Date of Approval: July 15, 2021

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-545

TANOVEA®

rabacfosadine for injection

Powder for Injection

Dogs

TANOVEA® is indicated for the treatment of lymphoma in dogs

Sponsored by:

VetDC, Inc.

Executive Summary

TANOVEA® (rabacfosadine for injection) is approved for the treatment of lymphoma in dogs. FDA conditionally approved the drug in December 2016 for the same use. At that time, the sponsor demonstrated that TANOVEA® was safe and had a reasonable expectation of effectiveness for treating lymphoma in dogs. The sponsor has now demonstrated that the drug meets the standard of substantial evidence of effectiveness for full approval. The labeled dosage regimen for TANOVEA® is a starting dose of 1 mg/kg given by intravenous (IV) infusion every 21 days for up to five doses.

TANOVEA® is a small molecule that mimics a nucleoside called guanine, one of the key building blocks of DNA. TANOVEA® preferentially targets rapidly dividing lymphoma cells and interferes with DNA synthesis in those cells, resulting in reduced proliferation, and ultimately, cell death. The cancerous lymph nodes are expected to shrink in size.

Proprietary Name	Established Name	Dosage Form	Application Type and Number	Sponsor
TANOVEA®	rabacfosadine for injection	Powder for injection	New Animal Drug Application (NADA) 141-545	VetDC, Inc.

Safety and Effectiveness

The sponsor conducted a field effectiveness study comparing TANOVEA® to a placebo in client-owned dogs. The study included dogs of any breed (except West Highland White Terriers) and either sex diagnosed with multicentric B-cell or T-cell lymphoma. Enrolled dogs represented a range of weights and ages (all were at least 1 year of age). Three times as many dogs were enrolled in the TANOVEA® group (112 dogs) than the placebo group (36 dogs). Approximately half of the dogs in both groups had prior chemotherapy treatment. The staging of the dogs' lymphoma, as defined by the World Health Organization, was also similar in both groups. Most dogs were staged as IIIa (generalized lymph node involvement without systemic signs) or IVa (generalized lymph node involvement with liver and/or spleen involvement without systemic signs). On Day 0, the dogs received an IV infusion of either TANOVEA® or the placebo (0.9% sodium chloride) over 30 minutes. The dogs continued to receive either TANOVEA® or the placebo every 21 days (considered one cycle), for up to five cycles, until their lymphoma progressed (their cancerous lymph nodes increased in size or they developed new lesions related to the lymphoma) or the dog was withdrawn from the study.

The primary endpoint was progression free survival (PFS), which is the time from the start of the study to when the dog's lymphoma progressed or the dog died. Dogs in the TANOVEA® group had a median PFS of 82 days compared to 21 days in dogs in the placebo group. The median PFS in dogs in the TANOVEA® group that had either a complete or partial response was 151 days. For those with a complete response, the median PFS was 168 days. (A complete response is when there is no evidence of disease. A partial response is when the cancerous lymph nodes decrease in size by at least 30% compared to baseline.) Five dogs in the TANOVEA® group still had a complete response on Day 365, which was the end of the study.

The most common adverse events seen in dogs in both the TANOVEA® and placebo groups were diarrhea, decreased appetite, vomiting, lethargy, and weight loss, although these adverse events occurred more often and were more severe in dogs treated with TANOVEA®. Neutropenia was also seen in dogs in the TANOVEA® group. Serious adverse events were reported more often in dogs treated with TANOVEA® and mainly included pulmonary fibrosis and dermatopathies (such as ear infections, hair loss, dermatitis, erythema, pruritus, hyperpigmentation, skin ulcerations, and bacterial skin infections). Few injection site reactions were seen in either group.

The type and frequency of reported adverse events did not vary greatly by cycle of TANOVEA® treatment. However, most of the adverse events seen in Cycles 1 and 2 were diarrhea, decreased appetite, vomiting, lethargy, and weight loss, while dermatopathies began to occur more often in Cycles 3, 4, and 5. In some cases, the veterinarian decided to reduce or delay the dose of TANOVEA® to manage a dog's adverse events.

Three laboratory studies were conducted to evaluate the safety and toxicity of rabacfosadine administered by IV infusion at various dosage regimens (the studies did not use the commercial formulation in TANOVEA®).

1) Young, healthy, male and female Beagle dogs were administered one 30-minute IV infusion. Half the dogs were necropsied on Day 3 and half were given a 21-day recovery period and necropsied on Day 21. Dogs were administered rabacfosadine at 0.25, 0.82, 2.5, or 8.2 mg/kg. A control group received 5% Dextrose for Injection.

2) Young, healthy, male and female Beagle dogs were administered 30-minute IV infusions daily for 5 days. Half the dogs were necropsied on Day 6 and half were given a 21-day recovery period and necropsied on Day 27. Dogs were administered rabacfosadine at 0.082, 0.25 and 0.82 mg/kg. A control group received 5% Dextrose for Injection.

3) Young, healthy, male and female Beagle dogs were administered 30-minute IV infusions weekly for 3 doses (on Days 1, 8, and 15). Half the dogs were necropsied on Day 16 and half were given a 21-day recovery period and necropsied on Day 36. Dogs were administered rabacfosadine at 0.25, 0.50, and 1.0 mg/kg. A control group received 5% Dextrose for Injection.

   In the first study, a single dose of rabacfosadine at 8.2 mg/kg resulted in mortality due to gastrointestinal toxicity and severe neutropenia. Dogs in this dose group were either found dead or were euthanized 6 to 7 days after treatment due to the severity of the adverse reactions.

   In the second study, supportive care was needed for dogs in the 0.82 mg/kg dose group.

   Across all three studies, the following adverse reactions were observed in dogs treated with rabacfosadine: vomiting, abnormal feces (described as black, green, red, soft, mucoid, or liquid stool), decreased activity, fever, dehydration, thinness (based on visual assessments), weight loss (based on scale measurements), and decreased food consumption. There was a dose-dependent leukopenia, with the lowest white blood cell (WBC) counts reported on Days 6 and 9. The WBC counts

returned to normal by Day 12 at all but the highest doses. In all three studies, dermatopathies were reported in all groups, including the control group, but were more common in dogs administered rabacfosadine.

Pathology changes were seen in the gastrointestinal tract, lymphoid tissue, bone marrow, male reproductive system, adrenal cortex, pancreas, salivary glands, and kidneys of treated dogs. Following a 21-day recovery period, some tissues returned to normal, and some tissues improved but did not completely return to normal.

In addition, one laboratory study was conducted to assess the potential cardiac effects of rabacfosadine after one 30-minute IV infusion in healthy, young, male Beagle dogs (the study did not use the commercial formulation in TANOVEA®). One IV infusion at 0.25 and 2.5 mg/kg did not affect arterial blood pressure (mean, systolic, and diastolic), heart rate, or electrocardiogram parameters.

In two pilot studies used to support the labeled dosage regimen for TANOVEA®, a total of 22 client-owned dogs with untreated, relapsed, or refractory lymphoma received rabacfosadine as an IV infusion at doses of 0.66 to 1.2 mg/kg administered once every 21 days for one to six doses (the studies did not use the commercial formulation in TANOVEA®). The drug had a narrow margin of safety in the pilot studies. Adverse reactions were common but manageable by regular monitoring of the dogs. With the exception of pulmonary fibrosis, the adverse reactions resolved spontaneously, with supportive care, or by reducing or delaying the next dose.

TANOVEA® has a narrow margin of safety, which is not unexpected for an antineoplastic drug. The target animal safety studies described above support the safety of TANOVEA® to treat lymphoma in dogs at the labeled dosage regimen. Veterinarians can manage adverse reactions in dogs by regular monitoring and by reducing the dose in a stepwise manner or delaying the next dose.

Safety Warnings
Because West Highland White Terriers are genetically predisposed to develop idiopathic pulmonary fibrosis, they were excluded from the field effectiveness study and TANOVEA® should not be used to treat lymphoma in this breed.

TANOVEA® is cytotoxic and may cause birth defects and affect fertility in males and females. Therefore, the drug should not be used to treat lymphoma in dogs that are pregnant, lactating, or intended for breeding.

User Safety
TANOVEA® is an antineoplastic drug with potential safety concerns for people who handle, prepare, administer, or are exposed to the drug. Based on data about how rabacfosadine is excreted in dogs and an extrapolation of the data to estimate the potential exposure risk for people after contact with a treated dog's various bodily fluids, FDA recommends a 5-day precautionary period. People should avoid direct contact with a treated dog's feces, urine, vomit, and saliva for 5 days after each treatment.

The package insert includes special instructions for veterinarians about how to handle, prepare, and administer TANOVEA®. The drug also comes with a Client Information Sheet for veterinarians to give to their clients. The Client Information

Sheet is written specifically for dog owners and contains a summary of important information about TANOVEA®. The sheet explains possible side effects of the drug, how dog owners should clean up after their dog for 5 days after each treatment, and other safety information.

TANOVEA® is cytotoxic and may cause birth defects and affect fertility in men and women. Women who are pregnant, may become pregnant, or are nursing shouldn't handle, prepare, or administer the drug or come into contact with a treated dog's feces, urine, vomit, and saliva for 5 days after each treatment. Children also should not have contact with TANOVEA® or a treated dog's bodily fluids for 5 days after each treatment.

Conclusions

Based on the data submitted by the sponsor for the approval of TANOVEA®, FDA determined that the drug is safe and effective when used according to the label.

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I. GENERAL INFORMATION

A. File Number

NADA 141-545

B. Sponsor

VetDC, Inc.
320 E. Vine Dr., suite 218
Fort Collins, CO 80524

Drug Labeler Code: 086072

C. Proprietary Name

TANOVEA®

D. Drug Product Established Name

rabacfosadine for injection

E. Pharmacological Category

Antineoplastic

F. Dosage Form

Powder for injection

G. Amount of Active Ingredient

16.4 mg per vial

H. How Supplied

TANOVEA® is supplied in a 3 mL amber Type I glass vial with rubber stopper, aluminum over-seal, and plastic flip-off cap, packaged in a carton. Each vial contains 16.4 mg of rabacfosadine, as succinate salt.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Administer TANOVEA® at 1.0 mg/kg body weight as a 30-minute intravenous infusion, once every three weeks, for up to five doses. Stepwise dose reductions to 0.8 mg/kg and 0.66 mg/kg or dose delays may be used to manage adverse reactions.

K. Route of Administration

Intravenous injection

L. Species/Class

Dog

M. Indication

TANOVEA® is indicated for the treatment of lymphoma in dogs.

II. EFFECTIVENESS

TANOVEA® is a small molecule that mimics a nucleoside called guanine, one of the key building blocks of DNA. TANOVEA® preferentially targets rapidly dividing lymphoma cells and interferes with DNA synthesis in those cells, resulting in reduced proliferation and ultimately, cell death. The expected outcome is cancerous lymph nodes shrinking in size.

The effectiveness of TANOVEA® was demonstrated in one adequate and well-controlled clinical field study. The study enrolled 158 dogs of any breed, except West Highland White Terrier, or any sex diagnosed with multicentric lymphoma, either B-cell or T-cell immunophenotypes, with at least one measurable peripheral lymph node. One hundred and twenty dogs received TANOVEA® at a dose of 1.0 mg/kg every three weeks for up to five total treatments as a 30-minute intravenous infusion, while 38 dogs received a placebo infusion of saline solution.

