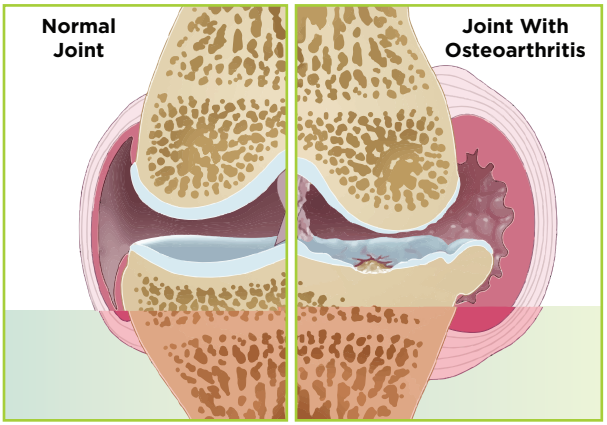

Librela™
(bedinvetmab injection)
GIVE YOUR DOG
MORE DAYS OF
PLAY
Control dog osteoarthritis (OA) pain
with monthly, long-lasting Librela

What Is Dog OA Pain?

It's a painful, chronic condition that causes your dog to hurt all the time if it's not treated[1]



OA is a type of arthritis that happens when **protective tissue in the joints is worn down**, causing bones to rub against one another.

Dogs of all ages, sizes, and breeds can have OA pain—it's not just a condition seen in older dogs.[2]

OA pain impacts how your dog moves and feels, and it can make it hard for you both to do the things you love to do together.

OA pain hurts, decreases your dog's willingness to play, and **affects their quality of life**.[1]

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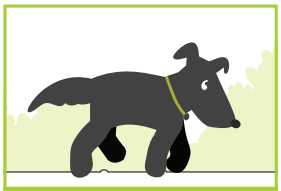
Is Your Dog Showing Signs of OA Pain?

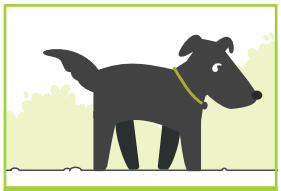
An OA diagnosis can be missed in some dogs because the signs may be subtle or overlooked as normal changes related to aging

Nearly 40% of dogs show signs of OA pain, but less than half are actually diagnosed[3,4]

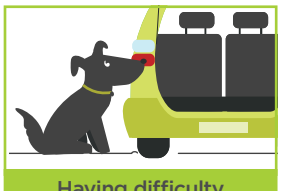
Your dog could be suffering from OA pain if they're displaying the following behaviors:


Limping after exercise


Slow to rise


Feeling stiff


Lagging behind on walks


Having difficulty jumping


Having difficulty with stairs

If your dog is showing any of these behaviors, speak to a veterinary professional.

Take the Dog OA Pain Checklist quiz to see if your dog could be showing signs of OA.

Scan the code with your phone's camera to take the quiz.

IMPORTANT SAFETY INFORMATION: For use in dogs only. Women who are pregnant, trying to conceive or breastfeeding should take extreme care to avoid self-injection. Hypersensitivity reactions, including anaphylaxis, could potentially occur with self-injection. LIBRELA should not be used in breeding, pregnant or lactating dogs. LIBRELA should not be administered to dogs with known hypersensitivity to bedinvetmab. The most common adverse events reported in a clinical study were urinary tract infections, bacterial skin infections and dermatitis. See full Prescribing Information in pocket.

Give Your Dog More Days of Play With Librela

Librela provides long-term OA pain control for your dog with a **once-a-month injection** given by your veterinary professional.[5,6]

In clinical studies, Librela was shown to control signs of OA pain in dogs, **which helped them be more active and improved their overall quality of life**.[5-8]

With long-lasting Librela, **your dog can feel better**, and you can **feel good about their treatment**, so you can **get back to the activities you both love**.[6-8]

Ask Your Vet About Librela

Librela is a monoclonal antibody that specifically targets a key driver of OA pain. It works to reduce pain signals, making it easier for your dog to move and play.[9,10]

Librela reduces OA pain, which can help your dog move and feel better.[6-8]

Librela is a once-monthly injection given by a veterinary professional, which means you don't have to worry about giving your dog daily oral medication for their OA pain.

In a clinical study, the most common side effects in dogs taking Librela vs placebo (no medicine) were urinary tract infection, bacterial skin infection, and dermatitis, and were similar for dogs taking placebo.[5]

How to Prepare for Your Vet Visits

Here are some tips to make your appointments with your vet as productive as possible

Pay attention to the physical and emotional behaviors of your dog before your appointment

How is your dog acting? Do they have trouble playing, jumping, or climbing stairs? How do they seem to be feeling?

Take videos and write down notes of your dog's activity and behaviors to share with your vet

It's important to talk to your vet about how your dog is moving and feeling so they can assess progress.

Schedule monthly appointments

Before you leave an appointment, be sure to schedule your next visit to stay on track.

Your next vet visit is scheduled for:

For the best possible results, Librela should be given to your dog by your veterinary professional once a month, every month. Because OA pain is chronic, it needs to be treated continually to see and maintain improvement.

See How Librela Can Make a Difference

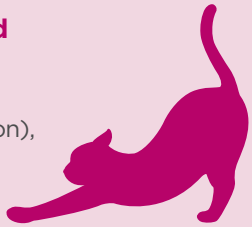
More than 6.8 million doses of Librela have been given to dogs in Europe since 2021[11]

Scan the codes with your phone's camera to see real results with Librela.

Meet Bella | Meet Emma | Meet Shiva

Do you own a cat that could be showing signs of OA?

Ask your veterinarian about Solensia™ (frunevetmab injection), the FIRST and ONLY treatment approved by the FDA for the control of OA pain in cats.



FDA=US Food and Drug Administration.

IMPORTANT SAFETY INFORMATION FOR SOLENSIA: For use in cats only. Women who are pregnant, trying to conceive or breastfeeding should take extreme care to avoid self-injection. Allergic reactions, including anaphylaxis, could potentially occur with self-injection. SOLENSIA should not be used in breeding cats or in pregnant or lactating queens. SOLENSIA should not be administered to cats with a known allergy to frunevetmab. The most common adverse events reported in a clinical study were vomiting and injection site pain. See full Prescribing Information in pocket.

Librela™
(bedinvetmab injection)

Feel Confident About Choosing Librela to Treat Your Dog's OA Pain

- Provides long-term OA pain control for your dog[5,6]
- A once-monthly injection given by your veterinary professional
- A monoclonal antibody that works to reduce pain signals, making it easier for your dog to move and play[9,10]
- Controls signs of OA pain in dogs, which can help them be more active and improve their overall quality of life[5-8]*

*Results from clinical studies.

