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ORIGINAL ARTICLE

Multicentered masked placebo-controlled phase 3 clinical study of an extended duration transdermal buprenorphine solution for post-operative pain in cats

Terrence P. Clark | **Deborah D. Linton** | **Kevin J. Freise** | **Ting-Li Lin**

Nexcyon Pharmaceuticals, Inc., Madison, Wisconsin, USA

Correspondence
Terrence P. Clark, Nexcyon Pharmaceuticals, Inc., PO Box 259158, Madison, WI 53725, USA.
Email: clarktp@nexcyon.com

Present address
Deborah D. Linton, DL Veterinary Consulting, LLC, Florida, USA

Kevin J. Freise, AbbVie Inc., North Chicago, Illinois, USA

Ting-Li Lin, Briostat, LLC, Madison, Wisconsin, USA

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Abstract

A prospective, double masked, placebo-controlled, multicentered phase 3 clinical study was conducted to evaluate the safety and effectiveness of transdermal buprenorphine solution (TBS) for the control of post-operative pain in cats. A total of 228 cats from 12 US investigational sites met the enrollment criteria of which 107 placebo- and 112 TBS-treated cats were included into the per protocol efficacy analysis. The dose of TBS was 8 mg (0.4 ml) to cats 1.2 to 3 kilograms and 20 mg (1 ml) to cats >3 to 7.5 kilograms applied topically to the dorsal unclipped cervical skin 1–2 h prior to the undergoing elective surgical reproductive sterilization in conjunction with forelimb onychectomy. Interactive pain assessments and physiological variables were quantified through 96 h following recovery from anesthesia, and rescue analgesia was administered any time that pain control was scored inadequate. Cats requiring rescue analgesia or experiencing an adverse event suspected to be treatment related were considered treatment failures. Sixty-five and 23 cats were considered treatment failures in the placebo and TBS groups, respectively, with most occurring on the day of surgery. The treatment success rates were 0.40 (95% confidence interval [CI]: [0.28–0.53]) and 0.81 (95% CI: [0.70–0.89]) in the placebo and TBS groups, respectively, and the difference was significant ($p < .05$). Adverse events occurred at a similar frequency and were not clinically meaningful in either treatment group. The post-operative body temperatures over the duration of the study were on average 0.35 (95% CI: [0.20–0.50]) °C higher than baseline in TBS-treated cats and were not clinically meaningful, an observation typical of opioids in cats. These results serve as substantial evidence that TBS is safe and effective for the control of orthopedic and soft tissue post-operative pain in cats when a single topical dose is applied 1–2 h prior to surgery.

KEYWORDS
analgesia, buprenorphine, cat, clinical study, pain, transdermal

1 | INTRODUCTION

Opioids are regarded as an important part of multi-modal post-operative analgesia (Pascoe, 2000). In human medicine, the use of opioids during and after surgery for most soft tissue and orthopedic surgeries is considered the standard of care and is included in procedure specific treatment algorithms (Neugebauer et al., 2007). In veterinary medicine, there are limited opioid options to treat moderate-to-severe pain in conscious cats beyond the immediate postoperative period because of inherent limitations of most

opioids, including poor oral bioavailability and rapid elimination (Pascoe, 2000).

In cats, opioid use is primarily limited to single or repeated parenteral injections in the immediate pre- and post-operative period (Bortolami & Love, 2015). Buprenorphine is effective for the control of post-operative pain in cats. There are two approved injectable formulations. The first, a low concentration buprenorphine solution (0.3 mg/ml) was approved for use as IM and IV injection (0.01–0.02 mg/kg) in 1995 in the United Kingdom ('Vetergesic; Ceva Animal Health', 1995), and later, several other regulatory jurisdictions. It has not been approved in the United States (US) to date. Parenteral injections of this formulation in cats have a short duration-of-action, possibly as short as 4 h, particularly in the absence of non-steroidal anti-inflammatory drugs (NSAID) (Steagall et al., 2009) and per the label, repeated injections are limited to a single injection 1 to 2 h following the first. The second, a high concentration injectable solution (1.8 mg/ml) ('Simbadol; Zoetis', 2014) was developed to extend the analgesic duration-of-action compared with the low concentration solution. A single subcutaneous dose (0.24 mg/kg) has an approximate 24-h analgesic duration (Doodnaught et al., 2017; Doodnaught et al., 2018; Sramek et al., 2015), whereas this extends the single injection duration-of-action compared with the low concentration formulation, prolonging analgesia beyond the day of surgery requires repeated daily injections. However, repeated injections are limited to a total of three per the label and the product cannot be dispensed to owners for home injection, limiting the practicality of extending the duration beyond in-hospital use.

Attempts to extend the duration-of-action of buprenorphine through investigational formulations (Catbagan et al., 2011; Enomoto et al., 2016; Johnson et al., 2017) or extralabel use (Doodnaught et al., 2017; Doodnaught et al., 2018; Murrell et al., 2007) have not resulted in newly approved products. Buprenorphine administered by the oral transmucosal (OTM) route is approximately 30% bioavailable (Hedges et al., 2014). It obviates the need for parenteral injections but requires frequent administrations for use over extended periods (Catbagan et al., 2011; Robertson et al., 2005). To make available an approved, extended duration formulation of buprenorphine for the control of post-operative pain in cats, a novel transdermal buprenorphine solution (TBS) has been developed (Zorbium™, Elanco US Inc., Greenfield, IN, USA, NADA 141-547).

A prior study demonstrated that following a single topical application of TBS, buprenorphine forms a depot in the skin resulting in prolonged systemic release with half-lives of 78.3–91.2 h, typical of flip-flop pharmacokinetics (PK) (Freise, Reinemeyer, Warren, et al., 2022) whereby the downward slope on a buprenorphine plasma concentration-time plot is the result of drug absorption rather than drug elimination mechanisms (Toutain & Bousquet-Melou, 2004). Two candidate doses were examined in a phase 2 clinical study (Clark et al., 2022a). In the phase 2 study, a TBS dose that was administered 1–2 h prior to surgery was differentiated from a lower TBS dose that was administered 2–4 h prior to surgery. Although the doses were differentiated, a larger phase 3 study of the selected dose is necessary in order to demonstrate substantial evidence of effectiveness. Therefore, the present study is a prospective, randomized, masked, placebo-controlled, multicentered, phase 3 clinical study of TBS in client-owned cats undergoing surgery that was designed and powered on the results of the phase 2 study, such that the results can be confirmed with the selected dosage a priori. The objective is to confirm the effectiveness and safety of TBS for the control of soft tissue and orthopedic pain following a single TBS dose administered 1–2 h prior to elective surgical sterilization in conjunction with onychectomy. This study was conducted in accordance with the principles of Good Clinical Practice, VICH GL9 CVM Guidance 85, (EMEA/CVMP/VICH/595/98) as described in the protocol and all amendments (FDA-CVM, 2001).

2 | MATERIALS AND METHODS

2.1 | Investigational and control veterinary products

The investigational veterinary product was TBS prepared as previously described. It is a clear ethanol solution that contains 20 mg/ml buprenorphine (calculated as free base) and 5% w/v (50 mg/ml) padimate O. It was packaged in single use, unit dose applicator tubes that deliver 8 mg (0.4 ml) or 20 mg (1 ml) of buprenorphine. The control veterinary product was placebo solution (5% w/v padimate O in ethanol) manufactured in single use, unit dose, applicator tubes that deliver 0.4 ml or 1 ml solution.

2.2 | Protocol concurrence and investigational site training

Prior to study initiation, the study protocol underwent peer review and concurrence by subject matter experts at the US Food and Drug Administration (FDA). Following protocol concurrence, all study participants simultaneously attended a study protocol training session at a central geographic location to ensure the accuracy, integrity, and correctness of data, to facilitate consistency in study performance, and in compliance with regulations (FDA-CVM, 2001) that each individual involved in the study conduct be qualified by education, training, and expertise to perform their respective task(s). Training on all aspects of the study was provided and all individuals conducting pain assessments were given specific training on the interactive pain assessment method used in the study (Appendix). There was an average of 2 trained pain assessors at each site (range of 1 to 4).

