



**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

FINAL REPORT

VOLUME I OF II

RTC Study no.: 41950

Sponsor

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**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

RTC Study no.: 41950

FINAL REPORT

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

C. Longobardi, Biol. D. *Giorgia Lepore* Date *12 - Jul - 2006*
(Study Director)

R. A. Manno, Biol. D. *R. A. Manno* Date *12 July 2006*
(Study Pathologist)

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. With the exception of the historical control data, that were not revised by Q.A., all the other 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).*

Study phases delegated to external site(s) were performed under the supervision of designated Principal Investigator(s). These parts of the study were performed in compliance with OECD Principles of Good Laboratory Practice and UK Principles of Good Laboratory Practice (The United Kingdom GLP Regulations 1999).

The related GLP Statement(s) is(are) included in this study report.

C. Longobardi, Biol. D.


(Study Director)

Date 12-Jul-2006

J. Brightwell, Ph. D.


(Scientific Director)

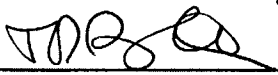
Date 12 Jul 2006

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	<u>Quality Assurance Inspections</u> (Day Month Year)		
	Inspection	Report to Study Director	Report to Company Management
PROTOCOL CHECK	07.04.2005	07.04.2005	07.04.2005
PROTOCOL AMENDMENT (1) CHECK	16.08.2005	17.08.2005	17.08.2005
PROTOCOL AMENDMENT (2) CHECK	16.08.2005	17.08.2005	17.08.2005
PROTOCOL AMENDMENT (3) CHECK	12.09.2005	12.09.2005	12.09.2205
PROTOCOL AMENDMENT (4) CHECK	05.10.2005	05.10.2005	05.10.2005
PROTOCOL AMENDMENT (5) CHECK	26.10.2005	27.10.2005	27.10.2005
PROTOCOL AMENDMENT (6) CHECK	02.12.2005	05.12.2005	05.12.2005
STUDY BASED INSPECTIONS RELATED TO THIS STUDY			
Dose preparation	14.04.2005	14.04.2005	14.04.2005
Dosing (oral)	13.04.2005	01.06.2005	09.06.2005
Pre post dose observation	13.04.2005	01.06.2005	09.06.2005
Body weight	04.05.2005	29.06.2005	06.07.2005
Food consumption	18.05.2005	01.07.2005	06.07.2005
Clinical observations	09.06.2005	06.07.2005	13.07.2005
Functional observation battery	09.06.2005	06.07.2005	13.07.2005
Motor activity	04.07.2005	01.08.2005	04.08.2005
Sensory reactivity to stimuli	05.07.2005	21.07.2005	21.07.2005
Blood sampling	11.07.2005	01.08.2005	04.08.2005
Urine collection	11.07.2005	13.07.2005	13.07.2005
Timed bleed	31.05.2005	29.06.2005	06.07.2005
Timed urine/faecas collection	31.05.2005	08.07.2005	13.07.2005
Despatch to necropsy	13.07.2005	01.08.2005	04.08.2005
Bleed at necropsy	13.07.2005	15.07.2005	04.08.2005
Liver collection	13.07.2005	15.07.2005	04.08.2005
Necropsy	13.07.2005	15.07.2005	04.08.2005
Necropsy	08.09.2005	05.10.2005	18.10.2005
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.			

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

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 12 July 2006



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

12 July 2006

Date

Study phases delegated to external sites were performed under the supervision of designated Principal Investigator(s). The related QA Statement(s) is (are) included in this report.

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GLP COMPLIANCE STATEMENT FOR HISTOLOGY

AT PROPATH UK LIMITED

STUDY/PROJECT NUMBER: 41950

DATE: 12 September 2005

I, the undersigned, accept responsibility for the validity of the Histology phase of this study and confirm that it was conducted in compliance with the UK Principles of Good Laboratory Practice (The United Kingdom GLP Regulations 1999), Statutory Instrument No. 3106 as amended by the Good Laboratory Practice (Codification Amendment Etc) Regulations 2004 Statutory Instrument No. 994. These are in accordance with the Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (1997) (ENV/MC/CHEM (98) 17)

PRINCIPAL INVESTIGATOR

Mr T Hilling
Laboratory Manager



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Audit Date: 06 June 2005

Reported to
Propath management: 09 June 2005

Scope: Histology laboratory facilities and procedures were inspected for compliance with the requirements of the OECD Principles of Good Laboratory Practice 1997 Revision (ENV/MC/CHEM(98)17) and the United Kingdom GLP Regulations 1999, Statutory Instrument No. 3106 as amended by the Good Laboratory Practice (Codification Amendment Etc) Regulations 2004 Statutory Instrument No. 994.

Signed: *anne fox*

Date: 09 June 2005

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GLP COMPLIANCE STATEMENT FOR HISTOLOGY

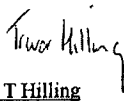
AT PROPATH UK LIMITED

STUDY/PROJECT NUMBER: 41950 (Additional Work Request)

DATE: 25 January 2006

I, the undersigned, accept responsibility for the validity of the Histology phase of this study and confirm that it was conducted in compliance with the UK Principles of Good Laboratory Practice (The United Kingdom GLP Regulations 1999) which are in accordance with the Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (1997) (ENV/MC/CHEM (98) 17)

PRINCIPAL INVESTIGATOR


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Audit Date: 31 August 2005

Reported to
Propath management: 01 September 2005

Scope: Histology laboratory facilities and procedures were inspected for compliance with the requirements of the OECD Principles of Good Laboratory Practice 1997 Revision (ENV/MC/CHEM(98)17) and the United Kingdom GLP Regulations 1999, Statutory Instrument No. 3106 as amended by the Good Laboratory Practice (Codification Amendment Etc) Regulations 2004 Statutory Instrument No. 994.

Signed: *any*

Date: 01 Sept 05

Anne Fox
AF International Consultancy

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1. SUMMARY

1.1 The oral toxicity of [REDACTED] when given by daily administration to rats, has been investigated over a period of 13 consecutive weeks and recovery from any potential treatment-related effects over a period of 8 consecutive weeks. Three groups, each of 10 male and 10 female Sprague Dawley rats, received the test item by gavage at dosages of 0.03, 0.13 and 0.5 mg/kg/day for 13 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 males, dosed at 0.5 mg/kg/day, for toxicokinetic evaluations.

1.2 Mortality

No mortality occurred during the study.

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

No reaction to treatment was seen at daily post-dose examinations.

Detailed clinical signs with neurotoxicity assessment did generally not show any signs which could be correlated to the treatment with the test item.

No toxicological importance was attributed to the small masses observed on the perigenital or mammary area in some animals from all treated and control groups (mainly in the males). These latter data are not tabulated in the report among the clinical signs.

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 clearly attributable to the test item.

1.5 Body weight

Body weights were slightly statistically significantly reduced in the high dose males on days 85 and 92 and in the high dose females from day 78 of the treatment period when compared to controls. These slight reductions were no longer evident up to the end of the recovery period.

1.6 Food consumption

No significant changes were observed in food consumption.

1.7 Ophthalmoscopy

No significant findings were seen at the ophthalmic examination.

1.8 Haematology

Very slight reductions of red blood cell count, haemoglobin and haematocrit were observed in the males receiving 0.13 and 0.5 mg/kg/day in a dose related trend.

The statistically significant changes of neutrophils and lymphocytes count observed in some females receiving 0.03 mg/kg/day were considered to be incidental.

The reductions observed during the dosing phase showed a complete recovery after the 8 week treatment-free period.

1.9 Clinical chemistry

Alkaline phosphatase was increased in 0.13 and 0.5 mg/kg/day animals when compared to controls. Increments were dose related.

Animals receiving 0.5 mg/kg/day showed slight but statistically significant changes in alanine aminotransferase, total bilirubin, cholesterol, urea, triglycerides, creatinine, protein, albumin, globulin, chloride and calcium. On some occasions some of these changes were observed in animals receiving 0.13 mg/kg/day.

At the end of the treatment-free period, some parameters which were altered in the dosing phase analyses, showed a trend for recovery while most of them had completely recovered.

No recovery was observed for alkaline phosphatase, triglycerides and urea levels, which remained higher when compared to controls.

1.10 Urinalysis

Urine specific gravity was slightly increased in a number of males treated with 0.5 mg/kg/day and pH was slightly reduced in the same group animals.

In addition, animal No. 90 had a concentration of glucose, bilirubin and urobilinogen higher than controls.

The slight changes observed during the dosing phase were no longer observed at the end of the recovery period.

1.11 Toxicokinetic analysis

Detectable plasma levels of the test item were measured between 2 and 168 hours after single dosing in the male animals of the satellite group dosed at 0.5 mg/kg. The maximum plasma level (C_{max}) was 580 ng/ml. C_{max} was measured 24 hours after dosing (t_{max}). A half-life ($t_{1/2}$) of approximately 1037 hours was estimated. The $AUC_{(24-168h)}$ was calculated to be 84686 ng/ml·h and the $AUC_{(inf)}$ was calculated to be 830571 ng/ml·h. Analysis of plasma levels in males and females treated for 13 weeks showed an increase of plasma levels of [REDACTED] of approximately 100 folds at the end of the 13 week treatment period. Reductions of approximately 45% and 35% were seen in plasma samples obtained after 7 days of recovery.

1.12 Organ weights

Dose-related, statistically significant increases in absolute and relative liver weights were noted in the animals dosed at 0.13 and 0.5 mg/kg/day at the end of the treatment period. This increase, although slightly reduced, was still present at the end of the recovery period. Statistically significant increase of the weight of the kidneys was seen in the animals dosed at 0.5 mg/kg/day at the end of treatment. This change was no longer present at the end of recovery. In addition, statistically significant reductions of spleen, testes, thymus and adrenals absolute weights were observed in the males dosed at 0.13 and 0.5 mg/kg/day. None of these changes were still present at the end of recovery.

1.13 Liver enzymes

Marked increases in mean cyanyde-insesitive palmitoyl CoA oxidase activity were observed in both sexes animals treated with the test item. Increases were generally dose-related, being approximately 11-times the mean control activities in the males and approximately 9-times control activities in the females receiving 0.5 mg/kg/day (activities expressed per mg protein).

In males and females, mean activities were statistically significantly different from control values at the mid- and high dose groups. Mean 3,000 x g supernatant protein concentrations

(mg/g liver) were statistically significantly increased in animals treated at 0.5 mg/kg/day. However, the protein concentrations of female rats dosed at 0.03 and 0.13 mg/kg/day were statistically significantly reduced.

Following an 8-week recovery period, the level of increase in the cyanide-insensitive palmitoyl CoA oxidase activity of male rats was reduced from approximately 11-times the mean control activities to approximately 5-times. In the female, the degree of reduction was less, with the activities being reduced from approximately 9- or 11-times to approximately 5-6-times the mean control activities, when related to mg protein or g liver, respectively.

1.14 Macroscopic observations

No relevant changes were observed at *post mortem* examination in the treated animals when compared with controls, either in animals killed at termination or after 8 weeks of recovery period.

1.15 Microscopic observations

Treatment-related changes were seen in the liver and lungs of treated animals receiving ≥ 0.13 mg/kg/day, when compared with controls and are summarised as follows:

Liver: hepatocytic hypertrophy was seen in 9/10 males and 9/10 females receiving 0.5 mg/kg/day. This change was also seen in 2/10 animals, both sexes, receiving 0.13 mg/kg/day. In addition, slight yellow/brown pigmentation was seen in the Kupffer's cells and occasionally in the hepatocytes of 2/10 females dosed at ≥ 0.13 mg/kg/day, in 1/10 females receiving 0.03 mg/kg/day and in 1/10 male dosed at 0.5 mg/kg/day.

Lungs: changes suggestive of phospholipidosis, represented by alveolar foamy macrophages, associated with interstitial inflammatory cell infiltrate, showed an increased incidence in the females receiving ≥ 0.13 mg/kg/day, when compared with controls.

Treatment-related changes were still present in the liver and lungs of treated animals, killed after 8 weeks of recovery period, when compared with controls.

Liver: hepatocytic hypertrophy was seen in the majority of treated animals; slight yellow/brown pigmentation was still observed in 2/5 treated females;

Lungs: alveolar foamy macrophages were clearly seen in treated males and females.

No toxicological significance was attributed to other findings observed in the stomach, spleen or uterus of individual animals from different dose groups.

The remaining lesions were considered to be an expression of spontaneous pathology, commonly seen in this species under our experimental conditions.

1.16 Conclusion

A treatment-related effect of the test item was seen at the 2 higher dose levels investigated (0.13 and 0.5 mg/kg/day). This effect was demonstrated by changes in clinical pathology parameters and *post mortem* examinations. A main target organ, the liver, was identified on the basis of the organ weights data and histopathological findings. In addition, the evaluation of the activity of cyanide-insensitive palmitoyl CoA oxidase, suggested that the test item acts as a strong peroxisome proliferator. A second target organ of the test item appeared to be the lungs. The above effects showed a dose-related trend and appeared to be only partially reversible after the 8-week recovery period. No significant effects were observed at the low dose level (0.03 mg/kg/day). Therefore, the dose level of 0.03 mg/kg/day, when administered daily for 13 consecutive weeks to both rat sexes, 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 13 consecutive weeks, and to investigate possible recovery from any treatment-related effects, during an 8 week recovery period.

The study design was in agreement with the procedures described in OECD Guideline No. 408 'Repeated Dose 90-day Oral Toxicity Study in Rodents' adopted 21 September 1998.

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 0.03, 0.13 and 0.5 mg/kg/day were defined in agreement with the Sponsor based on information from previous studies.

Each main group comprised 10 male and 10 female rats. Control and high dose groups included 5 additional animals per sex that were killed after 8 weeks of recovery. One satellite group for toxicokinetics comprised 9 male animals.

No treatment was given during the recovery period.

The animals were assigned to treatment groups on 7 April 2005 and dosing began on 13 April 2005. Necropsies of main phase animals were completed by 14 July 2005 and recovery groups by 8 September 2005.

The protocol and protocol amendments are presented in Addendum IX.

The study was carried out at:

Research Toxicology Centre S.p.A.
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00040 Pomezia (Rome)
Italy

Study Director: C. Longobardi

All stages of this study, with the exception of that detailed for the other Test Site.

Test Sites:

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Huntingdon Research Centre
Huntingdon
Cambridgeshire
PE28 4HS
UK
Department of *In Vitro* Metabolism

Principal Investigator: Anne Matthews

Delegated phases: Liver enzymes

Liver enzymes start date: 8 August 2005

Liver enzymes finish date: 25 November 2005

Propath UK Ltd
Willow Court, Netherwood Road
Hereford, HR2 6JU
England

Principal Investigator: Trevor Hilling
Delegated phase: Histological processing
Histological processing start date: 26 July 2005
Histological processing finish date: 6 September 2005
Additional histological processing start date: 26 September 2005
Additional histological processing finish date: 12 October 2005

The check of the protocol was not carried out by the Q.A. of the test site. However, it was revised by the lead Q.A.

The study was conducted on behalf of:

SOLVAY SOLEXIS S.p.A.
Viale 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	:	25 th 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 0.003, 0.013 and 0.05 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 assessed for content check in a previous study (RTC Study no. 27080). Samples of the formulations prepared in weeks 1 and 13 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 Animal management

4.1.1 Animal supply and acclimatisation

A total of 133 Hsd: Sprague Dawley SD rats (72 males and 61 females), 27-29 days old and with body weight of approximately 75-99 g, were obtained from Harlan Italy s.r.l., San Pietro al Natisone (UD), Italy. Animals were delivered in the weight range of 93-110 g, therefore slightly outside the range indicated in the protocol.

After arrival, on 25 March 2005, the weight range for each sex was determined and the animals were temporarily identified within the cage by means of a coloured mark on the tail. A health check was then performed by a veterinarian.

An acclimatisation period of 19 days was allowed before the start of treatment, during which time the health status of the animals were assessed by thorough 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 $22^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $55\% \pm 15\%$ respectively; actual conditions were monitored, recorded and the records retained. No relevant deviations from these ranges were recorded during the study. 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 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 at least 3 times a week.

Drinking water was supplied *ad libitum* to each cage via water bottles, except as noted in section 4.4.

A commercially available laboratory rodent diet (4 RF 21, Mucedola S.r.l., Via G. Galilei, 4, 20019, Settimo Milanese (MI), Italy) was offered *ad libitum* throughout the study, except as noted in section 4.4.

There was 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 in a Study Day Book.

4.1.3 Allocation to groups

On the day of allocation (6 days prior to the start of treatment) all animals were weighed. Animals at the extremes of the weight distribution were excluded to leave the required number of animals. The rats were allocated to groups by computerised stratified randomisation to give approximately equal initial group mean body weights.

Individuals were uniquely identified within the study by sex, tattoo on the hind feet and ear notch and housed 5 of one sex per cage (main groups) and 3 of one sex per cage (single dose toxicokinetic group).

The cages were identified by a label recording the study number, animal numbers and details of treatment. The arrangement of cages in batteries was such that cages from each treatment group were evenly distributed across the battery (Figure 1) to minimise possible environmental effects. 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 Selection of dose levels

Dose levels were selected in consultation with the Sponsor based on information from previous studies.

4.2.2 Dose levels, group size and identification

Each main group comprised 10 male and 10 female rats. Control and high dose groups included 5 additional animals per sex to be sacrificed after 8 weeks of recovery. One satellite group for toxicokinetics comprised 9 male animals. The group identification and animal numbers assigned to the treatment are summarised below:

MAIN AND RECOVERY GROUPS

Group Number	Treatment (mg/kg/day)+	Level	Rat Numbers			
			Main phase		Recovery phase	
			M (even)	F (odd)	M (even)	F (odd)
1	0	Control	2-20	1-19	22-30	21-29
2	0.03	Low	32-50	31-49		
3	0.13	Medium	52-70	51-69		
4	0.5	High	72-90	71-89	92-100	91-99
+: in terms of test item as supplied						

SATELLITE GROUP

Group Number	Treatment (mg/kg)	Level	Rat numbers Males (even)
5	0.5	High	102 - 118
+: in terms of test item as supplied			

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

4.2.3 Administration of test item

The test item was administered orally by gavage at a dose volume of 10 ml/kg 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.

4.2.4 Duration of treatment

All animals were dosed once a day, 7 days a week, for a minimum of 13 consecutive weeks. Satellite group animals were dosed once only. Animals in the main phase were dosed up until the day before necropsy. No treatment was given during the 8 week recovery period.

4.3 *In vivo* observations

Full records were maintained for all measurements and observations.

4.3.1 Mortality

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

4.3.2 Pre- and post-dose observations

All observations were recorded for individual animals. Examination of individual animals for signs of reaction to treatment was carried out daily before dosing, immediately after, and approximately 1 and 2 hours after dosing up to Day 9 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 a minimum of three minutes. Observed parameters, described by an evaluation scale, are indicated below:

Removal (from cage):	Easy, Difficult, Very difficult
Handling reactivity:	Normal, Slow, 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 (Slightly, Moderately, Severely)
 Pronation
 Forelimbs drag (Slight, Moderate, Marked)
 Hindlimbs 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 weeks 12/13 of treatment and once during week 8 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 (MA) of all animals was measured once during weeks 12/13 of treatment and once during week 8 of recovery by an automated activity recording. Measurements were performed using a computer generated random order.

4.3.5 Body weight

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

4.3.6 Food consumption (Main groups)

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

4.3.7 Ophthalmoscopy (Main groups)

Both eyes of all animals assigned to the study were examined just prior to the commencement of treatment by means of an ophthalmoscope, and by a slit-lamp microscope, after the instillation of 0.5% Tropicamide (Visumidriatic®, Visufarma, Rome, Italy). One animal with non-resolving lesions (No. 41950091) was replaced with a spare animal showing no ocular abnormality, from the batch initially ordered for the study. The eyes of all animals from high-dose and control groups were re-examined during week 13 of treatment.

4.4 Clinical pathology investigations (Main groups)

Once during week 13 of treatment and once during week 8 of recovery, samples of blood were withdrawn under isoflurane anaesthesia from the retro-orbital sinus of the first 10 surviving male and the first 10 surviving female animals from each group, under conditions of food and water deprivation. At the same time interval, individual overnight (approximately 16 hours) urine samples were collected from the same animals under the same conditions. Before starting urine collection water bottles were removed from each cage and each animal received approximately 10 ml/kg of drinking water by gavage, in order to obtain urine samples suitable for analysis.

Prior to necropsy, blood samples were taken from the abdominal vena cava of the same rats from each group, under isoflurane anaesthesia, to perform coagulation tests.

Blood samples were collected and analysed in the same order, a computer-generated random cage order being used.

OWS:

are listed below:

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 (Main and Satellite groups)

Blood samples were collected at 9 points on the day of dosing from the animals of the satellite group. Individual urine and faeces samples were also collected from the same animals at the time intervals indicated in following scheme:

Group Number	Treatment (mg/kg)	Animal Number (Males)	Time points (h) Blood samples	Time points (h) Urine/faeces samples
5	0.5	102,104,106	0, 4, 24	6-12 and 42-48
		108,110,112	2, 8, 96	18-24 and 162-168
		114,116,118	6, 48, 168	0-6 and 90-96

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. Urine and faeces samples were also frozen and stored at -20°C but were not analysed. Analysis of the blood samples were carried out by the Analytical Chemistry Department of RTC.

Satellite group animals were dosed once only and no necropsy was performed on animals dying during the study or sacrificed at the end of the study. Surviving satellite group animals were killed after the last sample has been collected. No necropsy examination was performed in these animals.

Additional blood samples of 0.8 ml were collected as described above, approximately 2 h after the last dosing, from the first 3 male and 3 female animals of groups 2, 3 and 4 at the end of weeks 11, 12 and 13.

On the last day of dosing approximately 24, 48, 96, 144 and 192 hours after last dosing, blood samples of 0.8 ml were withdrawn from group 4 recovery animals (5 males and 5 females).

Individual urine and faeces samples were also collected from the same animals at the following time intervals: 0-6, 6-12, 12-24, 48, 72, 96, 120, 144, 168 and 192 hours after the last dosing. All these samples were frozen and stored at -20°C but were not analysed. For analysed blood samples, the following parameters were calculated according to standard non-compartmental analysis:

C_{max} : maximum observed plasma concentration
 T_{max} : time to C_{max}
 $t_{1/2}$: 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 mean and standard deviation for plasma levels.

4.6 Terminal studies

4.6.1 Euthanasia

Animals from the main and recovery groups *in extremis* or killed for humane reasons and those that have completed the scheduled test period were killed by exsanguination under isoflurane anaesthesia. Satellite group animals were killed with carbon dioxide.

4.6.2 Necropsy (Main Groups)

The clinical history of the animal was studied and a detailed *post mortem* examination was conducted (including examination of the external surface and orifices). Changes were noted, the requisite organs weighed and the required tissue samples preserved in fixative and processed for histopathological examination (see sections 4.6.3 to 4.6.5).

4.6.3 Organ weights (Main Groups)

From all animals completing the scheduled test period, the organs indicated in Annex 1 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 (Main Groups)

Samples of all the tissues listed in section 4.6.7 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 4.6.6).

4.6.5 Histopathological examination (Main Groups)

The tissues required for histopathological examination are listed in section 4.6.7. After dehydration and embedding in paraffin wax, sections of the tissues were cut at 5 micrometre thickness and stained with haematoxylin and eosin. Histological processing was subcontracted to a GLP certified site. In the first instance the examination was as detailed below:

- a) Tissues specified in section 4.6.7 from all animals in the control and high dose groups dying during the treatment period or killed at the end of the 13 weeks of treatment.
- b) Tissues specified in section 4.6.7 from all animals in the low and medium dose groups killed or dying during the treatment period.
- c) All abnormalities in all groups.

The examination was then extended to the liver, lungs and spleen from all other animals killed after 13 weeks of treatment or 8 weeks of recovery.

4.6.6 Liver enzymes

Following removal of liver sections for histopathological examination, all remaining tissue (at least 4 g in the first instance, preferably taken from the left and right lateral lobes) was rinsed in ice-cold physiological saline, then placed into individual packages (one per animal) and immediately frozen in liquid nitrogen.

Frozen samples were maintained at -80°C pending despatch for analysis. The liver samples taken for enzyme analysis were transported frozen on dry ice to:

Department of *In Vitro* Metabolism
Building Numbers: E04
Laboratory Numbers: 1038, 1039, 1040
Huntingdon Life Sciences Ltd
Huntingdon Research Centre
Huntingdon
Cambridgeshire
PE28 4HS
UK

Telephone: +44(0) 1480 892833 – Principal Investigator
Facsimile: +44(0) 1480 892281 – Department
Facsimile: +44(0) 1480 890693 – Company

In the first instance, only samples from the first 5 surviving male and the first 5 surviving female rats from control and high dose groups were examined. Treatment related changes of the hepatic peroxisome proliferation were observed in the high dose animals examined and liver samples from the first 5 males and 5 females of the low and mid-dose groups and from all recovery group animals were processed and analysed in a similar manner to that used previously. The determination of cyanide-insensitive palmitoyl-CoA oxidation activity was done for the evaluation of hepatic peroxisome proliferation according to the procedures described in Annex 3 of study protocol (see Addendum VII of this report). These tests were undertaken and interpreted by the Test Site indicated above under the responsibility of the Principal Investigator, Anne Matthews (Ref. No. RTS0047). A QAU revised report can be found in Addendum VI of this report.

4.6.7 Annex 1 of study protocol

Organs / Tissues	Weight	Fixation Preservation	Microscopic Examination
Abnormalities		✓	✓
Adrenal glands	✓	✓	✓
Aorta		✓	✓
Bone marrow (from sternum)		✓	✓
Brain	✓	✓	✓
Caecum		✓	✓
Colon		✓	✓
Duodenum		✓	✓
Epididymides	✓	✓	✓
Eyes		✓	*
Femur with joint		✓	*
Heart	✓	✓	✓
Ileum (including Peyer's patches)		✓	✓
Jejunum		✓	✓
Kidneys	✓	✓	✓
Liver	✓	✓	✓
Lungs (including mainstem bronchi)		✓	✓
Lymph nodes - cervical		✓	✓
Lymph nodes - mesenteric		✓	✓
Mammary area		✓	✓
Oesophagus		✓	✓
Ovaries	✓	✓	✓
Oviducts ^a		✓	✓
Pancreas		✓	✓
Parathyroid glands ^b		✓	✓
Pituitary gland		✓	✓
Prostate gland		✓	✓
Rectum		✓	✓
Salivary glands		✓	✓
Sciatic nerve		✓	✓
Seminal vesicles		✓	*
Skeletal muscle		✓	*
Skin		✓	✓
Spinal column		✓	
Spinal cord		✓	✓
Spleen	✓	✓	✓
Stomach		✓	✓
Testes	✓	✓	✓
Thymus (where present)	✓	✓	✓
Thyroid		✓	✓
Trachea		✓	✓
Urinary bladder		✓	✓
Uterus - cervix	✓	✓	✓

*: Not examined as no signs of toxicity or target organ involvement observed

a: weighed and preserved with ovaries

b: preserved with thyroid gland

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. All raw data, records and documentation generated during the histological processing at the Test Site Propath UK Limited, were sent back to RTC and will be archived together with the remaining study data.

All raw data, records and documentation generated during the liver enzymes analysis at the Test Site Huntingdon Life Sciences Ltd, will be kept for a period of 5 years from the date on which the Study Director signs the final report. After such time, the Study Director will be contacted for instructions regarding despatch or disposal of the material.

5. RESULTS

5.1 Mortality

No mortality occurred during the study.

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

No reaction to treatment was seen at daily post-dose examinations.

Detailed clinical signs with neurotoxicity assessment did generally not show any signs which could be correlated to the treatment with the test item.

No toxicological importance was attributed to the small masses observed on the perigenital or mammary area in some animals from all treated and control groups (mainly in the males). Most of these masses were not found at necropsy examination or were recognised as abscesses or inflammation essentially noted around the preputial gland, which are usually observed in this strain and age of animal. These latter data are not tabulated in the report among the clinical signs.

5.3 Sensory reaction to stimuli and motor activity (Table 2; Appendices 1 and 2)

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.

Slight but statistically significant reductions in motor activity were observed in the males dosed at 0.13 and 0.5 mg/kg/day at the end of the treatment period.

5.4 Body weight (Figure 2; Tables 3, 4 and 8; Appendices 3 and 4)

Slight but statistically significantly reductions of the body weight were observed in the high dose males on days 85 and 92 of the treatment period (6% and 10% of reduction). Body weights were also slightly reduced (5% to 10%) in the high dose females by day 78 of the treatment period and in recovery animals, up to day 8 of recovery. The slight body weight losses observed in the last week of the treatment period were ascribed to the overnight fast prior to the bleeding procedure for clinical pathology investigations. These slight reductions were no longer evident up to the end of the recovery period.

5.5 Food consumption (Appendix 5)

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

5.6 Ophthalmoscopy (Table 5)

No significant findings were seen at the ophthalmic examination.

5.7 Haematology (Table 6; Appendix 6)

The statistically significant changes observed are described in the following table:

Parameters	2M	3M	4M	4M Rec	2F	3F	4F	4F Rec
RBC		-5%	-10%					
HGB		-4%	-6%					
HCT		-5%	-6%					
MCV			+4%					
MCH			+4%					
Neu					+65%			
Lym					-9%			

Treatment period

Very slight but statistically significant reductions in red blood cell count, haemoglobin and haematocrit and increases mean red blood cell volume and mean corpuscular haemoglobin were observed in males receiving 0.5 and 0.13 mg/kg/day. These changes were insufficient in magnitude to be of toxicological significance.

The statistically significant changes of neutrophils and lymphocytes count observed in some females receiving 0.03 mg/kg/day were considered to be incidental since no dose-relation was observed.

Recovery period

The changes observed during the dosing phase showed a complete recovery after the 8-week treatment-free period.

5.8 Clinical chemistry (Table 7; Appendix 7)

The statistically significant changes observed are described in the following table:

Parameters	2M	3M	4M	4M Rec	2F	3F	4F	4F Rec
AP	-11%	+25%	+101%	+47%			+65%	+29%
ALT		+30%						-14%
BILT			-25%				-31%	
CHOL		-27%				-20%		
TRI						+40%	+63%	+54%
Urea			+36%	+29%				
Crea		-13%	-23%					
Prot		-7%	-14%				+5%	
Alb			-7%			+8%	+14%	+13%
Glo			-23%					-19%
A/G Ratio			+24%			+20%	+32%	+38%
Ca	-3%	-4%	-8%					
Cl			+2%					
Phos				+18%				
Na				-1%				+1%

Treatment period

Alkaline phosphatase was statistically significantly increased in 0.5 and 0.13 mg/kg/day male animals when compared to controls and in the females dosed at 0.5 mg/kg/day. Since no indications of cholestasis or bone pathology were observed, this change could be due to an enzyme induction caused by the treatment.

Changes of total bilirubin, triglycerides, urea and creatinine were also observed in animals treated with 0.13 and/or 0.5 mg/kg/day. In the absence of notable pathology these could represent adaptive changes in the liver.

All other inter-group differences were slight, not dose-related and/or not consistent between sexes, therefore they were considered to be incidental.

Recovery period

At the end of the treatment-free period, some parameters which were altered in the dosing phase analyses showed a trend for recovery (alkaline phosphatase and triglycerides), while most of them had completely recovered.

No significant recovery was observed for urea levels, which remained higher when compared to controls.

5.9 Urinalysis (Table 8; Appendix 8)

Treatment period

Urine specific gravity was slightly increased in a number of males treated with 0.5 mg/kg/day and pH was slightly reduced in the same group animals.

In addition, animal No. 90 had a concentration of glucose, bilirubin and urobilinogen higher than controls.

These changes were not dose-related, not consistent between sexes and/or insufficient in magnitude to be of toxicological significance.

Recovery period

The slight changes observed during the dosing phase were no longer observed at the end of the recovery period.

5.10 Toxicokinetic analysis (Figure 3; Addendum IV)

Detectable plasma levels of the test item were measured between 2 and 168 hours after a single dose in the male animals of the satellite group treated at 0.5 mg/kg. The maximum plasma level (C_{max}) was 580 ng/ml. C_{max} was measured 24 hours after dosing (t_{max}). A half-life ($t_{1/2}$) of approximately 1037 hours was estimated. The $AUC_{(24-168h)}$ was calculated to be 84686 ng/ml·h and the $AUC_{(inf)}$ was calculated to be 830571 ng/ml·h.

Plasma levels were also determined at the end of weeks 11, 12 and 13 in 3 males and 3 females from each dose group approximately 2 hours after dosing in order to calculate the accumulation at the end of treatment. Results are summarised in Addendum VI. An increase of approximately 100 folds of test item concentration was observed in the males of the high dose groups when compared to those measured following a single administration at the same dose level (0.5 mg/kg). A partial decrease of plasma levels (45% and 35% in males and females, respectively) was observed after 7 days of recovery. C_{max} values of 45726 and 30364 ng/ml were estimated in males and females following analysis of plasma samples obtained during the first week of recovery. The half-life ($t_{1/2}$) was 187 hours in the males and 274 hours in the females. The $AUC_{(24-168h)}$ was 5787840 and 3825012 ng/ml·h and the $AUC_{(inf)}$ was 12595837 and 11627070 ng/ml·h (males and females, respectively).

5.11 Organ weights (Tables 10 and 11; Appendices 9 and 10)

Dose-related, statistically significant increases in absolute (13% and 28% in the males, 16% and 56% in the females) and relative (14% and 43% in the males, 15% and 61% in the females) liver weights were noted in the animals dosed at 0.13 and 0.5 mg/kg/day at the end of the treatment period. Although a trend of recovery was evident, the weight of the liver was still significantly increased at the end of the 8-week treatment-free period.

Slight, often, statistically significant increases of the weights of the kidneys (6% and 11% the absolute in males and females; 18% and 14% the relative in the 2 sexes), were also seen in the animals dosed at 0.5 mg/kg/day at the end of treatment. This change was no longer present at the end of recovery.

In addition, statistically significant reductions of the absolute weights of the spleen (19% in the males dosed at 0.5 mg/kg/day), testes (5% and 6% in the animals dosed at 0.13 and 0.5 mg/kg/day), thymus (28% and 12% in males and females respectively dosed at 0.5 mg/kg/day) and adrenals (16% in the high dose males) were observed in the animals from the 2 higher dose groups. None of these changes were still present at the end of recovery.

These last changes, not supported by findings observed at macroscopic and microscopic examination of these organs and completely reversible, were considered of no toxicological significance.

5.12 Liver enzymes (Addendum VI)

In male and female rats of the main dose groups, there were statistically significant increases in protein concentration, to 1.2-times the mean control value following administration of the test item at the high dose level (0.5 mg/kg/day). Decreases of 0.1-times and 0.2-times the mean control value were observed in the females treated at 0.03 and 0.13 mg/kg/day. In the female animals from the high dose group, there was a statistically significant increase in protein concentration (to 1.1-times the mean control value) at the end of recovery. There were no statistically significant increases in the males at the end of recovery.

Marked increases in mean cyanide-insensitive palmitoyl CoA oxidase activity were observed in both sexes animals treated with the test item. Increases were generally dose-related, being approximately 11-times the mean control activities in the males and approximately 9-times control activities in the females receiving 0.5 mg/kg/day (activities expressed per mg protein). In males and females, mean activities were statistically significantly different from control values at the mid- and high dose groups. Mean 3,000 x g supernatant protein concentrations (mg/g liver) were statistically significantly increased in animals treated at 0.5 mg/kg/day. However, the protein concentrations of female rats dosed at 0.03 and 0.13 mg/kg/day were statistically significantly reduced.

Following an 8-week recovery period, the level of increase in the cyanide-insensitive palmitoyl CoA oxidase activity of male rats was reduced from approximately 11-times the mean control activities to approximately 5-times. In the female, the degree of reduction was less, with the activities being reduced from approximately 9- or 11-times to approximately 5- 6-times the mean control activities, when related to mg/protein or g/liver, respectively.

5.13 Macroscopic observations (Table 12; Appendix 11)

No relevant changes were observed at *post mortem* examination in the treated animals when compared with controls, either in animals killed at termination or after 8 weeks of recovery period.

5.14 Microscopic observations (Table 13; Appendix 11)

Final sacrifice

Treatment-related changes were seen in the liver and lungs of treated animals receiving ≥ 0.13 mg/kg/day, when compared with controls and are summarised as follows:

Liver: hepatocytic hypertrophy was seen in 9/10 males and 9/10 females receiving 0.5 mg/kg/day. This change was also seen in 2/10 animals, both sexes, receiving 0.13 mg/kg/day. In addition, slight yellow/brown pigmentation was seen in the Kupffer's cells and occasionally in the hepatocytes of 2/10 females dosed at ≥ 0.13 mg/kg/day, in 1/10 females receiving 0.03 mg/kg/day and in 1/10 male dosed at 0.5 mg/kg/day. Although pigmentation in Kupffer's cells is occasionally seen in control animals of these species and strain, however lipofuscin-like pigment has been reported in hepatocytes and Kupffer cells in animals treated with different classes of drugs, for example agents which produce peroxisome proliferation ⁽¹⁾.

Lungs: changes suggestive of phospholipidosis, represented by alveolar foamy macrophages, associated with interstitial inflammatory cell infiltrate, showed an increased incidence in the females receiving ≥ 0.13 mg/kg/day, when compared with controls.

Recovery sacrifice

Treatment-related changes were still present in the liver and lungs of treated animals, killed after 8 weeks of recovery period, when compared with controls and are summarised as follows:

Liver: hepatocytic hypertrophy was seen in the majority of treated animals; slight yellow/brown pigmentation was still observed in 2/5 treated females;

Lungs: alveolar foamy macrophages were clearly seen in treated males and females.

Other findings

Two males receiving 0.5 mg/kg/day showed inflammatory reactions with oedema in the stomach. In 1 male, focal ulceration of the gastric mucosa was seen associated to the above-mentioned changes.

Increased incidence of yellow/brown pigmentation was seen in the spleen of females given ≥ 0.03 mg/kg/day. Control animals, killed after the recovery period showed the same change with similar incidence to those seen in treated animals. This change was considered of no toxicological significance.

Increased incidence of hydrometra in the uterus was seen in females dosed at 0.5 mg/kg/day in comparison to controls. No correspondent pathological changes were described in the cervix and vagina, where tissue appearance was representative for normal specific cycle stages. Therefore, this finding was seen incidental in origin.

The remaining lesions were considered to be an expression of spontaneous pathology, commonly seen in this species under our experimental conditions.

⁽¹⁾ Greaves "Histopathology of preclinical toxicity studies" (page 465)

6. CONCLUSION

The oral toxicity of [REDACTED] when given by daily administration to rats, has been investigated over a period of 13 consecutive weeks and recovery from any potential treatment-related effects over a period of 8 consecutive weeks.

No significant clinical signs or post-dose reactions were observed during the “in-life” phase of the study at any of the dose levels investigated.

Male animals dosed at 0.5 mg/kg/day showed very slight reductions in body weight when compared to controls. These slight reductions were no longer evident up to the end of the recovery period. Very slight reductions in red blood cell count, haemoglobin and haematocrit were observed in males dosed at 0.5 mg/kg/day. The reductions observed during the dosing phase showed a complete recovery after the 8-week treatment-free period. Alkaline phosphatase and alanine aminotransferase were statistically significantly increased in the high dose males. Other clinical chemistry parameters showed slight changes at the end of treatment in these animals. Most of the observed variations were no longer evident at the end of recovery. The absolute and relative weights of the liver were significantly increased in animals of both sexes receiving 0.5 mg/kg/day at the end of treatment period. Liver hepatocytic hypertrophy and instances of slight yellow/brown pigmentation in the Kupffer's cells or hepatocytes were seen at the end of treatment in animals (both sexes and females, respectively) receiving 0.5 mg/kg/day at microscopic examination. Changes, suggestive of phospholipidosis, were also observed in the lungs of these animals. Liver hepatocytic hypertrophy and phospholipidosis in lungs were still present in the high dose animals at the end of recovery. In addition, peroxisomal palmitoyl CoA oxidase activity was significantly induced, following treatment with the test item at a dose level of 0.5 mg/kg/day. Following an 8-week recovery period the enzyme activities of these animals remained significantly higher than those of the control group.

The toxicological significance of the kidneys weight increase observed in both sex animals dosed at 0.5 mg/kg/day is unclear, as no changes were seen in this organ at microscopic examination. No other changes of toxicological significance were observed in the organ weights of the high dose animals.

The majority of the changes observed in clinical pathology parameters as well as the increase in liver weight, liver enzymes activity and microscopic pathology findings observed in the liver, which were described for the high dose animals, were also noted in the animals receiving 0.13 mg/kg/day. The incidence and severity of the above changes was generally lower in the mid-dose animals when compared to the high dose ones.

Detectable plasma levels of the test item were measured between 2 and 168 hours after dosing in the animals dosed at 0.5 mg/kg ($C_{\max}$ was 580 ng/ml). $C_{\max}$ was measured 24 hours after dosing ($t_{\max}$). An estimated half-life ($t_{1/2}$) of approximately 1037 hours has been determined. This value was obtained by an extrapolation, as no decrement of test item plasma levels was observed after 168 post-dose. This situation did not allow the determined of a significant value of the AUC. An increase of 100 fold of test item plasma levels was observed at the end of the treatment period. The measured plasma levels showed a decrease of approximately 45% and 35% in males and females, respectively.

On the basis of these results, signs of an evident adverse effect of the test item were seen at the 2 higher dose levels investigated (0.13 and 0.5 mg/kg/day). Most of the observed effects were not reversible over an 8-week recovery period in the high dose animals. This effect was demonstrated by changes in clinical pathology parameters and *post mortem* examinations. A main target organ, the liver, was identified on the basis of the organ weights data and histopathological findings. In addition, the evaluation of the activity of cyanide-insensitive palmitoyl CoA oxidase, suggested that the test item acts as a strong peroxisome proliferator. A second target organ of the test item appeared to be the lungs. The above effects showed a dose-related trend and appeared to be only partially reversible after the 8-week recovery period. No significant effects were observed at the low dose level (0.03 mg/kg/day). Therefore, the dose level of 0.03 mg/kg/day, when administered daily for 13 consecutive weeks to both rat sexes, may be considered the No Observed Effect Level (NOEL) in this study.

**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

FIGURE 1 - Group and cage arrangement on battery

STUDY NO.: 41950

MAIN PHASE						
Group Number	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
1	0	Control	2-20	1-19	1 - 2	11 - 12
2	0.03	Low	32-50	31-49	4 - 5	14 - 15
3	0.13	Medium	52-70	51-69	6 - 7	16 - 17
4	0.5	High	72-90	71-89	8 - 9	18 - 19
RECOVERY PHASE°						
Group Number	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
1	0	Control	22-30	21-29	3	13
4	0.5	High	92-100	91-99	10	20

+ In terms of test item as supplied
° No treatment was given during the recovery period

MAIN PHASE

Group/Sex		Cage no.	
Males		Females	
1M	4M	1F	4F
1	9	11	19
2M	1M	2F	1F
4	2	14	12
3M		3F	
6		16	
4M		4F	
8		18	
2M	4M ^R	2F	4F ^R
5	10	15	20
3M	1M ^R	3F	1F ^R
7	3	17	13

^R = Recovery

**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

FIGURE 1 - Group and cage arrangement on battery - continued

STUDY NO.: 41950

RECOVERY PHASE

Group/Sex		Cage no.
Males	Females	
1M ^R		3
4M ^R		10
	1F ^R	13
	4F ^R	20

^R = Recovery

SATELLITE GROUP

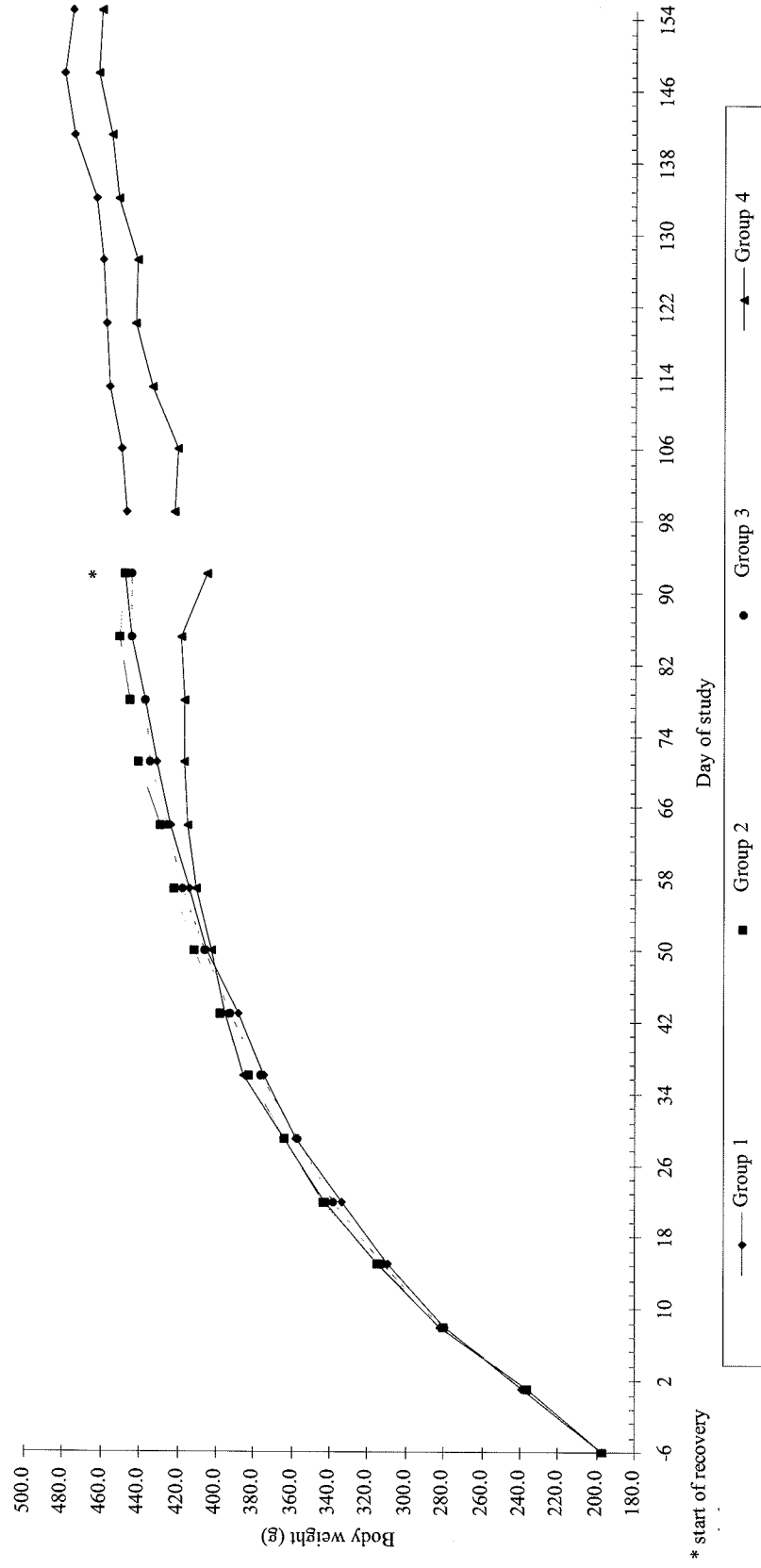
Group Number	Treatment (mg/kg)+	Level	Rat numbers Females (odd)	Cage numbers
5	0.5	High	102 - 118	21-23
+: in terms of test item as supplied				

Group/Sex		Cage no.
Males		
5M		
21		
5M		
22		
5M		
23		

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

FIGURE 2.1 - Body weight versus day of study - Males

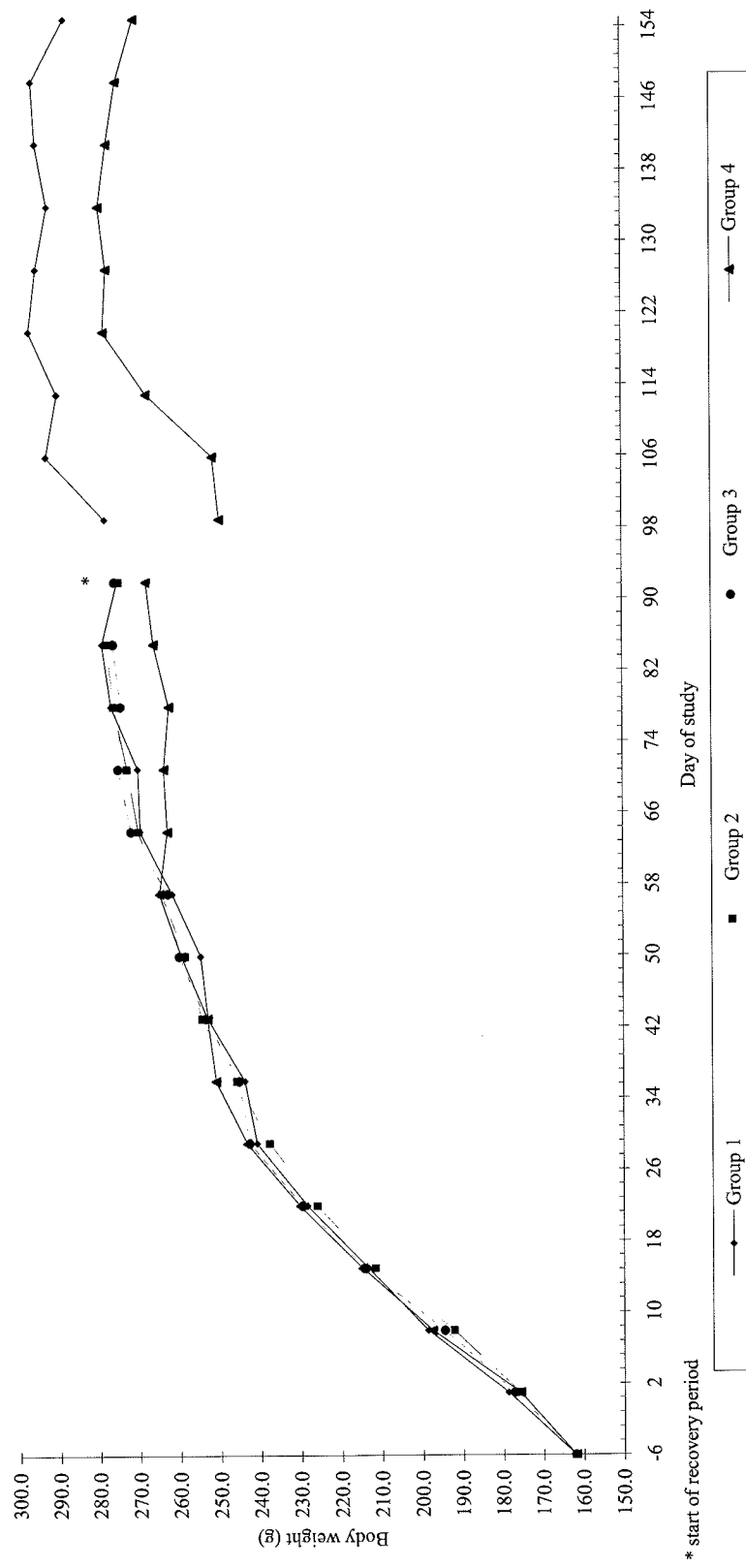
STUDY NO.: 41950



13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

FIGURE 2.2 - Body weight versus day of study - Females

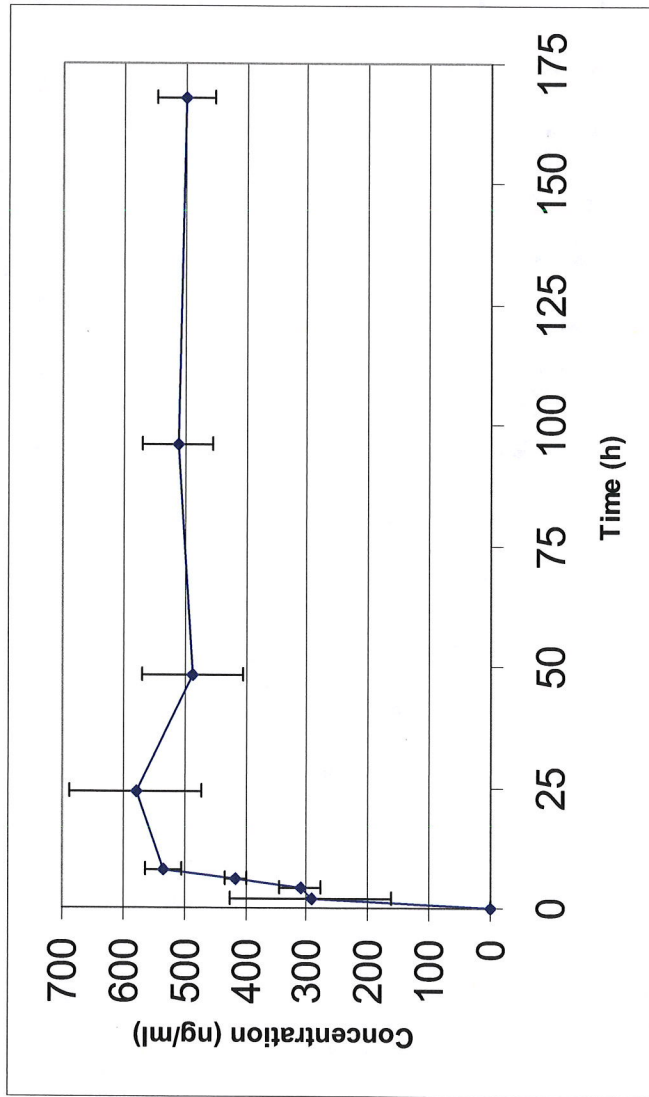
STUDY NO.: 41950



13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

FIGURE 3.1 - Plasma levels of [REDACTED] - Single dose - Males

STUDY NO.: 41950



13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

FIGURE 3.2 - Plasma levels of [REDACTED] - Week 1 of recovery - Males

STUDY NO.: 41950

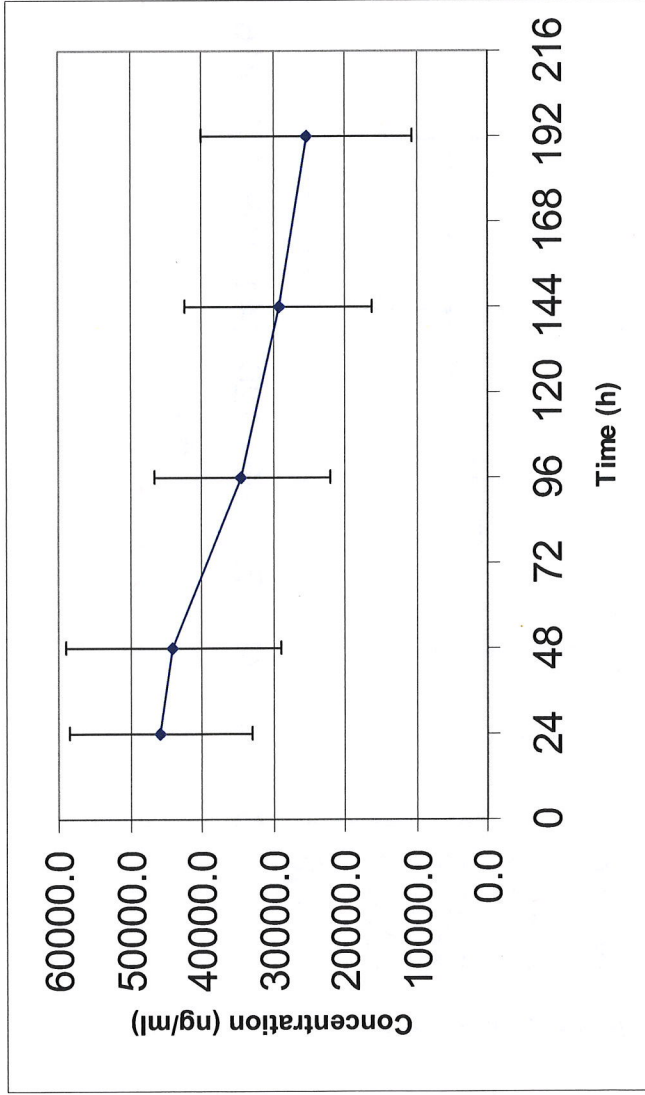
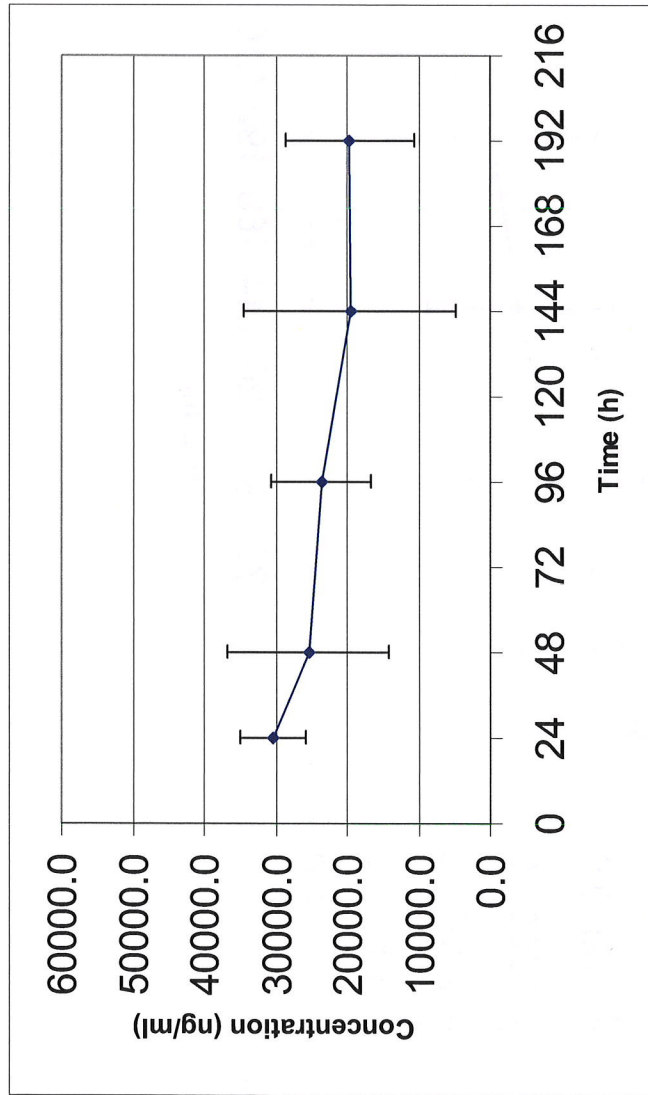


FIGURE 3.3 - Plasma levels of [REDACTED] - Week 1 of recovery - Females

STUDY NO.: 41950



REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: 41950

MALES

Interval: 1 - 13 Weeks Group Observation	1 (15)		2 (10)		3 (10)		4 (15)	
	a	b	a	b	a	b	a	b
EYE - EAR - MOUTH								
Tooth/Teeth broken	0	0.0	1	1.0	0	0.0	0	0.0
REMOVAL								
Removal easy	15	13.0	10	13.0	10	13.0	15	13.0
HANDLING REACTIVITY								
Handling reactivity normal	15	13.0	10	13.0	10	13.0	15	13.0
LACHRYMATION								
Lachrymation absent	15	13.0	10	13.0	10	13.0	15	13.0
PALPEBRAL CLOSURE								
Palpebral closure absent	15	13.0	10	13.0	10	13.0	15	13.0
SALIVATION								
Salivation absent	15	13.0	10	13.0	10	13.0	15	13.0
PILOERECTOR								
Piloerection absent	15	13.0	10	13.0	10	13.0	15	13.0
REARING								
Rearing absent	1	1.0	1	1.0	1	1.0	4	1.0
Rearing 1-3	4	1.3	1	1.0	4	1.5	9	1.4
Rearing 4-7	8	2.3	6	2.7	6	2.5	10	2.5
Rearing 8-10	12	1.8	8	3.5	7	3.0	13	3.6
Rearing 11-14	13	4.3	8	3.1	9	3.7	13	3.2
Rearing 15-20	13	3.7	9	3.9	8	4.3	11	4.2
Rearing 21-30	13	3.5	5	4.6	7	2.7	9	2.1
Rearing more than 30	1	1.0	1	1.0	1	1.0	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 AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: 41950

MALES

Interval: 1 - 13 Weeks									
Group Observation	1 (15)		2 (10)		3 (10)		4 (15)		
	a	b	a	b	a	b	a	b	
SPASMS									
Spasms absent	15	13.0	10	13.0	10	13.0	15	13.0	
MYOCLONIA									
Myoclonia absent	15	13.0	10	13.0	10	13.0	15	13.0	
GAIT									
Normal gait	15	13.0	10	13.0	10	13.0	15	13.0	
MOBILITY IMPAIRMENT									
Mobility impairment absent	15	13.0	10	13.0	10	13.0	15	13.0	
AROUSAL									
Arousal normal	15	13.0	10	12.8	10	13.0	14	12.7	
Arousal slow	0	0.0	1	2.0	0	0.0	3	5.7	
VOCALISATION									
Vocalisation absent	15	13.0	10	13.0	10	13.0	15	13.0	
STEREOTYPES									
Stereotypes absent	15	13.0	10	13.0	10	13.0	15	13.0	
UNUSUAL RESPIRATION									
Unusual respiration absent	15	13.0	10	13.0	10	13.0	15	13.0	
BIZARRE BEHAVIOUR									
Bizarre behaviour absent	15	13.0	10	13.0	10	13.0	15	13.0	

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

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: 41950

MALES

Interval: 1 - 13 Weeks										
Group		1		2		3		4		
Observation		(15)		(10)		(10)		(15)		
		a	b	a	b	a	b	a	b	
URINATION										
Urination absent		13	4.6	9	4.9	10	8.1	15	7.6	
Urination 1-3		15	5.4	10	4.8	10	2.8	13	2.9	
Urination 4-6		9	1.8	5	2.2	6	1.5	7	1.9	
Urination 7-9		5	2.4	5	1.8	2	1.0	3	2.0	
Urination more than 10		7	3.7	5	3.6	3	3.3	8	3.0	
DEFECATION										
Defecation absent		15	12.9	10	13.0	10	12.7	15	13.0	
Defecation 1-3		1	1.0	0	0.0	1	2.0	0	0.0	
Defecation 4-6		0	0.0	0	0.0	1	1.0	0	0.0	
TREMORS										
Tremors absent		15	13.0	10	13.0	10	13.0	15	13.0	

