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

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

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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. :



Study Director :



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

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QUALITY ASSURANCE UNIT (QAU)



Inspection of Study no. CD-98/6289T

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- 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

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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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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. <u>Supply</u>

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 $32.7 \times 19 \text{ cm}$), 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 $32.7 \times 19 \text{ cm}$), 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 19°C and 25°C. 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. <u>Diet</u>

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 $23G (0.6 \times 25 \text{ mm})$ 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.

		Dose Anim		nal no.	Colour
Group	Treatment	(mg/kg/day)	Males	Females	code
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. <u>Recovery period</u>

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:

			Anim	al no.
Group	Treatment	Dose (mg/kg/day)	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. <u>Clinical signs</u>

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. <u>Haematology</u>

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.	mmol/L
Potassium	Ion selective electrode.	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	Macroscopic observation
Volume	
Specific gravity	Refractometry
pН	
Proteins	
Glucose	
Bilirubin	Combur 8 test
Ketones	
Urobilinogen	
Haemoglobin	

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



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 method¹ (p<0.05).

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

^{a) Duncan D.B. Multiple range and multiple F test.} Biometrics <u>11</u>, 1-42 (1955).
b) Kramer C.Y. Extension of multiple range test to group means with unequal number of replication.

b) Kramer C.Y. Extension of multiple range test to group means with unequal number of replication Biometrics <u>12</u>, 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).

⁽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. <u>RESULTS</u>

14.1. <u>Mortality</u>

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. <u>Clinical signs</u>

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. <u>Water intake</u>

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. <u>Macroscopic observations</u>

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. <u>Microscopic observations</u>

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

<u>LIVER</u>

Lymphocytary infiltrate, portal IQB-9302.HCl (2.25 mg/kg/day): 92F <u>Microgranuloma</u> Control: 55F IQB-9302.HCl (2.25 mg/kg/day): 91F

<u>PITUITARY</u>

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

<u>EYES</u>

Lymphocytary infiltrate in Harder's gland, unilateral IQB-9302.HCl (2.25 mg/kg/day): 94F <u>LUNGS</u> <u>Intraalveolar histiocytosis, focal</u> Control: 7M, 54F IQB-9302.HCl (2.25 mg/kg/day): 36M, 38M

<u>KIDNEYS</u> <u>Dilation of renal pelvis</u> 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

<u>TESTES</u> <u>Tubular atrophy</u> IQB-9302.HCl (1.25 mg/kg/day): 29M

<u>THYMUS</u> <u>Multifocal congestion</u> IQB-9302.HCl (2.25 mg/kg/day): 38M

<u>URINARY BLADDER</u> <u>Cystitis, acute, non-specific</u> 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

<u>LIVER</u>

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

<u>KIDNEYS</u>

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.: 2





-J 48 .46 4 4 ų 4 4 * 4 4

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

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













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

NUMBER OF ANIMALS WITH CLINICAL SIGNS IN THE COURSE OF TREATMENT

					I	QB-93 mg/k	02.HC g/day	21	
CLINICAL SIGNS	Treatment group	CONT	FROL	0.′	75	1.2	25	2.2	25
	Sex	М	F	М	F	Μ	F	Μ	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

48

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

BODYWEIGHTS (g) Mean values

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

	TREATMENT				H	reatment	day					
	DOSE mg/kg/day		2-	۲-	4	8	.	15	18	22	25	29
A I	CONTROL	MEAN S.D.	191.5 8.10 15	258.2 13.65 15	273.7 14.92 15	296.8 18.50 15	313.9 21.45 15	332.2 25.54 15	347.5 26.98 15	366.5 32.31 15	367.7 30.06 15	389.9 33.70 15
à	IQB-9302.HCI 0.75	MEAN S.D.	188.6 11.04 10	247.4 15.50 10	265.9 16.28 10	287.7 18.15 10	303.5 21.39 10	320.6 24.65 10	333.9 26.78 10	350.6 30.81 10	346.6 31.13 10	370.1 34.37 10
Ö	IQB-9302.HCI 1.25	MEAN S.D.	193.2 7.18 10	254.3 10.90 10	276.1 12.91 10	300.7 17.38 10	318.0 20.49 10	336.7 23.66 10	352.4 28.34 10	366.7 33.53 10	364.7 33.43 10	387.0 34.57 10
Ö	IQB-9302.HCI 2.25	MEAN S.D.	189.5 9.26 15	253.7 13.98 15	274.5 15.38 15	300.1 21.89 15	318.1 24.73 15	338.8 29.42 15	356.6 34.31 15	374.9 37.61 15	374.1 42.31 15	401.8 46.73 15
One-\ of var	way analysis iance (p<0.05)		N.S.	N.S.	N.N.	N.S.	N.S.	N.S.	N.S.	N.S.	N. N	N.S.

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

BODYWEIGHTS (g) Mean values

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

	TREATMENT					Treatment	day					
	DOSE mg/kg/day		2-	~	4	80	11	15	18	22	25	29
A .	CONTROL	MEAN S.D.	162.5 10.00 15	193.2 10.32 15	201.3 10.17 15	211.6 11.51 15	218.6 13.22 15	230.1 14.37 15	236.0 14.82 15	244.9 14.94 15	241.3 14.11 15	251.1 14.57 15
i iii	IQB-9302.HCI 0.75	MEAN S.D.	160.4 7.09 10	186.7 7.82 10	195.7 8.60 10	206.7 10.51 10	212.8 11.29 10	222.0 10.77 10	228.3 13.39 10	236.6 13.91 10	231.3 13.98 10	239.2 11.82 10
i ii	IQB-9302.HCI 1.25	MEAN S.D.	160.9 8.23 10	189.9 14.36 10	196.9 14.43 10	206.1 13.19 10	216.0 10.70 10	225.9 11.67 10	231.8 14.11 10	239.7 16.17 10	234.5 14.75 10	239.7 14.45 10
	IQB-9302.HCI 2.25	MEAN S.D. n	160.9 6.94 15	189.1 8.11 15	199.5 10.94 15	211.2 11.45 15	219.4 12.01 15	226.7 13.02 15	233.2 12.48 15	241.6 12.29 15	237.4 14.81 15	248.9 14.96 15
One- of val	way analysis riance (p<0.05)		N.S.	N.S.	S. Z	N.S.	N.S.	N.S.	N.S.	N.N.	N.S.	N.N.

CENT DESA Toxici Table	PRO DE INVESTIGAC ARROLLO APLICADC ology Department no∴ 4	ción Υ , S.A.L.	Q v ž	DYWEIGHTS (g) ecovery period ean values		Study no∴ CD-9 Sex: Male	38/6289T
	TREATMENT			Study day			
	розе mg/kg/day		29	32	36	39	43
		MEAN	393.4	408.0	426.0	409.8	434.2
Ä	CONTROL	S.D.	28.27	29.93	28.00	32.18	30.29
:	1	C	S	S	5	5	£
		MEAN	428.0	446.6	466.2	453.0	463.0
á	10B-9302.HCI	S.D.	43.20	41.49	45.96	46.64	56.77
i	2.25	C	£	S	5	5	£
Stud (p*	ent t test <0.05)		N.S.	N.S.	N.S.	N. N.	Z.S.

1

18/6289T		43	262.0	10.32	S
Study no.: CD-9 Sex: Female		39	247.6	12.28	ഹ
		36	262.4	13.09	ъ
DYWEIGHTS (g) ecovery period ean values	Study day	32	256.0	15.65	5
08 v ≥		29	252.2	17.14	5 2
IÓN Y S.A.L.			MEAN	S.D.	c
RO DE INVESTIGACI RROLLO APLICADO, blogy Department no.: 5	TREATMENT	DOSE mg/kg/day		CONTROL	
CENT DESA Toxic Table				Ä	

Study day 32 36 39 43 256.0 262.4 247.6 262.0 15.65 13.09 12.28 10.32 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 13.09 N.S. N.S. N.S. B: IQB-9302.HCI S.D. 8.49 2.25 n 5 Student t test N.S. (p<0.05) = ł ÷



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)

]			IQ	B-9302.H	Cl (mg/kg/da	ay)	
		0	.75	1	.25	2	.25
Study week	Control	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)

]	. <u> </u>		IQI	B-9302.H	Cl (mg/kg/d	ay)	
		0	.75	1	.25	2	.25
Study week	Control	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

WATER INTAKE

Mean values (mL/animal/day)

				IQI	B-9302.H	Cl (mg/kg/d	ay)	
			0	.75	1	.25	2	2.25
Study week	Sex	Control	Mean	% with respect to Control	Mean	% with respect to Control	Mean	% with respect to Control
3	М	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)	М	30.0					32.0	106.7
	F	23.6					24.8	105.1

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

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

HAEMATOLOGY Mean values Week 4 PROTHR. 24.14 22.90 4.188 20.36 18.63 3.926 DCBA 6.102 3.292 TIME 9 9 6 5 *i* s PLATEL. 1121.5 1136.8 1128.3 1087.5 121.87 x10³/µL 135.94 52.15 77.01 N.S. 6 5 5 9 LYMPHO. MONOC. EOSINO. BASOPH. 0.000 0.00 0.000 0.000 0.00 0.0 0.00 ŝ 0.0 9 9 9 5 DIFFERENTIAL LEUKOCYTE COUNT (x10³/µL) 0.105 0.072 0.094 0.14 0.05 0.097 0.08 S.N. 0.08 6 9 5 6 CBDA 0.269 0.399 0.302 0.171 0.26 0.47 0.74 0.30 6 9 9 5 ю́ 2.445 2.813 1.643 1.398 10.78 8.83 N.S. 9.41 9.38 9 6 6 6 0.658 Segmen 0.558 NEUTROPHILS 0.625 1.26 0.461 1.50 1.41 N.S. 1.77 9 9 9 6 0.000 0.000 Rods 0.000 0.000 0.00 0.0 0.0 0.00 N.S. 9 9 9 9 LEUKOCYT. TOTAL x10³/µL 12.80 2.049 11.25 1.615 2.586 3.405 10.44 11.97 N.S. 9 5 6 9 g/100mL MCHC 0.745 0.528 37.31 36.50 0.680 36.82 1.074 36.85 S.S. 9 9 9 9 0.733 21.32 0.935 21.79 21.00 1.121 0.702 21.27 MOH S.S. 9 g 5 6 6 58.44 2.615 57.86 2.768 1.724 57.04 58.32 1.791 MCV N,S, 6 5 9 6 ᆔ HAEMOGL. HAEMATOC. 2.573 2.600 41.50 2.109 1.259 43.23 43.19 43.61 N.S. 9 9 9 5 * g/100mL 16.06 15.47 0.633 15.76 0.455 15.90 0.702 0.841 S.S. 6 9 5 9 ERYTHR. x10⁶/µL 0.456 0.443 0.442 0.271 7.55 S. N 7.58 7.11 9 9 7.41 ç 6 MEAN MEAN MEAN MEAN S.D. s. D. S.D. S.D. c c c c of variance (p<0.05) One-way analysis IQB-9302.HCI IQB-9302.HCI IQB-9302.HCI TREATMENT mg/kg/day CONTROL DOSE 2.25 0.75 1.25 .. 0 ... 0 ... ∢ ഫ

Duncan-Kramer test (p<0.05)

Study no∴ CD-98/6289T Sex: Female

> HAEMATOLOGY Mean values Week 4

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

											VIECE DENTIA		LE COUNT	(x10 ³ /uL)		PLATEL. F	PROTHR.
			сеутия	HAFMOGL	HAEMATOC.	MCV	MCH	MCHC	TOTAL								
	I KEA MEN								I FUKOCYT.	NEUTRO	DPHILS	гүмрно.	MONOC.	EOSINO. B	ASOPH.		TIME
	DOSE		•						~10 ³ /11	100	Seamen					×10 ³ /µL	s
	ma/ka/dav		x10°/µL	g/100mL	%	ų	рg	g/100mL	ALCTRE	enou	Cedital.						1 22
	(app)Au/Au	ME AN	G 78	15.0R	38.67	57.06	22.26	39.00	8.86	00'0	0.82	7.48	0.38	0.18	0.00	1142.4	15.6/
		MEAN	0.70	0000	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
×	CONTROL	S.D.	0.220	007.0	- 00: - 00:	200	- C - F	Ę	10	10	10	10	0	10	10	10	6
	1	د	10	2	2	2	2	2		000	100	0 7	0.03	0.062	00 0	1154.8	15.75
		MEAN	6.77	15.1	38.88	57.49	22.34	38.86	9.56	0.00	0.0	0.47	04.0	4 00.0		10 01	• • •
4		C G	0.406	0 867	2.418	1.518	0.688	0.855	1.811	000.0	0.423	1.644	0.146	0.088	0.000	120.02	-
 00	10B-9302.HCI	0.C	001.0		ç	0	10	10	10	10	10	10	10	10	10	6	6
	0.75	c	01	2	2	2		0000	- C 4 0		1 10	7 88	0.33	0.12	0.00	1213.5	14.94
		MEAN	6.64	14.76	37.80	56.93	22.23	39.95	70.8	00.0	2			001.0		11100	1 17E
		6	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	14.33	0.1.1
 0	10B-9302.HCI	ה. ס	0.400	120.0		ç	0	ç	0	10	10	<u>5</u>	5	10	10	6	9
	1.25	e	<u>6</u>	2	2	2	2			800	çõ	6 78	70.0	0.061	00.0	1162.4	14.99
		MEAN	6.61	14.57	38.36	58.05	22.08	38.09	8.10	0.00	0.33	0.00	1.2				776
ł		6	101.0	0 856	3 315	3.619	0.745	1.550	2.407	0.000	0.915	1.660	0.130	0.069	0.000	00.c/L	c//.D
 0	10B-9302.HCI	Ċ.		0000	ç	ç	0	10	10	10	10	6	10	10	6	<u>5</u>	10
	2.25	٢	2	2	2	2											
				:		2	U Z	u Z	۲ ۲	S N	N.S.N	N.S.	N.S.	S	N.S.	N.S.	N.S.
One-w	ay analysis		N.S.	N.S.	N.Z.	.0.Z	<u>.</u>)								
of varia	ance (p<0.05)																

Duncan-Kramer test (p<0.05)

BDCA

ENTRO DE INVESTIGACIÓN Y	oxicology Department	able no.: 11
		Tabl

BIOCHEMISTRY Mean values Week 4

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

TDCATMENT		GLICOSE	URFA	CREATININE	TOTAL	AST	ALT	HOS	ALKALINE	TOTAL	CALCIUM	INORGANIC	SODIUM F	POTASSIUM	CHLORIDE	TOTAL	ALBUMIN A	ALB./GLOB.
			}		AIL IRUBIN	(GOT)	(GPT)		PHOSPH	CHOLEST.	ц	HOSPHORUS			-	PROTEIN		RATIO
		ma/100ml	ma/100mL	ma/100mL	mg/100mL	n Vn	ΩΓ	ν'n	Ν	mg/100mL	mg/100mL	mg/100mL	mmol/L	mmoVL	mmol/L	g/100mL	g/100mL	
mg/kg/uay			7.80	0.44	60.0	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				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
	i c o	40. 1			10	10	10	10	10	10	10	10	10	10	10	ę	10	10
		0	376	0.43	0 11	1416	27.2	9.14	351.3	43.53	10.25	10.09	144.48	5.29	101.5	6.03	3.65	1.55
	MEAN	11.0	0.17		0.053	23.97	919	1.501	63.90	6.318	0.948	0.946	0.745	0.387	1.84	0.142	0.158	0.181
0.75	ה מ	60-11 7	- t. C		0000	10	10	10	10	10	10	10	10	10	10	10	10	10
2.5			906	240	000	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
	MEAN	0.10		11-00 12-00	20.0 ACA A	15 36	ря с	3 580	83.48	9.504	0.753	0.981	1.219	0.730	2.63	0.445	0.250	0.145
1.14 1.75	S. D	9.33	3.87 10	20.0	10	000	10	10	10	10	10	10	10	10	10	10	10	10
07.1				0.04	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. 108-9302 HCI	MEAL	7.60	0.07 V. V. V.	0 DAR	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	י ה מ	9.39 10	5 0	10	6	0	10	10	10	10	10	10	10	10	10	9	10	10
One-way analysis of variance (p<0.0	2)	N.S.	N.S.	ν. Σ	N.N.	ν. Ζ	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.N.	N.S.	N.S.	N.S.



NTRO DE INVESTIGACIÓN Y SARROLLO APLICADO, S.A.L.	cicology Department be no.: 12
CENT	Toxico Table I

BIOCHEMISTRY Mean values Week 4

Study no∴ CD-98/6289T Sex: Female

TREATMENT		GLUCOSE	UREA	CREATININE	TOTAL	AST	ALT	SDH	ALKALINE	TOTAL	CALCIUM	INORGANIC	SODIUM F	OTASSIUM	CHLORIDE	TOTAL	ALBUMIN	ALB./GLOB.
DOSE					BILIRUBIN	(GOT)	(GPT)		PHOSPH.	CHOLEST.	ų.	HOSPHORUS	(6)			PROTEIN		RATIO
markardav		mg/100mL	mg/100mL	mg/100mL	mg/100mL	ΩΥ	η	Ω	UL	mg/100mL	mg/100mL	mg/100mL	mmol/L	mmoML	mmoML	g/100mL	g/100mL	
×	MFAN	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
A: CONTROL	C V	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
ł	- -	6	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	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
B: 10B-9302.HCI	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
0.75	C	10	10	10	თ	10	10	10	10	10	10	10	10	10	10	10	40	10
	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
C: 108-9302.HCI	S	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
1.25	c	10	10	0	10	10	10	10	10	10	10	10	10	10	10	10	10	9
	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
D: 1QB-9302.HCI	S	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
2.25	c	10	10	10	10	10	10	6	10	10	10	10	6	10	6	6	10	10
One-way analysis of variance (p<0.05	6	N.N.	N. N.	N.S.	ò	ι. Ο	N.S.	N.S.	N.S.	ю	N.S.	N.S.	ဟဲ	N.S.	N.S.	Ś	S.Z	N.S.
Duncan-Kramer tes	**				BACD	ADCB				CDBA			CDBA			CDBA		
(p<0.05)																		



Study no.: CD-98/6289T

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

URINALYSIS Mean values Week 4

			NA CION			Females	
			IVIDICS	•			1
TREATMENT		VOLUME	SPECIFIC	Hq	VOLUME	SPECIFIC	Ľď
DOSE			GRAVITY			GRAVITY	
mg/kg/day		mL			mL		
	MEAN	25.4	1012.4	8.1	15.7	1017.8	7.7
A: CONTROL	S.D.	11.18	3.95	0.88	8.27	7.21	1.16
ł	c	10	10	10	10	10	10
	MEAN	26.6	1011.9	8.6	11.6	1021.9	7.8
B: IQB-9302.HCI	S.D.	8.18	3.60	0.52	5.57	7.19	0.92
0.75	c	10	10	10	10	10	10
	MEAN	20.7	1014.4	8.7	13.1	1019.8	7.5
C: IQB-9302.HCI	S.D.	6.93	4.55	0.48	5.91	8.32	1.35
1.25	c	10	10	10	10	10	10
	MEAN	20.0	1014.7	8.7	10.8	1021.3	7.4
D: 1QB-9302.HCI	S.D.	7.07	6.09	0.67	5.06	7.73	1.43
2.25	c	10	10	10	10	10	10
One-way analysis of variance (p<0.05)		N. N.	N.S.	N.S.	N.N.	N.S.	N.S.