The effectiveness analysis demonstrated a statistically significant improvement in progression free survival (PFS) for dogs in the TANOVEA® group compared to the placebo group. The median PFS for dogs in the TANOVEA® group was significantly longer ($P < 0.0001$) than that observed for the dogs in the placebo group (82 days versus 21 days). The most common adverse reactions observed in the field study included diarrhea, decreased appetite, vomiting, lethargy, weight loss, and neutropenia.

A. Dosage Characterization

The dose of TANOVEA® (rabacfosadine for injection) administered intravenously at 1.0 mg/kg once every three weeks for up to five doses, with dose reductions to 0.8 mg/kg and 0.66 mg/kg or dose delays to manage adverse reactions, is based on two pilot studies (PC-193-2001 and PC-193-2017) and three toxicity studies (TX-193-2009, TX-193-2010, and TX-193-2015). During development, rabacfosadine was also referred to as GS-9219.

1. Pilot Study

   Title: Efficacy Evaluation of GS-9219 in Naturally Occurring Non-Hodgkin's Lymphoma and Leukemia in Dogs. (Study No. PC-193-2001)

   Study Design: The study evaluated several dosage regimens of rabacfosadine (not commercial formulation) in treatment-naïve dogs with T- or B-cell canine lymphoma and in dogs with relapsed or refractory, T- or B-cell canine lymphoma. Fifty dogs with lymphoma were enrolled and received one of four dosing regimens and were observed for dose-limiting adverse events.

Rabacfosadine was administered using a 30-minute intravenous infusion in 5% Dextrose Solution for Injection, USP (2 mL/kg body weight).

Variables Measured: Response to treatment was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST).[1] The following criteria were used to assess response outcomes for individual dogs:

- Complete response (CR): complete disappearance of all measurable lymphoma.
- Partial response (PR): a > 30% decrease in the sums of the longest diameters of measurable affected nodes.
- Stable disease (SD): a 30% decrease to 20% increase in the sums of the longest diameters of measurable affected nodes.
- Progressive disease (PD): a > 20% increase in the sums of the longest diameters of measurable affected nodes or newly arising lesions.

Progression free survival (PFS) duration: the time from first dose to the first observation of disease progression or death due to any cause.

Results: Seventeen dogs received rabacfosadine at a dose between 0.66 and 1.2 mg/kg by intravenous infusion once every three weeks.

Three dogs received rabacfosadine at a dose of 1.2 mg/kg body weight by intravenous infusion, once every three weeks, for one to four doses. A summary of the results in these dogs is presented in Table II.1 below.

Table II.1. Effectiveness results for dogs receiving 1.2 mg/kg of rabacfosadine once every three weeks

Dog	Naïve or Relapsed/Refractory*	Doses	Best Response	PFS (days)
GS-1001B	Naïve	4	CR	370
GS-1002B	Relapsed/Refractory	1	PR	8**
GS-1003B	Naïve	1	PR	8

* Relapsed vs. refractory disease not stated.
** The dog was withdrawn from the study by the owner while still in remission.

Five dogs received rabacfosadine at a dose of 1.0 mg/kg body weight by intravenous infusion, once every three weeks, for one to five doses. A summary of the results in these dogs is presented in Table II.2 below.

Table II.2. Effectiveness results for dogs receiving 1.0 mg/kg of rabacfosadine once every three weeks

Dog	Naïve or Relapsed/Refractory*	Doses	Best Response	PFS (days)
GS-1004B	Relapsed/Refractory	2	PR	35
GS-1005B	Relapsed/Refractory	1	PR	22
GS-1006B	Naïve	5	CR	179
GS-1008B	Naïve	1	CR	23
GS-1011B	Relapsed/Refractory	5	CR	119

* Relapsed vs. refractory disease not stated.

Six dogs received rabacfosadine at a dose of 0.82 mg/kg body weight by intravenous infusion, once every three weeks, for one to five doses. A summary of the results in these dogs is presented in Table II.3 below.

Table II.3. Effectiveness results for dogs receiving 0.82 mg/kg of rabacfosadine once every three weeks

Dog	Naïve or Relapsed/Refractory*	Doses	Best Response	PFS (days)
UW017**	Naïve	5	CR	751
UW018	Relapsed/Refractory	1	PD	9
UW019	Naïve	5	CR	280
UW020	Naïve	2	PR	30***
UW023	Relapsed/Refractory	3	PR	50
GS-1012B	Relapsed/Refractory	1	PD	8

* Relapsed vs. refractory disease not stated.
** The dog was administered 0.82 mg/kg for doses 1, 3, 4, and 5, and 1.0 mg/kg for dose 2.
*** The dog was withdrawn by the owner while still in remission.

Three dogs received rabacfosadine at a dose of 0.66 mg/kg body weight by intravenous infusion once every three weeks for two to five doses. A summary of the results in these dogs is presented in Table II.4 below.

Table II.4. Effectiveness results for dogs receiving 0.66 mg/kg of rabacfosadine once every three weeks

Dog	Naïve or Relapsed/Refractory*	Doses	Best Response	PFS (days)
UW012	Relapsed/Refractory	5	CR	170
UW013	Naïve	5	CR	134
GS-1013	Relapsed/Refractory	2	PR	48

* Relapsed vs. refractory disease not stated.

Ten dogs administered rabacfosadine at various dosing regimens that achieved a complete or partial response (nine dogs with CR and one dog with PR), and then experienced recurrence of lymphoma, were subsequently retreated with rabacfosadine at a dose of 0.82 mg/kg once every three weeks for one to five doses. During the retreatment following recurrence of lymphoma, five of the dogs experienced a best response of CR, one dog experienced a best response of PR, two dogs experienced a best response of SD, and two dogs had a best response of PD. PFS in the six dogs with CR or PR during retreatment ranged from 43 to 99 days.

Safety: Adverse events were reported using Veterinary Cooperative Oncology Group – common terminology criteria, VCOG-CTCAE v1.1.[2] Adverse reactions associated with rabacfosadine treatment when administered once every three weeks included lethargy, dehydration, fever, hyporexia/anorexia, weight loss, vomiting, diarrhea, tachypnea, dyspnea, pulmonary fibrosis, aspiration pneumonia, neurologic signs, otitis externa, alopecia, dermatopathy, proteinuria, increased creatinine, elevated liver enzymes, elevated bilirubin, neutropenia, thrombocytopenia, anemia, hypertriglyceridemia,

hypoglobulinemia, hypoalbuminemia, increased creatine kinase, hypokalemia, and hypophosphatemia.

Most adverse reactions were Grade 1 (mild) or 2 (moderate). Grade 3 (severe) reactions included hyporexia/anorexia, weight loss, vomiting, diarrhea, dehydration, otitis externa, aspiration pneumonia, neutropenia, thrombocytopenia, anemia, and bilirubinemia. Grade 4 (life-threatening) reactions included tachypnea and neutropenia. Grade 5 (death) reactions included dyspnea (secondary to pulmonary fibrosis) resulting in a life-threatening or fatal outcome. With the exception of pulmonary fibrosis, adverse reactions resolved either spontaneously, with supportive treatment, or by dose modification.

Additional adverse reactions seen at the other dosing regimens (i.e., more frequent dosing) included pruritic and erythemic lesions on the dorsum; exudation, crusting, erythema, and necrosis with epidermal sloughing on the ears, face, ventral neck and/or forelimbs; glucosuria; and type II pneumocyte hyperplasia.

Pharmacokinetics: Plasma concentrations of rabacfosadine and its active metabolites were measured in eight dogs with lymphoma. Rabacfosadine was rapidly eliminated from plasma with a half-life of <0.5 hours. The primary metabolite, 9-(2-phosphonylmethoxyethyl)-N6-cyclopropyl-2,6-diaminopurine (cPrPMEDAP), had a plasma half-life of six hours. The cytotoxic metabolite 9-(2-phosphonylmethoxyethyl) guanine (PMEG) was not detected in plasma samples but was detected in high levels in peripheral blood mononuclear cells (PBMCs) within 24 hours of dosing and persisted with subsequent dosing in a similar manner in all dosage groups. The PBMC concentrations in the group treated with rabacfosadine doses of 0.82 mg/kg once every two weeks or once every three weeks were 131 and 1,420 nM for cPrPMEDAP and PMEG, respectively (median values from five dogs).

2. Pilot Study

Title: Randomized Trial of 3 Dose Regimens of GS-9219 in Dogs with Relapsed B-cell Non-Hodgkin's Lymphoma. (Study No. PC-193-2017)

Study Design: The study evaluated several dosage regimens of rabacfosadine (not commercial formulation) in dogs with relapsed, B-cell canine lymphoma. Fifteen dogs with lymphoma were enrolled and received one of three dosing regimens. Dogs were between five to 10 years old and weighed 5.6 to 65 kg. Ten male castrated and five female spayed dogs were enrolled.

Variables Measured: Response to treatment was evaluated using RESIST criteria.

Results: Five dogs were administered rabacfosadine intravenously at a dose of 1.0 mg/kg in a volume of 2 mL/kg in 0.9% Sodium Chloride Injection, USP, over 30 minutes, once every three weeks, for one to six doses. A summary of the results in these dogs is presented in Table II.5 below.

Table II.5. Effectiveness results for dogs receiving 1.0 mg/kg of rabacfosadine once every three weeks

Dog	Doses	Best Response	PFS (days)
001	6	CR	449
002	6	CR	365
007	1	PD	14
012*	5	SD	92**
017	2	SD	44

* The dog was administered 1.0 mg/kg for doses 1 and 5, 0.8 mg/kg for doses 2 and 3, and 0.92 mg/kg for dose 4.
** Censored

Safety: Adverse events were reported using Veterinary Cooperative Oncology Group – common terminology criteria, VCOG-CTCAE v1.1.[2] Adverse reactions associated with rabacfosadine treatment when administered once every three weeks included hyporexia/anorexia, vomiting, diarrhea, pulmonary fibrosis, aspiration pneumonia, tachycardia, injected sclera, dermatopathy, neutropenia, anemia, increased blood urea nitrogen, elevated liver enzymes, hypertriglyceridemia, hypoglobulinemia, proteinuria, pyuria, and bacteriuria.

Most adverse reactions were Grade 1-2. Grade 3 reactions included vomiting, aspiration pneumonia, and hypertriglyceridemia. Adverse reactions resolved either spontaneously, with supportive treatment, or by dose modification.

Additional adverse reactions seen at the other dosing regimens (i.e., more frequent dosing) included dehydration; weight loss; lethargy; polyuria; hematuria; glucosuria; otitis externa; pruritic and erythemic lesions on the dorsum; exudation, crusting, erythema, and necrosis with epidermal sloughing on the ears, face, ventral neck and/or forelimbs; type II pneumocyte hyperplasia in the lungs; thrombocytopenia; increased bilirubin; increased creatine kinase; increased creatinine; hypomagnesemia; hypoalbuminemia; and hypoproteinemia.

3. Toxicity Studies

The three toxicity studies (TX-193-2009, TX-193-2010, and TX-193-2015) used to support target animal safety provided information supporting dosage characterization. The label dosage of rabacfosadine was based on determining the highest non-severely toxic dose (HNSTD) in dogs. Refer to the Target Animal Safety section for more information.