2.3 | Inclusion and exclusion criteria

Cats that qualified for inclusion were client-owned animals intending to undergo elective surgical reproductive sterilization (castration/ovariohysterectomy) in conjunction with forelimb onychectomy that weighed 1.2–7.5 kg and were at least 4 months old. There was no

restriction on breed or sex; however, pregnant or lactating females and males intended for breeding were not eligible for enrollment. Cats were excluded if they had a history of blood dyscrasia, hepatic, renal or cardiac disease, seizures, or any other clinically relevant medical abnormalities that conflicted with the ability of the patient to undergo the surgery or other study procedures, and/or if they had severe systemic disease (i.e., American Society of Anesthesiologists [ASA] physical status classification score of P3 or greater). Animals were also excluded if they had recently received corticosteroids or NSAIDs prior to surgery that might interfere with post-operative pain assessments, had a known sensitivity to opioids, amide-type local anesthetics, or anesthetic agents, or had an abnormal application site (i.e., injured or diseased skin). Screening for entrance into the study was as a result of owners seeking elective reproductive sterilization in conjunction with forelimb onychectomy; at no point were owners encouraged to have their cats undergo surgical procedures that they had not desired. Participation was voluntary. As incentive to participate, the procedures and services described in this study were provided without cost to the owners. All owners were informed of the study procedures and risks and gave signed informed consent prior to screening for inclusion into the study.

2.4 | Enrollment and treatment administration

All cats underwent a screening physical examination, including blood collection for hematology and clinical chemistry. The hematology variables measured included red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, white blood cell count with differential, prothrombin time, activated partial thromboplastin time, and fibrinogen. The clinical chemistry variables measured included albumin, alkaline phosphatase, alanine aminotransferase, amylase, aspartate aminotransferase, blood urea nitrogen (BUN), calcium, chloride, cholesterol, creatine kinase, creatinine, gamma glutamyl transpeptidase, globulin, glucose, phosphorus, potassium, sodium, total bilirubin, total protein, albumin: globulin ratio, sodium: potassium ratio, and BUN:creatinine ratio. After meeting eligibility criteria, cats were hospitalized and randomized to treatment in blocks of two within each investigational site (i.e., clinic). Enrollment was restricted to a maximum of 40% of cats from any one site. A minimum enrollment of 100 cats per treatment group was selected based the outcome of a phase 2 study in order to maintain a power of >90% (Clark et al., 2022a). All clinic personnel and cat owners were blinded to the identity of the treatment assignments, except for the treatment administrator. The treatment administrators did not participate in animal observations or pain assessments.

Cats were randomized to a single pre-operative dose of placebo or TBS according to body weight on the day of surgery. The dose administered was based on unit dosing for cats that fit into a body weight range (Clark et al., 2022a). For cats allocated to TBS, smaller cats (1.2–3 kg) received 8 mg and larger cats (>3–7.5 kg) received 20 mg in dose volumes of 0.4 and 1 ml, respectively. Transdermal buprenorphine solution was administered 1–2 h prior to surgery according to its onset-of-action (Clark et al., 2022a). Cats randomized to placebo received placebo solution 1–2 h prior to surgery in a volume equivalent to the volume of TBS based on bodyweight.

Treatments were administered topically to the dorsal cervical region (i.e., base of the skull). The applicator tube tip was placed directly onto the skin at the application site by parting the hair, if necessary, and the entire dose volume was administered at a single location without moving the applicator tube. Cats were gently restrained for 2 min post-dosing to prevent shaking or grooming prior to complete drying of the solution. Cats were hospitalized throughout the 4-day study duration. In addition to protocol required observations and procedures, cats were observed according to the investigational site's standard practices.

2.5 | Anesthesia and surgery

To provide a basal level of preemptive analgesia to both treatment groups, 30 min prior to anesthetic induction, a single intramuscular injection of 5 μg/kg dexmedetomidine hydrochloride (Dexdomitor®, Zoetis Inc., Florham Park, NJ, USA) was administered and following anesthetic induction, a lidocaine metacarpal 4-point ring block was conducted on the forelimbs (Skarda & Tranquilli, 2007). To induce anesthesia, induction agents were constrained to the following drugs, alone or in combination, according to the investigational site's preference: propofol, ketamine, diazepam, midazolam, and tiletamine-zolazepam. Selection of inhalant anesthetic maintenance agents was limited to isoflurane or sevoflurane. Reproductive sterilization and forelimb onychectomy were performed in a single surgical period on all study animals. Onychectomy was performed by excisional/disarticulation via scalpel, laser, or guillotine nail trimmers according to the surgeon's preference. Ovariohysterectomy was performed by a midline approach. Castrations were performed via the scrotal approach. During anesthesia, the inhalant anesthetic vaporizer setting, and oxygen flow were intermittently recorded. Indirect mean arterial blood pressure (MAP) as measured by the oscillometric method on the tail or hind limb, heart rate, respiratory rate, body temperature, oxygen hemoglobin saturation (SpO_2), end tidal carbon dioxide ($ETCO_2$), and heart rhythm via electrocardiography were monitored and recorded every 10 min beginning at the time of intubation and extending through extubation. Normal ranges for these variables were as follows: MAP 60–120 mm Hg; heart rate 88–180 beats/min; respiratory rate 24–44 breaths/min; body temperature 38.1–39.2°C (100.5–102.5°F); SpO_2 > 90%. There was no defined normal range for $ETCO_2$. Supplemental heat (i.e., circulating warm water pad) and intravenous fluids during surgery were administered according to the investigational site's standard procedures.

2.6 | Post-Operative monitoring, pain assessments, and rescue analgesia

Following surgery, cats were continuously monitored through sternal recumbency. The time from vaporizer shut off to extubation, head lift, and sternal recumbency were recorded. The overall quality of anesthetic recovery was recorded according to the following:

0: Excellent, quickly assumes sternal recumbency following extubation with little or no struggling, and may attempt to stand or walk with little or no difficulty.
1: Acceptable, some struggling following extubation, requires assistance to achieve sternal recumbency ± standing, responsive to external stimuli, becomes quiet in sternal recumbency.
2: Unacceptable, prolonged struggling following extubation, unable to assume sternal recumbency quickly or difficulty in maintaining sternal or standing position, becomes agitated when assisted, prolonged paddling, and swimming motion.

At the time of sternal recumbency (time 0) and at 0.5, 1, 2, 4, 8, 12, 24, 28, 48, 72, and 96 h post-sternal recumbency, MAP, heart rate, respiratory rate, and body temperature were recorded as well as assessments of heart and lung auscultation, the presence of urine and feces, and food consumption. Body weights were measured daily.

At sternal recumbency (time 0) and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 28, 32, 48, 52, 56, 72, 76, 80, and 96 h following sternal recumbency, interactive pain assessments were conducted. At each time point, the presence of sedation (yes/no) and dysphoria, that is, a disquieted state of consciousness (yes/no) was scored. Pain was assessed based on a modification of King et al. (2012) and used in a phase 2 clinical study with TBS in cats (Clark et al., 2022a) as shown in Appendix. Cats that were considered to have inadequate pain control were immediately administered 0.4 mg/kg subcutaneous butorphanol (Torbugesic®-SA, Zoetis, Inc.) as a rescue drug and considered treatment failures. Following the initial analgesic rescue, additional butorphanol could be administered according to the approved label every 6 h for up to 2 days, and/or other analgesics could be administered at any time at the investigator's discretion. Cats that were administered rescue drugs due to inadequate pain control remained at the investigational site and continued to be observed at the scheduled assessment intervals until the scheduled study conclusion.

