettes	
8.10	Common glassware	

9. SAMPLING AND SAMPLES

9.1 Nature of the Sample; Samples shall be such as to enable the detection of substance in the relevant formulations.

9.2 Size of Sample; The size of the sample must be large enough to allow the method to be carried out and to allow repeat analysis where required.

9.3 The samples must be taken and packed in such a way as to allow proper identification in the laboratory.

9.4 The method of packing, preservation and transport must maintain the integrity of the sample and not prejudice the results of the examination. Samples for the analysis of [redacted] must be stored at room temperature.

10. PROCEDURE

10.1 Sampling

The solution is transferred into a suitable flask and diluted with water.

10.2 Blank and unknown samples

Samples are diluted with water as follows:

		Expected			
Step	Action	0 mg/ml	0.05 mg/ml	0.25 mg/ml	0.8 mg/ml
1	transfer	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	dilute to	250 ml	250 ml	250 ml	100 ml
2	transfer			2 ml	0.5 ml
	dilute to			10 ml	20 ml

For other concentrations samples will be prepared with an appropriate dilution.
Transfer into HPLC vials.

10.3 **Recovery samples**

Low Level (0.05 mg/ml in water): About 12.50 mg of [redacted] are transferred into a 250 ml volumetric flask and diluted with water, obtaining a 0.05 mg/ml solution. Six dilutions are performed: 0.5 ml of solution are transferred into 250 ml volumetric flask and diluted with water (100 ng/ml in water - working concentration).
High Level (0.8 mg/ml in water): About 80 mg of [redacted] are transferred into a 100 ml volumetric flask and diluted with water, obtaining a 0.8 mg/ml solution. Six dilutions are performed: 0.5 ml of solution are transferred into 100 ml volumetric flask and diluted with water. Each solution is diluted a second time: 0.5 ml are transferred into 20 ml volumetric flask and diluted with water (100 ng/ml in water - working concentration).
Transfer into HPLC vials.

10.4 **LC-MS/MS**

10.4.1 The following HPLC system is set up:

10.4.1.1	Precolumn	:	Phenomenex C18 ODS 4 mm * 2 mm ID
10.4.1.2	Mobile phase	:	Eluent A: Methanol
10.4.1.3	Flow	:	0.2 ml/min
10.4.1.4	Autosampler	:	+4°C
10.4.1.5	Injection vol.	:	10 µl
10.4.1.6	Run time	:	~ 2 minutes
10.4.1.7	Retention time	:	~ 30 sec.

10.4.2 Mass parameters:

Scan type : MRM
Polarity : positive

[redacted]

Precursor Ion Q1 Mass (m/z)	Product Ion Q3 Mass (m/z)
345.0	84.9
345.0	112.8
345.0	228.8
295.0	84.6
295.0	112.8
295.0	247.7

10.4.3 The HPLC is calibrated using the chromatographic software which generates a linear fit calibration curve drawing the best fit of a line, passing through the origin, to the amounts of [redacted] in ng/ml and the peaks areas. The software uses linear least-squares fit formula. The result of the fitting is:

$y = Bx$

where
B = Slope of the calibration curve
y = [redacted]
x = [redacted] amount in ng/ml

Unknown samples are injected after the HPLC calibration. Results of the [redacted] amount in ng/ml are obtained directly from the Analyst report. The result is calculated by the software as:

$x = (y) / B$

11. EXPRESSION OF RESULTS

11.1 [redacted] contents for formulations in mg/ml are obtained as follows:

$C = (x \bullet FD) / 1000000$

where:
C = content of [redacted] in the formulation as mg/ml
x = [redacted] concentration in ng/ml as read in the chromatogram result table
FD = Dilution factor
1000000 = conversion factor from ng/ml to mg/ml

12. SPECIAL CASES
Not applicable

13. NOTES ON PROCEDURE
Not applicable

14. TEST REPORT
Not applicable

15. SCHEMATIC REPRESENTATION OF PROCEDURE

Sampling ⟶ Dilution
↓
LC-MS/MS

16. BIBLIOGRAPHY
Not applicable

17. **VALIDATION**

17.1 **Linearity**

Calibration samples in triplicate at three levels ranging from 50 ng/ml to 200 ng/ml were processed as described in the analytical method. The following correlation was found:

Added ng/ml	Response
52.45	1.5302e+004
52.45	1.5395e+004
52.45	1.5399e+004
104.9	3.0275e+004
104.9	3.0329e+004
104.9	3.0253e+004
209.8	6.1965e+004
209.8	6.1703e+004
209.8	6.1640e+004

Equation : Response = +293* [redacted] concentration
r : 1.0000
Response type : area
Fit type : linear through zero
Weighting : none

17.2 **Selectivity**

No interfering peaks were present at the [redacted] retention time.

17.3 **Accuracy and precision**

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
mg/ml	mg/ml	Mean (mg/ml)	%	CV %
0.0502	0.0507 0.0503 0.0510 0.0494 0.0494 0.0506	**0.0502**	**100.06**	**1.37**
0.8109	0.8184 0.8157 0.7953 0.7972 0.8129 0.8091	**0.8081**	**99.65**	**1.20**

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Formulation analysis - Pre-treatment - Content check

STUDY NO.: 27080

Group	Intended Concentration mg/ml	Found Concentration mg/ml	Recovery %	Recovery Limits %
1	0	0	-	-
2	0.05	0.05224	104.49	95-105
3	0.25	0.2487	99.48	95-105
4	0.8	0.8278	103.47	95-105

[redacted]4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Formulation analysis - Stability 24 hours at room temperature - Content check

STUDY NO.: 27080

Group	Intended Concentration mg/ml	Found Concentration mg/ml	Recovery %	Recovery Limits %
2	0.05	0.05073	101.46	95-105
4	0.8	0.8089	101.11	95-105

[redacted]4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Formulation analysis - Week 1 of treatment - Content check

STUDY NO.: 27080

Group	Sex	Intended Concentration mg/ml	Found Concentration mg/ml	Recovery %	Recovery Limits %
1	M/F	0	0	-	-
2	M/F	0.05	0.05207	104.14	95-105
3	M/F	0.25	0.2573	102.91	95-105
4	M/F	0.8	0.8192	102.40	95-105

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Formulation analysis - Week 4 of treatment for main groups and Day 1 for satellite group - Content check

STUDY NO.: 27080

Group	Sex	Intended Concentration mg/ml	Found Concentration mg/ml	Recovery %	Recovery Limits %
1	M/F	0	0	-	-
2	M/F	0.05	0.050	98.41	95-105
3	M/F	0.25	0.250	99.84	95-105
4/5	M/F	0.8	0.793	99.16	95-105

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM IV - Analytical method and validation report for toxicokinetic analysis and toxicokinetic analysis

STUDY NO.: 27080

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Analytical method and validation report for toxicokinetic analysis
[redacted] Determination in Rat Plasma with LC-MS/MS detection

STUDY NO.: 27080

WARNING AND SAFETY PRECAUTIONS

SAFETY

Organic solvents - all organic solvents must be treated as potentially hazardous and all procedures using them must be performed in a fume cupboard.

[redacted]

Appropriate eye protection, impervious gloves and lab coat should be worn.
This method requires the use of corrosive and toxic reagents. It is the responsibility of the analyst to perform the method consistent with safe laboratory practices. The analyst should wear eye protection, impervious gloves, and a lab coat when preparing standards and processing samples. Caution statements have been included in the method giving specific guidance to certain procedural steps. Detailed hazard information should be obtained from the current MSDS available from the manufacturer of the solvent or reagent.