B. Substantial Evidence

1. Clinical Field Study

Title: A Randomized, Blinded, Placebo-Controlled Field Study to Determine the Efficacy and Safety of TANOVEA®-CA1 (rabacfosadine for injection) in Dogs. (Study No. VC-014)

Study Dates: September 25, 2018 to January 14, 2021

Study Locations:

Bedford Hills, NY
Culver City, CA
Dallas, TX
Fort Collins, CO
Malvern, PA
Norwalk, CT
San Diego, CA

Study Design: This was a multi-center, prospective, randomized, masked, placebo-controlled field study.

Objective: To evaluate the effectiveness and safety of TANOVEA® when administered as an intravenous injection for the treatment of lymphoma in dogs.

Study Animals: The study enrolled 158 dogs of any breed, except West Highland Terrier, or sex diagnosed with multicentric lymphoma, with at least one measurable peripheral lymph node. All 158 dogs were evaluable for safety (120 in the TANOVEA® group and 38 in the Placebo group), and 148 dogs were evaluable for effectiveness (112 in the TANOVEA® group and 36 in the Placebo group). The most commonly enrolled breed was large mixed breed. Dogs ranged from one to 15 years old in the TANOVEA® group and 3.2 to 16 years old in the Placebo group. Weights ranged from 3.3 to 65 kg in the TANOVEA® group and 3.4 to 63 kg in the Placebo group at the time of first treatment.

There were 51 neutered males, 57 spayed females, nine intact males, and three intact females enrolled in the TANOVEA® group and 21 neutered males, 10 spayed females, six intact males, and one intact female in the Placebo group. There were 100 dogs diagnosed with B-cell lymphoma and 20 dogs diagnosed with T-cell lymphoma in the TANOVEA® group. There were 32 dogs diagnosed with B-cell lymphoma and six dogs diagnosed with T-cell lymphoma in the Placebo group. The distribution of dogs receiving prior chemotherapy treatment was similar across groups. In the TANOVEA® group, 57, 39, 17, six, and one dogs had zero, one, two, three, and four previous treatments for lymphoma, respectively. In the Placebo group, 20, 14, three, and one dogs had zero, one, two, and three previous treatments for lymphoma, respectively. The distribution of World Health Organization (WHO) staging[3] was similar between groups with most dogs being staged as IIIa (generalized lymph node involvement without systemic signs) or IVa

(generalized lymph node involvement with liver and/or spleen involvement without systemic signs).

Experimental Design:

Table II.6. Control and Treatment Groups

Treatment Group	Number of Dogs in Group	Dose
TANOVEA®	120	1.0 mg/kg administered IV every 21 days (stepwise dose reductions to 0.8 mg/kg and 0.66 mg/kg were allowed)
Placebo (0.9% Sodium Chloride)	38	Dose volume corresponding to the TANOVEA® dose volume administered IV every 21 days

Randomization and Masking: At each study site, dogs were randomly allocated at a 3:1 ratio to either TANOVEA® or Placebo groups in sets of four dogs based on order of presentation. Dogs were randomized to treatment groups regardless of previous chemotherapy treatment for lymphoma (yes or no) or immunophenotype (T cell or B cell).

All study personnel conducting observations, collecting data, and administering treatment were masked to treatment group. Owners were also masked to their dog's treatment assignment. Each site had at least one Treatment Dispenser that was unmasked and had the responsibility of following the randomization plan for all dogs and for preparing the infusion solution for treatment. The study was conducted in accordance with Good Clinical Practice.

Inclusion Criteria:
- At least one year old on Day 0.
- Confirmed histologic or cytologic diagnosis of lymphoma by a veterinary pathologist
- May have been previously treated or untreated.
- Must have peripherally accessible and measurable disease.
- At least one peripheral lymph node >/= 20mm
- Adequate organ function as demonstrated by:
  - Absolute neutrophil count (ANC) > 2,000 cells/µL
  - Hematocrit > 25%
  - Platelet count > 75,000/µL
  - Serum creatinine < 2.5 mg/dL
  - Bilirubin ≤ the upper normal limit
  - Transaminases ≤ three times the upper normal limit or if > three times the upper normal limit then fasting and postprandial serum bile acids must be ≤ the upper normal limit
- Constitutional Clinical Signs General Performance score of either zero or one on Day 0, (VCOG- CTCAE v1.1)
- Signed owner informed consent

Exclusion Criteria:
- Received chemotherapy within two weeks of Day 0
- Received radiation therapy within six weeks of Day 0

- Received long-acting corticosteroids within four weeks, or short-acting corticosteroids within one week of Day 0
- Received immunotherapy to treat lymphoma
- Received bleomycin
- Constitutional Clinical Signs General Performance score > two on Day 0 (VCOG-CTCAE v1.1).
- Pulmonary fibrosis or a history of chronic pulmonary disease that could lead to fibrosis, such as chronic bronchitis
- West Highland White Terrier breed, which has a genetic predisposition towards idiopathic pulmonary fibrosis
- Concurrent malignancy or other serious systemic disorder or infection which, in the Investigator's opinion, could result in a life expectancy of less than three months
- Pregnant, lactating or intended for breeding
- Currently enrolled in another clinical trial
- Owned by an Investigator or his/her staff or family
- Any other reason which according to the Investigator, would affect the safety of the dog or interfere with study procedures

Concomitant Medications: Concomitant medications were used primarily for diarrhea, decreased appetite, and dermatopathy (bacterial skin infections). The most commonly used concomitant medications included antiemetics, antibiotics, electrolyte solutions, sedatives, appetite stimulants, analgesics, and topical corticosteroids with anti-infectives. No other chemotherapies or systemic corticosteroids were used in the study.

Drug Administration: TANOVEA® was administered intravenously at a dose of 1.0 mg/kg. After adding 2 mL of 0.9% Sodium Chloride for Injection, USP to the vial, the volume of reconstituted solution was 0.12 mL/kg, which was further diluted with saline to achieve a total infusion volume of 2 mL/kg.

The Placebo consisted solely of 0.9% Sodium Chloride for Injection, USP.

Doses were administered using a syringe pump or infusion pump with an intravenous fluid bag over 30 minutes.

A single “cycle” of treatment was the day of treatment and the 20 days after treatment (total of 21 days). Each dog received up to five treatments (cycles).

TANOVEA® (or Placebo group) doses could be incrementally reduced from 1.0 mg/kg to 0.8 mg/kg and then further to 0.66 mg/kg to manage adverse events.

Forty-four dogs in the TANOVEA® group completed five cycles of treatment. One Placebo dog completed five cycles of treatment.

Measurements and Observations: At the screening visit a fine needle aspirate or biopsy was collected to confirm the diagnosis of lymphoma. Tumor immunophenotype was determined by flow cytometry. Investigators staged the lymphoma according to the WHO staging criteria.

Study observations included:

- Physical examination at pre-enrollment screening and on Day 0, 7, 21, 28, 42, 49, 63, 70, 84, 91 and monthly beginning on Day 112.
- Clinical chemistry and urinalysis at pre-enrollment screening and on Day 0, 21, 42, 63, 84 and monthly beginning on Day 112.
- Complete blood count at pre-enrollment screening and on Day 0, 7, 21, 28, 42, 49, 63, 70, 84, 91 and monthly beginning on Day 112.
- Radiography (2 abdominal view, 3 thoracic views) on Day 0, 42, 84 and every other month during rechecks beginning on Day 140.
- Target lesion(s) (peripheral lymph node(s)) measurements and non-target lesion evaluation at pre-enrollment screening and on Day 0, 21, 42, 63, 84 and monthly beginning on Day 112. Lesion measurements were made by two independent, masked evaluators.
- Changes in existing non-target lesions and the appearance of new lesions since the pre-enrollment screening visit were recorded at each visit.

Response assessments were made according to the VCOG Response Evaluation Criteria for Peripheral Nodal Lymphoma in Dogs (v1.0).[4] The sum of the longest diameter (LD) for target lesions were compared to the Day 0 sum for calculating percent reduction or increase.

- Complete response (CR): Target lesions: Disappearance of all evidence of disease. All lymph nodes must be non-pathologic in size in the judgment of the evaluator(s) (Within normal limits, WNL). Non-target lesions: Any pathologic lymph nodes must be considered to have returned to normal and no new sites of disease should be observed. Spleen and liver should be considered WNL by the evaluator(s).
- Partial response (PR): Target lesions: At least a 30% decrease in the LD of target lesions, taking as reference the baseline LD. Non-target lesions: Not applicable.
- Stable disease (SD): Target lesions: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest LD since treatment. Non-target lesions: Not applicable.
- Progressive disease (PD): Target lesions: At least a 20% increase in the Mean Sum LD taking as reference the smallest mean sum LD at Day 0 or during follow-up. The LD of at least one of the target lesions must demonstrate an absolute increase of at least 5 mm compared with its nadir for PD to be defined. For target lesions < 10 mm at nadir, an increase in LD of any single previously identified target lesion to ≥ 15 mm. *Non-target lesions:* unequivocal progression of existing non-target lesions, in the judgment of the evaluator. (Note: the appearance of one or more new lesions is also considered progression).

The primary endpoint for this study was progression free survival (PFS), defined as the time from the start of study (randomization) until tumor progression or death.

Secondary Study Endpoints:

- Overall response rate (ORR): percentage of dogs with either CR or PR was evaluated at each scheduled treatment visit (Day 21, 42, 63, and 84).
- Best overall response rate (BORR): percentage of dogs with either CR or PR as their highest response at any scheduled treatment visit (Day 21, 42, 63, or 84).

- Percentage of dogs that were progression free at Month 4.

Statistical Methods: The statistical analysis consisted of a Cox regression analysis of PFS. The model included treatment group as a fixed effect and study site as a random effect. The treatment difference was expressed as the hazard ratio which was presented with its 95% confidence interval and the associated p-value. If PFS was longer for TANOVEA® compared with Placebo and the p-value for treatment difference was less than 0.05, a statistically significant difference in favor of TANOVEA® was concluded.

Results: Effectiveness was evaluated in 148 dogs (112 in the TANOVEA® group and 36 in the Placebo group). TANOVEA® demonstrated a statistically significant improvement in PFS compared to Placebo (82 days vs. 21 days, $p < 0.0001$). See Table II.7 below.

Table II.7. Summary of PFS

Treatment Group	Progression Free Survival Interval (Median Days, 95% confidence interval)	Hazard Ratio	95% Confidence Interval	P-value
TANOVEA®	82 (63, 140) *n = 112*	6.265	3.947, 9.945	< 0.0001
Placebo	21 (11, 21) *n = 36*	6.265	3.947, 9.945	< 0.0001

Secondary Study Endpoints:

The median PFS in dogs in the TANOVEA® group that had a response to treatment (i.e., dogs exhibiting a CR or PR) was 151 days and 168 days for those dogs with a CR.

For dogs with B-cell lymphoma, the median PFS was greater for dogs in the TANOVEA® group compared to dogs in the Placebo group (126 vs. 21 days, respectively). A smaller trend was observed for dogs with T-cell lymphoma (29 vs. 17 days, respectively).

For dogs naïve to prior chemotherapy regimens, the median PFS was greater for dogs in the TANOVEA® group compared to dogs in the Placebo group (143 vs. 19 days, respectively). A smaller trend was observed for dogs that had received prior chemotherapy (63 vs. 21 days, respectively). Dogs in the TANOVEA® group with one prior chemotherapy regimen had a median PFS of 82 days (127 days in dogs with CR or PR), and dogs with B-cell lymphoma in the TANOVEA® group with one prior chemotherapy had a median PFS of 107 days (172 days in dogs with CR or PR). Dogs with T-cell lymphoma in the TANOVEA® group with one prior chemotherapy regimen had a median PFS of 21 days.