2.7 | Adverse events and removal from study

An adverse event was considered to be any observation that was unfavorable and unintended and occurred after the use of the investigational or control veterinary product whether or not considered to be product related (FDA-CVM, 2001). In addition, physiological variables observed during anesthesia and post-operatively were considered adverse events if there was an excursion outside the normal range at any monitoring time. Values outside the defined ranges were documented as adverse events, consistent with regulations (FDA-CVM, 2010). At the time of occurrence, each adverse event was scored as mild, moderate, or severe and further classified as unknown, unrelated, possibly related, or related to the investigational veterinary product. If the adverse event resulted in death, was life-threatening, or resulted in persistent or significant disability, it was further categorized as a serious adverse event. A cat could be removed at any time if the investigator determined that an illness, injury, complication, or adverse reaction prohibited the animal from completing the study. At the time of withdrawal, a physical examination, including blood collection for hematology and serum chemistry, was completed. Cats removed from the study remained at the clinic and continued to be observed at the scheduled assessment intervals and per the investigational site's standard practices until the scheduled discharge 4 days post-surgery.

2.8 | Study end

After the 96-h assessment, a physical examination was conducted; blood samples for hematology and clinical chemistry were drawn and submitted to the clinical pathology laboratory, and the cats were discharged from the investigational site.

2.9 | Statistical analysis

The primary efficacy variable was treatment success as a composite measure of safety and effectiveness. Treatment success was defined as cats that were judged to have adequate pain control by interactive pain assessment and did not experience a treatment related adverse event that resulted in early study removal. Treatment failures were therefore defined as cats that were judged to have inadequate pain control by interactive pain assessment and required rescue analgesia, or cats that were removed from the study early as the result of an adverse event judged to be related to the investigational or control veterinary product. Animals that were withdrawn from study due to an adverse event that was classified as unlikely to be related to the investigational or control veterinary product were excluded from the primary variable analysis altogether. For the primary variable efficacy analysis, a generalized linear mixed effects model (GLMM) with a logit link function was fitted to the binary outcome of treatment success over the 4-day study duration in the per protocol dataset. The per protocol population was defined as cats that completed the study without major protocol deviations. Sensitivity analysis was done on the intent-to-treat dataset that included all randomized cats. The safety population was defined as all cats that were confirmed to be administered investigational or control product following randomization. The model included treatment as a fixed effect and site and site*treatment interaction as random effects. The overall treatments success rates and 95% confidence

intervals (CI) between TBS and placebo were constructed with the fitted GLMM model.

The dose of TBS selected for this study was based on the outcomes of PK laboratory studies and a phase 2 randomized controlled clinical study (Clark et al., 2022a). In the phase 2 study with the selected dose, the estimated overall treatment success rates from a GLMM analysis were 0.10 (95% CI: [0.02–0.36]) and 0.71 (95% CI: [0.38–0.91]) in the placebo and TBS dose groups, respectively. The estimated odds ratio was 22.6 (95% CI: [4.0–127.4]). Assuming a true success rate in the placebo group of 0.10 and the odds ratio of the success rates between the two treatment groups of 4.0 to 22.6, the number of cats necessary to detect a difference with 90% power was between 28 and 87 cats per treatment group. Therefore, a minimum of 100 cats per treatment group were targeted.

Secondary variables included time to treatment failure, anesthetic recovery times, continuous safety observations measured repeatedly throughout the study, and adverse events. A Kaplan–Meier estimate was used to analyze time to treatment failure. Clinical pathology values were summarized. A two sample Student's *t*-test was conducted to compare anesthetic recovery times between treatments. Cats that were administered atipamezole post-operatively to reverse the effects of dexmedetomidine were excluded from the recovery time analyses. A repeated measures GLMM model was fitted to bodyweights, variables measured during anesthesia (i.e., heart rate, respiratory rate, body temperature, MAP, vaporizer setting, oxygen flow, $ETCO_2$, and SpO_2), and variables measured post-anesthetic recovery (i.e., heart rate, respiratory rate, body temperature, and MAP). The model included treatment, time, and time-by-treatment interaction as fixed effects and site and site-by-treatment interaction as random effects. The baseline values were included as a covariate. The covariance structure in the repeated measures analysis was investigated using two structural assumptions, namely, heterogeneous compound symmetry and spatial power. The covariance structure yielding the minimum Akaike's Information Criterion (AIC) value was selected in the final analysis. A *post hoc* two-sided Fisher's Exact Test was used to test for differences in adverse event incidences by treatment. Statistically significant differences were determined at the $\alpha = 0.05$ significance level. All statistical analyses were conducted using SAS for Windows 9.3 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Demographics

Two hundred and thirty-nine cats were screened for enrollment from 12 US investigational sites across 7 states (i.e., Colorado, Florida, Indiana, Minnesota, Missouri, North Carolina, and Tennessee) of which 228 cats met enrollment criteria. This resulted in the intent-to-treat population of 115 allocated to TBS and 113 cats allocated to placebo. There were 6 cats excluded (3 allocated to placebo- and 3 allocated to TBS) that lacked documentation to confirm correct treatment tube selection and application. One additional cat allocated to placebo was inadvertently administered TBS and was included into the TBS group. This resulted in 222 cats in the safety population from 12 investigational sites (8 to 40 cats per site) of which 113 and 109 were allocated to TBS and placebo, respectively (Figure 1, Table 1). One cat in the TBS group was discovered to have been previously spayed at the time of surgery and did not meet enrollment criteria. Two cats in the placebo group were withdrawn; one did not meet enrollment criteria body weight requirement and one had an adverse event not considered related to treatment (i.e., bleeding at the surgical site). This resulted in the per protocol population of 112 allocated to TBS and 107 allocated to placebo (Figure 1). Gender distribution was composed of 53.9% females and 46.1% males. The most common breed enrolled was non-pedigree domestic short-hair (76.1%) and the most common pedigree breed was Siamese (2.7%). Cats averaged 10.3 (range: [4.0–60]) months of age and 2.9 (range: [1.1–5.7]) kg of bodyweight. The actual dosage of TBS administered on a bodyweight basis was 3.5–6.7 mg/kg.

3.2 | Anesthesia

The drugs used for anesthetic induction and maintenance were used in approximate similar proportions across both treatment groups; 47.8% of cats received propofol as an anesthetic induction agent and the remainder received ketamine (20.1%) or ketamine/diazepam (32.1%). Isoflurane (86.8%) was the predominant inhalant anesthetic with the remainder receiving sevoflurane. The proportions of cats that received supplemental heat during surgery in the safety population were 81% (92/113) and 83% (95/115) in the placebo and TBS groups, respectively. The proportions of cats that received IV fluids during surgery in the safety population were 36% (41/113) and 37% (42/115) in the placebo and TBS groups, respectively. The use of supplemental heat or IV fluids did not correlate to altered recovery times or adverse events.

During anesthesia, there were no differences ($p > .05$) between treatment groups in temperature, heart rate, respiratory rate, vaporizer setting, oxygen flow, MAP, and SpO_2. In TBS-treated cats, mean $ETCO_2$ was increased 2.5 (95% CI: [0.2–4.7]) mm Hg from baseline which was greater compared with placebo-treated cats ($p < .05$). When data were analyzed by anesthetic induction drug(s) or the inhalant anesthetic used, there were no correlations to increased $ETCO_2$. There were no arrythmias. In both groups, the most-common adverse events during surgery were hypothermia, hypotension, and hypertension and there were no significant differences ($p > .05$) between treatments in any of the adverse event incidences from anesthetic induction through recovery (Table 2).