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

MICROSCOPIC EXAMINATION OF SEDIMENT

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

URINALYSIS Group results Week 4

												BLOOD/	EPITH.								:
TREATMENT		YELLOW	PROT	EINS	GLUCO	SE SE	(ETONE:	s UR	OBILINOGEN	BILIRL	NIBI	HAEMOGLOBIN	CELLS	ЕКҮТН.	LEUKO.	BACT	ERIA	CAST	<u>ر</u> م	CRYSTAL	
													no./field	no./field	no./field						
mg/kg/day		COLOUR		1		╉		╀		ļ	T			6	0-5	0	+	0	+	0	+
			0	+	0	+			+	-	+	+	5	-		'					
A: CONTROL	4	ç	V	ű	0	0	10		0	10	0	3 7	10	10	10	0	6	6	0	.	თ
	=	2	r)	2				c c	001	C	30 70	100	100	100	0	100	100 100	0	10	8
1	%	100	4	8	100 1		00	1		3	,						1	1		c	
B: 10B-9302.HCI	2	¢	~	2	10	0	10		0	10	0	3 7	10	10	10	0	6	0		þ	2
	=	2)	1					c	001	c	30 70	100	100	100	0	100	100	•	0	8
¢7.0	*	100 1	8	20	100		00			3	,	2							c	c	
C: 10B-9302.HCI	5	10	~~~~	7	10	0	10		0	10	0	7 3	6	6	10	0	0	0	>	5	2
	:	2			001		00	 	ç	00	c	70 30	001	100	100	0	100	100	0	0	8
C7.I	%	100	8	20	001		3								9	•	ç	ç	c	c	ć
D: 10B-9302.HCI	5	¢	9	4	0	0	10	0	0	6	0	4 6	0	6	0		2	2		5	2
L C	=	2	•					; 	ç	100	C	40 60	100	100	100	0	100	100	0	0	8
CZ.Z	%	100	8	9	ğ						,										

Chi² test (p<0.05)

(1) : Magnesium ammonium phosphate



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

MICROSCOPIC EXAMINATION OF SEDIMENT

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

URINALYSIS Group results Week 4

													LOOD/	EPITH.	-							ŧ
TREATMENT		VELLOW	PROTE	EINS	GLUCO	 SE	(ETONE)	S D	OBILINOG	EN BII	LIRUBIN	HAEI	NIGOLOBIN	CELLS	ERYTH.	LEUKO.	BACTI	ERIA	CAS	TS	CRYST	ALS
malibaliau														no./field	no./field	no./field						
635 A		COLOUR				+			+		+	0	+	0-1	0-1	0-5	0	+	0	+	0	+
A: CONTROL		ç	- ~	+	- e	+ 0		-			0	0	10	10	10	1	0	10	10	0	ю	7
	= 3		> ç				00		0	÷	0	0	100	100	100	100	0	100	100	0	30	70
B: 10B-9302.HCI	<u>ج</u>		n ,	2 ~	10	, , ,	2 0	-	0		0	8	2*	10	10	10	0	10	10	0	5	80
0.75	= ;	2		- - -	2			÷	0		0 00	80	20	100	100	100	0	100	100	0	20	80
	8	100	3	2		- 						ۍ ا	4*	0	10	10	0	10	10	0	4	9
C: 100-3002-11C	c	10	9	4	თ	- 1	2						- Q	001	100	100	0	100	100	0	40	60
CZ.1	*	100	99	4	60	<u>0</u>	00			-		3	P									
D: 10B-9302.HCI	c	10	4	9	10	0	10 (0 0		0 0	S.	5*	10	10	10	•	10	9	0	4	9
2.25	*	100	40	60	100	, 0	00	1	0 00	-	0	20	50	100	100	100	•	<u>1</u> 00	100 1	0	4	80

Chi² test (p<0.05)

 * : Statistically significant difference with respect to the Control group

(1) : Magneslum ammonium phosphate

HAEMATOLOGY Mean values Recovery period

Study no∴ CD-98/6289T Sex: Male

THE ATARCHE		EPVTHR	HAFMOGI	HAEMATOC	MCV	MCH	MCHC	TOTAL		DIFFERENTI	AL LEUKOCY1	re count	(x10 ³ /µL)		PLATEL.	PROTHR.
								LEUKOCYT.	NEUTR	OPHILS	ГҮМРНО.	MONOC.	EOSINO. E	BASOPH.		TIME
DOSE		0,40 ⁶ /,1		5	Ģ	2	а/100ml	х10 ³ /µL	Rods	Segmen.					х10 ³ /µL	S
mg/kg/day		xio/ht	g/100mL	ę		R1	1000-00				00.01		20.0	000	1070 B	19.87
	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	0.0	0.0.0	10.01
			0.750	1 860	1 645	0 564	1.214	1.076	0.000	0.225	1.216	0.406	0.068	0.000	148.11	4.396
A: CONTROL	s.u.	0.130	607.0		2) .	i i	u	ď	ſ	ις.	S	S	5	S	5
:	c	ŝ	5	5	£	٥	n	0	2	,	, ,	,				1
	ME AN	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./4
				0000	010	002.0	0 847	2 151	0000	0.607	1.698	0.372	0.118	0.000	172.81	4.641
B : IQB-9302.HCI	S.D.	0.723	1.159	3.390	C/0.1	0.120	10.0	2.14			ı	ι	U	u	ų	Ľ
2.25	c	S	ß	S	5	5	5	5	£	5	n	0	•	n		,
						1	¢	0	0 7	U Z	S N	с Z	S Z	N.S.	N.S.	N.S.
Student t test		N.S.	N.S.	N.S.	N.S.	N.S.	'n		0.2			<u>.</u>				
(p<0.05)																





TDEATMENT		FRYTHR	HAEMOGL.	HAEMATOC.	MCV	МСН	MCHC	TOTAL		DIFFERENTIA	IL LEUKOCY1	re count	(×10 ³ /µL)		PLATEL.	PROTHR.
								LEUKOCYT.	NEUTR	OPHILS	LYMPHO .	MONOC.	EOSINO. E	BASOPH.	ç	TIME
ma/ka/dav		x10°/µL	a/100mL	*	Ļ	6d	g/100mL	×10 ³ /µL	Rods	Segmen.					x10²/µL	s
(mp/Bu/Bill	MFAN	699	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
		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
	י ר ס	с С. ч	20. u	1 5 1	ιΩ	ъ	5	S	S	S	S	5	5	5	5	5
		202	15.1R	40.1R	57.04	21.56	37.78	7.78	00.0	1.18	6.09	0.40	0.11	00.0	1039.4	15.20
		10.7	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
	י ה ס	- 4 - 4	с С	1 2 2	ъ	ŝ	ŝ	S	ъ	ß	5	5	5	5	5	S
Student t test	=	N. N.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	S.Z	N.S.
(p<0.05)																

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

> HAEMATOLOGY Mean values Recovery period

CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L.

Toxicology Department Table no.: 17



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

BIOCHEMISTRY Mean values Recovery period

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

TREATMENT		GLUCOSE	UREA	CREATININE	TOTAL	AST	ALT	SDH	ALKALINE	TOTAL	CALCIUM	INORGANIC	SODIUM F	OTASSIUM	CHLORIDE	TOTAL	ALBUMIN	ALB./GLOB.
DOSE					BILIRUBIN	(GOT)	(GPT)		PHOSPH	CHOLEST.	u	HOSPHORUS			Ŀ			RATIO
mg/kg/day		mg/100mL	mg/100mL	mg/100mL	mg/100mL	Ч'n	٦'n	η	Nυ	mg/100mL	mg/100mL	mg/100mL	mmol/L	mmoVL	mmoML	g/100mL	g/100mL	
	MEAN	8.66	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
A: CONTROL	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
ł	C	ŝ	5	5	S	4	4	4	5	5	5	5	5	5	5	5	5	5
	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
B: 1QB-9302.HCI	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
2.25	Ę	5	5	5	5	5	9	5	5	5	5	5	5	5	5	5	5	5
Student t test		N.S.	N.S.	N.S.	N.S.	N, S,	N.S.	N.S.	N.S.	Ś	ග	N.S.	N.S.	N.S.	N.S.	N.S.	N. N.	N.S.
(p<0.05)																		



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

> BIOCHEMISTRY Mean values Recovery period

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

			< L		TOTAL	AST	ALT	HOS	ALKALINE	TOTAL	CALCIUM	INORGANIC	SODIUM F	OTASSIUM (CHLORIDE			VLB./GLUD.
TREATMENT		GLUCUSE				- C										NDUCTON		RATIO
					BILIRUBIN	(GOT)	(GPT)		PHOSPH.	CHOLEST.	<u>a</u>	HOSPHORUS)
JOOH					1		011	-NU	Π	mg/100mL	mg/100mL	mg/100mL	mmol/L	mmol/L	mmol/L	g/100mL	g/100mL	
mg/kg/day		mg/100mL	mg/100mL	mg/100mL		10										o T	0	
		001	28.7	050	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	
	MEAN	103.4	70.7	10.0			1				326.0	0711	0.796	0.164	1.41	0.492	0.292	0.050
A: CONTROL	C ()	16.66	6.53	0.069	0.029	15.29	1.87	1.91/	11.79	040.17	0.000	-						ı
	i ò		L	u	u	ŭ	ſ	łс.	5	5	5	S	5	5	5	ռ	5	ç
:	c	D	n			,	,									10		1 24
		06.4	35 7	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	0.90	t 7.1
	MEAN	40. 1	30.0	5	5				Ĩ				1 570	0.431	0.45	0.391	0.324	0.120
B: IQB-9302.HCI	C S	3.91	6.18	0.055	0.019	15.79	2.88	2.131	47.7U	10017	1.424		0				ı	ı
10.0			ı	L	u	ų	ť	ſ	ŝ	5	5	5	5	5	5	5	5	0
CZ-7	٢	5	0	0	0	2	>	,										
Student t test		S Z	N.S.	N.S.	Ś	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N S	N.N.	N.S.	N.S.
(p<0.05)																		

- de

• * 4 h Study no.: CD-98/6289T

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

Recovery period

URINALYSIS Mean values

0.89 1.22 6.6 7.0 Hd S ഹ SPECIFIC GRAVITY Females 1027.2 1020.2 5.40 6.53 Ś ŝ VOLUME 5.50 13.2 2.28 8.8 8 Ē S S 0.55 0.00 8.0 7.6 F ŝ S SPECIFIC GRAVITY 1015.6 1019.2 Males 8.70 4.72 S S VOLUME 8.76 22.3 4.94 20.6 Ц ഹ ഹ MEAN MEAN S.D. s.D. c C IQB-9302.HCI A: CONTROL TREATMENT DOSE mg/kg/day 2.25 ł ä

Student t test

N.S. N.S.

S.S.

N.S.

S.S.

N.S.

e >

(b<0.05)

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

MICROSCOPIC EXAMINATION OF SEDIMENT

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

URINALYSIS Group results Recovery period

	S ⁽¹⁾		+		5	8		ц.	8	
	RYSTAL		0		0	0		0	0	
		┨	+		0	0			0	
	CASTS		0		ŝ	100		c,	100	
	3IA	+	+		5	100		сı	100	
	BACTEF		0		0	0		0	0	
	LEUKO.	no./field	0-5		5	100		ŝ	100	
	ERYTH.	no./fiełd	0		S	100		5	100	
EPITH.	CELLS	no./field	0		5	100		2	100	
/ao	GLOBIN		+		4	80		*0	0	
BLO	HAEMO		0		-	20		2	100	
	NIBIN		+		0	c	,	0	0	,
	BILIR		c	,	5	100	2	5	100	
	INOGEN		+		0	c	>	0	c	,
	UROBIL		-	,	5	001	nn	S	001	2
	NES		-	-	0	c	,	0	c	,
	KETO		6	,	5	227	3	5	001	
	COSE			+	0	¢	-	0	c	-
	GLUG		•	-	<u>ې</u>		₽	ۍ ا	2	3
	TEINS			+	ę		30	ŝ	001	BL
	PRO.		ſ	-	5	!	₽	0		-
	VELLOW		CULUUR		Ş		100	5		100
	- 12				c	: :	%	c	. :	%
	TREATMENT	ma/kn/dav	(a) (b) (b) (b) (b) (b) (b) (b) (b) (b) (b		A: CONTROL		1	B: IQB-9302.HCI	ц С С	2.20

Chi² test (p<0.05)

 \star : Statistically significant difference with respect to the Control group

(1) : Magnesium ammonium phosphate

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

ABSOLUTE ORGAN WEIGHTS Sacrificed after end of treatment Mean values

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

	TREATMENT DOSE	-	BODY WEIGHT	ADRENAL GLANDS	TESTES	THYROID GLANDS	KIDNEYS	BRAIN	HEART	LIVER	SPLEEN P	PROSTATE	LUNGS	THYMUS	PITUIT. GLAND
	mg/kg/day		ຽ	вш	D	вш	D	თ	თ	D	Ð	თ	D	ס	вш
:		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
A	CONTROL	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
:	1	Ę	6	10	10	10	10	10	10	10	10	10	10	0	10
-		MFAN	376.4	61.3	4.76	23.6	2.95	2.07	1.26	16.14	0.85	2.25	1.60	0.53	<u>6</u> .6
ά	10B-9302 HCI	SD	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
ć	0.75	c	10	10	10	10	10	10	10	10	10	10	10	10	10
i i		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
ċ	10B-9302 HCI	SD	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
5	1.25	c	10	10	10	10	10	10	10	0	6	10	10	10	6
		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
ċ	10B-9302 HCI	SD	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
ć	2.25	c	10	10	10	0	10	10	10	6	0	10	9	0	0
One- of va	way analysis riance (p<0.05)		N.S.	N.S.	N.S.	N.S.	S.Z.	N.S.	N.S.	N.S.	S	N. N	N.S.	N.S.	N.S.



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CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. oxicology Department able no.: 22

Recovery period URINALYSIS Group results

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

	÷	sTALS ⁽¹⁾		+	Ş	100	2	100	
		CRYS		0	0	0	0	0	
IN		STS		+	0	0	0	٥	
SEDIM		Š.		0	2	100	S	100	
TON OF		TERIA		+	ų	100	ŝ	100	
AMINAT		BAC		0	0	•	0	0	
OSCOPIC EX		LEUKO.	no./field	0-5	5	100	2	100	
MICRO		ERVTH.	no./field	0	5	100	5	100	
	EPITH.	CELLS	no./field	0	5	100	5	100	
	/qo	GLOBIN		+	0	0	0	0	
	вго	HAEMO		0	ۍ	100	ъ	100	
		UBIN		+	0	0	0	0	
		BILIR		0	5	100	5	100	
		BILINOGEN		+	0	0	0	0	
		UROI		0	с Ч	100	ۍ ا	100	
		ONES		+	0	0	0	0	
		KET		-	2	100	2	100	
		COSE		+	0	0	0	0	_
		GLU			, s	100	ۍ	100	
		TEINS		+	~	40	-	20	
		PRO		6	~ ~	60	4	80	
		VELLOW	COLOUR		2	100	5	100	
					2	: %	2 5	%	2
		TREATMENT	mg/kg/day		A: CONTROL	ł	B: 1QB-9302.HCI	2.25	

:hi² test (p<0.05)

t) : Magnesium ammonium phosphate

4 **b**.

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

ABSOLUTE ORGAN WEIGHTS Sacrificed after end of treatment

Mean values

DESARROLLO APLICADO, S.A.L. CENTRO DE INVESTIGACIÓN Y Toxicology Department Table no.: 24 PITUIT. GLAND 15.0 4.00 10 Bu 18.9 6.69 15.4 6.02 17.0 6.88 10 ŚŻ 9 9 THYMUS 0.55 0.108 0.52 0.110 0.55 0.110 0.57 0.095 N.S. 6 6 9 9 တ LUNGS 1.43 0.240 10 1.38 0.176 1.40 0.124 10 1.44 0.179 10 Ś 9 σ SPLEEN UTERUS 0.56 0.176 0.65 0.136 10 0.61 0.209 10 0.63 0.162 N.S. 9 6 D ACDB 0.79 0.143 0.63 0.115 0.78 0.132 0.80 0.180 10 9 9 9 Ś σ LIVER 1.295 10 10.58 0.600 10 10.14 0.995 10.36 0.877 11.01 ŚŻ 10 6 σ HEART 1.01 0.105 0.93 0.074 0.98 0.098 0.96 0.074 N.S. 9 5 9 9 ŋ BRAIN 1.99 0.096 1.97 0.110 0.114 1.90 0.106 10 1.93 s. Z 6 9 5 D KIDNEYS 2.01 0.128 2.00 0.210 10 2.02 0.133 10 1.99 0.223 10 N.S. 9 σ THYROID GLANDS 22.6 11.26 26.2 14.33 10 ίς Σ 21.3 7.97 10 21.3 6.50 10 g 6 OVARIES 128.5 21.12 157.9 22.95 146.1 35.80 138.7 31.37 10 S.S. B 9 9 9 ADRENAL GLANDS 75.5 11.12 72.0 10.93 10 78.**4** 13.17 76.2 14.41 N.S. B 9 6 9 VEIGHT ворү 256.6 17.68 10 245.3 13.57 246.9 14.79 247.3 16.38 N.S. σ 9 9 9 MEAN S.D. MEAN MEAN S.D. MEAN S.D. S.D. c c c c IQB-9302.HCI IQB-9302.HCI IQB-9302.HCI TREATMENT mg/kg/day CONTROL Duncan-Kramer test of variance (p<0.05) DOSE One-way analysis 0.75 1.25 2.25 ſ

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(p<0.05)

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

RELATIVE ORGAN WEIGHTS Sacrificed after end of treatment Mean values

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

	TREATMENT		BODY WEIGHT	ADRENAL GI ANDS	TESTES	THYROID GLANDS	KIDNEYS	BRAIN	HEART	LIVER	SPLEEN I	PROSTATE	LUNGS	THYMUS	PITUIT. GLAND
	лозе mg/kg/day		G	%(x100)	%	%(x100)	%	%	%	%	%	%	%	%	%(x100)
, A	CONTROL	MEAN S.D.	396.2 40.71	1.49 0.332	1.19 0.156	0.46 0.172	0.83 0.100	0.53 0.060	0.35 0.030	4.37 0.643	0.22 0.049	0.60 0.078	0.43 0.072	0.17 0.041	0.26 0.082
		C	0	10	10	6	10	10	9	9	0	6	10	10	0
		MFAN	376.4	161	1.27	0.62	0.78	0.55	0.34	4.31	0.23	0.60	0.43	0.14	0.27
à	10B-9302 HCI	S D S	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
i	0.75	, c	6	6	10	10	10	10	0	10	0	0	9	6	10
		MFAN	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
ċ	10B-9302.HCI	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
j	1.25	C	10	10	10	10	10	0	5	6	5	10	0	2	2
		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
ö	IQB-9302.HCI	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	0.0/0
	2.25	c	10	10	10	6	10	10	5	01	2	2	2	2	2
One-	way analysis		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.
of vai	riance (p<0.05)														

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

RELATIVE ORGAN WEIGHTS Sacrificed after end of treatment Mean values

CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. Toxicology Department Table no.: 26

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

Duncan-Kramer test (p<0.05)

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

ABSOLUTE ORGAN WEIGHTS Sacrificed after end of recovery period Mean values

CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. Toxicology Department Table no.: 27