Get more information at Librela.com.

Scan the code with your phone's camera to explore more.

References: 1. Lascelles BDX et al. *Vet J*. 2019;250:71-78. doi:10.1016/j.tvjl.2019.07.001 **2.** Anderson KL et al. *Front Vet Sci*. 2020;7:200. doi:10.3389/fvets.2020.00220 **3.** Wright A et al. *J Small Anim Pract*. 2022;63(8):609-618. doi:10.1111/jsap.13500 **4.** Librela Quant PMR: Pricing Sensitivity. Data on file. Zoetis Inc; May 2023. **5.** Michels GM et al. *Vet Anaesth Analg*. 2023;50(5):446-458. doi:10.1016/j.vaa.2023.06.003 **6.** Corral MJ et al. *Vet Anaesth Analg*. 2021;48:943-955. doi:10.1016/j.vaa.2021.08.001 **7.** Brown DC et al. *Am J Vet Res*. 2007;68(6):631-637. doi:10.2460/ajvr.68.6.631 **8.** Brown DC et al. *J Am Vet Med Assoc*. 2008;233(8):1278-1283. doi:10.2460/javma.233.8.1278 **9.** Keizer RJ et al. *Clin Pharmacokinet*. 2010;49(8):493-507. doi:10.2165/11531280 **10.** Isola M et al. *Vet Comp Orthop Traumatol*. 2011;24(4):279-284. doi:10.3415/VCOT-10-04-0051 **11.** Data on file. Zoetis Inc. May 2023.

zoetis

Librela™
(bedinvetmab injection)

Canine anti-nerve growth factor monoclonal antibody for subcutaneous use in dogs only.

Single-Use Vial

CAUTION
Federal law restricts this product to use by or on the order of a licensed veterinarian.

DESCRIPTION
LIBRELA (bedinvetmab injection) is a sterile injectable solution containing 5, 10, 15, 20, or 30 mg/mL of bedinvetmab in 20 mM histidine buffer pH 5.0 [(0.027% w/v L-histidine and 0.382% w/v histidine HCl monohydrate), 8.5% w/v trehalose dihydrate, 0.005% w/v disodium EDTA dihydrate, 0.01% w/v L-methionine, and 0.1% w/v poloxamer 188]. Bedinvetmab is a canine IgG monoclonal antibody (mAb), in which the variable regions from canine B cell sequence were joined with canine IgG constant sequences, and is expressed through recombinant DNA techniques in Chinese hamster ovary (CHO) cells. Bedinvetmab binds to nerve growth factor (NGF) to reduce NGF's effects. Such mAbs are commonly referred to as anti-NGF mAbs.

INDICATION
LIBRELA is indicated for the control of pain associated with osteoarthritis in dogs.

DOSAGE AND ADMINISTRATION
The minimum target dose of LIBRELA is 0.23 mg/lb (0.5 mg/kg) body weight, administered subcutaneously once a month. Dogs should be dosed by weight range according to the specific dosing information below.

The product does not contain a preservative. The full content of each vial is for single-use only. Once punctured, contents of the vial should be used immediately and any remaining solution should be discarded.

Dogs weighing ≥ 11 lb (≥ 5 kg):
Dogs should be dosed by weight range according to the Dosing Table below (Table 1). Dogs are given the full content of 1 or 2 vials of the appropriate concentration based on body weight. Aseptically withdraw the total dose into a single syringe and administer immediately.

Table 1. Dosing Table

Dog Body Weight in Pounds (lb)	Dog Body Weight in Kilograms (kg)	Number and Strength (mg/mL) of LIBRELA Vials to be Administered				
		5 mg/mL orange	10 mg/mL blue	15 mg/mL green	20 mg/mL gold	30 mg/mL purple
11-22.1	5-10	1 vial				
22.2-44.1	10.1-20		1 vial			
44.2-66.1	20.1-30			1 vial		
66.2-88.2	30.1-40				1 vial	
88.3-132.3	40.1-60					1 vial
132.4-176.4	60.1-80				2 vials	
176.5-220.5	80.1-100				1 vial	1 vial
220.6-264.6	100.1-120					2 vials

Dogs < 11 lb:
Aseptically withdraw 0.045 mL/lb (0.1 mL/kg) from a 5 mg/mL vial (orange vial) into a single syringe and administer immediately. Discard the vial after the dose has been withdrawn.

Effectiveness may not be achieved until after the second dose (see **EFFECTIVENESS**).

CONTRAINDICATIONS
LIBRELA should not be administered to dogs with known hypersensitivity to bedinvetmab.

LIBRELA should not be used in breeding dogs or in pregnant or lactating dogs. Immunoglobulin G class antibodies such as LIBRELA can pass through the placental blood barrier and be excreted in milk. Fetal abnormalities, increased rates of stillbirths and increased postpartum fetal mortality were noted in rodents and primates receiving anti-NGF monoclonal antibodies.

WARNINGS
User Safety Warnings
Not for use in humans. Keep this and all drugs out of reach of children. For use in dogs only.

Hypersensitivity reactions, including anaphylaxis, could potentially occur in the case of accidental self-injection.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet, vial or carton to the physician.

Pregnant women, women trying to conceive, and breastfeeding women should take extreme care to avoid accidental self-injection.

The importance of Nerve Growth Factor in ensuring normal fetal nervous system development is well-established and laboratory studies conducted on nonhuman primates with human anti-NGF antibodies have shown evidence of reproductive and developmental toxicity.

PRECAUTIONS
Administration of monoclonal antibodies may be associated with hypersensitivity reactions and delayed hypersensitivity reactions. If anaphylaxis or other hypersensitivity reaction occurs, discontinue use and institute appropriate therapy.

The safe use of this product with other monoclonal antibodies has not been evaluated. Use with caution in dogs with known hypersensitivity to other immunoglobulin therapy.

Evaluations were not made to determine if interactions occurred between LIBRELA and veterinary vaccines.

Treatment with LIBRELA may result in the formation of anti-bedinvetmab antibodies and potentially the loss of product effectiveness (see **IMMUNOGENICITY**).

The safe use of anti-NGF monoclonal antibodies with concurrent non-steroidal anti-inflammatory drugs (NSAIDs) has not been established in dogs. In human clinical trials, rapidly progressing osteoarthritis (RPOA) has been reported in a small number of patients receiving humanized anti-NGF monoclonal antibody therapy. The incidence of these events increased in human patients receiving NSAID treatment long term in combination with an anti-NGF monoclonal antibody. RPOA has not been characterized or reported in dogs.

The safety and effectiveness of LIBRELA has not been evaluated in dogs less than 12 months of age.