Key: () = Number of animals alive at start of interval

a = Number of animals affected

b = Number of weeks with clinical sign/animal

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: 41950

FEMALES

Interval: 1 - 13 Weeks

Group Observation	1 (15)		2 (10)		3 (10)		4 (15)	
	a	b	a	b	a	b	a	b
APPEARANCE								
Damaged tail	1	2.0	0	0.0	0	0.0	0	0.0
Scab(s)	0	0.0	0	0.0	1	1.0	0	0.0
Hairloss	2	3.0	2	1.5	1	2.0	5	2.2
EYE - EAR - MOUTH								
Damaged eye	0	0.0	1	11.0	0	0.0	0	0.0
REMOVAL								
Removal easy	15	13.0	10	13.0	10	13.0	15	13.0
HANDLING REACTIVITY								
Handling reactivity normal	15	13.0	10	13.0	10	13.0	15	13.0
LACHRYMATION								
Lachrymation absent	15	13.0	10	13.0	10	13.0	15	13.0
PALPEBRAL CLOSURE								
Palpebral closure absent	15	13.0	10	13.0	10	13.0	15	13.0
SALIVATION								
Salivation absent	15	13.0	10	13.0	10	13.0	15	13.0
PILOERECTION								
Piloerection absent	15	13.0	10	13.0	10	13.0	15	13.0

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

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: 41950

FEMALES

Interval: 1 - 13 Weeks Group Observation	1 (15)		2 (10)		3 (10)		4 (15)	
	a	b	a	b	a	b	a	b
REARING								
Rearing 1-3	0	0.0	1	1.0	0	0.0	1	1.0
Rearing 4-7	0	0.0	1	1.0	0	0.0	1	1.0
Rearing 8-10	0	0.0	2	1.0	1	1.0	2	2.0
Rearing 11-14	3	1.7	5	2.2	1	1.0	2	1.0
Rearing 15-20	10	3.1	9	3.2	5	3.8	13	3.2
Rearing 21-30	15	7.1	10	6.1	10	6.7	15	6.6
Rearing more than 30	14	3.8	8	3.1	9	4.7	12	3.8
SPASMS								
Spasms absent	15	13.0	10	13.0	10	13.0	15	13.0
MYOCLONIA								
Myoclonia absent	15	13.0	10	13.0	10	13.0	15	13.0
GAIT								
Normal gait	15	13.0	10	13.0	10	13.0	15	13.0
MOBILITY IMPAIRMENT								
Mobility impairment absent	15	13.0	10	13.0	10	13.0	15	13.0
AROUSAL								
Arousal normal	15	13.0	10	13.0	10	13.0	15	13.0
VOCALISATION								
Vocalisation absent	15	13.0	10	13.0	10	13.0	15	13.0

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

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: 41950

FEMALES

Interval: 1 - 13 Weeks

Group Observation	1 (15)		2 (10)		3 (10)		4 (15)	
	a	b	a	b	a	b	a	b
STEREOTYPES								
Stereotypies absent	15	13.0	10	13.0	10	13.0	15	13.0
UNUSUAL RESPIRATION								
Unusual respiration absent	15	13.0	10	13.0	10	13.0	15	13.0
BIZARRE BEHAVIOUR								
Bizarre behaviour absent	15	13.0	10	13.0	10	13.0	15	13.0
URINATION								
Urination absent	15	10.3	10	9.7	10	11.2	15	11.6
Urination 1-3	12	2.8	8	3.1	8	2.1	9	1.9
Urination 4-6	4	1.3	4	1.8	1	1.0	3	1.0
Urination 7-9	1	1.0	0	0.0	0	0.0	0	0.0
Urination more than 10	1	1.0	1	1.0	0	0.0	1	1.0
DEFECATION								
Defecation absent	15	13.0	10	13.0	10	13.0	15	13.0
TREMORS								
Tremors absent	15	13.0	10	13.0	10	13.0	15	13.0

Key: () = Number of animals alive at start of interval

a = Number of animals affected

b = Number of weeks with clinical sign/animal

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: 41950

MALES

Interval: 1 - 8 Weeks

Group Observation	1 (5)	4 (5)

	a	b	a	b

APPEARANCE

Scab(s)	0	0.0	2	2.0

EYE - EAR - MOUTH

Damaged ear	0	0.0	1	6.0

REMOVAL

Removal easy	5	8.0	5	8.0

HANDLING REACTIVITY

Handling reactivity normal	5	8.0	5	8.0

LACHRYMATION

Lachrymation absent	5	8.0	5	8.0

PALPEBRAL CLOSURE

Palpebral closure absent	5	8.0	5	8.0

SALIVATION

Salivation absent	5	8.0	5	8.0

PILORECTION

Pilorection absent	5	8.0	5	8.0

REARING

Rearing absent	0	0.0	1	1.0
Rearing 1-3	1	6.0	3	2.3
Rearing 4-7	3	1.0	4	2.0
Rearing 8-10	4	1.0	5	2.4

Key: () = Number of animals alive at start of interval

a = Number of animals affected

b = Number of weeks with clinical sign/animal

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: 41950

MALES

Interval: 1 - 8 Weeks

Group Observation	1 (5)		4 (5)	
	a	b	a	b
REARING				
Rearing 11-14	3	1.7	4	1.3
Rearing 15-20	5	2.4	2	2.5
Rearing 21-30	4	2.5	2	1.0
SPASMS				
Spasms absent	5	8.0	5	8.0
MYOCLONIA				
Myoclonia absent	5	8.0	5	8.0
GAIT				
Normal gait	5	8.0	5	8.0
MOBILITY IMPAIRMENT				
Mobility impairment absent	5	8.0	5	8.0
AROUSAL				
Arousal normal	5	8.0	5	7.6
Arousal slow	0	0.0	1	2.0
VOCALISATION				
Vocalisation absent	5	8.0	5	8.0
STEREOTYPIES				
Stereotypies absent	5	8.0	5	8.0

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

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: 41950

MALES

Interval: 1 - 8 Weeks
Group 1 4
Observation (5) (5)

UNUSUAL RESPIRATION

Unusual respiration absent 5 8.0 5 8.0

BIZARRE BEHAVIOUR

Bizarre behaviour absent 5 8.0 5 8.0

URINATION

Urination absent 4 3.5 4 2.5
Urination 1-3 4 3.0 5 2.2
Urination 4-6 0 0.0 4 2.8
Urination 7-9 3 1.7 3 1.3
Urination more than 10 2 4.5 2 2.0

DEFECATION

Defecation absent 5 8.0 5 8.0

TREMORS

Tremors absent 5 8.0 5 8.0

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

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: 41950

FEMALES

Interval: 1 - 8 Weeks

Group Observation	1 (5)		4 (5)	
	a	b	a	b
APPEARANCE				
Scab(s)	0	0.0	1	6.0
Hairloss	2	3.5	1	5.0
REMOVAL				
Removal easy	5	8.0	5	8.0
HANDLING REACTIVITY				
Handling reactivity normal	5	8.0	5	8.0
LACHRYMATION				
Lachrymation absent	5	8.0	5	8.0
PALPEBRAL CLOSURE				
Palpebral closure absent	5	8.0	5	8.0
SALIVATION				
Salivation absent	5	8.0	5	8.0
PILOERECTION				
Piloerection absent	5	8.0	5	8.0
REARING				
Rearing 11-14	2	1.5	0	0.0
Rearing 15-20	3	4.3	4	1.8
Rearing 21-30	4	3.3	5	4.0
Rearing more than 30	4	2.8	4	3.3

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

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: 41950

FEMALES

Interval: 1 - 8 Weeks Group Observation	1 (5)		4 (5)	
	a	b	a	b
SPASMS				
Spasms absent	5	8.0	5	8.0
MYOCLONIA				
Myoclonia absent	5	8.0	5	8.0
GAIT				
Normal gait	5	8.0	5	8.0
MOBILITY IMPAIRMENT				
Mobility impairment absent	5	8.0	5	8.0
AROUSAL				
Arousal normal	5	8.0	5	8.0
VOCALISATION				
Vocalisation absent	5	8.0	5	8.0
STEREOTYPES				
Stereotypies absent	5	8.0	5	8.0
UNUSUAL RESPIRATION				
Unusual respiration absent	5	8.0	5	8.0
BIZARRE BEHAVIOUR				
Bizarre behaviour absent	5	8.0	5	8.0

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

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: 41950

FEMALES

Interval: 1 - 8 Weeks

Group	1	4
Observation	(5)	(5)

URINATION	a	b	a	b
Urination absent	5	6.2	5	4.4
Urination 1-3	3	2.0	3	3.7
Urination 4-6	1	2.0	3	1.0
Urination 7-9	1	1.0	1	2.0
Urination more than 10	0	0.0	2	1.0

DEFECATION

Defecation absent	5	8.0	5	8.0

TREMORS

Tremors absent	5	8.0	5	8.0

Key: () = Number of animals alive at start of interval

a = Number of animals affected

b = Number of weeks with clinical sign/animal

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 2.1 - Motor activity - At the end of treatment - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control		Group 2		Group 3		Group 4	
	Mean	SD	Mean	n	Mean	n	Mean	n
Counter display	1054.1	186.9	995.4	15	855.0*	10	879.1*	15

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 (\$)

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 2.1 - Motor activity - At the end of treatment - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control		Group 2		Group 3		Group 4					
	Mean	SD	n	Mean	SD	n	Mean	SD	n			
Counter display	1017.2	170.6	15	992.1	122.5	10	1007.3	84.7	10	1022.7	212.6	15

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 (\$)

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 2.2 - Motor activity - At the end of recovery - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	n
Counter display	813.4	264.9	797.6	396.3 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)

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 2.2 - Motor activity - At the end of recovery - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	SD
Counter display	841.2	85.4	908.8	182.2
		5		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 (\$)

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 3.1 - Body weight (g) - During treatment - Group mean data

STUDY NO.: 41950

MALES

Group(s)	1!	1"	8	D a y o f P h a s e				29	36	43
				15	15	15	15			
1	(n) 15 Mean SD	15 238.73 7.01	15 279.14 9.17	15 309.50 12.41	15 333.36 14.00	15 357.88 15.44	15 374.82 17.55	15 388.33 17.34	15 398.08 28.69	15 393.17 16.57
2	(n) 10 Mean SD	10 236.20 9.70	10 279.92 15.14	10 314.78 18.38	10 343.16 21.30	10 364.00 22.04	10 383.13 26.24	10 398.08 28.69	10 398.08 28.69	10 393.17 16.57
3	(n) 10 Mean SD	10 238.18 7.40	10 280.60 9.81	10 312.17 12.50	10 338.61 15.16	10 356.90 14.10	10 377.08 17.66	10 393.17 16.57	10 393.17 16.57	10 393.17 16.57
4	(n) 15 Mean SD	15 235.90 9.29	15 281.50 11.23	15 314.64 15.52	15 343.01 20.73	15 364.36 22.08	15 385.63 23.58	15 395.02 26.49	15 395.02 26.49	15 395.02 26.49

Note: ! = Pre-test 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 AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 3.1 - Body weight (g) - During treatment - Group mean data

STUDY NO.: 41950

MALES

Group(s)		50!	57	64	D a y				P h a s e			
					71	78	85	92				
1	(n)	15	15	15	15	15	15	10				
	Mean	404.86	414.60	423.84	431.35	437.28	444.93	448.43				
	SD	18.42	18.05	20.04	19.61	20.80	20.88	16.37				
2	(n)	10	10	10	10	10	10	10				
	Mean	411.34	422.15	429.83	440.96	443.44	451.05	448.00				
	SD	25.35	25.63	27.92	29.82	27.97	28.60	27.49				
3	(n)	10	10	10	10	10	10	10				
	Mean	405.91	417.67	425.64	435.11	437.84	444.22	444.19				
	SD	17.70	20.07	18.69	19.97	20.69	23.16	22.67				
4	(n)	15	15	15	15	15	15	10				
	Mean	402.45	410.62	414.86	416.57	416.70	418.90*	405.64**				
	SD	25.94	27.20	27.53	32.37	33.32	32.79	24.36				

Note: ! = Dosing phase; " = 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 (\$)

TABLE 3.1 - Body weight (g) - During treatment - Group mean data

STUDY NO.: 41950

FEMALES

Group (s)	1!	1"	8	Day of Phase				29	36	43
				15	22	29	36			
1	(n)	15	15	15	15	15	15	15	15	15
	Mean	162.17	178.80	198.72	213.41	228.46	243.88	240.85	243.88	253.03
2	SD	5.99	10.09	12.28	11.70	14.69	13.80	19.00	13.80	12.36
	(n)	10	10	10	10	10	10	10	10	10
	Mean	162.21	176.00	192.34	211.85	226.13	245.88	237.80	245.88	254.63
	SD	5.86	8.00	11.13	8.87	12.15	11.52	8.96	11.52	11.53
3	(n)	10	10	10	10	10	10	10	10	10
	Mean	162.10	177.27	194.61	214.44	229.74	245.34	242.79	245.34	253.61
	SD	5.94	6.31	7.24	5.86	10.77	11.29	11.26	11.29	12.61
4	(n)	15	15	15	15	15	15	15	15	15
	Mean	162.09	175.90	197.71	214.87	230.26	251.07	243.28	251.07	253.10
	SD	6.36	7.35	9.75	8.02	8.48	13.07	15.38	13.07	10.54

Note: ! = Pre-test 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 AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 3.1 - Body weight (g) - During treatment - Group mean data

STUDY NO.: 41950

FEMALES

Group(s)	50!		57	64	D a y			P h a s e			92
	(n)	Mean SD			71	78	85				
1	15		15	15	15	15	15	15	15	10	
	254.78 14.74		261.68 14.95	269.66 18.20	270.19 14.71	276.71 20.11	278.95 20.18	275.31 18.36			
2	10		10	10	10	10	10	10	10	10	
	258.67 11.19		264.32 10.65	270.11 10.21	272.90 11.66	276.19 11.72	277.88 11.12	274.83 10.17			
3	10		10	10	10	10	10	10	10	10	
	260.02 12.25		262.82 8.74	271.92 10.48	275.05 13.44	274.47 13.98	276.28 13.08	275.89 13.29			
4	15		15	15	15	15	15	15	15	10	
	259.55 13.48		264.80 12.25	262.88 12.59	263.69 13.57	262.43* 11.68	266.18 11.15	268.04 10.29			

Note: ! = 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 AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 3.2 - Body weight (g) - During recovery - Group mean data

STUDY NO.: 41950

MALES

Group(s)	1"	8	15	D a y		P h a s e		43	50	57
				22	29	36	43			
1	(n) Mean SD	5 447.06 34.07	5 449.67 35.13	5 456.21 34.01	5 457.77 33.77	5 459.39 39.16	5 463.58 42.57	5 474.71 43.23	5 479.96 37.64	5 476.29 40.64
4	(n) Mean SD	5 422.41 43.41	5 420.44 37.58	5 433.56 40.09	5 442.74 36.24	5 441.47 38.92	5 451.33 38.23	5 454.92 35.07	5 462.49 35.15	5 460.85 39.90

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 (\$)

TABLE 3.2 - Body weight (g) - During recovery - Group mean data

STUDY NO.: 41950

FEMALES

Group(s)	1"	8	15	D a y		o f		P h a s e		43	50	57
				22	29	36	43	50	57			
1	(n)	5	5	5	5	5	5	5	5	5	5	5
	Mean	278.21	292.69	289.90	296.90	295.15	295.11	296.04	287.97	295.11	296.04	287.97
4	SD	14.40	16.71	16.65	17.64	13.90	18.00	17.20	17.62	18.00	17.20	17.62
	(n)	5	5	5	5	5	5	5	5	5	5	5
	Mean	249.82*	251.49**	267.80	278.47	277.72	277.54	275.14	270.66	277.54	275.14	270.66
	SD	14.65	17.04	20.41	19.66	17.17	14.82	16.13	14.41	14.82	16.13	14.41

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 (§)

TABLE 4 - Body weight (g) change* - Group mean data

STUDY NO.: 41950

MALES

Group(s)	Phase															
	8	15	22	29	36	43	50	57	64	71	78	85				
1	(n)	15	15	15	15	15	15	15	15	15	15	15				
	Mean	40.41	70.77	94.63	119.15	136.09	149.60	166.13	175.87	185.11	192.62	198.55	206.20	206.20	206.20	206.20
	SD	3.53	8.48	9.23	10.63	12.42	12.64	13.45	12.73	14.83	14.56	15.88	15.33	15.33	15.33	15.33
2	(n)	10	10	10	10	10	10	10	10	10	10	10				
	Mean	43.72	78.59	106.96*	127.80	146.94	161.88	175.15	185.95	193.64	204.76	209.24	214.85	214.85	214.85	214.85
	SD	6.51	10.71	14.76	15.66	19.82	22.98	19.84	20.41	21.39	24.07	21.83	22.67	22.67	22.67	22.67
3	(n)	10	10	10	10	10	10	10	10	10	10	10				
	Mean	42.42	73.99	100.43	118.72	138.90	154.99	167.72	179.49	187.46	196.93	199.66	206.03	206.03	206.03	206.03
	SD	4.35	6.25	9.25	8.24	11.88	10.22	11.83	13.62	12.27	13.14	13.79	16.22	16.22	16.22	16.22
4	(n)	15	15	15	15	15	15	15	15	15	15	15				
	Mean	45.59*	78.74*	107.10*	128.45	149.73	159.12	166.55	174.72	178.96	180.67	180.79	183.00*	183.00*	183.00*	183.00*
	SD	4.92	8.59	13.56	15.37	16.95	21.13	19.13	21.27	21.99	26.95	27.85	27.81	27.81	27.81	27.81

Note: Data for 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 (S)

* = mean body weight change relevant to Day 1 of the study

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 4 - Body weight (g) change^a - Group mean data

STUDY NO.: 41950

MALES

Group (s)	92!	1"	8	Day of Phase				43	50	57
				15	22	29	36			
1	(n)	10	5	5	5	5	5	5	5	5
	Mean	210.35	207.04	209.66	216.20	217.76	219.38	234.69	239.94	236.27
	SD	12.09	25.01	26.16	24.82	24.62	30.27	34.40	28.92	32.20
2	(n)	10								
	Mean	211.80								
	SD	21.26								
3	(n)	10								
	Mean	206.01								
	SD	16.09								
4	(n)	10	5	5	5	5	5	5	5	5
	Mean	168.95**	188.07	186.10	199.22	208.40	207.13	220.58	228.15	226.51
	SD	18.16	36.22	30.75	33.34	29.66	32.32	28.65	28.89	33.72

Note: ! = Dosing phase; " = 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

° = mean body weight change relevant to Day 1 of the study

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 4 - Body weight (g) change* - Group mean data

STUDY NO.: 41950

FEMALES

Group(s)	Day of Phase											
	8	15	22	29	36	43	50	57	64	71	78	85
1	(n)	15	15	15	15	15	15	15	15	15	15	15
	Mean	19.92	34.61	49.66	62.06	65.08	74.23	75.98	82.88	90.86	91.39	97.91
	SD	9.31	8.37	10.57	12.05	9.03	7.78	8.82	10.13	12.24	8.81	12.01
2	(n)	10	10	10	10	10	10	10	10	10	10	10
	Mean	16.34	35.85	50.12	61.79	69.88	78.63	82.66	88.31	94.10	96.90	101.87
	SD	4.59	7.70	10.16	11.04	12.25	8.92	7.77	7.51	6.01	8.57	9.93
3	(n)	10	10	10	10	10	10	10	10	10	10	10
	Mean	17.34	37.17	52.47	65.52	68.07	76.35	82.75	85.55	94.65	97.79	99.02
	SD	6.03	3.49	7.88	12.49	11.30	7.71	9.62	8.42	6.85	13.47	11.25
4	(n)	15	15	15	15	15	15	15	15	15	15	15
	Mean	21.82	38.98	54.36	67.39	75.18*	77.20	83.66	88.90	86.98	87.80	90.28*
	SD	5.92	5.87	5.42	10.71	9.67	7.18	10.08	8.64	8.90	8.47	7.07

Note: Data for 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 (\$)

* = mean body weight change relevant to Day 1 of the study

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 4 - Body weight (g) change* - Group mean data

STUDY NO.: 41950

FEMALES

Group(s)	92!	1"	8	Day of Phase				43	50	57
				15	22	29	36			
1	(n) Mean SD	5 103.74 11.93	5 118.22 17.82	5 115.44 16.92	5 122.43 18.90	5 120.68 7.43	5 117.71 10.31	5 120.64 13.17	5 121.57 14.38	5 113.50 15.53
2	(n) Mean SD	10 98.82 9.07								
3	(n) Mean SD	10 98.62 9.30								
4	(n) Mean SD	10 90.68 7.41	5 76.85** 6.86	5 78.52** 10.54	5 94.83 12.26	5 105.50 11.54	5 104.75* 9.94	5 104.57* 7.16	5 102.17* 8.30	5 97.69 9.46

Note: ! = Dosing phase; " = 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

° = mean body weight change relevant to Day 1 of the study

TABLE 5.1 - Ophthalmoscopy - Before treatment - Group mean data

STUDY NO.: 41950

MALES

Group Observation	1		2		3		4	
	a	b	a	b	a	b	a	b
	15	100.0	10	100.0	10	100.0	15	100.0
No significant lesions								

Key: () = Number of animals observed
a = Number of animals affected
b = % of observation in group

TABLE 5.1 - Ophthalmoscopy - Before treatment - Group mean data

STUDY NO.: 41950

FEMALES

Group	1	2	3	4
Observation	(15)	(10)	(10)	(15)
	a b	a b	a b	a b
	15 100.0	10 100.0	10 100.0	15 100.0

No significant lesions

Key: () = Number of animals observed
a = Number of animals affected
b = % of observation in group

TABLE 5.2 - Ophthalmoscopy - At the end of treatment - Group mean data

STUDY NO.: 41950

MALES

Group	1	4
Observation	(15)	(15)
	a	b
	15	15
	100.0	100.0

No significant lesions

Key: () = Number of animals observed
a = Number of animals affected
b = % of observation in group

TABLE 5.2 - Ophthalmoscopy - At the end of treatment - Group mean data

STUDY NO.: 41950

FEMALES

Group	1	4
Observation	(15)	(15)
	a	b
No significant lesions	15	15
	100.0	100.0

Key: () = Number of animals observed
a = Number of animals affected
b = % of observation in group

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 6.1 - Haematology - At the end of treatment - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control			Group 2			Group 3			Group 4			
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	
RED BLOOD CELL COUNT 10 ¹² /l	8.871	0.270	10	8.710	0.410	10	8.463*	0.342	10	8.019**	0.354	10	
HAEMOGLOBIN g/dl	(S)	16.16	0.27	10	15.88	0.37	10	15.44*	0.72	10	15.26**	0.63	10
HAEMATOCRIT %	(S)	46.53	0.70	10	45.70	1.11	10	44.41*	2.03	10	43.63**	1.79	10
MEAN RED BLOOD CELL VOLUME fl		52.47	1.51	10	52.52	1.54	10	52.52	1.13	10	54.39**	1.19	10
MEAN CORPUSCULAR Hb pg		18.23	0.49	10	18.25	0.57	10	18.23	0.41	10	19.03**	0.38	10
MEAN CORPUSCULAR Hb CONC. g/dl		34.74	0.31	10	34.76	0.25	10	34.74	0.41	10	34.95	0.28	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 (S)

Note: Data for Dosing phase

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 6.1 - Haematology - At the end of treatment - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control		Group 2		Group 3		Group 4	
	Mean	SD	Mean	n	Mean	n	Mean	n
PLATELETS 10 ⁹ /l	860.1	77.7	791.9	10	830.4	10	877.7	10
PROTHROMBIN TIME sec	17.21	0.34	16.91	10	16.65*	10	17.18	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 Note: Modified t test if group variances are inhomogeneous (\$) Note: Data for Dosing phase								

TABLE 6.1 - Haematology - At the end of treatment - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control		Group 2		Group 3		Group 4	
	Mean	SD	n	Mean	n	Mean	SD	n
WHITE BLOOD CELL COUNT 10 ⁹ /l	10.906	1.764	10	10.099	10	10.715	2.038	10
NEUTROPHILS %	15.45	5.14	10	16.77	10	16.01	5.69	10
LYMPHOCYTES %	77.45	4.65	10	75.96	10	77.09	6.26	10
MONOCYTES %	4.32	0.99	10	4.23	10	3.97	1.01	10
EOSINOPHILS %	1.55	0.35	10	1.91	10	1.81	0.54	10
BASOPHILS %	0.25	0.07	10	0.16*	10	0.22	0.08	10
LARGE UNSTAINED CELLS %	1.00	0.18	10	0.91	10	0.92	0.19	10

Controls from group(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 Dosing phase

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 6.1 - Haematology - At the end of treatment - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control			Group 2			Group 3			Group 4		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
RED BLOOD CELL COUNT 10 ¹² /l	7.837	0.290	10	7.717	0.236	10	7.558	0.343	10	7.701	0.204	10
HAEMOGLOBIN g/dl	14.96	0.60	10	14.62	0.44	10	14.63	0.51	10	14.94	0.46	10
HAEMATOCRIT %	42.16	1.64	10	41.57	1.48	10	41.50	1.53	10	41.87	1.00	10
MEAN RED BLOOD CELL VOLUME fl	53.83	0.94	10	53.88	0.95	10	54.94	0.81	10	54.37	1.34	10
MEAN CORPUSCULAR Hb pg	19.09	0.29	10	18.94	0.38	10	19.38	0.32	10	19.38	0.58	10
MEAN CORPUSCULAR Hb CONC. g/dl	35.45	0.26	10	35.18	0.67	10	35.26	0.30	10	35.67	0.35	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

TABLE 6.1 - Haematology - At the end of treatment - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control		Group 2		Group 3		Group 4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PLATELETS 10 ⁹ /l	888.9	77.8	10	865.4	138.2	10	870.1	79.5
PROTHROMBIN TIME sec	(S)	16.70	1.65	10	16.93	0.97	9	16.40
							10	16.35
							0.24	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

TABLE 6.1 - Haematology - At the end of treatment - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control		Group 2		Group 3		Group 4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
WHITE BLOOD CELL COUNT 10 ⁹ /l	7.578	1.254	6.531	1.364	7.034	1.264	7.605	2.482
NEUTROPHILS %	9.89	3.91	16.32**	5.54	12.27	3.70	11.42	3.82
LYMPHOCYTES %	83.70	4.37	76.16**	7.15	81.16	4.30	81.06	4.77
MONOCYTES %	3.28	0.80	3.95	1.46	3.64	0.87	4.22	1.11
EOSINOPHILS %	2.14	0.37	2.47	0.68	1.85	0.45	2.17	0.48
BASOPHILS %	0.19	0.07	0.16	0.07	0.21	0.13	0.21	0.06
LARGE UNSTAINED CELLS %	0.80	0.09	0.96	0.27	0.89	0.23	0.92	0.27

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

TABLE 6.2 - Haematology - At the end of recovery - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	n
RED BLOOD CELL COUNT 10 ¹² /l	8.482	0.179	8.520	5
HAEMOGLOBIN g/dl	15.70	0.23	15.86	5
HAEMATOCRIT %	46.78	0.77	46.88	5
MEAN RED BLOOD CELL VOLUME fl	55.16	0.71	55.08	5
MEAN CORPUSCULAR Hb pg	18.50	0.19	18.64	5
MEAN CORPUSCULAR Hb CONC. g/dl	33.52	0.33	33.82	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

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 6.2 - Haematology - At the end of recovery - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	n
PLATELETS 10 ⁹ /l	799.0	58.9	846.0	5
PROTHROMBIN TIME sec	17.73	0.67	16.70	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 Note: Data for Recovery phase				

TABLE 6.2 - Haematology - At the end of recovery - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	n
WHITE BLOOD CELL COUNT 10 ⁹ /l	10.776	4.068	9.176	5
NEUTROPHILS %	18.22	6.21	17.40	5
LYMPHOCYTES %	74.78	6.52	75.68	5
MONOCYTES %	3.18	0.72	3.14	5
EOSINOPHILS %	1.84	0.51	1.76	5
BASOPHILS %	0.18	0.04	0.22	5
LARGE UNSTAINED CELLS %	1.80	0.37	1.82	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

TABLE 6.2 - Haematology - At the end of recovery - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	SD
RED BLOOD CELL COUNT 10 ¹² /l	7.654	0.175	7.738	0.493
HAEMOGLOBIN g/dl	14.66	0.27	15.16	0.94
HAEMATOCRIT %	42.36	0.88	43.74	2.64
MEAN RED BLOOD CELL VOLUME fl	55.38	1.13	56.56	0.82
MEAN CORPUSCULAR Hb pg	19.16	0.37	19.60*	0.14
MEAN CORPUSCULAR Hb CONC. g/dl	34.62	0.24	34.66	0.34

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

Note: Data for Recovery phase

TABLE 6.2 - Haematology - At the end of recovery - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	n
PLATELETS 10 ⁹ /l	903.4	102.2	886.2	5
PROTHROMBIN TIME sec	17.40	0.41	17.24	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

Note: Modified t test if group variances are inhomogeneous (\$)

Note: Data for Recovery phase

TABLE 6.2 - Haematology - At the end of recovery - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	SD
WHITE BLOOD CELL COUNT 10 ⁹ /l	5.980	0.733	5.204	1.252
NEUTROPHILS %	15.96	3.67	20.16	6.11
LYMPHOCYTES %	77.20	4.10	74.18	5.58
MONOCYTES %	3.64	1.06	2.54	0.72
EOSINOPHILS % (S)	1.80	0.25	1.96	1.06
BASOPHILS %	0.16	0.05	0.22	0.16
LARGE UNSTAINED CELLS %	1.28	0.19	0.96*	0.17

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 AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 7.1 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control			Group 2			Group 3			Group 4		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
ALKALINE PHOSPHATASE U/l	227.25	17.00	10	202.52*	29.55	10	284.35**	39.27	10	457.61**	66.88	10
ALANINE AMINO-TRANSFERASE U/l	44.77	5.27	10	44.63	5.07	10	56.82**	11.98	10	50.43	6.85	10
ASPARTATE AMINO-TRANSFERASE U/l	81.09	8.02	10	84.34	9.43	10	91.63	18.10	10	91.15	10.75	10
GAMMA-GLUTAMYL TRANSFERASE U/l	0.970	0.996	10	0.640	0.901	10	0.350	0.268	10	0.530	0.732	10
TOTAL BILIRUBIN mg/dl	0.219	0.034	10	0.536	0.878	10	0.200	0.067	10	0.165**	0.032	10
TOTAL CHOLESTEROL mg/dl	74.47	6.73	10	65.73*	5.94	10	54.71**	6.61	10	67.42	9.07	10
TRIGLYCERIDES mg/dl	32.21	11.48	10	37.20	9.62	10	28.86	8.07	10	33.97	7.33	10
GLUCOSE mg/dl	120.50	7.55	10	118.19	10.50	10	128.55	19.30	10	123.88	6.01	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 AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 7.1 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control			Group 2			Group 3			Group 4		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
UREA mg/dl	34.84	3.84	10	32.93	3.14	10	35.94	4.63	10	47.37**	3.70	10
CREATININE mg/dl	0.412	0.041	10	0.389	0.040	10	0.357**	0.031	10	0.317**	0.028	10
CHLORIDE mmol/l	91.51	0.80	10	92.23	0.72	10	92.34	1.03	10	93.64**	0.76	10
INORGANIC PHOSPHORUS mg/dl	6.38	0.32	10	6.33	0.40	10	6.59	0.56	10	6.36	0.29	10
CALCIUM mmol/l	2.718	0.057	10	2.626**	0.038	10	2.618**	0.062	10	2.502**	0.046	10
SODIUM mmol/l	144.10	0.65	10	144.83	1.44	10	144.56	1.41	10	143.45	1.07	10
POTASSIUM mmol/l	4.215	0.084	10	4.229	0.209	10	4.456	0.402	10	4.338	0.150	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 AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 7.1 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control			Group 2			Group 3			Group 4		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
TOTAL PROTEIN g/dl	7.16	0.29	10	6.94	0.27	10	6.68**	0.18	10	6.18**	0.38	10
ALBUMIN g/dl	4.13	0.12	10	3.93	0.29	10	4.02	0.17	10	3.86*	0.22	10
GLOBULIN g/dl	3.03	0.27	10	3.01	0.47	10	2.66	0.16	10	2.32**	0.38	10
ALBUMIN/GLOBULIN RATIO	1.37	0.12	10	1.34	0.27	10	1.52	0.13	10	1.70**	0.27	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 AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 7.1 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control			Group 2			Group 3			Group 4		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
ALKALINE PHOSPHATASE U/l	164.25	21.87	10	213.14	137.30	10	170.01	33.66	10	271.10**	35.10	10
ALANINE AMINO-TRANSFERASE U/l	37.27	5.23	10	108.38	228.67	10	34.95	3.91	10	38.02	7.04	10
ASPARTATE AMINO-TRANSFERASE U/l	76.60	11.21	10	132.52	175.07	10	80.67	8.20	10	74.52	6.13	10
GAMMA-GLUTAMYL TRANSFERASE U/l	0.580	0.620	10	1.460	2.072	10	0.720	0.531	10	0.600	0.589	10
TOTAL BILIRUBIN mg/dl	0.233	0.034	10	0.341	0.277	10	0.240	0.136	10	0.161*	0.087	10
TOTAL CHOLESTEROL mg/dl	90.01	11.34	10	90.35	17.61	10	71.80**	10.50	10	80.15	10.76	10
TRIGLYCERIDES mg/dl	24.45	2.44	10	30.74	9.77	10	34.28**	7.20	10	39.89**	8.63	10
GLUCOSE mg/dl	121.28	10.02	10	123.86	9.87	10	133.54	16.61	10	129.44	13.24	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

Note: Data for Dosing phase Modified t test if group variances are inhomogeneous (\$)

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 7.1 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control			Group 2			Group 3			Group 4		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
UREA mg/dl	39.92	3.23	10	43.33	6.00	10	40.68	3.94	10	44.04	3.54	10
CREATININE mg/dl	0.460	0.041	10	0.544	0.138	10	0.463	0.061	10	0.440	0.030	10
CHLORIDE mmol/l	94.43	1.01	10	94.60	1.64	10	94.57	1.14	10	93.51	2.50	10
INORGANIC PHOSPHORUS mg/dl	5.74	0.42	10	5.32	0.46	10	5.56	0.45	10	6.06	0.75	10
CALCIUM mmol/l	2.641	0.067	10	2.647	0.082	10	2.661	0.049	10	2.673	0.067	10
SODIUM mmol/l	144.16	1.32	10	145.40	1.84	10	144.77	1.50	10	144.25	0.78	10
POTASSIUM mmol/l	4.308	0.375	10	4.224	0.308	10	4.021	0.301	10	4.024	0.443	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 AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 7.1 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control		Group 2		Group 3		Group 4	
	Mean	SD	n	Mean	SD	n	Mean	SD
TOTAL PROTEIN g/dl	6.82	0.26	10	7.09	0.27	10	6.97	0.28
ALBUMIN g/dl	4.36	0.15	10	4.49	0.20	10	4.72**	0.21
GLOBULIN g/dl	2.46	0.15	10	2.60	0.17	10	2.25	0.28
ALBUMIN/GLOBULIN RATIO	1.78	0.10	10	1.73	0.13	10	2.13**	0.28
							2.35**	0.42

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 AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 7.2 - Clinical chemistry - At the end of recovery - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	SD
ALKALINE PHOSPHATASE U/l	220.16	29.09	5 323.96*	78.42
ALANINE AMINO-TRANSFERASE U/l	46.08	4.51	5 52.54	7.74
ASPARTATE AMINO-TRANSFERASE U/l	75.82	7.87	5 76.64	9.02
GAMMA-GLUTAMYL TRANSFERASE U/l	0.720	0.729	5 0.080	0.130
TOTAL BILIRUBIN mg/dl	0.148	0.026	5 0.180	0.107
TOTAL CHOLESTEROL mg/dl	77.88	12.75	5 73.26	9.27
TRIGLYCERIDES mg/dl	38.88	13.94	5 38.10	4.67
GLUCOSE mg/dl	131.36	14.48	5 126.34	10.20

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

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 7.2 - Clinical chemistry - At the end of recovery - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control		Group 4	
	Mean	SD	n	Mean
UREA mg/dl	35.66	2.28	5	46.04**
CREATININE mg/dl	0.438	0.022	5	0.424
CHLORIDE mmol/l	92.08	0.41	5	92.10
INORGANIC PHOSPHORUS mg/dl	6.19	0.31	5	7.29**
CALCIUM mmol/l	2.698	0.038	5	2.696
SODIUM mmol/l	138.44	0.77	5	137.44*
POTASSIUM mmol/l	4.182	0.139	5	4.086

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

TABLE 7.2 - Clinical chemistry - At the end of recovery - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	n
TOTAL PROTEIN g/dl	7.04	0.21	6.96	5
ALBUMIN g/dl	3.98	0.11	3.92	5
GLOBULIN g/dl	3.06	0.27	3.04	5
ALBUMIN/GLOBULIN RATIO	1.31	0.14	1.30	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 AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 7.2 - Clinical chemistry - At the end of recovery - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	SD
ALKALINE PHOSPHATASE U/l	135.38	19.65	175.12*	19.50
ALANINE AMINO-TRANSFERASE U/l	36.58	3.42	31.46*	2.06
ASPARTATE AMINO-TRANSFERASE U/l	75.52	8.25	68.08	10.35
GAMMA-GLUTAMYL TRANSFERASE U/l	0.480	0.327	0.980	1.455
TOTAL BILIRUBIN mg/dl	0.254	0.036	0.212	0.061
TOTAL CHOLESTEROL mg/dl	84.48	9.59	88.36	13.34
TRIGLYCERIDES mg/dl	24.16	6.56	37.20*	7.84
GLUCOSE mg/dl	127.14	9.08	134.36	8.63

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

TABLE 7.2 - Clinical chemistry - At the end of recovery - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	SD
UREA mg/dl	47.70	6.62	53.80	14.13
CREATININE mg/dl	0.540	0.044	0.514	0.015
CHLORIDE mmol/l	93.58	1.03	92.90	0.74
INORGANIC PHOSPHORUS (s) mg/dl	4.97	0.72	4.68	0.21
CALCIUM mmol/l	2.690	0.073	2.712	0.049
SODIUM mmol/l	136.52	0.58	137.82**	0.50
POTASSIUM mmol/l	3.758	0.165	3.590	0.137

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

TABLE 7.2 - Clinical chemistry - At the end of recovery - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	n
TOTAL PROTEIN g/dl	7.42	0.15	7.48	5
ALBUMIN g/dl	4.56	0.21	5.16**	5
GLOBULIN g/dl	(S)	0.34	2.32*	5
ALBUMIN/GLOBULIN RATIO	1.62	0.30	2.23**	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

TABLE 8.1 - Urinalysis - At the end of treatment - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control		Group 2		Group 3		Group 4	
	Mean	SD	n	Mean	SD	n	Mean	SD
URINE VOLUME (OVERNIGHT)	11.35	2.27	10	12.15	1.51	10	11.45	2.49
ml								
SPECIFIC GRAVITY	1.0135	0.0047	10	1.0150	0.0053	10	1.0155	0.0028
							1.0210**	0.0066
								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 AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 8.1 - Urinalysis - At the end of treatment - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control		Group 2		Group 3		Group 4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
URINE VOLUME (OVERNIGHT)	5.85	2.00	6.05	2.49	5.85	1.40	6.85	1.55
ml								
SPECIFIC GRAVITY	1.0220	0.0063	1.0210	0.0061	1.0225	0.0049	1.0255	0.0037

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

TABLE 8.2 - Urinalysis - At the end of recovery - Group mean data

STUDY NO.: 41950

MALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	n
URINE VOLUME (OVERNIGHT) ml	7.40	1.75	7.30	5
SPECIFIC GRAVITY	1.0180	0.0067	1.0170	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

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 8.2 - Urinalysis - At the end of recovery - Group mean data

STUDY NO.: 41950

FEMALES

Parameter/units	Control		Group 4	
	Mean	SD	Mean	n
URINE VOLUME (OVERNIGHT) ml	3.40	1.08	3.60	5
SPECIFIC GRAVITY	1.0240	0.0042	1.0270	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

TABLE 9.1 - Terminal body weight (g) - Final sacrifice - Group mean data

STUDY NO.: 41950

MALES

Controls from group(s): 1		Data homogeneous by Bartlett's test (Dunnett's test)			
Group	Control	2		3	
Number/group	10	10	10	10	4
Mean	447.94	443.94	441.62	403.03	
Standard deviation	15.50	27.60	20.48	25.09	
Group diff. at p < 0.05		24.83	24.83	24.83*	
Group diff. at p < 0.01		31.49	31.49	31.49*	
Analysis of variance: F ratio = 8.52 Df = 3/ 36 F probability = 0.000					
Note: a * indicates group mean is significantly different from control at level of significance shown.					

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 9.1 - Terminal body weight (g) - Final sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Controls from group(s): 1		Data homogeneous by Bartlett's test (Dunnett's test)			
Group	Number/group	2	3	4	
Control	10	10	10	10	
Mean	274.20	274.82	277.13	265.99	
Standard deviation	18.24	10.49	14.38	11.28	
Group diff. at p < 0.05		15.28	15.28	15.28	
Group diff. at p < 0.01		19.38	19.38	19.38	

Analysis of variance: F ratio = 1.22 Df = 3/ 36 F probability = 0.317

Note: a * indicates group mean is significantly different from control at level of significance shown.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 9.2 - Terminal body weight (g) - Recovery sacrifice - Group mean data

STUDY NO.: 41950

MALES

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

Group	Control	4
Number/group	5	5
Mean	475.76	460.38
Standard deviation	39.13	39.07
Group diff. at p < 0.05		57.20
Group diff. at p < 0.01		83.24

Analysis of variance: F ratio = 0.39 Df = 1/ 8 F probability = 0.557

Note: a * indicates group mean is significantly different from control at level of significance shown.

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 9.2 - Terminal body weight (g) - Recovery sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Controls from group(s): 1		Data homogeneous by Bartlett's test (Dunnett's test)	
Group	Control	4	
Number/group	5	5	
Mean	289.92	272.04	
Standard deviation	17.67	12.11	
Group diff. at p < 0.05		22.16	
Group diff. at p < 0.01		32.26	
Analysis of variance: F ratio = 3.48 Df = 1/ 8 F probability = 0.097			
Note: a * indicates group mean is significantly different from control at level of significance shown.			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 41950

MALES

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

Group	2	3	4
Number/group	10	10	10
Mean	0.0551	0.0505	0.0462
Standard deviation	0.0078	0.0057	0.0023
Group diff. at p < 0.05		0.0069	0.0058*
Group diff. at p < 0.01		0.0098	0.0083*

Analysis of variance: F ratio = 4.32 Df = 3/ 36 F probability = 0.011

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 (Dunnnett's test)

Group	2	3	4
Number/group	10	10	10
Mean	1.868	1.796	1.827
Standard deviation	0.091	0.084	0.113
Group diff. at p < 0.05		0.101	0.101
Group diff. at p < 0.01		0.128	0.128

Analysis of variance: F ratio = 1.30 Df = 3/ 36 F probability = 0.290

Note: a * indicates group mean is significantly different from control at level of significance shown.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 41950

MALES

Organ: Epididymides	Controls from group: 1	Data inhomogeneous by Bartlett's test (Modified t test)
Group	2	3
Number/group	Control 10	10
Mean	1.4252	1.4014
Standard deviation	0.1625	1.3732
Group diff. at p < 0.05		0.1191
Group diff. at p < 0.01		0.1441
		0.2067
		0.1751
		0.2192
Analysis of variance: F ratio = 2.70 Df = 3/ 36 F probability = 0.059		
Note: * 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	2	3
Number/group	Control 10	10
Mean	1.446	1.393
Standard deviation	0.122	0.170
Group diff. at p < 0.05		0.145
Group diff. at p < 0.01		0.184
Analysis of variance: F ratio = 4.29 Df = 3/ 36 F probability = 0.011		
Note: * indicates group mean is significantly different from control at level of significance shown.		

TABLE 10.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 41950

MALES

Organ: Kidneys	Controls from group: 1				Data homogeneous by Bartlett's test (Dunnnett's test)			
	Group	Control	2	3	4			
Number/group	10		10	10	10			
Mean	2.650		2.610	2.736	2.816			
Standard deviation	0.132		0.222	0.245	0.157			
Group diff. at p < 0.05			0.213	0.213	0.213			
Group diff. at p < 0.01			0.271	0.271	0.271			

Analysis of variance: F ratio = 2.23 Df = 3/ 36 F probability = 0.100
 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 (Dunnnett's test)			
	Group	Control	2	3	4			
Number/group	10		10	10	10			
Mean	12.753		12.417	14.363	16.339			
Standard deviation	1.063		1.236	0.992	1.364			
Group diff. at p < 0.05			1.286	1.286*	1.286*			
Group diff. at p < 0.01			1.631	1.631	1.631*			

Analysis of variance: F ratio = 23.41 Df = 3/ 36 F probability = 0.000
 Note: a * indicates group mean is significantly different from control at level of significance shown.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 41950

MALES

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

Group	Control	2	3	4
Number/group	10	10	10	10
Mean	0.8852	0.9106	0.8318	0.7200
Standard deviation	0.0837	0.0904	0.0924	0.0633
Group diff. at p < 0.05		0.0913	0.0913	0.0913*
Group diff. at p < 0.01		0.1158	0.1158	0.1158*

Analysis of variance: F ratio = 10.32 Df = 3/ 36 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	10	10	10	10
Mean	4.0349	3.9290	3.8247	3.7806
Standard deviation	0.2200	0.4808	0.1314	0.1851
Group diff. at p < 0.05		0.3782	0.1833*	0.2057*
Group diff. at p < 0.01		0.5427	0.2630	0.2951

Analysis of variance: F ratio = 1.56 Df = 3/ 36 F probability = 0.215
 Note: a * indicates group mean is significantly different from control at level of significance shown.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 41950

MALES

Organ: Thymus	Controls from group: 1		Data homogeneous by Bartlett's test (Dunnnett's test)			
	Group	2	3	4		
Number/group	10	10	10	10		
Mean	0.3336	0.2925	0.3020	0.2390		
Standard deviation	0.0798	0.0850	0.0618	0.0485		
Group diff. at p < 0.05		0.0771	0.0771	0.0771*		
Group diff. at p < 0.01		0.0978	0.0978	0.0978		

Analysis of variance: F ratio = 3.13 Df = 3/ 36 F probability = 0.037

Note: a * indicates group mean is significantly different from control at level of significance shown.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

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

Group	Control	2	3	4
Number/group	10	10	10	10
Mean	0.0590	0.0609	0.0597	0.0576
Standard deviation	0.0066	0.0066	0.0044	0.0055
Group diff. at p < 0.05		0.0064	0.0064	0.0064
Group diff. at p < 0.01		0.0082	0.0082	0.0082

Analysis of variance: F ratio = 0.55 Df = 3/ 36 F probability = 0.654
 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 (Dunnnett's test)

Group	Control	2	3	4
Number/group	10	10	10	10
Mean	1.728	1.757	1.719	1.761
Standard deviation	0.082	0.073	0.056	0.057
Group diff. at p < 0.05		0.074	0.074	0.074
Group diff. at p < 0.01		0.094	0.094	0.094

Analysis of variance: F ratio = 0.95 Df = 3/ 36 F probability = 0.430
 Note: a * indicates group mean is significantly different from control at level of significance shown.

TABLE 10.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Heart		Controls from group: 1				Data homogeneous by Bartlett's test (Dunnnett's test)			
		Control							
		10				2			
						10			
Number/group									

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

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

Group	Control	2	3	4
Number/group	10	10	10	10
Mean	7.454	7.731	8.630	11.610
Standard deviation	0.714	0.403	0.701	0.688
Group diff. at p < 0.05		0.701	0.701*	0.701*
Group diff. at p < 0.01		0.889	0.889*	0.889*

Analysis of variance: F ratio = 88.58 Df = 3/ 36 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	10	10	10	10
Mean	0.1292	0.1253	0.1265	0.1267
Standard deviation	0.0196	0.0249	0.0188	0.0198
Group diff. at p < 0.05		0.0229	0.0229	0.0229
Group diff. at p < 0.01		0.0291	0.0291	0.0291

Analysis of variance: F ratio = 0.06 Df = 3/ 36 F probability = 0.974
 Note: a * indicates group mean is significantly different from control at level of significance shown.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Spleen		Controls from group: 1		Data homogeneous by Bartlett's test (Dunnett's test)	
Group	Number/group	Control		3	
		10	2	10	4
Mean		0.6557	0.7505	0.7101	0.6152
Standard deviation		0.0765	0.1527	0.0649	0.0983
Group diff. at p < 0.05			0.1137	0.1137	0.1137
Group diff. at p < 0.01			0.1442	0.1442	0.1442
Analysis of variance: F ratio = 3.29 Df = 3/ 36 F probability = 0.031					
Note: a * indicates group mean is significantly different from control at level of significance shown.					

Organ: Thymus		Controls from group: 1		Data inhomogeneous by Bartlett's test (Modified t test)	
Group	Number/group	Control		3	
		10	2	10	4
Mean		0.2720	0.2337	0.2455	0.2395
Standard deviation		0.1094	0.0528	0.0309	0.0443
Group diff. at p < 0.05			0.0869	0.0813	0.0844
Group diff. at p < 0.01			0.1247	0.1167	0.1212
Analysis of variance: F ratio = 0.65 Df = 3/ 36 F probability = 0.593					
Note: a * indicates group mean is significantly different from control at level of significance shown.					

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Uterus	Controls from group: 1		Data inhomogeneous by Bartlett's test (Modified t test)					
Group	Control		2		3		4	
Number/group	10		10		10		10	
Mean	0.5265		0.5459		0.5256		0.7661	
Standard deviation	0.1395		0.1310		0.1788		0.4072	
Group diff. at p < 0.05			0.1369		0.1622		0.3079	
Group diff. at p < 0.01			0.1964		0.2327		0.4418	
Analysis of variance: F ratio = 2.34 Df = 3/ 36 F probability = 0.089								
Note: a * indicates group mean is significantly different from control at level of significance shown.								

TABLE 10.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 41950

MALES

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

Group	4	5
Number/group		
Mean	0.0474	0.0504
Standard deviation	0.0032	0.0032
Group diff. at p < 0.05	0.0064	0.0064
Group diff. at p < 0.01	0.0093	0.0093

Analysis of variance: F ratio = 1.18 Df = 1/ 8 F probability = 0.310
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	4	5
Number/group		
Mean	1.861	1.899
Standard deviation	0.053	0.067
Group diff. at p < 0.05		0.089
Group diff. at p < 0.01		0.129

Analysis of variance: F ratio = 1.00 Df = 1/ 8 F probability = 0.348
Note: a * indicates group mean is significantly different from control at level of significance shown.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 41950

MALES

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

Group	Control	4	5
Number/group	5		
Mean	1.4924	1.4646	
Standard deviation	0.0629	0.0652	
Group diff. at p < 0.05		0.0937	
Group diff. at p < 0.01		0.1364	

Analysis of variance: F ratio = 0.47 Df = 1/ 8 F probability = 0.517
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	5
Number/group	5		
Mean	1.462	1.484	
Standard deviation	0.065	0.079	
Group diff. at p < 0.05		0.106	
Group diff. at p < 0.01		0.154	

Analysis of variance: F ratio = 0.23 Df = 1/ 8 F probability = 0.647
Note: a * indicates group mean is significantly different from control at level of significance shown.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 41950

MALES

Organ: Kidneys		Controls from group: 1		Data homogeneous by Bartlett's test (Dunnett's test)	
Number/group	Group	Control			
	Mean	5	4	5	
Standard deviation		2.782		2.928	
Group diff. at p < 0.05		0.164		0.314	
Group diff. at p < 0.01				0.367	
				0.534	
Analysis of variance: F ratio = 0.85 Df = 1/ 8 F probability = 0.387					
Note: * 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)	
Number/group	Group	Control			
	Mean	5	4	5	
Standard deviation		12.715		16.831	
Group diff. at p < 0.05		1.402		1.584	
Group diff. at p < 0.01				2.189*	
				3.185*	
Analysis of variance: F ratio = 18.92 Df = 1/ 8 F probability = 0.003					
Note: * indicates group mean is significantly different from control at level of significance shown.					

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 41950

MALES

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

Group	Control
Number/group	5
Mean	0.9304
Standard deviation	0.1165
Group diff. at $p < 0.05$	0.8138
Group diff. at $p < 0.01$	0.1126
	0.1676
	0.2439

Analysis of variance: F ratio = 2.59 Df = 1/ 8 F probability = 0.144
 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 (Dunnnett's test)

Group	Control
Number/group	5
Mean	4.1282
Standard deviation	0.2748
Group diff. at $p < 0.05$	3.9220
Group diff. at $p < 0.01$	0.2524
	0.3860
	0.5617

Analysis of variance: F ratio = 1.53 Df = 1/ 8 F probability = 0.251
 Note: a * indicates group mean is significantly different from control at level of significance shown.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 41950

MALES

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

Group	Control	4	5
Number/group	5		
Mean	0.2996	0.2560	
Standard deviation	0.0469	0.0241	
Group diff. at p < 0.05		0.0545	
Group diff. at p < 0.01		0.0794	

Analysis of variance: F ratio = 3.42 Df = 1/ 8 F probability = 0.099

Note: a * indicates group mean is significantly different from control at level of significance shown.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Adrenals	Controls from group: 1	Data homogeneous by Bartlett's test (Dunnnett's test)
Group	Control	4
Number/group	5	5
Mean	0.0586	0.0584
Standard deviation	0.0060	0.0129
Group diff. at p < 0.05		0.0147
Group diff. at p < 0.01		0.0214
Analysis of variance: F ratio = 0.00 Df = 1/ 8 F probability = 0.926		
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 (Dunnnett's test)
Group	Control	4
Number/group	5	5
Mean	1.764	1.680
Standard deviation	0.053	0.095
Group diff. at p < 0.05		0.113
Group diff. at p < 0.01		0.164
Analysis of variance: F ratio = 2.97 Df = 1/ 8 F probability = 0.120		
Note: a * indicates group mean is significantly different from control at level of significance shown.		

TABLE 10.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Heart	Controls from group: 1	Data homogeneous by Bartlett's test (Dunnett's test)
	Control	4
Group	5	5
Number/group	1.048	0.940
Mean	0.102	0.110
Standard deviation		0.155
Group diff. at p < 0.05		0.225
Group diff. at p < 0.01		
Analysis of variance: F ratio = 2.59 Df = 1/ 8 F probability = 0.144		
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		1.832		1.882	
Standard deviation		0.081		0.213	
Group diff. at p < 0.05				0.236	
Group diff. at p < 0.01				0.343	
Analysis of variance: F ratio = 0.25 Df = 1/ 8 F probability = 0.637					
Note: a * indicates group mean is significantly different from control at level of significance shown.					

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Liver		Controls from group: 1		Data homogeneous by Bartlett's test (Dunnnett's test)	
Group	Number/group	Control		4	5
Mean		8.020		10.423	
Standard deviation		0.707		0.751	
Group diff. at p < 0.05				1.067*	
Group diff. at p < 0.01				1.553*	
Analysis of variance: F ratio = 27.13 Df = 1/ 8 F probability = 0.001					
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 (Dunnnett's test)	
Group	Number/group	Control		4	5
Mean		0.1158		0.1196	
Standard deviation		0.0164		0.0152	
Group diff. at p < 0.05				0.0231	
Group diff. at p < 0.01				0.0337	
Analysis of variance: F ratio = 0.14 Df = 1/ 8 F probability = 0.712					
Note: a * indicates group mean is significantly different from control at level of significance shown.					

TABLE 10.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

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

Group	Control	4
Number/group	5	5
Mean	0.6724	0.6098
Standard deviation	0.0792	0.0560
Group diff. at p < 0.05		0.1003
Group diff. at p < 0.01		0.1460

Analysis of variance: F ratio = 2.08 Df = 1/ 8 F probability = 0.185
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	0.2012	0.1892
Standard deviation	0.0415	0.0357
Group diff. at p < 0.05		0.0566
Group diff. at p < 0.01		0.0824

Analysis of variance: F ratio = 0.24 Df = 1/ 8 F probability = 0.640
Note: a * indicates group mean is significantly different from control at level of significance shown.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 10.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Uterus	Controls from group: 1	Data homogeneous by Bartlett's test (Dunnnett's test)
Group	Control	4
Number/group	5	5
Mean	0.7270	0.5026
Standard deviation	0.3759	0.1652
Group diff. at p < 0.05		0.4248
Group diff. at p < 0.01		0.6182
Analysis of variance: F ratio = 1.49 Df = 1/ 8 F probability = 0.256		
Note: a * indicates group mean is significantly different from control at level of significance shown.		

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.1 - Relative organ weights* - Final sacrifice - Group mean data

STUDY NO.: 41950

MALES

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

Group	2	3	4
Number/group	10	10	10
Mean	0.0123	0.0114	0.0115
Standard deviation	0.0015	0.0011	0.0011
Group diff. at p < 0.05	0.0014	0.0014	0.0014
Group diff. at p < 0.01	0.0018	0.0018	0.0018

Analysis of variance: F ratio = 1.71 Df = 3/ 36 F probability = 0.180

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	2	3	4
Number/group	10	10	10
Mean	0.417	0.414	0.463
Standard deviation	0.025	0.023	0.032
Group diff. at p < 0.05	0.031	0.031	0.031*
Group diff. at p < 0.01	0.039	0.039	0.039*

Analysis of variance: F ratio = 8.58 Df = 3/ 36 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

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.1 - Relative organ weights* - Final sacrifice - Group mean data

STUDY NO.: 41950

MALES

Organ: Epididymides		Controls from group: 1		Data homogeneous by Bartlett's test (Dunnett's test)	
Group	Number/group	Control	2	3	4
Mean	10	0.3180	0.3171	0.3115	0.3170
Standard deviation		0.0317	0.0371	0.0182	0.0288
Group diff. at p < 0.05			0.0327	0.0327	0.0327
Group diff. at p < 0.01			0.0414	0.0414	0.0414

Analysis of variance: F ratio = 0.10 Df = 3/ 36 F probability = 0.956
 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	Number/group	Control	2	3	4
Mean	10	0.323	0.331	0.315	0.316
Standard deviation		0.027	0.036	0.021	0.015
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 = 0.78 Df = 3/ 36 F probability = 0.516
 Note: a * indicates group mean is significantly different from control at level of significance shown.
 * = expressed as % organ to body weight ratio

TABLE 11.1 - Relative organ weights* - Final sacrifice - Group mean data

STUDY NO.: 41950

MALES

Organ: Kidneys	Controls from group: 1				Data homogeneous by Bartlett's test (Dunnett's test)			
	Group	2	3	4				
Number/group	Control	10	10	10				
Mean		0.592	0.588	0.619			0.700	
Standard deviation		0.027	0.039	0.044			0.032	
Group diff. at p < 0.05			0.040	0.040			0.040*	
Group diff. at p < 0.01			0.050	0.050			0.050*	

Analysis of variance: F ratio = 20.46 Df = 3/ 36 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 homogeneous by Bartlett's test (Dunnett's test)			
	Group	2	3	4				
Number/group	Control	10	10	10				
Mean		2.846	2.793	3.254			4.056	
Standard deviation		0.198	0.144	0.214			0.258	
Group diff. at p < 0.05			0.228	0.228*			0.228*	
Group diff. at p < 0.01			0.289	0.289*			0.289*	

Analysis of variance: F ratio = 78.84 Df = 3/ 36 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

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.1 - Relative organ weights* - Final sacrifice - Group mean data

STUDY NO.: 41950

MALES

Organ: Spleen		Controls from group: 1		Data homogeneous by Bartlett's test (Dunnnett's test)	
Group	Number/group	Control	2	3	4
Mean	10	0.1976	0.2057	0.1882	0.1786
Standard deviation		0.0171	0.0229	0.0174	0.0102
Group diff. at p < 0.05			0.0192	0.0192	0.0192
Group diff. at p < 0.01			0.0243	0.0243	0.0243

Analysis of variance: F ratio = 4.50 Df = 3/ 36 F probability = 0.009
 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	Number/group	Control	2	3	4
Mean	10	0.9007	0.8895	0.8672	0.9404
Standard deviation		0.0368	0.1341	0.0371	0.0604
Group diff. at p < 0.05			0.0995	0.0374	0.0506
Group diff. at p < 0.01			0.1427	0.0537	0.0727

Analysis of variance: F ratio = 1.55 Df = 3/ 36 F probability = 0.218
 Note: a * indicates group mean is significantly different from control at level of significance shown.
 * = expressed as % organ to body weight ratio

TABLE 11.1 - Relative organ weights* - Final sacrifice - Group mean data

STUDY NO.: 41950

MALES

Organ: Thymus	Controls from group: 1		Data homogeneous by Bartlett's test (Dunnnett's test)			
	Group	2	3	4		
Number/group	Control	10	10	10		
Mean		0.0744	0.0684	0.0592		
Standard deviation		0.0170	0.0136	0.0112		
Group diff. at p < 0.05		0.0161	0.0161	0.0161		
Group diff. at p < 0.01		0.0204	0.0204	0.0204		
Analysis of variance: F ratio = 1.84 Df = 3/ 36 F probability = 0.156						
Note: a * indicates group mean is significantly different from control at level of significance shown.						
° = expressed as % organ to body weight ratio						

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13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.1 - Relative organ weights* - Final sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

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

Group	Control	2	3	4
Number/group	10	10	10	10
Mean	0.0216	0.0222	0.0216	0.0217
Standard deviation	0.0030	0.0025	0.0019	0.0021
Group diff. at p < 0.05		0.0026	0.0026	0.0026
Group diff. at p < 0.01		0.0033	0.0033	0.0033

Analysis of variance: F ratio = 0.14 Df = 3/ 36 F probability = 0.935
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 (Dunnnett's test)

Group	Control	2	3	4
Number/group	10	10	10	10
Mean	0.633	0.640	0.621	0.663
Standard deviation	0.052	0.040	0.024	0.042
Group diff. at p < 0.05		0.044	0.044	0.044
Group diff. at p < 0.01		0.056	0.056	0.056

Analysis of variance: F ratio = 1.93 Df = 3/ 36 F probability = 0.140
Note: a * indicates group mean is significantly different from control at level of significance shown.
* = expressed as % organ to body weight ratio

TABLE 11.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Heart	Controls from group: 1				Data homogeneous by Bartlett's test (Dunnett's test)			
	Group	2	3	4				
Number/group	Control	10	10	10				
Mean		0.371	0.352	0.365				0.350
Standard deviation		0.038	0.019	0.031				0.021
Group diff. at p < 0.05			0.031	0.031				0.031
Group diff. at p < 0.01			0.040	0.040				0.040
Analysis of variance: F ratio = 0.14 Df = 3/ 36 F probability = 0.935								
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	2	3	4				
Number/group	Control	10	10	10				
Mean		0.603	0.616	0.632				0.687
Standard deviation		0.039	0.034	0.036				0.039
Group diff. at p < 0.05			0.041	0.041				0.041*
Group diff. at p < 0.01			0.052	0.052				0.052*
Analysis of variance: F ratio = 9.84 Df = 3/ 36 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								

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.1 - Relative organ weights* - Final sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

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

Group	2	3	4
Number/group	10	10	10
Mean	2.716	3.113	4.370
Standard deviation	0.136	0.166	0.283
Group diff. at p < 0.05		0.214*	0.214*
Group diff. at p < 0.01		0.271*	0.271*

Analysis of variance: F ratio = 153.43 Df = 3/ 36 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 (Dunnnett's test)

Group	2	3	4
Number/group	10	10	10
Mean	0.0470	0.0455	0.0476
Standard deviation	0.0060	0.0052	0.0071
Group diff. at p < 0.05		0.0079	0.0079
Group diff. at p < 0.01		0.0100	0.0100

Analysis of variance: F ratio = 0.20 Df = 3/ 36 F probability = 0.893
Note: a * indicates group mean is significantly different from control at level of significance shown.
* = expressed as % organ to body weight ratio

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13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.1 - Relative organ weights* - Final sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Spleen	Controls from group: 1				Data inhomogeneous by Bartlett's test (Modified t test)			
	Group	2	3	4				
Number/group	Control	10	10	10				
Mean		0.2387	0.2739	0.2561			0.2308	
Standard deviation		0.0180	0.0608	0.0161			0.0322	
Group diff. at p < 0.05			0.0453	0.0173*			0.0264	
Group diff. at p < 0.01			0.0651	0.0248			0.0378	
Analysis of variance: F ratio = 2.78 Df = 3/ 36 F probability = 0.054								
Note: a * indicates group mean is significantly different from control at level of significance shown.								

