Date of Approval: July 18, 2014

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-434

SIMBADOL

Buprenorphine injection

Injectable

Cats

For the control of postoperative pain associated with surgical procedures in cats.

Sponsored by:

Abbott Laboratories

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I. GENERAL INFORMATION

A. File Number

NADA 141-434

B. Sponsor

Abbott Laboratories
North Chicago, IL 60064

Drug Labeler Code: 000044

C. Proprietary Name

SIMBADOL

D. Established Name

Buprenorphine injection

E. Pharmacological Category

Partial opioid agonist

F. Dosage Form

Injectable

G. Amount of Active Ingredient

1.8 mg base equivalent/mL

H. How Supplied

SIMBADOL is supplied in a carton containing one 10 mL amber glass vial. Each multidose vial contains 1.8 mg/mL of buprenorphine.

I. Dispensing Status

Rx

J. Dosage Regimen

0.24 mg/kg, once daily for up to 3 days. Administer the first dose approximately 1 hour prior to surgery.

K. Route of Administration

Subcutaneous injection

L. Species/Class

Cats

M. Indication

For the control of postoperative pain associated with surgical procedures in cats.

II. EFFECTIVENESS

A. Dosage Characterization

A dose of 0.24 mg/kg (0.11 mg/lb) administered subcutaneously (SQ) once daily for up to three treatments was selected based on the results of thermal threshold and pilot post-operative pain studies in cats.

Thermal threshold testing was performed in 12 healthy, adult cats of both sexes in single dose pharmacokinetic/pharmacodynamic studies. An injectable buprenorphine formulation containing preservatives was administered at 0.06, 0.12, and 0.24 mg/kg SQ. A 5% dextrose injection was administered as the control. The objective of the studies was to determine duration of analgesic effect of different doses of buprenorphine injectable solution in the cat. Blood samples were collected and clinical endpoints (starting and reaction temperature of skin to thermal stimulation, reaction to thermal stimulation, attitude, general condition, mydriasis, and euphoria) were assessed at multiple time points prior to dosing and up to 72 hours following dosing. These subcutaneous doses of injectable buprenorphine solution were determined to have an onset of analgesia of approximately one hour and a duration of effect of 24-28 hours. Differences in buprenorphine plasma concentrations did not appear to correlate to differences in the thermal threshold data.

Forty-six cats were enrolled in three pilot studies to evaluate effectiveness of buprenorphine injectable solution at doses of 0.02 (3 cats) mg/kg administered SQ every eight hours for nine treatments; or 0.06 (9 cats), 0.12 (9 cats), or 0.24 (25 cats) mg/kg administered SQ once daily for three treatments for the control of post-operative pain. The 46 cats were enrolled in six groups representing the above dosage variations and underwent one surgical procedure, either ovariohysterectomy (OHE) or onychectomy. Each cat received pre-anesthetic agents and the assigned dose of buprenorphine injectable solution approximately one hour prior to surgery, and then received buprenorphine for two days post-operatively according to the assigned dose and treatment regimen. Cats were evaluated post-operatively at predetermined times to assess the overall response to treatment. Effectiveness variables included observation from a distance, presence of sedation or excitation, behavior during social interaction, pain on palpation (incision site), overall pain, and need for rescue therapy. The need for rescue was based on clinical judgment in consideration of the other effectiveness variables. In the first study, OHEs were performed to assess doses in soft tissue surgery. In that study, zero out of nine (0/9) cats required rescue therapy in the 0.24 mg/kg group compared to 2/3 cats in the 0.02 mg/kg group, 2/9 cats in the 0.06 mg/kg group, and 4/9 cats in the 0.12 mg/kg group. In the second study, an onychectomy was performed on 10 cats to assess effectiveness of the 0.24 mg/kg dose in an orthopedic surgery. Three out of ten cats required rescue therapy. In the third study, an OHE was performed to evaluate post-operative pain in six cats using the pilot formulation (2.4 mg/mL) dosed at 0.24 mg/kg.

One out of six cats required rescue therapy. Based on the three surgical studies, a dose of 0.24 mg/kg administered once daily for three days was selected for controlling pain associated with both soft tissue and orthopedic surgical procedures.

B. Substantial Evidence

The effectiveness of SIMBADOL for the control of postoperative pain associated with surgery was evaluated in cats presented for ovariohysterectomy, various soft tissue surgeries, and onychectomy. Two field studies were conducted simultaneously at 19 veterinary clinics throughout various geographic regions within the U.S. Results of the studies demonstrate that SIMBADOL is safe and effective when administered at a dose of 0.24 mg/kg of body weight once daily for 3 days.

1. Field Study Evaluation of Buprenorphine for Control of Postoperative Pain Associated with Soft Tissue Surgery in Cats

   a. Title
   Evaluation of Buprenorphine for Control of Postoperative Pain Associated with Soft Tissue Surgery in Cats.

   b. Study Number
   08-30-MC-D-CT-BP

   c. Investigators and Study Locations

Dr. Clifton G. Barnett Seminole, FL	Dr. Lorin R. Bilhorn Hickory, NC
Dr. Paul Brandt Austin, TX	Dr. Nicole Eaton Lewis Center, OH
Dr. James Gaynor Colorado Springs, CO	Dr. Samuel J. Geller Quakertown, PA
Dr. David Griffin New Port Richey, FL	Dr. Edwin A. Howe Ocala, FL
Dr. Lorin D. Lawrence Rock Hill, SC	Dr. Sara Mark Littleton, CO
Dr. David H. Menard Ocala, FL	Dr. Julie C. Michels Burnsville, MN
Dr. Edward B. Peurifoy Kannapolis, NC	Dr. Stephen T. Pittenger Houston, TX
Dr. Howard T. Robinson Fort Collins, CO	Dr. Roger L. Sifferman Springfield, MO
Dr. Amy L. Smith Franklin, IN	Dr. Erik G. Tysklind Indianapolis, IN
Dr. Ann Valenti Inver Grove Heights, MN	Dr. Julie White Seminole, FL

d. Study Design

This was a multicenter, prospective, randomized, double-masked, placebo controlled field study.

(1) Objective

The study was designed to determine the clinical effectiveness and safety of buprenorphine (SIMBADOL), at a dose of 0.24 mg/kg, for the control of postoperative pain associated with soft tissue surgery over a 72 hour period.

(2) Study Animals

A total of 221 client-owned cats were enrolled and received at least one treatment in this study. Cats ranged in age from 0.33 to 16 years and in weight from 1.2 to 9.1 kg. Overall, more intact females were enrolled (45.2%) compared with spayed females (22.6%), neutered males (27.6%), and intact males (4.5%).

The largest percentage of cats underwent ovariohysterectomy (40.7%). Other surgeries performed in 5% or more cats were lumpectomy (18.1%), perineal urethrostomy (7.7%), cystotomy (6.8%), and enucleation (5.9%).

(3) Treatment Groups

Cats were randomly assigned into two treatment groups in a 1:1 ratio of buprenorphine or saline control (placebo).

Table 1. Treatment Groups

Treatment Group	Dose (mg/kg)	Dose Volume (mL/kg)	Number of Cats
SIMBADOL (buprenorphine)	0.24	0.13	109 (37 male, 72 female)
Placebo (saline control)	0	0.13	112 (34 male, 78 female)

(4) Drug Administration and Duration

The dosage was 0.13 mL/kg of SIMBADOL or placebo administered as a subcutaneous (SQ) injection. No treatment site preparation was required before injection. SIMBADOL or placebo was administered every 24 hours for 3 days as follows: at 1 hour before anesthetic induction, and at 24 and 48 hours after the initial drug administration.

(5) Randomization and Masking

Randomization occurred at a 1 to 1 ratio at the site in blocks of 2. The person administering the buprenorphine or placebo was masked to the treatment. The person(s) performing the sedation, excitation, and pain assessments and clinical observations was also masked to the treatment received.