Nineteen cats (13 TBS- and 6 placebo-treated) had the pre-anesthetic dexmedetomidine dose reversed with atipamezole during recovery period. Fourteen of the 19 reversed cats were from a single investigational site that represented site preference. Anesthesia recovery times from the time the vaporizer were shut-off to time-to-head lift and time-to-sternal recumbency were increased

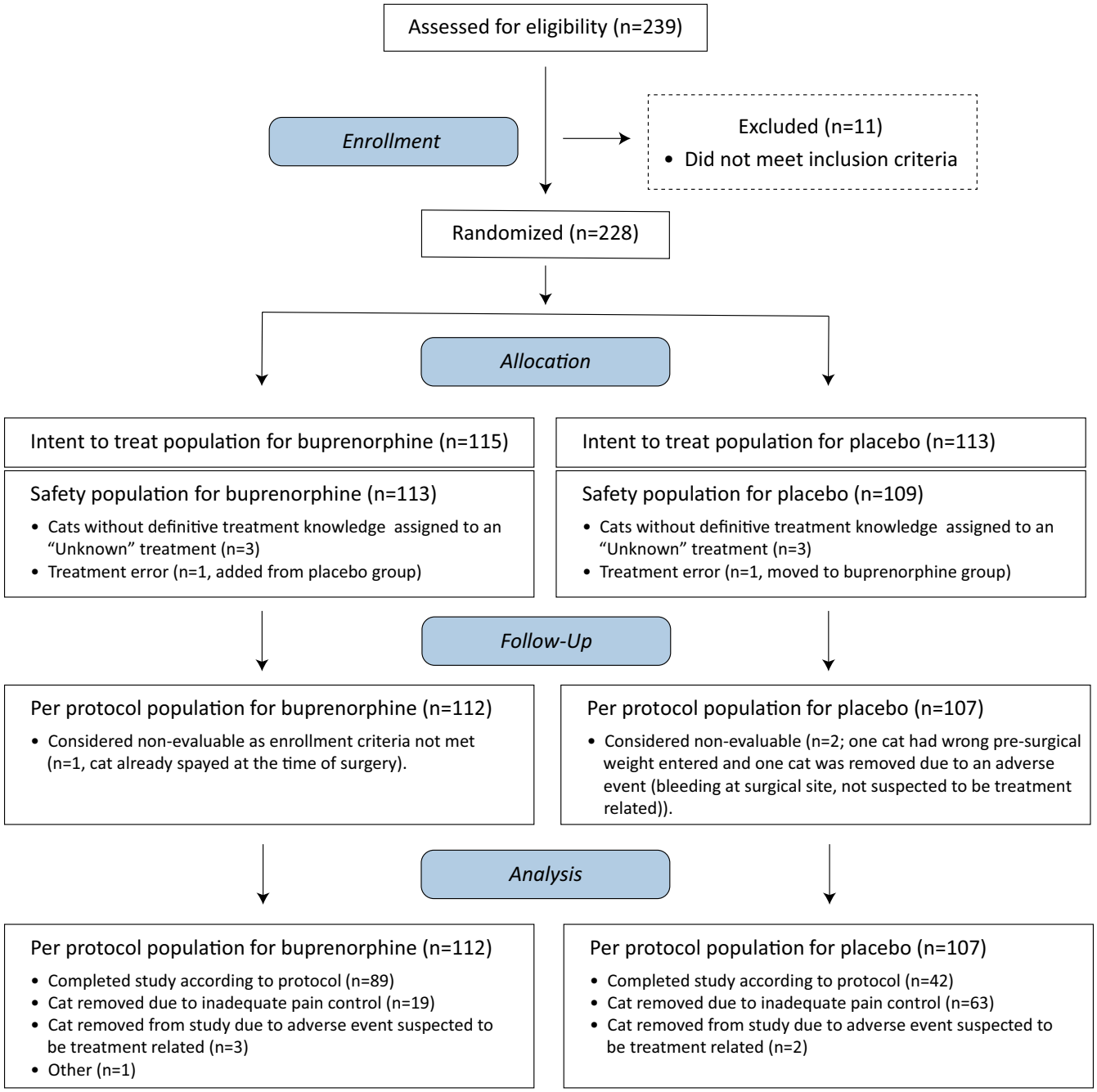

FIGURE 1 Consolidated standards of reporting trials (CONSORT) case flow diagram indicating randomized, intent-to-treat, safety, and per protocol populations for cats allocated to TBS and placebo treatment groups

($p < .05$) by 5 to 6 min in cats administered TBS compared with placebo (Figure 2). Time from vaporizer shut-off to extubation was not statistically different ($p > .05$). The majority of anesthesia recovery scores were excellent or acceptable in both treatment groups; however, there were 9 (8.3%) placebo- and 3 (2.7%) TBS-treated cats that were scored as having an unacceptable recovery (Table 3).

Sedation was commonly observed within the first 30 min following sternal recumbency at a similar frequency between treatment groups. At 15 and 30 min post-sternal recumbency, sedation proportions were 36.4% and 16.5% in TBS-treated cats and 29.1% and 16.5% in placebo-treated cats. Sedation was not observed in any cat after 1-h post-sternal recumbency, other than a single placebo-treated cat at the 2- and 3-h assessments. At 15 and 30 min post-sternal recumbency, dysphoria proportions were 13.1% and 10.7% in TBS-treated cats and 12.8% and 9.4% in placebo-treated cats. There were 4 remaining dysphoria observations in TBS-treated cats, 3 at 2 h- and 1 at 3 h-post-sternal recumbency.

3.3 | Physical examinations, physiological variables, and clinical pathology

The mean body weight in TBS-treated cats, adjusted for baseline value, was greater at study conclusion ($p < .05$) compared with

TABLE 1 Demographic information by treatment in the safety population

Variable	Treatment group		Overall
	TBS (n = 113)	Placebo (n = 109)	(N = 222)
Gender			
Female	57 (50.4%)	61 (56.0%)	118 (53.2%)
Male	56 (49.6%)	48 (44.0%)	104 (46.8%)
Breed			
Bengal	1 (0.9%)	3 (2.8%)	4 (1.8%)
Domestic long-hair	8 (7.1%)	5 (4.6%)	13 (5.9%)
Domestic medium-hair	14 (12.4%)	8 (7.3%)	22 (9.9%)
Domestic short-hair	83 (73.5%)	86 (78.9%)	169 (76.1%)
Himalayan	1 (0.9%)	0 (0.0%)	1 (0.5%)
Maine Coon Cat	2 (1.8%)	0 (0.0%)	2 (0.9%)
Manx	0 (0.0%)	1 (0.9%)	1 (0.5%)
Ragdoll	0 (0.0%)	1 (0.9%)	1 (0.5%)
Scottish Fold	0 (0.0%)	1 (0.9%)	1 (0.5%)
Siamese	3 (2.7%)	3 (2.8%)	6 (2.7%)
Sphynx	1 (0.9%)	0 (0.0%)	1 (0.5%)
Other	0 (0.0%)	1 (0.9%)	1 (0.5%)
Age (months)			
Mean	10.3	10.2	10.3
SD	9.4	8.2	8.8
Minimum	4.0	4.0	4.0
Median	7.0	7.0	7.0
Maximum	60.0	39.0	60.0
Body weight (kg)			
Mean	2.9	3.0	2.9
SD	1.1	1.1	1.1
Minimum	1.2	1.1	1.1
Median	2.9	2.9	2.9
Maximum	5.7	5.5	5.7
TBS dosage administered (mg/kg)	3.5–6.7	0	N/A

placebo-treated cats. The difference was 0.04 (95% CI: [0.02–0.17]) kg. Post-operatively, there were no differences between treatment groups in the physiological variables except for body temperature. The post-operative body temperatures over the duration of the study were on average 0.35 (95% CI: [0.20–0.50]) °C higher ($p < .05$) in TBS-treated cats compared with placebo-treated cats (Figure 3). Body temperatures in both groups were low during the first hour after sternal recumbency and from 4 through 8 h post-sternal recumbency the mean temperatures in the TBS treatment group were above the normal range of 38.1–39.2°C (Table 4). In both groups, the mean body temperature was within the normal range beyond the 8-h observation and the maximum body temperature at each observation time was not different between treatment groups (Table 4). When data were analyzed by anesthetic induction drug(s) or the inhalant anesthetic used, there was no correlation to increased body temperature.

From anesthetic recovery through study conclusion (i.e., 96 h), the most common adverse events were hypothermia, hyperthermia, sedation, and tachypnea (Table 5). The post-operative hyperthermia incidence was higher ($p < .05$) in TBS-treated cats and post-operative tachypnea was higher ($p < .05$) in placebo-treated cats. There were no other statistically significant differences between treatments in any of the post-operative adverse event incidences. When post-operative adverse events are parsed by study day, nearly all adverse events occurred on the day of surgery in both treatment groups (Table 6). Hyperthermia was the only adverse event that occurred in more than 10% of TBS-treated cats beyond the day of surgery.

