

**IQB-9302: A 28 DAY INTRAVENOUS  
TOXICITY STUDY IN DOGS**

**FOR**

**LABORATORIOS INBSA  
CRTA DE SABADELL A GRANOLLERS, KM.14.5  
08185 LLIÇA DE VALL (BARCELONA)  
SPAIN**

**Study Director  
L. J. Clare, D.V.M.**

**Performing Laboratory  
T.P.S., Inc.  
10424 Middle Mt. Vernon Road  
Mt. Vernon, Indiana 47620**

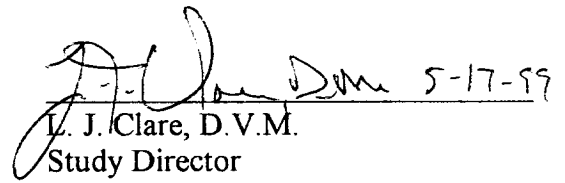
**T.P.S. Study Number  
616C-503-532-98**

**Sponsor I.D. No.:  
032b**



## CERTIFICATION OF GOOD LABORATORY PRACTICE

The enclosed report for T.P.S. Study No. 616C-503-532-98 accurately describes the methods and procedures used in the study and accurately reflects the raw data obtained. The study was conducted in compliance with the FDA Good Laboratory Practice for Nonclinical Laboratory Studies regulations as described in the Federal Register: 21 CFR Part 58. There were no differences discovered between practices used in conducting the study and those required by Good Laboratory Practice regulations.

  
L. J. Clare, D.V.M.  
Study Director  
T.P.S., Inc.

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## QUALITY ASSURANCE STATEMENT

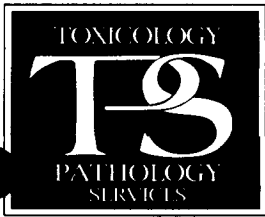
Quality Assurance inspections of Study 616C-503-532-98 were made and the findings reported on the following dates:

<u>Inspection Date</u>	<u>Date Reported</u>
10/12/98	10/12/98
11/02/98	11/05/98
11/03/98	11/03/98
11/05/98	11/05/98
11/09/98	11/09/98
11/10/98	11/10/98
11/23/98	11/23/98
12/08/98	12/08/98
12/22/98	12/22/98
01/21/99	01/21/99
01/26/99	01/26/99
02/01/99	02/01/99
03/25/99	03/25/99

This study was conducted in accordance with FDA Good Laboratory Practice for Nonclinical Laboratory Studies regulations (21 CFR 58). Data reported were compared to original raw data records and found to be accurate.

V. E. Alldredge 17 MAY 99  
V. E. Alldredge  
Quality Assurance Auditor  
T.P.S., Inc.

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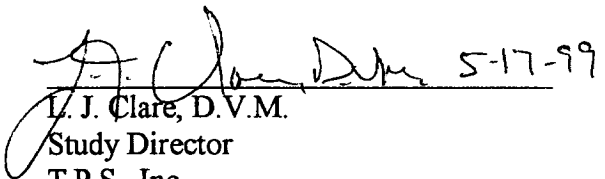
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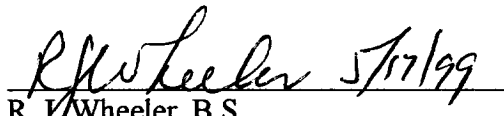
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Study Initiation: 10/28/98  
Animal Phase Initiation: 11/10/98  
Animal Phase Termination: 12/22/98

REPORTED BY:

  
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Vice President of Operations  
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## **IQB-9302: A 28 DAY INTRAVENOUS TOXICITY STUDY IN DOGS**

### **SUMMARY**

Groups of 5 male and 5 female dogs were dosed intravenously daily for at least 28 days at levels of 0 (Group BKG1), 1 (Group BKG2), 2 (Group BKG3), and 3 (Group BKG4) mg IQB-9302/kg/day. The test article was dissolved in the vehicle (0.9% Sterile Saline for Injection, USP) at concentrations that allowed the appropriate dose to be delivered in a volume of 1 mL/kg body weight. Initially, the test article dose solutions were infused at a rate of 3 mL/minute but clinical signs necessitated slowing the infusion rate to 1 and/or 2 mL/minute. The control group was administered 0.9% Sterile Saline for Injection, USP at 3 mL/minute. The last 1 dog/sex/group was allowed 14 days for recovery before sacrifice for evaluation. Physical examinations, including ophthalmology, were made during the pretest period and just before scheduled termination of each dog and clinical observations were conducted a minimum of twice daily during the treatment and recovery period. Body weights were taken pretest, weekly during the evaluation, and just prior to sacrifice. Food consumption was measured weekly. Urine and blood samples were obtained pretest, in Week 4, and from recovery animals in Week 6. Blood samples were obtained on Days 1 and 28 for determination of plasma drug levels. Electrocardiograms and indirect blood pressure measurements were made pretest, in Week 4, and from recovery animals in Week 6. Electrocardiograms were evaluated by a board certified Veterinary Cardiologist. Each dog was euthanized and subjected to a complete gross necropsy in which tissues were collected for histopathologic evaluation by a board certified Veterinary Pathologist and organ weights were taken for statistical evaluation.

There were no test article related effects observed based on physical examinations, ophthalmology, electrocardiograms, indirect blood pressure measurements, clinical pathology, clinical observations (other than dose/postdose), or the macroscopic and microscopic appearance of organs and tissues. Dose/postdose observations revealed clinical signs primarily related to the central nervous system. The effects were generally of short duration and no animals died or were considered moribund during this evaluation. Ataxia was the most frequently noted clinical sign followed by muscle twitching, salivation and seizure activity for both males and females. Muscle twitching and salivation were most commonly noted during infusion of the test article while ataxia and seizures were most commonly observed immediately following completion of the infusion. Ataxia was observed after dosing at least one or more times in every dog in the mid and high-dose groups and in one female dog in the low-dose group. Muscle twitching was noted on at least one occasion for one low-dose male, three low-dose females, three mid-dose males,

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four mid-dose females, and all high-dose dogs. Salivation was observed at least once for two mid-dose males, two mid-dose females, three high-dose males and all high-dose females except one. Seizure activity was observed at least once for one male and one female in the mid-dose group. Three high-dose males had at least one seizure episode while one high-dose female had three seizure episodes and another three high-dose females each had at least four seizures. All dosing/post-dosing clinical signs were resolved, and the dogs appeared normal, within 10-15 minutes postdosing. There were no adverse clinical signs noted during the entire 14-day recovery period.

In conclusion, it would appear that daily intravenous administration of up to 3 mg/kg/day of IQB-9302 to beagle dogs had, with the exception of dosing/postdosing clinical signs, no meaningful, distinct or consistent adverse effects relating to drug safety. Clinical signs during dosing and immediately thereafter, primarily related to the central nervous system, were prevalent in mid and high-dose groups but less frequent (primarily one male and three females) in the low-dose group. The initial dose infusion rate of 3 mL/minute was slowed to 1 and/or 2 mL/minute to minimize the severity of the dosing/postdosing clinical signs. With cessation of treatment all remarkable clinical signs ceased and all other parameters remained normal. Consequently, by strict definition, the no-observed-adverse-effect-level (NOAEL) with regard to clinical signs noted during and immediately after dosing was 0 mg IQB-9302/kg body weight/day; however, a dose of 1 mg/kg/day produced virtually no adverse effects in six of ten dogs.



## INTRODUCTION

The purpose of this study was to evaluate the intravenous toxicity potential of IQB-9302 when administered as a bolus dose intravenously to male and female Beagle dogs once daily for 28 days followed by a 14 day recovery period. The materials and methods used, the observations made, and the results obtained during the study are the subject of this report.

This study was conducted by T.P.S., Inc., 10424 Middle Mt. Vernon Road, Mt. Vernon, Indiana 47620 under the sponsorship of Laboratorios INIBSA to generate animal safety data which may be submitted to regulatory authorities. The laboratories of T.P.S., Inc. are licensed by the U.S.D.A. to conduct research in laboratory animals and all conditions of testing conformed to requirements of the Animal Welfare Act and its amendments. Maintenance of all records and performance of testing procedures were done in accordance with T.P.S. Standard Operating Procedures.

All work reported herein was done according to the requirements specified in the study protocol (Appendix XII). The protocol was reviewed and approved by the sponsor.

The names, titles, and job functions of T.P.S., Inc. supervisory personnel involved in the conduct of the study are listed in Appendix XIII.

All data reported herein were compared to original data and found to be valid and accurate. No known circumstances occurred during the study that may have adversely affected the quality or integrity of the data.

## MATERIALS AND METHODS

**TEST ARTICLE/VEHICLE.** The test article was received from LEBSA on 10/10/98 and identified as follows:

Name:	IQB-9302.HCl
Lot Number:	9454.001
Description:	White Powder
Storage Conditions:	Room temperature

All data relating to the identity, purity and stability of the test article are the responsibility of the sponsor. The Certificate of Analysis for the test article provided by the manufacturer is included in Appendix XI.

The vehicle was received from Henry Schein, Inc. and identified as follows:

Vehicle Name:	0.9% Saline for Injection, USP
Lot Number:	J8H672, J8L530
Physical Description:	Clear liquid
Storage Condition:	Room temperature

**DOSE SOLUTIONS PREPARATION AND CONCENTRATION.** Dose solutions containing test article were prepared under aseptic conditions the night prior to administration by dissolving the appropriate amount of IQB-9302.HCl in 0.9% Saline for Injection, USP such that a volume of 1 mL/kg body weight delivered the desired dosage. The dissolved solution was then passed through a 0.2  $\mu$ m Acrodisc<sup>®</sup> filter into a sterile glass vial and stored at 2 – 8 ° C until used. The concentration of IQB-9302 for Groups BKG2, BKG3, and BKG4 was 1, 2, and 3 mg/mL, respectively. The appropriate amount of test article needed for each dose concentration was determined by calculating the amount of IQB-9302.HCl required and multiplying that amount by the salt/free base correction factor of 1.1249. Animals in Group BKG1 were given 1 mL/kg of the 0.9% Saline for Injection, USP.

**DESCRIPTION OF THE TEST SYSTEM.** Young adult beagle dogs (24 male and 24 female) were obtained from Ridgman Farms, Inc., Mt. Horeb, Wisconsin for this study. The dogs were housed individually in adjacent runs with resting boards, chain link wire sides, and epoxy coated concrete floors with hardwood shavings as bedding in a dedicated temperature and humidity controlled animal room (Room B, Bldg. 106) with filtered air supply (10-15 changes/hour) and cycled lighting (12 hours of light and 12

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hours of darkness). Temperature (minimum, maximum, and current) readings (64–75 °F) were recorded daily and humidity (30–70 %) was recorded weekly. Fresh, dry wood shavings were supplied daily; all shavings were removed and the runs washed down every other week. PMI® Laboratory Canine Diet #5006 or PMI® Certified Canine Diet #5007 was provided *ad libitum* except for an overnight fast (16–18 hours) prior to blood collection for clinical pathology and prior to necropsy. Each dog was identified by a unique permanent marking (ear tattoo) in addition to an appropriately labeled cage card. Cage cards indicated the study number, animal number, tattoo number, dose level and color code consistent with the dose level.

Tested tap water (from a deep well) was provided *ad libitum* except when the dogs were housed in metabolism cages overnight for collection of urine samples. The tap water, provided via an automatic watering system, was analyzed for levels of possible contaminants. To the best of our knowledge, the concentration of contaminants in the bedding, drinking water, and canine diet were below levels known to be capable of compromising the study.

Following an acclimation period of at least 2 weeks, 40 of the dogs in this shipment were selected for study based on body weight, general physical condition, and clinical pathology results.

**ROUTE, METHOD AND RATE OF ADMINISTRATION.** Dose solutions were administered intravenously via an indwelling catheter placed in a cephalic vein. The indwelling catheter was placed just prior to administration of the dose solution and removed immediately after completion of the infusion. A new, sterile catheter was used for each animal each day. All dose groups were initially dosed at an infusion rate of 3 mL/minute. Clinical signs encountered, particularly in mid and high-dose animals, during and immediately after the infusion necessitated slowing the infusion rate to 2 mL/minute and/or 1 mL/minute.

**JUSTIFICATION OF DOSE ROUTE AND METHOD OF ADMINISTRATION.** The route of administration was chosen to determine the toxicopathologic effects of the test article when administered intravenously. The cephalic vein is ideal for intravenous administration in the dog.

**FREQUENCY AND DURATION OF ADMINISTRATION.** Each dog was dosed once daily for at least 28 days. Doses were administered at approximately the same time every day.

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**EXPERIMENTAL DESIGN.** Dogs (males weighing 10.529-13.362 kg; females weighing 8.841-11.162 kg) were assigned to the following groups using a computer generated randomization list:

Group Number	Test Article	Dose (mg/kg/day)	Dose Volume (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

The test article was administered by intravenous infusion once a day for at least 28 days. Dosages were adjusted weekly based on the most current body weights. Following the 28 days of dosing, 1 dog/sex/group was retained for a 14-day reversibility phase.

**JUSTIFICATION OF DOSE LEVELS.** The doses for this study were selected by the sponsor based on information gathered from previous studies with IQB-9302 in beagle dogs.

**PHYSICAL EXAMINATION AND OPHTHALMOLOGY.** All dogs were given a physical and ophthalmoscopic examination by a qualified veterinarian prior to selection for the study and within the final week of the dosing and reversibility phases.

**ELECTROCARDIOGRAM AND BLOOD PRESSURE EVALUATIONS:** Standard ECG tracings (Lead II was evaluated) and indirect blood pressure measurements (systolic, diastolic, and mean) were obtained on all dogs pretest, during Week 4, and on recovery animals prior to necropsy. The ECG tracings were evaluated by a board certified veterinary cardiologist (Dr. Robert L. Hamlin, DVM, Ph.D, DACVIM, 1520 Grenoble Road, Columbus, Ohio).

**CLINICAL SIGNS.** All dogs were observed by a qualified animal technician once in the morning and once in the late afternoon every day for general health, physical appearance, and for any sign of toxicity or clinical effect including behavioral changes. The date of onset, degree, progression, and duration of any clinical signs was recorded in the raw data. The twice daily observation regimen was maintained throughout the reversibility phase. Standard and acceptable veterinary health care practices were adhered to during this evaluation to ensure or maintain good health of the animals.

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**BODY WEIGHT.** Individual body weights were recorded prior to dose initiation and once weekly throughout the dosing and reversibility phases of the study. Body weights used for calculation of the relative organ weights at necropsy were obtained immediately prior to the final or recovery necropsy after an overnight fast.

**FOOD CONSUMPTION.** Individual food consumption was recorded pretest, and weekly throughout the study.

### **CLINICAL PATHOLOGY AND PLASMA TOXICOKINETICS.**

Clinical Pathology: Blood samples were collected after an overnight fast pretest, during Week 4, and prior to necropsy of the recovery animals. Blood was drawn from the jugular vein of each dog on each collection day.

Hematology: Blood was collected into EDTA tubes and used to determine the following hematology parameters:

Leukocyte Count	Mean Corpuscular Hemoglobin
Erythrocyte Count	Mean Corpuscular Hemoglobin Concentration
Hemoglobin	Leukocyte Differential Count
Hematocrit	Platelet Count
Mean Corpuscular Volume	

Clinical Chemistry: Blood was collected and processed to determine the following serum chemistry parameters:

Sodium	Total Bilirubin
Potassium	Calcium
Chloride	Total Protein
Urea Nitrogen	Albumin
Glucose	Globulin
Creatinine	Albumin/Globulin Ratio
Total Cholesterol	Inorganic Phosphorus
Alanine Aminotransferase	Triglycerides
Aspartate Aminotransferase	Alkaline Phosphase

Urinalysis: Following hydration by oral gavage (20 mL tap water/kg body weight), each dog was placed in a metabolism cage and urine collected during the overnight fasting

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period (approximately 16-18 hours) prior to the collection of blood samples. Urine samples were evaluated for the following:

Appearance	Color
Nitrite	Volume
Specific Gravity	Bilirubin
pH	Urobilinogen
Protein	Occult Blood
Glucose	Leukocytes
Ketones	Microscopic Examination

**Plasma Levels:** On Study Days 1 and 28, blood samples (approximately 7 mL) were collected from the jugular vein of each dog in the 3 treated groups at 0 (predose), 5, 15, 30, 60, and 90 minutes and 3 hours post dose, transferred to EDTA tubes, and placed on ice. The plasma was separated within 2 hours after collection, placed in properly labeled tubes, and frozen (approximately -20° C) until analyzed by HPLC for levels of IQB-9302. An equal amount of blood (approximately 49 mL) was drawn from the control dogs on Day 1 and processed to be used as control blanks for the toxicokinetic study.

**Plasma Analyses:** The plasma samples are being held frozen and may be analyzed pending HPLC method development.

## **PATHOLOGY.**

**Gross Necropsy:** A complete gross necropsy on surviving animals was conducted in a random order. The first 4 dogs/sex/group were necropsied at the end of the dosing phase (termination necropsy) and the remaining 1 dog/sex/group was necropsied after a 14-day recovery period (recovery necropsy). All gross necropsy findings were recorded on appropriate forms at the time of necropsy by the necropsy supervisor.

**Method of Euthanasia:** At the completion of the dosing and reversibility phases, surviving dogs were fasted overnight (approximately 16-18 hours) before euthanasia. They were euthanized with an intravenous injection of a sodium pentobarbital solution (approximately 1 mL/4.5 kg body weight).

**Organ Weights.** The following organs were weighed (paired organs weighed together) from each dog.

Liver	Kidneys
Brain	Adrenals

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Testes/Epididymides  
Thyroids/parathyroids  
Ovaries

Spleen  
Heart

Tissue Preservation: The following tissues (when present) from each animal were collected and preserved in 10% neutral buffered formalin:

adrenal glands	Pituitary
aorta	Prostate
bone (femur)	Rectum
bone marrow	Salivary gland (submaxillary)
brain	Sciatic nerve
cecum	Skeletal muscle (biceps femoris)
cervix	Skin
colon	Spinal cord (thoracic)
diaphragm	Spleen
duodenum	Sternebrae
epididymides*	Stomach
esophagus	Testes*
eyes	Thymus (or thymic region)
gallbladder	Thyroid (with parathyroid, if Present)
heart	Trachea
ileum	Urinary bladder
jejunum	Uterus (both horns)
kidneys	Vagina
liver	all gross lesions (to include apparently normal contiguous tissue)
lungs (with mainstem bronchi)	
mammary gland	
mesenteric lymph node	
mandibular lymph node	
ovaries	* Bouin's Fixative
pancreas	

Histopathology: All tissues collected at necropsy were embedded in paraffin, processed into blocks, sectioned, and stained with hematoxylin and eosin. Slides were examined microscopically by a board certified Veterinary Pathologist (D. Barnett, D.V.M., Ph.D., ACVP) employed by T.P.S., Inc.

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**STATISTICS** Statistical methods used in the evaluation of numerical data were those of Dunnett (1) which is a post hoc analysis of variance procedure used to compare one or more treatment groups to a control group. Statistical analysis was performed on body weight, food consumption, organ weight, hematology, clinical chemistry and applicable urinalysis data. Tabulated mean values with p values equal to or less than 0.05 or 0.01 were flagged with an asterisk (\*) or plus (+), respectively. Statistical evaluation of numerical data for the recovery animals could not be performed (i.e., less than 5 degrees of freedom by Dunnett's Test).

**KEY TO TABLES.** Each key, where applicable, is preceded by a key to the abbreviations and symbols used in the tables.

### **PROTOCOL DEVIATIONS.**

Protocol Section Page 4 of 13. Dose Solution Preparation. Per the request of Scientific Director, James A. Botta, Jr., D.V.M., Ph.D., dose solutions from Day 1 and Day 28 were analyzed for IQB-9302 concentration by HPLC using a method validated at T.P.S., Inc.

Protocol Section Page 4 of 13. Dosing Solution Preparation Storage. The protocol states the dosing solutions will be used immediately after preparation. The Scientific Director, James A. Botta, Jr., D.V.M., Ph.D., approved preparation of the dose solutions the night prior to dosing. Dose solutions were stored at 2 – 8 ° C until used. In the validation report for dosing solutions analyzed by HPLC, stability was confirmed up to 2 days when stored at 2 – 8 ° C.

Protocol Section Page 4 of 13. Control Article/Vehicle. Sterile Water for Injection, USP was to be used as the Vehicle Control. However, water was demonstrated to be inappropriate for IV injection by osmolality testing. 0.9% Saline for Injection, USP was selected as the appropriate vehicle. (See Form 120 p. 36865.)

Protocol Section Page 5 of 13. Age and Body Weight. The protocol indicates that dogs will weigh 6-10 kg at study initiation; however, due to delay in study initiation, BKG1F04, BKG2F01, BKG2F03, BKG3F02, BKG3F04, BKG4F01, BKG4F03, and BKG4F04 were the only dogs within the protocol range of 6-10 kg at the start of dosing.

Protocol Section Page 7 of 13. Frequency and Duration of Administration. On Study Day 5, due to excessive movement of Dog BKG1M03 (control), several attempts to place the indwelling cephalic catheter failed and the dog was not dosed.

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Protocol Section Page 7 of 13. Electrocardiogram and Blood Pressure Evaluations. Blood pressure values from Dog BKG3M05 at the Pretest evaluation were inadvertently not recorded.

The deviations listed above did not adversely affect the integrity or evaluation of the data.

**CHRONOLOGICAL TABLE OF SIGNIFICANT EVENTS.**

Animal Receipt:	09-25-98
Test Article Receipt:	10-10-98
Study Initiation	10-28-98
Pretest Blood Collection for Clinical Pathology:	11-03-98
Pretest Urine Collection:	11-02/03-98
Pretest Physical and Ophthalmic Examinations:	11-05-98
Pretest Blood Pressure Measurements:	11-05-98
Pretest ECG Recordings:	11-05-98
Randomization:	11-09-98
Animal Phase Initiation:	11-10-98
Day 1 Pharmacokinetic Blood Collection:	11-10-98
Week 4 Blood Collection for Clinical Pathology:	12-03-98
Week 4 Urine Collection:	12-02/03-98
Week 4 Physical and Ophthalmic Examinations:	12-03/04-98
Week 4 Blood Pressure Measurements:	12-03/04-98

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Week 4 ECG Recordings:	12-03/04-98
Date of Last Dose:	12-07-98 (males) 12-08-98 (females)
Day 28 Pharmacokinetic Blood Collection:	12-07-98
Termination Necropsy:	12-08-98 (males) 12-09-98 (females)
Recovery Blood Collection for Clinical Pathology:	12-22-98
Recovery Urine Collection:	12-21/22-98
Recovery Physical and Ophthalmic Examinations:	12-21-98
Recovery Blood Pressure Measurements:	12-21-98
Recovery ECG Recordings:	12-21-98
Recovery Necropsy:	12-22-98 (males and females)

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## RESULTS

**PHYSICAL EXAMINATION AND OPHTHALMOLOGY.** Physical and ophthalmoscopic examinations made during pretest and prior to sacrifice did not reveal any consistent or distinct treatment related effect.

**CLINICAL SIGNS.** No animals were found dead or considered to moribund during this evaluation. Daily observations prior to dosing revealed minimal clinical signs associated with this evaluation. These included animals with instances of skin lesion (1) and prominent 3<sup>rd</sup> eyelid (1). None of these findings were related to treatment with the test article. These observations are presented in Appendix I. A.

**DOSING/POST-DOSING OBSERVATIONS.** All animals were observed continuously during infusion of the test article and postdosing until clinical signs, if noted, had abated. Individual Dosing/Post-Dosing Observations by group indicating the numbers of animals per group affected by remarkable events are given in Appendix I. B. The most frequently noted event was ataxia, followed by muscle twitching, salivation and seizure activity for both males and females. Muscle twitching and salivation were most commonly noted during the infusion while ataxia and seizures were noted most commonly immediately following completion of the infusion. Ataxia was noted after dosing at least one or more times in every dog in the mid and high-dose groups and in one female dog (BKG2F05) in the low group. Muscle twitching was observed on at least one occasion for one male (BKG2M04) and three female low-dose dogs (BKG2F01, BKG2F03, and BKG2F05), three mid-dose males (BKG3M01, BKG3M03, and BKG3M04), four mid-dose females (BKG3F02, BKG3F03, BKG3F04, and BKG3F05), and all high-dose dogs. Salivation was observed at least once for two mid-dose males (BKG3M02 and BKG3M03), two mid-dose females (BKG3F01 and BKG3F03), three high-dose males (BKG4M03, BKG4M04, and BKG4M05) and all high-dose females except BKG4F02. Seizure activity was observed at least once for one mid-dose male (BKG3M01) and one mid-dose female (BKG3F01). Three male high-dose dogs (BKG4M02, BKG4M03 and BKG4M05) had at least one seizure episode while one high-dose female (BKG4F04) had three seizure episodes and another three high-dose females (BKG4F02, BKG4F03, and BKG4F05) each had at least four seizures. All dosing/post-dosing clinical signs had resolved, and the dogs appeared normal, within 10-15 minutes postdosing.

Following cessation of treatment, no remarkable clinical signs were observed.

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**ELECTROCARDIOGRAMS.** Electrocardiograms (ECGs) taken pretest and during Week 4 and prior to necropsy of the recovery animals were evaluated by a board certified Veterinary Cardiologist. All ECGs on all dogs were within normal limits. There were no drug-related differences when comparing ECGs from dogs receiving any dose with those receiving vehicle at the same recording times, or when compared with pretest recordings. As expected, there were many alterations in amplitudes of component deflections, but these occurred no more frequently in dogs receiving compound than in those receiving vehicle. The report from the Cardiologist is included in Appendix II.

**BLOOD PRESSURE.** Indirect blood pressure measurements (systolic, diastolic, and mean arterial pressure, and pulse) were obtained on all dogs pretest, during Week 4, and on recovery animals prior to necropsy. There were no meaningful differences indicative of a physiological or toxicological effect of the test article.

**BODY WEIGHT.** Body weights were recorded prior to dose initiation and weekly thereafter. These data were evaluated statistically on a weekly basis. Body weights are summarized in Table 1 and Body Weight Change is summarized in Table 2. Individual values are provided in Appendix III. A. and B.

Body Weight: There were no remarkable differences in group mean body weight between treated and control dogs of either sex at any time during the dosing and reversibility phases of this evaluation.

Body Weight Change: There were no remarkable difference in group mean body weight change between treated and control dogs of either sex at any time during the dosing and reversibility phases of this evaluation.

**FOOD CONSUMPTION.** Food consumption was measured, and evaluated statistically, weekly throughout the entire study period. Weekly Food Consumption (g/kg/day) is summarized in Table 3 and given individually in Appendix IV. There were no remarkable differences in group mean food consumption between treated and control dogs of either sex at any time during the dosing and reversibility phases of this evaluation.

#### **CLINICAL PATHOLOGY.**

Hematology: Blood samples were obtained from all dogs after an overnight fast (16-18 hours) pretest, during Week 4, and prior to necropsy of the recovery animals. These data were evaluated statistically, by parameter, according to the time of collection, and are summarized in Table 5 and provided individually in Appendix VI. A.-C.

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There were no biologically relevant differences in hematology parameters between treated and control animals of either sex at any time during the dosing and reversibility phases of this evaluation. Hematology parameters flagged as statistically significant were within the expected range of normal, were significant by variation in a direction not associated with adverse effect, or were not supported by similar changes in the opposite sex group.

Clinical Chemistry: Blood samples were taken at the same frequency as hematology: pretest, during Week 4, and prior to necropsy of the recovery animals. These data were evaluated statistically, by parameter, according to the time of collection, and are summarized in Table 6 and provided individually in Appendix VII. A.-C.

There were no remarkable differences in clinical chemistry parameters between treated and control animals of either sex at any time during the dosing and reversibility phases of this evaluation. Values flagged as statistically significant at pretest were within the expected range of normal and/or were significant by variation in a direction not associated with adverse effect.

Urinalysis: Urine samples were obtained at the same frequency as hematology and clinical chemistry: pretest, during Week 4, and prior to necropsy of the recovery animals. Those elements (Specific Gravity and pH) of the urinalysis evaluation which were evaluated statistically are summarized in Table 4. Individual data are provided in Appendix V. A.-C.

There were no biologically relevant differences in urine specific gravity and pH between treated and control animals at any time during the dosing and reversibility phases of this evaluation. The only statistically significant finding was a lower pH (5) for the Group BKG3 (mid-dose) females at pretest. This was considered incidental as a pH value of 5 is within the expected range (5-8) of normal values.

**DRUG BLOOD LEVELS.** Blood samples for toxicokinetic evaluations were taken from all dogs/sex/group in Groups BKG2-BKG4, immediately prior to dosing and at 5, 15, 30, 60, and 90 minutes and 3 hours postdosing on Days 1 and 28. The rate of drug administration on Study Day 1 was 3 mL/minute. Adverse clinical signs noted during the study (seizure activity, muscle twitching, ataxia, and salivation) made it necessary to reduce the rate of infusion for the Day 28 toxicokinetic evaluation to 2 mL/minute.

Results of the drug blood analyses will be appended when available.

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**ORGAN WEIGHTS.** At termination of dosing (designated Final Necropsy on the Organ Weight tables) a complete gross necropsy was conducted on the first 4 animals/sex/group and the major organs were weighed. The remaining 1 animal/sex/group was held for a 14-day recovery period and then necropsied (designated Recovery Necropsy on the Organ Weight tables).

Statistical evaluation of absolute organ weights (g) revealed no distinct or definitive differences between treated and control groups at the Final Necropsy. Significantly heavier spleens for the low-dose (Group BKG2) males was considered incidental and likely related to the pentobarbital euthanasia. There were no biologically relevant differences in absolute organ weights between treated and control animals of either sex at the Recovery Necropsy. Absolute organ weights are summarized in Table 7 and given individually in Appendix VIII. A. 1. and 2.

When evaluated statistically on the basis of organ weights relative to body weight (%), the only significant difference was heavier spleens for the Group BKG2 males. There were no biologically relevant differences in relative organ weights between treated and control animals of either sex at the Recovery Necropsy. Organ weights relative to body weight are summarized in Table 8 and given individually in Appendix VIII. B. 1. and 2.

**NECROPSY.** Gross necropsy findings are presented individually in Appendix IX. There were few gross necropsy findings noted. One low-dose female (BKG2F01) had an enlarged superficial gland of the third eyelid. This was noted pretest for this dog and is a common occurrence in young dogs that rarely produces detrimental clinical signs. The testicle of one mid-dose male (BKG3M02) was small and one high-dose male (BKG4M05) had two pale areas (streaks) on the surface of the spleen. Otherwise, most animals in each group were not remarkable at termination of treatment.

The only gross finding noted at the Recovery Necropsy was the spleen of one control female (BKG1F05) which had two small areas (streaks) on the surface of the spleen. All other animals were unremarkable at the Recovery Necropsy.

**HISTOPATHOLOGY.** Histopathological evaluation of major organs and tissues from all dogs by a board certified Veterinary Pathologist (ACVP) did not reveal any distinct or consistent microscopic tissue changes related to daily treatment with IQB-9302 for at least 28 days at dosages up to 3 mg/kg/day. The complete reports of the Histopathological Evaluation are provided in Appendix X.

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## DISCUSSION AND CONCLUSIONS

Groups of 5 male and 5 female dogs were dosed intravenously daily for at least 28 days at levels of 1, 2, or 3 mg/kg/day of IQB-9302. All comparisons were made to a similar control group dosed with the vehicle, 0.9% Saline for Injection, USP. Physical examinations, ophthalmology, electrocardiology, clinical pathology, clinical signs (other than dose/postdosing), and the gross and microscopic evaluation of organs and tissues at necropsy did not reveal any treatment related effects. Clinical signs noted during infusion of the test article and immediately postdosing were related primarily to the central nervous system and were generally of short duration. Ataxia was most frequently noted followed by muscle twitching, salivation and seizure activity for both males and females. Muscle twitching and salivation were most commonly noted during the infusion while ataxia and seizures were noted most commonly immediately following completion of the infusion. Ataxia was noted after dosing at least one or more times in every dog in the mid and high-dose groups and in one female dog in the low-dose group. Muscle twitching was observed on at least one occasion for one low-dose male, three low-dose females, three mid-dose males, four mid-dose females, and all high-dose dogs. Salivation was observed at least once for two mid-dose males, two mid-dose females, three high-dose males and all high-dose females except one. Seizure activity was observed at least once for one mid-dose male and one mid-dose female. Three male high-dose dogs had at least one seizure episode while one high-dose female had three seizure episodes and another three high-dose females each had at least four seizures. All dosing/post-dosing clinical signs had resolved, and the dogs appeared normal, within 10-15 minutes postdosing. There were no adverse clinical signs noted during the entire 14-day recovery period.