FIRST AID

Solvents, acids and alkalis in contact with skin - wash with copious amounts of cold water. Splashes in the eye - irrigate with water and seek medical attention immediately.
Cuts - seek assistance of first aid immediately.
Burns and frostbite - run affected part under cold water (burns) or tepid water (frostbite) for 10 minutes and seek medical attention.

INTRODUCTION

[redacted] is a product developed by the sponsor.

1. **SCOPE**
This method of analysis describes the analysis of [redacted] (or simply [redacted] in rat plasma.

2. **FIELD OF APPLICATION**
The method is described to be used for [redacted] in rat plasma.
The range of application is from 10 ng/ml to 330 ng/ml.

3. **REFERENCES**
ISO Standard 78/2-1982 Layout for standards - Part 2: Standard for Chemical Analysis

4. **DEFINITIONS**
[redacted] content is taken to mean the amount of [redacted] in rat plasma determined according to the described method and expressed as mg of analyte per ml test sample.

5. **PRINCIPLE**

The method essentially consists of three steps:
- Sampling
- Precipitation
- Centrifugation
- Evaporation
- LC-MS/MS

6. **REACTIONS**

7. **REAGENTS AND MATERIALS**

Note: The reagents (and equipment) for which examples of their sources are quoted are known to be satisfactory, nevertheless reagents and equipment from other sources may be equally suitable. All the reagents must be of analytical grade or better.

7.1 **Chemicals**

7.1.1 Acetonitrile HPLC grade (Baker 9017)

7.1.2 Methanol HPLC grade (Baker 8402)

7.1.3 Water HPLC grade (produced by EASYPURE)

7.1.4 [redacted] (Batch n° 90156/96-2, Purity 99%), Reference Standard can be ordered from Solvay - Solexis. Throughout the study this reference Standard will be mentioned as [redacted]

7.1.5 Diclofenac Sodium SW (Batch DS 0005/075, purity 100%), Internal Reference Standard can be ordered from Sigma. Throughout the study this reference Standard will be mentioned as ISTD - DICLOFENAC.

7.2 **Solutions**

7.2.1 Mobile phase A: Acetonitrile

7.2.2 Mobile phase B: Water

7.3 **Standard solutions**

7.3.1 [redacted] STOCK A:
About 10 mg of [redacted] are transferred into a 50 volumetric flask and dissolved with water obtaining a concentration corrected for purity of 198 µg/ml solution. This solution needs to be mixed with a magnetic stirrer for 5 minutes.

7.3.2 SOL B:
1 mL of STOCK A is transferred into a 10 mL volumetric flask and diluted with water obtaining a 19.8 µg/ml solution for [redacted]

7.3.3 SOL 8:
2 mL of SOL B are transferred into a 20 mL volumetric flask and diluted with water obtaining a 1.98 µg/ml solution for [redacted]

7.3.4 SOL 7:
1 mL of SOL B is transferred into a 15 mL volumetric flask and diluted with water obtaining a 1.32 µg/ml solution for [redacted]

7.3.5 SOL 6:
1 mL of SOL B is transferred into a 25 mL volumetric flask and diluted with water obtaining a 0.792 µg/ml solution for [redacted]

7.3.6 SOL 5:
1.5 mL of SOL 8 are transferred into a 5 mL volumetric flask and diluted with water obtaining a 0.594 µg/ml solution for [redacted]

7.3.7 SOL 4:
1 mL of SOL 8 is transferred into a 5 mL volumetric flask and diluted with water obtaining a 0.396 µg/ml solution for [redacted]

7.3.8 SOL 3:
1 mL of SOL 8 is transferred into a 10 mL volumetric flask and diluted with water obtaining a 0.198 µg/ml solution for [redacted]

7.3.9 SOL 2:
1 mL of SOL 8 is transferred into a 15 mL volumetric flask and diluted with water obtaining a 0.132 µg/ml solution for [redacted]

7.3.10 SOL 1:
1.5 ml of SOL 8 are transferred into a 50 mL volumetric flask and diluted with water obtaining a 0.0594 µg/ml solution for [redacted]

7.3.11 SOL HIGH:
1.7 mL of SOL B are transferred into a 20 mL volumetric flask and diluted with water obtaining a 1.68 µg/ml solution for [redacted]

7.3.12 STOCK ISTD:
About 25 mg of ISTD - DICLOFENAC are transferred into a 25 volumetric flask and dissolved with Methanol obtaining of 1000 µg/ml solution.

7.3.13 ISTD:
0.5 mL of STOCK ISTD are transferred into a 100 mL volumetric flask and diluted with Methanol obtaining a 5 µg/ml solution for ISTD - DICLOFENAC.

8. **APPARATUS**

Analytical balance	Mettler AT 261 Delta range
HPLC system	Agilent 1100 series
Detector	Applied BioSystems API2000 LC-MS/MS
Software	Analyst
Printer	HP Laser Jet 2200 Series PCL6
Column	Waters Atlantis C18 100 x 2.1 mm ID
Centrifuge	ALC 4236 A
Vortex	New ZX VELP
Heating Module	Pierce Reacti Therm III
HPLC microvials	
Eppendorf	
Volumetric pipettes	
Common glassware	

9. **SAMPLING AND SAMPLES**

Nature of the Sample; Samples shall be such as to enable the detection of residues in rat plasma.

Size of Sample; The size of the sample must be large enough to allow the method to be carried out and to allow repeat analysis where required.

The samples must be taken and packed in such a way as to allow proper identification in the laboratory.

The method of packing, preservation and transport must maintain the integrity of the sample and not prejudice the results of the examination. Samples for the analysis of [redacted] must be stored at temperature below -18°C.

10. **PROCEDURE**

10.1 **Blank and unknown samples**

The whole sample of rat plasma is centrifuged at 13000 rpm for 5 minutes.

300 µl of rat plasma are spiked with 10 µl ISTD and 50 µl of methanol, vortexed and then 900µL of Acetonitrile are added. Samples are vortexed. After centrifugation for 10 minutes at 14000 rpm, the supernatant is transferred in to 1.5mL Eppendorf. Samples are then evaporated up to about 100 µL under a gentle stream of Nitrogen at 40°C.

Sample are transferred into HPLC vials and analysed with LC-MS/MS.

10.2 **Calibration samples**

To 300 µl of rat plasma an adequate aliquot of working standard solution and 10 µl ISTD – DICLOFENAC (see table below) are added:

Samples are then processed as previously described.

The compounds concentration in matrix:

Name	Added	From solution	[redacted] concentration in matrix (ng/ml)	ISTD - DICLOFENAC Concentration (ng/ml)
Std 1	50 µL	SOL 1	≈9.90	≈167
Std 2	50 µL	SOL 2	≈22.0	≈167
Std 3	50 µL	SOL 3	≈33.0	≈167
Std 4	50 µL	SOL 4	≈66.0	≈167
Std 5	50 µL	SOL 5	≈99.0	≈167
Std 6	50 µL	SOL 6	≈132	≈167
Std 7	50 µL	SOL 7	≈220	≈167
Std 8	50 µL	SOL 8	≈330	≈167

10.3 **Accuracy and Precision samples (QC samples):**

To 300 µl of rat plasma an adequate aliquot of working standard solution and 10 µl ISTD – DICLOFENAC (see table below) are added:

Samples are then processed as previously described.