Compared with pre-treatment values, post-treatment (i.e., 96 h) clinical pathology results were generally similar across treatment groups with no clinically relevant changes. At study conclusion, there were no instances of hair loss, pruritus, erythema, edema, pain, or heat at the application site in any treatment group.

TABLE 2 Adverse events from anesthetic induction through recovery by treatment in the safety population

Adverse event[a]	Treatment group	
	TBS ($n = 113$)	Placebo ($n = 109$)
Hypothermia	37 (32.7%)	29 (26.6%)
Hypotension	31 (27.4%)	28 (25.7%)
Hypertension	27 (23.9%)	18 (16.5%)
Tachycardia	14 (12.4%)	14 (12.8%)
Sedation	12 (10.6%)	7 (6.4%)
Oxygen saturation ≤ 90%	6 (5.3%)	2 (1.8%)
Bradycardia	4 (3.5%)	2 (1.8%)
Hyperthermia	3 (2.7%)	4 (3.7%)

Note: Values are the number (%) of cats.

aPhysiological adverse events were defined as any single excursion outside the normal anesthetic range at any 10 min interval over the duration of anesthesia. Normal ranges for physiological variables: MAP 60–120 mm Hg; heart rate 88–180 beats/min; respiratory rate 24–44 breaths/min; body temperature 38.1–39.2°C (100.5–102.5°F); and $SpO_2 > 90\%$.

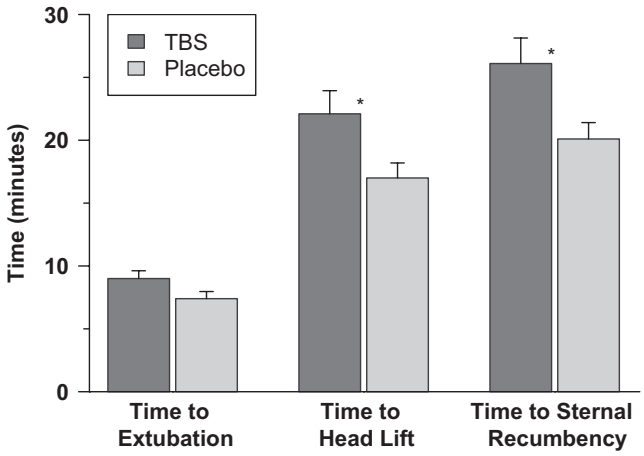

FIGURE 2 Time from end of anesthesia to recovery by treatment. *Within recovery endpoint, significantly different ($p < .05$) than placebo. Bars indicate the standard error

3.4 | Adverse events related to withdrawals and treatment failures

One placebo-treated cat was withdrawn from the study due to bleeding at the surgical site that was judged to be severe and not treatment related. It was administered additional dexmedetomidine approximately 45 min following sternal recumbency without further incident. Five cats (3 TBS- and 2 placebo-treated) were considered treatment failures due to hyperthermia that were judged as moderate and treatment related. Each was treated with dexamethasone and observed for the remainder of the study without further incident. One TBS-treated cat was considered a treatment failure due to fractious behavior 30 min following anesthetic recovery that was judged to be severe and treatment related. It was observed for the remainder of the study without further incident. These 6 cats were considered treatment failures for the purpose of the efficacy analysis because each adverse event was judged to be treatment related (Table 7). No adverse events resulted in death, were life-threatening, or resulted in persistent or significant disability, that is, serious adverse events.

TABLE 3 Anesthetic recovery scores by treatment in the safety population

Treatment group	N	Score		
		0	1	2
TBS	113	53 (46.9%)	57 (50.4%)	3 (2.7%)
Placebo	109	32 (29.4%)	67 (61.5%)	9 (8.3%)

Note: There were no significant differences.

0—Excellent, quickly assumes sternal recumbency following extubation with little or no struggling, and may attempt to stand or walk with little or no difficulty.

1—Acceptable, some struggling following extubation, requires assistance to sternal recumbency ± standing, responsive to external stimuli, becomes quiet in sternal recumbency.

2—Unacceptable, prolonged struggling following extubation, unable to assume sternal recumbency quickly or difficulty in maintaining sternal or standing position, becomes agitated when assisted, prolonged paddling, and swimming motion.

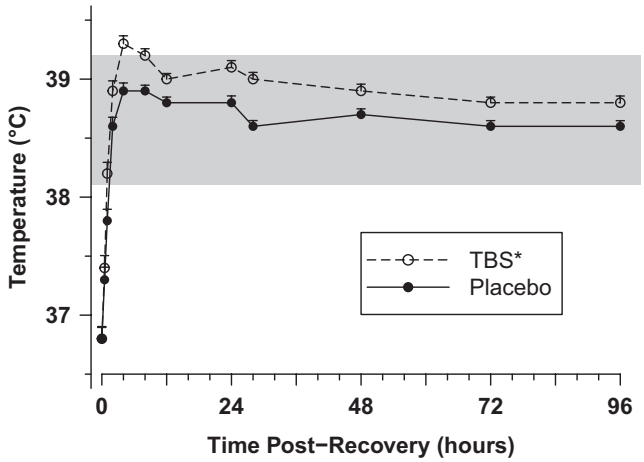

FIGURE 3 Mean body temperatures by treatment. *Across all time points post-recovery, statistically different ($p < .05$) from placebo. Bars indicate the standard error. Shaded region indicates the normal reference range

3.5 | Efficacy

A total of 63 (58.9%) placebo-treated cats were considered treatment failures due to inadequate pain control in contrast to 19 (17.0%) TBS-treated cats. There were 6 cats considered treatment failures for the purpose of the efficacy analysis due to adverse events judged

TABLE 4 Body temperature (°C) summary statistics after anesthetic recovery through study completion (i.e., 96 h) in TBS- and placebo-treated cats in the safety population

	TBS					Placebo				
Time (h)	Mean	Std dev	Min	Median	Max	Mean	Std dev	Min	Median	Max
0	36.8	1.1	33.4	37.0	39.7	36.8	1.0	33.9	37.0	39.1
0.5	37.4	1.1	34.7	34.7	40.3	37.3	1.1	34.4	37.5	39.7
1	38.2	1.0	35.4	38.2	40.3	37.8	1.0	35.5	38.0	40.3
2	38.9	0.9	36.4	39.0	40.9	38.6	0.8	36.3	38.8	40.6
4	39.3	0.7	37.7	39.3	40.6	38.9	0.7	36.1	39.0	40.8
8	39.2	0.6	37.9	39.2	40.4	38.9	0.5	37.6	38.9	40.3
12	39.0	0.5	37.8	39.1	40.4	38.8	0.5	37.4	38.8	40.0
24	39.1	0.6	36.7	39.1	40.8	38.8	0.6	37.4	38.8	40.9
28	39.0	0.6	37.6	39.0	40.3	38.6	0.5	37.3	38.5	39.9
48	38.9	0.6	36.4	39.0	40.6	38.7	0.5	37.4	38.7	40.4
72	38.8	0.5	37.7	38.8	40.2	38.6	0.5	37.3	38.7	40.0
96	39.8	0.6	36.4	38.8	40.8	38.6	0.5	37.6	38.6	40.3

TABLE 5 Adverse events after anesthetic recovery (i.e., sternal recumbency) through study completion (i.e., 96 h) in TBS- and placebo-treated cats in the safety population

	Treatment group	
Adverse event[1]	TBS ($n = 113$)	Placebo ($n = 109$)
Hypothermia	107 (94.7%)	105 (96.3%)
Hyperthermia	84 (74.3%)[a]	62 (56.9%)[b]
Sedation	64 (56.6%)	48 (44.0%)
Tachypnea	56 (49.6%)[a]	70 (64.2%)[b]
Hypotension	50 (44.2%)	51 (46.8%)
Hypertension	42 (37.2%)	34 (31.2%)
Bradycardia	34 (30.1%)	45 (41.3%)
Tachycardia	32 (28.3%)	39 (35.8%)
Anorexia	25 (22.1%)	32 (29.4%)
Dysphoria	20 (17.7%)	29 (26.6%)
Diarrhea	11 (9.7%)	11 (10.1%)
Bradypnea	11 (9.7%)	7 (6.4%)
Leukocytosis	6 (5.3%)	4 (3.7%)
Hyperactivity	2 (1.8%)	9 (8.3%)

Note: Values are the number (%) of cats.

