T.P.S. Inc., 10424 Middle Mt. Vernon Road, Mount Vernon, Indiana 47620 - Tel: 812/985-5900 - FAX 812/985-3403

IQB-9302: AN ACUTE INTRAVENOUS TOXICITY STUDY IN BEAGLE DOGS

FOR

LABORATORIOS INIBSA
CRTA DE SABADELL A GRANOLLERS, KM.14.5
08185 LLICA 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
616A-501-510-98

Sponsor I.D. No.:
032a

CERTIFICATION OF GOOD LABORATORY PRACTICE

The enclosed report for T.P.S. Study No. 616A-501-510-98 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.

DJm 3-17-99

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

T.P.S. Study No.: 616A-501-510-98
Sponsor I.D. No.: 032a

QUALITY ASSURANCE STATEMENT

Quality Assurance inspections of Study 616A-501-510-98 were made and the findings reported on the following dates:

11/10/98
11/16/98
11/25/98
12/24/98

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.

G L Ingram 17 MAR 99
G. L. Ingram, B.S.
Quality Assurance Auditor
T.P.S., Inc.

M J Bandoli 17 Mar 99
M. J. Bandoli, M.S.
Director of Quality Assurance
T.P.S., Inc.

T.P.S. Study No.: 616A-501-510-98
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FOR

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CRTA DE SABADELL A GRANOLLERS, KM.14.5
08185 LLICA DE VALL (BARCELONA)
SPAIN

T.P.S. Study No.: 616A-501-510-98

Study Initiation:	10/28/98
Animal Phase Initiation:	11/16/98
Animal Phase Termination:	11/25/98

REPORTED BY:

3-17-99
L. J. Clare, D.V.M.
Study Director
T.P.S., Inc.

APPROVED FOR RELEASE BY:

3-17-99
J. B. Botta, B.S., B.A.
President
T.P.S., Inc.

TABLE OF CONTENTS

IQB-9302: AN ACUTE INTRAVENOUS TOXICITY STUDY IN BEAGLE DOGS

SUMMARY

One male and one female adult beagle dogs were dosed intravenously with 1.25, 2.5, 4.0, 5.0, and 6.0 mg of the test article IQB-9302/kg body weight. The test article was dissolved in 0.9% Saline for Injection, USP at concentrations that allowed the appropriate dose to be delivered in a volume of 5 mL/kg body weight. All doses were delivered at an infusion rate of 3 mL/minute. Dosages were increased and administered after a minimum washout period of 24 hours between doses until a maximum tolerated non-lethal dose was determined. Body weights obtained just prior to the first dose and weekly thereafter were used to determine the appropriate dosage to be administered. Each dog was observed for clinical effects hourly for 6 hours following dosing and a minimum of twice daily throughout the evaluation.

There were no clinical indications of toxicity when IQB-9302 was administered at 1.25 and 2.50 mg/kg. Muscle twitching during dosing and ataxia after dosing were noted in both dogs at dosages of 4.0 and 5.0 mg/kg. Emesis was also noted in the male dog after administration of both the 4.0 and 5.0 mg/kg dosages while salivation was noted in the female dog at the 5.0 mg/kg dose level. At 6.0 mg IQB-9302/kg, muscle twitching during the infusion, emesis after dosing and marked ataxia for approximately 10 minutes following dosing were noted in the male dog. When the 6.0 mg IQB-9302/kg dosage was administered to the female dog, muscle twitching was observed during the infusion, emesis occurred following infusion, and a seizure began at the end of the infusion. The seizure lasted approximately 5 minutes and the dog remained recumbent for an additional 30 minutes. Because of the nature and duration of the seizure in the female dog, dosages above 6.0 mg/kg were not administered.

In summary, the intravenous administration of the test article IQB-9302 at dosages up to 6.0 mg/kg body weight produced muscle twitching, ataxia, salivation, emesis, and seizures. Based on the results of this study, the no-observable-effects-level for IQB-9302 delivered in a dose volume of 5 mL/kg at a rate of 3 mL/minute is 2.50 mg/kg while the maximum tolerated non-lethal dose is estimated to be 6.0 mg/kg.