Overall Response Rate (ORR)
Depending on the study day, dogs in the TANOVEA® group had an ORR ranging from 48.2 to 63.4%. Dogs in the Placebo had an ORR ranging from 0 to 5.6%. See Table II.8 below. In the TANOVEA® group, the ORR by study day ranged from 55.4 to 71.7% in dogs with B-cell lymphoma and 15 to 30% in dogs with T-cell lymphoma. In the Placebo group, the ORR by study day ranged from 0 to 6.7% in dogs with B-cell lymphoma and was 0% in dogs with T-cell lymphoma.

Table II.8. Summary of ORR by Study Day

Study Day	Treatment	Percent Dogs with PR or CR	N	Percent Dogs with SD or PD	N
21	TANOVEA®	63.4	71	36.6	41
	Placebo	5.6	2	94.4	34
42	TANOVEA®	60.4	67[a]	39.6	44
	Placebo	2.8	1	97.2	35
63	TANOVEA®	49.6	55[a]	50.5	56
	Placebo	0	0	100	36
84	TANOVEA®	48.2	54	51.8	58
	Placebo	0	0	100	36

[a.] One dog had missing data on Day 42 and Day 63

The ORR by study day was impacted by the level of prior chemotherapy treatment. See Table II.9 below.

Table II.9. Summary of ORR by Prior Chemotherapy Treatment Strata

No. of Prior Treatments	TANOVEA® Percent ORR	Placebo Percent ORR
0	62.3 to 83.0	0 to 5.3
1	45.9 to 56.8	0 to 7.1
2	20.0 to 40.0	0
3	16.7 to 33.3	0
4	0	0

Best Overall Response Rate (BORR)
The BORR was 73.2% (82/12 dogs) for dogs in the TANOVEA® group (50.9% CR; 57/112 dogs) compared to 5.6% (2/36 dogs) for dogs in the Placebo group (0% CR; 0/36 dogs). The BORR was 80.4% (74/92 dogs) for dogs in the TANOVEA® group with B-cell lymphoma (58.7% CR; 54/92 dogs), and 40.0% (8/20 dogs) in dogs in the TANOVEA® group with T-cell lymphoma (15.0% CR; 3/20 dogs).

In the TANOVEA® group, response rates were impacted by the number of prior chemotherapies, with a BORR of 88.7% (47/53 dogs) in naïve dogs (62.3% CR; 33/53 dogs), 70.3% (26/37 dogs) in dogs with one prior chemotherapy (54.1% CR; 20/37 dogs), and 40.9% (9/22 dogs) in dogs with more than one prior chemotherapy (18.2% CR; 4/22 dogs).

Percentage of dogs that were progression free at Month 4 Following Completion of Cycle 5
At the time of the Day 112 visit (one month after the last treatment), 33% (37/112 dogs) of dogs in the TANOVEA® group were progression free compared to 0 dogs (0/36 dogs) in the Placebo group.

Overall Response Summary in dogs treated with TANOVEA®
A response summary in dogs treated with TANOVEA® by immunophenotype and prior chemotherapy is provided in Table II.10 below.

Table II.10. Response Summary in TANOVEA®-Treated Dogs

Parameter	Overall	B-cell	T-cell	Naive	1 prior[a]	> 1 prior[a]	1 prior (B-cell)[a]	1 prior (T-cell)[a]	> 1 prior (B-cell)[a]	> 1 prior (T-cell)[a]
n	112	92	20	53	37	22	30	7	18	4
Median PFS (days)	82	126	29	143	82	41	107	21	39	60
Median PFS, Dogs with PR or CR only (days)	151	161	55	160	127	64	172	N/A[b]	64	N/A[c]
Median PFS, Dogs with CR only (days)	168	168	63	168	172	NE[d]	172	N/A[b]	NE[d]	NO[e]
% BORR	73.2	80.4	40	88.7	70.3	40.9	83.3	14.3	44.4	25
% CR (anytime)	50.9	58.7	15	62.3	54.1	18.2	63.3	14.3	22.2	0
% PR (anytime)	22.3	21.7	25	26.4	16.2	22.7	20	0	22.2	25

[a] Refers to number of prior chemotherapy regimens (e.g., 0, 1, > 1)
[b] N/A: Not applicable. Includes one dog with a PFS of 43 days
[c] N/A: Not applicable. Includes one dog with a PFS of 60 days
[d] NE: Not estimable. Includes four dogs with PFS of 50, 63, 161, and 360 days
[e] NO: No observations

Five dogs in the TANOVEA® group had a CR on Day 365 (end of study).

The primary reason for early withdrawal from the study for all dogs in both groups was disease progression, followed by death and adverse reactions.

Physical Examination: In the TANOVEA® group, as the study progressed, the incidence of abnormalities on physical examination for ears and skin increased compared to Day 0 which corresponded to the adverse reactions reported related to the skin (e.g., dermatitis) and ears (e.g., otitis). In the Placebo group, there were no increases in incidences of abnormalities on physical examination compared to Day 0.

There was a higher incidence of weight loss in dogs in the TANOVEA® group (110 dogs; 92%) compared to dogs in the placebo group (22 dogs; 58%), and there was a higher incidence of Grade 2 and Grade 3 weight loss in dogs in the TANOVEA® group compared to the Placebo group.

Clinical Pathology: There was a TANOVEA®-related effect on neutrophils, eosinophils, and leukocytes. Neutropenia occurred in up to 54% of TANOVEA®-treated dogs seven days after each treatment visit (i.e., 22 of 41 dogs in Cycle 5). Eosinopenia occurred in up to 93% of TANOVEA®-treated dogs seven days after each treatment visit (i.e., 70 of 75 dogs in Cycle 3). Leukopenia occurred in up to 17% of TANOVEA®-treated dogs seven days after each treatment visit (i.e., 16 of 95 dogs in Cycle 2). Neutrophil, eosinophil, and leukocyte values generally returned to the normal range by the next treatment cycle.

There was a TANOVEA®-related effect on urine glucose. In the TANOVEA® group, 17 dogs had glucosuria (trace to 4+). In the Placebo group, one dog was reported with trace glucosuria. No dogs had hyperglycemia at the time of glucosuria.

Adverse Reactions: Field safety was evaluated in 120 dogs treated with TANOVEA® and 38 dogs in the Placebo group. The Veterinary Cooperative Oncology Group - common terminology criteria for adverse events (VCOG-CTCAE[2]) definitions were used to grade the adverse reactions observed: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (death or euthanasia). Most adverse reactions were Grade 1 or 2. The adverse reactions observed in the study and number of dogs experiencing each adverse reaction is summarized in Table II.11 below.

The most common adverse reactions included diarrhea, decreased appetite, vomiting, lethargy, weight loss, and neutropenia. Though diarrhea, decreased appetite, vomiting, lethargy, and weight loss were observed in both groups, the incidence was higher in the TANOVEA® group and there were more Grade 2 and 3 adverse reactions compared to the Placebo group.

Table II.11. Adverse Reactions Reported During the Field Study

Adverse Reaction	TANOVEA® (n=120)		Placebo (n=38)	
	n	%	n	%
Diarrhea	105	87.5	19	50
Decreased appetite	82	68.3	15	39.5
Emesis	82	68.3	9	23.7
Lethargy	76	63.3	24	63.2
Weight loss	58	48.3	4	10.5
Neutropenia[a]	55	45.8	0	
Polydipsia	40	33.3	6	15.8
Anorexia	34	28.3	7	18.4
Otitis[b]	31	25.8	0	
Alopecia	30	25	2	5.3
Adipsia	29	24.2	5	13.2
Polyuria	29	24.2	2	5.3
Dermatitis	25	20.8	0	
Increased appetite	24	20	6	15.8
Hypoalbuminemia	24	20	5	13.2
Anemia	20	16.7	3	7.9
Hematochezia	20	16.7	0	
Dehydration	17	14.2	1	2.6
Nausea	15	12.5	2	5.3
Erythema	15	12.5	1	2.6
Pruritus	15	12.5	1	2.6
Hyperpigmentation	14	11.7	0	
Leukopenia	14	11.7	0	
Monocytosis	13	10.8	3	7.9
Elevated alanine aminotransferase (ALT)	13	10.8	2	5.3
Proteinuria	13	10.8	2	5.3
Pulmonary disorder[c]	13	10.8	0	
Elevated creatine-kinase (CK)	12	10	1	2.6
Oliguria	12	10	1	2.6
Urinary tract infection	12	10	1	2.6
Cough	11	9.2	3	7.9
Increased blood urea nitrogen (BUN) or creatinine	11	9.2	2	5.3
Elevated aspartate aminotransferase (AST)	11	9.2	0	
Neutrophilia	10	8.3	3	7.9
Hematuria	10	8.3	1	2.6
Mass[d]	10	8.3	0	
Hyperthermia	9	7.5	4	10.5
Thrombocytopenia	9	7.5	3	7.9
Elevated symmetrical dimethylarginine (SDMA)	9	7.5	2	5.3
Hypocalcemia	9	7.5	2	5.3
Glucosuria[e]	9	7.5	0	

Adverse Reaction	TANOVEA® (n=120)		Placebo (n=38)	
	n	%	n	%
Skin ulceration	9	7.5	0	
Tachypnea	8	6.7	5	13.2
Dyspnea	7	5.8	5	13.2
Elevated total bilirubin	7	5.8	1	2.6
Hypokalemia	7	5.8	1	2.6
Bacterial skin infection	7	5.8	0	
Desquamation	7	5.8	0	
Leukocytosis	6	5	5	13.2
Pinnal irritation	6	5	1	2.6
Digestive tract disorders NOS[f]	6	5	0	
Hypoproteinemia	6	5	0	

[a]Most neutropenia was Grade 1 or 2. However, eight instances of Grade 3 and three instances of Grade 4 neutropenia were reported. Neutropenia was reported seven days after treatment and returned to the normal range in all but two instances by the next cycle.
[b]Represents combined terms of Otitis Externa and Otitis Not Otherwise Specified (NOS).
[c]Pulmonary disorders included pulmonary fibrosis or possible pulmonary fibrosis (five dogs), pulmonary interstitial pattern (three dogs), pneumonia (three dogs), alveolar pattern on radiographs (two dogs), pneumomediastinum (one dog), pneumonitis (one dog), and pulmonary infiltrates on radiographs (one dog). Some dogs were reported with more than one abnormality.
[d]Masses included skin and subcutaneous masses.
[e]Glucosuria ranges from 1+ to 4+. In one dog, a 1+ ketonuria was reported at the same time as a 4+ glucosuria.
[f]Digestive tract disorders NOS included regurgitation (three dogs) and abnormal stool color (three dogs).

The type and frequency of reported adverse events did not vary greatly by cycle of TANOVEA® treatment. A single cycle was the day of treatment and the 20 days after treatment (total of 21 days). However, during Cycles 1 and 2 (after the first or second dose), the majority of adverse reactions were primarily related to gastrointestinal and constitutional signs (i.e., lethargy, weight loss), while dermatopathies began to occur more frequently in Cycles 3 through 5 (after the third through fifth dose).

