REPORT NO. CD-98/6289T

FOUR-WEEK TOXICITY STUDY IN RATS BY INTRAVENOUS ADMINISTRATION WITH A TWO-WEEK RECOVERY PERIOD.

TEST SUBSTANCE: IQB-9302.HCl

VOLUME I

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TEST SUBSTANCE: IQB-9302.HCl

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No. pages in Report : 226

This Study was carried out according to the Good Laboratory Practice regulations specified in:
- Real Decreto (Royal Decree) 822/1993 of 28th May (Spain).
- OECD Principles of Good Laboratory Practice (as revised in 1997), C(97) 186/Final, Paris, 26th November, 1997.
- Directive 87/18/EEC of 18th December 1986 (EU).

No circumstances which could affect the reliability of the data obtained were recorded.

Head Toxicology Dpt. :

J. Zapatero — 30 June 1998 — Date

Study Director :

L. Canut — 30 June 1998 — Date

Histopathologist:

J. Alumà — 30 June 1998 — Date

Haematology and Biochemistry:

M. de Luna — 30 JUNE 1998 — Date

Formulation:

C. Santasusagna — 30 JUNE 1998 — Date

The results presented in this Report refer only to the sample(s) received and tested, as indicated in the corresponding section.

QUALITY ASSURANCE UNIT (QAU)

Inspection of Study no. **CD-98/6289T**

This Study was carried out according to the Good Laboratory Practice regulations specified in:
- Real Decreto (Royal Decree) 822/1993 of 28th May (Spain).
- OECD Principles of Good Laboratory Practice (as revised in 1997), C(97) 186/Final, Paris, 26th November, 1997.
- Directive 87/18/EEC of 18th December 1986 (EU).

The Quality Assurance Unit at the Centro de Investigación y Desarrollo Aplicado, S.A.L. has inspected different phases of the Study. The Final Report has been audited and reflects the raw data obtained in the course of the Study.

The list of the inspections made and their dates, including the dates the inspection results were reported to the Study Director (S.D.) and Principal Investigator(s) (P.I.), if applicable, and the Management are the following:

DATE OF INSPECTION	*STUDY PHASE*	*QAU No.*	*REPORT TO* S.D. / P.I.	*REPORT TO MANAGEMENT*
30.SEP.98	*PROTOCOL*	15384	30.SEP.98	01.OCT.98
25.JAN.99	*WEIGHING, i.v. ADMINISTRATION AND CLINICAL SIGNS*	15857	25.JAN.99	25.JAN.99
02.FEB.99	*FORMULATION*	15909	02.FEB.99	03.FEB.99
16.FEB.99	*SACRIFICE, NECROPSIES AND WEIGHING OF ORGANS*	15980	16.FEB.99	16.FEB.99
22.FEB.99	*WATER INTAKE*	16004	22.FEB.99	01.MAR.99
11.MAY.99	*PARTIAL RESULTS*	16328	11.MAY.99	29.JUN.99
19.JUN.99	*FINAL REPORT*	16557	19.JUN.99	29.JUN.99

G. Segarra
Quality Assurance Unit

30 June 1999
Date

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REPORT NO. CD-98/6289T

FOUR-WEEK TOXICITY STUDY IN RATS BY INTRAVENOUS ADMINISTRATION WITH A TWO-WEEK RECOVERY PERIOD.

TEST SUBSTANCE: IQB-9302.HCl

SUMMARY

The test substance IQB-9302.HCl was administered intravenously, by bolus, to Crl:CD® (SD) BR Sprague-Dawley rats, for 4 consecutive weeks at the doses of 0.75, 1.25 and 2.25 mg/kg/day.

The rats were distributed in four treatment groups including the Control group.

The Control group and the one treated at 2.25 mg/kg/day consisted of 15 males and 15 females each and the groups treated at 0.75 and 1.25 mg/kg/day consisted of 10 males and 10 females each.

At the end of the four weeks of treatment, the animals were sacrificed, except for five males and five females of the Control and high dose groups, which underwent a two-week observation period.

During this period, whose purpose was to study the evolution of the alterations observed, the animals were not treated. At the end of the period, the animals were sacrificed.

The main results are detailed below:

IQB-9302.HCl, 2.25mg/kg/day

- No mortalities were recorded among the animals treated at this dose.
- The main clinical sign observed was ataxia. This alteration was accompanied occasionally in most of the animals by clonic convulsions, salivation, prostration, mydriasis, rigidity of the tail and hindquarters, decreased motor activity, dyspnoea and pallor. All the clinical signs started immediately after treatment and disappeared two minutes afterwards.
- The bodyweight increase in males and females was similar to that recorded in the Control group.

- The food and water intake in males and females was similar to that recorded in the Control animals.
- No alterations were registered in the ophthalmoscopic examinations carried out.
- No noticeable alterations were recorded in the haematological and biochemical analyses nor in the analyses of urine made at the end of the treatment period. There were no alterations at the end of the recovery period either.
- There were no alterations related to the treatment given in the organ weight at the end of the treatment and recovery period.
- The microscopic examination of the samples taken from the animals sacrificed at the end of the treatment period and at the end of the recovery period did not reveal any alteration associated with the administration of the test substance.

IQB-9302.HCl, 1.25mg/kg/day

- No mortalities were recorded among the animals treated at this dose.
- The main clinical sign was ataxia. In two animals, this alteration was occasionally accompanied by: decreased muscle tone and pallor (in one male) and prostration, dyspnoea, salivation, clonic convulsions, mydriasis and rigidity of the tail (in one female). All the clinical signs were observed immediately after administration and had disappeared two minutes after the treatment.
- The bodyweight increase in males and females was similar to that recorded for the Control group.
- The food and water intake in males and females was similar to that recorded in the Control animals.
- No alterations were registered in the ophthalmoscopic examinations carried out.
- No noticeable alterations were recorded in the haematological and biochemical analyses nor in the analysis of urine made at the end of the treatment period. There were no alterations at the end of the recovery period either.
- There were no alterations related to the treatment given in the organ weight at the end of the treatment and recovery period.

IQB-9302.HCl, 0.75mg/kg/day

- No mortality was registered among the animals treated at this dose.

- Only one male sporadically presented ataxia after treatment which disappeared after two minutes post-administration.
- The bodyweight increase in males and females was similar to that registered for the Control animals.
- No noticeable alterations were registered in the food and water intake.
- No alterations were observed in the ophthalmoscopic examinations carried out.
- No noticeable alterations were recorded in the haematological and biochemical analyses nor in the analysis of urine made at the end of the treatment period nor at the end of the recovery period.
- There were no alterations related to the treatment given in the organ weight at the end of the treatment and recovery period.

CONCLUSIONS

No mortalities were registered among the animals treated with the substance IQB-9302.HCl at the doses of 0.75, 1.25 and 2.25 mg/kg/day.

The main clinical signs recorded were ataxia, clonic convulsions, salivation, mydriasis, rigidity of the tail and decreased motor activity. These clinical signs were registered at the doses of 2.25 and 1.25 mg/kg/day. At the dose of 0.75 mg/kg/day only ataxia was observed occasionally in one animal.

No noticeable alterations were recorded in the haematological and biochemical analyses.

There were no alterations related to the treatment given in the organ weight.

The microscopic examination of the samples taken did not reveal any alterations related to the administration of the test substance.

The microscopic examination of the samples taken did no reveal any alterations related to the administration of the test substance.

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FOUR-WEEK TOXICITY STUDY IN RATS BY INTRAVENOUS ADMINISTRATION WITH A TWO-WEEK RECOVERY PERIOD.

TEST SUBSTANCE: IQB-9302.HCl

INTRODUCTION

The aim of this Study is to evaluate the toxicity of the test substance IQB-9302.HCl, a local anaesthetic, when administered intravenously to rats during a period of four consecutive weeks, so as to provide a rational base for the evaluation of the toxicological risk to man and indicate potential target organs.

This route has been chosen because it is the proposed route for administration to humans.

EXPERIMENTAL PROCEDURE

1. ANIMALS

1.1. Supply

A total of 120 rats (60 males and 60 females) of the Crl:CD® (SD) BR Sprague-Dawley strain with an approximate age of 28 days and from CHARLES RIVER were supplied by CRIFFA, S.A. (c/Paraires, 1-7, Nave 5, Polígono Industrial Santiga, 08130-STA. PERPÈTUA DE MOGODA, Barcelona, Spain) on 30th December 1998.

On their arrival a sample of animals was chosen at random and weighed to ensure compliance with the age requested. The mean weights of males and females were 80g and 82 g respectively.

The animals were housed in Makrolon cages (55 x 32.7 x 19 cm), with sawdust litter, in such a way that each cage contained a maximum of 5 animals of the same sex.

All animals underwent a period of 20 days of observation and acclimatisation between the date of arrival and the start of treatment. During the course of this period, the animals were inspected by a veterinary surgeon to ensure that they fulfilled the health requirements necessary for initiation of the Study.

During the acclimatisation period, 100 animals (50 males and 50 females) were selected for the Study. They were distributed among the experimental groups using a random distribution method. This procedure allows approximate equalisation of initial bodyweights whilst allowing random allocation to experimental groups.

1.2. Identification

The rats were individually identified by numbers tattooed on the ears.

The marking of the animals was performed when the animals were distributed among the study groups.

1.3. Housing

The rats were housed in Makrolon cages (55 x 32.7 x 19 cm), placed on racks. The cages had sawdust on the floor (Ultrasorb, Panlab, S.L. Mejía Lequerica, 34, Barcelona, Spain) as litter. From the week before initiation of the treatment, each cage contained a maximum of 5 rats of the same sex and treatment group.

Each cage was identified by a card, colour coded according to the dose level. This card stated the cage number, number and sex of the animals it contained, Study number, test substance code, administration route, dose level and Study Director's name, date of the arrival of the animals and initiation of treatment.

The temperature and relative humidity were continuously monitored. The temperature was between 19ºC and 25ºC. The relative humidity was generally maintained at 40-70%. Humidity indices lower than 40% and higher than 70% were avoided for prolonged periods.

Lighting was controlled to supply 12 hours of light (7:00 to 19:00 hours) and 12 hours of dark for each 24-hour period.

The cages corresponding to each experimental group were distributed on racks in such a manner that external factors, such as environmental conditions, were balanced as far as possible.

2. DIET AND WATER

2.1. Diet

All the rats had free access to a pelleted rat diet UAR A04C (Usine d'Alimentation Rationnelle, 91360-Villemoisson sur Orge, France) batches no. 80507 and 80609.

The diet was analyzed by the manufacturer to check its composition and to detect possible contaminants.

Appendix I shows the diet analysis certificates.

2.2. Water

The water, supplied by Compañía de Aguas de Sabadell, S.A., was offered *ad libitum* in bottles. The water was periodically analyzed to detect the presence of possible contaminants.

Appendix II shows the water analysis certificate.

3. TEST SUBSTANCE

3.1. Identification

The test substance IQB-9302.HCl, a local anaesthetic, was tested. This product was supplied by the Sponsor.

On 9th October 1998, Centro de Investigación y Desarrollo Aplicado, S.A.L. received approximately 8 g of IQB-9302.HCl lot 9454.001 in the form of a white powder supplied in a topaz crystal vial. It was stored at room temperature.

Appendix III contains the analysis certificate of IQB-9302.HCl.

At the end of the Study a sample of the product was taken, which will be stored in the archives of Centro de Investigación y Desarrollo Aplicado, S.A.L. for 5 years from the date of issue of the Final Report or until its expiry date. The remainder will be returned to the Sponsor.

3.2. Formulation of the test substance

The test substance was prepared daily and dissolved in physiological saline (Fisiológico Braun. B. Braun) isotonic solution of 0.9% sodium chloride.

The doses tested refer to the concentration of the base form of the test substance.

Taking into account that the molecular weight of the base form of the test substance is 286.42 and of the hydrochloride form is 322.88, a factor of 1.127 was used for the preparation of the formulations.

3.3. Formulation analysis

In the course of the first and third weeks of administration, samples of the formulations to be administered were sent to LABORATORIOS INIBSA, S.A. for the quantification of their IQB-9302.HCl content. The samples were sent at room temperature.

The results of the formulation analyses are shown in Appendix IV.

3.4. Administration route and procedure

The test substance, IQB-9302.HCl, was administered intravenously, by bolus, in the tail vein, using a 23G (0.6 x 25 mm) sterile disposable needle.

The duration of injection was 2 minutes.

This route has been chosen because it is the proposed route for administration to humans.

The rats belonging to the Control group were treated with the vehicle (physiological saline), at the same administration volume as the rest of the treatment groups.

3.5. Administration volume

The administration volume was 4 mL/kg.

The quantity of test substance administered to each animal was calculated from its bodyweight on the day of treatment.

3.6. Frequency and duration of treatment

The test substance was administered once a day, seven days a week during 4 weeks.

3.7. Dose levels and group sizes

The 100 rats selected for the Study were distributed into four groups using a random distribution method.

Two groups (Control and high dose) consisted of 15 males and 15 females each and a further two groups (intermediate and low dose) consisted of 10 males and 10 females each.

Group	Treatment	Dose (mg/kg/day)	Animal no.		Colour code
			Males	Females	
1	CONTROL (vehicle)	-	1-15	51-65	White
2	IQB-9302.HCl	0.75	16-25	66-75	Blue
3	IQB-9302.HCl	1.25	26-35	76-85	Green
4	IQB-9302.HCl	2.25	36-50	86-100	Red

3.8. Recovery period

Five males and five females of the Control and high dose group were selected at random to undergo a recovery period of two weeks after the last administration.

This recovery period included weeks 5 and 6 of the Study.

The aim of the recovery period was to study the evolution of the possible alterations recorded during the treatment period.

The animals assigned to the recovery period, chosen at random into each group, were the following:

Group	Treatment	Dose (mg/kg/day)	Animal no.	
			Males	Females
1	CONTROL	-	11, 12, 13, 14, 15	61, 62, 63, 64, 65
4	IQB-9302.HCl	2.25	46, 47, 48, 49, 50	96, 97, 98, 99, 100

4. OBSERVATIONS

4.1. Clinical signs

All the rats were observed at least twice daily with the purpose of recording any symptoms of ill-health or behavioural changes. These observations were also performed on week-ends. The observations included but were not limited to changes in skin and fur, in the eyes and mucous membranes, in the respiratory, circulatory, central nervous and autonomous systems, somatomotor activity and behaviour.

4.2. Bodyweight

The bodyweight of each rat was recorded one week before the start of treatment, daily during the course of the same and on the day of sacrifice. The rats selected for the recovery period were weighed twice a week and on the day of sacrifice. The mean weights for the different groups and sexes were calculated from the individual weights.

4.3. Food intake

Prior to the beginning of treatment, and afterwards once a week, the food intake of each cage was recorded and the mean weekly intake per rat was calculated.

4.4. Water intake

Water intake was checked by visual observation during the Study. In addition, the water consumption in each cage was measured daily for a period of 5 days, during the 3rd week of treatment and, subsequently, during the 2nd week of the recovery period.

4.5. Ophthalmoscopy

Before treatment started, the eyes of all animals were examined. These examinations included the cornea, the conjunctivae, the sclera, the iris and fundus.

The observations were made with the aid of an indirect ophthalmoscope.

Before the end of the treatment and before the end of the recovery period, additional examinations of the eyes of the animals from the Control and high dose groups were made.

Prior to each examination, the pupils of the rats were dilated by instillation of one drop of cyclopentholate chlorhydrate eyedrops. (Colircusí Ciclopléjico®, Laboratorios Cusí, S.A. Batches no. L09 and M08).

5. LABORATORY STUDIES

During the 4th week of treatment, samples of blood were withdrawn from the orbital sinus of 10 males and 10 females from each group, under light ether anaesthesia after fasting for 16 hours.

The blood samples were taken from each animal approximately between 7:30 and 10:00 hours in order to reduce biological variation caused by circadian rhythms.

In addition, samples of the urine produced during 16 hours by 10 males and 10 females were taken. To this end the rats were deprived of food for this period of time.

5.1. Haematology

The following determinations were performed:

Parameter	Method/Instrumentation	Units
Erythrocyte count	Haematological counter. SYSMEX F-800	10^6/µL
Haemoglobin	Haematological counter. SYSMEX F-800	g/100 mL
Haematocrit	Haematological counter. SYSMEX F-800	%
Mean corpuscular volume (MCV)	Calculation. SYSMEX F-800	fL
Mean corpuscular haemoglobin (MCH)	Calculation. SYSMEX F-800	pg

Parameter	Method/Instrumentation	Units
Mean corpuscular haemoglobin concentration (MCHC)	Calculation. SYSMEX F-800	g/100 mL
Reticulocyte count*	New methylene blue stain. Microscope	%
Total leukocyte count	Haematological counter. SYSMEX F-800	10^3/µL
Differential leukocyte count - Neutrophils - Lymphocytes - Eosinophils - Basophils - Monocytes	May Grünwald-Giemsa stain. Microscope	10^3/µL
Platelet count	Haematological counter. SYSMEX F-800	10^3/µL
Prothrombin time	Coagulometer. KC-4A	s

*Slides were prepared.

5.2. Biochemistry

The following blood chemistry determinations were carried out:

Parameter	Method/Instrumentation	Units
Glucose	Glucose dehydrogenase. COBAS MIRA	mg/100 mL
Urea	Urease-GLDH. COBAS MIRA	mg/100 mL
Creatinine	Jaffé. COBAS MIRA	mg/100 mL
Total bilirubin	Jendrassik-Grof reaction. COBAS MIRA	mg/100 mL
Aspartate aminotransferase (AST/GOT)	Malate dehydrogenase. DGKC. COBAS MIRA	U/L
Alanine aminotransferase (ALT/GPT)	Lactate dehydrogenase. DGKC. COBAS MIRA	U/L
Sorbitol dehydrogenase (SDH)	Reduction of fructose. COBAS MIRA	U/L
Alkaline phosphatase	p-nitrophenylphosphate. DGKC. COBAS MIRA	U/L
Total cholesterol	CHOD-PAP. COBAS MIRA	mg/100 mL

Parameter	Method/Instrumentation	Units
Sodium	Ion selective electrode. NOVA I	mmol/L
Potassium	Ion selective electrode. NOVA I	mmol/L
Chloride	Coulombimetric. CORNING 925	mmol/L
Calcium	MTB. COBAS MIRA	mg/100 mL
Inorganic phosphorus	Phosphomolybdate without deproteinization. COBAS MIRA	mg/100 mL
Total protein	Biuret. COBAS MIRA	g/100 mL
Albumin	Bromocresol green. COBAS MIRA	g/100 mL

The albumin/globulin ratios were calculated from the total protein and albumin values.

5.3. Analysis of urine

The following determinations were made:

Parameters	Method
Colour Volume	Macroscopic observation
Specific gravity	Refractometry
pH Proteins Glucose Bilirubin Ketones Urobilinogen Haemoglobin	Combur 8 test

The Combur 8 test is a diagnostic strip kit obtained from Boehringer Mannheim and it is used as a qualitative indicator of the concentration of the different parameters. The results are presented using the following scale:

0 = negative
\+ = small quantity of the parameter analyzed
++ = moderate quantity of the parameter analyzed

+++ = large quantity of the parameter analyzed

The urinary sediment was examined for the detection of:

- Epithelial cells
- Leukocytes
- Erythrocytes
- Organisms (bacteria, etc.)
- Crystals
- Other abnormal constituents (casts, sperm, etc.)

6. TERMINAL STUDIES

6.1. Sacrifice and macroscopic examination

On completion of the 4 weeks of treatment, 80 rats were sacrificed by CO_2 inhalation. The remaining 20 rats were sacrificed at the end of the recovery period. A full autopsy was performed on all animals which included examination of the external surface of the body, all orifices, cranial, thoracic and abdominal cavities and their contents both *in situ* and after evisceration.

As the number of animals exceeded the number that could be sacrificed in one day, the autopsies were carried out over three consecutive days at the end of the treatment period. However, each rat continued to receive the test substance until the day prior to its sacrifice.

The rats chosen for the recovery period were sacrificed at the end of it, all in one day.

6.2. Organ weights

After the macroscopic examination the following organs were weighed after separating the superficial fat:

Adrenals	Pituitary gland
Brain	Prostate and seminal vesicles
Heart	Spleen
Kidneys	Testes and epididymides
Liver	Thymus
Lungs	Thyroids
Ovaries	Uterus

6.3. Taking of histological samples

Samples of the following organs and tissues were taken and fixed in 10% neutral buffered formalin, with the exception of the eyes, which were preserved in Davidson's fixative:

Adrenals
Aorta
Bone (sternum)
Brain (bulbar, cerebellar and cortical sections)
Caecum
Colon
Eyes and optic nerves
Femur (with joint)
Heart
Injection site (tail)
Kidneys
Liver
Lungs and mainstem bronchi
Lymph nodes (submandibular and mesenteric)
Mammary gland
Oesophagus
Ovaries
Pancreas
Pituitary gland
Prostate
Rectum
Salivary glands
Sciatic nerve
Seminal vesicles
Skeletal muscle
Skin (abdominal)
Small intestine (duodenum, ileum, jejunum)
Spinal cord (cervical, thoracic and lumbar)
Spleen
Stomach
Testes and epididymides
Thymus
Thyroid and parathyroids
Tissue masses or tumours (including regional lymph nodes)
Tongue
Trachea
Urinary bladder
Uterus (corpus and cervix)
Vagina
Whatever other organ or tissue with macroscopic alterations.

A marrow smear from the femur was prepared, air-dried and fixed with anhydrous methanol.

6.4. Histopathological examination

Samples of the above-mentioned organs and tissues, except the marrow smear of which no examination was planned, were embedded in paraffin-wax, sectioned and stained with haematoxylin-eosin (phloxine variant).

Sections of liver obtained after freezing were stained using the Fat Red 7B method for examination of fat.

The microscopic examination was restricted to:

I. All animals pertaining to the Control and high dose groups.

II. All organs and tissues of animals from the low and intermediate dose groups which show any macroscopic alterations.

7. STATISTICAL EVALUATION

Bodyweight, organ weight, the results of the haematological and clinical biochemical analyses, and urinary volume, pH and specific gravity, were evaluated by a one-way analysis of variance ($p<0.05$) and, if found significant, the degree of significance was evaluated using the Duncan-Kramer method[1] ($p<0.05$).

During the recovery period, the above-mentioned parameters were evaluated statistically using the Student's t test ($p<0.05$)[2].

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[1] a) Duncan D.B. Multiple range and multiple F test.
Biometrics 11, 1-42 (1955).
b) Kramer C.Y. Extension of multiple range test to group means with unequal number of replication.
Biometrics 12, 307 (1956).

[2] Manual of Pharmacologic Calculations.
Ronald J. Tallarida and Rodney B. Murray.
Springer-Verlag (1987)

In the tables, the letters N.S. mean that, for the corresponding parameters, the differences between mean values for the stated groups are not statistically significant.

In the tables statistical significance is represented by an S. ($p<0.05$) at the foot of the corresponding column. The letters A, B, C and D represent the mean values for the Control group and groups 2, 3 and 4 respectively.

The letters are placed in ascending order and may be interpreted statistically as follows:

- The difference between two means underlined by the same line is not statistically significant, according to the Duncan-Kramer test ($p < 0.05$).
- The difference between two means not underlined by the same line is statistically significant, according to the Duncan-Kramer test ($p < 0.05$).

The remainder of the urine parameters were evaluated statistically using the homogeneity test (χ^2 test $p < 0.01$)[(2)].

8. ARCHIVES

All the data pertaining to the Study will be kept for at least five years in the archives at Centro de Investigación y Desarrollo Aplicado, S.A.L. All tissues preserved in formalin will be stored for a period of two years after the completion of the Study.

No material relating to this Study will be destroyed without the prior written consent of the Sponsor.

9. STUDY FACILITIES

This Study was conducted in the laboratories and animal housing of the Toxicology Department of Centro de Investigación y Desarrollo Aplicado, S.A.L., Centro Industrial Santiga, c/Argenters 6, 08130-SANTA PERPÈTUA DE MOGODA, Barcelona (Spain).

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(2) Manual of Pharmacologic Calculations.
Ronald J. Tallarida and Rodney B. Murray.
Springer-Verlag (1987)

The histopathological examination of the histological preparations was performed in the Centro de Histopatología Veterinaria, c/Castellnou, 21, 08017-BARCELONA (Spain).

10. STUDY DATES

The duration of the Study was as follows:

Protocol signed: 9th October 1998

Protocol amendment no. 1 accepted: 18th January 1999

Protocol amendment no. 2 accepted: 3rd February 1999

Arrival date of animals: 30th December 1998

Treatment started: 18th January 1999

End of treatment: 16th February 1999

Recovery period: 15th February to 1st March 1999

Final Report: See Page I

11. EXPERIMENTAL PROTOCOL

Appendix V contains the experimental protocol.

The protocol amendments approved in the course of the Study are shown in Appendix VI.

12. STANDARD OPERATING PROCEDURES

All procedures of this Study were carried out according to the Centro de Investigación y Desarrollo Aplicado, S.A.L. Standard Operating Procedures.

13. DIRECTIVES

The Study procedures described in this Report are in accordance with Directive 91/507/EEC relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of testing of medicinal products (Annex, Part 3, referring to Toxicological and Pharmacological testing) and Annex I of Recommendation 83/571/EEC.

14. RESULTS

14.1. Mortality

No mortalities were recorded among the animals treated with the substance IQB-9302.HCl at the different doses administered nor among the Control group animals.

14.2. Clinical signs

The frequency of the clinical signs according to sex and treatment group is shown in Table no. 1.