INTRODUCTION

The objective of this study was to determine the acute toxicopathologic effects of IQB-9302 when given intravenously to dogs using and up and down procedure. 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 II). 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 III.

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 I.

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

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

DOSE SOLUTION PREPARATION. Dosing solutions were prepared under aseptic conditions just prior to administration by dissolving the appropriate amount of IQB-9302.HCl in 0.9% Saline for Injection, USP such that a volume of 5 mL/kg body weight delivered the desired dosage. The dissolved solution was then passed through a 0.2 µm Acrodisc® filter into a sterile glass vial. Dose 1 was prepared by weighing out 33.8 mg (30 mg x 1.1249 [salt/free base factor]) into a tared container and q.s.'d to 120 g with 0.9% Saline. Doses 2 through 5 were prepared by weighing out 67.5 mg, 108 mg, 135 mg, and 162 mg, respectively, q.s.'d to 120 g with 0.9% Saline.

DOSE CONCENTRATIONS. The dose solutions were prepared such that all doses were administered in a dose volume of 5 mL/kg body weight.

DESCRIPTION OF THE TEST SYSTEM. Adult beagle dogs were obtained from Ridglan Farms Inc., Mt. Horeb, Wisconsin. The dogs were housed individually, in concrete floored kennel runs within an isolated temperature and humidity controlled animal room (Room A, Bldg. 106) with filtered air supply (10-15 changes/hour) and cycled lighting (12 hours of light and 12 hours of darkness). Temperature (minimum, maximum and current) readings were recorded daily (64-74 °F) and humidity (31%) was recorded weekly. PMI® Laboratory Canine Diet #5006 (OCT 07 98 3) was provided *ad libitum*. Tested tap water

(via an automatic water system) was provided *ad libitum*. Each dog was identified by a unique permanent marking (USDA ear tattoo) in addition to an appropriately labelled cage card indicating the study number, animal number, tattoo number and sex.

ROUTE, METHOD AND RATE OF ADMINISTRATION. The test article dose solutions were administered intravenously via a cephalic vein. All dose solutions were administered at a rate of 3 mL/minute.

JUSTIFICATION OF ROUTE OF ADMINISTRATION. The route of administration was chosen to determine the systemic effects of the test article when administered intravenously.

FREQUENCY AND DURATION OF ADMINISTRATION. The study design was that of an Up and Down procedure. Each dog was dosed with the initial dose (1.25 mg/kg) and subsequent doses were increased based on the results obtained from the previous dose. Doses were administered every other day (Monday, Wednesday, Friday).

EXPERIMENTAL DESIGN. Following an adequate acclimation period, 2 adult beagle dogs (1 male and 1 female) were selected for study and assigned to the following treatment group:

Group	Number of Dogs	Test Article	Initial Treatment*
BKE1	2	IQB-9302	1.25 mg/kg

* Subsequent doses were increased based on results of the previous dose after a washout period of at least 1 day.

CLINICAL OBSERVATIONS. The dogs were observed hourly for 6 hours following dosing and once in the morning and once in the late afternoon every day throughout the study for signs of pharmacologic, toxicologic, or clinical effects including behavioral changes.

BODY WEIGHTS. Body weights were obtained prior to the first dose and weekly thereafter and used to determine the appropriate dosage to be administered.

NECROPSY. There was no need to necropsy apparently healthy animals at the conclusion of the study. The dogs were returned to the stock colony at animal phase termination.

CHRONOLOGICAL TABLE OF SIGNIFICANT EVENTS.

Animal Receipt:	09-25-98
Study Initiation	10-28-98
Test Article Receipt:	10-10-98
Animal Phase Initiation:	11-16-98
Dose 1 (1.25 mg/kg)	11-16-98
Dose 2 (2.5 mg/kg)	11-18-98
Dose 3 (4.0 mg/kg)	11-20-98
Dose 4 (5.0 mg/kg)	11-23-98
Dose 5 (6.0 mg/kg)	11-25-98
Animal Phase Termination:	11-25-98

PROTOCOL DEVIATIONS.

Protocol Section Initial Dose Level (Page 6 of 7): Due to a calculation error by the dose prep technician, the initial dose level was 1.25 mg/kg instead of 1.0 mg/kg as indicated in the protocol.