TREATMEN'		вору	ADRENAL	TESTES	THYROID	KIDNEYS	BRAIN	HEART	LIVER	SPLEEN 1	PROSTATE	LUNGS	THYMUS	PITUIT. GI AND
DOSE mg/kg/day		WEIGHT g	GLANDS mg	Ø	GLANDS	ວ	Ø	D	თ	D	נס	б	ס	вш
A: CONTROL 	MEAN S.D.	434.2 30.29 5	59.6 4.10 5	4.85 0.413 5	32.0 7.65 5	3.15 0.276 5	2.09 0.043 5	1.41 0.073 5	18.92 2.000 5	0.78 0.068 5	2.56 0.324 5	1.68 0.157 5	0.66 0.118 5	16.0 1.87 5
B: IQB-9302.H 2.25	CI MEAN	463.0 56.77 5	71.0 12.51 5	5.35 0.421 5	32.8 10.23 5	3.50 0.404 5	2.15 0.110 5	1.62 0.136 5	19.26 4.433 5	0.92 0.109 5	2.82 0.516 5	1.98 0.186 5	0.78 0.202 5	16.0 4.36 5
Student t test (p<0.05)		N.S.	N.N.	N.S.	N.S.	N.S.	N.N.	တ်	N.S.	Ś	N.S.	Ś	N.S.	S N



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

Sacrificed after end of recovery period ABSOLUTE ORGAN WEIGHTS

Mean values

DESARROLLO APLICADO, S.A.L. CENTRO DE INVESTIGACIÓN Y Toxicology Department Table no.: 28

GLAND PITUIT. Вш 19.8 4.49 16.4 4.72 5 N.S. S LIVER SPLEEN UTERUS LUNGS THYMUS 0.49 0.070 5 0.50 0.075 5 s. N D 1.33 0.105 5 1.59 0.106 5 ഗ് ວ 0.58 0.110 0.67 0.139 5 N.S. S ວ 0.81 0.174 5 0.65 0.091 5 N.S. σ 10.57 1.166 5 10.76 0.398 5 N.S. σ HEART 0.98 0.079 5 0.99 0.105 5 s. Z D BRAIN 1.97 0.045 5 1.92 0.084 5 N.S. D KIDNEYS 2.06 0.113 5 2.00 0.215 5 s. N σ THYROID GLANDS 23.0 6.96 5 22.2 6.80 5 S.S. ĝ OVARIES 26.65 155.4 24.91 5 144.6 N.S. g ŝ ADRENAL GLANDS 67.6 14.43 В 69.6 7.09 5 N.S. ഗ BODY WEIGHT 14.36 262.0 10.32 270.2 N.S. D S ю MEAN MEAN S.D. S.D. c 1QB-9302.HCI 2.25 TREATMENT DOSE CONTROL mg/kg/day ł Student t test (p<0.05)

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

> CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. Toxicology Department Table no.: 29

RELATIVE ORGAN WEIGHTS Sacrificed after end of recovery period Mean values

	TREATMENT		BODY WEIGHT	ADRENAL GI ANDS	TESTES	THYROID GLANDS	KIDNEYS	BRAIN	HEART	LIVER	SPLEEN P	ROSTATE	LUNGS	THYMUS	PITUIT. GLAND
	mg/kg/day		0	%(x100)	%	%(x100)	%	%	%	%	%	%	%	%	%(x100)
Ä	CONTROL -	MEAN S.D.	434.2 30.29 5	1.38 0.088 5	1.12 0.138 5	0.74 0.155 5	0.73 0.056 5	0.48 0.029 5	0.33 0.018 5	4.35 0.158 5	0.18 0.008 5	0.60 0.097 5	0.39 0.043 5	0.15 0.032 5	0.37 0.049 5
ä	1QB-9302.HCl 2.25	MEAN S.D.	463.0 56.77 5	1.55 0.345 5	1.16 0.073 5	0.70 0.150 5	0.76 0.039 5	0.46 0.044 5	0.35 0.016 5	4.12 0.475 5	0.20 0.008 5	0.61 0.070 5	0.43 0.024 5	0.17 0.025 5	0.34 0.066 5
Studen (p<0.	t t test 05)		N.S.	S.Z.	N.S.	N.S.	N,S.	N.S.	N.S.	N.S.	Ś	N.S.	N.S.	N.S.	N.S.

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

> 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

	TREATMENT DOSE		BODY WEIGHT	ADRENAL GLANDS	OVARIES	THYROID GLAND %(Y100)	KIDNEYS %	BRAIN %	HEART %	LIVER %	SPLEEN %	UTERUS %	KUNGS	THYMUS %	PITUIT. GLAND %(x100)
	mg/kg/day		ß	(001X)%	(2010)0/	(001v)n/	2								
¥:	CONTROL	MEAN S.D.	262.0 10.32 5	2.65 0.206 5	5.95 1.064 5	0.88 0.255 5	0.79 0.047 5	0.75 0.038 5	0.37 0.018 5	4.11 0.210 5	0.25 0.037 5	0.22 0.040 5	0.51 0.038 5	0.19 0.027 5	0.75 0.149 5
ä	IQB-9302.HCI 2.25	MEAN S.D.	270.2 14.36 5	2.50 0.507 5	5.36 0.998 5	0.82 0.245 5	0.74 0.095 5	0.71 0.066 5	0.37 0.051 5	3.91 0.389 5	0.30 0.064 5	0.25 0.048 5	0.59 0.043 5	0.18 0.039 5	0.61 0.180 5
Stude (p<0	nt t test .05)		N.N.	N.S.	N.S.	N.N.	N.S.	N.N.	N.S.	N.S.	N.S.	N.N.	Ś	N.S.	N.S.



CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L.

Toxicology Department

Table no.: 31

FREQUENCY OF MACROSCOPIC OBSERVATIONS BY ORGAN/SEX/GROUP

Animals sacrificed at the end of the 4 weeks of treatment

		CONT	FROI	IQ	B-930)2.HC	l (mg/	kg/day	y)
			ROL	0.7	75	1.2	25	2.2	25
Organs/Macroscopic	Sex	М	F	М	F	М	F	M	F
observations	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						1			
in size									
SPLEEN									
Nodular surface								1	
Whitish nodule of 0.5 cm in							1		
diameter									

Study no.: CD-98/62897

CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. Toxicology Department

Table no.: 32

FREQUENCY OF MACROSCOPIC OBSERVATIONS BY ORGAN/SEX/GROUP

Animals sacrificed at the end of the recovery period

				IQB-93	02.HCl
		CON	TKOL	(2.25 mg	/kg/day)
Organs/Macroscopic	Sex	M	F	М	F
observations	Animals/Group	5	5	5	5
KIDNEYS					
Dilation of renal calices					
- Unilateral					1



CENTRO DE INVESTIGACIÓN Y

DESARROLLO APLICADO, S.A.L.

Toxicology Department

Table no.: 33

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

ORGAN	Treatment group:	1		2	2	3		4	
Microscopic observations	Sex:	M	F	Μ	F	Μ	F	Μ	<u> </u>
······	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			l						1
Microgranuloma			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					ļ				1
LUNGS	Animals exam:	10	10				L	10	10
Intraalveolar histiocytosis, focal		1	1	<u> </u>	L	ļ	L	2	
KIDNEYS	Animals exam:	10	10	L	1	1		10	10
Dilation of renal pelvis		2	L	ļ	1	1	1	ļ	<u> </u>
Interstitial nephritis, focal		ļ	 	ļ	 	ļ	ļ		
Pyelitis, acute, non-specific		<u> </u>	<u> </u>	 			ļ		2
TESTES	Animals exam:	10		<u> </u>	<u> </u>	1	 	10	
Tubular atrophy		\perp	<u> </u>	L	<u> </u>	1	ļ	4	
THYMUS	Animals exam:	10	10		1			10	10
Multifocal congestion				1		L	L	1	
URINARY BLADDER	Animals exam:	10	10		_	1	ļ	10	10
Cystitis, acute, non-specific									1


CENTRO DE INVESTIGACIÓN Y

DESARROLLO APLICADO, S.A.L.

Toxicology Department

Table no.: 34

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	Treatment group:	1		2	ł
Microscopic observations	Sex:	Μ	F	М	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

BODYWEIGHTS (g) Individual results

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

with the

ANI	MAL				Treatm	nent day			arrende -		
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	м	183	250	263	285	303	319	336	355	356	385
3	М	181	239	253	274	291	304	318	327	329	353
4	М	178	241	258	279	298	313	331	351	352	369
5	M	188	257	269	294	317	333	350	363	362	385
6	М	201	289	303	336	358	386	405	443	429	463
7	М	191	261	280	302	322	338	352	365	357	381
8	М	194	262	283	302	323	341	362	385	370	398
9	М	197	271	292	320	344	373	389	411	407	440
10	М	185	246	263	285	297	313	325	345	334	362
11	М	194	257	271	296	313	332	347	362	381	395
12	М	190	252	265	286	296	316	327	344	356	369
13	М	199	262	274	292	304	318	331	345	361	373
14	М	203	269	289	321	338	363	382	406	415	440
15	М	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

BODYWEIGHTS (g) Individual results

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

ANI	MAL				Treatm	ient day					
No.	Sex	-7	1	4	8	11	15	18	22	25	29
16	NA	210	269	286	314	331	350	366	381	386	400
10	111	180	239	258	284	302	321	340	359	360	386
17	111	177	235	257	279	295	309	323	338	341	363
18	1/1	104	200	262	285	296	320	333	353	352	375
19	NI NI	104	240	255	271	285	295	305	318	318	332
20	M	100	200	200	260	270	286	297	311	299	323
21	M	174	224	240	200	209	323	335	345	339	366
22	M	192	204	275	200	338	360	377	404	392	425
23	M	200	2/1	294	200	321	344	356	379	368	402
24	м	195	260	2/5	290	200	208	307	318	311	329
25	M	189	239	257	2/0	200					
		199.6	247 4	265.9	287.7	303.5	320.6	333.9	350.6	346.6	370.1
	MEAN	100.0	15 50	16 28	18 15	21.39	24.65	26.78	30.81	31.13	34.37
	S.D. n	10	10.00	10.20	10	10	10	10	10	10	10
		164	189	196	204	205	211	216	224	218	232
66	۲ ۲	150	194	103	204	210	217	220	229	230	243
67	F	159	175	181	194	199	211	212	219	214	226
68	F	152	100	108	209	222	235	232	242	246	260
69	+	158	109	190	103	205	217	220	228	222	238
70	+	153	1//	100	200	200	218	229	236	227	232
71	F	158	187	190	209	200	223	231	239	235	239
72	F	161	193	203	210	210	236	253	262	254	249
73	F	171	193	206	224	204	230	248	257	248	251
74	F	173	200	208	222	227	200	270	230	219	222
75	F	155	180	190	198	204	215		200		
		160.4	186.7	195 7	206 7	212.8	222.0	228.3	236.6	231.3	239.2
		7.00	7 80	8.60	10.51	11.29	10.77	13.39	13.91	13.98	11.82
	S.U.	7.09	1.02	10	10	10	10	10	10	10	10
	n	10	10	10	10						

BODYWEIGHTS (g) Individual results

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

ANII	MAL				Treatm	nent day					
No.	Sex	-7	1	4	8	11	15	18	22	25	29
26	м	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

BODYWEIGHTS (g) Individual results

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

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ANI	MAL				Treatm	ent 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	М	173	237	266	291	315	343	367	393	392	421
38	М	185	248	271	298	316	336	352	363	372	391
39	М	178	229	249	268	290	308	323	347	346	369
40	М	185	245	255	267	278	290	301	312	308	321
41	М	185	254	271	303	319	338	352	371	360	396
42	М	186	248	265	282	292	311	323	338	319	360
43	Μ	181	248	272	300	317	335	349	369	346	381
44	М	206	283	304	338	360	387	409	437	418	461
45	М	197	272	292	325	347	378	404	420	394	447
46	М	192	257	279	304	324	341	355	376	387	402
47	М	191	255	271	295	306	326	342	349	362	374
48	М	190	252	277	302	324	348	375	389	410	432
49	М	201	264	290	320	337	361	378	403	420	444
50	М	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

ANIM		Ŧ	Recovery po Individual re	eriod sults	Dose:	
	IAL		Study	y day		
No.	Sex	29	32	36	39	43
1	Σ	395	406	428	411	436
12	Σ	369	382	400	377	410
: []	ž	373	388	408	398	413
4	Σ	440	458	472	463	485
15	Σ	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
	E	S	5	5	5	ŝ
61	u	262	256	266	252	264
62	ш	236	249	255	240	255
63	u.	275	277	281	266	277
64	ш	235	235	246	234	250
65	LL.	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
	c	5	5	ъ	5	S

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CENTR(DESARF Toxicolo(Table no	D DE INVES ⁻ RoLLO APLI gy Departmei .: 40	TIGACIÓN Υ CADO, S.A.L. nt	BODYWEIG Recovery pr Individual re	iHTS (g) eriod sults	Study no.: CD-9f Test substance: Dose: 2.25 mg/k	8/6289T IQB-9302.HC g/day
AN	IMAL		Study	y day		
No.	Sex	29	32	36	39	43
46	Σ	402	421	433	427	439
47	Σ	374	396	410	402	427
48	Σ	432	454	474	438	406
49	Σ	444	456	487	477	500
50	Σ	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
	Ę	S	5	5	5	Ω
96	u.	246	243	241	239	246
97	u.	256	269	274	252	274
86	. LL	268	274	287	271	284
66	L	261	251	254	254	271
100	ш	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
	c	5	5	5 2	5	5

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

Individual results HAEMATOLOGY Week 4

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

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

Individual results Week 4 HAEMATOLOGY

ITRO DE INVESTIGACIÓN Y ARROLLO APLICADO, S.A.L. cology Department e no.: 42

										ICCCRENTIA		F COUNT	(x10 ³ /uL)		PLATEL.	PROTHR.
<u>a</u>	ERY	THR.	HAEMOGL.	HAEMATOC.	MCV	MCH	MCHC	IOIAL	1 1			UCIVOR I		RACOPH HGOSA		TIME
								LEUKOCYT.	NEUTR	OPHILS	LYMPHO.				x10 ³ /µL	ഗ
U.	Ax x10	0°/µL	a/100mL	%	Ļ	Бd	g/100mL	x10 ⁻ /µL	Rods	Segmen.				0	1001	7.00
Ί	a M	g	14.8	40.5	57.9	21.2	36.5	9.7	0.0	0.7	8.3	0.4	0.3	0.0		1 2
		0.00	0 W	45.3	59.2	20.8	35.1	11.8	0.0	1.4	9.8	0.6	0.0	0.0	101	22.4
	Σ	0.		0.0 7	58.4	202	35.4	12.8	0.0	1.5	10.5	0.8	0.0	0.0	889	19.7
	α Σ	3.18	10.9	0. 74			26.1	6.0	0.0	1.0	8.1	0.2	0.0	0.0	1269	22.6
	7 M	7.70	15.8	43.8	0.0 0.0	0.02	00 26 7	0.0 Q	00	0.6	7.0	0.2	0.0	0.0	1239	28.0
	8 N	3.07	16.5	44.9		4. 00 4. 00 7. 00	- 00 0 / 0	0. 4 A A		1.8	11.7	0.1	0.1	0.0	1202	30.7
	Z M	7.95	16.6	43.9	20.7 2 F 2	6.U2	0.10 47.4	10.6	0.0	2.0	8.6	0.0	0.0	0.0	940	24.5
	~ V	7.56	15.3	41.2	0.40 0.60	7.07		ο. Ο. α		1.0	7.1	0.2	0.0	0.0	1207	16.2
	9 2	6.79	15.5	40.5			0.00	1 (4) 1 (4)		1.5	7.1	0.0	0.1	0.0	1257	19.3
_	Σ	7.70	16.5	44.4	5/./C	4 4 7	37.75 38.0	11.8	0.0	<u>;</u> ,	10.1	0.6	0.0	0.0	1111	22.9
	2 W	7.22	15.2	40.0	t ,00	21.12	0.00			1 JA	8 83 8	030	0.05	0.00	1121.5	22.90
Z	2	7.58	15.90	43.23	57.04	21.00	30.82	10.44	0.00	0.461	1 643	0 269	0.097	0.000	135.94	4,188
Ö	Ö).456	0.702	2.573	1.791	0.733	1.074	2.049			<u></u>	10	10	10	10	10
		10	10	t	10	10	10	01	2	2	2		2 0		000	43.A
	u	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	809	0.0 4
	, u		15.4	39.6	59.3	23.1	38.9	8.9	0.0	0 [.] 0	7.5	0.4	0.2	0.0	1320	0.0
				38.7	56.4	22.0	39.0	9.6	0.0	0.7	8.5	0.4	0.0	0.0	1052	14.8
~	ш	6.77	14.U	20.6	r 000	5 - 6	38.6	11.3	0,0	1.8	8.8 8	0.5	0.2	0.0	1000	16.7
~	Ĵ.	6.98	15.4	0,00 0,00 0,00			37.0	119	0.0	8.0	10.9	0.1	0.0	0.0	1258	16.6
~		7.05	16.0	42.2	09.9 E		0.10	10.7	0.0	0.6	9.8	0.2	0.0	0.0	1080	15.3
_		7.13	14.9	2.95 2.00		5.07 70 70	30.0	84	0.0	0.6	7.8	0.0	0.0	0.0	1229	14.7
~	٣ س	6.14	14.1	30.2 20.0	0.80	2.03 C	2.00	6.7	0.0	0.3	6.0	0.3	0.1	0.0	1076	17.2
m	Ű.	6.00	13.6	33.8	20.0			a 19		t.	10.6	0.2	0.0	0.0	1271	16.9
4	u.	7.03	15.9	30.9	20:02 1	0.77 7	0.90. 20.6	5. C	0.0	. . .	6.8	0.1	0.1	0.0	1273	15.9
2	LL.	7.17	16.3	41.2	c./c	1.22		0.56		0.85	8 42	0.23	0.06	0.00	1154.8	15.75
AN	-	6.77	15.1	38.88	57.49	22.34	00.00 00.00	0.00 101		20:0	1 644	0.146	0.088	0.000	126.82	111
Ö	J	0.406	0.867	2.418	1.518	0.688	0.855	110.1	0.0			ç	0	10	10	Ċ
_		10	1 0	10	6	9	6	01	2	2	2	2	2			
7																
13																-

