Date of Approval: May 5, 2023

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-562

Librela™

(bedinvetmab injection)

Injectable Solution

Dogs

Librela™ is indicated for the control of pain associated with osteoarthritis in dogs.

Sponsored by:

Zoetis Inc.

Executive Summary

Librela™ (bedinvetmab injection) is approved for the control of pain associated with osteoarthritis in dogs. Bedinvetmab is a canine monoclonal antibody that binds to and inhibits the biological activity of canine nerve growth factor (NGF), which has been found to be elevated in dogs with osteoarthritis (OA). Monoclonal antibodies, such as bedinvetmab, are a specific subclass of therapeutic proteins.

Librela™ is given by subcutaneous (SC) injection once a month and dosed by weight range to target a minimum dose of 0.5 mg/kg.

Safety and Effectiveness

The sponsor conducted two field studies—one in the United States and one in the European Union (EU)—to evaluate the effectiveness of Librela™ to control pain associated with OA in dogs. Both studies enrolled client-owned dogs diagnosed with OA based on physical examination, orthopedic examination, and radiography. Enrolled dogs were both sexes and represented a variety of breeds, ages, and weights. Half the dogs received Librela™ and half received sterile saline by SC injection every 28 days for a total of 3 doses.

Before treatment on Day 0 and on various days throughout the study, owners used the Canine Brief Pain Inventory (CBPI) assessment tool to measure the dog's overall pain (pain severity score, or PSS) and the degree to which the pain interfered with the dog's daily activities (pain interference score, or PIS). A dog was considered a treatment success if there was a reduction of ≥ 1 in PSS and ≥ 2 in PIS on Day 28 compared to baseline.

There was a significant difference in treatment success rates between the treatment and control groups on Day 28 in the EU study but not in the US study. While the US and EU studies had similar success rates in the treatment groups (48% and 45.2%, respectively), there was a large variability in the success rates in the control groups (36.1% and 17.0%, respectively). Based on these results, there was a larger treatment effect between the treatment and control groups in the EU study compared to the US study. In both the US and EU studies, more dogs in the treatment group were treatment successes on Day 42 (14 days after the second dose) compared to the control group, and more dogs treated with Librela™ were treatment successes on Day 42 than on Day 28. This higher success rate relative to Day 28 was maintained in both studies through Day 84 (following a third dose on Day 56) and was also consistently higher compared to the control group. Taken together, the weight of evidence from the two field studies demonstrates that Librela™ is effective at controlling pain associated with OA in dogs when at least two doses are given 28 days apart. Reported adverse reactions included increased blood urea nitrogen, urinary tract infection, bacterial skin infection, dermatitis, erythema or pain at injection site, emesis, and anorexia.

Some dogs from the EU field study were enrolled in a continuation phase to evaluate the safety of 6 additional monthly SC injections of Librela™ (there was no control group in this phase of the study). The adverse reactions were similar to those reported in the two field studies.

The sponsor conducted a 6-month laboratory safety study in young, healthy, intact Beagles. The dogs were administered Librela™ by SC injection every 28 days for a

total of 7 doses at 0X (0 mg/kg), 1X (1 mg/kg), 3X (3 mg/kg), or 10X (10 mg/kg) the high end of the inherent dose band. Dogs in the 3X and 10X treatment groups had scabbing lesions of the head and neck. Boney changes, including boney remodeling and cartilage degeneration, were seen in one dog in the 3X treatment group. The dog may have had an underlying musculoskeletal condition that caused the boney changes; however, a relationship to treatment cannot be ruled out.

In a 2-week laboratory safety study, young, healthy Beagles concurrently received one SC injection of Librela™ at the high end of the inherent dose band and 14 days of an injectable non-steroidal anti-inflammatory drug (NSAID). Although there were no significant findings, this limited laboratory study did not provide sufficient data to support the safety of concurrent use of Librela™ and NSAIDs.

In a 3-month exploratory laboratory safety study, dogs were administered a non-final formulation of bedinvetmab by SC injection every 28 days for a total of 4 doses at 0X (0 mg/kg), 1X (1 mg/kg), 4X (4 mg/kg), and 12X (12 mg/kg) the high end of the inherent dose band. Both gross and microscopic skin lesions were observed at the injection site in all treatment groups.

Immunogenicity
All therapeutic proteins, including monoclonal antibodies, can trigger an immune response (immunogenicity) in an animal. The sponsor used a multi-tiered testing approach to evaluate immunogenicity caused by Librela™. Antibodies binding to Librela™ (called anti-drug antibodies or ADAs) were detected in a small number of dogs in the 6-month laboratory safety study and the two field studies. Some dogs in both the treatment and control groups were confirmed to have ADAs present prior to treatment administration, or confirmed to develop ADAs following treatment with Librela™ or saline. However, due to assay limitations, the clinical effects of this immunogenicity could not be determined.

User Safety
Women who are pregnant, trying to conceive, or breastfeeding should take extreme caution to avoid accidental self-injection of Librela™. NGF is important in the normal development of the fetal nervous system, and laboratory studies in nonhuman primates have shown that human antibodies to NGF can cause reproductive and developmental toxicity.

Conclusion
Based on the data submitted by the sponsor for the approval of Librela™, FDA determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-562

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

Librela™

D. Drug Product Established Name

bedinvetmab injection

E. Pharmacological Category

Monoclonal antibody

F. Dosage Form

Injectable solution

G. Amount of Active Ingredient

5, 10, 15, 20, and 30 mg bedinvetmab/mL in sterile solution

H. How Supplied

Librela™ injectable solution is supplied as a sterile buffered solution of 5, 10, 15, 20, and 30 mg bedinvetmab/mL in single-use vials containing an extractable volume of 1 mL of clear solution.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The dose of Librela™ (bedinvetmab) is 0.23 mg bedinvetmab/lb (0.5 mg bedinvetmab/kg) body weight, administered subcutaneously once a month.