Organ: Thymus	Controls from group: 1				Data inhomogeneous by Bartlett's test (Modified t test)			
	Group	2	3	4				
Number/group	Control	10	10	10				
Mean		0.0990	0.0849	0.0885			0.0899	
Standard deviation		0.0381	0.0187	0.0091			0.0156	
Group diff. at p < 0.05			0.0304	0.0280			0.0295	
Group diff. at p < 0.01			0.0436	0.0402			0.0423	
Analysis of variance: F ratio = 0.68 Df = 3/ 36 F probability = 0.573								
Note: a * indicates group mean is significantly different from control at level of significance shown.								
* = expressed as % organ to body weight ratio								

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.1 - Relative organ weights* - Final sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Uterus	Controls from group: 1	Data inhomogeneous by Bartlett's test (Modified t test)
Group	Control	3
Number/group	10	10
Mean	0.1927	0.1905
Standard deviation	0.0431	0.0663
Group diff. at p < 0.05	0.0473	0.0595
Group diff. at p < 0.01	0.0679	0.0854
		0.1585
Analysis of variance: F ratio = 2.87 Df = 3/ 36 F probability = 0.049		
Note: a * indicates group mean is significantly different from control at level of significance shown.		
° = expressed as % organ to body weight ratio		

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13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.2 - Relative organ weights^o - Recovery sacrifice - Group mean data

STUDY NO.: 41950

MALES

Organ: Adrenals		Controls from group: 1		Data homogeneous by Bartlett's test (Dunnnett's test)	
Group	Number/group	Control		4	5
Mean		0.0100		0.0110	
Standard deviation		0.0007		0.0009	
Group diff. at p < 0.05				0.0012	
Group diff. at p < 0.01				0.0017	
Analysis of variance: F ratio = 4.27 Df = 1/ 8 F probability = 0.071					
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 (Dunnnett's test)	
Group	Number/group	Control		4	5
Mean		0.393		0.414	
Standard deviation		0.037		0.024	
Group diff. at p < 0.05				0.046	
Group diff. at p < 0.01				0.067	
Analysis of variance: F ratio = 1.09 Df = 1/ 8 F probability = 0.330					
Note: a * indicates group mean is significantly different from control at level of significance shown.					
^o = expressed as % organ to body weight ratio					

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13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.2 - Relative organ weights* - Recovery sacrifice - Group mean data

STUDY NO.: 41950

MALES

Organ: Epididymides	Controls from group: 1	Data homogeneous by Bartlett's test (Dunnett's test)
Group	Control	4
Number/group	5	5
Mean	0.3154	0.3205
Standard deviation	0.0290	0.0377
Group diff. at p < 0.05		0.0492
Group diff. at p < 0.01		0.0715
Analysis of variance: F ratio = 0.06 Df = 1/ 8 F probability = 0.799		
Note: * 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	0.309	0.324
Standard deviation	0.021	0.025
Group diff. at p < 0.05		0.034
Group diff. at p < 0.01		0.049
Analysis of variance: F ratio = 1.09 Df = 1/ 8 F probability = 0.330		
Note: * indicates group mean is significantly different from control at level of significance shown.		
* = expressed as % organ to body weight ratio		

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.2 - Relative organ weights^a - Recovery sacrifice - Group mean data

STUDY NO.: 41950

MALES

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

Group	Control	4
Number/group	5	5
Mean	0.586	0.636
Standard deviation	0.029	0.041
Group diff. at p < 0.05		0.052
Group diff. at p < 0.01		0.076

Analysis of variance: F ratio = 4.93 Df = 1/ 8 F probability = 0.055
 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	2.668	3.664
Standard deviation	0.094	0.293
Group diff. at p < 0.05		0.382*
Group diff. at p < 0.01		0.637*

Analysis of variance: F ratio = 52.41 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 AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.2 - Relative organ weights* - Recovery sacrifice - Group mean data

STUDY NO.: 41950

MALES

Organ: Spleen	Controls from group: 1	Data homogeneous by Bartlett's test (Dunnett's test)
Group	Control	4
Number/group	5	5
Mean	0.1956	0.1763
Standard deviation	0.0192	0.0138
Group diff. at p < 0.05		0.0245
Group diff. at p < 0.01		0.0356
Analysis of variance: F ratio = 3.31 Df = 1/ 8 F probability = 0.104		
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	0.8700	0.8556
Standard deviation	0.0553	0.0727
Group diff. at p < 0.05		0.0945
Group diff. at p < 0.01		0.1375
Analysis of variance: F ratio = 0.12 Df = 1/ 8 F probability = 0.730		
Note: a * indicates group mean is significantly different from control at level of significance shown.		
* = expressed as % organ to body weight ratio		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.2 - Relative organ weights* - Recovery sacrifice - Group mean data

STUDY NO.: 41950

MALES

Organ: Thymus	Controls from group: 1	Data homogeneous by Bartlett's test (Dunnett's test)
Group	Control	4
Number/group	5	5
Mean	0.0629	0.0556
Standard deviation	0.0076	0.0030
Group diff. at p < 0.05		0.0085
Group diff. at p < 0.01		0.0124
Analysis of variance: F ratio = 3.90	Df = 1/ 8	F probability = 0.082
Note: a * indicates group mean is significantly different from control at level of significance shown.		
* = expressed as % organ to body weight ratio		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.2 - Relative organ weights* - Recovery sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

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

Group	Control	
Number/group	5	4
Mean	0.0203	0.0214
Standard deviation	0.0024	0.0043
Group diff. at p < 0.05		0.0050
Group diff. at p < 0.01		0.0073

Analysis of variance: F ratio = 0.27 Df = 1/ 8 F probability = 0.620
 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 (Dunnnett's test)

Group	Control	
Number/group	5	4
Mean	0.611	0.618
Standard deviation	0.043	0.023
Group diff. at p < 0.05		0.051
Group diff. at p < 0.01		0.074

Analysis of variance: F ratio = 0.11 Df = 1/ 8 F probability = 0.745
 Note: a * indicates group mean is significantly different from control at level of significance shown.
 * = expressed as % organ to body weight ratio

TABLE 11.2 - Relative organ weights* - Recovery sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Heart	Controls from group: 1		Data homogeneous by Bartlett's test (Dunnett's test)	
	Group	Control	4	5
Number/group	5			
Mean		0.361	0.345	
Standard deviation		0.020	0.027	
Group diff. at p < 0.05			0.035	
Group diff. at p < 0.01			0.051	

Analysis of variance: F ratio = 1.14 Df = 1/ 8 F probability = 0.319
 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	5
Number/group	5			
Mean		0.634	0.692	
Standard deviation		0.048	0.068	
Group diff. at p < 0.05			0.087	
Group diff. at p < 0.01			0.126	

Analysis of variance: F ratio = 2.42 Df = 1/ 8 F probability = 0.156
 Note: a * indicates group mean is significantly different from control at level of significance shown.
 * = expressed as % organ to body weight ratio

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 11.2 - Relative organ weights* - Recovery sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Liver	Controls from group: 1	Data homogeneous by Bartlett's test (Dunnett's test)
	Control	4
Group	5	5
Number/group	2.766	3.832
Mean	0.178	0.226
Standard deviation		
Group diff. at p < 0.05		0.298*
Group diff. at p < 0.01		0.433*
Analysis of variance: F ratio = 68.62 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			
Number/group		5	4		
Mean		0.0398	5	0.0440	
Standard deviation		0.0036		0.0053	
Group diff. at p < 0.05				0.0066	
Group diff. at p < 0.01				0.0096	
Analysis of variance: F ratio = 2.12 Df = 1/ 8 F probability = 0.181					
Note: a * indicates group mean is significantly different from control at level of significance shown.					

TABLE 11.2 - Relative organ weights^o - Recovery sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Spleen	Controls from group: 1	Data homogeneous by Bartlett's test (Dunnnett's test)
Group	Control	4
Number/group	5	5
Mean	0.2314	0.2238
Standard deviation	0.0168	0.0123
Group diff. at p < 0.05		0.0216
Group diff. at p < 0.01		0.0314
Analysis of variance: F ratio = 0.67 Df = 1/ 8 F probability = 0.443		
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 (Dunnnett's test)
Group	Control	4
Number/group	5	5
Mean	0.0690	0.0692
Standard deviation	0.0113	0.0106
Group diff. at p < 0.05		0.0161
Group diff. at p < 0.01		0.0234
Analysis of variance: F ratio = 0.00 Df = 1/ 8 F probability = 0.927		
Note: a * indicates group mean is significantly different from control at level of significance shown.		
^o = expressed as % organ to body weight ratio		

TABLE 11.2 - Relative organ weights* - Recovery sacrifice - Group mean data

STUDY NO.: 41950

FEMALES

Organ: Uterus	Controls from group: 1	Data homogeneous by Bartlett's test (Dunnnett's test)
Group	Control	4
Number/group	5	5
Mean	0.2570	0.1852
Standard deviation	0.1505	0.0625
Group diff. at p < 0.05		0.1686
Group diff. at p < 0.01		0.2453
Analysis of variance: F ratio = 0.97 Df = 1/ 8 F probability = 0.356		
Note: a * indicates group mean is significantly different from control at level of significance shown.		
* = expressed as % organ to body weight ratio		

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13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 12.1 - Macroscopic observations - Final sacrifice - Group incidence

STUDY NO.: 41950

	Group:	-- Males --				-- Females --			
		1	2	3	4	1	2	3	4
Number in group:		10	10	10	10	10	10	10	10
Cervical nodes									
Abnormal colour	0	0	1	0		3	4	1	2
Abnormal size	1	2	3	1		0	1	1	1
Cervix									
Abnormal colour						0	0	1	0
Epididymides									
Abnormal size	0	1	0	0					
Eyes									
Abnormal area(s)	0	0	0	0		1	3	1	0
Liver									
Abnormal area(s)	0	0	1	1		0	0	0	0
Abnormal colour	0	0	0	0		0	1	0	0
Abnormal shape	0	0	0	0		0	1	0	0
Abnormal size	0	1	0	1		0	0	0	0
Lungs									
Abnormal area(s)	2	1	1	3		0	2	1	0
Abnormal colour	0	0	1	0		0	0	0	1
Ovaries									
Abnormal size						2	0	0	1
Pituitary									
Abnormal shape	0	0	0	0		1	1	1	3
Skin									
Subcutaneous mass(es)	0	0	0	1		0	0	0	0
Mass(es) not confirmed	0	0	1	0		0	0	0	0
Spleen									
Abnormal shape	2	3	1	0		0	2	0	0
Stomach									
Abnormal area(s)	0	0	0	1		0	0	0	0
Abnormal size	0	0	0	2		0	0	0	0
Testes									
Abnormal size	0	1	0	0					

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 12.1 - Macroscopic observations - Final sacrifice - Group incidence

STUDY NO.: 41950

	Group:	-- Males --				-- Females --			
		1	2	3	4	1	2	3	4
Number in group:	10	10	10	10	10	10	10	10	10
Thymus									
Abnormal area(s)	1	1	1	1	1	1	0	0	0
Abnormal colour	1	0	1	1	1	1	0	0	0
Abnormal size	0	0	0	0	1	1	1	0	0
Uterus									
Abnormal size						1	1	2	3
Abnormal contents						0	1	1	3
Ears									
Abnormal area(s)	0	0	0	0	0	0	1	0	0
Teeth									
Missing	0	0	0	0	1	0	0	0	0
Whole animal									
No abnormalities detected	6	2	2	4	4	3	2	4	2

TABLE 12.2 - Macroscopic observations - Recovery sacrifice - Group incidence

STUDY NO.: 41950

	-- Males --		-- Females --	
	1	4	1	4
Group:	5	5	5	5
Number in group:	5	5	5	5
Adrenals				
Abnormal area (s)	0	0	1	0
Abnormal size	0	0	0	1
Cervical nodes				
Abnormal area(s)	1	0	0	0
Abnormal colour	0	0	0	1
Abnormal size	1	3	2	0
Eyes				
Abnormal area(s)	0	1	0	0
Abnormal colour	1	0	0	1
Kidneys				
Abnormal area(s)	1	0	0	0
Liver				
Abnormal size	2	0	3	0
Lungs				
Abnormal area(s)	0	1	0	0
Skin				
Subcutaneous mass(es)	2	0	1	0
Spleen				
Abnormal shape	1	0	0	0
Stomach				
Abnormal size	1	0	0	0
Uterus				
Abnormal size			1	0
Abnormal contents			1	0
Whole animal				
No abnormalities detected	1	1	2	4

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 13.1 - Microscopic observations - Final sacrifice - Group incidence

STUDY NO.: 41950

		-- Animals --				Affected --			
Controls from group(s): 1		Animal sex:		-- Males --		-- Females --			
Tissues With Diagnoses		Dosage group:		Ctl's		Ctl's			
		No. in group:		10 10 10 10		10 10 10 10			
Cervical nodes		Number examined:		10 2 3 10		10 4 1 10			
REACTIVE HYPERPLASIA				1 1 3 3		0 1 0 1			
CONGESTION/HAEMORRHAGE				0 0 1 0		0 6 4 1			
Epididymides		Number examined:		10 1 0 10					
REDUCTION OF SPERM				0 1 0 0					
Heart		Number examined:		10 0 0 10		10 0 0 10			
INFLAMMATORY CELL FOCI				9 0 0 5		0 0 0 1			
VALVULAR HEMATOCYST (S)				0 0 0 0		0 0 0 1			
Kidneys		Number examined:		10 0 0 10		10 0 0 10			
NEPHROPATHY				8 0 0 9		6 0 0 6			
CALCULI				1 0 0 0		0 0 0 0			
MEDULLARY MINERALIZATION				0 0 0 1		0 0 0 0			
Liver		Number examined:		10 10 10 10		10 10 10 10			
INFLAMMATORY CELL FOCI				8 10 9 10		10 10 10 10			
HEPATOCYTIC HYPERTROPHY				0 0 2 -9		0 0 2 -9			
PIGMENTATION				0 0 0 1		0 1 2 2			
CHOLANGITIS				0 0 0 1		0 0 0 0			
HEPATOCYTIC NECROSIS				0 0 0 0		0 0 0 1			
CHRONIC INFLAMMATION				0 0 1 0		0 0 0 0			
CLEAR CELL CHANGE				0 0 0 0		0 0 0 0			
Lungs		Number examined:		10 10 10 10		10 10 10 10			
INFLAMMATORY CELL FOCI				9 10 8 9		10 10 10 9			
VASCULAR MINERALIZATION				2 1 1 2		1 0 0 0			
ALVEOLAR HAEMORRHAGE				3 1 0 3		0 2 1 0			
ALVEOLAR EPITHELIALIZATION				2 0 0 0		0 1 1 0			
AGGREGATIONS OF ALVEOLAR MACROPHAGES				1 3 3 2		3 3 5 7			
FRAGMENTS OF BONE				0 0 0 2		0 0 0 0			
Prostate		Number examined:		10 0 0 10					
INFLAMMATORY CELL FOCI				3 0 0 3					

Note: Entries flagged with a - (minus) are significantly higher than control at the 0.05 level using the Kolmogorov-Smirnov one-tailed test.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 13.1 - Microscopic observations - Final sacrifice - Group incidence

STUDY NO.: 41950

		-- Animals --				Affected --			
Controls from group(s): 1		-- Males --		-- Females --					
Tissues With Diagnoses	No. in group	Ctl's		Ctl's					
		10	10	10	10	10	10	10	10
Spleen	Number examined:	10	10	10	10	10	10	10	10
PIGMENTATION		0	0	1	0	1	4	4	4
Stomach	Number examined:	10	0	0	10	10	0	0	10
CHRONIC INFLAMMATION		0	0	0	2	0	0	0	0
OEDEMA		0	0	0	2	0	0	0	0
MUCOSAL ULCERATION		0	0	0	1	0	0	0	0
Testes	Number examined:	10	1	0	10	10	0	0	0
TESTICULAR ATROPHY		0	1	0	0				
Thymus	Number examined:	10	1	2	10	10	1	0	10
CONGESTION/HAEMORRHAGE		1	1	2	1	0	0	0	1
PIGMENTATION		0	0	0	2	0	0	0	0
Thyroid	Number examined:	10	0	0	10	10	0	0	9
ECTOPIC THYMIC TISSUE		1	0	0	0	0	0	0	0
Trachea	Number examined:	10	0	0	10	10	0	0	10
INFLAMMATORY CELL FOCI		1	0	0	2	0	0	0	0
Urinary bladder	Number examined:	10	0	0	10	10	0	0	10
INFLAMMATORY CELL FOCI		0	0	0	0	0	0	0	1
Uterus	Number examined:					10	1	2	10
HYDROMETRA						1	1	1	4
Preputial gland	Number examined:	0	0	0	1	0	0	0	0
CHRONIC INFLAMMATION		0	0	0	1	0	0	0	0
Teeth	Number examined:	0	0	0	1	0	0	0	0
ACUTE INFLAMMATION		0	0	0	1	0	0	0	0
Eyes	Number examined:	0	0	0	0	1	3	1	0
ULCERATION OF THE CORNEA		0	0	0	0	1	0	0	0
ACUTE INFLAMMATION		0	0	0	0	1	0	0	0
PHTHISIS BULBI		0	0	0	0	0	2	0	0

Note: Entries flagged with a - (minus) are significantly higher than control at the 0.05 level using the Kolmogorov-Smirnov one-tailed test.

TABLE 13.1 - Microscopic observations - Final sacrifice - Group incidence

STUDY NO.: 41950

		-- Animals --		Affected --	
		-- Males --		-- Females --	
		Ctls	4	Ctls	4
		10	10	10	10
Tissues With Diagnoses		No. in group:			
Ears		0	0	0	0
HAEMORRHAGE		0	0	0	0
Pancreas		10	0	10	0
CHRONIC INFLAMMATION		1	0	0	0

Note: Entries flagged with a - (minus) are significantly higher than control at the 0.05 level using the Kolmogorov-Smirnov one-tailed test.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TABLE 13.2 - Microscopic observations - Recovery sacrifice - Group incidence

STUDY NO.: 41950				-- Animals --		Affected --	
				-- Males --		-- Females --	
Controls from group(s): 1				Ctl's		Ctl's	
Tissues With Diagnoses				No. in group:			
				Number examined:			
Liver				5	5	5	5
INFLAMMATORY CELL FOCI				3	5	5	5
HEPATOCYTIC HYPERTROPHY				0	5	0	4
PIGMENTATION				0	0	0	2
CHOLANGITIS				0	0	0	0
HEPATOCYTIC NECROSIS				0	0	0	0
CHRONIC INFLAMMATION				0	0	0	0
CLEAR CELL CHANGE				1	4	4	0
Lungs				5	5	4	5
INFLAMMATORY CELL FOCI				5	5	4	4
VASCULAR MINERALIZATION				3	2	1	0
ALVEOLAR HAEMORRHAGE				1	0	1	0
ALVEOLAR EPITHELIALIZATION				0	0	0	0
AGGREGATIONS OF ALVEOLAR MACROPHAGES				0	4	1	3
FRAGMENTS OF BONE				0	0	0	0
Spleen				5	5	5	5
PIGMENTATION				3	5	5	4

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 1.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUPI	RIGH
41950002	1	1	1	2	1	+	1
41950004		1	1	2	1	+	1
41950006		1	1	2	1	+	1
41950008		1	1	1	2	+	1
41950010		1	1	1	2	+	1
41950012		1	1	2	1	+	1
41950014		1	1	1	1	+	1
41950016		2	1	1	1	+	1
41950018		1	1	1	1	+	1
41950020		1	1	2	1	+	1
41950022		1	1	1	1	+	1
41950024		1	1	1	1	+	1
41950026		1	1	2	1	+	1
41950028		1	1	1	1	+	1
41950030		1	1	2	1	+	1
41950032	2	1	1	1	1	+	1
41950034		1	1	1	1	+	1
41950036		1	1	2	1	+	1
41950038		1	1	1	3	+	1
41950040		1	1	1	1	+	1
41950042		1	1	1	1	+	1
41950044		1	1	1	1	+	1
41950046		2	1	1	1	+	1
41950048		1	1	1	1	+	1
41950050		1	1	1	1	+	1

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 1.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUI	RIGH
41950052	3	1	1	1	1	+	1
41950054		1	1	1	1	+	1
41950056		1	1	2	1	+	1
41950058		1	1	3	1	+	1
41950060		1	1	2	1	+	1
41950062		1	1	1	1	+	1
41950064		1	1	1	1	+	1
41950066		1	1	2	3	+	1
41950068		1	1	1	2	+	1
41950070		1	1	1	2	+	1
41950072	4	1	1	1	1	+	1
41950074		1	1	1	1	+	1
41950076		1	1	1	1	+	1
41950078		1	1	2	1	+	1
41950080		1	1	2	2	+	1
41950082		1	1	1	1	+	1
41950084		2	1	1	1	+	1
41950086		1	1	1	1	+	1
41950088		1	1	1	1	+	1
41950090		1	1	1	1	+	1
41950092		1	1	1	1	+	1
41950094		1	1	1	1	+	1
41950096		1	1	1	1	+	1
41950098		1	1	2	1	+	1
41950100		1	1	1	1	+	1

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 1.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	GR1 S	GR12 S	GR1M S	BW g	LAN1 cm	LAN2 cm	LANM cm
41950002	1	2	2	2.0	476.3	6.2	4.6	5.40
41950004		4	4	4.0	465.5	4.3	4.5	4.40
41950006		9	4	6.5	450.9	6.6	6.3	6.45
41950008		7	3	5.0	453.1	4.9	4.3	4.60
41950010		8	4	6.0	433.5	4.0	4.8	4.40
41950012		5	6	5.5	431.1	7.8	7.3	7.55
41950014		15	3	9.0	439.9	10.4	9.0	9.70
41950016		5	3	4.0	427.1	7.0	6.5	6.75
41950018		5	6	5.5	447.7	8.6	7.6	8.10
41950020		5	4	4.5	436.7	9.8	9.8	9.80
41950022		4	6	5.0	430.1	4.0	4.0	4.00
41950024		6	3	4.5	458.3	4.0	5.2	4.60
41950026		5	5	5.0	465.9	3.0	3.0	3.00
41950028		10	8	9.0	386.3	6.0	6.9	6.45
41950030		6	8	7.0	440.5	4.6	4.5	4.55
Mean		6.4	4.6	5.50	442.86	6.08	5.89	5.983
SD		3.1	1.8	1.84	21.52	2.27	1.95	2.077
41950032	2	17	5	11.0	498.6	9.0	10.2	9.60
41950034		9	4	6.5	461.0	5.8	6.0	5.90
41950036		14	4	9.0	446.8	5.6	6.3	5.95
41950038		6	3	4.5	448.6	6.0	4.6	5.30
41950040		9	2	5.5	410.8	6.4	6.8	6.60
41950042		4	2	3.0	467.6	7.0	6.0	6.50
41950044		6	11	8.5	403.1	4.8	4.7	4.75
41950046		5	5	5.0	459.1	7.2	5.8	6.50
41950048		10	2	6.0	470.9	8.6	9.4	9.00
41950050		20	4	12.0	423.4	4.0	4.2	4.10
Mean		10.0	4.2	7.10	448.99	6.44	6.40	6.420
SD		5.4	2.7	2.92	29.36	1.57	1.98	1.723

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 1.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	GR11 s	GR12 s	GRIM s	BW g	LAN1 cm	LAN2 cm	LANM cm
41950052	3	2	4	3.0	454.1	6.8	5.2	6.00
41950054		3	4	3.5	416.7	6.0	3.8	4.90
41950056		27	5	16.0	419.3	6.8	6.1	6.45
41950058		6	7	6.5	479.2	7.6	8.2	7.90
41950060		8	4	6.0	440.4	8.0	6.4	7.20
41950062		4	1	2.5	419.2	2.0	2.1	2.05
41950064		5	2	3.5	462.4	4.4	4.0	4.20
41950066		1	1	1.0	441.3	4.1	4.6	4.35
41950068		1	1	1.0	437.2	5.6	5.3	5.45
41950070		4	1	2.5	473.0	4.0	4.5	4.25
Mean		6.1	3.0	4.55	444.28	5.53	5.02	5.275
SD		7.7	2.1	4.41	22.50	1.88	1.66	1.704
41950072	4	4	6	5.0	445.1	7.0	7.6	7.30
41950074		11	5	8.0	450.9	7.0	4.3	5.65
41950076		6	3	4.5	438.7	1.8	1.6	1.70
41950078		4	5	4.5	425.2	3.0	4.2	3.60
41950080		4	6	5.0	432.7	4.8	5.2	5.00
41950082		6	10	8.0	430.6	4.0	4.0	4.00
41950084		4	4	4.0	382.7	7.2	7.8	7.50
41950086		3	4	4.5	389.8	5.3	4.1	4.70
41950088		6	5	5.5	372.9	6.8	7.6	7.20
41950090		4	4	4.0	378.5	6.0	5.0	5.50
41950092		2	2	2.0	476.2	3.8	4.0	3.90
41950094		5	4	4.5	433.7	6.9	8.0	7.45
41950096		4	3	3.5	457.4	6.3	6.8	6.55
41950098		4	4	4.0	376.3	6.2	6.8	6.50
41950100		4	4	4.0	400.9	6.2	6.8	6.50
Mean		4.7	4.7	4.73	419.44	5.49	5.59	5.537
SD		2.1	1.9	1.55	33.27	1.66	1.90	1.707

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 1.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUPI	RIGH
41950001	1	1	1	1	1	+	1
41950003		1	2	1	1	+	1
41950005		1	1	1	1	+	1
41950007		1	1	1	1	+	1
41950009		1	1	1	1	+	1
41950011		1	1	2	2	+	1
41950013		1	1	1	2	+	1
41950015		1	1	1	1	+	1
41950017		1	1	1	1	+	1
41950019		1	1	1	1	+	1
41950021		1	1	1	1	+	1
41950023		1	1	1	1	+	1
41950025		1	1	2	1	+	1
41950027		1	1	1	1	+	1
41950029		1	1	1	2	+	1
41950031	2	1	1	1	1	+	1
41950033		1	1	1	2	+	1
41950035		1	1	1	1	+	1
41950037		1	1	1	2	+	1
41950039		1	1	1	1	+	1
41950041		1	1	2	1	+	1
41950043		1	1	1	1	+	1
41950045		2	1	1	1	+	1
41950047		1	1	2	2	+	1
41950049		1	1	1	1	+	1

° = lack of pupil reflex left eye

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 1.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUPI	RIGH
41950051	3	1	1	1	1	+	1
41950053		1	1	1	1	+	1
41950055		1	1	1	2	+	1
41950057		1	1	2	1	+	1
41950059		1	1	1	1	+	1
41950061		1	1	2	1	+	1
41950063		1	1	1	1	+	1
41950065		1	1	1	1	+	1
41950067		1	1	1	1	+	1
41950069		1	1	1	1	+	1
41950071	4	1	1	1	1	+	1
41950073		1	1	1	1	+	1
41950075		1	1	1	2	+	1
41950077		1	1	2	1	+	1
41950079		1	1	1	1	+	1
41950081		1	1	1	1	+	1
41950083		2	1	1	1	+	1
41950085		1	1	1	1	+	1
41950087		1	1	1	1	+	1
41950089		1	1	1	1	+	1
41950091		1	1	1	1	+	1
41950093		1	1	1	1	+	1
41950095		1	1	1	1	+	1
41950097		1	1	1	1	+	1
41950099		1	1	1	1	+	1

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 1.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	GR11 s	GR12 s	GRIM s	BW g	LAN1 cm	LAN2 cm	LANM cm
41950001	1	54	3	28.5	241.1	5.7	4.2	4.95
41950003		19	2	10.5	299.9	4.2	3.5	3.85
41950005		25	11	18.0	294.8	8.0	5.2	6.60
41950007		22	2	12.0	314.1	3.5	3.6	3.55
41950009		39	4	21.5	272.2	4.9	2.5	3.70
41950011		12	6	9.0	256.1	2.7	4.6	3.65
41950013		8	19	13.5	287.8	3.9	3.9	3.90
41950015		57	3	30.0	272.4	2.4	3.0	2.70
41950017		36	3	19.5	292.9	6.0	5.4	5.70
41950019		43	4	23.5	268.0	5.7	4.9	5.30
41950021		11	2	6.5	299.4	2.5	3.0	2.75
41950023		26	3	14.5	272.5	5.0	4.0	4.50
41950025		8	4	6.0	285.1	3.5	3.5	3.50
41950027		9	10	9.5	249.9	5.9	6.1	6.00
41950029		16	2	9.0	278.2	6.7	4.2	5.45
Mean		25.7	5.2	15.43	278.96	4.71	4.11	4.407
SD		16.5	4.7	7.72	20.18	1.65	0.99	1.197
41950031	2	19	3	11.0	281.0	5.8	5.1	5.45
41950033		2	8	5.0	297.0	5.1	5.8	5.45
41950035		11	4	7.5	272.0	7.1	4.6	5.85
41950037		11	1	6.0	278.8	2.6	3.1	2.85
41950039		21	3	12.0	266.1	6.2	6.2	6.20
41950041		3	1	2.0	282.9	7.7	7.2	7.45
41950043		13	3	8.0	288.3	6.1	5.8	5.95
41950045		49	2	25.5	269.0	1.5	1.6	1.55
41950047		28	10	19.0	260.1	4.9	3.5	4.20
41950049		16	6	11.0	283.6	5.9	4.4	5.15
Mean		17.3	4.1	10.70	277.88	5.29	4.73	5.010
SD		13.6	3.0	6.97	11.11	1.91	1.66	1.721

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 1.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	GR11 S	GR12 S	GRIM S	BW g	LAN1 cm	LAN2 cm	LANM cm
41950051	3	14	5	9.5	275.5	4.0	3.9	3.95
41950053		27	28	27.5	259.9	3.4	2.2	2.80
41950055		22	3	12.5	274.7	6.6	4.4	5.50
41950057		11	11	11.0	272.3	4.7	3.9	4.30
41950059		15	41	28.0	269.8	6.0	5.0	5.50
41950061		16	14	15.0	263.7	3.6	5.9	4.75
41950063		2	6	4.0	284.3	6.9	3.5	5.20
41950065		26	3	14.5	307.6	4.9	2.7	3.80
41950067		10	20	15.0	276.6	3.7	3.8	3.75
41950069		6	2	4.0	278.4	6.5	6.4	6.45
Mean		14.9	13.3	14.10	276.28	5.03	4.17	4.600
SD		8.2	12.9	8.25	13.07	1.36	1.31	1.082
41950071	4	11	3	7.0	281.2	2.8	2.2	2.50
41950073		4	10	7.0	262.5	2.1	2.5	2.30
41950075		10	22	16.0	267.8	7.6	6.3	6.95
41950077		10	2	6.0	271.4	5.0	4.6	4.80
41950079		2	10	6.0	281.1	4.4	3.8	4.10
41950081		14	7	10.5	270.5	7.7	5.4	6.55
41950083		17	1	9.0	262.1	7.5	7.4	7.45
41950085		32	11	21.5	251.4	3.8	4.4	4.10
41950087		10	15	12.5	257.5	8.3	7.6	7.95
41950089		1	2	1.5	270.5	6.3	6.0	6.15
41950091		43	3	23.0	250.1	5.3	5.0	5.15
41950093		1	18	9.5	272.1	5.0	5.2	5.10
41950095		14	4	9.0	281.4	2.1	2.4	2.25
41950097		12	14	13.0	266.2	3.6	3.2	3.40
41950099		2	6	4.0	246.8	4.8	3.6	4.20
Mean		12.2	8.5	10.37	266.17	5.09	4.64	4.863
SD		11.7	6.5	6.04	11.15	2.04	1.72	1.851

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 1.2 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of recovery - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUPI	RIGH
41950022	1	1	1	1	2	+	1
41950024		1	1	2	2	+	1
41950026		1	1	2	2	+	1
41950028		1	1	1	2	+	1
41950030	4	1	1	2	2	+	1
41950092		1	1	2	2	+	1
41950094		1	1	2	2	+	1
41950096		1	1	1	2	+	1
41950098		1	1	1	2	+	1
41950100		1	1	2	2	+	1

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 1.2 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of recovery - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	GR11 S	GR12 S	GRIM S	BW g	LAN1 cm	LAN2 cm	LANM cm
41950022	1	6	8	7.0	470.3	8.7	8.0	8.35
41950024		2	3	2.5	505.1	4.3	4.2	4.25
41950026		5	4	4.5	527.1	6.0	8.1	7.05
41950028		9	3	6.0	423.2	7.3	7.9	7.60
41950030		9	3	6.0	480.8	7.8	6.7	7.25
Mean		6.2	4.2	5.20	481.30	6.82	6.98	6.900
SD		2.9	2.2	1.75	39.25	1.71	1.65	1.562
41950092	4	9	3	6.0	493.4	7.3	8.2	7.75
41950094		5	4	4.5	482.0	6.7	5.9	6.30
41950096		7	2	4.5	492.5	8.0	8.0	8.00
41950098		6	6	6.0	407.9	8.8	8.5	8.65
41950100		7	5	6.0	446.0	7.5	8.5	8.00
Mean		6.8	4.0	5.40	464.36	7.66	7.82	7.740
SD		1.5	1.6	0.82	36.98	0.79	1.09	0.871

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 1.2 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of recovery - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUPI	RIGH
41950021	1	1	1	2	2	+	1
41950023		1	2	1	2	+	1
41950025		2	1	2	2	+	1
41950027		1	1	2	2	+	1
41950029		1	1	2	2	+	1
41950091	4	1	1	2	2	+	1
41950093		1	1	2	2	+	1
41950095		1	1	2	1	+	1
41950097		1	2	1	2	+	1
41950099		1	1	2	2	+	1

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 1.2 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of recovery - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	GR11 S	GR12 S	GRIM S	BW g	LAN1 cm	LAN2 cm	LANM cm
41950021	1	5	4	4.5	321.1	3.8	4.0	3.90
41950023		4	6	5.0	281.2	5.3	4.2	4.75
41950025		8	6	7.0	305.4	4.2	3.8	4.00
41950027		8	3	5.5	268.3	4.5	5.0	4.75
41950029		2	2	2.0	297.9	5.2	4.7	4.95
Mean		5.4	4.2	4.80	294.78	4.60	4.34	4.470
SD		2.6	1.8	1.82	20.62	0.64	0.50	0.483
41950091	4	10	3	6.5	255.9	6.0	3.8	4.90
41950093		6	8	7.0	267.4	5.8	3.3	4.55
41950095		9	7	8.0	286.1	4.9	3.9	4.40
41950097		9	4	6.5	288.8	4.3	3.9	4.10
41950099		11	6	8.5	272.9	5.5	4.0	4.75
Mean		9.0	5.6	7.30	274.22	5.30	3.78	4.540
SD		1.9	2.1	0.91	13.58	0.70	0.28	0.311

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 2.1 - Motor activity - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	COUN
41950002	1	1143
41950004		1185
41950006		1008
41950008		882
41950010		1058
41950012		793
41950014		1162
41950016		1026
41950018		1229
41950020		1186
41950022		795
41950024		1217
41950026		1222
41950028		669
41950030		1237
		Mean 1054.1
		SD 186.9
41950032	2	1214
41950034		1084
41950036		880
41950038		1088
41950040		967
41950042		1025
41950044		996
41950046		763
41950048		1070
41950050		867
		Mean 995.4
		SD 131.3

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 2.1 - Motor activity - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	COUN
41950052	3	890
41950054		717
41950056		314
41950058		999
41950060		952
41950062		690
41950064		1159
41950066		1004
41950068		939
41950070		886
Mean		855.0
SD		234.0
41950072	4	732
41950074		1150
41950076		1244
41950078		1124
41950080		752
41950082		989
41950084		587
41950086		1051
41950088		1013
41950090		768
41950092		636
41950094		722
41950096		586
41950098		866
41950100		966
Mean		879.1
SD		213.6

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 2.1 - Motor activity - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	COUN
41950001	1	1116
41950003		714
41950005		802
41950007		1135
41950009		919
41950011		982
41950013		1130
41950015		980
41950017		1358
41950019		1080
41950021		923
41950023		809
41950025		981
41950027		1208
41950029		1121
Mean		1017.2
SD		170.6
41950031	2	972
41950033		904
41950035		1049
41950037		1140
41950039		1054
41950041		861
41950043		804
41950045		891
41950047		1103
41950049		1143
Mean		992.1
SD		122.5

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 2.1 - Motor activity - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	COUN
41950051	3	879
41950053		907
41950055		975
41950057		1079
41950059		1084
41950061		1102
41950063		1023
41950065		966
41950067		1113
41950069		945
Mean		1007.3
SD		84.7
41950071	4	936
41950073		884
41950075		449
41950077		1232
41950079		1022
41950081		897
41950083		1194
41950085		929
41950087		958
41950089		917
41950091		1035
41950093		1235
41950095		1223
41950097		1167
41950099		1263
Mean		1022.7
SD		212.6

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 2.2 - Motor activity - At the end of recovery - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	COUN
41950022	1	909
41950024		684
41950026		1089
41950028		419
41950030		966
Mean		813.4
SD		264.9
41950092	4	679
41950094		1209
41950096		937
41950098		174
41950100		989
Mean		797.6
SD		396.3

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 2.2 - Motor activity - At the end of recovery - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	COUN
41950021	1	886
41950023		756
41950025		839
41950027		960
41950029		765
Mean		841.2
SD		85.4
41950091	4	769
41950093		772
41950095		938
41950097		855
41950099		1210
Mean		908.8
SD		182.2

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 3.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	1!	1"	8	Day	15	22	29	36	43
41950002	1	203.0	245.1	292.6	323.4	352.2	374.7	395.4	410.9	
41950004		201.7	245.1	288.1	322.9	351.8	381.5	394.7	407.7	
41950006		198.8	238.8	277.9	309.7	333.5	361.1	379.4	401.3	
41950008		199.6	243.2	281.7	313.9	343.0	367.5	386.0	400.4	
41950010		194.8	237.5	269.7	292.7	317.3	337.0	354.5	369.4	
41950012		190.9	229.0	270.9	306.9	328.9	352.6	364.4	376.0	
41950014		195.1	241.8	281.4	302.4	329.1	353.8	369.8	375.6	
41950016		188.9	228.3	265.5	296.7	315.5	341.4	360.4	370.9	
41950018		195.3	237.0	279.1	309.8	336.9	363.3	382.1	394.4	
41950020		197.9	235.1	276.6	310.4	326.9	355.9	375.4	393.9	
41950022		204.5	237.7	279.6	317.1	337.9	354.9	373.4	383.8	
41950024		207.7	244.7	286.6	328.2	347.8	372.9	390.8	403.0	
41950026		187.9	247.8	290.3	315.0	334.4	361.6	380.3	392.7	
41950028		186.3	224.7	261.0	281.0	302.3	322.4	328.9	347.9	
41950030		203.4	245.2	285.9	312.7	342.9	367.9	386.7	397.3	
(n)		15	15	15	15	15	15	15	15	
Mean		197.05	238.73	279.14	309.50	333.36	357.88	374.82	388.33	
SD		6.50	7.01	9.17	12.41	14.00	15.44	17.55	17.34	
41950032	2	202.3	244.6	297.1	338.5	370.9	388.1	418.3	438.2	
41950034		194.7	236.1	282.6	316.5	344.6	370.8	387.9	402.9	
41950036		185.9	229.2	276.6	316.7	355.8	374.2	385.3	402.7	
41950038		188.7	231.0	274.2	316.0	346.3	370.1	393.6	420.6	
41950040		197.4	234.3	271.8	302.6	327.6	339.1	357.4	368.3	
41950042		200.9	237.7	278.1	309.3	342.9	367.3	400.2	408.4	
41950044		204.4	221.4	255.4	282.2	302.5	325.0	335.4	345.8	
41950046		206.6	246.1	297.6	325.4	353.3	380.6	399.9	411.3	
41950048		198.2	253.8	301.8	343.3	367.8	386.7	401.4	416.5	
41950050		190.1	227.9	264.0	297.3	320.0	338.3	351.9	366.2	
(n)		10	10	10	10	10	10	10	10	
Mean		196.92	236.20	279.92	314.78	343.16	364.00	383.13	398.08	
SD		6.97	9.70	15.14	18.38	21.30	22.04	26.24	28.69	

Note: ! = Pre-test phase; " = Dosing phase

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 3.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	1!	1"	8	Day	15	Phase	22	29	36	43
41950052	3	202.4	240.8	285.0	317.4	346.9	362.4	378.5	400.5		
41950054		193.0	228.9	267.6	291.0	315.2	331.3	353.6	368.4		
41950056		195.3	233.2	279.4	310.3	330.4	352.5	368.9	383.2		
41950058		206.6	248.7	288.2	328.0	353.0	370.5	396.0	417.3		
41950060		195.3	234.6	273.8	306.8	334.5	352.9	366.0	384.0		
41950062		188.6	229.1	268.3	301.5	320.5	342.0	357.9	375.0		
41950064		201.3	242.6	289.5	317.5	356.2	372.4	402.4	412.7		
41950066		197.7	234.3	279.5	309.2	341.5	358.9	381.9	394.4		
41950068		204.0	240.0	286.0	306.4	328.9	350.0	365.4	386.3		
41950070		186.8	249.6	298.5	333.6	359.1	376.1	400.4	409.9		
(n)		10	10	10	10	10	10	10	10		
Mean		197.10	238.18	280.60	312.17	338.61	356.90	377.08	393.17		
SD		6.55	7.40	9.81	12.50	15.16	14.10	17.66	16.57		
41950072	4	206.8	252.1	301.8	331.9	363.8	391.5	409.1	422.7		
41950074		208.0	252.0	293.7	328.8	365.9	384.9	402.5	384.8		
41950076		196.5	234.9	288.7	325.7	356.8	380.1	402.2	412.1		
41950078		201.8	241.3	281.8	317.9	349.5	381.0	393.2	406.6		
41950080		199.8	243.8	288.3	325.8	357.7	373.7	399.0	418.2		
41950082		194.8	235.7	283.8	314.6	342.1	345.2	391.8	402.0		
41950084		186.5	221.9	284.1	292.8	326.5	350.4	366.7	375.7		
41950086		188.3	227.9	279.1	304.6	328.6	354.1	372.6	381.2		
41950088		203.9	230.1	276.9	303.6	327.1	344.8	363.4	373.6		
41950090		190.9	227.2	266.1	294.5	319.0	337.2	354.7	364.5		
41950092		199.6	243.7	291.0	338.5	374.9	398.3	423.5	445.1		
41950094		186.6	233.1	278.9	314.7	341.9	369.1	393.8	395.8		
41950096		198.3	239.6	291.2	332.5	365.1	384.2	409.1	423.9		
41950098		195.5	226.1	271.1	296.0	309.6	331.4	346.2	351.3		
41950100		190.9	229.2	266.0	298.0	316.8	339.6	356.9	368.0		
(n)		15	15	15	15	15	15	15	15		
Mean		196.55	235.90	281.50	314.64	343.01	364.36	385.63	395.02		
SD		6.95	9.29	11.23	15.52	20.73	22.08	23.58	26.49		

Note: ! = Pre-test phase; " = Dosing phase

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 3.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	50	57	64	Day 71	Phase 78	85	92
41950002	1	426.2	434.1	450.7	462.9	467.9	476.7	477.1
41950004		434.2	440.9	442.4	448.8	456.6	460.4	469.5
41950006		413.1	424.8	435.4	441.0	440.8	449.0	457.2
41950008		412.4	427.7	430.2	441.3	446.4	460.9	454.1
41950010		389.1	399.3	408.4	421.8	423.7	433.7	431.6
41950012		396.1	403.1	419.5	420.4	431.5	430.6	430.2
41950014		392.5	413.2	422.7	431.6	437.9	447.5	440.4
41950016		392.1	401.7	411.0	421.4	430.3	432.6	431.5
41950018		402.6	421.6	426.7	435.8	444.6	451.1	452.0
41950020		407.2	408.0	416.8	430.6	432.5	437.6	440.8
41950022		399.0	406.1	409.8	413.0	415.7	434.2	
41950024		420.3	426.2	443.1	440.0	449.1	458.5	
41950026		413.2	424.2	444.6	452.6	462.5	469.4	
41950028		358.2	367.2	370.0	379.5	381.9	389.3	
41950030		416.8	421.0	426.4	429.5	437.9	442.2	
(n)		15	15	15	15	15	15	10
Mean		404.86	414.60	423.84	431.35	437.28	444.93	448.43
SD		18.42	18.05	20.04	19.61	20.80	20.88	16.37
41950032	2	448.3	460.1	471.1	486.5	491.2	496.1	483.0
41950034		416.6	431.5	440.2	454.5	449.3	463.0	451.3
41950036		414.2	424.6	433.7	448.6	445.7	453.1	450.4
41950038		431.6	436.0	429.0	450.0	451.5	453.3	460.1
41950040		387.6	392.4	399.3	404.6	409.5	410.2	409.1
41950042		420.7	432.5	447.5	452.5	460.5	467.3	464.8
41950044		368.4	369.3	375.9	386.0	395.1	402.9	400.1
41950046		418.1	430.0	441.4	454.7	458.5	463.4	458.8
41950048		429.7	435.6	451.4	457.2	464.8	470.2	475.6
41950050		378.2	409.4	408.9	415.0	428.3	431.1	426.9
(n)		10	10	10	10	10	10	10
Mean		411.34	422.15	429.83	440.96	445.44	451.05	448.00
SD		25.35	25.63	27.92	29.82	27.97	28.60	27.49

Data for Dosing phase

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 3.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Day of Phase					92
		50	57	64	71	78	
41950052	3	414.7	420.4	432.0	441.3	443.2	442.9
41950054		380.5	388.6	400.8	409.6	412.7	413.3
41950056		390.5	403.6	419.5	419.5	416.1	417.3
41950058		419.2	440.7	453.3	465.7	470.4	472.8
41950060		402.3	414.4	426.8	433.0	433.4	437.8
41950062		384.9	394.1	399.0	413.9	415.5	427.6
41950064		432.0	442.4	442.5	446.5	458.9	468.9
41950066		408.3	418.6	426.5	430.6	431.5	442.8
41950068		398.6	408.4	415.7	424.4	433.6	440.4
41950070		428.1	445.5	447.2	466.7	463.2	478.5
(n)		10	10	10	10	10	10
Mean		405.91	417.67	425.64	435.11	437.84	444.19
SD		17.70	20.07	18.69	19.97	20.69	22.67
41950072	4	435.6	429.5	442.6	444.0	449.6	438.5
41950074		414.5	420.5	415.3	412.5	408.8	404.0
41950076		418.8	433.0	430.0	438.3	437.2	418.3
41950078		420.2	424.0	424.9	423.4	426.4	416.7
41950080		414.3	421.8	427.9	434.3	433.5	438.4
41950082		404.5	424.4	420.2	429.5	421.2	417.1
41950084		383.3	388.3	402.4	390.4	384.5	384.9
41950086		386.0	395.6	389.9	387.8	391.6	393.1
41950088		380.6	386.2	383.0	372.0	371.1	370.7
41950090		367.2	373.1	380.2	379.9	375.9	374.7
41950092		451.4	460.2	464.1	478.4	477.9	481.6
41950094		405.2	413.2	424.3	432.6	437.8	441.4
41950096		417.6	439.7	451.8	454.8	458.8	461.2
41950098		358.9	362.0	368.8	368.5	371.3	372.7
41950100		378.6	388.0	397.4	402.2	404.9	407.6
(n)		15	15	15	15	15	10
Mean		402.45	410.62	414.86	416.57	416.70	405.64
SD		25.94	27.20	27.53	32.37	33.32	24.36

Data for Dosing phase

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 3.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	1!	1"	8	Day	15	22	29	36	43
41950001	1	154.2	164.9	171.2	186.2	199.8	200.0	213.8	224.2	
41950003		169.7	185.7	207.9	221.1	240.4	260.8	259.8	266.3	
41950005		171.0	201.6	208.4	224.0	237.3	263.0	254.1	263.5	
41950007		166.0	193.4	210.3	227.8	253.4	274.1	255.1	266.9	
41950009		163.5	177.2	212.8	224.0	239.1	246.1	245.9	255.8	
41950011		161.4	167.1	186.6	204.9	210.4	219.5	225.2	236.8	
41950013		163.8	181.4	199.4	217.5	228.4	247.7	258.7	259.6	
41950015		152.1	180.7	186.7	218.1	218.2	227.9	249.4	252.1	
41950017		160.5	178.3	198.0	206.3	226.1	240.9	246.9	254.7	
41950019		155.9	179.3	210.7	206.1	241.3	256.2	235.1	258.5	
41950021		159.9	173.6	195.7	224.6	241.0	237.7	248.2	255.6	
41950023		157.8	171.0	191.7	205.8	214.2	227.4	238.2	246.0	
41950025		171.3	177.7	213.2	221.6	237.0	247.8	255.8	266.6	
41950027		158.7	165.5	187.3	198.6	214.2	226.4	224.3	237.5	
41950029		166.7	184.6	201.1	214.6	226.2	237.3	247.8	251.4	
(n)		15	15	15	15	15	15	15	15	
Mean		162.17	178.80	198.72	213.41	228.46	240.85	243.88	253.03	
SD		5.99	10.09	12.28	11.70	14.69	19.00	13.80	12.36	
41950031	2	161.0	176.9	197.3	210.9	229.4	227.2	246.5	243.5	
41950033		171.2	188.4	207.0	224.9	244.1	247.2	249.6	268.1	
41950035		164.8	167.6	187.7	198.1	217.0	232.4	231.6	248.9	
41950037		169.7	185.1	200.8	219.3	228.5	239.8	247.6	268.6	
41950039		153.2	164.6	172.5	202.6	226.7	252.9	238.6	240.9	
41950041		165.5	182.4	202.5	209.3	231.3	244.9	245.0	260.1	
41950043		155.3	170.0	181.3	224.7	235.7	240.9	272.4	270.0	
41950045		157.9	170.5	187.4	211.0	200.8	226.6	237.0	242.6	
41950047		163.4	173.6	185.3	205.8	215.8	229.3	237.1	246.7	
41950049		160.1	181.0	201.7	211.9	232.1	236.7	253.5	256.9	
(n)		10	10	10	10	10	10	10	10	
Mean		162.21	176.00	192.34	211.85	226.13	237.80	245.88	254.63	
SD		5.86	8.00	11.13	8.87	12.15	8.96	11.52	11.53	

Note: ! = Pre-test phase; " = Dosing phase

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 3.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	11	1"	8	Day	15	of	Phase	22	29	36	43
41950051	3	165.0	176.7	199.6		218.7		226.0		249.9	258.9	255.5
41950053		154.5	172.3	182.7		206.9		213.6		216.7	236.1	234.8
41950055		159.8	182.8	194.6		212.5		236.4		245.8	250.0	256.7
41950057		160.1	173.5	186.3		210.5		233.6		239.4	250.0	251.8
41950059		158.6	174.4	193.0		215.1		226.7		244.1	252.2	250.5
41950061		161.6	173.3	188.9		212.5		219.9		236.7	230.1	249.9
41950063		168.9	184.6	201.1		219.6		225.9		240.4	248.9	258.8
41950065		171.8	183.2	206.8		221.4		242.2		251.9	263.6	272.8
41950067		166.8	185.2	197.7		221.9		249.6		244.0	232.9	270.6
41950069		153.9	166.6	195.3		205.4		223.5		259.0	236.9	234.8
(n)		10	10	10		10		10		10	10	10
Mean		162.10	177.27	194.61		214.44		229.74		242.79	245.34	253.61
SD		5.94	6.31	7.24		5.86		10.77		11.26	11.29	12.61
41950071	4	167.2	185.4	215.8		222.7		245.0		266.7	278.8	266.9
41950073		165.2	178.5	210.9		224.2		226.7		262.6	261.9	252.5
41950075		162.2	179.0	196.3		218.3		234.6		244.6	246.3	250.3
41950077		164.3	183.6	210.9		219.0		247.2		268.1	255.8	262.3
41950079		172.4	180.6	190.7		216.2		228.0		249.2	258.2	260.1
41950081		171.3	183.7	204.2		214.4		227.3		238.6	247.7	249.3
41950083		160.1	174.5	193.9		210.9		225.1		229.0	240.7	244.7
41950085		156.8	168.4	190.7		209.1		222.0		239.9	249.7	246.8
41950087		155.4	170.1	196.6		222.1		224.2		228.7	241.2	249.9
41950089		157.9	169.9	191.6		216.0		228.5		237.8	264.0	263.6
41950091		151.2	169.0	183.0		199.8		226.9		232.6	231.7	238.8
41950093		160.4	164.8	187.4		198.8		216.9		226.9	234.3	242.9
41950095		163.6	183.4	200.5		221.3		238.8		263.1	261.7	266.2
41950097		169.3	182.3	204.7		221.8		236.7		239.6	257.7	266.7
41950099		154.1	165.3	188.7		208.6		226.2		221.7	236.5	235.4
(n)		15	15	15		15		15		15	15	15
Mean		162.09	175.90	197.71		214.87		230.26		243.28	251.07	253.10
SD		6.36	7.35	9.75		8.02		8.48		15.38	13.07	10.54

Note: ! = Pre-test phase; " = Dosing phase

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 3.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	50	57	64	Day	71	Phase	78	85	92
41950001	1	223.9	235.0	230.6	241.1	244.3	241.1	245.5		
41950003		265.7	280.8	285.4	276.3	280.2	299.9	293.3		
41950005		280.4	280.3	294.2	288.9	305.1	294.8	291.6		
41950007		270.4	267.5	286.4	290.5	319.2	314.1	294.7		
41950009		256.4	260.6	268.9	264.6	276.1	272.2	259.7		
41950011		241.1	244.0	252.4	245.0	252.3	256.1	259.1		
41950013		266.6	270.8	282.0	280.9	284.1	287.8	293.0		
41950015		240.2	258.1	259.3	266.9	279.2	272.4	260.4		
41950017		251.1	252.7	255.6	265.3	275.6	282.9	285.8		
41950019		253.9	274.8	288.7	276.4	274.3	268.0	270.0		
41950021		266.2	269.6	280.3	284.9	279.0	299.4			
41950023		253.6	250.4	261.4	267.4	264.3	272.5			
41950025		259.1	280.2	282.9	274.9	292.2	285.1			
41950027		235.8	239.9	247.1	254.2	246.4	249.9			
41950029		257.3	260.5	269.8	275.7	278.4	278.2			
(n)		15	15	15	15	15	15	10		
Mean		254.78	261.68	269.66	270.19	276.71	278.95	275.31		
SD		14.74	14.95	18.20	14.71	20.11	20.18	18.36		
41950031	2	255.4	270.1	276.9	268.5	280.0	281.0	274.4		
41950033		279.5	279.0	283.7	297.4	281.9	297.0	281.8		
41950035		250.8	264.4	257.9	262.5	259.7	272.0	276.4		
41950037		276.5	275.0	275.7	271.5	281.5	278.8	283.5		
41950039		249.6	255.5	265.1	258.5	264.0	266.1	257.7		
41950041		262.0	269.4	283.5	276.7	286.1	282.9	279.6		
41950043		257.9	263.5	266.9	285.2	295.4	288.3	290.2		
41950045		254.0	254.8	261.5	264.5	266.6	269.0	264.3		
41950047		255.7	243.2	255.3	267.1	264.3	260.1	263.2		
41950049		245.4	268.4	274.5	277.0	282.5	283.6	277.2		
(n)		10	10	10	10	10	10	10		
Mean		258.67	264.32	270.11	272.90	276.19	277.88	274.83		
SD		11.19	10.65	10.21	11.66	11.72	11.12	10.17		
Data for Dosing phase										

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 3.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	Day					Phase		
		50	57	64	71	78	85	92	
41950051	3	271.5	274.8	282.6	280.0	279.4	275.5	276.4	
41950053		237.5	255.7	258.1	256.9	261.1	259.9	266.6	
41950055		260.7	261.1	271.7	272.3	274.7	274.1	274.1	
41950057		257.8	258.7	268.0	276.6	266.9	272.3	269.8	
41950059		253.1	262.1	266.0	266.7	272.4	269.8	265.6	
41950061		250.6	251.5	268.4	259.7	261.3	263.7	264.0	
41950063		269.7	262.1	279.1	275.3	281.2	284.3	284.9	
41950065		281.2	281.0	287.3	303.4	308.5	307.6	305.6	
41950067		262.5	261.4	283.6	273.2	264.3	276.6	287.1	
41950069		255.6	259.9	258.6	287.0	277.1	278.4	264.7	
(n)		10	10	10	10	10	10	10	
Mean		260.02	262.82	271.92	275.05	274.47	276.28	275.89	
SD		12.25	8.74	10.48	13.44	13.98	13.08	13.29	
41950071	4	269.9	296.1	286.1	287.1	279.3	281.2	282.1	
41950073		261.2	285.1	262.3	267.2	259.3	262.5	268.1	
41950075		253.9	261.6	262.9	264.4	271.6	267.8	266.2	
41950077		286.2	282.1	263.3	273.2	265.2	271.4	270.9	
41950079		273.1	267.6	266.7	279.9	280.2	281.1	280.9	
41950081		256.2	268.8	260.4	271.1	269.3	270.5	273.0	
41950083		249.0	253.8	261.2	253.5	255.0	262.1	257.0	
41950085		252.9	249.4	254.3	245.8	250.3	251.4	258.3	
41950087		265.2	266.8	260.0	252.2	251.4	257.5	250.5	
41950089		266.1	261.8	263.0	272.3	261.4	270.5	273.4	
41950091		244.0	259.5	244.5	245.0	242.1	250.1		
41950093		242.4	248.7	249.5	254.7	258.5	272.1		
41950095		277.7	260.2	266.6	272.5	275.1	281.4		
41950097		255.7	272.6	292.5	272.5	269.6	266.2		
41950099		239.9	257.8	249.9	243.9	248.4	246.8		
(n)		15	15	15	15	15	15	10	
Mean		259.55	264.80	262.88	263.69	262.43	266.18	268.04	
SD		13.48	12.25	12.59	13.57	11.68	11.15	10.29	

Data for Dosing phase

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 3.2 - Body weight (g) - During recovery - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	1"	8	15	Day 22	29	Phase 36	43	50	57
41950022	1	442.4	443.9	446.5	452.4	459.0	438.9	460.4	466.0	468.2
41950024		468.2	470.8	472.9	473.9	484.7	487.9	499.8	505.2	504.0
41950026		479.5	485.5	491.1	492.0	495.3	510.7	524.0	521.9	521.9
41950028		391.6	393.5	402.4	402.9	394.7	403.3	410.0	424.5	415.8
41950030		453.7	454.7	468.2	467.6	463.3	477.2	479.4	482.3	471.6
(n)		5	5	5	5	5	5	5	5	5
Mean		447.06	449.67	456.21	457.77	459.39	463.58	474.71	479.96	476.29
SD		34.07	35.13	34.01	33.77	39.16	42.57	43.23	37.64	40.64
41950092	4	473.2	458.6	471.3	476.8	480.3	488.6	483.8	491.3	492.2
41950094		415.6	427.3	444.2	459.7	457.7	463.9	470.5	480.7	478.7
41950096		457.7	447.7	464.5	466.9	464.4	478.4	481.8	486.7	488.9
41950098		366.6	364.3	374.0	391.1	383.4	395.5	402.2	408.7	396.7
41950100		399.0	404.4	413.8	419.3	421.6	430.1	436.3	445.1	447.9
(n)		5	5	5	5	5	5	5	5	5
Mean		422.41	420.44	433.56	442.74	441.47	451.33	454.92	462.49	460.85
SD		43.41	37.58	40.09	36.24	38.92	38.23	35.07	35.15	39.90

Note: " = Recovery phase

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 3.2 - Body weight (g) - During recovery - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	1"	8	15	Day 22	Phase 29	Phase 36	43	50	57
41950021	1	288.5	302.9	294.9	314.4	292.6	306.9	311.0	317.6	310.1
41950023		288.8	277.3	273.9	268.3	282.6	282.3	282.6	287.3	274.5
41950025		294.2	316.5	316.3	304.4	306.1	300.9	306.2	304.2	300.4
41950027		258.9	287.8	284.4	304.0	281.7	274.4	269.8	272.2	267.7
41950029	(n)	280.8	279.0	280.0	293.4	312.7	296.5	306.0	298.9	287.1
		5	5	5	5	5	5	5	5	5
Mean		278.21	292.69	289.90	296.90	295.15	292.18	295.11	296.04	287.97
SD		14.40	16.71	16.65	17.64	13.90	13.47	18.00	17.20	17.62
41950091	4	236.7	249.7	249.1	262.6	265.0	278.5	269.6	258.8	249.9
41950093		243.3	224.7	259.3	266.4	269.5	268.8	269.3	265.8	267.9
41950095		269.5	266.2	287.1	293.0	286.6	293.7	300.2	295.5	286.1
41950097		261.2	266.4	292.3	305.7	303.7	284.6	284.6	289.1	282.5
41950099	(n)	238.5	250.4	251.3	264.5	263.8	272.3	264.0	266.5	266.9
		5	5	5	5	5	5	5	5	5
Mean		249.82	251.49	267.80	278.47	277.72	279.54	277.54	275.14	270.66
SD		14.65	17.04	20.41	19.66	17.17	9.93	14.82	16.13	14.41