[1]Physiological adverse events were defined as any single excursion outside the normal range between anesthetic recovery (sternal recumbency) through 4 days post-operatively. Normal ranges for physiological variables: MAP 60–120 mm Hg; heart rate 88–180 beats/min; respiratory rate 24–44 breaths/min; body temperature 38.1–39.2°C (100.5–102.5°F); and $SpO_2 > 90\%$. Within an adverse event, percentages with different *a*, *b* superscripts are statistically different ($p < .05$) per a post hoc two-sided Fisher's exact test.

to be treatment related (see *Adverse Event Related Withdrawal and Treatment Failures* above). Therefore, a total of 65 (60.7%) placebo- and 23 (20.5%) TBS-treated cats were considered treatment failures (Table 7). Most treatment failures occurred on the day of surgery in both groups (Figure 4). Beyond the day of surgery, there were 5 placebo- and 4 TBS-treated cats removed due to inadequate pain control between 1- and 3-days post-surgery. There were 110 rescue pain interventions in placebo-treated cats and 27 rescue pain interventions in TBS-treated cats resulting in an intervention per cat ratio of 1.7 (110/63) for placebo and 1.4 (27/19) for TBS.

In the per protocol population, the estimated overall treatment success rates by GLMM analysis were 0.81 (95% CI: [0.70–0.89]) and 0.40 (95% CI: [0.28–0.53]) for TBS- and placebo-treated cats, respectively (Table 7). The difference in success proportions between the TBS and placebo treatment group was 0.40 (95% CI: [0.27–0.52]). Comparison of the success rates between TBS and placebo treatment groups was statistically different ($p < .05$). A sensitivity analysis in the intent-to-treat dataset that included all 228 enrolled cats resulted in similar statistical significance (p-value = .0073).

4 | DISCUSSION

The number of cats enrolled into the study ($N = 228$) is consistent with an adequately sized phase 3 study to identify differences between treatment groups and was based on effect size differences in a phase 2 dosage characterization study (Clark et al., 2022a). The overall mean age of cats enrolled into the study of 10.3 months was representative of the age where cats are typically presented for surgical sterilization. There were slightly more females (53.2%) compared with males (46.8%) as a reflection of more ovariohysterectomies being enrolled compared with orchiectomies.

The results from this study serve as substantial evidence that TBS is safe and effective for the control of orthopedic and soft tissue post-operative pain in cats when a single topical dose is applied 1–2 h prior to surgery. The per protocol TBS treatment success rate of 0.81 (95% CI: [0.70–0.89]) was superior to the placebo success

TABLE 6 Adverse events after from anesthetic recovery (i.e., sternal recumbency) through study completion (i.e., 96 h) by study day for TBS-treated cats in the safety population ($n = 113$)

	Day post-surgery				
Adverse event[a]	Day 0	Day 1	Day 2	Day 3	Day 4
Hypothermia	106 (93.8%)	2 (1.8%)	2 (1.8%)	2 (1.8%)	2 (1.8%)
Hyperthermia	75 (66.4%)	32 (28.3%)	18 (15.9%)	14 (12.4%)	7 (6.2%)
Sedation	64 (56.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tachypnea	51 (45.1%)	5 (4.4%)	2 (1.8%)	3 (2.7%)	4 (3.5%)
Hypotension	42 (37.2%)	2 (1.8%)	1 (0.9%)	4 (3.5%)	2 (1.8%)
Hypertension	28 (24.8%)	2 (1.8%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
Anorexia	25 (22.1%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Bradycardia	24 (21.2%)	3 (2.7%)	2 (1.8%)	3 (2.7%)	5 (4.4%)
Tachycardia	24 (21.2%)	4 (3.5%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Dysphoria	20 (17.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bradypnea	8 (7.1%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperactivity	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

Note: Values are the number (%) of cats.

aPhysiological adverse events were defined as any single excursion outside the normal range between anesthetic recovery (sternal recumbency) through 4 days post-operatively. Normal ranges for physiological variables: MAP 60–120 mm Hg; heart rate 88–180 beats/min; respiratory rate 24–44 breaths/min; body temperature 38.1–39.2°C (100.5–102.5°F); and $SpO_2 > 90\%$.

TABLE 7 Treatment failures and estimated treatment success rate by GLMM in the per protocol population ($N = 219$)

	Treatment group	
Reason	TBS ($n = 112$)	Placebo ($n = 107$)
Treatment failure		
Inadequate pain control	19 (17.0%)	63 (58.9%)
Adverse event		
Hyperthermia	3 (2.7%)	2 (1.9%)
Fractious behavior	1 (0.9%)	0 (0.0%)
Total treatment failures	23 (20.5%)	65 (60.7%)
Overall treatment success	89 (79.5%)	42 (39.3%)
Estimated success rate (GLMM)	0.81[a]	0.40
95% CI of estimated success rate	0.70–0.89	0.28–0.53

Note: Values are the number (%) of cats.

[a]Superior to placebo ($p < .05$).

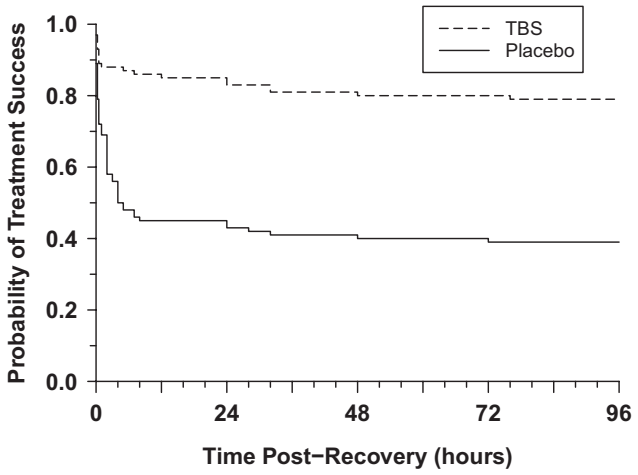

FIGURE 4 Kaplan–Meier curve of probability of treatment success from post-recovery time (i.e., sternal recumbency = time 0) through 96 h

rate resulting in a large treatment difference of 0.40 (95% CI: [0.27–0.52]). A sensitivity analysis in the intent-to-treat dataset that included all 228 enrolled cats resulted in similar statistical significance (p-value = .0073) and identical conclusions of effectiveness, further demonstrating that the primary efficacy analysis was robust and insensitive to protocol adherence. The basal level of preemptive analgesia of dexmedetomidine and lidocaine metacarpal 4-point ring block that was provided to all cats did not fully prevent breakthrough pain in most cats and did not confound the outcomes. However, lidocaine metacarpal 4-point ring blocks were administered following anesthetic induction and could not be tested for full effectiveness.