K. Route of Administration

Subcutaneous injection

L. Species

Dogs

M. Indication

Librela™ is indicated for the control of pain associated with osteoarthritis in dogs.

II. EFFECTIVENESS

A. Dosage Characterization

Bedinvetmab is a canine monoclonal antibody (mAb) that has been shown to bind to nerve growth factor (NGF) with high affinity and to be a potent inhibitor of the biological activity of canine NGF.

Based upon a dose finding study evaluating an anti-NGF mAb similar to bedinvetmab, Zoetis selected a dose of 0.5 mg/kg administered subcutaneously once per month for the control of pain associated with osteoarthritis.

The role of NGF in canine osteoarthritis was investigated in a dose-finding clinical field study of 346 dogs with naturally occurring osteoarthritis. In this study dogs were administered an investigational anti-NGF mAb that neutralizes NGF:TrkA signaling and behaves similarly in binding affinity, selectivity, and potency to bedinvetmab. Dogs were randomized to treatment with a single subcutaneous injection of a negative control (saline) or anti-NGF mAb at one of four dose levels (0.25, 0.5, 1.0, or 2.0 mg/kg). The control of pain was assessed by the owner using the Canine Brief Pain Inventory (CBPI) assessment tool. A positive response was seen in all anti-NGF mAb treatment groups. The results supported the use of a minimum target dose of 0.5 mg/kg for further evaluation in a field effectiveness and safety study to assess a one-month duration of effectiveness.

B. Substantial Evidence

Substantial evidence of effectiveness is demonstrated by the results of two field studies in dogs with naturally occurring osteoarthritis: one conducted in the United States (US Study C161C-US-17-178) and one conducted in Europe (EU Study C866C-XC-17-194). These studies, taken together, establish the effectiveness of 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.

The US field study and the EU field study were conducted using a similar study design. The primary endpoint used to evaluate the effectiveness of Librela™ for the control of osteoarthritic pain in dogs was an observer-reported measure conducted by owners using the CBPI. Both studies included a group administered Librela™ and a negative control group that was administered sterile saline. 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. The US study did not demonstrate a significant difference in treatment success at the pre-specified primary endpoint (Day 28), while the EU study demonstrated a significant difference in treatment effect at Day 28. However, the success rates in the Librela™ groups from Day 42 (14 days after the second monthly injection of Librela™) onward were

consistently higher compared to the control groups across both the US and EU studies.

Because of the similar treatment success of Librela™ throughout these two field studies and the large variability in the treatment success of the control groups, a weight of evidence approach was employed to determine if the overall evidence supported the conclusion that Librela™ was effective for the control of pain associated with osteoarthritis in dogs. When taken together, the results of the two studies described below support the conclusion that Librela™ is effective for the control of pain associated with osteoarthritis in dogs when administered as a minimum of two monthly injections.

1. US Field Study for the Control of Pain Associated with Osteoarthritis in Dogs

   Title: Field Safety and Efficacy of Librela™ Compared to Placebo for the Treatment of Pain Associated with Osteoarthritis in Dogs. (Study No. C161C-US-17-178)

   Study Dates: March 19, 2018 to October 11, 2018

   Study Locations: Veterinary clinics in the United States from the following locations participated in this study.

   Fort Collins, CO (2)
   Denver, CO
   Bradenton, FL
   Gainesville, FL
   Lake Worth, FL
   West Palm Beach, FL
   Savannah, GA
   Decatur, IL
   Lisle, IL
   Lawrence, KS
   Baton Rouge, LA
   Metairie, LA
   Zachary, LA
   Battle Creek, MI
   Caledonia, MI
   Canton, MI
   Grand Rapids, MI
   Wyoming, MI
   Springfield, MO
   Bartlesville, OK
   Farragut, TN
   Grapevine, TX
   Seguin, TX

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

   Objective: The study evaluated the effectiveness and field safety of Librela™ (bedinvetmab injection) administered by subcutaneous injection for the control of pain associated with osteoarthritis in dogs.

   Study Animals: The study enrolled 272 client-owned dogs with osteoarthritis (155 females; 117 males). Enrolled dogs had been diagnosed with osteoarthritis based on physical examination, orthopedic examination, and radiography. The enrolled dogs were at least 1 year of age (1.0 to 17.0 years), weighed between 1.8 to 62.7 kg (4.0 to 138.2 lb), and were of various breeds or non-purebred.

   Experimental Design: The dogs were randomized at a ratio of 1:1 to receive Librela™ or a negative control (sterile saline). Of the 272 dogs enrolled, 135 dogs received Librela™ and 137 received the negative control. This study was conducted in accordance with Good Clinical Practice (GCP).