The compounds concentration in matrix:

Name	Added	From solution	[redacted] concentration in matrix (ng/ml)	ISTD - DICLOFENAC Concentration (ng/ml)
LLOQ	50 µl	SOL. 1	≈9.90	≈167
1st level	50 µl	SOL 3	≈33.0	≈167
2nd level	50 µl	SOL 6	≈132	≈167
3th level	50 µl	SOL HIGH	≈281	≈167

10.4 **HPLC**

The following system is set up:

Column: Atlantis dC_{18} 3 µm 2.1x100 mm

Autosampler: 4°C

Mobile phase:

Eluent A : Acetonitrile

Eluent B: Water

	Time (Min)	A%	B%	Flow (ml)
Equilibration	8.00	50.0	50.0	0.2
Run	1.00	50.0	50.0	0.2
	1.10	100.0	0.0	0.4
	6.00	100.0	0.0	0.4

Injection vol.: 40 µl

Run time: 6 minutes

10.5 **Mass parameters:**

Scan type: MRM
Polarity: Negative
[redacted]

Precursor Ion Q1 Mass (m/z)	Product Ion Q3 Mass (m/z)	Quantitation
240.0	181.60	Total Ion Current (TIC)
	113.00	
215.10	113.00	
228.90	113.00	
182.00	112.80	

Retention time: ≈2.0 min

ISTD – DICLOFENAC

Precursor Ion Q1 Mass (m/z)	Product Ion Q3 Mass (m/z)	Quantitation
294.10	250.0	Total Ion Current (TIC)

Retention time: ≈2.0 min

The LC-MS analysis is calibrated using the software Analyst which generates a linear fit calibration curve drawing the best fit of a line to the amounts and peak areas of standard. The software uses linear least-squares fit formula with a 1/X weighting. The result of the fitting is:
$y = A + Bx$
where
A = y-intercept of the calibration curve
B = Slope of the calibration curve
y = peak IS area / analyte area
x = [redacted] amount in ng/ml
Unknown samples are injected after the LC-MS calibration. Results of the [redacted] amount in ng/ml are obtained directly from the LC/MS report. The result is calculated by the software as:

$x = (y-A) / B$

11. **EXPRESSION OF RESULTS**

[redacted] contents in ng/ml are obtained directly from the chromatogram result table as follows:
C = x
Where:
C = content of [redacted] as ng/ml
x = [redacted] amount in ng/ml as read in the chromatogram result table

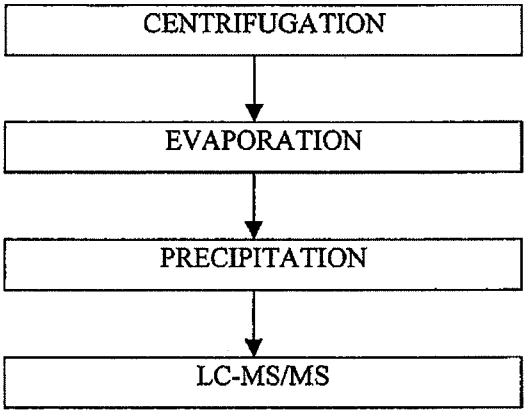
Individual data are reported in Section 17.

12. **SPECIAL CASES**

13. **NOTES ON PROCEDURE**

14. **TEST REPORT**

15. **SCHEMATIC REPRESENTATION OF PROCEDURE**



16. **BIBLIOGRAPHY**

17. **RESULTS VALIDATION**

17.1 [redacted] **Linearity**

Calibration samples in single at eight levels ranging from 10 ng/ml to 330 ng/ml were processed as described in the analytical method. The following correlation was found:

Added ng/ml	Response (IS Analyte/ Analyte area)	Calculated Concentration (ng/mL)	Deviation %
10.0188	1.7777 e-001	10.852	8.32
22.264	4.5018 e-001	22.176	-0.394
33.396	8.3243 e-001	38.066	14.0
66.792	1.3967 e+000	61.522	-7.89
100.188	2.0372 e+000	88.144	-12.0
133.584	2.7894 e+000	119.42	-10.6
222.64	5.4019 e+000	228.01	2.41
333.96	8.4485 e+000	354.65	6.20

Equation: Response = -0.0833 + 0.0241* [redacted] Conc.
r: 0.9956
Response type: area
Fit type: linear
Weighting: 1/X

17.2 **Selectivity**
No interfering peaks were present at the [redacted] retention times.

17.3 **Accuracy and precision (Low Level)**

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Mean Accuracy	Precision
ng/ml	ng/ml	Mean (ng/ml)	%	%	CV %
33.396	37.452 37.839 37.867 38.346 37.604 37.765	**37.812**	112.2 113.3 113.4 114.8 112.6 113.1	**113.2**	**0.81**
	n =6				

n: number of samples used for calculations.

17.4 **Accuracy and precision (Medium Level)**

Sextuplicates at the following concentration were prepared and analysed:

Amount added	Amount found		Accuracy	Mean Accuracy	Precision
ng/ml	ng/ml	Mean (ng/ml)	%	%	CV %
133.584	135.82 148.79 116.82 125.71 132.66 139.68	**133.247**	101.7 111.4 87.45 94.11 99.31 104.6	**99.75**	**8.33**
	n =6				

n: number of samples used for calculations.

17.5 **Accuracy and precision (Highest Level)**

Sextuplicates at the following concentration were prepared and analysed:

Amount added	Amount found		Accuracy	Mean Accuracy	Precision
ng/ml	ng/ml	Mean (ng/ml)	%	%	CV %
283.866	292.03 268.46 279.43 280.76 300.34 290.35	**285.23**	102.9 94.57 98.44 98.91 105.8 102.3	**100.5**	**3.95**
	n =6				

n: number of samples used for calculations.

17.6 **Accuracy and precision at LLOQ**

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Mean Accuracy	Precision
ng/ml	ng/ml	Mean (ng/ml)	%	%	CV %
10.0188	10.865 11.421 11.228 11.406 11.206 11.469	**11.266**	108.4 114.0 112.1 113.8 111.8 114.5	**112.4**	**1.99**
	n = 6				

n: number of samples used for calculations.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Analytical method and extention of validation report for toxicokinetic analysis of [redacted] Determination in Rat Plasma with LC-MS/MS detection

STUDY NO.: 27080

WARNING AND SAFETY PRECAUTIONS

SAFETY

Organic solvents - all organic solvents must be treated as potentially hazardous and all procedures using them must be performed in a fume cupboard.
[redacted]
Appropriate eye protection, impervious gloves and lab coat should be worn.
This method requires the use of corrosive and toxic reagents. It is the responsibility of the analyst to perform the method consistent with safe laboratory practices. The analyst should wear eye protection, impervious gloves, and a lab coat when preparing standards and processing samples. Caution statements have been included in the method giving specific guidance to certain procedural steps. Detailed hazard information should be obtained from the current MSDS available from the manufacturer of the solvent or reagent.

FIRST AID

Solvents, acids and alkalis in contact with skin - wash with copious amounts of cold water. Splashes in the eye - irrigate with water and seek medical attention immediately.
Cuts - seek assistance of first aid immediately.
Burns and frostbite - run affected part under cold water (burns) or tepid water (frostbite) for 10 minutes and seek medical attention.