In conclusion, it would appear that daily intravenous administration of up to 3 mg/kg/day of IQB-9302 to beagle dogs had, with the exception of dosing/postdosing clinical signs, no meaningful, distinct or consistent adverse effects relating to drug safety. Clinical signs during dosing and immediately thereafter, primarily related to the central nervous system, were prevalent in mid and high-dose groups but less frequent (primarily one male and three females) in the low-dose group. The initial dose infusion rate of 3 mL/minute was slowed to 1 and/or 2 mL/minute to minimize the severity of the dosing/postdosing clinical signs. Therefore, by strict definition, the no-observed-adverse-effect-level (NOAEL) with regard to clinical signs noted during and immediately after dosing was 0 mg IQB-9302/kg body weight/day; however, a dose of 1 mg/kg/day produced virtually no adverse effects in six of ten dogs.

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- (1) Dunnett, C. W. 1955. J. Amer. Statis. Assoc., 50, 1096-1121.
- (2) Dunnett, C. W. 1964. Biometrics 20, 482-491.

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## ARCHIVES

**RECORDS.** Original data entries made in laboratory notebooks or other data input forms and one copy of the final report with original signatures will be maintained in the T.P.S., Inc. archives for a period of at least 5 years. Laboratorios INIBSA will be notified to approve the destruction of these records, transfer to their facility or agree to additional archiving charges.

**TEST MATERIAL.** The unused test material was returned to the sponsor, Laboratorios INIBSA, following completion of this study. Data relating to the identity, purity, and stability of the test article will be maintained by the sponsor.

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## T.P.S. RAW DATA REFERENCES

- Form 102A Urine/Feces Collection Record: Nos. 236-238, 246-252
- Form 102B Urinalysis (Qualitative): Nos. 180-182, 190-192, 198-201
- Form 102C Urinalysis (Microscopic): Nos. 170-172, 179-181, 187-189
- Form 103 Clinical Exam Record: Nos. 7542-7589, 7594-7687
- Form 104 Hematology Record: Nos. 2662-2665, 2693-2696, 2714-2716, 2723
- Form 105 Necropsy Record: Nos. 28347-28386
- Form 108 Room Log: Nos. 8439-8441, 8491-8493, 8537-8539, 8583-8585
- Form 108A Notification of Out-of-Range Temperature/Humidity Value(s): Nos. 2322, 2324
- Form 112 Histology Worksheet: Nos. 2615-2622
- Form 116A Clinical Chemistry (Computer Generated): Nos. 651, 654, 658, 659
- Form 120 Test Data Sheet: Nos. 36817-36821, 36910-36921, 36796-36799, 36836, 36837, 36855-36857, 36865, 36881-36887, 36922-36937, 37006-37008, 37013-37023, 37063-37082, 37153-37155, 37162, 37180, 37230, 37231, 37250,
- Form 121 Test Material/Control Article Storage Record: Nos. 1986, 2008, 2021
- Form 122 Animal Receipt Record: No. 766
- Form 128 Study Maintenance Log: Nos. 3424-3426, 3436-3438, 3456-3458, 3473-3475
- Form 132 Body Weights: Nos. 31817-31820, 31871, 31872, 31882, 31883, 31935-31938, 31975-31978, 32035-32038, 32092, 32093, 32095, 32096, 32161-32164, 32170, 32171, 32211, 32212, 32268, 32355, 32356, 32269, 32387, 32388, 32420, 32431, 32460, 32461, 32508, 32509, 32526, 32531, 32532, 32874-32877

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- Form 132A Record of Food Supplementation: Nos. 583-592
- Form 133 Clinical Sign/Palpation Record: Nos. 11078, 11199, 11200, 11243, 11244, 11273, 11274, 11302, 11321, 11372
- Form 133A Observation Record: Nos. 442, 443, 451, 452
- Form 135 Weekly Dosing Record: Nos. 30748-30751, 30814-30817, 30857-30860, 30916-30919, 31002-31005
- Form 143 Test/Control Article Usage Log Sheet: Nos. 8633, 8694, 8697-8701, 8702-8709
- Form 143D Test/Control Solution Dispensing Log: Nos. 1616-1619, 1690-1693
- Form 146 Histopathology Worksheet: Nos. 4555-4570
- Form 148 Histology Laboratory Processing Record: No. 367
- Form 156 Clinical Chemistry Load List (Computer Generated): Nos. 758, 761, 765, 766
- Form 164 Study Director Notification: Nos. 689, 690, 699
- Form 169 HPLC Worksheet: Nos. 516, 517, 526, 527
- Form 170 Sample Inventory Log: Nos. 6502-6506, 6642, 6657-6662, 6665-6672, 6706-6710, 6721-6727, 6752-6756
- Form 177 Electrocardiogram Tracings: Nos. 2194-2368
- Form 177A Blood Collection Container: Nos. 513, 534, 538, 540, 541, 547, 550, 560
- Form 177B Blood Collection Record: Nos. 427, 440-444
- Form 190 Analytical Reference Standard Usage Log: No. 04

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**TABLE 1**

**Summary of Body Weights**

**Dosage Key**

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

**Dunnett's Test Key**

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

TABLE 1

## Summary of Body Weights (kg)

Group Number		Day -1	Week 1	Week 2	Week 3	Week 4	Week 5
Ç BKG1M	Mn:	11.383	11.363	11.608	11.777	11.704	12.362<
	SD:	1.189	1.393	1.396	1.646	1.551	.000
	N:	5	5	5	5	5	1
BKG2M	Mn:	11.937	11.603	12.015	12.064	12.011	11.544<
	SD:	.984	1.007	1.226	1.183	1.065	.000
	N:	5	5	5	5	5	1
BKG3M	Mn:	11.640	11.570	11.630	11.817	11.661	11.086<
	SD:	.589	.612	.720	.683	.541	.000
	N:	5	5	5	5	5	1
BKG4M	Mn:	12.458	12.340	12.514	12.715	12.852	12.904<
	SD:	.836	.806	.905	.965	.984	.000
	N:	5	5	5	5	5	1

TABLE 1

Summary of Body Weights (kg)

Group Number		Week 6
Ç BKG1M	Mn:	13.032<
Ç	SD:	.000
Ç	N:	1
BKG2M	Mn:	12.056<
	SD:	.000
	N:	1
BKG3M	Mn:	11.233<
	SD:	.000
	N:	1
BKG4M	Mn:	13.076<
	SD:	.000
	N:	1

TABLE 1

## Summary of Body Weights (kg)

Group Number		Day -1	Week 1	Week 2	Week 3	Week 4	Week 5
Ç BKG1F	Mn:	10.129	10.025	10.364	10.306	10.457	10.333<
	SD:	.840	.728	.655	.638	.719	.000
	N:	5	5	5	5	5	1
BKG2F	Mn:	10.154	10.044	10.162	10.252	10.292	11.193<
	SD:	.498	.475	.484	.555	.683	.000
	N:	5	5	5	5	5	1
BKG3F	Mn:	10.136	9.778	10.012	10.155	10.117	11.138<
	SD:	.804	.800	.930	.846	.835	.000
	N:	5	5	5	5	5	1
BKG4F	Mn:	9.820	9.596	9.749	9.962	10.043	10.856<
	SD:	.614	.697	.658	.708	.722	.000
	N:	5	5	5	5	5	1

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TABLE 1

## Summary of Body Weights (kg)

Group Number		Week 6
Ç BKG1F	Mn:	10.243<
Ç	SD:	.000
Ç	N:	1
BKG2F	Mn:	11.482<
	SD:	.000
	N:	1
BKG3F	Mn:	11.205<
	SD:	.000
	N:	1
BKG4F	Mn:	10.761<
	SD:	.000
	N:	1

**TABLE 2**

**Summary of Total Body Weight Change**

**Dosage Key**

<b>Group Number</b>	<b>Test Article</b>	<b>Dose (mg/kg/day)</b>	<b>Dose (mL/kg)</b>	<b>Number of Animals*</b>	
				<b>Males</b>	<b>Females</b>
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

**Dunnett's Test Key**

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

TABLE 2

## Summary of Total Body Weight Change (kg)

Group Number		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Ç BKG1M	Mn:	-.020	.225	.394	.321	.718<	1.388<
	SD:	.209	.227	.497	.372	.000	.000
	N:	5	5	5	5	1	1
BKG2M	Mn:	-.335	.077	.127	.074	-.259<	.253<
	SD:	.236	.336	.463	.480	.000	.000
	N:	5	5	5	5	1	1
BKG3M	Mn:	-.070	-.010	.177	.021	-.126<	.021<
	SD:	.591	.310	.327	.281	.000	.000
	N:	5	5	5	5	1	1
BKG4M	Mn:	-.118	.055	.257	.394	.411<	.583<
	SD:	.305	.263	.283	.401	.000	.000
	N:	5	5	5	5	1	1

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TABLE 2

## Summary of Total Body Weight Change (kg)

Group Number		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Ç BKG1F	Mn:	-.103	.235	.177	.328	.134<	.044<
	SD:	.251	.519	.455	.469	.000	.000
	N:	5	5	5	5	1	1
BKG2F	Mn:	-.110	.008	.097	.138	.444<	.733<
	SD:	.186	.206	.321	.251	.000	.000
	N:	5	5	5	5	1	1
BKG3F	Mn:	-.358	-.124	.019	-.019	.143<	.210<
	SD:	.142	.131	.168	.140	.000	.000
	N:	5	5	5	5	1	1
BKG4F	Mn:	-.224	-.071	.143	.223	.253<	.158<
	SD:	.087	.132	.118	.120	.000	.000
	N:	5	5	5	5	1	1

**TABLE 3**

**Summary of Food Consumption**

**Dosage Key**

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

**Dunnett's Test Key**

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

TABLE 3

## Summary of Food Consumption (g/kg/day)

Group Number		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Ç BKG1M	Mn:	29.961	30.548	29.754	26.935	23.933<	26.824<
	SD:	2.416	1.843	1.858	2.385	.000	.000
	N:	5	5	5	5	1	1
BKG2M	Mn:	25.535	30.469	28.431	27.147	25.208<	29.446<
	SD:	2.009	3.568	3.391	4.306	.000	.000
	N:	5	5	5	5	1	1
BKG3M	Mn:	29.827	33.622	31.626	29.990	31.146<	31.781<
	SD:	6.312	6.717	5.315	5.546	.000	.000
	N:	5	5	5	5	1	1
BKG4M	Mn:	27.665	28.921	27.286	26.227	28.341<	30.110<
	SD:	6.184	4.273	3.017	2.665	.000	.000
	N:	5	5	5	5	1	1

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TABLE 3

## Summary of Food Consumption (g/kg/day)

Group Number		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Ç BKG1F	Mn:	31.711	34.320	33.634	29.768	26.061<	39.762<
	SD:	8.773	5.170	5.888	4.438	.000	.000
	N:	5	5	5	5	1	1
BKG2F	Mn:	29.585	32.108	33.360	27.565	33.197<	25.133<
	SD:	2.199	.911	2.786	2.682	.000	.000
	N:	5	5	5	5	1	1
BKG3F	Mn:	30.758	33.719	33.264	31.653	19.278<	23.982<
	SD:	6.657	9.167	7.282	6.248	.000	.000
	N:	5	5	5	5	1	1
BKG4F	Mn:	26.709	30.542	30.201	31.225	35.504<	25.157<
	SD:	4.135	2.302	4.028	4.857	.000	.000
	N:	5	5	5	5	1	1

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**TABLE 4**

**Summary of Urinalysis Data**

**Dosage Key**

<b>Group Number</b>	<b>Test Article</b>	<b>Dose (mg/kg/day)</b>	<b>Dose (mL/kg)</b>	<b>Number of Animals*</b>	
				<b>Males</b>	<b>Females</b>
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

**Abbreviation Key**

SG Specific Gravity

**Dunnett's Test Key**

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

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TABLE 4

## Summary of Urinalysis Data

Group Number		SG Pretest	SG Week 4	SG Recovery	pH Pretest	pH Week 4	pH Recovery
Ç BKG1M	Mn:	1.036	1.055	1.042<	6	6	5<
	Ç SD:	.019	.026	.000	1	1	0
	Ç N:	5	5	1	5	5	1
BKG2M	Mn:	1.047	1.035	1.025<	5	6	6<
	SD:	.019	.003	.000	1	1	0
	N:	5	5	1	5	5	1
BKG3M	Mn:	1.025	1.040	1.040<	6	6	6<
	SD:	.005	.016	.000	1	1	0
	N:	5	5	1	5	5	1
BKG4M	Mn:	1.030	1.035	1.012<	6	6	7<
	SD:	.009	.027	.000	1	1	0
	N:	5	5	1	5	5	1

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TABLE 4  
Summary of Urinalysis Data

Group Number		SG	SG	SG	pH	pH	pH
		Pretest	Week 4	Recovery	Pretest	Week 4	Recovery
Ç BKG1F	Mn:	1.044	1.038	1.041<	6	6	5<
	Ç SD:	.027	.024	.000	1	1	0
	Ç N:	5	5	1	5	5	1
BKG2F	Mn:	1.021	1.020	1.014<	5	6	7<
	SD:	.007	.009	.000	1	1	0
	N:	5	5	1	5	5	1
BKG3F	Mn:	1.040	1.049	1.077<	5*	6	7<
	SD:	.009	.019	.000	0	1	0
	N:	5	5	1	5	5	1
BKG4F	Mn:	1.032	1.045	1.074<	6	6	8<
	SD:	.021	.011	.000	1	1	0
	N:	5	5	1	5	5	1

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**TABLE 5**

**Summary of Hematology Data**

**Dosage Key**

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

**Abbreviation Key**

WBC	White Blood Cells	Thousands/Cubic mm
NEUT	Neutrophils	Percent
LYMP	Lymphocytes	Percent
MONO	Monocytes	Percent
EOS	Eosinophils	Percent
BASO	Basophils	Percent
RBC	Red Blood Cells	Million/Cubic mm
HGB	Hemoglobin	g/dL
HCT	Hematocrit	Percent
MCV	Mean Corpuscular Volume	Cubic Microns
MCH	Mean Corpuscular Hemoglobin	pg
MCHC	Mean Corpuscular Hemoglobin Concentration	g/dL
PLAT	Platelet Count	Thousands/Cubic mm

**Dunnett's Test Key**

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

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TABLE 5A

Summary of Hematology Data  
Pretest

Group Number		WBC	NEUT	LYMP	MONO	EOS	BASO
Ç BKG1M	Mn:	10.7	65	28	5	3	0
	SD:	1.2	9	5	2	3	0
	N:	5	5	5	5	5	5
BKG2M	Mn:	9.8	63	30	4	3	0
	SD:	1.6	7	6	2	2	0
	N:	5	5	5	5	5	5
BKG3M	Mn:	8.6*	59	34	4	3	0
	SD:	.8	10	9	2	1	0
	N:	5	5	5	5	5	5
BKG4M	Mn:	10.9	64	28	5	2	0
	SD:	.7	2	4	2	2	0
	N:	5	5	5	5	5	5

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Sponsor I.D. No.: 032b

TABLE 5A

Summary of Hematology Data  
Pretest

Group Number		RBC	HGB	HCT	MCV	MCH	MCHC
Ç BKG1M	Mn:	6.38	14.4	43.0	67	22.5	33.4
	Ç SD:	.31	.6	1.2	2	.3	.8
	Ç N:	5	5	5	5	5	5
BKG2M	Mn:	6.47	14.1	42.3	65	21.8	33.3
	SD:	.39	.5	1.2	3	.7	.4
	N:	5	5	5	5	5	5
BKG3M	Mn:	6.30	13.8	41.4	66	22.0	33.4
	SD:	.47	.6	2.0	4	1.2	.3
	N:	5	5	5	5	5	5
BKG4M	Mn:	6.62	14.4	43.2	65	21.8	33.4
	SD:	.40	.4	2.3	3	.8	.9
	N:	5	5	5	5	5	5

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TABLE 5A

Summary of Hematology Data  
Pretest

Group Number		PLAT
Ç BKG1M	Mn:	307
Ç	SD:	56
Ç	N:	5
BKG2M	Mn:	292
	SD:	49
	N:	5
BKG3M	Mn:	276
	SD:	64
	N:	5
BKG4M	Mn:	278
	SD:	56
	N:	5

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TABLE 5A  
Summary of Hematology Data  
Pretest

Group Number			WBC	NEUT	LYMP	MONO	EOS	BASO
Ç BKG1F	Mn:		10.7	69	25	5	2	0
	SD:		2.0	9	9	2	2	0
	N:		5	5	5	5	5	5
BKG2F	Mn:		10.7	64	30	5	1	0
	SD:		2.1	12	13	2	1	0
	N:		5	5	5	5	5	5
BKG3F	Mn:		10.8	69	26	4	1	0
	SD:		2.4	12	9	3	1	0
	N:		5	5	5	5	5	5
BKG4F	Mn:		10.3	68	25	6	1	0
	SD:		.8	8	9	3	1	0
	N:		5	5	5	5	5	5

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Sponsor I.D. No.: 032b

TABLE 5A

Summary of Hematology Data  
Pretest

Group Number		RBC	HGB	HCT	MCV	MCH	MCHC
Ç BKG1F	Mn:	7.01	15.3	46.0	66	21.9	33.3
	Ç SD:	.49	.9	3.0	2	.7	.2
	Ç N:	5	5	5	5	5	5
BKG2F	Mn:	7.47	15.2	46.2	62+	20.4+	32.9
	SD:	.56	.9	2.7	1	.5	.9
	N:	5	5	5	5	5	5
BKG3F	Mn:	6.85	15.3	46.2	67	22.3	33.2
	SD:	.33	.7	2.5	1	.3	.5
	N:	5	5	5	5	5	5
BKG4F	Mn:	6.89	15.3	46.4	67	22.2	32.9
	SD:	.76	1.6	4.3	2	.9	.5
	N:	5	5	5	5	5	5



TABLE 5A  
 Summary of Hematology Data  
 Pretest

Group Number		PLAT
Ç BKG1F	Mn:	276
	SD:	38
	N:	5
BKG2F	Mn:	336
	SD:	71
	N:	5
BKG3F	Mn:	352
	SD:	52
	N:	5
BKG4F	Mn:	219
	SD:	43
	N:	5

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TABLE 5B

Summary of Hematology Data  
Week 4

Group Number		WBC	NEUT	LYMP	MONO	EOS	BASO
Ç BKG1M	Mn:	9.4	56	34	8	2	0
	Ç SD:	1.1	7	6	3	3	0
	Ç N:	5	5	5	5	5	5
BKG2M	Mn:	10.3	63	29	5	3	0
	SD:	1.7	8	7	3	3	0
	N:	5	5	5	5	5	5
BKG3M	Mn:	9.0	65	28	5	2	0
	SD:	.7	9	6	4	2	0
	N:	5	5	5	5	5	5
BKG4M	Mn:	11.1	61	32	5	2	0
	SD:	1.7	9	9	4	1	0
	N:	5	5	5	5	5	5

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TABLE 5B

Summary of Hematology Data  
Week 4

Group Number		RBC	HGB	HCT	MCV	MCH	MCHC
Ç BKG1M	Mn:	7.27	16.7	48.3	66	23.0	34.6
	SD:	.13	.2	.5	1	.2	.3
	N:	5	5	5	5	5	5
BKG2M	Mn:	7.22	16.1	46.9	65	22.3	34.3
	SD:	.49	.8	2.6	2	.7	.5
	N:	5	5	5	5	5	5
BKG3M	Mn:	6.63	15.1+	43.8*	66	22.9	34.6
	SD:	.63	.8	2.7	4	1.2	.7
	N:	5	5	5	5	5	5
BKG4M	Mn:	6.86	15.4*	44.5*	65	22.4	34.5
	SD:	.40	.7	2.1	3	.9	.2
	N:	5	5	5	5	5	5

TABLE 5B

Summary of Hematology Data  
Week 4

Group Number		PLAT
Ç BKG1M	Mn:	342
	SD:	61
	N:	5
BKG2M	Mn:	306
	SD:	26
	N:	5
BKG3M	Mn:	303
	SD:	57
	N:	5
BKG4M	Mn:	313
	SD:	34
	N:	5

TABLE 5B

Summary of Hematology Data  
Week 4

Group Number		WBC	NEUT	LYMP	MONO	EOS	BASO
Ç BKG1F	Mn:	10.2	64	29	5	2	0
	SD:	1.9	5	5	2	2	0
	N:	5	5	5	5	5	5
BKG2F	Mn:	9.5	62	32	5	1	0
	SD:	1.0	8	8	2	1	0
	N:	5	5	5	5	5	5
BKG3F	Mn:	10.0	69	27	3	1	0
	SD:	3.9	8	9	2	1	0
	N:	5	5	5	5	5	5
BKG4F	Mn:	8.4	66	29	3	2	0
	SD:	.7	5	6	1	2	0
	N:	5	5	5	5	5	5

TABLE 5B

Summary of Hematology Data  
Week 4

Group Number		RBC	HGB	HCT	MCV	MCH	MCHC
Ç BKG1F	Mn:	7.77	17.2	50.7	65	22.2	33.9
	SD:	.90	1.5	4.3	2	1.0	.6
	N:	5	5	5	5	5	5
BKG2F	Mn:	8.01	17.2	50.1	63	21.5	34.3
	SD:	.63	1.4	3.7	2	.6	.7
	N:	5	5	5	5	5	5
BKG3F	Mn:	7.29	16.6	48.5	67	22.8	34.3
	SD:	.51	.9	2.8	1	.5	.2
	N:	5	5	5	5	5	5
BKG4F	Mn:	7.21	16.5	48.4	67	22.9	34.2
	SD:	.95	2.2	6.6	2	.6	.5
	N:	5	5	5	5	5	5

TABLE 5B

Summary of Hematology Data  
Week 4

Group Number		PLAT
Ç BKG1F	Mn:	311
	SD:	12
	N:	5
BKG2F	Mn:	362
	SD:	31
	N:	5
BKG3F	Mn:	361
	SD:	79
	N:	5
BKG4F	Mn:	221*
	SD:	69
	N:	5

TABLE 5C

Summary of Hematology Data  
Recovery

Group Number		WBC	NEUT	LYMP	MONO	EOS	BASO
Ç BKG1M	Mn:	12.2<	67<	25<	7<	1<	0<
	SD:	.0	0	0	0	0	0
	N:	1	1	1	1	1	1
BKG2M	Mn:	7.4<	71<	27<	1<	1<	0<
	SD:	.0	0	0	0	0	0
	N:	1	1	1	1	1	1
BKG3M	Mn:	7.8<	61<	36<	2<	1<	0<
	SD:	.0	0	0	0	0	0
	N:	1	1	1	1	1	1
BKG4M	Mn:	12.2<	58<	32<	2<	8<	0<
	SD:	.0	0	0	0	0	0
	N:	1	1	1	1	1	1



TABLE 5C

Summary of Hematology Data  
Recovery

Group Number		RBC	HGB	HCT	MCV	MCH	MCHC
Ç BKG1M	Mn:	7.65<	17.2<	49.8<	65<	22.5<	34.5<
	SD:	.00	.0	.0	0	.0	.0
	N:	1	1	1	1	1	1
BKG2M	Mn:	7.36<	15.9<	46.1<	63<	21.6<	34.5<
	SD:	.00	.0	.0	0	.0	.0
	N:	1	1	1	1	1	1
BKG3M	Mn:	7.60<	16.4<	47.2<	62<	21.6<	34.7<
	SD:	.00	.0	.0	0	.0	.0
	N:	1	1	1	1	1	1
BKG4M	Mn:	7.13<	16.6<	48.5<	68<	23.3<	34.2<
	SD:	.00	.0	.0	0	.0	.0
	N:	1	1	1	1	1	1

TABLE 5C

Summary of Hematology Data  
Recovery

Group Number		PLAT
Ç BKG1M	Mn:	358<
	SD:	0
	N:	1
BKG2M	Mn:	345<
	SD:	0
	N:	1
BKG3M	Mn:	254<
	SD:	0
	N:	1
BKG4M	Mn:	284<
	SD:	0
	N:	1

TABLE 5C

Summary of Hematology Data  
Recovery

Group Number		WBC	NEUT	LYMP	MONO	EOS	BASO
Ç BKG1F	Mn:	10.7<	59<	39<	1<	1<	0<
	SD:	.0	0	0	0	0	0
	N:	1	1	1	1	1	1
BKG2F	Mn:	7.1<	66<	30<	2<	2<	0<
	SD:	.0	0	0	0	0	0
	N:	1	1	1	1	1	1
BKG3F	Mn:	7.8<	65<	30<	2<	3<	0<
	SD:	.0	0	0	0	0	0
	N:	1	1	1	1	1	1
BKG4F	Mn:	7.6<	77<	21<	2<	0<	0<
	SD:	.0	0	0	0	0	0
	N:	1	1	1	1	1	1

TABLE 5C

Summary of Hematology Data  
Recovery

Group Number		RBC	HGB	HCT	MCV	MCH	MCHC
Ç BKG1F	Mn:	8.17<	17.4<	50.2<	61<	21.3<	34.7<
	SD:	.00	.0	.0	0	.0	.0
	N:	1	1	1	1	1	1
BKG2F	Mn:	8.08<	17.7<	50.1<	62<	21.9<	35.3<
	SD:	.00	.0	.0	0	.0	.0
	N:	1	1	1	1	1	1
BKG3F	Mn:	7.17<	16.4<	47.6<	66<	22.9<	34.5<
	SD:	.00	.0	.0	0	.0	.0
	N:	1	1	1	1	1	1
BKG4F	Mn:	7.19<	16.9<	48.9<	68<	23.5<	34.6<
	SD:	.00	.0	.0	0	.0	.0
	N:	1	1	1	1	1	1

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TABLE 5C

Summary of Hematology Data  
Recovery

Group Number		PLAT
Ç BKG1F	Mn:	232<
	SD:	0
	N:	1
BKG2F	Mn:	284<
	SD:	0
	N:	1
BKG3F	Mn:	298<
	SD:	0
	N:	1
BKG4F	Mn:	258<
	SD:	0
	N:	1

**TABLE 6**

**Summary of Clinical Chemistry Data**

**Dosage Key**

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

**Abbreviation Key**

CL	Chloride	mEq/L
K	Potassium	mEq/L
NA	Sodium	mEq/L
ALP	Alkaline Phosphatase	IU/L
AST	Aspartate Aminotransferase	IU/L
ALT	Alanine Aminotransferase	IU/L
GLU	Glucose	mg/dL
BUN	Blood Urea Nitrogen	mg/dL
CRE	Creatinine	mg/dL
CHOL	Cholesterol (Total)	mg/dL
TRIG	Triglycerides	mg/dL
PHOS	Phosphorus, Inorganic	mg/dL
TP	Total Protein	g/dL
ALBG	Albumin	g/dL
GLOB	Globulin	g/dL
A/G	Albumin/Globulin Ratio	
CA	Calcium	mg/dL
TBIL	Total Bilirubin	mg/dL

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**TABLE 6**

**Summary of Clinical Chemistry Data (cont'd)**

**Dunnett's Test Key**

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

TABLE 6A

Summary of Clinical Chemistry Data  
Pretest

Group Number			CL	K	NA	ALP	AST	ALT
Ç BKG1M	Mn:		111.3	4.84	146.6	81.9	32.5	34.4
	SD:		2.3	.37	1.4	15.4	4.3	6.3
	N:		5	5	5	5	5	5
BKG2M	Mn:		112.3	4.62	147.1	74.3	34.0	33.1
	SD:		1.2	.22	1.8	11.2	4.7	3.2
	N:		5	5	5	5	5	5
BKG3M	Mn:		111.4	4.56	146.5	72.3	26.2	32.1
	SD:		1.9	.32	.9	16.5	2.5	5.9
	N:		5	5	5	5	5	5
BKG4M	Mn:		112.8	4.67	147.1	83.1	32.0	72.7
	SD:		1.1	.30	1.3	20.6	4.5	84.9
	N:		5	5	5	5	5	5

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TABLE 6A

Summary of Clinical Chemistry Data  
Pretest

Group Number		GLU	BUN	CRE	CHOL	TRIG	PHOS
Ç BKG1M	Mn:	111.4	13.0	.76	173.2	21.5	8.1
	Ç SD:	4.0	1.5	.12	15.9	3.7	.8
	Ç N:	5	5	5	5	5	5
BKG2M	Mn:	119.3*	13.8	.79	175.9	23.6	7.8
	SD:	6.0	1.7	.04	16.3	5.4	.3
	N:	5	5	5	5	5	5
BKG3M	Mn:	107.2	13.9	.79	166.0	19.2	7.7
	SD:	3.9	2.7	.09	23.1	5.7	.4
	N:	5	5	5	5	5	5
BKG4M	Mn:	110.8	15.1	.74	186.4	19.0	7.7
	SD:	4.1	2.8	.17	23.6	4.0	.9
	N:	5	5	.5	5	5	5

TABLE 6A

Summary of Clinical Chemistry Data  
Pretest

Group Number			TP	ALBG	GLOB	A/G	CA	TBIL
Ç	BKG1M	Mn:	5.6	3.3	2.4	1.4	11.1	.13
		SD:	.3	.1	.2	.1	.4	.02
		N:	5	5	5	5	5	5
	BKG2M	Mn:	5.8	3.4	2.4	1.4	11.3	.16
		SD:	.2	.1	.2	.1	.4	.02
		N:	5	5	5	5	5	5
	BKG3M	Mn:	5.6	3.3	2.3	1.4	10.9	.15
		SD:	.3	.2	.2	.2	.3	.03
		N:	5	5	5	5	5	5
	BKG4M	Mn:	5.5	3.3	2.2	1.5	11.2	.14
		SD:	.2	.2	.1	.1	.3	.02
		N:	5	5	5	5	5	5

TABLE 6A

Summary of Clinical Chemistry Data  
Pretest

Group Number			CL	K	NA	ALP	AST	ALT
Ç	BKG1F	Mn:	112.4	4.44	147.2	88.6	34.6	35.7
		SD:	.4	.31	.5	29.9	3.4	3.9
		N:	5	5	5	5	5	5
	BKG2F	Mn:	112.4	4.77	147.4	66.0	30.6	36.9
		SD:	.6	.11	.6	16.5	6.2	4.9
		N:	5	5	5	5	5	5
	BKG3F	Mn:	113.5	4.63	148.6	81.7	32.6	35.2
		SD:	2.6	.16	2.2	15.1	7.6	3.5
		N:	5	5	5	5	5	5
	BKG4F	Mn:	111.2	4.59	146.7	62.4	27.1	33.2
		SD:	1.4	.20	1.3	14.3	5.6	3.6
		N:	5	5	5	5	5	5

TABLE 6A

Summary of Clinical Chemistry Data  
Pretest

Group Number			GLU	BUN	CRE	CHOL	TRIG	PHOS
Ç	BKG1F	Mn:	109.0	15.8	.80	155.3	27.4	7.8
		SD:	3.8	4.8	.14	16.6	5.2	.4
		N:	5	5	5	5	5	5
	BKG2F	Mn:	105.0	14.1	.83	144.1	20.7*	7.3
		SD:	7.5	.8	.16	17.7	3.0	.5
		N:	5	5	5	5	5	5
	BKG3F	Mn:	112.0	16.2	.90	159.2	22.6	7.7
		SD:	12.4	4.1	.07	22.8	3.9	.6
		N:	5	5	5	5	5	5
	BKG4F	Mn:	103.9	15.0	.75	147.8	25.8	7.6
		SD:	3.4	2.1	.05	5.0	3.5	.4
		N:	5	5	5	5	5	5

TABLE 6A

Summary of Clinical Chemistry Data  
Pretest

Group Number		TP	ALBG	GLOB	A/G	CA	TBIL
Ç BKG1F	Mn:	5.8	3.5	2.3	1.5	11.1	.17
	SD:	.3	.2	.1	.0	.2	.04
	N:	5	5	5	5	5	5
BKG2F	Mn:	5.6	3.3	2.3	1.5	10.9	.16
	SD:	.2	.2	.2	.1	.2	.02
	N:	5	5	5	5	5	5
BKG3F	Mn:	5.7	3.5	2.3	1.5	11.1	.15
	SD:	.2	.1	.1	.1	.2	.02
	N:	5	5	5	5	5	5
BKG4F	Mn:	5.6	3.3	2.3	1.5	11.1	.18
	SD:	.3	.2	.1	.1	.4	.03
	N:	5	5	5	5	5	5