Table II.1 Treatment Groups and Dose of Librela™ and a Negative Control in Study No. C161C-US-17-178

Treatment Group	Dose of Librela™	Schedule for Administration of Librela™ and Control	Number of Dogs
Librela™ (bedinvetmab injection)	0.5 mg/kg	Days 0, 28 (± 3 days), and 56 (± 5 days)	135
Negative Control*	0 mg/kg	Days 0, 28 (± 3 days), and 56 (± 5 days)	137

*Control was sterile saline

Inclusion Criteria: The study included client-owned dogs that had been diagnosed with osteoarthritis based on owner history, physical examination, and radiographs. Dogs were in good general health or had stable chronic conditions that would not interfere with the study assessments. Dogs were required to have a Canine Brief Pain Index (CBPI) pain severity score (PSS) and pain interference score (PIS) ≥ 2 at the screening visit and again on Day 0; dogs were additionally required to have a veterinary assessment of 'Moderate', 'Severe', or 'Nearly Incapacitated' at the screening visit and again on Day 0 for at least one of the Veterinary Categorical Assessments for 'lameness/weight-bearing', 'pain on palpation/manipulation of joints', and 'general musculoskeletal condition' in at least one joint of the pelvic or thoracic limbs.

Exclusion Criteria: Dogs intended for breeding, pregnant or lactating female dogs, or dogs with conditions that would confound the study assessments or prevent completion of the study were excluded, including dogs that had a lameness known to be related to neoplasia or that had a primary neurological condition that precluded owner and veterinary assessments of pain associated with osteoarthritis. Additionally, dogs that had a cranial cruciate ligament rupture less than 6 months before the time of enrollment were excluded.

Prior to study start, dogs were withdrawn from other drugs or treatments that might have interfered with the assessment of effectiveness.

Drug Administration: Dogs were administered Librela™ (bedinvetmab injection) at a minimum of 0.23 mg/lb (0.5 mg/kg) or an equivalent volume of control (sterile saline) by subcutaneous injection. All dogs > 5.0 kg received a complete vial, as indicated in Table II.2. below. Dogs weighing < 5.0 kg received 0.045 mL/lb (0.1 mL/kg) from a 5 mg/mL vial or an equivalent volume of control. Treatment administration occurred in the veterinary clinic at scheduled visits.

Table II.2. 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	10 mg/mL	15 mg/mL	20 mg/mL	30 mg/mL
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

Measurements and Observations: Baseline physical examination, body weight, hematology, serum chemistry, urine protein-creatinine ratio, urinalysis, immunological assessment, CBPI, veterinary categorical assessment (for lameness/weight bearing, pain on palpation/manipulation of joints, and general musculoskeletal condition), orthopedic examination, owner categorical assessments (for lameness/weight bearing, musculoskeletal pain, and overall musculoskeletal condition) and orthopedic radiographs were collected at screening (prior to Day 0) and, except for blood and urine collection and orthopedic radiographs, again on Day 0 prior to enrollment. On Days 7, 14, 28, 42, 56, and 84, the veterinarian completed a physical examination, orthopedic examination, and injection site evaluation; the owner completed the CBPI during the clinic visit and completed the owner categorical assessments; and blood samples were collected for immunological assessment. In addition, hematology, serum chemistry, urinalysis, and urine protein-creatinine ratio were evaluated on Days 7 (hematology only), 28, 56, and 84.

Statistical Methods:

Effectiveness was determined by the owner's evaluation of the CBPI at Days 7, 14, 28, 42, 56, and 84 compared to baseline (Day 0, before treatment). For each day, treatment success was defined as a reduction ≥ 1 in PSS, the owner's assessment of the dog's overall pain, and ≥ 2 in PIS, the owner's assessment of how the pain interferes with the dog's daily activities, compared to baseline. The primary effectiveness endpoint was treatment success on Day 28.

Treatment success (Yes /No) was analyzed on each day as a binary response using a generalized linear mixed model with binomial distribution and logit link. The model included the fixed effect of treatment. The random effects included clinic and the interaction between clinic and treatment. Back-transformed least squares means were used as estimates of the treatment proportions and corresponding 95% confidence intervals were constructed.

Treatment comparisons were evaluated using log-odds ratios using a two-sided test at the 5% level of significance ($P < 0.05$).

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.

Results:

CBPI

A significant difference in treatment success rates based on the CBPI assessment was not observed at Day 28 ($P = 0.0719$). However, the percentage of dogs considered treatment successes based on the CBPI assessment was numerically greater in the Librela™ group compared to the control group on all post Day 0 assessment days, increased further after the second dose, and was maintained with the third dose (See Table II.3). The increase in treatment success in the Librela™-treated group demonstrated a clinically relevant effect. There was a greater increase in treatment success in the Librela™-treated group than in the control group through Day 56; and, thereafter, the frequency of treatment success was maintained in the Librela™-treated group but declined in the control group.

Table II.3: Least Squares Mean Percent Success by Assessment Day

Assessment Day	Treatment 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

CBPI PIS and PSS

Mean PIS and PSS were lower in the Librela™ group compared to the control group at Days 7, 14, 28, 42, 56, and 84.

CBPI Overall Impression

The CBPI Overall Impression was scored by the owner as poor, fair, good, very good, or excellent. A higher percentage of dogs in the Librela™ group were scored as excellent or very good compared to the control group at Days 7, 14, 28, 42, 56, and 84 (see Table II.4).

Table II.4. Summary of CBPI Overall Impression Scores

Study Day	Treatment	% Poor	% Fair	% Good	% Very Good	% Excellent	N
0	Librela™	4.5	27.8	55.6	10.5	1.5	133
	Control	3.0	23.9	57.5	15.7	0	134
7	Librela™	1.6	11.2	56.0	25.6	5.6	125
	Control	0.8	19.4	54.3	24.0	1.6	129
14	Librela™	0.0	12.7	46.0	37.3	4.0	126
	Control	0.0	13.3	59.4	24.2	3.1	128
28	Librela™	0.0	14.2	42.5	37.5	5.8	120
	Control	3.2	15.3	44.4	32.3	4.8	124
42	Librela™	0.0	9.6	38.3	40.9	11.3	115
	Control	0.8	13.4	47.1	28.6	10.1	119
56	Librela™	0.0	8.7	36.5	42.6	12.2	115
	Control	0.9	18.1	44.8	27.6	8.6	116
84	Librela™	0.0	9.1	29.1	50.9	10.9	110
	Control	1.8	19.3	41.3	28.4	9.2	109

Adverse Reactions: The safety of Librela™ administered at 28-day intervals was assessed in 135 dogs treated with Librela™, compared to 137 dogs treated with negative control. The most common adverse reactions reported during the field study are presented below in Table II.5.

