JOURNAL OF
Veterinary Pharmacology and Therapeutics

J. vet. Pharmacol. Therap. **35** (Suppl. 2), 53–64. doi: 10.1111/j.1365-2885.2012.01408.x

The effectiveness of a long-acting transdermal fentanyl solution compared to buprenorphine for the control of postoperative pain in dogs in a randomized, multicentered clinical study

D. D. LINTON*,
M. G. WILSON†,
G. C. NEWBOUND*,
K. J. FREISE* &
T. P. CLARK*

*Nexcyon Pharmaceuticals Inc., Madison, WI, USA; †Indiana University School of Medicine, Department of Clinical Pharmacology, Indianapolis, IN, USA

Linton, D. D., Wilson, M. G., Newbound, G. C., Freise, K. J., Clark, T. P. The effectiveness of a long-acting transdermal fentanyl solution compared to buprenorphine for the control of postoperative pain in dogs in a randomized, multicentered clinical study. *J. vet. Pharmacol. Therap.* **35** (Suppl. 2), 53–64.

A prospective, double-blinded, positive-controlled, multicenter, noninferiority clinical study was conducted to evaluate the safety and effectiveness of a long-acting transdermal fentanyl solution (TFS) for the control of postoperative pain. Four hundred forty-five client-owned dogs of various breeds were randomly assigned to receive a single dose of TFS (2.6 mg/kg [~50 μL/kg]) (N = 223) applied 2–4 h prior to surgery or buprenorphine (20 μg/kg) (N = 222) administered intramuscularly 2–4 h prior to surgery and every 6 h through 90 h. There were 159 (35.7%) males and 286 (64.3%) females ranging from 0.5 to 16 years of age and 3 to 98.5 kg enrolled. Pain was scored using the modified Glasgow Composite Pain Scale with an *a priori* dropout criteria of ≥8 (20 maximum score). The one-sided upper 95% confidence interval of the mean difference between fentanyl and buprenorphine treatment failures was 5.6%, which was not greater than the *a priori* selected margin difference of 15%. Adverse events attributed to either treatment were minimal in impact and were approximately equal between groups. Sustained plasma fentanyl concentrations provided by a single pre-emptive dose of TFS are safe and effective and are noninferior to repeated injections of buprenorphine in controlling postoperative pain over 4 days. This long-acting fentanyl formulation provides veterinarians with a novel, registered option for the control of postoperative pain in dogs that improves dosing compliance and potentially mitigates the disadvantages of oral, parenteral, and patch delivered opioids.

(Paper received 30 January 2012; accepted for publication 16 April 2012)

Dr Terrence Clark, Nexcyon Pharmaceuticals Inc., 644 W Washington Ave., Madison, WI 53703, USA. E-mail: clarktp@nexcyon.com

INTRODUCTION

Opioids are generally regarded as an important part of multimodal, perioperative analgesia, especially for moderate to severe pain. In human health, the use of opioids before, during, and after most soft tissue and orthopedic surgeries is considered the standard of care and are included in procedure-specific treatment algorithms (Neugebauer *et al.*, 2007). In veterinary medicine, there are limited opioid options for the treatment of moderate to severe pain in conscious, ambulatory dogs beyond the immediate postoperative period because of inherent limitations of most opioids that include poor oral bioavailability and rapid clearance (Pascoe, 2000). As a result, opioid use is often limited to single or repeat perioperative parenteral injections or intravenous (IV) constant rate infusions delivered during anesthesia and immediately postoperatively while dogs are hospitalized.

The approval of transdermal fentanyl solution[1] (TFS) for use in dogs by the European Medicines Agency (EMA) makes available a long-acting opioid for the control of postoperative pain in dogs and potentially mitigates the disadvantages of oral, parenteral, and extra-label patch delivered opioids. A single, rapid drying, small volume (~50 μL/kg), topically applied dose administered 2–4 h prior to surgery delivers fentanyl into the stratum corneum and provides sustained therapeutic plasma fentanyl concentrations over a period of at least 4 days (Freise *et al.*, 2012a, 2012c, 2012d). As a delivery method, the

[1] Recuvyra™ 50 mg/mL transdermal solution for dogs, Nexcyon Pharmaceuticals Ltd, London, UK.

transdermal route has several potential strengths over oral and parenteral administration. These include noninvasive dosing, avoidance of the gastrointestinal tract, and lack of first-pass metabolism. Steady, continuous drug delivery can avoid potential side effects associated with repeated postdose peaks in plasma concentrations as well as end of dose breakthrough pain associated with sub-analgesic plasma troughs. Additionally, reduced dose frequency allows for convenience and increased compliance (Urquhart, 2000).

The study presented here is a double-blinded, positive-controlled, parallel-arm, multicenter clinical study carried out by recruiting client-owned dogs that presented for orthopedic or various types of soft tissue surgery from 33 veterinary practices in France, Germany, and the United Kingdom. The study was conducted in compliance with veterinary international committee on harmonization (VICH) guideline 9 (GL9), good clinical practice guidance. The study objective was to evaluate the field safety and effectiveness of TFS when administered as a single, topical dose, 2–4 h prior to surgery compared to repeated intramuscularly (IM) injections of buprenorphine.

MATERIALS AND METHODS

Investigational drug

The investigational drug was TFS[1]. It is a clear, colorless to light yellow solution that contains 5% w/v (50 mg/mL) fentanyl base, 5% w/v (50 mg/mL) octyl salicylate (octisalate [2-ethylhexyl salicylate]), and isopropanol qs (quantum satis). Dogs randomized to TFS were administered a single dose according to the dosing table (Appendix I) of 2.6 mg/kg (~50 μL/kg) to the skin of the dorsal scapular area 2–4 h prior to surgery using a proprietary syringe and applicator tip (Freise *et al.*, 2012c, 2012d).

The skin over the dorsal scapular area required no specific preparation prior to liquid application. If the haircoat allowed direct contact of the proprietary applicator tips to the skin, no specific hair clipping or preparation was necessary. For thick-coated dogs such as Siberian Huskies, where the applicator tips could not directly deposit liquid onto the skin, clipping hair from the application site was required. To maintain blinding, the decision and actual clipping of the application site was carried out without knowledge of the treatment group assignment. Once the calculated volume of liquid was collected and applicator was attached to the syringe, the liquid was applied as follows: (i) the applicator tips were placed directly onto the skin of the dorsal scapular area, making sure that tips were in direct contact with the skin; (ii) up to 0.5 mL was applied onto the skin without moving the applicator tip; (iii) if the dosing volume was >0.5 mL, the applicator tip was then re-positioned at least 2.5 cm (1 inch) from the initial site and up to an additional 0.5 mL was applied; (iv) the reposition and application steps were repeated until the entire calculated volume was applied to the dog. The dog was then restrained for approximately 2 min to prevent removal by shaking or rolling and no contact was made with the site for 5 min following application to allow full drying of the liquid and fentanyl penetration into the skin. To prevent accidental application of the liquid to humans, animal health technicians wore latex or nitrile gloves, safety glasses, and a laboratory coat while administering the drug to dogs. There were no restrictions for interaction with the application site by professional staff or dog owners beyond 5 min following topical application.