LIBRELA has not been studied in dogs that have a history of cruciate ligament rupture within six months before initial product use as these cases were excluded from the field studies.

Long term effects which may occur more than 9 months after the use of LIBRELA have not been evaluated.

NGF is expressed within the heart and vasculature, and the long-term effects of reduced NGF in dogs with cardiac disease are unknown.

Primates receiving high doses of anti-NGF monoclonal antibodies had anatomical changes in postganglionic cell bodies (reduced size and number of neurons). The change in cell body size returned to normal after anti-NGF monoclonal antibody administration was discontinued. NGF is involved in the normal development of sensory and sympathetic nerve fibers in developing animals. This may be important with use of LIBRELA in young growing dogs.

ADVERSE REACTIONS
The safety of LIBRELA was assessed in a masked, controlled 84-day US field study evaluating the effectiveness of LIBRELA for the control of pain associated with osteoarthritis. Enrollment included 272 dogs, 135 dogs treated with LIBRELA and 137 dogs treated with a negative control (sterile saline). The enrolled dogs were at least 1 year of age (1 to 17 years old), weighed between 1.8 to 62.7 kg and were of various breeds or non-purebred. Dogs were dosed at 28-day intervals and received up to three injections. The most common adverse reactions reported during the study are summarized in Table 2 below.

Table 2. Number (%) of Dogs with Adverse Reactions Reported in the US Field Study

Adverse Reaction*	LIBRELA n (%) (Total N = 135)	Negative Control n (%) (Total N = 137)
Urinary tract infection	15 (11.1)	11 (8.0)
Bacterial skin infection	11 (8.1)	9 (6.6)
Dermatitis	10 (7.4)	8 (5.8)
Dermal mass	8 (5.9)	5 (3.6)
Erythema	6 (4.4)	5 (3.6)
Dermal cyst(s)	4 (3.0)	2 (1.5)
Pain on injection	4 (3.0)	2 (1.5)
Inappropriate urination**	4 (3.0)	1 (0.7)
Histiocytoma	3 (2.2)	0 (0.0)

*An adverse reaction may have occurred more than once in a dog; only the first occurrence was counted.
** Of these, two dogs treated with LIBRELA were among those reported with a urinary tract infection.

The safety of LIBRELA was also evaluated in a masked, controlled 84-day European field study evaluating the effectiveness of LIBRELA for the control of pain associated with osteoarthritis. Enrollment included 281 dogs, 138 dogs were treated with LIBRELA and 143 treated with a negative control (sterile saline). The enrolled dogs were at least 1 year of age (1 to 17.5 years old), weighed between 1.7 to 66 kg and were of various breeds or non-purebred. Dogs were dosed at 28-day intervals and received up to three injections. The most common adverse reactions reported during the study are summarized in Table 3 below.

Table 3. Number (%) of dogs with Adverse Reactions Reported in the European Field Study

Adverse Event Reported*	LIBRELA n (%) (Total N = 138)	Negative Control n (%) (Total N = 143)
Increased Blood Urea Nitrogen (BUN)**	19 (13.8)	7 (4.9)
Lethargy	5 (3.6)	0 (0.0)
Emesis	4 (2.9)	1 (0.7)
Anorexia	3 (2.2)	0 (0.0)
Lameness	3 (2.2)	1 (0.7)
Cough	3 (2.2)	1 (0.7)

*An adverse reaction may have occurred more than once in a dog; only the first occurrence was counted.
** Two dogs treated with LIBRELA suffered serious adverse events and were euthanized during or after study completion: A 13-year old Bichon Frise had pre-existing increased urine protein-creatinine ratio and heart failure that worsened during study; the dog also had an increase in creatinine during the study and was diagnosed with renal failure and was euthanized 3 days after completing the study. An 8-year-old mixed breed dog had pancreatitis and was euthanized on Day 74. The remainder of the dogs that had elevations in the BUN did not have any obvious adverse events associated with this finding.

One dog in the LIBRELA group was diagnosed with pyelonephritis on Day 15; this dog had pre-existing increased serum BUN and creatinine and a recent history of urinary tract infection that was not confirmed resolved prior to enrollment. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen were initiated on Day 7 for osteoarthritis-associated joint pain but NSAIDs were discontinued on Day 10 due to anorexia and gastroenteritis; azotemia worsened at Day 13 and the dog received no further LIBRELA treatment.

One dog in the LIBRELA group with a history of atopy, developed mild alopecia and mild erythema on the injection site on Days 5 and 23. Both episodes of alopecia and erythema resolved with treatment.

A total of 89 dogs were enrolled in a 6-month, single arm, open labeled, uncontrolled continuation of the EU field study and received monthly subcutaneous injections of LIBRELA. The study provided additional field safety information.

One dog experienced acute gastroenteritis and recovered following treatment for abdominal pain, fever, vomiting, and anorexia. One large breed dog enrolled for stifle osteoarthritis developed acute forelimb lameness that was diagnosed as elbow dysplasia. Two dogs presented with rear limb paresis of unknown etiology, one of whom responded to ongoing NSAID treatment and one who did not.

CONTACT INFORMATION
To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Zoetis Inc. at 1-888-963-8471.

For additional information about reporting adverse drug experience for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY
Mechanism of Action
Bedinvetmab is a recombinant canine monoclonal antibody that binds to nerve growth factor (NGF), reduces NGF binding to the tropomyosin receptor kinase A (TrkA) and p75 neurotrophin receptor ($p75^{NTR}$) receptors and decreases TrkA signal transduction in cell types involved in pain. *In vitro* binding studies suggest that bedinvetmab binds with high affinity to NGF but does not bind to other neurotrophins including human neurotrophin-3 (NT-3), canine and human NT-4, and human brain-derived neurotrophic factor (BDNF).

NGF has been found to be elevated in the osteoarthritic joints of dogs. Following a noxious stimulus, inflammatory cytokines and NGF are released by tissues of the joint.

NGF binds to TrkA/$p75^{NTR}$ receptors found on peripheral nerves, immune cells, endothelial cells, synoviocytes, and chondrocytes to induce peripheral sensitization, neurogenic inflammation, and increased pain perception. Bedinvetmab binds to NGF and prevents NGF/TrkA/$p75^{NTR}$ cellular signaling. In *in vitro* studies, bedinvetmab potently inhibits NGF-mediated signaling as measured by a reduction in TF-1 cell proliferation and functionally blocks NGF-induced neurite outgrowth in rat PC-12 neuronal cells.