Table II.5. 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.

Conclusion: This study provides evidence that the administration of Librela™ (bedinvetmab injection) at a dose of 0.23 mg/lb (0.5 mg/kg) subcutaneously 28 days apart is safe and effective for the control of pain associated with osteoarthritis in dogs. Although this study did not demonstrate treatment success based on the established primary effectiveness outcome measure at Day 28, the treatment success rate and the numerical difference between the success rates of the two groups from Day 42 (14 days after the second

treatment) onward demonstrate a clinically relevant effect in the Librela™ group compared to the control group. The results support the effectiveness of Librela™ for the control of pain associated with osteoarthritis when given as a minimum of two doses administered one month apart. See further discussion below in "Weight of the Evidence."

2. EU Field Study for the Control of Pain Associated with Osteoarthritis in Dogs

Title: EU Field Safety and Efficacy Study of Librela™ Compared to Placebo for the Treatment of Pain Associated with Osteoarthritis in Client-Owned Dogs. (Study No. C866C-XC-17-194)

Study Dates: May 14, 2018 to September 17, 2018

Study Locations: Study sites were located in Portugal (n=9), Hungary n=8), Ireland (n=6), and Germany (n=3).

Portugal
Ferreiros Amares
Vila Nova de Famalicão
Chaves
Vila Verde
Pardilhó
Esmoriz
Braga
Porto
Vila Mea

Hungary
Sümeg
Székesfehérvár
Kaposvar (2 sites)
Paks
Veszprém
Mosonmagyaróvár
Teskánd

Ireland
Virginia
Ballyshannon
Ballina
Drogheda
Trim
Tullamore

Germany
Münchsteinach
Berlin
München

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

Objective: The study evaluated the effectiveness and field safety of Librela™ (bedinvetmab injection) administered by subcutaneous injection for the control of pain associated with osteoarthritis in dogs.

Study Animals: The study enrolled 287 client-owned dogs with osteoarthritis (154 females, 133 males). Enrolled dogs had been diagnosed with osteoarthritis based on physical examination, orthopedic examination, and radiography. The enrolled dogs were at least 1 year of age (1.0 to 17.5 years old), weighed between 1.7 to 66.0 kg (3.7 to 145.5 lb), and were of various breeds or non-purebred.

Experimental Design: The dogs were randomized at a ratio of 1:1 to receive Librela™ or a negative control (sterile saline). Of the 287 dogs enrolled, 141 dogs received bedinvetmab and 146 received the negative control. This study was conducted in accordance with Good Clinical Practices (GCP).

Table II.6. Treatment Groups in Study No. C866C-XC-17-194

Treatment Group	Dose of Librela™	Schedule for Administration of Librela™ and Control	Number of Enrolled Dogs
Librela™ (bedinvetmab injection)	0.5 mg/kg	Days 0, 28 (±3 days) and 56 (± 5 days)	141
Negative Control*	0 mg/kg	Days 0, 28 (±3 days) and 56 (± 5 days)	146

*Control was sterile saline

Inclusion Criteria: The study included client-owned dogs that had been diagnosed with osteoarthritis based on owner history, physical examination, and radiographs. Dogs were in good general health or had stable chronic conditions that would not interfere with the study assessments. Dogs were required to have a CBPI PSS and PIS ≥ 2 at the screening visit and again on Day 0; dogs were additionally required to have a veterinary assessment of 'Moderate', 'Severe', or 'Nearly Incapacitated' for at least one of the Veterinary Categorical Assessments for 'lameness/weight-bearing', 'pain on palpation/manipulation of joints', and 'general musculoskeletal condition' in at least one joint of the pelvic or thoracic limbs.

Exclusion Criteria: Dogs intended for breeding, pregnant or lactating female dogs, or dogs with conditions that would confound the study assessments or prevent completion of the study were excluded, including dogs that had a lameness known to be related to neoplasia or that had a primary neurological condition that precluded owner and veterinary assessments of pain associated with osteoarthritis. Additionally, dogs that had a cranial cruciate ligament rupture less than 6 months before the time of enrollment were excluded.

Prior to study start, dogs were withdrawn from other drugs or treatments that might have interfered with the assessment of effectiveness.

Drug Administration: Dogs were administered Librela™ (bedinvetmab injection) at a minimum of 0.23 mg/lb (0.5 mg/kg) or an equivalent volume of control by subcutaneous injection. All dogs > 5.0 kg received a complete vial, as indicated in Table II.2. above. Dogs weighing < 5.0 kg received 0.045

mL/lb (0.1 mL/kg) from a 5 mg/mL vial or an equivalent volume of control. Treatment administration occurred in the veterinary clinic at scheduled visits.