Serious Adverse Reactions Events
Serious adverse events (SAEs) were reported in 20% of dogs in the TANOVEA® group (24 of 120 dogs) and 13% of dogs in the Placebo group (five of 38 dogs). In the 24 TANOVEA® dogs, SAEs included pulmonary fibrosis (five dogs) and dermatopathy (six dogs) as described below. Other SAEs included three cases of progressive disease (Grade 5), three cases of unrelated neoplasia/comorbidities, and one case each of hepatopathy (Grade 3), renal insufficiency (Grade 3), neutropenia (Grade 4), nausea (Grade 3), lymph node abscess (Grade 3), colitis (Grade 3), and hematochezia (Grade 3).

Pulmonary Fibrosis
Five dogs in the TANOVEA® group developed severe adverse reactions associated with pulmonary fibrosis. The clinical signs included dyspnea, tachypnea, and orthopnea. Four of these dogs also had pneumomediastinum, pneumothorax, and/or emphysema diagnosed radiographically. All five dogs had radiographic findings that could be associated with pulmonary fibrosis along with accompanying pulmonary clinical signs. All five dogs were euthanized (four dogs) or died (one dog) due to the pulmonary fibrosis (either during the study or after removal from the study). Two of these dogs had a histologic confirmation of fibrosis on necropsy. The median time from randomization to first detection of clinical signs was 87 days (range 84 to 140) and the median time from randomization to death was 127 days (range 112 to 172). At the time of withdrawal (due to adverse reactions), all five dogs had a complete response to treatment. Pulmonary fibrosis may be an idiosyncratic adverse reaction with an unknown mechanism of action.

Dermatopathy
Over half of the patients (67/120 dogs) treated with TANOVEA® experienced one or more dermatologic adverse reactions during their treatment. These adverse reactions were predominantly Grade 1 and primarily included otitis, alopecia, dermatitis, erythema, pruritus, hyperpigmentation, skin ulcerations, and bacterial skin infections.

Dermatologic adverse reactions typically presented by Cycle 3 (after the third dose), suggesting a cumulative effect of TANOVEA®-associated dermatopathy. Dose reductions and dose delays were implemented to mitigate dermal adverse reactions. Six dogs in the TANOVEA® group had Grade 3 or Grade 4 dermal adverse reactions which appeared in Cycle 2 (two dogs), Cycle 3 (three dogs), and Cycle 5 (one dog). Grade 3 adverse reactions included bacterial skin infections, skin ulcerations, desquamation, and dermatitis. Grade 4 adverse reactions included skin ulceration (severe erythema and ulceration of skin on limbs, ventrum, and foot pads) and desquamation (moist desquamation along the inguinal region and encompassing perivulvar area).

Euthanasia
Nine dogs in the TANOVEA® group (8%) and two dogs in the Placebo group (5%) were euthanized while on study. Reasons for euthanasia included four cases of progressive lymphoma (one with multiple comorbidities and pre-existing dermatopathy), two cases of pulmonary fibrosis, one case of probable hemangiosarcoma, one case of pyelonephritis/renal failure, and one case was unspecified. An additional three dogs died/were euthanized after withdrawal from the study due to suspected pulmonary fibrosis. One dog was euthanized after withdrawal from the study due to sepsis secondary to dermatopathy.

Dose Reductions and Dose Delays
Twenty-nine dogs in the TANOVEA® group dogs received dose reductions (from 1 to 0.8 mg/kg), which were typically employed on the second to fourth dose of TANOVEA®. Four dogs received a second stepwise reduction (from 0.8 to 0.66 mg/kg), which were employed on the third to fifth dose. The primary reason for dose reduction was gastrointestinal toxicity (diarrhea, vomiting, nausea), followed by dermatopathies, weight loss, anorexia/hyporexia,

neutropenia, thrombocytopenia, and hypoalbuminemia. All dogs continued on the reduced dose(s) for the remainder of the study or until withdrawn.

Fourteen dogs in the TANOVEA® group had a dose delay, which typically was one week beyond the intended treatment day. The primary reason cited in all cases was dermatopathy, and one case also cited weight loss. Eight dogs had both a dose reduction and delay, primarily attributable to dermatopathies.

Infusion Site Observations
On the day of treatment, two incidences of bruising were reported in dogs in the TANOVEA® group. Infusion site observations seven days after treatment in dogs in the TANOVEA® group included pigmentation (seven incidences), scaling (five incidences), erythema (three incidences), and swelling (two incidences).

One dog in the TANOVEA® group had an adverse reaction suggestive of mild extravasation. The dog had erythema at the infusion site and a slightly ulcerated skin surface seven days after the third infusion of TANOVEA®, and the dog had been licking the area. No treatment of the site was conducted.

Conclusion: TANOVEA® at a dose of 1.0 mg/kg as a 30-minute intravenous infusion, once every three weeks, for up to five doses is effective and has an adequate safety profile for the treatment of lymphoma in dogs.

III. TARGET ANIMAL SAFETY

The margin of safety and toxicity of rabacfosadine (not commercial formulation) was evaluated in three laboratory toxicity studies, one laboratory cardiovascular study, and the two pilot studies supporting dosage characterization.

The three laboratory toxicity studies included an acute toxicity study, a 5-day toxicity study, and a 3-cycle weekly toxicity study. The acute toxicity study with a recovery period was conducted in 30 male and 30 female Beagle dogs. A single IV dose of 0, 0.25, 0.82, and 2.5 mg/kg were tolerated. A dose of 8.2 mg/kg resulted in mortality due to gastrointestinal toxicity and severe neutropenia. The 5-day toxicity study with a 21-day recovery period was conducted in 24 male and 24 female Beagle dogs. Daily IV doses of 0.082, 0.25, and 0.82 mg/kg were tolerated, however therapeutic intervention was needed in dogs administered the 0.82 mg/kg dose. The 3-cycle, once weekly toxicity study with a 21-day recovery period was conducted in 24 male and 24 female dogs. Weekly IV doses of 0, 0.25, 0.50, and 1.0 were tolerated. Across the three studies, treatment-related findings included vomiting, abnormal feces, dehydration, thinness, body weight loss, decreased food consumption, decreased activity, and fever. Dermatologic changes were reported in all groups, including the control group, with a higher incidence in the dogs administered rabacfosadine. Hematological changes included dose-dependent reductions in white blood cell counts that reached a nadir on Days 6 and 9 and were reversible by Day 12 at most doses. Pathology changes included effects on the gastrointestinal tract, lymphoid tissue, bone marrow, male reproductive system, pancreas, salivary gland, prostate, adrenal cortex, and kidney. Following a 21-day recovery period, there was partial reversibility of the pathology changes.

The cardiovascular laboratory study was conducted to assess the potential effects of rabacfosadine on the cardiovascular system following a single 30-min IV infusion of rabacfosadine in 4 healthy, 2 to 4-year-old intact male Beagles. There were no treatment-related effects on arterial blood pressure, heart rate, or ECG parameters.

In two pilot studies, dogs with lymphoma were treated with an IV infusion at doses of rabacfosadine at 0.66 to 1.2 mg/kg body weight administered once every three weeks for one to six doses. Most adverse reactions were VCOG-CTCAE Grade 1-2. Grade 3 reactions included hyporexia/anorexia, weight loss, vomiting, diarrhea, otitis externa, dehydration, aspiration pneumonia, neutropenia, thrombocytopenia, anemia, bilirubinemia, and hypertriglyceridemia. Grade 4 reactions included tachypnea and neutropenia. Grade 5 reactions included dyspnea (secondary to pulmonary fibrosis).

A. Toxicity Study

Title: An Acute Intravenous Infusion Toxicity Study of GS-9219 in the Beagle Dog. (Study No. TX-193-2009)

Study Date: June 2006 to March 2007

Study Location: Senneville, Quebec, Canada

Study Design:

Objective: The objective of the study was to investigate the potential acute toxicity of rabacfosadine (not commercial formulation) following a single 30-minute intravenous infusion in the dog.

Study Animals: There were six male and six female Beagle dogs per treatment group. Dogs were 7 to 8 months old and weighed 5.7 to 10.9 kg at the start of treatment. All dogs were healthy based on physical examination and clinical pathology (hematology and serum chemistry).

Experimental Design: Thirty male and thirty female dogs were randomly assigned to five treatment groups of twelve dogs each (six males and six females). Males and females were randomized separately. Three dogs/sex/group were necropsied on Day 3 (main study) and three dogs/sex/group were necropsied on Day 21 (recovery group). The study was unmasked. The study was conducted in accordance with Good Laboratory Practice (GLP) regulations.

Table III.1. Control and Treatment Groups

Treatment Group	Dose (mg/kg)	Number and Sex of Dogs
1	Vehicle (5% Dextrose for Injection, USP)	6 males 6 females
2	0.25	6 males 6 females
3	0.82	6 males 6 females
4	2.5	6 males 6 females
5	8.2	6 males 6 females

Drug Administration: The test and control articles were administered by a 30-minute intravenous infusion on Day 1, into the saphenous or cephalic vein. The test article was added to 5% Dextrose for Injection, USP for the infusion. The dose volume was 2 mL/kg bodyweight.

Measurements and Observations: Mortality and signs of ill health or reaction to treatment were evaluated twice daily. Physical examinations were performed daily. Food consumption was measured daily. Body weight was measured weekly and prior to necropsy. Hematology was evaluated three times pretreatment and on Days 1, 2, 3, 6, 9, 12, 15, 18, and 21. Serum chemistry was evaluated once pretreatment and on Days 1, 3 (main study animals only), weekly during the observation period, and on Day 21. Gross necropsy and histopathology were performed on Day 3 (main study) and Day 21 (recovery group). Toxicokinetics were evaluated on Day 1.

Statistical Methods: For variables measured more than once throughout the study, a repeated measures analysis of covariance was used with treatment, sex, day, treatment by sex, treatment by day, sex by day and treatment by sex by day terms as fixed effects. Pretreatment values were used as a covariate and remained in the model regardless of statistical significance. All tests were conducted at alpha=0.10, except for the test for the three-way interaction, which was conducted at alpha=0.05. No additional analysis was performed if the three-way interaction was significant. Pairwise comparisons of each treatment group against control group (within sex, within day or overall) were evaluated at alpha=0.10 to follow up on significant effects involving treatment. No adjustments were made for multiple comparisons.

Results:

Mortality
All main study dogs survived to scheduled euthanasia on Day 3. All recovery dogs administered 8.2 mg/kg were either found dead or preterminally euthanized due to poor and deteriorating condition on Days 6 or 7. All remaining recovery dogs survived to scheduled euthanasia on Day 21.

Clinical Observations
Between Days 4-7, dogs in the recovery groups administered 8.2 mg/kg were observed to have decreased activity, weakness, dehydration, abnormal feces (black, green, liquid, red, soft, mucoid), vomiting, fur staining, salivation, thinness, prominent backbone, eyes partially closed, cold to touch, thin fur, head shaking, tremors, hunched posture, lying on side, decreased respiration, fever, tachycardia, and dermatologic changes (dry skin, red skin, scabs).

Starting on Day 4, there was an increased frequency of abnormal feces in dogs in the recovery group administered 2.5 mg/kg. This observation resolved by Day 10. Sporadic abnormal feces were reported in all treatment groups, including the control group.