No clinical signs were recorded among the animals pertaining to the Control group.

One male administered with IQB-9302.HCl at the dose of 0.75 mg/kg/day presented, on day 23 of the treatment, ataxia after the administration which disappeared two minutes afterwards.

All of the animals treated at the dose of 1.25 mg/kg/day presented ataxia. This alteration was accompanied occasionally, in one male, by decreased muscle tone and pallor and in one female by prostration, dyspnoea, salivation, clonic convulsions, mydriasis and rigidity of the tail. All the clinical signs were observed immediately after administration and had disappeared two minutes after the treatment.

All of the animals treated at the dose of 2.25 mg/kg/day presented ataxia. This alteration was accompanied occasionally, in most of the animals, by clonic convulsions, salivation and prostration. Similarly, some of the animals presented mydriasis, rigidity of the tail and hindquarters, decreased motor activity and pallor. All clinical signs started immediately after treatment and disappeared two minutes afterwards.

14.3. Bodyweight

The bodyweight increase, according to sex and treatment group, during the treatment and recovery period, is shown in Figures nos. 1 to 4 and Tables nos. 2 to 5.

The individual values for each animal are shown in Tables nos. 35 to 40.

The bodyweight increase in males and females treated with IQB-9302.HCl at the three treatment doses was, in the course of the treatment and recover period, similar to that recorded for the Control group animals and no statistically significant differences were recorded.

14.4. Food intake

Tables nos. 6 and 7 contain the weekly mean food intake of the males and females pertaining to the different treatment groups.

During the treatment period, the food intake in males and females treated with the test substance at the three doses administered was similar to that recorded in the animals of the Control group.

During the recovery period, the food intake in the males and females treated at 2.25 mg/kg/day was similar to that recorded in the Control group.

14.5. Water intake

The mean water intake by sex and treatment group during the course of the 3rd week of treatment and during the second week of the recovery period is shown in Table no. 8.

No noticeable alterations were recorded in the water intake during the third week of treatment.

During the treatment period, the food intake in males and females treated with the test substance at the three doses administered was similar to that recorded in the animals of the Control group.

During the recovery period, the food intake in the males and females of the 2.25 mg/kg/day treatment group was similar to that recorded in the Control group.

15.5. Water intake

The mean water intake by sex and treatment group during the course of the third week of treatment and during the second week of the recovery period is shown in Table no. 8.

No noticeable alterations were recorded in the water intake during the third week of treatment.

During the recovery period, the water intake in the males and females of the 2.25 mg/kg/day treatment group was similar to the one recorded in the Control group.

15.6. Ophthalmoscopy

No alterations were recorded in the examinations carried out before the start of treatment, nor in the observations made during the 4th week of treatment and at the end of the recovery period.

16. LABORATORY STUDIES

16.1. Haematology

The mean values by sex and treatment group corresponding to the haematological analyses made in the 4th week of treatment and at the end of the recovery period can be found in Tables nos. 9, 10 and 16, 17, respectively.

The individual results are presented in Tables nos. 41 to 44 and 53, 54.

No noticeable alterations were recorded in the analyses carried out at the end of the treatment period nor at the end of the recovery period.

16.2. Biochemistry

The mean values by sex and treatment group corresponding to the biochemical analyses made in the 4th week of treatment and at the end of the recovery period can be found in Tables nos. 11, 12 and 18, 19, respectively.

The individual results are presented in Tables nos. 45 to 48 and 55, 56.

The statistically significant differences detected, in comparison with the Control group, at the end of the treatment, for the parameters, such as AST, total cholesterol, sodium and total protein, are considered to be within the normal range without correlation with the doses administered.

No noticeable alterations were recorded in the analyses carried out at the end of the recovery period.

16.3. Analysis of urine

Tables nos. 13 to 15 and 20 to 22 contain the mean values by sex and treatment group corresponding to urine analyses made in the 4th week of treatment and at the end of the recovery period, respectively.

The individual results are presented in Tables no. 49 to 52 and 57, 58.

No alterations related to the treatment carried out were observed in the urine parameters examined.

In the females, the absolute and relative weight of the lungs at 2.25 mg/kg/day was statistically higher than that recorded in the Control group.

16.2. Macroscopic observations

16.2.1. Animals sacrificed at the end of the treatment period

Table no. 31 shows the frequency of the macroscopic observations by organ, sex and treatment group of the animals sacrificed at the end of the treatment.

The autopsies carried out revealed some renal alterations such as unilateral dilation of the renal calices in one male belonging to the Control group and one female treated at 1.25 mg/kg/day. A bilateral dilation of renal calices was registered in one male pertaining to the Control group and one female, one male and two females treated at the doses of 0.75, 1.25 and 2.25 mg/kg/day, respectively.

One female treated at the dose of 0.75 mg/kg/day and one male treated at the dose of 2.25 mg/kg/day presented petechial areas in the thymus.

One male administered at the dose of 1.25 mg/kg/day presented both testes decreased in size.

One female treated at the dose of 1.25 mg/kg/day presented a whitish nodule of 0.5 cm in diameter in the spleen. Similarly, the spleen of one male treated at 2.25 mg/kg/day presented a nodular surface.

16.2.2. Animals sacrificed at the end of the recovery period

Table no. 32 shows the frequency of the macroscopic observations by organ, sex and treatment group.

In the autopsies carried out at the end of the recovery period, one male belonging to the Control group and one female treated at the dose of 2.25 mg/kg/day presented unilateral dilation of renal calices.

16.3. Microscopic observations

16.3.1. Animals sacrificed at the end of the treatment period

The frequencies of the microscopic observations by organ, sex and treatment group can be found in Table no. 33.

MICROSCOPIC ALTERATIONS NOT ASSOCIATED WITH THE TREATMENT

SPLEEN

Lymphoid hyperplasia

IQB-9302.HCl (2.25 mg/kg/day): 44M

LIVER

Lymphocytary infiltrate, portal

IQB-9302.HCl (2.25 mg/kg/day): 92F

Microgranuloma

Control: 55F

IQB-9302.HCl (2.25 mg/kg/day): 91F

PITUITARY

Simple cyst

IQB-9302.HCl (2.25 mg/kg/day): 40M

EYES

Lymphocytary infiltrate in Harder's gland, unilateral

IQB-9302.HCl (2.25 mg/kg/day): 94F

LUNGS

Intraalveolar histiocytosis, focal

Control: 7M, 54F

IQB-9302.HCl (2.25 mg/kg/day): 36M, 38M

KIDNEYS

Dilation of renal pelvis

Control: 8M, 10M

IQB-9302.HCl (0.75 mg/kg/day): 69F

(1.25 mg/kg/day): 29M, 85F

Interstitial nephritis, focal

IQB-9302.HCl (2.25 mg/kg/day): 43M

Pyelitis, acute, non-specific

IQB-9302.HCl (2.25 mg/kg/day): 94F, 95F

TESTES

Tubular atrophy

IQB-9302.HCl (1.25 mg/kg/day): 29M

THYMUS

Multifocal congestion

IQB-9302.HCl (2.25 mg/kg/day): 38M

URINARY BLADDER

Cystitis, acute, non-specific

IQB-9302.HCl (2.25 mg/kg/day): 94F

16.3.2. Animals sacrificed at the end of the recovery period

The frequencies of the microscopic observations by organ, sex and treatment group can be found in Table no. 34.

MICROSCOPIC ALTERATIONS NOT ASSOCIATED WITH THE TREATMENT

LIVER

Hepatocytary vacuolisation, centrolobular

Control: 15M

PITUITARY

Simple cyst

Control: 65F

LUNGS

Intraalveolar histiocytosis, focal

Control: 15M

IQB-9302.HCl (2.25 mg/kg/day): 50M

KIDNEYS

Dilation of renal pelvis

Control: 15M

IQB-9302.HCl (2.25 mg/kg/day): 99F

16.4. Histopathological summary

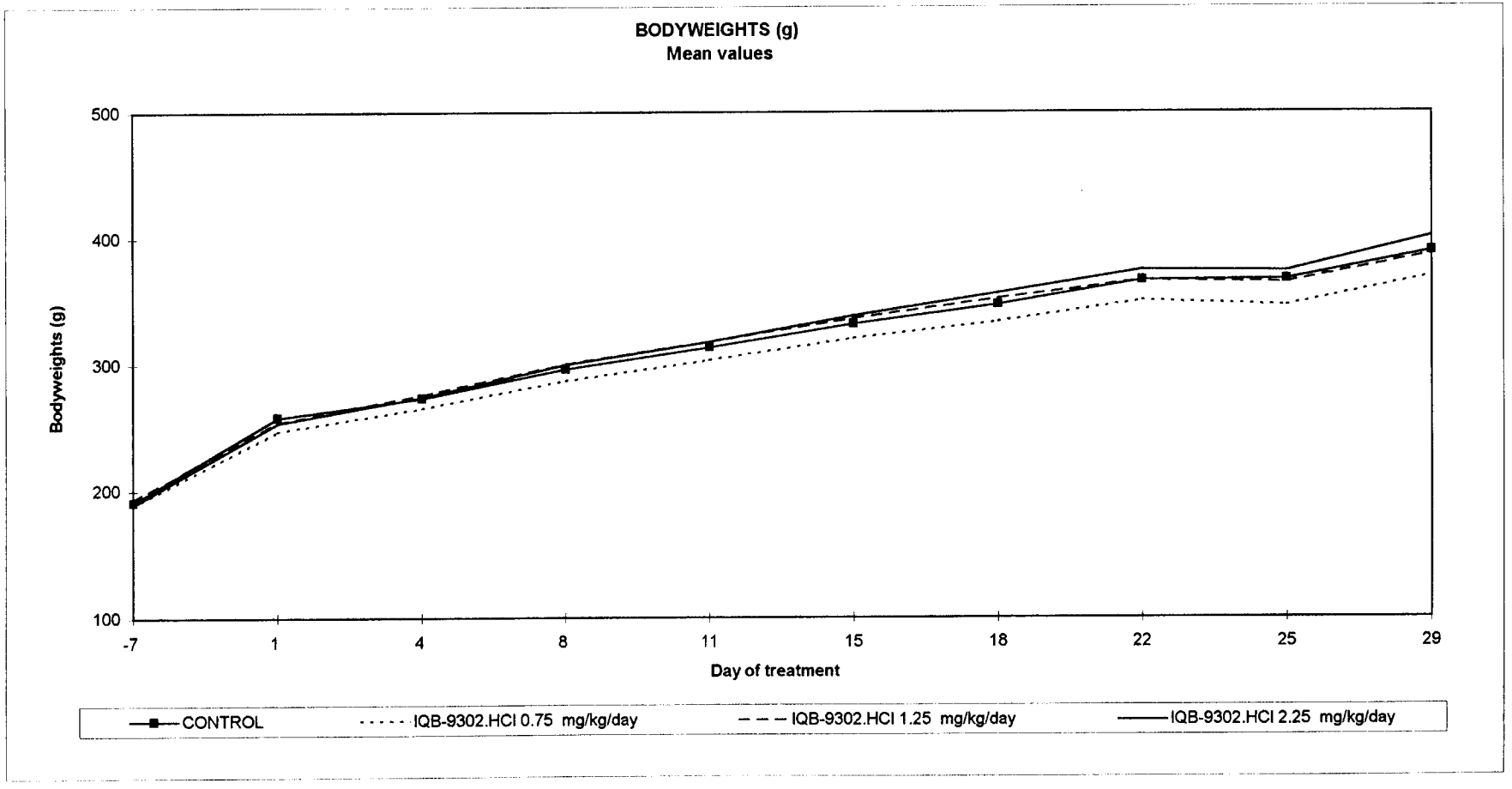
The microscopic observation of the samples corresponding to the animals sacrificed at the end of the treatment period did not reveal any alteration associated with the intravenous administration of the substance IQB-9302.HCl.

Similarly, the histopathological study of the samples belonging to the animals that underwent the recovery period did not reveal any alteration associated with the administration of the test substance.

The histopathological findings described are quite frequent in this type of laboratory animals. No evident relation with the intravenous administration of the test substance IQB-9302.HCl is observed.

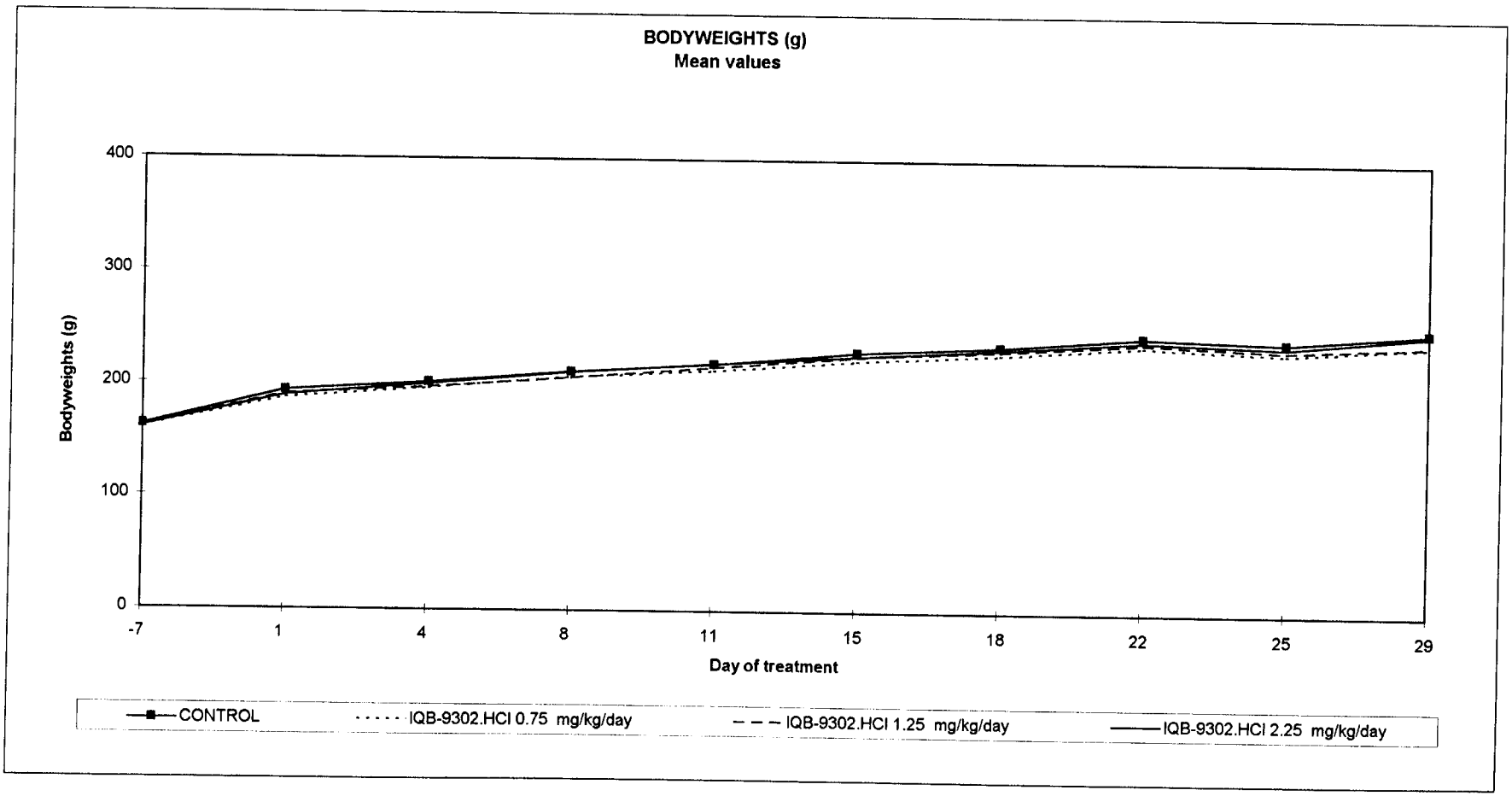
CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Figure no.: 1

Study no.: CD-98/6289T
Sex: Male



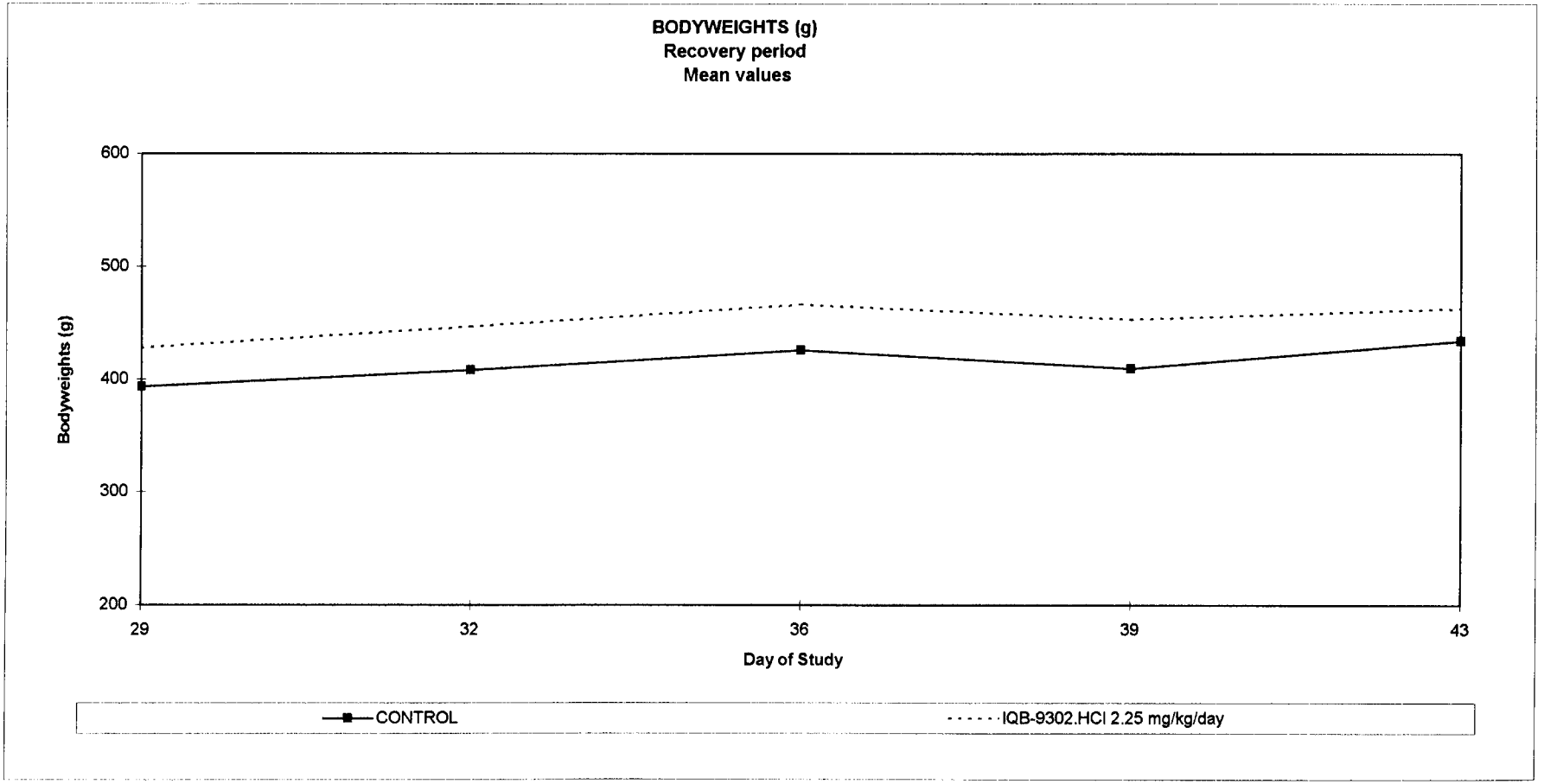
CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Figure no.: 2

Study no.: CD-98/6289T
Sex: Female



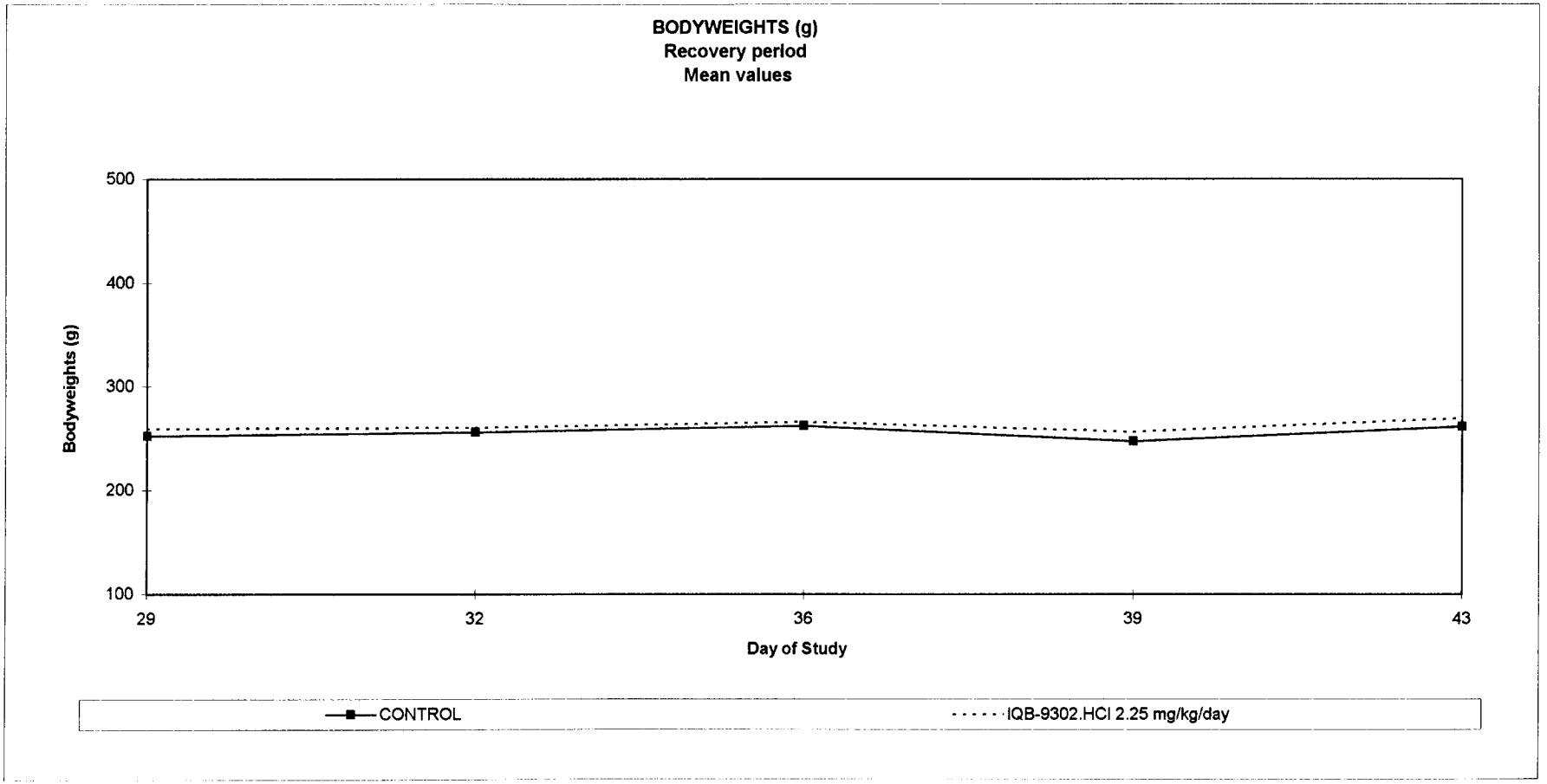
CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Figure no.: 3

Study no.: CD-98/6289T
Sex: Male



CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Figure no.:4

Study no.: CD-98/6289T
Sex: Female



CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 1

Study no.: CD-98/628

NUMBER OF ANIMALS WITH CLINICAL SIGNS IN THE COURSE OF TREATMENT

				IQB-9302.HCl mg/kg/day					
CLINICAL SIGNS	Treatment group	CONTROL		0.75		1.25		2.25	
	Sex	M	F	M	F	M	F	M	F
	Animal/Group	15	15	10	10	10	10	15	15
Ataxia				1		10	10	15	15
Clonic convulsions							1	10	8
Decreased motor activity								5	4
Decreased muscle tone						1			
Dyspnoea							1	5	8
Mydriasis							1	6	6
Pallor						1		1	
Prostration							1	11	10
Rigidity of hindquarters								1	
Rigidity of tail							1	10	6
Salivation							1	10	8

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 2

BODYWEIGHTS (g)
Mean values

Study no.: CD-98/6289T
Sex: Male

	TREATMENT DOSE mg/kg/day		Treatment day -7	1	4	8	11	15	18	22	25	29
A:	CONTROL --	MEAN	191.5	258.2	273.7	296.8	313.9	332.2	347.5	366.5	367.7	389.9
		S.D.	8.10	13.65	14.92	18.50	21.45	25.54	26.98	32.31	30.06	33.70
		n	15	15	15	15	15	15	15	15	15	15
B:	IQB-9302.HCl 0.75	MEAN	188.6	247.4	265.9	287.7	303.5	320.6	333.9	350.6	346.6	370.1
		S.D.	11.04	15.50	16.28	18.15	21.39	24.65	26.78	30.81	31.13	34.37
		n	10	10	10	10	10	10	10	10	10	10
C:	IQB-9302.HCl 1.25	MEAN	193.2	254.3	276.1	300.7	318.0	336.7	352.4	366.7	364.7	387.0
		S.D.	7.18	10.90	12.91	17.38	20.49	23.66	28.34	33.53	33.43	34.57
		n	10	10	10	10	10	10	10	10	10	10
D:	IQB-9302.HCl 2.25	MEAN	189.5	253.7	274.5	300.1	318.1	338.8	356.6	374.9	374.1	401.8
		S.D.	9.26	13.98	15.38	21.89	24.73	29.42	34.31	37.61	42.31	46.73
		n	15	15	15	15	15	15	15	15	15	15
One-way analysis of variance ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 3