TABLE 6B

Summary of Clinical Chemistry Data  
Week 4

Group Number			CL	K	NA	ALP	AST	ALT
Ç BKG1M	Mn:		111.8	4.88	147.2	82.9	30.9	38.9
	SD:		1.5	.16	1.3	16.6	4.1	6.9
	N:		5	5	5	5	5	5
BKG2M	Mn:		111.0	4.66	146.1	69.4	32.4	35.9
	SD:		1.3	.15	1.3	9.3	5.5	6.5
	N:		5	5	5	5	5	5
BKG3M	Mn:		111.8	4.62	146.5	73.3	28.5	37.9
	SD:		.7	.18	1.0	28.6	5.9	6.6
	N:		5	5	5	5	5	5
BKG4M	Mn:		112.4	4.71	146.8	72.0	29.9	59.1
	SD:		1.1	.25	1.5	12.6	5.5	47.7
	N:		5	5	5	5	5	5

TABLE 6B

Summary of Clinical Chemistry Data  
Week 4

Group Number		GLU	BUN	CRE	CHOL	TRIG	PHOS
Ç BKG1M	Mn:	99.5	14.9	.81	172.7	23.9	7.3
	SD:	5.6	2.6	.21	19.0	3.5	.9
	N:	5	5	5	5	5	5
BKG2M	Mn:	99.8	12.9	.91	158.8	22.0	6.5
	SD:	10.9	1.1	.12	14.7	4.0	.5
	N:	5	5	5	5	5	5
BKG3M	Mn:	99.7	13.6	.88	160.7	19.1	6.5
	SD:	.7	2.1	.21	26.7	5.3	.3
	N:	5	5	5	5	5	5
BKG4M	Mn:	101.0	13.8	.98	179.5	18.6	6.9
	SD:	4.5	2.8	.16	23.9	4.9	.6
	N:	5	5	5	5	5	5

TABLE 6B

Summary of Clinical Chemistry Data  
Week 4

Group Number			TP	ALBG	GLOB	A/G	CA	TBIL
Ç	BKG1M	Mn:	5.9	3.4	2.4	1.4	10.8	.15
		SD:	.2	.0	.2	.1	.3	.02
		N:	5	5	5	5	5	5
	BKG2M	Mn:	5.8	3.4	2.4	1.4	10.7	.19
		SD:	.2	.1	.2	.2	.2	.04
		N:	5	5	5	5	5	5
	BKG3M	Mn:	5.7	3.4	2.4	1.4	10.5	.15
		SD:	.3	.2	.2	.1	.1	.02
		N:	5	5	5	5	5	5
	BKG4M	Mn:	5.7	3.3	2.3	1.4	10.7	.15
		SD:	.2	.2	.1	.1	.2	.03
		N:	5	5	5	5	5	5



TABLE 6B

Summary of Clinical Chemistry Data  
Week 4

Group Number			CL	K	NA	ALP	AST	ALT
Ç BKG1F	Mn:		111.8	4.69	147.0	83.8	31.0	34.4
	SD:		.8	.26	.7	30.5	4.2	9.6
	N:		5	5	5	5	5	5
BKG2F	Mn:		112.5	4.78	147.1	59.0	29.6	36.8
	SD:		1.2	.18	1.0	14.4	6.5	5.6
	N:		5	5	5	5	5	5
BKG3F	Mn:		113.6	4.81	148.5	76.4	32.1	34.9
	SD:		2.8	.44	2.1	15.5	5.5	5.8
	N:		5	5	5	5	5	5
BKG4F	Mn:		111.5	4.81	146.5	62.9	29.5	32.6
	SD:		1.6	.51	.8	18.0	7.0	7.2
	N:		5	5	5	5	5	5

TABLE 6B

Summary of Clinical Chemistry Data  
Week 4

Group Number		GLU	BUN	CRE	CHOL	TRIG	PHOS
Ç BKG1F	Mn:	93.7	14.4	.84	146.0	25.8	6.3
	SD:	4.5	2.6	.10	14.4	5.5	.6
	N:	5	5	5	5	5	5
BKG2F	Mn:	91.8	14.1	.95	141.5	22.9	5.8
	SD:	6.5	2.3	.13	21.9	6.0	.3
	N:	5	5	5	5	5	5
BKG3F	Mn:	98.7	15.5	.83	150.6	22.8	5.8
	SD:	8.1	3.5	.11	25.5	3.2	.4
	N:	5	5	5	5	5	5
BKG4F	Mn:	91.9	15.6	.85	135.0	23.4	6.0
	SD:	4.6	1.5	.14	15.0	5.9	.3
	N:	5	5	5	5	5	5

TABLE 6B

Summary of Clinical Chemistry Data  
Week 4

Group Number		TP	ALBG	GLOB	A/G	CA	TBIL
Ç BKG1F	Mn:	5.8	3.5	2.3	1.5	10.1	.20
	SD:	.3	.2	.1	.0	.3	.04
	N:	5	5	5	5	5	5
BKG2F	Mn:	5.6	3.4	2.2	1.5	10.1	.19
	SD:	.3	.3	.2	.1	.2	.03
	N:	5	5	5	5	5	5
BKG3F	Mn:	5.7	3.5	2.2	1.6	10.1	.18
	SD:	.1	.1	.1	.1	.1	.04
	N:	5	5	5	5	5	5
BKG4F	Mn:	5.6	3.4	2.3	1.5	10.1	.20
	SD:	.5	.3	.3	.1	.2	.03
	N:	5	5	5	5	5	5

TABLE 6C

Summary of Clinical Chemistry Data  
Recovery

Group Number			CL	K	NA	ALP	AST	ALT
Ç BKG1M	Mn:		109.3<	5.33<	144.8<	96.6<	26.4<	30.8<
	SD:		.0	.00	.0	.0	.0	.0
	N:		1	1	1	1	1	1
BKG2M	Mn:		109.8<	5.05<	144.0<	64.4<	28.3<	35.3<
	SD:		.0	.00	.0	.0	.0	.0
	N:		1	1	1	1	1	1
BKG3M	Mn:		108.5<	4.51<	143.1<	61.0<	28.4<	39.7<
	SD:		.0	.00	.0	.0	.0	.0
	N:		1	1	1	1	1	1
BKG4M	Mn:		111.8<	4.80<	144.3<	85.3<	23.5<	26.8<
	SD:		.0	.00	.0	.0	.0	.0
	N:		1	1	1	1	1	1

TABLE 6C

Summary of Clinical Chemistry Data  
Recovery

Group Number		GLU	BUN	CRE	CHOL	TRIG	PHOS
Ç BKG1M	Mn:	95.4<	12.0<	.86<	181.8<	26.5<	7.0<
	SD:	.0	.0	.00	.0	.0	.0
	N:	1	1	1	1	1	1
BKG2M	Mn:	108.0<	13.4<	.98<	152.8<	18.0<	6.4<
	SD:	.0	.0	.00	.0	.0	.0
	N:	1	1	1	1	1	1
BKG3M	Mn:	86.6<	12.9<	.81<	162.4<	17.2<	6.0<
	SD:	.0	.0	.00	.0	.0	.0
	N:	1	1	1	1	1	1
BKG4M	Mn:	85.7<	10.5<	.88<	172.4<	22.1<	6.9<
	SD:	.0	.0	.00	.0	.0	.0
	N:	1	1	1	1	1	1

TABLE 6C

Summary of Clinical Chemistry Data  
Recovery

Group Number		TP	ALBG	GLOB	A/G	CA	TBIL
Ç BKG1M	Mn:	5.7<	3.4<	2.3<	1.5<	10.1<	.13<
	SD:	.0	.0	.0	.0	.0	.00
	N:	1	1	1	1	1	1
BKG2M	Mn:	5.9<	3.4<	2.5<	1.4<	10.7<	.18<
	SD:	.0	.0	.0	.0	.0	.00
	N:	1	1	1	1	1	1
BKG3M	Mn:	5.9<	3.6<	2.3<	1.6<	10.7<	.22<
	SD:	.0	.0	.0	.0	.0	.00
	N:	1	1	1	1	1	1
BKG4M	Mn:	5.8<	3.4<	2.4<	1.4<	10.6<	.14<
	SD:	.0	.0	.0	.0	.0	.00
	N:	1	1	1	1	1	1

TABLE 6C

Summary of Clinical Chemistry Data  
Recovery

Group Number		CL	K	NA	ALP	AST	ALT
Ç BKG1F	Mn:	109.0<	4.27<	143.9<	52.5<	25.0<	30.1<
	SD:	.0	.00	.0	.0	.0	.0
	N:	1	1	1	1	1	1
BKG2F	Mn:	107.9<	4.65<	144.4<	49.6<	30.4<	40.9<
	SD:	.0	.00	.0	.0	.0	.0
	N:	1	1	1	1	1	1
BKG3F	Mn:	110.7<	4.95<	144.1<	55.8<	28.5<	30.1<
	SD:	.0	.00	.0	.0	.0	.0
	N:	1	1	1	1	1	1
BKG4F	Mn:	112.3<	4.39<	147.3<	66.8<	29.2<	38.1<
	SD:	.0	.00	.0	.0	.0	.0
	N:	1	1	1	1	1	1

TABLE 6C

Summary of Clinical Chemistry Data  
Recovery

Group Number		GLU	BUN	CRE	CHOL	TRIG	PHOS
Ç BKG1F	Mn:	92.7<	14.5<	.94<	163.2<	21.0<	5.5<
	SD:	.0	.0	.00	.0	.0	.0
	N:	1	1	1	1	1	1
BKG2F	Mn:	91.8<	12.7<	.70<	177.0<	26.5<	5.7<
	SD:	.0	.0	.00	.0	.0	.0
	N:	1	1	1	1	1	1
BKG3F	Mn:	94.1<	18.2<	.99<	169.4<	25.2<	6.8<
	SD:	.0	.0	.00	.0	.0	.0
	N:	1	1	1	1	1	1
BKG4F	Mn:	102.0<	16.2<	1.01<	146.6<	13.7<	5.3<
	SD:	.0	.0	.00	.0	.0	.0
	N:	1	1	1	1	1	1



TABLE 6C

Summary of Clinical Chemistry Data  
Recovery

Group Number		TP	ALBG	GLOB	A/G	CA	TBIL
Ç BKG1F	Mn:	6.1<	3.7<	2.4<	1.5<	10.6<	.21<
	SD:	.0	.0	.0	.0	.0	.00
	N:	1	1	1	1	1	1
BKG2F	Mn:	6.2<	3.5<	2.7<	1.3<	10.8<	.19<
	SD:	.0	.0	.0	.0	.0	.00
	N:	1	1	1	1	1	1
BKG3F	Mn:	5.5<	3.4<	2.1<	1.6<	10.7<	.17<
	SD:	.0	.0	.0	.0	.0	.00
	N:	1	1	1	1	1	1
BKG4F	Mn:	6.2<	3.9<	2.3<	1.7<	10.7<	.20<
	SD:	.0	.0	.0	.0	.0	.00
	N:	1	1	1	1	1	1

**TABLE 7**

**Summary of Absolute Organ Weights**

**Dosage Key**

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

**Abbreviation Key**

BR	Brain	g
HE	Heart	g
KI	Kidneys	g
AD	Adrenals	g
LI	Liver	g
SP	Spleen	g
TE/EP	Testes/Epididymides (males)	g
OV	Ovaries (females)	g
TR/PA	Thyroid/Parathyroids	g

**Dunnett's Test Key**

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

TABLE 7A

Summary of Absolute Organ Weights (g)  
Final Necropsy

Group Number		BR	HE	KI	AD	LI	SP
Ç BKG1M	Mn:	76.364	92.213	51.018	1.188	283.675	52.196
	SD:	4.341	6.782	4.386	.179	42.117	4.927
	N:	4	4	4	4	4	4
BKG2M	Mn:	79.634	96.468	54.660	1.157	302.315	81.078*
	SD:	6.263	9.173	4.130	.245	27.015	17.725
	N:	4	4	4	4	4	4
BKG3M	Mn:	83.647	97.650	59.596	1.240	296.063	56.143
	SD:	6.562	11.197	8.326	.241	40.045	16.470
	N:	4	4	4	4	4	4
BKG4M	Mn:	82.188	96.298	58.389	1.162	313.558	56.998
	SD:	3.480	8.282	9.043	.343	25.030	11.795
	N:	4	4	4	4	4	4

TABLE 7A

Summary of Absolute Organ Weights (g)  
Final Necropsy

Group Number		TE/EP	TR/PA
Ç BKG1M	Mn:	18.886	1.459
	SD:	1.736	.111
	N:	4	4
BKG2M	Mn:	23.087	1.747
	SD:	3.803	.137
	N:	4	4
BKG3M	Mn:	22.603	1.442
	SD:	3.640	.374
	N:	4	4
BKG4M	Mn:	19.568	1.481
	SD:	3.313	.336
	N:	4	4

TABLE 7A

Summary of Absolute Organ Weights (g)  
Final Necropsy

Group Number			BR	HE	KI	AD	LI	SP
Ç BKG1F	Mn:		80.784	83.277	49.426	1.128	249.445	70.167
	SD:		2.462	5.695	5.777	.162	22.071	14.101
	N:		4	4	4	4	4	4
BKG2F	Mn:		78.727	83.878	45.538	1.248	249.043	71.942
	SD:		5.163	2.845	1.622	.271	23.936	11.949
	N:		4	4	4	4	4	4
BKG3F	Mn:		74.869	80.706	48.285	.980	249.535	52.621
	SD:		3.434	5.443	6.181	.158	48.257	11.822
	N:		4	4	4	4	4	4
BKG4F	Mn:		79.629	80.818	45.619	1.219	257.770	77.628
	SD:		8.948	7.715	2.500	.277	28.083	25.002
	N:		4	4	4	4	4	4

TABLE 7A

Summary of Absolute Organ Weights (g)  
Final Necropsy

Group Number		OV	TR/PA
Ç BKG1F	Mn:	.985	1.233
	SD:	.178	.237
	N:	4	4
BKG2F	Mn:	.777	1.364
	SD:	.171	.354
	N:	4	4
BKG3F	Mn:	.765	1.155
	SD:	.181	.159
	N:	4	4
BKG4F	Mn:	.889	1.397
	SD:	.297	.258
	N:	4	4

TABLE 7B

Summary of Absolute Organ Weights (g)  
Recovery Necropsy

Group Number		BR	HE	KI	AD	LI	SP
Ç BKG1M	Mn:	71.305<	84.220<	59.209<	.993<	302.350<	50.832<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1
BKG2M	Mn:	82.540<	103.140<	59.737<	1.006<	334.840<	72.995<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1
BKG3M	Mn:	80.820<	89.830<	49.834<	1.359<	287.020<	76.386<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1
BKG4M	Mn:	87.990<	88.070<	72.627<	1.011<	278.570<	87.810<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1

TABLE 7B

Summary of Absolute Organ Weights (g)  
Recovery Necropsy

Group Number		TE/EP	TR/PA
Ç BKG1M	Mn:	23.862<	1.276<
	SD:	.000	.000
	N:	1	1
BKG2M	Mn:	15.878<	1.423<
	SD:	.000	.000
	N:	1	1
BKG3M	Mn:	17.692<	1.621<
	SD:	.000	.000
	N:	1	1
BKG4M	Mn:	34.494<	1.634<
	SD:	.000	.000
	N:	1	1



TABLE 7B

Summary of Absolute Organ Weights (g)  
Recovery Necropsy

Group Number		BR	HE	KI	AD	LI	SP
Ç BKG1F	Mn:	82.380<	89.460<	44.989<	1.499<	266.320<	97.550<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1
BKG2F	Mn:	77.362<	94.550<	51.074<	1.298<	248.380<	73.551<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1
BKG3F	Mn:	82.410<	77.422<	52.644<	1.372<	263.700<	64.504<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1
BKG4F	Mn:	75.420<	80.500<	40.430<	1.064<	236.140<	60.104<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1

TABLE 7B

Summary of Absolute Organ Weights (g)  
Recovery Necropsy

Group Number		OV	TR/PA
Ç BKG1F	Mn:	1.206<	1.187<
	SD:	.000	.000
	N:	1	1
BKG2F	Mn:	1.084<	.797<
	SD:	.000	.000
	N:	1	1
BKG3F	Mn:	.982<	1.590<
	SD:	.000	.000
	N:	1	1
BKG4F	Mn:	.918<	.899<
	SD:	.000	.000
	N:	1	1

**TABLE 8**

**Summary of Organ Weights Relative to Body Weight**

**Dosage Key**

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

**Abbreviation Key**

BW	Body Weight	kg
BR	Brain	%
HE	Heart	%
KI	Kidneys	%
AD	Adrenals	%
LI	Liver	%
SP	Spleen	%
TE/EP	Testes/Epididymides (males)	%
OV	Ovaries (females)	%
TR/PA	Thyroid/Parathyroids	%

**Dunnett's Test Key**

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

TABLE 8A

Summary of Organ Weights Relative to Body Weight (%)  
Final Necropsy

Group Number		BW	BR	HE	KI	AD	LI
Ç BKG1M	Mn:	11.364	.688	.826	.454	.011	2.510
	SD:	1.935	.125	.130	.049	.003	.266
	N:	4	4	4	4	4	4
BKG2M	Mn:	11.986	.666	.809	.458	.010	2.526
	SD:	1.273	.026	.084	.027	.002	.084
	N:	4	4	4	4	4	4
BKG3M	Mn:	11.685	.716	.834	.513	.011	2.536
	SD:	.610	.049	.068	.092	.002	.336
	N:	4	4	4	4	4	4
BKG4M	Mn:	12.497	.662	.772	.467	.009	2.514
	SD:	1.105	.073	.050	.053	.003	.149
	N:	4	4	4	4	4	4

TABLE 8A

Summary of Organ Weights Relative to Body Weight (%)  
Final Necropsy

Group Number		SP	TE/EP	TR/PA
Ç BKG1M	Mn:	.466	.168	.013
	SD:	.070	.022	.002
	N:	4	4	4
BKG2M	Mn:	.671*	.193	.015
	SD:	.076	.023	.001
	N:	4	4	4
BKG3M	Mn:	.486	.195	.012
	SD:	.167	.041	.003
	N:	4	4	4
BKG4M	Mn:	.455	.157	.012
	SD:	.079	.026	.002
	N:	4	4	4

TABLE 8A

Summary of Organ Weights Relative to Body Weight (%)  
Final Necropsy

Group Number		BW	BR	HE	KI	AD	LI
Ç BKG1F	Mn:	10.348	.785	.807	.479	.011	2.410
	SD:	.815	.081	.068	.065	.002	.063
	N:	4	4	4	4	4	4
BKG2F	Mn:	9.764	.808	.862	.468	.013	2.547
	SD:	.558	.060	.071	.037	.003	.112
	N:	4	4	4	4	4	4
BKG3F	Mn:	9.775	.771	.828	.494	.010	2.541
	SD:	.869	.079	.045	.044	.001	.320
	N:	4	4	4	4	4	4
BKG4F	Mn:	9.728	.818	.832	.469	.012	2.647
	SD:	.516	.076	.084	.025	.002	.219
	N:	4	4	4	4	4	4

TABLE 8A

Summary of Organ Weights Relative to Body Weight (%)  
Final Necropsy

Group Number		SP	OV	TR/PA
Ç BKG1F	Mn:	.677	.010	.012
	SD:	.127	.002	.002
	N:	4	4	4
BKG2F	Mn:	.741	.008	.014
	SD:	.146	.002	.003
	N:	4	4	4
BKG3F	Mn:	.549	.008	.012
	SD:	.169	.001	.002
	N:	4	4	4
BKG4F	Mn:	.797	.009	.014
	SD:	.251	.003	.003
	N:	4	4	4

TABLE 8B

Summary of Organ Weights Relative to Body Weight (%)  
Recovery Necropsy

Group Number		BW	BR	HE	KI	AD	LI
Ç BKG1M	Mn:	12.693<	.562<	.664<	.466<	.008<	2.382<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1
BKG2M	Mn:	11.945<	.691<	.863<	.500<	.008<	2.803<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1
BKG3M	Mn:	11.304<	.715<	.795<	.441<	.012<	2.539<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1
BKG4M	Mn:	12.814<	.687<	.687<	.567<	.008<	2.174<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1



TABLE 8B

Summary of Organ Weights Relative to Body Weight (%)  
Recovery Necropsy

Group Number		SP	TE/EP	TR/PA
Ç BKG1M	Mn:	.400<	.188<	.010<
	SD:	.000	.000	.000
	N:	1	1	1
BKG2M	Mn:	.611<	.133<	.012<
	SD:	.000	.000	.000
	N:	1	1	1
BKG3M	Mn:	.676<	.157<	.014<
	SD:	.000	.000	.000
	N:	1	1	1
BKG4M	Mn:	.685<	.269<	.013<
	SD:	.000	.000	.000
	N:	1	1	1

TABLE 8B

Summary of Organ Weights Relative to Body Weight (%)  
Recovery Necropsy

Group Number		BW	BR	HE	KI	AD	LI
Ç BKG1F	Mn:	10.336<	.797<	.866<	.435<	.015<	2.577<
	Ç SD:	.000	.000	.000	.000	.000	.000
	Ç N:	1	1	1	1	1	1
BKG2F	Mn:	11.022<	.702<	.858<	.463<	.012<	2.253<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1
BKG3F	Mn:	11.012<	.748<	.703<	.478<	.012<	2.395<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1
BKG4F	Mn:	10.744<	.702<	.749<	.376<	.010<	2.198<
	SD:	.000	.000	.000	.000	.000	.000
	N:	1	1	1	1	1	1

TABLE 8B

Summary of Organ Weights Relative to Body Weight (%)  
Recovery Necropsy

Group Number		SP	OV	TR/PA
Ç BKG1F	Mn:	.944<	.012<	.011<
	Ç SD:	.000	.000	.000
	Ç N:	1	1	1
BKG2F	Mn:	.667<	.010<	.007<
	SD:	.000	.000	.000
	N:	1	1	1
BKG3F	Mn:	.586<	.009<	.014<
	SD:	.000	.000	.000
	N:	1	1	1
BKG4F	Mn:	.559<	.009<	.008<
	SD:	.000	.000	.000
	N:	1	1	1

**TABLE 9**

**Summary of Histologic Findings**

**Dosage Key**

<b>Group Number</b>	<b>Test Article</b>	<b>Dose (mg/kg/day)</b>	<b>Dose (mL/kg)</b>	<b>Number of Animals*</b>	
				<b>Males</b>	<b>Females</b>
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

**Abbreviation Key**

**SEVERITY CODES**

- 1 Minimal
- 2 Slight
- 3 Moderate
- 4 Marked
- 5 Severe; Extensive

**SECTION CODES**

- P Present

**TABLE 9A**

**Summary of Histologic Findings  
Final Necropsy**

	BKG1M		BKG2M		BKG3M		BKG4M	
	Inci- dence	Sev- erity	Inci- dence	Sev- erity	Inci- dence	Sev- erity	Inci- dence	Sev- erity
<b>THYROID(S)</b>								
Activity	4/4	(2)	4/4	(2)	4/4	(2)	4/4	(2)
Focal C Cell Hyperplasia	1/4	(1)	0/4		1/4	(2)	0/4	
<b>LUNGS</b>								
Focal Pneumonitis	2/4	(1)	0/4		0/4		0/4	
<b>SPLEEN</b>								
Congestion	4/4	(2)	4/4	(2)	4/4	(2)	4/4	(2)
<b>KIDNEYS</b>								
Mineralized Deposit(s)	3/4	(1)	4/4	(1)	3/4	(1)	2/4	(1)
<b>STOMACH</b>								
Mineralized Deposit(s)	2/4	(2)	1/4	(1)	1/4	(1)	1/4	(1)
<b>EPIDIDYMIDES</b>								
Hyospermia	1/4	(1)	0/4		1/4	(1)	0/4	
<b>TESTES</b>								
Atrophy	1/4	(1)	0/4		1/4	(1)	0/4	
Spermatogenesis	4/4	(2-3)	4/4	(3)	4/4	(2-3)	4/4	(3)
<b>BONE MARROW</b>								
Cellularity	4/4	(3)	4/4	(3)	4/4	(3)	4/4	(3)

Available sections from the following organs/tissues were found to be within the limits of expected histologic appearance:

BRAIN | SPINAL CORD | PITUITARY | ADRENALS | SALIVARY GLANDS | MANDIBULAR LYMPH NODES | THYMUS  
DIAPHRAGM | MESENTERIC LYMPH NODE | AORTA | ESOPHAGUS | TRACHEA | HEART | LIVER | GALLBLADDER  
PANCREAS | DUODENUM | JEJUNUM | ILEUM | CECUM | COLON | RECTUM | SKELETAL MUSCLE  
SCIATIC NERVE | MAMMARY GLAND | SKIN | URINARY BLADDER | PROSTATE | EYES | BONE

**TABLE 9A**

**Summary of Histologic Findings  
Final Necropsy**

	BKG1F		BKG2F		BKG3F		BKG4F	
	Inci- dence	Sev- erity	Inci- dence	Sev- erity	Inci- dence	Sev- erity	Inci- dence	Sev- erity
<b>THYROID(S)</b>								
Activity	4/4	(2)	4/4	(2)	4/4	(2)	4/4	(2)
Focal C Cell Hyperplasia	1/4	(2)	3/4	(1)	0/4		0/4	
<b>LUNGS</b>								
Focal Pneumonitis	1/4	(1)	0/4		0/4		1/4	(1)
<b>SPLEEN</b>								
Congestion	4/4	(2)	4/4	(2)	4/4	(2)	4/4	(2)
<b>KIDNEYS</b>								
Mineralized Deposit(s)	4/4	(1)	4/4	(1)	3/4	(1)	2/4	(1)
<b>OVARIES</b>								
Follicular Development	4/4	(P)	4/4	(P)	4/4	(P)	4/4	(P)
<b>BONE MARROW</b>								
Cellularity	4/4	(3)	4/4	(3)	4/4	(3)	4/4	(3)
<b>HARDERIAN GLANDS</b>								
Hyperplasia	0/0		1/1	(2)	0/0		0/0	

Available sections from the following organs/tissues were found to be within the limits of expected histologic appearance:

BRAIN | SPINAL CORD | PITUITARY | ADRENALS | SALIVARY GLANDS | MANDIBULAR LYMPH NODES | THYMUS  
 DIAPHRAGM | MESENTERIC LYMPH NODE | AORTA | ESOPHAGUS | TRACHEA | HEART | LIVER | GALLBLADDER  
 STOMACH | PANCREAS | DUODENUM | JEJUNUM | ILEUM | CECUM | COLON | RECTUM | SKELETAL MUSCLE  
 SCIATIC NERVE | MAMMARY GLAND | SKIN | URINARY BLADDER | UTERUS | CERVIX | VAGINA | EYES  
 BONE

**TABLE 9B**

**Summary of Histologic Findings  
Recovery Necropsy**

	BKG1M		BKG2M		BKG3M		BKG4M	
	Inci- dence	Sev- erity	Inci- dence	Sev- erity	Inci- dence	Sev- erity	Inci- dence	Sev- erity
<b>THYROID(S)</b>								
Activity	1/1	(2)	1/1	(2)	1/1	(2)	1/1	(2)
Focal C Cell Hyperplasia	0/1		1/1	(2)	1/1	(2)	1/1	(1)
<b>SPLEEN</b>								
Congestion	1/1	(2)	1/1	(2)	1/1	(2)	1/1	(2)
<b>KIDNEYS</b>								
Mineralized Deposit(s)	1/1	(1)	1/1	(1)	1/1	(1)	1/1	(1)
<b>STOMACH</b>								
Mineralized Deposit(s)	1/1	(2)	0/1		0/1		0/1	
<b>PROSTATE</b>								
Focal Inflammatory Infiltrate	0/1		0/1		0/1		1/1	(2)
<b>TESTES</b>								
Spermatogenesis	1/1	(3)	1/1	(3)	1/1	(3)	1/1	(3)
<b>BONE MARROW</b>								
Cellularity	1/1	(3)	1/1	(3)	1/1	(3)	1/1	(3)

Available sections from the following organs/tissues were found to be within the limits of expected histologic appearance:

BRAIN | SPINAL CORD | PITUITARY | ADRENALS | SALIVARY GLANDS | MANDIBULAR LYMPH NODES | THYMUS  
 DIAPHRAGM | MESENTERIC LYMPH NODE | AORTA | ESOPHAGUS | TRACHEA | HEART | LUNGS | LIVER  
 GALLBLADDER | PANCREAS | DUODENUM | JEJUNUM | ILEUM | CECUM | COLON | RECTUM  
 SKELETAL MUSCLE | SCIATIC NERVE | MAMMARY GLAND | SKIN | URINARY BLADDER | EPIDIDYMIDES  
 EYES | BONE

**TABLE 9B**

**Summary of Histologic Findings  
Recovery Necropsy**

	BKG1F		BKG2F		BKG3F		BKG4F	
	Inci- dence	Sev- erity	Inci- dence	Sev- erity	Inci- dence	Sev- erity	Inci- dence	Sev- erity
<b>THYROID(S)</b>								
Activity	1/1	(2)	1/1	(2)	1/1	(2)	1/1	(2)
Focal C Cell Hyperplasia	0/1		0/1		1/1	(2)	0/1	
<b>SPLEEN</b>								
Congestion	1/1	(2)	1/1	(2)	1/1	(2)	1/1	(2)
Focal Fibrosis	1/1	(2)	0/1		0/1		0/1	
<b>KIDNEYS</b>								
Cyst(s)	0/1		1/1	(2)	0/1		0/1	
Mineralized Deposit(s)	1/1	(1)	1/1	(1)	1/1	(1)	1/1	(1)
<b>OVARIES</b>								
Follicular Development	1/1	(P)	1/1	(P)	1/1	(P)	1/1	(P)
<b>BONE MARROW</b>								
Cellularity	1/1	(3)	1/1	(3)	1/1	(3)	1/1	(3)

Available sections from the following organs/tissues were found to be within the limits of expected histologic appearance:

BRAIN | SPINAL CORD | PITUITARY | ADRENALS | SALIVARY GLANDS | MANDIBULAR LYMPH NODES | THYMUS  
 DIAPHRAGM | MESENTERIC LYMPH NODE | AORTA | ESOPHAGUS | TRACHEA | HEART | LUNGS | LIVER  
 GALLBLADDER | STOMACH | PANCREAS | DUODENUM | JEJUNUM | ILEUM | CECUM | COLON | RECTUM  
 SKELETAL MUSCLE | SCIATIC NERVE | MAMMARY GLAND | SKIN | URINARY BLADDER | UTERUS | CERVIX  
 VAGINA | EYES | BONE



## **APPENDIX I**

### **INDIVIDUAL ANIMAL OBSERVATIONS**

- A. Clinical Sign/Palpation Record**
- B. Dose/Post-Dosing Observations**
- C. Blood Pressure Measurements**

## Key to Individual Animal Observations

### Dosage Key

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

**A. Clinical Sign/Palpation Record**

T.P.S. Study No.: 616C-503-532-98  
Sponsor I.D. No.: 032b

CLINICAL SIGN/PALPATION RECORD

ANIMAL	WEEK FIRST OBSERVED	WEEK LAST OBSERVED	OBSERVATION
BKG 3 M 3	1	4	Lesion Neck (Left)
BKG 2 F 1	1	*	Prominent Third Eyelid (Right)