NGF binds to TrkA receptors located on immune cells to elicit the release of additional proinflammatory mediators, including NGF itself. These inflammatory mediators lead to further peripheral sensitization involved in pain perception. Bedinvetmab reduces the expression of these inflammatory mediators in rat PC-12 neuronal cells.

Pharmacokinetics
In a 6-month laboratory study of healthy, adult Beagles administered LIBRELA at monthly doses ranging from 1-10 mg/kg, the area under the curve (AUC) and the maximum concentration (C_{max}) increased nearly in proportion to dose and steady-state was achieved after approximately 2 doses. In a laboratory pharmacokinetic study in Beagles at 0.5-1.0 mg/kg, peak serum drug levels were observed at 4-7 days after subcutaneous dosing, the mean bioavailability relative to an intravenous dose was approximately 86%, and the elimination half-life was approximately 12 days.

In a field study at the labeled dose in dogs with osteoarthritis, the half-life was highly variable and averaged approximately 19 days (harmonic mean 15.8 days). Steady-state was achieved after 2 doses.

The metabolic pathway of bedinvetmab has not been characterized. As a canine IgG monoclonal antibody, bedinvetmab is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.

IMMUNOGENICITY
Antibodies binding to bedinvetmab (i.e., an anti-drug antibody, ADA), were detected using a multi-tiered ADA testing approach (screening, confirmatory, and titration). Testing the confirmed ADA samples for neutralizing activity of bedinvetmab was not performed. Due to limitations of the assay methods performed to evaluate immunogenicity (confirmatory and titration), clinically relevant conclusions or correlations were not determined from the immunogenicity data reported.

In the US Field Effectiveness Study, 267 of 272 enrolled dogs with osteoarthritis were evaluated for immunogenicity after receiving up to 3 doses of LIBRELA. The presence of pre-existing ADAs was confirmed in 5 out of 267 dogs; 4 dogs in the LIBRELA group and 1 dog in the control group. Three of these LIBRELA-treated dogs continued to have ADAs confirmed after treatment with LIBRELA. Of the remaining dogs evaluated for immunogenicity, the presence of ADAs was confirmed on Day 84 in 1 dog in the LIBRELA-treated group and 1 dog in the control group.

In the EU Field Effectiveness Study, 281 of 287 enrolled dogs with osteoarthritis were evaluated for immunogenicity after receiving up to 3 doses of LIBRELA. The presence of pre-existing ADAs was confirmed in 2 out of 281 dogs; both in the control group. Of the other 141 dogs in the control group, the presence of ADA was confirmed in 1 dog after receiving treatment with placebo (on Study Visit Day 56). Of the 138 LIBRELA-treated dogs, the presence of ADA was confirmed in 2 dogs after treatment with LIBRELA (1 dog on Study Visit Day 84 and 1 dog on Study Visit Study Day 28). Eighty-nine LIBRELA-treated dogs continued on with once monthly treatment for an additional six months, and 82 of these dogs were evaluated for immunogenicity after receiving up to 6 additional doses of LIBRELA. The presence of ADA was confirmed in an additional 2 dogs.

In the 6-Month Safety Study, the presence of ADAs was confirmed in 2 out of 8 negative control dogs and no ADAs were confirmed in any of the 24 dogs administered 7 doses of LIBRELA.

The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to LIBRELA with the incidence of antibodies to other products may not be appropriate.

EFFECTIVENESS
The overall evidence, based on the results of two field studies, supports the conclusion that LIBRELA is effective for the control of pain associated with osteoarthritis in dogs when given as a minimum of two doses administered one month apart.

A US field effectiveness study and a European (EU) field effectiveness study were conducted using a similar study design. Both studies included a group administered LIBRELA and a negative control group that was administered sterile saline. The primary effectiveness endpoint was treatment success (Yes/No) at Day 28 based on owner assessment of pain measured on the Canine Brief Pain Inventory (CBPI).[1-2] CBPI treatment success was a secondary endpoint at Days 7, 14, 42, 56 and 84. Treatment success was defined as a reduction of ≥ 2 in Pain Interference Score (PIS) and ≥ 1 in Pain Severity Score (PSS) vs. Day 0. Dogs receiving rescue treatment (e.g., for lack of efficacy (LOE)) or withdrawn for LOE were counted as treatment failures starting on the day of rescue or withdrawal, respectively.

While the studies had similar success rates on Day 28 in the treatment groups administered LIBRELA (48% and 45.2%), the studies had differences in the success rates in the control groups. The success rate in the control group in the US study was 36.1% and the success rate of the control group in the EU study was 17.0%. Based on these results, there was a larger treatment effect size in the EU study as compared to the US study, such that the US study did not demonstrate a significant difference at Day 28. In the EU study, the primary effectiveness variable was successful and met statistical significance at Day 28 (P = 0.0018).

The CBPI data from both studies demonstrated a greater percentage of dogs achieving treatment success in the LIBRELA-treated vs. control groups at Day 42. This success rate was maintained with a third administration at Day 56 through the end of the study at Day 84. Taken together, the US and EU studies establish the effectiveness for LIBRELA (bedinvetmab injection) for the control of pain associated with osteoarthritis in dogs when given as a minimum of two doses administered one month apart.

US Field Effectiveness Study
An 84-day masked, randomized, controlled field study was conducted at 24 US veterinary clinics. The study enrolled 272 client-owned dogs with clinical signs of osteoarthritis confirmed by radiography and orthopedic examination. Enrolled dogs were randomized at an equal ratio into one of two treatment groups: LIBRELA (0.5 mg/kg, n = 135) or control (sterile saline, n = 137) and were treated on Days 0, 28, and 56. Dog age and body weight ranged from 1.0 to 17.0 years and 1.8 to 62.7 kg, respectively. The percentage of dogs considered treatment successes based on the owner CBPI assessment was greater in the LIBRELA-treated dogs compared to the control group for all assessments. The study failed to demonstrate statistical significance for effectiveness at Day 28; however, the difference in the percentage of treatment successes from Day 42 onward demonstrated a clinical effect in the LIBRELA group compared to the control group.