Control drug

Field studies conducted to support a Marketing Authorization (MA) by EMA must be adequate and well controlled and the selected active control must be approved for the indication and species being examined. Buprenorphine[2] is approved by the Veterinary Medicines Directorate in the United Kingdom (MA number Vm 00063/4001) for postoperative analgesia in dogs to be administered IM or IV every 3–6 h. Dogs randomized to buprenorphine were administered the approved dose of 20 μg/kg IM, 2–4 h prior to intubation with additional doses at extubation and then every 6 h through 90-h postextubation. To maintain blinding, dogs allocated to TFS were physically handled every 6-h (±1 h) postextubation, in a manner similar to those administered buprenorphine injections, but no treatment was administered.

Inclusion and exclusion criteria

Dogs that qualified for inclusion into the study were client-owned animals. Normal, healthy, nonpregnant, nonlactating female and male dogs, with the exception of the condition requiring soft tissue or orthopedic surgery and conditions allowed under inclusion/exclusion criteria that in the opinion of the Investigator were suitable to undergo surgery, were enrolled. There was no restriction on breed or sex; both intact and castrated males and intact and ovariohysterectomized females were enrolled. A dog was eligible for inclusion in the study if: (i) it was at least 6 months of age or older; (ii) weighed >2.7 kg at the time of enrollment; (iii) it was presented for soft tissue or orthopedic surgery that was limited to ovariohysterectomy, anal saculectomy, mastectomy, lateral ear resection, or laparotomy procedures: cystotomy, enterotomy, splenectomy (partial or full), liver lobectomy or biopsy, kidney removal or biopsy, or tumor removal (including cryptorchid testes); (iv) it was presented for surgical cranial or caudal cruciate ligament stabilization. Dogs were required to have a score of P1 or P2 according to the American Society of Anesthesiologists system (Appendix II).

A dog was excluded from the study if it had received short-acting systemic corticosteroids within the last 14 days, had received nonsteroidal anti-inflammatory drugs (NSAIDs) within 24 h prior to surgery, or long-acting corticosteroids within the last 30 days.

[2]Vetergesic® (buprenorphine) Multidose, 0.3 mg/mL, solution for injection for dogs and cats; Alstoe Limited, Sheriff Hutton, York, UK.

Treatment randomization

Day 0 was defined as the day in which investigational or control drug was first administered. After meeting eligibility criteria on Day 1 or Day 0, dogs were hospitalized and randomized to treatment. Dogs within each clinic and surgery type were blocked on the basis of entry order into the study into blocks of two, and the two treatments were randomly assigned within each block. The ratio of soft surgery types was restricted to approximately 40% ovariohysterectomies to 60% other soft surgery types by the randomization schedule. Blocking was utilized to maintain enrollment balance and was not included in the statistical analysis as a design variable. Because this study was designed to evaluate postoperative pain in a clinical setting, there was no grouping or restriction to randomization to equalize for gender, weight, or age.

Blinding

All clinic personnel were blinded to the identity of the treatment assignments with the exception of the Treatment Administrator. The Treatment Administrator was the individual who allocated animals to treatment and administered treatments to qualified dogs, including the mock injections to dogs allocated to TFS. The Treatment Administrator was not involved in any post-treatment observations.

Study procedures

A screening physical examination, including opthalmoscopy and blood samples for hematology[3] and clinical chemistry[4], was performed for all candidate dogs up to Day −1 to qualify for entry into the study. After meeting eligibility criteria on Day −1 or Day 0, dogs were hospitalized throughout the study for observation through discharge on Day 4. A subsequent presurgical physical examination was performed prior to surgery on Day 0. A termination physical examination, including opthalmoscopy and blood samples for hematology and clinical chemistry, was conducted prior to discharge on Day 4.

Animal observations

Dogs were observed according to the hospital's standard practice. All observations of suspected abnormal health by any hospital personnel at any time were reported to the Investigator to verify the observations as adverse events.

[3]Hematocrit, RBC, Hemoglobin, MCV, MCH, MCHC, WBC, Segmented Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, and Platelets.

[4]Glucose, BUN, Creatinine, BUN/Creatinine ratio, Total Protein, Albumin, Globulin, Albumin/Globulin ratio, Total Bilirubin, ALT, AST, Alkaline Phosphatase, Amylase, CPK, Calcium, Phosphorus, Sodium, Potassium, Sodium/Potassium, Chloride, and Cholesterol.

Anesthesia

The anesthetic protocol was restricted to using combinations of the following agents according to the Investigator's practice standards: (i) anesthetic premedication: glycopyrrolate, acepromazine, atropine, midazolam, and/or diazepam; (ii) anesthetic induction: propofol, thiopental, ketamine/diazepam, or tiletamine/zolazepam; and (iii) anesthetic maintenance: isoflurane or sevoflurane in oxygen (with or without nitrous oxide). Heat, such as from a circulating water blanket, could be applied directly to the TFS application site or control injection site without restriction at any time during or after surgery.

Pain assessment

Pain assessments were based on a modification (deletion of section B) of the Glasgow Composite Pain Scale (GCPS) (Holton *et al.*, 2001; Murrell *et al.*, 2008) (Appendix III). The pain assessments were made by the same Pain Assessor for each dog. Assessments were performed in the order listed (Appendix III) by a trained observer, the Pain Assessor, prior to treatment (up to Day −1 or on Day 0), on Day 0 (1-h postextubation ± 30 min, 2-, 4-, 6-, 8-, 12-h postextubation ± 1 h), Day 1 (24-h postinitial treatment ± 4 h, then 6–8 h later), Day 2 (48-h postinitial treatment ± 4 h, then 6–8 h later), Day 3 (72-h postinitial treatment ± 4 h, then 6–8 h later), and Day 4 (96-h postinitial treatment ± 4 h). Prior to each pain assessment, a sedation score based on the scoring system used in laboratory safety studies (Savides *et al.*, 2012) was assigned as determined in Appendix IV. If the sedation score was ≥2, then the dog was considered to be too sedated to adequately assess analgesia and the pain score assessment was not conducted at that time. Following each sedation scoring and pain assessment (if conducted), rectal temperature, pulse rate, and respiratory rate were also recorded.

Pain intervention

At each pain assessment time point, dogs were evaluated for adequacy of pain control. The *a priori* criterion for the administration of pain intervention was a composite pain score ≥8 (of the 20 maximum score) at any time (FDA-CVM, 2007). If pain intervention was necessary, the dog was considered a treatment failure. Any dog removed from the study owing to lack of pain control was treated for pain using the Investigator's standard of care such as administration of NSAIDs and remained at the clinic for safety observations until the scheduled discharge on Day 4.

Adverse events

For the purpose of this study, the definition of an adverse event was that provided in VICH GL9: '*Any observation in animals that is unfavorable and unintended and occurs after the use of a veterinary product or investigational veterinary product, whether or not*

considered to be product related'. As a result, all safety observations are reported in this study whether or not they are considered to be causally related to TFS or buprenorphine. Adverse event recording began after animals had been administered the investigational or control drug beginning on Day 0. Following an adverse event, a physical examination was conducted and any tests deemed necessary were completed. All treatments as the result of an adverse event were documented. The relationship of all adverse events (including severe adverse events and deaths) to the administered investigational veterinary or control product was made by the blinded clinical investigators.