(6) Inclusion criteria
- Was undergoing a soft tissue surgical procedure, excluding castration and caesarian section
- Major lumpectomies were allowed on a case-by-case basis
- Had an American Society of Anesthesiologists (ASA) Classification of Physical Status score I, II, III, or IV requiring analgesia for soft tissue surgery. The inclusion of a cat with an ASA Classification of Physical Status score of IV was at the discretion of the investigator.
- Was 4 months of age or older
- Was in good health
- Had not received any investigational drug or had been enrolled in an investigational drug study within 7 days before admission to the study

(7) Exclusion criteria
- Had a medical condition (ASA Classification of Physical Status V) that precludes the use of anesthesia protocol procedures
- Was undergoing castration, caesarian section, or dental surgery
- Was undergoing orthopedic procedures, including joint surgeries
- Had diabetes mellitus
- Had uncontrolled hyperthyroid disease

(8) Anesthesia

Anesthetic protocols were similar across all clinics. If possible, the cat was fasted at least 12 hours before surgery if an elective surgery was performed. All cats were administered acepromazine +/- glycopyrrolate as a premedication at the same time as the study drug. Intravenous (IV) fluids were optional according to the site's standard of care. Cats were induced with propofol and maintenance anesthesia was inhaled isoflurane or sevoflurane.

(9) Surgery

The soft tissue surgeries were performed according to each site's standard surgical procedures. Surgical incisions could have been midline or flank and closed with a combination of suture, staples, or tissue glue, as appropriate.

(10) Measurements and Observations

Before administration of any medications or performing surgery, a physical examination; hematology, serum chemistry, and urinalysis; and baseline sedation, excitation, and pain assessments were performed.

Safety was monitored during the study through clinical observations, collection of adverse events, electrocardiograms (during surgery only), and vital sign measurements (heart rate, respiratory rate, body temperature, and blood pressure).

(a) Pain Assessments

Cats were assessed for pain by a trained assessor, using a descriptive, interactive pain assessment system at the following time points: prior to treatment; within 30 minutes after anesthetic recovery; at 1, 2, 3, 4, 8, and 12 hours after anesthetic recovery;

prior to the second dose (24 hours after the first dose), and 4 and 8 hours after the second dose; prior to the third dose (48 hours after the first dose), and 4 and 8 hours after the third dose; and 24 hours after the third dose.

The interactive pain assessment involved the following observations:

1. Behavior from a distance
   Cats were quietly observed in their cage from approximately 10 feet away for general appearance, behavior, body tension, and the level of comfort. The investigator assessed the cat as one of the following:

   a. Comfortable (content and quiet when unattended; interested in or curious about surroundings; minimal body tension).
   b. Mild signs of discomfort or withdrawal (appears slightly unsettled; less interested in surroundings but will look at what is going on; mild body tension).
   c. Moderate signs of discomfort or withdrawal (quiet; loss of brightness in eyes; lays curled up or sits tucked up; hair coat may appear rough; may intensively groom an area that is painful or irritating; moderate body tension).
   d. Severe signs of discomfort or withdrawal (prostrate; potentially unresponsive or unaware of surroundings; constantly yowling, growling, or hissing when unattended; may be rigid to avoid painful movement; severe body tension).

2. Behavior during social interaction
   The assessor observed the behavior of the cat upon approach of the cage. The cage door was then opened and the cat was stroked. The resulting behavior, including body tension, was observed. The investigator assessed the cat as one of the following:

   a. Comfortable (interested in or curious about surroundings; interested in the assessor as they approach the cage; seeks attention when cage is approached or door opened; minimal body tension when stroked).
   b. Mild signs of discomfort or withdrawal (less interested in surroundings, but will look around to see what is going on; may or may not be interested in assessor as they approach cage; allows touching of non-operated area without hesitation; mild body tension when stroked).
   c. Moderate signs of discomfort or withdrawal (decreased responsiveness, seeks solitude; tolerates attention, may even perk up when stroked, as long as painful area is avoided; moderate body tension when stroked).

d. Severe signs of discomfort or withdrawal (potentially unresponsive or unaware of surroundings, difficult to distract from pain; receptive to care [even mean or wild cats will be more tolerant of contact]; growls or hisses when stroked; severe body tension when stroked).

3. Response to palpation
The surgical site was gently palpated. The response to palpation of both the nonsurgical and surgical areas was observed. The investigator assessed the cat as one of the following:

a. Normal response (not bothered by palpation of surgery site or to palpation elsewhere).
b. Mild response (may or may not react to palpation of surgery site).
c. Moderate response (responds aggressively or tries to escape if painful area is palpated or approached).
d. Severe response (growls or hisses at non-painful palpation [may be experiencing allodynia, wind-up, or fear pain may be made worse]; reacts aggressively to palpation, adamantly pulls away to avoid contact; may be rigid to avoid painful movement or not respond to palpation).

4. Overall pain assessment
After assessments were made for behavior from a distance, sedation and excitation, behavior during social interaction, and response to palpation assessments, the assessor made an overall assessment of the pain control at that time point. The investigator assessed the cat as one of the following:

a. Well controlled.
b. Moderately controlled.
c. Poorly controlled.

(b) Sedation and Excitation
Prior to pain assessments, each cat was assessed for the presence or absence of sedation and excitation. If sedation or excitation was present, the cat was considered to be too sedated to adequately assess analgesic effects, and the pain assessment at that time was not conducted.

(c) Rescue
After all sedation, excitation, and pain assessments were performed, the assessor used clinical judgment to determine if the cat needed rescue.

(11) Statistical Methods

(a) Analysis Sets

The effectiveness analysis included all cats that were randomly assigned to and received at least one dose of the study drug and met the following criteria:

- Not from a low enrollment site (less than two evaluable cases per treatment group)
- Did not have sedation/excitation at more than two scheduled time points
- Did not take interfering concomitant medication, and
- Was not withdrawn by owner for reasons not related to treatment.

The safety analysis included all cats that received at least one dose of the study drug.

(b) Effectiveness

The primary effectiveness endpoint was the treatment success rate, defined as a cat that made it through the 72-hour time period without needing rescue analgesia. A cat that was removed from the study due to an adverse event was considered a treatment failure for the purpose of statistical analysis of effectiveness.

The primary analysis for effectiveness was a comparison of the treatment success rates in each group using a generalized linear mixed model (GLMM) via the GLIMMIX procedure in SAS. The statistical model included treatment as a fixed effect and site and the site-by-treatment interaction as random effects. The model employed the binomial distribution with logit link. The experimental unit was the individual cat. The difference between treatment groups was evaluated at a 2-sided α =0.05. Estimates of percentage success in each group were generated by back-transforming the least squares (LS) mean estimates from the analysis.

Frequencies and counts of secondary effectiveness categorical outcomes (sedation, excitation, and pain assessment) were summarized by treatment group by time points.

e. Results

(1) Effectiveness

Effectiveness was evaluated in 195 cats (93 cats in the SIMBADOL group and 102 cats in the placebo group) and field safety was evaluated in 221 cats (109 cats in the SIMBADOL group and 112 cats in the placebo group). The results from this study demonstrated a significant difference (P=0.005) between the SIMBADOL and placebo groups based on the primary effectiveness endpoint of the treatment success rate. The success rate in the SIMBADOL group (71.0%) was significantly different from and greater than the placebo group (44.1%). See Table 2 below.

Table 2. Results of the Effectiveness Analysis

Treatment Group	N	# of Successes (%)	# of Failures (%)	P-value[1]
SIMBADOL	93	66 (71.0%)	27 (29.0%)	0.005
Placebo	102	45 (44.1%)	57 (55.9%)	0.005

1. P-value for the difference between investigational veterinary product and control product, based on a generalized linear mixed model that includes treatment as a fixed effect and site and the site-by-treatment interaction as random effects. The model employed the binomial distribution with logit link.