BODYWEIGHTS (g)
Mean values

Study no.: CD-98/6289T
Sex: Female

	TREATMENT DOSE mg/kg/day		Treatment day -7	1	4	8	11	15	18	22	25	29
A:	CONTROL --	MEAN	162.5	193.2	201.3	211.6	218.6	230.1	236.0	244.9	241.3	251.1
		S.D.	10.00	10.32	10.17	11.51	13.22	14.37	14.82	14.94	14.11	14.57
		n	15	15	15	15	15	15	15	15	15	15
B:	IQB-9302.HCl 0.75	MEAN	160.4	186.7	195.7	206.7	212.8	222.0	228.3	236.6	231.3	239.2
		S.D.	7.09	7.82	8.60	10.51	11.29	10.77	13.39	13.91	13.98	11.82
		n	10	10	10	10	10	10	10	10	10	10
C:	IQB-9302.HCl 1.25	MEAN	160.9	189.9	196.9	206.1	216.0	225.9	231.8	239.7	234.5	239.7
		S.D.	8.23	14.36	14.43	13.19	10.70	11.67	14.11	16.17	14.75	14.45
		n	10	10	10	10	10	10	10	10	10	10
D:	IQB-9302.HCl 2.25	MEAN	160.9	189.1	199.5	211.2	219.4	226.7	233.2	241.6	237.4	248.9
		S.D.	6.94	8.11	10.94	11.45	12.01	13.02	12.48	12.29	14.81	14.96
		n	15	15	15	15	15	15	15	15	15	15
One-way analysis of variance ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 4

BODYWEIGHTS (g)
Recovery period
Mean values

Study no.: CD-98/6289T
Sex: Male

	TREATMENT DOSE mg/kg/day		Study day 29	32	36	39	43
A:	CONTROL --	MEAN	393.4	408.0	426.0	409.8	434.2
		S.D.	28.27	29.93	28.00	32.18	30.29
		n	5	5	5	5	5
B:	IQB-9302.HCl 2.25	MEAN	428.0	446.6	466.2	453.0	463.0
		S.D.	43.20	41.49	45.96	46.64	56.77
		n	5	5	5	5	5
Student t test ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 5

BODYWEIGHTS (g)
Recovery period
Mean values

Study no.: CD-98/6289T
Sex: Female

	TREATMENT DOSE mg/kg/day		Study day 29	32	36	39	43
A:	CONTROL --	MEAN	252.2	256.0	262.4	247.6	262.0
		S.D.	17.14	15.65	13.09	12.28	10.32
		n	5	5	5	5	5
B:	IQB-9302.HCl 2.25	MEAN	259.0	260.2	266.2	256.4	270.2
		S.D.	8.49	12.87	18.40	12.58	14.36
		n	5	5	5	5	5
Student t test ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no. : 6

Study no.: CD-98/6289T
Sex: Males

FOOD INTAKE
Mean values
(g/animal/day)

Study week	Control	IQB-9302.HCl (mg/kg/day)					
		0.75		1.25		2.25	
		Mean	% with respect to Control	Mean	% with respect to Control	Mean	% with respect to Control
-1	25.6	24.9	97.3	25.5	99.6	26.2	102.3
1	24.7	23.9	96.8	25.3	102.4	25.3	102.4
2	24.7	23.9	96.8	24.9	100.8	25.7	104.0
3	24.6	23.2	94.3	24.7	100.4	25.7	104.5
4	25.8	24.8	96.1	25.9	100.4	27.0	104.7
Weekly means (1 to 4)	24.95	23.95	96.0	25.20	101.0	25.93	103.9
5	30.0					33.7	112.3
6	22.9					23.3	101.7
Weekly means (5 to 6)	26.45					28.50	107.5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no. : 7

Study no.: CD-98/6289T
Sex: Females

FOOD INTAKE
Mean values
(g/animal/day)

Study week	Control	IQB-9302.HCl (mg/kg/day)					
		0.75		1.25		2.25	
		Mean	% with respect to Control	Mean	% with respect to Control	Mean	% with respect to Control
-1	18.0	17.4	96.7	18.1	100.6	17.5	97.2
1	17.3	16.8	97.1	16.9	97.7	17.4	100.6
2	18.1	17.3	95.6	17.6	97.2	17.8	98.3
3	18.2	16.7	91.8	17.4	95.6	17.0	93.4
4	18.4	18.0	97.8	18.2	98.9	18.5	100.5
Weekly means (1 to 4)	18.00	17.20	95.6	17.53	97.4	17.68	98.2
5	20.0					21.2	106.0
6	16.0					16.6	103.8
Weekly means (5 to 6)	18.00					18.90	105.0

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no. : 8

Study no.: CD-98/6289T

WATER INTAKE
Mean values
(mL/animal/day)

Study week	Sex	Control	IQB-9302.HCl (mg/kg/day)					
			0.75		1.25		2.25	
			Mean	% with respect to Control	Mean	% with respect to Control	Mean	% with respect to Control
3	M	30.4	28.7	94.4	31.4	103.3	32.9	108.2
	F	23.7	20.6	86.9	21.9	92.4	23.8	100.4
6 (recovery period)	M	30.0					32.0	106.7
	F	23.6					24.8	105.1

CENTRO DE INVESTIGACION Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 9

HAEMATOLOGY
Mean values
Week 4

Study no.: CD-98/6289T
Sex: Male

	TREATMENT DOSE mg/kg/day		ERYTHR.	HAEMOGL.	HAEMATOC.	MCV	MCH	MCHC	TOTAL LEUKOCYT.	DIFFERENTIAL LEUKOCYTE COUNT ($x10^3/\mu L$)						PLATEL.	PROTHR. TIME
										NEUTROPHILS		LYMPHO.	MONOC.	EOSINO.	BASOPH.		
			$x10^6/\mu L$	g/100mL	%	fL	pg	g/100mL	$x10^3/\mu L$	Rods	Segmen.					$x10^3/\mu L$	s
A :	CONTROL	MEAN	7.41	15.76	43.19	58.32	21.27	36.50	11.97	0.00	1.77	9.38	0.74	0.08	0.00	1128.3	24.14
	--	S.D.	0.271	0.455	1.259	1.724	0.702	0.680	3.405	0.000	0.625	2.813	0.302	0.094	0.000	52.15	6.102
		n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
B :	IQB-9302.HCl	MEAN	7.58	15.90	43.23	57.04	21.00	36.82	10.44	0.00	1.26	8.83	0.30	0.05	0.00	1121.5	22.90
	0.75	S.D.	0.456	0.702	2.573	1.791	0.733	1.074	2.049	0.000	0.461	1.643	0.269	0.097	0.000	135.94	4.188
		n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
C :	IQB-9302.HCl	MEAN	7.55	16.06	43.61	57.86	21.32	36.85	11.25	0.00	1.50	9.41	0.26	0.08	0.00	1087.5	20.36
	1.25	S.D.	0.443	0.841	2.600	2.768	0.935	0.528	1.615	0.000	0.558	1.398	0.171	0.072	0.000	77.01	3.292
		n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
D :	IQB-9302.HCl	MEAN	7.11	15.47	41.50	58.44	21.79	37.31	12.80	0.00	1.41	10.78	0.47	0.14	0.00	1136.8	18.63
	2.25	S.D.	0.442	0.633	2.109	2.615	1.121	0.745	2.586	0.000	0.658	2.445	0.399	0.105	0.000	121.87	3.926
		n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
One-way analysis of variance ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	S.	N.S.	N.S.	N.S.	S.
Duncan-Kramer test ($p<0.05$)													CBDA				DCBA

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 10

HAEMATOLOGY
Mean values
Week 4

Study no.: CD-98/6289T
Sex: Female

	TREATMENT DOSE mg/kg/day		ERYTHR. x10^6/µL	HAEMOGL. g/100mL	HAEMATOC. %	MCV fL	MCH pg	MCHC g/100mL	TOTAL LEUKOCYT. x10^3/µL	DIFFERENTIAL LEUKOCYTE COUNT (x10^3/µL) NEUTROPHILS Rods	NEUTROPHILS Segmen.	LYMPHO.	MONOC.	EOSINO.	BASOPH.	PLATEL. x10^3/µL	PROTHR. TIME s
		MEAN	6.78	15.08	38.67	57.06	22.26	39.00	8.86	0.00	0.82	7.48	0.38	0.18	0.00	1142.4	15.67
A :	CONTROL	S.D.	0.220	0.266	1.001	1.307	0.574	0.651	2.009	0.000	0.361	1.867	0.288	0.111	0.000	119.20	0.726
	--	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
		MEAN	6.77	15.1	38.88	57.49	22.34	38.86	9.56	0.00	0.85	8.42	0.23	0.062	0.00	1154.8	15.75
B :	IQB-9302.HCl	S.D.	0.406	0.867	2.418	1.518	0.688	0.855	1.811	0.000	0.423	1.644	0.146	0.088	0.000	126.82	1.111
	0.75	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
		MEAN	6.64	14.76	37.80	56.93	22.23	39.06	9.52	0.00	1.19	7.88	0.33	0.12	0.00	1213.5	14.94
C :	IQB-9302.HCl	S.D.	0.265	0.622	1.694	1.423	0.606	0.558	3.181	0.000	0.647	2.739	0.253	0.128	0.000	114.99	1.176
	1.25	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
		MEAN	6.61	14.57	38.36	58.05	22.08	38.09	8.10	0.00	0.99	6.78	0.27	0.061	0.00	1162.4	14.99
D :	IQB-9302.HCl	S.D.	0.491	0.856	3.315	3.619	0.745	1.550	2.407	0.000	0.915	1.660	0.130	0.069	0.000	175.00	0.775
	2.25	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
One-way analysis of variance ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	S.	N.S.	N.S.	N.S.
Duncan-Kramer test ($p<0.05$)														BDCA			

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 11

BIOCHEMISTRY
Mean values
Week 4

Study no.: CD-98/6289T
Sex: Male

TREATMENT DOSE mg/kg/day		GLUCOSE mg/100mL	UREA mg/100mL	CREATININE mg/100mL	TOTAL BILIRUBIN mg/100mL	AST (GOT) U/L	ALT (GPT) U/L	SDH U/L	ALKALINE PHOSPH. U/L	TOTAL CHOLEST. mg/100mL	CALCIUM mg/100mL	INORGANIC PHOSPHORUS mg/100mL	SODIUM mmol/L	POTASSIUM mmol/L	CHLORIDE mmol/L	TOTAL PROTEIN g/100mL	ALBUMIN g/100mL	ALB./GLOB. RATIO
	MEAN	80.0	28.7	0.44	0.09	142.9	27.6	10.19	337.4	46.70	10.44	10.04	143.94	5.20	101.7	6.06	3.66	1.53
A: CONTROL	S.D.	11.84	5.50	0.064	0.035	20.31	3.66	2.411	62.92	8.618	0.734	0.711	1.095	0.407	1.83	0.280	0.151	0.118
--	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	MEAN	77.6	27.6	0.43	0.11	141.6	27.2	9.14	351.3	43.53	10.25	10.09	144.48	5.29	101.5	6.03	3.65	1.55
B: IQB-9302.HCl	S.D.	11.05	3.41	0.047	0.053	23.97	3.19	1.501	63.90	6.318	0.948	0.946	0.745	0.387	1.84	0.142	0.158	0.181
0.75	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	MEAN	81.0	30.6	0.47	0.09	132.6	25.3	8.26	360.7	49.00	10.35	10.88	144.83	5.58	101.6	6.24	3.67	1.44
C: IQB-9302.HCl	S.D.	9.33	3.92	0.077	0.026	15.36	3.89	3.580	83.48	9.504	0.753	0.981	1.219	0.730	2.63	0.445	0.250	0.145
1.25	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	MEAN	89.2	28.9	0.44	0.13	127.9	25.7	7.99	338.6	44.87	10.13	10.39	144.30	5.54	102.3	6.04	3.61	1.49
D: IQB-9302.HCl	S.D.	9.39	2.64	0.068	0.035	12.09	3.43	3.337	78.52	7.800	0.874	1.145	1.003	0.609	1.83	0.310	0.191	0.117
2.25	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
One-way analysis of variance ($p<0.05$)		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 12

BIOCHEMISTRY
Mean values
Week 4

Study no.: CD-98/6289T
Sex: Female

TREATMENT DOSE mg/kg/day		GLUCOSE mg/100mL	UREA mg/100mL	CREATININE mg/100mL	TOTAL BILIRUBIN mg/100mL	AST (GOT) U/L	ALT (GPT) U/L	SDH U/L	ALKALINE PHOSPH. U/L	TOTAL CHOLEST. mg/100mL	CALCIUM mg/100mL	INORGANIC PHOSPHORUS mg/100mL	SODIUM mmol/L	POTASSIUM mmol/L	CHLORIDE mmol/L	TOTAL PROTEIN g/100mL	ALBUMIN g/100mL	ALB./GLOB. RATIO
A: CONTROL --	MEAN	85.0	39.0	0.52	0.14	123.5	24.3	9.23	184.2	59.21	10.89	9.13	144.34	5.14	101.3	6.97	4.22	1.55
	S.D.	13.73	6.04	0.043	0.036	17.65	6.25	1.816	75.70	12.670	0.798	0.646	1.488	0.429	3.59	0.517	0.230	0.130
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
B: IQB-9302.HCl 0.75	MEAN	84.9	35.1	0.49	0.11	143.9	22.3	9.01	166.4	54.98	10.87	9.19	143.95	5.07	102.6	6.61	3.97	1.52
	S.D.	6.51	3.28	0.040	0.034	15.80	3.27	3.079	49.96	10.787	0.891	0.669	0.883	0.415	1.78	0.407	0.343	0.195
	n	10	10	10	9	10	10	10	10	10	10	10	10	10	10	10	10	10
C: IQB-9302.HCl 1.25	MEAN	89.3	33.9	0.48	0.15	139.2	21.4	9.36	185.0	46.29	10.82	8.91	142.67	5.04	101.1	6.50	4.00	1.61
	S.D.	9.80	5.07	0.073	0.058	12.18	2.12	2.704	33.42	5.671	0.527	0.882	1.126	0.464	1.91	0.258	0.287	0.213
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
D: IQB-9302.HCl 2.25	MEAN	87.0	33.6	0.47	0.17	126.9	23.5	8.87	166.3	49.07	10.44	8.49	143.74	5.04	103.3	6.53	3.94	1.55
	S.D.	12.68	4.12	0.053	0.033	13.74	15.04	1.389	47.89	7.965	0.409	0.801	1.090	0.312	2.16	0.343	0.347	0.293
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
One-way analysis of variance (p<0.05)		N.S.	N.S.	N.S.	S.	S.	N.S.	N.S.	N.S.	S.	N.S.	N.S.	S.	N.S.	N.S.	S.	N.S.	N.S.
Duncan-Kramer test (p<0.05)					BACD	ADCB				CDBA			CDBA			CDBA		

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 13

URINALYSIS
Mean values
Week 4

Study no.: CD-98/6289T

TREATMENT DOSE mg/kg/day		Males VOLUME mL	Males SPECIFIC GRAVITY	Males pH	Females VOLUME mL	Females SPECIFIC GRAVITY	Females pH
A: CONTROL --	MEAN	25.4	1012.4	8.1	15.7	1017.8	7.7
	S.D.	11.18	3.95	0.88	8.27	7.21	1.16
	n	10	10	10	10	10	10
B: IQB-9302.HCl 0.75	MEAN	26.6	1011.9	8.6	11.6	1021.9	7.8
	S.D.	8.18	3.60	0.52	5.57	7.19	0.92
	n	10	10	10	10	10	10
C: IQB-9302.HCl 1.25	MEAN	20.7	1014.4	8.7	13.1	1019.8	7.5
	S.D.	6.93	4.55	0.48	5.91	8.32	1.35
	n	10	10	10	10	10	10
D: IQB-9302.HCl 2.25	MEAN	20.0	1014.7	8.7	10.8	1021.3	7.4
	S.D.	7.07	6.09	0.67	5.06	7.73	1.43
	n	10	10	10	10	10	10
One-way analysis of variance ($p<0.05$)		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 14

URINALYSIS
Group results
Week 4

Study no.: CD-98/6289T
Sex: Male

TREATMENT mg/kg/day		YELLOW COLOUR	PROTEINS		GLUCOSE		KETONES		UROBILINOGEN		BILIRUBIN		BLOOD/ HAEMOGLOBIN		MICROSCOPIC EXAMINATION OF SEDIMENT							
															EPITH. CELLS no./field	ERYTH. no./field	LEUKO. no./field	BACTERIA		CASTS		CRYSTALS[1]	
			0	+	0	+	0	+	0	+	0	+	0	+	0-1	0-1	0-5	0	+	0	+	0	+
A: CONTROL	n	10	4	6	10	0	10	0	10	0	10	0	3	7	10	10	10	0	10	10	0	1	9
--	%	100	40	60	100	0	100	0	100	0	100	0	30	70	100	100	100	0	100	100	0	10	90
B: IQB-9302.HCl	n	10	8	2	10	0	10	0	10	0	10	0	3	7	10	10	10	0	10	10	0	0	10
0.75	%	100	80	20	100	0	100	0	100	0	100	0	30	70	100	100	100	0	100	100	0	0	100
C: IQB-9302.HCl	n	10	8	2	10	0	10	0	10	0	10	0	7	3	10	10	10	0	10	10	0	0	10
1.25	%	100	80	20	100	0	100	0	100	0	100	0	70	30	100	100	100	0	100	100	0	0	100
D: IQB-9302.HCl	n	10	6	4	10	0	10	0	10	0	10	0	4	6	10	10	10	0	10	10	0	0	10
2.25	%	100	60	40	100	0	100	0	100	0	100	0	40	60	100	100	100	0	100	100	0	0	100

Chi^2 test ($p<0.05$)

(1) : Magnesium ammonium phosphate

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 15

URINALYSIS
Group results
Week 4

Study no.: CD-98/6289T
Sex: Female

TREATMENT mg/kg/day		YELLOW COLOUR	PROTEINS		GLUCOSE		KETONES		UROBILINOGEN		BILIRUBIN		BLOOD/ HAEMOGLOBIN		MICROSCOPIC EXAMINATION OF SEDIMENT							
															EPITH. CELLS no./field	ERYTH. no./field	LEUKO. no./field	BACTERIA		CASTS		CRYSTALS(1)	
			0	+	0	+	0	+	0	+	0	+	0	+	0-1	0-1	0-5	0	+	0	+	0	+
A: CONTROL	n	10	3	7	10	0	10	0	10	0	10	0	0	10	10	10	10	0	10	10	0	3	7
--	%	100	30	70	100	0	100	0	100	0	100	0	0	100	100	100	100	0	100	100	0	30	70
B: IQB-9302.HCl	n	10	3	7	10	0	10	0	10	0	10	0	8	2*	10	10	10	0	10	10	0	2	8
0.75	%	100	30	70	100	0	100	0	100	0	100	0	80	20	100	100	100	0	100	100	0	20	80
C: IQB-9302.HCl	n	10	6	4	9	1	10	0	10	0	10	0	6	4*	10	10	10	0	10	10	0	4	6
1.25	%	100	60	40	90	10	100	0	100	0	100	0	60	40	100	100	100	0	100	100	0	40	60
D: IQB-9302.HCl	n	10	4	6	10	0	10	0	10	0	10	0	5	5*	10	10	10	0	10	10	0	4	6
2.25	%	100	40	60	100	0	100	0	100	0	100	0	50	50	100	100	100	0	100	100	0	40	60

Chi^2 test ($p<0.05$)

* : Statistically significant difference with respect to the Control group

(1) : Magnesium ammonium phosphate

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 16

HAEMATOLOGY
Mean values
Recovery period

Study no.: CD-98/6289T
Sex: Male

TREATMENT		ERYTHR.	HAEMOGL.	HAEMATOC.	MCV	MCH	MCHC	TOTAL LEUKOCYT.	DIFFERENTIAL LEUKOCYTE COUNT ($x10^3/\mu L$)						PLATEL.	PROTHR. TIME
DOSE									NEUTROPHILS		LYMPHO.	MONOC.	EOSINO.	BASOPH.		
mg/kg/day		$x10^6/\mu L$	g/100mL	%	fL	pg	g/100mL	$x10^3/\mu L$	Rods	Segmen.					$x10^3/\mu L$	s
	MEAN	8.10	15.98	46.36	57.22	19.74	34.50	12.08	0.00	1.57	10.02	0.41	0.07	0.00	1070.8	19.82
A : CONTROL	S.D.	0.190	0.259	1.869	1.645	0.564	1.214	1.076	0.000	0.225	1.216	0.406	0.068	0.000	148.11	4.396
--	n	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	MEAN	7.50	15.46	42.08	56.16	20.64	36.78	11.34	0.00	1.51	9.12	0.54	0.17	0.00	1043.2	18.74
B : IQB-9302.HCl	S.D.	0.723	1.159	3.996	1.873	0.720	0.847	2.151	0.000	0.607	1.698	0.372	0.118	0.000	172.81	4.641
2.25	n	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Student t test		N.S.	N.S.	N.S.	N.S.	N.S.	S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
($p<0.05$)																

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 17

HAEMATOLOGY
Mean values
Recovery period

Study no.: CD-98/6289T
Sex: Female

TREATMENT DOSE mg/kg/day		ERYTHR. x10^6/µL	HAEMOGL. g/100mL	HAEMATOC. %	MCV fL	MCH pg	MCHC g/100mL	TOTAL LEUKOCYT. x10^3/µL	DIFFERENTIAL LEUKOCYTE COUNT (x10^3/µL) NEUTROPHILS Rods	NEUTROPHILS Segmen.	LYMPHO.	MONOC.	EOSINO.	BASOPH.	PLATEL. x10^3/µL	PROTHR. TIME s
	MEAN	6.99	14.82	39.40	56.36	21.18	37.62	8.52	0.00	1.13	6.99	0.35	0.05	0.00	1153.4	15.26
A : CONTROL	S.D.	0.375	1.057	2.632	1.417	0.482	0.691	1.103	0.000	0.819	0.987	0.139	0.046	0.000	144.95	1.155
--	n	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	MEAN	7.04	15.18	40.18	57.04	21.56	37.78	7.78	0.00	1.18	6.09	0.40	0.11	0.00	1039.4	15.20
B : IQB-9302.HCl	S.D.	0.241	0.785	1.842	1.367	0.754	0.844	1.457	0.000	0.609	1.089	0.135	0.148	0.000	125.47	0.938
2.25	n	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Student t test (p<0.05)		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 18

BIOCHEMISTRY
Mean values
Recovery period

Study no.: CD-98/6289T
Sex: Male

TREATMENT DOSE mg/kg/day		GLUCOSE mg/100mL	UREA mg/100mL	CREATININE mg/100mL	TOTAL BILIRUBIN mg/100mL	AST (GOT) U/L	ALT (GPT) U/L	SDH U/L	ALKALINE PHOSPH. U/L	TOTAL CHOLEST. mg/100mL	CALCIUM mg/100mL	INORGANIC PHOSPHORUS mg/100mL	SODIUM mmol/L	POTASSIUM mmol/L	CHLORIDE mmol/L	TOTAL PROTEIN g/100mL	ALBUMIN g/100mL	ALB./GLOB. RATIO
A: CONTROL --	MEAN	99.8	26.8	0.47	0.16	139.3	28.0	8.73	313.2	46.24	11.52	9.04	145.56	5.05	103.2	6.62	3.66	1.24
	S.D.	12.28	2.17	0.025	0.025	27.35	5.60	3.261	64.91	5.263	0.217	0.416	0.716	0.209	0.84	0.130	0.114	0.133
	n	5	5	5	5	4	4	4	5	5	5	5	5	5	5	5	5	5
B: IQB-9302.HCl 2.25	MEAN	97.8	27.4	0.46	0.14	133.0	22.2	11.62	270.6	58.08	11.18	8.68	145.82	5.06	102.4	6.48	3.54	1.21
	S.D.	20.97	1.67	0.022	0.042	16.57	3.11	4.061	21.16	9.730	0.217	0.522	0.955	0.279	1.82	0.327	0.207	0.119
	n	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Student t test (p<0.05)		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	S.	S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 19

BIOCHEMISTRY
Mean values
Recovery period

Study no.: CD-98/6289T
Sex: Female

TREATMENT DOSE mg/kg/day		GLUCOSE mg/100mL	UREA mg/100mL	CREATININE mg/100mL	TOTAL BILIRUBIN mg/100mL	AST (GOT) U/L	ALT (GPT) U/L	SDH U/L	ALKALINE PHOSPH. U/L	TOTAL CHOLEST. mg/100mL	CALCIUM mg/100mL	INORGANIC PHOSPHORUS mg/100mL	SODIUM mmol/L	POTASSIUM mmol/L	CHLORIDE mmol/L	TOTAL PROTEIN g/100mL	ALBUMIN g/100mL	ALB./GLOB. RATIO
A: CONTROL	MEAN	103.2	38.2	0.52	0.21	115.6	18.0	9.00	122.4	62.34	10.84	7.00	145.26	4.43	103.0	7.18	4.10	1.33
	S.D.	16.66	6.53	0.069	0.029	15.29	1.87	1.917	62.77	21.548	0.336	0.711	0.796	0.164	1.41	0.492	0.292	0.050
--	n	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	MEAN	96.4	35.2	0.54	0.15	120.4	16.6	9.20	155.4	60.76	10.70	6.92	144.70	4.57	103.2	7.04	3.90	1.24
B: IQB-9302.HCl	S.D.	3.91	6.18	0.055	0.019	15.79	2.88	2.131	47.70	21.507	0.424	0.409	1.570	0.431	0.45	0.391	0.324	0.120
2.25	n	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Student t test (p<0.05)		N.S.	N.S.	N.S.	S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 20