Opioid reversal

Naloxone[5], a full μ opioid receptor antagonist (Veng-Pedersen *et al.*, 1995), was to be administered to any dog that showed severe adverse effects consistent with opioid intoxication such as nonresponsive unconsciousness, seizure, or marked abdominal breathing. The dose to be administered was 0.04 mg/kg IV or IM as an initial dose. If clinical reversal was not observed after 2–3 min, administration of naloxone at the same dose was to be repeated. This dose regimen of naloxone has been shown to completely reverse the adverse effects of an overdose of TFS in dogs (Freise *et al.*, 2012b). Any dog requiring reversal with naloxone was considered a treatment failure, but remained at the clinic until the scheduled study discharge on Day 4 for safety observations per standard clinic practice.

Removal from the study

Once qualified for inclusion into the study, a dog could be removed at any time if the Investigator determined that pain, illness, injury, complication, or adverse reaction prohibited the animal from completing the study. In the event of removal from the study, dogs allotted to buprenorphine were not administered additional injections. At the time of withdrawal, a physical examination, including hematology and serum chemistry, was to be completed at the time of removal. Any dog removed from the study was considered a treatment failure if it was removed for lack of effectiveness or safety reasons and remained at the clinic until the scheduled study discharge on Day 4 for safety observations.

Statistical analysis

The primary variable for determining effectiveness and safety was the combined treatment failure rate owing to lack of pain control (pain score ≥8) or withdrawal from the study owing to adverse events or naloxone reversal. A one-sided upper 95% confidence bound of the TFS–buprenorphine treatment failure rate difference was calculated to test for noninferiority. The *a priori* noninferiority margin was based on the published NSAID–placebo treatment failure difference where the modified GCPS was used (FDA-CVM, 2007). In this study, the placebo failure rate was 24.2% (31/128) and the NSAID failure rate was 6.4% (8/126). The difference in the failure rate was 17.8% and therefore, taking a more conservative approach in the present study, a margin of 15% was selected.

Secondary variables included time-wise pain scores and sedation, rectal temperatures, heart rates, and respiratory rates collected at each pain assessment time point. No hypothesis testing was carried out for these secondary variables and two-sided 95% confidence intervals of the mean difference between the TFS–buprenorphine were constructed. For other data such as age, body weight, breed, and adverse events, summary statistics are provided.

All statistical calculations were conducted using SAS for Windows 9.1.3 (Service Pack 4; SAS Institute Inc., Cary, NC, USA).

Sample size determination

The sample size was selected to achieve 90% power to demonstrate noninferiority of TFS to buprenorphine when the true fentanyl dropout rate is 5 percentage points higher than the buprenorphine dropout rate. The buprenorphine dropout rate was assumed to be 15% for power calculations. A group size of 247 dogs results in 90% power to demonstrate noninferiority. To achieve at least 90% power, a group size of 250 dogs was set as the target for enrollment.

RESULTS

Demographics

A total of 445 dogs enrolled; 159 (35.7%) males and 286 (64.3%) females ranging from 6 month to 16 years of age approximately equally divided between TFS (N = 223) and buprenorphine (N = 222). The greater portion of females is a reflection of the allotment procedure in the soft tissue population that fixed at least 40% of the soft tissue enrollment to be ovariohysterectomies. There were 75 breeds of dogs represented (Table 1).

An 11.7% (26/223) of fentanyl- and 8.6% (19/222) of buprenorphine-treated dogs had the hair over the dorsal scapular area clipped prior to treatment. There were 199 and 235 dogs allotted to orthopedic and soft tissue surgeries, respectively (Table 2). The types of cruciate stabilization and soft tissue surgery were approximately equally divided between TFS- and buprenorphine-treated dogs. The 54.3% (121/223) of dogs allotted to fentanyl and 53.6% (119/222) of dogs allotted to buprenorphine were provided external heat during surgery to support core body temperature.

Treatment failures

Pain scores were highest 1 h following extubation in both groups where values were 2.98 ± 2 (mean ± SD) in TFS- and 2.67 ± 1.9 in buprenorphine-treated dogs (Fig. 1). Pain score declined over the 4-day study duration such that by Day 4, mean

[5]Naloxone HCl, Hospira Inc., Lake Forest, IL, USA.

Table 1. Breeds of dogs enrolled in the study

Breed	Total $N = 445$ *n* (%)
Crossbred	61 (13.7)
Boxer	25 (5.6)
Labrador Retriever	40 (9.0)
Rottweiler	21 (4.7)
Yorkshire Terrier	26 (5.8)
Poodle	20 (4.5)
Golden Retriever	16 (3.6)
German Shepherd Dog	15 (3.4)
Border Collie	9 (2.0)
English Springer Spaniel	14 (3.1)
Bichon Frise	11 (2.5)
Greyhound	12 (2.7)
Staffordshire Bull Terrier	13 (2.9)
Cocker Spaniel	10 (2.2)
French Bulldog	8 (1.8)
West Highland White Terrier	13 (2.9)
Cavalier King Charles Spaniel	9 (2.0)
Other pure breeds	122 (27.4)

Table 2. The types and numbers of orthopedic and soft tissue surgeries

Surgery Type	Total *n* (%)
Orthopedic	
Total orthopedic	199 (44.7)
TPLO	57 (12.8)
Fabellar suture	128 (28.8)
TTA	25 (5.6)
Soft tissue	
Total soft tissue	235 (52.8)
Ovariohysterectomy	90 (20.2)
Mastectomy	40 (9.0)
Cryptorchid testes removal	15 (3.4)
Anal sac removal	18 (4.0)
Perineal hernia	13 (2.9)
Lateral ear resection	11 (2.5)
Enterectomy	7 (1.6)
Splenectomy	7 (1.6)
Kidney removal/biopsy	4 (0.9)
Cystotomy	12 (2.7)
Liver lobectomy/biopsy	2 (0.4)
Pyometra	6 (1.3)
Total ear ablation	7 (1.6)
Intra-abdominal tumor removal	3 (0.7)

pain scores were 1.2 ± 1.8 in TFS- and 1.4 ± 1.9 in buprenorphine-treated dogs. The 95% CI contained 0 at each pain assessment time point further supporting the finding that TFS is noninferior to buprenorphine.