Of the 27 cats rescued in the SIMBADOL group in the effectiveness population, 24 were rescued in the first 4 hours of recovery. Of the 56 cats rescued in the placebo group in the effectiveness population, 51 were rescued in the first 4 hours of recovery. In addition, one cat from the placebo group was removed due to an adverse reaction and was considered a treatment failure.

(2) Sedation and Excitation

The greatest proportion of cats showed sedation at 30 minutes after recovery with slightly higher sedation seen in the SIMBADOL group (36 of 105 [34.3%] and 30 of 100 [30.0%] in the SIMBADOL and placebo groups, respectively). At 1 hour after recovery, 20 of 101 (19.8%) and 15 of 91 (16.5%) cats in the SIMBADOL and placebo groups, respectively showed sedation. At 2, 3, and 4 hours after recovery slightly more cats in the SIMBADOL group (9.4%, 6.5%, and 4.4%, respectively) showed sedation compared with the placebo group (3.9%, 4.3%, and 1.5%, respectively). Only 1 cat, in the placebo group, showed sedation at the 4 hours after dose 3 timepoint. No other cats showed sedation beyond the 4 hours after recovery timepoint.

The greatest proportion of cats showed excitation at 30 minutes after recovery, and a higher proportion of cats in the SIMBADOL group showed excitation (9 of 105 cats [8.6%]) compared with the placebo group (3 of 99 cats [3.0%]). No cat in the placebo group showed excitation after 30 minutes after recovery. In the SIMBADOL group, 1 cat showed excitation at 1 hour after recovery and 1 cat showed excitation at 4 hours after recovery.

(3) Safety

(a) During Surgery
Mean heart rates and mean body temperatures were similar between the SIMBADOL and placebo groups throughout surgery.

Twenty-six cats in the SIMBADOL group (highest heart rate of 260 bpm) and 15 cats in the placebo group (highest heart rate of 252 bpm) experienced 1 or more episodes of tachycardia during surgery.

Thirteen cats in the SIMBADOL group had respiratory rates less than 10 breaths per minute during surgery compared to 5 cats in the control group.

Thirty-nine cats in the SIMBADOL group were reported with hypotension; the lowest blood pressure reported was 28 mmHg. Thirty-three cats in the control group were reported with hypotension; the lowest blood pressure reported was 28 mmHg. Seven cats in the SIMBADOL group were reported with hypertension; the highest blood pressure reported was 140 mmHg. Nine cats in the control group were reported with hypertension; the highest blood pressure reported was 182 mmHg.

There was no evidence of cardioactive or cardiovascular adverse reactions due to SIMBADOL.

(b) Post-Surgery
Post-surgery, mean heart rates in the SIMBADOL group were higher than the placebo group at all time points up to 24 hours after the 3rd dose. In the cats reported with tachycardia, heart rates ranged from 200 to 280 beats per minute in the SIMBADOL group compared to 200 to 243 beats per minute in the placebo group.

Post-surgery, mean respiratory rates and mean blood pressures were similar between groups. In the cats reported with hypertension, blood pressures ranged from 160 to 200 mmHg in the SIMBADOL group compared to 160 to 180 mmHg in the placebo group. In the cats reported with hypotension, blood pressures ranged from 42 to 90 mmHg in both groups.

Post-surgery, temperatures were higher in the SIMBADOL group compared to the placebo group at all time points. In the cats reported with hyperthermia, temperatures ranged from 103.0 to 105.7°F in the SIMBADOL group compared to 103.0 to 105.0°F in the placebo group.

(c) Pain on Injection
The number of cats with pain on injection was higher in the SIMBADOL group (12 cats, 18 incidences) compared to the placebo group (4 cats, 5 incidences).

(4) Adverse Reactions
The most commonly reported adverse reactions were hypotension, tachycardia, hypothermia, hyperthermia, hypertension, and anorexia. The adverse reactions and number of cats experiencing each adverse reaction are summarized in Table 3 below.

Table 3. Adverse Reactions in the Soft Tissue Field Study

Adverse Reaction[1]	SIMBADOL (N=109) During Surgery[2]	SIMBADOL (N=109) After Surgery	Placebo (N=112) During Surgery[2]	Placebo (N=112) After Surgery
Hypotension[3]	39 (35.8%)	29 (26.6%)	33 (29.5%)	24 (21.4%)
Tachycardia[4]	26 (23.9%)	29 (26.6%)	15 (13.4%)	20 (17.9%)
Hypothermia (≤98.0°F)	30 (27.5%)	1 (0.9%)	31 (27.7%)	0
Hyperthermia (≥103.0°F)	0	40 (36.7%)	0	19 (17.0%)
Hypertension[5]	7 (6.4%)	20 (18.3%)	9 (8.0%)	6 (5.4%)
Anorexia	0	18 (16.5%)	0	15 (13.4%)
Hyperactivity	0	10 (9.2%)	0	4 (3.6%)
Reduced Oxygen Saturation of Hemoglobin (pulse oximetry ≤90%)	5 (4.6%)	1 (0.9%)	8 (7.1%)	0
Bradycardia (≤90 beats/min)	2 (1.8%)	1 (0.9%)	1 (0.9%)	0
Tachypnea (≥72 breaths/min)	0	3 (2.8%)	0	2 (1.8%)
Arrhythmia	1 (0.9%)	0	1 (0.9%)	0
Hyperesthesia	0	1 (0.9%)	0	0
Blindness	0	1 (0.9%)	0	0
Apnea/Death	0	1 (0.9%)	0	0

1. Cats may have experienced more than one type or occurrence of an adverse reaction. Cats experiencing the same reaction both during and after surgery are presented in both time periods.
2. During surgery is the time from the administration of the anesthetic induction agent until discontinuation of the gas anesthetic.
3. Hypotension is defined as a mean blood pressure of ≤60 mmHg during surgery and ≤90 mmHg after surgery.
4. Tachycardia is defined as a heart rate ≥180 beats per minute during surgery and ≥200 beats per minute after surgery.
5. Hypertension is defined as a mean blood pressure of ≥120 mmHg during surgery and ≥160 mmHg after surgery.

(a) Deaths
A 15-year-old neutered male cat in the SIMBADOL group had a prolonged recovery following an exploratory laparotomy followed by apnea and death. A necropsy was performed and a specific cause of death was not found, although other remarkable findings included metastatic neoplasia affecting multiple systems.

An 11-year-old spayed female cat in the SIMBADOL group in was euthanized after completion of the study due to pulmonary complications. The complications were considered likely related to the severity of the cat's injuries prior to surgery. The cat was attacked by a raccoon and required scapular amputation.

(b) Blindness
A 1.5-year-old female in the SIMBADOL group undergoing ovariohysterectomy was reported with blindness approximately 9.75 hours after surgery. During surgery, blood pressure intervention (increasing intravenous fluid rate) was performed because a blood pressure reading could not be captured by the instrument. She improved neurologically over the next 30 days, and although not blind, seemed to have some visual and minor balance deficits. The event of blindness was considered possibly related to study drug by the investigator.

f. Conclusions
Administration of SIMBADOL at a dose of 0.24 mg/kg (0.11 mg/lb) once daily for three days, with the first dose administered approximately one hour prior to surgery, was effective and considered safe for the control of postoperative pain associated with soft tissue surgery in cats.