INTRODUCTION

[redacted] is a product developed by the sponsor.

1. **SCOPE**
This method of analysis describes the analysis of [redacted] [redacted] (or simply [redacted] in rat plasma.

2. **FIELD OF APPLICATION**
The method is described to be used for [redacted] in rat plasma.
The range of application is from 10 ng/ml to 33000 ng/ml.

3. **REFERENCES**
ISO Standard 78/2-1982 Layout for standards - Part 2: Standard for Chemical Analysis.

4. **DEFINITIONS**
[redacted] content is taken to mean the amount of [redacted] in rat plasma determined according to the described method and expressed as mg of analyte per ml test sample.

5. **PRINCIPLE**

The method essentially consists of three steps:
- Sampling
- Precipitation
- Centrifugation
- Evaporation
- LC-MS/MS

6. **REACTIONS**

7. **REAGENTS AND MATERIALS**

Note: The reagents (and equipment) for which examples of their sources are quoted are known to be satisfactory, nevertheless reagents and equipment from other sources may be equally suitable. All the reagents must be of analytical grade or better.

7.1 Chemicals

7.1.1 Acetonitrile HPLC grade (Baker 9017)

7.1.2 Methanol HPLC grade (Baker 8402)

7.1.3 Water HPLC grade (produced by EASYPURE)

7.1.4 [redacted] (Batch n° 90156/96-2, Purity 99%), Reference Standard can be ordered from Solvay - Solexis. Throughout the study this reference Standard will be mentioned as [redacted]

7.1.5 Diclofenac Sodium SW (Batch DS 0005/075, purity 100%), Internal Reference Standard can be ordered from Sigma. Throughout the study this reference Standard will be mentioned as ISTD - DICLOFENAC.

7.2 Solutions

7.2.1 Mobile phase A: Acetonitrile

7.2.2 Mobile phase B: Water

7.3 Standard solutions

7.3.1 [redacted] STOCK A:
About 10 mg of [redacted] are transferred into a 50 volumetric flask and dissolved with water obtaining a concentration corrected for purity of 198 µg/ml solution. This solution needs to be mixed with a magnetic stirrer for 5 minutes.

7.3.2 SOL B:
1 mL of STOCK A is transferred into a 10 mL volumetric flask and diluted with water obtaining a 19.8 µg/ml solution for [redacted]

7.3.3 SOL 8:
2 mL of SOL B are transferred into a 20 mL volumetric flask and diluted with water obtaining a 1.98 µg/ml solution for [redacted]

7.3.4 SOL 1:
1.5 ml of SOL 8 are transferred into a 50 mL volumetric flask and diluted with water obtaining a 0.0594 µg/ml solution for [redacted]

7.3.5 STOCK ISTD:
About 25 mg of ISTD - DICLOFENAC are transferred into a 25 volumetric flask and dissolved with Methanol obtaining of 1000 µg/ml solution.

7.3.6 ISTD:
0.5 mL of STOCK ISTD are transferred into a 100 mL volumetric flask and diluted with Methanol obtaining a 5 µg/ml solution for ISTD - DICLOFENAC.

8. APPARATUS

Analytical balance	Mettler AT 261 Delta range
HPLC system	Agilent 1100 series
Detector	Applied BioSystems API2000 LC-MS/MS
Software	Analyst
Printer	HP Laser Jet 2200 Series PCL6
Column	Waters Atlantis C18 100 x 2.1 mm ID
Centrifuge	ALC 4236 A
Vortex	New ZX VELP
Heating Module	Pierce Reacti Therm III
HPLC microvials	
Eppendorf	
Volumetric pipettes	
Common glassware	

9. SAMPLING AND SAMPLES
Nature of the Sample; Samples shall be such as to enable the detection of residues in rat plasma.
Size of Sample; The size of the sample must be large enough to allow the method to be carried out and to allow repeat analysis where required.
The samples must be taken and packed in such a way as to allow proper identification in the laboratory.
The method of packing, preservation and transport must maintain the integrity of the sample and not prejudice the results of the examination. Samples for the analysis of [redacted] must be stored at temperature below -18°C.

10. PROCEDURE

10.1 Blank and unknown samples
The whole sample of rat plasma is centrifuged at 13000 rpm for 5 minutes.
300 µl of rat plasma are spiked with 10 µl ISTD and 50 µl of methanol, vortexed and then 900µL of Acetonitrile are added. Samples are vortexed. After centrifugation for 10 minutes at 14000 rpm, the supernatant is transferred in to 1.5mL Eppendorf. Samples are then evaporated up to about 100 µL under a gentle stream of Nitrogen at 40°C.
Sample are transferred into HPLC vials and analysed with LC-MS/MS.

10.2 **Calibration samples**

To 300 µl of rat plasma an adequate aliquot of working standard solution and 10 µl ISTD – DICLOFENAC (see table below) are added:

Samples are then processed as previously described.

The compounds concentration in matrix:

Name	Added	From solution	aliquot methanol addition	[redacted] concentration in matrix (ng/ml)	ISTD - DICLOFENAC Concentration (ng/ml)
Std 1	50 µl	SOL 1	-	≈9.90	≈167
Std 2	50 µl	SOL 8	-	330	≈167
Std 3	25 µl	SOL B	25 µl	≈1650	≈167
Std 4	50 µl	SOL B	-	≈3300	≈167
Std 5	10 µl	STOCK A	40 µl	≈6600	≈167
Std 6	20 µl	STOCK A	30 µl	≈13200	≈167
Std 7	35 µl	STOCK A	15 µl	≈23100	≈167
Std 8	50 µl	STOCK A	-	≈33000	≈167

10.3 **HPLC**

The following system is set up:

Column: Atlantis dC18 3 µm 2.1x100 mm
Autosampler: 4°C
Mobile phase:
Eluent A : Acetonitrile
Eluent B: Water

	Time (Min)	A%	B%	Flow (ml)
Equilibration	8.00	50.0	50.0	0.2
Run	1.00	50.0	50.0	0.2
	1.10	100.0	0.0	0.4
	6.00	100.0	0.0	0.4

Injection vol.: 40 µl
Run time: 6 minutes

10.4 **Mass parameters:**

Scan type: MRM
Polarity: Negative
[redacted]

Precursor Ion Q1 Mass (m/z)	Product Ion Q3 Mass (m/z)	Quantitation
240.0	181.60	Total Ion Current (TIC)
	113.00	
215.10	113.00	
228.90	113.00	
182.00	112.80	

Retention time: ≈2.0 min

ISTD – DICLOFENAC

Precursor Ion Q1 Mass (m/z)	Product Ion Q3 Mass (m/z)	Quantitation
294.10	250.0	Total Ion Current (TIC)

Retention time: ≈2.0 min

The LC-MS analysis is calibrated using the software Analyst which generates a linear fit calibration curve drawing the best fit of a line to the amounts and peak areas of standard. The software uses linear least-squares fit formula with a 1/X weighting. The result of the fitting is:
y = A + Bx
where
A = y-intercept of the calibration curve
B = Slope of the calibration curve
y = peak area
x = [redacted] amount in ng/ml
Unknown samples are injected after the LC-MS calibration. Results of the [redacted] amount in ng/ml are obtained directly from the LC/MS report. The result is calculated by the software as:

x = (y-A) / B

11. EXPRESSION OF RESULTS

[redacted] contents in ng/ml are obtained directly from the chromatogram result table as follows:
C = x
Where:
C = content of [redacted] as ng/ml
x = [redacted] amount in ng/ml as read in the chromatogram result table