In the soft tissue population, 10 dogs were considered treatment failures (Table 3). Five dogs (3 TFS, 2 buprenorphine) were withdrawn owing to lack of pain control. The three dogs administered TFS that were treatment failures were withdrawn

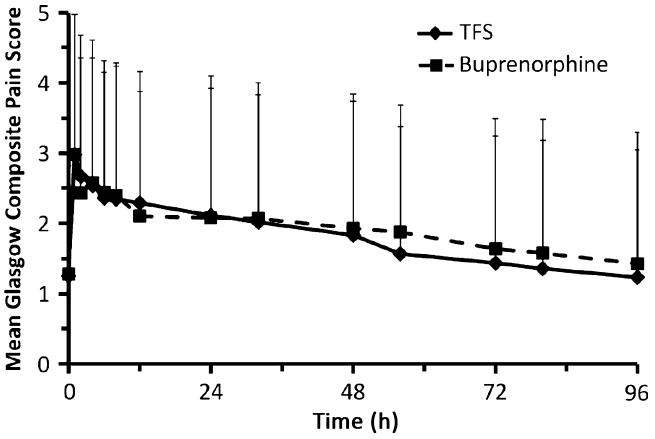

Fig. 1. Mean ± SD modified Glasgow Composite Pain Scale (GCPS) scores for transdermal fentanyl solution (TFS)- and buprenorphine-treated dogs at each pain assessment time point.

Table 3. The number and reasons for treatment failure in TFS- and buprenorphine-treated dogs

Reason	TFS ($N = 223$) *n* (%)	Buprenorphine ($N = 222$) *n* (%)
Soft tissue		
Safety		
Adverse event	0 (0.0)	1 (0.5)
Opioid reversal	3 (1.3)	0 (0.0)
Death	1 (0.4)	0 (0.0)
Effectiveness		
Lack of pain control	3 (1.3)	2 (0.9)
Orthopedic		
Safety		
Adverse event	1 (0.4)	1 (0.5)
Opioid reversal	2 (0.9)	0 (0.0)
Death	1 (0.4)	0 (0.0)
Effectiveness		
Lack of pain control	4 (1.8)	4 (1.8)
Total	15 (6.7)	8 (3.6)

TFS, transdermal fentanyl solution.

on Day 0 at 6-h postextubation, and at the first and second assessments on Day 1 with pain scores of 11, 11, and 9, respectively. The two buprenorphine-treated dogs were withdrawn on Day 0 at 4-h postextubation and on Day 2 at the first assessment of the day, with scores of 12 and 10, respectively. Three TFS-treated dogs did not complete the study owing to adverse events, all of which were administered naloxone, and one buprenorphine-treated dog did not complete the study owing to adverse events. One TFS-treated dog undergoing soft tissue surgery did not complete the study owing to death not attributable to investigational drug treatment and is discussed in the *Deaths* section below.

In the orthopedic population, 13 dogs were considered treatment failures (Table 3). Eight dogs (4 TFS, 4 buprenorphine) were withdrawn owing to lack of pain control. The four

TFS-treated dogs were withdrawn at the following study times as the result of the following pain scores: during surgery prior to any pain scoring (1 dog), on Day 0 at 4- (1 dog) and 8-h (1 dog) postextubation, and at the first assessment on Day 1 (1 dog) with pain scores of 10, 8, and 8, respectively. The four buprenorphine-treated dogs were withdrawn on Day 0 at 4-h postextubation (1 dog) and on Day 1 at the first (one dog) and second (two dogs) assessments of the day, with scores of 8–12. Three TFS-treated dogs did not complete the study owing to adverse events, two of which were administered naloxone, and one buprenorphine-treated dog did not complete the study owing to adverse events. One TFS-treated dog that underwent orthopedic surgery did not complete the study owing to death. Death was not attributed to investigational drug treatment and is discussed in the *Deaths* section below.

The primary variable for determining effectiveness was a noninferiority evaluation of the TFS and buprenorphine treatment failure rate which were 6.7% (15/223) and 3.6% (8/220), respectively (Table 4). The one-sided upper 95% confidence bound was 5.6%, which was not >15%. Therefore, based on the treatment failure rate, TFS was noninferior to buprenorphine.

Sedation

Sedation scores were highest at the first pain assessment time, 1-h postextubation where the scores were 2.2 ± 0.97 (mean ± SD) and 2.1 ± 0.97 in TFS- and buprenorphine-treated dogs, respectively (Fig. 2). By 6-h postextubation, mean sedation scores in both groups were <1 (mild), 0.9 and 0.8 for TFS and buprenorphine, respectively. The 95% CI of the mean difference of TFS–buprenorphine sedation scores contained 0 at each assessment time point suggesting that treatment with TFS resulted in no greater sedation compared to repeated injections of buprenorphine. At 1-h postextubation, 76% of TFS-treated dogs had a sedation scores ≥2 and by 12 h this had diminished to 5.5% of dogs (Fig. 3). By 24 h, 2.8% of TFS-treated dogs had a sedation scores ≥2 and none beyond 56 h. The number of buprenorphine-treated dogs with sedation scores ≥2 was similar over time compared to TFS. At 1-h postextubation, 76% of buprenorphine-treated dogs had a sedation scores ≥2 and 6% of dogs remained moderately sedated at 12 h. By 24 h, 0.5% of buprenorphine-treated dogs had a sedation scores ≥2 and none beyond 32 h.

Table 4. Noninferiority analysis of treatment failures

TFS (N = 223)	Buprenorphine (N = 220*)	Difference		
Treatment failures	Treatment failures			
n (%)	n (%)	Mean	SE	Upper 95% CI†
15 (6.7)	8 (3.6)	3.1	1.5	5.6

TFS, transdermal fentanyl solution.
*The safety and efficacy population contained 222 and 220, respectively. Two dogs with planned intra-abdominal soft tissue surgeries were treated with buprenorphine but did not require laparotomy following enrollment and were excluded from the efficacy population.
†The TFS treatment failure rate was noninferior to the buprenorphine dropout rate as the upper 95% CI of the percent difference was less than or equal to the 15% *a priori* margin of difference.

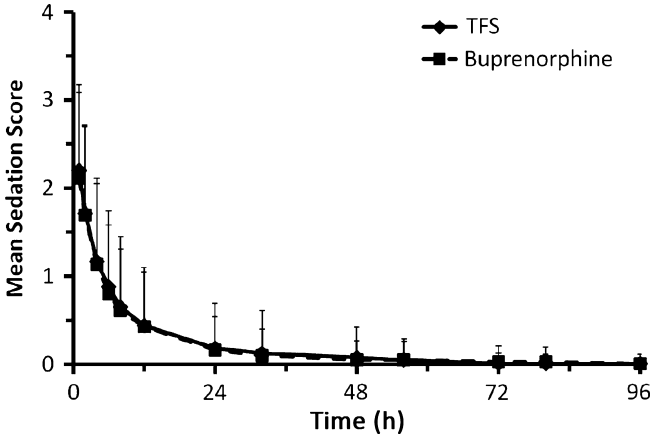

Fig. 2. Mean ± SD sedation scores for transdermal fentanyl solution (TFS)- and buprenorphine-treated dogs at each pain assessment time.

Temperature, pulse, and respiration

Rectal temperatures were lowest at the first pain assessment time, 1-h postextubation where the temperatures were 36.8 °C ± 1.2 (98.2 °F ± 2.1) (mean ± SD) and (36.8 °C ± 1.2) (98.2 °F ± 2.1) in TFS- and buprenorphine-treated dogs, respectively (Fig. 4). Mean temperatures exceeded 37.8 °C (100 °F) in TFS- and buprenorphine-treated dogs at 24-h and 6-h postextubation, respectively. At the study conclusion on Day 4, temperatures were 38.4 °C ± 0.5 (101.1 °F ± 0.9) and 38.5 °C ± 0.5 (100.8 °F ± 0.8) in TFS- and buprenorphine-treated dogs, respectively.