2. Field Study Evaluation of Buprenorphine for Control of Postoperative Pain Associated with Orthopedic Surgery (Onychectomy) in Cats

a. Title
Evaluation of Buprenorphine for Control of Postoperative Pain Associated with Orthopedic Surgery (Onychectomy) in Cats.

b. Study Number
08-31-MC-D-CT-BP

c. Investigators and Study Locations

Dr. Clifton G. Barnett Seminole, FL	Dr. Lorin R. Bilhorn Hickory, NC
Dr. Paul Brandt Austin, TX	Dr. Nicole Eaton Lewis Center, OH
Dr. James Gaynor Colorado Springs, CO	Dr. Samuel J. Geller Quakertown, PA
Dr. David Griffin New Port Richey, FL	Dr. Edwin A. Howe Ocala, FL
Dr. Lorin D. Lawrence Rock Hill, SC	Dr. Sara Mark Littleton, CO
Dr. David H. Menard Ocala, FL	Dr. Julie C. Michels Burnsville, MN
Dr. Edward B. Peurifoy Kannapolis, NC	Dr. Stephen T. Pittenger Houston, TX
Dr. Howard T. Robinson Fort Collins, CO	Dr. Roger L. Sifferman Springfield, MO
Dr. Amy L. Smith Franklin, IN	Dr. Erik G. Tysklind Indianapolis, IN
Dr. Ann Valenti Inver Grove Heights, MN	Dr. Julie White Seminole, FL

d. Study Design

This was a multicenter, prospective, randomized, double-masked, placebo controlled field study.

(1) Objective

The study was designed to determine the clinical effectiveness and safety of buprenorphine (SIMBADOL) at a dose of 0.24 mg/kg, for the control of postoperative pain associated with orthopedic (onychectomy) surgery over a 72 hour period.

(2) Study Animals

A total of 229 client-owned cats were enrolled and received at least one treatment in this study. Cats ranged in age from 0.33 to 10 years and in weight from 1.5 to 9.0 kg. Overall, less intact males were enrolled (15.7%) compared with intact females (24.5%), neutered males (31.9%), and spayed females (27.9%)

The majority of cats underwent onychectomy alone (62.0%), while the remaining cats underwent either onychectomy and ovariohysterectomy (22.7%) or onychectomy and orchiectomy (15.3%).

(3) Treatment Groups

Cats were randomly assigned into two treatment groups in a 1:1 ratio of SIMBADOL or saline control (placebo).

Table 4. Treatment Groups

Treatment Group	Dose (mg/kg)	Dose Volume (mL/kg)	Number of Cats
SIMBADOL (buprenorphine)	0.24	0.13	115 (54 males, 61 females)
Placebo (saline control)	0	0.13	114 (55 males, 59 females)

(4) Drug Administration
The dosage was 0.13 mL/kg of SIMBADOL or placebo administered as a subcutaneous (SQ) injection. No treatment site preparation was required before injection. SIMBADOL or placebo was administered every 24 hours for 3 days as follows: at 1 hour before anesthetic induction, and at 24 and 48 hours after the initial drug administration.

(5) Randomization and Masking
Randomization occurred at a 1 to 1 ratio at the site in blocks of 2. The person administering SIMBADOL or placebo was masked to the treatment. The person(s) performing the sedation, excitation, and pain assessments and clinical observations was also masked to the treatment received.

(6) Inclusion criteria
- Was undergoing an orthopedic surgery (onychectomy) ± neuter (ovariohysterectomy or orchiectomy)
- Had an ASA Classification of Physical Status score I, II, III, or IV requiring analgesia for soft tissue surgery. The inclusion of a cat with an ASA Classification of Physical Status score of IV was at the discretion of the investigator.
- Was 4 months of age or older
- Was in good health
- Had not received any investigational drug or had been enrolled in an investigational drug study within 7 days before admission to the study

(7) Exclusion criteria
- Had a medical condition (ASA Classification of Physical Status V) that precludes the use of anesthesia protocol procedures
- Was pregnant
- Was undergoing orthopedic procedures other than onychectomy, including joint surgeries
- Had diabetes mellitus
- Had uncontrolled hyperthyroid disease

(8) Anesthesia
Anesthetic protocols were similar across all clinics. All cats were administered acepromazine +/- glycopyrrolate as a premedication at the same time as the study drug. Intravenous (IV) fluids were optional according to the site's standard of care. Cats were induced with propofol and maintenance anesthesia was inhaled isoflurane or sevoflurane.

(9) Surgery
The onychectomy was performed according to each site's standard surgical procedures using a sterilized nail trimmer, scalpel, or laser. If the cat was also undergoing an ovariohysterectomy or orchiectomy, the procedure was performed according to each site's standard surgical practices.

(10) Measurements and Observations
Before administration of any medications or performing surgery, a physical examination; hematology, serum chemistry, and urinalysis; and baseline sedation, excitation, and pain assessments were performed.

Safety was monitored during the study through clinical observations, collection and monitoring of adverse events, electrocardiograms (during surgery only), and vital sign measurements (heart rate, respiratory rate, body temperature, and blood pressure).

(a) Pain Assessments
Cats were assessed for pain by a trained assessor, using a descriptive, interactive pain assessment system at the following time points: prior to treatment; within 30 minutes after anesthetic recovery; at 1, 2, 3, 4, 8, and 12 hours after anesthetic recovery; prior to the second dose (24 hours after the first dose), and 4 and 8 hours after the second dose; prior to the third dose (48 hours after the first dose), and 4 and 8 hours after the third dose; and 24 hours after the third dose.

The interactive pain assessment involved the following observations

1. Behavior from a distance
Cats were quietly observed in their cage from approximately 10 feet away for general appearance, behavior, and body tension, and the level of comfort. The investigator assessed the cat as one of the following:

a. Comfortable (content and quiet when unattended; interested in or curious about surroundings; minimal body tension).

b. Mild signs of discomfort or withdrawal (appears slightly unsettled; less interested in surroundings but will look at what is going on; mild body tension).
c. Moderate signs of discomfort or withdrawal (quiet; loss of brightness in eyes; lays curled up or sits tucked up; hair coat may appear rough; may intensively groom an area that is painful or irritating; moderate body tension).
d. Severe signs of discomfort or withdrawal (prostrate; potentially unresponsive or unaware of surroundings; constantly yowling, growling, or hissing when unattended; may be rigid to avoid painful movement; severe body tension).

2. Behavior during social interaction
The assessor observed the behavior of the cat upon approach of the cage. The cage door was then opened and the cat was stroked. The resulting behavior, including body tension, was observed. The investigator assessed the cat as one of the following:

a. Comfortable (interested in or curious about surroundings; interested in the assessor as they approach the cage; seeks attention when cage is approached or door opened; minimal body tension when stroked).
b. Mild signs of discomfort or withdrawal (less interested in surroundings, but will look around to see what is going on; may or may not be interested in assessor as they approach cage; allows touching of non-operated area without hesitation; mild body tension when stroked).
c. Moderate signs of discomfort or withdrawal (decreased responsiveness, seeks solitude; tolerates attention, may even perk up when stroked, as long as painful area is avoided; moderate body tension when stroked).
d. Severe signs of discomfort or withdrawal (potentially unresponsive or unaware of surroundings, difficult to distract from pain; receptive to care [even mean or wild cats will be more tolerant of contact]; growls or hisses when stroked; severe body tension when stroked).

3. Response to palpation
The surgical site was gently palpated. The response to palpation of both the nonsurgical and surgical areas was observed. The investigator assessed the cat as one of the following:

a. Normal response (not bothered by palpation of surgery site or to palpation elsewhere).
b. Mild response (may or may not react to palpation of surgery site).
c. Moderate response (responds aggressively or tries to escape if painful area is palpated or approached).

d. Severe response (growls or hisses at non-painful palpation [may be experiencing allodynia, wind-up, or fear pain may be made worse]; reacts aggressively to palpation, adamantly pulls away to avoid contact; may be rigid to avoid painful movement or not respond to palpation).

4. Overall pain assessment
After assessments were made for behavior from a distance, sedation and excitation, behavior during social interaction, and response to palpation assessments, the assessor made an overall assessment of the pain control at that time point. The investigator assessed the cat as one of the following:

a. Well controlled.
b. Moderately controlled.
c. Poorly controlled.

(b) Sedation and Excitation
Prior to pain assessments, each cat was assessed for the presence or absence of sedation and excitation. If sedation or excitation was present, the cat was considered to be too sedated to adequately assess analgesic effects, and the pain assessment at that time was not conducted.