Measurements and Observations: Baseline physical examination, body weight, hematology, serum chemistry, urine protein-creatinine ratio, urinalysis, immunological assessment, CBPI, veterinary categorical assessment (for lameness/weight-bearing, pain on palpation/manipulation of joints and general musculoskeletal condition), orthopedic examination, owner categorical assessments (for lameness/weight-bearing, musculoskeletal pain and overall musculoskeletal condition), and orthopedic radiographs were collected at screening (prior to Day 0) and, except for blood and urine collection and orthopedic radiographs, again on Day 0 prior to enrollment. On Days 7, 14, 28, 42, 56, and 84, the veterinarian completed a physical examination, orthopedic examination, veterinary categorical assessments and injection site evaluation; the owner completed the CBPI during the clinic visit; and blood samples were collected for immunological assessment. In addition, hematology and serum chemistry were evaluated on Days 28, 56, and 84. Urinalysis and urine protein creatinine ratio were evaluated at Day 84 only.

Statistical Methods:

Effectiveness was determined by the owner's evaluation of the CBPI at Days 7, 14, 28, 42, 56, and 84 compared to baseline (Day 0, before treatment). For each day, treatment success was defined as a reduction ≥ 1 in PSS, the owner's assessment of the dog's overall pain, and ≥ 2 in PIS, the owner's assessment of how the pain interferes with the dog's daily activities, compared to baseline. The primary effectiveness endpoint was treatment success on Day 28.

Treatment success (Yes/No) was analyzed on each day as a binary response using a generalized linear mixed model with binomial distribution and logit link. The model included the fixed effect of treatment. The random effects included clinic and the interaction between clinic and treatment. Back-transformed least squares means were used as estimates of the treatment proportions and corresponding 95% confidence intervals were constructed. Treatment comparisons were evaluated using log-odds ratios using a two-sided test at the 5% level of significance ($P < 0.05$).

Dogs receiving rescue treatment (e.g., for LOE) or withdrawn for LOE were counted as treatment failures starting on the day of rescue or withdrawal, respectively.

Results:

<u>CBPI</u>

The primary effectiveness variable was successful and met statistical significance at Day 28 ($P = 0.0018$). The proportion of dogs considered treatment successes based on the CBPI assessment was greater in the Librela™ group compared to the control group on all assessment days (See Table II.7).

Table II.7: Least Squares Mean Percent Success by Assessment Day

Assessment Day	Treatment 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

CBPI PIS and PSS

Mean PIS and PSS were lower in the Librela™ group compared to the control group at Days 7, 14, 28, 42, 56, and 84.

CBPI Overall Impression

The CBPI Overall Impression was scored by the owner as poor, fair, good, very good, or excellent. A higher percent of dogs in the Librela™ group were scored as excellent or very good compared to the control group at Days 7, 14, 28, 42, 56, and 84 (see Table II.8).

Table II.8. Summary of CBPI Overall Impression Scores

Study Day	Treatment	% Poor	% Fair	% Good	% Very Good	% Excellent	N
0	Librela™	10.9	42.8	39.9	6.5	0	138
	Control	6.3	49.7	36.4	7.0	0.7	143
7	Librela™	1.6	33.3	48.8	14.7	1.6	129
	Control	2.2	48.1	37.8	11.1	0.7	135
14	Librela™	0.7	24.6	47.0	23.9	3.7	134
	Control	2.2	42.0	40.6	14.5	0.7	138
28	Librela™	0.8	16.9	45.4	30.8	6.2	130
	Control	2.3	39.2	42.3	14.6	1.5	130
42	Librela™	0.8	13.7	38.2	35.9	11.5	131
	Control	2.3	34.1	43.4	17.8	2.3	129
56	Librela™	0.8	15.9	37.9	34.8	10.6	132
	Control	2.4	31.7	44.4	18.3	3.2	126
84	Librela™	2.3	17.2	35.2	32.8	12.5	128
	Control	0.8	36.1	42.9	16.8	3.4	119

Veterinary Categorical Assessments

The Veterinary Categorical Assessments for lameness/weight bearing, pain on palpation/manipulation of joints, and general musculoskeletal condition were

made by the veterinarian on Days 0, 7, 14, 28, 42, 56, and 84. Assessment categories were "clinically normal", "mild", "moderate", "severe", or "nearly incapacitated". The percentage of dogs where these conditions were categorized as "clinically normal" or "mild" increased during the study and was higher at all post Day 0 time points in the Librela™-treated group compared to the control group for all three assessments.

Adverse Reactions: The safety of Librela™ administered at 28-day intervals was assessed in 141 dogs treated with Librela™, compared to 146 dogs treated with negative control. The most common adverse reactions reported during the study are presented below in Table II.9.

Table II.9. Number (%) of Dogs with Adverse Reactions Reported in the European Field Study

Adverse Reaction*	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 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 had a history of atopy and was treated with oclacitinib. The dog developed mild alopecia and mild erythema at the injection site on Day 5. Treatment with oral and topical antimicrobials, and a medicated shampoo was initiated. The reaction resolved by Day 11, but mild erythema and mild alopecia were reported at the same location on Day 23. With continued treatment, the erythema resolved on Day 33 and the alopecia resolved on Day 40.

Conclusion: This study provides evidence that the administration of Librela™ (bedinvetmab injection) at a dose of 0.23 mg/lb (0.5 mg/kg) subcutaneously

28 days apart is safe and effective for the control of pain associated with osteoarthritis in dogs. The primary effectiveness variable was successful and met statistical significance at Day 28 (P = 0.0018). The proportion of dogs considered treatment successes based on the owner CBPI assessment was greater in the Librela™ group compared to the control group at Days 7, 14, 28, 42, 56, and 84. See further discussion below in 'Weight of the Evidence'.

3. Continuation Therapy Field Safety Study (Study C866C-XC-17-195)

A total of 89 dogs were enrolled in a single arm, open label, uncontrolled continuation of the EU field study (Study C866C-XC-17-194). The dogs received monthly subcutaneous injections of Librela™ (0.5 mg/kg) for an additional 6 months. Adverse findings in this study included the following events.