Note: " = Recovery phase

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 4 - Body weight (g) change* - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Day of Phase												
		8	15	22	29	36	43	50	57	64	71	78	85	
41950002	1	47.5	78.3	107.2	129.6	150.4	165.8	181.2	189.0	205.6	217.9	222.9	231.7	
41950004		43.0	77.8	106.7	136.4	149.7	162.6	189.1	195.8	197.3	203.7	211.5	215.3	
41950006		39.2	70.9	94.7	122.3	140.6	162.5	174.3	186.1	196.6	202.3	202.0	210.3	
41950008		38.6	70.7	99.9	124.3	142.8	157.2	169.3	184.5	193.0	198.1	203.2	217.8	
41950010		32.2	55.1	79.7	99.4	116.9	131.9	151.5	161.7	170.9	184.3	186.1	196.2	
41950012		42.0	77.9	99.9	123.6	135.5	147.1	167.2	174.2	190.5	191.5	202.5	201.6	
41950014		39.6	60.5	87.3	111.9	128.0	133.7	150.7	171.4	180.8	189.8	196.0	205.7	
41950016		37.2	68.4	87.1	113.0	132.1	142.6	163.8	173.4	182.7	193.1	202.0	204.3	
41950018		42.1	72.8	99.9	126.3	145.1	157.4	165.6	184.7	189.7	198.8	207.7	214.1	
41950020		41.5	75.3	91.7	120.8	140.3	158.7	172.1	172.9	181.7	195.5	197.4	202.4	
41950022		41.9	79.3	100.2	117.1	135.7	146.0	161.2	168.4	172.1	175.3	178.0	196.5	
41950024		41.9	83.5	103.1	128.2	146.1	158.3	175.6	181.5	198.4	195.3	204.4	213.8	
41950026		42.5	67.3	86.6	113.9	132.6	144.9	165.4	176.4	196.8	204.9	214.7	221.7	
41950028		36.3	56.2	77.6	97.7	104.2	123.2	133.5	142.5	145.3	154.8	157.2	164.6	
41950030		40.7	67.6	97.7	122.7	141.5	152.1	171.6	175.8	181.2	184.4	192.7	197.0	
(n)		15	15	15	15	15	15	15	15	15	15	15	15	
Mean		40.41	70.77	94.63	119.15	136.09	149.60	166.13	175.87	185.11	192.62	198.55	206.20	
SD		3.53	8.48	9.23	10.63	12.42	12.64	13.45	12.73	14.83	14.56	15.88	15.33	
41950032	2	52.5	93.9	126.3	143.5	173.7	193.5	203.7	215.4	226.5	241.9	246.6	251.5	
41950034		46.5	80.5	108.5	134.7	151.8	166.9	180.5	195.4	204.1	218.4	213.2	227.0	
41950036		47.4	87.5	126.6	145.0	156.1	173.5	185.0	195.4	204.5	219.4	216.5	223.9	
41950038		43.2	85.0	115.3	139.1	162.6	189.6	200.6	205.0	198.0	219.0	220.5	222.3	
41950040		37.5	68.3	93.3	104.8	123.1	134.0	153.3	158.1	165.0	170.3	175.2	175.9	
41950042		40.5	71.6	105.2	129.7	162.5	170.7	183.1	194.9	209.9	214.8	222.8	229.6	
41950044		34.0	60.8	81.2	103.6	114.1	124.5	147.1	148.0	154.6	164.7	173.7	181.5	
41950046		51.5	79.4	107.3	134.5	153.8	165.2	172.0	183.9	195.3	208.6	212.4	217.3	
41950048		48.0	89.5	114.0	132.9	147.7	162.7	175.9	181.9	197.6	203.4	211.0	216.4	
41950050		36.1	69.4	92.1	110.4	124.0	138.3	150.3	181.4	181.0	187.1	200.4	203.2	
(n)			10	10	10	10	10	10	10	10	10	10	10	10
Mean			43.72	78.59	106.96	127.80	146.94	161.88	175.15	185.95	193.64	204.76	209.24	214.85
SD			6.51	10.71	14.76	15.66	19.82	22.98	19.84	20.41	21.39	24.07	21.83	22.67

Note: Data for Dosing phase
* = mean body weight change relevant to Day 1 of the study

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 4 - Body weight (g) change° - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	8	15	22	29	36	Day	43	50	57	Phase	64	71	78	85	
41950052	3	44.2	76.6	106.1	121.6	137.7	159.7	173.9	179.6	191.2	200.5	202.4	211.0	202.4	211.0	
41950054		38.8	62.1	86.3	102.4	124.8	139.6	151.6	159.7	172.0	180.8	183.8	184.5	183.8	184.5	
41950056		46.2	77.0	97.1	119.3	135.6	150.0	157.3	170.3	179.5	186.2	182.9	189.0	182.9	189.0	
41950058		39.5	79.3	104.3	121.8	147.3	168.6	170.5	192.0	204.6	217.1	221.7	228.1	221.7	228.1	
41950060		39.2	72.2	99.9	118.3	131.3	149.4	167.7	179.8	192.0	204.6	217.1	221.7	228.1	221.7	228.1
41950062		39.2	72.4	91.4	112.9	128.8	145.9	155.8	165.0	169.9	184.8	186.4	190.1	184.8	186.4	190.1
41950064		46.9	74.9	113.6	129.8	159.7	170.1	189.3	199.8	199.8	203.9	216.3	223.0	216.3	223.0	223.0
41950066		45.2	74.9	107.1	124.6	147.5	160.1	174.0	184.3	192.1	196.3	197.2	206.6	196.3	197.2	206.6
41950068		36.1	66.4	89.0	110.0	125.4	146.4	158.7	168.4	175.7	184.4	193.6	196.4	184.4	193.6	196.4
41950070		48.9	84.0	109.5	126.5	150.8	160.3	178.5	195.9	197.6	217.1	213.6	227.5	217.1	213.6	227.5
(n)		10	10	10	10	10	10	10	10	10	10	10	10	10	10	
Mean		42.42	73.99	100.43	118.72	138.90	154.99	167.72	179.49	187.46	196.93	199.66	206.03	199.66	206.03	
SD		4.35	6.25	9.25	8.24	11.88	10.22	11.83	13.62	12.27	13.14	13.79	16.22	13.79	16.22	
41950072	4	49.7	79.8	111.7	139.4	157.0	170.6	183.5	177.4	190.5	191.9	197.5	191.9	197.5	191.0	
41950074		41.7	76.8	113.9	132.9	150.5	132.8	162.5	168.5	163.3	160.5	156.8	155.7	156.8	155.7	
41950076		53.9	90.8	121.9	145.2	167.3	177.2	184.0	198.1	195.1	203.4	202.4	204.8	203.4	204.8	
41950078		40.5	76.5	108.2	139.7	151.9	165.3	178.9	182.7	183.6	182.1	185.1	184.6	182.1	185.1	
41950080		44.5	81.9	113.8	129.9	155.2	174.3	170.5	177.9	184.1	190.5	189.7	195.2	189.7	195.2	
41950082		48.1	78.9	106.4	109.5	156.1	166.4	168.8	188.7	184.6	193.8	185.5	190.2	185.5	190.2	
41950084		42.3	70.9	104.7	128.5	144.8	153.8	161.4	166.5	180.5	168.6	162.6	166.7	168.6	166.7	
41950086		51.1	76.7	100.7	126.2	144.7	153.3	158.1	167.7	162.0	159.9	163.7	164.9	163.7	164.9	
41950088		46.9	73.5	97.1	114.7	133.4	143.6	150.6	156.2	153.0	141.9	141.0	146.4	141.0	146.4	
41950090		38.9	67.3	91.7	109.9	127.4	137.2	140.0	145.9	152.9	152.6	148.7	152.6	148.7	152.6	
41950092	47.3	94.9	131.2	154.6	179.8	201.4	207.7	216.5	220.4	234.7	234.2	237.9	234.7	234.2	237.9	
41950094	45.8	81.6	108.8	136.0	160.7	162.7	172.1	180.1	191.2	199.5	204.7	208.3	199.5	204.7	208.3	
41950096	51.5	92.9	125.4	144.6	169.5	184.3	178.0	200.1	212.2	215.2	219.2	221.6	215.2	219.2	221.6	
41950098	45.0	69.9	83.6	105.3	120.2	125.3	132.9	135.9	142.7	142.5	145.2	146.6	142.5	145.2	146.6	
41950100	36.8	68.8	87.6	110.4	127.7	138.7	149.4	158.7	168.2	173.0	175.6	178.4	173.0	175.6	178.4	
(n)		15	15	15	15	15	15	15	15	15	15	15	15	15	15	
Mean		45.59	78.74	107.10	128.45	149.73	159.12	166.55	174.72	178.96	180.67	180.79	183.00	180.79	183.00	
SD		4.92	8.59	13.56	15.37	16.95	21.13	19.13	21.27	21.99	26.95	27.85	27.81	27.85	27.81	

Note: Data for Dosing phase
° = mean body weight change relevant to Day 1 of the study

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 4 - Body weight (g) change° - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	92!	1"	8	15	Day 22	Phase 29	Phase 36	50	57
41950002	1	232.1								
41950004		224.4								
41950006		218.4								
41950008		210.9								
41950010		194.1								
41950012		201.3								
41950014		198.5								
41950016		203.2								
41950018		215.0								
41950020		205.6								
41950022			204.6	206.2	208.8	214.7	221.3	201.1	228.2	230.4
41950024			223.5	226.2	228.2	229.3	240.0	243.2	255.1	259.4
41950026			231.7	237.7	243.3	244.2	247.5	263.0	274.1	274.2
41950028			166.9	168.8	177.7	178.2	170.0	178.6	199.3	191.1
41950030			208.5	209.5	223.0	222.4	218.1	232.0	234.2	226.4
(n)		10	5	5	5	5	5	5	5	5
Mean		210.35	207.04	209.66	216.20	217.76	219.38	223.56	234.69	236.27
SD		12.09	25.01	26.16	24.82	24.62	30.27	33.68	28.92	32.20
41950032	2	238.3								
41950034		215.2								
41950036		221.2								
41950038		229.1								
41950040		174.8								
41950042		227.1								
41950044		178.7								
41950046		212.7								
41950048		221.9								
41950050		199.0								
(n)		10								
Mean		211.80								
SD		21.26								

Note: ! = Dosing phase; " = Recovery phase
° = mean body weight change relevant to Day 1 of the study

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 4 - Body weight (g) change° - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	92!	1"	8	Day of Phase					43	50	57
					15	22	29	36				
41950052	3	202.1										
41950054		184.3										
41950056		184.1										
41950058		224.1										
41950060		203.2										
41950062		198.5										
41950064		226.3										
41950066		208.4										
41950068		200.4										
41950070		228.8										
		(n)										
		10										
		Mean										
		SD										
41950072	4	186.4										
41950074		152.1										
41950076		183.4										
41950078		175.4										
41950080		194.6										
41950082		181.4										
41950084		163.1										
41950086		165.2										
41950088		140.6										
41950090		147.5										
41950092			229.5	214.9	227.6	233.1	236.6	245.0		240.1	247.6	248.5
41950094			182.5	194.1	211.1	226.6	224.6	230.8		237.4	247.6	245.6
41950096			218.1	208.1	224.9	227.3	224.8	238.8		242.1	247.1	249.3
41950098			140.5	138.3	148.0	165.0	157.3	169.5		176.2	182.6	170.6
41950100			169.7	175.1	184.6	190.0	192.4	200.9		207.1	215.8	218.7
		(n)	5	5	5	5	5	5		5	5	5
		Mean	168.95	188.07	199.22	208.40	207.13	216.99		220.58	228.15	226.51
		SD	18.16	36.22	33.34	29.66	32.32	31.48		28.65	28.89	33.72

Note: ! = Dosing phase; " = Recovery phase
° = mean body weight change relevant to Day 1 of the study

REDACTED AS TO TRADE NAMES
13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 4 - Body weight (g) change* - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	8	15	22	29	36	Day of Phase				64	71	78	85
							43	50	57					
41950001	1	6.2	21.3	34.9	35.1	48.9	59.3	59.0	70.1	65.7	76.2	79.4	76.2	76.2
41950003		22.1	35.4	54.6	75.1	74.1	80.6	80.0	95.1	99.7	90.5	94.5	114.1	114.1
41950005		6.8	22.3	35.7	61.4	52.5	61.9	78.8	78.7	92.6	87.3	103.5	93.2	93.2
41950007		16.8	34.3	60.0	80.7	61.7	73.4	76.9	74.1	93.0	97.1	125.8	120.6	120.6
41950009		35.5	46.8	61.8	68.9	68.7	78.6	79.2	83.3	91.7	87.4	98.8	94.9	94.9
41950011		19.5	37.8	43.3	52.4	58.1	69.8	74.0	76.9	85.2	77.9	85.2	89.0	89.0
41950013		18.0	36.1	47.0	66.3	77.3	78.2	85.2	89.4	100.6	99.5	102.7	106.4	106.4
41950015		5.9	37.4	37.5	47.2	68.7	71.4	59.5	77.4	78.6	86.2	98.5	91.7	91.7
41950017		19.8	28.0	47.9	62.6	68.7	76.4	72.8	74.4	77.3	87.0	97.3	114.7	114.7
41950019		31.4	26.8	62.0	76.9	55.8	79.2	74.6	95.5	109.4	97.2	95.0	88.7	88.7
41950021		22.1	51.0	67.4	64.1	74.6	82.0	92.6	96.0	106.6	111.3	105.4	125.8	125.8
41950023		20.7	34.9	43.2	56.5	67.2	75.0	82.7	79.4	90.4	96.5	93.3	101.6	101.6
41950025		35.6	44.0	59.4	70.2	78.1	89.0	81.4	102.5	105.3	97.2	114.6	107.4	107.4
41950027		21.8	33.1	48.7	60.9	58.8	72.0	70.3	74.4	81.6	88.7	80.9	84.4	84.4
41950029		16.5	30.0	41.6	52.7	63.2	66.8	72.7	75.9	85.2	91.1	93.8	93.6	93.6
(n)		15	15	15	15	15	15	15	15	15	15	15	15	15
Mean		19.92	34.61	49.66	62.06	65.08	74.23	75.98	82.88	90.86	91.39	97.91	100.15	100.15
SD		9.31	8.37	10.57	12.05	9.03	7.78	8.82	10.13	12.24	8.81	12.01	14.26	14.26
41950031	2	20.4	34.0	52.5	50.3	69.6	66.6	78.5	93.2	100.1	91.6	103.2	104.2	104.2
41950033		18.6	36.5	55.7	58.8	61.2	79.7	91.2	90.7	95.4	109.1	93.5	108.6	108.6
41950035		20.1	30.6	49.5	64.8	64.0	81.4	83.2	96.8	90.3	95.0	92.1	104.4	104.4
41950037		15.6	34.1	43.3	54.7	62.5	83.5	91.4	89.9	90.6	86.4	96.4	93.7	93.7
41950039		7.9	38.0	62.1	88.4	74.0	76.3	85.0	90.9	100.6	93.9	99.4	101.5	101.5
41950041		20.1	26.9	48.9	62.5	62.6	77.7	79.6	87.0	101.1	94.3	103.7	100.5	100.5
41950043		11.2	54.7	65.7	70.9	102.4	100.0	87.9	93.5	96.9	115.2	125.3	118.3	118.3
41950045		16.9	40.5	30.3	56.1	66.5	72.1	83.5	84.3	91.0	94.0	96.1	98.5	98.5
41950047		11.7	32.2	42.2	55.7	63.4	73.1	82.1	69.6	81.7	93.5	90.7	86.5	86.5
41950049		20.7	30.8	51.1	55.7	72.5	75.9	64.4	87.3	93.5	96.0	101.5	102.6	102.6
(n)		10	10	10	10	10	10	10	10	10	10	10	10	10
Mean		16.34	35.85	50.12	61.79	69.88	78.63	82.66	88.31	94.10	96.90	100.18	101.87	101.87
SD		4.59	7.70	10.16	11.04	12.25	8.92	7.77	7.51	6.01	8.57	9.93	8.47	8.47

Note: Data for Dosing phase
° = mean body weight change relevant to Day 1 of the study

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 4 - Body weight (g) change* - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	8	15	22	29	36	43	50	57	64	71	78	85
41950051	3	22.9	41.9	49.2	73.1	82.2	78.7	94.8	98.1	105.9	103.3	102.7	98.8
41950053		10.4	34.6	41.3	44.4	63.8	62.5	65.2	83.4	85.8	84.5	88.8	87.6
41950055		11.8	29.8	53.6	63.0	73.9	77.9	77.9	78.3	84.8	89.0	89.6	91.9
41950057		12.8	37.0	60.1	65.9	76.5	78.3	84.3	85.2	94.5	103.1	93.4	98.8
41950059		18.6	40.7	52.3	69.7	77.8	76.1	78.7	87.7	91.6	92.3	98.0	95.4
41950061		15.6	39.1	46.6	63.4	56.8	76.6	77.3	78.2	95.1	86.4	88.0	90.4
41950063		16.5	34.9	41.3	55.8	64.3	74.2	85.0	77.4	94.4	90.7	96.6	99.7
41950065		23.7	38.2	59.1	68.7	80.5	89.6	98.0	97.9	104.1	120.2	125.4	124.5
41950067		12.4	36.6	64.3	58.7	47.6	85.4	77.3	76.1	98.4	87.9	79.1	91.3
41950069		28.6	38.8	56.9	92.4	70.2	68.2	89.0	93.2	92.0	120.4	110.5	111.8
(n)		10	10	10	10	10	10	10	10	10	10	10	10
Mean		17.34	37.17	52.47	65.52	68.07	76.35	82.75	85.55	94.65	97.79	97.20	99.02
SD		6.03	3.49	7.88	12.49	11.30	7.71	9.62	8.42	6.85	13.47	13.15	11.25
41950071	4	30.4	37.3	59.6	81.3	93.4	81.5	84.6	110.7	100.7	101.8	93.9	95.9
41950073		32.4	45.7	48.1	84.1	83.4	74.0	82.6	86.6	83.8	88.6	80.8	84.0
41950075		17.2	39.3	55.5	65.6	67.2	71.3	74.9	82.6	83.9	85.4	92.6	88.8
41950077		27.4	35.4	63.7	84.6	72.3	78.7	102.6	98.5	79.7	89.7	81.6	87.8
41950079		10.1	35.6	47.4	68.6	77.6	79.5	92.5	87.0	86.1	99.3	99.6	100.5
41950081		20.4	30.7	43.6	54.9	64.0	65.6	72.5	85.1	76.7	87.4	85.6	86.8
41950083		19.4	36.4	50.6	54.6	66.2	70.3	74.6	79.3	86.8	79.1	80.6	87.7
41950085		22.3	40.7	53.6	71.5	81.4	78.5	84.5	81.0	85.9	77.4	81.9	83.1
41950087		26.5	52.0	54.1	58.6	71.1	79.7	95.0	96.7	89.9	82.1	81.3	87.4
41950089		21.7	46.1	58.6	68.0	94.2	93.7	96.2	92.0	93.2	102.4	91.5	100.7
41950091		14.0	30.8	57.9	63.6	62.7	69.8	75.0	90.5	75.5	76.0	73.1	81.1
41950093		22.5	34.0	52.0	62.1	69.4	78.0	77.6	83.9	84.7	89.9	93.7	107.2
41950095		17.1	37.9	55.4	79.7	78.3	82.8	94.3	76.8	83.2	89.1	91.7	98.0
41950097		22.3	39.5	54.3	57.2	75.3	84.4	73.4	90.3	110.1	90.2	87.3	83.9
41950099		23.4	43.3	60.9	56.4	71.2	70.1	74.6	92.5	84.6	78.6	83.1	81.5
(n)		15	15	15	15	15	15	15	15	15	15	15	15
Mean		21.82	38.98	54.36	67.39	75.18	77.20	83.66	88.90	86.98	87.80	86.54	90.28
SD		5.92	5.87	5.42	10.71	9.67	7.18	10.08	8.64	8.90	8.47	7.07	8.11

Note: Data for Dosing phase

* = mean body weight change relevant to Day 1 of the study

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 4 - Body weight (g) change° - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	92!	1"	8	15	Day	22	of	Phase	36	43	50	57
41950001	1	80.6											
41950003		107.6											
41950005		90.0											
41950007		101.3											
41950009		82.5											
41950011		92.1											
41950013		111.6											
41950015		79.7											
41950017		107.6											
41950019		90.7											
41950021			114.8	129.3	121.3	140.8	118.9	133.2	137.4	144.0	136.5		
41950023		97.8	106.3	102.9	97.3	111.6	111.3	111.3	111.6	116.3	103.5		
41950025		116.5	138.8	138.7	126.8	128.5	123.3	123.3	128.6	126.6	122.8		
41950027		93.4	122.3	118.9	138.5	116.2	108.9	108.9	104.3	106.7	102.2		
41950029		96.2	94.4	95.4	108.8	128.1	111.9	111.9	121.4	114.3	102.5		
(n)		10	5	5	5	5	5	5	5	5	5		
Mean		94.35	103.74	118.22	115.44	122.43	120.68	117.71	120.64	121.57	113.50		
SD		11.93	11.03	17.82	16.92	18.90	7.43	10.31	13.17	14.38	15.53		
41950031	2	97.5											
41950033		93.5											
41950035		108.8											
41950037		98.4											
41950039		93.1											
41950041		97.2											
41950043		120.2											
41950045		93.8											
41950047		89.5											
41950049		96.2											
(n)		10											
Mean		98.82											
SD		9.07											

Note: ! = Dosing phase; " = Recovery phase
° = mean body weight change relevant to Day 1 of the study

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 4 - Body weight (g) change° - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	92!	1"	8	D a y			P h a s e			50	57
					15	22	29	36	43	50		
41950051	3	99.7										
41950053		94.3										
41950055		91.3										
41950057		96.3										
41950059		91.2										
41950061		90.7										
41950063		100.3										
41950065		122.5										
41950067		101.9										
41950069		98.1										
		(n)										
		10										
		Mean										
		SD										
41950071	4	96.7										
41950073		89.6										
41950075		87.2										
41950077		87.3										
41950079		100.3										
41950081		89.3										
41950083		82.6										
41950085		89.9										
41950087		80.4										
41950089		103.6										
41950091		67.7	80.7		80.1	93.6	96.0	109.5	100.6	89.8	80.9	
41950093		78.5	59.9		94.5	101.6	104.7	104.0	104.5	101.0	103.1	
41950095		86.0	82.8		103.7	109.6	103.2	110.3	116.8	112.1	102.7	
41950097		78.9	84.1		109.9	123.4	121.4	102.2	102.3	106.8	100.2	
41950099		73.2	85.1		86.0	99.2	98.5	107.0	98.7	101.2	101.6	
		(n)	10		5	5	5	5	5	5	5	
		Mean	90.68	78.52	94.83	105.50	104.75	106.57	104.57	102.17	97.69	
		SD	7.41	10.54	12.26	11.54	9.94	3.45	7.16	8.30	9.46	
			6.86									

Note: ! = Dosing phase; " = Recovery phase
° = mean body weight change relevant to Day 1 of the study

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

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

STUDY NO.: 41950

MALES

Cage	Group	1	8	Day 15	of 22	Phase	29	36	43
1	1	22.9	24.4	26.0	25.8	27.4	27.8	26.2	26.2
2		23.2	24.9	26.9	25.4	26.8	26.5	25.8	25.8
3		24.1	25.7	26.5	26.8	28.2	27.1	26.3	26.3
	(n)	3	3	3	3	3	3	3	3
	Mean	23.43	24.98	26.44	26.02	27.46	27.11	26.09	26.09
	SD	0.61	0.63	0.45	0.74	0.74	0.64	0.30	0.30
4	2	23.1	24.9	27.4	26.5	28.6	27.6	26.5	26.5
5		23.4	24.5	26.5	26.9	28.4	27.3	26.2	26.2
	(n)	2	2	2	2	2	2	2	2
	Mean	23.22	24.73	26.95	26.71	28.47	27.44	26.35	26.35
6	3	23.4	24.7	26.5	26.4	27.3	27.3	26.8	26.8
7		24.9	25.9	27.7	28.0	28.6	27.7	26.8	26.8
	(n)	2	2	2	2	2	2	2	2
	Mean	24.17	25.29	27.11	27.21	27.96	27.51	26.81	26.81
8	4	24.2	25.2	26.7	27.8	28.4	28.3	25.6	25.6
9		22.4	24.0	24.7	25.3	26.6	26.0	25.2	25.2
10		23.4	25.4	26.7	26.3	27.4	27.4	26.4	26.4
	(n)	3	3	3	3	3	3	3	3
	Mean	23.33	24.86	26.06	26.45	27.46	27.23	25.74	25.74
	SD	0.93	0.74	1.14	1.23	0.92	1.15	0.61	0.61

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

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

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

STUDY NO.: 41950

MALES

Cage	Group	Day of Phase							
		50	57	64	71	78	85	92	
1	1	26.7	25.7	26.1	24.7	25.0	26.7	23.0	
2		26.8	25.7	25.8	24.8	24.4	25.4	21.7	
3		27.6	26.2	25.9	25.1	25.7	26.5	25.4	
	(n)	3	3	3	3	3	3	3	
	Mean	27.03	25.91	25.92	24.88	25.03	26.21	23.33	
	SD	0.47	0.29	0.14	0.18	0.65	0.69	1.87	
4	2	27.9	26.2	26.9	25.2	25.4	25.6	21.9	
5		27.5	26.1	26.3	25.1	25.9	25.6	22.3	
	(n)	2	2	2	2	2	2	2	
	Mean	27.69	26.15	26.62	25.17	25.67	25.62	22.13	
6	3	27.2	25.7	25.9	24.9	25.0	25.2	21.3	
7		28.7	26.8	25.6	24.8	26.2	26.8	23.3	
	(n)	2	2	2	2	2	2	2	
	Mean	27.98	26.22	25.71	24.85	25.58	25.98	22.29	
8	4	29.9	27.8	29.1	27.8	28.2	28.5	24.7	
9		26.4	25.9	26.5	24.5	26.3	26.5	22.6	
10		27.6	27.3	28.1	28.0	28.4	29.0	26.8	
	(n)	3	3	3	3	3	3	3	
	Mean	27.96	27.02	27.87	26.74	27.64	28.00	24.69	
	SD	1.81	1.01	1.30	1.98	1.20	1.33	2.06	

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

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

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

STUDY NO.: 41950

FEMALES

Cage	Group	1	8	15	Day of Phase	22	29	36	43
11	1	18.8	17.1	18.7	18.7	20.6	18.5	17.7	
12		17.4	18.1	18.5	19.1	19.0	19.1	19.5	
13		17.8	18.8	20.6	21.1	20.7	20.4	20.9	
	(n)	3	3	3	3	3	3	3	
	Mean	18.01	18.04	19.25	19.61	20.10	19.34	19.41	
	SD	0.68	0.85	1.14	1.27	0.98	0.95	1.60	
14	2	16.4	16.9	18.5	19.2	20.0	18.3	18.8	
15		17.3	17.4	19.5	19.5	20.3	21.3	20.1	
	(n)	2	2	2	2	2	2	2	
	Mean	16.88	17.13	19.01	19.36	20.14	19.80	19.45	
16	3	17.7	17.2	18.4	19.4	20.1	19.1	18.2	
17		17.6	18.6	20.5	20.4	22.3	19.7	20.4	
	(n)	2	2	2	2	2	2	2	
	Mean	17.66	17.91	19.48	19.91	21.21	19.42	19.32	
18	4	16.9	19.1	19.7	19.8	22.3	21.6	18.5	
19		16.9	16.8	19.6	17.8	21.1	20.2	19.3	
20		16.7	18.3	19.2	20.6	20.8	19.9	20.3	
	(n)	3	3	3	3	3	3	3	
	Mean	16.80	18.08	19.52	19.40	21.40	20.57	19.35	
	SD	0.11	1.13	0.29	1.46	0.77	0.90	0.89	

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

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

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

STUDY NO.: 41950

FEMALES

Cage	Group	Day of Phase									
		50	57	64	71	78	85	92			
11	1	19.1	18.0	19.6	16.9	19.4	19.6	15.8			
12		19.2	19.3	20.3	17.7	18.3	19.1	16.3			
13		22.5	19.9	21.7	21.2	20.7	21.5	19.7			
		3	3	3	3	3	3	3			
	2	20.25	19.09	20.54	18.61	19.48	20.09	17.27			
		1.96	0.97	1.03	2.29	1.19	1.26	2.10			
14		20.7	19.2	19.5	17.9	18.1	18.8	15.4			
15		19.8	19.5	20.9	19.6	21.0	19.6	17.1			
	3	2	2	2	2	2	2	2			
		20.24	19.38	20.19	18.74	19.57	19.21	16.28			
16		19.3	18.7	19.4	18.1	18.4	18.1	16.5			
17		21.2	19.4	21.2	19.9	20.1	20.1	18.3			
	4	2	2	2	2	2	2	2			
		20.22	19.04	20.32	18.99	19.24	19.11	17.40			
18		21.3	20.6	20.2	20.3	20.7	21.1	19.4			
19		19.2	18.3	18.8	18.9	19.3	20.7	18.0			
20		19.6	20.3	20.3	19.1	20.1	21.3	18.8			
		3	3	3	3	3	3	3			
		20.00	19.75	19.79	19.45	20.05	21.01	18.74			
		1.10	1.24	0.82	0.71	0.67	0.31	0.74			

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

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

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

STUDY NO.: 41950

MALES

Cage	Group	Phase							
		8	15	22	29	36	43	50	57
3	1 (n)	24.5	25.3	24.7	25.0	25.7	24.3	25.7	22.6
		1	1	1	1	1	1	1	1
10	4 (n)	27.8	27.2	25.2	25.0	26.1	25.1	25.8	22.4
		1	1	1	1	1	1	1	1

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

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

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

STUDY NO.: 41950

FEMALES

Cage	Group	8	15	22	D a y			P h a s e			50	57
					29	36	43	43	50	57		
13	1	22.9 1 (n)	21.6 1	20.1 1	21.5 1	19.9 1	18.9 1	20.1 1	16.8 1			
20	4	20.1 1 (n)	21.4 1	20.2 1	19.8 1	19.4 1	17.6 1	18.4 1	16.0 1			

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

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	RBC 10 ¹² /l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
41950002	1	9.05	16.4	47.2	52.2	18.2	34.8
41950004	1	9.16	16.8	47.6	52.0	18.3	35.2
41950006	1	9.35	15.9	45.9	49.0	17.1	34.8
41950008	1	8.82	16.1	46.7	52.9	18.3	34.5
41950010	1	8.80	16.1	46.8	53.2	18.3	34.5
41950012	1	8.52	15.9	45.1	52.9	18.6	35.2
41950014	1	8.76	16.0	46.6	53.2	18.2	34.2
41950016	1	8.70	16.2	46.9	53.9	18.6	34.6
41950018	1	9.02	16.1	46.2	51.2	17.8	34.8
41950020	1	8.53	16.1	46.3	54.2	18.9	34.8
		Mean 8.871	16.16	46.53	52.47	18.23	34.74
		SD 0.270	0.27	0.70	1.51	0.49	0.31
41950032	2	8.29	15.6	44.9	54.2	18.9	34.8
41950034	2	8.30	15.7	45.1	54.3	18.9	34.8
41950036	2	8.18	15.6	44.9	54.9	19.0	34.7
41950038	2	8.69	15.7	45.1	51.9	18.1	34.9
41950040	2	9.53	16.6	48.3	50.7	17.4	34.3
41950042	2	8.72	15.7	45.5	52.2	18.0	34.5
41950044	2	8.78	15.5	44.6	50.8	17.6	34.7
41950046	2	9.12	16.4	46.6	51.0	18.0	35.2
41950048	2	8.60	16.0	45.8	53.2	18.6	35.0
41950050	2	8.89	16.0	46.2	52.0	18.0	34.7
		Mean 8.710	15.88	45.70	52.52	18.25	34.76
		SD 0.410	0.37	1.11	1.54	0.57	0.25

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	RBC 10 ¹² /l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
41950052	3	8.50	15.1	43.6	51.3	17.8	34.8
41950054	3	8.10	15.0	43.9	54.3	18.5	34.2
41950056	3	8.20	14.6	41.9	51.2	17.8	34.7
41950058	3	8.87	16.3	46.8	52.8	18.3	34.8
41950060	3	8.43	15.7	44.3	52.6	18.6	35.4
41950062	3	8.90	15.9	45.7	51.4	17.9	34.8
41950064	3	8.57	15.6	45.2	52.8	18.2	34.4
41950066	3	7.81	14.2	40.5	51.8	18.1	35.0
41950068	3	8.63	15.5	45.4	52.7	18.0	34.1
41950070	3	8.62	16.5	46.8	54.3	19.1	35.2
Mean		8.463	15.44	44.41	52.52	18.23	34.74
SD		0.342	0.72	2.03	1.13	0.41	0.41
41950072	4	7.93	14.8	41.8	52.7	18.6	35.3
41950074	4	7.50	14.2	41.2	54.9	18.9	34.4
41950076	4	7.60	14.7	41.9	55.1	19.4	35.2
41950078	4	8.37	15.6	44.6	53.2	18.6	34.9
41950080	4	8.25	16.2	46.4	56.2	19.7	34.9
41950082	4	8.14	15.4	44.2	54.3	19.0	34.9
41950084	4	7.63	14.9	42.8	56.0	19.5	34.8
41950086	4	8.46	15.8	45.0	53.2	18.7	35.1
41950088	4	7.93	15.1	42.7	53.8	19.0	35.3
41950090	4	8.38	15.9	45.7	54.5	18.9	34.7
Mean		8.019	15.26	43.63	54.39	19.03	34.95
SD		0.354	0.63	1.79	1.19	0.38	0.28

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	PLT 10 ⁹ /l	PT sec
41950002	1	855	17.7
41950004	1	883	16.9
41950006	1	1026	16.8
41950008	1	920	17.7
41950010	1	827	17.1
41950012	1	788	17.4
41950014	1	810	17.3
41950016	1	873	17.2
41950018	1	744	16.7
41950020	1	875	17.3
		Mean 860.1	17.21
		SD 77.7	0.34
41950032	2	951	17.5
41950034	2	732	16.6
41950036	2	860	14.2
41950038	2	737	17.1
41950040	2	773	16.7
41950042	2	748	15.8
41950044	2	800	17.2
41950046	2	934	17.6
41950048	2	696	18.8
41950050	2	688	17.6
		Mean 791.9	16.91
		SD 93.7	1.23

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	PLT 10 ⁹ /l	PT sec
41950052	3	952	18.0
41950054	3	800	16.3
41950056	3	795	16.9
41950058	3	788	16.7
41950060	3	789	16.9
41950062	3	965	17.0
41950064	3	712	15.9
41950066	3	953	16.7
41950068	3	798	16.6
41950070	3	752	15.5
		Mean 830.4	16.65
		SD 91.2	0.67
41950072	4	969	17.3
41950074	4	738	16.7
41950076	4	927	17.0
41950078	4	884	16.5
41950080	4	837	16.5
41950082	4	898	17.3
41950084	4	817	17.2
41950086	4	1078	18.0
41950088	4	736	17.4
41950090	4	893	17.9
		Mean 877.7	17.18
		SD 103.6	0.52

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	WBC 10 ⁹ /l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
41950002	1	11.24	11.3	79.9	5.9	1.5	0.2	1.2
41950004	1	9.92	14.3	79.9	2.9	1.5	0.4	1.0
41950006	1	14.02	26.6	67.3	3.4	1.7	0.3	0.8
41950008	1	12.73	19.4	74.8	3.6	1.2	0.2	0.8
41950010	1	11.02	19.0	74.3	4.4	1.2	0.2	0.9
41950012	1	8.87	11.1	81.8	3.9	2.1	0.2	0.9
41950014	1	11.56	15.8	75.5	5.8	1.4	0.3	1.3
41950016	1	9.96	13.6	79.8	4.1	1.3	0.3	0.9
41950018	1	8.10	8.9	83.3	5.0	1.4	0.2	1.2
41950020	1	11.64	14.5	77.9	4.2	2.2	0.2	1.0
Mean		10.906	15.45	77.45	4.32	1.55	0.25	1.00
SD		1.764	5.14	4.65	0.99	0.35	0.07	0.18
41950032	2	12.80	20.2	72.0	4.7	1.9	0.2	1.0
41950034	2	11.94	7.3	87.3	2.8	1.4	0.2	0.8
41950036	2	9.00	10.1	84.8	3.3	0.7	0.1	0.9
41950038	2	10.01	30.4	63.8	3.1	1.9	0.1	0.6
41950040	2	9.52	11.3	80.5	4.6	2.3	0.2	1.0
41950042	2	10.15	25.3	66.2	5.2	2.2	0.1	0.9
41950044	2	8.79	12.4	80.7	3.6	2.4	0.1	0.8
41950046	2	8.77	12.9	80.8	3.6	1.7	0.2	0.8
41950048	2	10.92	11.8	78.7	6.1	1.8	0.3	1.2
41950050	2	9.09	26.0	64.8	5.3	2.8	0.1	1.1
Mean		10.099	16.77	75.96	4.23	1.91	0.16	0.91
SD		1.391	8.02	8.59	1.10	0.58	0.07	0.17

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	WBC 10 ⁹ /l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
41950052	3	15.17	12.2	79.8	4.0	2.6	0.4	1.1
41950054	3	8.69	12.5	82.0	2.9	1.8	0.2	0.6
41950056	3	12.05	25.1	65.7	5.9	1.8	0.2	1.2
41950058	3	8.94	13.7	79.7	3.7	2.0	0.2	0.8
41950060	3	9.32	16.0	78.3	2.8	2.2	0.2	0.7
41950062	3	10.06	9.6	83.8	3.2	2.3	0.2	0.9
41950064	3	12.24	20.4	71.8	5.2	1.3	0.2	1.1
41950066	3	8.82	23.9	69.5	4.7	0.8	0.2	1.0
41950068	3	10.70	17.8	76.0	3.6	1.3	0.1	1.0
41950070	3	11.16	8.9	84.3	3.7	2.0	0.3	0.8
Mean		10.715	16.01	77.09	3.97	1.81	0.22	0.92
SD		2.038	5.69	6.26	1.01	0.54	0.08	0.19
41950072	4	7.07	17.5	76.8	3.0	1.8	0.3	0.7
41950074	4	5.37	14.9	77.0	5.4	1.4	0.3	1.0
41950076	4	7.12	25.9	66.5	4.3	2.0	0.4	0.9
41950078	4	10.90	16.2	74.6	5.9	2.1	0.2	1.1
41950080	4	10.45	14.3	77.4	4.7	2.2	0.2	1.1
41950082	4	10.75	15.2	78.9	3.3	1.5	0.2	0.9
41950084	4	10.42	14.1	78.9	3.6	2.3	0.3	0.8
41950086	4	10.30	12.1	81.6	3.5	1.8	0.3	0.7
41950088	4	9.72	17.0	76.1	4.3	1.4	0.2	1.0
41950090	4	11.06	16.9	74.9	3.2	3.4	0.3	1.3
Mean		9.316	16.41	76.27	4.12	1.99	0.27	0.95
SD		2.019	3.71	4.01	0.98	0.59	0.07	0.19

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	RBC 10 ¹² /l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
41950001	1	7.35	14.2	40.2	54.7	19.3	35.3
41950003	1	8.01	15.3	43.2	53.9	19.0	35.3
41950005	1	7.82	15.2	42.4	54.2	19.4	35.8
41950007	1	8.17	15.4	43.1	52.8	18.9	35.7
41950009	1	7.50	14.3	40.4	54.0	19.1	35.3
41950011	1	7.98	14.9	42.2	52.9	18.7	35.3
41950013	1	8.17	16.0	45.1	55.2	19.6	35.4
41950015	1	7.64	14.3	39.9	52.3	18.7	35.8
41950017	1	7.65	14.6	41.8	54.7	19.1	35.0
41950019	1	8.08	15.4	43.3	53.6	19.1	35.6
		Mean	7.837	42.16	53.83	19.09	35.45
		SD	0.290	1.64	0.94	0.29	0.26
41950031	2	7.88	14.7	41.5	52.7	18.6	35.4
41950033	2	7.31	13.8	39.2	53.7	18.8	35.1
41950035	2	8.14	15.3	45.0	55.2	18.8	34.1
41950037	2	7.68	14.4	41.7	54.3	18.8	34.6
41950039	2	7.53	14.2	40.7	54.0	18.8	34.8
41950041	2	7.86	14.5	41.9	53.3	18.5	34.7
41950043	2	7.59	14.5	40.5	53.4	19.1	35.8
41950045	2	7.57	14.8	42.0	55.6	19.6	35.2
41950047	2	7.91	14.9	41.8	52.8	18.8	35.7
41950049	2	7.70	15.1	41.4	53.8	19.6	36.4
		Mean	7.717	41.57	53.88	18.94	35.18
		SD	0.236	1.48	0.95	0.38	0.67

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	RBC 10 ¹² /l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
41950051	3	6.97	13.9	39.0	55.9	20.0	35.8
41950053	3	6.96	13.7	39.0	56.1	19.7	35.1
41950055	3	7.74	14.9	42.6	55.1	19.3	35.0
41950057	3	7.65	14.8	42.0	54.9	19.4	35.2
41950059	3	7.80	15.3	43.1	55.3	19.6	35.5
41950061	3	7.69	14.8	42.4	55.1	19.3	34.9
41950063	3	7.94	15.0	42.7	53.8	18.9	35.2
41950065	3	7.79	15.0	42.6	54.7	19.2	35.1
41950067	3	7.65	14.6	40.9	53.5	19.1	35.7
41950069	3	7.39	14.3	40.7	55.0	19.3	35.1
		Mean	14.63	41.50	54.94	19.38	35.26
		SD	0.51	1.53	0.81	0.32	0.30
41950071	4	7.23	14.4	40.5	56.0	19.9	35.5
41950073	4	7.70	14.8	41.0	53.2	19.2	36.1
41950075	4	7.52	14.7	41.4	55.0	19.6	35.6
41950077	4	7.88	15.2	42.1	53.4	19.2	36.0
41950079	4	7.76	15.0	42.3	54.5	19.4	35.6
41950081	4	7.79	16.1	44.3	56.9	20.6	36.3
41950083	4	7.94	14.7	41.9	52.7	18.5	35.2
41950085	4	7.67	14.8	41.7	54.4	19.2	35.4
41950087	4	7.68	14.9	41.8	54.5	19.4	35.6
41950089	4	7.84	14.8	41.7	53.1	18.8	35.4
		Mean	14.94	41.87	54.37	19.38	35.67
		SD	0.46	1.00	1.34	0.58	0.35

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	PLT 10 ⁹ /l	PT sec
41950001	1	886	16.8
41950003	1	896	17.0
41950005	1	895	16.7
41950007	1	769	20.2
41950009	1	923	17.3
41950011	1	868	16.5
41950013	1	925	13.4
41950015	1	998	16.4
41950017	1	755	15.9
41950019	1	974	16.8
		Mean 888.9	16.70
		SD 77.8	1.65
41950031	2	911	17.6
41950033	2	925	19.1
41950035	2	898	17.1
41950037	2	477	NT
41950039	2	875	16.3
41950041	2	948	16.6
41950043	2	878	15.7
41950045	2	902	16.6
41950047	2	926	16.4
41950049	2	914	17.0
		Mean 865.4	16.93
		SD 138.2	0.97
NT = NOT TAKEN			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	PLT 10 ⁹ /l	PT sec
41950051	3	803	16.1
41950053	3	760	14.7
41950055	3	956	16.9
41950057	3	846	15.2
41950059	3	921	17.1
41950061	3	965	16.8
41950063	3	891	16.3
41950065	3	854	16.4
41950067	3	951	17.1
41950069	3	754	17.4
		Mean 870.1	16.40
		SD 79.5	0.87
41950071	4	919	16.4
41950073	4	1042	16.5
41950075	4	826	16.5
41950077	4	956	16.4
41950079	4	1045	16.4
41950081	4	840	16.2
41950083	4	991	16.2
41950085	4	909	16.2
41950087	4	979	16.8
41950089	4	983	15.9
		Mean 949.0	16.35
		SD 75.5	0.24

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	WBC 10 ⁹ /l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
41950001	1	5.77	15.8	78.7	2.3	2.2	0.1	0.8
41950003	1	7.81	5.1	88.9	2.9	2.2	0.2	0.7
41950005	1	8.08	8.4	83.9	4.3	2.2	0.3	0.9
41950007	1	7.54	15.3	76.6	4.5	2.4	0.2	0.9
41950009	1	10.60	6.5	87.1	3.6	1.9	0.2	0.7
41950011	1	7.93	9.6	84.5	3.0	2.0	0.2	0.8
41950013	1	7.16	11.9	82.1	2.5	2.3	0.3	0.9
41950015	1	6.98	6.1	89.3	2.5	1.3	0.1	0.7
41950017	1	6.88	7.1	86.3	3.1	2.7	0.1	0.7
41950019	1	7.03	13.1	79.6	4.1	2.2	0.2	0.9
		Mean	7.578	83.70	3.28	2.14	0.19	0.80
		SD	1.254	4.37	0.80	0.37	0.07	0.09
41950031	2	7.46	15.8	74.6	5.9	2.5	0.1	1.1
41950033	2	6.24	16.7	76.3	4.0	2.2	0.2	0.7
41950035	2	8.74	27.0	60.1	7.1	4.1	0.2	1.6
41950037	2	7.14	20.5	73.2	3.1	2.1	0.2	0.9
41950039	2	5.06	17.5	76.2	3.4	1.7	0.1	0.9
41950041	2	5.84	11.0	82.7	2.7	2.7	0.2	0.8
41950043	2	7.83	19.3	73.6	3.5	2.2	0.3	1.0
41950045	2	4.78	10.9	80.8	4.2	3.0	0.1	1.1
41950047	2	4.93	16.9	77.0	3.0	2.3	0.1	0.8
41950049	2	7.29	7.6	87.1	2.6	1.9	0.1	0.7
		Mean	6.531	76.16	3.95	2.47	0.16	0.96
		SD	1.364	7.15	1.46	0.68	0.07	0.27

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	WBC 10 ⁹ /l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
41950051	3	8.57	14.0	79.7	3.4	1.8	0.3	0.7
41950053	3	5.81	13.0	78.4	4.4	2.7	0.2	1.4
41950055	3	8.58	6.9	86.7	3.5	1.7	0.2	1.1
41950057	3	8.56	11.2	83.1	2.7	1.9	0.5	0.7
41950059	3	6.99	8.6	84.7	4.0	1.6	0.1	1.0
41950061	3	6.82	9.2	85.4	3.4	1.1	0.1	0.8
41950063	3	7.22	16.4	75.2	5.6	1.5	0.3	1.0
41950065	3	6.42	14.8	79.1	2.9	2.3	0.2	0.7
41950067	3	6.61	10.1	84.5	2.8	1.7	0.1	0.8
41950069	3	4.76	18.5	74.8	3.7	2.2	0.1	0.7
		Mean	7.034	81.16	3.64	1.85	0.21	0.89
		SD	1.264	4.30	0.87	0.45	0.13	0.23
41950071	4	11.71	18.2	73.5	3.9	2.9	0.3	1.2
41950073	4	7.50	14.2	76.3	6.1	2.0	0.2	1.2
41950075	4	9.80	13.0	79.7	4.7	1.7	0.2	0.7
41950077	4	9.87	6.0	87.7	3.6	1.6	0.2	0.9
41950079	4	9.25	9.3	80.5	5.9	2.7	0.2	1.4
41950081	4	7.29	8.8	85.7	2.8	1.8	0.2	0.8
41950083	4	5.47	13.7	78.9	4.0	2.7	0.1	0.5
41950085	4	5.74	12.1	80.9	4.1	2.0	0.2	0.7
41950087	4	4.00	6.2	88.1	2.8	1.8	0.2	0.9
41950089	4	5.42	12.7	79.3	4.3	2.5	0.3	0.9
		Mean	7.605	81.06	4.22	2.17	0.21	0.92
		SD	2.482	4.77	1.11	0.48	0.06	0.27

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Haematology - At the end of recovery - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	RBC 10 ¹² /l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
41950022	1	8.30	15.6	46.3	55.8	18.8	33.6
41950024	1	8.78	16.1	47.9	54.5	18.3	33.6
41950026	1	8.41	15.5	46.7	55.5	18.5	33.2
41950028	1	8.46	15.6	45.9	54.3	18.4	34.0
41950030	1	8.46	15.7	47.1	55.7	18.5	33.2
		Mean 8.482	15.70	46.78	55.16	18.50	33.52
		SD 0.179	0.23	0.77	0.71	0.19	0.33
41950092	4	8.70	16.1	46.8	53.9	18.5	34.3
41950094	4	8.70	16.2	48.1	55.3	18.7	33.7
41950096	4	8.46	15.3	45.4	53.7	18.1	33.7
41950098	4	8.67	16.0	47.5	54.8	18.4	33.6
41950100	4	8.07	15.7	46.6	57.7	19.5	33.8
		Mean 8.520	15.86	46.88	55.08	18.64	33.82
		SD 0.271	0.36	1.02	1.60	0.53	0.28

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Haematology - At the end of recovery - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	PLT 10 ⁹ /l	PT sec
41950022	1	858	17.5
41950024	1	864	18.6
41950026	1	732	NT
41950028	1	765	17.0
41950030	1	776	17.8
		Mean 799.0	17.73
		SD 58.9	0.67
41950092	4	972	16.7
41950094	4	763	16.9
41950096	4	904	16.9
41950098	4	874	16.5
41950100	4	717	16.5
		Mean 846.0	16.70
		SD 104.3	0.20

NT = NOT TAKEN

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Haematology - At the end of recovery - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	WBC 10 ⁹ /l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
41950022	1	7.84	14.0	79.6	2.2	2.3	0.2	1.7
41950024	1	10.34	15.6	77.4	3.2	1.3	0.2	2.4
41950026	1	8.65	13.1	80.0	3.0	2.3	0.1	1.4
41950028	1	9.18	20.2	72.5	3.3	2.0	0.2	1.8
41950030	1	17.87	28.2	64.4	4.2	1.3	0.2	1.7
	Mean	10.776	18.22	74.78	3.18	1.84	0.18	1.80
	SD	4.068	6.21	6.52	0.72	0.51	0.04	0.37
41950092	4	7.65	12.9	80.8	2.5	1.7	0.3	1.7
41950094	4	10.38	17.7	76.1	2.8	1.3	0.2	2.0
41950096	4	11.39	23.3	67.9	3.8	2.5	0.2	2.4
41950098	4	6.65	18.0	74.9	3.5	2.0	0.2	1.4
41950100	4	9.81	15.1	78.7	3.1	1.3	0.2	1.6
	Mean	9.176	17.40	75.68	3.14	1.76	0.22	1.82
	SD	1.966	3.90	4.92	0.52	0.51	0.04	0.39

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Haematology - At the end of recovery - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	RBC 10 ¹² /l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
41950021	1	7.73	14.7	42.4	54.9	19.0	34.7
41950023	1	7.64	14.8	43.2	56.5	19.3	34.2
41950025	1	7.87	15.0	43.2	54.9	19.1	34.7
41950027	1	7.64	14.3	41.2	54.0	18.7	34.7
41950029	1	7.39	14.5	41.8	56.6	19.7	34.8
	Mean	7.654	14.66	42.36	55.38	19.16	34.62
	SD	0.175	0.27	0.88	1.13	0.37	0.24
41950091	4	8.17	15.9	45.1	55.2	19.4	35.2
41950093	4	7.40	14.6	42.0	56.7	19.7	34.8
41950095	4	8.35	16.4	47.7	57.2	19.7	34.4
41950097	4	7.23	14.2	41.3	57.2	19.7	34.4
41950099	4	7.54	14.7	42.6	56.5	19.5	34.5
	Mean	7.738	15.16	43.74	56.56	19.60	34.66
	SD	0.493	0.94	2.64	0.82	0.14	0.34

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Haematology - At the end of recovery - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	PLT 10 ⁹ /l	PT sec
41950021	1	1027	16.8
41950023	1	852	17.4
41950025	1	771	17.9
41950027	1	981	17.3
41950029	1	886	17.6
		Mean 903.4	17.40
		SD 102.2	0.41
41950091	4	890	16.9
41950093	4	853	16.7
41950095	4	781	18.4
41950097	4	926	17.4
41950099	4	981	16.8
		Mean 886.2	17.24
		SD 75.4	0.70

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Haematology - At the end of recovery - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	WBC 10 ⁹ /l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
41950021	1	6.44	19.4	72.9	4.4	1.6	0.2	1.4
41950023	1	5.82	16.8	76.7	3.6	1.5	0.2	1.3
41950025	1	4.76	19.2	74.5	3.1	2.0	0.1	1.2
41950027	1	6.43	13.3	78.4	4.9	1.8	0.2	1.5
41950029	1	6.45	11.1	83.5	2.2	2.1	0.1	1.0
		Mean	15.96	77.20	3.64	1.80	0.16	1.28
		SD	3.67	4.10	1.06	0.25	0.05	0.19
41950091	4	4.80	21.7	72.5	1.8	2.8	0.1	1.1
41950093	4	5.35	23.3	70.6	2.3	2.5	0.4	1.0
41950095	4	3.32	12.8	79.6	3.6	2.7	0.4	0.9
41950097	4	5.93	27.8	67.8	2.9	0.3	0.1	1.1
41950099	4	6.62	15.2	80.4	2.1	1.5	0.1	0.7
		Mean	20.16	74.18	2.54	1.96	0.22	0.96
		SD	6.11	5.58	0.72	1.06	0.16	0.17

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 41950

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
41950002	1	232.6	47.5	84.7	0.10	0.21	67.9	26.8	116.6
41950004	1	246.4	42.9	72.5	2.90	0.29	86.1	32.0	116.0
41950006	1	241.2	48.9	84.2	0.60	0.19	76.7	28.7	118.1
41950008	1	221.5	33.9	65.3	0.80	0.22	76.6	23.9	123.8
41950010	1	208.9	51.2	80.7	0.40	0.20	72.4	43.8	125.7
41950012	1	216.8	46.8	91.1	0.50	0.20	72.4	19.0	114.6
41950014	1	214.7	43.1	78.4	2.70	0.24	75.7	22.0	123.3
41950016	1	222.0	39.0	89.4	0.60	0.25	61.1	38.1	119.8
41950018	1	259.2	49.5	87.5	0.90	0.17	76.0	57.2	137.2
41950020	1	209.2	44.9	77.1	0.20	0.22	79.8	30.6	109.9
		Mean	227.25	81.09	0.970	0.219	74.47	32.21	120.50
		SD	17.00	8.02	0.996	0.034	6.73	11.48	7.55
41950032	2	188.5	43.7	79.3	0.40	0.20	66.0	44.6	130.7
41950034	2	211.6	40.1	94.0	0.50	0.18	65.8	42.7	123.3
41950036	2	158.2	41.8	83.6	0.10	0.19	69.3	43.1	122.7
41950038	2	184.3	50.1	71.2	1.00	0.20	64.7	47.1	102.2
41950040	2	207.0	36.1	74.2	0.00	0.14	57.4	42.9	117.0
41950042	2	228.7	48.5	103.5	0.90	0.77	59.2	20.8	104.8
41950044	2	223.9	43.0	80.0	3.00	0.24	61.3	42.6	126.9
41950046	2	235.1	48.8	83.1	0.00	0.25	72.3	24.1	105.3
41950048	2	155.8	42.0	86.3	0.10	0.21	77.0	26.6	120.6
41950050	2	232.1	52.2	88.2	0.40	2.98	64.3	37.5	128.4
		Mean	202.52	84.34	0.640	0.536	65.73	37.20	118.19
		SD	29.55	9.43	0.901	0.878	5.94	9.62	10.50

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 41950

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
41950052	3	303.5	73.1	85.1	0.20	0.36	67.8	26.6	118.2
41950054	3	280.1	47.1	78.7	0.00	0.18	56.0	28.4	120.4
41950056	3	249.3	54.9	87.8	0.80	0.20	45.2	28.4	121.3
41950058	3	281.2	63.2	89.2	0.70	0.18	55.8	33.8	119.8
41950060	3	318.9	77.4	138.6	0.20	0.26	49.8	21.4	109.1
41950062	3	246.4	46.7	79.3	0.60	0.16	51.5	22.7	117.0
41950064	3	220.0	43.9	84.8	0.10	0.13	62.4	25.4	135.5
41950066	3	356.8	62.2	78.8	0.20	0.20	53.9	25.2	163.0
41950068	3	288.3	44.0	90.3	0.30	0.14	48.9	27.0	163.1
41950070	3	299.0	55.7	103.7	0.40	0.19	55.8	49.7	118.1
		Mean	284.35	91.63	0.350	0.200	54.71	28.86	128.55
		SD	39.27	18.10	0.268	0.067	6.61	8.07	19.30
41950072	4	469.4	50.3	86.9	0.10	0.15	57.4	28.6	124.8
41950074	4	423.3	56.9	95.2	0.20	0.16	84.5	35.0	133.2
41950076	4	450.8	48.5	106.3	0.10	0.16	64.1	28.7	115.6
41950078	4	633.6	38.4	76.6	0.70	0.17	76.0	30.7	117.9
41950080	4	433.8	43.8	77.8	0.20	0.18	72.3	52.8	124.8
41950082	4	478.9	53.3	106.8	2.50	0.14	55.6	32.0	123.0
41950084	4	415.7	46.7	89.5	0.10	0.23	67.4	33.5	126.3
41950086	4	423.7	55.0	99.6	0.50	0.12	63.0	37.6	133.2
41950088	4	452.3	49.0	89.7	0.70	0.20	60.6	27.4	122.1
41950090	4	394.6	62.4	83.1	0.20	0.14	73.3	33.4	117.9
		Mean	457.61	91.15	0.530	0.165	67.42	33.97	123.88
		SD	66.88	10.75	0.732	0.032	9.07	7.33	6.01

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 41950

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
41950002	1	30.1	0.38	91.9	6.6	2.76	143.6	4.21
41950004	1	31.7	0.43	90.8	6.8	2.73	143.2	4.40
41950006	1	32.8	0.44	90.4	6.6	2.79	143.7	4.10
41950008	1	31.5	0.38	92.0	6.2	2.64	143.6	4.23
41950010	1	36.2	0.49	92.1	6.2	2.65	145.3	4.21
41950012	1	38.7	0.42	92.0	6.2	2.71	144.3	4.16
41950014	1	32.1	0.40	92.9	6.9	2.78	144.1	4.23
41950016	1	35.2	0.41	91.1	6.2	2.64	145.0	4.22
41950018	1	38.3	0.34	90.6	6.1	2.72	143.9	4.27
41950020	1	41.8	0.43	91.3	6.0	2.76	144.3	4.12
		Mean	34.84	91.51	6.38	2.718	144.10	4.215
		SD	3.84	0.80	0.32	0.057	0.65	0.084
41950032	2	32.8	0.42	93.2	7.0	2.65	145.5	4.14
41950034	2	30.0	0.36	91.8	6.4	2.59	145.1	4.36
41950036	2	35.8	0.46	92.5	6.2	2.61	146.2	4.03
41950038	2	36.0	0.39	92.5	5.8	2.64	146.5	4.06
41950040	2	32.2	0.36	92.0	6.5	2.60	146.9	4.26
41950042	2	29.2	0.40	91.9	6.8	2.60	142.7	4.72
41950044	2	28.9	0.32	91.9	6.2	2.58	144.1	4.15
41950046	2	31.7	0.40	92.0	6.5	2.71	143.8	4.09
41950048	2	38.2	0.42	91.0	5.7	2.64	144.3	4.11
41950050	2	34.5	0.36	93.5	6.4	2.64	143.2	4.37
		Mean	32.93	92.23	6.33	2.626	144.83	4.229
		SD	3.14	0.72	0.40	0.038	1.44	0.209

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 41950

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
41950052	3	32.6	0.40	91.7	6.8	2.68	144.8	5.20
41950054	3	32.3	0.30	94.5	6.4	2.58	146.4	4.46
41950056	3	32.4	0.36	93.5	7.3	2.64	147.0	4.59
41950058	3	36.8	0.34	91.0	5.9	2.65	144.8	4.25
41950060	3	37.0	0.34	91.6	7.4	2.50	143.5	5.11
41950062	3	31.7	0.37	92.1	6.6	2.64	145.5	4.14
41950064	3	38.1	0.33	92.0	6.3	2.58	144.1	4.03
41950066	3	35.2	0.36	93.0	5.7	2.58	142.8	4.25
41950068	3	35.9	0.37	91.9	6.4	2.61	143.1	4.35
41950070	3	47.4	0.40	92.1	7.2	2.72	143.6	4.18
Mean		35.94	0.357	92.34	6.59	2.618	144.56	4.456
SD		4.63	0.031	1.03	0.56	0.062	1.41	0.402
41950072	4	41.4	0.32	93.6	6.7	2.46	142.6	4.40
41950074	4	45.8	0.29	93.0	6.1	2.50	141.1	4.47
41950076	4	43.4	0.33	93.4	6.3	2.51	144.7	4.14
41950078	4	47.1	0.28	94.1	6.7	2.56	143.8	4.36
41950080	4	47.8	0.37	93.6	6.0	2.57	143.4	4.36
41950082	4	50.0	0.31	94.3	6.4	2.49	143.9	4.25
41950084	4	50.8	0.35	92.5	6.2	2.43	142.9	4.62
41950086	4	44.6	0.29	95.2	6.0	2.45	143.3	4.30
41950088	4	49.1	0.31	93.7	6.8	2.54	144.4	4.37
41950090	4	53.7	0.32	93.0	6.4	2.51	144.4	4.11
Mean		47.37	0.317	93.64	6.36	2.502	143.45	4.338
SD		3.70	0.028	0.76	0.29	0.046	1.07	0.150