(c) Rescue
After all sedation, excitation, and pain assessments were performed, the assessor used clinical judgment to determine if the cat needed rescue.

(11) Statistical Methods:

(a) Analysis Sets
The effectiveness analysis included all cats that were randomly assigned to and received at least one dose of the study drug and met the following criteria:

- Not from a low enrollment site (less than two evaluable cases per treatment group),
- Did not have sedation/excitation at more than two scheduled time points,
- Did not take interfering concomitant medication, and
- Was not withdrawn by owner for reasons not related to treatment.

The safety analysis included all cats that received at least one dose of the study drug.

(b) Effectiveness

The primary effectiveness endpoint was the treatment success rate, defined as a cat that made it through the 72-hour time period without needing rescue analgesia. A cat that was removed from the study due to an adverse event was considered a treatment failure for the purpose of statistical analysis of effectiveness. The primary analysis for effectiveness was a comparison of the treatment success rates in each group using a generalized linear mixed model (GLMM) via the GLIMMIX procedure in SAS. The statistical model included treatment as a fixed effect and site and the site-by-treatment interaction as random effects. The model employed the binomial distribution with logit link. The experimental unit was the individual cat. The difference between treatment groups was evaluated at a 2-sided α=0.05. Estimates of percentage success in each group were generated by back-transforming the least squares (LS) mean estimates from the analysis.

Frequencies and counts of secondary effectiveness categorical outcomes (sedation, excitation, and pain assessment) were summarized by treatment group by time points.

e. Results:

(1) Effectiveness

Effectiveness was evaluated in 207 cats (105 cats in the SIMBADOL group and 102 cats in the placebo group) and field safety was evaluated in 229 cats (115 cats in the SIMBADOL group and 114 cats in the placebo group). The results from this study demonstrated a significant difference (P=0.002) between SIMBADOL and placebo based on the primary effectiveness endpoint of the treatment success rate. The success rate in the SIMBADOL group (61.0%) was significantly different from and greater than the placebo group (32.4%). See Table 5 below.

Table 5. Results of the Effectiveness Analysis

Treatment Group	N	# of Successes (%)	# of Failures (%)	P-value[1]
SIMBADOL	105	64 (61.0%)	41 (39.0%)	0.0002
Placebo	102	33 (32.4%)	69 (67.6%)	0.0002

1. P-value for the difference between investigational veterinary product and control product, based on a generalized linear mixed model that includes treatment as a fixed effect and site and the site-by-treatment interaction as random effects. The model employed the binomial distribution with logit link.

Of the 40 cats rescued in the SIMBADOL group in the effectiveness population, 30 were rescued in the first 4 hours of recovery. Of the 68 cats rescued in the placebo group in the effectiveness population, 62 were rescued in the first 4 hours of recovery. In addition, one cat from each treatment group was removed due to an adverse reaction and they were considered treatment failures.

(2) Sedation and Excitation

The greatest proportion of cats showed sedation at 30 minutes after recovery with no difference between the treatment groups (31 of 111 [27.9%] and 29 of 103 [28.2%] in the SIMBADOL and placebo groups, respectively). At 1 hour after recovery, 25 of 104 (14.4%) and 11 of 88 (12.5%) of cats in the SIMBADOL and placebo groups, respectively showed sedation. At 2, 3, and 4 hours after recovery more cats in the placebo group (11.8%, 9.0%, and 5.1%, respectively) showed sedation compared with the SIMBADOL group (5.2%, 5.4%, and 2.2%, respectively). No cat showed sedation after 4 hours after recovery.

The greatest proportion of cats showed excitation at 30 minutes after recovery, and a higher proportion of cats in the SIMBADOL group showed excitation (16 of 111 cats [14.4%]) compared with the placebo group (7 of 103 cats [6.8%]). No cat in the placebo group showed excitation after 30 minutes after recovery. In the SIMBADOL group, at 1 hour into recovery, 9 of 104 (8.7%) cats in the SIMBADOL group showed excitation. One to 3 cats (1.3% to 8.7%) in the SIMBADOL group at every time point from 2 hours through 8 hours after recovery showed excitation; no cat in the SIMBADOL group showed excitation after 8 hours after recovery.

(3) Safety

(a) During Surgery

Mean heart rates and mean body temperatures were similar between the SIMBADOL and placebo groups throughout surgery.

Twenty-nine cats in the SIMBADOL group (high heart rate of 232 bpm) and 15 cats in the placebo group (high heart rate of 278 bpm) experienced 1 or more episodes of tachycardia during surgery.

Five cats in the SIMBADOL group had respiratory rates less than 10 breaths per minute during surgery compared to 2 cats in the placebo group.

Twenty-nine cats in the SIMBADOL group were reported with hypotension; the lowest blood pressure reported was 29 mmHg. Twenty-seven cats in the control group were reported with hypotension; the lowest blood pressure reported was 35 mmHg. Three cats in the SIMBADOL group were reported with hypertension; the highest blood pressure reported was 130 mmHg. Eight cats in the control group were reported with hypertension; the highest blood pressure reported was 165 mmHg.

There was no evidence of cardioactive or cardiovascular adverse reactions due to SIMBADOL.

(b) Post-Surgery

Post-surgery, mean heart rates were similar between groups on Day 1. Mean heart rates in the SIMBADOL group were higher than the placebo group at all time points on Day 2 and Day 3. In the cats reported with tachycardia, heart rates ranged from 200 to 280 beats per minute in the SIMBADOL group compared to 200 to 278 beats per minute in the placebo group.

Post-surgery, mean respiratory rates and mean blood pressures were similar between groups.

In the cats reported with hypertension, blood pressures ranged from 160 to 210 mmHg in the SIMBADOL group compared to 160 to 190 mmHg in the placebo group. In the cats reported with hypotension, blood pressures ranged from 40 to 90 mmHg in the SIMBADOL group compared to 43 to 90 mmHg in the placebo group.

Post-surgery, mean respiratory rates were lower in the SIMBADOL group compared to the placebo group at every time point post-surgery until 4 hours after the 3rd dose. The lowest reported respiratory rate was 16 breaths per minutes in the SIMBADOL group compared to 12 in the placebo group.

Post-surgery, temperatures were higher in the SIMBADOL group compared to the placebo group at all time points. In the cats reported with hyperthermia, temperatures ranged from 103.0 to 105.1°F in the SIMBADOL group compared to 103.0 to 104.0°F in the placebo group.

(c) Pain on Injection

The number of cats with pain on injection was higher in the SIMBADOL group (8 cats, 10 incidences) compared to the placebo group (4 cats, 5 incidences).

(4) Adverse Reactions

The most commonly reported adverse reactions were tachycardia, hypotension, hyperthermia, anorexia, hypertension, hypothermia, and hyperactivity. The adverse reactions and number of cats experiencing each adverse reaction are summarized in Table 6 below.