During the recovery period, vomiting was reported in one dog administered 0.82 mg/kg and two dogs administered 2.5 mg/kg; suspected dehydration was reported in one dog administered 0.82 mg/kg and two dogs administered 2.5 mg/kg; and thinness or prominent backbone was reported in one dog administered 0.82 mg/kg and two dogs administered 2.5 mg/kg.

In all groups, including control, there were dermatologic changes (fur loss, thin fur, dry skin, red skin, skin lesions, scabs) with a higher incidence in the dogs administered 2.5 mg/kg.

Body Weight
There was no treatment-related effect on body weight noted in the main study dogs euthanized on Day 3.

Male dogs in the recovery group administered 8.2 mg/kg lost 15-19% of their weight by Day 6 compared to Day -1 (female weights were not provided).

Dose-dependent weight loss was observed in dogs in the recovery groups administered 0.82 and 2.5 mg/kg and there was a trend towards weight recovery in these groups.

Food Consumption
Treatment-related decreases in food consumption were noted in dogs administered 2.5 and 8.2 mg/kg, starting on Day 2 to 3. By Day 8 or 9, dogs administered 2.5 mg/kg began consuming food amounts similar to pre-study; however, they were offered supplemental food from Day 7 or 8 until the end of the study. One dog administered 0.82 mg/kg was offered supplemental food from Day 11 until the end of the study; the dog had lower food intake on Days 7 and 8.

Hematology
There was a dose-dependent decrease in white blood cell (WBC) parameters in dogs administered 0.82, 2.5, and 8.2 mg/kg. The nadir for the leukopenia and monocytopenia was at Day 6. The nadir for the neutropenia, eosinopenia, and basopenia was between Day 6 and 9. Recovery of the WBC parameters was generally seen by Day 12.

For neutropenia the VCOG grade was Grade 1 in dogs administered 0.82 mg/kg; Grade 1 to 3 in dogs administered 2.5 mg/kg; and Grade 1 on Days 1 and 2 and Grade 4 on Day 6 in dogs administered 8.2 mg/kg.

Serum Chemistry
There were no serum chemistry findings attributable to the test article.

One dog in the recovery group administered 8.2 mg/kg had several abnormalities likely due to severe dehydration and gastrointestinal loss including increased creatinine, blood urea nitrogen, and phosphorus and decreased sodium and chloride.

Pathology
Main Study Day 3: Dose-related macroscopic and microscopic changes were noted in the gastrointestinal tract (stomach, small intestines, and large intestines) in all treatment groups administered the test article. Changes included minimal to slight single cell necrosis in the epithelium of the stomach and minimal to slight crypt necrosis was noted in the duodenum, jejunum, ileum, cecum, and colon.

Lymphoid atrophy and necrosis were noted in the thymus, spleen, mesenteric lymph node, and gut associated lymphoid tissue (GALT) in dogs administered 2.5 and 8.2 mg/kg.

Minimal to moderate bone marrow hematopoietic hypocellularity was observed in all dogs administered 8.2 mg/kg.

Minimal single cell necrosis of the acinar epithelium of the prostate was observed in all males administered 8.2 mg/kg.

Minimal increased mitotic figures/single cell necrosis in the adrenal cortex was observed in one dog administered 2.5 mg/kg and in one dog administered 8.2 mg/kg.

Minimal renal tubular vacuolation was observed in one dog administered 8.2 mg/kg, minimal basophilia of the kidney was observed in one dog administered 8.2 mg/kg, and minimal basophilia and fibrosis of the kidney was observed in one dog administered 2.5 mg/kg.

Recovery Group Day 21: Dose-dependent single cell necrosis of the epithelium, mucosal atrophy, and mucosal inflammation was observed in the glandular mucosa of the stomach and dose-dependent duodenal crypt dilatation and inflammation was observed.

Slight lymphoid atrophy/necrosis was noted in the thymus of one dog administered 0.25 mg/kg and one dog administered 2.5 mg/kg.

Dose-dependent tubular degeneration/necrosis of the kidney was characterized by nuclear karyomegaly, cytoplasmic basophilia, and occasional single cell necrosis. Tubular degeneration/necrosis was noted in the preterminally euthanized animals administered 8.2 mg/kg.

Conclusions: The administration of a single 30-minute intravenous infusion of rabacfosadine in dogs was tolerated at dose levels of 0, 0.25, 0.82, and 2.5 mg/kg. A single dose of rabacfosadine administered at 8.2 mg/kg resulted in mortality due to gastrointestinal toxicity and severe neutropenia. Treatment-related vomiting, dehydration, thinness, body weight loss, and decreased food consumption were observed at doses ≥ 0.82 mg/kg; and abnormal feces were observed at doses ≥ 2.5 mg/kg. Hematological changes included dose-dependent reductions in white blood cells that reached a nadir on Days 6 and 9 and were reversible by Day 12 for doses ≤ 2.5 mg/kg. Dermatologic changes were reported in all groups, including the control group with a higher incidence in the dogs administered 2.5 mg/kg. Pathology changes included dose-dependent effects on the gastrointestinal tract, lymphoid tissue, bone marrow, prostate, adrenal cortex, and kidney. Following a 21-day recovery period, the majority of the changes in the intestines and lymphoid tissues reversed. Dose-dependent renal tubular degeneration/necrosis was still observed.

B. Toxicity Study

Title: A 5-Day Intravenous Infusion Toxicity Study of GS-9219 (with a 21-Day Recovery Period) in the Beagle Dog. (Study No. TX-193-2010)

Study Dates: July 2006 to March 2007

Study Location: Senneville, Quebec, Canada

Study Design:

Objective: The objective of the study was to investigate the potential toxicity of rabacfosadine (not commercial formulation) following daily 30-minute IV infusions in the dog for 5 days and to assess the reversibility, persistence, or delayed occurrence of effects, if any, after a 21-day recovery period.

Study Animals: There were six male and six female Beagle dogs per treatment group. Dogs were 7 months old and weighed 5.7 to 9.7 kg at the start of treatment. All dogs were healthy based on physical examination, hematology, and chemistry.

Experimental Design: Twenty-four male and 24 female dogs were randomly assigned to four treatment groups of 12 dogs each (six males and six females). Males and females were randomized separately. Three dogs/sex/group were necropsied on Day 6 (main study) and three dogs/sex/group were necropsied on Day 27 (recovery group). The study was unmasked. The study was conducted in accordance with GLP regulations.

Table III.2. Control and Treatment Groups

Treatment Group	Dose (mg/kg)	Number and Sex of Dogs
1	Vehicle (5% Dextrose for Injection, USP)	6 males 6 females
2	0.082	6 males 6 females
3	0.25	6 males 6 females
4	0.82	6 males 6 females

Drug Administration: The test/control articles were administered once a day by a 30-minute intravenous infusion on Days 1 through 5, into the saphenous or cephalic veins. The test article was added to 5% Dextrose for Injection, USP for the infusion. The dose volume was 2 mL/kg bodyweight.

Measurements and Observations: Mortality and signs of ill health or reaction to treatment were evaluated twice daily. Physical examinations were performed daily. Food consumption was measured daily. Body weight was measured weekly and prior to necropsy. Hematology was evaluated three times pretreatment and on Days 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, and 27. Serum chemistry was evaluated once pretreatment and on Days 1, 6, 14, 21 and 27. Gross necropsy and histopathology were performed on Day 6 (main study) and Day 27 (recovery group). Toxicokinetics were evaluated on Day 1 and 5.

Statistical Methods: For variables measured more than once throughout the study, a repeated measures analysis of covariance was used with treatment, sex, day, treatment by sex, treatment by day, sex by day and treatment by sex by day terms as fixed effects. Pretreatment values were used as a covariate and remained in the model regardless of statistical significance. All tests were conducted at alpha=0.10, except for the test for the three-way interaction, which was conducted at alpha=0.05. No additional analysis was performed if the three-way interaction was significant. Pairwise comparisons of each treatment group against control group (within sex, within day or overall) were evaluated at alpha=0.10 to follow up on significant effects involving treatment. No adjustments were made for multiple comparisons.

Results:

Mortality
All dogs survived to scheduled euthanasia.

Clinical Observations
In the main and recovery groups, dogs administered 0.82 mg/kg had vomiting, abnormal feces (soft, liquid, green, red), and were observed as thin. During the recovery period, dogs administered 0.82 mg/kg also had decreased appetite, decreased activity, suspected dehydration, and fever. The vomiting was mainly reported between Days 5 and 11. Five dogs reported with suspected dehydration were administered Lactated Ringers Solution by subcutaneous injection on several days between Days 7 and 21.

One dog administered 0.082 mg/kg vomited on Day 20.

During the recovery period, one dog administered 0.082 mg/kg and one dog administered 0.25 mg/kg were observed as thin.

In all groups, including control, there were dermatologic changes (fur loss, thin fur, dry skin, red skin, skin lesions, scabs) with a higher incidence in the groups administered drug.

Body Weight
There was a dose-dependent effect on body weight loss in dogs administered 0.25 and 0.82 mg/kg. The largest amount of weight loss occurred between Days -1 and 7, followed by between Days 7 and 14. Most dogs started regaining weight by the end of the study; however, 4 of 6 dogs administered 0.25 mg/kg and 6 of 6 dogs administered 0.82 mg/kg weighed less at Day 27 compared to their Day -1 values.

Food Consumption
There was a dose-dependent decrease in food consumption in dogs administered 0.25 and 0.82 mg/kg starting on Day 2 to 3 and persisting through the end of the study. All dogs in the recovery group administered 0.82 mg/kg received supplemental food from Days 7 to 9 until the end of the recovery period. One dog administered 0.25 mg/kg received supplemental food from Day 15 until the end of the recovery period.

Hematology
There was a dose-dependent decrease of all WBC parameters in dogs administered 0.082, 0.25, and 0.82 mg/kg. The nadir for leukocytes was between Day 6 and 9. The nadir for lymphocytes and monocytes was at Day 6. The nadir for neutrophils, eosinophils, and basophils was at Day 9. Recovery of the WBC parameters was generally seen by Day 12.

Neutropenia was observed in dogs administered 0.25 and 0.82 mg/kg. In dogs administered 0.25 mg/kg, all neutropenia was VCOG Grade 1. In dogs administered 0.82 mg/kg, VCOG Grade 1 and 2 neutropenia was observed at Day 6 and VCOG Grade 4 neutropenia was observed at Day 6 and 9.

Serum Chemistry
Treatment-related changes in electrolytes (decreased sodium and chloride and increased phosphorus and potassium were noted in dogs administered 0.082, 0.25, and 0.82 mg/kg.

Incidences of Grade 1 hypoalbuminemia were observed in dogs administered 0.82 mg/kg during the study.

Pathology
Main Study Day 6: Decreased organ weight changes (absolute, percent body weight) were present in the spleen in dogs administered 0.25 and 0.82 mg/kg and in the thymus in dogs administered 0.82 mg/kg. A small thymus was observed in one dog administered 0.25 mg/kg and two dogs administered 0.82 mg/kg.

Dose-dependent macroscopic observations of dark foci of discoloration were noted in the small and large intestines in dogs administered 0.25 and 0.82 mg/kg.

Dose-dependent microscopic changes were noted in the gastrointestinal tract. In the stomach, minimal single cell necrosis was observed. In the small and large intestines, varying degrees and combinations of mucosal hemorrhage, dilatation of mucosal glands/crypts, necrosis of crypt epithelial cells, atrophy of the mucosa/villi, and edema and inflammation of the intestinal wall were present in dogs administered 0.25 and 0.82 mg/kg.