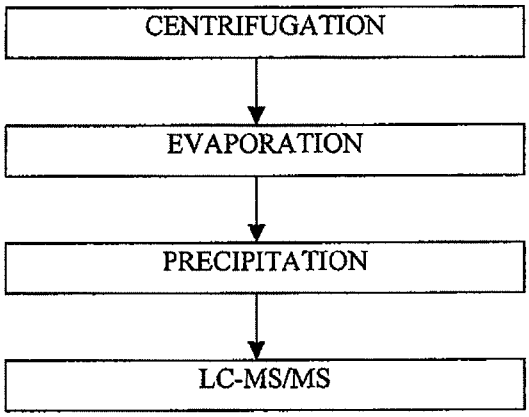
Individual data are reported in RTC Report no.: 27080

12. SPECIAL CASES

13. NOTES ON PROCEDURE

14. TEST REPORT

15. **SCHEMATIC REPRESENTATION OF PROCEDURE**



16. **BIBLIOGRAPHY**

17. **RESULTS VALIDATION**

17.1 [redacted] **Linearity**

Calibration samples in single at eight levels ranging from 10 ng/ml to 33000 ng/ml were processed as described in the analytical method. The following correlation was found:

Added ng/ml	Response (IS Analyte/ Analyte area)	Calculated Concentration (ng/mL)	Deviation %
10.0188	2.0947 e-001	11.285	12.6
333.960	7.5296 e+000	288.14	-13.7
1669.80	4.1948 e+001	1589.9	-4.78
3339.60	8.9953 e+001	3405.5	1.97
6679.20	1.8159 e+002	6871.3	2.88
13358.4	3.8058 e+002	14398	7.78
23377.2	5.5090 e+002	20839	-10.9
33396.0	9.1899 e+002	34761	4.09

Equation: Response = -0.0889 + 0.0264* [redacted] Conc.
r: 0.9974
Response type: area
Fit type: linear
Weighting: 1/X

17.2 **Selectivity**

No interfering peaks were present at the [redacted] retention times.

[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - [redacted] plasma levels (ng/ml) following oral administration of 8.0 mg/kg/day to female rats

STUDY NO.: 27080

Animal No.	Sampling times (hours post-dose)								
	0	2	4	6	8	24	48	96	168
27080061	BLQ		6224.8			10146.0			
27080063	BLQ		6889.4			7213.2			
27080065	BLQ		8364.2			15993.0			
27080067		4447.6			16780.0			3250.7	
27080069		3092.8			6786.1			3100.9	
27080071		3589.5			14597.0			3456.8	
27080073				8126.7			4553.4		3175.4
27080075				22565.0			7560.4		1825.7
27080077				17457.0			4116.3		1982.2
Mean*	0	3710	7159.5	16050	12721.0	11117.4	5410.0	3269.5	2327.8
SD	0	685.4	1095	7321	5254.4	4469.8	1875.0	178.7	738.2
CV%	0	18.47	15.29	45.62	41.30	40.21	34.66	5.47	31.71

* Estimated values since they were calculated with calibration curve ranging from 10.019 ng/mL to 333.96 ng/mL. In any case the linearity was successfully extended until 33396 ng/mL, but sample analysis was not repeated since no more additional aliquots were available.

BLQ = below the limit of quantitation

[redacted]4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - Toxicokinetic parameters

STUDY NO.: 27080

Dose level (mk/kg)	DAY 1				
	t_{max} (h)	C_{max} (ng/ml)	T ½ (h)	*$AUC_{(6\text{-}168)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
8.0	6	16050.0	58.72	850628.9	1047825.4

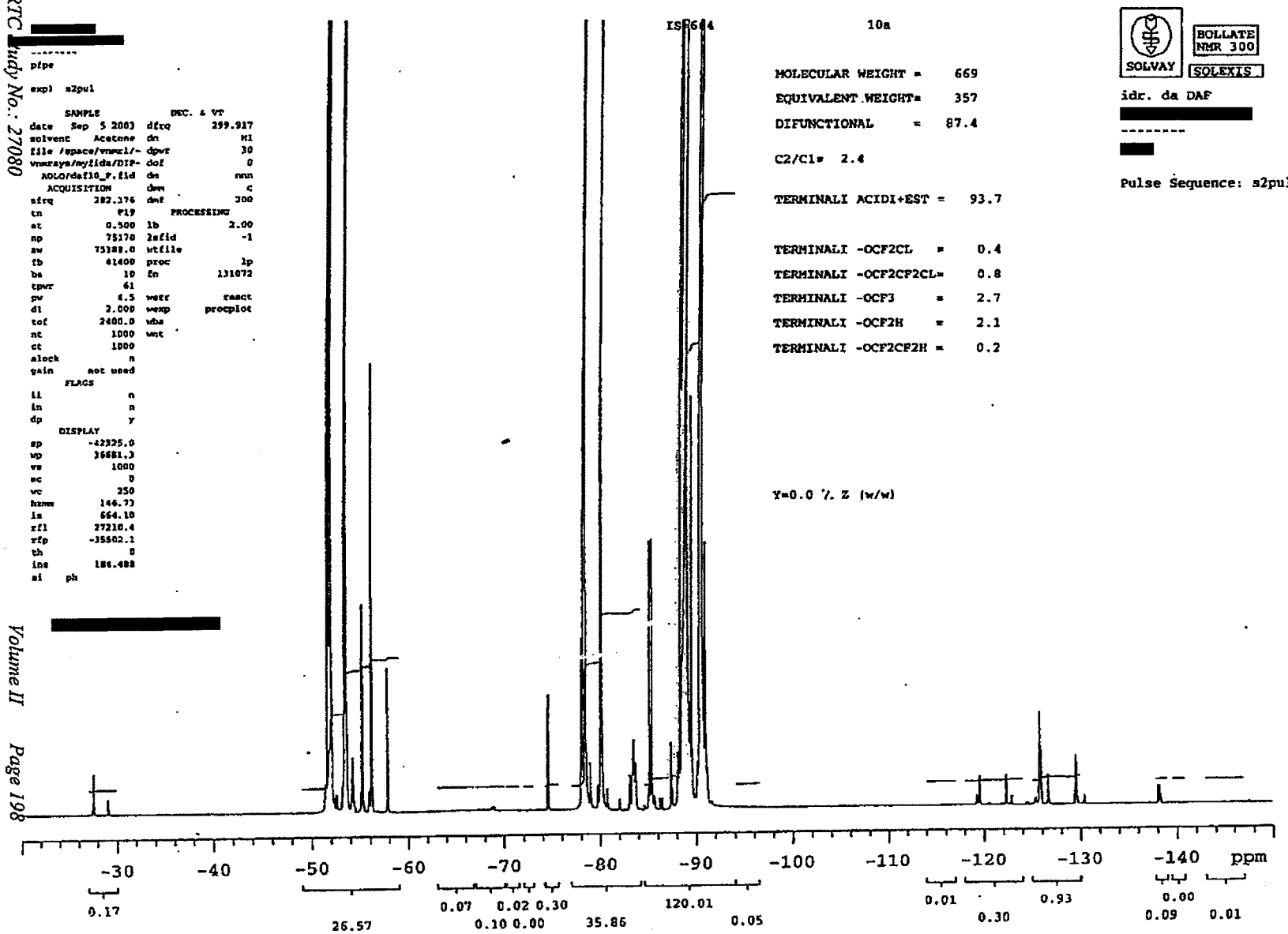
* Calculated from t_{max} (6 hours).