Table 6. Adverse Reactions in the Orthopedic Field Study

Adverse Reaction[1]	SIMBADOL (N = 15) During Surgery[2]	SIMBADOL (N = 115) After Surgery	Placebo (N = 114) During Surgery[2]	Placebo (N = 114) After Surgery
Tachycardia[3]	29 (25.2%)	44 (38.3%)	15 (13.2%)	24 (21.1%)
Hypotension[4]	29 (25.2%)	22 (19.1%)	27 (23.7%)	16 (14.0%)
Hyperthermia (≥103.0°F)	1 (0.9%)	51 (44.3%)	0	14 (12.3%)
Anorexia	0	22 (19.1%)	0	20 (17.5%)
Hypertension[5]	3 (2.6%)	20 (17.4%)	8 (7.0%)	12 (10.5%)
Hypothermia (≤98.0°F)	8 (7.0%)	0	16 (14.0%)	0
Hyperactivity	0	16 (13.9%)	0	7 (6.1%)
Bradycardia (≤90 beats/min)	3 (2.6%)	0	3 (2.6%)	1 (0.9%)
Tachypnea (≥72 breaths/min)	0	2 (1.8%)	1 (0.9%)	4 (3.5%)
Reduced Oxygen Saturation of Hemoglobin (pulse oximetry ≤90%)	3 (2.6%)	0	3 (2.6%)	0
Arrhythmia	0	1 (0.9%)	1 (0.9%)	0
Blindness	0	1 (0.9%)	0	1 (0.9%)
Ataxia	0	1 (0.9%)	0	0
Apnea/Death	1 (0.9%)	0	0	0

1. Cats may have experienced more than one type or occurrence of an adverse reaction. Cats experiencing the same reaction both during and after surgery are presented in both time periods.
2. During surgery is the time from the administration of the anesthetic induction agent until discontinuation of the gas anesthetic.
3. Tachycardia is defined as a heart rate ≥180 beats per minute during surgery and ≥200 beats per minute after surgery.
4. Hypotension is defined as a mean blood pressure of ≤60 mmHg during surgery and ≤90 mmHg after surgery.
5. Hypertension is defined as a mean blood pressure of ≥120 mmHg during surgery and ≥160 mmHg after surgery.

(a) Deaths

A 5-month-old intact male cat in the SIMBADOL group experienced apnea, followed by cardiopulmonary arrest, and death during endotracheal intubation. A necropsy was performed and a specific cause of death not found.

(b) Blindness

A 7-month-old female in the SIMBADOL group undergoing ovariohysterectomy and onychectomy was reported with blindness 12 hours after surgery. Throughout the surgical procedure the cat had low mean blood pressure readings therefore the fluid rate was increased and anesthetic gas was decreased. The cat had a slow and difficult recovery and after recovery the cat was disoriented. The cat appeared visual 7 days after surgery and was functioning normally. The event of blindness was considered possibly related to study drug by the investigator.

A 1-year-old male in the placebo group undergoing onychectomy and orchiectomy was reported with blindness after conclusion of the study. During surgery, 1 adverse event of mild bradycardia was reported. At 84 days after surgery, the owner reported that the cat was able to see, as determined by his ability to chase and track. The cause of the blindness was considered unknown.

f. Conclusions

Administration of SIMBADOL at a dose of 0.24 mg/kg (0.11 mg/lb) once daily for up to three days, with the first dose administered approximately one hour prior to surgery, was effective and considered safe for the control of postoperative pain associated with orthopedic surgery in cats.

III. TARGET ANIMAL SAFETY:

A. Target Animal Safety (TAS) Study of Buprenorphine in Cats.

1. Study Number
   09-06-WR-D-TS-BP

2. Type of Study
   Laboratory safety study

3. Study Dates
   May 26, 2011, to June 7, 2011

4. Study Director
   Matthew Haas, B.A
   WIL Research Laboratories, LLC
   Ashland, OH

5. General Design

   a. Purpose
   The objective of this laboratory study was to evaluate the safety of buprenorphine when administered to young cats subcutaneously once daily for 9 consecutive days at 0 (saline), 1X (0.24 mg/kg), 3X (0.72 mg/kg), or 5X (1.2 mg/kg) the proposed dose.

b. Test Animals
Sixteen male and 16 female healthy domestic shorthair (DSH) cats ≤ 4 months old were selected and randomly allocated to four treatment groups (4/sex/group). Cats weighed between 1.52 kg and 2.54 kg on the first day of dosing.

c. Test Article
Injectable solution, 1.8 mg/mL buprenorphine final market formulation

d. Control
0.9% Saline, injection

e. Dosages Used

Table 7. Treatment Groups for TAS Study

Treatment Group	Dose	Number and Sex of Animals
1	0X, saline (0.13 mL/kg)	4M, 4F
2	1X, 0.24 mg/kg (0.13 mL/kg)	4M, 4F
3	3X, 0.72 mg/kg (0.40 mL/kg)	4M, 4F
4	5X, 1.20 mg/kg (0.67 mL/kg)	4M, 4F

f. Dosing
The cats were dosed by subcutaneous injection in the dorsoscapular area once daily for 9 days. During acclimation, the dose site was shaved and marked for the 9 separate injections. The cats were shaved again on study day 7.

g. Variables Measured
Each injection site was visually inspected and palpated at least 1, 4, and 12 hours following dose administration on study day 0. Beginning on day 1, injection sites were examined twice daily. Behavioral response to injection was assessed throughout the study as shown below in Table 8. Detailed physical examinations were performed by a veterinarian pre-study and on study days 0, 2, 4, 6, and 8, at least 1 hour following dose administration. Clinical observations (including heart rate and respiratory rate) were conducted on all cats once daily at least 6 hours after the detailed physical examinations. On study days 1, 3, 5, and 7, the clinical observations were conducted at least 1 hour following dose administration and the second observation was conducted at least 6 hours following the first observation. Radiotelemetry data was collected for electrocardiographic, blood pressure, and temperature evaluation pre-study and twice daily during study days 0-8 (first measurement obtained at least 1 hour after dose administration and the second measurement obtained at least 6 hours after the first

measurement) and on study day 9 prior to necropsy. Body weight, food consumption, and water consumption were recorded pre-study and daily throughout the study. Monitoring for urination and defecation was conducted pre-study and once daily throughout the study. Hematology, coagulation, serum chemistry, and urinalysis were evaluated pre-study and on study days 0, 4, and 8 at approximately 1 hour following dose administration. Bleeding time was determined pre-study and on study day 8. A complete set of tissues was collected for gross pathology and histopathology evaluations. Selected organs were weighed. Histopathology evaluation included each injection site on all cats.

Table 8. Assessment of Behavioral Response

Assessment	Behavior
Normal Response	Cat was aware of injection but did not protest
Moderate Response	Cat had minor vocalization or wincing and quick resolution
Severe Response	Cat tried to bite or scratch or had marked vocalization or persistent attention to the injection site

h. Statistical Analysis

(1) Physiologic signs (heart rate, blood pressure, ECG, respiration rate, and body temperature), body weight, food and water consumption, and clinical pathology:
Continuous variables measured at multiple times during the study were analyzed by a repeated-measures analysis of covariance, with treatment, gender, day, treatment-by-gender, gender-by-day, treatment-by-day, and treatment-by-gender-by-day terms in the model as fixed effects, and animal identified as the subject in the repeated.

(2) Organ Weights
ANOVA was used to evaluate a model containing treatment, gender, and gender-by-treatment interaction as fixed effects.

(3) Bleeding time
ANCOVA was used to evaluate a model containing treatment, gender, and gender-by-treatment interaction as fixed effects.

(4) Categorical outcomes
For categorical variables, outcomes deemed clinically relevant, and where sufficient data were available (at least 4 unexpected findings within a dose group on any given study day), Fisher's exact test was used to evaluate the treatment groups versus control in a pair-wise fashion. Gender was ignored in this analysis.

6. Results
All cats survived to termination of the study.

a. Clinical Observations and Detailed Physical Examinations
The incidence of difficulty in handling, abnormal oral dryness, dilated pupils, and decreased pupillary light reflex was higher in the buprenorphine-treated groups.

One 1X cat on study day 4 and one 3X cat on study day 2 were reported with hyperactivity, difficulty in handling, slight disorientation, agitation, dilated pupils which were responsive to light, and respiratory sinus arrhythmia. One 1X cat (one episode) on study day 6 and one 3X cat (3 episodes) on study days 0, 6, and 8 were reported with nystagmus. One 1X cat on study day 2 and one 3X cat on study day 0 (first treatment day) were reported with decreased blink response.

b. Behavioral Responses to Injection
The incidence of moderate responses and severe responses to injection was higher in the buprenorphine-treated groups and occurred on all dosing days. All responses were normal except as described below:

In the 0X group, 3 cats exhibited a moderate response at 1 timepoint each and 1 cat exhibited 4 moderate and 2 severe responses.