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

HAEMATOLOGY Individual results Week 4

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

		i i		UARMATOC	MCV	ЧСН	MCHC	TOTAL		NFFERENTIA	L LEUKOCYT	E COUNT	(x10 ³ /µL)		PLATEL.	PROTHR.
ā	ш	RYTHR.	HAEMOGL	HAEMALOC.					NEUTR	OPHILS	LYMPHO .	MONOC.	EOSINO.	BASOPH.	c	TIME
		10 ⁶ /		2	Ŧ	ç	o/100ml.	x10 ³ /µL	Rods	Segmen.					x10 ³ /µL	S
	Sex	X10 /µL	g/100mL	<u>e</u> ,	- - - -	R to	27.6	101	c c	1.8	9.1	1.0	0.2	0.0	1066	25.4
	Σ	7.48	16.0	42.6	n. /c	4. U				о. С	83	0.5	0.0	0.0	1015	14.1
	Σ	6.55	15.5	40.9	62.4	23.1	0/. 0	t. () (4 *	101	40	, 1	0.0	1381	23.6
	Σ	7.71	15.3	42.5	55.1	19.8	36.0	14.2	0.0	- (1193	20.2
	Σ	714	15.4	41.4	58.0	21.6	37.2	10.3	0.0	0.0	9.7	0.1			0004	
	2	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	1200	7.77
_	5 2	69.9	14.7	38.0	56.8	21.2	37.4	13.2	0.0	1.2	11.7	0.0	0.3	0.0	1016	D. C. L.
_	2 2	0.00 775	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
	≅ :		0.0 4		R1 7	23.1	37.4	17.4	0.0	1.4	14.8	1.2	0.0	0.0	1124	15.8
	Σ	0.01	1.0.1				37.2	15.7	0.0	0.6	14.1	0.6	0.3	0.0	1049	15.9
 _ ,	Σ:	6.93 7 70	15.6	4-1.0 אסג ג	90.0 59 0	222	37.7	13.1	0.0	1.7	10.7	0.5	0.1	0.0	1068	17.4
	Σ	0.70		5 5	50 44	04 70	37 31	12 AN	00 0	1.41	10.78	0.47	0.14	0.00	1136.8	18.63
Ž		7.11	15.47	0C.14	10.00 11.00 11.00	21.12	10.10	0 505- C		0.658	2 445	0.399	0.105	0.000	121.87	3.926
õ		0.442	0.633	2.109	2.615	1.121.1	0./ 1 0		0.00	100	0	10	10	10	10	10
		6	10	10	01	2	0	2	2	2		Ċ	c		1768	14.4
	L	6.96	14.6	36.9	53.0	21.0	39.6	6.4	0.0	0.8	5.4	0.3	0.0		1000	r u r u
	. u	6 75	14.0	36.1	57.8	22.4	38.8	10.0	0.0	0.4	9.2	4.0	0.0	0.0		
	. L		8 0 7	32.2	55.5	22.1	39.8	5.8	0.0	0.2	5.5	0.1	0.1	0.0	G//	1.01
~ `	L I	0.0 0.0		37.7	56.9	216	37.9	5.6	0.0	1.0	4.6	0.1	0.0	0.0	1200	15.5
m	L :	6.62	0.4- 0.4	200	0.00 0 L U	2.14	30.2	7.8	0.0	0.8	6.7	0.2	0.1	0.0	1327	14.8
0	LL.	6.65	10.1	000	0. 10 A A A	24 F	38.1	7.6	0.0	1.0	6.2	0.3	0.1	0.0	1131	13.7
-	U.,	7.34	15.8	0.14	0.00 1 2 2	0 F	37.8	6 8	0.0	0.6	7.3	0.3	0.0	0.0	1163	16.4
~	LL.	6.88	14.9	4. F		20.1	346	61	0.0	0.4	5.4	0.2	0.1	0.0	957	14.3
ო	ш	6.50	0.61	40.4		- c	285	105	00	1.5	8.4	0.4	0.2	0.0	1340	14.7
ব	ш	6.00	13.9	36.1	2.U0 2.00	40.4 7 Л	36.6 26.6	13.0	0.0	3.4	9.1	0.4	0.1	0.0	1203	15.4
ß	ᇿ	7.13	15.3	41.0	0.00	00 00		010		00 U	6.78	0.27	0 [.] 0	0.00	1162.4	14.99
AN		6.61	14.57	38.36	28.U2	on:77	50.00	2.0		0 015	1 660	0 130	0.069	000.0	175.00	9-775
ġ		0.491	0.856	3.315	3.619	0./45	nec I	2.407	0000		, c		ç	10	10	đ
~		5	10	10	₽	5	0	10	2	2	2	2	2			
75.																
•																

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

> HAEMATOLOGY Individual results Week 4

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

THR.	ЧĒ		5.	2.2	0.4	2.7	5.4	3.5	4.1	7.8	3.7	0.7	.36	292	0	3.4	3.9	5.6	5.5	6.4	3.8	3.5	5.1	6.0	6.2	1.94	176	Ģ		
PRO.	Ψ	*	21	Я	54	ĸ	25	15	12	12	15	3	8	Э.		1	¥	1	ĩ	11	ť	¥	Ť	÷	1	14	. -	·	7	
PLATEL.		х10 ³ /µL	1126	1009	1069	1033	1057	987	1083	1234	1090	1187	1087.5	77.01	10	1194	1376	1375	1165	1220	1055	1250	1025	1220	1255	1213.5	114.99	10		
	BASOPH.		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.00	0.000	10	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.00	0.000	10		
(x10 ³ /µL)	EOSINO.		0.1	0.2	0.1	0.0	0.0	0.1	0.1	0.0	0.0	0.1	0.08	0.072	6	0.2	0.0	0.2	0.0	0.0	0.2	0.2	0.0	0.4	0.1	0.12	0.128	10		
E COUNT	MONOC.		0.0	0.3	0.1	0.3	0.5	0.2	0.2	0.1	0.3	0.5	0.26	0.171	6	0.6	0.1	0.1	0.1	0.5	0.8	0.1	0.4	0.5	0.2	0.33	0.253	t		
. LEUKOCYT	гүмрно.		11.4	7.8	10.1	9.6	6.5	9.2	9.7	9.3	10.2	10.3	9.41	1.398	10	6.9	11.9	8.3	5.8	6.7	13.8	6.1	6.5	6.7	6.2	7.88	2.739	10		
FFERENTIAL	OPHILS	Segmen.	0.7	1.3	1.5	14	0 7	4	. 6	1.5	2.6	1.9	1.50	0.558	10	1.9	1.6	4	0.4	0.7	1.5	1.4	0.4	2.1	0.6	1.19	0.647	10		
ā	NEUTRO	Rods	00	00	0.0				0.0	0.0		0.0	00.0	0.000	10	0.0			0.0		00	0.0	0.0	0.0	0.0	0.00	000.0	10		
TOTAI	EUKOCYT.	x10 ³ /µL	12.3	9.9	119	, ,	0:	- F	8.1	10.9	19.1	12.9	11 25	1 615	10	96	2.0		6.5	4.0	16.0	7.7	7.2	2.6	7.0	9.52	3,181	10		
UHUW		o/100ml	36.0	37.0	2.10	38.8	0.00	2.10	20.00 27 A	35.7	36 B	37.5	36.85	0.528	10	28.2		20.00	20.00	507	- 00	38.8	39.4	38.0	39.5	39.06 39	0.558	10	2	
		Č	21.2	2 c 2 a	0. 14 0. 10 0. 10		7.07	19.2	γ. 1. α	ο ο α	0 C	214 24	21 32	0 035	10	24 0	6 FC	1.14	- 5	7.77 0 FC	0.12	21.5	23.3	20 C	23.1	22.23	0,606	10	2	
1004		Į	57 G		0.00 • • • •		0.0 0	0.1.0 2.0	00.0 7 0.0	7 7 7 7		57.1	57 BG	00.10 2768	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	57.7	7.10	0.00	1.00	0.0C	0.00 7 1	0.70 6.77	20.00	4.00 4. 4	- 90	56.93	1 473		2	
	HAEWALOC.	70	× 4	40.0	0.44 0.04	40.9	42.1	44.1	40.3		4/	41.U	10.01	43.01	7.000	2 9	1 0 0 0 0	31.1	00.4 11 10 0	C./E	4.90 0.00	0.00	0.40	0.00		37.80	1 604	-00+	2	
	HAEMUGL.		g/ LUUTIL	0.01 0.01	16.6	2.71	15.4	16.4	16.9	10.1	10.8	10.1 15.1	10.1	10.00	0.041	2	14.1	14./	14.4	14.9	15.4	14 10 10	0.0 7 u t		10.0	14.76		0.022	2	
	ЕКУІНК.	~10 ⁶ /l	×10 /µL	cn./	7.63	¢¢./	7.44	8.52	7.91	7.40 1.40	1.1	7.06	8 L	00.7	0.443		6.43	6.78	6.53	6.70	7.06	/0.9	0.73 0	0.4/	80.7	0.40		C07.U	2	
	=	C	Xex	Σ	Z :	Σ	Σ	Σ	Σ :	Σ	Σ	Σ:	2	7			LL I	LL I	u. I	LL I	LL I	ι	⊥ι	L 1	ι		z			
- 1	g			~		~	~	~		~ .	~ ·	 1	.1	7	n'	_ 1	()		ന	m	0	- (N		α ι	51 م	τı	_ن	~	

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

BIOCHEMISTRY Individual results Week 4

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

ALB./GLOB.	RATIO		1.68	1.68	1.58	1 44	163		1.50	1.36	1.38	1.59	1.48	1.53	0.118	10	1.54	1.50	1.52	1 75		+	1.03	1.50	1.50	1.35	1.41	1.55	0.130	10	
ALBUMIN		g/100mL	3.7	3.7	3.8	36	0.0	0.0 1	3.6	3.8	3.6	3.5	3.4	3.66	0.151	10	4.0	3.9	4 4	r c F T	4 4	0. 4 0. 0	4.3	4.5	4.2	4.6	4.1	4.22	0.230	10	
TOTAL	PROTEIN	g/100mL	5.9	5.9	62			0.0	6.0	6.6	6.2	5.7	5.7	6.06	0.280	10	6.6	6.5	4 2	2 0	0.0	0.3	6.9	7.5	7.0	8.0	7.0	6.97	0.517	10	
CHLORIDE		mmol/L	102	102	102	101	201	106	100	102	66	101	101	101.7	1.83	10	97	109	6	70	101	98	100	98	101	105	102	101.3	3 59	10	
POTASSIUM		mmol/L	5.73	5.28	77.4		4.99	4.83	5.47	5.60	4.78	4.82	5.73	5.20	0.407	10	5 20	0.20 7 7	14.0	0.40	4.62	4.52	5.29	5.68	5.65	4.88	4.69	5.14	0.429	10	2
SODIUM F		mmol/L	143.0	143.9	9 4 4 4	144.0	144.2	145.2	141.5	143.4	144.6	144.0	145.0	143.94	1.095	10	145 0	4.04	1 42.0	142.4	144.9	143.9	147.0	144.3	145.0	145.5	142.6	144.34	1 488	10.4	2
NORGANIC	HORPHORUS	ma/100mL	10.8	10.6	0.0	9.9	11.2	9.5	10.3	9.6	10.1	8.8	9.6	10.04	0.711	10	č	- c 5 c	9.2 9.0	6.6	9.8	8.9	7.9	9.1	10.0	8.8	8.6	0 13	0.10	0.040 10	2
CALCIUM 1	ā	ma/100ml	10.1	4 C	9. G	10.1	10.4	11.0	10.2	11.4	11.8	9.6	10.2	10.44	0.734	10	2	0.0L	10.3	10.5	10.3	10.0	11.4	11.0	12.1	11.2	12.1	10 00	0.00	1./30	2
TOTAL	CHOLEST	ma/100ml	A1 0	0.14	47.8	47.1	60.7	38.9	59.1	34.8	41.4	46.4	53.8	46.70	8618	10.00	2	86.U	61.7	63.1	44.0	61.1	40.5	63.3	51.5	65.0	55.9	2000	17.80	12.6/U	2
AI KAI INF	PHOSPH		01F		GRE	399	297	263	447	281	342	282	295	337.4	62 92	10.20	2	111	258	134	287	313	122	199	152	152	114	t	184.2	75.70	1
SDH				0.11	11.8	10.4	6.6	11.6	5.4	12.1	10.0	12.5	9.7	10.19	2 111		2	8.0	10.5	10.2	9.8	10.7	6.2	11.3	69	0.0	0.1	10.0	9.23	1.816	10
11		(119)	4	77	30	28	30	29	24	32	- cc	1 2	- 28	27 G	0.12 09 C	00.0	2	19	26	27	20	34	22	19	PC PC	r 4 4	85		24.3	6.25	10
ACT	TSA TCC	(109)	۲.	140	160	126	135	116	142	182	137	101 AC1	165		142.3	10.31	2	107	108	143	111	150	122	136	108	001		107	123.5	17.65	10
10101		BILIKUBIN	mg/100mL	0.06	0.07	0.07	0.12	0.09	0.00	0.12	2.00	0.03	0.10	0.00	60.0 2022	0.035	10	0.08	0.08	0.17	0.16	0.12	0.16			0.19	0.10 5.5	0.13	0.14	0.036	10
	CREATININE		mg/100mL	0.37	0.36	0.37	0.41	0.41	0.50	0.54		0.47	0.40 i	0.47	0.44	0.064	10	0.50	0.50	0.50	0.50	0.46	0.40 P.8-0		0.0	70'N	0.57	0.49	0.52	0.043	10
	UREA		mg/100mL	42	25	27	28	2	5 V	5 8	67 G	5 5	26	32	28.7	5.50	10	30	38	33	38	35	2	5 U	cr S	44	45	43	39.0	6.04	10
	GLUCOSE		mg/100mL	68	72	80	62	40	80	90	4	85	101	66	80.0	11.84	6	76	105	74		4 6	6		6/	83	103	85	85.0	13.73	10
	Animal		No. Sex	۲	2 W	¥ ۳	2	5 : r 1	≅ : Ω (z ∞	× ×	8	₩ 6	10 M	MEAN	S.D.	c	51 F	52 F	. Ц С. 4	- LL	 5 :		26 1	57 F	58 F	59 F	60 F	MEAN	S.D.	c

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

> BIOCHEMISTRY Individual results Week 4

CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. Toxicology Department Table no.: 46 ALBUMIN ALB./GLOB. RATIO 0.195 0.181 1.52 55. 33 .50 .48 .34 6 30 1.52 4 . 1.61 6 .68 83 .67 .17 5 10 58 .65 65 .31 54 2 3.65 0.158 3.97 0.343 q/100ml 3.9 4.0 9 4.0 3.6 3.4 3.7 3.8 3.8 3.8 3.5 3.5 3.5 3.5 3.7 9 4.5 4.2 4.4 4.0 3.7 TOTAL PROTEIN 6.03 0.142 6.61 0.407 10 g/100mL 6.8 5.8 6.0 6.0 6.8 7.0 6.0 6.7 6.3 6.0 ₽ 7.3 6.7 6.4 6.1 6.2 5.8 6.1 6.2 6.1 6.1 CALCIUM INORGANIC SODIUM POTASSIUM CHLORIDE 101 101 101 101 101.5 1.84 102.6 1.78 10 mmol/L 102 105 105 102 102 102 8 104 9 00 5.07 0.415 5.29 0.387 5.06 5.59 4.75 5.45 5.76 4.66 5.21 4.85 4.66 4.68 5.89 5.05 4.96 mmol/l 5.42 5.39 4.92 5.05 4.96 5.31 9 5.99 9 143.95 0.883 10 144.48 0.745 143.5 143.4 144.9 143.9 145.4 142.8 143.8 143.1 143.6 143.7 143.5 144.1 144.5 143.8 145.0 145.3 145.1 mmol/L 144.8 144.3 145.8 9 PHOSPHORUS mg/100mL 10.09 0.946 0.669 10 9.19 10.3 9.0 10.1 11.6 10.7 8.9 9.9 9.3 9.5 9.8 8.4 11.4 9,9 9.4 9.4 8.8 9.3 8.1 10.3 9 8.7 mg/100mL 10.25 0.948 10.87 0.891 10 12.6 10.0 12.6 9.8 10.2 11.2 10.2 10.3 10.6 10.8 10.8 9.8 11.3 12.1 10.2 9.8 9.5 9.8 9 9.9 9.7 mg/100mL CHOLEST 6.318 54.98 10.787 43.53 62.9 TOTAL 66.2 51.4 53.4 38.9 48.1 51.7 30.9 70.7 57.7 42.7 62.2 51.6 43.7 38.4 42.8 9 39.7 42.7 43.7 10 45.7 ALKALINE PHOSPH. 166.4 49.96 10 351.3 63.90 140 145 137 156 310 402 354 238 300 369 375 473 321 9 136 134 157 207 295 157 371 Ч 3.079 10 8.5 8.9 8.7 9.7 9.14 1.501 11.8 11.0 11.1 9.01 12.7 11.7 10.2 8.8 8.3 3.0 9.7 SDH 10.1 6.0 8.7 8.1 4.8 9.7 9 ALT (GPT) 27 24 26 30 30 32 30 30 30 30 30 319 22.3 3.27 10 9 h 141.6 23.97 143.9 15.80 10 AST (GOT) 144 138 159 154 131 145 154 148 104 114 169 177 152 113 135 159 165 137 9 141 116 z BILIRUBIN mg/100ml 0.034 0.11 0.053 0.13 0.07 TOTAL 0.06 0.13 0.11 0.06 0.15 0.18 0.12 0.19 0.03 0.09 0.1 0.11 0.09 0.17 0.06 0.08 0.11 0.11 9 ი CREATININE mg/100mL 0.040 10 0.047 0.49 0.49 0.52 0.52 0.52 0.43 0.43 0.48 0.52 0.42 0.38 0.55 0.45 0.44 0.40 0.46 0.43 0.53 0.43 0.39 0.43 0.41 5 mg/100mL UREA 35.1 3.28 10 28 29 30 30 30 30 30 22 28 23 23 23 23 341 35 36 38 38 9 37 40 37 35 34 37 GLUCOSE mg/100mL 77.6 11.05 84.9 6.51 77 76 69 82 82 104 85 73 64 74 9 82 8 75 79 88 87 82 87 98 2 24 M 25 M MEAN Sex LL. MEAN Animal LL. Σ Σ Σ Σ Σ Σ Σ LL. LL. LL. LL. ц. Ŀ S.D. S.D. 73 75 69 2 72 74 99 68 71 Ś 16 17 18 19 20 3 22 23 67

Parameter not determined

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

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

ALB./GLOB.	RATIO		1.48	1.56	1 66	DC.1	1.68	1.26	1.30	1.32	1.48	1.27	1.48	1.44	0 145	2 - F		0.1.	1.96	1.76	1.86	1.39	1.58	1.67	4 63	20.1	1.38	1.32	1.61	0.213	10	
ALBUMIN		g/100mL	3.7	9.6		0. 1	3.7	3.9	3.9	3.3	3.7	3.3	3.4	3.67	0.250	0.200	2	3.9	4.5	4.4	4,1	3.9	ন ব	40	, c	0 0	3.6	3.7	4.00	0.287	10	
TOTAL	PROTEIN	g/100mL	6.2	R 4	r ·	6.4	5.9	7.0	6.9	5.8	6.2	5,9	5.7	6.24	0.445		2	6.2	6.8	6.9	6.3	67	67	49	i d	6.3	6.2	6.5	6.50	0.258	10	
CHLORIDE		mmol/L	96	00	5	103	103	102	102	104	105	102	100	101 Ê	2.52	20.7 7	n	100	66	100	103	103	00 80	, c,	401 701	103	100	103	101.1	1.91	10	
POTASSIUM		mmol/L	5.66	0.00 1 1 1	9. I /	5.11	5.17	5.05	7.41	5.68	5 96	563	4 91	5.58	0022 0	U. / 3U	01	4.83	4.94	5.33	465	00 ¥	0.40 4	0.11	00. †	4.88	5.28	4.64	5.04	0.464	10	
SODIUM		mmol/L	4 AF A		146./	144.5	144.3	143.2	147.0	144.6	1446	144.4	1436	20 4 4 4	144.00	1.219	9	141.4	143.0	141.8	147.6	1 11 1			143.0	142.3	141.7	143.7	142.67	1.126	10	
NORGANIC	HOSPHORUS	mo/100ml		- 7	11.8	11.4	11.8	9.6	10.7	11 2			0.0 0	9.2	10.00	0.981	6	9.8	9.1	88) (- c 5 c	5. G	ۍ ۱۵.3 ۲	8.U	7.8	8.1	8.2	8.91	0.882	0	2
		ma/100ml		0.0	9.7	10.2	<u>6</u> ,9	9.9	1 1 1		0.0- 7	D. C	0.1	10.1	10.35	0.753	10	9.9	10.7	10.6) u) (0.01	10.3	11.4	10.9	11.3	11.0	11.6	10.82	0.527	10	2
TOTAL		0.10cc01.		60.1	50.8	46.6	34.3	5.02		00.00 8 C ¥	0.70	0.04	40.4	39.4	49.00	9.504	10	40.8	50 B		0.00	47.0	47.6	47.8	43.6	44.6	39.5	42.2	46.29	5.671		2
			OLL.	451	299	334	444	390		393 167	407	212	399	353	360.7	83.48	10	264	103	001		175	176	175	212	152	157	156	185.0	0.00-	× 100	2
	NUN NUN	-	0,F	7.4	8.7	7.2	1	t C V C	10.9	- C	0.7	4.8	9.3	13.2	8.26	3,580	10	6 6	, u		10.9	11.6	10.4	2.3	11.5	10.5	10.0	87	0.26	9.90 704	z./04	٦U
	ALT	(LHD)	N۲	27	30	00	0 0	n S	67	5 2	24	26	19	23	25.3	3.89	10	10	<u>-</u>	7	77	21	23	20	20	20	33	26 26	27	4 . t	71.7	10
	AST	(GOI)	U/L	119	125	118	0.1	07.1	124	162	148	146	140	118	132.6	15.36	10	133	200	131	142	120	143	146	153	144	157	123	0.001	139.2	12.18	10
	TOTAL	BILIRUBIN	mg/100mL	0.10	0.08		0.00	0.12	0.06	0.07	0.07	0.14	0.09	0.12	0.09	0.026	0	C 7 0	0.12	0.12	0,10	0.18	0.07	0.28	0.18	0 13	21.0		0.10	0.15	0.058	9
	CREATININE		mg/100mL	0.46	0.40	91-0 14-0	0.40	0.45	0.37	0.64	0.50	0.53	0.47	0.40	0.47	0 077	10	5	0.47	0.39	0.41	0.39	0.45	0.60	0.53	0.54		. 4.	0.00	0.48	0.073	10
	UREA		mg/100mL	36	Ūč	3	31	32	25	30	30	36	32	24	30.6	3 97	10	2	38	31	38	28	40	37	35		er e	74	32	33.9	5.07	10
	GLUCOSE		mg/100mL	74		00	91	6 3	66	78	81	84	91	83	810	0 33		2	94	91	94	103	78	68	007	201	6/	14	89	89.3	9.80	07
	Animal		No. Sex	об М		M /7	28 M	29 M	30 M	31 M	32 M	33 M	34 M	35 M	MEAN		י ב ס	=	76 F	77 F	78 F	79 F	80 F	81 Г	. L	97 1	83 +	84 F	85 F	MEAN	S.D.	c