Dose-dependent lymphoid atrophy and necrosis was observed in the thymus and spleen in all dogs administered the test article. Dose-dependent lymphoid atrophy and necrosis was observed in the mesenteric lymph node, mandibular lymph node, and GALT in dogs administered 0.25 and 0.82 mg/kg.

Dose-dependent minimal to slight hematopoietic hypocellularity was observed in the bone marrow in all groups administered the test article.

Minimal to moderate degeneration/atrophy of the testicular seminiferous epithelium was present in male dogs from the groups administered 0.25 and 0.82 mg/kg.

Recovery Group Day 27: Decreased organ weights (absolute, percent body weight) were present in the thymus in dogs administered 0.25 and 0.82 mg/kg.

The histopathological changes in the recovery groups were only partially reversed in all treatment groups at all dose levels. Following the 21-day recovery period, treatment-related microscopic findings were present in the gastrointestinal tract, thymus, bone marrow, testis, pancreas, salivary gland, and kidney.

Dose-dependent minimal to slight mucosal hemorrhage and glandular or cryptal dilatation in the small and large intestines was observed in dogs administered 0.25 and 0.82 mg/kg. Dose-dependent single cell necrosis, mucosal atrophy, and inflammation in the stomach were noted in dogs from all groups administered the test article.

Dose-dependent lymphoid atrophy/necrosis in the thymus was observed in dogs from all groups administered the test article.

Slight hematopoietic hypocellularity was observed in the bone marrow in dogs administered 0.82 mg/kg.

Dose-dependent minimal to moderate degeneration/atrophy of the testicular seminiferous epithelium was present in males in all groups administered the test article.

Dose-dependent acinar cell necrosis in the pancreas was observed in dogs administered 0.25 and 0.82 mg/kg.

Dose-dependent glandular cell necrosis, atrophy, and/or inflammation were observed in the mandibular salivary gland in all groups administered the test article.

Dose-dependent minimal to slight tubular changes were observed in the kidneys characterized by varying combinations of dilatation, increased cellular basophilia, tubular cell degeneration and necrosis of individual tubular epithelial cells were present in all groups administered the test article.

Conclusions: The administration of rabacfosadine once daily for 5 days by a 30-minute intravenous infusion was tolerated at dose levels of 0.082, 0.25, and 0.82 mg/kg; however, at 0.82 mg/kg therapeutic intervention was necessary. Body weight loss and decreased food consumption were observed at doses ≥ 0.25 mg/kg; and vomiting, abnormal feces, decreased appetite, decreased activity, suspected dehydration, and fever were observed at 0.82 mg/kg. Hematological changes included dose dependent reductions in white blood cells that reached a nadir on Days 6 and 9 and were reversible by Day 12. Dermatologic changes were reported in all groups, including the control group with a higher incidence in the groups administered rabacfosadine. Pathology changes included dose-dependent effects on the gastrointestinal tract, lymphoid tissue, bone marrow, male reproductive system, pancreas, salivary gland, and kidney. Following a 21-day recovery period, microscopic findings were present in the gastrointestinal tract, salivary gland, kidney and testes in all treated dogs, in the pancreas and thymus in dogs administered ≥ 0.25 mg/kg and in the bone marrow in dogs administered 0.82 mg/kg. The microscopic changes following the recovery period were minimal to slight in dogs administered 0.082 and 0.25 mg/kg, except for the changes in the testes.

C. Toxicity Study

Title: A 3-Cycle Once Weekly Intravenous Infusion Toxicity Study of GS-9219 (with a 21-Day Recovery Period) in the Beagle Dog. (Study No. TX-193-2015)

Study Dates: August 2007 to May 2008

Study Location: Senneville, Quebec, Canada

Study Design:

Objective: The objective of the study was to investigate the potential toxicity of rabacfosadine (not commercial formulation) following daily 30-minute intravenous infusion once every 7 days in the dog for 3 doses and to assess the reversibility, persistence, or delayed occurrence of effects, if any, after a 21-day recovery period.

Study Animals: There were six male and six female Beagle dogs per treatment group. Dogs were 7 months old and weighed 4.9 to 8.9 kg at the start of treatment. All dogs were healthy based on physical examination, hematology, chemistry, and urinalysis.

Experimental Design: Twenty-four male and 24 female dogs were randomly assigned to four treatment groups of 12 dogs each (six males and six females).

Males and females were randomized separately. Three dogs/sex/group were necropsied on Day 16 (Main Study) and three dogs/sex/group were necropsied on Day 36 (Recovery Group). The study was unmasked. The study was conducted in accordance with GLP regulations.

Table III.3. Control and Treatment Groups

Treatment Group	Dose (mg/kg)	Number and Sex of Dogs
1	Vehicle (5% Dextrose for Injection, USP)	6 males 6 females
2	0.25	6 males 6 females
3	0.50	6 males 6 females
4	1.0	6 males 6 females

Drug Administration: The test/control articles were administered by a 30-minute intravenous infusion once every 7 days for 3 administrations (Days 1, 8, and 15), into the cephalic vein. The test article was added to 5% Dextrose for Injection, USP for the infusion. The dose volume was 2 mL/kg bodyweight.

Measurements and Observations: Mortality and signs of ill health or reaction to treatment was evaluated twice daily. Physical examinations were performed daily. Food consumption was measured daily. Body weight was measured twice weekly and prior to necropsy. Hematology and serum chemistry was evaluated once pretreatment and on Days 7, 10, 16, 22, 29, and 36. Urine was evaluated once pretreatment and on Days 16, 22, and 36. Electrocardiography was evaluated once pretreatment and on Days 1 and 15 at 1 to 2 hours after infusion initiation and at the end of the recovery period. Ophthalmic examination was performed once pretreatment, once during the week following the last dose, and once during the last week of the recovery phase. Gross necropsy and histopathology were performed on Day 16 (main study) and Day 36 (recovery group). Toxicokinetics were evaluated on Day 1 and 15.

Statistical Methods: For variables measured more than once throughout the study, a repeated measures analysis of covariance was used with treatment, sex, day, treatment by sex, treatment by day, sex by day and treatment by sex by day terms as fixed effects. Pretreatment values were used as a covariate and remained in the model regardless of statistical significance. All tests were conducted at alpha=0.10, except for the test for the three-way interaction, which was conducted at alpha=0.05. No additional analysis was performed if the three-way interaction was significant. Pairwise comparisons of each treatment group against control group (within sex, within day or overall) were evaluated at alpha=0.10 to follow up on significant effects involving treatment. No adjustments were made for multiple comparisons.

Results:

Mortality
All dogs survived to scheduled euthanasia.

Clinical Observations
Mainly starting after the second dose, one dog in the control group, two dogs administered 0.50 mg/kg, and three dogs administered 1.0 mg/kg were observed as thin.

In all groups, including control, there were dermatologic changes (fur loss, thin fur, dry skin, red skin, skin lesions, scabs) with a higher incidence in the groups administered drug.

Body Weight
Dogs administered 1.0 mg/kg had decreased body weight.

Food Consumption
Dogs administered 1.0 mg/kg had decreased food consumption.

Hematology
Leukopenia was reported in one dog administered 1.0 mg/kg. VCOG Grade 1 neutropenia was observed in one dog administered 0.25 mg/kg and four dogs administered 1.0 mg/kg. Dose-dependent eosinopenia was seen in dogs administered the test article. Recovery of the WBC parameters was seen by Day 29.

Serum Chemistry
There were no serum chemistry findings attributable to the test article.

Urinalysis
There were no urinalysis findings attributable to the test article.

Electrocardiography
There were no electrocardiography findings attributable to the test article.

Ophthalmic Examination
There were no ophthalmic examination findings attributable to the test article.

Pathology
Main Study Day 16: Decreased organ weights (absolute, percent body weight) were present in the testes in male dogs in all groups administered the test article and in the thymus in dogs administered 0.50 and 1.0 mg/kg.

Dose-related minimal to moderate glandular necrosis with or without inflammation was observed in the stomach and minimal to moderate cryptal necrosis was observed in the cecum and colon in dogs from all groups administered the test article. Minimal cryptal necrosis of the ileum was noted in dogs administered 0.50 and 1.0 mg/kg.

Dose-related minimal to moderate lymphoid atrophy/necrosis was noted in the lymph nodes and GALT in in dogs from all groups administered the test article. Minimal to slight lymphoid atrophy was observed in the thymus in dogs administered 0.50 and 1.0 mg/kg. Minimal lymphoid atrophy/necrosis of the spleen was observed in dogs administered 1.0 mg/kg.

Non-dose dependent minimal to slight acute glandular necrosis was observed in the salivary gland in dogs from all groups administered the test article.

Macroscopically, small testes and epididymides were reported in 2 of 3 males administered 1.0 mg/kg. Non-dose dependent minimal to marked degeneration/atrophy of the seminiferous epithelium was observed in the testes in in male dogs from all groups administered the test article.

Non-dose dependent minimal tubular degeneration/necrosis with evidence of karyomegaly was observed in the kidneys in dogs from all groups administered the test article. Minimal to slight tubular vacuolation was observed in dogs administered 1.0 mg/kg.

Moderate pleural fibrosis was observed in one dog administered 0.25 mg/kg. Minimal splenic fibrosis was observed in one dog administered 0.25 mg/kg.

Recovery Group Day 36: Decreased organ weights (absolute, percent body weight) were present in the testes in male dogs in all groups administered the test article and in the thymus in dogs administered 0.50 and 1.0 mg/kg on Day 36.

Non-dose dependent minimal to slight glandular necrosis of the stomach was observed in dogs from all groups administered the test article.

Minimal necrosis/atrophy in the lymphoid tissues was observed in one dog administered 0.50 mg/kg and two dogs administered 1.0 mg/kg. Dose-dependent minimal lymphoid atrophy in the thymus was observed in dogs administered 0.50 and 1.0 mg/kg.

Dose-dependent minimal to moderate necrosis in the salivary glands was observed in dogs from all groups administered the test article.

Macroscopically, small testes and epididymides were reported in males in all groups administered the test article. Non-dose dependent degeneration/atrophy of the seminiferous epithelium in the testes was observed in dogs administered the test article with a slight increase in severity compared to the main study dogs.

Dose-dependent tubular regeneration was observed in the kidneys of dogs administered the test article, characterized by minimal to moderate tubular basophilia, dilatation, and thinning of the tubular epithelium. Karyomegaly and minimal tubular degeneration/necrosis was also observed.

Minimal adrenal fibrosis was observed in one dog administered 1.0 mg/kg.

Conclusions: The administration of a 30-minute intravenous infusion of rabacfosadine in dogs at dose levels of 0, 0.25, 0.50 and 1.0 mg/kg once every 7 days for 3 treatments was tolerated at all dose levels. Treatment-related findings included decreased body weight and food consumption at 1.0 mg/kg. Hematological changes included mild neutropenia predominantly at 1.0 mg/kg. Dermatologic changes were reported in all groups, including the control group with a higher incidence in the groups administered rabacfosadine. Pathology

changes included dose-dependent effects on the gastrointestinal tract and lymphoid tissue, and non-dose dependent effects on the salivary gland, male reproductive tract, and kidney. Following a 21-day recovery period there was partial reversibility of the pathology changes.