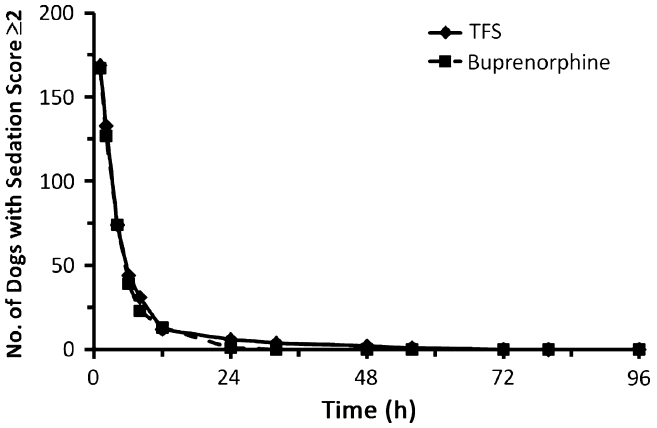

Fig. 3. The number of transdermal fentanyl solution (TFS)- and buprenorphine-treated dogs with a sedation score of ≥2 at each pain assessment time point over the 4-day study duration.

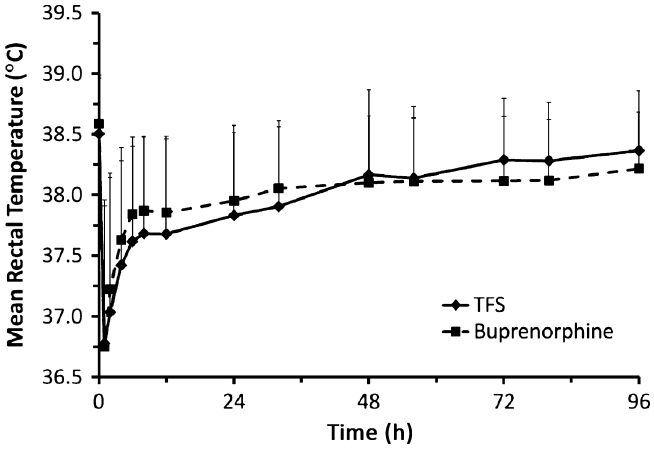

Fig. 4. Mean ± SD rectal temperatures for transdermal fentanyl solution (TFS)- and buprenorphine-treated dogs at each pain assessment time point.

Mean heart rates ranged from 94.2 to 100.6 bpm and 91.5–103.1 bpm over the 4-day study for TFS- and buprenorphine-treated dogs, respectively (Fig. 5). From 36 to 96 h, the 95% CI of the mean difference of TFS–buprenorphine heart rates did not contain 0 suggesting that treatment with buprenorphine resulted in lower heart rates compared to TFS during these time periods. The mean heart rate from 32 to 96 h in buprenorphine-treated dogs was 91.5–93.9 bpm.

Mean respiratory rates ranged from 36.6 to 46.6 rpm and 33.9–44.2 rpm over the 4-day study for TFS- and buprenorphine-treated dogs, respectively (Fig. 6). The 95% CI of the mean difference of TFS–buprenorphine respiratory rates contained 0 at all time points suggesting that the effect of TFS and buprenorphine on respiratory rate was not different.

Body weight

A 24.3% of TFS-treated dogs and 28.4% of buprenorphine-treated dogs did not lose body weight over the 4-day study period. The 46.7% of TFS-treated dogs and 40.8% of buprenorphine-treated dogs lost up to 5% of their body weight. Approximately 25% of buprenorphine- and TFS-treated dogs lost between 5% and 10% and another approximate 4% of buprenorphine- and TFS-treated dogs lost between 10% and 15% body weight. One buprenorphine-treated dog lost >15% of body weight.

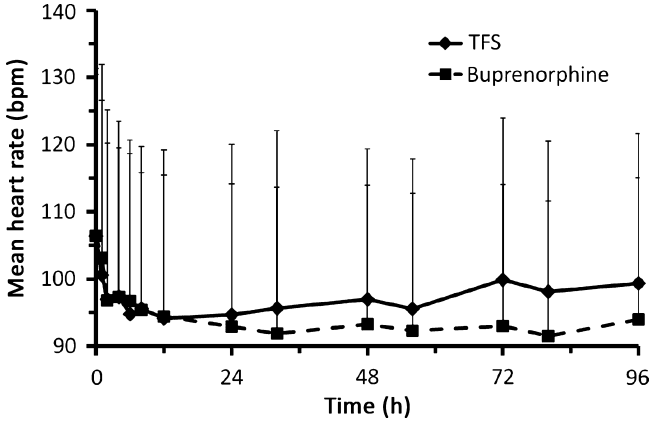

Fig. 5. Mean ± SD heart rates for transdermal fentanyl solution (TFS)- and buprenorphine-treated dogs at each pain assessment time point.

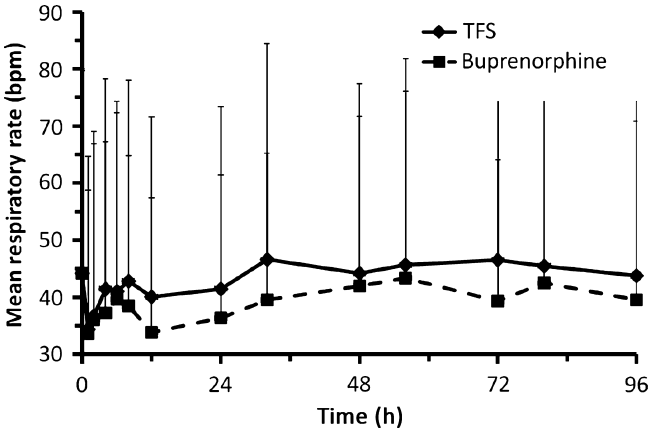

Fig. 6. Mean ± SD respiratory rates for transdermal fentanyl solution (TFS)- and buprenorphine-treated dogs at each pain assessment time point.

Clinical pathology

In all instances, the mean value for all clinical pathology variables was within the reference range for both treatment groups at baseline and at study conclusion on Day 4. Individual excursions outside the normal ranged were not judged to be treatment related but rather causally related to the surgical disease being treated.

Adverse events

The type and frequency of adverse events was approximately equal between treatment groups (Table 5). There were a total of 47 (21.1%) TFS-treated dogs that experienced adverse events and those with an event rate of ≥1% included emesis, diarrhea, sedation, anorexia, hypersalivation, ataxia, bradycardia, conjunctivitis, and hypothermia. In buprenorphine-treated dogs, 48 (21.6%) dogs experienced an adverse event and those with an event rate of ≥1% included emesis, diarrhea, sedation, anorexia, bradycardia, conjunctivitis, hypothermia, and tachycardia.