Study no.: CD-98/6289T

URINALYSIS
Mean values
Recovery period

TREATMENT DOSE mg/kg/day		Males VOLUME mL	Males SPECIFIC GRAVITY	Males pH	Females VOLUME mL	Females SPECIFIC GRAVITY	Females pH
A: CONTROL	MEAN	20.6	1019.2	8.0	8.8	1027.2	6.6
	S.D.	8.76	8.70	0.00	2.28	6.53	0.89
--	n	5	5	5	5	5	5
	MEAN	22.3	1015.6	7.6	13.2	1020.2	7.0
B: IQB-9302.HCl	S.D.	4.94	4.72	0.55	5.50	5.40	1.22
2.25	n	5	5	5	5	5	5
Student t test		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

($p<0.05$)

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 21

URINALYSIS
Group results
Recovery period

Study no.: CD-98/6289T
Sex: Male

TREATMENT mg/kg/day		YELLOW COLOUR	PROTEINS		GLUCOSE		KETONES		UROBILINOGEN		BILIRUBIN		BLOOD/ HAEMOGLOBIN		MICROSCOPIC EXAMINATION OF SEDIMENT							
															EPITH. CELLS no./field	ERYTH. no./field	LEUKO. no./field	BACTERIA		CASTS		CRYSTALS(1)	
			0	+	0	+	0	+	0	+	0	+	0	+	0	0	0-5	0	+	0	+	0	+
A: CONTROL	n	5	2	3	5	0	5	0	5	0	5	0	1	4	5	5	5	0	5	5	0	0	5
--	%	100	40	60	100	0	100	0	100	0	100	0	20	80	100	100	100	0	100	100	0	0	100
B: IQB-9302.HCl	n	5	0	5	5	0	5	0	5	0	5	0	5	0*	5	5	5	0	5	5	0	0	5
2.25	%	100	0	100	100	0	100	0	100	0	100	0	100	0	100	100	100	0	100	100	0	0	100

Chi^2 test ($p<0.05$)

* : Statistically significant difference with respect to the Control group

(1) : Magnesium ammonium phosphate

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 23

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of treatment
Mean values

Study no.: CD-98/6289T
Sex: Male

	TREATMENT DOSE mg/kg/day		BODY WEIGHT g	ADRENAL GLANDS mg	TESTES g	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	PROSTATE g	LUNGS g	THYMUS g	PITUIT. GLAND mg
A:	CONTROL --	MEAN	396.2	59.3	4.70	18.5	3.25	2.07	1.38	17.24	0.84	2.36	1.70	0.68	10.1
		S.D.	40.71	15.23	0.472	7.85	0.314	0.144	0.126	2.585	0.199	0.315	0.307	0.185	3.11
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
B:	IQB-9302.HCl 0.75	MEAN	376.4	61.3	4.76	23.6	2.95	2.07	1.26	16.14	0.85	2.25	1.60	0.53	9.9
		S.D.	35.03	16.05	0.422	8.36	0.395	0.094	0.114	2.001	0.136	0.295	0.300	0.107	2.42
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
C:	IQB-9302.HCl 1.25	MEAN	396.6	60.1	4.43	19.6	3.01	2.01	1.39	17.36	0.91	2.37	1.85	0.63	10.3
		S.D.	37.44	7.87	0.973	5.66	0.324	0.115	0.204	3.084	0.142	0.341	0.215	0.144	3.37
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
D:	IQB-9302.HCl 2.25	MEAN	395.1	61.3	4.64	20.9	3.06	2.08	1.36	17.17	1.02	2.32	1.78	0.70	11.0
		S.D.	45.90	9.13	0.297	8.18	0.421	0.125	0.154	2.946	0.274	0.299	0.237	0.150	2.79
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
One-way analysis of variance ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 22

URINALYSIS
Group results
Recovery period

Study no.: CD-98/6289T
Sex: Female

TREATMENT mg/kg/day		YELLOW COLOUR	PROTEINS		GLUCOSE		KETONES		UROBILINOGEN		BILIRUBIN		BLOOD/ HAEMOGLOBIN		MICROSCOPIC EXAMINATION OF SEDIMENT							
															EPITH. CELLS no./field	ERYTH. no./field	LEUKO. no./field	BACTERIA		CASTS		CRYSTALS(1)	
			0	+	0	+	0	+	0	+	0	+	0	+	0	0	0-5	0	+	0	+	0	+
A: CONTROL	n	5	3	2	5	0	5	0	5	0	5	0	5	0	5	5	5	0	5	5	0	0	5
--	%	100	60	40	100	0	100	0	100	0	100	0	100	0	100	100	100	0	100	100	0	0	100
B: IQB-9302.HCl	n	5	4	1	5	0	5	0	5	0	5	0	5	0	5	5	5	0	5	5	0	0	5
2.25	%	100	80	20	100	0	100	0	100	0	100	0	100	0	100	100	100	0	100	100	0	0	100

Chi^2 test ($p<0.05$)

(1) : Magnesium ammonium phosphate

CENTRO DE INVESTIGACIÓN Y
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Toxicology Department
Table no.: 24

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of treatment
Mean values

Study no.: CD-98/6289T
Sex: Female

	TREATMENT DOSE mg/kg/day		BODY WEIGHT g	ADRENAL GLANDS mg	OVARIES mg	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	UTERUS g	LUNGS g	THYMUS g	PITUIT. GLAND mg
A:	CONTROL --	MEAN	256.6	72.0	138.7	26.2	2.01	1.99	1.01	11.01	0.63	0.56	1.40	0.57	18.9
		S.D.	17.68	10.93	31.37	14.33	0.128	0.096	0.105	1.295	0.115	0.176	0.124	0.095	6.69
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
B:	IQB-9302.HCl 0.75	MEAN	245.3	75.5	128.5	22.6	2.00	1.97	0.93	10.58	0.80	0.65	1.44	0.55	15.4
		S.D.	13.57	11.12	21.12	11.26	0.210	0.110	0.074	0.600	0.180	0.136	0.179	0.108	6.02
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
C:	IQB-9302.HCl 1.25	MEAN	246.9	78.4	157.9	21.3	2.02	1.93	0.98	10.14	0.78	0.61	1.43	0.52	17.0
		S.D.	14.79	13.17	22.95	7.97	0.133	0.114	0.098	0.995	0.132	0.209	0.240	0.110	6.88
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
D:	IQB-9302.HCl 2.25	MEAN	247.3	76.2	146.1	21.3	1.99	1.90	0.96	10.36	0.79	0.63	1.38	0.55	15.0
		S.D.	16.38	14.41	35.80	6.50	0.223	0.106	0.074	0.877	0.143	0.162	0.176	0.110	4.00
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
One-way analysis of variance (p<0.05)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	S.	N.S.	N.S.	N.S.	N.S.
Duncan-Kramer test (p<0.05)											ACDB				

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 25

RELATIVE ORGAN WEIGHTS
Sacrificed after end of treatment
Mean values

Study no.: CD-98/6289T
Sex: Male

	TREATMENT DOSE mg/kg/day		BODY WEIGHT g	ADRENAL GLANDS %(x100)	TESTES %	THYROID GLANDS %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	PROSTATE %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
A:	CONTROL --	MEAN	396.2	1.49	1.19	0.46	0.83	0.53	0.35	4.37	0.22	0.60	0.43	0.17	0.26
		S.D.	40.71	0.332	0.156	0.172	0.100	0.060	0.030	0.643	0.049	0.078	0.072	0.041	0.082
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
B:	IQB-9302.HCl 0.75	MEAN	376.4	1.61	1.27	0.62	0.78	0.55	0.34	4.31	0.23	0.60	0.43	0.14	0.27
		S.D.	35.03	0.303	0.074	0.201	0.085	0.043	0.024	0.573	0.035	0.072	0.069	0.023	0.066
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
C:	IQB-9302.HCl 1.25	MEAN	396.6	1.52	1.12	0.49	0.76	0.51	0.35	4.36	0.23	0.60	0.47	0.16	0.26
		S.D.	37.44	0.172	0.260	0.122	0.060	0.048	0.026	0.472	0.025	0.089	0.061	0.031	0.083
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
D:	IQB-9302.HCl 2.25	MEAN	395.1	1.58	1.18	0.53	0.77	0.53	0.35	4.35	0.25	0.59	0.45	0.18	0.28
		S.D.	45.90	0.332	0.104	0.208	0.060	0.042	0.022	0.575	0.042	0.052	0.048	0.024	0.070
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
One-way analysis of variance ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

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Toxicology Department
Table no.: 26

RELATIVE ORGAN WEIGHTS
Sacrificed after end of treatment
Mean values

Study no.: CD-98/6289T
Sex: Female

	TREATMENT DOSE mg/kg/day		BODY WEIGHT g	ADRENAL GLANDS %(x100)	OVARIES %(x100)	THYROID GLAND %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
A:	CONTROL --	MEAN	256.6	2.81	5.40	1.02	0.78	0.78	0.40	4.29	0.25	0.22	0.55	0.22	0.74
		S.D.	17.68	0.443	1.119	0.550	0.039	0.064	0.037	0.328	0.040	0.069	0.035	0.037	0.271
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
B:	IQB-9302.HCl 0.75	MEAN	245.3	3.09	5.24	0.93	0.81	0.81	0.38	4.32	0.32	0.27	0.59	0.22	0.63
		S.D.	13.57	0.492	0.807	0.492	0.069	0.041	0.035	0.273	0.057	0.058	0.069	0.037	0.272
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
C:	IQB-9302.HCl 1.25	MEAN	246.9	3.18	6.40	0.85	0.82	0.78	0.40	4.12	0.32	0.25	0.58	0.21	0.68
		S.D.	14.79	0.543	0.876	0.291	0.051	0.032	0.035	0.402	0.049	0.090	0.087	0.043	0.243
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
D:	IQB-9302.HCl 2.25	MEAN	247.3	3.09	5.87	0.86	0.81	0.77	0.39	4.19	0.32	0.26	0.56	0.22	0.60
		S.D.	16.38	0.607	1.249	0.256	0.088	0.073	0.021	0.214	0.049	0.068	0.075	0.037	0.146
		n	10	10	10	10	10	10	10	10	10	10	10	10	10
One-way analysis of variance ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	S.	N.S.	N.S.	N.S.	N.S.
Duncan-Kramer test ($p<0.05$)											ACDB				

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DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 27

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of recovery period
Mean values

Study no.: CD-98/6289T
Sex: Male

	TREATMENT DOSE mg/kg/day		BODY WEIGHT g	ADRENAL GLANDS mg	TESTES g	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	PROSTATE g	LUNGS g	THYMUS g	PITUIT. GLAND mg
A:	CONTROL	MEAN	434.2	59.6	4.85	32.0	3.15	2.09	1.41	18.92	0.78	2.56	1.68	0.66	16.0
	--	S.D.	30.29	4.10	0.413	7.65	0.276	0.043	0.073	2.000	0.068	0.324	0.157	0.118	1.87
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
B:	IQB-9302.HCl	MEAN	463.0	71.0	5.35	32.8	3.50	2.15	1.62	19.26	0.92	2.82	1.98	0.78	16.0
	2.25	S.D.	56.77	12.51	0.421	10.23	0.404	0.110	0.136	4.433	0.109	0.516	0.186	0.202	4.36
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
Student t test (p<0.05)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	S.	N.S.	S.	N.S.	S.	N.S.	N.S.

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DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 28

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of recovery period
Mean values

Study no.: CD-98/6289T
Sex: Female

	TREATMENT DOSE mg/kg/day		BODY WEIGHT g	ADRENAL GLANDS mg	OVARIES mg	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	UTERUS g	LUNGS g	THYMUS g	PITUIT. GLAND mg
A:	CONTROL --	MEAN	262.0	69.6	155.4	23.0	2.06	1.97	0.98	10.76	0.65	0.58	1.33	0.50	19.8
		S.D.	10.32	7.09	24.91	6.96	0.113	0.045	0.079	0.398	0.091	0.110	0.105	0.075	4.49
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
B:	IQB-9302.HCl 2.25	MEAN	270.2	67.6	144.6	22.2	2.00	1.92	0.99	10.57	0.81	0.67	1.59	0.49	16.4
		S.D.	14.36	14.43	26.65	6.80	0.215	0.084	0.105	1.166	0.174	0.139	0.106	0.070	4.72
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
Student t test (p<0.05)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	S.	N.S.	N.S.

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DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 29

RELATIVE ORGAN WEIGHTS
Sacrificed after end of recovery period
Mean values

Study no.: CD-98/6289T
Sex: Male

	TREATMENT DOSE mg/kg/day		BODY WEIGHT g	ADRENAL GLANDS %(x100)	TESTES %	THYROID GLANDS %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	PROSTATE %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
A:	CONTROL --	MEAN	434.2	1.38	1.12	0.74	0.73	0.48	0.33	4.35	0.18	0.60	0.39	0.15	0.37
		S.D.	30.29	0.088	0.138	0.155	0.056	0.029	0.018	0.158	0.008	0.097	0.043	0.032	0.049
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
B:	IQB-9302.HCl 2.25	MEAN	463.0	1.55	1.16	0.70	0.76	0.46	0.35	4.12	0.20	0.61	0.43	0.17	0.34
		S.D.	56.77	0.345	0.073	0.150	0.039	0.044	0.016	0.475	0.008	0.070	0.024	0.025	0.066
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
Student t test ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	S.	N.S.	N.S.	N.S.	N.S.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 30

RELATIVE ORGAN WEIGHTS
Sacrificed after end of recovery period
Mean values

Study no.: CD-98/6289T
Sex: Female

	TREATMENT DOSE mg/kg/day		BODY WEIGHT g	ADRENAL GLANDS %(x100)	OVARIES %(x100)	THYROID GLAND %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
A:	CONTROL --	MEAN	262.0	2.65	5.95	0.88	0.79	0.75	0.37	4.11	0.25	0.22	0.51	0.19	0.75
		S.D.	10.32	0.206	1.064	0.255	0.047	0.038	0.018	0.210	0.037	0.040	0.038	0.027	0.149
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
B:	IQB-9302.HCl 2.25	MEAN	270.2	2.50	5.36	0.82	0.74	0.71	0.37	3.91	0.30	0.25	0.59	0.18	0.61
		S.D.	14.36	0.507	0.998	0.245	0.095	0.066	0.051	0.389	0.064	0.048	0.043	0.039	0.180
		n	5	5	5	5	5	5	5	5	5	5	5	5	5
Student t test ($p<0.05$)			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	S.	N.S.	N.S.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 31

Study no.: CD-98/6289T

FREQUENCY OF MACROSCOPIC OBSERVATIONS
BY ORGAN/SEX/GROUP

Animals sacrificed at the end of the 4 weeks of treatment

		CONTROL		IQB-9302.HCl (mg/kg/day)					
				0.75		1.25		2.25	
Organs/Macroscopic observations	Sex	M	F	M	F	M	F	M	F
	Animals/Group	10	10	10	10	10	10	10	10
KIDNEYS									
Dilation of renal calices									
- Unilateral		1					1		
- Bilateral		1			1	1			2
THYMUS									
Petechial areas					1			1	
TESTES									
Both testes decreased in size						1			
SPLEEN									
Nodular surface								1	
Whitish nodule of 0.5 cm in diameter							1		

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 32

Study no.: CD-98/6289T

FREQUENCY OF MACROSCOPIC OBSERVATIONS
BY ORGAN/SEX/GROUP

Animals sacrificed at the end of the recovery period

		CONTROL		IQB-9302.HCl (2.25 mg/kg/day)	
Organs/Macroscopic observations	Sex	M	F	M	F
	Animals/Group	5	5	5	5
KIDNEYS Dilation of renal calices - Unilateral		1			1

CENTRO DE INVESTIGACIÓN Y
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Toxicology Department
Table no.: 33

Study no.: CD-98/62891

MICROSCOPIC OBSERVATIONS BY ORGAN/SEX/GROUP
(Animals sacrificed at the end of treatment)

Codes for treatment groups and doses:

Group 1: CONTROL - mg/kg/day
Group 2: IQB-9302.HCl 0.75 mg/kg/day
Group 3: IQB-9302.HCl 1.25 mg/kg/day
Group 4: IQB-9302.HCl 2.25 mg/kg/day

ORGAN Microscopic observations	Treatment group:	1		2		3		4	
	Sex:	M	F	M	F	M	F	M	F
	Animals/group:	10	10	10	10	10	10	10	10
SPLEEN	Animals exam:	10	10					10	10
Lymphoid hyperplasia								1	
LIVER	Animals exam:	10	10					10	10
Lymphocytary infiltrate, portal									1
Microgranuloma			1						1
PITUITARY	Animals exam:	10	10					10	10
Simple cyst								1	
EYES	Animals exam:	10	10					10	10
Lymphocytary infiltrate in Harder's gland, unilateral									1
LUNGS	Animals exam:	10	10					10	10
Intraalveolar histiocytosis, focal		1	1					2	
KIDNEYS	Animals exam:	10	10		1	1	1	10	10
Dilation of renal pelvis		2			1	1	1		
Interstitial nephritis, focal								1	
Pyelitis, acute, non-specific									2
TESTES	Animals exam:	10				1		10	
Tubular atrophy						1			
THYMUS	Animals exam:	10	10		1		1	10	10
Multifocal congestion								1	
URINARY BLADDER	Animals exam:	10	10					10	10
Cystitis, acute, non-specific									1

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 34

Study no.: CD-98/628~~97~~

MICROSCOPIC OBSERVATIONS BY ORGAN/SEX/GROUP
(Animals sacrificed at the end of recovery)

Codes for treatment group and dose:

Group 1: CONTROL - mg/kg/day Group 4: IQB-9302.HCl 2.25 mg/kg/day

ORGAN Microscopic observations	Treatment group:	1		4	
	Sex:	M	F	M	F
	Animals/group:	5	5	5	5
LIVER	Animals exam:	5	5	5	5
Hepatocytary vacuolisation, centrolobular		1			
PITUITARY	Animals exam:	5	4	5	5
Simple cyst			1		
LUNGS	Animals exam:	5	5	5	5
Intraalveolar histiocytosis, focal		1		1	
KIDNEYS	Animals exam:	5	5	5	5
Dilation of renal pelvis		1			1

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Toxicology Department
Table no.: 35

BODYWEIGHTS (g)
Individual results

Study no.: CD-98/62891
Test substance: CONTROL
Dose: --

ANIMAL		Treatment day									
No.	Sex	-7	1	4	8	11	15	18	22	25	29
1	M	185	244	255	271	280	296	312	328	329	345
2	M	183	250	263	285	303	319	336	355	356	385
3	M	181	239	253	274	291	304	318	327	329	353
4	M	178	241	258	279	298	313	331	351	352	369
5	M	188	257	269	294	317	333	350	363	362	385
6	M	201	289	303	336	358	386	405	443	429	463
7	M	191	261	280	302	322	338	352	365	357	381
8	M	194	262	283	302	323	341	362	385	370	398
9	M	197	271	292	320	344	373	389	411	407	440
10	M	185	246	263	285	297	313	325	345	334	362
11	M	194	257	271	296	313	332	347	362	381	395
12	M	190	252	265	286	296	316	327	344	356	369
13	M	199	262	274	292	304	318	331	345	361	373
14	M	203	269	289	321	338	363	382	406	415	440
15	M	203	273	288	309	324	338	346	367	377	390
	MEAN	191.5	258.2	273.7	296.8	313.9	332.2	347.5	366.5	367.7	389.9
	S.D.	8.10	13.65	14.92	18.50	21.45	25.54	26.98	32.31	30.06	33.70
	n	15	15	15	15	15	15	15	15	15	15
51	F	150	177	190	202	207	218	225	232	235	245
52	F	156	191	196	209	215	228	236	251	240	257
53	F	175	206	211	225	226	242	245	253	257	271
54	F	156	184	192	201	210	221	225	232	227	242
55	F	148	179	186	194	198	210	214	227	221	237
56	F	166	188	197	207	221	233	239	248	237	238
57	F	173	205	214	222	232	242	249	253	248	255
58	F	164	197	204	212	220	229	230	235	229	233
59	F	179	205	218	234	252	263	274	282	266	274
60	F	166	204	211	222	228	241	246	255	246	253
61	F	177	208	211	221	220	231	238	250	252	262
62	F	157	187	197	202	209	218	222	232	227	236
63	F	161	190	206	216	222	239	243	256	263	275
64	F	157	185	188	197	203	207	220	225	226	235
65	F	152	192	199	210	216	230	234	243	245	253
	MEAN	162.5	193.2	201.3	211.6	218.6	230.1	236.0	244.9	241.3	251.1
	S.D.	10.00	10.32	10.17	11.51	13.22	14.37	14.82	14.94	14.11	14.57
	n	15	15	15	15	15	15	15	15	15	15

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 36

BODYWEIGHTS (g)
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 0.75 mg/kg/day

ANIMAL		Treatment day									
No.	Sex	-7	1	4	8	11	15	18	22	25	29
16	M	210	269	286	314	331	350	366	381	386	400
17	M	180	239	258	284	302	321	340	359	360	386
18	M	177	235	257	279	295	309	323	338	341	363
19	M	184	245	262	285	296	320	333	353	352	375
20	M	185	238	255	271	285	295	305	318	318	332
21	M	174	224	240	260	270	286	297	311	299	323
22	M	192	254	275	293	309	323	335	345	339	366
23	M	200	271	294	317	338	360	377	404	392	425
24	M	195	260	275	298	321	344	356	379	368	402
25	M	189	239	257	276	288	298	307	318	311	329
	MEAN	188.6	247.4	265.9	287.7	303.5	320.6	333.9	350.6	346.6	370.1
	S.D.	11.04	15.50	16.28	18.15	21.39	24.65	26.78	30.81	31.13	34.37
	n	10	10	10	10	10	10	10	10	10	10
66	F	164	189	196	204	205	211	216	224	218	232
67	F	159	184	193	204	210	217	220	229	230	243
68	F	152	175	181	194	199	211	212	219	214	226
69	F	158	189	198	209	222	235	232	242	246	260
70	F	153	177	186	193	205	217	220	228	222	238
71	F	158	187	196	209	209	218	229	236	227	232
72	F	161	193	203	210	213	223	231	239	235	239
73	F	171	193	206	224	234	236	253	262	254	249
74	F	173	200	208	222	227	239	248	257	248	251
75	F	155	180	190	198	204	213	222	230	219	222
	MEAN	160.4	186.7	195.7	206.7	212.8	222.0	228.3	236.6	231.3	239.2
	S.D.	7.09	7.82	8.60	10.51	11.29	10.77	13.39	13.91	13.98	11.82
	n	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 37

BODYWEIGHTS (g)
Individual results

Study no.: CD-98/62891
Test substance: IQB-9302.HCl
Dose: 1.25 mg/kg/day

ANIMAL		Treatment day									
No.	Sex	-7	1	4	8	11	15	18	22	25	29
26	M	187	246	267	292	307	332	345	360	359	383
27	M	186	243	258	270	278	298	301	309	309	333
28	M	198	262	287	315	334	356	380	396	403	428
29	M	190	251	273	296	318	343	360	375	373	387
30	M	197	252	273	298	311	317	333	334	333	352
31	M	205	274	300	331	352	377	393	419	416	440
32	M	183	242	268	293	319	341	361	378	373	396
33	M	193	248	265	287	301	311	320	333	332	351
34	M	202	269	289	309	327	335	355	369	360	386
35	M	191	256	281	316	333	357	376	394	389	414
	MEAN	193.2	254.3	276.1	300.7	318.0	336.7	352.4	366.7	364.7	387.0
	S.D.	7.18	10.90	12.91	17.38	20.49	23.66	28.34	33.53	33.43	34.57
	n	10	10	10	10	10	10	10	10	10	10
76	F	155	182	188	197	213	221	228	238	228	231
77	F	159	189	197	204	214	223	227	231	229	244
78	F	153	178	183	192	202	212	220	224	225	238
79	F	154	178	182	198	213	218	229	231	232	241
80	F	163	194	201	210	217	228	229	235	228	241
81	F	166	194	211	222	224	240	255	268	248	254
82	F	156	180	189	198	209	217	217	225	216	217
83	F	166	195	203	214	219	231	241	250	239	236
84	F	157	183	187	194	208	219	217	229	231	226
85	F	180	226	228	232	241	250	255	266	269	269
	MEAN	160.9	189.9	196.9	206.1	216.0	225.9	231.8	239.7	234.5	239.7
	S.D.	8.23	14.36	14.43	13.19	10.70	11.67	14.11	16.17	14.75	14.45
	n	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 38