\* Still present at last observation

## **B. Dose/Post-Dosing Observations**

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Sponsor I.D. No.: 032b

Dose / Post Dose Observations

ANIMAL NO	OBSERVATION	DAY OF STUDY											
BKG 2 M 4	Muscle Twitching	9	28										
BKG 3 M 1	Ataxia	1	18	24	27								
	Muscle Twitching	3	4	13	20	28							
	Seizure	1											
BKG 3 M 2	Ataxia	1	4	6	18	24	26						
	Salivation	8	9	10	12	14	15	17	18	19	21	22	23
		24	25	26	27	28							
BKG 3 M 3	Ataxia	1	2	6	24	25	26	27					
	Muscle Twitching	8	17	25									
	Salivation	20											
BKG 3 M 4	Ataxia	1	2	3	4	5	6	8	14	15	17	18	21
		24	25	26									
	Muscle Twitching	4	24										
BKG 3 M 5	Ataxia	1	2	5	6	17	18	27					
BKG 4 M 1	Ataxia	1	2	5	6	8	11	12	14	15	16	17	18
		19	20	21	22	23	24	25	26	27	28		
	Muscle Twitching	2	3	4	5	6	8	9	11	12	14	15	18
		21	23	25	27	28							
BKG 4 M 2	Ataxia	1	2	3	6	7	11	12	13	14	15	16	17
		18	19	20	21	22	23	24	25	26	27	28	
	Muscle Twitching	2	4	5	6	15	17	18	19	20	21	22	23
	Seizure	24	5										
BKG 4 M 3	Ataxia	1	2	3	5	6	12	14	15	16	17	18	19
		20	21	23	25	26	27	28					
	Muscle Twitching	4	8	17	22	24							
	Salivation	3	4	5	7	15	16	17	21	23	24	25	26
		1	28										
BKG 4 M 4	Ataxia	1	7	8	10	13	14	15	16	17	18	19	20
		21	22	23	24	25	26	27	28				
	Muscle Twitching	21	22	25	26	27	28						
	Salivation	1	2	9	11	12	13	14	15	16	17	18	19
		20	21	22	23	24	25	26	27	28			
BKG 4 M 5	Ataxia	1	2	3	4	6	7	8	11	12	14	15	16
		17	18	19	20	21	22	23	24	25	26	27	28
	Muscle Twitching	5	7	8	9	10	11	13	14	15	16	17	18
		20	21	22	23	24	26	27	28				
	Salivation	1	3	4	5	7	8	9	10	11	12	13	16
	17	19	20	21	22	23	25	26	27	28			
		5	28										
	Seizure	5	28										

ANIMAL NO	OBSERVATION	Dose / Post Dose Observations											
		DAY OF STUDY											
BKG 2 F 1	Muscle Twitching	3											
BKG 2 F 3	Muscle Twitching	17	19	20	21	22	23	24	25	26	27		
BKG 2 F 5	Ataxia	17											
	Muscle Twitching	17											
BKG 3 F 1	Ataxia	1	24										
	Salivation	5											
	Seizure	1											
BKG 3 F 2	Ataxia	1											
	Muscle Twitching	5	6	8	10	16	17	18	19	21	22	23	24
		25	26	27	28	29							
BKG 3 F 3	Ataxia	1	3	6	12	14	17	21	22	24	25	26	
	Muscle Twitching	17	18	24	25								
	Salivation	8	13	18	24	27							
BKG 3 F 4	Ataxia	1	6	7	17	18	22	23	24	25	26	27	
	Muscle Twitching	10	23	28									
BKG 3 F 5	Ataxia	1	14	22	24	26							
	Muscle Twitching	24	28										
BKG 4 F 1	Ataxia	1	2	3	8	11	13	14	16	17	18	19	20
		21	22	24	25	28							
	Muscle Twitching	3	14	22	24	28							
	Salivation	12	18	20	21	22	23	25	27				
BKG 4 F 2	Ataxia	1	2	3	4	5	6	7	8	11	12	13	14
		15	16	21	22	24	25	27	28	29			
	Muscle Twitching	2	3	6	8	9	10	11	12	13	14	15	16
		17	18	19	22	23	24	25	26	27	28		
	Seizure	1	14	16	28								
BKG 4 F 3	Ataxia	1	2	5	6	9	13	14	15	16	17	18	19
		20	21	22	23	24	25	26	27	28	29		
	Muscle Twitching	3	5	6	7	8	9	10	12	13	15	16	17
		18	19	20	21	22	23	24	25	26	27	28	29
	Salivation	2	3	4	5	6	7	8	9	10	12	14	15
		16	17	18	19	20	21	22	23	24	25	26	29
	Seizure	7	21	23	27								
BKG 4 F 4	Ataxia	1	2	3	4	5	6	7	9	11	14	15	16
		17	18	19	20	21	22	23	24	27	28	29	
	Muscle Twitching	4	5	6	12	13	14	16	18	19	20	21	22
		23	25	27									
	Salivation	2	3	4	5	6	7	8	9	10	11	12	13
		14	15	16	17	18	19	20	21	22	23	24	25
		26	27	28	29								
	Seizure	1	14	21									
BKG 4 F 5	Ataxia	1	2	5	6	9	10	13	14	17	21	23	24

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ANIMAL NO	OBSERVATION	Dose / Post Dose Observations													
		DAY OF STUDY													
		26	28	29											
	Muscle Twitching	2	3	5	6	7	8	9	10	11	12	13	14		
		15	16	17	18	19	20	21	22	24	25	26	27		
		28	29												
	Salivation	5	9												
	Seizure	1	9	14	28										

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### **C. Blood Pressure Measurements**

T.P.S. Study No.: 616C-503-532-98  
Sponsor I.D. No.: 032b

## BLOOD PRESSURE MEASUREMENTS

### Mean Arterial Pressure

ANIMAL NUMBER	PRETEST 11-05-98	WEEK 4 12-03-98	RECOVERY 12-21-98
BKG1M01	122	104A	S
BKG1M02	90	91	S
BKG1M03	107	110	S
BKG1M04	90	146	S
BKG1M05	77	122	72
BKG2M01	106	115	S
BKG2M02	141	76	S
BKG2M03	70	102	S
BKG2M04	78	129	S
BKG2M05	105	116	91
BKG3M01	100	102	S
BKG3M02	117	117	S
BKG3M03	125	104	S
BKG3M04	83	104	S
BKG3M05	I	97	106
BKG4M01	71	90	S
BKG4M02	124	100	S
BKG4M03	119	124	S
BKG4M04	111	65	S
BKG4M05	82	101	106

I = Inadvertently not recorded

S = Scheduled sacrificed

A = Blood pressure measurements were obtained on 12-04-98 for Animal BKG1M01

## BLOOD PRESSURE MEASUREMENTS

### Pulse

ANIMAL NUMBER	PRETEST 11-05-98	WEEK 4 12-03-98	RECOVERY 12-21-98
BKG1M01	76	121A	S
BKG1M02	111	90	S
BKG1M03	126	153	S
BKG1M04	133	126	S
BKG1M05	90	117	145
BKG2M01	123	125	S
BKG2M02	123	126	S
BKG2M03	153	133	S
BKG2M04	148	101	S
BKG2M05	111	119	98
BKG3M01	57	94	S
BKG3M02	119	148	S
BKG3M03	111	111	S
BKG3M04	117	117	S
BKG3M05	I	125	129
BKG4M01	150	98	S
BKG4M02	135	126	S
BKG4M03	129	119	S
BKG4M04	121	114	S
BKG4M05	125	135	86

I = Inadvertently not recorded

S = Scheduled sacrificed

A = Blood pressure measurements were obtained on 12-04-98 for Animal BKG1M01

## BLOOD PRESSURE MEASUREMENTS

### Systolic/Diastolic Pressure

ANIMAL NUMBER	PRETEST 11-05-98	WEEK 4 12-03-98	RECOVERY 12-21-98
BKG1M01	129/108	116/98A	S
BKG1M02	137/71	130/75	S
BKG1M03	155/83	122/97	S
BKG1M04	109/71	156/135	S
BKG1M05	91/66	135/101	120/56
BKG2M01	135/101	141/93	S
BKG2M02	183/121	112/62	S
BKG2M03	91/52	106/97	S
BKG2M04	124/65	146/113	S
BKG2M05	147/92	136/97	123/69
BKG3M01	137/77	119/91	S
BKG3M02	125/112	130/96	S
BKG3M03	172/100	157/76	S
BKG3M04	109/78	136/87	S
BKG3M05	I/I	131/76	129/85
BKG4M01	105/57	112/77	S
BKG4M02	131/116	112/91	S
BKG4M03	174/91	164/96	S
BKG4M04	138/93	105/50	S
BKG4M05	125/69	167/96	137/88

I = Inadvertently not recorded

S = Scheduled sacrificed

A = Blood pressure measurements were obtained on 12-04-98 for Animal BKG1M01

T.P.S. Study No.: 616C-503-532-98

Sponsor I.D. No.: 032b

## BLOOD PRESSURE MEASUREMENTS

### Mean Arterial Pressure

ANIMAL NUMBER	PRETEST 11-05-98	WEEK 4 12-04-98	RECOVERY 12-21-98
BKG1F01	58	78	S
BKG1F02	92	120	S
BKG1F03	92	102	S
BKG1F04	92	71	S
BKG1F05	117	86	104
BKG2F01	83	82	S
BKG2F02	41	59	S
BKG2F03	92	96	S
BKG2F04	94	88	S
BKG2F05	66	101	78
BKG3F01	129	96	S
BKG3F02	80	99	S
BKG3F03	83	113	S
BKG3F04	100	92	S
BKG3F05	114	87	109
BKG4F01	124	105	S
BKG4F02	70	102	S
BKG4F03	97	97	S
BKG4F04	110	111	S
BKG4F05	120	88	96

S = Scheduled sacrificed

## BLOOD PRESSURE MEASUREMENTS

### Pulse

ANIMAL NUMBER	PRETEST 11-05-98	WEEK 4 12-04-98	RECOVERY 12-21-98
BKG1F01	166	105	S
BKG1F02	137	137	S
BKG1F03	163	88	S
BKG1F04	97	112	S
BKG1F05	145	111	129
BKG2F01	66	74	S
BKG2F02	153	160	S
BKG2F03	98	82	S
BKG2F04	112	91	S
BKG2F05	111	109	129
BKG3F01	129	106	S
BKG3F02	129	156	S
BKG3F03	150	148	S
BKG3F04	94	86	S
BKG3F05	140	142	119
BKG4F01	137	129	S
BKG4F02	52	88	S
BKG4F03	145	117	S
BKG4F04	103	103	S
BKG4F05	125	150	98

S = Scheduled sacrificed

## BLOOD PRESSURE MEASUREMENTS

### Systolic/Diastolic Pressure

ANIMAL NUMBER	PRETEST 11-05-98	WEEK 4 12-04-98	RECOVERY 12-21-98
BKG1F01	112/47	137/61	S
BKG1F02	146/73	167/100	S
BKG1F03	110/86	129/83	S
BKG1F04	147/69	119/57	S
BKG1F05	146/90	138/80	130/76
BKG2F01	130/69	131/61	S
BKG2F02	71/36	112/46	S
BKG2F03	140/76	130/90	S
BKG2F04	121/74	134/83	S
BKG2F05	113/52	115/81	110/67
BKG3F01	177/112	144/73	S
BKG3F02	185/65	112/85	S
BKG3F03	150/67	139/92	S
BKG3F04	106/95	110/75	S
BKG3F05	148/97	101/82	123/93
BKG4F01	151/103	139/94	S
BKG4F02	127/56	115/81	S
BKG4F03	118/81	150/72	S
BKG4F04	124/90	138/90	S
BKG4F05	148/100	175/76	136/74

S = Scheduled sacrificed

**APPENDIX II**  
**ELECTROCARDIOGRAM EVALUATION REPORT**

T.P.S. Study No.: 616C-503-532-98  
Sponsor I.D. No.: 032b



Robert L. Hamlin, DVM, PhD, DACVIM  
1520 Grenoble Rd.  
Columbus, Ohio 43221  
614-486-7542  
Fax: 614-486-7545

January 6, 1999

Lisa J. Clare, DVM  
Study Director  
TPS  
10424 Middle Mt. Vernon Road  
Mount Vernon, Indiana 47620

RE: ECG findings on 40 dogs for Study No. TPS 616C.

Dear Dr. Clare,

All ECGs are within normal limits. There are no drug-related differences when comparing ECGs from dogs receiving any dose with those receiving vehicle at the same recording times, or when compared with pretest recordings. As expected, there are many alterations in amplitudes of component deflections, but these occur no more frequently in dogs receiving compound than in those receiving vehicle.

Sincerely,



Robert L. Hamlin, DVM, PhD, DACVIM (Cardiology/Internal Medicine)

T.P.S. Study No.: 616C-503-532-98  
Sponsor I.D. No.: 032b

**APPENDIX III**

**INDIVIDUAL BODY WEIGHT DATA**

- A. Body Weights**
- B. Total Body Weight Change**

## Key to Individual Body Weight Data

### Dosage Key

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

### Abbreviation Key

S = Scheduled Sacrifice

### Dunnett's Test Key

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

**A. Body Weights**

Individual Body Weights (kg)

Animal Number	Day -1	Week 1	Week 2	Week 3	Week 4	Week 5
BKG1M 1	10.614	10.546	10.844	11.103	10.845	S
BKG1M 2	10.651	10.487	10.671	10.613	10.621	S
BKG1M 3	10.643	10.441	10.638	10.581	10.754	S
BKG1M 4	13.362	13.685	13.898	14.519	14.297	S
BKG1M 5	11.644	11.656	11.989	12.069	12.002	12.362
Ç BKG1M Mn:	11.383	11.363	11.608	11.777	11.704	12.362<
BKG2M 1	10.529	10.437	10.550	10.815	10.925	S
BKG2M 2	13.138	13.067	13.789	13.929	13.729	S
BKG2M 3	11.677	11.195	11.475	11.842	11.929	S
BKG2M 4	12.540	12.092	12.578	12.336	12.091	S
BKG2M 5	11.803	11.223	11.682	11.400	11.381	11.544
BKG2M Mn:	11.937	11.603	12.015	12.064	12.011	11.544<
BKG3M 1	11.506	11.537	11.685	11.826	11.568	S
BKG3M 2	12.669	11.962	12.657	12.748	12.416	S
BKG3M 3	11.506	12.381	11.890	12.175	11.984	S
BKG3M 4	11.306	10.983	11.118	11.288	11.168	S
BKG3M 5	11.212	10.987	10.801	11.047	11.168	11.086
BKG3M Mn:	11.640	11.570	11.630	11.817	11.661	11.086<
BKG4M 1	13.161	13.303	13.514	13.911	14.203	S
BKG4M 2	12.487	12.448	12.274	12.610	12.895	S
BKG4M 3	13.078	12.814	13.267	13.215	13.078	S
BKG4M 4	11.073	11.218	11.254	11.301	11.457	S
BKG4M 5	12.493	11.919	12.260	12.540	12.627	12.904
BKG4M Mn:	12.458	12.340	12.514	12.715	12.852	12.904<

Individual Body Weights (kg)

Animal Number	Week 6
BKG1M 1	S
BKG1M 2	S
BKG1M 3	S
BKG1M 4	S
BKG1M 5	13.032
Ç BKG1M Mn:	13.032<
BKG2M 1	S
BKG2M 2	S
BKG2M 3	S
BKG2M 4	S
BKG2M 5	12.056
BKG2M Mn:	12.056<
BKG3M 1	S
BKG3M 2	S
BKG3M 3	S
BKG3M 4	S
BKG3M 5	11.233
BKG3M Mn:	11.233<
BKG4M 1	S
BKG4M 2	S
BKG4M 3	S
BKG4M 4	S
BKG4M 5	13.076
BKG4M Mn:	13.076<

Individual Body Weights (kg)

Animal Number	Day -1	Week 1	Week 2	Week 3	Week 4	Week 5
BKG1F 1	10.025	9.852	9.883	9.863	9.900	S
BKG1F 2	11.162	11.143	11.489	11.368	11.645	S
BKG1F 3	10.417	10.003	10.339	10.388	10.559	S
BKG1F 4	8.841	9.108	9.945	9.793	9.911	S
BKG1F 5	10.199	10.021	10.163	10.116	10.269	10.333
Ç BKG1F Mn:	10.129	10.025	10.364	10.306	10.457	10.333<
BKG2F 1	9.797	9.845	9.939	10.298	9.948	S
BKG2F 2	10.559	10.575	10.271	10.831	11.040	S
BKG2F 3	9.568	9.558	9.685	9.635	9.548	S
BKG2F 4	10.098	9.712	9.972	9.739	9.925	S
BKG2F 5	10.749	10.530	10.943	10.755	10.998	11.193
BKG2F Mn:	10.154	10.044	10.162	10.252	10.292	11.193<
BKG3F 1	10.822	10.241	10.822	10.817	10.651	S
BKG3F 2	9.383	9.000	9.181	9.496	9.354	S
BKG3F 3	10.237	10.031	10.142	10.474	10.422	S
BKG3F 4	9.243	8.895	8.935	9.035	9.125	S
BKG3F 5	10.995	10.724	10.981	10.951	11.035	11.138
BKG3F Mn:	10.136	9.778	10.012	10.155	10.117	11.138<
BKG4F 1	9.389	9.128	9.208	9.458	9.459	S
BKG4F 2	10.340	10.201	10.486	10.661	10.703	S
BKG4F 3	9.216	8.923	9.154	9.225	9.382	S
BKG4F 4	9.550	9.246	9.465	9.700	9.743	S
BKG4F 5	10.603	10.482	10.430	10.767	10.928	10.856
BKG4F Mn:	9.820	9.596	9.749	9.962	10.043	10.856<

Individual Body Weights (kg)

Animal Number	Week 6
BKG1F 1	S
BKG1F 2	S
BKG1F 3	S
BKG1F 4	S
BKG1F 5	10.243
Ç BKG1F Mn:	10.243<
BKG2F 1	S
BKG2F 2	S
BKG2F 3	S
BKG2F 4	S
BKG2F 5	11.482
BKG2F Mn:	11.482<
BKG3F 1	S
BKG3F 2	S
BKG3F 3	S
BKG3F 4	S
BKG3F 5	11.205
BKG3F Mn:	11.205<
BKG4F 1	S
BKG4F 2	S
BKG4F 3	S
BKG4F 4	S
BKG4F 5	10.761
BKG4F Mn:	10.761<



## **B. Total Body Weight Change**

T.P.S. Study No.: 616C-503-532-98  
Sponsor I.D. No.: 032b

Individual Total Body Weight Change (kg)

Animal Number	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
BKG1M 1	-.068	.230	.489	.231	S	S
BKG1M 2	-.164	.020	-.038	-.030	S	S
BKG1M 3	-.202	-.005	-.062	.111	S	S
BKG1M 4	.323	.536	1.157	.935	S	S
BKG1M 5	.012	.345	.425	.358	.718	1.388
Ç BKG1M Mn:	-.020	.225	.394	.321	.718<	1.388<
BKG2M 1	-.092	.021	.286	.396	S	S
BKG2M 2	-.071	.651	.791	.591	S	S
BKG2M 3	-.482	-.202	.165	.252	S	S
BKG2M 4	-.448	.038	-.204	-.449	S	S
BKG2M 5	-.580	-.121	-.403	-.422	-.259	.253
BKG2M Mn:	-.335	.077	.127	.074	-.259<	.253<
BKG3M 1	.031	.179	.320	.062	S	S
BKG3M 2	-.707	-.012	.079	-.253	S	S
BKG3M 3	.875	.384	.669	.478	S	S
BKG3M 4	-.323	-.188	-.018	-.138	S	S
BKG3M 5	-.225	-.411	-.165	-.044	-.126	.021
BKG3M Mn:	-.070	-.010	.177	.021	-.126<	.021<
BKG4M 1	.142	.353	.750	1.042	S	S
BKG4M 2	-.039	-.213	.123	.408	S	S
BKG4M 3	-.264	.189	.137	0.000	S	S
BKG4M 4	.145	.181	.228	.384	S	S
BKG4M 5	-.574	-.233	.047	.134	.411	.583
BKG4M Mn:	-.118	.055	.257	.394	.411<	.583<

Individual Total Body Weight Change (kg)

Animal Number	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
BKG1F 1	-.173	-.142	-.162	-.125	S	S
BKG1F 2	-.019	.327	.206	.483	S	S
BKG1F 3	-.414	-.078	-.029	.142	S	S
BKG1F 4	.267	1.104	.952	1.070	S	S
BKG1F 5	-.178	-.036	-.083	.070	.134	.044
Ç BKG1F Mn:	-.103	.235	.177	.328	.134<	.044<
BKG2F 1	.048	.142	.501	.151	S	S
BKG2F 2	.016	-.288	.272	.481	S	S
BKG2F 3	-.010	.117	.067	-.020	S	S
BKG2F 4	-.386	-.126	-.359	-.173	S	S
BKG2F 5	-.219	.194	.006	.249	.444	.733
BKG2F Mn:	-.110	.008	.097	.138	.444<	.733<
BKG3F 1	-.581	0.000	-.005	-.171	S	S
BKG3F 2	-.383	-.202	.113	-.029	S	S
BKG3F 3	-.206	-.095	.237	.185	S	S
BKG3F 4	-.348	-.308	-.208	-.118	S	S
BKG3F 5	-.271	-.014	-.044	.040	.143	.210
BKG3F Mn:	-.358	-.124	.019	-.019	.143<	.210<
BKG4F 1	-.261	-.181	.069	.070	S	S
BKG4F 2	-.139	.146	.321	.363	S	S
BKG4F 3	-.293	-.062	.009	.166	S	S
BKG4F 4	-.304	-.085	.150	.193	S	S
BKG4F 5	-.121	-.173	.164	.325	.253	.158
BKG4F Mn:	-.224	-.071	.143	.223	.253<	.158<

**APPENDIX IV**  
**INDIVIDUAL FOOD CONSUMPTION DATA**

T.P.S. Study No.: 616C-503-532-98  
Sponsor I.D. No.: 032b

## Key to Individual Food Consumption Data

### Dosage Key

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

- \* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

### Abbreviation Key

S = Scheduled Sacrifice

### Dunnett's Test Key

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

Individual Food Consumption (g/kg/day)

Animal Number	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
BKG1M 1	27.295	29.773	28.911	27.702	S	S
BKG1M 2	28.947	29.854	30.838	30.048	S	S
BKG1M 3	30.772	29.906	27.745	27.857	S	S
BKG1M 4	29.110	33.825	32.416	24.311	S	S
BKG1M 5	33.680	29.384	28.858	24.758	23.933	26.824
Ç BKG1M Mn:	29.961	30.548	29.754	26.935	23.933<	26.824<
BKG2M 1	28.552	30.210	30.830	28.127	S	S
BKG2M 2	26.337	30.638	26.863	25.514	S	S
BKG2M 3	24.539	36.259	32.361	34.214	S	S
BKG2M 4	24.963	28.349	23.705	24.056	S	S
BKG2M 5	23.281	26.891	28.396	23.824	25.208	29.446
BKG2M Mn:	25.535	30.469	28.431	27.147	25.208<	29.446<
BKG3M 1	25.954	24.317	23.930	22.179	S	S
BKG3M 2	29.009	41.210	30.512	32.885	S	S
BKG3M 3	40.252	37.108	38.030	35.037	S	S
BKG3M 4	30.007	36.101	34.908	33.678	S	S
BKG3M 5	23.911	29.376	30.752	26.172	31.146	31.781
BKG3M Mn:	29.827	33.622	31.626	29.990	31.146<	31.781<
BKG4M 1	29.587	30.496	27.989	27.225	S	S
BKG4M 2	27.520	26.141	25.286	25.879	S	S
BKG4M 3	27.381	32.242	27.487	26.413	S	S
BKG4M 4	35.523	32.840	31.787	29.477	S	S
BKG4M 5	18.314	22.885	23.878	22.141	28.341	30.110
BKG4M Mn:	27.665	28.921	27.286	26.227	28.341<	30.110<

Individual Food Consumption (g/kg/day)

Animal Number		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
BKG1F	1	28.406	36.869	36.374	35.195	S	S
BKG1F	2	35.000	33.088	32.221	25.186	S	S
BKG1F	3	25.835	32.415	30.145	26.396	S	S
BKG1F	4	45.480	41.510	42.287	33.657	S	S
BKG1F	5	23.836	27.720	27.142	28.407	26.061	39.762
Ç BKG1F	Mn:	31.711	34.320	33.634	29.768	26.061<	39.762<
BKG2F	1	32.489	33.634	32.983	27.026	S	S
BKG2F	2	30.409	32.088	38.243	29.710	S	S
BKG2F	3	26.799	31.212	32.308	24.268	S	S
BKG2F	4	28.110	31.832	31.655	30.817	S	S
BKG2F	5	30.118	31.775	31.613	26.005	33.197	25.133
BKG2F	Mn:	29.585	32.108	33.360	27.565	33.197<	25.133<
BKG3F	1	40.316	48.569	43.679	40.425	S	S
BKG3F	2	25.286	27.744	26.598	26.940	S	S
BKG3F	3	33.482	35.424	36.681	33.281	S	S
BKG3F	4	30.916	31.673	32.983	33.174	S	S
BKG3F	5	23.792	25.186	26.377	24.442	19.278	23.982
BKG3F	Mn:	30.758	33.719	33.264	31.653	19.278<	23.982<
BKG4F	1	25.917	33.372	33.411	34.570	S	S
BKG4F	2	28.429	30.912	27.617	28.523	S	S
BKG4F	3	19.852	27.888	24.421	26.281	S	S
BKG4F	4	30.005	31.982	33.564	28.783	S	S
BKG4F	5	29.343	28.558	31.989	37.968	35.504	25.157
BKG4F	Mn:	26.709	30.542	30.201	31.225	35.504<	25.157<

**APPENDIX V**

**INDIVIDUAL URINALYSIS DATA**

- A. Qualitative Evaluation**
- B. Microscopic Examination**
- C. Statistical Analysis**



## Key to Individual Urinalysis Data

### Dosage Key

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

### Abbreviation Key

Amor Phos	Amorphous Phosphates
Amor Urate	Amorphous Urates
Bact	Bacteria
Bili	Bilirubin
Bld	Blood
Ca Ox	Calcium Oxalate
Epith Cells	Epithelial Cells
Glu	Glucose
Gran Casts	Granular Casts
Hyal Casts	Hyaline Casts
Ket	Ketones
Leuk	Leukocytes
Nit	Nitrite
Pro	Protein
RBC	Red Blood Cells
S	Scheduled Sacrifice
SG	Specific Gravity
Tri Phos	Triple Phosphates
Urob	Urobilinogen
WBC	White Blood Cells
^	Greater than (Section C. Statistical Analysis)

## Key to Individual Urinalysis Data (cont'd)

### Dunnett's Test Key

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

### QUALITATIVE CODES

<b>BLOOD</b> - Negative 10 Ery/ $\mu$ L 50 Ery/ $\mu$ L 250 Ery/ $\mu$ L	<b>BILIRUBIN</b> - Negative 1 mg/dL 3 mg/dL 6 mg/dL	<b>KETONES</b> - Negative 15 mg/dL 50 mg/dL 150 mg/dL	<b>LEUKOCYTES</b> - Negative 25 Leu/ $\mu$ L 75 Leu/ $\mu$ L 500 Leu/ $\mu$ L
<b>GLUCOSE</b> N Normal 50 mg/dL 100 mg/dL > 250 mg/dL	<b>PROTEIN</b> - Negative Tr Trace 30 mg/dL 100 mg/dL 500 mg/dL	<b>UROBILINOGEN</b> N Normal 1 mg/dL 4 mg/dL $\geq$ 8 mg/dL	<b>NITRITE</b> - Negative + Positive

### MICROSCOPIC CODES

WBC/high power field	- Negative
RBC/high power field	Tr Trace
Epith Cells/low power field	+ Few
Hyal Casts/low power field	++ Moderate
Gran Casts/low power field	+++ Many
	++++ Loaded

## **A. Qualitative Evaluation**

## URINALYSIS

### Qualitative Pretest

Animal I.D.	pH	Leuk	Nit	Pro	Glu	Ket	Urob	Bili	Bld	Spec Grav	Color, Appearance
BKG1M01	6	75	-	-	N	-	N	-	10	1.022	Yellow, Clear
BKG1M02	5	500	-	-	N	-	N	-	10	1.038	Dark Yellow, Clear
BKG1M03	6	500	-	-	N	-	N	-	10	1.051	Dark Yellow, Clear
BKG1M04	5	-	-	-	N	-	N	-	-	1.058	Dark Yellow, Clear
BKG1M05	8	-	-	-	N	-	N	-	-	1.012	Pale Yellow, Clear
BKG2M01	6	500	-	-	N	-	N	-	50	1.034	Yellow, Clear
BKG2M02	5	500	-	-	N	-	N	-	50	1.034	Yellow, Slightly Cloudy
BKG2M03	5	500	-	TR	N	-	N	-	50	1.067	Dark Yellow, Clear
BKG2M04	5	75	-	TR	N	-	N	-	10	1.067	Dark Yellow, Clear
BKG2M05	6	500	-	-	N	-	N	-	10	1.031	Yellow, Clear
BKG3M01	6	25	-	-	N	-	N	-	10	1.024	Yellow, Clear
BKG3M02	5	-	-	-	N	-	N	-	10	1.034	Yellow, Clear
BKG3M03	5	-	-	-	N	-	N	-	250	1.020	Pale Yellow, Clear
BKG3M04	6	-	-	-	N	-	N	-	-	1.023	Yellow, Clear
BKG3M05	7	500	-	-	N	-	N	-	250	1.022	Yellow, Clear
BKG4M01	5	500	-	-	N	-	N	-	250	1.032	Yellow, Clear
BKG4M02	6	-	-	-	N	-	N	-	10	1.024	Pale Yellow, Clear
BKG4M03	5	500	-	-	N	-	N	-	10	1.045	Dark Yellow, Clear
BKG4M04	7	75	-	-	N	-	N	-	10	1.028	Yellow, Clear
BKG4M05	5	500	-	-	N	-	N	-	250	1.021	Yellow, Clear

## URINALYSIS

### Qualitative Pretest

Animal I.D.	pH	Leuk	Nit	Pro	Glu	Ket	Urob	Bili	Bld	Spec Grav	Color, Appearance
BKG1F01	7	-	-	TR	N	-	N	-	10	1.074	Dark Yellow, Clear
BKG1F02	6	500	-	-	N	-	N	-	50	1.027	Yellow, Slightly Cloudy
BKG1F03	5	-	-	-	N	-	N	-	-	1.074	Dark Yellow, Clear
BKG1F04	6	-	-	-	N	-	N	-	10	1.026	Yellow, Slightly Cloudy
BKG1F05	7	500	-	-	N	-	N	-	250	1.020	Pale Yellow, Clear
BKG2F01	5	-	-	-	N	-	N	-	10	1.016	Pale Yellow, Clear
BKG2F02	5	-	-	-	N	-	N	-	50	1.030	Yellow, Clear
BKG2F03	5	-	-	-	N	-	N	-	10	1.015	Pale Yellow, Clear
BKG2F04	6	-	-	-	N	-	N	-	10	1.018	Yellow, Clear
BKG2F05	6	-	-	-	N	-	N	-	-	1.028	Yellow, Clear
BKG3F01	5	-	-	-	N	-	N	-	10	1.045	Yellow, Clear
BKG3F02	5	25	-	-	N	-	N	-	50	1.040	Yellow, Clear
BKG3F03	5	500	+	-	N	-	N	-	250	1.035	Yellow, Slightly Cloudy
BKG3F04	5	-	-	-	N	-	N	-	-	1.052	Dark Yellow, Clear
BKG3F05	5	75	-	-	N	-	N	-	250	1.029	Yellow, Slightly Cloudy
BKG4F01	6	-	-	-	N	-	N	-	-	1.030	Yellow, Clear
BKG4F02	7	-	-	-	N	-	N	-	-	1.009	Colorless, Clear
BKG4F03	5	-	-	-	N	-	N	-	-	1.020	Yellow, Clear
BKG4F04	6	-	-	-	N	-	N	-	-	1.036	Yellow, Clear
BKG4F05	6	75	-	-	N	-	N	-	10	1.064	Dark Yellow, Slightly Cloudy

# URINALYSIS

## Qualitative Week 4

Animal I.D.	PH	Leuk	Nit	Pro	Glu	Ket	Urob	Bili	Bid	Spec Grav	Color, Appearance
BKG1M01	6	500	-	TR	N	-	N	-	10	1.051	Yellow, Clear
BKG1M02	5	75	-	-	N	-	N	-	10	1.051	Yellow, Clear
BKG1M03	6	-	-	30	N	-	1	-	10	>1.086	Dark Yellow, Slightly Cloudy
BKG1M04	6	75	-	TR	N	-	1	-	10	1.070	Dark Yellow, Clear
BKG1M05	5	-	-	-	N	-	N	-	-	1.017	Yellow, Clear
BKG2M01	7	500	-	-	N	-	N	-	50	1.036	Yellow, Clear
BKG2M02	5	500	-	-	N	-	N	-	10	1.034	Yellow, Clear
BKG2M03	5	-	-	-	N	-	N	-	10	1.035	Yellow, Clear
BKG2M04	7	500	-	-	N	-	N	-	10	1.030	Yellow, Clear
BKG2M05	8	75	-	-	N	-	N	-	-	1.039	Yellow, Clear
BKG3M01	7	75	-	30	N	-	1	-	10	1.061	Dark Yellow, Slightly Cloudy
BKG3M02	5	-	-	-	N	-	N	-	10	1.038	Yellow, Clear
BKG3M03	5	500	-	-	N	-	N	-	10	1.034	Yellow, Clear
BKG3M04	6	500	-	-	N	-	1	-	10	1.051	Dark Yellow, Clear
BKG3M05	6	500	-	-	N	-	N	-	50	1.018	Yellow, Slightly Cloudy
BKG4M01	6	25	-	-	N	-	N	-	10	1.029	Yellow, Clear
BKG4M02	7	-	-	-	N	-	N	-	10	1.025	Yellow, Clear
BKG4M03	5	500	-	-	N	-	1	-	10	1.083	Dark Yellow, Clear
BKG4M04	7	-	-	-	N	-	N	-	-	1.022	Pale Yellow, Clear
BKG4M05	7	-	-	-	N	-	N	-	250	1.018	Yellow, Clear