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

RESULTS

CLINICAL OBSERVATIONS.

DOSE 1
IQB-9302: 1.25 mg/kg

Animal No.	Observation
BKE1M01	No Remarkable Clinical Signs
BKE1F01	No Remarkable Clinical Signs

DOSE 2
IQB-9302: 2.50 mg/kg

Animal No.	Observation
BKE1M01	No Remarkable Clinical Signs
BKE1F01	No Remarkable Clinical Signs

DOSE 3
IQB-9302: 4.0 mg/kg

Animal No.	Observation
BKE1M01	Muscle twitching during dosing Emesis immediately after dosing Ataxia for approximately 10 minutes after dosing Clinically recovered by 1 hour postdosing
BKE1F01	Muscle twitching during dosing Ataxia for approximately 10 minutes after dosing Clinically recovered by 1 hour postdosing

CLINICAL OBSERVATIONS. (cont'd.)

DOSE 4
IQB-9302: 5.0 mg/kg

Animal No.	Observation
BKE1M01	Muscle twitching during dosing Emesis immediately after dosing Ataxia for approximately 10 minutes after dosing Clinically recovered by 1 hour postdosing
BKE1F01	Muscle twitching during dosing Salivation during dosing Ataxia for approximately 10 minutes after dosing Clinically recovered by 1 hour postdosing

DOSE 5
IQB-9302: 6.0 mg/kg

Animal No.	Observation
BKE1M01	Muscle twitching during dosing Emesis immediately after dosing Marked ataxia for approximately 10 minutes after dosing Clinically recovered by 1 hour postdosing
BKE1F01	Muscle twitching during dosing Emesis immediately after dosing Seizure immediately after dosing lasting 5 minutes Recumbent for approximately 30 minutes following seizure Clinically recovered by 1 hour postdosing

BODY WEIGHT AND DOSE LEVELS.

Dog BKE1M01

Study Day	Body Weight	Dose Number	Dose Level	Dose Rate	Dose Volume
Day 1	11.9 kg	Dose 1	1.25 mg/kg	3 mL/minute	5 mL/kg
Day 3	11.9 kg	Dose 2	2.50 mg/kg	3 mL/minute	5 mL/kg
Day 5	11.9 kg	Dose 3	4.0 mg/kg	3 mL/minute	5 mL/kg
Day 8	12.4 kg	Dose 4	5.0 mg/kg	3 mL/minute	5 mL/kg
Day 10	12.4 kg	Dose 5	6.0 mg/kg	3 mL/minute	5 mL/kg

Dog BKE1F01

Study Day	Body Weight	Dose Number	Dose Level	Dose Rate	Dose Volume
Day 1	10.5 kg	Dose 1	1.25 mg/kg	3 mL/minute	5 mL/kg
Day 3	10.5 kg	Dose 2	2.50 mg/kg	3 mL/minute	5 mL/kg
Day 5	10.5 kg	Dose 3	4.0 mg/kg	3 mL/minute	5 mL/kg
Day 8	11.1 kg	Dose 4	5.0 mg/kg	3 mL/minute	5 mL/kg
Day 10	11.1 kg	Dose 5	6.0 mg/kg	3 mL/minute	5 mL/kg

DISCUSSION AND CONCLUSIONS

The test article IQB-9302 was dissolved in the vehicle at concentrations that allowed the 1.25, 2.5, 4.0, 5.0, and 6.0 mg/kg dosages to be delivered in a dose volume of 5 mL/kg. All dosages were administered intravenously at an infusion rate of 3 mL/minute. Subsequent dosages were increased based on results from the previous dosage after a minimum two day washout period. There were no clinical indications of toxicity in either Dog BKE1M01 or Dog BKE1F01 when IQB-9302 was administered intravenously at 1.25 and 2.50 mg/kg. Muscle twitching during dosing and ataxia after dosing were noted in both dogs at dosages of 4.0 and 5.0 mg/kg. Emesis was also noted in Dog BKE1M01 after administration of both the 4.0 and 5.0 mg/kg dosages while salivation was noted in Dog BKE1F01 at the 5.0 mg/kg dose level. At 6.0 mg IQB-9302/kg, muscle twitching during the infusion, emesis after dosing and marked ataxia for approximately 10 minutes following dosing were noted in Dog BKE1M01. When the 6.0 mg IQB-9302/kg dosage was administered to Dog BKE1F01, muscle twitching was observed during the infusion, emesis after dosing, and an epileptiform-like seizure began at the end of the infusion. The seizure lasted approximately 5 minutes and the dog remained recumbent for an additional 30 minutes. Because of the nature and duration of the seizure in Dog BKE1F01, dosages above 6.0 mg/kg were not administered.