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	PROT g/dl	ALB g/dl	GLO g/dl	AGR
41950002	1	7.7	4.1	3.6	1.1
41950004	1	7.3	4.2	3.1	1.4
41950006	1	7.5	4.2	3.3	1.3
41950008	1	6.9	3.9	3.0	1.3
41950010	1	7.2	4.2	3.0	1.4
41950012	1	6.8	4.2	2.6	1.6
41950014	1	6.9	4.0	2.9	1.4
41950016	1	7.0	4.1	2.9	1.4
41950018	1	7.0	4.1	2.9	1.4
41950020	1	7.3	4.3	3.0	1.4
		Mean	4.13	3.03	1.37
		SD	0.12	0.27	0.12
41950032	2	7.0	4.2	2.8	1.5
41950034	2	6.9	4.2	2.7	1.6
41950036	2	6.8	4.2	2.6	1.6
41950038	2	7.2	3.9	3.3	1.2
41950040	2	6.5	4.1	2.4	1.7
41950042	2	7.5	3.6	3.9	0.9
41950044	2	6.8	3.8	3.0	1.3
41950046	2	7.0	4.0	3.0	1.3
41950048	2	6.8	4.0	2.8	1.4
41950050	2	6.9	3.3	3.6	0.9
		Mean	3.93	3.01	1.34
		SD	0.29	0.47	0.27

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	PROT g/dl	ALB g/dl	GLO g/dl	AGR
41950052	3	6.9	4.0	2.9	1.4
41950054	3	6.5	4.0	2.5	1.6
41950056	3	6.5	3.9	2.6	1.5
41950058	3	6.9	4.3	2.6	1.7
41950060	3	6.7	3.8	2.9	1.3
41950062	3	6.9	4.3	2.6	1.7
41950064	3	6.7	3.9	2.8	1.4
41950066	3	6.5	3.9	2.6	1.5
41950068	3	6.5	4.1	2.4	1.7
41950070	3	6.7	4.0	2.7	1.5
		Mean	4.02	2.66	1.52
		SD	0.17	0.16	0.13
41950072	4	6.2	4.0	2.2	1.8
41950074	4	5.9	3.7	2.2	1.7
41950076	4	5.9	3.9	2.0	2.0
41950078	4	5.9	3.9	2.0	2.0
41950080	4	5.8	3.7	2.1	1.8
41950082	4	6.1	4.1	2.0	2.1
41950084	4	6.8	3.6	3.2	1.1
41950086	4	5.9	3.5	2.4	1.5
41950088	4	6.6	4.1	2.5	1.6
41950090	4	6.7	4.1	2.6	1.6
		Mean	3.86	2.32	1.70
		SD	0.22	0.38	0.27

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 41950

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
41950001	1	136.9	44.8	77.7	0.40	0.27	104.0	25.8	112.7
41950003	1	183.0	38.5	68.7	0.10	0.22	86.7	25.2	144.3
41950005	1	168.5	33.7	70.7	1.10	0.24	73.7	24.0	122.3
41950007	1	158.1	34.1	77.2	0.30	0.18	86.1	25.1	128.1
41950009	1	171.1	45.3	107.5	0.10	0.28	89.7	22.9	121.1
41950011	1	175.9	30.1	73.9	0.20	0.25	102.6	19.8	114.0
41950013	1	142.6	35.5	71.4	0.30	0.20	105.5	24.1	113.9
41950015	1	159.5	32.5	72.3	1.80	0.27	74.7	22.2	127.4
41950017	1	207.4	36.2	74.3	0.10	0.22	84.5	28.1	117.3
41950019	1	139.5	42.0	72.3	1.40	0.20	92.6	27.3	111.7
		Mean	164.25	76.60	0.580	0.233	90.01	24.45	121.28
		SD	21.87	11.21	0.620	0.034	11.34	2.44	10.02
41950031	2	188.1	42.0	71.2	0.60	0.22	119.8	30.2	120.3
41950033	2	138.2	39.9	76.7	0.80	0.34	70.5	25.4	124.5
41950035	2	597.3	759.1	630.4	7.20	1.12	112.7	57.2	147.4
41950037	2	155.3	33.1	65.7	0.50	0.31	87.0	31.3	121.6
41950039	2	202.1	34.3	84.2	0.30	0.20	71.8	30.1	121.8
41950041	2	200.0	37.1	84.9	1.30	0.23	84.8	27.1	121.4
41950043	2	147.7	37.5	86.1	0.50	0.23	70.9	30.2	109.4
41950045	2	199.9	33.9	76.9	1.80	0.29	90.5	29.4	131.1
41950047	2	143.8	28.3	69.5	0.40	0.23	88.9	24.0	122.8
41950049	2	159.0	38.6	79.6	1.20	0.24	106.6	22.5	118.3
		Mean	213.14	132.52	1.460	0.341	90.35	30.74	123.86
		SD	137.30	228.67	2.072	0.277	17.61	9.77	9.87

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 41950

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
41950051	3	182.1	32.8	97.6	0.20	0.20	70.6	36.2	145.1
41950053	3	148.0	36.0	78.3	0.20	0.15	61.4	45.6	158.0
41950055	3	153.3	38.1	81.4	0.50	0.22	78.8	24.2	121.3
41950057	3	233.9	37.4	81.2	1.30	0.21	79.3	36.5	128.0
41950059	3	163.4	34.0	68.6	0.60	0.20	68.4	32.8	133.4
41950061	3	137.8	28.7	85.9	1.80	0.22	88.2	23.0	139.5
41950063	3	124.2	36.3	77.0	1.10	0.62	75.9	30.4	112.3
41950065	3	161.2	34.4	86.5	0.70	0.15	67.1	36.7	158.1
41950067	3	211.7	41.9	78.9	0.60	0.23	77.2	43.1	112.6
41950069	3	184.5	29.9	71.3	0.20	0.20	51.1	34.3	127.1
Mean		170.01	34.95	80.67	0.720	0.240	71.80	34.28	133.54
SD		33.66	3.91	8.20	0.531	0.136	10.50	7.20	16.61
41950071	4	274.5	55.8	83.3	0.80	0.09	86.0	38.7	119.4
41950073	4	276.5	40.1	72.7	1.00	0.15	93.6	47.9	136.3
41950075	4	314.2	35.1	67.2	0.20	0.40	74.9	28.2	118.8
41950077	4	308.9	37.3	76.4	0.50	0.14	69.0	33.4	114.7
41950079	4	202.1	33.2	70.3	0.20	0.15	92.7	52.8	146.7
41950081	4	266.6	40.1	69.2	0.50	0.16	70.4	31.9	119.8
41950083	4	296.4	32.6	82.4	0.70	0.15	65.8	39.6	131.9
41950085	4	259.7	39.9	73.8	0.00	0.15	90.6	53.0	153.6
41950087	4	285.7	31.3	81.7	2.00	0.11	86.5	35.4	119.4
41950089	4	226.4	34.8	68.2	0.10	0.11	72.0	38.0	133.8
Mean		271.10	38.02	74.52	0.600	0.161	80.15	39.89	129.44
SD		35.10	7.04	6.13	0.589	0.087	10.76	8.63	13.24

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 41950

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
41950001	1	37.9	0.40	95.3	5.7	2.71	144.6	4.28
41950003	1	36.5	0.46	93.4	5.6	2.65	144.3	4.49
41950005	1	42.9	0.49	94.1	5.8	2.74	144.9	4.43
41950007	1	39.2	0.47	96.4	5.7	2.65	144.8	4.45
41950009	1	38.4	0.40	94.0	6.7	2.54	144.7	5.19
41950011	1	41.3	0.43	94.6	5.6	2.58	145.4	4.23
41950013	1	41.1	0.48	93.3	6.1	2.70	140.8	4.16
41950015	1	39.4	0.48	94.7	5.3	2.65	144.9	3.92
41950017	1	46.7	0.53	93.3	5.7	2.55	144.0	4.00
41950019	1	35.8	0.46	95.2	5.2	2.64	143.2	3.93
Mean		39.92	0.460	94.43	5.74	2.641	144.16	4.308
SD		3.23	0.041	1.01	0.42	0.067	1.32	0.375
41950031	2	39.0	0.51	93.7	5.7	2.72	146.4	3.98
41950033	2	36.0	0.44	92.9	5.5	2.61	144.8	3.83
41950035	2	47.5	0.92	98.0	4.7	2.83	141.7	4.75
41950037	2	36.6	0.52	92.7	5.4	2.61	145.2	4.52
41950039	2	45.6	0.52	96.0	5.0	2.63	145.8	4.52
41950041	2	41.7	0.50	93.6	5.6	2.58	145.4	4.01
41950043	2	46.0	0.50	95.6	5.8	2.61	143.1	4.26
41950045	2	42.7	0.47	95.4	4.5	2.55	146.9	3.86
41950047	2	41.8	0.47	94.3	5.5	2.63	147.1	4.30
41950049	2	56.4	0.59	93.8	5.7	2.70	147.6	4.21
Mean		43.33	0.544	94.60	5.32	2.647	145.40	4.224
SD		6.00	0.138	1.64	0.46	0.082	1.84	0.308

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 41950

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
41950051	3	44.1	0.52	94.6	5.7	2.68	143.3	4.49
41950053	3	43.5	0.49	92.2	5.1	2.63	144.8	3.82
41950055	3	40.8	0.46	95.7	5.7	2.77	145.8	4.08
41950057	3	33.4	0.44	94.3	5.6	2.66	145.9	4.41
41950059	3	38.1	0.38	95.4	6.0	2.64	145.6	4.33
41950061	3	34.7	0.41	94.4	5.6	2.65	146.0	4.02
41950063	3	41.8	0.40	95.3	6.3	2.69	146.6	3.90
41950065	3	43.5	0.57	93.7	4.7	2.58	142.1	3.80
41950067	3	43.7	0.44	94.0	5.6	2.65	143.0	3.75
41950069	3	43.2	0.52	96.1	5.3	2.66	144.6	3.61
Mean		40.68	0.463	94.57	5.56	2.661	144.77	4.021
SD		3.94	0.061	1.14	0.45	0.049	1.50	0.301
41950071	4	41.2	0.44	94.7	6.8	2.70	143.8	4.51
41950073	4	43.6	0.42	88.7	5.6	2.67	145.1	3.56
41950075	4	45.8	0.46	93.9	7.3	2.78	143.9	3.89
41950077	4	38.1	0.41	93.7	6.7	2.59	143.9	4.32
41950079	4	40.1	0.44	89.2	5.9	2.70	142.8	3.86
41950081	4	46.9	0.51	94.5	5.8	2.69	143.9	3.77
41950083	4	50.1	0.45	94.4	5.2	2.61	144.1	3.85
41950085	4	46.0	0.44	94.5	5.0	2.65	145.5	3.71
41950087	4	43.4	0.41	95.8	6.5	2.58	144.6	4.99
41950089	4	45.2	0.42	95.7	5.8	2.76	144.9	3.78
Mean		44.04	0.440	93.51	6.06	2.673	144.25	4.024
SD		3.54	0.030	2.50	0.75	0.067	0.78	0.443

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	PROT g/dl	ALB g/dl	GLO g/dl	AGR
41950001	1	7.3	4.7	2.6	1.8
41950003	1	6.5	4.3	2.2	2.0
41950005	1	7.1	4.5	2.6	1.7
41950007	1	6.9	4.4	2.5	1.8
41950009	1	6.7	4.3	2.4	1.8
41950011	1	6.7	4.3	2.4	1.8
41950013	1	7.0	4.3	2.7	1.6
41950015	1	6.5	4.2	2.3	1.8
41950017	1	6.7	4.2	2.5	1.7
41950019	1	6.8	4.4	2.4	1.8
		Mean 6.82	4.36	2.46	1.78
		SD 0.26	0.15	0.15	0.10
41950031	2	7.6	4.9	2.7	1.8
41950033	2	6.9	4.4	2.5	1.8
41950035	2	7.2	4.4	2.8	1.6
41950037	2	7.1	4.6	2.5	1.8
41950039	2	6.8	4.3	2.5	1.7
41950041	2	6.9	4.6	2.3	2.0
41950043	2	7.2	4.4	2.8	1.6
41950045	2	6.7	4.2	2.5	1.7
41950047	2	7.3	4.5	2.8	1.6
41950049	2	7.2	4.6	2.6	1.8
		Mean 7.09	4.49	2.60	1.73
		SD 0.27	0.20	0.17	0.13

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	PROT g/dl	ALB g/dl	GLO g/dl	AGR
41950051	3	7.6	4.6	3.0	1.5
41950053	3	7.1	4.9	2.2	2.2
41950055	3	7.0	5.0	2.0	2.5
41950057	3	7.2	5.1	2.1	2.4
41950059	3	6.7	4.5	2.2	2.0
41950061	3	6.9	4.8	2.1	2.3
41950063	3	6.7	4.5	2.2	2.0
41950065	3	6.8	4.6	2.2	2.1
41950067	3	6.7	4.6	2.1	2.2
41950069	3	7.0	4.6	2.4	1.9
Mean		6.97	4.72	2.25	2.13
SD		0.28	0.21	0.28	0.28
41950071	4	7.7	4.7	3.0	1.6
41950073	4	7.3	5.0	2.3	2.2
41950075	4	7.2	4.7	2.5	1.9
41950077	4	6.7	4.7	2.0	2.4
41950079	4	7.2	5.3	1.9	2.8
41950081	4	7.3	5.0	2.3	2.2
41950083	4	7.1	5.2	1.9	2.7
41950085	4	7.1	5.2	1.9	2.7
41950087	4	6.8	5.0	1.8	2.8
41950089	4	7.3	5.1	2.2	2.3
Mean		7.17	4.99	2.18	2.35
SD		0.28	0.22	0.37	0.42

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Clinical chemistry - At the end of recovery - Individual data

STUDY NO.: 41950

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
41950022	1	207.3	43.3	72.1	0.10	0.15	75.2	38.3	114.9
41950024	1	221.7	51.9	80.9	0.20	0.18	79.9	61.1	151.3
41950026	1	226.0	42.7	72.4	1.70	0.14	61.8	40.3	140.6
41950028	1	262.7	50.0	86.7	0.30	0.16	75.3	24.6	126.3
41950030	1	183.1	42.5	67.0	1.30	0.11	97.2	30.1	123.7
	Mean	220.16	46.08	75.82	0.720	0.148	77.88	38.88	131.36
	SD	29.09	4.51	7.87	0.729	0.026	12.75	13.94	14.48
41950092	4	356.4	43.7	68.7	0.00	0.11	77.4	33.2	111.2
41950094	4	192.5	53.1	72.1	0.30	0.14	86.7	41.8	126.5
41950096	4	360.3	62.0	83.5	0.00	0.37	68.9	43.8	123.0
41950098	4	393.9	46.0	70.0	0.00	0.14	62.2	37.7	137.5
41950100	4	316.7	57.9	88.9	0.10	0.14	71.1	34.0	133.5
	Mean	323.96	52.54	76.64	0.080	0.180	73.26	38.10	126.34
	SD	78.42	7.74	9.02	0.130	0.107	9.27	4.67	10.20

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Clinical chemistry - At the end of recovery - Individual data

STUDY NO.: 41950

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
41950022	1	37.4	0.43	92.1	6.1	2.75	139.1	4.09
41950024	1	35.9	0.47	92.5	5.7	2.72	137.3	4.35
41950026	1	36.7	0.44	92.1	6.5	2.68	138.4	4.31
41950028	1	36.6	0.41	92.3	6.4	2.69	139.2	4.12
41950030	1	31.7	0.44	91.4	6.3	2.65	138.2	4.04
Mean		35.66	0.438	92.08	6.19	2.698	138.44	4.182
SD		2.28	0.022	0.41	0.31	0.038	0.77	0.139
41950092	4	47.9	0.40	91.2	7.0	2.79	137.4	4.10
41950094	4	48.4	0.47	91.7	7.3	2.76	138.2	4.16
41950096	4	46.4	0.43	92.5	7.8	2.67	137.1	4.11
41950098	4	47.3	0.36	92.9	7.9	2.63	137.4	4.14
41950100	4	40.2	0.46	92.2	6.4	2.63	137.1	3.92
Mean		46.04	0.424	92.10	7.29	2.696	137.44	4.086
SD		3.35	0.045	0.67	0.60	0.075	0.45	0.096

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Clinical chemistry - At the end of recovery - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	PROT g/dl	ALB g/dl	GLO g/dl	AGR
41950022	1	6.9	4.0	2.9	1.4
41950024	1	7.0	4.1	2.9	1.4
41950026	1	6.8	4.0	2.8	1.4
41950028	1	7.3	4.0	3.3	1.2
41950030	1	7.2	3.8	3.4	1.1
	Mean	7.04	3.98	3.06	1.31
	SD	0.21	0.11	0.27	0.14
41950092	4	7.3	4.2	3.1	1.4
41950094	4	6.9	3.7	3.2	1.2
41950096	4	6.7	3.7	3.0	1.2
41950098	4	6.8	4.1	2.7	1.5
41950100	4	7.1	3.9	3.2	1.2
	Mean	6.96	3.92	3.04	1.30
	SD	0.24	0.23	0.21	0.14

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Clinical chemistry - At the end of recovery - Individual data

STUDY NO.: 41950

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
41950021	1	152.3	34.8	65.2	0.80	0.24	76.3	23.2	122.2
41950023	1	139.6	37.0	86.2	0.70	0.23	78.4	16.7	136.9
41950025	1	152.9	39.9	80.9	0.30	0.27	93.0	19.9	126.8
41950027	1	106.4	31.7	74.4	0.00	0.22	78.0	27.6	114.9
41950029	1	125.7	39.5	70.9	0.60	0.31	96.7	33.4	134.9
Mean		135.38	36.58	75.52	0.480	0.254	84.48	24.16	127.14
SD		19.65	3.42	8.25	0.327	0.036	9.59	6.56	9.08
41950091	4	198.2	32.2	71.9	0.10	0.25	99.0	27.2	125.9
41950093	4	168.0	31.4	58.3	0.10	0.16	104.3	34.1	136.5
41950095	4	185.5	34.5	71.1	0.00	0.17	85.0	48.6	136.8
41950097	4	146.4	29.2	81.9	1.30	0.30	82.4	39.6	126.1
41950099	4	177.5	30.0	57.2	3.40	0.18	71.1	36.5	146.5
Mean		175.12	31.46	68.08	0.980	0.212	88.36	37.20	134.36
SD		19.50	2.06	10.35	1.455	0.061	13.34	7.84	8.63

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Clinical chemistry - At the end of recovery - Individual data

STUDY NO.: 41950

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
41950021	1	46.0	0.51	92.8	6.1	2.76	136.0	3.53
41950023	1	51.6	0.58	94.0	4.5	2.66	136.2	3.82
41950025	1	51.5	0.59	94.9	5.0	2.60	136.2	3.98
41950027	1	36.8	0.49	93.9	4.2	2.66	136.8	3.76
41950029	1	52.6	0.53	92.3	5.0	2.77	137.4	3.70
	Mean	47.70	0.540	93.58	4.97	2.690	136.52	3.758
	SD	6.62	0.044	1.03	0.72	0.073	0.58	0.165
41950091	4	62.5	0.52	91.7	5.0	2.76	137.7	3.65
41950093	4	43.7	0.51	93.5	4.6	2.77	138.1	3.62
41950095	4	44.2	0.52	92.7	4.6	2.68	138.2	3.43
41950097	4	74.6	0.53	93.4	4.4	2.68	138.1	3.77
41950099	4	44.0	0.49	93.2	4.8	2.67	137.0	3.48
	Mean	53.80	0.514	92.90	4.68	2.712	137.82	3.590
	SD	14.13	0.015	0.74	0.21	0.049	0.50	0.137

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Clinical chemistry - At the end of recovery - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	PROT g/dl	ALB g/dl	GLO g/dl	AGR
41950021	1	7.4	4.4	3.0	1.5
41950023	1	7.4	4.6	2.8	1.6
41950025	1	7.6	4.4	3.2	1.4
41950027	1	7.5	4.5	3.0	1.5
41950029	1	7.2	4.9	2.3	2.1
Mean		7.42	4.56	2.86	1.62
SD		0.15	0.21	0.34	0.30
41950091	4	7.8	5.3	2.5	2.1
41950093	4	7.7	5.4	2.3	2.3
41950095	4	7.3	5.0	2.3	2.2
41950097	4	7.3	5.0	2.3	2.2
41950099	4	7.3	5.1	2.2	2.3
Mean		7.48	5.16	2.32	2.23
SD		0.25	0.18	0.11	0.10



**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

FINAL REPORT

VOLUME II OF II

RTC Study no.: 41950

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REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	VOL ml	SG
41950002	1	12.5	1.010
41950004	1	12.0	1.010
41950006	1	9.5	1.025
41950008	1	9.5	1.010
41950010	1	13.0	1.015
41950012	1	10.0	1.015
41950014	1	12.0	1.010
41950016	1	7.0	1.015
41950018	1	14.0	1.010
41950020	1	14.0	1.015
		Mean 11.35	1.0135
		SD 2.27	0.0047
41950032	2	14.0	1.010
41950034	2	13.0	1.010
41950036	2	9.5	1.020
41950038	2	11.5	1.020
41950040	2	10.0	1.025
41950042	2	13.0	1.010
41950044	2	12.0	1.015
41950046	2	12.0	1.010
41950048	2	12.5	1.015
41950050	2	14.0	1.015
		Mean 12.15	1.0150
		SD 1.51	0.0053

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	VOL ml	SG
41950052	3	12.5	1.015
41950054	3	13.0	1.015
41950056	3	10.0	1.020
41950058	3	13.0	1.015
41950060	3	14.0	1.015
41950062	3	9.5	1.015
41950064	3	10.5	1.020
41950066	3	12.0	1.015
41950068	3	6.0	1.010
41950070	3	14.0	1.015
		Mean 11.45	1.0155
		SD 2.49	0.0028
41950072	4	14.0	1.015
41950074	4	14.0	1.015
41950076	4	11.5	1.030
41950078	4	12.0	1.025
41950080	4	10.0	1.025
41950082	4	11.0	1.020
41950084	4	7.0	1.030
41950086	4	12.0	1.010
41950088	4	13.0	1.020
41950090	4	8.0	1.020
		Mean 11.25	1.0210
		SD 2.35	0.0066

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
41950002	1	1	0	8.0	0	30	0.06	0	0.0
41950004	1	1	0	7.5	0	100	0.00	15	0.0
41950006	1	1	0	7.0	0	300	0.00	0	0.0
41950008	1	1	0	7.5	0	30	0.00	0	0.0
41950010	1	1	0	7.5	0	30	0.00	0	0.0
41950012	1	1	0	7.5	0	30	0.00	0	0.0
41950014	1	1	0	7.5	0	30	0.00	0	0.0
41950016	1	1	0	7.0	0	100	0.00	0	0.0
41950018	1	1	0	7.5	0	30	0.00	0	0.0
41950020	1	1	0	7.5	0	100	0.00	0	0.0
41950032	2	1	0	7.5	0	30	0.00	0	0.0
41950034	2	1	0	7.5	0	100	0.00	0	0.0
41950036	2	1	0	7.0	0	100	0.00	0	0.0
41950038	2	1	0	7.0	0	300	0.00	0	0.0
41950040	2	1	0	6.5	0	100	0.00	0	0.0
41950042	2	1	0	7.5	0	30	0.00	0	0.0
41950044	2	1	0	7.0	0	30	0.00	0	0.0
41950046	2	1	0	7.5	0	30	0.00	0	0.0
41950048	2	1	0	7.0	0	300	0.00	0	0.0
41950050	2	1	0	7.5	0	30	0.00	0	0.0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
41950052	3	1	0	7.0	0	100	0.00	0	0.0
41950054	3	1	0	7.5	0	100	0.00	15	0.0
41950056	3	1	0	7.0	0	100	0.00	15	0.0
41950058	3	1	0	7.0	0	100	0.00	0	0.0
41950060	3	1	0	7.5	0	30	0.00	0	0.0
41950062	3	1	0	7.0	0	100	0.00	0	0.0
41950064	3	1	0	7.0	0	100	0.00	0	0.0
41950066	3	1	0	7.5	0	100	0.00	0	0.0
41950068	3	1	0	8.0	0	100	0.00	0	0.0
41950070	3	1	0	7.0	0	100	0.00	0	0.0
41950072	4	0	0	7.0	0	100	0.00	0	0.0
41950074	4	0	0	7.0	0	100	0.00	0	0.0
41950076	4	1	0	6.5	0	100	0.00	0	0.0
41950078	4	0	0	7.0	0	100	0.00	0	0.5
41950080	4	0	0	6.5	0	100	0.00	0	0.0
41950082	4	1	0	7.0	0	100	0.00	0	0.0
41950084	4	1	0	6.5	0	100	0.00	0	0.0
41950086	4	1	0	8.0	0	15	0.00	0	0.0
41950088	4	1	0	7.0	0	30	0.00	0	0.0
41950090	4	1	0	7.5	50	100	0.00	15	2.0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	URO mg/dl
41950002	1	1.0
41950004	1	1.0
41950006	1	1.0
41950008	1	1.0
41950010	1	1.0
41950012	1	1.0
41950014	1	1.0
41950016	1	1.0
41950018	1	1.0
41950020	1	1.0
41950032	2	1.0
41950034	2	1.0
41950036	2	1.0
41950038	2	1.0
41950040	2	1.0
41950042	2	1.0
41950044	2	1.0
41950046	2	1.0
41950048	2	1.0
41950050	2	1.0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	URO mg/dl
41950052	3	1.0
41950054	3	1.0
41950056	3	1.0
41950058	3	1.0
41950060	3	1.0
41950062	3	1.0
41950064	3	1.0
41950066	3	1.0
41950068	3	2.0
41950070	3	1.0
41950072	4	1.0
41950074	4	1.0
41950076	4	1.0
41950078	4	1.0
41950080	4	1.0
41950082	4	1.0
41950084	4	1.0
41950086	4	1.0
41950088	4	1.0
41950090	4	4.0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
41950002	1	1	0	0	2	1	0
41950004	1	0	0	0	1	1	0
41950006	1	1	0	0	1	1	0
41950008	1	0	0	0	2	1	0
41950010	1	1	0	0	2	1	0
41950012	1	1	0	0	2	1	0
41950014	1	0	0	0	2	1	0
41950016	1	1	0	0	1	1	0
41950018	1	0	0	0	3	2	0
41950020	1	0	0	0	1	1	0
41950032	2	0	0	0	1	1	0
41950034	2	1	0	0	1	1	0
41950036	2	1	0	0	1	2	0
41950038	2	0	0	0	1	1	0
41950040	2	0	0	0	1	2	0
41950042	2	0	0	0	2	1	0
41950044	2	0	0	0	1	1	0
41950046	2	0	0	0	1	1	0
41950048	2	0	0	0	2	1	0
41950050	2	0	0	0	2	1	0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
41950052	3	0	0	0	2	2	0
41950054	3	0	0	0	1	2	0
41950056	3	0	0	0	2	2	0
41950058	3	1	0	0	1	2	0
41950060	3	0	0	0	1	2	0
41950062	3	0	0	0	1	1	0
41950064	3	0	0	0	1	1	0
41950066	3	0	0	0	3	1	0
41950068	3	0	0	0	2	1	0
41950070	3	0	0	0	2	1	0
41950072	4	1	0	0	0	1	0
41950074	4	0	0	0	1	1	0
41950076	4	0	0	0	0	1	0
41950078	4	0	0	0	1	1	0
41950080	4	1	0	0	0	1	0
41950082	4	0	0	0	1	1	0
41950084	4	0	0	0	0	1	0
41950086	4	1	0	0	1	1	0
41950088	4	1	0	0	1	1	0
41950090	4	0	0	0	1	1	0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	VOL ml	SG
41950001	1	5.0	1.020
41950003	1	6.0	1.025
41950005	1	10.0	1.020
41950007	1	5.0	1.010
41950009	1	3.5	1.025
41950011	1	3.0	1.030
41950013	1	7.5	1.020
41950015	1	6.5	1.025
41950017	1	5.5	1.030
41950019	1	6.5	1.015
		Mean 5.85	1.0220
		SD 2.00	0.0063
41950031	2	5.0	1.020
41950033	2	2.0	1.025
41950035	2	10.5	1.010
41950037	2	7.0	1.025
41950039	2	5.0	1.025
41950041	2	4.0	1.030
41950043	2	7.0	1.015
41950045	2	4.5	1.020
41950047	2	6.5	1.025
41950049	2	9.0	1.015
		Mean 6.05	1.0210
		SD 2.49	0.0061

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	VOL ml	SG
41950051	3	5.0	1.020
41950053	3	4.0	1.030
41950055	3	5.0	1.025
41950057	3	5.0	1.020
41950059	3	4.5	1.020
41950061	3	7.5	1.025
41950063	3	8.0	1.020
41950065	3	5.5	1.020
41950067	3	7.0	1.015
41950069	3	7.0	1.030
Mean		5.85	1.0225
SD		1.40	0.0049
41950071	4	8.5	1.030
41950073	4	6.0	1.025
41950075	4	4.0	1.025
41950077	4	7.0	1.025
41950079	4	9.5	1.030
41950081	4	6.0	1.020
41950083	4	6.5	1.025
41950085	4	6.0	1.030
41950087	4	7.0	1.020
41950089	4	8.0	1.025
Mean		6.85	1.0255
SD		1.55	0.0037

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
41950001	1	0	0	7.0	0	15	0.00	0	0.0
41950003	1	0	0	6.5	0	30	0.00	0	0.0
41950005	1	0	0	7.0	0	15	0.00	0	0.0
41950007	1	0	0	7.5	0	30	0.00	0	0.0
41950009	1	0	0	7.0	0	30	0.00	0	0.0
41950011	1	0	0	6.5	0	30	0.00	0	0.0
41950013	1	0	0	7.0	0	300	0.00	0	0.0
41950015	1	0	0	7.0	0	15	0.00	0	0.0
41950017	1	0	0	6.5	0	15	0.00	0	0.0
41950019	1	0	0	7.0	0	15	0.00	0	0.0
41950031	2	0	0	7.0	0	15	0.00	0	0.0
41950033	2	0	0	7.0	0	30	0.00	0	0.0
41950035	2	1	0	8.0	100	300	0.00	15	0.5
41950037	2	0	0	7.0	0	30	0.00	0	0.0
41950039	2	0	0	6.5	0	30	0.00	0	0.0
41950041	2	0	0	6.5	0	30	0.00	0	0.0
41950043	2	0	0	7.0	0	15	0.00	0	0.0
41950045	2	0	0	7.0	0	30	0.00	15	2.0
41950047	2	0	0	7.0	0	15	0.00	0	0.0
41950049	2	0	0	7.0	0	0	0.00	0	0.0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
41950051	3	0	0	7.0	0	30	0.00	0	0.0
41950053	3	0	0	7.0	0	30	0.00	0	0.0
41950055	3	0	0	7.0	0	15	0.00	0	0.0
41950057	3	0	0	7.0	0	15	0.00	0	0.0
41950059	3	0	0	7.0	0	0	0.00	0	0.0
41950061	3	0	0	6.5	0	15	0.00	0	0.0
41950063	3	0	0	7.0	0	15	0.00	0	0.0
41950065	3	0	0	7.0	0	30	0.00	0	0.0
41950067	3	0	0	7.0	0	15	0.00	0	0.0
41950069	3	0	0	6.5	0	30	0.00	0	0.0
41950071	4	0	0	6.5	0	30	0.00	0	0.0
41950073	4	0	0	7.0	0	15	0.00	0	0.0
41950075	4	0	0	7.0	0	30	0.00	0	0.0
41950077	4	0	0	7.0	0	30	0.00	0	0.0
41950079	4	0	0	6.5	0	30	0.00	0	0.0
41950081	4	0	0	7.0	0	30	0.00	0	0.0
41950083	4	0	0	7.0	0	15	0.00	0	0.0
41950085	4	0	0	7.0	0	30	0.00	0	0.0
41950087	4	0	0	7.0	0	30	0.00	0	0.0
41950089	4	0	0	7.0	0	100	0.00	0	0.0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	URO mg/dl
41950001	1	1.0
41950003	1	1.0
41950005	1	1.0
41950007	1	1.0
41950009	1	1.0
41950011	1	1.0
41950013	1	1.0
41950015	1	1.0
41950017	1	1.0
41950019	1	1.0
41950031	2	1.0
41950033	2	1.0
41950035	2	1.0
41950037	2	1.0
41950039	2	1.0
41950041	2	1.0
41950043	2	1.0
41950045	2	4.0
41950047	2	1.0
41950049	2	1.0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	URO mg/dl
41950051	3	1.0
41950053	3	1.0
41950055	3	1.0
41950057	3	1.0
41950059	3	1.0
41950061	3	1.0
41950063	3	1.0
41950065	3	1.0
41950067	3	1.0
41950069	3	1.0
41950071	4	1.0
41950073	4	1.0
41950075	4	1.0
41950077	4	1.0
41950079	4	1.0
41950081	4	1.0
41950083	4	1.0
41950085	4	1.0
41950087	4	1.0
41950089	4	1.0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
41950001	1	1	1	0	0	0	0
41950003	1	1	1	0	0	0	0
41950005	1	1	1	0	1	0	0
41950007	1	1	2	0	1	0	0
41950009	1	1	1	0	1	0	0
41950011	1	2	1	0	1	0	0
41950013	1	1	1	0	1	0	0
41950015	1	1	2	0	1	0	0
41950017	1	2	1	0	1	0	0
41950019	1	1	1	0	1	0	0
41950031	2	1	1	0	1	0	0
41950033	2	1	2	0	1	0	0
41950035	2	2	2	0	2	0	0
41950037	2	1	1	0	1	0	0
41950039	2	1	2	0	1	0	0
41950041	2	1	1	0	1	0	0
41950043	2	1	1	0	1	0	0
41950045	2	1	1	0	1	0	0
41950047	2	1	2	0	1	0	0
41950049	2	1	2	0	1	0	0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
41950051	3	1	1	0	1	0	0
41950053	3	1	1	0	1	0	0
41950055	3	1	2	0	1	0	0
41950057	3	1	2	0	1	0	0
41950059	3	2	2	0	1	0	0
41950061	3	1	2	0	1	0	0
41950063	3	1	1	0	1	0	0
41950065	3	1	1	0	1	0	0
41950067	3	1	1	0	0	0	0
41950069	3	1	1	0	1	0	0
41950071	4	2	1	0	1	0	0
41950073	4	1	1	0	1	0	0
41950075	4	2	2	1	1	0	0
41950077	4	1	1	0	1	0	0
41950079	4	1	1	0	1	0	0
41950081	4	1	1	0	1	0	0
41950083	4	2	1	0	1	0	0
41950085	4	1	1	0	1	0	0
41950087	4	1	1	0	1	0	0
41950089	4	1	1	0	1	0	0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	VOL ml	SG
41950022	1	7.5	1.015
41950024	1	9.5	1.015
41950026	1	8.5	1.010
41950028	1	6.5	1.025
41950030	1	5.0	1.025
		Mean 7.40	1.0180
		SD 1.75	0.0067
41950092	4	7.5	1.025
41950094	4	5.5	1.015
41950096	4	8.0	1.020
41950098	4	9.5	1.010
41950100	4	6.0	1.015
		Mean 7.30	1.0170
		SD 1.60	0.0057

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
41950022	1	0	0	7.5	0	>400	0.00	0	0.0
41950024	1	0	0	7.5	0	300	0.00	0	0.0
41950026	1	0	0	7.5	0	300	0.00	0	0.0
41950028	1	0	0	7.0	0	100	0.00	40	0.0
41950030	1	0	0	7.0	0	>400	0.00	15	0.0
41950092	4	0	0	7.0	0	300	0.00	0	0.0
41950094	4	0	0	7.5	0	>400	0.00	0	0.0
41950096	4	0	0	7.0	0	300	0.00	0	0.0
41950098	4	0	0	7.5	0	100	0.00	0	0.0
41950100	4	0	0	7.5	0	>400	0.00	15	0.0

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	URO mg/dl
41950022	1	1.0
41950024	1	1.0
41950026	1	1.0
41950028	1	1.0
41950030	1	1.0
41950092	4	1.0
41950094	4	1.0
41950096	4	1.0
41950098	4	1.0
41950100	4	1.0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
41950022	1	0	0	0	2	1	0
41950024	1	0	0	0	2	0	0
41950026	1	0	0	0	2	2	0
41950028	1	0	0	0	2	2	0
41950030	1	0	0	0	2	3	0
41950092	4	0	0	0	1	1	0
41950094	4	0	0	0	1	0	0
41950096	4	1	0	0	1	2	0
41950098	4	1	0	0	1	1	0
41950100	4	0	0	0	0	0	0

REDACTED AS TO TRACE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	VOL ml	SG
41950021	1	4.5	1.020
41950023	1	4.0	1.020
41950025	1	2.5	1.025
41950027	1	2.0	1.030
41950029	1	4.0	1.025
		Mean 3.40	1.0240
		SD 1.08	0.0042
41950091	4	1.5	1.025
41950093	4	3.0	1.030
41950095	4	5.0	1.030
41950097	4	2.0	1.030
41950099	4	6.5	1.020
		Mean 3.60	1.0270
		SD 2.10	0.0045

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
41950021	1	0	0	7.0	0	15	0.00	0	0.0
41950023	1	0	0	7.0	0	30	0.00	0	0.0
41950025	1	0	0	7.0	0	300	0.00	0	0.0
41950027	1	0	0	6.5	0	30	0.00	0	0.0
41950029	1	0	0	6.5	0	30	0.00	0	0.0
41950091	4	0	0	6.5	0	100	0.00	0	0.0
41950093	4	0	0	7.0	0	100	0.00	0	0.0
41950095	4	0	0	6.5	0	30	0.00	0	0.0
41950097	4	0	0	6.5	0	100	0.00	0	0.0
41950099	4	0	0	7.0	0	15	0.00	0	0.0

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	URO mg/dl
41950021	1	1.0
41950023	1	1.0
41950025	1	1.0
41950027	1	1.0
41950029	1	1.0
41950091	4	1.0
41950093	4	1.0
41950095	4	1.0
41950097	4	2.0
41950099	4	1.0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
41950021	1	0	0	0	0	0	0
41950023	1	0	0	0	0	0	0
41950025	1	1	0	0	1	0	0
41950027	1	1	0	0	0	0	0
41950029	1	1	0	0	1	0	0
41950091	4	1	0	0	1	0	0
41950093	4	0	0	0	1	0	0
41950095	4	0	0	0	0	0	0
41950097	4	0	0	0	0	0	0
41950099	4	1	0	0	2	0	0

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
41950002	1	477.1	0.060	1.83	1.556	1.34	2.81	13.69
41950004	1	464.2	0.056	1.83	1.777	1.54	2.64	12.69
41950006	1	456.8	0.060	1.79	1.318	1.44	2.75	14.78
41950008	1	451.3	0.071	2.01	1.327	1.61	2.60	11.75
41950010	1	435.6	0.046	1.97	1.253	1.20	2.61	12.39
41950012	1	429.4	0.048	1.85	1.357	1.43	2.43	11.48
41950014	1	440.1	0.054	1.90	1.589	1.51	2.89	13.78
41950016	1	429.8	0.054	1.80	1.379	1.43	2.59	11.64
41950018	1	453.5	0.057	1.97	1.361	1.57	2.57	12.92
41950020	1	441.6	0.045	1.73	1.335	1.39	2.61	12.42
Mean		447.94	0.0551	1.868	1.4252	1.446	2.650	12.753
SD		15.50	0.0078	0.091	0.1625	0.122	0.132	1.063
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)
41950032	2	486.9	0.057	1.94	1.428	1.38	2.93	14.89
41950034	2	449.5	0.045	1.74	1.216	1.20	2.48	12.99
41950036	2	447.4	0.042	1.76	1.417	1.69	2.32	11.61
41950038	2	454.0	0.059	1.76	1.440	1.61	2.53	13.07
41950040	2	406.1	0.044	1.81	1.330	1.31	2.52	11.18
41950042	2	459.8	0.046	1.83	1.431	1.63	2.71	12.27
41950044	2	394.5	0.049	1.66	1.473	1.28	2.39	10.88
41950046	2	454.9	0.046	1.72	1.476	1.60	3.01	12.36
41950048	2	460.7	0.049	1.85	1.209	1.44	2.70	13.53
41950050	2	425.6	0.052	1.88	1.594	1.53	2.52	11.39
Mean		443.94	0.0489	1.796	1.4014	1.467	2.610	12.417
SD		27.60	0.0056	0.084	0.1191	0.170	0.222	1.236
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
41950052	3	441.2	0.049	1.92	1.338	1.26	2.79	14.19
41950054	3	414.8	0.051	1.71	1.392	1.43	2.72	15.12
41950056	3	417.2	0.042	1.92	1.350	1.27	2.42	12.55
41950058	3	473.6	0.049	1.64	1.311	1.39	2.73	15.11
41950060	3	433.1	0.050	1.74	1.432	1.44	2.68	13.02
41950062	3	426.1	0.047	1.71	1.337	1.28	2.32	13.98
41950064	3	460.8	0.057	1.92	1.467	1.50	3.21	14.14
41950066	3	440.1	0.044	1.87	1.317	1.35	2.75	14.72
41950068	3	440.3	0.059	1.94	1.413	1.40	2.89	15.65
41950070	3	469.0	0.057	1.90	1.375	1.62	2.87	15.16
Mean		441.62	0.0505	1.827	1.3732	1.393	2.736	14.363
SD		20.48	0.0057	0.113	0.0520	0.112	0.245	0.992
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)
41950072	4	434.5	0.047	1.88	1.461	1.51	3.07	18.00
41950074	4	397.3	0.049	1.92	1.271	1.29	2.82	14.55
41950076	4	428.3	0.045	1.79	1.304	1.33	2.87	16.75
41950078	4	411.0	0.045	1.94	1.564	1.30	2.80	15.67
41950080	4	432.0	0.044	1.80	1.259	1.33	2.83	16.69
41950082	4	417.3	0.042	1.91	1.132	1.29	2.91	18.81
41950084	4	382.7	0.049	1.78	1.242	1.25	2.84	16.00
41950086	4	388.1	0.049	1.97	1.236	1.17	2.87	16.61
41950088	4	366.4	0.046	1.76	1.158	1.08	2.67	14.45
41950090	4	372.7	0.046	1.85	1.144	1.19	2.47	15.86
Mean		403.03	0.0462	1.861	1.2771	1.274	2.816	16.339
SD		25.09	0.0023	0.075	0.1387	0.115	0.157	1.364
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus
41950002	1	477.1	0.994	4.371	0.415
41950004	1	464.2	0.902	4.193	0.323
41950006	1	456.8	0.963	3.929	0.262
41950008	1	451.3	0.976	3.978	0.500
41950010	1	435.6	0.812	3.745	0.231
41950012	1	429.4	0.859	3.865	0.288
41950014	1	440.1	0.824	4.313	0.388
41950016	1	429.8	0.938	3.748	0.324
41950018	1	453.5	0.734	4.079	0.312
41950020	1	441.6	0.850	4.128	0.293
Mean		447.94	0.8852	4.0349	0.3336
SD		15.50	0.0837	0.2200	0.0798
	(n)	(10)	(10)	(10)	(10)
41950032	2	486.9	0.839	4.024	0.449
41950034	2	449.5	0.943	2.817	0.347
41950036	2	447.4	1.079	4.068	0.216
41950038	2	454.0	1.019	3.759	0.210
41950040	2	406.1	0.966	4.538	0.176
41950042	2	459.8	0.844	4.301	0.354
41950044	2	394.5	0.805	4.012	0.220
41950046	2	454.9	0.917	4.338	0.306
41950048	2	460.7	0.862	3.635	0.333
41950050	2	425.6	0.832	3.798	0.314
Mean		443.94	0.9106	3.9290	0.2925
SD		27.60	0.0904	0.4808	0.0850
	(n)	(10)	(10)	(10)	(10)

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus
41950052	3	441.2	0.886	3.807	0.283
41950054	3	414.8	0.724	3.819	0.237
41950056	3	417.2	0.735	3.556	0.226
41950058	3	473.6	0.767	3.945	0.256
41950060	3	433.1	0.810	3.863	0.352
41950062	3	426.1	0.717	3.848	0.288
41950064	3	460.8	0.946	4.007	0.274
41950066	3	440.1	0.946	3.719	0.320
41950068	3	440.3	0.868	3.945	0.423
41950070	3	469.0	0.919	3.738	0.361
Mean		441.62	0.8318	3.8247	0.3020
SD		20.48	0.0924	0.1314	0.0618
(n)		(10)	(10)	(10)	(10)
41950072	4	434.5	0.765	4.072	0.194
41950074	4	397.3	0.644	3.870	0.223
41950076	4	428.3	0.739	3.840	0.251
41950078	4	411.0	0.729	3.856	0.330
41950080	4	432.0	0.846	3.755	0.268
41950082	4	417.3	0.750	3.509	0.251
41950084	4	382.7	0.717	3.536	0.196
41950086	4	388.1	0.670	4.001	0.293
41950088	4	366.4	0.628	3.636	0.179
41950090	4	372.7	0.712	3.731	0.205
Mean		403.03	0.7200	3.7806	0.2390
SD		25.09	0.0633	0.1851	0.0485
(n)		(10)	(10)	(10)	(10)

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
41950001	1	247.9	0.055	1.83	0.92	1.67	7.10	0.122
41950003	1	293.0	0.065	1.73	1.01	1.77	8.32	0.149
41950005	1	294.5	0.054	1.72	1.01	1.66	8.28	0.142
41950007	1	295.8	0.057	1.69	1.14	1.89	7.91	0.150
41950009	1	258.6	0.062	1.68	0.93	1.64	7.05	0.104
41950011	1	255.8	0.067	1.70	1.02	1.62	6.56	0.091
41950013	1	287.5	0.062	1.87	0.99	1.69	8.39	0.126
41950015	1	260.1	0.065	1.60	1.21	1.48	6.60	0.144
41950017	1	281.9	0.058	1.67	0.95	1.59	7.37	0.126
41950019	1	266.9	0.045	1.80	0.97	1.52	6.95	0.138
Mean		274.20	0.0590	1.728	1.015	1.652	7.454	0.1292
SD		18.24	0.0066	0.082	0.092	0.118	0.714	0.0196
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)
41950031	2	278.9	0.065	1.65	0.97	1.75	7.39	0.104
41950033	2	283.2	0.062	1.90	0.98	1.87	7.66	0.105
41950035	2	256.6	0.055	1.82	0.88	1.76	8.02	0.110
41950037	2	281.5	0.053	1.74	1.09	1.75	8.61	0.128
41950039	2	264.1	0.070	1.81	0.99	1.59	7.39	0.185
41950041	2	286.4	0.068	1.72	1.06	1.70	7.82	0.116
41950043	2	285.1	0.056	1.72	0.93	1.65	7.94	0.151
41950045	2	267.9	0.065	1.68	0.90	1.64	7.18	0.115
41950047	2	264.8	0.051	1.76	0.93	1.57	7.65	0.121
41950049	2	279.7	0.064	1.77	0.96	1.64	7.64	0.118
Mean		274.82	0.0609	1.757	0.966	1.692	7.731	0.1253
SD		10.49	0.0066	0.073	0.066	0.092	0.403	0.0249
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
41950051	3	291.0	0.064	1.73	1.03	1.84	9.68	0.137
41950053	3	271.1	0.064	1.68	1.01	1.66	8.54	0.100
41950055	3	280.5	0.059	1.71	1.04	1.64	9.50	0.130
41950057	3	272.3	0.057	1.76	0.87	1.67	8.06	0.118
41950059	3	262.0	0.063	1.69	1.12	1.75	8.19	0.111
41950061	3	258.9	0.060	1.63	0.98	1.70	8.12	0.127
41950063	3	276.6	0.055	1.76	1.07	1.83	7.87	0.119
41950065	3	306.5	0.064	1.75	1.11	2.10	9.32	0.170
41950067	3	285.5	0.051	1.81	0.93	1.82	9.10	0.120
41950069	3	266.9	0.060	1.66	0.92	1.54	7.92	0.133
Mean		277.13	0.0597	1.719	1.009	1.754	8.630	0.1265
SD		14.38	0.0044	0.056	0.082	0.154	0.701	0.0188
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)
41950071	4	287.4	0.062	1.76	1.05	1.98	12.76	0.154
41950073	4	258.7	0.053	1.81	0.99	1.83	11.77	0.125
41950075	4	288.2	0.056	1.66	0.92	1.69	10.45	0.103
41950077	4	269.4	0.063	1.77	0.97	1.90	11.01	0.153
41950079	4	277.7	0.056	1.76	0.92	1.91	11.37	0.110
41950081	4	270.2	0.059	1.71	0.96	1.83	11.60	0.110
41950083	4	257.2	0.066	1.78	0.82	1.71	11.37	0.105
41950085	4	253.6	0.061	1.73	0.90	1.60	11.24	0.131
41950087	4	250.8	0.050	1.87	0.92	1.90	12.06	0.127
41950089	4	266.7	0.050	1.79	0.87	1.94	12.48	0.149
Mean		265.99	0.0576	1.761	0.932	1.828	11.610	0.1267
SD		11.28	0.0055	0.057	0.065	0.124	0.688	0.0198
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Uterus
41950001	1	247.9	0.494	0.216	0.539
41950003	1	293.0	0.695	0.328	0.661
41950005	1	294.5	0.704	0.164	0.507
41950007	1	295.8	0.788	0.260	0.408
41950009	1	258.6	0.627	0.159	0.590
41950011	1	255.8	0.602	0.296	0.499
41950013	1	287.5	0.676	0.275	0.797
41950015	1	260.1	0.652	0.266	0.546
41950017	1	281.9	0.638	0.542	0.296
41950019	1	266.9	0.681	0.214	0.422
Mean		274.20	0.6557	0.2720	0.5265
SD		18.24	0.0765	0.1094	0.1395
(n)		(10)	(10)	(10)	(10)
41950031	2	278.9	0.724	0.290	0.516
41950033	2	283.2	0.717	0.201	0.577
41950035	2	256.6	1.035	0.118	0.455
41950037	2	281.5	0.991	0.194	0.411
41950039	2	264.1	0.772	0.218	0.500
41950041	2	286.4	0.683	0.258	0.546
41950043	2	285.1	0.655	0.275	0.825
41950045	2	267.9	0.680	0.268	0.465
41950047	2	264.8	0.529	0.280	0.446
41950049	2	279.7	0.719	0.235	0.718
Mean		274.82	0.7505	0.2337	0.5459
SD		10.49	0.1527	0.0528	0.1310
(n)		(10)	(10)	(10)	(10)

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Uterus
41950051	3	291.0	0.767	0.306	0.433
41950053	3	271.1	0.731	0.209	0.456
41950055	3	280.5	0.665	0.219	0.457
41950057	3	272.3	0.688	0.275	0.451
41950059	3	262.0	0.731	0.220	0.597
41950061	3	258.9	0.639	0.231	0.603
41950063	3	276.6	0.671	0.249	0.954
41950065	3	306.5	0.859	0.263	0.586
41950067	3	285.5	0.680	0.262	0.287
41950069	3	266.9	0.670	0.221	0.432
	Mean	277.13	0.7101	0.2455	0.5256
	SD	14.38	0.0649	0.0309	0.1788
	(n)	(10)	(10)	(10)	(10)
41950071	4	287.4	0.679	0.258	0.401
41950073	4	258.7	0.666	0.225	0.819
41950075	4	268.2	0.680	0.251	0.548
41950077	4	269.4	0.757	0.307	0.978
41950079	4	277.7	0.647	0.264	1.600
41950081	4	270.2	0.688	0.247	1.254
41950083	4	257.2	0.487	0.280	0.734
41950085	4	253.6	0.555	0.224	0.423
41950087	4	250.8	0.469	0.162	0.367
41950089	4	266.7	0.524	0.177	0.537
	Mean	265.99	0.6152	0.2395	0.7661
	SD	11.28	0.0983	0.0443	0.4072
	(n)	(10)	(10)	(10)	(10)

REDACTED AS TO TRADE NAMES

13 WEEK OFAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Absolute organ weights (g) - Recovery sacrifice - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
41950022	1	464.8	0.048	1.86	1.543	1.48	2.82	11.93
41950024	1	505.4	0.046	1.80	1.470	1.43	2.73	14.16
41950026	1	516.5	0.056	1.93	1.556	1.49	3.00	14.06
41950028	1	416.9	0.042	1.89	1.494	1.37	2.55	10.89
41950030	1	475.2	0.045	1.83	1.399	1.54	2.82	12.53
Mean		475.76	0.0474	1.861	1.4924	1.462	2.782	12.715
SD		39.13	0.0053	0.053	0.0629	0.065	0.164	1.402
(n)		(5)	(5)	(5)	(5)	(5)	(5)	(5)
41950092	4	491.6	0.050	1.98	1.496	1.44	3.37	19.25
41950094	4	476.4	0.049	1.93	1.507	1.62	2.86	15.90
41950096	4	490.1	0.056	1.90	1.358	1.50	3.12	17.59
41950098	4	399.2	0.049	1.80	1.515	1.42	2.67	16.04
41950100	4	444.6	0.048	1.89	1.447	1.44	2.63	15.37
Mean		460.38	0.0504	1.899	1.4646	1.484	2.928	16.831
SD		39.07	0.0032	0.067	0.0652	0.079	0.314	1.584
(n)		(5)	(5)	(5)	(5)	(5)	(5)	(5)

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Absolute organ weights (g) - Recovery sacrifice - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus
41950022	1	464.8	0.911	4.113	0.283
41950024	1	505.4	0.897	4.250	0.351
41950026	1	516.5	0.994	4.518	0.282
41950028	1	416.9	0.769	3.957	0.239
41950030	1	475.2	1.081	3.803	0.343
Mean		475.76	0.9304	4.1282	0.2996
SD		39.13	0.1165	0.2748	0.0469
(n)		(5)	(5)	(5)	(5)
41950092	4	491.6	0.916	4.321	0.262
41950094	4	476.4	0.930	3.737	0.249
41950096	4	490.1	0.804	3.793	0.286
41950098	4	399.2	0.660	3.736	0.220
41950100	4	444.6	0.759	4.023	0.263
Mean		460.38	0.8138	3.9220	0.2560
SD		39.07	0.1126	0.2524	0.0241
(n)		(5)	(5)	(5)	(5)

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Absolute organ weights (g) - Recovery sacrifice - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
41950021	1	309.5	0.056	1.81	1.11	1.84	8.29	0.138
41950023	1	282.3	0.061	1.76	1.07	1.71	8.53	0.114
41950025	1	304.2	0.055	1.68	1.17	1.91	8.74	0.126
41950027	1	265.4	0.053	1.76	0.91	1.90	7.12	0.099
41950029	1	288.2	0.068	1.81	0.99	1.81	7.43	0.102
Mean		289.92	0.0586	1.764	1.048	1.832	8.020	0.1158
SD		17.67	0.0060	0.053	0.102	0.081	0.707	0.0164
(n)		(5)	(5)	(5)	(5)	(5)	(5)	(5)
41950091	4	255.3	0.054	1.58	0.82	1.78	9.93	0.107
41950093	4	268.0	0.063	1.58	0.91	1.93	10.77	0.132
41950095	4	283.5	0.067	1.72	0.96	1.73	10.17	0.103
41950097	4	284.3	0.070	1.77	1.12	2.24	11.56	0.138
41950099	4	269.1	0.038	1.75	0.90	1.74	9.70	0.118
Mean		272.04	0.0584	1.680	0.940	1.882	10.423	0.1196
SD		12.11	0.0129	0.095	0.110	0.213	0.751	0.0152
(n)		(5)	(5)	(5)	(5)	(5)	(5)	(5)

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Absolute organ weights (g) - Recovery sacrifice - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Uterus
41950021	1	309.5	0.737	0.206	0.555
41950023	1	282.3	0.588	0.202	0.555
41950025	1	304.2	0.734	0.259	0.411
41950027	1	265.4	0.584	0.142	1.364
41950029	1	288.2	0.719	0.197	0.750
	Mean	289.92	0.6724	0.2012	0.7270
	SD	17.67	0.0792	0.0415	0.3759
	(n)	(5)	(5)	(5)	(5)
41950091	4	255.3	0.536	0.136	0.420
41950093	4	268.0	0.569	0.203	0.788
41950095	4	283.5	0.673	0.219	0.504
41950097	4	284.3	0.643	0.218	0.396
41950099	4	269.1	0.628	0.170	0.405
	Mean	272.04	0.6098	0.1892	0.5026
	SD	12.11	0.0560	0.0357	0.1652
	(n)	(5)	(5)	(5)	(5)

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Relative organ weights* - Final sacrifice - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
41950002	1	477.1	0.013	0.38	0.326	0.28	0.59	2.87
41950004	1	464.2	0.012	0.39	0.383	0.33	0.57	2.73
41950006	1	456.8	0.013	0.39	0.289	0.32	0.60	3.24
41950008	1	451.3	0.016	0.44	0.294	0.36	0.58	2.60
41950010	1	435.6	0.011	0.45	0.288	0.28	0.60	2.84
41950012	1	429.4	0.011	0.43	0.316	0.33	0.57	2.67
41950014	1	440.1	0.012	0.43	0.361	0.34	0.66	3.13
41950016	1	429.8	0.013	0.42	0.321	0.33	0.60	2.71
41950018	1	453.5	0.013	0.43	0.300	0.35	0.57	2.85
41950020	1	441.6	0.010	0.39	0.302	0.31	0.59	2.81
Mean		447.94	0.0123	0.417	0.3180	0.323	0.592	2.846
SD		15.50	0.0015	0.025	0.0317	0.027	0.027	0.198
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)
41950032	2	486.9	0.012	0.40	0.293	0.28	0.60	3.06
41950034	2	449.5	0.010	0.39	0.271	0.27	0.55	2.89
41950036	2	447.4	0.009	0.39	0.317	0.38	0.52	2.59
41950038	2	454.0	0.013	0.39	0.317	0.35	0.56	2.88
41950040	2	406.1	0.011	0.45	0.328	0.32	0.62	2.75
41950042	2	459.8	0.010	0.40	0.311	0.36	0.59	2.67
41950044	2	394.5	0.012	0.42	0.373	0.32	0.61	2.76
41950046	2	454.9	0.010	0.38	0.324	0.35	0.66	2.72
41950048	2	460.7	0.011	0.40	0.262	0.31	0.59	2.94
41950050	2	425.6	0.012	0.44	0.375	0.36	0.59	2.68
Mean		443.94	0.0110	0.405	0.3171	0.331	0.588	2.793
SD		27.60	0.0012	0.023	0.0371	0.036	0.039	0.144
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)

* = expressed as % organ to body weight ratio

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Relative organ weights* - Final sacrifice - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
41950052	3	441.2	0.011	0.43	0.303	0.29	0.63	3.22
41950054	3	414.8	0.012	0.41	0.336	0.34	0.65	3.64
41950056	3	417.2	0.010	0.46	0.324	0.30	0.58	3.01
41950058	3	473.6	0.035	0.35	0.277	0.29	0.58	3.19
41950060	3	433.1	0.012	0.40	0.331	0.33	0.62	3.01
41950062	3	426.1	0.011	0.40	0.314	0.30	0.54	3.28
41950064	3	460.8	0.012	0.42	0.318	0.30	0.70	3.07
41950066	3	440.1	0.010	0.42	0.299	0.31	0.62	3.34
41950068	3	440.3	0.013	0.44	0.321	0.32	0.66	3.55
41950070	3	469.0	0.012	0.41	0.293	0.34	0.61	3.23
Mean		441.62	0.014	0.414	0.3115	0.315	0.619	3.254
SD		20.48	0.0011	0.030	0.0182	0.021	0.044	0.214
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)
41950072	4	434.5	0.011	0.43	0.336	0.35	0.71	4.14
41950074	4	397.3	0.012	0.48	0.320	0.32	0.71	3.66
41950076	4	428.3	0.011	0.42	0.304	0.31	0.67	3.91
41950078	4	411.0	0.011	0.47	0.381	0.32	0.68	3.81
41950080	4	432.0	0.010	0.42	0.291	0.31	0.65	3.86
41950082	4	417.3	0.010	0.46	0.271	0.31	0.70	4.51
41950084	4	382.7	0.013	0.46	0.325	0.33	0.74	4.18
41950086	4	388.1	0.013	0.51	0.318	0.30	0.74	4.28
41950088	4	366.4	0.013	0.48	0.316	0.30	0.73	3.94
41950090	4	372.7	0.012	0.50	0.307	0.32	0.66	4.26
Mean		403.03	0.0115	0.463	0.3170	0.316	0.700	4.056
SD		25.09	0.0011	0.032	0.0288	0.015	0.032	0.258
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)

* = expressed as % organ to body weight ratio

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Relative organ weights^o - Final sacrifice - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Terminal B.W. (g)	Testes			Thymus
			Spleen			
41950002	1	477.1	0.208	0.916	0.087	0.087
41950004	1	464.2	0.194	0.903	0.070	0.070
41950006	1	456.8	0.211	0.860	0.057	0.057
41950008	1	451.3	0.216	0.881	0.111	0.111
41950010	1	435.6	0.186	0.860	0.053	0.053
41950012	1	429.4	0.200	0.900	0.067	0.067
41950014	1	440.1	0.187	0.980	0.088	0.088
41950016	1	429.8	0.218	0.872	0.075	0.075
41950018	1	453.5	0.162	0.899	0.069	0.069
41950020	1	441.6	0.192	0.935	0.066	0.066
Mean		447.94	0.1976	0.9007	0.0744	0.0744
SD		15.50	0.0171	0.0368	0.0170	0.0170
(n)		(10)	(10)	(10)	(10)	(10)
41950032	2	486.9	0.172	0.826	0.092	0.092
41950034	2	449.5	0.210	0.627	0.077	0.077
41950036	2	447.4	0.241	0.909	0.048	0.048
41950038	2	454.0	0.224	0.828	0.046	0.046
41950040	2	406.1	0.238	1.117	0.043	0.043
41950042	2	459.8	0.184	0.935	0.077	0.077
41950044	2	394.5	0.204	1.017	0.056	0.056
41950046	2	454.9	0.202	0.954	0.067	0.067
41950048	2	460.7	0.187	0.789	0.072	0.072
41950050	2	425.6	0.195	0.892	0.074	0.074
Mean		443.94	0.2057	0.8895	0.0653	0.0653
SD		27.60	0.0229	0.1341	0.0162	0.0162
(n)		(10)	(10)	(10)	(10)	(10)