# URINALYSIS

## Qualitative Week 4

Animal I.D.	pH	Leuk	Nit	Pro	Glu	Ket	Urob	Bili	Bld	Spec Grav	Color, Appearance
BKG1F01	6	-	-	-	N	-	N	-	-	1.074	Yellow, Clear
BKG1F02	5	500	-	-	N	-	N	-	10	1.027	Yellow, Clear
BKG1F03	6	-	-	-	N	-	N	-	-	1.051	Dark Yellow, Clear
BKG1F04	7	-	-	-	N	-	N	-	-	1.020	Yellow, Clear
BKG1F05	6	25	-	-	N	-	N	-	10	1.020	Pale Yellow, Clear
BKG2F01	7	-	-	-	N	-	N	-	-	1.012	Pale Yellow, Clear
BKG2F02	6	-	-	-	N	-	N	-	-	1.024	Yellow, Clear
BKG2F03	7	-	-	-	N	-	N	-	-	1.014	Pale Yellow, Clear
BKG2F04	6	-	-	-	N	-	N	-	-	1.034	Yellow, Slightly Cloudy
BKG2F05	5	-	-	-	N	-	N	-	-	1.015	Yellow, Clear
BKG3F01	5	-	-	-	N	-	N	-	-	1.029	Yellow, Clear
BKG3F02	6	25	-	-	N	-	N	-	-	1.064	Yellow, Clear
BKG3F03	5	75	-	-	N	-	N	-	250	1.028	Yellow, Slightly Cloudy
BKG3F04	7	-	-	TR	N	-	N	-	-	1.067	Dark Yellow, Clear
BKG3F05	6	25	-	-	N	-	N	-	-	1.058	Yellow, Clear
BKG4F01	7	-	-	-	N	-	N	-	-	1.051	Yellow, Slightly Cloudy
BKG4F02	6	-	-	-	N	-	N	-	-	1.033	Yellow, Clear
BKG4F03	5	-	-	-	N	-	N	-	-	1.040	Yellow, Clear
BKG4F04	5	25	-	-	N	-	N	-	-	1.061	Yellow, Clear
BKG4F05	5	-	-	-	N	-	N	-	-	1.040	Yellow, Clear

**URINALYSIS**

**Qualitative  
Termination Recovery**

Animal I.D.	pH	Leuk	Nit	Pro	Glu	Ket	Urob	Bili	Bld	Spec Grav	Color, Appearance
BKG1M05	5	-	-	-	N	-	N	-	-	1.042	Yellow, Clear
BKG2M05	6	500	-	-	N	-	N	-	10	1.025	Yellow, Clear
BKG3M05	6	500	-	-	N	-	N	-	10	1.040	Yellow, Clear
BKG4M05	7	-	-	-	N	-	N	-	250	1.012	Yellow, Clear
BKG1F05	5	-	-	-	N	-	N	-	-	1.041	Yellow, Clear
BKG2F05	7	-	-	-	N	-	N	-	-	1.014	Pale Yellow, Clear
BKG3F05	7	500	-	-	N	-	N	-	50	1.077	Yellow, Clear
BKG4F05	8	75	-	-	N	-	N	-	-	1.074	Yellow, Clear



## **B. Microscopic Examination**

# URINALYSIS

## Microscopic Pretest

Animal I.D.	WBC	RBC	Epith Cells	Hyal Casts	Gran Casts	Bact	Mucus	Amor Phos	Amor Urate	Tri Phos	Ca Ox	Other
BKG1M01	2-5	5-10	5-10	0	0	+++	-	-	-	-	-	
BKG1M02	0-2	0-2	2-5	0	0	+	-	-	-	-	-	
BKG1M03	0-2	0-2	2-5	0	0	++	-	-	-	-	-	
BKG1M04	2-5	0-2	5-10	0	0	+	-	-	-	-	-	
BKG1M05	0	0	0-2	0	0	+	-	-	-	-	-	
BKG2M01	2-5	5-10	15-20	0	0	++++	-	-	-	++	-	Sperm
BKG2M02	5-10	2-5	10-15	0	0	+	-	-	-	-	-	
BKG2M03	5-10	10-15	5-10	0	0	++	-	-	-	-	-	
BKG2M04	0-2	2-5	15-20	0	0	++	-	-	-	-	-	Sperm
BKG2M05	5-10	5-10	10-15	0	0	++++	-	-	-	-	-	
BKG3M01	0-2	2-5	10-15	0	0	++	-	-	-	-	-	Sperm
BKG3M02	0	0	10-15	0	0	+	-	-	-	-	-	
BKG3M03	2-5	0	2-5	0	0	+	-	-	-	-	-	Sperm
BKG3M04	0-2	5-10	15-20	0	0	++	-	-	-	-	-	Sperm
BKG3M05	15-20	10-15	15-20	0	0	++++	-	-	-	++	-	
BKG4M01	5-10	10-15	15-20	0	0	++	-	-	-	-	-	Sperm
BKG4M02	0-2	0-2	50-60	0	0	+++	-	-	-	-	-	Sperm
BKG4M03	0-2	0-2	2-5	0	0	+	-	-	-	-	-	Sperm
BKG4M04	0-2	2-5	40-50	0	0	++	-	-	-	+	-	
BKG4M05	5-10	15-20	15-20	0	0	+++	-	-	-	-	-	Sperm

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 Sponsor I.D. No.: 032b

# URINALYSIS

## Microscopic Pretest

Animal I.D.	WBC	RBC	Epith Cells	Hyal Casts	Gran Casts	Bact	Mucus	Amor Phos	Amor Urate	Tri Phos	Ca Ox	Other
BKG1F01	0	0	5-10	0	0	+	-	+	-	+	-	
BKG1F02	5-10	20-30	15-20	0	0	++++	-	-	-	-	-	
BKG1F03	0-2	0-2	10-15	0	0	++	-	-	-	-	-	
BKG1F04	5-10	0-2	15-20	0	0	++	-	-	-	+	-	
BKG1F05	5-10	2-5	15-20	0	0	++++	-	-	-	-	-	
BKG2F01	2-5	0-2	2-5	0	0	++	-	-	-	-	-	
BKG2F02	2-5	2-5	10-15	0	0	++++	-	-	-	-	-	
BKG2F03	2-5	0-2	5-10	0	0	++++	-	-	-	-	-	
BKG2F04	5-10	0-2	10-15	0	0	+++	-	-	-	-	-	
BKG2F05	2-5	2-5	15-20	0	0	++	-	-	-	-	-	
BKG3F01	5-10	0	5-10	0	0	+	-	-	-	-	-	
BKG3F02	15-20	5-10	25-30	0	0	++	-	-	-	-	-	
BKG3F03	0	0	2-5	0	0	+++	-	-	-	-	-	
BKG3F04	2-5	0-2	5-10	0	0	+	-	-	-	-	-	
BKG3F05	5-10	5-10	10-15	0	0	++	-	-	-	-	-	
BKG4F01	2-5	0	25-30	0	0	+	-	-	-	-	-	
BKG4F02	0	0	0-2	0	0	+++	-	-	-	-	-	
BKG4F03	2-5	0	5-10	0	0	+	-	-	-	-	-	
BKG4F04	0-2	5-10	5-10	0	0	+	-	-	-	-	-	
BKG4F05	5-10	2-5	5-10	0	0	++	-	-	-	++++	-	

# URINALYSIS

## Microscopic Week 4

Animal I.D.	WBC	RBC	Epith Cells	Hyal Casts	Gran Casts	Bact	Mucus	Amor Phos	Amor Urate	Tri Phos	Ca Ox	Other
BKG1M01	0-2	5-10	10-15	0	0	++	-	-	-	-	-	Sperm
BKG1M02	0-2	0-2	0-2	0	0	+	-	-	-	+	-	Sperm
BKG1M03	2-5	5-10	2-5	0	0	++	-	-	-	+	++	Sperm
BKG1M04	2-5	5-10	2-5	0	0	+	+	-	-	++++	-	Sperm
BKG1M05	2-5	5-10	5-10	0	0	+	-	-	-	-	-	-
BKG2M01	0-2	0-2	0-1	0-1	0	+	-	-	-	+	-	Sperm
BKG2M02	5-10	2-4	20-25	0	0	+	-	-	-	-	-	Sperm
BKG2M03	0-2	0	5-10	0	0	+	-	-	-	-	-	Sperm
BKG2M04	0-2	5-10	2-5	0	0	+	-	-	-	-	-	Sperm
BKG2M05	0-2	2-5	0-2	0	0	+	-	-	-	++	-	Sperm
BKG3M01	2-5	0-2	5-10	0	0	++	-	-	-	+	-	Sperm
BKG3M02	0-2	0-2	5-10	0	0	+	-	-	-	-	-	Sperm
BKG3M03	0-2	2-5	0-2	0	0	+	-	-	-	-	-	Sperm
BKG3M04	2-5	2-5	0-2	0	0	+	-	-	-	+	-	Sperm
BKG3M05	5-10	15-20	40-50	0	0	+++	-	-	-	-	-	Sperm
BKG4M01	8-10	5-10	20-25	0	0	++	-	-	-	-	-	Sperm
BKG4M02	0-2	0-2	5-10	0	0	+	-	-	-	+	-	Sperm
BKG4M03	2-5	5-10	0-2	0	0	++	-	-	-	-	-	Sperm
BKG4M04	0-2	0	2-5	0	0	+	-	-	-	-	-	-
BKG4M05	2-5	15-20	10-15	0	0	+	-	-	-	-	-	Sperm

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Sponsor I.D. No.: 032b

# URINALYSIS

## Microscopic Week 4

Animal I.D.	WBC	RBC	Epith Cells	Hyal Casts	Gran Casts	Bact	Mucus	Amor Phos	Amor Urate	Tri Phos	Ca Ox	Other
BKG1F01	0-2	0-2	5-10	0	0	+	-	-	-	-	-	
BKG1F02	25-30	0-2	2-5	0	0	++	-	-	-	-	-	
BKG1F03	0-2	0	0	0	0	+	-	-	-	++	-	
BKG1F04	0-2	0	5-10	0	0	+	-	-	-	-	-	
BKG1F05	10-15	2-5	30-40	0	0	++++	-	-	-	-	-	
BKG2F01	0	0	0-2	0	0	+++	-	-	-	-	-	
BKG2F02	5-10	0-2	5-10	0	0	++	-	-	-	+	-	
BKG2F03	2-5	0-2	10-15	0	0	+++	-	-	-	-	-	
BKG2F04	0-2	2-5	5-10	0	0	+	-	-	-	+	-	
BKG2F05	2-5	0-2	10-15	0	0	+++	-	-	-	-	-	
BKG3F01	0-2	0	5-10	0	0	+	-	-	-	-	-	
BKG3F02	5-10	5-10	0-2	0	0	+	-	-	-	+	-	
BKG3F03	0	2-5	5-10	0	0	++++	-	-	-	-	-	
BKG3F04	2-5	0	0	0	0	+	-	-	-	++++	-	
BKG3F05	2-5	0	0	0	0	+	-	-	-	++	-	
BKG4F01	0	0	0	0	0	++	-	-	-	++++	-	
BKG4F02	0-2	0-2	5-10	0	0	+	-	-	-	-	-	
BKG4F03	0-2	0-2	5-10	0	0	+	-	-	-	-	-	
BKG4F04	0-2	5-10	15-20	0	0	+	-	-	-	-	-	
BKG4F05	2-5	0	5-10	0	0	+	-	-	-	-	-	

# URINALYSIS

## Microscopic Termination Recovery

Animal I.D.	WBC	RBC	Epith Cells	Hyal Casts	Gran Casts	Bact	Mucus	Amor Phos	Amor Urate	Tri Phos	Ca Ox	Other
BKG1M05	0-1	0	0-2	0	0	+	-	-	-	-	-	Sperm
BKG2M05	20-25	30-40	15-20	0	0	++	-	-	-	-	-	Sperm
BKG3M05	2-5	0-2	0-2	0	0	+	-	-	-	+	-	Sperm
BKG4M05	0-2	2-5	5-10	0	0	++	-	-	-	-	-	Sperm
BKG1F05	2-5	0	2-5	0	0	+++	-	-	-	+	-	
BKG2F05	0-2	0-2	15-20	0	0	++	-	-	-	-	-	
BKG3F05	0-2	0	2-5	0	0	++	-	++	-	+++	-	
BKG4F05	5-10	0-2	2-5	0	0	+++	-	-	-	++++	-	

## **C. Statistical Analysis**

Individual Urinalysis Data

Animal Number		SG Pretest	SG Week 4	SG Recovery	pH Pretest	pH Week 4	pH Recovery
BKG1M	1	1.022	1.051	S	6	6	S
BKG1M	2	1.038	1.051	S	5	5	S
BKG1M	3	1.051	1.086 <sup>^</sup>	S	6	6	S
BKG1M	4	1.058	1.070	S	5	6	S
BKG1M	5	1.012	1.017	1.042	8	5	5
Ç BKG1M	Mn:	1.036	1.055	1.042<	6	6	5<
BKG2M	1	1.034	1.036	S	6	7	S
BKG2M	2	1.034	1.034	S	5	5	S
BKG2M	3	1.067	1.035	S	5	5	S
BKG2M	4	1.067	1.030	S	5	7	S
BKG2M	5	1.031	1.039	1.025	6	8	6
BKG2M	Mn:	1.047	1.035	1.025<	5	6	6<
BKG3M	1	1.024	1.061	S	6	7	S
BKG3M	2	1.034	1.038	S	5	5	S
BKG3M	3	1.020	1.034	S	5	5	S
BKG3M	4	1.023	1.051	S	6	6	S
BKG3M	5	1.022	1.018	1.040	7	6	6
BKG3M	Mn:	1.025	1.040	1.040<	6	6	6<
BKG4M	1	1.032	1.029	S	5	6	S
BKG4M	2	1.024	1.025	S	6	7	S
BKG4M	3	1.045	1.083	S	5	5	S
BKG4M	4	1.028	1.022	S	7	7	S
BKG4M	5	1.021	1.018	1.012	5	7	7
BKG4M	Mn:	1.030	1.035	1.012<	6	6	7<



Individual Urinalysis Data

Animal Number		SG Pretest	SG Week 4	SG Recovery	pH Pretest	pH Week 4	pH Recovery
BKG1F	1	1.074	1.074	S	7	6	S
BKG1F	2	1.027	1.027	S	6	5	S
BKG1F	3	1.074	1.051	S	5	6	S
BKG1F	4	1.026	1.020	S	6	7	S
BKG1F	5	1.020	1.020	1.041	7	6	5
Ç BKG1F	Mn:	1.044	1.038	1.041<	6	6	5<
BKG2F	1	1.016	1.012	S	5	7	S
BKG2F	2	1.030	1.024	S	5	6	S
BKG2F	3	1.015	1.014	S	5	7	S
BKG2F	4	1.018	1.034	S	6	6	S
BKG2F	5	1.028	1.015	1.014	6	5	7
BKG2F	Mn:	1.021	1.020	1.014<	5	6	7<
BKG3F	1	1.045	1.029	S	5	5	S
BKG3F	2	1.040	1.064	S	5	6	S
BKG3F	3	1.035	1.028	S	5	5	S
BKG3F	4	1.052	1.067	S	5	7	S
BKG3F	5	1.029	1.058	1.077	5	6	7
BKG3F	Mn:	1.040	1.049	1.077<	5*	6	7<
BKG4F	1	1.030	1.051	S	6	7	S
BKG4F	2	1.009	1.033	S	7	6	S
BKG4F	3	1.020	1.040	S	5	5	S
BKG4F	4	1.036	1.061	S	6	5	S
BKG4F	5	1.064	1.040	1.074	6	5	8
BKG4F	Mn:	1.032	1.045	1.074<	6	6	8<

**APPENDIX VI**  
**INDIVIDUAL HEMATOLOGY DATA**

- A. Pretest**
- B. Week 4**
- C. Recovery**

## Key to Individual Hematology Data

### Dosage Key

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

### Abbreviation Key

WBC	White Blood Cells	Thousands/Cubic mm
NEUT	Neutrophils	Percent
LYMP	Lymphocytes	Percent
MONO	Monocytes	Percent
EOS	Eosinophils	Percent
BASO	Basophils	Percent
RBC	Red Blood Cells	Million/Cubic mm
HGB	Hemoglobin	g/dL
HCT	Hematocrit	Percent
MCV	Mean Corpuscular Volume	Cubic Microns
MCH	Mean Corpuscular Hemoglobin	pg
MCHC	Mean Corpuscular Hemoglobin Concentration	g/dL
PLAT	Platelet Count	Thousands/Cubic mm

## Key to Individual Hematology Data (cont'd)

### Dunnett's Test Key

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

### Additional Hematology Findings (A)

#### Pretest

BKG3F02      7 band cells included in the neutrophil count

#### Week 4

BKG1M04      5 band cells included in the neutrophil count

BKG3M04      6 band cells included in the neutrophil count

## **A. Pretest**

Individual Hematology Data  
Pretest

Animal Number	WBC	NEUT	LYMP	MONO	EOS	BASO
BKG1M 1	10.9	69	24	2	5	0
BKG1M 2	10.2	67	28	5	0	0
BKG1M 3	9.2	54	34	8	4	0
BKG1M 4	12.5	75	22	3	0	0
BKG1M 5	10.5	58	30	6	6	0
Ç BKG1M Mn:	10.7	65	28	5	3	0
BKG2M 1	9.0	70	26	3	1	0
BKG2M 2	9.2	59	34	3	4	0
BKG2M 3	9.9	55	37	3	5	0
BKG2M 4	12.5	61	30	7	2	0
BKG2M 5	8.3	70	23	5	2	0
BKG2M Mn:	9.8	63	30	4	3	0
BKG3M 1	8.4	47	45	5	3	0
BKG3M 2	9.3	59	31	8	2	0
BKG3M 3	7.3	59	34	4	3	0
BKG3M 4	9.2	57	37	2	4	0
BKG3M 5	8.7	75	21	3	1	0
BKG3M Mn:	8.6*	59	34	4	3	0
BKG4M 1	10.5	66	30	2	2	0
BKG4M 2	10.4	63	26	8	3	0
BKG4M 3	10.5	65	31	4	0	0
BKG4M 4	12.0	61	33	5	1	0
BKG4M 5	11.0	66	22	7	5	0
BKG4M Mn:	10.9	64	28	5	2	0

Individual Hematology Data  
Pretest

Animal Number	RBC	HGB	HCT	MCV	MCH	MCHC
BKG1M 1	6.68	14.9	43.5	65	22.3	34.3
BKG1M 2	6.12	13.9	41.2	67	22.7	33.7
BKG1M 3	5.99	13.7	42.5	71	22.9	32.2
BKG1M 4	6.48	14.3	43.5	67	22.1	32.9
BKG1M 5	6.64	15.1	44.5	67	22.7	33.9
Ç BKG1M Mn:	6.38	14.4	43.0	67	22.5	33.4
BKG2M 1	5.82	13.3	40.2	69	22.9	33.1
BKG2M 2	6.44	14.1	43.1	67	21.9	32.7
BKG2M 3	6.85	14.4	42.7	62	21.0	33.7
BKG2M 4	6.66	14.6	43.3	65	21.9	33.7
BKG2M 5	6.59	14.1	42.2	64	21.4	33.4
BKG2M Mn:	6.47	14.1	42.3	65	21.8	33.3
BKG3M 1	6.70	14.8	44.2	66	22.1	33.5
BKG3M 2	6.77	13.9	41.5	61	20.5	33.5
BKG3M 3	5.82	13.0	38.5	66	22.3	33.8
BKG3M 4	5.78	13.7	41.6	72	23.7	32.9
BKG3M 5	6.43	13.7	41.1	64	21.3	33.3
BKG3M Mn:	6.30	13.8	41.4	66	22.0	33.4
BKG4M 1	6.85	14.5	42.3	62	21.2	34.3
BKG4M 2	6.95	14.7	45.7	66	21.2	32.2
BKG4M 3	6.95	14.9	45.4	65	21.4	32.8
BKG4M 4	6.21	13.8	40.1	65	22.2	34.4
BKG4M 5	6.16	14.2	42.5	69	23.1	33.4
BKG4M Mn:	6.62	14.4	43.2	65	21.8	33.4

Individual Hematology Data  
Pretest

Animal Number		PLAT
BKG1M	1	247
BKG1M	2	360
BKG1M	3	255
BKG1M	4	308
BKG1M	5	365
Ç BKG1M	Mn:	307
BKG2M	1	357
BKG2M	2	276
BKG2M	3	224
BKG2M	4	295
BKG2M	5	310
BKG2M	Mn:	292
BKG3M	1	354
BKG3M	2	214
BKG3M	3	336
BKG3M	4	232
BKG3M	5	244
BKG3M	Mn:	276
BKG4M	1	239
BKG4M	2	213
BKG4M	3	354
BKG4M	4	279
BKG4M	5	307
BKG4M	Mn:	278



Individual Hematology Data  
Pretest

Animal Number		WBC	NEUT	LYMP	MONO	EOS	BASO
BKG1F	1	10.8	67	28	5	0	0
BKG1F	2	8.6	61	31	3	5	0
BKG1F	3	12.2	66	30	3	1	0
BKG1F	4	8.7	68	25	7	0	0
BKG1F	5	13.0	84	9	5	2	0
Ç BKG1F	Mn:	10.7	69	25	5	2	0
BKG2F	1	13.1	67	29	4	0	0
BKG2F	2	8.8	48	48	4	0	0
BKG2F	3	12.9	79	12	8	1	0
BKG2F	4	9.3	68	27	4	1	0
BKG2F	5	9.5	57	36	6	1	0
BKG2F	Mn:	10.7	64	30	5	1	0
BKG3F	1	8.9	73	21	5	1	0
BKG3F	2	11.1	84A	16	0	0	0
BKG3F	3	14.3	60	30	7	3	0
BKG3F	4	11.5	75	23	2	0	0
BKG3F	5	8.3	55	38	6	1	0
BKG3F	Mn:	10.8	69	26	4	1	0
BKG4F	1	10.2	78	16	5	1	0
BKG4F	2	10.9	66	29	5	0	0
BKG4F	3	11.2	73	19	7	1	0
BKG4F	4	9.2	59	38	1	2	0
BKG4F	5	10.2	64	24	10	2	0
BKG4F	Mn:	10.3	68	25	6	1	0

Individual Hematology Data  
Pretest

Animal Number	RBC	HGB	HCT	MCV	MCH	MCHC
BKG1F 1	6.68	14.1	42.3	63	21.1	33.3
BKG1F 2	7.19	15.8	47.6	66	22.0	33.2
BKG1F 3	7.11	15.9	47.4	67	22.4	33.5
BKG1F 4	6.39	14.5	43.4	68	22.7	33.4
BKG1F 5	7.67	16.2	49.3	64	21.1	32.9
Ç BKG1F Mn:	7.01	15.3	46.0	66	21.9	33.3
BKG2F 1	7.31	14.9	45.4	62	20.4	32.8
BKG2F 2	7.82	15.3	48.7	62	19.6	31.4
BKG2F 3	8.20	16.6	49.2	60	20.2	33.7
BKG2F 4	7.27	15.0	45.3	62	20.6	33.1
BKG2F 5	6.75	14.2	42.6	63	21.0	33.3
BKG2F Mn:	7.47	15.2	46.2	62+	20.4+	32.9
BKG3F 1	6.50	14.6	43.2	66	22.5	33.8
BKG3F 2	6.95	15.3	46.4	67	22.0	33.0
BKG3F 3	6.70	14.8	45.6	68	22.1	32.5
BKG3F 4	6.74	15.3	45.6	68	22.7	33.6
BKG3F 5	7.36	16.5	50.1	68	22.4	32.9
BKG3F Mn:	6.85	15.3	46.2	67	22.3	33.2
BKG4F 1	7.19	15.3	47.0	65	21.3	32.6
BKG4F 2	5.77	13.2	40.5	70	22.9	32.6
BKG4F 3	7.85	17.6	52.7	67	22.4	33.4
BKG4F 4	7.00	14.9	45.8	65	21.3	32.5
BKG4F 5	6.66	15.4	45.8	69	23.1	33.6
BKG4F Mn:	6.89	15.3	46.4	67	22.2	32.9

Individual Hematology Data  
Pretest

Animal Number		PLAT
BKG1F	1	262
BKG1F	2	320
BKG1F	3	226
BKG1F	4	308
BKG1F	5	266
Ç BKG1F	Mn:	276
BKG2F	1	410
BKG2F	2	329
BKG2F	3	401
BKG2F	4	295
BKG2F	5	244
BKG2F	Mn:	336
BKG3F	1	398
BKG3F	2	344
BKG3F	3	413
BKG3F	4	300
BKG3F	5	306
BKG3F	Mn:	352
BKG4F	1	234
BKG4F	2	258
BKG4F	3	227
BKG4F	4	146
BKG4F	5	231
BKG4F	Mn:	219

**B. Week 4**

Individual Hematology Data  
Week 4

Animal Number	WBC	NEUT	LYMP	MONO	EOS	BASO
BKG1M 1	9.0	55	31	13	1	0
BKG1M 2	8.7	59	34	7	0	0
BKG1M 3	9.2	46	44	9	1	0
BKG1M 4	11.3	65A	28	6	1	0
BKG1M 5	9.0	56	32	4	8	0
Ç BKG1M Mn:	9.4	56	34	8	2	0
BKG2M 1	8.0	72	22	4	2	0
BKG2M 2	9.8	52	34	11	3	0
BKG2M 3	10.2	65	22	5	8	0
BKG2M 4	12.6	57	37	4	2	0
BKG2M 5	10.7	68	29	3	0	0
BKG2M Mn:	10.3	63	29	5	3	0
BKG3M 1	9.1	59	35	2	4	0
BKG3M 2	10.0	61	30	6	3	0
BKG3M 3	8.3	62	31	4	3	0
BKG3M 4	9.5	60A	28	10	2	0
BKG3M 5	8.3	81	18	1	0	0
BKG3M Mn:	9.0	65	28	5	2	0
BKG4M 1	13.6	67	24	7	2	0
BKG4M 2	10.5	53	40	4	3	0
BKG4M 3	9.1	54	43	1	2	0
BKG4M 4	10.3	59	29	10	2	0
BKG4M 5	12.0	73	25	1	1	0
BKG4M Mn:	11.1	61	32	5	2	0

Individual Hematology Data  
Week 4

Animal Number	RBC	HGB	HCT	MCV	MCH	MCHC
BKG1M 1	7.49	17.1	48.9	65	22.8	35.0
BKG1M 2	7.25	16.5	48.2	66	22.8	34.2
BKG1M 3	7.25	16.7	48.4	67	23.0	34.5
BKG1M 4	7.15	16.5	47.5	66	23.1	34.7
BKG1M 5	7.21	16.8	48.5	67	23.3	34.6
Ç BKG1M Mn:	7.27	16.7	48.3	66	23.0	34.6
BKG2M 1	6.63	15.5	44.5	67	23.4	34.8
BKG2M 2	6.87	15.4	45.7	67	22.4	33.7
BKG2M 3	7.63	16.3	47.6	62	21.4	34.2
BKG2M 4	7.77	17.4	51.1	66	22.4	34.1
BKG2M 5	7.19	15.9	45.6	63	22.1	34.9
BKG2M Mn:	7.22	16.1	46.9	65	22.3	34.3
BKG3M 1	6.72	15.6	46.8	70	23.2	33.3
BKG3M 2	7.55	16.2	46.5	62	21.5	34.8
BKG3M 3	6.26	14.4	41.3	66	23.0	34.9
BKG3M 4	5.87	14.5	41.2	70	24.7	35.2
BKG3M 5	6.77	15.0	43.4	64	22.2	34.6
BKG3M Mn:	6.63	15.1+	43.8*	66	22.9	34.6
BKG4M 1	6.75	14.7	42.9	64	21.8	34.3
BKG4M 2	7.35	16.0	46.4	63	21.8	34.5
BKG4M 3	7.19	15.9	45.8	64	22.1	34.7
BKG4M 4	6.45	14.5	41.7	65	22.5	34.8
BKG4M 5	6.54	15.7	45.8	70	24.0	34.3
BKG4M Mn:	6.86	15.4*	44.5*	65	22.4	34.5

Individual Hematology Data  
Week 4

Animal	Number	PLAT
BKG1M	1	275
BKG1M	2	383
BKG1M	3	278
BKG1M	4	370
BKG1M	5	404
Ç BKG1M	Mn:	342
BKG2M	1	311
BKG2M	2	321
BKG2M	3	261
BKG2M	4	322
BKG2M	5	316
BKG2M	Mn:	306
BKG3M	1	335
BKG3M	2	263
BKG3M	3	365
BKG3M	4	227
BKG3M	5	326
BKG3M	Mn:	303
BKG4M	1	274
BKG4M	2	318
BKG4M	3	363
BKG4M	4	292
BKG4M	5	318
BKG4M	Mn:	313

Individual Hematology Data  
Week 4

Animal Number		WBC	NEUT	LYMP	MONO	EOS	BASO
BKG1F	1	8.9	59	35	5	1	0
BKG1F	2	10.2	64	29	5	2	0
BKG1F	3	13.0	71	22	7	0	0
BKG1F	4	8.2	58	30	7	5	0
BKG1F	5	10.8	67	30	2	1	0
Ç BKG1F	Mn:	10.2	64	29	5	2	0
BKG2F	1	11.2	57	35	6	2	0
BKG2F	2	8.9	58	35	5	2	0
BKG2F	3	9.1	75	21	3	1	0
BKG2F	4	9.1	63	29	7	1	0
BKG2F	5	9.0	55	42	3	0	0
BKG2F	Mn:	9.5	62	32	5	1	0
BKG3F	1	6.4	56	40	2	2	0
BKG3F	2	9.6	76	21	3	0	0
BKG3F	3	16.6	75	18	7	0	0
BKG3F	4	8.6	70	28	2	0	0
BKG3F	5	8.7	69	29	1	1	0
BKG3F	Mn:	10.0	69	27	3	1	0
BKG4F	1	8.8	69	26	4	1	0
BKG4F	2	8.2	60	33	2	5	0
BKG4F	3	7.6	73	20	4	3	0
BKG4F	4	9.5	61	36	2	1	0
BKG4F	5	8.1	66	32	2	0	0
BKG4F	Mn:	8.4	66	29	3	2	0



Individual Hematology Data  
Week 4

Animal Number	RBC	HGB	HCT	MCV	MCH	MCHC
BKG1F 1	7.35	15.9	47.6	65	21.6	33.4
BKG1F 2	8.26	18.2	53.5	65	22.0	34.0
BKG1F 3	7.17	15.9	47.8	67	22.2	33.3
BKG1F 4	6.94	16.6	47.5	68	23.9	34.9
BKG1F 5	9.11	19.3	56.9	62	21.2	33.9
Ç BKG1F Mn:	7.77	17.2	50.7	65	22.2	33.9
BKG2F 1	7.21	15.3	45.4	63	21.2	33.7
BKG2F 2	7.78	16.2	47.1	61	20.8	34.4
BKG2F 3	8.95	18.9	53.7	60	21.1	35.2
BKG2F 4	7.99	17.7	52.8	66	22.2	33.5
BKG2F 5	8.13	17.9	51.6	63	22.0	34.7
BKG2F Mn:	8.01	17.2	50.1	63	21.5	34.3
BKG3F 1	6.66	15.3	44.4	67	23.0	34.5
BKG3F 2	7.99	17.8	51.9	65	22.3	34.3
BKG3F 3	7.45	16.6	48.8	66	22.3	34.0
BKG3F 4	6.97	16.3	47.4	68	23.4	34.4
BKG3F 5	7.37	17.1	49.9	68	23.2	34.3
BKG3F Mn:	7.29	16.6	48.5	67	22.8	34.3
BKG4F 1	6.91	15.5	44.6	65	22.4	34.8
BKG4F 2	5.78	13.4	39.9	69	23.2	33.6
BKG4F 3	8.35	19.3	57.1	68	23.1	33.8
BKG4F 4	7.47	16.6	48.3	65	22.2	34.4
BKG4F 5	7.52	17.8	51.9	69	23.7	34.3
BKG4F Mn:	7.21	16.5	48.4	67	22.9	34.2