In summary, the intravenous administration of the test article IQB-9302 at dosages up to 6.0 mg/kg body weight produced muscle twitching, ataxia, salivation, emesis, and seizures. Based on the results of this study, the no-observable-effects-level for IQB-9302 delivered in a dose volume of 5 mL/kg at a rate of 3 mL/minute is 2.50 mg/kg while the maximum-tolerated-non-lethal-dose is 6.0 mg/kg.

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.

T.P.S. RAW DATA REFERENCES

Form 101	Body Weight and Food Consumption: Nos. 12688, 12689
Form 108	Room Log: No. 8535
Form 120	Test Data Sheet: Nos. 36998-37000, 37032
Form 121	Test Material/Control Article Storage Record: Nos. 1986, 2008
Form 122	Animal Receipt Record: No. 766
Form 128	Study Maintenance Log: No. 3465
Form 133	Clinical Observation Record: Nos. 11191-11194, 11256
Form 133A	Observation Record: No. 459
Form 135A	Weekly Dosing Record: Nos. 30812, 30856
Form 143	Test/Control Article Usage Log Sheet: Nos. 8710, 8711

APPENDIX I

TEST ARTICLE CERTIFICATE OF ANALYSIS

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@sefes.es
Telex. 93051 LEB-E

CERTIFICATE OF ANALYSIS

PRODUCT: CIPROCAINE HYDROCHLORIDE **CONTROL #:** 9810034

LOT #: 9454.001 **DATE:** 8th 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. 1.584, F. 171, H. 13.690 - CIF/VAT - ESA/ 08150460

T.P.S. Study No.: 616A-501-510-98
Sponsor I.D. No.: 032a

APPENDIX II

PROTOCOL

IQB-9302: AN ACUTE INTRAVENOUS TOXICITY STUDY IN BEAGLE DOGS

FACILITY NAME & ADDRESS:	**SPONSOR NAME & ADDRESS:**
T.P.S., Inc. 10424 Middle Mt. Vernon Road Mt. Vernon, IN 47620 Telephone: (812) 985-5900 Facsimile: (812) 985-3403	Laboratorios INIBSA Crta de Sabadell a Granollers, KM.14.5 08185 Llica de Vall (Barcelona) Spain
T.P.S. **STUDY NO.:** 616A-501-510-98	**SPONSOR** **STUDY NO.:** 032a
APPROVED BY: 10-28-98 L. J. Clare, D.V.M. Date	**APPROVED BY:** 29-10-98 Alvaro Galiano Ramos Instituto Quimico y Biologico Date
REVIEWED BY: 10/28/98 R. J. Wheeler, B.S. Date Vice President of Marketing	**REVIEWED BY:** Date

IQB-9302: AN ACUTE INTRAVENOUS TOXICITY STUDY IN BEAGLE DOGS

GENERAL INFORMATION

Identification:

T.P.S. Study No.: 616A-501-510-98
Sponsor Study No.: 032a

Sponsor:

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

Objective: To determine the acute toxicopathologic effects of IQB-9302 when given intravenously to dogs using an up and down procedure.

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.

Personnel:

Sponsor:	Laboratorios INIBSA
Study Monitor:	Alvaro Galiano Ramos Instituto Quimico y Biologico 28230 Las Rozas (Madrid) Spain
Telephone:	+ 34 91 631 60 26
Facsimile:	+ 34 91 631 65 03
e-mail:	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

Study Director:	L. J. Clare, D.V.M.
Study Manager:	M. A. Kempf, LAT
Colony Manager:	M. A. Kempf, LAT
Director of QAU:	M. J. Bandoli, M.S.
Veterinarian:	L. J. Clare, D.V.M.