In a phase 2 randomized, controlled trial (Clark et al., 2022a), two TBS doses were differentiated, and a dose was selected for inclusion in the present study, whereas treatments were differentiated in the present study, the majority of treatment failures occurred on the day of surgery. There was a total of 65 (60.7%) placebo- and 23 (20.5%) TBS-treated cats considered treatment failures, and beyond the day of surgery, there were 5 placebo- and 4 TBS-treatment failures between 1- and 3-days post-surgery. These outcomes reduce statistical inferences beyond the day of surgery. Comparable results were reported with two other drugs in randomized, controlled trials of similar design. In a placebo-controlled field study, a high concentration buprenorphine injectable solution was administered once

prior to surgery and daily for 2 additional injections to 221 cats undergoing various surgeries ('Simbadol; Zoetis', 2014). The drop-out rates (i.e., cats that required rescue analgesia) for placebo- and buprenorphine-treated cats were 55.9% and 29.0%, respectively, and of the 83 total treatment failures, 75 (90.4%) were rescued in the first 4 h of recovery. In a placebo-controlled field study, robenacoxib was administered once prior to surgery and 2 additional daily doses to 249 cats undergoing various surgeries. The success rates for the robenacoxib and placebo groups were 83.5% and 53.7%, respectively (King et al., 2012; 'Onsior; Elanco', 2011), and of the 64 total treatment failures, 49 (76.5%) were rescued within 24 h post-surgery. Elucidation of treatment differences beyond the first 24 h following surgery may be aided by the inclusion of additional assessment methods in future multicentered, randomized clinical trials. For example, in a unilateral onychectomy model study in cats, a pressure platform gait analysis was able to distinguish limb function improvement in two onychectomy surgical techniques (Robinson et al., 2007). Cats undergoing laser onychectomy had significantly higher ground reaction forces on Days 1 and 2 following surgery, and a significantly higher peak vertical force ratio on Day 12 compared with cats undergoing scalpel onychectomy. In a placebo-controlled laboratory study with an investigational extended-release buprenorphine injectable formulation, ground reaction forces from landing on a pressure sensitive walkway were compared in cats undergoing unilateral laser onychectomy (Enomoto et al., 2016). Over 72 h, extended-release buprenorphine resulted in significantly decreased asymmetry in limb use during landing and walking, and no cats required rescue analgesics based on a subjective pain score.

The observation of treatment failures in TBS treated cats is not unexpected. In some cats undergoing surgery, it may be that buprenorphine is not sufficient as a monotherapy for post-operative pain. For example, in a study of 100 cats undergoing ovariohysterectomy that were administered buprenorphine by various routes, 40 needed rescue therapy (Giordano et al., 2010). In a second study of 12 cats undergoing ovariohysterectomy following 20 μg/kg IM buprenorphine, all required rescue intervention (Warne et al., 2016). It is not certain why these differences are observed although variable responses to analgesics in cats have been hypothesized as the result of genetic variability that could include the number, morphology, and distribution of opioid receptors, or variations in uptake, biotransformation, transport, and elimination (Steagall et al., 2014). There is some direct evidence in cats that there is a variable response to opioids as the result of polymorphisms. Thermal thresholds and minimum alveolar concentration (MAC) suppression variability were examined in 5 groups of cats (Taylor et al., 2007): 3 of the 5 groups were from published thermal threshold or MAC suppression studies (Lascelles & Robertson, 2004; Pypendop et al., 2006; Robertson, 2006). Thermal thresholds were examined before and after treatment with buprenorphine, butorphanol, and morphine, and MAC suppression was tested following epidural buprenorphine or morphine. Some cats did not respond with an increased thermal threshold or decreased MAC following treatment with one or more opioids. Results were reproducible in some cats that were administered the same treatment more than once. This outcome supports the idea that some cats are "non-responders" to various opioids and that alternative opioids should be used if the first administered opioid is ineffective. It was hypothesized that these differences may be genetic and a follow-up pilot study examined antinociceptive phenotypes in cats with demonstrated polymorphisms (Slingsby et al., 2014). The 5 exons of the μ opioid receptor gene were sequenced from 12 laboratory cats with historical thermal threshold data (Slingsby et al., 2012). There were several single nucleotide polymorphisms and insertion/deletions identified that divided cats into 2 haplotypes groups. In one group, the thermal threshold responses were different for fentanyl and butorphanol. There were no differences between groups for buprenorphine and methadone. In subsequent work, genetic markers that predict clinical opioid responsiveness could be identified to aid opioid clinical selection.

Transdermal buprenorphine solution was safe when used in conjunction with a variety of anesthetic agents similar to that reported in a phase 2 clinical study (Clark et al., 2022a). There were no differences in the intraoperative physiological variables in TBS-treated cats except for $ETCO_2$, nor were there any differences in the adverse event incidences from anesthetic induction through recovery (Table 2). The mean $ETCO_2$ was increased 2.5 (95% CI: [0.2–4.7]) mm Hg greater than baseline in TBS-treated cats compared with placebo. This small difference was not influenced by the drugs used during anesthesia and was not associated with hypercapnia during surgery. There were no differences in respiratory rates. Therefore, the small observed difference in $ETCO_2$ was not considered clinically meaningful. Similar to the present study, buprenorphine has not been associated with clinically meaningful changes in CO_2. When physiological variables were compared following buprenorphine/acepromazine premedication with midazolam/ketamine and medetomidine/propofol, pCO_2 increased equally in all groups (Akkerdaas et al., 2001). The increased pCO_2 was considered acceptable given the depth of anesthesia. However, the study was not placebo controlled, and therefore, the increased pCO_2 could not be causally isolated to any particular drug. In other studies that included buprenorphine, there was no clinically meaningful changes to pCO_2 (Bellini et al., 2017; Grint et al., 2009).

Transdermal buprenorphine solution had no adverse effect on the quality of anesthetic recovery. In most TBS-treated cats, anesthetic recovery was qualitatively scored as excellent (46.9%) or acceptable (50.4%) (Table 3). There were 3 (2.7%) cats where recovery was scored as unacceptable, a result that was less than in placebo-treated cats (8.3%). Instances of dysphoria and sedation were largely limited to the first 30 min following recovery and were no different than placebo. The anesthetic recovery outcomes of time-to-head lift and time-to-sternal recumbency were slightly longer ($p < .05$) by 5 to 6 min in TBS-treated cats compared with placebo-treated cats (Figure 2). The small difference in recovery times was not associated with any adverse event instances and is not considered clinically meaningful. In a smaller phase 2 clinical study with TBS, there were no differences in recovery times when a 5 μg/kg preanesthetic dexmedetomidine dosage was utilized, but recovery times were

prolonged when the FDA approved preanesthetic dexmedetomidine dosage of 40 μg/kg was used (Clark et al., 2022a). The observed difference from the present study was likely revealed due to the larger sample size. Atipamezole was administered to 13 TBS- and 6 placebo-treated cats which were excluded from the recovery times analysis. Most of the reversed cats (14/19) were from a single investigational site that represented site preference rather than concern for prolonged recoveries. Importantly, atipamezole does not interfere with post-operative pain scores (Warne et al., 2016) and therefore did not confound pain assessment outcomes.

From the time of anesthetic recovery through 96 h post-operatively, adverse events were largely confined to the immediate post-operative period and were mostly related to surgery or recovery from anesthesia. There was a small difference in mean body weights between groups at study conclusion that was not considered clinically meaningful. There were two adverse events that were significantly different between treatment groups: tachypnea and hyperthermia. There were greater instances of post-operative ($p < .05$) tachypnea in placebo-treated cats (64.2%) compared with TBS-treated cats (49.6%) (Table 5). The majority of tachypnea instances (55.8%) occurred on the day of surgery following anesthetic recovery. The increased respiratory rate proportion in placebo-treated cats was likely related to the need for rescue analgesia. There were 54.2% (58/107) of placebo-treated cats administered rescue analgesia on the day of surgery, a proportion similar to tachypnea. Over the study duration, mean body temperatures were on average 0.35 (95% CI: [0.20–0.50])°C (Figure 3) higher than baseline in TBS-treated cats. The temperature increase was similar in magnitude to that consistently observed in two laboratory studies and a clinical study of TBS in cats (Clark et al., 2022a). As before, the increased body temperature was not considered clinically meaningful. The maximum individual cat temperature recorded in both treatment groups was similar (Table 4). The majority (66.4%) of the post-operative hyperthermia in TBS-treated cats occurred on the day of surgery (Table 6). Three TBS-treated cats and 2 placebo-treated cats were considered treatment failures due to hyperthermia. Each were treated with dexamethasone and observed for the remainder of the study without further incident. As with other opioid-induced hyperthermia in cats (Cannarozzo et al., 2021; Posner et al., 2010), clinicians should be aware that TBS may cause small and transient increases in body temperature following surgery and not mistake this observation for inflammation or infection.