Table 4. Study #1: Least Squares Mean Percent Success by Assessment Day

Day	Group	N	% Success
7	LIBRELA	125	30.3
	Control	129	24.8
14	LIBRELA	129	41.4
	Control	130	30.5
28	LIBRELA	128	48.0
	Control	131	36.1
42	LIBRELA	121	54.8
	Control	126	38.9
56	LIBRELA	122	57.8
	Control	124	42.1
84	LIBRELA	118	57.1
	Control	118	33.4

EU Field Effectiveness Study
An 84-day masked, randomized, controlled field study was conducted at 26 different study sites located in Portugal, Hungary, Ireland and Germany. The study enrolled 287 client-owned dogs with clinical signs of osteoarthritis confirmed by radiography and orthopedic examination. Dogs were randomized at an equal ratio into one of two treatment groups: LIBRELA (0.5 mg/kg, n = 141) or control (sterile saline, n = 146) and were treated on Days 0, 28, and 56. Dog age and body weight ranged from 1.0 to 17.5 years and 1.7 to 66.0 kg, respectively. The percentage of dogs considered treatment successes based on the owner CBPI assessment was greater for LIBRELA-treated dogs compared to the control group for all assessments. The study met statistical significance compared to the control at Day 28 (primary effectiveness endpoint; P = 0.0018). The difference in the percentage of treatment successes from Day 42 onward continued to demonstrate a clinical effect in the LIBRELA group compared to the control group.

Table 5. Study #2: Least Squares Mean Percent Success by Assessment Day

Day	Group	N	% Success
7	LIBRELA	128	18.5
	Control	130	4.0
14	LIBRELA	132	35.7
	Control	132	9.6
28	LIBRELA	131	45.2
	Control	131	17.0
42	LIBRELA	133	53.5
	Control	134	21.4
56	LIBRELA	133	52.9
	Control	134	20.6
84	LIBRELA	129	49.9
	Control	132	24.3

TARGET ANIMAL SAFETY
6 Month Margin of Safety Study:
LIBRELA (bedinvetmab injection) 15 mg/mL and 30 mg/mL concentrations were administered subcutaneously to 11 to 12-month old, healthy Beagles (8 dogs per group) at doses of 1 mg/kg (1X), 3 mg/kg (3X), and 10 mg/kg (10X) every 28 days for seven consecutive doses. The control group (8 dogs) received sterile saline injections. Dogs weighed 5.6-11.7 kg at study initiation.

There were no clinically significant changes noted in neurological examinations, body temperature, heart and respiratory rate, blood pressure, electrocardiography, and organ weights. Detailed pathology evaluation of the shoulder, elbow, hip, and knee joints were conducted.

Vomiting and soft stool were noted across all groups throughout the study. Scabbing on the face, neck and thorax was seen across all groups except the 1 mg/kg group. Injection site redness was noted sporadically for 1 control dog, 2 dogs in the 1 mg/kg treatment group, 5 dogs in the 3 mg/kg treatment group, and 5 dogs in the 10 mg/kg treatment group. One dog in the 3 mg/kg treatment group had a temporary, mild swollen facial area 26 days after the first dose that resolved spontaneously. Two dogs in the 3 mg/kg treatment group had lymphadenopathy on the last study day with no related histopathology findings. One dog in the 10 mg/kg treatment group had an approximately 2.5 cm X 3.5 cm circular raised firm erythematous lesion with slight serosanguinous discharge and mild scabs of the shaved cervical area that resolved over 14 days.

One dog in the 1 mg/kg treatment group had an increasing ALP value over the course of the study that increased threefold above the high end of the reference range at study completion. There was no gross or histopathology correlate.

One dog in the 1 mg/kg treatment group had mild cartilage necrosis in the left ulna and an erosion in the cartilage of the right ulna. One dog in the 3 mg/kg treatment group had mild bilateral, femoral neck enthesophytes observed on radiographs pre-treatment. On end of study radiography and pathology evaluation, this dog had an osteophyte of the left acetabulum, mild left acetabulum remodeling and severe left femoral neck enthesophytes. Microscopically, mild to moderate cartilage degeneration with erosion and proteoglycan depletion was also noted in the left proximal femur and acetabulum. The mild right femoral neck enthesophytes were the same grade as pre-treatment. The findings may be progression of an underlying musculoskeletal condition; however, a potential relation to treatment cannot be ruled out.

None of the LIBRELA-treated dogs developed anti-drug antibodies due to bedinvetmab administration.

Additional Safety Studies:
In a two-week laboratory safety study, eight dogs concurrently received one subcutaneous injection of LIBRELA at the high end of the inherent dose band (1 mg/kg) and fourteen days of an injectable NSAID. This limited laboratory study did not provide sufficient data to support a conclusion on the safety of concurrent use of LIBRELA and NSAIDs.

In a 3-month exploratory laboratory safety study using a non-final formulation of bedinvetmab administered by subcutaneous injection monthly for four doses, a dog administered a 4 mg/kg dose had a reddened and/or swollen muzzle abrasion, with an elevated white blood cell count, and elevated globulin level and fibrinogen level. At one of the injection administrations, one dog administered a 4 mg/kg dose had a 4 cm X 2 cm injection site erythema with an eschar that resolved; and one dog administered a 1 mg/kg dose had 3 cm X 1 cm injection site erythema that resolved. Another dog administered a 1 mg/kg dose had injection site erythema, scabbing, and mucopurulent discharge for 18 days.

STORAGE CONDITIONS
LIBRELA (bedinvetmab injection) should be stored in a refrigerator, 2° – 8°C (36° – 46° F). Do not freeze. Store vials in their boxes to protect from prolonged exposure to light. Once punctured, contents of the vial should be used immediately and any remaining solution should be discarded.

HOW SUPPLIED
LIBRELA is available in 5 strengths packaged in 4 mL glass vials containing an extractable volume of 1 mL of clear solution. Each strength is available in cartons containing 2 or 6 vials.

REFERENCES

1. Brown DC, Bell M, Rhodes L. Power of treatment success definitions when the Canine Brief Pain Inventory is used to evaluate carprofen treatment for the control of pain and inflammation in dogs with osteoarthritis. Amer J Vet Rsch 2013; 74(12):1467-1473.

2. Brown DC, Bell M, Rhodes L. ERRATUM to: Power of treatment success definitions when the Canine Brief Pain Inventory is used to evaluate carprofen treatment for the control of pain and inflammation in dogs with osteoarthritis. Amer J Vet Rsch 2014; 75(4):353.

Approved by FDA under NADA # 141-562

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007
March 2023

Solensia™
(frunevetmab injection)

7 mg/mL

Feline anti-nerve growth factor monoclonal antibody for subcutaneous injection in cats only.

Single-Use Vial

CAUTION
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
SOLENSIA (frunevetmab injection) is a sterile injectable solution containing 7mg/mL of frunevetmab in histidine buffer (10 mM L-histidine monohydrochloride, 5% D-sorbitol, 0.01%polysorbate 20, adjusted to pH 6.0 by HCl/NaOH, quantity sufficient to 1 mL by Water for Injection.). Frunevetmab is a felinized immunoglobulin G monoclonal antibody (mAb), a murine antibody in which all regions of the mouse antibody are replaced with feline counterparts except for the complementarity-determining regions. Frunevetmab binds to nerve growth factor (NGF) to block NGF's effects. Such mAbs are commonly referred to as anti-NGF mAbs.