^o = expressed as % organ to body weight ratio

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Relative organ weights* - Final sacrifice - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus
41950052	3	441.2	0.201	0.863	0.064
41950054	3	414.8	0.175	0.921	0.057
41950056	3	417.2	0.176	0.852	0.054
41950058	3	473.6	0.162	0.833	0.054
41950060	3	433.1	0.187	0.892	0.081
41950062	3	426.1	0.168	0.903	0.068
41950064	3	460.8	0.205	0.870	0.059
41950066	3	440.1	0.215	0.845	0.073
41950068	3	440.3	0.197	0.896	0.096
41950070	3	469.0	0.196	0.797	0.077
Mean		441.62	0.1882	0.8672	0.0684
SD		20.48	0.0174	0.0371	0.0136
(n)		(10)	(10)	(10)	(10)
41950072	4	434.5	0.176	0.937	0.045
41950074	4	397.3	0.162	0.974	0.056
41950076	4	428.3	0.173	0.897	0.059
41950078	4	411.0	0.177	0.938	0.080
41950080	4	432.0	0.196	0.869	0.062
41950082	4	417.3	0.180	0.841	0.060
41950084	4	382.7	0.187	0.924	0.051
41950086	4	388.1	0.173	1.031	0.075
41950088	4	366.4	0.171	0.992	0.049
41950090	4	372.7	0.191	1.001	0.055
Mean		403.03	0.1786	0.9404	0.0592
SD		25.09	0.0102	0.0604	0.0112
(n)		(10)	(10)	(10)	(10)

* = expressed as % organ to body weight ratio

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Relative organ weights* - Final sacrifice - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
41950001	1	247.9	0.022	0.74	0.37	0.67	2.86	0.049
41950003	1	293.0	0.022	0.59	0.34	0.60	2.84	0.051
41950005	1	294.5	0.018	0.59	0.34	0.56	2.81	0.048
41950007	1	295.8	0.019	0.57	0.38	0.64	2.67	0.051
41950009	1	258.6	0.024	0.65	0.36	0.63	2.73	0.040
41950011	1	255.8	0.026	0.66	0.40	0.63	2.56	0.036
41950013	1	287.5	0.022	0.65	0.35	0.59	2.92	0.044
41950015	1	260.1	0.025	0.61	0.47	0.57	2.54	0.055
41950017	1	281.9	0.021	0.59	0.34	0.56	2.62	0.045
41950019	1	266.9	0.017	0.67	0.36	0.57	2.61	0.052
Mean		274.20	0.0216	0.633	0.371	0.603	2.716	0.0470
SD		18.24	0.0030	0.052	0.038	0.039	0.136	0.0060
	(n)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
41950031	2	278.9	0.023	0.59	0.35	0.63	2.65	0.037
41950033	2	283.2	0.022	0.67	0.34	0.66	2.70	0.037
41950035	2	256.6	0.021	0.71	0.34	0.68	3.12	0.043
41950037	2	281.5	0.019	0.62	0.39	0.62	3.06	0.045
41950039	2	264.1	0.027	0.69	0.37	0.60	2.80	0.070
41950041	2	286.4	0.024	0.60	0.37	0.59	2.73	0.041
41950043	2	285.1	0.020	0.60	0.33	0.58	2.79	0.053
41950045	2	267.9	0.024	0.63	0.33	0.61	2.68	0.043
41950047	2	264.8	0.019	0.66	0.35	0.59	2.89	0.046
41950049	2	279.7	0.023	0.63	0.34	0.59	2.73	0.042
Mean		274.82	0.0222	0.640	0.352	0.616	2.815	0.0457
SD		10.49	0.0025	0.040	0.019	0.034	0.161	0.0097
	(n)	(10)	(10)	(10)	(10)	(10)	(10)	(10)

* = expressed as % organ to body weight ratio

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Relative organ weights* - Final sacrifice - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
41950051	3	291.0	0.022	0.59	0.35	0.63	3.32	0.047
41950053	3	271.1	0.024	0.62	0.37	0.61	3.15	0.037
41950055	3	280.5	0.021	0.61	0.37	0.59	3.39	0.046
41950057	3	272.3	0.021	0.65	0.32	0.61	2.96	0.043
41950059	3	262.0	0.024	0.65	0.43	0.67	3.12	0.042
41950061	3	258.9	0.023	0.63	0.38	0.66	3.13	0.049
41950063	3	276.6	0.020	0.64	0.39	0.66	2.85	0.043
41950065	3	306.5	0.021	0.57	0.36	0.68	3.04	0.055
41950067	3	285.5	0.018	0.64	0.33	0.64	3.19	0.042
41950069	3	266.9	0.022	0.62	0.35	0.58	2.97	0.050
Mean		277.13	0.0216	0.621	0.365	0.632	3.113	0.0455
SD		14.38	0.0019	0.024	0.031	0.036	0.166	0.0052
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)
41950071	4	287.4	0.022	0.61	0.37	0.69	4.44	0.054
41950073	4	258.7	0.020	0.70	0.38	0.71	4.55	0.048
41950075	4	268.2	0.021	0.62	0.34	0.63	3.90	0.038
41950077	4	269.4	0.023	0.66	0.36	0.71	4.09	0.057
41950079	4	277.7	0.020	0.63	0.33	0.69	4.09	0.040
41950081	4	270.2	0.022	0.63	0.35	0.68	4.29	0.041
41950083	4	257.2	0.026	0.69	0.32	0.66	4.42	0.041
41950085	4	253.6	0.024	0.68	0.35	0.63	4.43	0.052
41950087	4	250.8	0.020	0.74	0.37	0.76	4.81	0.051
41950089	4	266.7	0.019	0.67	0.33	0.73	4.68	0.056
Mean		265.99	0.0217	0.663	0.350	0.687	4.370	0.0476
SD		11.28	0.0021	0.042	0.021	0.039	0.283	0.0071
(n)		(10)	(10)	(10)	(10)	(10)	(10)	(10)

* = expressed as % organ to body weight ratio

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Relative organ weights* - Final sacrifice - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Uterus
41950001	1	247.9	0.199	0.087	0.217
41950003	1	293.0	0.237	0.112	0.226
41950005	1	294.5	0.239	0.056	0.172
41950007	1	295.8	0.266	0.088	0.138
41950009	1	258.6	0.242	0.061	0.228
41950011	1	255.8	0.235	0.116	0.195
41950013	1	287.5	0.235	0.096	0.277
41950015	1	260.1	0.251	0.102	0.210
41950017	1	281.9	0.226	0.192	0.105
41950019	1	266.9	0.255	0.080	0.158
Mean		274.20	0.2387	0.0990	0.1927
SD		18.24	0.0180	0.0381	0.0502
(n)		(10)	(10)	(10)	(10)
41950031	2	278.9	0.260	0.104	0.185
41950033	2	283.2	0.253	0.071	0.204
41950035	2	256.6	0.403	0.046	0.177
41950037	2	281.5	0.352	0.069	0.146
41950039	2	264.1	0.292	0.083	0.189
41950041	2	286.4	0.238	0.090	0.191
41950043	2	285.1	0.230	0.096	0.289
41950045	2	267.9	0.254	0.100	0.174
41950047	2	264.8	0.200	0.106	0.168
41950049	2	279.7	0.257	0.084	0.257
Mean		274.82	0.2739	0.0849	0.1980
SD		10.49	0.0608	0.0187	0.0431
(n)		(10)	(10)	(10)	(10)

* = expressed as % organ to body weight ratio

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Relative organ weights* - Final sacrifice - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Uterus
41950051	3	291.0	0.264	0.105	0.149
41950053	3	271.1	0.270	0.077	0.168
41950055	3	280.5	0.237	0.078	0.163
41950057	3	272.3	0.253	0.101	0.166
41950059	3	262.0	0.279	0.084	0.228
41950061	3	258.9	0.247	0.089	0.233
41950063	3	276.6	0.243	0.090	0.345
41950065	3	306.5	0.280	0.086	0.191
41950067	3	285.5	0.238	0.092	0.101
41950069	3	266.9	0.251	0.083	0.162
Mean		277.13	0.2561	0.0885	0.1905
SD		14.38	0.0161	0.0091	0.0663
(n)		(10)	(10)	(10)	(10)
41950071	4	287.4	0.236	0.090	0.140
41950073	4	258.7	0.257	0.087	0.317
41950075	4	268.2	0.254	0.094	0.204
41950077	4	269.4	0.281	0.114	0.363
41950079	4	277.7	0.233	0.095	0.576
41950081	4	270.2	0.255	0.091	0.464
41950083	4	257.2	0.189	0.109	0.285
41950085	4	253.6	0.219	0.088	0.167
41950087	4	250.8	0.187	0.065	0.146
41950089	4	266.7	0.196	0.066	0.201
Mean		265.99	0.2308	0.0899	0.2864
SD		11.28	0.0322	0.0156	0.1460
(n)		(10)	(10)	(10)	(10)

* = expressed as % organ to body weight ratio

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 10.2 - Relative organ weights* - Recovery sacrifice - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
41950022	1	464.8	0.010	0.40	0.332	0.32	0.61	2.57
41950024	1	505.4	0.009	0.36	0.291	0.28	0.54	2.80
41950026	1	516.5	0.011	0.37	0.301	0.29	0.58	2.72
41950028	1	416.9	0.010	0.45	0.358	0.33	0.61	2.61
41950030	1	475.2	0.009	0.38	0.294	0.32	0.59	2.64
Mean		475.76	0.0100	0.393	0.3154	0.309	0.586	2.668
SD		39.13	0.0007	0.037	0.0290	0.021	0.029	0.094
(n)		(5)	(5)	(5)	(5)	(5)	(5)	(5)
41950092	4	491.6	0.010	0.40	0.304	0.29	0.69	3.91
41950094	4	476.4	0.010	0.40	0.316	0.34	0.60	3.34
41950096	4	490.1	0.011	0.39	0.277	0.31	0.64	3.59
41950098	4	399.2	0.012	0.45	0.380	0.36	0.67	4.02
41950100	4	444.6	0.011	0.42	0.325	0.32	0.59	3.46
Mean		460.38	0.0110	0.414	0.3205	0.324	0.636	3.664
SD		39.07	0.0009	0.024	0.0377	0.025	0.041	0.293
(n)		(5)	(5)	(5)	(5)	(5)	(5)	(5)

* = expressed as % organ to body weight ratio

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 10.2 - Relative organ weights* - Recovery sacrifice - Individual data

STUDY NO.: 41950

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus
41950022	1	464.8	0.196	0.885	0.061
41950024	1	505.4	0.177	0.841	0.069
41950026	1	516.5	0.192	0.875	0.055
41950028	1	416.9	0.184	0.949	0.057
41950030	1	475.2	0.227	0.800	0.072
	Mean	475.76	0.1956	0.8700	0.0629
	SD	39.13	0.0192	0.0553	0.0076
	(n)	(5)	(5)	(5)	(5)
41950092	4	491.6	0.186	0.879	0.053
41950094	4	476.4	0.195	0.784	0.052
41950096	4	490.1	0.164	0.774	0.058
41950098	4	399.2	0.165	0.936	0.055
41950100	4	444.6	0.171	0.905	0.059
	Mean	460.38	0.1763	0.8556	0.0556
	SD	39.07	0.0138	0.0727	0.0030
	(n)	(5)	(5)	(5)	(5)

* = expressed as % organ to body weight ratio

REDACTED AS TO TRADE NAMES

13 WEEK CRAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 10.2 - Relative organ weights* - Recovery sacrifice - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
41950021	1	309.5	0.018	0.58	0.36	0.59	2.68	0.045
41950023	1	282.3	0.022	0.62	0.38	0.60	3.02	0.040
41950025	1	304.2	0.018	0.55	0.38	0.63	2.87	0.041
41950027	1	265.4	0.020	0.66	0.34	0.72	2.68	0.037
41950029	1	288.2	0.024	0.63	0.34	0.63	2.58	0.035
Mean		289.92	0.0203	0.611	0.361	0.634	2.766	0.0398
SD		17.67	0.0024	0.043	0.020	0.048	0.178	0.0036
(n)		(5)	(5)	(5)	(5)	(5)	(5)	(5)
41950091	4	255.3	0.021	0.62	0.32	0.70	3.89	0.042
41950093	4	268.0	0.024	0.59	0.34	0.72	4.02	0.049
41950095	4	283.5	0.024	0.61	0.34	0.61	3.59	0.036
41950097	4	284.3	0.025	0.62	0.39	0.79	4.07	0.049
41950099	4	269.1	0.014	0.65	0.33	0.64	3.60	0.044
Mean		272.04	0.0214	0.618	0.345	0.692	3.832	0.0440
SD		12.11	0.0043	0.023	0.027	0.068	0.226	0.0053
(n)		(5)	(5)	(5)	(5)	(5)	(5)	(5)

* = expressed as % organ to body weight ratio

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 10.2 - Relative organ weights* - Recovery sacrifice - Individual data

STUDY NO.: 41950

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Uterus
41950021	1	309.5	0.238	0.067	0.179
41950023	1	282.3	0.208	0.072	0.197
41950025	1	304.2	0.241	0.085	0.135
41950027	1	265.4	0.220	0.054	0.514
41950029	1	288.2	0.249	0.068	0.260
	Mean	289.92	0.2314	0.0690	0.2570
	SD	17.67	0.0168	0.0113	0.1505
	(n)	(5)	(5)	(5)	(5)
41950091	4	255.3	0.210	0.053	0.165
41950093	4	268.0	0.212	0.076	0.294
41950095	4	283.5	0.237	0.077	0.178
41950097	4	284.3	0.226	0.077	0.139
41950099	4	269.1	0.233	0.063	0.151
	Mean	272.04	0.2238	0.0692	0.1852
	SD	12.11	0.0123	0.0106	0.0625
	(n)	(5)	(5)	(5)	(5)

* = expressed as % organ to body weight ratio

REDACTED AS TO TRACE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950002		Sex: Male	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Heart		INFLAMMATORY CELL FOCI, Multifocal, Slight, Myocardial.		
Kidneys		NEPHROPATHY, Bilateral, Slight.		
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.		
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.		
Thymus	 Abnormal colour, Red	CONGESTION/HAEMORRHAGE, Slight.		
The following tissues are normal microscopically:				
Adrenals	Bronchi	Bone marrow	Brain	
Caecum	Cervical nodes	Colon	Duodenum	
Epididymides	Ileum	Jejunum	Mesenteric nodes	
Parathyroid gl.	Pituitary	Prostate	Rectum	
Sciatic nerve	Spinal cord	Spleen	Stomach	
Testes	Thyroid	Trachea	Urinary bladder	
Aorta	Mammary area	Oesophagus	Skin	
Salivary gland	Pancreas			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950004	Sex: Male	Status: Final phase sacrifice	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase				
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Heart		INFLAMMATORY CELL FOCI, Focal, Slight, Myocardial.		
Kidneys		NEPHROPATHY, Bilateral, Slight.		
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.		
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.		
		VASCULAR MINERALIZATION, Focal, Slight.		
Thyroid		ECTOPIC THYMIC TISSUE, Slight.		

Whole animal . . . No abnormalities detected

The following tissues are normal macroscopically:	Adrenals	Bronchi	Bone marrow	Brain
	Caecum	Cervical nodes	Colon	Duodenum
	Epididymides	Ileum	Jejunum	Mesenteric nodes
	Parathyroid gl.	Pituitary	Prostate	Rectum
	Sciatic nerve	Spinal cord	Spleen	Stomach
	Testes	Thymus	Trachea	Urinary bladder
	Aorta	Mammary area	Oesophagus	Skin
	Salivary gland	Pancreas		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950006	Sex: Male	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Cervical nodes . . . Abnormal size, Single, Enlarged/ 13x7x3mm		REACTIVE HYPERPLASIA, Mild.	
Heart		INFLAMMATORY CELL FOCI, Focal, Slight, Myocardial.	
Kidneys		NEPHROPATHY, Bilateral, Mild.	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
Spleen Abnormal shape, Swollen		Tissue is unremarkable.	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Colon	Duodenum	Epididymides
Ileum	Jejunum	Lungs	Mesenteric nodes
Parathyroid gl.	Pituitary	Prostate	Rectum
Sciatic nerve	Spinal cord	Stomach	Testes
Thymus	Thyroid	Trachea	Urinary bladder
Aorta	Mammary area	Oesophagus	Skin
Salivary gland	Pancreas		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950008 Sex: Male Group: 1 Dose level: 0.00 mg/kg/day
 Day of death: 92 Dosing phase Status: Final phase sacrifice
 Tissue Gross observations / Comments Microscopic observations / Comments
 Heart
 Liver
 Lungs

Whole animal . . . No abnormalities detected

The following tissues are normal
 macroscopically:
 Adrenals Bronchi Bone marrow Brain
 Caecum Cervical nodes Colon Duodenum
 Epididymides Ileum Jejunum Kidneys
 Mesenteric nodes Parathyroid gl. Pituitary Prostate
 Rectum Sciatic nerve Spinal cord Spleen
 Stomach Testes Thymus Thyroid
 Trachea Urinary bladder Aorta Mammary area
 Oesophagus Skin Salivary gland Pancreas

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950010		Sex: Male	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Heart		INFLAMMATORY CELL FOCI, Focal, Slight, Myocardial.		
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.		
		ALVEOLAR HAEMORRHAGE, Focal, Slight.		

Whole animal . . . No abnormalities detected

The following tissues are normal microscopically:		Bronchi	Bone marrow	Brain
		Cervical nodes	Colon	Duodenum
		Ileum	Jejunum	Kidneys
		Mesenteric nodes	Parathyroid gl.	Pituitary
		Rectum	Sciatic nerve	Spinal cord
		Stomach	Testes	Thymus
		Trachea	Urinary bladder	Aorta
		Oesophagus,	Skin	Salivary gland
		Pancreas		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950012		Sex: Male	Group: 1	Dose level: 0.00 mg/kg/day	
Day of death: 92 Dosing phase		Status: Final phase sacrifice			
Tissue	Gross observations / Comments	Microscopic observations / Comments			
Heart		INFLAMMATORY CELL FOCI, Focal, Slight, Myocardial.			
Kidneys		NEPHROPATHY, Bilateral, Slight.			
		CALCULI, Unilateral, Slight, Pelvic.			
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.			
Lungs		INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.			
		VASCULAR MINERALIZATION, Focal, Mild.			
Prostate		INFLAMMATORY CELL FOCI, Slight, Interstitial.			
Pancreas		CHRONIC INFLAMMATION, Focal, Slight.			
Whole animal	. . . No abnormalities detected				
The following tissues are normal					
microscopically:					
Adrenals	Bronchi	Bone marrow	Brain		
Caecum	Cervical nodes	Colon	Duodenum		
Epididymides	Ileum	Jejunum	Mesenteric nodes		
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve		
Spinal cord	Spleen	Stomach	Testes		
Thymus	Thyroid	Trachea	Urinary bladder		
Aorta	Mammary area	Oesophagus	Skin		
Salivary gland					

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950014	Sex: Male	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Heart		INFLAMMATORY CELL FOCI, Focal, Slight, Vascular.	
Kidneys		NEPHROPATHY, Unilateral, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Whole animal	No abnormalities detected		
The following tissues are normal microscopically:			
	Adrenals	Bronchi	Bone marrow
	Caecum	Cervical nodes	Colon
	Epididymides	Ileum	Jejunum
	Mesenteric nodes	Parathyroid gl.	Pituitary
	Rectum	Sciatic nerve	Spinal cord
	Stomach	Testes	Thymus
	Trachea	Urinary bladder	Aorta
	Oesophagus	Skin	Salivary gland
			Mammary area
			Pancreas

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950016		Sex: Male	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Heart		INFLAMMATORY CELL FOCI, Focal, Slight, Vascular.		
Kidneys		NEPHROPATHY, Bilateral, Slight.		
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.		
Lungs	Abnormal area(s), Multiple, Dark/ up to 5x4mm	INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.		
		ALVEOLAR HAEMORRHAGE, Focal, Mild.		
		ALVEOLAR EPITHELIALIZATION, Focal, Slight.		
Prostate		INFLAMMATORY CELL FOCI, Slight, Interstitial.		
Spleen	Abnormal shape, Swollen	Tissue is unremarkable.		
Thymus	Abnormal area(s), Multiple, Red, Pinpoint/ right lobe	Tissue is unremarkable.		
The following tissues are normal macroscopically:				
	Adrenals	Bronchi	Bone marrow	Brain
	Caecum	Cervical nodes	Colon	Duodenum
	Epididymides	Ileum	Jejunum	Mesenteric nodes
	Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
	Spinal cord	Stomach	Testes	Thyroid
	Trachea	Urinary bladder	Aorta	Mammary area
	Oesophagus	Skin	Salivary gland	Pancreas

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950018			Sex: Male	Group: 1	Dose level: 0.00 mg/kg/day	
Day of death: 92 Dosing phase			Status: Final phase sacrifice			
Tissue	Gross observations / Comments			Microscopic observations / Comments		
Kidneys				NEPHROPATHY, Bilateral, Slight.		
Liver				INFLAMMATORY CELL FOCI, Focal, Slight.		
Lungs	 Abnormal area(s), Single, Dark/ 20x3mm, right caudal lobe			INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.		
				ALVEOLAR HAEMORRHAGE, Focal, Mild.		
				ALVEOLAR EPITHELIALIZATION, Focal, Slight.		
				AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.		
Prostate				INFLAMMATORY CELL FOCI, Slight, Interstitial.		
Trachea				INFLAMMATORY CELL FOCI, Focal, Slight, Submucosal.		
The following tissues are normal microscopically:						
Adrenals		Bronchi		Bone marrow		Brain
Caecum		Cervical nodes		Colon		Duodenum
Epididymides		Heart		Ileum		Jejunum
Mesenteric nodes		Parathyroid gl.		Pituitary		Rectum
Sciatic nerve		Spinal cord		Spleen		Stomach
Testes		Thymus		Thyroid		Urinary bladder
Aorta		Mammary area		Oesophagus		Skin
Salivary gland		Pancreas				

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950020	Sex: Male	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Heart		INFLAMMATORY CELL FOCI, Focal, Slight, Myocardial.	
Kidneys		NEPHROPATHY, Bilateral, Slight.	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	

Whole animal . . . No abnormalities detected

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Ileum	Jejunum	Mesenteric nodes
Parathyroid gl.	Pituitary	Prostate	Rectum
Sciatic nerve	Spinal cord	Spleen	Stomach
Testes	Thymus	Thyroid	Trachea
Urinary bladder	Aorta	Mammary area	Oesophagus
Skin	Salivary gland	Pancreas	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950022	Sex: Male	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 58 Recovery phase	Status: Final phase sacrifice		

Tissue	Gross observations / Comments	Microscopic observations / Comments	

Kidneys	Abnormal area(s), Single, Pale/ 7x5mm, right	Tissue not examined microscopically.	
Liver	Abnormal size, Small	INFLAMMATORY CELL FOCI, Multifocal, Mild.	
Lungs		INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
Spleen		PIGMENTATION, Slight, Yellow/brown.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950024		Sex: Male	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 58 Recovery phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
			VASCULAR MINERALIZATION, Focal, Slight.	
Whole animal . . . No abnormalities detected				
The following tissues are normal microscopically:				
				Spleen

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950026		Sex: Male	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 58 Recovery phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Liver			CLEAR CELL CHANGE, Slight, Panlobular.	
Lungs			INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
Spleen			PIGMENTATION, Mild, Yellow/brown.	
Eyes	 Abnormal colour, Red/ sclera		Miscellaneous tissue not examined.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950028	Sex: Male	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 58 Recovery phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Cervical nodes	Abnormal area(s), Multiple, Red, Pinpoint	Tissue not examined microscopically.	
	Abnormal size, Single, Enlarged/ 9x5x2mm		
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		VASCULAR MINERALIZATION, Focal, Slight.	
Stomach	Abnormal size, Thickened/ glandular non glandular region	Tissue not examined microscopically.	
Skin	Subcutaneous mass(es), Mass 1, Firm/ 2x2x1mm, c/s pale, firm	Tissue not examined microscopically.	

The following tissues are normal microscopically: Spleen

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950030		Sex: Male	Group: 1	Dose level: 0.00 mg/kg/day	
Day of death: 58 Recovery phase		Status: Final phase sacrifice			
Tissue	Gross observations / Comments		Microscopic observations / Comments		
Liver	Abnormal size, Small		Tissue is unremarkable.		
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.		
			VASCULAR MINERALIZATION, Multifocal, Slight.		
Spleen	Abnormal shape, Swollen		PIGMENTATION, Slight, Yellow/brown.		
Skin	Subcutaneous mass(es), Mass 1, Pale, Firm/ 10x9x7mm, c/s green creamy		Tissue not examined microscopically.		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950032 Sex: Male Status: Final phase sacrifice Group: 2 Dose level: 0.03 mg/kg/day

Day of death: 92 Dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments

Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.

Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.

Thymus	Abnormal area(s), Multiple, Dark, Pinpoint/ right lobe	CONGESTION/HAEMORRHAGE, Slight.

The following tissues are normal
microscopically: Spleen

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950034	Sex: Male	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Epididymides . . . Abnormal size, Small		REDUCTION OF SPERM, Unilateral, Moderate.	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Testes Abnormal size, Small/ 11x8x7mm, left		TESTICULAR ATROPHY, Unilateral, Moderate.	
The following tissues are normal microscopically:			
		Spleen	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950036	Sex: Male	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		VASCULAR MINERALIZATION, Focal, Slight.	
Spleen	Abnormal shape, Swollen	Tissue is unremarkable.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950038		Sex: Male	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Liver			INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Spleen	 Abnormal shape, Swollen		Tissue is unremarkable.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950040	Sex: Male	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs	Abnormal area(s), Multiple, Pale, Pinpoint	INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	

The following tissues are normal Spleen
microscopically:

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950042	Sex: Male	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Cervical nodes	. . Abnormal size, Enlarged/ up to 11x6x2mm	REACTIVE HYPERPLASIA, Mild.	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
The following tissues are normal microscopically:			
		Spleen	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950044		Sex: Male	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Multifocal, Slight.		
Whole animal . . . No abnormalities detected				
The following tissues are normal microscopically:		Spleen		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950046		Sex: Male	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Liver			INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
			ALVEOLAR HAEMORRHAGE, Focal, Slight.	
Spleen	Abnormal shape, Swollen		Tissue is unremarkable.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950048 Sex: Male Status: Final phase sacrifice Group: 2 Dose level: 0.03 mg/kg/day

Day of death: 92 Dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments

Liver		INFLAMMATORY CELL FOCI, Focal, Slight.

Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.

Whole animal . . . No abnormalities detected

The following tissues are normal microscopically: Spleen

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950050	Sex: Male	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Cervical nodes	. . Abnormal size, Single, Enlarged/ 11x6x2mm	Tissue is unremarkable.	
Liver	 Abnormal size, Small	INFLAMMATORY CELL FOCI, Multifocal, Mild.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Mild.	
The following tissues are normal microscopically:		Spleen	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950052	Sex: Male	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
Skin	Mass(es) not confirmed, Mass 1, No abnormalities detected	Tissue is unremarkable.	

The following tissues are normal microscopically: Spleen

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950054		Sex: Male	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
Whole animal		. . No abnormalities detected		
The following tissues are normal		Spleen		
Microscopically:				

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950056	Sex: Male	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Cervical nodes	Abnormal size, Two, Enlarged/ up to 11x7x2mm	REACTIVE HYPERPLASIA, Slight.	
Liver	Abnormal area(s), Single, Pale/ 4x4mm, right median lobe	CHRONIC INFLAMMATION, Focal, Mild, Capsule.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	

The following tissues are normal microscopically:		Spleen	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950058	Sex: Male	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
		VASCULAR MINERALIZATION, Focal, Slight.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	

Whole animal . . . No abnormalities detected			

The following tissues are normal
microscopically: Spleen

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950060	Sex: Male	Status: Final phase sacrifice	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 92 Dosing phase				
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.		
Whole animal . . . No abnormalities detected				
The following tissues are normal				
microscopically:		Lungs	Spleen	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950062	Sex: Male	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	

Whole animal . . . No abnormalities detected

The following tissues are normal
microscopically: Spleen

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950064	Sex: Male	Status: Final phase sacrifice	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 92 Dosing phase				
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Cervical nodes	Abnormal size, Single, Enlarged/ 13x9x3mm	REACTIVE HYPERPLASIA, Moderate.		
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.		
		HEPATOCYTIC HYPERTROPHY, Focal, Slight, Centrilobular.		
Lungs		INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.		
The following tissues are normal microscopically:				
			Spleen	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950066		Sex: Male	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Cervical nodes	. . Abnormal size, Single, Enlarged/ 10x7x3mm		REACTIVE HYPERPLASIA, Mild.	
	Abnormal colour, Single, Red		CONGESTION/HAEMORRHAGE, Slight.	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs	 Abnormal area(s), Multiple, Pale, Pinpoint		INFLAMMATORY CELL FOCI, Slight, Perivascular, interstitial.	
			AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
The following tissues are normal microscopically:				
				Spleen

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950068	Sex: Male	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
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Tissue	Gross observations / Comments	Microscopic observations / Comments	
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Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs	Abnormal colour, Dark	INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Spleen		PIGMENTATION, Slight, Yellow/brown.	
Thymus	Abnormal colour, Red/ right lobe	CONGESTION/HAEMORRHAGE, Slight.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950070	Sex: Male	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
		HEPATOCYTIC HYPERTROPHY, Focal, Slight, Centrilobular.	
Spleen	Abnormal shape, Swollen	Tissue is unremarkable.	
Thymus	Abnormal area(s), Multiple, Red, Pinpoint	CONGESTION/HAEMORRHAGE, Mild.	
The following tissues are normal microscopically:			
		Lungs	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950072		Sex: Male	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Heart		INFLAMMATORY CELL FOCI, Focal, Slight, Myocardial.		
Kidneys		NEPHROPATHY, Bilateral, Mild.		
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.		
		HEPATO CYTIC HYPERTROPHY, Slight, Centrilobular.		
Thymus	Abnormal size, Small	PIGMENTATION, Slight, Yellow/brown.		

The following tissues are normal microscopically:

Adrenals	Bone marrow	Brain
Caecum	Colon	Duodenum
Epididymides	Jejunum	Lungs
Mesenteric nodes	Pituitary	Prostate
Rectum	Spinal cord	Spleen
Stomach	Thyroid	Trachea
Urinary bladder	Mammary area	Oesophagus
Skin	Pancreas	
	Salivary gland	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950074	Sex: Male	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Heart		INFLAMMATORY CELL FOCI, Focal, Slight, Myocardial.	
Kidneys		NEPHROPATHY, Bilateral, Slight.	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
		HEPATOCYTIC HYPERTROPHY, Slight, Panlobular.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Whole animal	No abnormalities detected		

The following tissues are normal microscopically:	Adrenals	Bronchi	Bone marrow	Brain
	Caecum	Cervical nodes	Colon	Duodenum
	Epididymides	Ileum	Jejunum	Mesenteric nodes
	Parathyroid gl.	Pituitary	Prostate	Rectum
	Sciatic nerve	Spinal cord	Spleen	Stomach
	Testes	Thymus	Thyroid	Trachea
	Urinary bladder	Aorta	Mammary area	Oesophagus
	Skin	Salivary gland	Pancreas	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950076		Sex: Male	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations	Comments	Microscopic observations / Comments	
Kidneys			NEPHROPATHY, Bilateral, Mild.	
Liver			INFLAMMATORY CELL FOCI, Multifocal, Slight.	
			HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
			VASCULAR MINERALIZATION, Focal, Slight.	
			ALVEOLAR HAEMORRHAGE, Focal, Slight.	

Whole animal . . . No abnormalities detected

The following tissues are normal microscopically:		Adrenals	Bronchi	Bone marrow	Brain
		Caecum	Cervical nodes	Colon	Duodenum
		Epididymides	Heart	Ileum	Jejunum
		Mesenteric nodes	Parathyroid gl.	Pituitary	Prostate
		Rectum	Sciatic nerve	Spinal cord	Spleen
		Stomach	Testes	Thymus	Thyroid
		Trachea	Urinary bladder	Aorta	Mammary area
		Oesophagus	Skin	Salivary gland	Pancreas

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950078	Sex: Male	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Cervical nodes . . . Abnormal size, Single, Enlarged/ 12x6x3mm		REACTIVE HYPERPLASIA, Moderate.	
Kidneys		NEPHROPATHY, Bilateral, Mild.	
Liver Abnormal size, Small/ caudal, caudate lobe		INFLAMMATORY CELL FOCI, Multifocal, Mild.	
Abnormal area(s), Single, Dark/ 5x5mm, caudal, caudate lobe		HEPATOCYTIC HYPERTROPHY, Mild, Panlobular.	
Lungs Abnormal area(s), Multiple, Dark/ up to 1x1mm, right lobes		PIGMENTATION, Moderate, Caudal caudate lobe.	
		CHOLANGITIS, Mild, Caudal caudate lobe.	
		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		ALVEOLAR HAEMORRHAGE, Focal, Slight.	
Prostate		INFLAMMATORY CELL FOCI, Moderate, Interstitial.	
Stomach Abnormal size, Thickened/ glandular region		CHRONIC INFLAMMATION, Focal, Mild, non-glandular region.	
Abnormal area(s), Single, Pale, Soft, Raised/ 15x6x5mm, non glandular region		OEDEMA, Moderate, non-glandular region.	
Thymus Abnormal colour, Dark		MUCOSAL ULCERATION, Focal, Slight, non-glandular region.	
Abnormal area(s), Multiple, Red/ up to 1x1mm		CONGESTION/HAEMORRHAGE, Slight.	
		PIGMENTATION, Slight.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950078	Sex: Male	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Trachea		INFLAMMATORY CELL FOCI, Slight, Submucosal.	
The following tissues are normal microscopically:			
Adrenals	Bronchi	Bone marrow	Brain
Caecum	Colon	Duodenum	Epididymides
Heart	Ileum	Jejunum	Mesenteric nodes
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
Spinal cord	Spleen	Testes	Thyroid
Urinary bladder	Aorta	Mammary area	Oesophagus
Skin	Salivary gland	Pancreas	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950080	Sex: Male	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Kidneys		NEPHROPATHY, Bilateral, Mild.	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
		HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular.	
Lungs		INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
Prostate		FRAGMENTS OF BONE, Focal, Slight.	
Whole animal	No abnormalities detected	INFLAMMATORY CELL FOCI, Slight, Interstitial.	
The following tissues are normal microscopically:			
Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Heart	Ileum	Jejunum
Mesenteric nodes	Parathyroid gl.	Pituitary	Rectum
Sciatic nerve	Spinal cord	Spleen	Stomach
Testes	Thymus	Thyroid	Trachea
Urinary bladder	Aorta	Mammary area	Oesophagus
Skin	Salivary gland	Pancreas	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950082		Sex: Male	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Heart			INFLAMMATORY CELL FOCI, Focal, Slight, Myocardial.	
Kidneys			NEPHROPATHY, Bilateral, Mild.	
Liver			INFLAMMATORY CELL FOCI, Multifocal, Slight.	
			HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Stomach	Abnormal size, Thickened/ glandular region		Tissue is unremarkable.	
The following tissues are normal microscopically:				
Adrenals		Bronchi	Bone marrow	Brain
Caecum		Cervical nodes	Colon	Duodenum
Epididymides		Ileum	Jejunum	Mesenteric nodes
Parathyroid gl.		Pituitary	Prostate	Rectum
Sciatic nerve		Spinal cord	Spleen	Testes
Thymus		Thyroid	Trachea	Urinary bladder
Aorta		Mammary area	Oesophagus	Skin
Salivary gland		Pancreas		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950084		Sex: Male	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Heart		INFLAMMATORY CELL FOCI, Focal, Slight, Myocardial.		
Kidneys		NEPHROPATHY, Bilateral, Slight.		
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.		
		HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular.		
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.		
		VASCULAR MINERALIZATION, Focal, Slight.		
Trachea		INFLAMMATORY CELL FOCI, Slight, Submucosal.		
Preputial gland		CHRONIC INFLAMMATION, Focal, Mild, Refers to Mass 1.		
Skin	Subcutaneous mass(es), Mass 1, Pale, Firm/ 5x4x3mm, c/s green soft	Tissue is unremarkable.		
			/ For Mass 1 see Preputial gland.	
The following tissues are normal microscopically:				
	Adrenals	Bronchi	Bone marrow	
	Caecum	Cervical nodes	Colon	
	Epididymides	Ileum	Jejunum	
	Parathyroid gl.	Pituitary	Prostate	
	Sciatic nerve	Spinal cord	Spleen	
	Testes	Thymus	Thyroid	
	Aorta	Mammary area	Oesophagus	
	Pancreas		Urinary bladder	
			Salivary gland	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950086	Sex: Male	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Heart		INFLAMMATORY CELL FOCI, Focal, Slight, Myocardial.	
Kidneys		MEDULLARY MINERALIZATION, Unilateral, Slight.	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
		HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular.	
Lungs	Abnormal area(s), Multiple, Pale, Pinpoint	INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
		ALVEOLAR HAEMORRHAGE, Focal, Mild.	
Prostate		INFLAMMATORY CELL FOCI, Slight, Interstitial.	
The following tissues are normal macroscopically:			
Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Ileum	Jejunum	Mesenteric nodes
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
Spinal cord	Spleen	Stomach	Testes
Thymus	Thyroid	Trachea	Urinary bladder
Aorta	Mammary area	Oesophagus	Skin
Salivary gland	Pancreas		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950088	Sex: Male	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Cervical nodes		REACTIVE HYPERPLASIA, Moderate.	
Kidneys		NEPHROPATHY, Unilateral, Slight.	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs		HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular.	
		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Stomach		CHRONIC INFLAMMATION, Mild, Glandular, non-glandular region.	
		OEDEMA, Mild, Glandular, non-glandular region.	

Whole animal . . . No abnormalities detected

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Colon	Duodenum	Epididymides
Heart	Ileum	Jejunum	Mesenteric nodes
Parathyroid gl.	Pituitary	Prostate	Rectum
Sciatic nerve	Spinal cord	Spleen	Testes
Thymus	Thyroid	Trachea	Urinary bladder
Aorta	Mammary area	Oesophagus	Skin
Salivary gland	Pancreas		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950090	Sex: Male	Status: Final phase sacrifice	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 92 Dosing phase				
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Cervical nodes		REACTIVE HYPERPLASIA, Mild.		
Kidneys		NEPHROPATHY, Bilateral, Slight.		
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.		
Lungs	Abnormal area(s), Multiple, Pale, Pinpoint	INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.		

AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
 FRAGMENTS OF BONE, Focal, Slight.
 ACUTE INFLAMMATION, Focal, Moderate.

Teeth Missing/ upper incisor, left

The following tissues are normal
 microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Colon	Duodenum	Epididymides
Heart	Ileum	Jejunum	Mesenteric nodes
Parathyroid gl.	Pituitary	Prostate	Rectum
Sciatic nerve	Spinal cord	Spleen	Stomach
Testes	Thymus	Thyroid	Trachea
Urinary bladder	Aorta	Mammary area	Oesophagus
Skin	Salivary gland	Pancreas	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950092		Sex: Male	Group: 4
Day of death: 58 Recovery phase		Status: Final phase sacrifice	
Tissue		Gross observations / Comments	Microscopic observations / Comments
Cervical nodes		Abnormal size, Single, Enlarged/ 9x7x4mm	Tissue not examined microscopically.
Liver			INFLAMMATORY CELL FOCI, Multifocal, Slight.
			HEPATOCYTIC HYPERTROPHY, Focal, Slight, Centrilobular.
Lungs			CLEAR CELL CHANGE, Slight, Periportal, Midzonal.
			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.
			/ Focal slight, yellow/brown macrophages were also seen.
Spleen			PIGMENTATION, Mild, Yellow/brown.
Eyes		Abnormal area(s), Single, Red/ 3x2mm, sclera	Miscellaneous tissue not examined.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950094	Sex: Male	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 58 Recovery phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Cervical nodes	. . Abnormal size, Single, Enlarged/ 11x7x3mm	Tissue not examined microscopically.	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
		HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		VASCULAR MINERALIZATION, Focal, Slight.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
Spleen		PIGMENTATION, Slight, Yellow/brown.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950096	Sex: Male	Status: Final phase sacrifice	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 58 Recovery phase				
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Liver				INFLAMMATORY CELL FOCI, Multifocal, Slight.
				HEPATOCYTIC HYPERTROPHY, Focal, Slight, Centrilobular.
				CLEAR CELL CHANGE, Slight, Periportal, Midzonal.
Lungs	Abnormal area(s), Multiple, Pale/ up to 2x1mm			INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.
				AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
Spleen				PIGMENTATION, Mild, Yellow/brown.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950098	Sex: Male	Status: Final phase sacrifice	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 58 Recovery phase				
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.		
		HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular.		
		CLEAR CELL CHANGE, Mild, Periportal, Midzonal.		
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.		
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Multifocal, Moderate.		
Spleen		PIGMENTATION, Slight, Yellow/brown.		
Whole animal . . . No abnormalities detected				

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950100		Sex: Male	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 58 Recovery phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Cervical nodes	. . Abnormal size, Single, Enlarged/ 11x8x4mm		Tissue not examined microscopically.	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
			HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular.	
			CLEAR CELL CHANGE, Slight, Periportal, Midzonal.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
			VASCULAR MINERALIZATION, Focal, Slight.	
			AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Mild.	
Spleen			PIGMENTATION, Mild, Yellow/brown.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950001		Sex: Female	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Cervical nodes			CONGESTION/HAEMORRHAGE, Slight.	
Kidneys			NEPHROPATHY, Bilateral, Slight.	
Liver			INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Thymus	 Abnormal area(s), Single, Dark/ 4x4mm, right lobe		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
		Tissue is unremarkable.		

The following tissues are normal microscopically:				
Adrenals	Bronchi	Bone marrow	Brain	
Caecum	Cervix	Colon	Duodenum	
Heart	Ileum	Jejunum	Mesenteric nodes	
Ovaries	Oviducts	Parathyroid gl.	Pituitary	
Rectum	Sciatic nerve	Spinal cord	Spleen	
Stomach	Thyroid	Trachea	Urinary bladder	
Uterus	Aorta	Mammary area	Oesophagus	
Skin	Salivary gland	Pancreas		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950003 Sex: Female Group: 1 Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase Status: Final phase sacrifice
Tissue Gross observations / Comments Microscopic observations / Comments
Liver
Lungs
Uterus
Whole animal No abnormalities detected

The following tissues are normal
microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Kidneys	Mesenteric nodes	Ovaries	Oviducts
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
Spinal cord	Spleen	Stomach	Thymus
Thyroid	Trachea	Urinary bladder	Aorta
Mammary area	Oesophagus	Skin	Salivary gland
Pancreas			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950005	Sex: Female	Status: Final phase sacrifice	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase				
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Kidneys		NEPHROPATHY, Bilateral, Slight.		
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.		
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.		
		VASCULAR MINERALIZATION, Focal, Slight.		
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.		
Ovaries	Abnormal size, Enlarged/ up to 6mm diam	Tissue is unremarkable.		
Spleen		PIGMENTATION, Slight, Yellow/brown.		
Thymus	Abnormal size, Small	Tissue is unremarkable.		

The following tissues are normal microscopically:				
Adrenals	Bronchi	Bone marrow	Brain	
Caecum	Cervical nodes	Cervix	Colon	
Duodenum	Heart	Ileum	Jejunum	
Mesenteric nodes	Oviducts	Parathyroid gl.	Pituitary	
Rectum	Sciatic nerve	Spinal cord	Stomach	
Thyroid	Trachea	Urinary bladder	Uterus	
Aorta	Mammary area	Oesophagus	Skin	
Salivary gland	Pancreas			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950007		Sex: Female	Group: 1
Day of death: 92 Dosing phase		Status: Final phase sacrifice	
Dose level: 0.00 mg/kg/day			
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Cervical nodes	Abnormal colour, Single, Dark	CONGESTION/HAEMORRHAGE, Mild.	
Kidneys		NEPHROPATHY, Bilateral, Slight.	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	

The following tissues are normal microscopically:

Adrenals	Bone marrow	Brain
Caecum	Colon	Duodenum
Heart	Jejunum	Mesenteric nodes
Ovaries	Parathyroid gl.	Pituitary
Rectum	Spinal cord	Spleen
Stomach	Thyroid	Trachea
Urinary bladder	Aorta	Mammary area
Oesophagus	Salivary gland	Pancreas

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950009	Sex: Female	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Kidneys		NEPHROPATHY, Unilateral, Slight.	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Eyes	Abnormal area(s), Ruptured/ right	ULCERATION OF THE CORNEA, Unilateral, Marked.	
		ACUTE INFLAMMATION, Unilateral, Marked, Cornea, Anterior Chamber, sclera.	
The following tissues are normal microscopically:			
Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Mesenteric nodes	Ovaries	Oviducts	Parathyroid gl.
Pituitary	Rectum	Sciatic nerve	Spinal cord
Spleen	Stomach	Thymus	Thyroid
Trachea	Urinary bladder	Uterus	Aorta
Mammary area	Oesophagus	Skin	Salivary gland
Pancreas			

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950011		Sex: Female	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Cervical nodes	. . Abnormal colour, Dark	CONGESTION/HAEMORRHAGE, Mild.		
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.		
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.		
The following tissues are normal microscopically:				
	Adrenals	Bronchi	Bone marrow	Brain
	Caecum	Cervix	Colon	Duodenum
	Heart	Ileum	Jejunum	Kidneys
	Mesenteric nodes	Ovaries	Oviducts	Parathyroid gl.
	Pituitary	Rectum	Sciatic nerve	Spinal cord
	Spleen	Stomach	Thymus	Thyroid
	Trachea	Urinary bladder	Uterus	Aorta
	Mammary area	Oesophagus	Skin	Salivary gland
	Pancreas			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950013		Sex: Female	Group: 1	Dose level: 0.00 mg/kg/day		
Day of death: 92 Dosing phase		Status: Final phase sacrifice				
Tissue	Gross observations / Comments		Microscopic observations / Comments			
Cervical nodes	. . Abnormal colour, Two, Red		CONGESTION/HAEMORRHAGE, Slight.			
Kidneys			NEPHROPATHY, Bilateral, Mild.			
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.			
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.			
Pituitary	 Abnormal shape, Swollen		Tissue is unremarkable.			
The following tissues are normal microscopically:						
Adrenals		Bronchi		Brain		
Caecum		Cervix		Duodenum		
Heart		Ileum		Mesenteric nodes		
Ovaries		Oviducts		Parathyroid gl.		
Sciatic nerve		Spinal cord		Rectum		
Thymus		Thyroid		Stomach		
Uterus		Aorta		Urinary bladder		
Skin		Salivary gland		Oesophagus		
				Mammary area		
				Pancreas		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950015		Sex: Female	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Cervical nodes			CONGESTION/HAEMORRHAGE, Slight.	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Ovaries	 Abnormal size, Enlarged/ up to 6x5x3mm		Tissue is unremarkable.	
Thymus	 Abnormal colour, Red/ right lobe		Tissue is unremarkable.	
Uterus	 Abnormal size, Thickened		Tissue is unremarkable.	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervix	Colon	Duodenum
Heart	Ileum	Jejunum	Kidneys
Mesenteric nodes	Oviducts	Parathyroid gl.	Pituitary
Rectum	Sciatic nerve	Spinal cord	Spleen
Stomach	Thyroid	Trachea	Urinary bladder
Aorta	Mammary area	Oesophagus	Skin
Salivary gland	Pancreas		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950017		Sex: Female	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Cervical nodes			CONGESTION/HAEMORRHAGE, Mild.	
Kidneys			NEPHROPATHY, Unilateral, Slight.	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
				AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.

Whole animal . . . No abnormalities detected

The following tissues are normal microscopically:		Adrenals	Bronchi	Bone marrow	Brain
		Caecum	Cervix	Colon	Duodenum
		Heart	Ileum	Jejunum	Mesenteric nodes
		Ovaries	Oviducts	Parathyroid gl.	Pituitary
		Rectum	Sciatic nerve	Spinal cord	Spleen
		Stomach	Thymus	Thyroid	Trachea
		Urinary bladder	Uterus	Aorta	Mammary area
		Oesophagus	Skin	Salivary gland	Pancreas

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950019	Sex: Female	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 92 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	

Whole animal . . . No abnormalities detected

The following tissues are normal microscopically:	Adrenals	Bronchi	Bone marrow	Brain
	Caecum	Cervical nodes	Cervix	Colon
	Duodenum	Heart	Ileum	Jejunum
	Kidneys	Mesenteric nodes	Ovaries	Oviducts
	Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
	Spinal cord	Spleen	Stomach	Thymus
	Thyroid	Trachea	Urinary bladder	Uterus
	Aorta	Mammary area	Oesophagus	Skin
	Salivary gland	Pancreas		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950021		Sex: Female	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 58 Recovery phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Adrenals	Abnormal area (s), Multiple, Dark, Pinpoint		Tissue not examined microscopically.	
Cervical nodes	Abnormal size, Single, Enlarged/ 11x8x2mm		Tissue not examined microscopically.	
Liver	Abnormal size, Small		INFLAMMATORY CELL FOCI, Focal, Slight.	
			CLEAR CELL CHANGE, Slight, Panlobular.	
Spleen			PIGMENTATION, Slight, Yellow/brown.	
Skin	Subcutaneous mass(es), Mass 1, Firm/ 17x11x6mm, c/s pale, firm		Tissue not examined microscopically.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950023	Sex: Female	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 58 Recovery phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
		CLEAR CELL CHANGE, Slight, Panlobular.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Multifocal, Slight.	
Spleen		PIGMENTATION, Mild, Yellow/brown.	
Whole animal	No abnormalities detected		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950025		Sex: Female	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 58 Recovery phase		Status: Final phase sacrifice		
Tissue		Gross observations / Comments	Microscopic observations / Comments	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
			CLEAR CELL CHANGE, Slight, Panlobular.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
			VASCULAR MINERALIZATION, Focal, Mild.	
Spleen			PIGMENTATION, Slight, Yellow/brown.	
Whole animal . . .		No abnormalities detected		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950027		Sex: Female	Group: 1	
Day of death: 58 Recovery phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments		Dose level: 0.00 mg/kg/day
Cervical nodes	. . Abnormal size, Single, Enlarged/ 10x5x2mm	Tissue not examined microscopically.		
Liver	 Abnormal size, Small	INFLAMMATORY CELL FOCI, Focal, Slight.		
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.		
Spleen		PIGMENTATION, Slight, Yellow/brown.		
Uterus	 Abnormal size, Distended/ 7mm diam	Tissue not examined microscopically.		
	Abnormal contents, Clear, Fluid			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950029		Sex: Female	Group: 1	Dose level: 0.00 mg/kg/day
Day of death: 58 Recovery phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Liver	Abnormal size, Small	INFLAMMATORY CELL FOCI, Focal, Slight.		
Lungs		CLEAR CELL CHANGE, Slight, Panlobular.		
		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.		
		ALVEOLAR HAEMORRHAGE, Focal, Slight.		
Spleen		PIGMENTATION, Mild, Yellow/brown.		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950031	Sex: Female	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, slight.	
Whole animal	No abnormalities detected		
The following tissues are normal microscopically:	Spleen		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950033	Sex: Female	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver	Abnormal colour, Red	INFLAMMATORY CELL FOCI, Multifocal, Slight.	
	Abnormal shape, Swollen		
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	

The following tissues are normal
microscopically: Spleen

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950035	Sex: Female	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Cervical nodes . . Abnormal colour, Dark		CONGESTION/HAEMORRHAGE, Mild.	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Mild.	
Lungs Abnormal area(s), Multiple, Pale, Pinpoint		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Spleen Abnormal shape, Swollen		Tissue is unremarkable.	
Eyes Abnormal area(s), Ruptured/ right		PHTHISIS BULBI, Unilateral, Marked.	
Ears Abnormal area(s), Ruptured/ right		HAEMORRHAGE, Focal, Mild, Auricle, Connective tissue.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950037		Sex: Female	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 93 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Liver			INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
Spleen	 Abnormal shape, Swollen		Tissue is unremarkable.	
Thymus	 Abnormal size, Small		Tissue is unremarkable.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950039		Sex: Female	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 93 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Cervical nodes	. . Abnormal colour, Red		CONGESTION/HAEMORRHAGE, Mild.	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
			PIGMENTATION, Slight, Yellow/brown, Kupffer's cells.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Spleen			PIGMENTATION, Slight, Yellow/brown.	
Eyes	 Abnormal area(s), Ruptured/ left		Tissue is unremarkable.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950041	Sex: Female	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 93 Dosing phase		Status: Final phase sacrifice	
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
Pituitary	Abnormal shape, Swollen	Tissue is unremarkable.	
Spleen		PIGMENTATION, Slight, Yellow/brown.	
Eyes	Abnormal area(s), Ruptured/ left	PHTHISIS BULBI, Unilateral, Marked.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950043		Sex: Female	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 93 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Cervical nodes	. . Abnormal size, Single, Enlarged/ 11x7x3mm		REACTIVE HYPERPLASIA, Mild.	
	Abnormal colour, Two, Red		CONGESTION/HAEMORRHAGE, Mild.	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
Uterus	 Abnormal size, Distended/ 5mm diam		ALVEOLAR HAEMORRHAGE, Focal, Slight.	
	Abnormal contents, Clear, Fluid		HYDROMETRA, Mild.	
The following tissues are normal microscopically:				
			Spleen	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950045	Sex: Female	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Whole animal . . .	No abnormalities detected		
The following tissues are normal microscopically:		Spleen	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950047	Sex: Female	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.
Lungs	Abnormal area(s), Single, Dark, 6x6mm, left lobe		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.
			ALVEOLAR HAEMORRHAGE, Focal, Slight.
Spleen			PIGMENTATION, Mild, Yellow/brown.

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950049		Sex: Female	Group: 2	Dose level: 0.03 mg/kg/day
Day of death: 93 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Cervical nodes	. . Abnormal colour, Red		CONGESTION/HAEMORRHAGE, Slight.	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
			ALVEOLAR EPITHELIALIZATION, Focal, Slight.	
			AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
Spleen			PIGMENTATION, Slight, Yellow/brown.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950051		Sex: Female	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 93 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Cervical nodes	. . Abnormal colour, Red		CONGESTION/HAEMORRHAGE, Mild.	
Abnormal size, Enlarged/ up to 11x5x6mm				
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
Spleen			AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight. PIGMENTATION, Slight, Yellow/brown.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950053		Sex: Female	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 93 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Cervix	Abnormal colour, Red		Tissue is unremarkable.	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
			ALVEOLAR EPITHELIALIZATION, Focal, Slight.	
			AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
Pituitary	Abnormal shape, Swollen		Tissue is unremarkable.	
The following tissues are normal microscopically:		Spleen		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950055	Sex: Female	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		ALVEOLAR HAEMORRHAGE, Focal, Slight.	
Eyes	Abnormal area(s), Ruptured/ left	Tissue is unremarkable.	

The following tissues are normal		Spleen	
microscopically:			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950057		Sex: Female	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 93 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Liver			INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs	Abnormal area(s), Multiple, Pale, Pinpoint		PIGMENTATION, Slight, Yellow/brown, Kupffer's cells.	
Spleen			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
			PIGMENTATION, Slight, Yellow/brown.	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950059	Sex: Female	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
Uterus	Abnormal size, Thickened	Tissue is unremarkable.	
The following tissues are normal			
microscopically:			Spleen

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950061		Sex: Female	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 93 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Liver			INFLAMMATORY CELL FOCI, Multifocal, Slight.	
			HEPATOCYTIC HYPERTROPHY, Focal, Slight, Centrilobular.	
			PIGMENTATION, Slight, Yellow/brown, Kupffer's cells, Intrahepatocyte	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
			AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
Spleen			PIGMENTATION, Slight, Yellow/brown.	
Whole animal	. . . No abnormalities detected			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950063	Sex: Female	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Multifocal, Slight.	
Uterus	Abnormal contents, Clear, Fluid	HYDROMETRA, Mild.	

Abnormal size, Distended/ 4mm diam

The following tissues are normal microscopically: Spleen

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950065	Sex: Female	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	

Whole animal . . . No abnormalities detected

The following tissues are normal microscopically:	Spleen

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950067	Sex: Female	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs		HEPATOCYTIC HYPERTROPHY, Focal, Slight, Centrilobular.	
Whole animal	No abnormalities detected	INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
The following tissues are normal			
microscopically:			
Spleen			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950069	Sex: Female	Status: Final phase sacrifice	Group: 3	Dose level: 0.13 mg/kg/day
Day of death: 93 Dosing phase				
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.		
Lungs		INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.		
Spleen		PIGMENTATION, Slight, Yellow/brown.		
Whole animal	. . . No abnormalities detected			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950071		Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 93 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Cervical nodes	. . Abnormal size, Single, Enlarged/ 12x7x4mm		REACTIVE HYPERPLASIA, Mild.	
	Abnormal colour, Single, Red		CONGESTION/HAEMORRHAGE, Slight.	
Kidneys			NEPHROPATHY, Bilateral, Slight.	
Liver			INFLAMMATORY CELL FOCI, Multifocal, Slight.	
			HEPATOCYTIC HYPERTROPHY, Mild, Panlobular.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Ovaries	 Abnormal size, Enlarged/ up to 7x5x3mm		Tissue is unremarkable.	
The following tissues are normal microscopically:				
	Adrenals	Bronchi	Bone marrow	Brain
	Caecum	Cervix	Colon	Duodenum
	Heart	Ileum	Jejunum	Mesenteric nodes
	Oviducts	Parathyroid gl.	Pituitary	Rectum
	Sciatic nerve	Spinal cord	Spleen	Stomach
	Thymus	Thyroid	Trachea	Urinary bladder
	Uterus	Aorta	Mammary area	Oesophagus
	Skin	Salivary gland	Pancreas	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950073	Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
		HEPATOCYTIC HYPERTROPHY, Slight, Panlobular.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Multifocal, Slight.	
Uterus	Abnormal size, Distended/ 5mm diam	HYDROMETRA, Mild.	

Abnormal contents, Clear, Fluid

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Kidneys	Mesenteric nodes	Ovaries	Oviducts
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
Spinal cord	Spleen	Stomach	Thymus
Thyroid	Trachea	Urinary bladder	Aorta
Mammary area	Oesophagus	Skin	Salivary gland
Pancreas			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950075	Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
		HEPATOCYTIC HYPERTROPHY, Slight, Panlobular.	
		PIGMENTATION, Slight, Yellow/brown, Kupffer's cells, Intrahepatocyte	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	

Whole animal . . . No abnormalities detected

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Kidneys	Mesenteric nodes	Ovaries	Oviducts
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
Spinal cord	Spleen	Stomach	Thymus
Thyroid	Trachea	Urinary bladder	Uterus
Aorta	Mammary area	Oesophagus	Skin
Salivary gland	Pancreas		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950077	Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Kidneys		NEPHROPATHY, Bilateral, Mild.	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
		HEPATOCYTIC HYPERTROPHY, Slight, Panlobular.	
		PIGMENTATION, Slight, Yellow/brown, Kupffer's cells.	
Lungs	Abnormal colour, Dark	INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
Pituitary	Abnormal shape, Swollen	Tissue is unremarkable.	
Uterus		HYDROMETRA, Mild.	
The following tissues are normal microscopically:			
Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Mesenteric nodes	Ovaries	Oviducts	Parathyroid gl.
Rectum	Sciatic nerve	Spinal cord	Spleen
Stomach	Thymus	Thyroid	Trachea
Urinary bladder	Aorta	Mammary area	Oesophagus
Skin	Salivary gland	Pancreas	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950079	Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Heart		INFLAMMATORY CELL FOCI, Focal, Slight, Vascular.	
Kidneys		NEPHROPATHY, Bilateral, Slight.	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
		HEPATOCYTIC HYPERTROPHY, Mild, Panlobular.	
Uterus	Abnormal size, Distended/ 7mm diam	HYDROMETRA, Moderate.	
	Abnormal contents, Clear, Fluid		

The following tissues are normal microscopically:	Adrenals	Bronchi	Bone marrow	Brain
	Caecum	Cervical nodes	Cervix	Colon
	Duodenum	Ileum	Jejunum	Lungs
	Mesenteric nodes	Ovaries	Oviducts	Parathyroid gl.
	Pituitary	Rectum	Sciatic nerve	Spinal cord
	Spleen	Stomach	Thymus	Thyroid
	Trachea	Urinary bladder	Aorta	Mammary area
	Oesophagus	Skin	Salivary gland	Pancreas

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950081	Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Kidneys		NEPHROPATHY, Bilateral, Mild.	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
Spleen		PIGMENTATION, Slight, Yellow/brown.	
Uterus	Abnormal size, Distended/ 6mm daim	HYDROMETRA, Moderate.	
	Abnormal contents, Clear, Fluid		

The following tissues are normal microscopically:

Adrenals	Bone marrow	Brain
Caecum	Cervix	Colon
Duodenum	Ileum	Jejunum
Mesenteric nodes	Oviducts	Parathyroid gl.
Pituitary	Sciatic nerve	Spinal cord
Stomach	Thyroid	Trachea
Urinary bladder	Mammary area	Oesophagus
Skin	Pancreas	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950083	Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Mild.	
		HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
Parathyroid gl.		Tissue is missing.	
Spleen		PIGMENTATION, Slight, Yellow/brown.	
Thymus		CONGESTION/HAEMORRHAGE, Slight.	
Thyroid		Tissue is missing.	
Whole animal	No abnormalities detected		

The following tissues are normal microscopically:		Adrenals	Bronchi	Bone marrow	Brain
		Caecum	Cervical nodes	Cervix	Colon
		Duodenum	Heart	Ileum	Jejunum
		Kidneys	Mesenteric nodes	Ovaries	Oviducts
		Pituitary	Rectum	Sciatic nerve	Spinal cord
		Stomach	Trachea	Urinary bladder	Uterus
		Aorta	Mammary area	Oesophagus	Skin
		Salivary gland	Pancreas		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950085	Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 93 Dosing phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Mild.	
		HEPATOCYTTIC HYPERTROPHY, Mild, Panlobular.	
		HEPATOCYTTIC NECROSIS, Focal, Mild.	
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
Pituitary	Abnormal shape, Swollen	Tissue is unremarkable.	
Urinary bladder		INFLAMMATORY CELL FOCI, Focal, Slight, Submucosal.	
The following tissues are normal microscopically:			
Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Kidneys	Mesenteric nodes	Ovaries	Oviducts
Parathyroid gl.	Rectum	Sciatic nerve	Spinal cord
Spleen	Stomach	Thymus	Thyroid
Trachea	Uterus	Aorta	Mammary area
Oesophagus	Skin	Salivary gland	Pancreas

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950087		Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 93 Dosing phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments		
Cervical nodes	. Abnormal colour, Single, Red	CONGESTION/HAEMORRHAGE, Mild.		
Heart		VALVULAR HEMATOCYST(S), Focal, Mild.		
Kidneys		NEPHROPATHY, Bilateral, Slight.		
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.		
		HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular.		
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.		
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.		
Spleen		PIGMENTATION, Slight, Yellow/brown.		
The following tissues are normal microscopically:				
Adrenals	Bronchi	Bone marrow	Brain	
Caecum	Cervix	Colon	Duodenum	
Ileum	Jejunum	Mesenteric nodes	Ovaries	
Oviducts	Parathyroid gl.	Pituitary	Rectum	
Sciatic nerve	Spinal cord	Stomach	Thymus	
Thyroid	Trachea	Urinary bladder	Uterus	
Aorta	Mammary area	Oesophagus	Skin	
Salivary gland	Pancreas			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950089 Sex: Female Status: Final phase sacrifice Group: 4 Dose level: 0.50 mg/kg/day

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Bilateral, Slight.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.
		HEPATOCYTIC HYPERTROPHY, Slight, Panlobular.
Lungs		INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Multifocal, Slight.