[redacted]4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM V - Certificate of analysis

STUDY NO.: 27080

[redacted]



[redacted]

[redacted] idr. da DAF

[redacted]

IS=66410

SOLVAY BOLLATE NMR 300 SOLEXIS

idr. da DAF

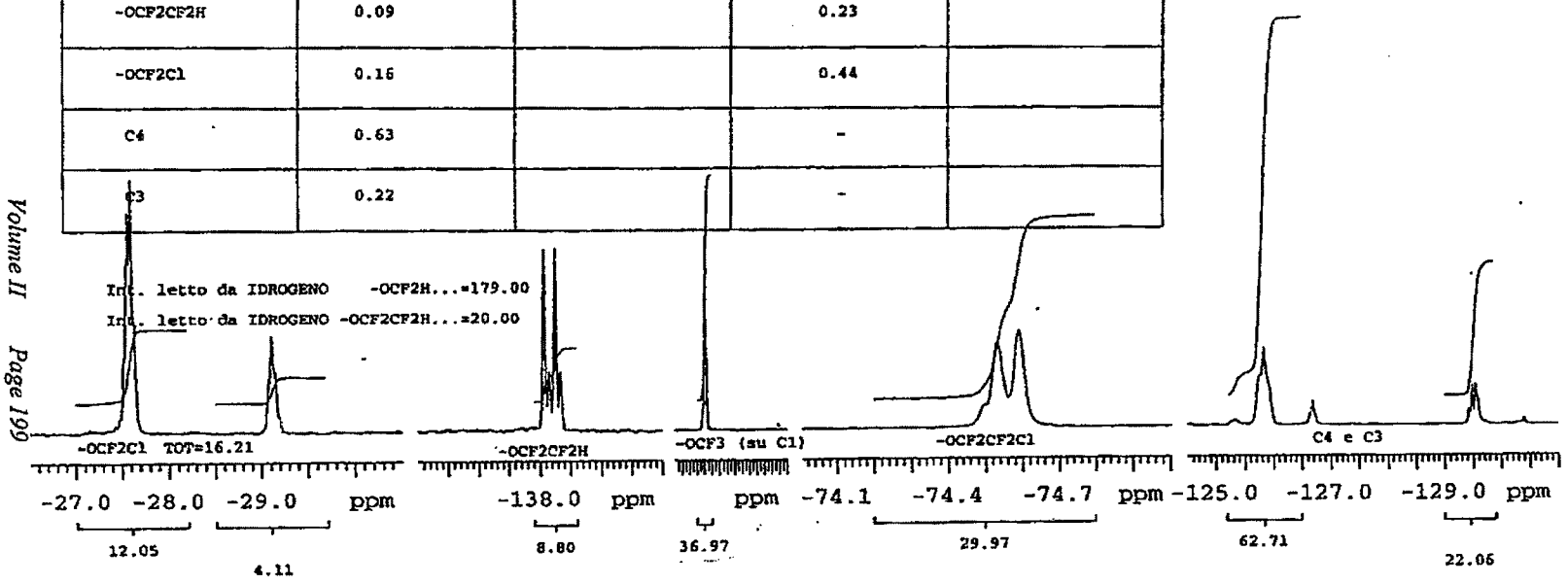
[redacted]

Pulse Sequence: s2pul

IS x 100

Pulse Sequence: s2pul	INT letto MAGIC '	INT misurato	DISTR. TERM MAGIC	DISTR. TERM. PC
C1	25.00		-	
C2	118.45		-	
-OCF3	1.02		2.75	
-OCF2CF2Cl	0.30		0.81	
TERMINALE 1	34.73		93.68	
TERMINALE 2	0.00		0.00	
-OCF2H	0.77		2.09	
-OCF2CF2H	0.09		0.23	
-OCF2Cl	0.16		0.44	
C4	0.63		-	
C3	0.22		-	

MOLECOLAR WEIGHT= 669
EQUIVALENT WEIGHT= 357
DIFUNZIONALE= 87.4
C2/C1= 2.4



[redacted]4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM VI - Study protocol and protocol amendment

STUDY NO.: 27080

RESEARCH TOXICOLOGY CENTRE - ROMA

[redacted]

4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Final Protocol
prepared for

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

by

RESEARCH TOXICOLOGY CENTRE S.p.A.
Via Tito Speri, 12
00040 Pomezia (Rome)
Italy

RTC Enquiry Number: 27080

April 2004

Commercial Office

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RTC S.p.A.
Capitale sociale Euro 5.154.000
C.C.I.A.A. n° 375376
Reg. Soc. Trib. di Roma n° 2828/72
Cod. Fisc.: 00653120584
Partita IVA: 00920611001

1. INTRODUCTION

1.1 Objective

The purpose of this study is to evaluate the toxicity of [redacted] in rats after daily oral administration for 4 weeks and recovery from any treatment related effects during a recovery period of 2 weeks.

1.2 Species

The Sprague Dawley 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 by oral route. 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 will be conducted in compliance with the GLP regulations of:

- Commission Directive 1999/11/EC of 8 March 1999 (adoption of the "OECD principles on Good Laboratory Practice - as revised in 1997") and subsequent revisions.
- Decreto Legislativo no. 120 of 27 January 1992 and subsequent revisions.

This study design is in agreement with the procedures described in OECD Guideline no. 407 adopted 27 July 1995 and with those described by Japanese METI (Ministry of Economy, Trade and Industry) of 13 July 1974 and subsequent revisions.

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 Legislativo No. 116 of 27 January 1992. Aspects of the protocol concerning animal welfare have been approved by the Company'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	:	90156/96-2
Purity	:	>99%
Appearance	:	White granules
Storage conditions	:	Ambient temperature, away from direct sunlight

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 the 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 in the vehicle. The formulations will be prepared daily (concentrations of 0.05, 0.25 and 0.8 mg/ml). Concentrations will be calculated and expressed in terms of test item as supplied.

2.6 Formulation analysis

Analysis will be performed to confirm that the proposed formulation procedure is acceptable and the stability of formulation is satisfactory.
Samples of the formulations prepared in weeks 1 and 4 of the study will also be analysed to check the concentration. Chemical analysis will be carried out by the Analytical Chemistry Department at RTC (additional cost).

2.7 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 returned to the Sponsor.

3. TEST SYSTEM

3.1 Animal supply and acclimatisation

A total of 80 Hsd Sprague Dawley rats (35 males and 45 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 rats 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 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 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, except as noted in section 4.3.
A commercially available laboratory rodent diet (Altromin MT pelleted diet, Altromin, Lange Str. 42, D-3279 Lage, Germany or 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 noted 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 5 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 up to 5 of one sex per cage.
The cages will be identified by a label and recording the study number, animal numbers and details of treatment.
The arrangement of cages in 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 based on information from preliminary studies.