INDICATION
SOLENSIA is indicated for the control of pain associated with osteoarthritis in cats.

DOSAGE AND ADMINISTRATION
Cats should be dosed by weight range according to the Dosing Chart (Table 1) below. Cats are given the full content of 1 or 2 vials based on body weight to target a minimum dosage of 0.45 mg/lb. (1 mg/kg) body weight, administered subcutaneously once a month. Aseptically withdraw the total dose into a single syringe and administer immediately.

The product does not contain a preservative. The full content of each vial is for single use only. Once punctured, contents of the vial should be used immediately and any remaining solution should be discarded.

Table 1. Dosing Chart

Weight of Cat (lb.)	Weight of Cat (kg)	Volume	Number of Vials*
5.5-15.4	2.5-7 kg	1 mL	1
15.5-30.8	7.1-14 kg	2 mL	2

*1 mL frunevetmab injection per vial

CONTRAINDICATIONS
SOLENSIA should not be administered to cats with known hypersensitivity to frunevetmab.

SOLENSIA should not be used in breeding cats or in pregnant or lactating queens because it may pass through the placental blood barrier and be excreted in milk. Fetal abnormalities, increased rates of stillbirths and increased postpartum fetal mortality were noted in rodents and primates receiving anti-NGF mAbs.

WARNINGS
User SafetyWarnings
Not for use in humans. Keep out of reach of children.

Hypersensitivity reactions, including anaphylaxis, could potentially occur in the case of accidental self-injection.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Pregnant women, women trying to conceive, and breastfeeding women should take extreme care to avoid accidental self-injection.

The importance of NGF in ensuring normal fetal nervous system development is well-established and laboratory studies conducted on nonhuman primates with human anti-NGF antibodies have shown evidence of reproductive and developmental toxicity.

PRECAUTIONS
Administration of mAbs may be associated with hypersensitivity reactions and delayed hypersensitivity reactions. If anaphylaxis or other hypersensitivity reaction occurs, discontinue use and institute appropriate therapy.

Administration of SOLENSIA may be associated with scabbing on the head and neck, dermatitis, and pruritus; however, pre-approval data suggest that these signs do not require cessation of SOLENSIA administration (see **ADVERSE REACTIONS** and **TARGET ANIMAL SAFETY**).

Evaluations were not made to determine if interactions occurred between SOLENSIA and veterinary vaccines.

Treatment with SOLENSIA may result in the formation of anti-frunevetmab antibodies and potentially the loss of product effectiveness (see **Immunogenicity**).

The safe use of SOLENSIA with concurrent non-steroidal anti-inflammatory drugs (NSAIDs) has not been established in cats. In human clinical trials, rapidly progressing osteoarthritis (RPOA) has been reported in a small number of patients receiving humanized anti-NGF mAb therapy. The incidence of these events increased in human patients receiving NSAID treatment long term in combination with an anti-NGF mAb. RPOA has not been characterized or reported in cats.

SOLENSIA has not been evaluated in cats less than 7 months or 5.5 lbs.

Long term effects, which may occur more than 6 months after the use of SOLENSIA, have not been evaluated. Primates receiving high doses of anti-NGF mAbs had reduced cell size in postganglionic neuronal cell bodies. The change in cell body size returned to normal after anti-NGF mAb administration was discontinued. NGF is involved in the normal development of sensory and sympathetic nerve fibers in developing animals. This may be important with use of SOLENSIA in young growing cats.

The safe use of this product with other mAbs has not been evaluated.

ADVERSE REACTIONS
The safety of SOLENSIA was evaluated in a masked, controlled 112-day field study to evaluate the effectiveness of SOLENSIA for the control of pain associated with osteoarthritis in cats. Enrollment included 275 cats weighing 2.5-to 11.4 kg and 1.6-to 22.4 years old; 182 cats were treated with SOLENSIA and 93 cats were administered a vehicle control. Cats were dosed at 28-day intervals and received up to three injections. The most common adverse reactions reported during the field study are presented below.

Table 2. Adverse Reactions Reported in the Field Study[1]

Adverse Reaction	Solensia N=182 (%)	Vehicle Control N=93 (%)
Vomiting	24 (13.2%)	10 (10.8%)
Injection site pain[2]	20 (10.9%)	13 (14%)
Diarrhea	12 (6.6%)	5 (5.4%)
Abnormal behavior and behavioral disorders[3]	12 (6.6%)[4]	5 (5.4%)[5]
Renal insufficiency[6]	12 (6.6%)	4 (4.3%)
Anorexia	12 (6.6%)	4 (4.3%)
Lethargy	11 (6.0%)	3 (3.2%)
Dermatitis	11 (6.0%)	1 (1.1%)
Alopecia	10 (5.5%)	2 (2.2%)
Dehydration	8 (4.4%)	0 (0.0%)
Lameness[7]	8 (4.4%)	2 (2.2%)
Pruritus	7 (3.8%)	0 (0.0%)
Weight loss	6 (3.3%)	5 (5.4%)
Scabbing on head/neck	6 (3.3%)	1 (1.1%)
Gingival disorder	5 (2.7%)	0 (0.0%)
Bacterial skin infection	4 (2.2%)	1 (1.1%)
Otitis externa	4 (2.2%)	0 (0.0%)

[1] If a cat experienced the same event more than once, only the first occurrence is reported
[2] The control product was the vehicle without active ingredient
[3] Behavior abnormal for the individual cat
[4] Individual cats had at least one of the following behavior changes: anxiety (1), hiding (1), hypersomnia (1), inappropriate urination (5), sleeping with owner (1), vocalization (3), increased aggressive behavior (1)
[5] Individual cats had at least one of the following behavior changes: anxiety (2), disorientation (1), inappropriate urination (2), and vocalization (1)
[6] Worsening of existing disease
[7] New lameness or worsening of previous lameness

The safety of SOLENSIA was also evaluated in a masked, controlled 56-day exploratory field study to evaluate the effectiveness of SOLENSIA for the control of pain associated with osteoarthritis in cats. Enrollment included 126 cats; 85 cats were treated with frunevetmab injection manufactured similar to SOLENSIA and 41 cats were administered a vehicle control. Cats were dosed at 28-day intervals and received up to two injections. The most frequently reported adverse reactions were digestive tract disorders, including vomiting and diarrhea, and skin disorders, including dermatitis/eczema and alopecia that were mostly attributed to irritation by an activity monitor collar required for the study.