In the 1X group, 7 cats exhibited a moderate response at 1 to 4 timepoints each with 1 of these cats also experiencing 1 severe response.

In the 3X group, 7 cats exhibited a moderate response at 1 to 4 timepoints each with 2 of these cats also experiencing 1 severe response. One cat had no moderate responses but had a severe response at 1 timepoint.

In the 5X group, 6 cats exhibited a moderate response at 1 to 5 timepoints each with 3 of these cats also experiencing 1 severe response. One cat had no moderate responses but had a severe response at 1 timepoint.

c. Injection Site Inspections
There were no differences in the injection site inspections between any groups, including the 0X group.

d. Monitoring for Urination and Defecation
The incidence of urination was lower in the buprenorphine-treated groups. During the study period, no urination was reported 15 times in the 0X group, 28 times in the 1X group, 17 times in the 3X group, and 33 times in the 5X group.

e. Body Weights and Food and Water Consumption
Three cats in the 5X group lost body weight (79 g or less) from study day 0 to study day 9 which correlated with decreased food consumption. All other cats gained weight from study day 0 to study day 9.

On study days 0 and 8, food consumption in the 1X and 3X groups was significantly higher than that of the 0X group ($P<0.10$). During the study,

food consumption was lower in the 5X group compared to the 0X group, but was only statistically significant on study days 4 and 5 (P<0.10).

f. Electrocardiographic (ECG), Blood Pressure, and Temperature
There were no clinically significant changes or abnormalities in ECGs and blood pressure during the study.

The incidence of temperatures ≥103°F was higher in the buprenorphine-treated groups compared to the control group. On study day 0, at 1 and 6 hours post-dosing, body temperature was elevated in the 1X, 3X, and 5X groups compared to the 0X group. Temperatures were significantly higher (P<0.10) in the 1X and 3X groups as compared to the 0X group during the study. Mean body temperatures did not exceed 102°F and the highest temperature observed in the buprenorphine-treated group was 103.8°F in a 5X cat.

g. Respiratory and Heart Rate
There were no clinically significant changes in respiratory and heart rates during the study.

h. Clinical Pathology
There were no clinically significant changes in hematology, coagulation, bleeding times, or urinalysis during the study. Creatine kinase (CK) values were higher (P<0.10) in the 3X and 5X groups compared to the 0X group and correlated with subcutaneous inflammation. Table 9 below shows the mean CK values by treatment group.

Table 9. Mean CK Value (U/L) by Treatment Group (male and female)

Group	N	Day -1	Day 0[1]	Day 4	Day 8
1	8	344.9	377.6	362.3	242.0
2	8	273.8	353.3	374.4	267.8
3	8	556.3	851.8	441.9	439.6
4	8	308.3	723.6	399.3	710.3

[1.] Approximately 1 hour after the first dose

i. Gross Pathology and Histopathological Findings
Histologic lesions included minimal to moderate subacute inflammation at the injection sites and correlated with the administration of buprenorphine versus the control. No severe inflammation was noted. Table 10 below shows the incidence of injection site inflammation by treatment group. Table 11 below shows the incidence of histologic findings.

Table 10. Incidence of Injection Site Inflammation by Treatment Group[1]

Treatment Group	Group 1 (0 mg/kg)	Group 2 (0.24 mg/kg)	Group 3 (0.72 mg/kg)	Group 4 (1.20 mg/kg)
Inflammation, Subacute	5	64	67	67
Minimal	5	42	43	23
Mild	0	22	24	43
Moderate	0	0	0	1

[1.] Seventy-two injection sites evaluated per group (nine injection sites per cat; eight cats per group)

Table 11. Incidence of Histologic Findings

Histologic Finding	Incidence
Mineralization at an injection site	One 1X cat and one 3X cat
Chronic inflammation in the heart (valve or myocardium)	Two 5X cats
Subacute liver inflammation	One control cat, two 1X cats, three 3X cats, and three 5X cats
Lymphoid hyperplasia of the mediastinal lymph node	One 1X cat
Acute inflammation was seen in the mediastinal lymph node	One 3X cat
Lymphoid hyperplasia of the Peyer's Patches	Two 1X cats and one 5X cat
Lymphoid hyperplasia, lymphocytic infiltrate, or subacute inflammation of the stomach	Four 1X cats, four 3X cats, and three 5X cats
Subacute inflammation or lymphocytic infiltrate of the thyroid glands	Two 1X cats, one 3X cat, and four 5X cats

7. Conclusions

This study demonstrated an adequate safety margin to support the use of 0.24 mg/kg buprenorphine for the control of postoperative pain associated with surgical procedures in cats. Test article related findings included difficulty in handling, lower incidence of urination, abnormal oral dryness, dilated pupils, decreased pupillary light reflex, and increased body temperatures. One 1X and one 3X cat experienced hyperactivity, slight disorientation, and agitation. Subcutaneous injection of buprenorphine caused an increased incidence in moderate to severe responses to the injection in cats compared to cats receiving the control and caused inflammatory histological changes at the injection site that was associated with increased serum CK values in the 3X and 5X groups.

B. Arterial Blood Pressure Study in Cats Administered Buprenorphine.

1. Study Number
   10-41-SN-D-GLP-BP

2. Type of Study
   Laboratory safety study

3. Study Dates
   May 10, 2011, to May 13, 2011

4. Study Director
   Timothy Madsen, B.A.
   Sinclair Research Center LLC.
   Auxvasse, MO

5. General Design

   a. Purpose
      The objective of this laboratory study was to determine the effect of 0.24 mg/kg of buprenorphine administered subcutaneously on arterial blood pressure during a surgical procedure in cats.

   b. Test Animals
      Eight male and 8 female healthy adult DSH cats > 8 months of age were selected and randomly allocated to two treatment groups (4/sex/group). Cats weighed between 2.75 kg and 5.64 kg.

   c. Test Article
      Injectable solution, 1.8 mg/mL buprenorphine final market formulation

   d. Control
      Injectable solution, 5 mg/mL meloxicam

   e. Route of Administration
      Subcutaneous injection

   f. Dosages Used

      Table 12. Control and Treatment Groups for Blood Pressure Study

Treatment Group	Dose	Number and Sex of Animals
1	0.24 mg/kg buprenorphine	4M, 4F
2	0.3 mg/kg meloxicam	4M, 4F

   g. Study Design
      Cats in both groups were dosed once approximately 1 hour prior to anesthetic induction. All cats received 0.05 mg/kg acepromazine subcutaneously, 1 hour prior to anesthetic induction. Premedication was administered separately from the test or control article. Anesthesia was

induced with intravenous propofol and maintained, following intubation, with 0.5 to 5% isoflurane delivered via 100% oxygen. Cats received intravenous lactated ringers solution at a rate of 5 mL/kg/hour beginning prior to induction and discontinued at the end of surgery. An exploratory laparotomy was performed for 1 hour. Following surgery, cats were monitored for 8 hours.

h. Variables Measured
Prior to surgery, animals were weighed and physical examination, hematology, serum chemistry, and urinalysis were conducted. Heart rate, respiration rate, body temperature, and blood pressure were measured prior to surgery, every 5 minutes during surgery, within 30 minutes of extubation, and 2, 4, and 8 hours after extubation. Indirect blood pressures were measured pre- and post-surgery and arterial blood pressures were measured during surgery. During surgery, ECGs, end tidal CO_2, and oxygen hemoglobin saturation were also recorded. Clinical observations were performed post-surgery within 30 minutes of extubation, and at 2, 4, and 8 hours post-extubation.

i. Statistical Analysis
Physiologic variables (heart rate, blood pressure [direct and indirect], respiration rate, and body temperature): These outcomes were analyzed by a repeated measures analysis of covariance, with treatment, gender, time, treatment-by-gender, gender-by-time, treatment-by-time, and treatment-by-gender-by-time terms in the model as fixed effects, and cat identified as the subject in the repeated statement.