4.1.2 Dose levels, group size and identification

Each main group will comprise 5 male and 5 female rats. Control and high dose groups will include 5 additional animals per sex to be sacrificed after 2 weeks of recovery. One satellite group for toxicokinetics will comprise 9 female animals. The group identification and animal numbers assigned to the treatment are summarised below:

MAIN GROUPS

Group Number:	Treatment (mg/kg/day)+	Level	Main phase		Rat numbers Recovery phase	
			M (even)	F (odd)	M (even)	F (odd)
1	0.0	Control	2 – 10	1 – 9	12 – 20	11 – 19
2	0.5	Low	22 – 30	21 – 29		
3	2.5	Medium	32 – 40	31 – 39		
4	8.0	High	42 – 50	41 – 49	52 – 60	51 – 59
+: in terms of test item as supplied						

SATELLITE GROUP

Group Number:	Treatment (mg/kg)	Level	Rat numbers Females (odd)
5	8.0	High	61 - 77

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).

4.1.3 Administration of test item

The test item will be administered orally, by gavage, at a dose volume of 10 ml/kg body weight. 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 main group animals will be dosed once a day, 7 days a week, for a minimum of 4 consecutive weeks followed by a recovery period of 2 weeks for 5 males and 5 females from groups 1 and 4. Satellite group animals will be dosed once only, during week 4 of the study.
All animals from the main groups will be dosed up until the day before necropsy.
No treatment will be given during the recovery period.

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 early in the morning and 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 in all cases as detailed in section 5.4.2 below.

4.2.2 Pre- and post-dose observations (Main groups)

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 and at suitable intervals after dosing. The number and timing of these daily observations will be reviewed by the Study Director at the end of the first week of treatment and, if appropriate, at subsequent intervals. The number of observations may be reduced, but all animals will be observed at least three times daily during treatment. If more than three daily observations are required after the first week of treatment, an additional cost may be incurred.

4.2.3 Clinical signs and neurotoxicity assessment (Main groups)

Once before commencement of treatment and at least once per week from the start of treatment, each animal will be given a detailed clinical examination. Each animal will be observed in an open arena. The test will include observation of changes in gait and posture, reactivity to handling, presence of clonic or tonic movements, stereotypies or bizarre behaviour and effects on the autonomic nervous system (e.g. lachrymation, piloerection, pupil size, unusual respiratory pattern).

Once during week 4 of treatment and once during week 2 of recovery an evaluation of sensory reactivity to stimuli of different modalities (e.g. auditory, visual and proprioceptive stimuli) and an assessment of grip strength will also be performed.

4.2.4 Motor activity assessment (MA) (Main groups)

The motor activity (MA) of all animals will be measured once during week 4 of treatment and once during week 2 of recovery by an automated activity recording. Measurements will be performed using a computer generated random order.

4.2.5 Body weight

Each animal will be weighed on the day of allocation to treatment groups, on the day that treatment commences, weekly thereafter and just prior to necropsy. Satellite group animals will be weighed only on the day of dosing.

4.2.6 Food consumption (Main groups)

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 (Main groups)

During week 4 of treatment, samples of blood will be withdrawn under light ether anaesthesia from the retro-orbital sinus of all surviving male and female rats from each group, under conditions of food and water deprivation. At the same time interval individual overnight urine samples will also be collected from the same animals under the same conditions. Before starting urine collection, water bottles will be removed from each cage and each animal will receive approximately 10 ml/kg of drinking water by gavage, in order to obtain urine samples suitable for analysis.
During week 2 of the recovery period blood and urine samples may also be taken (after consultation with the Sponsor) from all surviving animals under identical conditions in order to re-evaluate any parameters which showed treatment-related changes at measurements performed during the treatment period (additional cost).
Blood samples will be collected and analysed in the same order, a computer-generated random cage order being used.

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 tests

The measurements to be performed on blood and urine 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
Gamma -glutamyltransferase
Urea
Creatinine
Glucose
Triglycerides
Phosphorus
Total bilirubin
Total cholesterol
Total protein
Albumin
Globulin
A/G Ratio
Sodium
Potassium
Calcium
Chloride

4.3.3 Urinalysis

Appearance
Volume
Specific gravity
PH
Protein
Total reducing substances
Glucose
Ketones
Bilirubin
Urobilinogen
Blood

The sediment, obtained from centrifugation at approximately 3000 rpm for 10 minutes, will be examined microscopically for:

Epithelial cells
Poly morphonuclear leucocytes
Erythrocytes
Crystals
Spermatozoa and precursors
Other abnormal components

4.4 Toxicokinetics (Satellite group)

Blood samples will be collected at 9 points on the day of dosing from all animals of the satellite group as indicated in following scheme:

Group Number:	Treatment (mg/kg)	Animal Number (Males)	Time points (hours)
5	8.0	61 ,63, 65 67, 69, 71 73, 75, 77	0, 4, 24 2, 8, 96 6, 48, 168

At each sampling time approximately 0.8 ml blood samples will be collected from the tail vein of each animal as indicated above. Samples will be transferred into tubes containing heparin anticoagulant, centrifuged and the plasma frozen at –20°C. Analysis of the samples will be carried out by the Analytical Chemistry Department of RTC (additional cost).
Satellite group animals will be dosed once only and no necropsy will be performed on animals dying during the study or sacrificed at the end of the study. Surviving satellite group animals will be killed at the end of the last bleeding procedure. No necropsy examination will be performed in these animals.

5.4 Terminal studies

5.4.1 Euthanasia

Animals *in extremis* or killed for humane reasons and those that have completed the scheduled test period will be killed with carbon dioxide. All animals of the main groups, including those found dead, will be subjected to necropsy, supervised by a pathologist, as detailed below.

5.4.2 Necropsy (Main groups)

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 5.4.3 to 5.4.5).

5.4.3 Organ weights (Main groups)

From all animals completing the scheduled test period, the organs indicated in Annex 1 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.

5.4.4 Tissues fixed and preserved (Main groups)

Samples of all the tissues listed in Annex 1 will be fixed and preserved in 10% buffered formol saline (except eyes which will be fixed in Davidson's fluid; and testes and epididymides which will be fixed in Bouin's solution and all preserved in 70% ethyl alcohol). An extra liver sample will be taken from all main group animals and frozen at −80°C (see section 5.4.6).

5.4.5 Histopathological examination

The tissues required for histopathological examination are listed in Annex 1. After dehydration and embedding in paraffin wax, sections of the tissues will be cut at 5 micrometre thickness and stained with haematoxylin and eosin.
If considered necessary, histological processing may be subcontracted to a GLP certified test site. In such cases, a protocol amendment will be issued; the Sponsor will be informed of the location of the test site and the complete address and name of the Principal Investigator will be presented in the final report.

In the first instance the examination will be restricted as detailed below:

a) Tissues specified in Annex 1 from all animals in the control and high dose group killed after 4 weeks of treatment.
b) Tissues specified in Annex 1 from all animals killed or dying during the treatment period
c) All abnormalities in all main groups

The examination could then be extended to include, from all other animals killed after 4 weeks of treatment or 2 weeks of recovery those tissues in which there is any suspicion of treatment-related change at the high dose level.
All histopathological activities which cannot be foreseen before the start of the study (i.e. processing of all abnormalities, tissues of unscheduled deaths in the low, medium dose and recovery groups, target tissues in the low, medium dose and liver enzymes for the evaluation of hepatic peroxisome proliferation) will incur an additional cost.