Immunogenicity
All therapeutic proteins, including monoclonal antibodies, have the potential for immunogenicity, including the production of antibodies that bind to the therapeutic protein and may decrease effectiveness. Such host-derived antibodies are termed anti-drug antibodies (ADA). SOLENSIA, therefore has the potential to cause the cat to produce ADAs against frunevetmab.

The presence of binding antibodies to frunevetmab in cats was assessed using a screening and confirmatory assay approach. In controlled field effectiveness studies in cats with osteoarthritis (see **EFFECTIVENESS**), four out of 259 cats that received SOLENSIA once monthly developed anti-drug antibodies (ADAs). One cat tested positive for ADAs on Days 0, 28, 56, and 84. This cat had non-detectable plasma drug concentration levels of SOLENSIA on Days 28 and 56, and was a treatment failure in the effectiveness analysis, suggesting that the ADAs may have clinical significance. No assessment for neutralizing antibodies was performed.

The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SOLENSIA with the incidence of antibodies to other products may not be appropriate.

CONTACT INFORMATION
To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Zoetis Inc. at 1-888-963-8471.

For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY
Mechanism of Action
Frunevetmab is a felinized monoclonal antibody that binds to nerve growth factor (NGF), reduces NGF binding to the tropomyosin receptor kinase A (TrkA) and $p75^{NTR}$ receptors, and decreases signal transduction in cell types involved in pain. *In vitro* binding studies suggest that frunevetmab binds with high affinity to NGF, but does not bind to other neurotrophins, including human neurotrophin-3 (NT-3), feline and human neurotrophin-4 (NT-4), and human brain-derived neurotrophic factor (BDNF).

NGF has been found to be elevated in osteoarthritic joints of multiple species. Following a noxious stimulus, inflammatory cytokines and NGF are released by tissues of the joint. NGF binds to TrkA/$p75^{NTR}$ receptors found on peripheral nerves, immune cells, endothelial cells, synoviocytes, and chondrocytes to induce peripheral sensitization, neurogenic inflammation, and increased pain perception.

Frunevetmab binds to NGF and prevents NGF/TrkA/$p75^{NTR}$ cellular signaling. In *in vitro* studies, frunevetmab potently inhibits NGF-mediated signaling as measured by reducing proliferation of TF-1 cells, a human erythroleukemia cell line, and functionally blocks NGF-induced neurite outgrowth in rat PC-12 neuronal cells.

NGF binds to TrkA receptors located on immune cells to elicit the release of additional proinflammatory mediators, including NGF itself. These inflammatory mediators lead to further peripheral sensitization involved in pain perception. Frunevetmab reduces the expression of these inflammatory mediators in rat PC-12 neuronal cells.

Pharmacokinetics
In a laboratory safety study in healthy cats administered SOLENSIA (frunevetmab injection) subcutaneously once every twenty-eight days for six consecutive doses (2.8 mg/kg), area under the plasma concentration time curve from time zero to the end of the dose interval (AUC) and maximum plasma concentration (C_{max}) increased in a less than dose proportional manner. Dosing every 28 days resulted in minimal accumulation over the course of five consecutive SOLENSIA doses of 2.8 mg/kg.

Table 3. Mean ± Standard Deviation frunevetmab pharmacokinetic parameters following subcutaneous dosing to laboratory and osteoarthritic cats.

Parameter	Laboratory Cats	Osteoarthritic Cats
Dose (mg/kg)	2.8	3.0
C_{max} (µg/mL)	42.8 ± 10.4	30.2 ± 5.5
T_{max}[#] (day)	3.5 (1-7)	7.0 (3-7)
AUC (day*µg/mL)	596 ± 245	653.0 ± 132
$t_{1/2}$ (day)	9.8 ± 3.1	11.0 ± 2.5
Bioavailability (%)	Not determined	73.2 ± 14.8

[#]Median and range

In a cross-study comparison of the pharmacokinetics in healthy laboratory cats and cats with naturally occurring osteoarthritis, the median time to maximum concentration (T_{max}) was approximately 3.5 days longer in cats with osteoarthritis compared to healthy cats. C_{max} was greater in healthy cats compared to cats with osteoarthritis. Overall drug exposure (AUC) and half-life were similar between healthy cats and cats with osteoarthritis. Compared to an intravenous dose, subcutaneously-administered frunevetmab had a bioavailability of approximately 73% in cats with osteoarthritis.

In a field effectiveness study at the label dose in cats with osteoarthritis, steady-state was achieved after approximately 2 doses.

EFFECTIVENESS

Because of the limitations currently inherent in studies designed to assess chronic pain and the response to drugs intended to control chronic pain in cats, a weight of evidence approach was employed to determine if the overall evidence supported the conclusion that SOLENSIA was effective for the control of pain associated with osteoarthritis in cats. Based on current thinking, the endpoints used to evaluate the effectiveness of SOLENSIA for the control of osteoarthritic pain in cats are observer-reported measures conducted by either owners or veterinarians. When taken together, the results of the two studies described below demonstrate the effectiveness of SOLENSIA for the control of pain associated with osteoarthritis in cats. Additional information related to the evaluation of these studies, including the study endpoints, is available in the Freedom of Information Summary available at https://animaldrugsatfda.fda.gov.

Field Effectiveness Study #1

A 56-day, masked, randomized, controlled field study was conducted at 14 U.S. veterinary clinics. The study enrolled 126 client-owned cats with clinical signs of osteoarthritis (OA) confirmed by radiography and orthopedic examination; enrolled cats weighed 3.3 to 10.5 kg and were over 6 months old. The enrolled cats were randomized to treatment with frunevetmab injection (n=85) manufactured similar to SOLENSIA or vehicle control (n=41), administered subcutaneously on Days 0 and 28 or intravenously on Day 0 and subcutaneously on Day 28. Cats were dosed with frunevetmab injection or vehicle control based on body weight (2.5-7 kg cats received 1 mL, 7.1-14 kg cats received 2 mL).

Outcome measures for the control of pain associated with OA included comparison of the owner's evaluation of Client Specific Outcomes Measures (CSOM) at Days 14, 28, 42, and 56 compared to baseline (Day 0, before treatment); Owner Global Assessments on Days 28 and 56; and total orthopedic pain score completed by the veterinarian at screening and on Days 28 and 56. For the CSOM, treatment success was defined as a reduction of at least 2 in the total CSOM score compared with the score at baseline. Cats that had an increase in any individual CSOM activity score (regardless of the total CSOM score) were considered treatment failures. For the Owner Global Assessment, success was defined as an owner's impression of the response to treatment as Good or Excellent (versus Fair or Poor). Success was not defined for the veterinarian-assessed total orthopedic pain score. The proportion of cats considered treatment successes based on the owner CSOM assessment and the Owner Global Assessment was greater in the frunevetmab injection group compared to the control group for all assessments. The mean total orthopedic pain score was lower in the frunevetmab injection group compared to the control group at all post-dosing assessments.