Individual Hematology Data  
Week 4

Animal Number		PLAT
BKG1F	1	309
BKG1F	2	312
BKG1F	3	310
BKG1F	4	330
BKG1F	5	296
Ç BKG1F	Mn:	311
BKG2F	1	373
BKG2F	2	391
BKG2F	3	384
BKG2F	4	350
BKG2F	5	314
BKG2F	Mn:	362
BKG3F	1	423
BKG3F	2	363
BKG3F	3	452
BKG3F	4	300
BKG3F	5	267
BKG3F	Mn:	361
BKG4F	1	283
BKG4F	2	257
BKG4F	3	182
BKG4F	4	118
BKG4F	5	266
BKG4F	Mn:	221*

## **C. Recovery**

Individual Hematology Data  
Recovery

Animal Number		WBC	NEUT	LYMP	MONO	EOS	BASO
BKG1M	5	12.2	67	25	7	1	0
Ç BKG1M	Mn:	12.2<	67<	25<	7<	1<	0<
BKG2M	5	7.4	71	27	1	1	0
BKG2M	Mn:	7.4<	71<	27<	1<	1<	0<
BKG3M	5	7.8	61	36	2	1	0
BKG3M	Mn:	7.8<	61<	36<	2<	1<	0<
BKG4M	5	12.2	58	32	2	8	0
BKG4M	Mn:	12.2<	58<	32<	2<	8<	0<

Individual Hematology Data  
Recovery

Animal Number	RBC	HGB	HCT	MCV	MCH	MCHC
BKG1M 5	7.65	17.2	49.8	65	22.5	34.5
Ç BKG1M Mn:	7.65<	17.2<	49.8<	65<	22.5<	34.5<
BKG2M 5	7.36	15.9	46.1	63	21.6	34.5
BKG2M Mn:	7.36<	15.9<	46.1<	63<	21.6<	34.5<
BKG3M 5	7.60	16.4	47.2	62	21.6	34.7
BKG3M Mn:	7.60<	16.4<	47.2<	62<	21.6<	34.7<
BKG4M 5	7.13	16.6	48.5	68	23.3	34.2
BKG4M Mn:	7.13<	16.6<	48.5<	68<	23.3<	34.2<

Individual Hematology Data  
Recovery

Animal Number		PLAT
BKG1M	5	358
Ç BKG1M	Mn:	358<
BKG2M	5	345
BKG2M	Mn:	345<
BKG3M	5	254
BKG3M	Mn:	254<
BKG4M	5	284
BKG4M	Mn:	284<

Individual Hematology Data  
Recovery

Animal Number	WBC	NEUT	LYMP	MONO	EOS	BASO
BKG1F 5	10.7	59	39	1	1	0
Ç BKG1F Mn:	10.7<	59<	39<	1<	1<	0<
BKG2F 5	7.1	66	30	2	2	0
BKG2F Mn:	7.1<	66<	30<	2<	2<	0<
BKG3F 5	7.8	65	30	2	3	0
BKG3F Mn:	7.8<	65<	30<	2<	3<	0<
BKG4F 5	7.6	77	21	2	0	0
BKG4F Mn:	7.6<	77<	21<	2<	0<	0<

Individual Hematology Data  
Recovery

Animal Number	RBC	HGB	HCT	MCV	MCH	MCHC
BKG1F 5	8.17	17.4	50.2	61	21.3	34.7
Ç BKG1F Mn:	8.17<	17.4<	50.2<	61<	21.3<	34.7<
BKG2F 5	8.08	17.7	50.1	62	21.9	35.3
BKG2F Mn:	8.08<	17.7<	50.1<	62<	21.9<	35.3<
BKG3F 5	7.17	16.4	47.6	66	22.9	34.5
BKG3F Mn:	7.17<	16.4<	47.6<	66<	22.9<	34.5<
BKG4F 5	7.19	16.9	48.9	68	23.5	34.6
BKG4F Mn:	7.19<	16.9<	48.9<	68<	23.5<	34.6<



Individual Hematology Data  
Recovery

Animal Number		PLAT
BKG1F	5	232
Ç BKG1F	Mn:	232<
BKG2F	5	284
BKG2F	Mn:	284<
BKG3F	5	298
BKG3F	Mn:	298<
BKG4F	5	258
BKG4F	Mn:	258<

**APPENDIX VII**

**INDIVIDUAL CLINICAL CHEMISTRY DATA**

- A. Pretest**
- B. Week 4**
- C. Recovery**

## Key to Individual Clinical Chemistry Data

### Dosage Key

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

### Abbreviation Key

CL	Chloride	mEq/L
K	Potassium	mEq/L
NA	Sodium	mEq/L
ALP	Alkaline Phosphatase	IU/L
AST	Aspartate Aminotransferase	IU/L
ALT	Alanine Aminotransferase	IU/L
GLU	Glucose	mg/dL
BUN	Blood Urea Nitrogen	mg/dL
CRE	Creatinine	mg/dL
CHOL	Cholesterol (Total)	mg/dL
TRIG	Triglycerides	mg/dL
PHOS	Phosphorus, Inorganic	mg/dL
TP	Total Protein	g/dL
ALBG	Albumin	g/dL
GLOB	Globulin	g/dL
A/G	Albumin/Globulin Ratio	
CA	Calcium	mg/dL
TBIL	Total Bilirubin	mg/dL
a	Light hemolysis	
b	Moderate hemolysis	

## Key to Individual Clinical Chemistry Data (cont'd)

### Dunnett's Test Key

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

## **A. Pretest**

Individual Clinical Chemistry Data  
Pretest

Animal Number		CL	K	NA	ALP	AST	ALT
BKG1M	1	109.5	4.46	145.5	76.2	30.5	39.9
BKG1M	2	108.8	5.15	145.1	69.1	28.4	37.9
BKG1M	3	113.8	4.64	148.4	71.4	39.0	24.2
BKG1M	4	110.8	4.62	146.4	85.9	34.6	37.3
BKG1M	5	113.4	5.32	147.6	107.0	29.9	32.6
Ç BKG1M	Mn:	111.3	4.84	146.6	81.9	32.5	34.4
BKG2M	1	113.4	4.62	146.2	68.8	38.2	28.5
BKG2M	2	112.4	4.91	146.9	70.1	28.2	35.6
BKG2M	3	111.3a	4.73a	146.5a	61.8a	39.4a	31.0a
BKG2M	4	110.8	4.35	145.7	90.3	32.8	35.9
BKG2M	5	113.4	4.48	150.2	80.6	31.5	34.4
BKG2M	Mn:	112.3	4.62	147.1	74.3	34.0	33.1
BKG3M	1	109.7	4.66	145.3	53.8	25.6	28.5
BKG3M	2	109.2	5.03	146.2	67.6	26.4	30.7
BKG3M	3	112.2	4.49	146.7	98.9	24.0	38.0
BKG3M	4	113.6	4.49	146.9	69.0	24.6	24.9
BKG3M	5	112.2	4.14	147.6	72.4	30.4	38.2
BKG3M	Mn:	111.4	4.56	146.5	72.3	26.2	32.1
BKG4M	1	112.7	5.05	149.0	114.0	31.1	42.7
BKG4M	2	111.7	4.49	146.5	81.8	39.2	224.1
BKG4M	3	112.9	4.83	145.5	65.9	31.3	37.9
BKG4M	4	112.2	4.28	146.9	63.5	31.7	29.2
BKG4M	5	114.5	4.71	147.8	90.5	26.7	29.4
BKG4M	Mn:	112.8	4.67	147.1	83.1	32.0	72.7

Individual Clinical Chemistry Data  
Pretest

Animal Number		GLU	BUN	CRE	CHOL	TRIG	PHOS
BKG1M	1	116.9	13.8	.88	189.8	24.3	7.5
BKG1M	2	113.1	11.1	.77	154.7	19.3	7.3
BKG1M	3	111.3	13.9	.75	189.7	26.5	8.0
BKG1M	4	109.2	14.5	.57	163.6	18.1	9.3
BKG1M	5	106.4	11.6	.83	168.3	19.2	8.3
Ç BKG1M	Mn:	111.4	13.0	.76	173.2	21.5	8.1
BKG2M	1	118.2	12.2	.78	188.8	15.1	7.9
BKG2M	2	114.0	14.8	.86	152.4	24.4	8.2
BKG2M	3	117.0a	12.1a	.77a	171.9a	25.2a	7.5a
BKG2M	4	117.8	16.0	.79	172.5	23.2	7.4
BKG2M	5	129.6	13.8	.75	193.7	30.1	8.0
BKG2M	Mn:	119.3*	13.8	.79	175.9	23.6	7.8
BKG3M	1	105.3	11.2	.72	130.5	27.0	7.5
BKG3M	2	110.6	18.2	.88	159.3	21.9	8.3
BKG3M	3	101.7	13.6	.88	184.9	13.3	7.6
BKG3M	4	107.4	12.2	.69	167.5	19.5	7.9
BKG3M	5	111.1	14.4	.79	187.7	14.2	7.4
BKG3M	Mn:	107.2	13.9	.79	166.0	19.2	7.7
BKG4M	1	105.3	19.3	.90	206.7	18.4	7.3
BKG4M	2	112.1	16.1	.66	206.0	24.1	6.7
BKG4M	3	113.0	12.6	.58	165.7	21.3	7.7
BKG4M	4	107.9	14.9	.95	156.7	13.7	7.8
BKG4M	5	115.6	12.4	.60	197.1	17.3	9.2
BKG4M	Mn:	110.8	15.1	.74	186.4	19.0	7.7

Individual Clinical Chemistry Data  
Pretest

Animal Number		TP	ALBG	GLOB	A/G	CA	TBIL
BKG1M	1	6.0	3.4	2.6	1.3	11.5	.14
BKG1M	2	5.6	3.2	2.4	1.3	10.5	.16
BKG1M	3	5.3	3.2	2.1	1.5	11.2	.12
BKG1M	4	5.8	3.3	2.5	1.3	11.4	.13
BKG1M	5	5.5	3.2	2.3	1.4	10.7	.11
Ç BKG1M	Mn:	5.6	3.3	2.4	1.4	11.1	.13
BKG2M	1	5.8	3.4	2.4	1.4	11.1	.16
BKG2M	2	5.8	3.3	2.5	1.3	11.3	.14
BKG2M	3	5.6a	3.4a	2.2a	1.5a	11.1a	.13a
BKG2M	4	5.8	3.4	2.4	1.4	11.1	.17
BKG2M	5	6.2	3.5	2.7	1.3	12.1	.18
BKG2M	Mn:	5.8	3.4	2.4	1.4	11.3	.16
BKG3M	1	5.6	3.4	2.2	1.5	10.9	.18
BKG3M	2	5.7	3.2	2.5	1.3	11.3	.16
BKG3M	3	5.3	3.0	2.3	1.3	10.7	.13
BKG3M	4	5.3	3.3	2.0	1.7	10.6	.12
BKG3M	5	6.0	3.5	2.5	1.4	11.1	.18
BKG3M	Mn:	5.6	3.3	2.3	1.4	10.9	.15
BKG4M	1	5.2	3.0	2.2	1.4	10.9	.11
BKG4M	2	5.7	3.4	2.3	1.5	11.1	.16
BKG4M	3	5.6	3.5	2.1	1.7	11.3	.17
BKG4M	4	5.3	3.2	2.1	1.5	11.0	.14
BKG4M	5	5.7	3.3	2.4	1.4	11.6	.14
BKG4M	Mn:	5.5	3.3	2.2	1.5	11.2	.14



Individual Clinical Chemistry Data  
Pretest

Animal Number		CL	K	NA	ALP	AST	ALT
BKG1F	1	112.2	4.30	146.8	86.0	34.5	34.2
BKG1F	2	112.4	4.88	148.1	64.0	34.7	41.5
BKG1F	3	112.9	4.60	147.1	120.6	32.5	31.0
BKG1F	4	112.7	4.33	146.8	117.3	40.0	37.2
BKG1F	5	112.0	4.08	147.3	55.1	31.2	34.4
Ç BKG1F	Mn:	112.4	4.44	147.2	88.6	34.6	35.7
BKG2F	1	112.9	4.81	147.3	46.1	37.6	30.3
BKG2F	2	112.2	4.88	147.9	89.4	33.8	39.4
BKG2F	3	112.2	4.81	147.7	73.1	22.1	33.3
BKG2F	4	111.5	4.59	146.5	65.0	33.0	42.1
BKG2F	5	113.1	4.75	147.7	56.3	26.6	39.2
BKG2F	Mn:	112.4	4.77	147.4	66.0	30.6	36.9
BKG3F	1	113.1	4.83	148.5	73.9	29.3	38.6
BKG3F	2	116.7	4.56	151.8	81.1	22.9	29.6
BKG3F	3	113.1	4.61	148.8	105.9	43.1	36.9
BKG3F	4	114.8	4.42	148.5	82.2	36.5	34.4
BKG3F	5	109.7	4.75	145.6	65.6	31.4	36.7
BKG3F	Mn:	113.5	4.63	148.6	81.7	32.6	35.2
BKG4F	1	110.8	4.67	144.8	51.1	22.6	35.0
BKG4F	2	112.9	4.84	147.0	45.4	23.4	28.7
BKG4F	3	109.9	4.63	146.4	63.7	24.1	30.5
BKG4F	4	112.4	4.34	148.4	72.0	35.8	33.9
BKG4F	5	110.1	4.45	146.8	80.0	29.5	37.8
BKG4F	Mn:	111.2	4.59	146.7	62.4	27.1	33.2

Individual Clinical Chemistry Data  
Pretest

Animal Number		GLU	BUN	CRE	CHOL	TRIG	PHOS
BKG1F	1	107.1	23.7	1.00	136.7	23.9	7.4
BKG1F	2	104.7	13.6	.63	143.2	20.8	8.4
BKG1F	3	107.3	12.1	.86	173.4	34.2	8.1
BKG1F	4	114.0	12.6	.80	151.5	28.6	7.8
BKG1F	5	111.8	17.0	.71	171.7	29.5	7.4
Ç BKG1F	Mn:	109.0	15.8	.80	155.3	27.4	7.8
BKG2F	1	103.7	13.1	.66	123.2	20.8	7.0
BKG2F	2	116.6	14.2	.76	141.4	20.7	7.3
BKG2F	3	96.1	15.3	.99	158.1	22.7	7.2
BKG2F	4	102.2	14.4	1.00	132.1	23.4	8.0
BKG2F	5	106.2	13.7	.74	165.6	15.8	6.8
BKG2F	Mn:	105.0	14.1	.83	144.1	20.7*	7.3
BKG3F	1	100.6	15.7	.84	171.5	24.9	7.6
BKG3F	2	132.2	14.7	.85	172.8	20.4	7.4
BKG3F	3	104.1	22.8	.89	142.2	18.0	8.6
BKG3F	4	108.9	16.2	1.01	128.1	21.6	7.0
BKG3F	5	114.0	11.7	.93	181.3	28.0	7.8
BKG3F	Mn:	112.0	16.2	.90	159.2	22.6	7.7
BKG4F	1	102.7	11.7	.73	141.4	28.6	6.9
BKG4F	2	104.1	15.1	.79	145.0	19.7	7.8
BKG4F	3	98.8	17.3	.68	153.6	26.3	7.5
BKG4F	4	106.1	15.1	.74	151.8	27.4	7.5
BKG4F	5	107.6	15.9	.79	147.3	26.9	8.1
BKG4F	Mn:	103.9	15.0	.75	147.8	25.8	7.6

Individual Clinical Chemistry Data  
Pretest

Animal Number	TP	ALBG	GLOB	A/G	CA	TBIL
BKG1F 1	5.5	3.3	2.2	1.5	11.1	.14
BKG1F 2	6.0	3.6	2.4	1.5	11.3	.14
BKG1F 3	5.8	3.4	2.4	1.4	11.3	.14
BKG1F 4	5.5	3.3	2.2	1.5	10.8	.23
BKG1F 5	6.2	3.7	2.5	1.5	11.0	.20
Ç BKG1F Mn:	5.8	3.5	2.3	1.5	11.1	.17
BKG2F 1	5.3	3.2	2.1	1.5	10.7	.19
BKG2F 2	5.4	3.2	2.2	1.5	10.8	.14
BKG2F 3	5.9	3.5	2.4	1.5	10.9	.17
BKG2F 4	5.7	3.5	2.2	1.6	11.0	.15
BKG2F 5	5.7	3.2	2.5	1.3	11.1	.16
BKG2F Mn:	5.6	3.3	2.3	1.5	10.9	.16
BKG3F 1	5.8	3.5	2.3	1.5	11.3	.15
BKG3F 2	5.9	3.6	2.3	1.6	11.1	.14
BKG3F 3	5.6	3.3	2.3	1.4	11.3	.13
BKG3F 4	5.5	3.4	2.1	1.6	10.8	.17
BKG3F 5	5.8	3.5	2.3	1.5	11.2	.18
BKG3F Mn:	5.7	3.5	2.3	1.5	11.1	.15
BKG4F 1	5.3	3.1	2.2	1.4	10.7	.19
BKG4F 2	5.5	3.3	2.2	1.5	11.3	.20
BKG4F 3	5.9	3.6	2.3	1.6	10.7	.22
BKG4F 4	5.4	3.2	2.2	1.5	11.2	.14
BKG4F 5	6.0	3.5	2.5	1.4	11.5	.16
BKG4F Mn:	5.6	3.3	2.3	1.5	11.1	.18

**B. Week 4**

Individual Clinical Chemistry Data  
Week 4

Animal Number		CL	K	NA	ALP	AST	ALT
BKG1M	1	113.2	4.82	148.3	78.8	30.5	48.1
BKG1M	2	109.5	4.78	145.5	64.1	27.5	39.4
BKG1M	3	113.2	4.78	147.5	74.5	35.6	30.1
BKG1M	4	111.5	4.87	148.3	89.2	34.4	42.1
BKG1M	5	111.5	5.17	146.2	107.9	26.3	34.6
Ç BKG1M	Mn:	111.8	4.88	147.2	82.9	30.9	38.9
BKG2M	1	110.5	4.55	144.8	66.0	34.5	28.3
BKG2M	2	112.5	4.64	146.5	60.3	28.9	30.6
BKG2M	3	110.2	4.69	144.6	63.4	41.2	39.3
BKG2M	4	109.7	4.53	147.3	83.2	29.1	36.8
BKG2M	5	112.2	4.91	147.2	74.1	28.4	44.3
BKG2M	Mn:	111.0	4.66	146.1	69.4	32.4	35.9
BKG3M	1	111.2	4.77	146.2	43.7	21.9	26.9
BKG3M	2	111.5	4.78	146.6	58.5	36.8	39.0
BKG3M	3	111.5b	4.64b	146.4b	119.6b	27.8b	44.1b
BKG3M	4	113.0	4.33	145.4	75.7	24.3	37.8
BKG3M	5	112.0	4.60	148.1	68.9	31.8	41.5
BKG3M	Mn:	111.8	4.62	146.5	73.3	28.5	37.9
BKG4M	1	111.0	4.95	146.0	84.7	30.8	41.3
BKG4M	2	112.5	4.56	148.2	71.7	37.4	144.0
BKG4M	3	112.2	4.61	144.9	61.7	30.2	43.5
BKG4M	4	112.2	4.45	146.5	57.4	29.3	35.6
BKG4M	5	114.2	5.00	148.3	84.3	21.9	31.1
BKG4M	Mn:	112.4	4.71	146.8	72.0	29.9	59.1

Individual Clinical Chemistry Data  
Week 4

Animal Number	GLU	BUN	CRE	CHOL	TRIG	PHOS
BKG1M 1	98.1	18.3	.82	160.2	29.1	6.6
BKG1M 2	109.5	12.3	.88	150.2	22.1	6.6
BKG1M 3	96.5	16.6	.57	195.6	25.5	6.7
BKG1M 4	96.6	15.1	1.11	169.4	19.8	8.0
BKG1M 5	96.8	12.4	.68	188.2	23.2	8.4
Ç BKG1M Mn:	99.5	14.9	.81	172.7	23.9	7.3
BKG2M 1	109.0	12.5	1.00	159.7	17.5	6.1
BKG2M 2	95.8	12.5	.80	133.4	24.2	6.9
BKG2M 3	83.0	14.0	.78	163.4	27.7	5.9
BKG2M 4	109.3	13.9	1.06	168.6	20.9	7.0
BKG2M 5	102.1	11.4	.91	168.8	19.7	6.4
BKG2M Mn:	99.8	12.9	.91	158.8	22.0	6.5
BKG3M 1	99.2	11.2	.60	117.9	25.5	7.0
BKG3M 2	99.5	16.7	1.15	155.2	22.2	6.3
BKG3M 3	98.9b	14.6b	.84b	184.7b	19.1b	6.5b
BKG3M 4	100.6	13.3	.80	165.1	17.0	6.5
BKG3M 5	100.2	12.3	.99	180.6	11.6	6.4
BKG3M Mn:	99.7	13.6	.88	160.7	19.1	6.5
BKG4M 1	103.8	16.5	1.07	210.3	14.9	7.7
BKG4M 2	96.9	15.4	.79	193.3	26.3	6.3
BKG4M 3	105.0	11.4	.83	160.1	20.2	6.5
BKG4M 4	103.9	15.4	1.02	151.9	17.4	6.7
BKG4M 5	95.5	10.2	1.18	182.0	14.1	7.4
BKG4M Mn:	101.0	13.8	.98	179.5	18.6	6.9

Individual Clinical Chemistry Data  
Week 4

Animal Number	TP	ALBG	GLOB	A/G	CA	TBIL
BKG1M 1	5.7	3.4	2.3	1.5	11.0	.16
BKG1M 2	5.9	3.5	2.4	1.5	10.7	.17
BKG1M 3	5.7	3.4	2.3	1.5	10.5	.16
BKG1M 4	6.2	3.4	2.8	1.2	11.1	.12
BKG1M 5	5.8	3.4	2.4	1.4	10.5	.14
Ç BKG1M Mn:	5.9	3.4	2.4	1.4	10.8	.15
BKG2M 1	5.6	3.4	2.2	1.5	10.5	.19
BKG2M 2	6.0	3.2	2.8	1.1	10.8	.16
BKG2M 3	5.9	3.5	2.4	1.5	10.5	.26
BKG2M 4	5.9	3.4	2.5	1.4	10.9	.19
BKG2M 5	5.8	3.5	2.3	1.5	11.0	.16
BKG2M Mn:	5.8	3.4	2.4	1.4	10.7	.19
BKG3M 1	5.6	3.5	2.1	1.7	10.5	.18
BKG3M 2	5.8	3.3	2.5	1.3	10.4	.17
BKG3M 3	5.4b	3.1b	2.3b	1.3b	10.4b	.13b
BKG3M 4	5.6	3.3	2.3	1.4	10.4	.14
BKG3M 5	6.2	3.6	2.6	1.4	10.6	.15
BKG3M Mn:	5.7	3.4	2.4	1.4	10.5	.15
BKG4M 1	5.4	3.1	2.3	1.3	10.8	.13
BKG4M 2	6.0	3.5	2.5	1.4	10.6	.19
BKG4M 3	5.8	3.6	2.2	1.6	10.5	.18
BKG4M 4	5.5	3.2	2.3	1.4	10.9	.13
BKG4M 5	5.6	3.3	2.3	1.4	10.8	.14
BKG4M Mn:	5.7	3.3	2.3	1.4	10.7	.15

Individual Clinical Chemistry Data  
Week 4

Animal Number		CL	K	NA	ALP	AST	ALT
BKG1F	1	112.2	4.43	147.7	89.3	32.0	49.8
BKG1F	2	111.2	5.12	147.4	53.3	33.3	32.5
BKG1F	3	112.5	4.70	147.3	106.5	27.4	24.3
BKG1F	4	112.2	4.65	146.7	118.3	36.3	36.3
BKG1F	5	110.7	4.56	145.9	51.5	26.2	29.3
Ç BKG1F	Mn:	111.8	4.69	147.0	83.8	31.0	34.4
BKG2F	1	114.2	4.88	148.0	44.9	40.0	34.2
BKG2F	2	111.7	4.72	146.4	79.4	27.3	41.4
BKG2F	3	111.5	4.78	146.3	56.3	23.8	28.4
BKG2F	4	113.5	4.53	148.4	67.2	31.8	41.6
BKG2F	5	111.7	5.01	146.6	47.2	25.2	38.5
BKG2F	Mn:	112.5	4.78	147.1	59.0	29.6	36.8
BKG3F	1	111.5	4.82	146.9	73.5	31.6	44.9
BKG3F	2	116.3	5.13	151.4	72.8	26.3	30.3
BKG3F	3	112.7	4.21	148.2	102.7	33.6	31.8
BKG3F	4	116.8	4.57	149.8	71.7	40.6	34.8
BKG3F	5	110.7	5.31	146.2	61.3	28.6	32.5
BKG3F	Mn:	113.6	4.81	148.5	76.4	32.1	34.9
BKG4F	1	112.7	4.64	145.9	55.1	25.1	36.3
BKG4F	2	113.2	4.42	146.3	38.1	24.9	23.4
BKG4F	3	109.2a	4.45a	145.6a	60.7a	23.8a	30.7a
BKG4F	4	112.0	5.66	147.6	83.1	33.8	30.0
BKG4F	5	110.5	4.87	147.1	77.5	39.8	42.4
BKG4F	Mn:	111.5	4.81	146.5	62.9	29.5	32.6



Individual Clinical Chemistry Data  
Week 4

Animal Number	GLU	BUN	CRE	CHOL	TRIG	PHOS
BKG1F 1	101.1	18.7	.98	134.3	23.8	6.2
BKG1F 2	89.9	12.4	.75	128.6	17.0	7.0
BKG1F 3	91.2	14.9	.77	160.9	29.4	6.4
BKG1F 4	91.3	12.9	.81	147.1	28.9	6.5
BKG1F 5	94.8	13.3	.90	158.9	29.8	5.3
Ç BKG1F Mn:	93.7	14.4	.84	146.0	25.8	6.3
BKG2F 1	90.4	16.5	.99	111.8	21.1	6.2
BKG2F 2	98.5	16.7	1.09	148.1	16.4	6.0
BKG2F 3	85.4	12.3	1.04	137.9	23.3	5.8
BKG2F 4	98.7	13.1	.81	137.1	32.7	5.8
BKG2F 5	86.1	11.8	.80	172.4	21.2	5.3
BKG2F Mn:	91.8	14.1	.95	141.5	22.9	5.8
BKG3F 1	93.8	15.2	.95	173.8	21.2	5.9
BKG3F 2	112.3	13.9	.85	165.6	22.3	5.4
BKG3F 3	99.4	20.9	.89	134.9	18.7	6.4
BKG3F 4	96.1	15.8	.83	113.6	27.1	5.3
BKG3F 5	91.8	11.5	.65	165.2	24.8	5.8
BKG3F Mn:	98.7	15.5	.83	150.6	22.8	5.8
BKG4F 1	97.5	14.1	.88	115.8	19.9	6.2
BKG4F 2	92.2	14.1	.65	127.1	25.7	6.3
BKG4F 3	86.7a	16.8a	.77a	155.9a	22.0a	5.8a
BKG4F 4	95.0	17.4	.94	136.0	32.4	5.5
BKG4F 5	88.0	15.7	1.00	140.1	17.1	6.2
BKG4F Mn:	91.9	15.6	.85	135.0	23.4	6.0

Individual Clinical Chemistry Data  
Week 4

Animal Number	TP	ALBG	GLOB	A/G	CA	TBIL
BKG1F 1	5.8	3.5	2.3	1.5	10.5	.19
BKG1F 2	6.0	3.6	2.4	1.5	10.1	.18
BKG1F 3	5.6	3.4	2.2	1.5	10.1	.15
BKG1F 4	5.5	3.3	2.2	1.5	10.0	.26
BKG1F 5	6.1	3.7	2.4	1.5	9.8	.22
Ç BKG1F Mn:	5.8	3.5	2.3	1.5	10.1	.20
BKG2F 1	5.2	3.1	2.1	1.5	9.9	.20
BKG2F 2	5.4	3.2	2.2	1.5	9.9	.15
BKG2F 3	5.7	3.5	2.2	1.6	10.5	.21
BKG2F 4	6.0	3.8	2.2	1.7	10.2	.21
BKG2F 5	5.9	3.4	2.5	1.4	10.1	.17
BKG2F Mn:	5.6	3.4	2.2	1.5	10.1	.19
BKG3F 1	5.8	3.5	2.3	1.5	10.3	.22
BKG3F 2	5.7	3.5	2.2	1.6	10.0	.16
BKG3F 3	5.7	3.3	2.4	1.4	10.0	.14
BKG3F 4	5.5	3.5	2.0	1.8	10.0	.22
BKG3F 5	5.7	3.5	2.2	1.6	10.0	.18
BKG3F Mn:	5.7	3.5	2.2	1.6	10.1	.18
BKG4F 1	5.2	3.1	2.1	1.5	9.8	.19
BKG4F 2	5.0	3.1	1.9	1.6	10.1	.16
BKG4F 3	5.9a	3.5a	2.4a	1.5a	10.3a	.24a
BKG4F 4	5.8	3.4	2.4	1.4	9.9	.18
BKG4F 5	6.2	3.7	2.5	1.5	10.3	.23
BKG4F Mn:	5.6	3.4	2.3	1.5	10.1	.20

## **C. Recovery**

Individual Clinical Chemistry Data  
Recovery

Animal Number		CL	K	NA	ALP	AST	ALT
BKG1M	5	109.3	5.33	144.8	96.6	26.4	30.8
Ç BKG1M	Mn:	109.3<	5.33<	144.8<	96.6<	26.4<	30.8<
BKG2M	5	109.8	5.05	144.0	64.4	28.3	35.3
BKG2M	Mn:	109.8<	5.05<	144.0<	64.4<	28.3<	35.3<
BKG3M	5	108.5	4.51	143.1	61.0	28.4	39.7
BKG3M	Mn:	108.5<	4.51<	143.1<	61.0<	28.4<	39.7<
BKG4M	5	111.8	4.80	144.3	85.3	23.5	26.8
BKG4M	Mn:	111.8<	4.80<	144.3<	85.3<	23.5<	26.8<

Individual Clinical Chemistry Data  
Recovery

Animal Number	GLU	BUN	CRE	CHOL	TRIG	PHOS
BKG1M 5	95.4	12.0	.86	181.8	26.5	7.0
Ç BKG1M Mn:	95.4<	12.0<	.86<	181.8<	26.5<	7.0<
BKG2M 5	108.0	13.4	.98	152.8	18.0	6.4
BKG2M Mn:	108.0<	13.4<	.98<	152.8<	18.0<	6.4<
BKG3M 5	86.6	12.9	.81	162.4	17.2	6.0
BKG3M Mn:	86.6<	12.9<	.81<	162.4<	17.2<	6.0<
BKG4M 5	85.7	10.5	.88	172.4	22.1	6.9
BKG4M Mn:	85.7<	10.5<	.88<	172.4<	22.1<	6.9<

Individual Clinical Chemistry Data  
Recovery

Animal Number	TP	ALBG	GLOB	A/G	CA	TBIL
BKG1M 5	5.7	3.4	2.3	1.5	10.1	.13
Ç BKG1M Mn:	5.7<	3.4<	2.3<	1.5<	10.1<	.13<
BKG2M 5	5.9	3.4	2.5	1.4	10.7	.18
BKG2M Mn:	5.9<	3.4<	2.5<	1.4<	10.7<	.18<
BKG3M 5	5.9	3.6	2.3	1.6	10.7	.22
BKG3M Mn:	5.9<	3.6<	2.3<	1.6<	10.7<	.22<
BKG4M 5	5.8	3.4	2.4	1.4	10.6	.14
BKG4M Mn:	5.8<	3.4<	2.4<	1.4<	10.6<	.14<