Deaths

There were two deaths in this study. The first dog was allotted to TFS and underwent a surgical liver lobectomy owing to liver pathology. The dog was proceeding on the study without incident, when it was discovered dead on the morning of Day 3. Necropsy indicated biliary duct perforation and associated peritonitis and the death was judged to be owing to the pre-existing pathology and not owing to TFS treatment. The second dog was allotted to TFS and 15 min following anesthetic induction with thiopental, the dog experienced cardiac arrest,

Table 5. Adverse event rate for TFS- and buprenorphine-treated dogs from the time of first treatment on Day 0 through Day 4 with an incidence of event rate of ≥1% in either treatment group

	TFS (N = 223)	Buprenorphine (N = 222)
Category	n (%)	n (%)
Emesis	12 (5.4)	11 (5.0)
Diarrhea	9 (4)	9 (4.1)
Sedation	8 (3.6)	3 (4.1)
Anorexia	7 (3.1)	3 (1.4)
Hypersalivation	4 (1.8)	1 (0.5)
Ataxia	4 (1.8)	0 (0.0)
Bradycardia	3 (1.3)	5 (2.3)
Conjunctivitis	3 (1.3)	4 (1.8)
Hypothermia	3 (1.3)	4 (1.8)
Tachycardia	1 (0.4)	3 (1.4)

TFS, transdermal fentanyl solution.

followed by respiratory arrest, and was not successfully resuscitated. Naloxone was not administered to this dog. Necropsy was unremarkable, except for thickening of the left ventricle of the wall of the heart, and the cause of death was judged to be barbiturate intolerance and not related to TFS treatment.

DISCUSSION

These study results demonstrate that a single dose of TFS applied topically 2–4 h prior to surgery is safe and effective for the control of pain associated with orthopedic and soft tissue surgery in dogs and provides analgesia for 4 days. As a primary endpoint, the treatment failure rate that encompassed both safety (i.e., adverse event) and effectiveness (i.e., inadequate pain control by *a priori* GCPS ≥8) in TFS-treated dogs was noninferior to those treated with IM buprenorphine injections every 6 h through 90 h (Table 4). There was a high degree of analgesic effectiveness as evidenced by the low treatment failure rate owing to a GCPS ≥8 alone; there were 7/223 (3.1%) and 6/222 (2.7%) of TFS- and buprenorphine-treated dogs, respectively, removed from the study (Table 3). This is further confirmed by the low pain scores over the 4-day study, where mean pain scores in both groups never exceeded three of a total possible score of 20 on the GCPS (Fig. 1). From a safety perspective, changes to postoperative physiological variables and adverse events were approximately similar between the two opioids.

A single dose of TFS provides sustained, systemic fentanyl delivery over a period of days as demonstrated in both laboratory dogs (Freise *et al.*, 2012c, 2012d) and in a randomized, multicentered clinical study (Freise *et al.*, 2012a). Buprenorphine[2] injection is an approved opioid for the control of postoperative pain in dogs and was therefore chosen as an active control. A single injection does not result in extended therapeutic concentrations, but repeated injections result in effective, long-term opioid exposure (Andaluz *et al.*, 2009). The decision to follow dogs for 4 days was based on the known natural course of pain following surgery. In a randomized, blinded study of dogs undergoing a variety of types of orthopedic and soft tissue surgeries, NSAIDs resulted in significant pain reduction compared to placebo for at least 3 or 4 days following surgery (Clark *et al.*, 2001; Martinez *et al.*, 2001).

A noninferiority trial was chosen because it would not be reasonable to hypothesize that a μ-agonist opioid would be superior to another opioid, even a full agonist (i.e., fentanyl) compared to a partial agonist (i.e., buprenorphine), at clinically useful doses and frequencies that provide analgesia with minimal side effects. An investigational drug is noninferior to an active control if there is a high degree of confidence that it is not inferior to control drug by more than a predetermined margin of difference. In regulated noninferiority trials, the margin of difference cannot be greater than the smallest effect size that the investigational drug would be reliably expected to have compared with placebo in the setting of the planned trial (ICH E10, Section 1.5.1.1). A placebo-controlled study with buprenorphine in dogs under similar design using the GCPS with discrete dropout criteria has not been reported in the literature and for ethical reasons was not undertaken for the sole purpose to generate a margin.

However, following completion of this transdermal fentanyl study, a small placebo-controlled clinical trial of subcutaneously (SQ) administered buprenorphine (20 μg/kg every 6 h) for postoperative pain associated with ovariohysterectomy was reported that used a similar behaviorally based pain scale (23-point University of Melbourne Pain Scale [UMPS] compared to the 20-point GCPS) (Moll *et al.*, 2009). That study reported that pain scores were >2-fold higher in the placebo control group than in the SQ buprenorphine group (7.89 ± 0.44 and 3.05 ± 0.27, respectively), clearly demonstrating that repeatedly extravascularly injected buprenorphine in dogs provides significant and sustained postoperative analgesia. The peak mean UMPS scores of 4.6 following repeated SQ buprenorphine injections were quantitatively similar to the peak mean GCPS scores in the current study of 2.59 following repeated IM buprenorphine injections (Fig. 1). In another study that compared a single 20 μg/kg IM buprenorphine injection to 4.4 mg/kg SQ carprofen for postoperative analgesia, the peak mean GCPS scores (using a 24-point GCPS) in the buprenorphine treatment group were also very similar at 4.4 (Shih *et al.*, 2008). Combined, these results indicate that the analgesic effects of injectable buprenorphine can be consistently and repeatedly demonstrated under similar study designs.

In addition to the important aspect in noninferiority trials of *a priori* selecting the margin of difference (e.g., 15%), an important *post hoc* aspect is ensuring that the positive control had the expected magnitude of effect (i.e., constancy assumption maintained, ICH E10, Section 1.5.1.1). The *a priori* selected noninferiority margin was based on a placebo-controlled trial of postoperative analgesia in dogs that used the same GCPS ≥8 as a treatment failure criteria (FDA-CVM, 2007). In that trial, the analgesic treatment group had a failure rate of 6.4% (compared to 24.2% for the placebo group), very similar to the buprenorphine positive control treatment failure rate owing to lack of pain control only (i.e., GCPS ≥8) of 2.7% (6/222, Table 3). Thus, the

magnitude of the positive control effect was consistent with the expected effect of the analgesic and the noninferiority trial constancy assumption was maintained.

Along with the desired analgesic effects, sedation is an expected extension of the pharmacological effect of opioids (Gutstein & Akil, 2006). Excessive sedation was not a key feature of either treatment in this study. Sedation was approximately moderate by 1 h following extubation with TFS- and buprenorphine-treated dogs having mean sedation scores of 2.2 and 2.1, respectively. Thereafter, sedation scores rapidly dropped such that by 24 h, there was 6/223 (2.7%) and 1/222 (0.5%) of dogs with sedation scores ≥2 for dogs treated with TFS and buprenorphine, respectively. No dogs beyond the second postoperative day had sedation scores ≥2. Throughout the 96-h postoperative period, the 95% CI of the mean difference between TFS and buprenorphine contained 0 consistent with no differences in these treatments. It should be noted that the magnitude and duration of sedation over a period of days following surgery in a placebo-controlled study has not been reported in veterinary medicine. However, in a positive-controlled study comparing a single 20 μg/kg IM buprenorphine injection to 4.4 mg/kg SQ carprofen following ovariohysterectomy in dogs, sedation was virtually absent by 6-h postextubation in the carprofen-treated dogs but still present in the buprenorphine-treated dogs (Shih *et al.*, 2008). Nevertheless, these data suggest that although sedation is an expected outcome when opioids are administered at therapeutic concentrations, analgesia can be delivered over 4 days with a single dose of TFS without concern for excessive sedation.