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 with no ossification of the humeral condyles on the left side and a fissure of the left medial coronoid process.

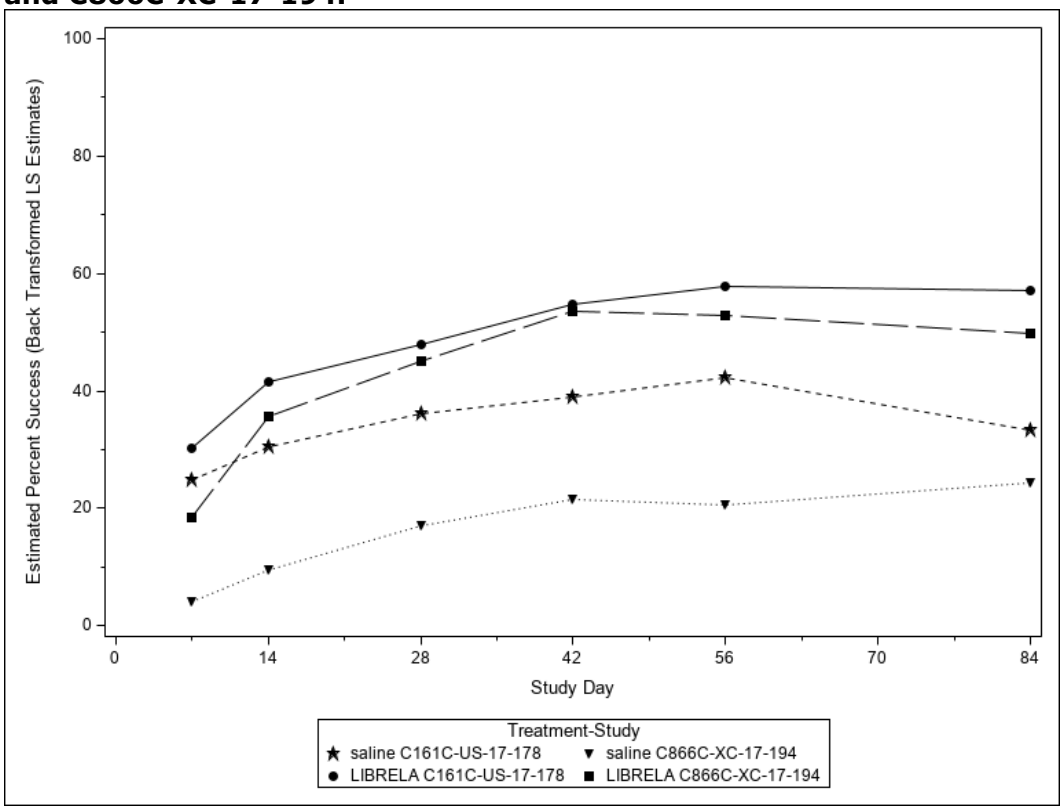
Two dogs presented with rear limb paresis of unknown etiology. One dog responded to ongoing NSAID treatment and one dog did not respond to NSAID treatment and was euthanized.

4. Weight of the Evidence

Substantial evidence of effectiveness is demonstrated by the results of the two field studies in dogs with naturally occurring osteoarthritis (Study C161C-US-17-178 and Study C866C-XC-17-194). These studies, taken together, establish the effectiveness of 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.

In US Study C161C-US-17-178, the treatment success rates and the numerical difference between the success rates of the two groups from Day 42 onward demonstrate a clinically relevant effect in the Librela™ group compared to the control group. However, the difference was not significant on Day 28, the primary effectiveness endpoint. In EU Study C866C-XC-17-194, the difference between the success rates of the two groups was significant ($P < 0.05$) on Day 28, the primary effectiveness endpoint. With monthly dosing, both studies demonstrated a greater percentage of dogs achieving treatment success, based on the CBPI endpoint, in the Librela™-treated versus the control groups at Day 42. Further, the percentage of dogs in the Librela™-treated group achieving treatment success was higher in both studies at Day 42 than at Day 28. This higher success rate relative to Day 28 was maintained in both studies through Day 84 (following a third administration at Day 56); see Figure II.1 below. The consistency of the results in the Librela™ group between the two studies, and the numerical difference between the success rates of the two groups from Day 42 onward in both studies, supports the effectiveness of the drug when administered at a minimum of two monthly doses.

Figure II.1. Canine Brief Pain Inventory (CBPI) Assessments of Treatment Success. Plot of Back-Transformed Least Squares Means for Librela™ and Control Treated Dogs in Studies C161C-US-17-178 and C866C-XC-17-194.



The results of other secondary variables from the US study (CBPI PIS and PSS and CBPI Overall Impression) and the EU Study (CBPI PIS and PSS, CBPI Overall Impression, and Veterinary Categorical Assessment) provide additional support that Librela™ reduced clinical signs of pain associated with osteoarthritis more than the negative control.

Conclusion:

The weight of evidence from these two studies demonstrates substantial evidence of 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.

III. TARGET ANIMAL SAFETY

The safety of Librela™ (bedinvetmab injection) was demonstrated in a well-controlled laboratory study using 11 to 12-month-old, healthy dogs. The purpose of the study was to demonstrate the safety of Librela™ in dogs when used according to label instructions.