Pituitary Abnormal shape, Swollen

Spleen

Tissue is unremarkable.

PIGMENTATION, Slight, Yellow/brown.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Mesenteric nodes	Ovaries	Oviducts	Parathyroid gl.
Rectum	Sciatic nerve	Spinal cord	Stomach
Thymus	Thyroid	Trachea	Urinary bladder
Uterus	Aorta	Mammary area	Oesophagus
Skin	Salivary gland	Pancreas	

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950091		Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 58 Recovery phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Liver			INFLAMMATORY CELL FOCI, Focal, Slight.	
Lungs			INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
Spleen			PIGMENTATION, Slight, yellow/brown.	
Whole animal		. . . No abnormalities detected		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950093	Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 58 Recovery phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Focal, Slight.	
		HEPATOCYTIC HYPERTROPHY, Slight, Panlobular.	
		PIGMENTATION, Slight, Yellow/brown, Kupffer's cells, Intrahepatocyte	
Lungs		INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
Spleen		PIGMENTATION, Mild, Yellow/brown.	
Whole animal	No abnormalities detected		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950095	Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 58 Recovery phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
		HEPATOCYTIC HYPERTROPHY, Mild, Panlobular.	
		PIGMENTATION, Slight, Yellow/brown, Kupffer's cells	
Lungs		INFLAMMATORY CELL FOCI, Mild, Perivascular, Interstitial.	
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.	
Spleen		PIGMENTATION, Mild, Yellow/brown.	
Whole animal	No abnormalities detected		

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950097		Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 58 Recovery phase		Status: Final phase sacrifice		
Tissue	Gross observations / Comments		Microscopic observations / Comments	
Liver			INFLAMMATORY CELL FOCI, Multifocal, Slight.	
			HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular.	
Lungs			INFLAMMATORY CELL FOCI, Slight, Perivascular, Interstitial.	
			AGGREGATIONS OF ALVEOLAR MACROPHAGES, Multifocal, Mild.	
Spleen			PIGMENTATION, Slight, Yellow/brown.	
Whole animal	. . . No abnormalities detected			

REDACTED AS TO TRADE NAMES

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

APPENDIX 11 - Macroscopic and microscopic observations - Individual data

STUDY NO.: 41950

Animal: 41950099	Sex: Female	Group: 4	Dose level: 0.50 mg/kg/day
Day of death: 58 Recovery phase	Status: Final phase sacrifice		
Tissue	Gross observations / Comments	Microscopic observations / Comments	
Adrenals	Abnormal size, Small/ 2mm diam, left	Tissue not examined microscopically.	
Cervical nodes	Abnormal colour, Red	Tissue not examined microscopically.	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight.	
		HEPATOCYTIC HYPERTROPHY, Focal, Slight, Centrilobular.	
Eyes	Abnormal colour, Dark red/ sclera, right	Miscellaneous tissue not examined.	
The following tissues are normal microscopically:			
	Lungs	Spleen	

13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM I - Computer abbreviations and symbols

STUDY NO.: 41950

Abbreviations	Parameter 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
PHOS	PHOSPHORUS	mg/dl
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
TRI	TRIGLYCERIDES	mg/dl
ALB	ALBUMIN	g/dl
GLO	GLOBULIN	g/dl
AGR	ALBUMIN/GLOBULIN RATIO	
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

**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

ADDENDUM I - Computer abbreviations and symbols

STUDY NO.: 41950

Abbreviations	Parameter 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	

**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

ADDENDUM II - Abbreviations of neurotoxicity tests

STUDY NO.: 41950

Abbreviations	Parameter names	Key
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
BW		Body weight

**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

ADDENDUM II - Abbreviations of neurotoxicity tests

STUDY NO.: 41950

Abbreviations	Parameter names	Key
STIMULUS REACTIVITY		
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)
COUN	COUNTER DISPLAY	The number of times the animal crosses the beam of the photoelectric cell.

 13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED
BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM III - Analytical method and validation report for formulation analysis and formulation
analysis

STUDY NO.: 41950

**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

ADDENDUM III - Analytical method and validation report for formulation analysis
Determination in water with LC-MS/MS detection

STUDY NO.: 41950

SAFETY

WARNING AND SAFETY PRECAUTIONS

Organic solvents - all organic solvents must be treated as potentially hazardous and all procedures using them must be performed in a fume cupboard.

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

(synonymous:) is a product developed by the Sponsor.

1.

SCOPE

This method of analysis describes the analysis of A Frazione 10 in water.

2.

FIELD OF APPLICATION

The method is described to be used for formulated product in water. The range of application is from 0.003 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**

Methanol HPLC grade (Baker 8402)

Water HPLC grade (produced by EASYPURE)

7.2 **Solutions**

Mobile phase A: Methanol

7.3 **Standard solutions**

[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.

[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).

[REDACTED] STOCK REC BASSO (extension to validation):
1 ml of STOCK A is transferred into a 15 ml volumetric flask and dissolved with water obtaining a 2.66 µg/ml solution of [REDACTED]
[REDACTED]

8.

APPARATUS

Analytical balance	Mettler AT 261 Delta range or equivalent
HPLC system	Agilent 1100 series
Detector	LC-MS/MS
Software	Analyst
Printer	HP Laser Jet 4050 Series PCL6
Precolumn	Phenomenex C18 ODS 4 mm x 2 mm ID
HPLC microvials	
Pasteur pipettes	
Volumetric pipettes	
Common glassware	

9.

SAMPLING AND SAMPLES

Nature of the Sample; Samples shall be such as to enable the detection of substance in the relevant formulations.

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 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:

Step	Action	Expected			
		0 mg/ml	0.03 mg/ml	0.013 mg/ml	0.05 mg/ml
1	transfer	1 ml	1 ml	1 ml	1 ml
	dilute to	25 ml	25 ml	100 ml	100 ml
2	transfer				1ml
	dilute to				5 ml

For other concentrations samples will be prepared with an appropriate dilution.

Transfer into HPLC vials.

10.3 Recovery samplesLow 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).

Extension to validation (0.003 mg/ml in water):

Six dilution are performed from STOCK REC BASSO, 1 ml of this solution is transferred into a 25 ml volumetric flask and diluted with water

Transfer into HPLC vials.

10.4

LC-MS/MS

10.4.1

The following HPLC system is set up:

Precolumn : Phenomenex C18 ODS 4 mm * 2 mm ID
 Mobile phase : Eluent A: Methanol
 Flow : 0.2 ml/min
 Autosampler : +4°C
 Injection vol. : 10 µl
 Run time : ~ 2 minutes
 Retention time : ~ 30 sec.

10.4.2

Mass parameters:

Scan type : MRM
 Polarity : positive

Precursor Ion Q1 Mass (m/z)	Product Ion Q3 Mass (m/z)
344.7	84.9
344.7	112.8
344.7	229.0
295.0	84.6
295.0	113.0
295.0	229.1

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 = peak area

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

_____ 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

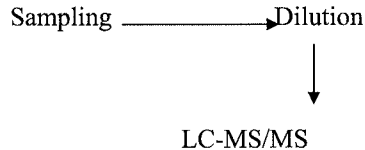
13. NOTES ON PROCEDURE

Not applicable

14. TEST REPORT

Not applicable

15. SCHEMATIC REPRESENTATION OF PROCEDURE



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]
[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	0.0502	100.06	1.37
	0.0503			
	0.0510			
	0.0494			
	0.0494			
	0.0506			
0.8109	0.8184	0.8081	99.65	1.20
	0.8157			
	0.7953			
	0.7972			
	0.8129			
	0.8091			

18.

EXTENSION TO VALIDATION

18.1

Accuracy and precision

Sextuplicates at the following concentration were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
mg/ml	mg/ml	Mean (mg/ml)	%	CV %
0.002696	0.002638 0.002664 0.002736 0.002659 0.002736 0.002739	0.002695	99.97	1.72

**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

ADDENDUM III - Summary of the validation

STUDY NO.: 41950

LEVEL mg/ml	ACCURACY %	CV %
0.002696	99.97	1.72
0.0502	100.06	1.37
0.8109	99.65	1.20

**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

ADDENDUM III - Formulation analysis - Pre-treatment formulation - Content check

STUDY NO.: 41950

Group	Sex	Intended Concentration mg/ml	Found Concentration mg/ml	Recovery %	Recovery Limits %
1	M-F	0	0	-	-
2	M-F	0.003	0.002922	97.39	95 -105
3	M-F	0.013	0.01267	97.45	95 -105
4	M-F	0.05	0.05006	100.12	95 -105

**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

ADDENDUM III - Formulation analysis - Day 1 - Content check

STUDY NO.: 41950

Group	Sex	Intended Concentration mg/ml	Found Concentration mg/ml	Recovery %	Recovery Limits %
1	M-F	0	0	-	-
2	M-F	0.003	0.003	103.4	95 -105
3	M-F	0.013	0.013	102.3	95 -105
4	M-F	0.05	0.049	98.69	95 -105

**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

ADDENDUM III - Formulation analysis - Day 1 of toxicokinetic group (Week 7 of main groups) -
Content check

STUDY NO.: 41950

Group	Sex	Intended Concentration mg/ml	Found Concentration mg/ml	Recovery %	Recovery Limits %
1	M-F	0	0	-	-
2	M-F	0.003	0.003	101.2	95 -105
3	M-F	0.013	0.013	98.40	95 -105
4-5	M-F	0.05	0.049	98.02	95 -105

**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

ADDENDUM III - Formulation analysis - Week 13 - Content check

STUDY NO.: 41950

Group	Sex	Intended Concentration mg/ml	Found Concentration mg/ml	Recovery %	Recovery Limits %
1	M-F	0	0	-	-
2	M-F	0.003	0.003	96.03	95 -105
3	M-F	0.013	0.013	96.89	95 -105
4	M-F	0.05	0.052	103.5	95 -105

 13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM IV - Analytical method and validation report for toxicokinetic analysis and
toxicokinetic analysis

STUDY NO.: 41950

**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

**ADDENDUM IV - Analytical method and validation report for toxicokinetic analysis
Determination in Rat Plasma with LC-MS/MS detection**

STUDY NO.: 41950

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.

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

is a product developed by the sponsor.

1.

SCOPE

This method of analysis describes the analysis of (or simply in rat plasma.

2.

FIELD OF APPLICATION

The method is described to be used for in rat plasma. The range of application is from 3 µg/ml to 33000 ng/ml.

3. **REFERENCES**

ISO Standard 78/2-1982 Layout for standards - Part 2: Standard for Chemical Analysis

4. **DEFINITIONS**

██████████ content is taken to mean the amount of ██████████ 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**

Acetonitrile HPLC grade (Baker 9017)

Methanol HPLC grade (Baker 8402)

Water HPLC grade (produced by EASYPURE)

██████████ (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 ██████████

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

Mobile phase A: Acetonitrile

Mobile phase B: Water

7.3

Standard solutions

7.3.1

STOCK A:

About 10 mg of [REDACTED] are transferred into a 50 mL 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 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]

7.3.5

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]

7.3.6

STOCK ISTD:

About 25 mg of ISTD - DICLOFENAC are transferred into a 25 mL volumetric flask and dissolved with Methanol obtaining a 1000 µg/mL solution.

7.3.7

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 Agilent Zorbax 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 water, 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	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	≈1650	≈167
Std 4	50 µL	SOL B	≈3300	≈167
Std 5	10 µL	STOCK A	≈6600	≈167
Std 6	20 µL	STOCK A	≈13000	≈167
Std 7	35 µL	STOCK A	≈23000	≈167
Std 8	50 µL	STOCK A	≈33000	≈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	concentration in matrix (ng/ml)	ISTD - DICLOFENAC Concentration (ng/ml)
LLOQ	50 µl	SOL. 1	≈9.90	≈167
1 st level	50 µl	SOL 3	≈33.0	≈167
2 nd level	50 µl	SOL B	≈3000	≈167
3 th level	50 µl	STOCK A	≈28000	≈167

10.4

HPLC

The following system is set up:

Column: Zorbax 80A extended C18 100 x 2:1 mm 3.5 µm

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



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.

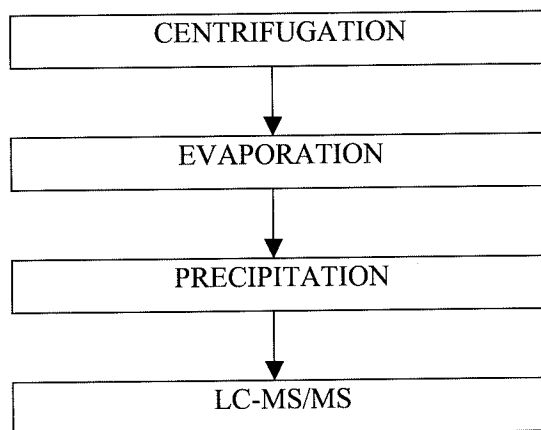
NOTES ON PROCEDURE

14.

TEST REPORT

15.

SCHEMATIC REPRESENTATION OF PROCEDURE



16.

BIBLIOGRAPHY

17. RESULTS VALIDATION

17.1 XXXXXXXXXX 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 * XXXXXXXXXX Conc.

r: 0.9956

Response type: area

Fit type: linear

Weighting: 1/X

17.2 Selectivity

No interfering peaks were present at the XXXXXXXXXX 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	37.812	112.2	113.2	0.81
	37.839		113.3		
	37.867		113.4		
	38.346		114.8		
	37.604		112.6		
	37.765		113.1		
	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	133.247	101.7	99.75	8.33
	148.79		111.4		
	116.82		87.45		
	125.71		94.11		
	132.66		99.31		
	139.68		104.6		
	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	285.23	102.9	100.5	3.95
	268.46		94.57		
	279.43		98.44		
	280.76		98.91		
	300.34		105.8		
	290.35		102.3		
	N =6				

n: number of samples used for calculations.

17.6

Accuracy and precision (Extended High 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 %
27245	31253	29308	114.71	107.57	5.93
	30760		112.90		
	29994		110.09		
	27835		102.17		
	29267		107.42		
	26740		98.15		
	n = 6				

n: number of samples used for calculations.

17.7

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	11.266	108.4	112.4	1.99
	11.421		114.0		
	11.228		112.1		
	11.406		113.8		
	11.206		111.8		
	11.469		114.5		
	n = 6				

n: number of samples used for calculations.

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

ADDENDUM IV - Analytical method and extention of validation report for toxicokinetic analysis of
████████████████████ Determination in Rat Plasma with LC-MS/MS detection

STUDY NO.: 41950

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.

████████████████████

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

██████████ is a product developed by the sponsor.

1.

SCOPE

This method of analysis describes the analysis of ██████████
██████████ (or simply ██████████ in rat plasma.

2.

FIELD OF APPLICATION

The method is described to be used for ██████████ 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**

██████████ content is taken to mean the amount of ██████████ 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**

Acetonitrile HPLC grade (Baker 9017)

Methanol HPLC grade (Baker 8402)

Water HPLC grade (produced by EASYPURE)

████████████████████ (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 ██████████

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**

Mobile phase A: Acetonitrile

Mobile phase B: Water

7.3 Standard solutions

- 7.3.1 **STOCK A:**
About 10 mg of [REDACTED] were 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 was 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 were transferred into a 20 mL volumetric flask and diluted with water obtaining a 1.98 µg/ml solution for [REDACTED]
- 7.3.4 **SOL 3:**
1 mL of SOL 8 was transferred into a 10 mL volumetric flask and diluted with water obtaining a 0.198 µg/ml solution for [REDACTED]
- 7.3.5 **SOL 1:**
1.5 mL of SOL 8 were transferred into a 50 mL volumetric flask and diluted with water obtaining a 0.0594 µg/ml solution for [REDACTED]
- 7.3.6 **STOCK ISTD:**
About 25 mg of ISTD - DICLOFENAC were transferred into a 25 volumetric flask and dissolved with Methanol obtaining of 1000 µg/ml solution.
- 7.3.7 **ISTD:**
0.5 mL of STOCK ISTD were 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 Agilent Zorbax 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 water, 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	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	≈13000	≈167
Std 7	35 µl	STOCK A	15 µl	≈23000	≈167
Std 8	50 µl	STOCK A	-	≈33000	≈167

10.3

HPLC

The following system is set up:

Column: Zorbax 80 C18 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



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.

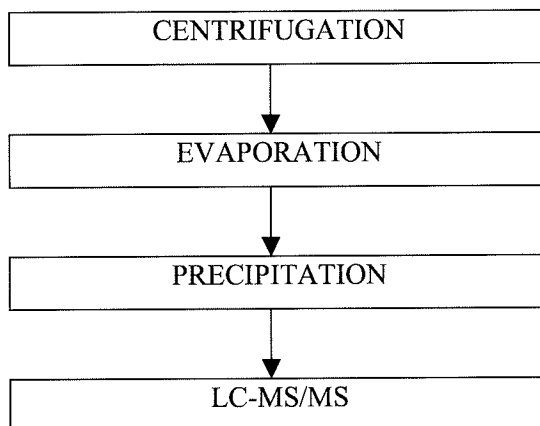
SPECIAL CASES

13.

NOTES ON PROCEDURE

14. **TEST REPORT**

15. **SCHEMATIC REPRESENTATION OF PROCEDURE**



16. **BIBLIOGRAPHY**

17. **RESULTS VALIDATION**

17.1 **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* Conc.

r: 0.9974

Response type: area

Fit type: linear

Weighting: 1/X

17.2 **Selectivity**

No interfering peaks were present at the retention times.

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM IV - Toxicokinetic analysis - [REDACTED] plasma levels (ng/ml) following oral administration of 0.5 mg/kg/day to male rats

STUDY NO.: 41950

Animal No.	Sampling times (hours post-dose)								
	0	2	4	6	8	24	48	96	168
419500102	BLQ		273.16			551.33			
419500104	BLQ		336.35			700.62			
419500106	BLQ		324.36			489.10			
419500108		393.86			556.24			461.16	
419500110		339.92			500.02			574.85	
419500112		144.39			544.71			499.03	
419500114				425.80			394.30		477.24
419500116				395.64			523.90		553.15
419500118				427.55			548.41		465.11
Mean*	0	292.72	311.29	416.33	533.66	580.35	488.57	511.68	498.50
SD	0	131.26	33.561	17.939	29.695	108.71	82.812	57.891	47.715
CV%	0	44.84	10.78	4.31	5.56	18.73	16.94	11.31	9.57

* Estimated values since they were calculated with calibration curve ranging from 0.019 ng/mL to 333.96 ng/mL. In any case the linearity was successfully extended until 333.96 ng/mL, but sample analysis was not repeated since no more additional aliquots were available.

BLO = below the limit of quantitation

* Estimated values since they were calculated with calibration curve ranging from 0.019 ng/mL to 333.96 ng/mL. In any case the linearity was successfully extended until 333.96 ng/mL, but sample analysis was not repeated since no more additional aliquots were available.
BLQ = below the limit of quantitation

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM IV - Plasma levels of [REDACTED] (ng/ml) in male rats at week 11, 12 and 13 of treatment

STUDY NO.: 41950

Group and dose level	Animal No.	Sampling times 2 hours post-dose		
		Week 11	Week 12	Week 13
2 0.03 mg/kg	419500032	1743.3	1073.3	2321.0
	419500034	1247.5	1461.1	2660.1
	419500036	1615.8	2788.1	4047.6
		MEAN SD CV %	1774.2 899.25 50.68	3009.6 914.81 30.40
3 0.13 mg/kg	419500052	6119.3	7044.9	11295
	419500054	7898.3	20827	10939
	419500056	8244.5	7689.0	11936
		MEAN SD CV %	11854 7777.8 65.61	11390 505.24 4.44
4 0.50 mg/kg	419500072	17384	83860 @	39469 @
	419500074	36063	71855 @	22471
	419500076	35612	49561 @	36058 @
		MEAN SD CV %	68425 17405 25.44	32666 8992.3 27.53
(@ = estimated (> validation range)).				

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM IV - Plasma levels of [REDACTED] (ng/ml) in female rats at week 11, 12 and 13 of treatment

STUDY NO.: 41950

Group and dose level	Animal No.	Sampling times 2 hours post-dose		
		Week 11	Week 12	Week 13
2 0.03 mg/kg	419500031	579.92	86.089	1078.6
	419500033	515.93	318.14	1097.0
	419500035	625.65	419.13	869.34
		MEAN SD CV %	274.45 1015.0 126.46 12.46	
3 0.13 mg/kg	419500051	2335.8	3303.9	5539.0
	419500053	2379.3	4114.3	6128.3
	419500055	3314.7	3515.8	9079.9
		MEAN SD CV %	3644.7 420.29 11.53	6915.7 1897.2 27.43
4 0.50 mg/kg	419500071	20855	28819	28957
	419500073	19530	6449.4	26250
	419500075	13131	4321.7	43394 @
		MEAN SD CV %	17838 4130.4 23.16	32867 9216.6 28.04
@ = estimated (> validation range).				

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM IV - Toxicokinetic analysis - Plasma levels of (ng/ml) following the last oral administration (2.0 mg/kg/day) to male rats

STUDY NO.: 41950

Animal No.	Sampling times (hours following the last dosing)			
	24	48	96	144
41950092	54192 @	62163 @	36683 @	38746 @
41950094	24285	20833	17569	9212
41950096	49675 @	49003 @	48231 @	39611 @
41950098	55915 @	45062 @	42307 @	35327 @
41950100	44565 @	42648 @	26937	23232
MEAN	45726	43942	34345	29226
SD	12769	14955	12227	12963
CV %	27.93	34.03	35.60	44.35
(@ = estimated (> validation range)).				
				49566 @
				10508
				25015
				19007
				22116
				25242
				14641
				58.00

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM IV - Toxicokinetic analysis - Plasma levels of (ng/ml) following the last oral administration (2.0 mg/kg/day) to female rats

STUDY NO.: 41950

Animal No.	Sampling times (hours following the last dosing)			
	24	48	96	144
41950091	37824 @	15153	17326	21445
41950093	28505	43665 @	21544	37312 @
41950095	26103	25540	30929	29658
41950097	31238	26025	30944	6679.8
41950099	28060	16721	17321	2731.8
MEAN	30346	25421	23613	19565
SD	4564	11340	6904.1	14746
CV %	15.05	44.61	29.24	75.37
@ = estimated (> validation range).				
				16548
				34481 @
				21104
				15172
				11272
				19715
				8971
				45.50

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM IV - Toxicokinetic analysis - Toxicokinetic parameters

STUDY NO.: 41950

DAY 1 - Treatment phase - Males					
Dose level (mg/kg)	t _{max} (h)	C _{max} (ng/ml)	T _{1/2} (h)	*AUC ₍₂₄₋₁₆₈₎ (ng/ml·h)	*AUC _(inf) (ng/ml·h)
0.5	24	580.35	1037	84686	830571
* Calculated from t _{max} (24 hours).					

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM IV - Toxicokinetic analysis - Toxicokinetic parameters

STUDY NO.: 41950

DAY 1 - Recovery phase - Males				
Dose level (mg/kg)	t _{max} (h)	C _{max} (ng/ml)	T ½ (h)	*AUC _(inf) (ng/ml·h)
0.5	24	45726	187	12595837
* Calculated from t _{max} (24 hours).				

13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM IV - Toxicokinetic analysis - Toxicokinetic parameters

STUDY NO.: 41950

DAY 1 - Recovery phase - Females				
Dose level (mg/kg)	t _{max} (h)	C _{max} (ng/ml)	T _{1/2} (h)	*AUC _(inf) (ng/ml·h)
0.5	24	30346	274	11627070
* Calculated from t _{max} (24 hours).				

 13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM V - Certificate of analysis

STUDY NO.: 41950

1984

MOLECULAR WEIGHT = 669

EQUIVALENT WEIGHT* 357

DIFUNCTIONAL **87.4**

C2/C1= 2.4

TERMINALI ACIDI+EST = 93.7

TERMINALI -OCF₂CL = 0.4

TERMINAL -OCF2CF2CL= 0.8

TERMINALI -OCF3 ■ 2.7

TERMINALI -OCF2H = 2.1

TERMINALI -OCF₂CF₂H = 0.2

 $Y \approx 0.0\% \text{ Z (w/w)}$

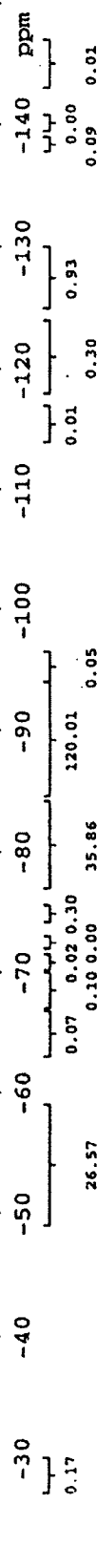
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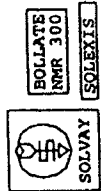
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file	respec/ncs1-0pwr		30	
transp	respec/ncs1-0pwr		0	
acqfile	12.1id	dm	new	
ACQUISITION				
sfreq	282.176	dm	PROCESSING	200
tn	719			
at	0.500	lb	2.00	
np	75170	isfile		
aw	75189.0	wcfile	-1	
fb	41000	proc	lp	131072
bs	10	fn		
tpw	61			
pu	4.5	werr	reset	
dl	2.000	wump	precplot	
tsf	2400.0	whw		
nt	1000	unit		
ct	1000			
alloc	n			
gain	not used			
FLAGS				
ll	n			
in	n			
dp	y			
DISPLAY				
app	-42235.0			
exp	76679.3			
res	1300			
sec	6			
uc	250			
hnum	146.73			
ls	664.10			
rt1	27210.4			
frfp	-35502.1			
th	0			
lne	184.408			
ai	ai			
ph				

RTC Study No.: 41950

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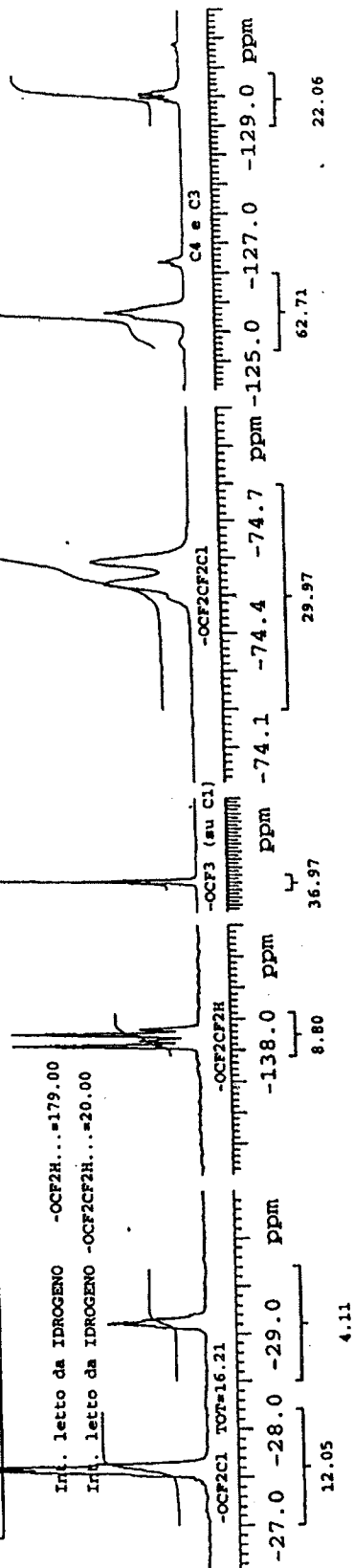
idr da DAF

Pulse Sequence: s2pul

IS x 100

MOLECULAR WEIGHT= 669
EQUIVALENT WEIGHT= 157
DIFUNZIONALE= 80.4
C2/C1= 80.4

INT letto MAGIC	INT misurato	DISTR. TERM MAGIC	DISTR. TERM. PC
25.00		-	
118.45		-	
1.02		2.75	
0.30		0.81	
34.73		93.68	
0.00		0.00	
0.77		2.09	
0.09		0.23	
0.16		0.44	
0.63		-	
0.22		-	



 13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM VI - Liver enzymes

STUDY NO.: 41950

RTS 0047/053623

**13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED
BY AN 8 WEEK RECOVERY PERIOD**

Sponsor

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Report issued 15 March 2006

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COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

**13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED
BY AN 8 WEEK RECOVERY PERIOD**

The study phase described in this report was conducted in compliance with the following Good Laboratory Practice standards and I consider the data generated to be valid.

The UK Good Laboratory Practice Regulations 1999 (Statutory Instrument No. 3106 as amended by Statutory Instrument 2004 No. 994).

EC Commission Directive 2004/10/EC of 11 February 2004 (Official Journal No. L 50/44).

OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM (98) 17.


.....
Anne Matthews, B.Sc.
Principal Investigator
Huntingdon Life Sciences Ltd

15 March 2006
Date

RTS 0047/053623

QUALITY ASSURANCE STATEMENT

The following inspections and audits have been carried out in relation to the phase of the study conducted at Huntingdon Life Sciences:

Study Phase	Date(s) of Inspection	Date of Reporting to Principal Investigator and Test Site Management	Date of Reporting to Study Director, Test Facility Management and Lead QA
Protocol Audit	9 August 2005	9 August 2005	9 August 2005
Study Based Inspections			
Liver processing	9 August 2005	9 August 2005	9 August 2005
microsomal preparation			
Report Audit	21 – 29 December 2005	29 December 2005	5 January 2006

In addition an inspection of the facility where this phase of the study was conducted was carried out on an annual basis. These inspections were promptly reported to Company Management.



 Tracy Scarfe, HNC, FRQA
 Group Manager
 Department of Quality Assurance
 Huntingdon Life Sciences Ltd.

15 March 2006.....
 Date

RTS 0047/053623

CONTRIBUTING SCIENTISTS

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SUMMARY

Samples received for analysis were livers from male and female rats (Sprague-Dawley) which had received [REDACTED] by oral administration for 13 weeks at dose levels of 0, 0.03, 0.13 or 0.5 mg/kg/day and those from the control and 0.5 mg/kg/day groups that had undergone an 8-week recovery period without any further dosing.

A 3,000 × g supernatant sub-cellular fraction was prepared from each liver sample by differential centrifugation. Cyanide-insensitive palmitoyl CoA oxidase activity (a marker for peroxisomal β-oxidation) and protein concentration were subsequently measured in this fraction.

Summary Tables 1 and 2 present mean data from male and female rats, from the main study and recovery groups, respectively. Mean results obtained from animals in the treated groups are expressed as a percentage of the corresponding control group mean.

Administration of [REDACTED] by oral administration for 13 weeks to rats at dose levels of 0.03, 0.13 or 0.5 mg/kg/day produced marked increases in mean cyanide-insensitive palmitoyl CoA oxidase activity in both male and female rats. Increases were generally dose-related, being approximately 11-times the mean control activities in males and approximately 9-times control activities in females of the highest dose group (activities expressed per mg protein). In males and females, mean activities (both units) were statistically significantly different ($p < 0.01$) from control values at the intermediate and high treatment levels. Mean 3,000 × g supernatant protein concentrations (mg/g liver) were statistically significantly increased in male and female animals treated at 0.5 mg/kg/day ($p < 0.01$). However, the protein concentrations of female rats statistically significantly decreased following treatment at 0.03 (80% of control; $p < 0.01$) and 0.13 (86% of control; $p < 0.05$) mg/kg/day.

Following an 8-week recovery period, the level of increase in the cyanide-insensitive palmitoyl CoA oxidase activity of male rats of the high dose group was reduced from approximately 11-times the mean control activities to approximately 5-times the mean control activities. In female animals, the degree of reduction was less, with the activities being reduced from approximately 9- or 11-times to approximately 5- or 6-times the mean control activities, when related to mg protein or g liver, respectively.

The data obtained following oral administration of [REDACTED] to male and female rats for 13 weeks suggest that the test compound was acting as a relatively strong peroxisome proliferator under the conditions used in this study, as evidenced by its effects on cyanide-insensitive palmitoyl CoA oxidase activity. The effects appeared more pronounced in male animals compared with those measured in females. Following an 8-week recovery period, during which time no further dosing was carried out, evidence for the compound being a peroxisome proliferator remained, since the activities measured were still increased in both male and female rats of the high dose groups compared with the controls.

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SUMMARY TABLE 1

Main groups

Data are group mean results expressed as a percentage of the respective control group mean

Male

Parameter	(mg/kg/day)		
	(0.03)	(0.13)	(0.5)
3,000 × g Supernatant protein - (mg/g liver)	94%	94%	117% **
Palmitoyl CoA oxidase - (nmoles/min/mg protein)	110%	309% **	1097% **
- (nmoles/min/g liver)	103%	292% **	1285% **

Female

Parameter	(mg/kg/day)		
	(0.03)	(0.13)	(0.5)
3,000 × g Supernatant protein - (mg/g liver)	80% ++	86% +	123% ++
Palmitoyl CoA oxidase - (nmoles/min/mg protein)	92%	188% **	911% **
- (nmoles/min/g liver)	73%	164% **	1121% **

** Significance level of comparison with control, using Williams' test: $p < 0.01$

+ Significance level of comparison with control, using Dunnett's test: $p < 0.05$

++ Significance level of comparison with control, using Dunnett's test: $p < 0.01$

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SUMMARY TABLE 2

Recovery groups

Data are group mean results expressed as a percentage of the respective control group mean

Male

Parameter	
	(mg/kg/day)
	(0.5)
3,000 × g Supernatant protein - (mg/g liver)	105%
Palmitoyl CoA oxidase - (nmoles/min/mg protein)	512%***
- (nmoles/min/g liver)	539%***

Female

Parameter	
	(mg/kg/day)
	0.5)
3,000 × g Supernatant protein - (mg/g liver)	114%***
Palmitoyl CoA oxidase - (nmoles/min/mg protein)	537%***
- (nmoles/min/g liver)	614%***

*** Significance level of comparison with control, using Student's *t* test: $p < 0.001$

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INTRODUCTION

Several compounds, in particular certain hypolipidaemic drugs and phthalate esters, have been shown to produce liver enlargement, hepatic peroxisome proliferation and induction of peroxisomal fatty acid oxidising enzyme activities in rodents (Cohen and Grasso 1981; Gibson 1993; Bosgra *et al* 2005).

In the present study, the effects of [REDACTED] on the activity of cyanide-insensitive palmitoyl coenzyme A (CoA) oxidase, a peroxisomal fatty acid β -oxidation marker activity, were evaluated in $3,000 \times g$ supernatant fractions prepared from the livers of rats that had been orally administered the test compound for 13 weeks. The dose levels investigated were 0 (control; dose vehicle), 0.03, 0.13 and 0.5 mg/kg/day. Animals that had an 8-week recovery period, following dosing at 0.5 mg/kg/day, without receiving any further test compound were also evaluated.

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RELEVANT STUDY DATES

Receipt of frozen livers: 28 July 2005 & 03 November 2005

Start of experimental period: 09 August 2005

End of experimental period: 24 November 2005

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EXPERIMENTAL PROCEDURES

CHEMICALS

Bovine serum albumin, palmitoyl CoA, β -NAD (sodium salt), CoA, FAD (di-sodium salt) and dithiothreitol were all obtained from Sigma-Aldrich Co Ltd.

Additional chemicals were purchased from Sigma-Aldrich Co Ltd, from Fisher Scientific or from VWR International.

Water (of super-purity grade) was distilled on the premises using an Elga water purification system (Vivendi Water Systems).

TEST SAMPLES

Liver samples from male and female Sprague-Dawley rats, which originated from RTC Study number 41950, were received into the Department of *In Vitro* Metabolism frozen in the presence of solid CO₂ and were subsequently stored at *ca* -75°C. Samples were identified with reference to animal number, sex and dose group, in accordance with those designations made on RTC Study number 41950, as shown below.

Main animals

Dose group	Male animals	Female animals
Control (Dose vehicle)	2, 4, 6, 8, 10	1, 3, 5, 7, 9
(0.03 mg/kg/day)	32, 34, 36, 38, 40	31, 33, 35, 37, 39
(0.13 mg/kg/day)	52, 54, 56, 58, 60	51, 53, 55, 57, 59
(0.5 mg/kg/day)	72, 74, 76, 78, 80	71, 73, 75, 77, 79

Recovery animals

Dose group	Male animals	Female animals
Control (Dose vehicle)	22, 24, 26, 28, 30	21, 23, 25, 27, 29
(0.5 mg/kg/day)	92, 94, 96, 98, 100	91, 93, 95, 97, 99

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METHODS

Preparation of buffers

Unless indicated otherwise, all buffers were adjusted to the stated pH value at a temperature of 25°C.

Liver processing

The following procedures were conducted in an environment maintained at *ca* 4°C. The liver samples (as received) were removed from storage and thawed by immersion for *ca* 20 minutes in ice-cold 50 mM Tris-HCl buffer, pH 7.4, containing 0.154 M KCl. A representative portion of each liver (*ca* 1 g) was homogenised in *ca* 9 volumes of 50 mM Tris-HCl buffer, pH 7.4, containing 0.154 M KCl, using an electrically-driven glass Potter-Elvehjem-type homogeniser fitted with a Teflon pestle. The homogenates were centrifuged at *ca* 3,000 × *g* for 7 minutes at 4°C (Beckman L8-70M ultracentrifuge, fixed angle rotor 50.2 Ti: 5,500 rpm) and the resulting supernatant decanted off and the volume measured. Aliquots of the supernatant were stored at *ca* -75°C for the subsequent determination of cyanide-insensitive palmitoyl CoA oxidase activity and at *ca* -20°C for the subsequent determination of protein concentration.

Measurement of protein concentration

Protein concentration was determined by the method of Lowry *et al* (1951). Aliquots (0.5 ml) of diluted 3,000 × *g* supernatant fraction (1 in 150 dilution with water, in duplicate) were mixed with alkaline copper tartrate reagent [1 part 2% (w/v) K/Na Tartrate : 1 part 1% (w/v) CuSO₄·5H₂O : 98 parts 2% (w/v) Na₂CO₃ in 0.1 M NaOH] (3 ml) and left to stand at room temperature for 20 minutes. Aliquots (0.3 ml) of Folin-Ciocalteu's phenol reagent (diluted 1 : 1 with water) were then added and samples allowed to stand at room temperature for a further 40 minutes before assaying spectrophotometrically (Philips PU-8700 Series UV/Vis Spectrophotometer) at 750 nm against a distilled water reference. The amount of protein was calculated from a standard curve prepared from 0 - 200 µg bovine serum albumin (BSA)/ml assayed under identical conditions. Results have been expressed as milligrams of protein (BSA equivalents) per gram of liver.

Measurement of cyanide-insensitive palmitoyl CoA oxidase activity

Cyanide-insensitive palmitoyl CoA oxidation was measured essentially as described by Gray *et al* (1983), a modification of the method of Lazarow and De Duve (1976). Enzyme activity was measured at 37°C in 3,000 × *g* supernatants using a Philips PU-8700 series UV/Vis spectrophotometer at 340 nm. Cuvettes contained 200 µl of diluted supernatant (1 in 2 to 1 in 64 dilutions with 50 mM Tris-HCl buffer, pH 7.4, containing 0.154 M KCl) and 800 µl of co-factor mix [2.5 mM β-NAD, 1.25 mM CoA, 62.5 mM dithiothreitol, 15 mM KCN, 1 mM FAD and 1.5 mg/ml BSA (1 volume of each, in 50 mM Tris-HCl buffer, pH 7.89) + 2 volumes 50 mM Tris-HCl buffer, pH 7.89]. The reaction was initiated by the addition of 5 mM palmitoyl CoA (20 µl; in 50 mM Tris-HCl buffer, pH 7.89) and the rate of NADH formation measured for a period of up to 12 minutes. Samples were assayed in duplicate as a

: 13 :

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minimum (refer to Data Analysis section for replicate acceptance criterion) and activity quantified as nanomoles of NADH formed per minute per milligram of $3,000 \times g$ supernatant protein and per gram of liver, employing an extinction coefficient of $6.22 \text{ cm}^{-1}\text{mM}^{-1}$.

DATA ANALYSIS

Data treatment

Data were produced for male and female rats of control and three treatment groups (0.03, 0.13 and 0.5 mg/kg/day) in the main study. For the recovery animals, data were produced for the control and high dose (0.5 mg/kg/day) treatment groups. For each assay, individual animal concentration or activity data were calculated using the measurements of the first two sample replicates only, providing that each replicate value was $\leq 5\%$ different from the duplicate mean. Where this acceptance criterion was not fulfilled, a third replicate value was used, either to achieve acceptance with one of the original two replicates or, if no replicate pair satisfied the criterion, to be included for derivation of the median value of all three replicates. Means and standard deviations for each dose group were then calculated from these individual animal results.

Statistical analysis

Significance testing of main group male protein concentration and male and female enzyme activity was carried out using Williams' test at the 5% and 1% levels. Significant differences have been marked on the tables using the conventional asterisk notation: ** $p < 0.01$. For the protein concentration of main group female animals, Dunnett's test was applied as monotonicity could not be assumed. Significant differences have been marked on the tables using the following notation: + $p < 0.05$ and ++ $p < 0.01$. For the recovery animals, significance testing of male and female protein concentration and male and female enzyme activity was carried out using Student's *t* test. Significant differences have been marked on the tables using the conventional asterisk notation: *** $p < 0.001$.

A detailed description of the statistical analysis of the data is presented in the Statistics Report (Appendix 2).

LOCATION OF DATA

All raw data (notebook reference numbers 2005/1620 and 2005/1656), supplementary files and other documents generated in the Department of *In Vitro* Metabolism, Huntingdon Life Sciences Ltd during the course of this study phase, together with a copy of this final report, will be stored for at least 5 years in the Archives of Huntingdon Life Sciences Ltd, UK. None of these records will be disposed of without the prior written consent of the Study Sponsor. Huntingdon Life Sciences will retain the Quality Assurance records relevant to this study phase and a copy of the final report in its archive indefinitely.

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RESULTS

Mean results are presented in Tables 1 and 2, with individual animal data given in Appendix 1.

3,000 × g SUPERNATANT PROTEIN CONCENTRATION

In male and female rats of the main dose groups, there were statistically significant increases in protein concentration, to 1.2-times the mean control value ($p < 0.01$) following administration of the test compound at the highest dose level (0.5 mg/kg/day). In female rats, there were decreases 0.2-times ($p < 0.01$) and 0.1-times the mean control value ($p < 0.05$) following administration of the test compound at 0.03 and 0.13 mg/kg/day, respectively.

In the female animals from the high dose recovery group, there was a statistically significant increase in protein concentration, to 1.1-times the mean control value ($p < 0.001$). There were no statistically significant increases noted in the recovery group male animals.

CYANIDE-INSENSITIVE PALMITOYL COA OXIDASE ACTIVITY

There were statistically significant increases in the mean activity of cyanide-insensitive palmitoyl CoA oxidase following a 13-week administration of [REDACTED] to male rats at the intermediate and highest dose levels. At 0.13 and 0.5 mg/kg/day the respective mean activities (per mg protein) were 3.1- and 11.0-times the mean control value (both $p < 0.01$). Although male animals dosed at 0.03 mg/kg/day showed an increase of 1.1-times the mean control value, this was not statistically significant. The pattern of increase was similar when mean male activities were expressed per g liver, being 2.9- and 12.9-times the mean control activity, in the intermediate and high dose groups respectively (both $p < 0.01$). In females, there were no statistically significant changes in mean activities relative to control following administration of the test compound at the lowest dose level (0.03 mg/kg/day). At 0.13 and 0.5 mg/kg/day, the respective mean activities were 1.9- and 9.1-times the mean control value with results expressed per mg protein and 1.6- and 11.2-times the mean control value with results expressed per g liver (all $p < 0.01$).

In the recovery animals, there were statistically significant increases in the mean activity of cyanide-insensitive palmitoyl CoA oxidase in the males following administration of [REDACTED] to 5.1-times the mean control activity when related to mg protein and to 5.4-times (both $p < 0.001$) relative to g liver. Similar increases were noted in the female animals, to 5.4-times the control activity relative to mg protein and to 6.1-times (both $p < 0.001$) relative to g liver.

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DISCUSSION

Among the early biochemical responses to exposure of rodents to a peroxisome proliferator is an increase in the number of peroxisomes within the liver, with a parallel increase in the activity of enzymes specific to these organelles. However, the synthesis of certain peroxisomal enzymes, including cyanide-insensitive palmitoyl CoA oxidase, is also selectively induced by these types of compound (Cohen and Grasso 1981). The extent of this induction varies depending on the xenobiotic in question, but can exceed 20-fold (Cohen and Grasso 1981; Bosgra *et al* 2005).

Data from the present study indicate that [REDACTED] when administered to male and female rats for 13 weeks, significantly induced peroxisomal palmitoyl CoA oxidase activity. Maximum increases to 11-times that of the control activities (per mg protein) in males and up to 9-times that of the control activities in females were observed following administration at a dose level of 0.5 mg/kg/day. There was also evidence for an increase in this activity following administration of [REDACTED] to male and female animals at 0.13 mg/kg/day. Following an 8-week recovery period, the enzyme activities of the animals from the high dose groups remained significantly higher than those of the control groups.

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CONCLUSIONS

The data obtained following oral administration of [REDACTED] to male and female rats for 13 weeks suggest that the test compound was acting as a relatively strong peroxisome proliferator under the conditions used in this study, as shown by its effects on cyanide-insensitive palmitoyl CoA oxidase activity. The effects appeared more pronounced in male animals compared with those measured in females. Following an 8-week recovery period, during which time no further dosing was carried out, evidence for the compound being a peroxisome proliferator remained, since the activities measured were still increased in both male and female rats of the high dose groups compared with the controls.

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RTS 0047/053623

TABLE 1

Mean hepatic $3,000 \times g$ supernatant protein concentrations and cyanide-insensitive palmitoyl CoA oxidase activities in rats following oral administration of [REDACTED] at dose levels of 0 (control), 0.03, 0.13 and 0.5 mg/kg/day for 13 weeks

Male

Treatment group	Protein concentration (mg/g liver)	Palmitoyl CoA oxidase activity	
		(nmoles NADH formed /min/mg protein)	(nmoles NADH formed /min/g liver)
Control (0)	160 $\pm$ 9	4.37 $\pm$ 0.50	698 $\pm$ 49
[REDACTED] (0.03 mg/kg/day)	150 $\pm$ 14 (94%)	4.80 $\pm$ 0.36 (110%)	719 $\pm$ 74 (103%)
[REDACTED] (0.13 mg/kg/day)	151 $\pm$ 17 (94%)	13.49** $\pm$ 2.13 (309%)	2037** $\pm$ 418 (292%)
[REDACTED] (0.5 mg/kg/day)	187** $\pm$ 4 (117%)	47.94** $\pm$ 8.28 (1097%)	8972** $\pm$ 1539 (1285%)

Female

Treatment group	Protein concentration (mg/g liver)	Palmitoyl CoA oxidase activity	
		(nmoles NADH formed /min/mg protein)	(nmoles NADH formed /min/g liver)
Control (0)	149 $\pm$ 9	4.45 $\pm$ 0.37	661 $\pm$ 47
[REDACTED] (0.03 mg/kg/day)	119++ $\pm$ 5 (80%)	4.08 $\pm$ 0.31 (92%)	485 $\pm$ 44 (73%)
[REDACTED] (0.13 mg/kg/day)	128+ $\pm$ 16 (86%)	8.38** $\pm$ 1.57 (188%)	1082** $\pm$ 251 (164%)
[REDACTED] (0.5 mg/kg/day)	183++ $\pm$ 12 (123%)	40.56** $\pm$ 10.02 (911%)	7409** $\pm$ 1951 (1121%)

Results are expressed as the mean of 5 animals $\pm$ standard deviation

(%) Data in parentheses are group mean data expressed as a percentage of the corresponding control group mean

** Significance level of comparison with control, using Williams' test: $p < 0.01$

+ Significance level of comparison with control, using Dunnett's test: $p < 0.05$

++ Significance level of comparison with control, using Dunnett's test: $p < 0.01$

RTS 0047/053623

TABLE 2

Mean hepatic 3,000 × g supernatant protein concentrations and cyanide-insensitive palmitoyl CoA oxidase activities in rats following oral administration of [REDACTED] at dose levels of 0 (control) and 0.5 mg/kg/day for 13 weeks followed by an 8-week recovery period

Male

Treatment group	Protein concentration (mg/g liver)	Palmitoyl CoA oxidase activity	
		(nmoles NADH formed /min/mg protein)	(nmoles NADH formed /min/g liver)
Control (0)	150 ± 11	4.10 ± 0.15	614 ± 60
[REDACTED] (0.5 mg/kg/day)	158 ± 16 (105%)	20.99 *** ± 6.93 (512%)	3310 *** ± 1115 (539%)

Female

Treatment group	Protein concentration (mg/g liver)	Palmitoyl CoA oxidase activity	
		(nmoles NADH formed /min/mg protein)	(nmoles NADH formed /min/g liver)
Control (0)	130 ± 5	3.80 ± 0.35	492 ± 57
[REDACTED] (0.5 mg/kg/day)	148 *** ± 3 (114%)	20.39 *** ± 4.05 (537%)	3019 *** ± 554 (614%)

Results are expressed as the mean of 5 animals ± standard deviation

(%) Data in parentheses are group mean data expressed as a percentage of the corresponding control group mean

*** Significance level of comparison with control, using Student's *t* test: $p < 0.001$

: 20 :

RTS 0047/053623

APPENDIX 1

Individual animal data

A. Main group animals

(a) 3,000 × g Supernatant protein concentrations

Male

Treatment group	Animal number	Protein concentration (mg/g liver)		
Control (0)	2	153		
	4	166		
	6	147		
	8	165		
	10	169		
	Mean ± sd	160	±	9
[REDACTED] (0.03 mg/kg/day)	32	145		
	34	130		
	36	167		
	38	155		
	40	153		
		150	±	14
[REDACTED] (0.13 mg/kg/day)	52	139		
	54	127		
	56	162		
	58	158		
	60	167		
		151	±	17
[REDACTED] (0.5 mg/kg/day)	72	188		
	74	192		
	76	190		
	78	184		
	80	182		
	Mean ± sd	187	±	4

sd Standard deviation

APPENDIX 1

(continued)

A. Main group animals - continued

(a) 3,000 × g Supernatant protein concentrations - continued

Female

Treatment Group	Animal number	Protein concentration (mg/g liver)
Control (0)	1	161
	3	153
	5	138
	7	149
	9	142
	Mean ± sd	149 ± 9
[REDACTED] (0.03 mg/kg/day)	31	127
	33	115
	35	119
	37	114
	39	119
		119 ± 5
[REDACTED] (0.13 mg/kg/day)	51	141
	53	109
	55	114
	57	141
	59	137
		128 ± 16
[REDACTED] (0.5 mg/kg/day)	71	197
	73	186
	75	180
	77	164
	79	186
	Mean ± sd	183 ± 12

sd Standard deviation

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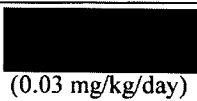
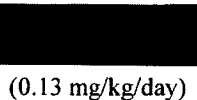
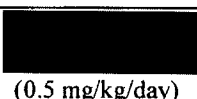
APPENDIX 1

(continued)

A. Main group animals - continued

(b) 3,000 × g Supernatant cyanide-insensitive palmitoyl CoA oxidase activities

Male

Treatment group	Animal number	Rate of NADH production			
		(nmoles/min/mg protein)		(nmoles/min/g liver)	
Control (0)	2	4.92		754	
	4	4.40		731	
	6	4.80		706	
	8	3.82		632	
	10	3.93		666	
	Mean ± sd	4.37	± 0.50	698	± 49
 (0.03 mg/kg/day)	32	4.85		701	
	34	5.09		663	
	36	4.99		831	
	38	4.18		649	
	40	4.89		749	
		4.80	± 0.36	719	± 74
 (0.13 mg/kg/day)	52	15.21		2115	
	54	11.49		1454	
	56	16.24		2627	
	58	12.80		2026	
	60	11.73		1963	
		13.49	± 2.13	2037	± 418
 (0.5 mg/kg/day)	72	51.03		9595	
	74	35.62		6847	
	76	56.40		10722	
	78	52.84		9708	
	80	43.80		7987	
	Mean ± sd	47.94	± 8.28	8972	± 1539

sd Standard deviation

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APPENDIX 1

(continued)

A. Main group animals - continued

(b) 3,000 × g Supernatant cyanide-insensitive palmitoyl CoA oxidase activities - continued

Female

Treatment group	Animal number	Rate of NADH production	
		(nmoles/min/mg protein)	(nmoles/min/g liver)
Control (0)	1	4.49	725
	3	4.04	619
	5	5.04	695
	7	4.32	646
	9	4.36	619
	Mean ± sd	4.45 ± 0.37	661 ± 47
[REDACTED] (0.03 mg/kg/day)	31	4.01	509
	33	3.66	421
	35	4.52	539
	37	4.14	472
	39	4.07	485
	Mean ± sd	4.08 ± 0.31	485 ± 44
[REDACTED] (0.13 mg/kg/day)	51	7.27	1027
	53	6.39	698
	55	9.98	1137
	57	9.82	1386
	59	8.45	1162
	Mean ± sd	8.38 ± 1.57	1082 ± 251
[REDACTED] (0.5 mg/kg/day)	71	45.30	8908
	73	40.68	7560
	75	53.71	9645
	77	36.20	5923
	79	26.89	5011
	Mean ± sd	40.56 ± 10.02	7409 ± 1951

sd Standard deviation

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APPENDIX 1

(continued)

B. Recovery group animals

(a) $3,000 \times g$ Supernatant protein concentrations

Male

Treatment group	Animal number	Protein concentration (mg/g liver)	
Control (0)	22	157	
	24	149	
	26	149	
	28	161	
	30	132	
	Mean $\pm$ sd	150	$\pm$ 11
 (0.5 mg/kg/day)	92	170	
	94	163	
	96	172	
	98	134	
	100	153	
	Mean $\pm$ sd	158	$\pm$ 16

sd Standard deviation

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APPENDIX 1**(continued)****B. Recovery group animals - continued****(a) 3,000 × g Supernatant protein concentrations - continued****Female**

Treatment group	Animal number	Protein concentration (mg/g liver)
Control (0)	21	126
	23	134
	25	124
	27	128
	29	136
	Mean ± sd	130 ± 5
[REDACTED] (0.5 mg/kg/day)	91	147
	93	149
	95	152
	97	144
	99	149
	Mean ± sd	148 ± 3

sd Standard deviation

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APPENDIX 1

(continued)

B. Recovery group animals - continued

(b) 3,000 × g Supernatant cyanide-insensitive palmitoyl CoA oxidase activities

Male

Treatment group	Animal number	Rate of NADH production					
		(nmoles/min/mg protein)			(nmoles/min/g liver)		
Control (0)	22	4.16			655		
	24	4.13			615		
	26	3.87			577		
	28	4.28			686		
	30	4.06			537		
	Mean ± sd	4.10	±	0.15	614	±	60
[REDACTED] (0.5 mg/kg/day)	92	27.62			4702		
	94	11.06			1798		
	96	21.96			3786		
	98	26.94			3613		
	100	17.39			2652		
	Mean ± sd	20.99	±	6.93	3310	±	1115

sd Standard deviation

RTS 0047/053623

APPENDIX 1

(continued)

B. Recovery group animals - continued

(b) 3,000 × g Supernatant cyanide-insensitive palmitoyl CoA oxidase activities - continued

Female

Treatment group	Animal number	Rate of NADH production			
		(nmoles/min/mg protein)		(nmoles/min/g liver)	
Control (0)	21	3.69		465	
	23	3.44		460	
	25	3.82		473	
	27	3.66		469	
	29	4.38		594	
	Mean ± sd	3.80	± 0.35	492	± 57
[REDACTED] (0.5 mg/kg/day)	91	16.62		2449	
	93	18.79		2809	
	95	20.94		3185	
	97	27.09		3893	
	99	18.51		2758	
	Mean ± sd	20.39	± 4.05	3019	± 554

sd Standard deviation

RTS 0047/053623

APPENDIX 2

Statistical analysis of hepatic enzyme data

**EFFECT ON HEPATIC LEVELS OF CYANIDE-INSENSITIVE PALMITOYL COA
OXIDASE IN THE MALE AND FEMALE SPRAGUE-DAWLEY RAT AFTER ORAL
ADMINISTRATION AT 0, 0.03, 0.13 AND 0.5 MG/KG/DAY FOR 13 WEEKS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

STATISTICAL ANALYSIS OF HEPATIC ENZYME DATA

Author

Susan C. Cook

Statistics Department

APPENDIX 2

(continued)

INTRODUCTION

The hepatic enzyme data were available for a control group and three treated groups receiving [REDACTED] at 0.03, 0.13 and 0.5 mg/kg/day for 13 weeks. The data were received for male and female rats, with five animals per group.

A recovery phase was also included in the study. This consisted of two groups; the control and 0.5 mg/kg/day for both males and females, with five animals in each group.

In this report, the statistical analyses of the following parameters are described:

3000 × g Supernatant protein concentration:	(mg/g liver)
Cyanide-insensitive palmitoyl CoA oxidase activity:	(nmoles/min/mg protein)
	(nmoles/min/g liver)

METHODOLOGY

The statistical analyses were performed using the following decision tree for each sex separately.

The Levene's test (Levene 1960) for homogeneity of variance was applied. If the test was significant at the 1% level, then a logarithmic transformation was tried. If Levene's test was still significant, then either the original analysis was retained or non-parametric tests (Kruskal and Wallis 1952, 1953) were applied, whichever was deemed most appropriate depending on the pattern of the variance heterogeneity.

A one-way analysis of variance was then applied, using treatment as a factor. If the F1 test for monotonicity of dose-response (Healey 1999a) was not significant at the 1% level, a Williams' test for a monotonic trend (Williams 1971, 1972) was applied, to compare the [REDACTED] treated groups with the control group. If the F1 test was significant, suggesting that the dose-response was not monotone, Dunnett's test (Dunnett 1955, 1964) was performed instead.

The non-parametric test, Kruskal-Wallis test (Kruskal and Wallis 1952, 1953) was applied. If the H1 test for monotonicity of dose-response (Healey 1999b) was not significant at the 1% level, Shirley's test for a monotonic trend (Shirley 1977) was applied. If the H1 test was significant, suggesting that the dose-response was not monotone, Steel's test (Steel 1959) was performed instead.

For the recovery data, one-way analyses of variance were again applied with treatment as a factor. Since there were only two groups this is equivalent to Student's *t* test. It should be noted that given the small number of degrees of freedom for the analyses, only gross differences between groups would be significant.

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APPENDIX 2**(continued)****DATA HANDLING**

Data were received as an Excel spreadsheet and converted to an ASCII file prior to the analysis. The software used for all the analyses was the in-house program StarTox (StarTox 2001).

RESULTS

The results for the statistical analyses have been summarised in Table 1 for the main study.

In order to obtain homogeneity of variance a logarithmic transformation was performed on both male and female cyanide-insensitive palmitoyl CoA oxidase activity (when expressed as nmoles/min/g liver and nmoles/min/mg protein (Levene's test $p < 0.01$)) prior to analysis. For 3000 x g supernatant protein concentration Levene's test was not significant ($p > 0.01$).

All comparisons with the control were made using Williams' test (Williams 1971, 1972) with the exception of female 3000 x g supernatant protein concentration where monotonicity could not be assumed and Dunnett's test (Dunnett 1955, 1964) was applied.

There was an increase in mean 3000 x g supernatant protein concentration for both males and females at the 0.5 mg/kg/day dose level ($p < 0.01$). However, for the females there was also evidence of a decrease at both the 0.03 and 0.13 mg/kg/day dose levels ($p < 0.01$ and $p < 0.05$ respectively).

Mean cyanide-insensitive palmitoyl CoA oxidase activity (nmoles/min/mg protein and nmoles/min/g liver) was significantly increased for males and females at both the 0.13 and 0.5 mg/kg/day dose levels ($p < 0.01$).

The results for the recovery data have been presented in Table 2.

In order to obtain homogeneity of variance a logarithmic transformation was performed on male cyanide-insensitive palmitoyl CoA oxidase activity (when expressed as nmoles/min/mg protein (Levene's test $p < 0.01$)) prior to analysis.

Following recovery, there was an increase in mean 3000 x g supernatant protein concentration for females at the 0.5 mg/kg/day dose level ($p < 0.001$).

Mean cyanide-insensitive palmitoyl CoA oxidase activity (when expressed as nmoles/min/g liver and nmoles/min/mg protein) was significantly increased for both males and females at the 0.5 mg/kg/day dose level ($p < 0.001$).