The product profile of TBS makes available a long-acting opioid for the control of post-operative pain in cats that potentially mitigates the disadvantages of other approved and extralabel buprenorphine uses in cats. As a delivery method, the transdermal route has several potential strengths over oral and parenteral administration. These include non-invasive dosing, avoidance of the gastrointestinal tract, and lack of first pass metabolism (Riviere & Papich, 2001). There has been one other attempt to deliver buprenorphine by the transdermal route to cats. In a laboratory study where a 35 μg/h buprenorphine patch ('Butrans Transdermal System; Purdue Pharma L.P', 2010) was applied to the clipped thorax of cats, there was no significant change in thermal thresholds despite a slow rise in plasma buprenorphine concentrations (Murrell et al., 2007). Even if there was a difference in thermal thresholds detected, for use in a pre-emptive manner, patches would have to be applied to cats 24 h prior to surgery. Moreover, poor patch adhesion was observed whereby patches fell off in four of the six cats, and although they were quickly reattached, this could present a practical safety hazard to owners and cats in a clinical or home setting. In contrast, without the need for a patch or a device, TBS can be applied to the skin 1–2 h prior to surgery which allows its ease of integration into preemptive, multimodal analgesia.

Transdermal buprenorphine solution is supplied in single use, unit dose, use-and-dispose applicator tubes. This is the second study where cats have been found to have a mean body weight of about 3 kg which lends to unit dosing to cats into two weight classes: those up to 3 kg and those greater than 3 kg. Using this paradigm, a previous phase 2 study showed that when cats that weighed 3 kg or less were administered 8 mg TBS and cats that weighed greater than 3 kg were administered 20 mg, TBS was superior to placebo (Clark et al., 2022a). The present study confirms this result in a larger population enrolled from a greater number of clinics across a broader geographic region. In this dosage form, TBS can be administered accurately without the need for injections or repeated OTM administrations (Bortolami & Love, 2015; Steagall et al., 2014) that are potentially painful or difficult to administer, contributing to stress and fear in both cats and medical personnel (Riemer et al., 2021). Injection stress and intolerance is a major concern in delivering medicines to cats. In a survey, 43.5% of cats show intolerance to a first injection and 26.9% of cats that accepted a first injection become intolerant to subsequent injections (Mariti et al., 2016). Moreover, the rationale for the TBS application site selection was to allow cats to be in a comfortable, stress free conformation during application and to prevent cats from immediately grooming the application site during the 2-min drying period. The area over the head is the least resisted examination area in cats. In a survey of veterinary examinations, cats resist examination in rank order: the abdomen (30.6%), the tail (22.7%), the genital area (11.4%), the mouth (9.6%), the claws (7.4%), the ears (6.8%), and over the head (4%) (Mariti et al., 2016). Transdermal buprenorphine solution was well tolerated at the application site, there were no adverse events on application site skin consistent with prior studies (Clark et al., 2022a; Freise, Reinemeyer, Warren, et al., 2022).

Finally, TBS is intended for use in a controlled hospital setting without the need to dispense controlled substance for at-home administrations by owners and eliminates compliance and mis-dosing concerns (Urquhart, 2000). In contrast, buprenorphine OTM syringes are typically dispensed to owners for repeated administrations at home because of the short analgesic duration-of-action (Steagall et al., 2014), whereas repeated OTM administrations may extend the analgesic duration and eliminate injection pain, it does not alleviate the legal responsibility of dispensing buprenorphine, a Class III controlled substance in the US (Kukanich & Papich, 2009).

5 | CONCLUSION

A single pre-operative TBS administration is safe and effective for the control of post-operative soft tissue and orthopedic pain in cats. TBS was superior to placebo in the number of treatment successes and the intraoperative and post-operative safety outcomes were similar to those observed with placebo. The success rate in TBS-treated cats was approximately 80%, therefore, TBS treatment alone may not be sufficient for the control of post-operative pain in some cats emphasizing the importance of continued pain assessment following surgery. The availability of this FDA approved, extended duration TBS can be readily included into a preventative pain management analgesic protocol in a stress- and fear-free manner without the need for repeated injections, dispensing controlled substances, or adverse effects associated with post-dose peaks in plasma concentrations, and the end-of-dose breakthrough pain associated with sub-analgesic plasma concentrations.

AUTHOR CONTRIBUTION

TPC contributed to study design, study execution, data analysis, and manuscript writing. DDL contributed to protocol development, data analysis, and study execution. KJF was involved in study design, data analysis, and manuscript preparation. TL contributed to study design, data analysis, and manuscript preparation. All authors have read and approved the final manuscript.

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ANIMAL WELFARE AND ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. Screening for entrance into the study was the result of owners seeking elective reproductive sterilization in conjunction with forelimb onychectomy, at no point were owners encouraged to have their cats undergo surgical procedures that they had not desired. Participation was voluntary. All owners were informed of the study procedures and risks and gave signed informed consent prior to screening for inclusion into the study. [Correction added on 26 August 2022, after first online publication: The Animal Welfare and Ethics Statement was included in this current version.]

CONFLICT OF INTEREST

All authors were paid employees of Nexcyon Pharmaceuticals, Inc. at the time the study was conducted. One author (Clark) was a paid consultant of Elanco Animal Health at the time the manuscript was written, and one author (Lin) was a paid consultant of Nexcyon Pharmaceuticals, Inc. at the time the manuscript was written.

DATA AVAILABILITY STATEMENT

Not applicable.

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APPENDIX

Pain Assessment

Behavior from a Distance (0–2)

0. Comfortable, may appear/exhibit: content and quiet, comfortable when resting, interested in or curious about surroundings, ambulates normally; minimal body tension.

1. Uncomfortable, may appear/exhibit: slightly unsettled; less interested in surroundings; hair coat appears rough or fluffed up; may constantly groom an area that is painful or irritating; ambulates with noticeable weight shifting behavior but still places affected limbs on floor; mild-to-moderate body tension.

2. Distressed, may appear/exhibit: constantly yowling, growling, or hissing; may bite or chew at wound; unlikely to move, prostrate; unaware of surroundings; barely or unable to ambulate, significant weight shifts or non-bearing behavior; moderate to severe body tension

Behavior following Social Interaction (0–3)

0. Normal, may appear/exhibit: content and quiet, interested in or curious in the assessor as he/she approaches; does not object to stroking; minimal body tension.

1. Mildly Abnormal, may appear/exhibit: content or slightly unsettled; less interested in assessor's approach, but will look around to see what is going on; slight reduction in level of social behavior but does not overtly object to stroking; mild body tension.

2. Moderately Abnormal, may appear/exhibit: decreased responsiveness to assessor's approach, seeks solitude; quiet, tolerates attention, may even perk up when stroked, as long as painful area is avoided; mild-to-moderate body tension.

3. Severely Abnormal, may appear/exhibit: refuses to be stroked and may display aggression without provocation; growls or hisses at non-painful stroking; unlikely to move, prostrate; unaware of surroundings; may be rigid to avoid painful movement; moderate to severe body tension.

Pain on Palpation (0–2)

0. Minimal, may appear/exhibit: may react to palpation of surgical site, but at a pressure level nearly equivalent to what could be applied in a cat that had not undergone surgery.

1. Moderate, may appear/exhibit: reacts to palpation of surgical site at a pressure level less than what could be applied in a cat that had not undergone surgery, response to moderate palpation may be aggressive, including growling or hissing, and/or cat may try to escape upon palpation.

2. Severe, may appear/exhibit: growls or hisses at non-painful palpation or any level of physical contact to surgical area; reacts aggressively to non-painful palpation, adamantly pulls away to avoid any contact; alternatively may be rigid to avoid painful movement.

Pain Control (0–1)*:

0. Adequate; no rescue needed.

1. Inadequate; rescue needed.

*After Behavior from a Distance, Behavior following Social Interaction, and Pain on Palpation were scored, the pain assessor determined if pain control was adequate (0) or inadequate (1). No specific score (i.e., cumulative or taken from any individual section) was calculated to determine the need for rescue analgesia.