A. Margin of Safety Study

Title: A 6-Month Study of Bedinvetmab by Subcutaneous Injection in Adult Beagle Dogs. (Study No. C362N-US-17-160)

Study Dates: April 4, 2018 to August 29, 2019

Study Location: Ashland, OH

Study Design:

Objective: This study was intended to demonstrate a margin of safety and the toxicokinetic profile of Librela™ (bedinvetmab injection) when administered once every 28 days by subcutaneous injection to Beagles for 7 treatments at 0X (0 mg/kg), 1X (1 mg/kg), 3X (3 mg/kg), and 10X (10 mg/kg) the high end of the inherent dose band.

Study Animals: Thirty-two (16 male, 16 female) young, healthy, intact Beagles approximately 11 to 12 months of age on Day 0, weighing 5.6 to 11.7 kg at the initiation of dosing.

Experimental Design: Dogs were randomly allocated to one of 4 treatment groups of 8 dogs per group (4 per sex). Dogs were administered Librela™ or a negative control (saline) every 28 days for 7 doses. This study was conducted in accordance with Good Laboratory Practice (GLP) Regulations.

Drug Administration: Librela™ 15 mg/mL and 30 mg/mL concentrations were administered subcutaneously on Days 0, 28, 56, 84, 112, 140, and 168 using a 23-gauge 1-inch needle.

Table III.1. Treatment Groups

Treatment Group; concentration	Number of dogs	Dose (mg/kg)	Route	Treatment Days
Control (saline); 0 mg/mL	4 male 4 female	0X (0 mg/kg)	Subcutaneous injection	Days 0, 28, 56, 84, 112, 140, and 168
Librela™; 15 mg/mL	4 male 4 female	1X (1 mg/kg)	Subcutaneous injection	Days 0, 28, 56, 84, 112, 140, and 168
Librela™; 30 mg/mL	4 male 4 female	3X (3 mg/kg)	Subcutaneous injection	Days 0, 28, 56, 84, 112, 140, and 168
Librela™; 30 mg/mL	4 male 4 female	10X (10 mg/kg)	Subcutaneous injection	Days 0, 28, 56, 84, 112, 140, and 168

Measurements and Observations: Body weights were measured weekly and food consumption was measured daily. Veterinary physical examinations, blood pressure, electrocardiographic evaluation, and respiratory rate were evaluated

pre-treatment, at 1 and 3 months, and prior to necropsy. Ophthalmic examinations and survey radiographs of the hip, knee, shoulder, and elbow were conducted pre-treatment and prior to necropsy. Veterinary neurologic exams were conducted pre-study, mid-study, and after the last dose. There were twice daily observations; and veterinary observations prior to each treatment, 2 hours post-treatment, once daily for 2 days following each dose, and prior to necropsy. Injection sites were observed pre-dose, 2- and 8-hours post-dose, once daily for 6 days after each dose, and prior to necropsy. Hematology, coagulation, serum chemistry, and urinalysis samples were collected prior to each dose and prior to necropsy. Blood samples were collected for toxicokinetics and antidrug antibody testing prior to each dose; at 7, 14, and 21 days following the first dose and sixth dose; and at 7 and 14 days after the seventh dose. Necropsy was performed two weeks following the final dose, and included gross pathology, organ weights, and histopathology. Histopathology included cranial cervical ganglion and dorsal root ganglia evaluation. Following tissue fixation, the hip, knee, shoulder, and elbow joints were evaluated by high-resolution radiography. Pathology evaluation of specified joints included weight-bearing surfaces, ligaments, acetabulum, synovial membrane, and subchondral bone. Orthopedic tissue sectioning was guided by high-resolution radiography to evaluate for possible lesions not grossly evident.

Statistical Methods: Body weight, temperature, average daily feed consumption, and continuous clinical pathology data were analyzed using a general linear mixed model for repeated measures with fixed effects of treatment, time, sex, and all their 2- and 3-way interactions. Where appropriate, a baseline covariate was included in the model. For organs collected from both sexes, organ weight, organ weight relative to final body weight, and organ weight relative to brain weight were analyzed using a general linear mixed model with sex, treatment, and the sex by treatment interaction as fixed effects.

For organs collected from a single sex, the organ weight variables were analyzed using a general linear mixed model with treatment as a fixed effect. Statistical significance was evaluated at a two-sided alpha equal to 0.10 except that the 3-way interaction term was evaluated at two-sided alpha equal to 0.05.

Results:

All dogs survived to study conclusion. There were no clinically significant changes noted in neurological examinations, body temperature, heart and respiratory rate, blood pressure, electrocardiography, and organ weights.

Clinical Observations: One dog in the 3 mg/kg treatment group and one dog in the 10 mg/kg treatment group were administered supplemental feeding for one week, starting at Days 176 and 172 of the study, respectively, due to low food consumption and weight loss. The dog in the 10 mg/kg group also had temporary lower food consumption pre-study.

Vomiting and soft stool were noted across all treatment 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 dog in the control group, 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 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 on shaved caudal dorsal cervical area that resolved over 14 days.

One dog in the 3 mg/kg treatment group had a temporary, mild swollen facial area 26 days after the first dose. The one-time finding resolved spontaneously without any treatment.

Another dog in the 3 mg/kg treatment group had a small dermal mass with some thickening and discoloration above the right eye for approximately 2.5 months. This dog had lymphadenopathy on Day 183 with no histopathology correlate and a mildly elevated white blood cell count from Days 140-168. A third dog in the 3 mg/kg treatment group, which was one of the dogs with soft feces during the study, also had lymphadenopathy on Day 183 with no histopathological correlate.