Proposed Schedule:

Animal Phase Initiation:	November 1998
Animal Phase Termination:	December 1998
Report Date:	January 1998

TEST ARTICLE AND DOSING

TEST ARTICLE

Name: IBQ-9302

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

Source and Manufacturer: LEBSA.

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.

VEHICLE:

Name: 0.9% Saline for Injection, USP

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

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

Storage: Room temperature in the original containers.

DOSING SOLUTION PREPARATION

Preparation of Dose Formulation: The test article will be prepared as a solution under aseptic conditions using 0.9% Saline for Injection, USP. The method of preparation will be documented in the raw data and final report

Frequency of Preparation: Once prior to dosing.

Dose Concentrations: The dosing solutions will be prepared such that each dose is administered in the same dose volume of 5 mL/kg.

Storage: Dosing solutions will be used immediately after preparation.

DESCRIPTION OF TEST SYSTEM

Species/Breed: Canine/Beagle

Source: T.P.S., Inc. stock colony obtained from a USDA licensed supplier.

Sex and Number: Two males and/or females.

Age and Body Weight: Adult dogs weighing 8-15 kg at study initiation.

Acclimation: Dogs will be acclimated at least one week prior to test initiation.

Identification: Animal runs will be marked with an identification card 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: Since the number of animals is small (two) and both will be receiving the same treatment, control of bias is not necessary.

Environment: Animals will be held in an isolated animal room 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.

Caging: Animals will be housed in individual 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.

Diet: PMI® Laboratory Canine Diet (#5006) will be provided *ad libitum*.

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 contaminants which would interfere with the conduct or purpose of this evaluation.

EXPERIMENTAL DESIGN

Route, Method and Rate of Administration: The test article solution will be administered intravenously via the cephalic or saphenous vein. The rate of administration will be documented in the raw data and final report.

Justification of Route of Administration: To determine acute systemic effects of the test article when administered intravenously.

Frequency and Duration of Administration: The study design is that of an **Up and Down** procedure. Each dog will be dosed with the initial dose (1.0 mg/kg) and subsequent doses will be increased or decreased depending on results obtained. Doses will be administered every other day (Monday, Wednesday, Friday) until clinical signs indicate that a maximum tolerated non-lethal dose has been reached.

Initial Dose Level:

Group	Initial Treatment mg/kg*	No. of Dogs
BKE1	1.0	2

* Additional doses will be increased or decreased depending on results obtained until a maximum tolerated non-lethal dose has been reached.

Clinical Signs: The animals will be observed hourly for 6 hours following each dose and then once in the morning and once in the late afternoon every day including weekends and holidays for signs of pharmacologic, toxicologic or clinical effects including behavioral changes.

Clinically Affected Dogs: Clinically affected dogs may be examined more frequently as determined necessary by the attending veterinarian. The date of onset, degree, progression and duration of any clinical sign will be recorded in the raw data.

Body Weights: Body weights will be recorded immediately prior to administration of test article. Body weights are the basis for determining the appropriate dosage to be administered.

Moribund and Dead Dogs: Moribund dogs or dogs not expected to survive until the next observation period will be humanely sacrificed using sodium pentobarbital for euthanasia administered intravenously at a minimum dose of approximately 1 mL/4.5 kg.

Gross Necropsy: There is no need to necropsy apparently healthy animals at the conclusion of the study. However, necropsies will be performed on all moribund animals and any animals found dead, while on study, to determine the possible cause of death.

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 final report will be issued within 30 days of study termination and will include all observations made during the evaluation, test article identification, description of administration and remarkable signs exhibited by the animals.

STATISTICS

Statistical evaluations are not applicable due to the small number of animals on the study.

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.

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 III

T.P.S. SUPERVISORY PERSONNEL

T.P.S., INC. SUPERVISORY PERSONNEL

Name/Title	Job Function
L. J. Clare, D.V.M. Toxicologist/Attending Veterinarian	Study Director
J. P. Devine, Jr., B.S., LAT Toxicologist I	Study Manager
M. J. Bandoli, M.S. Director of Quality Assurance	Quality Assurance