The repeated measures analysis was performed separately for direct and indirect blood pressure observations. The same pretreatment value (from indirect method) was used as a covariate for each cat.

6. Results
All cats survived to termination of the study.

a. Blood Pressure
There were no significant differences (P>0.10) in direct mean blood pressure between the buprenorphine and meloxicam groups during surgery. There were no significant differences (P>0.10) in indirect mean blood pressure between buprenorphine and meloxicam groups during the post-operative period. See Table 13 below.

Table 13. Mean Blood Pressure (mmHg) Least Squared Means (Standard Error of the Mean)

Timepoint	Buprenorphine Group	Meloxicam Group
During Surgery (direct)	78.02 (3.15)	82.48 (3.15)
Post-Operative (indirect)	119.44 (4.14)	129.03 (4.14)

b. Heart Rate
During surgery, significantly higher heart rates (P<0.10) were observed in the buprenorphine group compared to the meloxicam group. In the post-operative period, significantly higher heart rates (P<0.10) were observed in the buprenorphine group compared to the meloxicam group for combined genders at 2, 4, and 8 hours and for females overall. See Table 14 below.

Table 14. Heart Rate (Beats/Minute) Least Squared Means (Standard Error of the Mean)

Timepoint	Buprenorphine Group	Meloxicam Group
During Surgery	166.29 (6.41)	138.96 (6.41)[1]
<30 minutes post-extubation	170.16 (12.66)	164.44 (12.67)
2 hours post-extubation	197.66 (12.66)	131.56 (13.41)[1]
4 hours post-extubation	188.16 (12.66)	128.06 (12.67)[1]
8 hours post-extubation	197.53 (12.66)	132.06(12.67)[1]

[1.] P<0.10 vs. Buprenorphine Group

Six cats in the buprenorphine group experienced heart rates ≥180 beats/minute during surgery compared to two cats in the meloxicam group. Six cats in the buprenorphine group experienced heart rates ≥200 beats/minute post-extubation compared to three cats in the meloxicam group.

c. Respiration Rate
During surgery, significantly lower respiration rates (P<0.10) were observed in the buprenorphine group compared to the meloxicam group. Apnea was not reported in any cat. See Table 15 below.

Table 15. Respiration Rate (Breaths/Minute) Least Squared Means (Standard Error of the Mean)

Timepoint	Buprenorphine Group	Meloxicam Group
During Surgery	20.39 (2.19)	26.49 (2.19)[1]

[1.] P<0.10 vs. Buprenorphine Group

d. Body Temperature
During surgery, body temperatures were similar between groups. In the post-operative period, significantly higher body temperatures (P<0.10) were observed in the buprenorphine group compared to the meloxicam group. See Table 16 below.

Table 16. Body Temperature (°F) Least Squared Means (Standard Error of the Mean)

Timepoint	Buprenorphine Group	Meloxicam Group
During Surgery	97.17 (0.70)	97.48 (0.70)
Post-Operative	101.28 (0.39)	100.14 (0.39)[1]

[1.] P<0.10 vs. Buprenorphine Group

Post-operatively, four cats in the buprenorphine group had temperatures of ≥103.0°F compared to none in the meloxicam group. The highest temperature reported was 104.3°F.

Either during surgery or post-operatively, temperatures ≤98.0°F were seen in all cats, with a low temperature of 92.3°F in one buprenorphine cat and 95.0°F in one meloxicam cat.

e. ECG
ECGs were qualitatively normal in all cats.

f. Oxygen Hemoglobin Saturation
One cat in the buprenorphine group had hemoglobin saturation less than 90% (88%) at one timepoint.

g. Clinical Observations
All animals were clinically healthy for the duration of the study. Post-operatively, four buprenorphine and three meloxicam cats were reported as "irritable" or "growling".

7. Conclusions
The results of this study support the safe use of buprenorphine injection in cats undergoing anesthesia and surgery. A pre-operative subcutaneous dose of 0.24 mg/kg of buprenorphine had no effect on intraoperative arterial blood pressure in adult cats undergoing exploratory laparotomy. Test article related findings included increased heart rates, decreased respiration rates, and increased body temperatures compared to the control group.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in cats, which are non-food animals. 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:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to SIMBADOL, and regarding abuse potential:

CIII	HUMAN SAFETY WARNING

Abuse Potential
SIMBADOL contains buprenorphine (1.8 mg/mL), an opioid agonist and Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. Buprenorphine has certain opioid properties that in humans may lead to dependence of the morphine type. Abuse of buprenorphine may lead to physical dependence or psychological dependence. The risk of abuse by humans should be considered when storing, administering, and disposing of SIMBADOL. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (suicidal depression).

Life-Threatening Respiratory Depression
Respiratory depression, including fatal cases, may occur with abuse of SIMBADOL.

Additive CNS Depressant Effects
SIMBADOL has additive CNS depressant effects when used with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Accidental Exposure
Because of the potential for adverse reactions associated with accidental injection, SIMBADOL should only be administered by veterinarians or veterinary technicians who are trained in the handling of potent opioids.

See Human Safety for detailed information.

WARNINGS:

Human Safety:
Not for use in humans. Keep out of reach of children.

Adult Human User Safety while handling SIMBADOL in the hospital:

Mucous membrane or eye contact during administration:
Direct contact of SIMBADOL with the eyes, oral or other mucous membranes could result in absorption of buprenorphine and the potential for adverse reactions. If accidental eye, oral or other mucous membrane contact is made during administration, flush the area with water and contact a physician.

Skin contact during administration:
If human skin is accidentally exposed to SIMBADOL, wash the exposed areas with soap and water and contact a physician. Accidental exposure could result in absorption of buprenorphine and the potential for adverse reactions.

Drug Abuse, Addiction, and Diversion of Opioids:

Controlled Substance:
SIMBADOL contains buprenorphine, a mu opioid partial agonist and Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. SIMBADOL can be abused and is subject to misuse, abuse, addiction, and criminal diversion. SIMBADOL should be handled appropriately to minimize the risk of diversion, including restriction of access, the use of accounting procedures, and proper disposal methods, as appropriate to the clinical setting and as required by law.

Abuse:
Abuse of SIMBADOL poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances including other opioids and benzodiazepines. Buprenorphine has been diverted for non-medical use into illicit channels of distribution. All people handling opioids require careful monitoring for signs of abuse. Drug abuse is the intentional non-therapeutic use of a prescription drug for its rewarding psychological or physiological effects. Abuse of opioids can occur in the absence of true addiction.

Storage and Discard:
SIMBADOL is a Class III opioid. Store in a locked, substantially constructed cabinet according to DEA and local controlled substance guidelines. Discard broached vials after 28 days. Any unused or expired vials must be destroyed by a DEA registered reverse distributor; for further information, contact your local DEA field office or call Abbott Animal Health at 1-888-299-7416.

Information for physician:
SIMBADOL injectable solution is a mu opioid partial agonist (1.8 mg buprenorphine/mL). In the case of an emergency, provide the physician with the package insert. Naloxone may not be effective in reversing respiratory depression produced by buprenorphine. The onset of naloxone effect may be delayed by 30 minutes or more. Doxapram hydrochloride has also been used as a respiratory stimulant.

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 and 21 CFR part 514. The data demonstrate that SIMBADOL, when used according to the label, is safe and effective for the control of postoperative pain associated with surgical procedures in cats.

A. Marketing Status:

The drug is restricted to use by or on the order of a licensed veterinarian because the product is a highly concentrated, schedule III opioid with a potential for human abuse. Furthermore, professional expertise is needed to diagnose pain and provide guidance in the control of postoperative pain. The veterinarian also monitors patients for possible adverse effects of the drug.

B. Exclusivity:

SIMBADOL, 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 Federal Food, Drug, and Cosmetic Act because this is the first time we are approving this active ingredient in a new animal drug.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.