Individual Clinical Chemistry Data  
Recovery

Animal Number		CL	K	NA	ALP	AST	ALT
BKG1F	5	109.0	4.27	143.9	52.5	25.0	30.1
Ç BKG1F	Mn:	109.0<	4.27<	143.9<	52.5<	25.0<	30.1<
BKG2F	5	107.9	4.65	144.4	49.6	30.4	40.9
BKG2F	Mn:	107.9<	4.65<	144.4<	49.6<	30.4<	40.9<
BKG3F	5	110.7	4.95	144.1	55.8	28.5	30.1
BKG3F	Mn:	110.7<	4.95<	144.1<	55.8<	28.5<	30.1<
BKG4F	5	112.3	4.39	147.3	66.8	29.2	38.1
BKG4F	Mn:	112.3<	4.39<	147.3<	66.8<	29.2<	38.1<

Individual Clinical Chemistry Data  
Recovery

Animal Number		GLU	BUN	CRE	CHOL	TRIG	PHOS
BKG1F	5	92.7	14.5	.94	163.2	21.0	5.5
Ç BKG1F	Mn:	92.7<	14.5<	.94<	163.2<	21.0<	5.5<
BKG2F	5	91.8	12.7	.70	177.0	26.5	5.7
BKG2F	Mn:	91.8<	12.7<	.70<	177.0<	26.5<	5.7<
BKG3F	5	94.1	18.2	.99	169.4	25.2	6.8
BKG3F	Mn:	94.1<	18.2<	.99<	169.4<	25.2<	6.8<
BKG4F	5	102.0	16.2	1.01	146.6	13.7	5.3
BKG4F	Mn:	102.0<	16.2<	1.01<	146.6<	13.7<	5.3<



Individual Clinical Chemistry Data  
Recovery

Animal Number	TP	ALBG	GLOB	A/G	CA	TBIL
BKG1F 5	6.1	3.7	2.4	1.5	10.6	.21
Ç BKG1F Mn:	6.1<	3.7<	2.4<	1.5<	10.6<	.21<
BKG2F 5	6.2	3.5	2.7	1.3	10.8	.19
BKG2F Mn:	6.2<	3.5<	2.7<	1.3<	10.8<	.19<
BKG3F 5	5.5	3.4	2.1	1.6	10.7	.17
BKG3F Mn:	5.5<	3.4<	2.1<	1.6<	10.7<	.17<
BKG4F 5	6.2	3.9	2.3	1.7	10.7	.20
BKG4F Mn:	6.2<	3.9<	2.3<	1.7<	10.7<	.20<

## **APPENDIX VIII**

### **INDIVIDUAL ORGAN WEIGHT DATA**

- A. Absolute Organ Weight Data**
  - 1. Final Necropsy**
  - 2. Recovery Necropsy**
- B. Relative Organ Weight Data**
  - 1. Final Necropsy**
  - 2. Recovery Necropsy**

### **A. Absolute Organ Weight Data**

## Key to Individual Absolute Organ Weight Data

### Dosage Key

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

### Abbreviation Key

BR	Brain	g
HE	Heart	g
KI	Kidneys	g
AD	Adrenals	g
LI	Liver	g
SP	Spleen	g
TE/EP	Testes/Epididymides (males)	g
OV	Ovaries (females)	g
TR/PA	Thyroid/Parathyroids	g
A	Only right thyroid weighed on BKG2F05	

### Dunnett's Test Key

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison

## **1. Final Necropsy**

Individual Absolute Organ Weights (g)  
Final Necropsy

Animal Number		BR	HE	KI	AD	LI	SP
BKG1M	1	80.950	100.780	47.295	1.154	301.500	58.167
BKG1M	2	78.980	91.400	53.304	1.048	268.010	48.686
BKG1M	3	73.931	84.220	47.401	1.449	233.830	47.661
BKG1M	4	71.596	92.450	56.071	1.100	331.360	54.270
Ç BKG1M	Mn:	76.364	92.213	51.018	1.188	283.675	52.196
BKG2M	1	72.730	85.200	51.637	.796	277.500	68.387
BKG2M	2	86.490	95.060	58.996	1.274	336.020	107.270
BKG2M	3	76.266	98.160	50.659	1.221	283.760	72.870
BKG2M	4	83.050	107.450	57.347	1.336	311.980	75.783
BKG2M	Mn:	79.634	96.468	54.660	1.157	302.315	81.078*
BKG3M	1	78.027	87.990	69.829	.901	260.310	48.058
BKG3M	2	83.790	103.930	50.674	1.456	281.560	43.045
BKG3M	3	92.810	110.240	55.565	1.249	353.280	53.459
BKG3M	4	79.959	88.440	62.314	1.352	289.100	80.010
BKG3M	Mn:	83.647	97.650	59.596	1.240	296.063	56.143
BKG4M	1	84.290	97.900	60.267	1.098	351.030	70.447
BKG4M	2	79.375	98.640	55.157	1.650	302.640	41.734
BKG4M	3	79.098	104.070	69.801	1.051	298.950	58.872
BKG4M	4	85.990	84.580	48.332	.847	301.610	56.937
BKG4M	Mn:	82.188	96.298	58.389	1.162	313.558	56.998

Individual Absolute Organ Weights (g)  
Final Necropsy

Animal Number	TE/EP	TR/PA
BKG1M 1	18.567	1.609
BKG1M 2	20.210	1.430
BKG1M 3	16.556	1.342
BKG1M 4	20.211	1.454
Ç BKG1M Mn:	18.886	1.459
BKG2M 1	22.760	1.660
BKG2M 2	27.849	1.862
BKG2M 3	18.550	1.600
BKG2M 4	23.189	1.865
BKG2M Mn:	23.087	1.747
BKG3M 1	22.750	1.040
BKG3M 2	19.390	1.220
BKG3M 3	20.621	1.837
BKG3M 4	27.650	1.670
BKG3M Mn:	22.603	1.442
BKG4M 1	23.411	1.773
BKG4M 2	15.660	1.660
BKG4M 3	18.400	1.480
BKG4M 4	20.800	1.010
BKG4M Mn:	19.568	1.481

Individual Absolute Organ Weights (g)  
Final Necropsy

Animal Number		BR	HE	KI	AD	LI	SP
BKG1F	1	81.960	83.480	42.918	1.292	227.730	49.164
BKG1F	2	77.205	89.460	51.977	.922	275.220	78.351
BKG1F	3	81.240	75.689	46.744	1.084	260.010	74.802
BKG1F	4	82.730	84.480	56.064	1.215	234.820	78.350
Ç BKG1F	Mn:	80.784	83.277	49.426	1.128	249.445	70.167
BKG2F	1	82.340	82.420	46.844	1.488	254.970	68.884
BKG2F	2	81.870	83.290	43.384	.942	280.040	59.292
BKG2F	3	79.485	88.040	45.189	1.465	226.050	71.560
BKG2F	4	71.212	81.760	46.733	1.098	235.110	88.030
BKG2F	Mn:	78.727	83.878	45.538	1.248	249.043	71.942
BKG3F	1	71.273	88.450	56.757	1.030	318.000	40.650
BKG3F	2	72.690	76.118	41.920	.834	212.560	56.915
BKG3F	3	78.470	80.330	47.447	1.181	248.550	45.781
BKG3F	4	77.042	77.926	47.016	.875	219.030	67.139
BKG3F	Mn:	74.869	80.706	48.285	.980	249.535	52.621
BKG4F	1	82.030	83.670	46.511	1.006	254.940	82.620
BKG4F	2	91.230	80.430	47.818	1.565	281.970	79.036
BKG4F	3	71.685	70.442	42.032	.985	219.300	44.197
BKG4F	4	73.569	88.730	46.115	1.320	274.870	104.660
BKG4F	Mn:	79.629	80.818	45.619	1.219	257.770	77.628



Individual Absolute Organ Weights (g)  
Final Necropsy

Animal Number	OV	TR/PA
BKG1F 1	.890	1.442
BKG1F 2	.840	1.180
BKG1F 3	.970	1.390
BKG1F 4	1.240	.920
Ç BKG1F Mn:	.985	1.233
BKG2F 1	1.000	1.020
BKG2F 2	.820	1.860
BKG2F 3	.657	1.277
BKG2F 4	.630	1.300
BKG2F Mn:	.777	1.364
BKG3F 1	.820	1.220
BKG3F 2	.756	1.277
BKG3F 3	.959	1.201
BKG3F 4	.524	.921
BKG3F Mn:	.765	1.155
BKG4F 1	.780	1.470
BKG4F 2	1.240	1.170
BKG4F 3	.544	1.219
BKG4F 4	.990	1.730
BKG4F Mn:	.889	1.397

## **2. Recovery Necropsy**

Individual Absolute Organ Weights (g)  
Recovery Necropsy

Animal Number		BR	HE	KI	AD	LI	SP
BKG1M	5	71.305	84.220	59.209	.993	302.350	50.832
Ç BKG1M	Mn:	71.305<	84.220<	59.209<	.993<	302.350<	50.832<
BKG2M	5	82.540	103.140	59.737	1.006	334.840	72.995
BKG2M	Mn:	82.540<	103.140<	59.737<	1.006<	334.840<	72.995<
BKG3M	5	80.820	89.830	49.834	1.359	287.020	76.386
BKG3M	Mn:	80.820<	89.830<	49.834<	1.359<	287.020<	76.386<
BKG4M	5	87.990	88.070	72.627	1.011	278.570	87.810
BKG4M	Mn:	87.990<	88.070<	72.627<	1.011<	278.570<	87.810<

Individual Absolute Organ Weights (g)  
Recovery Necropsy

Animal Number		TE/EP	TR/PA
BKG1M	5	23.862	1.276
Ç BKG1M	Mn:	23.862<	1.276<
BKG2M	5	15.878	1.423
BKG2M	Mn:	15.878<	1.423<
BKG3M	5	17.692	1.621
BKG3M	Mn:	17.692<	1.621<
BKG4M	5	34.494	1.634
BKG4M	Mn:	34.494<	1.634<

Individual Absolute Organ Weights (g)  
Recovery Necropsy

Animal Number		BR	HE	KI	AD	LI	SP
BKG1F	5	82.380	89.460	44.989	1.499	266.320	97.550
Ç BKG1F	Mn:	82.380<	89.460<	44.989<	1.499<	266.320<	97.550<
BKG2F	5	77.362	94.550	51.074	1.298	248.380	73.551
BKG2F	Mn:	77.362<	94.550<	51.074<	1.298<	248.380<	73.551<
BKG3F	5	82.410	77.422	52.644	1.372	263.700	64.504
BKG3F	Mn:	82.410<	77.422<	52.644<	1.372<	263.700<	64.504<
BKG4F	5	75.420	80.500	40.430	1.064	236.140	60.104
BKG4F	Mn:	75.420<	80.500<	40.430<	1.064<	236.140<	60.104<

Individual Absolute Organ Weights (g)  
Recovery Necropsy

Animal Number		OV	TR/PA
BKG1F	5	1.206	1.187
Ç BKG1F	Mn:	1.206<	1.187<
BKG2F	5	1.084	.797A
BKG2F	Mn:	1.084<	.797<
BKG3F	5	.982	1.590
BKG3F	Mn:	.982<	1.590<
BKG4F	5	.918	.899
BKG4F	Mn:	.918<	.899<

## **B. Relative Organ Weight Data**

## Key to Individual Organ Weights Relative to Body Weight

### Dosage Key

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

### Abbreviation Key

BW	Body Weight	kg
BR	Brain	%
HE	Heart	%
KI	Kidneys	%
AD	Adrenals	%
LI	Liver	%
SP	Spleen	%
TE/EP	Testes/Epididymides (males)	%
OV	Ovaries (females)	%
TR/PA	Thyroid/Parathyroids	%
A	Only right thyroid weighed on BKG2F05	

### Dunnett's Test Key

- \* = .05 Significance by Dunnett's Test
- + = .01 Significance by Dunnett's Test
- < = Less than 5 degrees of freedom by Dunnett's Test
- Ç = Control group used for Dunnett's Test comparison



## **1. Final Necropsy**

Individual Organ Weights Relative to Body Weight (%)  
Final Necropsy

Animal Number	BW	BR	HE	KI	AD	LI
BKG1M 1	10.557	.767	.955	.448	.011	2.856
BKG1M 2	10.384	.761	.880	.513	.010	2.581
BKG1M 3	10.253	.721	.821	.462	.014	2.281
BKG1M 4	14.260	.502	.648	.393	.008	2.324
Ç BKG1M Mn:	11.364	.688	.826	.454	.011	2.510
BKG2M 1	10.624	.685	.802	.486	.007	2.612
BKG2M 2	13.671	.633	.695	.432	.009	2.458
BKG2M 3	11.583	.658	.847	.437	.011	2.450
BKG2M 4	12.067	.688	.890	.475	.011	2.585
BKG2M Mn:	11.986	.666	.809	.458	.010	2.526
BKG3M 1	11.427	.683	.770	.611	.008	2.278
BKG3M 2	12.426	.674	.836	.408	.012	2.266
BKG3M 3	11.883	.781	.928	.468	.011	2.973
BKG3M 4	11.005	.727	.804	.566	.012	2.627
BKG3M Mn:	11.685	.716	.834	.513	.011	2.536
BKG4M 1	13.823	.610	.708	.436	.008	2.539
BKG4M 2	12.175	.652	.810	.453	.014	2.486
BKG4M 3	12.800	.618	.813	.545	.008	2.336
BKG4M 4	11.189	.769	.756	.432	.008	2.696
BKG4M Mn:	12.497	.662	.772	.467	.009	2.514

Individual Organ Weights Relative to Body Weight (%)  
Final Necropsy

Animal Number		SP	TE/EP	TR/PA
BKG1M	1	.551	.176	.015
BKG1M	2	.469	.195	.014
BKG1M	3	.465	.161	.013
BKG1M	4	.381	.142	.010
Ç BKG1M	Mn:	.466	.168	.013
BKG2M	1	.644	.214	.016
BKG2M	2	.785	.204	.014
BKG2M	3	.629	.160	.014
BKG2M	4	.628	.192	.015
BKG2M	Mn:	.671*	.193	.015
BKG3M	1	.421	.199	.009
BKG3M	2	.346	.156	.010
BKG3M	3	.450	.174	.015
BKG3M	4	.727	.251	.015
BKG3M	Mn:	.486	.195	.012
BKG4M	1	.510	.169	.013
BKG4M	2	.343	.129	.014
BKG4M	3	.460	.144	.012
BKG4M	4	.509	.186	.009
BKG4M	Mn:	.455	.157	.012

Individual Organ Weights Relative to Body Weight (%)  
Final Necropsy

Animal Number	BW	BR	HE	KI	AD	LI
BKG1F 1	9.759	.840	.855	.440	.013	2.334
BKG1F 2	11.459	.674	.781	.454	.008	2.402
BKG1F 3	10.458	.777	.724	.447	.010	2.486
BKG1F 4	9.716	.851	.869	.577	.013	2.417
Ç BKG1F Mn:	10.348	.785	.807	.479	.011	2.410
BKG2F 1	9.731	.846	.847	.481	.015	2.620
BKG2F 2	10.515	.779	.792	.413	.009	2.663
BKG2F 3	9.168	.867	.960	.493	.016	2.466
BKG2F 4	9.643	.738	.848	.485	.011	2.438
BKG2F Mn:	9.764	.808	.862	.468	.013	2.547
BKG3F 1	10.547	.676	.839	.538	.010	3.015
BKG3F 2	9.113	.798	.835	.460	.009	2.332
BKG3F 3	10.504	.747	.765	.452	.011	2.366
BKG3F 4	8.937	.862	.872	.526	.010	2.451
BKG3F Mn:	9.775	.771	.828	.494	.010	2.541
BKG4F 1	9.215	.890	.908	.505	.011	2.767
BKG4F 2	10.390	.878	.774	.460	.015	2.714
BKG4F 3	9.444	.759	.746	.445	.010	2.322
BKG4F 4	9.863	.746	.900	.468	.013	2.787
BKG4F Mn:	9.728	.818	.832	.469	.012	2.647

Individual Organ Weights Relative to Body Weight (%)  
Final Necropsy

Animal Number	SP	OV	TR/PA
BKG1F 1	.504	.009	.015
BKG1F 2	.684	.007	.010
BKG1F 3	.715	.009	.013
BKG1F 4	.806	.013	.009
Ç BKG1F Mn:	.677	.010	.012
BKG2F 1	.708	.010	.010
BKG2F 2	.564	.008	.018
BKG2F 3	.781	.007	.014
BKG2F 4	.913	.007	.013
BKG2F Mn:	.741	.008	.014
BKG3F 1	.385	.008	.012
BKG3F 2	.625	.008	.014
BKG3F 3	.436	.009	.011
BKG3F 4	.751	.006	.010
BKG3F Mn:	.549	.008	.012
BKG4F 1	.897	.008	.016
BKG4F 2	.761	.012	.011
BKG4F 3	.468	.006	.013
BKG4F 4	1.061	.010	.018
BKG4F Mn:	.797	.009	.014

## **2. Recovery Necropsy**

Individual Organ Weights Relative to Body Weight (%)  
Recovery Necropsy

Animal Number		BW	BR	HE	KI	AD	LI
BKG1M	5	12.693	.562	.664	.466	.008	2.382
Ç BKG1M	Mn:	12.693<	.562<	.664<	.466<	.008<	2.382<
BKG2M	5	11.945	.691	.863	.500	.008	2.803
BKG2M	Mn:	11.945<	.691<	.863<	.500<	.008<	2.803<
BKG3M	5	11.304	.715	.795	.441	.012	2.539
BKG3M	Mn:	11.304<	.715<	.795<	.441<	.012<	2.539<
BKG4M	5	12.814	.687	.687	.567	.008	2.174
BKG4M	Mn:	12.814<	.687<	.687<	.567<	.008<	2.174<

Individual Organ Weights Relative to Body Weight (%)  
Recovery Necropsy

Animal Number		SP	TE/EP	TR/PA
BKG1M	5	.400	.188	.010
Ç BKG1M	Mn:	.400<	.188<	.010<
BKG2M	5	.611	.133	.012
BKG2M	Mn:	.611<	.133<	.012<
BKG3M	5	.676	.157	.014
BKG3M	Mn:	.676<	.157<	.014<
BKG4M	5	.685	.269	.013
BKG4M	Mn:	.685<	.269<	.013<



Individual Organ Weights Relative to Body Weight (%)  
Recovery Necropsy

Animal Number	BW	BR	HE	KI	AD	LI
BKG1F 5	10.336	.797	.866	.435	.015	2.577
Ç BKG1F Mn:	10.336<	.797<	.866<	.435<	.015<	2.577<
BKG2F 5	11.022	.702	.858	.463	.012	2.253
BKG2F Mn:	11.022<	.702<	.858<	.463<	.012<	2.253<
BKG3F 5	11.012	.748	.703	.478	.012	2.395
BKG3F Mn:	11.012<	.748<	.703<	.478<	.012<	2.395<
BKG4F 5	10.744	.702	.749	.376	.010	2.198
BKG4F Mn:	10.744<	.702<	.749<	.376<	.010<	2.198<

Individual Organ Weights Relative to Body Weight (%)  
Recovery Necropsy

Animal Number	SP	OV	TR/PA
BKG1F 5	.944	.012	.011
Ç BKG1F Mn:	.944<	.012<	.011<
BKG2F 5	.667	.010	.007A
BKG2F Mn:	.667<	.010<	.007<
BKG3F 5	.586	.009	.014
BKG3F Mn:	.586<	.009<	.014<
BKG4F 5	.559	.009	.008
BKG4F Mn:	.559<	.009<	.008<

**APPENDIX IX**  
**NECROPSY REPORT**

## NECROPSY REPORT

Following 28 days of dosing with either control article/vehicle or test article IQB-9302 as indicated in the table below, the first 4 dogs/sex/group were fasted overnight, euthanized with an intravenous injection of sodium pentobarbital solution and necropsied according to a randomization scheme on 08 December 1998 (males) or 09 December 1998 (females). Following a 14 day recovery period, the remaining 1 dog/sex/group was necropsied on 22 December 1998.

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

BKG1M01            Scheduled sacrifice during Week 5 (08 December 1998)  
Not Remarkable

BKG1M02            Scheduled sacrifice during Week 5 (08 December 1998)  
Not Remarkable

BKG1M03            Scheduled sacrifice during Week 5 (08 December 1998)  
Not Remarkable

BKG1M04            Scheduled sacrifice during Week 5 (08 December 1998)  
Not Remarkable

BKG1M05            Scheduled sacrifice during Week 7 (22 December 1998)  
Not Remarkable

BKG2M01            Scheduled sacrifice during Week 5 (08 December 1998)  
Not Remarkable

BKG2M02            Scheduled sacrifice during Week 5 (08 December 1998)  
Not Remarkable

### NECROPSY REPORT (cont'd)

BKG2M03	Scheduled sacrifice during Week 5 (08 December 1998) Not Remarkable
BKG2M04	Scheduled sacrifice during Week 5 (08 December 1998) Not Remarkable
BKG2M05	Scheduled sacrifice during Week 7 (22 December 1998) Not Remarkable
BKG3M01	Scheduled sacrifice during Week 5 (08 December 1998) Not Remarkable
BKG3M02	Scheduled sacrifice during Week 5 (08 December 1998) Left testicle small
BKG3M03	Scheduled sacrifice during Week 5 (08 December 1998) Not Remarkable
BKG3M04	Scheduled sacrifice during Week 5 (08 December 1998) Not Remarkable
BKG3M05	Scheduled sacrifice during Week 7 (22 December 1998) Not Remarkable
BKG4M01	Scheduled sacrifice during Week 5 (08 December 1998) Not Remarkable
BKG4M02	Scheduled sacrifice during Week 5 (08 December 1998) Not Remarkable
BKG4M03	Scheduled sacrifice during Week 5 (08 December 1998) Not Remarkable
BKG4M04	Scheduled sacrifice during Week 5 (08 December 1998) Not Remarkable
BKG4M05	Scheduled sacrifice during Week 7 (22 December 1998) Two (2) pale areas (streaks) on surface of spleen near the caudal end

### NECROPSY REPORT (cont'd)

BKG1F01	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG1F02	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG1F03	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG1F04	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG1F05	Scheduled sacrifice during Week 7 (22 December 1998) Two (2) pale areas (streaks) on surface of spleen
BKG2F01	Scheduled sacrifice during Week 5 (09 December 1998) Harderian gland enlarged, red and prominent – right eye
BKG2F02	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG2F03	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG2F04	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG2F05	Scheduled sacrifice during Week 7 (22 December 1998) Not Remarkable Note: Left thyroid lost at necropsy
BKG3F01	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG3F02	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG3F03	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable

### NECROPSY REPORT (cont'd)

BKG3F04	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG3F05	Scheduled sacrifice during Week 7 (22 December 1998) Red streaks on mucosa of ileum
BKG4F01	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG4F02	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG4F03	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG4F04	Scheduled sacrifice during Week 5 (09 December 1998) Not Remarkable
BKG4F05	Scheduled sacrifice during Week 7 (22 December 1998) Not Remarkable

## **APPENDIX X**

### **HISTOPATHOLOGY REPORT**

- A. Histopathologic Evaluation**
- B. Gross and Microscopic Correlation**
- C. Outline of Histologic Findings**



## **A. Histopathologic Evaluation**

## **HISTOPATHOLOGIC EVALUATION**

### **ABSTRACT**

Hematoxylin and eosin stained paraffin processed tissue sections were evaluated microscopically from 5 male and 5 female vehicle control dogs, Group BKG1 and 5 male and 5 female dogs given IQB-9302 at 1, Group BKG2, 2, Group BKG3, and 3, Group BKG4, mg/kg/day intravenously for 28 days. The last dog/sex/group was allowed 14 days for recovery after termination of dosing. All dogs in all groups survived the study. There were no distinct or consistent microscopic tissue changes related to treatment with IQB-9302 in this study.

### **TREATMENT RELATED FINDINGS**

There were no distinct or consistent microscopic tissue changes related to treatment with IQB-9302 at 1, 2 or 3 mg/kg/day intravenously for 28 days.

### **SPONTANEOUS OR INCIDENTAL FINDINGS**

The following microscopic findings were considered spontaneous or incidental and not related to treatment with IQB-9302 and were generally similar after 28 days and after recovery.

Thyroids for all Groups BKG1, BKG2, BKG3 and BKG4 dogs had the microscopic appearance of slight activity. Minimal or slight focal C-cell hyperplasia was noted in thyroids for 2 Group BKG1, 4 Group BKG2, 3 Group BKG3 and 1 of the Group BKG4 dogs.

Slight congestion, attributed to barbiturate euthanasia, was evident in spleen red pulp for all Groups BKG1, BKG2, BKG3 and BKG4 dogs and slight focal fibrosis occurred in spleen for 1 Group BKG1 dog. Lungs for 3 Group BKG1 and 1 of the Group BKG4 dogs had minimal focal pneumonitis. Harderian gland for 1 of the Group BKG2 dogs had slight hyperplasia.

Minimal mineralized deposits were noted in kidney medullary tissue for 9 Group BKG1, 10 Group BKG2, 8 Group BKG3, and 6 Group BKG4 dogs and 1 of the Group BKG2 dogs had slight cortical cysts. Fundic mucosa stomach sections for 3 Group BKG1, 1 Group BKG2, 1 Group BKG3 and 1 of the Group BKG4 dogs had minimal or slight mineralized deposits.

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Testes for 1 Group BKG1 and 1 Group BKG3 male dogs had bilateral or unilateral minimal segmental seminiferous tubule atrophy, subnormal slight spermatogenesis and minimal hypospermia in the epididymides. All other Group BKG1, BKG2, BKG3 and BKG4 male dogs had normal moderate spermatogenesis. Slight multifocal inflammatory infiltrate was noted in prostate for 1 of the Group BKG4 dogs.

Follicular development was present in ovaries for all Groups BKG1, BKG2, BKG3 and BKG4 female dogs. Bone marrow from all Groups BKG1, BKG2, BKG3 and BKG4 dogs had moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

Available sections of the following organs were within the limits of expected histologic appearance: brain (4 sections), spinal cord, pituitary, adrenals, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), liver (2 sections), gallbladder, pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

Histopathologic Evaluation Submitted by:

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Dean Barnett, DVM, Ph.D. (ACVP)  
Veterinary Pathologist

## **B. Gross and Microscopic Correlation**

BKG1M01  
Male  
Vehicle Control/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

EPIDIDYMIDES:

Gross: No alterations described.  
Microscopic: One had minimal hypospermia and the other was essentially normal.

TESTES:

Gross: No alterations described.  
Microscopic: Both had slight spermatogenesis and minimal segmental seminiferous tubule atrophy.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, kidneys, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, prostate, eyes and bone.

BKG1M02  
Male  
Vehicle Control/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDS:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG1M03  
Male  
Vehicle Control/Intravenous

GENERAL: Sacrifice, Week 5.

PITUITARY:

Gross: No alterations described.  
Microscopic: Not present in the available section.

THYROIDS:

Gross: No alterations described.  
Microscopic: One had minimal focal C cell hyperplasia and both had slight activity.

LUNGS:

Gross: No alterations described.  
Microscopic: One had minimal focal pneumonitis and the other was essentially normal.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

GALLBLADDER:

Gross: No alterations described.  
Microscopic: Not present in the available section.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

STOMACH:

Gross: No alterations described.  
Microscopic: The fundic section had slight multifocal mineralized deposits and the other two were essentially normal.

BKG1M03 (cont'd)  
Male  
Vehicle Control/Intravenous

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), liver (2 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.



BKG1M04  
Male  
Vehicle Control/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

LUNGS:

Gross: No alterations described.  
Microscopic: One had minimal focal pneumonitis and the other was essentially normal.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

STOMACH:

Gross: No alterations described.  
Microscopic: The fundic section had slight multifocal mineralized deposits and the other two were essentially normal.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

BKG1M04 (cont'd)  
Male  
Vehicle Control/Intravenous

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), liver (2 sections), gallbladder, pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG1M05  
Male  
Vehicle Control/Intravenous

GENERAL: Sacrifice, Week 7.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

STOMACH:

Gross: No alterations described.  
Microscopic: The fundic section had slight multifocal mineralized deposits and the other two were essentially normal.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG2M01  
Male  
1 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG2M02  
Male  
1 mg/kg/day IQB-9302/Intravenous

**GENERAL:** Sacrifice, Week 5.

**THYROIDS:**

Gross: No alterations described.  
Microscopic: Both had slight activity.

**SPLEEN:**

Gross: No alterations described.  
Microscopic: Slight congestion.

**KIDNEYS:**

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits.

**TESTES:**

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

**BONE MARROW:**

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG2M03  
Male  
1 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDIS:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits.

STOMACH:

Gross: No alterations described.  
Microscopic: The fundic section had minimal multifocal mineralized deposits and the other two were essentially normal.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG2M04  
Male  
1 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG2M05  
Male  
1 mg/kg/day IQB-9302/Intravenous

**GENERAL:** Sacrifice, Week 7.

**THYROIDS:**

Gross: No alterations described.

Microscopic: One had slight focal C cell hyperplasia and both had slight activity.

**SPLEEN:**

Gross: No alterations described.

Microscopic: Slight congestion.

**KIDNEYS:**

Gross: No alterations described.

Microscopic: Both had minimal mineralized deposits.

**TESTES:**

Gross: No alterations described.

Microscopic: Both had moderate spermatogenesis.

**BONE MARROW:**

Gross: No alterations described.

Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.



BKG3M01  
Male  
2 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDS:

Gross: No alterations described.  
Microscopic: Both had slight activity.

MESENTERIC LYMPH NODE:

Gross: No alterations described.  
Microscopic: Not present in the available section.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

STOMACH:

Gross: No alterations described.  
Microscopic: The fundic section had minimal multifocal mineralized deposits and the other two were essentially normal.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

BKG3M01 (cont'd)  
Male  
2 mg/kg/day IQB-9302/Intravenous

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG3M02  
Male  
2 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

EPIDIDYMIDES:

Gross: No alterations described.  
Microscopic: One had minimal hypospermia and the other was essentially normal.

TESTES:

Gross: Left testicle small.  
Microscopic: One had slight spermatogenesis and minimal segmental seminiferous tubule atrophy and the other had normal moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, kidneys, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, prostate, eyes and bone.

BKG3M03  
Male  
2 mg/kg/day IQB-9302/Intravenous °

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG3M04  
Male  
2 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.

Microscopic: One had slight focal C cell hyperplasia and both had slight activity.

SPLEEN:

Gross: No alterations described.

Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.

Microscopic: One had minimal mineralized deposits and the other was essentially normal.

TESTES:

Gross: No alterations described.

Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.

Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG3M05  
Male  
2 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 7.

THYROIDES:

Gross: No alterations described.  
Microscopic: One had slight focal C cell hyperplasia and both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG4M01  
Male  
3 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG4M02  
Male  
3 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, kidneys, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.



BKG4M03  
Male  
3 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG4M04  
Male  
3 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDS:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

STOMACH:

Gross: No alterations described.  
Microscopic: The fundic section had minimal multifocal mineralized deposits and the other two were essentially normal.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, kidneys, pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, prostate, eyes and bone.

BKG4M05  
Male  
3 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 7.

THYROIDES:

Gross: No alterations described.  
Microscopic: One had minimal focal C cell hyperplasia and both had slight activity.

SPLEEN:

Gross: Two pale areas (streaks) on surface of spleen near the caudal end.  
Microscopic: Both sections had slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits.

PROSTATE:

Gross: No alterations described.  
Microscopic: Slight focal inflammatory infiltrate.

TESTES:

Gross: No alterations described.  
Microscopic: Both had moderate spermatogenesis.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, epididymides, eyes and bone.

BKG1F01  
Female  
Vehicle Control/Intravenous

**GENERAL:** Sacrifice, Week 5.

**THYROID:**

Gross: No alterations described.  
Microscopic: Both had slight activity.

**SPLEEN:**

Gross: No alterations described.  
Microscopic: Slight congestion.

**KIDNEYS:**

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits.

**OVARIES:**

Gross: No alterations described.  
Microscopic: Both had follicular development.

**BONE MARROW:**

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG1F02  
Female  
Vehicle Control/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDS:

Gross: No alterations described.  
Microscopic: Both had slight activity.

LUNGS:

Gross: No alterations described.  
Microscopic: One had minimal focal pneumonitis and the other was essentially normal.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG1F03  
Female  
Vehicle Control/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG1F04  
Female  
Vehicle Control/Intravenous

**GENERAL:** Sacrifice, Week 5.

**THYROIDS:**

Gross: No alterations described.

Microscopic: One had slight focal C cell hyperplasia and both had slight activity.