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

BIOCHEMISTRY Individual results Week 4

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

VLB./GLOB.	RATIO		1.50	1.52	1.54	1.38	1.76	1.50	1.35	1.38	1.46	1.52	1 49		0.117		1.76	1.76	2.00	1.65	1.86	1.38	1.17	1.44	1.19	1 31	1 22 1	00°1	0.293	01
ALBUMIN 4		g/100mL	3.6	3.8	4.0	3.6	3.7	3.3	3.5	3.6	3.5	35	3.61	10.0	0.191	10	4.4	4.4	4.2	3.8	4.1	4.0	3.5	3.9	3.7	4	100	3.94	0.347	10
TOTAL	PROTEIN	g/100mL	6.0	6.3	6.6	6.2	5.8	5.5	6.1	6.2	5.9	5.8	e DA	10 .0	0.310	10	6.9	6.9	6.3	6.1	6.3	6.9	6.5	6.6	A A	0.0 9	0.0	6.53	0.343	₽
CHLORIDE		mmol/L	105	101	66	103	104	104	103	101	101	102	701	C.201	1.83	10	101	103	101	107	104	102	105	106	103	201	101	103.3	2.16	0
POTASSIUM		mmoVL	5.76	6.58	5.18	5.11	5.17	5.46	5.01	6.63	5.47	50 S	10.0	9.04	0.609	10	4.80	5.58	4.70	5.18	5.11	5.53	4.99	4 83	4 7 8		4.85	5.04	0.312	1 0
SODIUM		mmol/L	144.9	145.3	144.4	147 9	143.0	143.2	144.8	145.0	0.044	1.44	144.4	144.30	1.003	10	141.7	144.5	142.1	144.4	143.3	144.2	144.0	145.2		144.2	143.8	143.74	1.090	₽
INORGANIC	HOSPHORUS	ma/100mL	11.7	12.8	10.3	2.2 7	10 F	10.4		0.0	ה רי ה כ	9.7	C.UT	10.39	1.145	10	8.4	9.6	9.2	8.2	- -	- 6	0.0 0	0.0		3.2	8.1	8.49	0.801	10
CALCIUM	Ē	ma/100mL	99	96	10.0	0.01	t c	0.0	9.9	10.1	10.3	4.71	10.4	10.13	0.874	10	10.5	10.7	10.1	9.7	101		10.5		0.0	10.3	10.5	10.44	0.409	10
TOTAL	CHOLEST.	ma/100ml	375	0.10	46.0	40.4	0.90	4.10	40.0 3 2 6	32.3	5.90	40.6	53.1	44.87	7.800	10	38.0	60.9	64.2	76.4	t.o. t.	4. C	46.0		40.1	46.9	45.5	49.07	7.965	10
AI KAI INF	PHOSPH.	MI	100	60F		007	717	505	2007	440	253	297	297	338.6	78.52	10	66	150	104	215	012	210	107	190	717	111	163	166.3	47.89	10
HUS		111	10		n (13.U	P. /	8.D	0./	12.1	1.6	8.9	8.1	7.99	3.337	10	77	~ ~	7 8	t •	4. 0	0.11	10.3	4.0 4.0	0.0	10.1	8.1	8.87	1.389	10
Υ			0,1	8	40	29	25	23	23	25	24	25	23	25.7	3.43	10	66	, ,	2 7	6 C	77	50	16	70	16	19	17	23.5	15.04	10
ACT		(100)		4LL	141	130	11	130	115	136	144	138	120	127.9	12.09	0	134	10		/11	133	113	144	133	147	114	106	126.9	13.74	10
TOTAL		BILIRUBIN	mg/100mL	0.09	0.07	0.16	0.14	0.11	0.13	0.14	0.17	0.10	0.17	0.13	0.035	10	0000	07.0	0.23	0.10	0.13	0.12	0.17	0.16	0.18	0.15	0.18	0.17	0.033	10
	KEALININE		mg/100mL	0.40	0.45	0.41	0.36	0.33	0.50	0.48	0.56	0.47	0.45	0.44	0.068	10	00.0	0.39	0.45	0.44	0.47	0.40	0.54	0.46	0.55	0.51	0.46	0.47	0.053	10
	UREA		mg/100mL	28	32	30	27	26	26	33	30	31	26	28.9	2.64	5	2	45	33	29	29	33	34	30	33	41	40	33.6	4.10	1 1 1
	GLUCOSE		mg/100mL	73	84	88	81	92	108	87	94	96	68	80 7	1.00	80.8 CF	2	80	78	92	103	101	71	101	94	70	80	87 D	03.00	10
	Animal		No. Sex	36 M	37 M	38 M	39 M	40 M	41 M	42 M	43 M	44 M	45 M	MEAN		o. r.	=	86 F	87 F	88 F	89 F	90 F	91 F	92 F	93 F	94 F	. ц С			ה ה



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 $23G (0.6 \times 25 \text{ mm})$ 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.

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

URINALYSIS Individual results Week 4

ENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. oxicology Department able no.: 49

* : Magnesium ammonium phosphate

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

> Individual results URINALYSIS Week 4

ESARROLLO APLICADO, S.A.L.

oxicology Department able no∷ 50

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ENTRO DE INVESTIGACIÓN Y

CRYSTALS' + + + ‡ ‡ ++++ +++++ ++++ ‡ ‡ \$ ‡ +++++ ‡ ‡ ‡ +++++ ‡ 0 + 0 ‡ + MICROSCOPIC EXAMINATION OF SEDIMENT CASTS 5 . BACTERIA +++++ + + + ŧ ++++ ‡ + + + + ÷ +++++ ‡ ‡ ‡ ‡ +++++ ‡ ‡ ŧ ‡ ‡ LEUKO. no./field 2 Ϋ́ 6000000 0 0 0 0 0000 no./field ERYTH. 000000000 0 no./field CELL EPIT. 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 PROTEINS GLUCOSE KETONES UROBILINOGEN BILIRUBIN BLOOD/ HAEM. 5 ‡ + + + + 0 0 0 0 0 + 000 0 00 + + +0 ť ş 0 5 0 ÷ + + + + 0 0 0 0 0 0 00 ο + + + 0 Ο + Ha 0.92 0.52 7.8 8.6 9 9 ഗയ ω თ თ ω თ Ø თთთდთ თ თ თ 7 \sim ωω SPECIFIC GRAVITY 1011.9 021.9 1026 1006 1012 1014 1025 1029 1016 1011 1014 1015 1008 1011 1012 1009 3.60 1035 1017 1017 1024 1020 7.19 1017 9 6 COLOUR VOLUME 17 18 25 25 26 26 25 26.6 8.18 11.6 9.5 6.5 5.57 10 7 4 9 5 14 13 13 19 α ц ш Yellow Animal Sex * * * * * * * * * * * և և և և և MEAN டட LL u. MEAN S.D. S.D.

* : Magnesium ammonium phosphate 8 1

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rro DE INVESTIGACIÓN RROLLO APLICADO, S. ology Department	: no.: 51

URINALYSIS Individual results Week 4

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

												MICROS	COPIC EX	AMINATION C	OF SEDIME	۲,
Anim		R VOLUME	SPECIFIC	E	PROTEINS	GLUCOSE 1	KETONES	UROBILINOGEN	BILIRUBIN	BLOOD/	EPIT.	ERYTH.	LEUKO.	BACTERIA	CASTS	CRYSTALS*
			GRAVITY							HAEM.	CELL	:	ų	Č	į	ŤĊ
<u>o</u>	Sex	шĻ			+/0	+/0	+/0	+/0	;	+0	no./field	no./tield	no./tield	+/0	+ 5	+50
l e	M Yellow	16	1018	თ	0	0	0	0	0	+	0	0	0	+ + +	0	+ + +
22	M Yellow	17	1014	თ	0	0	0	0	0	0	0	0	9	‡	0	‡
iõ	M Yellow	21	1015	თ	0	0	0	0	0	0	0	0	9 -	+ + +	0	+ + +
a g	M Yellow	; 2	1022	თ	+	0	0	o	0	0	0	0	0	‡	0	‡
36	M Yellow	24	1010	Ø	0	0	0	0	0	0	0	0	9 1	‡	0	+
3 6	M Yellow	33	1006	Ø	0	0	0	0	0	0	0	0	0	‡	0	+
5 %	M Vellow	5	1018	ω	+	0	0	0	0	+	0	0	0	+ + +	0	+ + +
3 6	M Yallow	: F	1015	თ	0	0	0	0	0	0	0	0	0-1	* * *	0	‡
3 4	M Yellow	3	1015	თ	0	0	0	0	0	0	0	0	0	‡	0	+ + +
35	M Yellow	ы . 	1011	თ	0	0	0	0	0	+	0	0	0	*	0	+ + +
MEA	Z	20.7	1014.4	8.7												
SD		6.93	4.55	0.48												
C		10	6	10												,
76	F Yellow	17	1020	9	+	0	0	0	0	0	0	0	0	+	0	0
2. [2	F Yellow	, 15	1013	თ	0	0	0	0	0	+	0	0	0	‡	0 (+ :
78	F Yellow	, 22	1010	თ	0	0	0	0	0	0	0	0	0	‡	0	+ + +
62	F Yellow	12	1012	თ	0	0	0	ο	0	0	0	0	0	‡	0	+ + +
2 08	F Yellow	/ 18	1016	თ	0	0	0	0	0	0	0	0	0	* * *	0 0	‡ (
81	F Yellow	v 7.5	1028	9	+	÷	0	0	0	‡	0	0	- -	‡	5 0	5 0
82	F Yellow	v 7	1029	7	0	0	0	0	0	‡	0-1	0		‡ ·	- C	5 0
8	F Yellow	۷ ۲	1020	7	+	0	0	0	0	0	0	0) (+	5 0	· c
84	F Yellow	د 6	1035	ဖ	+	0	0	0	0	0	0	0	5 (+ 1	-	+ -
85	F Yellov	د 19	1015	7	0	0	0	0	0	ŧ	0	0	э	ŧ	5	÷
ME	N	13.1	1019.8	7.5												-
S.E	Ċ	5.91	8.32	1.35												
c		10	10	10												
	: Magnesiur	n ammonium	phosphate		í											<u>.</u>
82																

Individual results URINALYSIS Week 4

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

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RO DE INVE	RROLLO AP	ology Departn	no .: 52
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) i))			
9	Wi I IO	SPECIFIC	H	PROTEINS	GLUCOSE	KETONES U	ROBILINOGEN	BILIRUBIN	BLOOD/	EPIT.	ERYTH.	LEUKO.	BACTERIA	CASTS	CRYSTALS*
Ś			L						HAEM.	CELL					
	Ē			+/0	+/0	+/0	+/0	+/0	+/0	no./field	no./field	no./field	÷0	+/0	+/0
Ž	10	1010	æ	0	0	0	0	0	+	0	0	0	‡	0	‡
Ň	32	1010	თ	0	0	0	0	0	0	0	0	0	‡	0	+ + +
	6	1026	თ	+	0	0	0	0	÷	0	0	0	+ + +	0	+ + +
	י ר ר	1011	ი თ.	0	0	0	0	0	0	0	0	0	‡	0	+ + +
	24	1009	ι σ .	0	0	0	0	0	0	0	0	0	*	0	+ + +
	<u>1</u>	1014	- ~	0	0	0	0	0	+	0	0	0	‡	0	+
	<u>5</u>	1022	. თ	, +	0	0	0	0	+	0-1	0	0	* * *	0	+ + +
	5 10 10	1021	თ	÷	0	0	0	0	0	0	0	0	+ + +	0	+ + +
; ≩	5 6	1014	ത	+	0	0	0	0	+	0	0	0	‡	0	+ + +
s A	ي ۲	1010	თ	0	0	0	0	0	+	0	0	0	‡ +	0	‡
	20.0	1014.7	8.7												
	70.7	6.09	0.67												
	6	6	10											ſ	
ß	18	1014	œ	0	0	0	0	0	0	0	0	0 (‡	5 0	+ + +
ş	4	1030	ഹ	+	0	0	0	0	+	0	0	0	+	5 0	
ð 8	7	1021	æ	0	0	0	0	0	0	0	0	0	+ + +	5 0	+ +
Ň	16	1018	თ	0	0	0	0	0	0	0	0	0	+ + +	0	+ + +
N N	თ	1020	თ	0	0	0	0	0	0	0	0	0	‡	0 0	‡ (
ð	1 4	1013	9	+	0	0	0	0	+	0	0		‡ ·	5 0	. .
§	4.5	1038	9	+	0	0	0	0	+	0	0	0 (+	. .	5 0
Ř	95 9	1024	2	+	0	0	0	0	0	0	0	D	+++	כ	5
i M	16.5	1015	2	+	0	0	0	0	+	0	0	1.3	‡	0	*
ð	თ	1020	თ	+	0	0	0	0	+	0	0	3-2 3	‡	-	+
	10.8	1021.3	7.4												-
	5.06	7.73	1.43												4
	10	10	10												

* : Magnesium ammonium phosphate

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

HAEMATOLOGY Individual results Recovery period

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

EL. PROTHR.	TIME	/µL s	38 21.2	111	- 11.	c./1 00	20.4	0 25.9	0.8 19.82	.11 4.396	ß	157		J5 16.2	57 15.9	45 13.3	20 15.2	3.4 15.26	.95 1.155	L
PLAT		x10 ³ ,	110	110		100	120	85	107(148.	S	ð	5	110	115	124	132	115	144	U
	BASOPH.		0.0	Ċ	0.U	0.0	0.0	0.0	00.00	000.0	ß	c	0.0	0.0	0.0	0.0	0.0	0.0	0.000	L
(x10 ₃ /µL)	EOSINO.		00		0.1	<u>0</u>	0.0	0.1	0.07	0.068	പ	Ċ	5	0.0	0.1	0.0	0.1	0.05	0.046	ŧ
TE COUNT	MONOC.		с т		0.1	0.3	0.4	1.1	0.41	0.406	S	ç	0.3	0.3	0.2	0.5	0.5	0.35	0.139	ι
LEUKOCY	LYMPHO .		9 A A F	5	11.4	9.3	11.2	9.6	10.02	1.216	ъ	C L	D.G	7.9	7.1	8.0	6.1	6:99	0.987	ı
FFERENTIAL	OPHILS	Segmen.	10	2	1.6	1.6	1.3	1.5	1.57	0.225	ц.	ļ	0.8	1.2	2.3	0.1	с. С	1.13	0.819	
ā	NEUTR	Rods	c	2	0.0	0.0	0.0	0.0	00.0	0000	ι C		0.0	0.0	0.0	0.0	0.0	00.0		
TOTAL	LEUKOCYT	x10 ³ /µL	10.6	0.0	13.2	11.4	12.9	12.3	12.08	1 076	ָ 	,	7.0	9.4	2.6	86	5.2	8.52	1 103	00
MCHC		o/100ml	1	52.4	34.5	35.1	35.2	35.3	34 50	1 214	i u	,	36.8	37.7	37.5	37.4	38.7	37.67	1090	200
HOM		č	2	19.2	19.4	20.0	20.6	195	1974	0 FEA	r Su	, ,	21.0	21.8	214	100	24.0	24 18		101.0
MCV		.	- - - -	2.60	56.4	56.9	58.5	57 57 1	57 22	47.10 A 6 45	2 - -		57.1	57 Q	57 1 1			20.02		
		6	e i	49.4	46.1	44.7	46.6	45.0	AE 3E		-003 1	n	40.5	7 04	1 0 C	- 00. 9 A A	0.00	0.80	03.40 0 000 0	7007
			g/ I UUTITE	16.0	15.9	15.7	 	- u	10.0	0.00	807.0	ß	14.9)		+ (+ (0.0	10.4	14.82	
	באדוחא.	~10 ⁶ /!	X10 /µL	8.34	8.18	7 RG	30.4	02.7	0.0	0.10	0.130	Դ	209	200.7	6. C	0.73	0.40	07. /	0.99	0.3/5
	-	c	Xex	Σ	Σ	2	2	2 2	Σ	-			ш	. l	L 1	L	LI	L .	7	
	Animai		9 N	1	10	i (2	t L		MEAN	S.D.	c	ĩ	5 8	8 8	3	8	8	MEAN	S.D.