5.4.6 Liver enzymes (Main groups , if required)

Following removal of liver sections for histopathological examination, all remaining tissue (at least 4 g in the first instance preferably taken from the left lateral lobe) will be rinsed in ice-cold physiological saline then placed into individual packages (one per animal) and immediately frozen in liquid nitrogen (-80°C). In cases of changes in the liver noted at histopathological examination, the liver samples taken for enzyme analysis will be transported frozen on dry ice to:

BIBRA International
Woodmansterne Road
Carshalton, Surrey SM5 4DS
United Kingdom
Tel: +44 (0)181-652 1000
Fax: +44 (0)181-661 7029

In the first instance only samples from control and high dose groups will be examined. The determination of cyanide-insensitive palmitoyl-CoA oxidation and catalase activity will be done for the evaluation of hepatic peroxisome proliferation. These tests will be undertaken and interpreted by the test Site indicated above under the responsibility of the Principal Investigator, Brian G. Lake. A Q.A.U. revised report will be returned to RTC for inclusion in the Final Report.

5.4.7 Photomicrographs

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

6. ANALYSIS OF DATA

6.1 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.

6.2 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.

7. 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 retain the right to take independent action.

8. REPORTING

8.1 Interim report

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

8.2 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.

8.3 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.

9. 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 may 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.
If relevant, biological samples obtained for analytical chemistry measurements or similar will be destroyed shortly after the issue of the Final Report, unless otherwise requested by the Sponsor.

All specimens other than the samples described above, raw data, records and documentation generated during the course of this study will be retained at RTC. Archiving will be provided for a period of 3 years after which the Sponsor will be contacted for instructions regarding despatch or disposal of the material. As a further option, archiving space can be rented for an additional time.
All raw data, records and documentation generated at the # and # test sites will be archived there under the Principal Investigator responsibility.

10. TEST FACILITY

10.1 Test site location

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

Study Director:	Cristina Longobardi
Study phases:	all stages of the study, with the exception of those detailed below for the other Test Site(s).

BIBRA International
Woodmansterne Road
Carshalton, Surrey SM5 4DS
United Kingdom
Tel: +44 (0)181-652 1000
Fax: +44 (0)181-661 7029

Principal Investigator:	Brian G. Lake
Delegated phases:	enzymatic analyses, interpretation of data and production of a final report

10.2 Lead QA

Research Toxicology Centre S.p.A.
Via Tito Speri, 12
00040 Pomezia (Rome)
Italy
Head of QAU: M.M. Brunetti

10.3 Interactions between the test sites

All information/documentation between the test sites will be circulated to/through the Study Director/Principal Investigator(s). Details regarding delegated activities, timing and associated responsibilities will be clearly defined in a separate, written agreement between Study Director and Principal Investigator(s).

11. QUALITY ASSURANCE

The phases of the study carried out at RTC will be subjected to the following quality assurance procedures:

- the protocol will be inspected.
- all procedures relevant to the study will be inspected at intervals adequate to assure the integrity of the study.
- the report will be reviewed to assure that it accurately describes the methods and Standard Operating Procedures and that the results accurately reflect the raw data.

Periodic reports on these activities will be made to management and the Study Director.
All raw data pertaining to the study will be available for inspection by the Sponsor's representative and regulatory authorities (following authorisation from the Sponsor).

12. PROJECTED TIME PLAN

		Date
1.	Start of treatment	: First half of May 2004
2.	End of *in vivo* phase	: Second half of June 2004
3.	End of histopathological examination	: Second half of July 2004
4.	QAU audited draft report to Sponsor	: 3.5 months after the first day 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	✓	✓	✓
Eyes		✓	*
Heart	✓	✓	✓
Ileum (including Peyer's patches)		✓	✓
Jejunum		✓	✓
Kidneys	✓	✓	✓
Liver	✓	✓	✓
Lungs (including mainstem bronchi)		✓	✓
Lymph nodes - cervical		✓	✓
Lymph nodes - mesenteric		✓	✓
Ovaries	✓	✓	✓
Oviducts[a]		✓	✓
Parathyroid glands[b]		✓	✓
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		✓	✓

*: to be examined if indicated by signs of toxicity or target organ involvement.

a: weighed and preserved with ovaries

b: weighed and preserved with thyroid gland

ANNEX 2. GROUP AND CAGE ARRANGEMENT ON BATTERY

MAIN PHASE

Group Number:	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
1	0.0	Control	2 – 10	1 – 9	1	7
2	0.5	Low	22 – 30	21 – 29	3	9
3	2.5	Medium	32 – 40	31 – 39	4	10
4	8.0	High	42 – 50	41 – 49	5	11

RECOVERY PHASE

Group Number:	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
1	0.0	Control	12 – 20	11 – 19	2	8
4	8.0	High	52 – 60	51 – 59	6	12

+: in terms of test item as supplied
° No treatment will be given during the recovery period.

SATELLITE GROUP

Group Number:	Treatment (mg/kg)+	Level	Rat numbers Females (odd)	Cage numbers
5	8.0	High	61 - 77	13-15

+: in terms of test item as supplied
° No treatment will be given during the recovery period.

Group/Sex
Cage no.

#

To be inserted in the final report

PROTOCOL APPROVAL PAGE

STUDY TITLE : 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD.

TEST FACILITY : RESEARCH TOXICOLOGY CENTRE S.p.A.
Via Tito Speri, 12
00040 Pomezia (Rome)
Italy

RTC ENQUIRY NO. : 27080

TEST ITEM : [redacted]

APPROVED BY : _____ 07-04-2004
C. Longobardi, Biol. D. Date
Study Director

APPROVED BY : _____ 07.04.2004
L. Luperi, D.V.M. Date
Responsible for Animal Welfare

RELEASED BY : _____ 7 Apr 2004
J. Brightwell, Ph.D. Date
Scientific Director

SPONSOR : SOLVAY SOLEXIS S.p.A.
Via Lombardia, 20
20121 Bollate (MI)
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AUTHORISED BY SPONSOR* : _____ 14/04/2004
Date

Name and Title : ILARIA COLOMBO INDUSTRIAL TOXICOLOGY

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RESEARCH TOXICOLOGY CENTRE - ROMA

PROTOCOL AMENDMENT (1)

STUDY TITLE	:	[redacted] 4 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD
STUDY NO.	:	27080
DATE OF PROTOCOL APPROVAL	:	7 April 2005
DATE OF ISSUE OF AMENDMENT	:	Date signed

THE FOLLOWING SECTION IS TO BE AMENDED:

Section 2.2 Identity (Page 3)

Delete	:	Purity: > 99%
Insert	:	Purity: > 85% (referred to dicarboxy chain ends perfluoropolyethers).
Reason	:	Incorrect in the study protocol.

RTC Study Number: 27080

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Cod. Fisc. 00853120584
Partita IVA: 00920611001

PROTOCOL AMENDMENT (1)

APPROVAL PAGE

STUDY TITLE : 4 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY A 2 WEEK RECOVERY PERIOD

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RTC STUDY NO. : 27080

TEST ITEM : [redacted]

APPROVED BY : Cinzia Longobardi — 13-Jun-2005
C. Longobardi, Biol. D. — Date
Study Director

RELEASED BY : J. Brightwell — 13 Jun 2005
J. Brightwell, Ph.D. — Date
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