BODYWEIGHTS (g)
Individual results

Study no.: CD-98/62891
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day

ANIMAL		Treatment day									
No.	Sex	-7	1	4	8	11	15	18	22	25	29
36	M	189	244	260	276	290	299	310	325	321	340
37	M	173	237	266	291	315	343	367	393	392	421
38	M	185	248	271	298	316	336	352	363	372	391
39	M	178	229	249	268	290	308	323	347	346	369
40	M	185	245	255	267	278	290	301	312	308	321
41	M	185	254	271	303	319	338	352	371	360	396
42	M	186	248	265	282	292	311	323	338	319	360
43	M	181	248	272	300	317	335	349	369	346	381
44	M	206	283	304	338	360	387	409	437	418	461
45	M	197	272	292	325	347	378	404	420	394	447
46	M	192	257	279	304	324	341	355	376	387	402
47	M	191	255	271	295	306	326	342	349	362	374
48	M	190	252	277	302	324	348	375	389	410	432
49	M	201	264	290	320	337	361	378	403	420	444
50	M	203	270	295	333	357	381	409	431	456	488
	MEAN	189.5	253.7	274.5	300.1	318.1	338.8	356.6	374.9	374.1	401.8
	S.D.	9.26	13.98	15.38	21.89	24.73	29.42	34.31	37.61	42.31	46.73
	n	15	15	15	15	15	15	15	15	15	15
86	F	166	197	208	219	224	234	234	239	235	253
87	F	149	170	180	189	196	202	212	221	210	210
88	F	152	184	189	202	204	212	221	229	229	245
89	F	167	196	212	208	224	229	239	254	242	258
90	F	159	187	199	213	220	224	224	238	235	247
91	F	154	178	183	194	202	205	212	217	204	223
92	F	169	202	220	232	241	253	258	260	243	252
93	F	169	194	208	225	233	237	243	246	238	253
94	F	158	189	202	214	220	227	240	246	238	247
95	F	158	190	197	211	219	227	234	245	233	251
96	F	153	183	189	199	216	223	224	235	242	246
97	F	167	188	203	216	218	229	237	241	251	256
98	F	163	190	196	212	230	237	240	257	259	268
99	F	159	193	201	214	215	226	237	248	249	261
100	F	170	196	206	220	229	236	243	248	253	264
	MEAN	160.9	189.1	199.5	211.2	219.4	226.7	233.2	241.6	237.4	248.9
	S.D.	6.94	8.11	10.94	11.45	12.01	13.02	12.48	12.29	14.81	14.96
	n	15	15	15	15	15	15	15	15	15	15

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 39

BODYWEIGHTS (g)
Recovery period
Individual results

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --

ANIMAL		Study day				
No.	Sex	29	32	36	39	43
11	M	395	406	428	411	436
12	M	369	382	400	377	410
13	M	373	388	408	398	413
14	M	440	458	472	463	485
15	M	390	406	422	400	427
	MEAN	393.4	408.0	426.0	409.8	434.2
	S.D.	28.27	29.93	28.00	32.18	30.29
	n	5	5	5	5	5
61	F	262	256	266	252	264
62	F	236	249	255	240	255
63	F	275	277	281	266	277
64	F	235	235	246	234	250
65	F	253	263	264	246	264
	MEAN	252.2	256.0	262.4	247.6	262.0
	S.D.	17.14	15.65	13.09	12.28	10.32
	n	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 40

BODYWEIGHTS (g)
Recovery period
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day

ANIMAL		Study day				
No.	Sex	29	32	36	39	43
46	M	402	421	433	427	439
47	M	374	396	410	402	427
48	M	432	454	474	438	406
49	M	444	456	487	477	500
50	M	488	506	527	521	543
	MEAN	428.0	446.6	466.2	453.0	463.0
	S.D.	43.20	41.49	45.96	46.64	56.77
	n	5	5	5	5	5
96	F	246	243	241	239	246
97	F	256	269	274	252	274
98	F	268	274	287	271	284
99	F	261	251	254	254	271
100	F	264	264	275	266	276
	MEAN	259.0	260.2	266.2	256.4	270.2
	S.D.	8.49	12.87	18.40	12.58	14.36
	n	5	5	5	5	5

NTRO DE INVESTIGACIÓN Y
SARROLLO APLICADO, S.A.L.
icology Department
le no.: 41

HAEMATOLOGY
Individual results
Week 4

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --

nal		ERYTHR.	HAEMOGL.	HAEMATOC.	MCV	MCH	MCHC	TOTAL LEUKOCYT.	DIFFERENTIAL LEUKOCYTE COUNT ($x10^3/\mu L$)						PLATEL.	PROTHR. TIME
									NEUTROPHILS		LYMPHO.	MONOC.	EOSINO.	BASOPH.		
o.	Sex	$x10^6/\mu L$	g/100mL	%	fL	pg	g/100mL	$x10^3/\mu L$	Rods	Segmen.					$x10^3/\mu L$	s
	M	7.75	15.4	43.4	56.0	19.9	35.5	8.5	0.0	0.8	7.1	0.5	0.1	0.0	1035	22.6
2	M	7.13	15.6	42.0	58.9	21.9	37.1	8.1	0.0	2.2	5.2	0.7	0.0	0.0	1127	18.9
3	M	7.59	15.7	42.8	56.4	20.7	36.7	11.1	0.0	1.8	8.5	0.7	0.1	0.0	1145	25.3
4	M	7.70	16.9	45.2	58.7	21.9	37.4	7.8	0.0	1.0	6.4	0.3	0.1	0.0	1138	20.0
5	M	7.38	15.6	43.6	59.1	21.1	35.8	14.9	0.0	1.5	12.4	0.7	0.3	0.0	1188	39.6
6	M	6.99	15.6	43.3	61.9	22.3	36.0	14.3	0.0	2.4	10.4	1.3	0.1	0.0	1102	19.9
7	M	7.58	16.1	45.0	59.4	21.2	35.8	17.3	0.0	2.8	13.3	1.2	0.0	0.0	1227	24.2
8	M	7.39	15.6	42.1	57.0	21.1	37.1	12.7	0.0	1.7	10.4	0.5	0.1	0.0	1105	28.0
9	M	7.06	15.3	41.2	58.4	21.7	37.1	15.3	0.0	2.1	12.4	0.8	0.0	0.0	1104	21.9
10	M	7.55	15.8	43.3	57.4	20.9	36.5	9.7	0.0	1.5	7.6	0.7	0.0	0.0	1112	21.0
EAN		7.41	15.76	43.19	58.32	21.27	36.50	11.97	0.00	1.77	9.38	0.74	0.08	0.00	1128.3	24.14
D.		0.271	0.455	1.259	1.724	0.702	0.680	3.405	0.000	0.625	2.813	0.302	0.094	0.000	52.15	6.102
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
51	F	6.54	14.8	38.5	58.9	22.6	38.4	7.1	0.0	0.4	6.3	0.1	0.3	0.0	1072	15.7
52	F	6.72	15.2	38.5	57.3	22.6	39.5	8.2	0.0	1.1	6.8	0.1	0.2	0.0	1275	15.9
53	F	6.66	15.0	37.3	56.0	22.5	40.2	8.7	0.0	0.5	7.8	0.3	0.0	0.0	1263	14.8
54	F	7.01	15.4	40.1	57.2	22.0	38.4	7.9	0.0	0.7	6.6	0.4	0.2	0.0	1289	14.6
55	F	6.92	15.2	38.8	56.1	22.0	39.2	13.0	0.0	0.5	11.1	1.0	0.4	0.0	1038	16.6
56	F	6.50	15.2	38.9	59.8	23.4	39.1	6.8	0.0	0.9	5.4	0.3	0.1	0.0	1150	15.4
57	F	7.18	15.3	40.3	56.1	21.3	38.0	7.7	0.0	1.5	5.8	0.4	0.1	0.0	1203	15.6
58	F	6.58	14.6	37.2	56.5	22.2	39.2	7.6	0.0	0.6	6.3	0.5	0.2	0.0	929	16.0
59	F	6.86	15.3	38.8	56.6	22.3	39.4	10.8	0.0	1.3	8.9	0.5	0.1	0.0	1157	16.9
60	F	6.83	14.8	38.3	56.1	21.7	38.6	10.8	0.0	0.6	9.8	0.1	0.2	0.0	1048	15.2
EAN		6.78	15.08	38.67	57.06	22.26	39.00	8.86	0.00	0.82	7.48	0.38	0.18	0.00	1142.4	15.67
.D.		0.220	0.266	1.001	1.307	0.574	0.651	2.009	0.000	0.361	1.867	0.288	0.111	0.000	119.20	0.726
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

NTRO DE INVESTIGACIÓN Y
SARROLLO APLICADO, S.A.L.
cology Department
le no.: 42

HAEMATOLOGY
Individual results
Week 4

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 0.75 mg/kg/day

nal		ERYTHR.	HAEMOGL.	HAEMATOC.	MCV	MCH	MCHC	TOTAL LEUKOCYT.	DIFFERENTIAL LEUKOCYTE COUNT ($x10^3/\mu L$)						PLATEL.	PROTHR. TIME
									NEUTROPHILS		LYMPHO.	MONOC.	EOSINO.	BASOPH.		
.	Sex	$x10^6/\mu L$	g/100mL	%	fL	pg	g/100mL	$x10^3/\mu L$	Rods	Segmen.					$x10^3/\mu L$	s
6	M	6.99	14.8	40.5	57.9	21.2	36.5	9.7	0.0	0.7	8.3	0.4	0.3	0.0	1024	22.7
7	M	7.65	15.9	45.3	59.2	20.8	35.1	11.8	0.0	1.4	9.8	0.6	0.0	0.0	1077	22.4
8	M	8.18	16.9	47.8	58.4	20.7	35.4	12.8	0.0	1.5	10.5	0.8	0.0	0.0	889	19.7
9	M	7.70	15.8	43.8	56.9	20.5	36.1	9.3	0.0	1.0	8.1	0.2	0.0	0.0	1269	22.6
0	M	8.07	16.5	44.9	55.6	20.4	36.7	7.8	0.0	0.6	7.0	0.2	0.0	0.0	1239	28.0
1	M	7.95	16.6	43.9	55.2	20.9	37.8	13.8	0.0	1.8	11.7	0.1	0.1	0.0	1202	30.7
2	M	7.56	15.3	41.2	54.5	20.2	37.1	10.6	0.0	2.0	8.6	0.0	0.0	0.0	940	24.5
3	M	6.79	15.5	40.5	59.6	22.8	38.3	8.2	0.0	1.0	7.1	0.2	0.0	0.0	1207	16.2
4	M	7.70	16.5	44.4	57.7	21.4	37.2	8.6	0.0	1.5	7.1	0.0	0.1	0.0	1257	19.3
5	M	7.22	15.2	40.0	55.4	21.1	38.0	11.8	0.0	1.1	10.1	0.6	0.0	0.0	1111	22.9
AN		7.58	15.90	43.23	57.04	21.00	36.82	10.44	0.00	1.26	8.83	0.30	0.05	0.00	1121.5	22.90
D.		0.456	0.702	2.573	1.791	0.733	1.074	2.049	0.000	0.461	1.643	0.269	0.097	0.000	135.94	4.188
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
6	F	6.71	14.5	38.6	57.5	21.6	37.6	8.1	0.0	0.6	7.4	0.2	0.0	0.0	989	13.8
7	F	6.68	15.4	39.6	59.3	23.1	38.9	8.9	0.0	0.9	7.5	0.4	0.2	0.0	1320	15.6
8	F	6.77	14.9	38.2	56.4	22.0	39.0	9.6	0.0	0.7	8.5	0.4	0.0	0.0	1052	14.8
9	F	6.98	15.4	39.9	57.2	22.1	38.6	11.3	0.0	1.8	8.8	0.5	0.2	0.0	1000	16.7
0	F	7.05	16.0	42.2	59.9	22.7	37.9	11.9	0.0	0.8	10.9	0.1	0.0	0.0	1258	16.6
1	F	7.13	14.9	39.2	55.0	20.9	38.0	10.7	0.0	0.6	9.8	0.2	0.0	0.0	1080	15.3
2	F	6.14	14.1	36.2	59.0	23.0	39.0	8.4	0.0	0.6	7.8	0.0	0.0	0.0	1229	14.7
3	F	6.00	13.6	33.8	56.3	22.7	40.2	6.7	0.0	0.3	6.0	0.3	0.1	0.0	1076	17.2
4	F	7.03	15.9	39.9	56.8	22.6	39.8	11.9	0.0	1.1	10.6	0.2	0.0	0.0	1271	16.9
5	F	7.17	16.3	41.2	57.5	22.7	39.6	8.1	0.0	1.1	6.8	0.1	0.1	0.0	1273	15.9
EAN		6.77	15.1	38.88	57.49	22.34	38.86	9.56	0.00	0.85	8.42	0.23	0.06	0.00	1154.8	15.75
.D.		0.406	0.867	2.418	1.518	0.688	0.855	1.811	0.000	0.423	1.644	0.146	0.088	0.000	126.82	1.111
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

NTRO DE INVESTIGACIÓN Y
SARROLLO APLICADO, S.A.L.
icology Department
le no.: 44

HAEMATOLOGY
Individual results
Week 4

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day

mal		ERYTHR.	HAEMOGL.	HAEMATOC.	MCV	MCH	MCHC	TOTAL LEUKOCYT.	DIFFERENTIAL LEUKOCYTE COUNT ($x10^3/\mu L$)						PLATEL.	PROTHR. TIME
									NEUTROPHILS		LYMPHO.	MONOC.	EOSINO.	BASOPH.		
o.	Sex	$x10^6/\mu L$	g/100mL	%	fL	pg	g/100mL	$x10^3/\mu L$	Rods	Segmen.					$x10^3/\mu L$	s
6	M	7.48	16.0	42.6	57.0	21.4	37.6	12.1	0.0	1.8	9.1	1.0	0.2	0.0	1066	25.4
7	M	6.55	15.5	40.9	62.4	23.7	37.9	11.4	0.0	2.6	8.3	0.5	0.0	0.0	1015	14.1
8	M	7.71	15.3	42.5	55.1	19.8	36.0	14.2	0.0	1.3	12.4	0.4	0.1	0.0	1381	23.6
9	M	7.14	15.4	41.4	58.0	21.6	37.2	10.3	0.0	0.9	9.2	0.1	0.1	0.0	1193	20.2
0	M	7.37	15.5	40.3	54.7	21.0	38.5	12.2	0.0	2.1	10.0	0.0	0.1	0.0	1288	22.2
1	M	6.69	14.2	38.0	56.8	21.2	37.4	13.2	0.0	1.2	11.7	0.0	0.3	0.0	1016	15.9
2	M	7.75	16.6	45.9	59.2	21.4	36.2	8.4	0.0	0.5	7.5	0.3	0.1	0.0	1168	15.8
3	M	6.81	15.7	42.0	61.7	23.1	37.4	17.4	0.0	1.4	14.8	1.2	0.0	0.0	1124	15.8
4	M	6.93	15.6	41.9	60.5	22.5	37.2	15.7	0.0	0.6	14.1	0.6	0.3	0.0	1049	15.9
5	M	6.70	14.9	39.5	59.0	22.2	37.7	13.1	0.0	1.7	10.7	0.5	0.1	0.0	1068	17.4
AN		7.11	15.47	41.50	58.44	21.79	37.31	12.80	0.00	1.41	10.78	0.47	0.14	0.00	1136.8	18.63
D.		0.442	0.633	2.109	2.615	1.121	0.745	2.586	0.000	0.658	2.445	0.399	0.105	0.000	121.87	3.926
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
6	F	6.96	14.6	36.9	53.0	21.0	39.6	6.4	0.0	0.8	5.4	0.3	0.0	0.0	1268	14.4
7	F	6.25	14.0	36.1	57.8	22.4	38.8	10.0	0.0	0.4	9.2	0.4	0.0	0.0	1260	15.6
8	F	5.80	12.8	32.2	55.5	22.1	39.8	5.8	0.0	0.2	5.5	0.1	0.1	0.0	775	15.1
9	F	6.62	14.3	37.7	56.9	21.6	37.9	5.6	0.0	1.0	4.6	0.1	0.0	0.0	1200	15.5
0	F	6.65	15.1	38.5	57.9	22.7	39.2	7.8	0.0	0.8	6.7	0.2	0.1	0.0	1327	14.8
1	F	7.34	15.8	41.5	56.5	21.5	38.1	7.6	0.0	1.0	6.2	0.3	0.1	0.0	1131	13.7
2	F	6.88	14.9	39.4	57.3	21.7	37.8	8.2	0.0	0.6	7.3	0.3	0.0	0.0	1163	16.4
3	F	6.50	15.0	43.4	66.8	23.1	34.6	6.1	0.0	0.4	5.4	0.2	0.1	0.0	957	14.3
4	F	6.00	13.9	36.1	60.2	23.2	38.5	10.5	0.0	1.5	8.4	0.4	0.2	0.0	1340	14.7
5	F	7.13	15.3	41.8	58.6	21.5	36.6	13.0	0.0	3.4	9.1	0.4	0.1	0.0	1203	15.4
EAN		6.61	14.57	38.36	58.05	22.08	38.09	8.10	0.00	0.99	6.78	0.27	0.06	0.00	1162.4	14.99
.D.		0.491	0.856	3.315	3.619	0.745	1.550	2.407	0.000	0.915	1.660	0.130	0.069	0.000	175.00	0.775
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

NTRO DE INVESTIGACION Y
SARROLLO APLICADO, S.A.L.
icology Department
le no.: 43

HAEMATOLOGY
Individual results
Week 4

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 1.25 mg/kg/day

mal		ERYTHR.	HAEMOGL.	HAEMATOC.	MCV	MCH	MCHC	TOTAL LEUKOCYT.	DIFFERENTIAL LEUKOCYTE COUNT ($x10^3/\mu L$)						PLATEL.	PROTHR. TIME
									NEUTROPHILS		LYMPHO.	MONOC.	EOSINO.	BASOPH.		
o.	Sex	$x10^6/\mu L$	g/100mL	%	fL	pg	g/100mL	$x10^3/\mu L$	Rods	Segmen.					$x10^3/\mu L$	s
6	M	7.05	15.0	40.6	57.6	21.3	36.9	12.3	0.0	0.7	11.4	0.0	0.1	0.0	1126	21.5
7	M	7.63	16.6	44.6	58.5	21.8	37.2	9.6	0.0	1.3	7.8	0.3	0.2	0.0	1009	20.2
8	M	7.55	17.2	46.9	62.1	22.8	36.7	11.9	0.0	1.5	10.1	0.1	0.1	0.0	1069	24.0
9	M	7.44	15.4	42.1	56.6	20.7	36.6	11.3	0.0	1.4	9.6	0.3	0.0	0.0	1033	22.7
0	M	8.52	16.4	44.1	51.8	19.2	37.2	7.7	0.0	0.7	6.5	0.5	0.0	0.0	1057	25.4
1	M	7.91	16.9	46.3	58.5	21.4	36.5	11.0	0.0	1.4	9.2	0.2	0.1	0.0	987	18.5
2	M	7.40	16.1	43.1	58.2	21.8	37.4	11.8	0.0	1.8	9.7	0.2	0.1	0.0	1083	14.1
3	M	7.71	16.8	47.1	61.1	21.8	35.7	10.9	0.0	1.5	9.3	0.1	0.0	0.0	1234	17.8
4	M	7.18	15.1	41.0	57.1	21.0	36.8	13.1	0.0	2.6	10.2	0.3	0.0	0.0	1090	18.7
5	M	7.06	15.1	40.3	57.1	21.4	37.5	12.9	0.0	1.9	10.3	0.5	0.1	0.0	1187	20.7
AN		7.55	16.06	43.61	57.86	21.32	36.85	11.25	0.00	1.50	9.41	0.26	0.08	0.00	1087.5	20.36
D.		0.443	0.841	2.600	2.768	0.935	0.528	1.615	0.000	0.558	1.398	0.171	0.072	0.000	77.01	3.292
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
6	F	6.43	14.1	36.8	57.2	21.9	38.3	9.6	0.0	1.9	6.9	0.6	0.2	0.0	1194	13.4
7	F	6.78	14.7	37.7	55.6	21.7	39.0	13.7	0.0	1.6	11.9	0.1	0.0	0.0	1376	13.9
8	F	6.53	14.4	36.4	55.7	22.1	39.6	10.0	0.0	1.4	8.3	0.1	0.2	0.0	1375	15.6
9	F	6.70	14.9	37.5	56.0	22.2	39.7	6.2	0.0	0.4	5.8	0.1	0.0	0.0	1165	15.5
0	F	7.06	15.4	39.4	55.8	21.8	39.1	7.9	0.0	0.7	6.7	0.5	0.0	0.0	1220	16.4
1	F	6.57	14.9	38.0	57.8	22.7	39.2	16.2	0.0	1.5	13.8	0.8	0.2	0.0	1055	13.8
2	F	6.29	13.5	34.8	55.3	21.5	38.8	7.7	0.0	1.4	6.1	0.1	0.2	0.0	1250	13.5
3	F	6.47	15.1	38.3	59.2	23.3	39.4	7.2	0.0	0.4	6.5	0.4	0.0	0.0	1025	15.1
4	F	7.08	15.6	41.1	58.1	22.0	38.0	9.7	0.0	2.1	6.7	0.5	0.4	0.0	1220	16.0
5	F	6.48	15.0	38.0	58.6	23.1	39.5	7.0	0.0	0.6	6.2	0.2	0.1	0.0	1255	16.2
AN		6.64	14.76	37.80	56.93	22.23	39.06	9.52	0.00	1.19	7.88	0.33	0.12	0.00	1213.5	14.94
D.		0.265	0.622	1.694	1.423	0.606	0.558	3.181	0.000	0.647	2.739	0.253	0.128	0.000	114.99	1.176
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 45

BIOCHEMISTRY
Individual results
Week 4

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --

Animal No.	Sex	GLUCOSE mg/100mL	UREA mg/100mL	CREATININE mg/100mL	TOTAL BILIRUBIN mg/100mL	AST (GOT) U/L	ALT (GPT) U/L	SDH U/L	ALKALINE PHOSPH. U/L	TOTAL CHOLEST. mg/100mL	CALCIUM mg/100mL	INORGANIC PHOSPHORUS mg/100mL	SODIUM mmol/L	POTASSIUM mmol/L	CHLORIDE mmol/L	TOTAL PROTEIN g/100mL	ALBUMIN g/100mL	ALB./GLOB. RATIO
1	M	68	42	0.37	0.06	140	22	11.8	373	41.9	10.1	10.8	143.0	5.73	102	5.9	3.7	1.68
2	M	72	25	0.36	0.07	160	30	11.8	395	42.9	9.6	10.6	143.9	5.28	102	5.9	3.7	1.68
3	M	80	27	0.37	0.07	126	28	10.4	399	47.1	10.1	9.9	144.6	4.77	102	6.2	3.8	1.58
4	M	72	28	0.41	0.12	135	30	6.6	297	60.7	10.4	11.2	144.2	4.99	102	6.1	3.6	1.44
5	M	86	24	0.41	0.09	116	29	11.6	263	38.9	11.0	9.5	145.2	4.83	106	6.3	3.9	1.63
6	M	96	31	0.52	0.07	142	24	5.4	447	59.1	10.2	10.3	141.5	5.47	100	6.0	3.6	1.50
7	M	74	29	0.54	0.12	182	32	12.1	281	34.8	11.4	9.6	143.4	5.60	102	6.6	3.8	1.36
8	M	85	23	0.47	0.03	137	22	10.0	342	41.4	11.8	10.1	144.6	4.78	99	6.2	3.6	1.38
9	M	101	26	0.46	0.15	126	31	12.5	282	46.4	9.6	8.8	144.0	4.82	101	5.7	3.5	1.59
10	M	66	32	0.47	0.08	165	28	9.7	295	53.8	10.2	9.6	145.0	5.73	101	5.7	3.4	1.48
MEAN		80.0	28.7	0.44	0.09	142.9	27.6	10.19	337.4	46.70	10.44	10.04	143.94	5.20	101.7	6.06	3.66	1.53
S.D.		11.84	5.50	0.064	0.035	20.31	3.66	2.411	62.92	8.618	0.734	0.711	1.095	0.407	1.83	0.280	0.151	0.118
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
51	F	76	30	0.50	0.08	107	19	8.0	111	86.0	10.0	9.1	145.2	5.29	97	6.6	4.0	1.54
52	F	105	38	0.50	0.08	108	26	10.5	258	61.7	10.3	9.2	142.6	5.27	109	6.5	3.9	1.50
53	F	74	33	0.50	0.17	143	27	10.2	134	63.1	10.5	9.9	142.4	5.48	102	7.3	4.4	1.52
54	F	72	38	0.50	0.16	111	20	9.8	287	44.0	10.3	9.8	144.9	4.62	101	6.6	4.2	1.75
55	F	67	35	0.46	0.12	150	34	10.7	313	61.1	10.0	8.9	143.9	4.52	98	6.3	4.0	1.74
56	F	100	49	0.61	0.16	122	22	6.2	122	40.5	11.4	7.9	147.0	5.29	100	6.9	4.3	1.65
57	F	79	35	0.51	0.14	136	19	11.3	199	63.3	11.0	9.1	144.3	5.68	98	7.5	4.5	1.50
58	F	89	44	0.52	0.19	108	24	6.9	152	51.5	12.1	10.0	145.0	5.65	101	7.0	4.2	1.50
59	F	103	45	0.57	0.15	143	35	7.9	152	65.0	11.2	8.8	145.5	4.88	105	8.0	4.6	1.35
60	F	85	43	0.49	0.13	107	17	10.8	114	55.9	12.1	8.6	142.6	4.69	102	7.0	4.1	1.41
MEAN		85.0	39.0	0.52	0.14	123.5	24.3	9.23	184.2	59.21	10.89	9.13	144.34	5.14	101.3	6.97	4.22	1.55
S.D.		13.73	6.04	0.043	0.036	17.65	6.25	1.816	75.70	12.670	0.798	0.646	1.488	0.429	3.59	0.517	0.230	0.130
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 46