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

HAEMATOLOGY Individual results Recovery period

CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. Toxicology Department Table no.: 54

PROTHR.	TIME	S	23.6	10.0	10.01	24.0	14.8	15.3	18.74	4.641	S	15.3		14.3	15.9	16.3	14.2	15.20	0 038	0.500	۵
PLATEL.		x10°/µL	1100		4071	1057	776	1029	1043.2	172.81	ъ	1230		9/4	898	1014	1081	1039.4	175 47	14.07	5
	BASOPH.		00		0.0	0.0	0.0	0.0	0.00	0.000	ъ	0 C	o d o d	0.0	0.0	0.0	0.0	0.00		0,000	2
(x10 ³ /µL)	EOSINO.		5	- (0.0	0.2	0.2	0.3	0.17	0.118	ഹ	с т	- (; (0.0	0.0	0.4	0.1	0.11	0110	U.148	5
TE COUNT	MONOC.		ч С	<u>,</u>	0.5	0.2	0.3	1.2	0.54	0.372	ъ	۳ ر	5	0.6	0.4	0.4	0.3	040		0.130	5
LEUKOCYI	гүмрно.		77		8.1	11.1	7.9	10.9	9.12	1.698	S	e o	0	7.2	5.9	6.1	4.4	60.9		1.089	5
FFERENTIAL	OPHILS	Segmen.		D	1.2	0.7	1.7	2.4	1.51	0.607	S	۲ C		4.1	0.8	2.2	6.0	1 18	2	0.609	ъ С
ā	NEUTRO	Rods		0.0	0.0	0.0	0.0	0.0	0.00	0.000	ŝ	0	0.0	0.0	0.0	0.0	0.0		2.2	0.000	ъ С
TOTAL	FUKOCYT	x10°/uL		9.N	9.7	12.3	10.1	14.7	11.34	2 151	i L		α.U	9.2	7.0	0.6	2.2	7 70	01.1	1.457	ъ
MCHC	2	100ml		36.9	37.4	35.6	37.7	36.3	36 78	0.847	, u	, ,	38.0	37.2	39.0	37.9	36.8 8.75	07.70	01.10	0.844	ß
нОМ		2	R	19.7	20.7	20.7	217	20.4	20.64	0.720	2 u	,	21.1	21.2	9.00	21.3	1 6 1 6		0C.12	0.754	ъ
MCV		¥	-	53.5	55.4	58.3	575	56.1	56 16	1 873	ο δ _. α	>	55.4	56.8	58.8	56.0 56.0			57.U4	1.367	ß
		6	۶	42.5	41.4	47.2	36.1	43.2	10.08	2 006 2 006	0.93 0.73	2	40.0	40.3	41 B	0.14 C 76	1 1 1	o. 1.	40.18	1.842	ىر ا
	HAENUGL.		g/ I UUT	15.7	15.5	16.8	- 0.0 - 73 E	0, rt 0, rt	15.46		рсі. Н	0	15.2	15.0	n (2 - 7) ,	- c + u	0.01	15.18	0 785	
	באין וחא.	1.10012	X10 /µL	7.95	7 47	8 10		07.0	1.10	00.7	0./23 7	n	7.22	7 00	5.5		0.07	11.1	7.04	0 241	
		¢	xex	Σ	Σ	2	2 2	2 2	Ξ				ц.	u	L L	L L	ᇿᇉ	ъ			
	Animal	:	ÖN.	46	47	Ē	ç ç	24 u		MEAN	S. D.	-	ട്ര	07	in C	8	55	3	MEAN		



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

BIOCHEMISTRY Individual results Recovery period

CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. Toxicology Department Table no.: 55

ALB./GLOB.	RATIO		1 28		1.41	1.09	1.32	1.13	104	47.1 0 1 2 0	0.133	5	1 38	0.0	1.39	1.30	1.31	1 28		1.33	0.050	2	
ALBUMIN		a/100mL	27	2.5	3.8	3.5	3.7	36	99.0	0.00	0.114	5	4.4	r i	3.9	4.3	4.2	37		4.10	0.292	ŝ	
TOTAL	PROTEIN	a/100mL		0.0	6.5	6.7	6.5	89	200	20.0	0.130	5	7 6	2	6.7	7.6	7.4	5	2	7.18	0.492	¢,	,
CHLORIDE		mmol/	101	104	103	104	102	103	200	103.2	0.84	5	100	501	103	105	103	2 T	5	103.0	1.41	v	,
POTASSIUM		mmol/l		cn.c	4.85	4.85	я 15 15		40.0	5.05	0.209	5		4.14	4.40	4.38	4.55	1 64	4.01	4.43	0.164	ų	>
SODIUM F		1/100000		144.8	144.8	146.1	145.8	0.041	40.0	145.56	0.716	5		140.1	145.7	146.1	145.4		144.0	145.26	0.796	L.	
NORGANIC	HORDRUS		IIIG/ I UULIIL	9.5	9.2	8.4		n 0 0 0	9.Z	9.04	0.416	ŝ		6.4	8.0	6.6	4	5 1	c./	7.00	0711		•
CALCIUM 1	đ	,	TIMON L/BW	11.6	11.4	11 2	4 1		11.7	11.52	0.217	ŝ	,	11.0	10.7	10.8	, c , t		10.4	10.84	0.336		0
TOTAI	CHOLEST		mg/100mL	45.9	39.0	15.5		53.8	47.0	46.24	5.263	¢.	, ,	99.5	58.9	AR 7		40.1	58.5	62.34	21 5AR	oro. 14	2
ALKALINE			٨٢	356	390	090	607	229	322	313.2	64.91	Ľ	,	75	226	178		5	112	122.4	C7 77		2
спи	500		N۲	33.6*	4.7	4 C	0.0	11.6	10.5	8.73	3.261		Ŧ	8.5	8.8	r u	t .	9.6	11.7	9.00	FFC 7		2
117	AL .	(149)	U/L	107*	56	3	32	21	26	28.0	5 60	•	Ŧ	18	24			17	18	18.0		1.87	S
±04	ASI 1000	(109)	UL	243*	1 1 1		146	105	135	139.3	27 35		4	95	102	071	118	107	135	115.6	0.01	15.29	5
	IUIAL	BILIRUBIN	mg/100mL	0.16	0-10	0.20	0.15	0.14	0.14	0.16	0.025		5	0.21	5	17.0	0.16	0.21	0.24	2 2	1.0	0.029	s
	CREATININE		mg/100mL	0.47	F o	U.48	0.50	0.47	0.43	0.47	3000	0.ULO	2	0.50		0.00	0.62	0.48	0.44	0.60	70.0	0.069	5
	UREA		mg/100mL	25	3	25	30	28	26	26 B		11.7	2	90	8	c,	42	47	37	0.00	20.2	6.53	5
	GLUCOSE		ma/100mL		60	117	103	96	100	8 00	0.00	12.28	ъ	106	2	81	126	108	95	0.001	103.2	16.66	5
	Animal		No. Sex		W	12 M	13 M	14 M	15 M	MEAN		S.D.	Ē	5		62 F	63 F	64 F	85 T	-	MEAN	S.D.	c

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



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

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BIOCHEMISTRY Individual results Recovery period

CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. Toxicology Department Table no.: 56

ALB./GLOB. RATIO 1.10 1.19 1.19 1.19 1.21 1.09 5 1.18 1.19 5 1.10 1.124 0.120 5 5	
ALBUMIN 9/100mL 3.3 3.5 3.5 3.5 3.5 4 3.5 5 5 5 3.9 0.207 5 3.9 0.207 5 3.9 0.207 5 3.4 0.207 5 5 3.4 0.207 5 5 5 5 5 5 5 5 5 6 6 100mL	
TOTAL PROTEIN 9/100mL 6.3 6.6 6.0 6.7 6.8 6.3 6.8 7.4 7.4 7.4 7.4 7.4 7.7 7.0 4 7.0 4 7.0 4 7.0 7.0 7.0 7.0 7.0 7.0 7.0 7.0 7.0 7.0	
CHLORIDE mmol/L 104 101 102.4 103 103.2 103 103 103.2 0.45 5 5 5 5	
POTASSIUM mmol/L 4.72 4.96 5.09 5.06 5.20 5.20 6.279 5.30 4.47 4.57 4.57 4.57 4.57 0.431 5 5 5 5 5 5 5 5 5 5 6 4.47 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	
SODIUM mmol(L 147.4 145.3 146.0 145.8 0.955 5 0.955 145.0 144.0 144.0 144.70 144.70 1570 5 5 5 5 5 5 5 5 5 5 5 5 5	
INORGANIC HOSPHORUS 9.0 9.4 8.6 8.6 8.6 8.6 6.6 6.6 6.9 6.9 6.9 6.9 0.409 0.409	
CALCIUM p mg/100mL 11.1 11.1 11.1 11.1 11.1 11.1 11.1 11	
TOTAL TOTAL CHOLEST. mg/100mL 49.9 41.1 71.5 80.6 5 86.2 85.2 85.2 85.2 85.2 85.2 85.2 38.2 5 5 5 5 1.507 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	
ALKALINE PHOSPH. U/L 261 276 304 264 248 248 276 5 111 149 111 155.4 155.4 155.4 155.4 5 5 5	
SDH U/L 17.7 13.7 7.9 8.7 7.9 8.7 5 11.62 4.061 5 5 9.1 11.5 9.1 11.0 8.1 9.20 8.1 2.131	,
ALT (GPT) (U/L 255 211 25 222 23 211 55 15 26 26 26 26 26 26 26 26 26 26 26 26 26	,
AST (GOT) U// 115 133.0 133.0 133.0 133.0 134 134 134 138 133.0 15.7 137 137	D
TOTAL BILIRUBIN mg/100mL 0.09 0.14 0.14 0.14 0.14 0.14 0.14 0.15 0.15 0.15 0.15 0.15 0.15	a
CREATININE mg/100mL 0.46 0.43 0.47 0.47 0.46 0.47 0.46 0.47 0.54 0.54 0.54 0.54 0.55 0.055	5
UREA UREA mg/100mL 25 29 27.4 1.67 27.4 1.67 39 31 36 28 6.18 6.18	5
GLUCOSE mg/100mL 96 78 87 133 95 97.8 97.8 97.8 97.8 98 98 98 96.4 3.91	2
Animal Animal Animal Animal A8 M A9 A9 A9 M A10 Sex A10 M A10 Sex A10 M A10	5

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

Recovery period Individual results URINALYSIS

ESARROLLO APLICADO, S.A.L. ENTRO DE INVESTIGACIÓN Y oxicology Department able no.: 57

CRYSTALS* ‡ ++++ ţ ‡ ‡ + ‡ ‡ + + + MICROSCOPIC EXAMINATION OF SEDIMENT BACTERIA CASTS 0 0 0 0 0 \$ 0000 0 ‡ ‡ ‡ ++++ ‡ *0 +++ ‡ ‡ ‡ + LEUKO. no./field 0 0 0 0 0 00007 no./field ERYTH. 0 0 0 0 0 0 0 0 0 0 no./field CELL EPIT. 0 0 0 0 0 0 0 0 0 0 BLOOD/ HAEM. 0 0 0 0 0 ; ο + + BILIRUBIN 0 0 0 0 0 0 0 0 0 0 ÷ UROBILINOGEN 0000 0 0 0 0 0 \$ 0 KETONES 0 0 0 0 0 ÷ 0 0 0 0 0 PROTEINS GLUCOSE 0 0 0 0 0 ş 0000 0 + 0 0 \$ ο 0 + + + 0 + 0.89 0.00 8.0 6.6 S F **ထ ထ ထ ထ** ഗാ 0 N 0 ω GRAVITY SPECIFIC 1027.2 1019.2 1025 6.53 1016 8.70 1020 1024 1030 1013 1032 1024 1037 101 ഗ ŝ VOLUME 20.6 8.76 2.28 5 8.8 8 Ę S COLOUR Yellow MEAN MEAN Sex Σ Σ ΣΣ Σ L ц. ц. L u_ Animal S.D. S.D. c C



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

> URINALYSIS ndividual results Recovery period

SENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. oxicology Department able no.: 58

CRYSTALS* + + + ‡ ‡ \$ ‡ ‡ + ŧ + + MICROSCOPIC EXAMINATION OF SEDIMENT CASTS 0 0 0 0 0 0 0 0 0 0 \$ BACTERIA ‡ ‡ ‡ ‡ '0 ‡ ‡ ‡ ‡ ÷ no./field LEUKO. 0 3²5 000 0 0 0 0 0 ERYTH. no./field 0 0 0 0 0 0 0 0 0 0 no./field CELL EPIT 0 0 0 0 0 0 0 0 0 0 BLOOD/ HAEM. 00 000 \$ 0 0 0 0 0 BILIRUBIN ÷ 0 0 0 0 0 0 0 0 0 0 UROBILINOGEN 0 0 0 0 0 ÷ 0 0 0 0 0 KETONES ş 0 0 0 0 0 0 0 0 0 0 PROTEINS GLUCOSE ÷ 0 0 0 0 0 0 0 0 0 0 ş 0 0 0 ‡ 0 + 1.22 0.55 5 7.0 7.6 F 9 1 ω σ 8 ~ 8 7 ω SPECIFIC GRAVITY 1015.6 1020.2 1015 1026 1024 1014 5.40 1017 1022 1016 4.72 1022 1014 1009 ß ю VOLUME 5.50 22.3 13.2 17.5 4.94 18 27 ŝ Ч 28 З ഹ COLOUR Yellow MEAN Sex MEAN шшш L Σ Σ ΣΣ Σ ш Animal S.D. S.D. c c 96 97 98 99 20 Ś 48 49 46 47

* . 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.

		Dose	Anin	Colour	
Group	Treatment	(mg/kg/day)	Males	Females	code
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. <u>Recovery period</u>

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:

			Anim	al no.
Group	Treatment	Dose (mg/kg/day)	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

ABSOLUTE ORGAN WEIGHTS Sacrificed after end of treatment Individual results

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

Dose: --Sex: Male

CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. Toxicology Department Table no.: 59

PITUIT. 3LAND	бш	თ	ω	4	ω	11	13	14	5	4 0	ø	9	10.1	• • • • •	ن 1 ب	10
THYMUS	D	0.84	0.50	0.63	0.40	0.58	1.00	0.65	0.01	- 6 0	0.67	0.62	0.68	104 0	0.180	10
LUNGS	D	1.80	1.48	1.59	1.29	2.02	1.75	1.93		0.10	2.21	1.26	1 70		0.30/	6
PROSTATE	Ø	2.57	1.87	2.44	2.00	2.05	2.82	2 24		2 i	2.73	2.44	236		0.315	0
SPLEEN P	6	0.95	0.46	0.67	0.68	0.89	0.89	101	5	20.1	1.04 40	0.74	D B.A		0.199	9
LIVER	5	14.02	14.52	19 44	13.97	19.09	20.22	20.70		15.74	17.74	16.98	NC 71		2.585	10
HEART	D	1.44	1 26	61	138	148	1 64		00. 10.	1.35	1.46	1.29	00 7	5.	0.126	10
BRAIN	Ø	90 0	191	- 0 - 70	1 93	50 50.0	2.46	2 2	7.02	2.21	2.05	1.92	20.0	2.07	0.144	10
KIDNEYS	D	3 40			5 5 5 5 7 5 7 5 7 7 7 7 7 7 7 7 7 7 7 7	20.0			3.24	3.86	3.31	3.14	L C C	3.20	0.314	10
	GLAINUS mg	12	4 7	t (<u> </u>	- 6	8 C	6 G	20	27	20	7		18.5	7.85	10
TESTES	ס	201	- 4. d - C 1	4.04	4.07	4 0	40.4	40 00 -	4.68	5.61	4 98	5.10		4.70	0.472	10
ADRENAL	GLANUS	00	29 1	<u>,</u>	23 s	41 7	81	21	76	56	04	52		59.3	15 23	10
вору	WEIGHT		345	C2	353	377	392	472	395	408	16.7	378		396.2	40.71	
ANIMAL	Ö		, - (2	ი [.]	4	Ð	ю	7	œ	o c	» (†		MFAN		2 2

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

PITUIT. GLAND	бш	11	15	12	11	80	Ø	თ	۵	7	ç	2	9.9		1.4	10
THYMUS	D	0.67	0.55	0.54	0.42	0.50	0.52	0.38	0.72	0.57	0.40	0.43	0.53	204 0	0.10/	6
LUNGS	g	1.42	1.67	1.45	2.26	1.41	1.31	1.45	1.62	1.97		1.41	1.60	000 0	0.300	6
PROSTATE	Ð	2.42	2.53	1.76	2.54	2.14	1.85	2.18	2.60	2.09		2.41	2.25		0.295	10
SPLEEN	D	0.80	1.14	0.94	0.85	0.71	0.66	0.77	0.80	0.93		0.86	0.85		0.136	6
LIVER	σ	16.40	17.34	17.93	18.33	16.07	14.27	15.48	18 47	12.20		14.86	1614		2.001	10
HEART	б	1.27	1.38	1.33	1.39	111	1 07	1 24	1 33	1 25	3	1.17	1 26	-	0.114	10
BRAIN	ß	2.12	2.16	2.19	2.12	1 98	1 93	1.96	2 16 2 16	2 5	2.2	2.06	207	2.4	0.094	10
KIDNEYS	D	2.85	3.48	2 62	i 6	0 80 80	2010	2 1 R	0.0 87 8		20.7	2.78	7 05	20.4	0.395	10
	6 mg	Å	41	74	74	18	1 4	<u>5</u> 6	2 Ç	n c - c	S	15	200	0.02	8.36	6
TESTES	ŋ	4 73	5.74 5.74	4 78 7 78		0 F	- C	2 07	1 C C	00.0	0.00	4.72	97.1	4.70	0.422	0
	Bmg	G	88	8 6	3 6		0	9	5	0 Q	55	54	0.20	01.0	16.05	5
BODY	B	24	400 206	2000	202	0// 205	000	100	1/5	439	416	346	000	3/6.4	35.03	10
ANIMAL	Ň		<u> </u>	/ /	0	9L 00	2 2	5 8	33	53	24	25		MEAN	C V	; ; ;



ABSOLUTE ORGAN WEIGHTS Sacrificed after end of treatment Individual results

Study no.: CD-98/6289T Test substance: IQB-9302.HCI

Dose: 1.25 mg/kg/day Sex: Male

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

PITUIT. GLAND	бш	თ	ø	10	80	7	15		<u>0</u>	15	თ	7	-	10.3	10 0	0.01	6	
THYMUS	Ø	0.70	0.48	0.69	0.85	0.46	0.59		0.00	0.50	0.55	0 66	5	0.63		0.144	6	
LUNGS	D	1.77	1.59	1.86	1.56	1.87	171		1.8.1	2.08	2.08	, 0, 0	7.21	1 85	1.00	GLZ.0	10	!
PROSTATE	D	2.22	2.42	2.38	1.61	2.29	2 85		2.82	2.43	2.32	70.0	2.3	237		0.341	6	2
SPLEEN	ס	0.87	0.63	1.09	1.09	0.86	105		0.92	0.88	0.84		0.82	60		0.142	6	2
LIVER	D	14.78	12.61	18.31	16.03	17.23	73 58	20.00	16.14	15.62	19.44		19.04	17 26	2	3.084	ç	2
HEART	Ø	1.32	1.12	1.55	1.28	1 10	1 1 1	10.1	1.53	1.28	1.43	Ī	1.72	00	20.	0.204	5	2
BRAIN	ວ	2.14	1.96	2.09	1 83	001	8 - -	z.03	2.20	2,00	1.95		1.96	2 c	10.7	0.115	ç	2
KIDNEYS	D	2.41	2.57	00 8	806	2.07 2.85		3.31	3.31	3 00	0000 0000	5	3.33	200	3.01	0.324	¢	2
THYROID	GLANDS	20	5 5	: %	5 F F		± č	24	31	2	- 7	2	19		19.0	5.66		5
TESTES	ŋ	4 4U	95	00.4 ×			4.01	4.58	5.29	A GO		000	4.57		4.43	0 973	0.00	10
ADRENAL	GLANDS	54	5 4	t 0	0	8 8	6	67	74		9 9 9	00	61		60.1	7 87	5.9	10
ВОDУ	WEIGHT 9	000	ŝ	555 907	440	195	359	456	410		005 705	104	433		396.6	27 14	1 .5	0
ANIMAL	Ň	4	ę (17	87	52	ဓ	31		70	3	97 17	35		MFAN		o.r.	c