**SPLEEN:**

Gross: No alterations described.

Microscopic: Slight congestion.

**KIDNEYS:**

Gross: No alterations described.

Microscopic: Both had minimal mineralized deposits.

**OVARIES:**

Gross: No alterations described.

Microscopic: Both had follicular development.

**BONE MARROW:**

Gross: No alterations described.

Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG1F05  
Female  
Vehicle Control/Intravenous

GENERAL: Sacrifice, Week 7.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: Two (2) pale areas (streaks) on surface of spleen.  
Microscopic: Both sections had slight congestion and one had slight focal fibrosis.

KIDNEYS:

Gross: No alterations described.  
Microscopic: Both sections had minimal mineralized deposits.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.



BKG2F01  
Female  
1 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

HARDERIAN GLAND:

Gross: Enlarged, red and prominent - right eye.  
Microscopic: Slight hyperplasia.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG2F02  
Female  
1 mg/kg/day IQB-9302/Intravenous

**GENERAL:** Sacrifice, Week 5.

**THYROIDS:**

**Gross:** No alterations described.  
**Microscopic:** One had minimal focal C cell hyperplasia and both had slight activity.

**SPLEEN:**

**Gross:** No alterations described.  
**Microscopic:** Slight congestion.

**KIDNEYS:**

**Gross:** No alterations described.  
**Microscopic:** One had minimal mineralized deposits and the other was essentially normal.

**OVARIES:**

**Gross:** No alterations described.  
**Microscopic:** Both had follicular development.

**BONE MARROW:**

**Gross:** No alterations described.  
**Microscopic:** Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG2F03  
Female  
1 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: One had minimal focal C cell hyperplasia and both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG2F04  
Female  
1 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDS:

Gross: No alterations described.  
Microscopic: One had minimal focal C cell hyperplasia and both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG2F05  
Female  
1 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 7.

THYROID:

Gross: No alterations described.  
Microscopic: The available section had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits and one had slight cortical cysts.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG3F01  
Female  
2 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG3F02  
Female  
2 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDIS:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG3F03  
Female  
2 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDS:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.



BKG3F04  
Female  
2 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

PITUITARY:

Gross: No alterations described.  
Microscopic: No section available for evaluation.

THYROIDS:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, kidneys, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG3F05  
Female  
2 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 7.

THYROIDES:

Gross: No alterations described.  
Microscopic: One had slight focal C cell hyperplasia and both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

ILEUM:

Gross: Red streaks on mucosa of ileum.  
Microscopic: The available section was essentially normal.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG4F01  
Female  
3 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, kidneys, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG4F02  
Female  
3 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDS:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, kidneys, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG4F03  
Female  
3 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

LUNGS:

Gross: No alterations described.  
Microscopic: One had minimal focal pneumonitis and the other was essentially normal.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG4F04  
Female  
3 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 5.

THYROIDES:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: Both had minimal mineralized deposits.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

BKG4F05  
Female  
3 mg/kg/day IQB-9302/Intravenous

GENERAL: Sacrifice, Week 7.

THYROIDS:

Gross: No alterations described.  
Microscopic: Both had slight activity.

SPLEEN:

Gross: No alterations described.  
Microscopic: Slight congestion.

KIDNEYS:

Gross: No alterations described.  
Microscopic: One had minimal mineralized deposits and the other was essentially normal.

OVARIES:

Gross: No alterations described.  
Microscopic: Both had follicular development.

BONE MARROW:

Gross: No alterations described.  
Microscopic: Moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis.

The following organs were neither described grossly nor remarkable microscopically: brain (4 sections), spinal cord, pituitary, adrenal glands, salivary glands, mandibular lymph nodes, thymus, diaphragm, mesenteric lymph node, aorta, esophagus, trachea, heart (3 sections), lungs, liver (2 sections), gallbladder, stomach (3 sections), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, sciatic nerve, mammary gland, skin, urinary bladder, uterus (both horns), cervix, vagina, eyes and bone.

## **C. Outline of Histologic Findings**



## Key to Outline of Histologic Findings

### Dosage Key

Group Number	Test Article	Dose (mg/kg/day)	Dose (mL/kg)	Number of Animals*	
				Males	Females
BKG1	Vehicle	0	1	5	5
BKG2	IQB-9302	1	1	5	5
BKG3	IQB-9302	2	1	5	5
BKG4	IQB-9302	3	1	5	5

\* The last 1 dog per sex numerically in each group was carried into the reversibility phase.

### Abbreviation Key

#### STATUS CODE

S Scheduled Sacrifice

#### SEVERITY CODES

1 Minimal  
2 Slight  
3 Moderate  
4 Marked  
5 Severe; Extensive

#### SECTION CODES

A Not Present  
N No Section  
P Present  
X Not Remarkable

### Outline of Histologic Findings

Tissue / Lesion	1	1	1	2	2	2	3	3	3	4	4	4	4
DEATH STATUS	M	M	M	M	M	M	M	M	M	M	M	M	M
BRAIN	1	2	3	4	1	2	3	4	1	2	3	4	4
SPINAL CORD	S	S	S	S	S	S	S	S	S	S	S	S	S
PITUITARY	X	X	X	X	X	X	X	X	X	X	X	X	X
ADRENALS	X	X	X	X	X	X	X	X	X	X	X	X	X
THYROID(S) Activity	2	2	2	2	2	2	2	2	2	2	2	2	2
Focal C Cell Hyperplasia		1											
SALIVARY GLANDS	X	X	X	X	X	X	X	X	X	X	X	X	X
MANDIBULAR LYMPH NODES	X	X	X	X	X	X	X	X	X	X	X	X	X
THYMUS	X	X	X	X	X	X	X	X	X	X	X	X	X
DIAPHRAGM	X	X	X	X	X	X	X	X	X	X	X	X	X
MESENTERIC LYMPH NODE	X	X	X	X	X	X	X	X	X	X	X	X	X
AORTA	X	X	X	X	X	X	X	X	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X	X	X	X	X	X	X	X	X
TRACHEA	X	X	X	X	X	X	X	X	X	X	X	X	X
HEART	X	X	X	X	X	X	X	X	X	X	X	X	X
LUNGS Focal Pneumonitis	X	X	1	1									
SPLEEN Congestion	2	2	2	2	2	2	2	2	2	2	2	2	2
LIVER	X	X	X	X	X	X	X	X	X	X	X	X	X
GALLBLADDER	X	X	A	X	X	X	X	X	X	X	X	X	X
KIDNEYS Mineralized Deposit(s)	X	1	1	1	1	1	1	1	1	1	1	1	1
STOMACH Mineralized Deposit(s)	X	X	2	2	X	1							1
PANCREAS	X	X	X	X	X	X	X	X	X	X	X	X	X
DUODENUM	X	X	X	X	X	X	X	X	X	X	X	X	X

### Outline of Histologic Findings

Tissue / Lesion	1		1		2		2		3		3		4		4		4	
	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
JEJUNUM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ILEUM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CECUM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
COLON	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RECTUM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SKELETAL MUSCLE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SCIATIC NERVE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MAMMARY GLAND	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SKIN	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
URINARY BLADDER	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EPIDIDYMIDES Hyperemia	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PROSTATE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TESTES Spermatogenesis Atrophy	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
EYES	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BONE MARROW Cellularity	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
BONE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X





### Outline of Histologic Findings

Tissue / Lesion	1	2	3	4
	M	M	M	M
	5	5	5	5
DEATH STATUS	S	S	S	S
BRAIN	X	X	X	X
SPINAL CORD	X	X	X	X
PITUITARY	X	X	X	X
ADRENALS	X	X	X	X
THYROID(S) Activity	2	2	2	2
Focal C Cell Hyperplasia	2	2	2	1
SALIVARY GLANDS	X	X	X	X
MANDIBULAR LYMPH NODES	X	X	X	X
THYMUS	X	X	X	X
DIAPHRAGM	X	X	X	X
MESENTERIC LYMPH NODE	X	X	X	X
AORTA	X	X	X	X
ESOPHAGUS	X	X	X	X
TRACHEA	X	X	X	X
HEART	X	X	X	X
LUNGS	X	X	X	X
SPLEEN Congestion	2	2	2	2
LIVER	X	X	X	X
GALLBLADDER	X	X	X	X
KIDNEYS Mineralized Deposit(s)	1	1	1	1
STOMACH Mineralized Deposit(s)	2	X	X	X
PANCREAS	X	X	X	X
DUODENUM	X	X	X	X

**Outline of Histologic Findings**

Tissue / Lesion	1	2	3	4
	M S	M S	M S	M S
JEJUNUM	X	X	X	X
ILEUM	X	X	X	X
CECUM	X	X	X	X
COLON	X	X	X	X
RECTUM	X	X	X	X
SKELETAL MUSCLE	X	X	X	X
SCIATIC NERVE	X	X	X	X
MAMMARY GLAND	X	X	X	X
SKIN	X	X	X	X
URINARY BLADDER	X	X	X	X
EPIDIDYMIDES	X	X	X	X
PROSTATE Focal Inflammatory Infiltrate	X	X	X	2
TESTES Spermatogenesis	3	3	3	3
EYES	X	X	X	X
BONE MARROW Cellularity	3	3	3	3
BONE	X	X	X	X

**Outline of Histologic Findings**

Tissue / Lesion	1	2	3	4
DEATH STATUS	8	8	8	8
BRAIN	X	X	X	X
SPINAL CORD	X	X	X	X
PITUITARY	X	X	X	X
ADRENALS	X	X	X	X
THYROID(S) Activity	2	2	2	2
Focal C Cell Hyperplasia				
SALIVARY GLANDS	X	X	X	X
MANDIBULAR LYMPH NODES	X	X	X	X
THYMUS	X	X	X	X
DIAPHRAGM	X	X	X	X
MESENTERIC LYMPH NODE	X	X	X	X
AORTA	X	X	X	X
ESOPHAGUS	X	X	X	X
TRACHEA	X	X	X	X
HEART	X	X	X	X
LUNGS	X	X	X	X
SPLEEN Congestion	2	2	2	2
Focal Fibrosis	2			
LIVER	X	X	X	X
GALLBLADDER	X	X	X	X
KIDNEYS Mineralized Deposit(s)	1	1	1	1
Cyst(s)		2		
STOMACH	X	X	X	X
PANCREAS	X	X	X	X
DUODENUM	X	X	X	X



### Outline of Histologic Findings

Tissue / Lesion	1	2	3	4
	F	F	F	F
	5	5	5	5
JEJUNUM	X	X	X	X
ILEUM	X	X	X	X
CECUM	X	X	X	X
COLON	X	X	X	X
RECTUM	X	X	X	X
SKELETAL MUSCLE	X	X	X	X
SCIATIC NERVE	X	X	X	X
MAMMARY GLAND	X	X	X	X
SKIN	X	X	X	X
URINARY BLADDER	X	X	X	X
UTERUS	X	X	X	X
CERVIX	X	X	X	X
VAGINA	X	X	X	X
OVARIES Follicular Development	P	P	P	P
EYES	X	X	X	X
BONE MARROW Cellularity	3	3	3	3
BONE	X	X	X	X

**APPENDIX XI**  
**TEST ARTICLE CERTIFICATE OF ANALYSIS**

T.P.S. Study No.: 616C-503-532-98  
Sponsor I.D. No.: 032b

# LEBSA

LABORATORIOS ESPINOS Y BOFILL, S.A.  
Investigación y síntesis de productos químicos  
Ctra. de l'Hospitalet, 30  
08940 Cornellà (Barcelona)  
Apartado 14.012 de Barcelona  
Teléfono 93 377 00 51 Fax 93 377 51 58  
E-mail: lebsa@setes.es  
Telex. 93051 LEB-E

## CERTIFICATE OF ANALYSIS

PRODUCT: CIPROCAINE HYDROCHLORIDE      CONTROL #: 9810034  
LOT #: 9454.001      DATE: 8<sup>th</sup> Oct. 1998

ANALYTICAL DATA	SPECIFICATIONS	RESULT
Appearance	White powder	Conforms
Identification		
I.R. Spectrum	Similar to standard	Conforms
Chlorides	To pass test	Conforms
Appearance of solution	Clear and colourless	Conforms
Acidity or alkalinity	To pass test	Conforms
Related substances	Not more than 0.5%	Conforms
2,6-Dimethylaniline	Not more than 100ppm	Conforms
Heavy metals	Not more than 10 ppm	Conforms
Loss on drying	Not more than 1.0%	0.35%
Sulphates ash	Not more than 0.1%	0.04%
Assay	98.5 - 101.0%	101.0%
Residual Isopropanol	Not more than 0.5%	0.23%



Analyst  
Silvia Dieguez



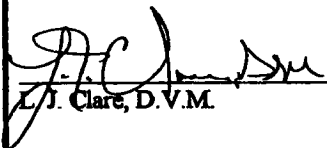

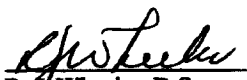
Analytical Department Manager  
Anna Pons

R.M. Barcelona, Insc. 1ª, Sec. 2ª, L. 1.025, T. 1.594, F. 171, H. 13.690 - CIF/VAT - ESA/ 08150450

T.P.S. Study No.: 616C-503-532-98  
Sponsor I.D. No.: 032b

**APPENDIX XII**  
**PROTOCOL**



<b>IQB-9302: A 28 DAY INTRAVENOUS TOXICITY STUDY IN DOGS</b>	
<b>FACILITY NAME &amp; ADDRESS:</b> T.P.S., Inc. 10424 Middle Mt. Vernon Road Mt. Vernon, IN 47620 Telephone: (812) 985-5900 Facsimile: (812) 985-3403	<b>SPONSOR NAME &amp; ADDRESS:</b> Laboratorios INIBSA Ctra de Sabadell a Granollers, KM 14.5 08185 Llica de Vall (Barcelona) Spain
<b>T.P.S. STUDY NO.:</b> 616C-503-532-98	<b>SPONSOR STUDY NO.:</b> 032b
<b>APPROVED BY:</b>  L.J. Clare, D.V.M.      10-28-98 Date	<b>APPROVED BY:</b>  Alvaro Galiano Ramos      29-10-98 Instituto Químico y Biológico      Date
<b>REVIEWED BY:</b>  R. J. Wheeler, B.S.      10/28/98 Vice President of Marketing      Date	<b>REVIEWED BY:</b> Asunción Soria      Date Instituto Químico Biológico

T.P.S. Study No.: 616C-503-532-98  
Sponsor I.D. No.: 032b



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**IQB-9302: A 28 DAY INTRAVENOUS  
TOXICITY STUDY IN DOGS**

**GENERAL INFORMATION**

**Identification:**

T.P.S. Study No.: 616C-503-532-98  
Sponsor Study No.: 032b

**Sponsor:**

Laboratorios INIBSA  
Crta de Sabadell a Granollers, KM.14.5  
08185 Llica de Vall (Barcelona)  
Spain

**Objective:** The purpose of this study is to evaluate the intravenous toxicity potential of IQB-9302 when administered as a bolus dose intravenously to male and female Beagle dogs once daily for 28 days followed by a 14 day recovery period.

**Location of Study and Conditions of Testing:**

It is the intention of Laboratorios INIBSA in sponsoring this study to generate animal safety data which may be submitted to regulatory authorities. The laboratories of T.P.S., Inc., 10424 Middle Mt. Vernon Road, Mt. Vernon, Indiana 47620 are licensed by the United States Department of Agriculture to conduct research in laboratory animals, and all the conditions of testing will conform to the Animal Welfare Act and its amendments. T.P.S., Inc. will follow all requirements specified in this approved protocol and all applicable governmental regulations regarding Good Laboratory Practices as well as T.P.S., Inc. Standard Operating Procedures. Changes in the protocol may be made by consultation with, and approval from, Laboratorios INIBSA, followed by written verification of the change. Laboratorios INIBSA, reserves the right to inspect facilities and procedures used in this study by means of announced or unannounced site visits.

T.P.S. Study No.: 616C-503-532-98  
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T.P.S. Study No.: 616C-503-532-98  
IQB-9302: A 28-Day IV Study in Dogs

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**Personnel:**

**Laboratorios INIBSA**

Study Monitor: Alvaro Galiano Ramos  
Instituto Químico y Biológico  
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Spain

Telephone: + 34-91 631 60 26  
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E-mail: [galiano@jet.es](mailto:galiano@jet.es)

**T.P.S., Inc.:**  
10424 Middle Mt. Vernon Road  
Mt. Vernon, IN 47620

Telephone: (812) 985-5900  
Facsimile: (812) 985-3403  
E-mail: [tps@toxpath.com](mailto:tps@toxpath.com)

Study Director:	L. J. Clare, D.V.M.
Study Manager:	M. A. Kempf, LAT
Colony Manager:	M. A. Kempf, LAT
Clinical Pathology Pathologist	S. E. Blessinger, B. S., MT (ASCP) Dean Barnett, D. V. M., Ph.D.
Director of QAU:	M. J. Bandoli, M.S.
Veterinarian:	L. J. Clare, D.V.M.
Necropsy Supervisor:	J. A. Botta, Jr., D. V. M., Ph.D.

**Proposed Schedule:**

Animal Phase Initiation:	November 1998
Animal Phase Termination:	December 1998
Final Necropsy:	December 1998
Report Date:	March 1999



T.P.S. Study No.: 616C-503-532-98  
IQB-9302: A 28-Day IV Study in Dogs

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#### **TEST ARTICLE AND CONTROL ARTICLE**

##### **TEST ARTICLE (Bulk Drug):**

**Name:** IQB-9302

**Source:** LEBSA

**Lot Number:** To be included in the raw data and final report.

**Purity:** To be given in the Certificate of Analysis to be provided by the manufacturer and included in the raw data and final report.

**Bulk Drug Storage:** To be stored at room temperature in the original containers.

**Stability:** The sponsor has data indicating the bulk drug is stable at room temperature for at least 4 years. The sponsor is conducting stability studies according to FDA and EMEA guidelines.

##### **CONTROL ARTICLE/VEHICLE**

**Name:** Sterile Water for Injection, USP.

**Source:** To be included in the raw data and final report.

**Lot Numbers and Expiration Date:** To be included in the raw data and final report.

**Storage:** Room temperature in the original containers.

##### **DOSING SOLUTION PREPARATION**

**Method of Preparation:** The dose solutions will be prepared at the appropriate concentrations in 0.9% Saline for Injection, USP. The method of preparation will be documented in the raw data and final report.

**Frequency of Preparation:** Fresh dosing solutions will be prepared daily.

**Dose Concentration:** The dosing solutions will be prepared such that all dogs receive a dose volume of 1 mL/kg.

**Storage:** Dosing solutions will be used immediately after preparation.





T.P.S. Study No.: 616C-503-532-98  
IQB-9302: A 28-Day IV Study in Dogs

October 28, 1998  
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### **DOSE VALIDATION AND DRUG ACCOUNTABILITY**

**Test Article Accountability:** Documentation for the following steps will be included in the raw data:

**Received:** Amount of IQB-9302 received by T.P.S., Inc.  
**Used:** Amount of IQB-9302 used during the study.  
**Returned:** Amount of IQB-9302 returned to Laboratorios INIBSA at the end of the study.

**Dosing Accountability:** Dosing solution containers will be weighed before and after intravenous administration to insure proper dosing has occurred. The exact amount of dosing solution used each day will be recorded in the raw data.

### **DESCRIPTION OF TEST SYSTEM**

**Species/Breed:** Canine/Beagle

**Source:** Dogs will be obtained from a USDA licensed supplier.

**Sex and Number:** 22 male and 22 female dogs will be used for pretest evaluations from which 20 males and 20 females (3 dose and one control group of 5 dogs/sex) will be selected.

**Age and Body Weight:** Young healthy adult dogs weighing 6-10 kg at study initiation.

**Acclimation:** Dogs will be acclimated at least two weeks prior to study initiation.

**Identification:** Animal runs will be marked with an identification card color coded by group and inscribed with the study number and animal number. Dogs will be identified by ear tattoo (USDA number).

**Justification:** The beagle is a standard non-rodent test animal used in drug safety evaluations.

**Control of Bias:** Treatment groups will be assigned using a computer generated randomization list. Cage position is not considered to be a source of experimental error.

**Environment:** Animals will be held in isolated animals rooms with filtered air supply (10-15 fresh changes per hour), temperature (64-84°F) and humidity (30-70%) control, and fluorescent lighting (12 hours on and 12 hours off). Temperature will be recorded daily and humidity will be recorded weekly.



T.P.S. Study No.: 616C-503-532-98  
IQB-9302: A 28-Day IV Study in Dogs

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**Housing:** Except during urine collection, animals will be housed individually in wire-mesh runs with concrete floors and resting boards. Fresh dry wood shavings will be supplied daily; all shavings will be removed and the runs washed down biweekly. During urine collection procedures, dogs will be housed in metabolism cages.

**Diet:** PMI® Laboratory Canine Diet (#5006) will be provided *ad libitum* except where deprivation is required for clinical tests and the night prior to necropsy. Lot numbers will be documented in the raw data.

**Water:** Tested tap water derived from a deep well will be provided *ad libitum* via an automatic watering system.

**Contaminants:** The Study Director is not aware of any dietary or water contaminants which would interfere with the conduct or purpose of this evaluation.

#### **EXPERIMENTAL DESIGN:**

**Route and Method of Administration:** Intravenous via a peripheral vessel (cephalic or saphenous vein).

**Justification of Route and Method of Administration:** To determine the toxicopathologic effects when doses are administered intravenously. The cephalic and saphenous veins are ideal for intravenous administration in the dog.

**Frequency and Duration of Administration:** Once daily via intravenous administration for 28 days. Doses will be administered at approximately the same time every day.

**Dose Volume and Rate of Administration:** The dosages will be administered in a total volume of 1 mL/kg body weight/day. The rate of administration will be determined based on results of the rangefinding study and will be documented in the raw data and final report.

**Justification of Dose Levels:** The dose levels will be selected by the sponsor based on previous studies conducted with the test article.

**Dose Group Identification:**

Group Number	Test Substance	Dose (mg/kg/day)	Study Animals*	
			Males	Females
BKG1	Control	0	5	5
BKG2	Test Article	1	5	5
BKG3	Test Article	2	5	5
BKG4	Test Article	3	5	5

\*After 28 days of dosing, 4 animals/sex/group will be necropsied with the remaining 1 animal/sex/group allowed to recover for 14 days.

**Detailed Physical and Ophthalmologic Examinations:** All dogs will be given detailed physical examinations including ophthalmology by a qualified veterinarian prior to selection to study and prior to each necropsy. Dogs will be examined closely at the weekly weigh period by a qualified animal technician.

**Clinical Signs:** All dogs will be observed by a qualified animal technician once in the morning and once in the late afternoon every day for general health, physical appearance, and for any sign of toxicity or clinical effect including behavioral changes. The date of onset, degree, progression, and duration of any clinical signs will be recorded in the raw data.

**Moribund and Dead Dogs:** Moribund dogs or dogs not expected to survive until the next observation period will be humanely sacrificed (intravenous sodium pentobarbital for euthanasia at a minimum dose of 1 mL/4.5 kg body weight) and a complete necropsy performed expeditiously to prevent loss of tissue from autolysis. All dogs whether dying during the course of the study (or sacrificed in moribund condition) will be examined and evaluated in the same manner as those surviving to terminal necropsy except that organ weights will not be taken. If possible, blood samples for clinical chemistry and plasma drug levels will be obtained from moribund animals prior to sacrifice.

**Body Weights:** To be recorded on all dogs pretest, Day -1, and weekly thereafter. Body weights will be obtained on fasted dogs immediately prior to necropsy.

**Food Consumption:** To be recorded pretest and then weekly throughout the study.

**Electrocardiogram and Blood Pressure Evaluations:** Standard ECG tracings (Lead II will be evaluated) and indirect blood pressure (systolic, diastolic, and mean) measurements will be obtained on all dogs pretest, during Week 4, and on recovery animals prior to necropsy. The ECG tracings will be evaluated by a board certified veterinary cardiologist.



### CLINICAL PATHOLOGY AND PLASMA TOXICOKINETICS

**Clinical Pathology:** Blood and urine samples will be collected from all dogs after an overnight fast (16-18 hours) pretest, during Week 4 and prior to necropsy of the recovery animals. Blood will be drawn from the jugular or cephalic vein. At unscheduled necropsies, if possible, blood samples will be collected prior to euthanasia.

**Hematology:** Blood will be collected in the proper anticoagulant for the following hematology parameters:

Erythrocyte Count	Mean Corpuscular Hemoglobin Concentration
Leukocyte Count	Mean Corpuscular Volume
Differential Leukocyte Count	Platelet Count
Hematocrit	Mean Corpuscular Hemoglobin
Hemoglobin	

**Serum Chemistry:** Blood will be collected and processed for the following serum chemistry parameters:

Aspartate Aminotransferase	Triglycerides
Alanine Aminotransferase	Total Cholesterol
Total Bilirubin	Creatinine
Total Protein	Urea Nitrogen
Albumin	Chloride
Globulin	Sodium
Albumin-Globulin Ratio	Potassium
Glucose	Calcium
Alkaline Phosphatase	Inorganic Phosphorus

**Urinalysis:** Dogs will be hydrated by oral gavage with tap water at 20 mL/kg body weight and placed in metabolism cages overnight for collection of urine sample for determination of the following routine urinalysis evaluations:

Appearance	Ketones
pH	Urobilinogen
Specific Gravity	Protein
Glucose	Microscopic Examination
Occult Blood	Color
Leukocytes	Nitrite
Bilirubin	Volume



**Plasma Levels (Toxicokinetics):** On Days 1 and 28, blood samples (7 mL) will be collected from each of the dogs in the 3 treated groups at 0 (predose) and at 5, 15, 30, 60 and 90 minutes and 3 hours post dose, transferred to EDTA tubes, and placed on ice. The plasma will be separated within 2 hours after collection, placed in properly labeled tubes, and frozen (approximately -20° C) until analyzed by HPLC for levels of IQB-9302.

An equal volume of blood (approximately 49 mL) will be drawn once from the control dogs on Day 1 and processed to be used as control blanks for the toxicokinetic study.

**Plasma Analysis:** The plasma samples will be analyzed by a laboratory selected by Laboratorios INIBSA for the presence of IQB-9302 using methods developed and validated by Laboratorios INIBSA.

**Sample Shipment:** The frozen plasma samples will be shipped directly from T.P.S., Inc. to the selected laboratory for analysis.

**Data Interpretation:** A copy of the analytical data will be sent to T.P.S, Inc. for incorporation into the final report.

#### **PATHOLOGY:**

**Gross Necropsy:** A complete postmortem examination will be performed on all study animals including those that die on study or are sacrificed in a moribund state. The gross observations will be recorded on the appropriate forms. A thorough visual examination is made of all organs and body tissues in situ before removal for detailed examination. The necropsy will include examination of:

- The external surfaces
- All orifices
- Cranial cavity
- Carcass
- External surfaces of the brain
- The thoracic, abdominal, and pelvic cavities and their viscera
- The cervical tissues and organs

**Scheduled Necropsy:** The day after the last dose, 4 dogs/sex/group will be fasted overnight, sacrificed (intravenous sodium pentobarbital for euthanasia administered at a minimum dose of 1 mL/4.5 kg body weight) and necropsied in the order of a computer-generated randomization list. Recovery dogs (1 sex/group) will be sacrificed after a 14 day recovery period. Terminal body weights will be taken after an overnight fast.



**Organ Weights:** The following organs will be weighed (paired organs will be weighed together) from animals at scheduled sacrifice:

Adrenals	Liver
Brain	Spleen
Heart	Testes/ Epididymides
Kidneys	Thyroid/Parathyroid
Ovaries	

Organ weights will be recorded directly on line or on the appropriate forms and later transferred to the computer system at T.P.S., Inc.

**Tissue Preservation:** The following tissues (when present) from each animal in the study will be collected and preserved in 10% neutral buffered formalin:

adrenal glands	pancreas
aorta	pituitary
bone (femur)	prostate
bone marrow	rectum
brain	salivary gland (submaxillary)
cecum	sciatic nerve
cervix	skeletal muscle (biceps femoris)
colon	skin
diaphragm	spinal cord (thoracic)
duodenum	spleen
epididymides*	sternbrae
esophagus	stomach
eyes	testes*
gallbladder	thymus (or thymic region)
heart	thyroid (with parathyroid, if present)
ileum	trachea
jejunum	urinary bladder
kidneys	uterus (both horns)
liver	vagina
lungs (with mainstem bronchi)	all gross lesions (to include apparently normal contiguous tissue)
mammary gland	
mesenteric lymph node	
mandibular lymph node	
ovaries	

\* Bouin's Fixative



**Histopathology:** The tissues listed above from all animals in the study will be embedded in paraffin, processed into blocks, sectioned, stained with hematoxylin and eosin, and examined microscopically by a board certified veterinary pathologist (ACVP) employed by T.P.S., Inc.

## RECORDS

All records generated during the course of the study will be retained in T.P.S., Inc. archives for a period of at least five years after which Laboratorios INIBSA will be notified and must approve destruction of these records, transfer to their facilities, or agree to additional archiving charges. Remaining test article and any specimens generated during the study will be returned to the sponsor.

## REPORT

A comprehensive audited final report will be issued within 90 days of necropsy and will include:

**Experimental Design:** Identification of the Sponsor (Laboratorios INIBSA), test article, and materials and methods used.

### **Results:**

- Bulk Drug Purity and Identity Assays
- Mortality
- Clinical Signs (appearance, behavior, and signs of toxic effects)
- Physical Examinations
- Body Weights and Body Weight Changes
- Food Consumption
- Clinical Pathology
- Toxicokinetics
- Organ Weights
- Gross Pathology
- Histopathology

**Statistical Evaluation:** Statistical methods used in the evaluation of numerical data will be those of Dunnett<sup>1</sup> and will include:

- Body Weights and Body Weight Changes
- Food Consumption
- Clinical Pathology

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<sup>1</sup> Dunnett CW, J Amer Statis Assoc. 1955; 50: 1096-1121.  
Dunnett CW, Biometrics. 1964; 20: 482-91.



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### Organ Weights

#### Summary Tables to include:

Group Mean Body Weights and Body Weight Changes  
Group Mean Food Consumption Data  
Group Mean Clinical Pathology Data  
Group Mean Organ Weight Data  
Incidence of Gross Pathology Findings  
Incidence of Histopathology Findings

#### Appendices to include:

Individual Clinical Signs  
Individual Body Weight Values  
Individual Food Consumption Values  
Individual Clinical Pathology Data  
Individual Organ Weight Data  
Individual Gross Pathology Findings  
Individual Histopathology Findings  
Pathology Report

### **SAFETY**

All safety precautions described in the T.P.S., Inc. standard operating procedures and material MSDS are to be strictly followed.

### **ANIMAL WELFARE COMPLIANCE**

This study will comply with all applicable sections of the final rules of the Animal Welfare Act regulations (9 CFR) and the "Guide for the Care and Use of Laboratory Animals" (National Academy Press, 1996). Wherever possible, procedures used in this study are designed to avoid or minimize discomfort, distress and pain to animals. All procedures are described in this study protocol or in written laboratory procedures. These procedures are based on the most currently available technologies concerning proper laboratory animal use and management.

In the event that any aspect of this study causes undue pain or distress to the animals, the Study Director shall determine if the administration of appropriate sedatives, analgesics or anesthetics would be contradicted by the objectives of the study and document the resultant course of actions. Animals that experience severe or chronic pain or distress that cannot be relieved will be painlessly euthanized. Methods of euthanasia used during this study are in conformance with the above referenced regulations.





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#### **QUALITY ASSURANCE AND GOOD LABORATORY PRACTICES**

This is a GLP study designed to conform to all applicable Good Laboratory Practice regulations. The entire study will be subjected to inspections, and the final report will be reviewed by the T.P.S. Quality Assurance Unit in accordance with T.P.S. Standard Operating Procedures.

**APPENDIX XIII**

**T.P.S. SUPERVISORY PERSONNEL**

## **T.P.S., INC. SUPERVISORY PERSONNEL**

<b>Name/Title</b>	<b>Job Function</b>
L. J. Clare, D.V.M. Toxicologist II	Study Director/ Attending Veterinarian
M. A. Kempf, LAT Lab Animal Care Supervisor	Study Manager
S. E. Blessinger, B.S., MT(ASCP) Clinical Pathology Supervisor	Clinical Pathology
M. J. Bandoli, M.S. Director of Quality Assurance	Quality Assurance
D. Barnett, D.V.M., Ph.D. (ACVP) Veterinary Pathologist	Histopathologist