BIOCHEMISTRY
Individual results
Week 4

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 0.75 mg/kg/day

Animal		GLUCOSE	UREA	CREATININE	TOTAL BILIRUBIN	AST (GOT)	ALT (GPT)	SDH	ALKALINE PHOSPH.	TOTAL CHOLEST.	CALCIUM	INORGANIC PHOSPHORUS	SODIUM	POTASSIUM	CHLORIDE	TOTAL PROTEIN	ALBUMIN	ALB./GLOB. RATIO
No.	Sex	mg/100mL	mg/100mL	mg/100mL	mg/100mL	U/L	U/L	U/L	U/L	mg/100mL	mg/100mL	mg/100mL	mmol/L	mmol/L	mmol/L	g/100mL	g/100mL	
16	M	77	28	0.43	0.06	116	27	10.1	371	45.7	9.9	10.3	145.8	5.99	100	6.1	3.7	1.54
17	M	76	29	0.43	0.06	145	24	6.0	310	39.7	9.7	11.4	144.8	5.42	100	6.2	3.8	1.58
18	M	69	28	0.41	0.15	154	26	10.2	402	51.6	10.0	11.6	143.8	5.39	104	6.1	3.8	1.65
19	M	72	28	0.39	0.08	148	30	8.8	354	43.7	9.8	9.9	144.3	4.92	103	5.8	3.8	1.90
20	M	82	30	0.38	0.11	104	25	11.8	238	38.4	9.5	10.7	145.0	5.05	101	6.1	3.8	1.65
21	M	104	34	0.55	0.18	137	32	8.7	300	42.7	9.8	9.4	145.3	4.96	100	6.2	3.5	1.30
22	M	85	26	0.45	0.11	114	26	8.5	369	42.8	12.6	9.4	143.7	5.89	101	6.0	3.4	1.31
23	M	73	28	0.43	0.12	169	30	8.9	375	48.1	9.8	10.3	143.5	5.31	101	5.8	3.5	1.52
24	M	64	23	0.44	0.19	177	30	8.7	473	51.7	10.2	9.0	144.1	5.05	100	6.0	3.5	1.40
25	M	74	22	0.40	0.03	152	22	9.7	321	30.9	11.2	8.9	144.5	4.96	105	6.0	3.7	1.61
MEAN		77.6	27.6	0.43	0.11	141.6	27.2	9.14	351.3	43.53	10.25	10.09	144.48	5.29	101.5	6.03	3.65	1.55
S.D.		11.05	3.41	0.047	0.053	23.97	3.19	1.501	63.90	6.318	0.948	0.946	0.745	0.387	1.84	0.142	0.158	0.181
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
66	F	81	37	0.46	0.06	113	19	8.1	136	43.7	10.2	8.8	145.1	4.66	102	7.3	4.5	1.61
67	F	82	40	0.43	0.13	135	26	12.7	134	66.2	10.3	9.3	143.4	5.45	102	6.7	4.2	1.68
68	F	90	37	0.53	0.09	141	22	4.8	157	51.4	10.6	10.1	144.9	5.76	105	6.8	4.4	1.83
69	F	75	35	0.48	-	159	30	8.3	207	70.7	10.8	9.9	143.9	5.21	105	6.4	4.0	1.67
70	F	79	34	0.52	0.11	165	22	3.0	140	57.7	10.8	9.3	145.4	4.85	105	7.0	4.0	1.33
71	F	88	37	0.52	0.11	144	21	9.7	295	42.7	9.8	9.5	142.8	4.66	100	6.0	3.6	1.50
72	F	87	35	0.52	0.09	138	21	11.0	157	62.2	11.3	8.7	143.8	5.06	102	6.7	4.0	1.48
73	F	82	32	0.52	0.13	159	21	11.7	145	53.4	12.1	9.8	143.1	5.59	102	6.3	3.4	1.17
74	F	87	36	0.49	0.07	154	21	11.1	137	62.9	12.6	8.4	143.5	4.75	102	6.8	3.9	1.34
75	F	98	28	0.42	0.17	131	20	9.7	156	38.9	10.2	8.1	143.6	4.68	101	6.1	3.7	1.54
MEAN		84.9	35.1	0.49	0.11	143.9	22.3	9.01	166.4	54.98	10.87	9.19	143.95	5.07	102.6	6.61	3.97	1.52
S.D.		6.51	3.28	0.040	0.034	15.80	3.27	3.079	49.96	10.787	0.891	0.669	0.883	0.415	1.78	0.407	0.343	0.195
n		10	10	10	9	10	10	10	10	10	10	10	10	10	10	10	10	10

-: Parameter not determined

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 47

BIOCHEMISTRY
Individual results
Week 4

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 1.25 mg/kg/day

Animal		GLUCOSE	UREA	CREATININE	TOTAL BILIRUBIN	AST (GOT)	ALT (GPT)	SDH	ALKALINE PHOSPH.	TOTAL CHOLEST.	CALCIUM	INORGANIC PHOSPHORUS	SODIUM	POTASSIUM	CHLORIDE	TOTAL PROTEIN	ALBUMIN	ALB./GLOB. RATIO
No.	Sex	mg/100mL	mg/100mL	mg/100mL	mg/100mL	U/L	U/L	U/L	U/L	mg/100mL	mg/100mL	mg/100mL	mmol/L	mmol/L	mmol/L	g/100mL	g/100mL	
26	M	74	36	0.46	0.10	119	27	7.4	451	60.1	9.6	12.1	145.4	5.66	96	6.2	3.7	1.48
27	M	69	30	0.40	0.08	125	30	8.7	299	50.8	9.7	11.8	146.7	5.17	99	6.4	3.9	1.56
28	M	91	31	0.45	0.08	118	20	7.2	334	46.6	10.2	11.4	144.5	5.11	103	6.4	3.9	1.56
29	M	93	32	0.45	0.12	126	30	12.4	444	34.3	9.3	11.8	144.3	5.17	103	5.9	3.7	1.68
30	M	66	25	0.37	0.06	124	29	10.9	265	50.7	9.8	9.6	143.2	5.05	102	7.0	3.9	1.26
31	M	78	30	0.64	0.07	162	25	1.1	393	66.6	11.1	10.7	147.0	7.41	102	6.9	3.9	1.30
32	M	81	30	0.50	0.07	148	24	7.6	457	52.8	10.5	11.2	144.6	5.68	104	5.8	3.3	1.32
33	M	84	36	0.53	0.14	146	26	4.8	212	43.3	11.6	10.1	144.6	5.96	105	6.2	3.7	1.48
34	M	91	32	0.47	0.09	140	19	9.3	399	45.4	11.0	10.9	144.4	5.63	102	5.9	3.3	1.27
35	M	83	24	0.40	0.12	118	23	13.2	353	39.4	10.7	9.2	143.6	4.91	100	5.7	3.4	1.48
MEAN		81.0	30.6	0.47	0.09	132.6	25.3	8.26	360.7	49.00	10.35	10.88	144.83	5.58	101.6	6.24	3.67	1.44
S.D.		9.33	3.92	0.077	0.026	15.36	3.89	3.580	83.48	9.504	0.753	0.981	1.219	0.730	2.63	0.445	0.250	0.145
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
76	F	94	38	0.47	0.12	133	19	9.2	264	40.8	9.9	9.8	141.4	4.83	100	6.2	3.9	1.70
77	F	91	31	0.39	0.12	131	20	8.5	193	50.8	10.7	9.1	143.0	4.94	99	6.8	4.5	1.96
78	F	94	38	0.41	0.10	142	22	10.9	190	59.0	10.6	8.8	141.8	5.33	100	6.9	4.4	1.76
79	F	103	28	0.39	0.18	120	21	11.6	175	47.0	10.5	9.1	142.6	4.65	103	6.3	4.1	1.86
80	F	78	40	0.45	0.07	143	23	10.4	176	47.6	10.3	9.9	141.7	5.20	103	6.7	3.9	1.39
81	F	89	37	0.60	0.28	146	20	2.3	175	47.8	11.4	10.3	144.9	6.11	98	6.7	4.1	1.58
82	F	102	35	0.53	0.18	153	20	11.5	212	43.6	10.9	8.0	143.6	4.56	102	6.4	4.0	1.67
83	F	79	36	0.54	0.13	144	20	10.5	152	44.6	11.3	7.8	142.3	4.88	103	6.3	3.8	1.52
84	F	74	24	0.47	0.17	157	23	10.0	157	39.5	11.0	8.1	141.7	5.28	100	6.2	3.6	1.38
85	F	89	32	0.55	0.16	123	26	8.7	156	42.2	11.6	8.2	143.7	4.64	103	6.5	3.7	1.32
MEAN		89.3	33.9	0.48	0.15	139.2	21.4	9.36	185.0	46.29	10.82	8.91	142.67	5.04	101.1	6.50	4.00	1.61
S.D.		9.80	5.07	0.073	0.058	12.18	2.12	2.704	33.42	5.671	0.527	0.882	1.126	0.464	1.91	0.258	0.287	0.213
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 48

BIOCHEMISTRY
Individual results
Week 4

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day

Animal No.	Sex	GLUCOSE mg/100mL	UREA mg/100mL	CREATININE mg/100mL	TOTAL BILIRUBIN mg/100mL	AST (GOT) U/L	ALT (GPT) U/L	SDH U/L	ALKALINE PHOSPH. U/L	TOTAL CHOLEST. mg/100mL	CALCIUM mg/100mL	INORGANIC PHOSPHORUS mg/100mL	SODIUM mmol/L	POTASSIUM mmol/L	CHLORIDE mmol/L	TOTAL PROTEIN g/100mL	ALBUMIN g/100mL	ALB./GLOB. RATIO
36	M	73	28	0.40	0.09	114	26	7.3	409	37.5	9.9	11.7	144.9	5.76	105	6.0	3.6	1.50
37	M	84	32	0.45	0.07	141	34	4.9	473	43.3	9.6	12.8	145.3	6.58	101	6.3	3.8	1.52
38	M	88	30	0.41	0.16	130	29	13.0	288	46.2	10.0	10.3	144.4	5.18	99	6.6	4.0	1.54
39	M	81	27	0.36	0.14	111	25	7.9	272	39.8	9.4	9.4	142.9	5.11	103	6.2	3.6	1.38
40	M	92	26	0.33	0.11	130	23	8.5	363	51.4	9.3	10.6	143.0	5.17	104	5.8	3.7	1.76
41	M	108	26	0.50	0.13	115	23	7.0	288	46.0	9.9	10.4	143.2	5.46	104	5.5	3.3	1.50
42	M	87	33	0.48	0.14	136	25	12.7	446	32.5	10.1	8.8	144.8	5.01	103	6.1	3.5	1.35
43	M	94	30	0.56	0.17	144	24	1.6	253	58.3	10.3	9.9	145.9	6.63	101	6.2	3.6	1.38
44	M	96	31	0.47	0.10	138	25	8.9	297	40.6	12.4	9.7	144.2	5.47	101	5.9	3.5	1.46
45	M	89	26	0.45	0.17	120	23	8.1	297	53.1	10.4	10.3	144.4	5.01	102	5.8	3.5	1.52
MEAN		89.2	28.9	0.44	0.13	127.9	25.7	7.99	338.6	44.87	10.13	10.39	144.30	5.54	102.3	6.04	3.61	1.49
S.D.		9.39	2.64	0.068	0.035	12.09	3.43	3.337	78.52	7.800	0.874	1.145	1.003	0.609	1.83	0.310	0.191	0.117
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
86	F	80	34	0.39	0.20	131	66	7.7	99	38.0	10.5	8.4	141.7	4.80	101	6.9	4.4	1.76
87	F	78	33	0.45	0.23	131	17	7.7	150	60.9	10.7	9.6	144.5	5.58	103	6.9	4.4	1.76
88	F	92	29	0.44	0.15	117	19	8.4	104	64.2	10.1	9.2	142.1	4.70	101	6.3	4.2	2.00
89	F	103	29	0.47	0.13	133	22	9.4	215	46.4	9.7	8.2	144.4	5.18	107	6.1	3.8	1.65
90	F	101	33	0.40	0.12	113	20	11.0	218	51.4	10.1	9.1	143.3	5.11	104	6.3	4.1	1.86
91	F	71	34	0.54	0.17	144	19	10.3	201	42.8	11.0	8.3	144.2	5.53	102	6.9	4.0	1.38
92	F	101	30	0.46	0.16	133	20	9.4	190	45.9	10.5	6.9	144.0	4.99	105	6.5	3.5	1.17
93	F	94	33	0.55	0.18	147	16	6.6	212	48.7	11.0	7.9	145.2	4.83	106	6.6	3.9	1.44
94	F	70	41	0.51	0.15	114	19	10.1	111	46.9	10.3	9.2	144.2	4.78	103	6.8	3.7	1.19
95	F	80	40	0.46	0.18	106	17	8.1	163	45.5	10.5	8.1	143.8	4.86	101	6.0	3.4	1.31
MEAN		87.0	33.6	0.47	0.17	126.9	23.5	8.87	166.3	49.07	10.44	8.49	143.74	5.04	103.3	6.53	3.94	1.55
S.D.		12.68	4.12	0.053	0.033	13.74	15.04	1.389	47.89	7.965	0.409	0.801	1.090	0.312	2.16	0.343	0.347	0.293
n		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

Taking into account that the molecular weight of the base form of the test substance is 286.42 and of the hydrochloride form is 322.88, a factor of 1.127 was used for the preparation of the formulations.

3.3. Formulation analysis

In the course of the first and third weeks of administration, samples of the formulations to be administered were sent to LABORATORIOS INIBSA, S.A. for the quantification of their IQB-9302.HCl content. The samples were sent at room temperature.

The results of the formulation analyses are shown in Appendix IV.

3.4. Administration route and procedure

The test substance, IQB-9302.HCl, was administered intravenously, by bolus, in the tail vein, using a 23G (0.6 x 25 mm) sterile disposable needle.

The duration of injection was 2 minutes.

This route has been chosen because it is the proposed route for administration to humans.

The rats belonging to the Control group were treated with the vehicle (physiological saline), at the same administration volume as the rest of the treatment groups.

3.5. Administration volume

The administration volume was 4 mL/kg.

The quantity of test substance administered to each animal was calculated from its bodyweight on the day of treatment.

3.6. Frequency and duration of treatment

The test substance was administered once a day, seven days a week during 4 weeks.

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 49

URINALYSIS
Individual results
Week 4

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --

Animal		COLOUR	VOLUME	SPECIFIC GRAVITY	pH	PROTEINS	GLUCOSE	KETONES	UROBIL.	BILIRUBIN	BLOOD/ HAEM.	MICROSCOPIC EXAMINATION OF SEDIMENT					
												EPIT. CELL	ERYTH.	LEUKO.	BACTERIA	CASTS	CRYSTALS*
No.	Sex		mL			0/+	0/+	0/+	0/+	0/+	0/+	no./field	no./field	no./field	0/+	0/+	0/+
1	M	Yellow	13	1018	8	+	0	0	0	0	0	0	0	0	+++	0	+++
2	M	Yellow	25	1012	9	0	0	0	0	0	0	0	0	0	++	0	++
3	M	Yellow	31	1007	9	0	0	0	0	0	0	0-1	0	0	++	0	+
4	M	Yellow	19	1015	9	0	0	0	0	0	++	0	0-1	1-2	+++	0	++
5	M	Yellow	21	1014	8	+	0	0	0	0	+	0	0-1	0	++	0	+
6	M	Yellow	21	1015	8	+	0	0	0	0	+	0	0-1	0	+++	0	+++
7	M	Yellow	54	1005	6	+	0	0	0	0	++	0	0	0-1	++	0	0
8	M	Yellow	19	1015	8	+	0	0	0	0	+	0	0	0	+++	0	++
9	M	Yellow	25	1011	8	0	0	0	0	0	+	0	0	0	++	0	++
10	M	Yellow	26	1012	8	+	0	0	0	0	+	0	0	0	+++	0	++
MEAN			25.4	1012.4	8.1												
S.D.			11.18	3.95	0.88												
n			10	10	10												
51	F	Yellow	10	1017	9	+	0	0	0	0	++	0	0	0-1	+++	0	+++
52	F	Yellow	15	1017	9	+	0	0	0	0	++	0	0	0	+++	0	++
53	F	Yellow	20	1012	9	0	0	0	0	0	+	0	0	0	++	0	+++
54	F	Yellow	35	1007	8	0	0	0	0	0	++	0	0	3-5	++	0	0
55	F	Yellow	21	1012	7	0	0	0	0	0	+	0	0	0	+++	0	++
56	F	Yellow	15.5	1018	8	+	0	0	0	0	+	0	0	0	+++	0	++
57	F	Yellow	11	1020	6	+	0	0	0	0	+	0	0	0	++	0	0
58	F	Yellow	5	1034	6	+	0	0	0	0	+	0	0	0	+	0	+
59	F	Yellow	11	1021	8	+	0	0	0	0	+	0-1	0	0	++	0	++
60	F	Yellow	13.5	1020	7	+	0	0	0	0	+	0	0	0-1	+++	0	0
MEAN			15.7	1017.8	7.7												
S.D.			8.27	7.21	1.16												
n			10	10	10												

* : Magnesium ammonium phosphate

ENTRO DE INVESTIGACIÓN Y
ESARROLLO APLICADO, S.A.L.
oxicology Department
able no.: 50

URINALYSIS
Individual results
Week 4

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 0.75 mg/kg/day

Animal												MICROSCOPIC EXAMINATION OF SEDIMENT					
		COLOUR	VOLUME	SPECIFIC GRAVITY	pH	PROTEINS	GLUCOSE	KETONES	UROBILINOGEN	BILIRUBIN	BLOOD/ HAEM.	EPIT. CELL	ERYTH.	LEUKO.	BACTERIA	CASTS	CRYSTALS*
o.	Sex		mL			0/+	0/+	0/+	0/+	0/+	0/+	no./field	no./field	no./field	0/+	0/+	0/+
6	M	Yellow	17	1017	9	+	0	0	0	0	+	0	0	0-1	+++	0	++
7	M	Yellow	18	1016	8	0	0	0	0	0	0	0	0	0	+++	0	+++
8	M	Yellow	25	1011	9	0	0	0	0	0	0	0	0	0	++	0	+
9	M	Yellow	27	1014	9	+	0	0	0	0	0	0	0	0	++	0	++
20	M	Yellow	28	1015	9	0	0	0	0	0	+	0	0	0	++	0	+++
21	M	Yellow	29	1008	8	0	0	0	0	0	+	0	0	0	++	0	+++
22	M	Yellow	26	1011	9	0	0	0	0	0	+	0	0	0	++	0	++
23	M	Yellow	25	1012	9	0	0	0	0	0	++	0	0	0	+++	0	+++
24	M	Yellow	47	1006	8	0	0	0	0	0	+	0-1	0	0-1	+++	0	++
25	M	Yellow	24	1009	8	0	0	0	0	0	+	0	0	0	++	0	+++
MEAN			26.6	1011.9	8.6												
S.D.			8.18	3.60	0.52												
n			10	10	10												
66	F	Yellow	5	1035	9	+	0	0	0	0	0	0	0	0	+++	0	+++
67	F	Yellow	14	1017	8	0	0	0	0	0	0	0	0	0	++	0	+++
68	F	Yellow	22	1012	8	0	0	0	0	0	0	0	0	0	++	0	++
69	F	Yellow	13	1017	9	+	0	0	0	0	0	0	0	0	+++	0	++
70	F	Yellow	19	1014	8	0	0	0	0	0	0	0	0	0	++	0	+++
71	F	Yellow	8	1025	8	+	0	0	0	0	+	0	0	0	+++	0	++
72	F	Yellow	9.5	1026	7	+	0	0	0	0	+	0	0	0	++	0	0
73	F	Yellow	6.5	1024	7	+	0	0	0	0	0	0	0	0	++	0	+
74	F	Yellow	7	1029	6	+	0	0	0	0	0	0	0	0-1	++	0	0
75	F	Yellow	12	1020	8	+	0	0	0	0	0	0	0	1-3	++	0	++
MEAN			11.6	1021.9	7.8												
S.D.			5.57	7.19	0.92												
n			10	10	10												

*: Magnesium ammonium phosphate

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 51

URINALYSIS
Individual results
Week 4

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 1.25 mg/kg/day

Animal		COLOUR	VOLUME	SPECIFIC GRAVITY	pH	PROTEINS	GLUCOSE	KETONES	UROBILINOGEN	BILIRUBIN	BLOOD/ HAEM.	MICROSCOPIC EXAMINATION OF SEDIMENT					
												EPIT. CELL	ERYTH.	LEUKO.	BACTERIA	CASTS	CRYSTALS*
No.	Sex		mL			0/+	0/+	0/+	0/+	0/+	0/+	no./field	no./field	no./field	0/+	0/+	0/+
26	M	Yellow	16	1018	9	0	0	0	0	0	+	0	0	0	+++	0	+++
27	M	Yellow	17	1014	9	0	0	0	0	0	0	0	0	0-1	++	0	++
28	M	Yellow	21	1015	9	0	0	0	0	0	0	0	0	0-1	+++	0	+++
29	M	Yellow	12	1022	9	+	0	0	0	0	0	0	0	0	+++	0	++
30	M	Yellow	24	1010	8	0	0	0	0	0	0	0	0	0-1	++	0	+
31	M	Yellow	32	1006	8	0	0	0	0	0	0	0	0	0	++	0	+
32	M	Yellow	12	1018	8	+	0	0	0	0	+	0	0	0	+++	0	+++
33	M	Yellow	21	1015	9	0	0	0	0	0	0	0	0	0-1	+++	0	++
34	M	Yellow	21	1015	9	0	0	0	0	0	0	0	0	0	++	0	+++
35	M	Yellow	31	1011	9	0	0	0	0	0	+	0	0	0	+++	0	+++
MEAN			20.7	1014.4	8.7												
S.D.			6.93	4.55	0.48												
n			10	10	10												
76	F	Yellow	17	1020	6	+	0	0	0	0	0	0	0	0	+	0	0
77	F	Yellow	15	1013	9	0	0	0	0	0	+	0	0	0	++	0	+++
78	F	Yellow	22	1010	9	0	0	0	0	0	0	0	0	0	++	0	+++
79	F	Yellow	12	1012	9	0	0	0	0	0	0	0	0	0	++	0	+++
80	F	Yellow	18	1016	9	0	0	0	0	0	0	0	0	0	+++	0	+++
81	F	Yellow	7.5	1028	6	+	+	0	0	0	++	0	0	0-1	++	0	0
82	F	Yellow	7	1029	7	0	0	0	0	0	++	0-1	0	0-1	++	0	0
83	F	Yellow	7	1020	7	+	0	0	0	0	0	0	0	0	+	0	0
84	F	Yellow	6	1035	6	+	0	0	0	0	0	0	0	0	+	0	+
85	F	Yellow	19	1015	7	0	0	0	0	0	++	0	0	0	++	0	+
MEAN			13.1	1019.8	7.5												
S.D.			5.91	8.32	1.35												
n			10	10	10												

* : Magnesium ammonium phosphate

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 52

URINALYSIS
Individual results
Week 4

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day

Animal		COLOUR	VOLUME	SPECIFIC GRAVITY	pH	PROTEINS	GLUCOSE	KETONES	UROBILINOGEN	BILIRUBIN	BLOOD/ HAEM.	MICROSCOPIC EXAMINATION OF SEDIMENT					
												EPIT. CELL	ERYTH.	LEUKO.	BACTERIA	CASTS	CRYSTALS*
No.	Sex		mL			0/+	0/+	0/+	0/+	0/+	0/+	no./field	no./field	no./field	0/+	0/+	0/+
36	M	Yellow	19	1010	8	0	0	0	0	0	+	0	0	0	++	0	++
37	M	Yellow	32	1010	9	0	0	0	0	0	0	0	0	0	++	0	+++
38	M	Yellow	10	1026	9	+	0	0	0	0	+	0	0	0	+++	0	+++
39	M	Yellow	25	1011	9	0	0	0	0	0	0	0	0	0	++	0	+++
40	M	Yellow	27	1009	9	0	0	0	0	0	0	0	0	0	++	0	+++
41	M	Yellow	19	1014	7	0	0	0	0	0	+	0	0	0	++	0	+
42	M	Yellow	10	1022	9	+	0	0	0	0	+	0-1	0	0	+++	0	+++
43	M	Yellow	15	1021	9	+	0	0	0	0	0	0	0	0	+++	0	+++
44	M	Yellow	22	1014	9	+	0	0	0	0	+	0	0	0	++	0	+++
45	M	Yellow	21	1010	9	0	0	0	0	0	+	0	0	0	+++	0	++
MEAN			20.0	1014.7	8.7												
S.D.			7.07	6.09	0.67												
n			10	10	10												
86	F	Yellow	18	1014	8	0	0	0	0	0	0	0	0	0	++	0	+++
87	F	Yellow	4	1030	5	+	0	0	0	0	+	0	0	0	+	0	0
88	F	Yellow	7	1021	8	0	0	0	0	0	0	0	0	0	+++	0	+++
89	F	Yellow	16	1018	9	0	0	0	0	0	0	0	0	0	+++	0	+++
90	F	Yellow	9	1020	9	0	0	0	0	0	0	0	0	0	++	0	+++
91	F	Yellow	14	1013	6	+	0	0	0	0	+	0	0	0-1	++	0	0
92	F	Yellow	4.5	1038	6	+	0	0	0	0	+	0	0	0	+	0	0
93	F	Yellow	9.5	1024	7	+	0	0	0	0	0	0	0	0	+++	0	0
94	F	Yellow	16.5	1015	7	+	0	0	0	0	+	0	0	1-3	++	0	++
95	F	Yellow	9	1020	9	++	0	0	0	0	+	0	0	3-5	++	0	+
MEAN			10.8	1021.3	7.4												
S.D.			5.06	7.73	1.43												
n			10	10	10												