Clinical chemistry evaluations: There was a significant treatment effect across time points for albumin. Compared to the control group, decreased albumin was observed in dogs in the 1 mg/kg treatment group and 3 mg/kg treatment group. Dogs in the 3 mg/kg treatment group had significantly different and numerically smaller mean albumin values compared to the control group on Days 84, 140, 168, and 182 ($p = 0.026$, 0.0002, 0.073, and 0.0079, respectively). Dogs in the 1 mg/kg treatment group had significantly different and numerically smaller mean albumin values compared to the control group on Day 182 ($p = 0.0146$). All albumin values remained within the reference range.

Additionally, one dog in the 1 mg/kg treatment group had an increasing serum alkaline phosphatase (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.

Pharmacokinetics: Serum concentrations of bedinvetmab were measured using a validated ligand binding assay method. The time to reach maximum concentration (Tmax) was 7 days. Toxicokinetic exposure [maximum observed concentration (Cmax) and area under the serum concentration-time curve from time zero to 28 days (AUC0-28d)] on Day 0 (1st dose) and Day 140 (6th dose) increased approximately in proportion to the bedinvetmab dose and exposures were similar in both sexes. The elimination half-life (T1/2) ranged from 8.8 days to 10.0 days. There was slight accumulation on Day 140 compared to Day 0 and steady-state was achieved after approximately 2 doses.

Pathology: One dog in the 1 mg/kg treatment group with focal proteoglycan depletion had mild focal cartilage necrosis in the left ulna and an erosion in the cartilage and degeneration 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.

Conclusions: Librela™ (bedinvetmab injection), administered to healthy 11-12-month-old Beagles, at 1, 3, or 10 times the high end of the inherent dose band, demonstrated an adequate margin of safety when administered subcutaneously once every four weeks for seven consecutive doses. Scabbing lesions of the head and neck are associated with bedinvetmab. The boney changes may be progression of an underlying musculoskeletal condition; however, a potential relation to treatment cannot be ruled out.

B. Concurrent Use Study

In a 2-week laboratory safety study, eight healthy 10-11 month old Beagles concurrently received one subcutaneous injection of Librela™ at the high end of the inherent dose band (1 mg/kg) and 14 days of an injectable NSAID. Shoulder, elbow, hip, and knee joints were evaluated by pathology, along with additional soft tissues considered possible targets of either drug. Although there were no significant findings, this limited laboratory study did not provide sufficient data to support the safety of concurrent use of Librela™ and NSAIDs.

C. Exploratory Safety Study

In a 3-month exploratory laboratory safety study using a non-final formulation of bedinvetmab administered by subcutaneous injection at 0X, 1X (1 mg/kg), 4x (4 mg/kg), and 12X (12 mg/kg) 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 4 mg/kg had a 4 cm X 2 cm area of erythema with eschar at the injection site that resolved; and one dog administered a 1 mg/kg dose had a 3 cm X 1 cm area of erythema at the injection site that resolved. A dog administered a 1 mg/kg dose had injection site erythema, scabbing, and mucopurulent discharge for 18 days. There was perivascular mononuclear infiltrate at the left lateral neck injection sites in all treatment groups administered bedinvetmab. The infiltrate was minimal to mild severity and localized to this tissue without any additional associated reaction.

D. Immunogenicity

All therapeutic protein products have the potential for inducing an immune response (immunogenicity) following administration to a host, like a humoral immune response and the production of antibodies in the host. These host-derived antibodies may bind to the therapeutic protein (drug product) and may result in decreased effectiveness or increased risk for an adverse reaction. Such host-derived antibodies specific for the therapeutic protein are also termed anti-drug antibodies (ADA). Monoclonal antibody drug products, such as Librela™, are a specific subclass of therapeutic protein products, have the potential for pre-existing ADAs (i.e., drug-specific ADAs present prior to therapeutic protein administration), and the potential for immunogenicity following administration. Antibodies binding to Librela™ (i.e., ADAs), were detected using a multi-tiered ADA testing approach (screening, confirmatory, and titration). Testing the

confirmed ADA samples for neutralizing activity of Librela™ 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 (132 dogs in the Librela™ group and 135 in the control group). 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 (138 dogs in the Librela™ group and 143 in the control group). 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 ADAs was confirmed in 1 dog on Day 56. Of the 138 Librela™-treated dogs, the presence of ADAs was confirmed in 2 dogs after treatment with Librela™ (1 dog on Day 84 and 1 dog on Day 28).

Eighty-nine Librela™-treated dogs in the EU field safety and effectiveness study continued on for further evaluation with once monthly treatment with Librela™ for an additional six months, and 82 of 89 enrolled dogs were evaluated for immunogenicity. The 2 Librela™-treated dogs previously confirmed with the presence of ADAs did not continue to have the presence of ADAs confirmed during the additional six months. Of the other 80 dogs, the presence of ADAs was confirmed in 2 additional dogs.

In the Six-Month Safety Study, the presence of ADAs was confirmed in 2 out of 8 dogs in the negative control group and no ADAs were confirmed in any of the 24 dogs treated with Librela™.

IV. HUMAN FOOD SAFETY

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

V. USER SAFETY

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

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 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 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.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Librela™, when used according to the label, is safe and effective for the control of pain associated with osteoarthritis in dogs.

A. Marketing Status

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

B. Exclusivity

The exclusivity provisions of section 512(c)(2)(F) of the FD&C Act do not apply to this drug because under section 106 of the Generic Animal Drug and Patent Term Restoration Act (Pub.L. 100-670), FDA cannot approve an abbreviated new animal drug application for a new animal drug that is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific gene manipulation techniques. Therefore, a sponsor cannot submit an ANADA to market a generic version of this drug.

C. Patent Information

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