Table 4. Percent CSOM Success by Assessment Day

Study Day	Frunevetmab Injection (%)	Vehicle Control (%)
14	61.8	60.6
28	68.6	55.9
42	73.5	55.9
56	80.0	47.1

Table 5. Percent Owner Global Assessment Success by Assessment Day

Study Day	Frunevetmab Injection (%)	Vehicle Control (%)
28	63.2	26.3
56	71.1	32.4

Table 6. Mean Veterinarian-Assessed Total Orthopedic Pain Score by Assessment Day

Study Day	Frunevetmab Injection (change from baseline)	Vehicle Control (change from baseline)
Screening	31.88	32.25
28	27.08 (-4.8)	28.03 (-4.22)
56	25.69 (-6.19)	27.75 (-4.5)

Field Effectiveness Study #2

A 112-day, masked, randomized, controlled field study was conducted at 21 U.S. veterinary clinics. The study enrolled 275 client-owned cats with clinical signs of osteoarthritis (OA) confirmed by radiography and orthopedic examination; enrolled cats weighed 2.5 to 11.4 kg and were 1.6 to 22.4 years old. The enrolled cats were randomized to treatment with SOLENSIA (n=182) or vehicle control (n=93), administered subcutaneously on Days 0, 28, and 56. Cats were dosed with SOLENSIA (frunevetmab injection) or vehicle control based on body weight (2.5-7 kg cats received 1 mL, 7.1-14 kg cats received 2 mL).

The primary outcome measure for success for the control of pain associated with OA was comparison of the owner's evaluation of CSOM at Day 56 compared to baseline (Day 0, before treatment). Treatment success was defined as a reduction of at least 2 in the total CSOM score at Day 56 compared with the score at baseline. Cats that had an increase in any individual CSOM activity score (regardless of the total CSOM score) or that received rescue analgesia prior to Day 56 were considered treatment failures. Secondary outcome measures included the total CSOM score on Days 28 and 84; Owner Global Assessments on Days 28, 56, and 84; and total orthopedic pain score completed by the veterinarian on Days 28, 56, and 84. For the Owner Global Assessment, success was defined as an owner's impression of the response to treatment as Good or Excellent (versus Fair or Poor). Success was not defined for the veterinary-assessed total orthopedic pain score. The proportion of cats considered treatment successes based on the owner CSOM assessment and the Owner Global Assessment was greater in the SOLENSIA group compared to the control group for all assessments. The mean total orthopedic pain score was lower in the SOLENSIA group compared to the control group at all post-dosing assessments.

Table 7. Percent CSOM Success by Assessment Day

Study Day	Solensia (%)	Vehicle Control (%)
28	66.9	51.6
56	75.1	64.8
84	76.5	67.3

Table 8. Percent Owner Global Assessment Success by Assessment Day

Study Day	Solensia (%)	Vehicle Control (%)
28	39.3	30.4
56	59.3	48.3
84	64.6	57.8

Table 9. Mean Veterinarian-Assessed Total Orthopedic Pain Score by Assessment Day

Study Day	Solensia (change from baseline)	Vehicle Control (change from baseline)
Screening	34.11	33.6
28	28.68 (-5.43)	29.1 (-4.5)
56	27.52 (-6.59)	28.67 (-4.93)
84	27.29 (-6.82)	28.54 (-5.06)

TARGET ANIMAL SAFETY

Frunevetmab injection was administered subcutaneously to healthy seven to eight-month-old cats (8 cats per group) at doses of 2.8 mg/kg (1X), 8.4 mg/kg (3X), and 14 mg/kg (5X) every 28 days for six consecutive doses. The control group (8 cats) received vehicle control injections. No clinically significant changes related to frunevetmab were observed among the cats for physical examination, lameness evaluation, and body weight.

The most common findings included vomiting and diarrhea observed sporadically in all groups. The highest frequency of vomiting occurred in the 1X group. Clinically relevant skin findings included abrasions, alopecia, or scabs mostly around the face and ears. These findings were noted in three 1X cats, three 3X cats, and one 5X cat. Another 1X cat developed a 2 cm ventral neck lesion following clipping and blood collection on Day 87. Although the initial irritation appeared related to the clipping, the unexpectedly severe and persistent pruritus and prolonged recovery were deemed possibly drug-related. The ulcerated skin lesion healed when self-trauma was prevented including the placement of an e-collar for the remainder of the study.

Flinching was occasionally associated with injections, most frequently noted during the first dosing in all dosing groups. Occasionally, scabs, small abrasions, or spot of alopecia were observed at the injection sites in all dosing groups. A few cats had transient swelling at injection sites.

Body tremors and shivering were noted in one 3X cat on Day 28.

Serum creatinine values in females were significantly higher in the 5X group compared to controls ($P < 0.10$). Creatinine values on Day 28 were significantly higher ($P= 0.0239$) in the 1X group compared to the control group. On Day 112, values were significantly higher ($P = 0.0443$) in the 5X group compared to the control group. Creatinine values did not exceed the reference ranges in cats of either sex at any time point.

There was one 1X cat with mild focal discoloration of the left tibiofemoral joint cruciate ligament on gross pathology. There was no correlative pathology on microscopic examination. No lameness was reported in this cat or any cat over the course of this study.

One 1X cat had a small amount of bilirubinuria on Day 43. This cat had dark urine and hematuria on Days 43-45 with no evidence of UTI on urinalysis. The cat responded to a canned prescription urinary diet and recovered. This cat also vomited food, bile or hair on three days and had diarrhea or dark, tarry stools on two days. Another 3X cat had a small amount of bilirubinuria on Day 83 and orange colored urine. This cat also had elevated serum lactate dehydrogenase activity at three time points.

There was one 5X cat that had a small amount of bilirubinuria at the end of the study with lipid sediment. This cat also had focal hepatic lipidosis on histopathology.

STORAGE CONDITIONS

SOLENSIA should be stored upright in a refrigerator, between 35°– 46°F (2°– 8°C). Do not freeze. Protect from light. See in-use instructions provided in the **DOSAGE AND ADMINISTRATION** section.

HOW SUPPLIED

SOLENSIA is supplied as a sterile buffered solution of 7mg/mL of frunevetmab in single-use 4 mL glass vials containing an extractable volume of 1mL of clear solution with a butyl rubber stopper and aluminum overseal. Vials are available in cartons containing 2 or 6 vials.

Approved by FDA under NADA # 141-546

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Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

August 2021