* : Magnesium ammonium phosphate

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 53

HAEMATOLOGY
Individual results
Recovery period

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --

Animal		ERYTHR.	HAEMOGL.	HAEMATOC.	MCV	MCH	MCHC	TOTAL LEUKOCYT.	DIFFERENTIAL LEUKOCYTE COUNT ($x10^3/\mu L$)						PLATEL.	PROTHR. TIME
									NEUTROPHILS		LYMPHO.	MONOC.	EOSINO.	BASOPH.		
No.	Sex	$x10^6/\mu L$	g/100mL	%	fL	pg	g/100mL	$x10^3/\mu L$	Rods	Segmen.					$x10^3/\mu L$	s
11	M	8.34	16.0	49.4	59.2	19.2	32.4	10.6	0.0	1.9	8.6	0.1	0.0	0.0	1108	21.2
12	M	8.18	15.9	46.1	56.4	19.4	34.5	13.2	0.0	1.6	11.4	0.1	0.1	0.0	1187	14.1
13	M	7.86	15.7	44.7	56.9	20.0	35.1	11.4	0.0	1.6	9.3	0.3	0.1	0.0	1000	17.5
14	M	7.96	16.4	46.6	58.5	20.6	35.2	12.9	0.0	1.3	11.2	0.4	0.0	0.0	1209	20.4
15	M	8.16	15.9	45.0	55.1	19.5	35.3	12.3	0.0	1.5	9.6	1.1	0.1	0.0	850	25.9
MEAN		8.10	15.98	46.36	57.22	19.74	34.50	12.08	0.00	1.57	10.02	0.41	0.07	0.00	1070.8	19.82
S.D.		0.190	0.259	1.869	1.645	0.564	1.214	1.076	0.000	0.225	1.216	0.406	0.068	0.000	148.11	4.396
n		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
61	F	7.09	14.9	40.5	57.1	21.0	36.8	7.0	0.0	0.8	5.9	0.3	0.1	0.0	940	15.7
62	F	7.38	16.1	42.7	57.9	21.8	37.7	9.4	0.0	1.2	7.9	0.3	0.0	0.0	1105	16.2
63	F	6.73	14.4	38.4	57.1	21.4	37.5	9.7	0.0	2.3	7.1	0.2	0.1	0.0	1157	15.9
64	F	6.48	13.3	35.6	54.9	20.5	37.4	8.6	0.0	0.1	8.0	0.5	0.0	0.0	1245	13.3
65	F	7.26	15.4	39.8	54.8	21.2	38.7	7.9	0.0	1.3	6.1	0.5	0.1	0.0	1320	15.2
MEAN		6.99	14.82	39.40	56.36	21.18	37.62	8.52	0.00	1.13	6.99	0.35	0.05	0.00	1153.4	15.26
S.D.		0.375	1.057	2.632	1.417	0.482	0.691	1.103	0.000	0.819	0.987	0.139	0.046	0.000	144.95	1.155
n		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

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HAEMATOLOGY
Individual results
Recovery period

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day

Animal		ERYTHR.	HAEMOGL.	HAEMATOC.	MCV	MCH	MCHC	TOTAL LEUKOCYT.	DIFFERENTIAL LEUKOCYTE COUNT (x10³/µL)						PLATEL.	PROTHR. TIME
									NEUTROPHILS		LYMPHO.	MONOC.	EOSINO.	BASOPH.		
No.	Sex	x10⁶/µL	g/100mL	%	fL	pg	g/100mL	x10³/µL	Rods	Segmen.					x10³/µL	s
46	M	7.95	15.7	42.5	53.5	19.7	36.9	9.9	0.0	1.6	7.7	0.5	0.1	0.0	1100	23.6
47	M	7.47	15.5	41.4	55.4	20.7	37.4	9.7	0.0	1.2	8.1	0.5	0.0	0.0	1254	16.0
48	M	8.10	16.8	47.2	58.3	20.7	35.6	12.3	0.0	0.7	11.1	0.2	0.2	0.0	1057	24.0
49	M	6.28	13.6	36.1	57.5	21.7	37.7	10.1	0.0	1.7	7.9	0.3	0.2	0.0	776	14.8
50	M	7.70	15.7	43.2	56.1	20.4	36.3	14.7	0.0	2.4	10.9	1.2	0.3	0.0	1029	15.3
MEAN		7.50	15.46	42.08	56.16	20.64	36.78	11.34	0.00	1.51	9.12	0.54	0.17	0.00	1043.2	18.74
S.D.		0.723	1.159	3.996	1.873	0.720	0.847	2.151	0.000	0.607	1.698	0.372	0.118	0.000	172.81	4.641
n		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
96	F	7.22	15.2	40.0	55.4	21.1	38.0	8.0	0.0	0.7	6.9	0.3	0.1	0.0	1230	15.3
97	F	7.09	15.0	40.3	56.8	21.2	37.2	9.2	0.0	1.4	7.2	0.6	0.0	0.0	974	14.3
98	F	7.11	16.3	41.8	58.8	22.9	39.0	7.0	0.0	0.8	5.9	0.4	0.0	0.0	898	15.9
99	F	6.62	14.1	37.2	56.2	21.3	37.9	9.0	0.0	2.2	6.1	0.4	0.4	0.0	1014	16.3
100	F	7.17	15.3	41.6	58.0	21.3	36.8	5.7	0.0	0.9	4.4	0.3	0.1	0.0	1081	14.2
MEAN		7.04	15.18	40.18	57.04	21.56	37.78	7.78	0.00	1.18	6.09	0.40	0.11	0.00	1039.4	15.20
S.D.		0.241	0.785	1.842	1.367	0.754	0.844	1.457	0.000	0.609	1.089	0.135	0.148	0.000	125.47	0.938
n		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

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BIOCHEMISTRY
Individual results
Recovery period

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --

Animal No.	Sex	GLUCOSE mg/100mL	UREA mg/100mL	CREATININE mg/100mL	TOTAL BILIRUBIN mg/100mL	AST (GOT) U/L	ALT (GPT) U/L	SDH U/L	ALKALINE PHOSPH. U/L	TOTAL CHOLEST. mg/100mL	CALCIUM mg/100mL	INORGANIC PHOSPHORUS mg/100mL	SODIUM mmol/L	POTASSIUM mmol/L	CHLORIDE mmol/L	TOTAL PROTEIN g/100mL	ALBUMIN g/100mL	ALB./GLOB. RATIO
11	M	83	25	0.47	0.16	243*	107*	33.6*	356	45.9	11.6	9.5	144.8	5.05	104	6.6	3.7	1.28
12	M	117	25	0.48	0.20	171	33	4.2	390	39.0	11.4	9.2	144.8	4.85	103	6.5	3.8	1.41
13	M	103	30	0.50	0.15	146	32	8.6	269	45.5	11.2	8.4	146.1	4.85	104	6.7	3.5	1.09
14	M	96	28	0.47	0.14	105	21	11.6	229	53.8	11.7	8.9	145.8	5.15	102	6.5	3.7	1.32
15	M	100	26	0.43	0.14	135	26	10.5	322	47.0	11.7	9.2	146.3	5.34	103	6.8	3.6	1.13
MEAN		99.8	26.8	0.47	0.16	139.3	28.0	8.73	313.2	46.24	11.52	9.04	145.56	5.05	103.2	6.62	3.66	1.24
S.D.		12.28	2.17	0.025	0.025	27.35	5.60	3.261	64.91	5.263	0.217	0.416	0.716	0.209	0.84	0.130	0.114	0.133
n		5	5	5	5	4	4	4	5	5	5	5	5	5	5	5	5	5
61	F	106	30	0.50	0.21	95	18	8.5	75	99.5	11.0	6.4	145.1	4.19	103	7.6	4.4	1.38
62	F	81	35	0.55	0.21	123	21	8.8	226	58.9	10.7	8.0	145.7	4.40	103	6.7	3.9	1.39
63	F	126	42	0.62	0.16	118	16	6.4	128	48.7	10.8	6.6	146.1	4.38	105	7.6	4.3	1.30
64	F	108	47	0.48	0.21	107	17	9.6	71	46.1	11.3	6.5	145.4	4.55	103	7.4	4.2	1.31
65	F	95	37	0.44	0.24	135	18	11.7	112	58.5	10.4	7.5	144.0	4.61	101	6.6	3.7	1.28
MEAN		103.2	38.2	0.52	0.21	115.6	18.0	9.00	122.4	62.34	10.84	7.00	145.26	4.43	103.0	7.18	4.10	1.33
S.D.		16.66	6.53	0.069	0.029	15.29	1.87	1.917	62.77	21.548	0.336	0.711	0.796	0.164	1.41	0.492	0.292	0.050
n		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

*: Abnormal values. Not included in the statistical analysis.

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BIOCHEMISTRY
Individual results
Recovery period

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day

Animal No.	Sex	GLUCOSE mg/100mL	UREA mg/100mL	CREATININE mg/100mL	TOTAL BILIRUBIN mg/100mL	AST (GOT) U/L	ALT (GPT) U/L	SDH U/L	ALKALINE PHOSPH. U/L	TOTAL CHOLEST. mg/100mL	CALCIUM mg/100mL	INORGANIC PHOSPHORUS mg/100mL	SODIUM mmol/L	POTASSIUM mmol/L	CHLORIDE mmol/L	TOTAL PROTEIN g/100mL	ALBUMIN g/100mL	ALB./GLOB. RATIO
46	M	96	25	0.46	0.09	115	25	17.7	261	49.9	11.4	9.0	147.4	4.72	104	6.3	3.3	1.10
47	M	78	29	0.43	0.12	148	21	13.7	276	47.3	11.1	8.2	145.3	4.96	100	6.6	3.8	1.36
48	M	87	27	0.49	0.16	151	20	7.9	304	61.1	10.9	8.2	146.0	5.09	103	6.8	3.7	1.19
49	M	133	27	0.47	0.20	133	26	8.7	264	71.5	11.4	9.4	145.4	5.06	104	6.0	3.4	1.31
50	M	95	29	0.47	0.13	118	19	10.1	248	60.6	11.1	8.6	145.0	5.49	101	6.7	3.5	1.09
MEAN		97.8	27.4	0.46	0.14	133.0	22.2	11.62	270.6	58.08	11.18	8.68	145.82	5.06	102.4	6.48	3.54	1.21
S.D.		20.97	1.67	0.022	0.042	16.57	3.11	4.061	21.16	9.730	0.217	0.522	0.955	0.279	1.82	0.327	0.207	0.119
n		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
96	F	98	39	0.54	0.17	134	13	6.3	128	41.4	10.3	6.6	145.9	5.30	104	6.8	3.9	1.34
97	F	98	31	0.54	0.14	118	15	11.5	149	79.9	10.7	6.6	145.7	4.18	103	7.4	4.3	1.39
98	F	91	33	0.47	0.15	98	20	9.1	111	85.2	11.3	6.9	142.0	4.52	103	7.4	4.0	1.18
99	F	94	44	0.62	0.12	137	16	11.0	235	38.2	10.3	7.6	144.9	4.36	103	6.5	3.4	1.10
100	F	101	29	0.51	0.16	115	19	8.1	154	59.1	10.9	6.9	145.0	4.47	103	7.1	3.9	1.22
MEAN		96.4	35.2	0.54	0.15	120.4	16.6	9.20	155.4	60.76	10.70	6.92	144.70	4.57	103.2	7.04	3.90	1.24
S.D.		3.91	6.18	0.055	0.019	15.79	2.88	2.131	47.70	21.507	0.424	0.409	1.570	0.431	0.45	0.391	0.324	0.120
n		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

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URINALYSIS
Individual results
Recovery period

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --

Animal No.	Sex	COLOUR	VOLUME mL	SPECIFIC GRAVITY	pH	PROTEINS 0/+	GLUCOSE 0/+	KETONES 0/+	UROBILINOGEN 0/+	BILIRUBIN 0/+	BLOOD/ HAEM. 0/+	MICROSCOPIC EXAMINATION OF SEDIMENT: EPIT. CELL no./field	ERYTH. no./field	LEUKO. no./field	BACTERIA 0/+	CASTS 0/+	CRYSTALS* 0/+
11	M	Yellow	30	1011	8	0	0	0	0	0	+	0	0	0	++	0	+++
12	M	Yellow	24	1013	8	+	0	0	0	0	+	0	0	0	+++	0	++
13	M	Yellow	9	1032	8	+	0	0	0	0	0	0	0	0	+++	0	+++
14	M	Yellow	26	1016	8	+	0	0	0	0	+	0	0	0	++	0	+
15	M	Yellow	14	1024	8	0	0	0	0	0	+	0	0	0-1	++	0	+
MEAN			20.6	1019.2	8.0												
S.D.			8.76	8.70	0.00												
n			5	5	5												
61	F	Yellow	6	1037	6	+	0	0	0	0	0	0	0	0	+	0	+
62	F	Yellow	12	1020	6	0	0	0	0	0	0	0	0	0	++	0	++
63	F	Yellow	8	1025	8	+	0	0	0	0	0	0	0	0	++	0	++
64	F	Yellow	10	1024	7	0	0	0	0	0	0	0	0	0	++	0	+
65	F	Yellow	8	1030	6	0	0	0	0	0	0	0	0	0	++	0	++
MEAN			8.8	1027.2	6.6												
S.D.			2.28	6.53	0.89												
n			5	5	5												

* : Magnesium ammonium phosphate

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URINALYSIS
Individual results
Recovery period

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day

Animal		COLOUR	VOLUME	SPECIFIC GRAVITY	pH	PROTEINS	GLUCOSE	KETONES	UROBILINOGEN	BILIRUBIN	BLOOD/ HAEM.	MICROSCOPIC EXAMINATION OF SEDIMENT					
												EPIT. CELL	ERYTH.	LEUKO.	BACTERIA	CASTS	CRYSTALS*
No.	Sex		mL			0/+	0/+	0/+	0/+	0/+	0/+	no./field	no./field	no./field	0/+	0/+	0/+
46	M	Yellow	28	1009	7	+	0	0	0	0	0	0	0	0	++	0	+
47	M	Yellow	17.5	1014	8	+	0	0	0	0	0	0	0	0	++	0	++
48	M	Yellow	21	1017	8	+	0	0	0	0	0	0	0	0	++	0	++
49	M	Yellow	18	1022	7	+	0	0	0	0	0	0	0	0	+	0	+
50	M	Yellow	27	1016	8	+	0	0	0	0	0	0	0	0	++	0	+
MEAN			22.3	1015.6	7.6												
S.D.			4.94	4.72	0.55												
n			5	5	5												
96	F	Yellow	9	1022	6	0	0	0	0	0	0	0	0	0	+++	0	+
97	F	Yellow	10	1026	7	0	0	0	0	0	0	0	0	0	++	0	++
98	F	Yellow	17	1015	6	0	0	0	0	0	0	0	0	0	++	0	++
99	F	Yellow	9	1024	9	++	0	0	0	0	0	0	0	3-5	++	0	+++
100	F	Yellow	21	1014	7	0	0	0	0	0	0	0	0	0	++	0	+
MEAN			13.2	1020.2	7.0												
S.D.			5.50	5.40	1.22												
n			5	5	5												

* : Magnesium ammonium phosphate

3.7. Dose levels and group sizes

The 100 rats selected for the Study were distributed into four groups using a random distribution method.

Two groups (Control and high dose) consisted of 15 males and 15 females each and a further two groups (intermediate and low dose) consisted of 10 males and 10 females each.

Group	Treatment	Dose (mg/kg/day)	Animal no.		Colour code
			Males	Females	
1	CONTROL (vehicle)	-	1-15	51-65	White
2	IQB-9302.HCl	0.75	16-25	66-75	Blue
3	IQB-9302.HCl	1.25	26-35	76-85	Green
4	IQB-9302.HCl	2.25	36-50	86-100	Red

3.8. Recovery period

Five males and five females of the Control and high dose group were selected at random to undergo a recovery period of two weeks after the last administration.

This recovery period included weeks 5 and 6 of the Study.

The aim of the recovery period was to study the evolution of the possible alterations recorded during the treatment period.

The animals assigned to the recovery period, chosen at random into each group, were the following:

Group	Treatment	Dose (mg/kg/day)	Animal no.	
			Males	Females
1	CONTROL	-	11, 12, 13, 14, 15	61, 62, 63, 64, 65
4	IQB-9302.HCl	2.25	46, 47, 48, 49, 50	96, 97, 98, 99, 100

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ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	TESTES g	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	PROSTATE g	LUNGS g	THYMUS g	PITUIT. GLAND mg
1	345	39	4.91	12	3.40	2.29	1.44	14.02	0.95	2.57	1.80	0.84	9
2	385	51	4.52	14	3.24	1.91	1.26	14.52	0.46	1.87	1.48	0.50	8
3	353	53	4.07	16	3.09	1.95	1.22	19.44	0.67	2.44	1.59	0.63	14
4	377	41	4.25	11	2.59	1.93	1.38	13.97	0.68	2.00	1.29	0.40	8
5	392	85	4.64	29	3.32	2.23	1.48	19.09	0.89	2.05	2.02	0.58	11
6	472	70	4.19	29	3.34	2.16	1.64	20.22	0.89	2.82	1.75	1.00	13
7	395	76	4.68	20	3.24	2.02	1.30	20.70	1.01	2.24	1.93	0.65	14
8	408	56	5.61	27	3.86	2.21	1.35	15.74	1.09	2.43	1.70	0.91	12
9	457	70	4.98	20	3.31	2.05	1.46	17.74	1.04	2.73	2.21	0.67	6
10	378	52	5.10	7	3.14	1.92	1.29	16.98	0.74	2.44	1.26	0.62	6
MEAN	396.2	59.3	4.70	18.5	3.25	2.07	1.38	17.24	0.84	2.36	1.70	0.68	10.1
S.D.	40.71	15.23	0.472	7.85	0.314	0.144	0.126	2.585	0.199	0.315	0.307	0.185	3.11
n	10	10	10	10	10	10	10	10	10	10	10	10	10

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ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 0.75 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	TESTES g	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	PROSTATE g	LUNGS g	THYMUS g	PITUIT. GLAND mg
16	400	60	4.73	26	2.85	2.12	1.27	16.40	0.80	2.42	1.42	0.67	11
17	386	68	5.24	41	3.48	2.16	1.38	17.34	1.14	2.53	1.67	0.55	15
18	363	53	4.48	24	2.62	2.19	1.33	17.93	0.94	1.76	1.45	0.54	12
19	377	60	4.90	24	3.21	2.12	1.39	18.33	0.85	2.54	2.26	0.42	11
20	335	50	4.11	22	2.89	1.98	1.11	16.07	0.71	2.14	1.41	0.50	8
21	331	46	4.10	13	2.21	1.93	1.07	14.27	0.66	1.85	1.31	0.52	8
22	371	48	4.94	19	3.18	1.96	1.24	15.48	0.77	2.18	1.45	0.38	9
23	439	75	5.00	19	3.48	2.16	1.33	18.47	0.80	2.60	1.62	0.72	8
24	416	99	5.33	33	2.80	2.01	1.35	12.20	0.93	2.09	1.97	0.57	7
25	346	54	4.72	15	2.78	2.06	1.17	14.86	0.86	2.41	1.41	0.43	10
MEAN	376.4	61.3	4.76	23.6	2.95	2.07	1.26	16.14	0.85	2.25	1.60	0.53	9.9
S.D.	35.03	16.05	0.422	8.36	0.395	0.094	0.114	2.001	0.136	0.295	0.300	0.107	2.42
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 61

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 1.25 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	TESTES g	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	PROSTATE g	LUNGS g	THYMUS g	PITUIT. GLAND mg
26	383	51	4.40	20	2.41	2.14	1.32	14.78	0.87	2.22	1.77	0.70	9
27	333	54	4.38	11	2.57	1.96	1.12	12.61	0.63	2.42	1.59	0.48	8
28	428	58	4.91	23	3.00	2.09	1.55	18.31	1.09	2.38	1.86	0.69	10
29	397	58	1.78	17	3.04	1.83	1.28	16.03	1.09	1.61	1.56	0.85	8
30	359	61	4.61	14	2.85	1.90	1.10	17.23	0.86	2.29	1.87	0.46	7
31	456	67	4.58	24	3.31	2.09	1.57	23.58	1.05	2.85	1.71	0.59	15
32	410	74	5.29	31	3.31	2.20	1.53	16.14	0.92	2.82	1.81	0.86	15
33	366	49	4.69	21	3.00	2.00	1.28	15.62	0.88	2.43	2.08	0.50	15
34	401	68	5.05	16	3.30	1.95	1.43	19.44	0.84	2.32	2.08	0.55	9
35	433	61	4.57	19	3.33	1.96	1.72	19.84	0.82	2.37	2.21	0.66	7
MEAN	396.6	60.1	4.43	19.6	3.01	2.01	1.39	17.36	0.91	2.37	1.85	0.63	10.3
S.D.	37.44	7.87	0.973	5.66	0.324	0.115	0.204	3.084	0.142	0.341	0.215	0.144	3.37
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 62

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	TESTES g	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	PROSTATE g	LUNGS g	THYMUS g	PITUIT. GLAND mg
36	340	54	4.15	11	2.43	2.01	1.19	14.56	0.83	1.95	1.91	0.59	7
37	421	55	5.14	17	2.83	2.20	1.47	15.10	1.07	2.35	1.76	0.72	10
38	391	62	4.68	22	3.04	1.92	1.29	19.48	1.02	2.14	1.73	0.65	13
39	369	58	4.29	27	2.84	2.06	1.21	15.32	0.81	1.82	1.66	0.63	12
40	329	72	4.53	14	2.79	1.83	1.15	13.19	0.65	2.24	1.45	0.50	7
41	402	70	4.42	33	2.91	2.16	1.42	15.09	1.17	2.44	1.58	0.90	14
42	372	60	4.67	18	3.09	2.12	1.49	19.02	0.94	2.30	1.78	0.51	14
43	399	75	4.88	35	3.17	2.09	1.28	20.17	0.95	2.53	1.60	0.79	12
44	471	45	4.79	15	3.62	2.22	1.58	22.22	1.67	2.80	2.15	0.93	8
45	457	62	4.83	17	3.88	2.15	1.52	17.56	1.06	2.62	2.17	0.77	13
MEAN	395.1	61.3	4.64	20.9	3.06	2.08	1.36	17.17	1.02	2.32	1.78	0.70	11.0
S.D.	45.90	9.13	0.297	8.18	0.421	0.125	0.154	2.946	0.274	0.299	0.237	0.150	2.79
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 63

RELATIVE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	TESTES %	THYROID GLANDS %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	PROSTATE %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
1	345	1.13	1.42	0.35	0.99	0.66	0.42	4.06	0.28	0.74	0.52	0.24	0.26
2	385	1.32	1.17	0.36	0.84	0.50	0.33	3.77	0.12	0.49	0.38	0.13	0.21
3	353	1.50	1.15	0.45	0.88	0.55	0.35	5.51	0.19	0.69	0.45	0.18	0.40
4	377	1.09	1.13	0.29	0.69	0.51	0.37	3.71	0.18	0.53	0.34	0.11	0.21
5	392	2.17	1.18	0.74	0.85	0.57	0.38	4.87	0.23	0.52	0.52	0.15	0.28
6	472	1.48	0.89	0.61	0.71	0.46	0.35	4.28	0.19	0.60	0.37	0.21	0.28
7	395	1.92	1.18	0.51	0.82	0.51	0.33	5.24	0.26	0.57	0.49	0.16	0.35
8	408	1.37	1.38	0.66	0.95	0.54	0.33	3.86	0.27	0.60	0.42	0.22	0.29
9	457	1.53	1.09	0.44	0.72	0.45	0.32	3.88	0.23	0.60	0.48	0.15	0.13
10	378	1.38	1.35	0.19	0.83	0.51	0.34	4.49	0.20	0.65	0.33	0.16	0.16
MEAN	396.2	1.49	1.19	0.46	0.83	0.53	0.35	4.37	0.22	0.60	0.43	0.17	0.26
S.D.	40.71	0.332	0.156	0.172	0.100	0.060	0.030	0.643	0.049	0.078	0.072	0.041	0.082
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 64

RELATIVE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 0.75 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	TESTES %	THYROID GLANDS %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	PROSTATE %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
16	400	1.50	1.18	0.65	0.71	0.53	0.32	4.10	0.20	0.61	0.36	0.17	0.28
17	386	1.76	1.36	1.06	0.90	0.56	0.36	4.49	0.30	0.66	0.43	0.14	0.39
18	363	1.46	1.23	0.66	0.72	0.60	0.37	4.94	0.26	0.48	0.40	0.15	0.33
19	377	1.59	1.30	0.64	0.85	0.56	0.37	4.86	0.23	0.67	0.60	0.11	0.29
20	335	1.49	1.23	0.66	0.86	0.59	0.33	4.80	0.21	0.64	0.42	0.15	0.24
21	331	1.39	1.24	0.39	0.67	0.58	0.32	4.31	0.20	0.56	0.40	0.16	0.24
22	371	1.29	1.33	0.51	0.86	0.53	0.33	4.17	0.21	0.59	0.39	0.10	0.24
23	439	1.71	1.14	0.43	0.79	0.49	0.30	4.21	0.18	0.59	0.37	0.16	0.18
24	416	2.38	1.28	0.79	0.67	0.48	0.32	2.93	0.22	0.50	0.47	0.14	0.17
25	346	1.56	1.36	0.43	0.80	0.60	0.34	4.29	0.25	0.70	0.41	0.12	0.29
MEAN	376.4	1.61	1.27	0.62	0.78	0.55	0.34	4.31	0.23	0.60	0.43	0.14	0.27
S.D.	35.03	0.303	0.074	0.201	0.085	0.043	0.024	0.573	0.035	0.072	0.069	0.023	0.066
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 65