Measures of safety were approximately similar for both TFS- and buprenorphine-treated dogs. Rectal temperature differences did not have any apparent clinical significance, and these data support the notion that postoperative hypothermia following TFS is not a primary concern requiring additional case management intervention. In addition, population PK analysis from a randomized clinical trial in dogs treated with TFS prior to orthopedic or soft tissue surgery suggests that fentanyl flux and analgesia are maintained in the presence of decreased body temperature during the postoperative period (Freise *et al.*, 2012a).

Heart rates were minimally affected in both treatments groups. Results from the present study suggest that reduced postoperative heart rates or arrhythmias during 4 days following treatment with TFS are not a clinical concern. In addition, hypoventilation and respiratory depression were not dose-limiting adverse reactions in this study. Throughout the study, respiratory rates were maintained and there were no dropouts owing to respiratory adverse events. Unlike in humans, spontaneous respirations are maintained independent of fentanyl concentration in dogs (Bailey *et al.*, 1987; Mathews, 2000). The present study demonstrates postoperative respiratory adverse events are not a clinical concern and that established tolerance to opioid-induced respiratory depression is not necessary prior to initiating treatment with TFS in dogs.

A standard preoperative practice is to limit food intake prior to anesthesia to eliminate the likelihood of intra- or postoperative regurgitation and aspiration. Postoperative food is gradually reintroduced at an amount and frequency appropriate for the condition that required surgery. Despite these common practices of nutritional management during the perioperative period, there are no data available regarding expected body weight changes in response to surgery in the veterinary literature. In the present study, 76% and 88% of TFS- and buprenorphine-treated dogs lost weight compared to baseline. Most body weight loss in both groups was between 0% and 5% but a small percentage of dogs lost >10% of body weight. There was no obvious morbidity problems associated with dogs that lost body weight over 4 days. The body weight change over a period of days following surgery in a placebo-controlled study has not been reported in veterinary medicine. Therefore, it cannot be concluded with certainty that the observed change in body weight was owing to opioid, anesthesia, or other surgically related postoperative comorbidity. However, in the absence of adverse events associated with the observed body weight loss, it is concluded that a small degree of weight loss must be a typical outcome of surgery but that a placebo-controlled study would be necessary to confirm this observation.

The adverse events that affected at least 1% of dogs included emesis, diarrhea, sedation, anorexia, hypersalivation, ataxia, bradycardia, conjunctivitis, and hypothermia. These are consistent with class effects of opioids and were approximately similar between TFS and buprenorphine.

CONCLUSION

In summary, this study demonstrates that a single, small volume of pre-emptive TFS administered 2–4 h prior to surgery provides analgesia that is noninferior to repeated injections of buprenorphine over 4 days. For safety observations that included sedation scores, body temperature, heart rate, respiratory rate, and adverse events, changes were minimal in magnitude and frequency and were approximately equal between groups. A readily available, EMA-approved, long-acting opioid may allow further optimization of postoperative analgesia in dogs for 4 days following surgery and potentially mitigate the disadvantages of extra-label oral, parenteral, and patch delivered opioids.

ACKNOWLEDGMENTS

The study was funded by Nexcyon Pharmaceuticals, Inc. The authors wish to acknowledge the clinical Investigators for recruitment and enrollment of the clinical cases included in this study.

CONFLICTS OF INTEREST

The authors were employees or paid contributors to Nexcyon Pharmaceuticals, Inc.

REFERENCES

Andaluz, A., Moll, X., Abellan, R., Ventura, R., Carbo, M., Fresno, L. & Garcia, F. (2009) Pharmacokinetics of buprenorphine after intravenous administration of clinical doses to dogs. *Veterinary Journal (London, England: 1997)*, **181**, 299–304.

Bailey, P.L., Port, J.D., McJames, S., Reinersman, L. & Stanley, T.H. (1987) Is fentanyl an anesthetic in the dog? *Anesthesia and Analgesia*, **66**, 542–548.

Clark, T.P., Curto, M., Huhn, J.C., Anway, S.D., Smothers, C.D. & Boy, M.G. (2001) *The Effect of Perioperative Carprofen Administration on the Alleviation of Pain Associated with Soft Tissue Surgery*. American College of Veterinary Anesthesia Annual Forum, New Orleans, LA, USA.

FDA-CVM (2007) *NADA 141-230 Freedom of Information Summary*. FDA-CVM, Rockville, MD.

Freise, K.J., Linton, D.D., Newbound, G.C., Tudan, C. & Clark, T.P. (2012a) Population pharmacokinetics of transdermal fentanyl solution following a single dose administered prior to soft tissue and orthopedic surgery in dogs. *Journal of Veterinary Pharmacology and Therapeutics*, **35**(Suppl. 2), 65–72.

Freise, K.J., Newbound, G.C., Linton, D.D., Tudan, C. & Clark, T.P. (2012b) Naloxone reversal of an overdose of a novel, long acting transdermal fentanyl solution in laboratory Beagles. *Journal of Veterinary Pharmacology and Therapeutics*, **35**(Suppl. 2), 45–51.

Freise, K.J., Newbound, G.C., Tudan, C. & Clark, T.P. (2012c) Pharmacokinetics and the effect of application site on a novel, long acting transdermal fentanyl solution in healthy laboratory Beagles. *Journal of Veterinary Pharmacology and Therapeutics*, **35**(Suppl. 2), 27–33.

Freise, K.J., Savides, M.C., Riggs, K.L., Owens, J.G., Newbound, G.C. & Clark, T.P. (2012d) Pharmacokinetics and dose selection of a novel, long-acting transdermal fentanyl solution in healthy laboratory Beagles. *Journal of Veterinary Pharmacology and Therapeutics*, **35**(Suppl. 2), 21–26.

Gutstein, H.B. & Akil, H. (2006) Opioid analgesics. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th edn. Eds Brunton, L.L., Lazo, J.S. & Parker, K.L., pp. 547–590. McGraw-Hill, New York.

Holton, L., Reid, J., Scott, E.M., Pawson, P. & Nolan, A. (2001) Development of a behaviour-based scale to measure acute pain in dogs. *The Veterinary Record*, **148**, 525–531.

Martinez, S., Clark, T.P., Curto, M., Huhn, J.C., Anway, S.D., Wang, C. & Boy, M.G. (2001) *The Effect of Perioperative Carprofen Administration on the Alleviation of Pain Associated with Cruciate Surgery*. American College of Veterinary Surgeons Annual Forum, Chicago, IL, USA.