APPENDIX 2**(continued)****REFERENCES**

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APPENDIX 2

(continued)

TABLE 1

Mean hepatic 3000 x g supernatant protein concentrations and cyanide-insensitive palmitoyl CoA oxidase activities in rats following oral administration of [REDACTED] at dose levels of 0 (control), 0.03, 0.13 and 0.5 mg/kg/day for 13 weeks

Male

Treatment group	n	Protein concentration mg/g liver		Palmitoyl CoA oxidase activity			
				nmoles NADH formed /min/mg protein ^a		nmoles NADH formed /min/g liver ^a	
		Mean	sd	Mean	sd	Mean	sd
Control (0)	5	160	9.49	4.37	0.50	698	49
[REDACTED] (0.03 mg/kg/day)	5	150	13.68	4.80	0.36	719	74
[REDACTED] (0.13mg/kg/day)	5	151	16.92	13.49 **	2.13	2037 **	418
[REDACTED] (0.5 mg/kg/day)	5	187 **	4.15	47.94 **	8.28	8972 **	1539

Female

Treatment group	n	Protein concentration mg/g liver		Palmitoyl CoA oxidase activity			
				nmoles NADH formed /min/mg protein ^a		nmoles NADH formed /min/g liver ^a	
		Mean	sd	Mean	sd	Mean	sd
Control (0)	5	149	9.07	4.45	0.37	661	47
[REDACTED] (0.03 mg/kg/day)	5	119 ++	5.12	4.08	0.31	485	44
[REDACTED] (0.13mg/kg/day)	5	128 +	15.61	8.38 **	1.57	1082 **	251
[REDACTED] (0.5 mg/kg/day)	5	183 ++	12.08	40.56 **	10.02	7409 **	1951

n Group size

sd Standard deviation

^a Analysis performed on logarithmically transformed data. Means and sd's presented for untransformed data** Significance level of comparison with control, using Williams' test: $p < 0.01$ + Significance level of comparison with control, using Dunnett's test: $p < 0.05$ ++ Significance level of comparison with control, using Dunnett's test: $p < 0.01$

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APPENDIX 2

(continued)

TABLE 2

Mean hepatic 3000 x g supernatant protein concentrations and cyanide-insensitive palmitoyl CoA oxidase activities in rats following oral administration of [REDACTED] at dose levels of 0 (control) and 0.5 mg/kg/day for 13 weeks followed by 8 weeks recovery

Male recovery

Treatment group	n	Protein concentration mg/g liver		Palmitoyl CoA oxidase activity			
				nmoles NADH formed /min/mg protein ^a		nmoles NADH formed /min/g liver ^a	
		Mean	sd	Mean	sd	Mean	sd
Control (0)	5	150	11.13	4.10	0.15	614	60
[REDACTED] (0.5 mg/kg/day)	5	158	15.53	20.99 ***	6.93	3310 ***	1115

Female recovery

Treatment group	n	Protein concentration mg/g liver		Palmitoyl CoA oxidase activity			
				nmoles NADH formed /min/mg protein ^a		nmoles NADH formed /min/g liver ^a	
		Mean	sd	Mean	sd	Mean	sd
Control (0)	5	130	5.18	3.80	0.35	492	57
[REDACTED] (0.5 mg/kg/day)	5	148 ***	2.95	20.39 ***	4.05	3019 ***	554

n Group size

sd Standard deviation

^a Analysis performed on logarithmically transformed data. Means and sd's presented for untransformed data

*** Significance level of comparison with control, using Student's *t* test: $p < 0.001$

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APPENDIX 3

Huntingdon Research Centre GLP Compliance Statement



THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE IN ACCORDANCE WITH DIRECTIVE 2004/9/EC

LABORATORY	TEST TYPE
Huntingdon Life Sciences Huntingdon Research Centre Woolley Road Alconbury Cambridgeshire PE28 4HS	Analytical Chemistry Clinical Chemistry Ecosystems Environmental Fate Environmental Toxicity Toxicology Phys/Chem Testing

DATE OF INSPECTION

7th March 2005

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of the UK GLP Compliance Programme.

At the time of inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

A handwritten signature in black ink, reading 'Bryan J. Wright' with the date '9/6/05' written below it.

Mr. Bryan J. Wright
Head, UK GLP Monitoring Authority

 13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM VII - Clinical pathology report

STUDY NO.: 41950

STUDY NO.: 41950

**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

Clinical Pathology Report

Haematology

The statistically significant changes observed are described in the following table:

Parameters	2M	3M	4M	4M Rec	2F	3F	4F	4F Rec
RBC		-5%	-10%					
HGB		-4%	-6%					
HCT		-5%	-6%					
MCV			+4%					
MCH			+4%					
Neu					+65%			
Lym					-9%			

Treatment period

Very slight but statistically significant reductions in red blood cell count, haemoglobin and haematocrit and increases mean red blood cell volume and mean corpuscular haemoglobin were observed in males receiving 0.5 and 0.13 mg/kg/day. These changes were insufficient in magnitude to be of toxicological significance.

The statistically significant changes of neutrophils and lymphocytes count observed in some females receiving 0.03 mg/kg/day were considered to be incidental since no dose-relation was observed.

Recovery period

The changes observed during the dosing phase showed a complete recovery after the 8-week treatment-free period.

Clinical Chemistry

The statistically significant changes observed are described in the following table:

Parameters	2M	3M	4M	4M Rec	2F	3F	4F	4F Rec
AP	-11%	+25%	+101%	+47%			+65%	+29%
ALT		+30%						-14%
BILT			-25%				-31%	
CHOL		-27%				-20%		
TRI						+40%	+63%	+54%
Urea			+36%	+29%				
Crea		-13%	-23%					
Prot		-7%	-14%				+5%	
Alb			-7%			+8%	+14%	+13%
Glo			-23%					-19%
A/G Ratio			+24%			+20%	+32%	+38%
Ca	-3%	-4%	-8%					
Cl			+2%					
Phos				+18%				
Na				-1%				+1%

Treatment period

Alkaline phosphatase was statistically significantly increased in 0.5 and 0.13 mg/kg/day male animals when compared to controls and in the females dosed at 0.5 mg/kg/day. Since no indications of cholestasis or bone pathology were observed, this change could be due to an enzyme induction caused by the treatment.

Changes of total bilirubin, triglycerides, urea and creatinine were also observed in animals treated with 0.13 and/or 0.5 mg/kg/day. In the absence of notable pathology these could represent adaptive changes in the liver.

All other inter-group differences were slight, not dose-related and/or not consistent between sexes, therefore they were considered to be incidental.

Recovery period

At the end of the treatment-free period, some parameters which were altered in the dosing phase analyses showed a trend for recovery (alkaline phosphatase and triglycerides), while most of them had completely recovered.

No significant recovery was observed for urea levels, which remained higher when compared to controls.

Urinalyses

Treatment period

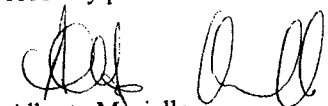
Urine specific gravity was slightly increased in a number of males treated with 0.5 mg/kg/day and pH was slightly reduced in the same group animals.

In addition, animal No. 90 had a concentration of glucose, bilirubin and urobilinogen higher than controls.

These changes were not dose-related, not consistent between sexes and/or insufficient in magnitude to be of toxicological significance.

Recovery period

The slight changes observed during the dosing phase were no longer observed at the end of the recovery period.



Alberto Mosiello
Study Clinical Pathologist

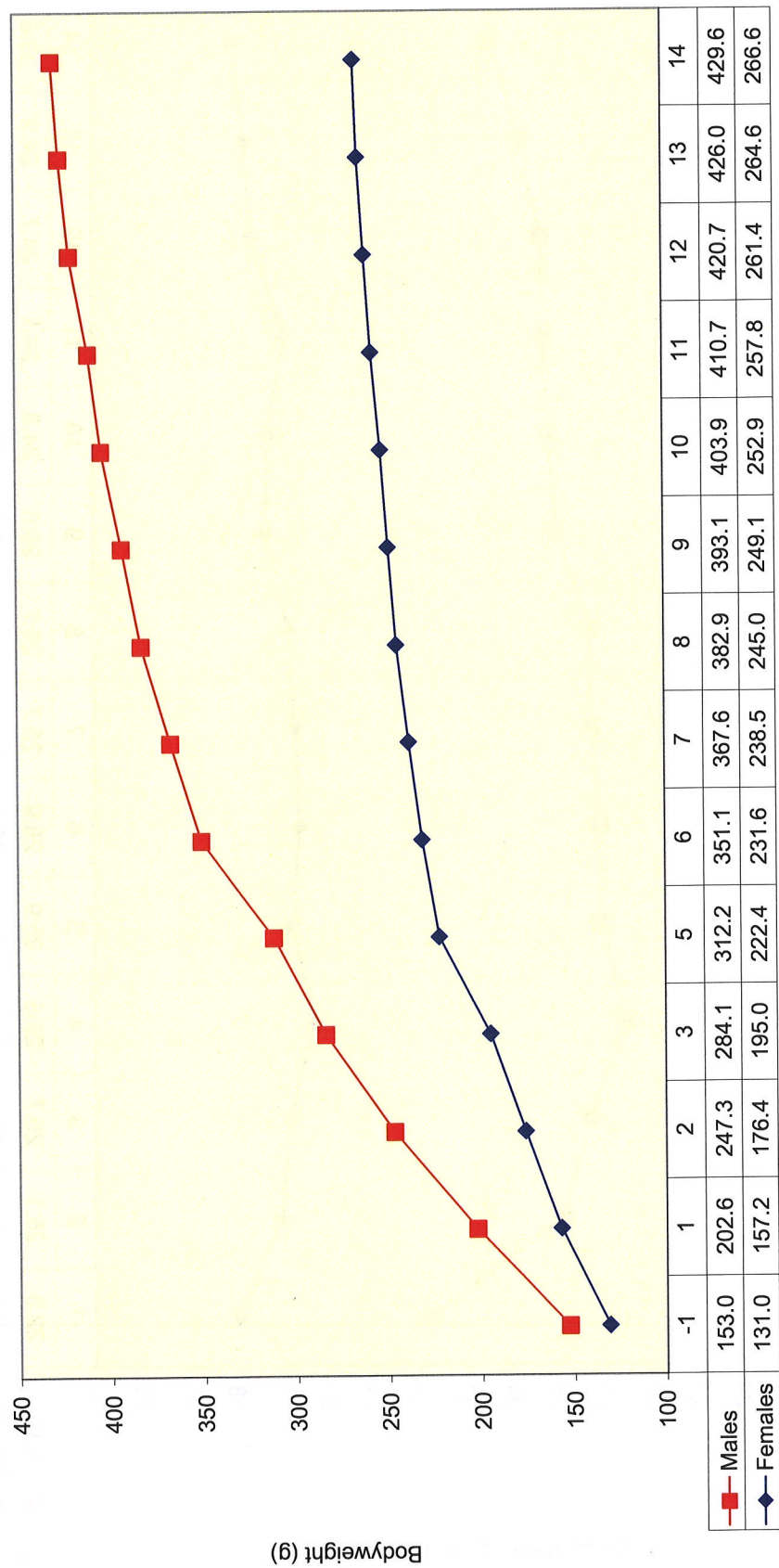
date: 3 March 2006

 13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM VIII - Historical control data

STUDY NO.: 41950

Fig. 1a: 13 week Studies - Bodyweight - Both sexes



Week number

Fig. 2a: 13 week Studies - Food consumption - Both sexes

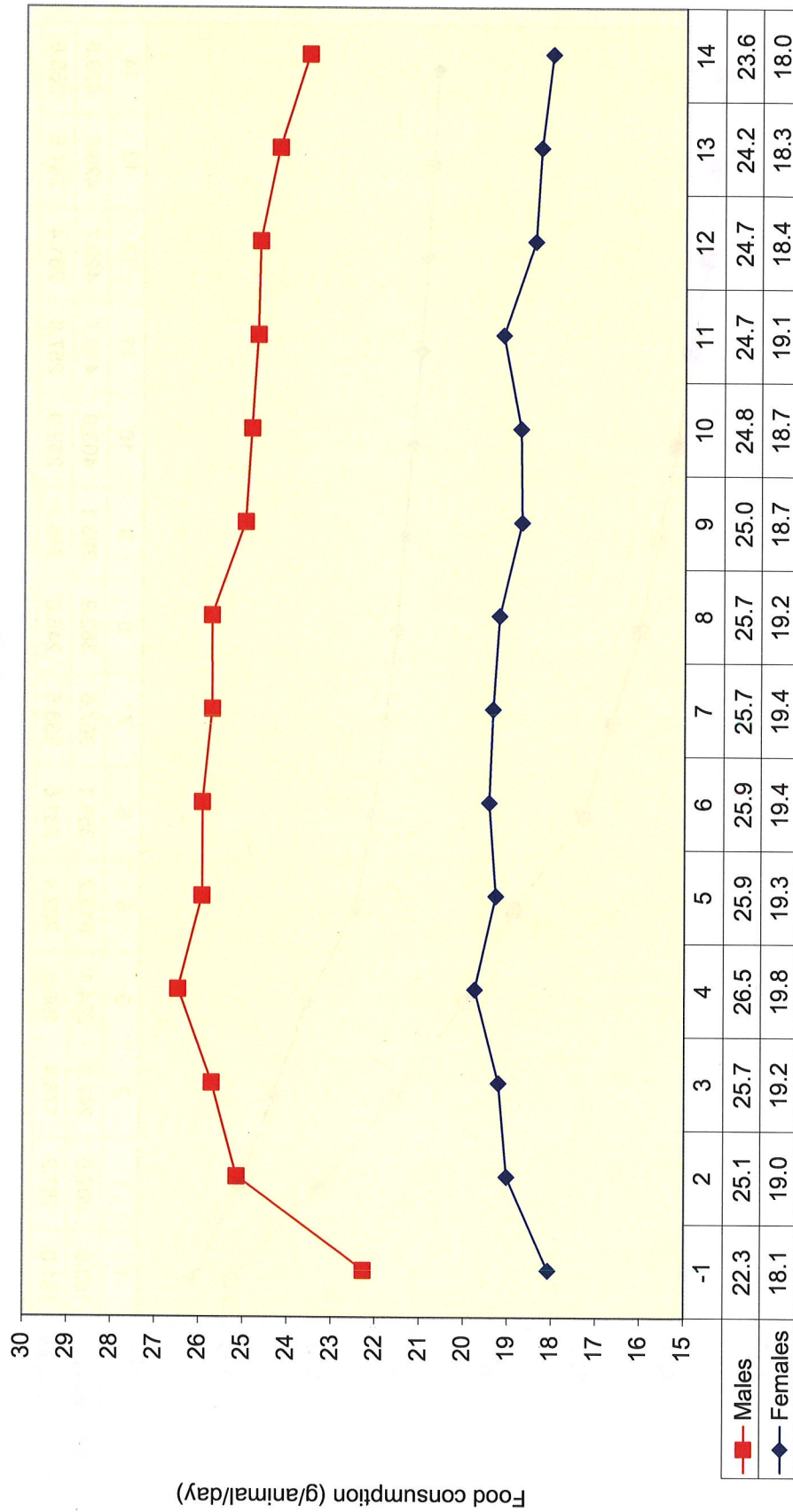


Fig. 3a: 13 week Studies – Haematology - Males

Parameter	Units	No.	Maximum	Minimum	Mean	Std Dev
Haemoglobin	g/dl	160	18.4	13.5	16.2	0.7
Red Blood Cell Count	$10^{12}/l$	160	10.2	7.8	9.1	0.5
Haematocrit	%	160	54.9	38.9	48.0	2.5
Mean Corpuscular Hb	pg	160	19.7	15.7	17.9	0.8
Mean Corpusc. Hb conc.	g/dl	160	35.8	31.6	33.9	1.1
Mean Red Blood Cell Vol.	fl	160	60.8	45.5	52.8	3.0
White Blood Cell Count	$10^9/l$	160	19.0	5.9	10.8	2.4
Neutrophils	%	160	45.1	5.3	15.6	5.9
Lymphocytes	%	160	89.7	51.8	78.4	6.3
Monocytes	%	160	6.0	1.3	2.8	0.9
Eosinophils	%	160	7.2	0.5	1.8	0.9
Basophils	%	160	0.6	0.0	0.3	0.1
Large Unstained Cells	%	160	2.4	0.5	1.2	0.4
Platelets	$10^9/l$	160	1383.0	529.0	959.0	136.2
Mean Platelet Volume	fl	10	4.5	4.1	4.4	0.2
Prothrombin Time	sec.	89	18.2	10.3	12.9	1.2

Fig. 3a: 13 week Studies – Haematology - Females

Parameter	Units	No.	Maximum	Minimum	Mean	Std Dev
Haemoglobin	g/dl	157	17.3	11.7	15.2	0.7
Red Blood Cell Count	10 ¹² /l	157	9.3	6.3	8.2	0.4
Haematocrit	%	157	49.8	35.2	44.3	2.1
Mean Corpuscular Hb	pg	157	19.8	16.5	18.4	0.6
Mean Corpusc. Hb conc.	g/dl	157	36.7	32.2	34.3	1.0
Mean Red Blood Cell Vol.	fl	157	59.5	48.8	53.8	2.1
White Blood Cell Count	10 ⁹ /l	157	17.7	2.9	7.8	2.4
Neutrophils	%	157	28.0	5.2	11.9	4.0
Lymphocytes	%	157	90.7	66.6	82.2	4.4
Monocytes	%	157	6.1	1.0	2.5	0.8
Eosinophils	%	157	5.9	0.6	2.1	0.8
Basophils	%	157	0.6	0.0	0.2	0.1
Large Unstained Cells	%	157	2.1	0.4	1.0	0.4
Platelets	10 ⁹ /l	157	1377.0	561.0	1037.9	140.9
Mean Platelet Volume	fl	9	4.4	3.6	4.0	0.3
Prothrombin Time	sec.	88	21.6	11.5	13.5	1.8

Fig. 4a: 13 week Studies – Serum Chemistry - Males

Parameter	Units	No.	Maximum	Minimum	Mean	Std Dev
Albumin/globulin ratio		10	0.8	0.6	0.7	0.1
Albumin	g/dl	90	4.1	2.9	3.4	0.3
Alanine Amino-Transferase	U/l	160	218.1	34.9	53.7	18.0
Alkaline Phosphatase	U/l	160	459.0	131.6	258.9	73.6
Aspartate Amino-Transferase	U/l	160	201.8	56.1	92.8	25.3
Total Bilirubin	mg/dl	160	0.3	0.0	0.1	0.0
Calcium	mmol/l	180	2.9	2.1	2.6	0.1
Total Cholesterol	mg/dl	160	176.1	71.9	104.1	17.9
Chloride	mmol/l	160	104.0	81.5	97.0	4.9
Creatinine	mg/dl	160	0.9	0.4	0.6	0.1
Globulin	g/dl	10	4.9	4.0	4.3	0.3
Glucose	mg/dl	160	203.0	91.9	130.7	19.3
Potassium	mmol/l	180	5.3	2.9	3.8	0.5
Sodium	mmol/l	179	162.6	121.9	144.0	9.0
Total Protein	g/dl	160	8.1	6.5	7.1	0.3
Triglycerides	mg/dl	20	40.5	21.4	29.3	6.1
Urea	mg/dl	160	96.4	30.2	45.5	12.3

Fig. 4a: 13 week Studies – Serum Chemistry - Females

Parameter	Units	No.	Maximum	Minimum	Mean	Std Dev
Albumin/globulin ratio		10	0.9	0.7	0.8	0.0
Albumin	g/dl	90	4.4	3.0	3.6	0.4
Alanine Amino-Transferase	U/l	158	64.0	22.9	40.5	7.9
Alkaline Phosphatase	U/l	158	324.3	77.6	188.5	53.0
Aspartate Amino-Transferase	U/l	158	172.2	47.0	86.4	16.8
Total Bilirubin	mg/dl	158	0.2	0.0	0.1	0.0
Calcium	mmol/ l	177	3.3	2.3	2.6	0.1
Total Cholesterol	mg/dl	158	221.6	52.5	104.4	23.9
Chloride	mmol/ l	158	103.7	79.6	96.8	4.9
Creatinine	mg/dl	158	1.0	0.4	0.7	0.1
Globulin	g/dl	10	4.3	4.0	4.1	0.1
Glucose	mg/dl	158	167.1	83.3	111.9	15.6
Potassium	mmol/ l	177	5.4	2.2	3.5	0.5
Sodium	mmol/ l	177	154.7	119.4	143.2	7.0
Total Protein	g/dl	158	8.7	6.1	7.1	0.4
Triglycerides	mg/dl	20	36.6	15.2	25.0	5.8
Urea	mg/dl	158	88.8	31.1	50.1	10.4

Fig. 5a: 13 week Studies – Urinalysis - Males

Parameter	Units	No.	Maximum	Minimum	Mean	Std Dev
Chloride	mmol/h	20	0.03	0.01	0.02	0.01
Potassium	mmol/h	20	0.12	0.03	0.07	0.02
Sodium	mmol/h	20	0.03	0.01	0.02	0.01
Specific Gravity		110	1.06	1.01	1.03	0.01
Urine Volume	ml	89	24.00	1.00	7.89	6.15

Fig. 5a: 13 week Studies – Urinalysis - Females

Parameter	Units	No.	Maximum	Minimum	Mean	Std Dev
Chloride	mmol/h	20	0.03	0.00	0.01	0.01
Potassium	mmol/h	20	0.06	0.01	0.03	0.01
Sodium	mmol/h	20	0.03	0.01	0.02	0.01
Specific Gravity		69	1.06	1.01	1.03	0.01
Urine Volume	ml	68	21.00	1.00	5.85	5.00

Fig. 6a: 13 week Studies – Terminal Bodyweight - Males

TBW	No.	Maximum	Minimum	Mean	Std Dev
TBW	96	486.7	375.6	430.9	22.7

Fig. 6a: 13 week Studies – Terminal Bodyweight - Females

TBW	No.	Maximum	Minimum	Mean	Std Dev
TBW	102	308.6	191.2	266.4	20.6

Fig. 7a: 13 week Studies – Organ Weights - Males
(% of bodyweight)

Organ	No.	Maximum	Minimum	Mean	Std Dev
Adrenals	102	0.020	0.009	0.013	0.002
Brain	101	0.510	0.378	0.430	0.023
Epididymides	65	0.394	0.271	0.322	0.021
Heart	102	0.403	0.290	0.344	0.021
Kidneys	102	0.924	0.560	0.685	0.073
Liver	102	4.980	2.929	3.718	0.393
Pituitary	37	0.004	0.002	0.003	0.001
Spleen	102	0.291	0.148	0.201	0.026
Testes	102	1.119	0.333	0.907	0.089
Thymus	65	0.093	0.038	0.064	0.015
Thyroid	52	0.008	0.003	0.005	0.001

Fig. 7a: 13 week Studies – Organ Weights - Females
(% of bodyweight)

Organ	No.	Maximum	Minimum	Mean	Std Dev
Adrenals	98	0.038	0.013	0.024	0.004
Brain	98	0.819	0.550	0.653	0.047
Heart	98	0.440	0.322	0.379	0.024
Kidneys	98	0.870	0.570	0.680	0.051
Liver	98	4.920	2.690	3.531	0.341
Ovaries	98	0.042	0.017	0.032	0.005
Pituitary	35	0.007	0.003	0.005	0.001
Spleen	98	0.365	0.181	0.257	0.035
Thymus	63	0.129	0.037	0.082	0.017
Thyroid	50	0.011	0.005	0.008	0.001
Uterus	98	0.572	0.095	0.189	0.071

**RTC - 13- week Oral Studies – Microscopic Pathology – Males
Harlan SD – (2003-2005)**

Organs/Tissues	Number Examined	Diagnoses	Incidence Observed %	
Adrenals	82	CORTICAL FOCAL HYPERPLASIA	1	1.22%
	82	CORTICAL HYPERTROPHY	1	1.22%
	82	HAEMATOCYST/S	1	1.22%
Cervical nodes	82	CYSTIC CHANGE	1	1.22%
	82	REACTIVE HYPERPLASIA	15	18.29%
Colon	82	DISTENSION	2	2.44%
Epididymides	82	ABSENCE OF SPERM	1	1.22%
Eyes	92	INJURY	4	4.35%
Harderian glands	22	CHRONIC INFLAMMATION	5	22.73%
Heart	92	CHRONIC INFLAMMATION	7	7.61%
Kidneys	92	CHRONIC INFLAMMATION	4	4.35%
	92	CHRONIC PROGRESSIVE NEPHROSIS	49	53.26%
	92	CORTICAL TUBULAR CELL BASOPHILIA	14	15.22%
	92	CORTICAL TUBULAR DILATATION	16	17.39%
	92	HYALINE DROPLETS IN THE PROXIMAL TUBULES	1	1.09%
	92	M-NEPHROBLASTOMA	1	1.09%
	92	MINERALIZATION	1	1.09%
Liver	92	BILE DUCT PROLIFERATION	2	2.17%
	92	CENTRIOBULAR HEPATOCYTIC VACUOLATION	11	11.96%
	92	CHRONIC INFLAMMATION	39	42.39%
	92	FIBROSIS	3	3.26%
	92	HEPATOCYTIC NECROSIS	2	2.17%
	92	CLEAR CELL CHANGE	6	6.52%
	92	PIGMENTATION	2	2.17%
Lungs	92	AGGREGATIONS OF ALVEOLAR MACROPHAGES	2	2.17%
	92	ALVEOLAR HAEMORRHAGE	5	5.43%
	92	CHRONIC INFLAMMATION	42	45.65%
	92	OSSEOUS METAPLASIA	1	1.09%
	92	PERIBRONCHIAL LYMPHOID HYPERPLASIA	3	3.26%
	92	PNEUMONIA	1	1.09%
	92	VASCULAR MINERALIZATION	27	29.35%
Mammary area	72	ABSCCESS	1	1.39%
Mesenteric nodes	82	HAEMORRHAGE	2	2.44%
Pancreas	82	ACINAR ATROPHY	1	1.22%
	82	CHRONIC INFLAMMATION	2	2.44%

Parathyroid glands	74	FIBROSIS	1	1.35%
Prostate	82	CHRONIC INFLAMMATION	9	10.98%
Pituitary	82	DEVELOPMENTAL CYST/S	2	2.44%
Skin	82	ABSCCESS(ES)	2	2.44%
Stomach	82	MIXED INFLAMMATORY CELL INFILTRATION	1	1.22%
Testes	92	SEMINIFEROUS TUBULES ATROPHY	3	1.09%
Thyroid	82	ECTOPIC THYMIC TISSUE	1	1.22%
Urinary bladder	82	DISTENSION	2	2.44%
	82	PROTEINACEOUS PLUG	10	12.20%

RTC - 13- week Oral Studies – Microscopic Pathology – Females
Harlan SD – (2003-2005)

Organs/Tissues	Number Examined	Diagnoses	Incidence Observed	%
Cervical nodes	82	REACTIVE HYPERPLASIA	6	7.32%
Colon	82	MIXED INFLAMMATORY CELL INFILTRATION	1	1.22%
Harderian glands	22	CHRONIC INFLAMMATION	4	18.18%
Heart	92	CHRONIC INFLAMMATION	6	6.52%
Ileum	82	VILLOUS NECROSIS	1	1.22%
Kidneys	92	CHRONIC INFLAMMATION	4	4.35%
	92	CHRONIC PROGRESSIVE NEPHROSIS	20	21.74%
	92	CORTICAL TUBULAR CELL BASOPHILIA	4	4.35%
	92	CORTICAL TUBULAR DILATATION	9	9.78%
	92	MINERALIZATION	20	21.74%
Liver	92	BILE DUCT PROLIFERATION	2	2.17%
	92	CHRONIC INFLAMMATION	33	35.87%
	92	EXTRAMEDULLARY HAEMOPOIESIS	3	3.26%
	92	CLEAR CELL CHANGE	3	3.26%
	92	PIGMENTATION	1	1.09%
Lungs	92	AGGREGATIONS OF ALVEOLAR MACROPHAGES	3	3.26%
	92	ALVEOLAR EPITHELIALIZATION	1	1.09%
	92	ALVEOLAR HAEMORRHAGE	2	2.17%
	92	CHRONIC INFLAMMATION	27	29.34%
	92	GRANULOMA/S	1	1.09%
	92	PERIBRONCHIAL LYMPHOID HYPERPLASIA	2	2.17%
	92	VASCULAR MINERALIZATION	11	11.96%
Ovaries	82	FOLLICULAR CYST/S	2	2.44%
Pancreas	82	CHRONIC INFLAMMATION	1	1.22%
Parathyroid glands	74	FIBROSIS	1	1.35%
Pituitary	82	DEVELOPMENTAL CYST/S	2	2.44%
Stomach	82	CHRONIC INFLAMMATION	1	1.22%
	82	KERATIN CYST/S	2	2.44%
Thymus	82	BRANCHIAL CYST/S	2	2.44%
	82	ECTOPIC THYROID TISSUE	2	2.44%
Uterus	73	HYDROMETRA	4	5.48%

 13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

ADDENDUM IX - Study protocol and protocol amendments

STUDY NO.: 41950



**13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD**

Final Protocol
prepared for

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RTC Enquiry Number: 41950

March 2005

- 1 of 17 -

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Partita IVA: 00920611001

1. INTRODUCTION

1.1 Objective

The purpose of this study is to investigate the toxicity of [REDACTED] 10 in rats after daily oral administration for 13 weeks and recovery from any treatment-related effects during a recovery period of 8 weeks.

1.2 Species

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

1.3 Route of administration

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

1.4 Regulatory compliance

This study will be conducted in compliance with the GLP regulations of:

- Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004;
- ENV/MC/CHEM(98)17 "OECD principles on Good Laboratory Practice – as revised in 1997";
- Decreto Legislativo no. 120 of 27 January 1992 and subsequent revisions.

The Sponsor has required the testing activity on this substance to develop notification/submission to regulatory authorities and produce a safety assessment for production and uses.

This study design is in agreement with the procedures described in OECD Guideline no. 408 'Repeated Dose 90-day Oral Toxicity Study in Rodents' adopted 21 September 1998.

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 RTC's Ethical Committee.

2. TEST ITEM

2.1 Characterisation

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

A certificate of analysis for the test item should also be supplied.

2.2 Identity

The test item will be [REDACTED]

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

Batch Number : 90156/96-2

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 test item received and used at RTC will be recorded according to RTC standard procedures.

2.3 Safety precautions

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

2.4 Vehicle

The vehicle will be distilled water.

2.5 Formulation procedure

The required amount of [REDACTED] will be dissolved/suspended in the vehicle. The formulation will be prepared daily (concentrations of 0.003, 0.013 and 0.05 mg/ml), unless specified otherwise. 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 that the stability of the formulation is satisfactory. Samples of the formulations prepared in weeks 1 and 13 of the study will also be analysed to check the homogeneity (in the case of suspensions) and concentration. Chemical analysis will be carried out by the Analytical Chemistry Department at RTC.

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 destroyed by incineration.

3. TEST SYSTEM

3.1 Animal supply and acclimatisation

A total of 130 Hsd: Sprague Dawley SD rats (70 males and 60 females), 27-29 days old and with body weight of approximately 75-99 g, will be ordered from Harlan Italy s.r.l., San Pietro al Natisone (UD), Italy.

After arrival the weight range for each sex will be determined and the animals will be temporarily identified within the cage by means of a coloured mark on the tail. A health check will then be performed by a veterinarian.

An acclimatisation period of approximately 2 weeks will be allowed before the start of treatment, during which time the health status of the animals will be assessed by thorough observations. Rats considered unsatisfactory will be killed and where appropriate subjected to pathological examination. Unsatisfactory batches of animals will be rejected before the start of treatment.

3.2 Animal husbandry

The animals will be housed in a limited access rodent facility. Animal room controls will be set to maintain temperature and relative humidity at $22^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $55\% \pm 15\%$ 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 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 (4 RF 21, 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.

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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 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 5 of one sex per cage (main groups) and 3 of one sex per cage (toxicokinetic group).

The cages will be identified by a label 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. No replacements will occur after the first dose is administered.

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 previous studies.

4.1.2 Dose levels, group size and identification

Each main group will comprise 10 male and 10 female rats. Control and high dose groups will include 5 additional animals per sex to be sacrificed after 8 weeks of recovery. One satellite group for toxicokinetics will comprise 9 male animals. The group identification and animal numbers assigned to the treatment are summarised below:

MAIN AND RECOVERY GROUPS

Group Number	Treatment (mg/kg/day)+	Level	Rat Numbers			
			Main phase		Recovery phase	
			M (even)	F (odd)	M (even)	F (odd)
1	0	Control	2-20	1-19	22-30	21-29
2	0.03	Low	32-50	31-49		
3	0.13	Medium	52-70	51-69		
4	0.5	High	72-90	71-89	92-100	91-99

+: in terms of test item as supplied

SATELLITE GROUP

Group Number:	Treatment (mg/kg)	Level	Rat numbers Males (even)
5	0.5	High	102 - 118
+: in terms of test item as supplied			

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

4.1.3 Administration of test item

The test item will be administered orally by gavage at a dose volume of 10 ml/kg 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 animals will be dosed once a day, 7 days a week, for a minimum of 13 consecutive weeks. Satellite group animals will be dosed once only. Animals in the main phase will be dosed up until the day before necropsy. No treatment will be given during the 8 week 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 and again in the afternoon. At weekends and Public Holidays a similar procedure will be followed except that the final check will be carried out at approximately mid-day. This will allow *post mortem* examinations to be carried out during the working period of that day. Severely debilitated animals will be observed carefully. Animals judged to be *in extremis* will be killed. A complete necropsy will be performed in all cases as detailed in section 4.5.2 below.

4.2.2 Pre- and post-dose observations

All observations will be recorded for individual animals. Examination of individual animals for signs of reaction to treatment will be carried out daily prior to dosing 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, unusual respiratory pattern).

Once during weeks 12 or 13 of treatment and once during week 8 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 12 or 13 of treatment and once during week 8 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 group, on the day that treatment commences, weekly thereafter and just prior to necropsy.

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.

4.2.7 Ophthalmoscopy (Main groups)

Both eyes of all animals assigned to the study will be examined just prior to the commencement of treatment by means of an ophthalmoscope, and by a slit-lamp microscope, after the instillation of 0.5% Tropicamide (Visumidriatic®, Visufarma, Rome, Italy). Where possible, animals with non-resolving lesions will be replaced with spare animals showing no ocular abnormality, from the batch initially ordered for the study. In the first instance the eyes of all animals from high-dose and control groups will be re-examined during week 13 of treatment. If treatment-related changes are observed the examination will be extended to the other treated groups (additional cost). Ophthalmoscopy will also be repeated during week 8 of recovery if considered necessary (additional cost).

4.3 Clinical pathology investigations (Main groups)

During week 13 of treatment, samples of blood will be withdrawn under isoflurane anaesthesia from the retro-orbital sinus of the first 10 surviving male and the first 10 surviving female animals from each group, under conditions of food and water deprivation. At the same time interval, individual overnight (approximately 16 hours) 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.

Prior to necropsy, blood samples will be taken from the abdominal vena cava of the same rats from each group, under isofluorane anaesthesia, to perform coagulation tests. During week 8 of the recovery period blood and/or urine samples may also be taken (after consultation with the Sponsor) from all surviving animals under identical conditions in order to re-evaluate all those 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
Polymorphonuclear 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 the animals of the satellite group. Individual urine and faeces samples will also be collected from the same animals at the time intervals indicated in following scheme:

Group Number:	Treatment (mg/kg)	Animal Number (Males)	Time points (h) Blood samples	Time points (h) Urine/faeces samples
5	0.5	102,104,106	0, 4, 24	6-12 and 42-48
		108,110,112	2, 8, 96	18-24 and 162-168
		114,116,118	6, 48, 168	0-6 and 90-96

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. Urine and faeces samples will also be frozen and stored at -20°C, pending analysis (if required, additional cost). Analysis of the samples will be carried out by the Analytical Chemistry Department of RTC. 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 after the last sample has been collected. No necropsy examination will be performed in these animals.

4.5 Terminal studies

4.5.1 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, including those found dead, will be subjected to necropsy, supervised by a pathologist, as detailed below.

4.5.2 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 4.5.3 to 4.5.5).

Representative photographs will be taken of any significant findings, if considered appropriate.

4.5.3 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.

4.5.4 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 4.5.6).

4.5.5 Histopathological examination (Main Groups)

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 as detailed below:

- a) Tissues specified in Annex 1 from all animals in the control and high dose groups dying during the treatment period or killed at the end of the 13 weeks of treatment.
- b) Tissues specified in Annex 1 from all animals in the low and medium dose groups killed or dying during the treatment period.
- c) All abnormalities in all groups.

The examination could then be extended to include, from all other animals killed after 13 weeks of treatment or 8 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: abnormalities in all groups, tissues of unscheduled deaths in the low and medium dose groups, target tissues in the low and medium dose groups and liver enzymes for the evaluation of hepatic peroxisome proliferation) will incur an additional cost.

4.5.6 Liver enzymes (Main groups, if required, additional cost)

Following removal of liver sections for histopathological examination, all remaining tissue (at least 4 g in the first instance, preferably taken from the left and right lateral lobes) will be rinsed in ice-cold physiological saline, then placed into individual packages (one per animal) and immediately frozen in liquid nitrogen (-80°C). The liver samples taken for enzyme analysis will be transported frozen on dry ice to:

#

In the first instance, only samples from the first 5 surviving male and the first 5 surviving female rats 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, #. A Q.A.U. revised report will be returned to RTC for inclusion in the Final Report.

= to be added in a protocol amendment

4.5.7 Photomicrographs

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

5. ANALYSIS OF DATA

5.1 Presentation of data

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

5.2 Statistics

For continuous variables the significance of the differences amongst group means will be assessed by Dunnett's test or a modified *t* test, depending on the homogeneity of data. Statistical analysis of histopathological findings will be carried out by means of the non-parametric Kolmogorov-Smirnov test.

6. AMENDMENTS TO THE PROTOCOL

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

7. REPORTING

7.1 Interim report

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

7.2 Final report

A draft report will be sent to the Sponsor. With the exception of the dated signature of scientists and other professional personnel, the draft report will contain all information and data included in the final report.

Comments made by the Sponsor may be incorporated into the draft, after which it will be issued as the final report.

The final report will include the information and data required by current internationally recognised regulations. One original unbound, one copy bound and a PDF version will be supplied.

7.3 Corrections or additions to the final report

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

8. RECORDS AND ARCHIVES

Full records will be maintained of all aspects of study conduct, together with results of all measurements and observations.

RTC will retain all relevant computer stored data generated by electronic on-line capture in a manner fully compliant with Good Laboratory Practice. At the end of the specified period, these data 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.

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.

Management of all raw data, records and documentation generated at each test site will be specified in the documents (Principal Investigator's Agreement), pertaining to the delegated phase.

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

9. 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.
- 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).

The QA of each Test Site will be responsible for quality assurance procedures pertaining to the delegated activities.

Any GLP deviations and findings from study specific inspections, noted by the QA of each Test Site, that could affect the quality and the integrity of the study will be notified to the Study Director and relevant Principal Investigator.

10. LOCATION OF THE STUDY

10.1 Test Site Location

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

Study Director: C. Longobardi

Study phases: All stages of the study, with the exception of those detailed below for the other Test Sites.

#

#

Principal Investigator: Dr.#

Delegated phases: enzymatic analyses, interpretation of data and production of a final report

10.2 Lead QAU

Research Toxicology Centre S.p.A.
Via Tito Speri, 12
00040 Pomezia (Roma)
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. PROJECTED TIME PLAN

	<u>Date</u>
1. Start of treatment	: First half of April 2005
2. End of <i>in vivo</i> phase	: First half of September 2005
3. End of histopathological examination	: First half of September 2005
4. QA-audited draft report to Sponsor	: 6 months after the first day of treatment

= to be added in a protocol amendment

ANNEX 1. TISSUE PROCESSING

Organs / Tissues	Weight	Fixation Preservation	Microscopic Examination
Abnormalities		✓	✓
Adrenal glands	✓	✓	✓
Aorta		✓	✓
Bone marrow (from sternum)		✓	✓
Brain	✓	✓	✓
Caecum		✓	✓
Colon		✓	✓
Duodenum		✓	✓
Epididymides	✓	✓	✓
Eyes		✓	*
Femur with joint		✓	*
Heart	✓	✓	✓
Ileum (including Peyer's patches)		✓	✓
Jejunum		✓	✓
Kidneys	✓	✓	✓
Liver	✓	✓	✓
Lungs (including mainstem bronchi)		✓	✓
Lymph nodes - cervical		✓	✓
Lymph nodes - mesenteric		✓	✓
Mammary area		✓	✓
Oesophagus		✓	✓
Ovaries	✓	✓	✓
Oviducts ^a		✓	✓
Pancreas		✓	✓
Parathyroid glands ^b		✓	✓
Pituitary gland		✓	✓
Prostate gland		✓	✓
Rectum		✓	✓
Salivary glands		✓	✓
Sciatic nerve		✓	✓
Seminal vesicles		✓	*
Skeletal muscle		✓	*
Skin		✓	✓
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	Control	2-20	1-19	1 - 2	11 - 12
2	0.03	Low	32-50	31-49	4 - 5	14 - 15
3	0.13	Medium	52-70	51-69	6 - 7	16 - 17
4	0.5	High	72-90	71-89	8 - 9	18 - 19
RECOVERY PHASE°						
Group Number	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
1	0	Control	22-30	21-29	3	13
4	0.5	High	92-100	91-99	10	20
+ 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	0.5	High	102 - 118	21-23
+: in terms of test item as supplied				

Group/Sex
Cage no.

To be inserted in the Final Report.

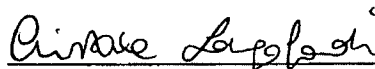
PROTOCOL APPROVAL PAGE

STUDY TITLE : 13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TEST FACILITY : RESEARCH TOXICOLOGY CENTRE S.p.A.
Via Tito Speri, 12
00040 Pomezia (Rome)
Italy

RTC ENQUIRY NO. : 41950

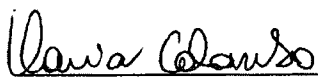
TEST ITEM : XXXXXXXXXX

APPROVED BY :  30-Mar-2005
C. Longobardi, Biol.D. Date
Study Director

APPROVED BY :  30-Mar-2005
L. Luperi, D.V.M. Date
Responsible for Animal Welfare

RELEASED BY :  31 Mar 2005
J. Brightwell, Ph.D. Date
Scientific Director

SPONSOR : SOLVAY SOLEXIS S.p.A.
Viale Lombardia, 20
20121 Bollate (MI)
Italy

AUTHORISED BY :  05/04/2005
SPONSOR* Date

Name and Title : LAURA COLOMBO INDUSTRIAL TOXICOLOGY
SOLVAY SOLEXIS S.p.A.
* Please print or type your name and company status below your signature.



PROTOCOL AMENDMENT (1)

STUDY TITLE : [REDACTED]
13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

STUDY NO. : 41950

DATE OF PROTOCOL APPROVAL : 30 March 2005

DATE OF ISSUE OF AMENDMENT : Date signed

THE FOLLOWING SECTION ARE TO BE AMENDED:

Section 4.4 Toxicokinetic (Satellite group) (Page 10)

Delete : (Satellite group)

Insert : (Main and Satellite groups)

Add at the end of second paragraph : Additional blood samples of 0.8 ml will be collected as described above, approximately 2 h after the last dosing, from the first 3 male and 3 female animals of groups 2, 3 and 4 at the end of weeks 11, 12 and 13.
On the last day of dosing approximately 24, 48, 96, 144 and 192 hours after last dosing, blood samples of 0.8 ml will be withdrawn from group 4 recovery animals (5 males and 5 females). Individual urine and faeces samples will also be collected from the same animals at the following time intervals: 0-6, 6-12, 12-24, 48, 72, 96, 120, 144, 168 and 192 hours after the last dosing.

Reason : Additional activities requested by the Sponsor.

RTC Study Number: 41950

- 1 of 3 -

Commercial Office

RTC S.p.A.
Via Tito Spert, 12
00040 Pomezia (Roma) - ITALY
Tel.: + 39.06.91095 1
Fax: + 39.06.910 5737
e-mail: mkt@rtc.it
www.rtc.it

Head Office and Administration

RTC S.p.A.
Via Tito Spert, 12
00040 Pomezia (Roma) - ITALY
Tel.: + 39.06.91095 1
Fax: + 39.06.912.2233
P.O. Box 15301-00143 - Roma Eur Laurentino

RTC S.p.A.
Capitale sociale Euro 5.164.000
C.C.I.A.A. n° 375376
Reg. Soc. Trib. di Roma n° 2828/72
Cod. Fisc.: 00653120584
Partita IVA: 00920611001

PROTOCOL AMENDMENT (1)

Section 4.5.1 Euthanasia (Page 10)

- Delete : Animals *in extremis* or killed for humane reasons and those that have completed the scheduled test period will be killed with carbon dioxide.
- Insert : Animals from the main and recovery groups *in extremis* or killed for humane reasons and those that have completed the scheduled test period will be killed by exanguination under isoflurane anaesthesia. Satellite group animals will be killed with carbon dioxide.
- Reason : Incorrect in the study protocol.

PROTOCOL AMENDMENT (1)

APPROVAL PAGE

STUDY TITLE : 13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TEST FACILITY : RESEARCH TOXICOLOGY CENTRE S.p.A.
Via Tito Speri, 12
00040 Pomezia (Roma)
Italy

RTC STUDY NO. : 41950

TEST ITEM : XXXXXXXXXX

APPROVED BY : C. Longobardi 13-Jul-2005
C. Longobardi, Biol.D. Date
Study Director

RELEASED BY : J. Brightwell 13 Jul 2005
J. Brightwell, Ph.D. Date
Scientific Director

SPONSOR : SOLVAY SOLEXIS S.p.A.
Viale Lombardia, 20
20121 Bollate (MI)
Italy

AUTHORISED BY : Ilaria Colombo 15/7/2005
SPONSOR* Date

Name and Title : ILARIA COLOMBO INDUSTRIAL TOXICOLOGY

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



PROTOCOL AMENDMENT (2)

STUDY TITLE : [REDACTED]
13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

STUDY NO. : 41950

DATE OF PROTOCOL APPROVAL : 30 March 2005

DATE OF ISSUE OF AMENDMENT : Date signed

THE FOLLOWING SECTIONS ARE TO BE AMENDED:

Section 4.5.6 Liver enzyme (Page 11)

Delete : Whole paragraph.

Insert : Following removal of liver sections for histopathological examination, all remaining tissue (at least 4 g in the first instance, preferably taken from the left and right lateral lobes) will be rinsed in ice-cold physiological saline, then placed into individual packages (one per animal) and immediately frozen in liquid nitrogen. Frozen samples will be maintained at -80°C pending despatch for analysis. The liver samples taken for enzyme analysis will be transported frozen on dry ice to:

Department of *In Vitro* Metabolism
Building Numbers: E04
Laboratory Numbers: 1038, 1039, 1040
Huntingdon Life Sciences Ltd
Huntingdon Research Centre
Huntingdon
Cambridgeshire
PE28 4HS
UK

Telephone: +44(0) 1480 892833 – Principal Investigator
Facsimile: +44(0) 1480 892281 – Department
Facsimile: +44(0) 1480 890693 – Company

RTC Study Number: 41950

- 1 of 3 -

Commercial Office

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www.rtc.it

Head Office and Administration

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Fax: +39.06.912.2233
P.O. Box 15301-00143 - Roma Eur Laurentino

RTC S.p.A.
Capitale sociale Euro 5.164.000
C.C.I.A.A. n° 375376
Reg. Soc. Trib. di Roma n° 2828/72
Cod. Fisc.: 00853120584
Partita IVA: 00820611001

PROTOCOL AMENDMENT (2)

In the first instance, only samples from the first 5 surviving male and the first 5 surviving female rats from control and high dose groups will be examined. The determination of cyanide-insensitive palmitoyl-CoA oxidation activity will be done for the evaluation of hepatic peroxisome proliferation according to the procedures described in Annex 3 of study protocol. These tests will be undertaken and interpreted by the test Site indicated above under the responsibility of the Principal Investigator, Anne Matthews (Ref. No. RTS0047). A QAU revised report will be returned to RTC for inclusion in the Final Report.

Reason : Information omitted in the study protocol.

Section 10.1 Test site location (Page 14)

Delete : #

Insert : Huntingdon Life Sciences Ltd
Huntingdon Research Centre
Huntingdon
Cambridgeshire
PE28 4HS
UK
Department of *In Vitro* Metabolism
Principal Investigator: Anne Matthews

ANNEX 3 (insert after Annex 2)

Reason : Information not present in the study protocol.

PROTOCOL AMENDMENT (2)

Reference Number: RTS0047

CONFIDENTIAL

1. GOOD LABORATORY PRACTICE

1.1 Good Laboratory Practice

This phase of the study will be conducted in compliance with the principles of Good Laboratory Practice Standards as set forth in:

The UK Good Laboratory Practice Regulations 1999 (Statutory Instrument No 3106, as amended by Statutory Instrument 2004 No. 994).

OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17.

EC Commission Directive 2004/10/EC of 11 February 2004 (Official Journal No L 50/44).

These principles of Good Laboratory Practice are accepted by the regulatory authorities of the United States of America and Japan on the basis of intergovernmental agreements.

1.2 Standard operating procedures

This phase of the study will be conducted according to the Standard Operating Procedures of the Department of *In Vitro* Metabolism.

1.3 Test guidelines

There are no test guidelines that are applicable to this phase of the study.

PROTOCOL AMENDMENT (2)

Reference Number: RTS0047

2. STUDY MANAGEMENT

2.1 Huntingdon Life Sciences Personnel

Head, Department of <i>In Vitro</i> Metabolism:	Michael Hall, Ph.D.
Principal Investigator:	Anne Matthews, B.Sc.

2.2 Location of study phase

Department of *In Vitro* Metabolism
Building Numbers: E04
Laboratory Numbers: 1038, 1039, 1040

Huntingdon Life Sciences Ltd
Huntingdon Research Centre
Huntingdon
Cambridgeshire
PE28 4HS

Telephone:	+44(0) 1480 892833 – Principal Investigator
Facsimile:	+44(0) 1480 892281 - Department
Facsimile:	+44(0) 1480 890693 - Company

3. SCHEDULED TIME PLAN

Date of expected arrival of frozen livers:	Week beginning 25 July 2005
Beginning of experimental period:	08 August 2005
End of experimental period:	26 August 2005
Availability of draft data:	02 September 2005
Despatch of QA audited draft phase report:	30 September 2005

Page 2

RTC Study Number: 41950

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PROTOCOL AMENDMENT (2)

Reference Number: RTS0047

4. TEST SAMPLES

4.1 Origin of livers

A total of up to 20 rat liver samples, originating from RTC S.p.A. and frozen in the presence of solid CO₂, are expected for analysis.

4.2 Sample identification

Each sample will be identified with reference to animal number, sex and dose group, in accordance with those designations made by RTC S.p.A.

5. LIVER PROCESSING

All stages involved in the preparation of hepatic 3000 × g supernatant subcellular fractions will be conducted in the Department of *In Vitro* Metabolism, in a low-temperature environment. Frozen liver samples will be thawed by standing in ice-cold 50 mM Tris-HCl buffer, pH 7.4, containing 0.154 M KCl. 3000 × g Supernatant subcellular fractions will then be prepared by differential centrifugation of liver homogenates using standard techniques. The 3000 × g supernatant will be divided into aliquots and stored at ca. -75°C until used for assay of protein and enzyme activities.

Any residual thawed liver remaining after completion of the 3000 × g supernatant preparation will be discarded at this point.

6. MEASUREMENTS

The following parameters will be measured:

1. 3000 × g Supernatant protein concentration: method of Lowry *et al* (1951) *J. Biol. Chem.*, 193, 265.
2. Cyanide-insensitive palmitoyl CoA oxidase activity: method of Gray *et al.* (1983) *Toxicol. Appl. Pharmacol.*, 67, 15.

All assays will be performed in duplicate (as a minimum).

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RTC Study Number: 41950

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PROTOCOL AMENDMENT (2)

Reference Number: RTS0047

7. DATA PROCESSING

Individual animal concentration and rate data will be calculated using the measured values of the first two sample replicates, only, providing that each replicate measured value is $\leq 5\%$ different from the duplicate mean. Where this acceptance criterion is not fulfilled, a third replicate measured value will be used, either to achieve acceptance with one of the original two replicates or, if no replicate pair satisfies the criterion, to be included for derivation of the median of all three replicates.

Enzyme activities (rates) will be reported as per milligram of $3000 \times g$ supernatant protein and per gram of liver. Results will be expressed as mean $\pm$ standard deviation for each treatment group.

Detailed statistical analysis of the data will be conducted to determine whether there is any significant effect of treatment on the parameters measured.

8. REPORTING

The results of the work described in this Plan will be reported to the Study Director, RTC S.p.A. in a form suitable for inclusion in the study report. This will include a Principal Investigator GLP Compliance Statement and a Huntingdon Life Sciences Quality Assurance Statement.

Page 4

RTC Study Number: 41950

- 6 of 8 -

PROTOCOL AMENDMENT (2)

Reference Number: RTS0047

9. QUALITY ASSURANCE AND ARCHIVING PROCEDURES

9.1 Quality assurance

Huntingdon Life Sciences QA (Test Site QA) will inspect or audit the following in relation to this phase of the study.

Protocol Audit : Sections of the protocol relating to the work to be carried out at Huntingdon Life Sciences.

Study based inspections : Critical parts of this phase of the study will be inspected.

QA findings will be reported promptly to the Principal Investigator, Huntingdon Life Sciences (Test Site) Management, Study Director Test Facility Management and Lead QA on completion of each action.

9.2 Archiving

All raw data, samples and specimens (if appropriate) arising from the performance of this phase of the study will remain the property of the Sponsor.

Types of sample and specimen which are unsuitable, by reason of instability, for long term retention and archiving may be disposed of after the periods stated in Huntingdon Life Sciences Standard Operating Procedures.

All other samples and specimens and all raw data will be retained by Huntingdon Life Sciences in its archive for a period of five years from the date on which the Study Director signs the final report. After such time, the Study Director will be contacted and their advice sought on the return, disposal or further retention of the materials. If requested, Huntingdon Life Sciences will continue to retain the materials subject to a reasonable fee being agreed with the Sponsor.

Huntingdon Life Sciences will retain the Quality Assurance records relevant to this phase of the study and a copy of the final report in its archive indefinitely.

9.3 Disposal of biological samples

Any remaining portions of thawed liver will be discarded at the time of 3000 × g supernatant preparation (see Section 6).

3000 × g Supernatants will be discarded following issue of the final report, unless requested otherwise by the Study Director. The Study Director will be contacted prior to disposal of the 3000 × g supernatant fractions, only.

10. STAFF SAFETY

The standard safety precautions within the Department of *In Vitro* Metabolism will apply to this phase of the study.

Page 5

RTC Study Number: 41950

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PROTOCOL AMENDMENT (2)

APPROVAL PAGE

STUDY TITLE : 13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TEST FACILITY : RESEARCH TOXICOLOGY CENTRE S.p.A.
Via Tito Speri, 12
00040 Pomezia (Rome)
Italy

RTC STUDY NO. : 41950

TEST ITEM : XXXXXXXXXX

APPROVED BY : *C. Longobardi* 04-Aug-2005
C. Longobardi, Biol.D. Date
Study Director

RELEASED BY : *J. Brightwell* 4 Aug 2005
J. Brightwell, Ph.D. Date
Scientific Director

SPONSOR : SOLVAY SOLEXIS S.p.A.
Viale Lombardia, 20
20121 Bollate (MI)
Italy

AUTHORISED BY : *Ilawaldanilo* 4-Aug-2005
SPONSOR* Date

Name and Title : ILARIA CANTUCCI

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

RTC Study Number: 41950

- 8 of 8 -



PROTOCOL AMENDMENT (3)

STUDY TITLE : [REDACTED]
13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

STUDY NO. : 41950

DATE OF PROTOCOL APPROVAL : 30 March 2005

DATE OF ISSUE OF AMENDMENT : Date signed

THE FOLLOWING SECTIONS ARE TO BE AMENDED:

Section 4.5.5 Histological Examination (Page 11)

Delete : 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.

Insert : Histological processing will be subcontracted to a GLP certified site.

Section 10.1 Test site location (Page 14)

Insert : Propath UK Ltd
Willow Court, Netherwood Road
Hereford, HR2 6JU
England

Principal Investigator: Trevor Hilling
Delegated phase: Histological processing

Reason : For internal organisational purposes the histological processing has been subcontracted to a test site, in agreement with the Sponsor.

RTC Study Number: 41950

- 1 of 2 -

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Partita IVA: 00920811001

PROTOCOL AMENDMENT (3)

APPROVAL PAGE

STUDY TITLE : 13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TEST FACILITY : RESEARCH TOXICOLOGY CENTRE S.p.A.
Via Tito Speri, 12
00040 Pomezia (Rome)
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RTC STUDY NO. : 41950

TEST ITEM : XXXXXXXXXX

APPROVED BY : *C. Longobardi* 09-Aug-2005
C. Longobardi, Biol.D.
Study Director Date

RELEASED BY : *J. Brightwell* 9 Aug 2005
J. Brightwell, Ph.D.
Scientific Director Date

SPONSOR : SOLVAY SOLEXIS S.p.A.
Viale Lombardia, 20
20121 Bollate (MI)
Italy

AUTHORISED BY : *Laura Colombo* 22 Aug 2005
SPONSOR* Date

Name and Title : LARIA COLOMBO, INDUSTRIAL TOXICOLOGY

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

RTC Study Number: 41950

- 2 of 2 -



PROTOCOL AMENDMENT (4)

STUDY TITLE : [REDACTED]
13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

STUDY NO. : 41950

DATE OF PROTOCOL APPROVAL : 30 March 2005

DATE OF ISSUE OF AMENDMENT : Date signed

THE FOLLOWING SECTIONS ARE TO BE AMENDED:

Section 4.5.6 Liver enzymes (Page 11)

Insert at the end of the second sentence : If treatment related changes of the hepatic peroxisome proliferation will be observed in the high dose animals examined, liver samples from the first 5 males and 5 females of the low and mid-dose groups will be processed and analysed in a similar manner to that used previously. Recovery animals may also be analysed following consultation with and approval of the Sponsor.

ANNEX 3 Section 3 Scheduled time plan (page 4 of Protocol Amendment 2)

Delete	: End of experimental period	: 26 August 2005
	Availability of draft data	: 02 September 2005
	Despatch of QA audited draft phase report	: 30 September 2005
Insert	: End of experimental period	: 30 September 2005
	Availability of draft data	: 07 October 2005
	Despatch of QA audited draft phase report	: 11 November 2005

ANNEX 3 Section 4.1 Origin livers (page 5 of Protocol Amendment 2)

Delete	: A total of up to 20 rat liver samples.....
Insert	: A total of up to 60 rat liver samples.....
Reason	: Additional activities required by the Sponsor.

RTC Study Number: 41950

- 1 of 2 -

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Cod. Fisc.: 00653120584
Partita IVA: 00920611001

PROTOCOL AMENDMENT (4)

APPROVAL PAGE

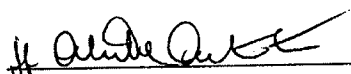
STUDY TITLE : 13 WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

TEST FACILITY : RESEARCH TOXICOLOGY CENTRE S.p.A.
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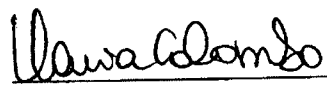
RTC STUDY NO. : 41950

TEST ITEM : XXXXXXXXXX

APPROVED BY :  15-Sep-2005
C. Longobardi, Biol.D.
Study Director Date

RELEASED BY :  15 Sept 2005
J. Brightwell, Ph.D.
Scientific Director Date

SPONSOR : SOLVAY SOLEXIS S.p.A.
Viale Lombardia, 20
20121 Bollate (MI)
Italy

AUTHORISED BY SPONSOR* :  20-Sept-2005
Date

Name and Title : MARIA COLOMBO INDUSTRIAL Toxicology

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

RTC Study Number: 41950

- 2 of 2 -



PROTOCOL AMENDMENT (5)

STUDY TITLE : [REDACTED] 13 WEEK ORAL
TOXICITY STUDY IN RATS FOLLOWED BY AN 8
WEEK RECOVERY PERIOD

STUDY NO. : 41950

DATE OF PROTOCOL APPROVAL : 30 March 2005

DATE OF ISSUE OF AMENDMENT : Date signed

THE FOLLOWING SECTION IS TO BE AMENDED:

Section 4.5.4 Histopathological examination (Page 11)

Delete : The examination could then be extended to include, from all other animals killed after 13 weeks of treatment or 8 weeks of recovery, those tissues in which there is any suspicion of treatment-related change.

Insert : The examination will then be extended to the liver, lungs and spleen from all other animals killed after 13 weeks of treatment or 8 weeks of recovery.

Reason : Histopathological changes were observed in the above organs of the high dose animals.

RTC Study Number: 41950

- 1 of 2 -

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Cod. Fisc.: 00653120584
Partita IVA: 00920611001

PROTOCOL AMENDMENT (5)

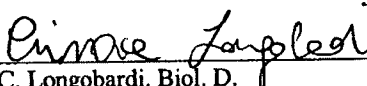
APPROVAL PAGE

STUDY TITLE : 13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8
WEEK RECOVERY PERIOD

TEST FACILITY : RESEARCH TOXICOLOGY CENTRE S.p.A.
Via Tito Speri, 12
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Italy

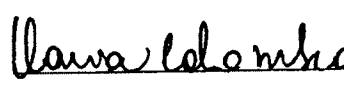
RTC STUDY NO. : 41950

TEST ITEM : XXXXXXXXXX

APPROVED BY :  05-Oct-2005
C. Longobardi, Biol. D. Date
Study Director

RELEASED BY :  5 Oct 2005
J. Brightwell, Ph. D. Date
Scientific Director

SPONSOR : SOLVAY SOLEXIS S.p.A.
Viale Lombardia, 20
20121 Bollate (Milano)
Italy

AUTHORISED BY :  18/10/2005
SPONSOR* Date

Name and Title : LARIA COLOMBO, INDUSTRIAL TOXICOLOGY

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

RTC Study Number: 41950

- 2 of 2 -



PROTOCOL AMENDMENT (6)

STUDY TITLE : [REDACTED] 13 WEEK ORAL
TOXICITY STUDY IN RATS FOLLOWED BY AN 8
WEEK RECOVERY PERIOD

STUDY NO. : 41950

DATE OF PROTOCOL APPROVAL : 30 March 2005

DATE OF ISSUE OF AMENDMENT : Date signed

THE FOLLOWING SECTIONS ARE TO BE AMENDED:

Section 4.5.5 Histopathological examination (Page 11)

Delete : Section 4.5.4

Insert : Section 4.5.5

Reason : Incorrect number of section in Protocol Amendment (5)

ANNEX 3 Section 3 Scheduled time plan (page 4 of Protocol Amendment 2)

Delete : End of experimental period : 30 September 2005
Availability of draft data : 07 October 2005
Despatch of QA audited draft
phase report : 11 November 2005

Insert : End of experimental period : 25 November 2005
Availability of draft data : 02 December 2005
Despatch of QA audited draft
phase report : 13 January 2006

Reason : Changes in scheduled time plan for additional activities required by the Sponsor.

RTC Study Number: 41950

- 1 of 2 -

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Partita IVA: 00920611001

PROTOCOL AMENDMENT (6)

APPROVAL PAGE

STUDY TITLE : 13 WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY AN 8
WEEK RECOVERY PERIOD

TEST FACILITY : RESEARCH TOXICOLOGY CENTRE S.p.A.
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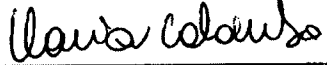
RTC STUDY NO. : 41950

TEST ITEM : XXXXXXXXXX

APPROVED BY :  10 - Nov - 2005
C. Longobardi, Biol. D.
Study Director Date

RELEASED BY :  10 Nov 2005
J. Brightwell, Ph. D.
Scientific Director Date

SPONSOR : SOLVAY SOLEXIS S.p.A.
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Italy

AUTHORISED BY :  14/Nov./2005
SPONSOR* Date

Name and Title : ILARIA COLOMBO, INDUSTRIAL Toxicology

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