D. Cardiovascular Study

Title: A Pharmacological Assessment of the Effect of GS-9219 on the Cardiovascular System of the Beagle Dog Using Telemetry (Study No. TX-193-2013)

Study Dates: July 2006 to March 2007

Study Location: Senneville, Quebec, Canada

Study Design:

Objective: The study evaluated the pharmacological effects of rabacfosadine (not commercial formulation) on hemodynamic and electrocardiographic (ECG) parameters following a 30-minute IV infusion (dose volume of 2 mL/kg) in the Beagle dog via telemetry.

Study Animals: There were four male Beagle dogs implanted with telemetry devices. Dogs were 7 to 8 months old and weighed 11.5 to 12.4 kg at the start of treatment. All dogs were healthy based on physical examination, hematology, and chemistry.

Experimental Design: The four dogs received vehicle (5% Dextrose for Injection) (dose 1), 0.25 (dose 2), and 2.5 mg/kg (dose 3) of rabacfosadine with a minimum washout period of 3 days and 7 days between dose 1 and 2, and dose 2 and 3, respectively. The study was conducted in accordance with GLP regulations.

Drug Administration: The test/control articles were administered by a 30-minute intravenous infusion. The dose volume was 2 mL/kg. 5% Dextrose for Injection, USP was used for the infusion.

Measurements and Observations: Mortality and signs of ill health or reaction to treatment was evaluated twice daily. Body weights were measured prior to randomization and on the day prior to dosing. Clinical observations were performed once pretreatment and following each dosing occasion. The following were evaluated: clinical signs, arterial blood pressures (mean arterial pressure, systolic blood pressure, diastolic blood pressure and pulse pressure), heart rate, quantitative ECG intervals, and a qualitative evaluation of the ECG waveforms were performed twice prior to each dose (at least 30 minutes apart) and at approximately 15, 30, 45 minutes and 1, 1.5, 2, 4, 6, 8, 10, 12, 24 hours post-dose for each dose level. On all dosing occasions the blood pressure and ECG waveforms were recorded continuously, and all derived parameters logged as 5-minute means from approximately 2 hours prior to each dose to approximately 24 hours post-dose.

Statistical Methods: The results were presented using summary statistics (treatment mean and standard error of the mean (SEM)) for each variable. Either baseline-adjusted values or absolute values were computed for each time interval.

Results:

Mortality
All dogs survived to scheduled euthanasia.

Cardiovascular Parameters
There were no treatment-related effects on arterial blood pressure (mean, systolic, diastolic), heart rate, or ECG parameters.

Conclusion: At single intravenous doses of 0.25 and 2.5 mg/kg, rabacfosadine had no effect on the cardiovascular system.

E. Pilot Studies

Study Summary
In two multi-institutional field studies (PC-193-2001 and PC-193-2017) used to support dosage characterization for the treatment of lymphoma (see **Dosage Characterization**), 22 dogs with untreated, relapsed, or refractory lymphoma received rabacfosadine (not commercial formulation) as an intravenous infusion at doses of 0.66 to 1.2 mg/kg body weight administered once every three weeks for one to six doses.

Adverse Reactions
All dogs experienced at least one adverse reaction, however not all adverse reactions were seen in each dog. Adverse reactions associated with rabacfosadine when administered once every three weeks included:

General: lethargy, dehydration, fever

Gastrointestinal: hyporexia/anorexia, vomiting, diarrhea

Renal: increased creatinine, increased blood urea nitrogen, proteinuria, pyuria, bacteruria

Hepatic: elevated liver enzymes, elevated bilirubin

Cardiorespiratory: pulmonary fibrosis, aspiration pneumonia, tachypnea, dyspnea, tachycardia

Metabolic: weight loss

Hematologic: neutropenia, thrombocytopenia, anemia, hypertriglyceridemia, hypoproteinemia, hypoglobulinemia, hypoalbuminemia, increased creatine kinase, hypokalemia, hypophosphatemia

Ocular: injected sclera

Dermatologic: otitis externa, alopecia, dermatitis, pyoderma, ulcerations, excoriations

Most adverse reactions were VCOG-CTCAE Grade 1-2. Grade 3 reactions included hyporexia/anorexia, weight loss, vomiting, diarrhea, otitis externa, dehydration, aspiration pneumonia, neutropenia, thrombocytopenia, anemia, bilirubinemia, and hypertriglyceridemia. Grade 4 reactions included tachypnea, and neutropenia. Grade 5 reactions included dyspnea (secondary to pulmonary fibrosis).

Additional adverse reactions seen in dogs administered rabacfosadine at more frequent dosing schedules include:

- Dermatopathy including pruritic and erythemic lesions on the dorsum and exudation, crusting, erythema, and necrosis with epidermal sloughing on the ears, face, ventral neck and/or forelimbs.
- Glucosuria
- Type II pneumocyte hyperplasia

Conclusion
Rabacfosadine had a narrow margin of safety in the pilot effectiveness studies. Adverse reactions were common but manageable by monitoring patients regularly. With the exception of pulmonary fibrosis, adverse reactions resolved either spontaneously, with supportive treatment, dose modification, or dose delay.

Overall Conclusion on Safety:

Rabacfosadine has a narrow margin of safety. The above studies support the safe use of TANOVEA® administered at a dose of 1.0 mg/kg as a 30-minute intravenous infusion, once every three weeks, for up to five doses for the treatment of lymphoma in dogs. Stepwise dose reductions to 0.8 mg/kg and 0.66 mg/kg or dose delays may be used to manage adverse reactions.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food-producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

Based on excretion data and an extrapolation of the data for exposure, a 5-day human user safety precautionary period is recommended following treatment with TANOVEA®. The excretion data from study AD-193-2001 entitled "Distribution and Excretion of [^{14}C]-GS-9219 Following Intravenous Administration to Dogs" demonstrated that the majority of the radioactivity following a radiolabeled dose (76.5%) of [^{14}C]-GS-9219 was excreted in feces (41.4%), urine (31.5%), and cage rinse (3.83%) within first 48 hours post-administration. An additional 3.2% of radioactivity was excreted by 120 hours post-administration. The radioactivity recovery was not complete. The collected urine and feces samples contained little parent drug and no active metabolite.

Assuming the excretion of the remaining radioactive dose is approximately 2% during each 24-hour period after the first 48 hours following dose administration, the extrapolated 90% recovery time for the full dose administered would be approximately 10 days.

TANOVEA® is not orally bioavailable. The accidental exposure to the full amount excreted over a 24hour period would be a worst-case scenario. Exposure to the full amount excreted would require that the exposed person would come into contact with all excretions for a full 24-hour period and that these excretions would be introduced systemically. Therefore, the potential risk for human exposure to the drug after the initial 48 hours following treatment is minimal and a 5-day precautionary period is recommended.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to TANOVEA®:

On the package insert:

USER SAFETY WARNINGS:

NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. Do not store near food or with medications intended for use in humans. Do not eat, drink, or smoke while handling the product.

CHILDREN SHOULD NOT COME INTO CONTACT WITH TANOVEA. Children should not come into contact with feces, urine, vomit, and saliva of treated dogs for **5 days** after each treatment.

Drug Handling and Administration
Pregnant women, women who may become pregnant, and nursing women should not handle, prepare, or administer TANOVEA. Rabacfosadine is cytotoxic and may cause birth defects and affect female and male fertility.

Use standard measures for the safe handling of all chemotherapeutic drugs. Refer to Occupational Safety and Health Administration (OSHA) for appropriate guidelines, recommendations, and regulations for handling antineoplastic agents.

Do not come into direct contact with TANOVEA. Wear chemotherapy-resistant gloves, goggles, and protective clothing when handling or administering TANOVEA. After removing and disposal of gloves, wash hands immediately and thoroughly with soap and water.

Accidental Exposure to TANOVEA
In the case of accidental self-injection:
- Remove glove.
- Let the wound bleed a few drops of blood.
- Rinse the wound thoroughly with tap water.
- Seek medical advice immediately and show the package insert, label, or client information sheet to the physician.

In case of accidental skin contact:
- Wash the affected area immediately and thoroughly with soap and water.

In the case of accidental eye exposure:
- Remove contact lenses.
- Rinse the eyes with large amounts of tap water (use eyewash station if present) for 10 minutes while holding back the eyelid.
- Seek medical advice immediately and show the package insert, label, or client information sheet to the physician.

In the case of accidental ingestion:
- Seek medical advice immediately and show the package insert, label, or client information sheet to the physician.

Handling of Excreta and Soiled Items
Do not come into direct contact with the treated dog's feces, urine, vomit, and saliva for **5 days** after each treatment with TANOVEA.

When cleaning up feces, urine, vomit, and saliva, wear disposable chemotherapy-resistant gloves to collect the contaminated substances with disposable absorptive material (such as paper towels) and place them into a plastic bag. Carefully remove the gloves and place them in the bag, and tie or fasten it securely before general disposal. Wash hands immediately and thoroughly with soap and water afterwards. Do not wash any items soiled with feces, urine, vomit, and saliva from the dog for **5 days** after each treatment with other laundry.

Wear disposable chemotherapy-resistant gloves when handling the dog's toys, food bowl, and water bowl. Wash food and water bowls separately from other items for **5 days** after each treatment.

Accidental Exposure to Excreta

In the case of direct skin contact with feces, urine, vomit, and saliva of dogs for **5 days** after each treatment:
- Wash the affected skin immediately and thoroughly with soap and water.

On the Client Information Sheet:

How do I safely clean up after my dog after treatment with TANOVEA?
Because TANOVEA is a chemotherapeutic drug used to treat cancer, extra care must be taken when handling and cleaning up after your dog for **5 days** after each treatment with TANOVEA.
- Avoid direct contact (particularly for children, pregnant women, women who may become pregnant and nursing women) with feces, urine, vomit, and saliva for **5 days** after each treatment.
- When cleaning up feces, urine, vomit, or saliva you should wear disposable chemotherapy-resistant gloves and collect the contaminated material with disposable absorptive material (such as paper towels) and place them into a plastic bag.
- Carefully remove the gloves and place them in the bag and tie or fasten it securely for general household disposal. Wash your hands thoroughly afterwards with soap and water. Check with your veterinarian to ensure you have the appropriate gloves.
- Any skin that comes in contact with feces, urine, vomit, and saliva should be washed immediately and thoroughly with soap and water.

- Do not wash any items soiled with feces, urine, vomit, and saliva from your dog for **5 days** after each treatment with other laundry.
- Take precautions in handling the dog's toys, food bowl, and water bowl. Wash food and water bowls separately from other items for **5 days** after each treatment.
- Do not let your dog urinate or defecate in areas where people may come in direct contact with the urine or stool.

What should I do in case of accidental contact with feces, urine, vomit, or saliva?
In the case of direct skin contact with feces, urine, vomit, and saliva of dogs for **5 days** after each treatment:

- Wash the affected skin immediately and thoroughly with soap and water.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that TANOVEA®, when used according to the label, is safe and effective for the treatment of lymphoma in dogs.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose lymphoma, and to monitor safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

TANOVEA®, as approved in our approval letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the FD&C Act because this is the first time we are approving this active ingredient in a new animal drug application submitted under section 512(b)(1) of the FD&C Act. Any applicable exclusive marketing rights and exclusivity for this drug run concurrently.

C. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.

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