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

ABSOLUTE ORGAN WEIGHTS Sacrificed after end of treatment Individual results

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

PITUIT. GLAND	Вш	7	10	13	12	7	14	14	12	ø	13	11.0	2.79	0	2
THYMUS	ס	0.59	0.72	0.65	0.63	0.50	06.0	0.51	0.79	0.93	0.77	0.70	0.150	0	2
LUNGS	ວ	1.91	1.76	1.73	1.66	1.45	1.58	1.78	1.60	2.15	2.17	1.78	0.237	ç	2
PROSTATE	IJ	1.95	2.35	2.14	1.82	2.24	2.44	2.30	2.53	2.80	2.62	2.32	0.299	0	2
SPLEEN	מ	0.83	1.07	1.02	0.81	0.65	1.17	0.94	0.95	1.67	1.06	1.02	0 274		2
LIVER	D	14.56	15.10	19.48	15.32	13.19	15.09	19.02	20.17	22.22	17.56	17.17	2 946		2
HEART	ŋ	1.19	1.47	1.29	1.21	1.15	1.42	1.49	1.28	1.58	1.52	1.36	0 154		כ
BRAIN	ס	2.01	2.20	1.92	2.06	1.83	2.16	2.12	2.09	2.22	2.15	2 08	0 125	24.0	10
KIDNEYS	ס	2.43	2.83	3.04	2.84	2 79	2.91	3.09	3.17	3.62	3.88	3.06	0.00	- 74.0	10
THYROID GI ANDS	bu	1	17	: 6	27	14	33	18	35) (17	906	010	0.10	10
TESTES	D	4 15	5.14	4.68	00 ⁻¹	4 53	4 47	4.67	4.88	02. 1	4.83	A EA		0.231	10
ADRENAL	B	54	5 42	3 C	4 Q 4	3 5	1 0		200	č K	62 67	c 13	0. <u>0</u> 0	9.13	10
BODY		340		100	195		670	404 272	210	200 174	457	205.4	1.020	45.90	10
ANIMAL	Ňo	30	0 0	58	8 6	n (4 v 0 v	1	4	0 1 1	44 45		MEAN	S.D.	c

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RO DE INVESTIGACIÓN Y	ology Department
\RROLLO APLICADO, S.A.L.	no.: 63
CENTRO D	Toxicology [
DESARROI	Table no.:

RELATIVE ORGAN WEIGHTS Sacrificed after end of treatment Individual results

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

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PITUIT. GLAND %(x100)	0.26	0.21	0.40	0.21	0.28	0.28	0.35	0.29	0.13	0.16	0.26	0.082	10
THYMUS %	0.24	0.13	0.18	0.11	0.15	0.21	0.16	0.22	0.15	0.16	0.17	0.041	9
KUNGS	0.52	0.38	0.45	0.34	0.52	0.37	0.49	0.42	0.48	0.33	0.43	0.072	10
PROSTATE %	0.74	0.49	0.69	0.53	0.52	09.0	0.57	09.0	09:0	0.65	0.60	0.078	10
SPLEEN %	0.28	0.12	0.19	0.18	0.23	0.19	0.26	0.27	0.23	0.20	0.22	0.049	10
LIVER %	4.06	3.77	5.51	3.71	4.87	4.28	5.24	3.86	3.88	4.49	4.37	0.643	10
HEART %	0.42	0.33	0.35	0.37	0.38	0.35	0.33	0.33	0.32	0.34	0.35	0:030	10
BRAIN %	0.66	0.50	0.55	0.51	0.57	0.46	0.51	0.54	0.45	0.51	0.53	0.060	10
KIDNEYS %	0.99	0.84	0.88	0.69	0.85	0.71	0.82	0.95	0.72	0.83	0.83	0.100	10
THYROID GLANDS %(x100)	0.35	0.36	0.45	0.29	0.74	0.61	0.51	0.66	0.44	0.19	0.46	0.172	10
TESTES %	1.42	1.17	1.15	1.13	1.18	0.89	1 18	1 38	1 09	1.35	1 19	0.156	10
ADRENAL GLANDS %(x100)	1.13	1.32	1.50	1 09	217	1 48	1 97	1.37	1 53	1.38	1 49	0.332	10
BODY WEIGHT 9	345	385	353	377	397	472	305	408 808	457	378	306.0	40 71	10
ANIMAL No.		~ ~	1.07) 4	۲u	» د	7 (-α	σσ	, t	MEAN		j c

NTRO DE INVESTIGACIÓN Y	SARROLLO APLICADO, S.A.L.	cicology Department	ble no.: 64
CENTE	DESAF	Toxicol	Table r

RELATIVE ORGAN WEIGHTS Sacrificed after end of treatment Individual results

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

AAL	ВОДУ	ADRENAL	TESTES	THYROID	KIDNEYS	BRAIN	HEART	LIVER	SPLEEN	PROSTATE	LUNGS	THYMUS	PITUIT. GI AND
	WEIGHT 9	GLANDS %(x100)	%	GLANDS %(x100)	%	%	%	%	%	%	%	%	%(x100)
		1 50	1 18	0.65	0.71	0.53	0.32	4.10	0.20	0.61	0.36	0.17	0.28
	004	- 1 - 1 - 1	1 26	106	06.0	0.56	0.36	4.49	0:30	0.66	0.43	0.14	0.39
	200	- 1 - 1	<u>8</u> 8 8	0.66	0 72	0.60	0.37	4.94	0.26	0.48	0.40	0.15	0.33
	200		0.1	0.64	0.85	0.56	0.37	4.86	0.23	0.67	0.60	0.11	0.29
	226	07.1	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	0.66	0.86	0.59	0.33	4.80	0.21	0.64	0.42	0.15	0.24
	555	061	1 24	0.39	0.67	0.58	0.32	4.31	0.20	0.56	0.40	0.16	0.24
	100	00 00 00 00	1 33	0.51	0.86	0.53	0.33	4.17	0.21	0.59	0.39	0.10	0.24
	- 10	1 7 4	00.1 1 1 4	0.43	0.79	0.49	0:30	4.21	0.18	0.59	0.37	0.16	0.18
	409	1.1	1 28	62 U	0.67	0.48	0.32	2.93	0.22	0.50	0.47	0.14	0.17
	4 I 0 346	1.56	1.36	0.43	0.80	09.0	0.34	4.29	0.25	0.70	0.41	0.12	0.29
1	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
	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
	10	10	10	10	10	10	0	10	6	10	10	10	10





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

> RELATIVE ORGAN WEIGHTS Sacrificed after end of treatment individual results

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

ANIMAL	вору	ADRENAL	TESTES		KIDNEYS	BRAIN	HEART	LIVER	SPLEEN	PROSTATE	LUNGS	тнүмис	PITUIT. GLAND
No	WEIGHI	GLANUS %(x100)	%	%(x100)	%	%	%	%	%	%	%	%	%(x100)
ę	000	1 23	1 15	0.52	0.63	0.56	0.34	3.86	0.23	0.58	0.46	0.18	0.23
86	2000 2000	- <u>-</u>	132	0.33	0.77	0.59	0.34	3.79	0.19	0.73	0.48	0.14	0.24
100		1.36	115	0.54	0.70	0.49	0.36	4.28	0.25	0.56	0.43	0.16	0.23
8	120 207 207	1 46	0.45	0.43	0.77	0.46	0.32	4.04	0.27	0.41	0.39	0.21	0.20
2 2	250		1 28	0.39	0.79	0.53	0.31	4.80	0.24	0.64	0.52	0.13	0.19
5 5	909 456	1.47		0.53	0.73	0.46	0.34	5.17	0.23	0.63	0.38	0.13	0.33
- 6		Ča t	00 F	0.76	0.81	0.54	0.37	3.94	0.22	0.69	0.44	0.21	0.37
25	- + C	8.6	ac 1 ac 1	0.57	0.87	0 55	0.35	4.27	0.24	0.66	0.57	0.14	0.41
55	005	+ + +	1 26 1 26	0.0	0.82	0.49	0.36	4.85	0.21	0.58	0.52	0.14	0.22
4 4 4	- 04 - 04	141	106	0.44	0.77	0.45	0.40	4.58	0.19	0.55	0.51	0.15	0.16
3	2												
	306.6	1 57	112	0.49	0.76	0.51	0.35	4.36	0.23	09.0	0.47	0.16	0.26
	0.000	0.170	0.260	0 122	0,060	0.048	0.026	0.472	0.025	0.089	0.061	0.031	0.083
o S C	10 10	10	10	10	10	10	10	10	10	10	6	6	6
									the second				

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

> RELATIVE ORGAN WEIGHTS Sacrificed after end of treatment Individual results

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

ANIMAL	вору	ADRENAL	TESTES	THYROID	KIDNEYS	BRAIN	HEART	LIVER	SPLEEN 1	PROSTATE	LUNGS	THYMUS	PITUIT. GI AND
Ő	WEIGHT g	GLANDS %(x100)	%	GLANDS %(x100)	%	%	%	%	%	%	%	%	%(x100)
ç	010	1	1 22	0 37	0.71	0 59	0.35	4.28	0.24	0.57	0.56	0.17	0.21
e l	2 5 0	80	<u>i</u> 5		0.67	0.57	0.35	3.59	0.25	0.56	0.42	0.17	0.24
3/	471	-0-4	<u>1</u> 1 2	0 C	0.78	0.49	0.33	4.98	0.26	0.55	0.44	0.17	0.33
89	190		140	0.00	27.0	0.56	0.33	4.15	0.22	0.49	0.45	0.17	0.33
99 99	50 G 50 G	10.1 0 F C	0- 1	0.0	0.85	0.56	0.35	4.01	0.20	0.68	0.44	0.15	0.21
4 :	329	81.7 7	00.4	5 5 6 6 6 7 6	0.00	0.54	0.35	3.75	0.29	0.61	0.39	0.22	0.35
41	40Z	4 +	0	40.0 87 C	0.83	0.57	0.40	5.11	0.25	0.62	0.48	0.14	0.38
42	3/2	10.1	9 9 8		0.70	0.52	0.32	5 06	0.24	0.63	0.40	0.20	0.30
4 3	995	- 20 - 20 - 20	<u>1</u> 2	20 20 20 20 20 20 20 20 20 20 20 20 20 2	24.0	0.02	0.34	4 72	0.35	0.59	0.46	0.20	0.17
4 45 45	4/1 457	0.90 1.36	1.06	0.37	0.85	0.47	0.33	3.84	0.23	0.57	0.47	0.17	0.28
	r acc	1 60	a, t	0 53	0 77	0.53	0.35	4.35	0.25	0.59	0.45	0.18	0.28
MEAN	1.000 A F 00	1.30 1337	0104	0.208	0.060	0.042	0.022	0.575	0.042	0.052	0.048	0.024	0.070
о С	10	10	10	10	10	10	10	10	10	6	6	10	9



ABSOLUTE ORGAN WEIGHTS Sacrificed after end of treatment

Individual results

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

Sex: Female

Dose: --

DESARROLLO APLICADO, S.A.L. Toxicology Department Table no.: 67 Table no.:

CENTRO DE INVESTIGACIÓN Y

GLAND PITUIT. 18.9 6.69 10 20 25 11 15 17 17 17 17 25 17 17 17 17 B THYMUS 0.57 0.095 10 $\begin{array}{c} 0.65\\ 0.75\\ 0.75\\ 0.56\\ 0.48\\ 0.53\\ 0.56\\ 0.56\\ 0.56\\ 0.63\\$ σ LUNGS 1.47 1.45 1.45 1.45 1.45 1.45 1.45 1.37 1.37 1.40 0.124 10 1.63 1.51 σ SPLEEN UTERUS 0.56 0.176 10 0.42 0.98 0.58 0.58 0.55 0.55 0.55 0.55 0.55 0.36 0.36 σ 0.63 0.115 10 0.71 0.69 0.69 0.62 0.70 0.70 0.70 0.70 0.73 0.73 0.73 σ LIVER 11.45 9.34 9.90 11.53 11.34 11.71 13.56 11.69 11.01 1.295 10 9.98 9.60 σ HEART 1.01 0.105 10 $\begin{array}{c} 1.03\\ 1.04\\ 0.87\\ 0.93\\ 0.93\\ 1.06\\ 1.06\\ 1.01\\ 1.23\\ 1.23\\ \end{array}$ σ BRAIN 2.10 1.98 1.97 1.96 1.98 1.98 1.98 2.10 2.10 2.10 1.99 0.096 10 σ KIDNEYS 2.01 0.128 10 2.187 2.187 2.12 2.12 2.197 2.05 2.05 2.11 2.08 2.08 σ THYROID GLANDS 26.2 14.33 10 B OVARIES 138.7 31.37 10 105 168 126 92 92 132 137 153 153 Вш ADRENAL GLANDS 72.0 10.93 10 ĝ WEIGHT вору 245 257 257 257 252 263 263 263 263 263 263 256.6 17.68 10 σ MEAN S.D. ANIMAL ġ

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ABSOLUTE ORGAN WEIGHTS Sacrificed after end of treatment Individual results

Test substance: IQB-9302.HCI Dose: 0.75 mg/kg/day Sex: Female

Study no.: CD-98/6289T

PITUIT. GLAND	đu	31	16	17	12	15	12	11	13	17	C *	2	15.4	6.02		2
THYMUS	σ	0.51	0.49	0.39	0.79	0.50	0.51	09.0	0.50	0.61	100	10.0	0.55	0 108		2
LUNGS	ຒ	1.37	1.56	1.27	1.67	1.49	1.24	1.16	1.38	1.67		- -	1,44	0 179		2
UTERUS	ס	0.91	0.65	0.46	0.60	0.68	0.76	0.53	0.77	0.52	000	0.03	0.65	0.136	2	0
SPLEEN	б	0.66	0.65	0.63	1.02	0.70	0.94	0.71	1.16	0.76	ľ	ς/.Π	0.80	0.180	0.0	01
LIVER	D	10.31	10.99	10.70	10.20	10.78	9.47	11.12	11.54	10.72		10.00	10.58	0 600	0,000	10
HEART	D	0.91	0.91	0.94	1.10	0.84	0.89	0.89	0.93	0.91		1.02	0.93	V 0 0	0.074	10
BRAIN	D	2.05	1.92	1.80	2.16	1.96	2.09	1 90	200	- -	2	1.86	1.97	077 0	0.10	10
KIDNEYS	D	2.02	2.07	181	2 47	1.76	1 86	1 80	0 13 13	2 0	5	2.01	00 6		0.210	10
	mg	47	: 6	2 40	77	16	- 6	?σ	ə 2	4 C	P V	18	27.6		11.26	10
OVARIES	бш	126	ζi β	3 2 2	891	<u>3</u> 5	149	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	<u>3</u>	121	<u>†</u>	117	108.5	0.041	21.12	10
ADRENAL	GLANUS	8	4 C	2 89	3 6	3 8	4 0 4 1	2.9	8 8	35	40	81	75 F	0.01	11.12	10
BODY	WEIGHI 9	000	202	242 206	250		747	++7 1	240 070		107	234	045 0	0.047	13.57	10
ANIMAL	No	, ec	0 0	10	88	0 0	5 5		2	5.1	74	75		MEAN	S.D.	c



ABSOLUTE ORGAN WEIGHTS Sacrificed after end of treatment Individual results

Test substance: IQB-9302.HCI Dose: 1.25 mg/kg/day Sex: Female

Study no.: CD-98/6289T

PITUIT. GLAND	6 m	12	16	22	20	4	17	თ	19	თ	32	17.0	6.88	10
THYMUS	ס	0.66	0.55	0.40	0.53	0.61	0.68	0.37	0.44	0.42	0.56	0.52	0.110	10
LUNGS	ס	1.27	1.62	1.15	1.20	1.59	1.49	1.19	1.28	1.77	1.75	1.43	0.240	10
UTERUS	ס	0.60	1.03	0.39	0.65	0.81	0.37	0.58	0.53	0.74	0.40	0.61	0.209	10
SPLEEN	D	0.78	0.62	0.75	1.00	0.67	0.87	0.66	0.99	0.75	0.74	0.78	0.132	10
LIVER	Ø	8.66	9.24	9.77	9.59	11.68	11.62	10.48	9.98	9.58	10.81	10.14	0.995	10
HEART	D	1.09	0.92	0.88	0.90	1.04	1.00	0.90	1.16	0.88	1.02	0.98	0.098	10
BRAIN	D	1.96	1.83	1.96	1.80	1.90	1.99	1.77	2.15	1.91	2.03	1.93	0.114	6
KIDNEYS	D	2.11	1.89	2.03	1.81	2.08	2.26	1.86	1.99	2.05	2.07	2.02	0.133	10
THYROID GI ANDS	Вш	12	17	23	8	15	21	10	26	25	35	21.3	7.97	10
OVARIES	Вш	152	128	122	150	175	150	163	199	163	177	157.9	22.95	10
ADRENAL	6m	78	76	22	28	99	85	88	84	5 5	80	78.4	13.17	10
BODY	g	241	244	238	241	039	266	206	258	241	275	246.9	11 70	10
ANIMAL	No.	76	2 4	78	0 0		2 2 2	- 6	4 C 0 4	2 a	85	MEAN		0 2 2 2

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

PITUIT. GLAND	бш	15	ი	12	16	16	15	21	0	2	18	თ		15.0	4.00	ç	2
THYMUS	ס	0.54	0.46	0.50	0.68	0.50	0.38	0.44		0.0	0.62	0.70		0.55	0.110	ç	2
LUNGS	σ	1.28	1.49	1.34	1.51	1.35	1.12	111		3	1.65	1.42		1.38	0.176		2
UTERUS	D	0.76	0.73	0.59	0.50	0.84	0.44	0.45		10.U	0.59	0.88		0.63	0 162		2
SPLEEN	D	0.69	0.61	0.82	0.80	0.78	0.58	1 00	40.4	0.88	0.98	0.78		0.79	0 143		2
LIVER	D	9.60	9.50	9.98	11.29	10.65	8.91	11 51	$\overline{\mathbf{o}}$	11 08	11.03	10.02		10.36	0 877	5.5	10
HEART	ס	0.94	0.82	0.99	1.00	0.89	0.91	 90	8	1.00	1.04	0 93)	0.96	0.074	+ 0.0	01
BRAIN	Ø	1.89	1.79	1.87	1.89	1 98	2 U3	8 2 1 c	5	1.74	1.99	1 79	2	1 90	3010	0.10	10
KIDNEYS	ס	1.87	1 98	1 69	214	217	1 64	40°-	CN.7	1.92	2.11	7 2 7	5.4	1 00		0.223	10
	b mg	33	9 4	5 5 7	2 5	- 5 7	5 8	5 6	87	18	19	2 7	t	21.3	2	0°.9	10
OVARIES	ßш	179	20	30 90	167	801	115		201	1 40	188	201	171	146.1		35.80	6
	mg	8	3 5	<u></u>	2 4	36	1		85	67	104	5	2	76.7	10.2	14.41	10
BODY	vvelGn i g	763		240	242	200	202 202	77	257	266	202	147	247	0110	C. 147	16.38	10
ANIMAL	Ňo	90	8 6	/0 00	88	50 G	3	61	92	5	3 6	4 L C	95		MEAN	S.D.	c