Mathews, K.A. (2000) Pain assessment and general approach to management. *The Veterinary Clinics of North America: Small Animal Practice*, **30**, 729–755, v.

Moll, X., Fresno, L., Garcia, F., Prandi, D. & Andaluz, A. (2009) Comparison of subcutaneous and transdermal administration of buprenorphine for pre-emptive analgesia in dogs undergoing elective ovariohysterectomy. *Veterinary Journal (London, England: 1997)*.

Murrell, J.C., Psatha, E.P., Scott, E.M., Reid, J. & Hellebrekers, L.J. (2008) Application of a modified form of the Glasgow pain scale in a veterinary teaching centre in the Netherlands. *The Veterinary Record*, **162**, 403–408.

Neugebauer, E.A., Wilkinson, R.C., Kehlet, H. & Schug, S.A. (2007) PROSPECT: a practical method for formulating evidence-based expert recommendations for the management of postoperative pain. *Surgical Endoscopy*, **21**, 1047–1053.

Pascoe, P.J. (2000) Opioid analgesics. *The Veterinary Clinics of North America: Small Animal Practice*, **30**, 757–772.

Savides, M.C., Pohland, R.C., Wilkie, D.A., Abbott, J.A., Newbound, G.C., Freise, K.J. & Clark, T.P. (2012) The margin of safety of a single application of transdermal fentanyl solution when administered at multiples of the therapeutic dose to laboratory dogs. *Journal of Veterinary Pharmacology and Therapeutics*, **35**(Suppl. 2), 35–43.

Shih, A.C., Robertson, S., Isaza, N., Pablo, L. & Davies, W. (2008) Comparison between analgesic effects of buprenorphine, carprofen, and buprenorphine with carprofen for canine ovariohysterectomy. *Veterinary Anaesthesia and Analgesia*, **35**, 69–79.

Urquhart, J. (2000) INTERNAL MEDICINE IN THE 21ST CENTURY: controlled drug delivery: therapeutic and pharmacological aspects. *Journal of Internal Medicine*, **248**, 357–376.

Veng-Pedersen, P., Wilhelm, J.A., Zakszewski, T.B., Osifchin, E. & Waters, S.J. (1995) Duration of opioid antagonism by nalmefene and naloxone in the dog: an integrated pharmacokinetic/pharmacodynamic comparison. *Journal of Pharmaceutical Sciences*, **84**, 1101–1106.

APPENDIX 1

The volume of TFS administered was based on body weight according to the following dosing table. The average dose in each weight band was approximately 2.6 mg/kg (~50 μL/kg)

Fentanyl dosing table

Body weight	
Kgs	Dose (mL)
3.0–4.2	0.2
4.3–6.1	0.3
6.2–8.0	0.4
8.1–9.9	0.5
10.0–11.7	0.6
11.8–13.6	0.7
13.7–15.5	0.8
15.6–17.4	0.9
17.5–19.3	1.0
19.4–21.2	1.1
21.3–23.1	1.2
23.2–25.0	1.3
25.1–26.9	1.4
27.0–28.8	1.5
28.9–30.6	1.6
30.7–32.5	1.7
32.6–34.4	1.8
34.5–36.3	1.9
36.4–38.2	2.0
38.3–40.1	2.1
40.2–42.0	2.2
42.1–43.9	2.3
44.0–45.8	2.4
45.9–47.7	2.5
47.8–49.6	2.6
49.7–51.4	2.7
51.5–53.3	2.8
53.4–55.2	2.9
55.3–57.1	3.0

Body weight	Dose (mL)	
Kgs*	Syringe 1	Syringe 2
57.2–59.0	2.0	1.1
59.1–60.9	2.0	1.2

APPENDIX 1

(*Continued*)

Body weight	Dose (mL)	
Kgs*	Syringe 1	Syringe 2
61.0–62.8	2.0	1.3
62.9–64.7	2.0	1.4
64.8–66.6	2.0	1.5
66.7–68.5	2.0	1.6
68.6–70.3	2.0	1.7
70.4–72.2	2.0	1.8
72.3–74.1	2.0	1.9
74.2–76.0	2.0	2.0
76.1–77.9	3.0	1.1
78.0–79.8	3.0	1.2
79.9–81.7	3.0	1.3
81.8–83.6	3.0	1.4
83.7–85.5	3.0	1.5
85.6–87.4	3.0	1.6
87.5–89.3	3.0	1.7
89.4–91.1	3.0	1.8
91.2–93.0	3.0	1.9
93.1–94.9	3.0	2.0
95.0–96.8	3.0	2.1
96.9–98.7	3.0	2.2
98.8–100.6	3.0	2.3
100.7–102.5	3.0	2.4
102.6–104.4	3.0	2.5
104.5–106.3	3.0	2.6
106.4–108.2	3.0	2.7
108.3–110.0	3.0	2.8
110.1–111.9	3.0	2.9
112.0–113.8	3.0	3.0

*For dogs weighing 57.2–113.8 kg, two different, unique syringes were used to apply doses. A single syringe was not re-used for dosing. The used syringe(s)/applicator tip(s) was/were disposed as a unit in an indicated container.

APPENDIX 2

American Society of Anesthesiologists Physical Status Classification System

P1	A normal healthy patient
P2	A patient with mild systemic disease
P3	A patient with severe systemic disease
P4	A patient with severe systemic disease that is a constant threat to life
P5	A moribund patient who is not expected to survive without the operation
P6	A declared brain-dead patient whose organs are being removed for donor purposes

APPENDIX 3

Modified Glasgow Composite Pain Scale Form

A. Look at dog in kennel. Is the dog:

(i)

0 Quiet
1 Crying or whimpering
2 Groaning
3 Screaming

(ii)

0 Ignoring any wound or painful area
1 Looking at wound or painful area
2 Licking wound or painful area
3 Rubbing wound or painful area
4 Chewing wound or painful area

C. If it has a wound or painful area including abdomen, apply gentle pressure 2 inches round the site. Does it:

(iv)

0 Do nothing
1 Look round
2 Flinch
3 Growl or guard area
4 Snap
5 Cry

D. Overall: Is the dog:

(v)

0 Happy and content and happy or bouncy
1 Quiet
2 Indifferent or nonresponsive to surroundings
3 Nervous or anxious or fearful
4 Depressed or nonresponsive to stimulation

(vi)

0 Comfortable
1 Unsettled
2 Restless
3 Hunched or tense
4 Rigid

APPENDIX 4

Sedation score scale

0 – No Sedation Present

1 – Slight Sedation – almost normal; able to stand easily, but appears somewhat fatigued, subdued, or somnolent.

2 – Moderate Sedation – able to stand but prefers to be recumbent; sluggish; ataxic or uncoordinated.

3 – Profound Sedation – unable to rise, but can exhibit some awareness of environment; responds to stimuli through body movement; may be lateral or sternal recumbency.

4 – Unresponsive – in a state of coma or semi-coma from which little or no response can be elicited; remains in lateral recumbency.

If the sedation score was ≥2, then the dog was considered to be too sedated to adequately assess analgesia and the pain score assessment was not conducted at that time.