RELATIVE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 1.25 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	TESTES %	THYROID GLANDS %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	PROSTATE %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
26	383	1.33	1.15	0.52	0.63	0.56	0.34	3.86	0.23	0.58	0.46	0.18	0.23
27	333	1.62	1.32	0.33	0.77	0.59	0.34	3.79	0.19	0.73	0.48	0.14	0.24
28	428	1.36	1.15	0.54	0.70	0.49	0.36	4.28	0.25	0.56	0.43	0.16	0.23
29	397	1.46	0.45	0.43	0.77	0.46	0.32	4.04	0.27	0.41	0.39	0.21	0.20
30	359	1.70	1.28	0.39	0.79	0.53	0.31	4.80	0.24	0.64	0.52	0.13	0.19
31	456	1.47	1.00	0.53	0.73	0.46	0.34	5.17	0.23	0.63	0.38	0.13	0.33
32	410	1.80	1.29	0.76	0.81	0.54	0.37	3.94	0.22	0.69	0.44	0.21	0.37
33	366	1.34	1.28	0.57	0.82	0.55	0.35	4.27	0.24	0.66	0.57	0.14	0.41
34	401	1.70	1.26	0.40	0.82	0.49	0.36	4.85	0.21	0.58	0.52	0.14	0.22
35	433	1.41	1.06	0.44	0.77	0.45	0.40	4.58	0.19	0.55	0.51	0.15	0.16
MEAN	396.6	1.52	1.12	0.49	0.76	0.51	0.35	4.36	0.23	0.60	0.47	0.16	0.26
S.D.	37.44	0.172	0.260	0.122	0.060	0.048	0.026	0.472	0.025	0.089	0.061	0.031	0.083
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 66

RELATIVE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	TESTES %	THYROID GLANDS %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	PROSTATE %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
36	340	1.59	1.22	0.32	0.71	0.59	0.35	4.28	0.24	0.57	0.56	0.17	0.21
37	421	1.31	1.22	0.40	0.67	0.52	0.35	3.59	0.25	0.56	0.42	0.17	0.24
38	391	1.59	1.20	0.56	0.78	0.49	0.33	4.98	0.26	0.55	0.44	0.17	0.33
39	369	1.57	1.16	0.73	0.77	0.56	0.33	4.15	0.22	0.49	0.45	0.17	0.33
40	329	2.19	1.38	0.43	0.85	0.56	0.35	4.01	0.20	0.68	0.44	0.15	0.21
41	402	1.74	1.10	0.82	0.72	0.54	0.35	3.75	0.29	0.61	0.39	0.22	0.35
42	372	1.61	1.26	0.48	0.83	0.57	0.40	5.11	0.25	0.62	0.48	0.14	0.38
43	399	1.88	1.22	0.88	0.79	0.52	0.32	5.06	0.24	0.63	0.40	0.20	0.30
44	471	0.96	1.02	0.32	0.77	0.47	0.34	4.72	0.35	0.59	0.46	0.20	0.17
45	457	1.36	1.06	0.37	0.85	0.47	0.33	3.84	0.23	0.57	0.47	0.17	0.28
MEAN	395.1	1.58	1.18	0.53	0.77	0.53	0.35	4.35	0.25	0.59	0.45	0.18	0.28
S.D.	45.90	0.332	0.104	0.208	0.060	0.042	0.022	0.575	0.042	0.052	0.048	0.024	0.070
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 67

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	OVARIES mg	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	UTERUS g	LUNGS g	THYMUS g	PITUIT. GLAND mg
51	245	57	105	26	1.87	2.10	1.03	9.98	0.71	0.42	1.47	0.65	20
52	257	72	168	62	2.18	1.98	1.04	9.60	0.69	0.98	1.39	0.75	33
53	271	76	126	24	2.12	1.97	0.87	11.45	0.62	0.49	1.45	0.55	18
54	236	85	128	22	1.78	2.11	0.94	9.34	0.49	0.58	1.41	0.50	25
55	238	61	92	11	1.89	1.80	0.93	9.90	0.70	0.65	1.27	0.48	9
56	252	86	132	17	1.97	1.96	0.92	11.53	0.58	0.50	1.37	0.53	17
57	263	80	203	34	2.04	1.98	1.06	11.34	0.65	0.52	1.33	0.59	22
58	243	56	137	14	2.05	1.94	1.01	11.71	0.40	0.36	1.19	0.42	13
59	293	70	143	23	2.11	1.93	1.10	13.56	0.78	0.66	1.63	0.56	15
60	268	77	153	29	2.08	2.10	1.23	11.69	0.71	0.44	1.51	0.63	17
MEAN	256.6	72.0	138.7	26.2	2.01	1.99	1.01	11.01	0.63	0.56	1.40	0.57	18.9
S.D.	17.68	10.93	31.37	14.33	0.128	0.096	0.105	1.295	0.115	0.176	0.124	0.095	6.69
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 68

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 0.75 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	OVARIES mg	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	UTERUS g	LUNGS g	THYMUS g	PITUIT. GLAND mg
66	232	92	126	47	2.02	2.05	0.91	10.31	0.66	0.91	1.37	0.51	31
67	243	70	95	13	2.07	1.92	0.91	10.99	0.65	0.65	1.56	0.49	16
68	226	68	133	26	1.81	1.80	0.94	10.70	0.63	0.46	1.27	0.39	17
69	260	63	168	24	2.47	2.16	1.10	10.20	1.02	0.60	1.67	0.79	12
70	242	84	102	31	1.76	1.96	0.84	10.78	0.70	0.68	1.49	0.50	15
71	244	75	149	18	1.86	2.09	0.89	9.47	0.94	0.76	1.24	0.51	12
72	245	66	133	9	1.80	1.90	0.89	11.12	0.71	0.53	1.16	0.60	11
73	270	92	128	12	2.13	2.02	0.93	11.54	1.16	0.77	1.38	0.50	13
74	257	64	134	28	2.04	1.95	0.91	10.72	0.76	0.52	1.67	0.61	17
75	234	81	117	18	2.01	1.86	1.02	10.00	0.75	0.63	1.54	0.61	10
MEAN	245.3	75.5	128.5	22.6	2.00	1.97	0.93	10.58	0.80	0.65	1.44	0.55	15.4
S.D.	13.57	11.12	21.12	11.26	0.210	0.110	0.074	0.600	0.180	0.136	0.179	0.108	6.02
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 69

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 1.25 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	OVARIES mg	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	UTERUS g	LUNGS g	THYMUS g	PITUIT. GLAND mg
76	241	78	152	12	2.11	1.96	1.09	8.66	0.78	0.60	1.27	0.66	12
77	244	76	128	17	1.89	1.83	0.92	9.24	0.62	1.03	1.62	0.55	16
78	238	52	122	22	2.03	1.96	0.88	9.77	0.75	0.39	1.15	0.40	22
79	241	58	150	30	1.81	1.80	0.90	9.59	1.00	0.65	1.20	0.53	20
80	239	86	175	15	2.08	1.90	1.04	11.68	0.67	0.81	1.59	0.61	14
81	266	85	150	21	2.26	1.99	1.00	11.62	0.87	0.37	1.49	0.68	17
82	226	88	163	10	1.86	1.77	0.90	10.48	0.66	0.58	1.19	0.37	9
83	258	84	199	26	1.99	2.15	1.16	9.98	0.99	0.53	1.28	0.44	19
84	241	91	163	25	2.05	1.91	0.88	9.58	0.75	0.74	1.77	0.42	9
85	275	86	177	35	2.07	2.03	1.02	10.81	0.74	0.40	1.75	0.56	32
MEAN	246.9	78.4	157.9	21.3	2.02	1.93	0.98	10.14	0.78	0.61	1.43	0.52	17.0
S.D.	14.79	13.17	22.95	7.97	0.133	0.114	0.098	0.995	0.132	0.209	0.240	0.110	6.88
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 70

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	OVARIES mg	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	UTERUS g	LUNGS g	THYMUS g	PITUIT. GLAND mg
86	253	60	179	23	1.87	1.89	0.94	9.60	0.69	0.76	1.28	0.54	15
87	218	73	90	16	1.98	1.79	0.82	9.50	0.61	0.73	1.49	0.46	9
88	245	70	126	15	1.69	1.87	0.99	9.98	0.82	0.59	1.34	0.50	12
89	266	65	167	21	2.14	1.89	1.00	11.29	0.80	0.50	1.51	0.68	16
90	253	97	128	35	2.17	1.98	0.89	10.65	0.78	0.84	1.35	0.50	16
91	221	71	115	24	1.64	2.03	0.91	8.91	0.58	0.44	1.12	0.38	15
92	257	85	201	28	2.05	2.04	1.06	11.51	1.02	0.45	1.11	0.44	21
93	266	67	140	18	1.92	1.74	1.00	11.08	0.88	0.51	1.53	0.65	19
94	247	104	188	19	2.11	1.99	1.04	11.03	0.98	0.59	1.65	0.62	18
95	247	70	127	14	2.37	1.79	0.93	10.02	0.78	0.88	1.42	0.70	9
MEAN	247.3	76.2	146.1	21.3	1.99	1.90	0.96	10.36	0.79	0.63	1.38	0.55	15.0
S.D.	16.38	14.41	35.80	6.50	0.223	0.106	0.074	0.877	0.143	0.162	0.176	0.110	4.00
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 71

RELATIVE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	OVARIES %(x100)	THYROID GLAND %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
51	245	2.33	4.29	1.06	0.76	0.86	0.42	4.07	0.29	0.17	0.60	0.27	0.82
52	257	2.80	6.54	2.41	0.85	0.77	0.40	3.74	0.27	0.38	0.54	0.29	1.28
53	271	2.80	4.65	0.89	0.78	0.73	0.32	4.23	0.23	0.18	0.54	0.20	0.66
54	236	3.60	5.42	0.93	0.75	0.89	0.40	3.96	0.21	0.25	0.60	0.21	1.06
55	238	2.56	3.87	0.46	0.79	0.76	0.39	4.16	0.29	0.27	0.53	0.20	0.38
56	252	3.41	5.24	0.67	0.78	0.78	0.37	4.58	0.23	0.20	0.54	0.21	0.67
57	263	3.04	7.72	1.29	0.78	0.75	0.40	4.31	0.25	0.20	0.51	0.22	0.84
58	243	2.30	5.64	0.58	0.84	0.80	0.42	4.82	0.16	0.15	0.49	0.17	0.53
59	293	2.39	4.88	0.78	0.72	0.66	0.38	4.63	0.27	0.23	0.56	0.19	0.51
60	268	2.87	5.71	1.08	0.78	0.78	0.46	4.36	0.26	0.16	0.56	0.24	0.63
MEAN	256.6	2.81	5.40	1.02	0.78	0.78	0.40	4.29	0.25	0.22	0.55	0.22	0.74
S.D.	17.68	0.443	1.119	0.550	0.039	0.064	0.037	0.328	0.040	0.069	0.035	0.037	0.271
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 72

RELATIVE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 0.75 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	OVARIES %(x100)	THYROID GLAND %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
66	232	3.97	5.43	2.03	0.87	0.88	0.39	4.44	0.28	0.39	0.59	0.22	1.34
67	243	2.88	3.91	0.53	0.85	0.79	0.37	4.52	0.27	0.27	0.64	0.20	0.66
68	226	3.01	5.88	1.15	0.80	0.80	0.42	4.73	0.28	0.20	0.56	0.17	0.75
69	260	2.42	6.46	0.92	0.95	0.83	0.42	3.92	0.39	0.23	0.64	0.30	0.46
70	242	3.47	4.21	1.28	0.73	0.81	0.35	4.45	0.29	0.28	0.62	0.21	0.62
71	244	3.07	6.11	0.74	0.76	0.86	0.36	3.88	0.39	0.31	0.51	0.21	0.49
72	245	2.69	5.43	0.37	0.73	0.78	0.36	4.54	0.29	0.22	0.47	0.24	0.45
73	270	3.41	4.74	0.44	0.79	0.75	0.34	4.27	0.43	0.29	0.51	0.19	0.48
74	257	2.49	5.21	1.09	0.79	0.76	0.35	4.17	0.30	0.20	0.65	0.24	0.66
75	234	3.46	5.00	0.77	0.86	0.79	0.44	4.27	0.32	0.27	0.66	0.26	0.43
MEAN	245.3	3.09	5.24	0.93	0.81	0.81	0.38	4.32	0.32	0.27	0.59	0.22	0.63
S.D.	13.57	0.492	0.807	0.492	0.069	0.041	0.035	0.273	0.057	0.058	0.069	0.037	0.272
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 73

RELATIVE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 1.25 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	OVARIES %(x100)	THYROID GLAND %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
76	241	3.24	6.31	0.50	0.88	0.81	0.45	3.59	0.32	0.25	0.53	0.27	0.50
77	244	3.11	5.25	0.70	0.77	0.75	0.38	3.79	0.25	0.42	0.66	0.23	0.66
78	238	2.18	5.13	0.92	0.85	0.82	0.37	4.11	0.32	0.16	0.48	0.17	0.92
79	241	2.41	6.22	1.24	0.75	0.75	0.37	3.98	0.41	0.27	0.50	0.22	0.83
80	239	3.60	7.32	0.63	0.87	0.79	0.44	4.89	0.28	0.34	0.67	0.26	0.59
81	266	3.20	5.64	0.79	0.85	0.75	0.38	4.37	0.33	0.14	0.56	0.26	0.64
82	226	3.89	7.21	0.44	0.82	0.78	0.40	4.64	0.29	0.26	0.53	0.16	0.40
83	258	3.26	7.71	1.01	0.77	0.83	0.45	3.87	0.38	0.21	0.50	0.17	0.74
84	241	3.78	6.76	1.04	0.85	0.79	0.37	3.98	0.31	0.31	0.73	0.17	0.37
85	275	3.13	6.44	1.27	0.75	0.74	0.37	3.93	0.27	0.15	0.64	0.20	1.16
MEAN	246.9	3.18	6.40	0.85	0.82	0.78	0.40	4.12	0.32	0.25	0.58	0.21	0.68
S.D.	14.79	0.543	0.876	0.291	0.051	0.032	0.035	0.402	0.049	0.090	0.087	0.043	0.243
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 74

RELATIVE ORGAN WEIGHTS
Sacrificed after end of treatment
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	OVARIES %(x100)	THYROID GLAND %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
86	253	2.37	7.08	0.91	0.74	0.75	0.37	3.79	0.27	0.30	0.51	0.21	0.59
87	218	3.35	4.13	0.73	0.91	0.82	0.38	4.36	0.28	0.33	0.68	0.21	0.41
88	245	2.86	5.14	0.61	0.69	0.76	0.40	4.07	0.33	0.24	0.55	0.20	0.49
89	266	2.44	6.28	0.79	0.80	0.71	0.38	4.24	0.30	0.19	0.57	0.26	0.60
90	253	3.83	5.06	1.38	0.86	0.78	0.35	4.21	0.31	0.33	0.53	0.20	0.63
91	221	3.21	5.20	1.09	0.74	0.92	0.41	4.03	0.26	0.20	0.51	0.17	0.68
92	257	3.31	7.82	1.09	0.80	0.79	0.41	4.48	0.40	0.18	0.43	0.17	0.82
93	266	2.52	5.26	0.68	0.72	0.65	0.38	4.17	0.33	0.19	0.58	0.24	0.71
94	247	4.21	7.61	0.77	0.85	0.81	0.42	4.47	0.40	0.24	0.67	0.25	0.73
95	247	2.83	5.14	0.57	0.96	0.72	0.38	4.06	0.32	0.36	0.57	0.28	0.36
MEAN	247.3	3.09	5.87	0.86	0.81	0.77	0.39	4.19	0.32	0.26	0.56	0.22	0.60
S.D.	16.38	0.607	1.249	0.256	0.088	0.073	0.021	0.214	0.049	0.068	0.075	0.037	0.146
n	10	10	10	10	10	10	10	10	10	10	10	10	10

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 75

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of recovery period
Individual results

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	TESTES g	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	PROSTATE g	LUNGS g	THYMUS g	PITUIT. GLAND mg
11	436	65	5.33	21	3.28	2.11	1.52	19.05	0.75	2.99	1.93	0.74	14
12	410	55	5.01	30	3.05	2.13	1.35	17.23	0.70	2.63	1.72	0.74	16
13	413	56	5.07	35	2.72	2.03	1.34	17.32	0.74	2.72	1.54	0.55	15
14	485	61	4.54	42	3.31	2.12	1.44	22.17	0.87	2.22	1.58	0.51	16
15	427	61	4.32	32	3.41	2.06	1.40	18.82	0.82	2.26	1.61	0.75	19
MEAN	434.2	59.6	4.85	32.0	3.15	2.09	1.41	18.92	0.78	2.56	1.68	0.66	16.0
S.D.	30.29	4.10	0.413	7.65	0.276	0.043	0.073	2.000	0.068	0.324	0.157	0.118	1.87
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 76

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of recovery period
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	TESTES g	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	PROSTATE g	LUNGS g	THYMUS g	PITUIT. GLAND mg
46	439	59	5.30	29	3.08	1.99	1.61	17.47	0.84	3.02	1.87	0.70	11
47	427	91	4.82	22	3.35	2.15	1.50	17.94	0.84	2.38	1.83	0.63	17
48	406	63	5.10	26	3.20	2.13	1.47	13.85	0.83	2.18	1.84	0.59	12
49	500	74	5.62	46	3.90	2.16	1.71	21.54	1.04	3.39	2.24	1.06	19
50	543	68	5.89	41	3.95	2.30	1.79	25.52	1.03	3.13	2.11	0.92	21
MEAN	463.0	71.0	5.35	32.8	3.50	2.15	1.62	19.26	0.92	2.82	1.98	0.78	16.0
S.D.	56.77	12.51	0.421	10.23	0.404	0.110	0.136	4.433	0.109	0.516	0.186	0.202	4.36
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 77

RELATIVE ORGAN WEIGHTS
Sacrificed after end of recovery period
Individual results

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	TESTES %	THYROID GLANDS %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	PROSTATE %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
11	436	1.49	1.22	0.48	0.75	0.48	0.35	4.37	0.17	0.69	0.44	0.17	0.32
12	410	1.34	1.22	0.73	0.74	0.52	0.33	4.20	0.17	0.64	0.42	0.18	0.39
13	413	1.36	1.23	0.85	0.66	0.49	0.32	4.19	0.18	0.66	0.37	0.13	0.36
14	485	1.26	0.94	0.87	0.68	0.44	0.30	4.57	0.18	0.46	0.33	0.11	0.33
15	427	1.43	1.01	0.75	0.80	0.48	0.33	4.41	0.19	0.53	0.38	0.18	0.44
MEAN	434.2	1.38	1.12	0.74	0.73	0.48	0.33	4.35	0.18	0.60	0.39	0.15	0.37
S.D.	30.29	0.088	0.138	0.155	0.056	0.029	0.018	0.158	0.008	0.097	0.043	0.032	0.049
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 78

RELATIVE ORGAN WEIGHTS
Sacrificed after end of recovery period
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day
Sex: Male

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	TESTES %	THYROID GLANDS %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	PROSTATE %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
46	439	1.34	1.21	0.66	0.70	0.45	0.37	3.98	0.19	0.69	0.43	0.16	0.25
47	427	2.13	1.13	0.52	0.78	0.50	0.35	4.20	0.20	0.56	0.43	0.15	0.40
48	406	1.55	1.26	0.64	0.79	0.52	0.36	3.41	0.20	0.54	0.45	0.15	0.30
49	500	1.48	1.12	0.92	0.78	0.43	0.34	4.31	0.21	0.68	0.45	0.21	0.38
50	543	1.25	1.08	0.76	0.73	0.42	0.33	4.70	0.19	0.58	0.39	0.17	0.39
MEAN	463.0	1.55	1.16	0.70	0.76	0.46	0.35	4.12	0.20	0.61	0.43	0.17	0.34
S.D.	56.77	0.345	0.073	0.150	0.039	0.044	0.016	0.475	0.008	0.070	0.024	0.025	0.066
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 79

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of recovery period
Individual results

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	OVARIES mg	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	UTERUS g	LUNGS g	THYMUS g	PITUIT. GLAND mg
61	264	62	113	26	2.03	1.91	1.04	11.24	0.50	0.64	1.19	0.39	24
62	255	66	163	29	1.88	2.03	0.90	10.29	0.71	0.50	1.27	0.53	16
63	277	79	156	29	2.08	1.97	1.08	10.48	0.66	0.66	1.46	0.53	23
64	250	66	177	16	2.13	1.94	0.91	10.72	0.63	0.66	1.37	0.45	14
65	264	75	168	15	2.17	1.98	0.97	11.08	0.73	0.42	1.38	0.58	22
MEAN	262.0	69.6	155.4	23.0	2.06	1.97	0.98	10.76	0.65	0.58	1.33	0.50	19.8
S.D.	10.32	7.09	24.91	6.96	0.113	0.045	0.079	0.398	0.091	0.110	0.105	0.075	4.49
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 80

ABSOLUTE ORGAN WEIGHTS
Sacrificed after end of recovery period
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS mg	OVARIES mg	THYROID GLANDS mg	KIDNEYS g	BRAIN g	HEART g	LIVER g	SPLEEN g	UTERUS g	LUNGS g	THYMUS g	PITUIT. GLAND mg
96	246	63	152	22	2.14	2.04	1.10	10.29	0.84	0.57	1.61	0.61	18
97	274	62	159	22	2.14	1.87	0.91	10.93	0.77	0.91	1.53	0.45	16
98	284	67	177	24	2.19	1.97	1.08	12.34	0.94	0.65	1.72	0.46	17
99	271	54	123	12	1.71	1.87	0.86	9.20	0.98	0.58	1.45	0.50	9
100	276	92	112	31	1.84	1.84	1.02	10.10	0.54	0.64	1.66	0.44	22
MEAN	270.2	67.6	144.6	22.2	2.00	1.92	0.99	10.57	0.81	0.67	1.59	0.49	16.4
S.D.	14.36	14.43	26.65	6.80	0.215	0.084	0.105	1.166	0.174	0.139	0.106	0.070	4.72
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 81

RELATIVE ORGAN WEIGHTS
Sacrificed after end of recovery period
Individual results

Study no.: CD-98/6289T
Test substance: CONTROL
Dose: --
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	OVARIES %(x100)	THYROID GLAND %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
61	264	2.35	4.28	0.98	0.77	0.72	0.39	4.26	0.19	0.24	0.45	0.15	0.91
62	255	2.59	6.39	1.14	0.74	0.80	0.35	4.04	0.28	0.20	0.50	0.21	0.63
63	277	2.85	5.63	1.05	0.75	0.71	0.39	3.78	0.24	0.24	0.53	0.19	0.83
64	250	2.64	7.08	0.64	0.85	0.78	0.36	4.29	0.25	0.26	0.55	0.18	0.56
65	264	2.84	6.36	0.57	0.82	0.75	0.37	4.20	0.28	0.16	0.52	0.22	0.83
MEAN	262.0	2.65	5.95	0.88	0.79	0.75	0.37	4.11	0.25	0.22	0.51	0.19	0.75
S.D.	10.32	0.206	1.064	0.255	0.047	0.038	0.018	0.210	0.037	0.040	0.038	0.027	0.149
n	5	5	5	5	5	5	5	5	5	5	5	5	5

CENTRO DE INVESTIGACIÓN Y
DESARROLLO APLICADO, S.A.L.
Toxicology Department
Table no.: 82

RELATIVE ORGAN WEIGHTS
Sacrificed after end of recovery period
Individual results

Study no.: CD-98/6289T
Test substance: IQB-9302.HCl
Dose: 2.25 mg/kg/day
Sex: Female

ANIMAL No.	BODY WEIGHT g	ADRENAL GLANDS %(x100)	OVARIES %(x100)	THYROID GLAND %(x100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	LUNGS %	THYMUS %	PITUIT. GLAND %(x100)
96	246	2.56	6.18	0.89	0.87	0.83	0.45	4.18	0.34	0.23	0.65	0.25	0.73
97	274	2.26	5.80	0.80	0.78	0.68	0.33	3.99	0.28	0.33	0.56	0.16	0.58
98	284	2.36	6.23	0.85	0.77	0.69	0.38	4.35	0.33	0.23	0.61	0.16	0.60
99	271	1.99	4.54	0.44	0.63	0.69	0.32	3.39	0.36	0.21	0.54	0.18	0.33
100	276	3.33	4.06	1.12	0.67	0.67	0.37	3.66	0.20	0.23	0.60	0.16	0.80
MEAN	270.2	2.50	5.36	0.82	0.74	0.71	0.37	3.91	0.30	0.25	0.59	0.18	0.61
S.D.	14.36	0.507	0.998	0.245	0.095	0.066	0.051	0.389	0.064	0.048	0.043	0.039	0.180
n	5	5	5	5	5	5	5	5	5	5	5	5	5