RELATIVE ORGAN WEIGHTS Sacrificed after end of treatment Individual results

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

Dose: --Sex: Female

PITUIT. GLAND	%(x100)	0.82	1.28	0.66	1.06	0.38	0.67	0.84	0.53	0.51	500	0.00	0.74	0.271	10	
THYMUS	%	0.27	0.29	0.20	0.21	0.20	0.21	0.22	0.17	0.19		U. 24	0.22	0.037	10	
LUNGS	%	0.60	0.54	0.54	09.0	0.53	0.54	0.51	0.49	0.56		96.0	0.55	0.035	10	
UTERUS	%	0.17	0.38	0.18	0.25	0.27	0.20	0.20	0.15	0 23		0.16	0.22	0.069	10	2
SPLEEN	%	0.29	0.27	0.23	0.21	0.29	0.23	0.25	0.16	0.27		0.26	0.25	0.040	10)
LIVER	%	4.07	3.74	4.23	3.96	4.16	4.58	4.31	4 82	463		4.36	4.29	0.328	6	2
HEART	%	0.42	0.40	0.32	0,40	0.39	0.37	0.40	0.42	1 0° 1 0° 1 0°	200	0.46	0.40	0.037	ç	2
BRAIN	%	0.86	0.77	0.73	0.89	0.76	0.78	0.75		0.00	00.0	0.78	0.78	0.064		2
KIDNEYS	%	0.76	0.85	0.78	0.75	0 79	0.78	0.78			0.12	0.78	0 78	0 039		2
	%(x100)	1 06	2.41	- 68 C	0.93	0.46	0.67	0.0	04.0	0 7 7 7	0.70	1.08	103	0 550		2
OVARIES	%(x100)	4 29	6 5.4	4.65	5 47	2 87	10.0 10	1 7 7 7 7	N		4.88	5.71	2 10	0.10		2
	%(x100)	2 33	2.00 PD	2 00 00 00 00 00 00 00 00 00 00	20 19 19 19	0.00	2 2 2 2 2 2 4 0 7 0			2.3U	2.39	2.87	10 C		0.440	0
BODY	WEIGH I	745	247 267	107	- 12	007	6.70 76.70	707	507	243	293	268	000	0.002	2Q./L	10
ANIMAL	Ňo	ŭ	ត	7 6	2	1 1 1	n n n	8 [/4	58	59	60		MEAN	S.D.	c



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

PITUIT.	GLAND %(v100)	(00. v)o	1.34	0.66	0.75	0.46	0.62	0.49	0.45	0.48	0.66	0.43	0.63	0.272	10
THYMUS	70	2	0.22	0.20	0.17	0:30	0.21	0.21	0.24	0.19	0.24	0.26	0.22	0.037	6
LUNGS	70	2	0.59	0.64	0.56	0.64	0.62	0.51	0.47	0.51	0.65	0.66	0.59	0.069	10
UTERUS	70	۲ ۲	0.39	0.27	0.20	0.23	0.28	0.31	0.22	0.29	0.20	0.27	0.27	0.058	10
SPLEEN	70	8	0.28	0.27	0.28	0.39	0.29	0.39	0.29	0.43	0.30	0.32	0.32	0.057	5
LIVER	2	8	4.44	4.52	4.73	3.92	4.45	3.88	4.54	4.27	4.17	4.27	4.32	0.273	10
HEART	2	%	0.39	0.37	0.42	0.42	0.35	0.36	0.36	0.34	0.35	0.44	0.38	0.035	10
BRAIN	2	0%	0.88	0.79	0.80	0.83	0.81	0.86	0.78	0.75	0.76	0.79	0.81	0.041	10
KIDNEYS	à	%	0.87	0.85	0.80	0.95	0.73	0.76	0.73	0.79	0.79	0.86	0.81	0.069	10
THYROID	GLAND	%(X1UU)	2.03	0.53	1.15	0.92	1.28	0.74	0.37	0.44	1.09	0.77	0.93	0.492	6
OVARIES		%(x100)	5.43	3.91	5.88	6,46	4.21	6.11	5.43	4.74	5.21	5.00	5.24	0.807	10
ADRENAL	GLANDS	%(x100)	3.97	2.88	3.01	2.42	3.47	3.07	2.69	3 41	2.49	3.46	3.09	0 492	6
вору	WEIGHT	D	232	243	226	260	242	244	245	2.2	257	234	245.3	13.57	10
ANIMAL		No	99	22	5 89 89	5	3 CZ	2 7		<u>4 5</u>	P 2 4	75	MFAN		., c



RELATIVE ORGAN WEIGHTS Sacrificed after end of treatment Individual results

Study no.: CD-98/6289T Test substance: IQB-9302.HCI

Dose: 1.25 mg/kg/day Sex: Female

PITUIT. GLAND	%(x100)	0.50	0.66	0.92	0.83	0.59	0.64	0.40	0.74	0.37	1.16	0.68	0.243	10
THYMUS	%	0.27	0.23	0.17	0.22	0.26	0.26	0.16	0.17	0.17	0.20	0.21	0.043	0
LUNGS	%	0.53	0.66	0.48	0.50	0.67	0.56	0.53	0.50	0.73	0.64	0.58	0.087	10
UTERUS	%	0.25	0.42	0.16	0.27	0.34	0.14	0.26	0.21	0.31	0.15	0.25	060.0	10
SPLEEN	%	0.32	0.25	0.32	0,41	0.28	0.33	0.29	0.38	0.31	0.27	0.32	0.049	10
LIVER	%	3.59	3.79	4.11	3.98	4.89	4.37	4.64	3.87	3.98	3.93	4.12	0.402	10
HEART	%	0.45	0.38	0.37	0.37	0.44	0.38	0.40	0.45	0.37	0.37	0.40	0.035	10
BRAIN	%	0.81	0.75	0.82	0.75	0.79	0.75	0.78	0.83	0.79	0.74	0.78	0.032	10
KIDNEYS	%	0.88	0.77	0.85	0.75	0.87	0.85	0.82	0.77	0.85	0.75	0.82	0.051	10
THYROID GLAND	%(x100)	0.50	0.70	0.92	1.24	0.63	0.79	0.44	1.01	1.04	1.27	0.85	0.291	10
OVARIES	%(x100)	6.31	5.25	5.13	6.22	7.32	5.64	7.21	7.71	6.76	6.44	6.40	0.876	10
ADRENAL GI ANDS	%(x100)	3.24	3.11	2.18	2.41	3.60	3.20	3.89	3.26	3.78	3.13	3.18	0.543	6
BODY WEIGHT	0	241	244	238	241	239	266	226	258	241	275	246.9	14.79	10
ANIMAL	No.	76	22	78	26	80	81	6	5	84	85	MFAN	SD	c

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.HCI

Dose: 2.25 mg/kg/day Sex: Female

THYMUS	č	%	0.21	0.21	0.20	0.26	0.20	0.17	0.17	0.24	0.25		07.0	0.22	0.037	0	2
LUNGS		%	0.51	0.68	0.55	0.57	0.53	0.51	0.43	0.58	0.67		70'N	0.56	0.075	ç	2
UTERUS		%	0:30	0.33	0.24	0.19	0.33	0.20	0.18	0.19	0.24	000	0. J	0.26	0.068	c	2
SPLEEN		%	0.27	0.28	0.33	0.30	0.31	0.26	0,40	0.33	0.40	000	0.32	0.32	0.049	0	2
I IVFR		%	3.79	4.36	4.07	4.24	4.21	4.03	4.48	4.17	4.47		4.06	4.19	0.214		2
HEART		%	0.37	0.38	0.40	0.38	0.35	0.41	0.41	0.38	0.42		0.38	0.39	0.021		<u>0</u>
NIVAB		%	0.75	0.82	0.76	0.71	0.78	0.92	0.79	0.65	0.81	2	0.72	0.77	0.073		01
KIDNEVS		%	0.74	0.91	0.69	0.80	0.86	0.74	0.80	0 72	2 2 2	200	0.96	0.81	0 088		10
	GLAND	%(x100)	0.91	0.73	0.61	0.79	1.38	1.09	601	0.68	8-0 		0.57	0.86	0.256	0.10	10
	UVARIES	%(x100)	7 08	4 13	5.14	6.28	5 06	5 20	7.87	10. r 90. r	1.40	10.1	5.14	587	1 249	247.1	0
	GLANDS	%(x100)	237	2 C C	0.00 AR	2 44	1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	3.01 2.02	2.21		70.7	4.21	2.83	3 09	0.607	0.001	10
	BODY WEIGHT	Ð	753	81C	0-4 740	245 266	253	200	757	100	007 C	24/	247	5 TAC		10.30	10
	ANIMAL	Ň	90	00	000	88	88	6 6	- 0	30		49	95	MEAN		S.D.	c

0.59 0.41 0.49 0.68 0.68 0.68 0.68 0.73 0.73 0.73 0.73 0.60 0.146

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PITUIT. GLAND %(x100)

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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

THYMUS	σ	0.74	0.74	0.55	0.51	0.75	0.66 0.118 5
FUNGS	0	1.93	1.72	1.54	1.58	1.61	1.68 0.157 5
PROSTATE	ס	2.99	2.63	2.72	2.22	2.26	2.56 0.324 5
SPLEEN	D	0.75	0.70	0.74	0.87	0.82	0.78 0.068 5
LIVER	ס	19.05	17.23	17.32	22.17	18.82	18.92 2.000 5
HEART	D	1.52	1.35	1.34	1.44	1.40	1.41 0.073 5
BRAIN	D	2.11	2.13	2.03 2.03	2.12	2.06	2.09 0.043 5
KIDNEYS	ບ	3.28	3.05	2.50 2.70	331	3.41	3.15 0.276 5
THYROID GLANDS	вш	2	i e	5 6	8 6	33	32.0 7.65 5
TESTES	6	5 33	5.00 10	- CC 4	454	4.32	4.85 0.413 5
	b mg	ц В	3 8	2 Y	5 æ	9 9	59.6 4.10 5
BODY		361	004	0 4 7 0 6	401	427	434.2 30.29 5
ANIMAL	No		- ;	2		4 <u>τ</u>	MEAN S.D.

PITUIT. GLAND mg

16.0 1.87 5



ABSOLUTE ORGAN WEIGHTS Sacrificed after end of recovery period Individual results

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

PITUIT. GLAND	вш	11	12	19	54	16.0 4.36 5
THYMUS	ס	0.70 0.63	0.59	1.06	0.92	0.78 0.202 5
LUNGS	ס	1.87 1.83	1.84	2.24	2.11	1.98 0.186 5
PROSTATE	B	3.02 2.02	2.18	3.39	3.13	2.82 0.516 5
SPLEEN	ß	0.84	0.83	1.04	1.03	0.92 0.109 5
LIVER	D	17.47	13.85	21.54	25.52	19.26 4.433 5
HEART	ס	1.61 4 £0	1.20	1.71	1.79	1.62 0.136 5
BRAIN	ס	1.99	01.2 01.2	2.16	2.30	2.15 0.110 5
KIDNEYS	Ø	3.08	3.30 0.6	3.90	3.95	3.50 0.404 5
	6 D D D D	29	ដង	46	4	32.8 10.23 5
TESTES	ס	5.30	4.82	00 7 60	5.89	5.35 0.421 5
ADRENAL	GLANUS	20	91	50	t 89	71.0 12.51 5
BODY	WEIGH I g	439	427	406	543	463.0 56.77 5
ANIMAL	No.	46	47	48 9	50 50	MEAN S.D.

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RELATIVE ORGAN WEIGHTS Sacrificed after end of recovery period Individual results

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

Dose: --Sex: Male

NTUIT.	6(x100)	0.32	0.39	0.36	0.33	0.44	0.37 0.049 5
THYMUS F	%	0.17	0.18	0.13	0.11	0.18	0.15 0.032 5
, SONUL	%	0.44	0.42	0.37	0.33	0.38	0.39 0.043 5
ROSTATE	%	0.69	0.64	0.66	0.46	0.53	0.60 0.097 5
SPLEEN P	%	0.17	0.17	0.18	0.18	0.19	0.18 0.008 5
LIVER	%	4.37	4.20	4.19	4.57	4.41	4.35 0.158 5
HEART	%	0.35	0.33	0.32	0.30	0.33	0.33 0.018 5
BRAIN	%	0.48	0.52	0.49	0.44	0.48	0.48 0.029 5
KIDNEYS	%	0.75	0.74	0.66	0.68	0.80	0.73 0.056 5
THYROID	GLANUS %(x100)	0.48	0.73	0.85	0.87	0.75	0.74 0.155 5
TESTES	%	1 23	15	10,1	200	1.01	1.12 0.138 5
ADRENAL	GLANDS %(x100)	1 40		 	 9,	1.43	1.38 0.088 5
вору	WEIGHT 9	324		5 c	4 - C	427	434.2 30.29 5
ANIMAL	N	*	- (4	<u>,</u>	15	MEAN S.D.

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.HCI Dose: 2.25 mg/kg/day Sex: Male

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PITUIT. GI AND	%(x100)	0.25	0.40	0.30	0.38	0.39	0.34 0.066 5
THYMUS	%	0.16	0.15	0.15	0.21	0.17	0.17 0.025 5
LUNGS	%	0.43	0.43	0.45	0.45	0.39	0.43 0.024 5
PROSTATE	%	0.69	0.56	0.54	0.68	0.58	0.61 0.070 5
SPLEEN	%	0.19	0.20	0.20	0.21	0.19	0.20 0.008 5
LIVER	%	3.98	4.20	3.41	4.31	4.70	4.12 0.475 5
HEART	%	0.37	0.35	0.36	0.34	0.33	0.35 0.016 5
BRAIN	%	0.45	0,50	0.52	0.43	0.42	0.46 0.044 5
KIDNEYS	%	0.70	0.78	0.70	0.78	0.73	0.76 0.039 5
THYROID	GLANDS %(x100)	0.66	0.52	0.64		0.76	0.70 0.150 5
TESTES	%	1 21	- -		0 7 7 7 7	1.08	1.16 0.073 5
ADRENAL	GLANDS %(x100)	1 34	- c		CC	1.25	1.55 0.345 5
вору	WEIGHT 9	OCT		421		543 543	463.0 56.77 5
ANIMAL	Ö	4	₽ Ç	/ 4	8 4 9	84 CC	MEAN S.D.



ENTRO DE INVESTIGACIÓN Y	ESARROLLO APLICADO, S.A.L.	xicology Department	ble no.: 79
CENI	DES/	Toxic	Table

ABSOLUTE ORGAN WEIGHTS Sacrificed after end of recovery period individual results

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

PITUIT. GLAND mg	24 16 2	53 44	19.8 4.49 5
THYMUS	0.39 0.53 0.53	0.45	0.50 0.075 5
LUNGS	1.19 1.27	1.37	1.33 0.105 5
UTERUS 9	0.64 0.50	0.66 0.42	0.58 0.110 5
SPLEEN 9	0.50 0.71	0.63	0.65 0.091 5
LIVER	11.24 10.29	10.72 10.72 11.08	10.76 0.398 5
HEART g	1.04 0.90	0.91 0.91 0.97	0.98 0.079 5
BRAIN g	1.91 2.03	1.97 1.94 1.98	1.97 0.045 5
KIDNEYS	2.03 1.88	2.13 2.13 2.17	2.06 0.113 5
THYROID GLANDS mg	8 8 S	5 15 15	23.0 6.96 5
OVARIES	113 163	156 177 168	155.4 24.91 5
ADRENAL GLANDS mg	62	79 66 75	69.6 7.09 5
BODY WEIGHT	264 255	277 250 264	262.0 10.32 5
ANIMAL No.	61	888	MEAN S.D. n



CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L.	Toxicology Department	Table no.: 80	CENTRO DE INVESTIGACIÓN Y DESARROLLO APLICADO, S.A.L. Toxicology Department Table no: 80
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ABSOLUTE ORGAN WEIGHTS Sacrificed after end of recovery period Individual results

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

PITUIT. GLAND mg	16 17 22 22	16.4 4.72 5
THYMUS 9	0.61 0.45 0.46 0.50 0.44	0.49 0.070 5
LUNGS	1.61 1.53 1.72 1.45	1.59 0.106 5
UTERUS	0.57 0.91 0.58 0.64	0.67 0.139 5
SPLEEN	0.84 0.77 0.94 0.98 0.54	0.81 0.174 5
LIVER	10.29 10.93 12.34 9.20	10.57 1.166 5
HEART g	1.10 0.91 0.86 0.86	0.99 0.105 5
BRAIN g	2.04 1.87 1.97 1.87 1.87	1.92 0.084 5
KIDNEYS	2.14 2.14 2.19 84	2.00 0.215 5
THYROID GLANDS mg	888828	22.2 6.80 5
OVARIES	152 159 177 123	144.6 26.65 5
ADRENAL GLANDS mg	8 5 5 5 6 7 8 6 7 8 9 8 9 8 9 8 9 8 9 8 9 8 9 8 9 8 9 8	67.6 14.43 5
BODY WEIGHT 9	246 274 284 271	270.2 14.36 5
ANIMAL No.	96 26 26 26 26 26 26 26 26 26 26 26 26 26	MEAN S.D.



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RELATIVE ORGAN WEIGHTS Sacrificed after end of recovery period Individual results

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

Study no.: CD-98/6289T Test substance: CONTROL Dose: --Sex: Female PITUIT. GLAND %(x100)

0.75 0.149 5

0.91 0.63 0.83 0.83 0.83

THYMUS	%	0.15	0.21	0.19	0.18	0.22	0.19	0.027	5
LUNGS	%	0.45	0.50	0.53	0.55	0.52	0.51	0.038	S
UTERUS	%	0.24	0.20	0.24	0.26	0.16	0.22	0.040	5
SPLEEN	%	0.19	0.28	0.24	0.25	0.28	0.25	0.037	ъ
LIVER	%	4.26	4.04	3.78	4.29	4.20	4.11	0.210	5
HEART	%	0.39	0.35	0.39	0.36	0.37	0.37	0.018	S
BRAIN	%	0.72	0.80	0.71	0.78	0.75	0.75	0.038	S
KIDNEYS	%	0.77	0.74	0.75	0.85	0.82	0.79	0.047	S
THYROID	GLAND %(x100)	0.98	1.14	1.05	0.64	0.57	0.88	0.255	5
OVARIES	%(x100)	4 28	6.39	5.63	7 08	6.36	5.95	1.064	S
ADRENAL	GLANDS %(x100)	2.35	2 59	2 R5	264	2.84	2.65	0.206	S
вору	WEIGHT 9	264	255 255	202	250	264	262.0	10.32	5
ANIMAL	ŏ	E.	5 6	3 6	3	5 5	MEAN	N D S	; ; ;

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

RELATIVE ORGAN WEIGHTS Sacrificed after end of recovery period individual results

PITUIT. GLAND	%(x100)	0.73	0.58	09.0	0.33	0.80	0.61 0.180 5
THYMUS	%	0.25	0.16	0.16	0.18	0.16	0.18 0.039 5
LUNGS	%	0.65	0.56	0.61	0.54	09.0	0.59 0.043 5
UTERUS	%	0.23	0.33	0.23	0.21	0.23	0.25 0.048 5
SPLEEN	%	0.34	0.28	0.33	0.36	0.20	0.30 0.064 5
LIVER	%	4.18	3.99	4.35	3.39	3.66	3.91 0.389 5
HEART	%	0.45	0.33	0,38	0.32	0.37	0.37 0.051 5
BRAIN	%	0.83	0.68	0.69	0.69	0.67	0.71 0.066 5
KIDNEYS	%	0.87	0.78	24.0	0.63	0.67	0.74 0.095 5
THYROID	GLAND %(x100)	0.89	0.80	0.85	0.00	1.12	0.82 0.245 5
OVARIES	%(x100)	6 18	5 80 2 80	0.00 8 2 3	0.50 A 54	4.06	5.36 0.998 5
ADRENAL	GLANDS %(x100)	0 F.G	2 0 0 2 0 2 0 2 0 2 0 2 0 2 0 2 0 2 0 2	2.20		3.33	2.50 0.507 5
вору	WEIGHT 9	3AG	042 7	4/7	407 774	276	270.2 14.36 5
ANIMAL	Ň	g	2 6	100	0 0	8 9 0	MEAN S.D.