RESEARCH PAPER

A prospective, randomized, double-blind, placebo-controlled multisite, parallel-group field study in dogs with osteoarthritis conducted in the United States of America evaluating bedinvetmab, a canine anti-nerve growth factor monoclonal antibody

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Abstract

Objective Bedinvetmab, a fully canine anti-nerve growth factor monoclonal antibody, was evaluated in dogs for control of osteoarthritis-related pain in a study conducted to support registration in the USA.

Study design Randomized, double-blind, placebo-controlled, multicenter, parallel-group study.

Animals General practice client-owned dogs with osteoarthritis ($n = 272$).

Methods Dogs were block randomized 1:1 to placebo (saline, $n = 137$) or bedinvetmab ($n = 135$; 0.5–1.0 mg kg^{-1}) administered subcutaneously, once monthly. The primary end point, day 28 Canine Brief Pain Inventory (CBPI) treatment success (TS), required pain severity score (PSS; 0–10) decrease $\geq$1 and pain interference score (PIS; 0–10) decrease $\geq$ 2. CBPI TS rates [and number needed to treat (NNT)], change in scores [and standardized effect size (ES)], change in quality of life (QoL) and bedinvetmab half-life were calculated.

Results Significant ($p < 0.05$) improvement with bedinvetmab over placebo occurred (days 28, 42, 56, 84) for CBPI TS. Of cases evaluable for day 28 CBPI TS (placebo, $n = 131$; bedinvetmab, $n = 128$), success rates were 36.6% and 47.4%, respectively ($p = 0.0410$) (NNT, 9.3; PSS and PIS ES, 0.3). CBPI TS increased after the second dose in both groups, plateaued for bedinvetmab at day 42 and decreased for placebo beginning day 84. Day 84 NNT (4.3), PSS (0.4) and PIS (0.5) showed continued improvement with monthly dosing. After the first dose, mean (± standard deviation) bedinvetmab half-life was 19.1 (8.3) days. Adverse events were similar between groups and not considered treatment-related. There was a significant effect of bedinvetmab *versus* placebo on all CBPI components (PIS, PSS, QoL).

Conclusions and clinical relevance These results corroborated those previously reported and provide further support of safety and effectiveness of bedinvetmab (0.5–1.0 mg kg^{-1}) administered subcutaneously at monthly intervals to dogs for control of osteoarthritis-related pain.

Keywords bedinvetmab, canine brief pain inventory, canine osteoarthritis, degenerative joint disease, monoclonal antibody, pain management.

Introduction

Chronic pain, a hallmark of osteoarthritis (OA), is the central focus of OA management in veterinary medicine where the main goal is to improve overall quality of life (QoL) (Johnston et al. 2008; Rialland et al. 2012; Meeson et al. 2019; Corral et al. 2021). Reported OA prevalence is nearly 40% in dogs and > 50% in cats (Lascelles et al. 2010; Gruen et al. 2022; Wright et al. 2022). Nerve growth factor (NGF), a neurotrophic factor associated with pain signal transduction and nociceptor receptor gene expression (Mantyh et al. 2011; Zhao et al. 2022), plays an important role in pain signaling in OA. NGF is a soluble signaling protein released after tissue injury or inflammation. It binds to high-affinity NGF-specific tropomyosin receptor kinase A (TrkA) and low-affinity p75 neurotrophin receptor (p75^{NTR}) (Enomoto et al. 2019), which can lead to central sensitization (Mantyh et al. 2011), induce the

expression of pain-related substances peripherally and centrally, and make adjacent pain-sensing neurons sensitive to inflammation, thereby mediating pain (Bannwarth & Kostine 2014; Cohen & Mao 2014; Eskander et al. 2015; Enomoto et al. 2019; Zhao et al. 2022). The expression of NGF is substantially increased at sites of trauma and inflammation (Hefti et al. 2006; Zhao et al. 2022). NGF concentrations in synovial fluid (Isola et al. 2011) and expression levels of NGF and TrkA in synovium (Yamazaki et al. 2021) are higher in dogs with OA than in those without OA and expression levels varied with severity of synovitis (Yamazaki et al. 2021).

Bedinvetmab and frunevetmab are anti-NGF monoclonal antibodies (mAbs) recently licensed for the control of pain associated with OA in dogs and cats, respectively (Corral et al. 2021; Gruen et al. 2021). These molecules bind to NGF and prevent interaction with its receptors, thereby interrupting NGF/TrkA signaling and decreasing the hyperalgesic response associated with OA (Enomoto et al. 2019). Anti-NGF mAbs represent the most significant clinical advance in OA pain management in veterinary medicine since registration of the first non-steroidal anti-inflammatory drug (NSAID) 25 years ago.

The objective of the current study was to demonstrate efficacy and safety of bedinvetmab in dogs for control of pain associated with OA. The study was conducted to support registration in USA and followed a similar study design as the placebo-controlled study phase reported by Corral et al. (2021).

Materials and methods

Study design

The study was a prospective, randomized, double-blind, placebo-controlled, multicenter, parallel-group study with balanced randomization (1:1) conducted in the USA (11 states; 24 general practices). Data collection complied with Veterinary International Conference on Harmonization and Good Clinical Practice Guideline principles (VICH Topic GL9 2000; EMEA 2000). The Sponsor Ethical Review Board reviewed and approved the protocol prior to study initiation (protocol ID C161C-US-17-178). All owners provided written confirmation of informed consent.

Sample size estimates were derived from power calculations based on variance and effect sizes observed in unpublished data from a proprietary placebo-controlled field study [proportions of Canine Brief Pain Inventory (CBPI) treatment successes (TS) were assumed at 0.307 and 0.614 for placebo and bedinvetmab, respectively) with the aim to achieve $\geq$ 80% power at $\alpha = 0.05$ (two-sided).

Study population

The study enrolled client-owned dogs from primary care veterinary clinics from March to July, 2018. Eligibility criteria ensured that efficacy and safety evaluations were not confounded by enrollment of dogs with uncontrolled concurrent disease or treatments.

Inclusion criteria

Clinical and radiographic evidence of OA in dogs $\geq$ 1 year of age were confirmed in $\geq$ one joint of a thoracic or pelvic limb at a screening visit. Dog was expected to benefit from continued treatment for a 1 month period for clinical signs of OA. Severity of at least one of the veterinarian categorical assessments [general musculoskeletal condition, pain on palpation/manipulation of joint(s), lameness/weight bearing] was at least 'moderate' (scale: clinically normal, mild, moderate, severe, nearly incapacitating) at screening and day 0. CBPI pain severity score (PSS) and pain interference score (PIS), assessed by the owner, were each $\geq$ 2 (scale, 0−10) at screening visit and day 0 (Brown et al. 2013). The CBPI overall impression of QoL was assessed but did not contribute to eligibility. Users adhered to all instructions in the CBPI User Guide (Brown 2017). Veterinarians confirmed dogs were generally in good health, concomitant diseases were well controlled and clinical pathology results (blood and urine) were satisfactory.

Exclusion criteria

Dogs enrolled in a clinical trial $\leq$ 30 days before day 0 or involving an injectable product < 90 days before day 0 or ever treated with an anti-NGF mAb; intended for breeding or lactating or pregnant; with lameness associated with primary immunologic, neurologic, infectious or neoplastic condition, ligament rupture < 6 months ago, or non-healed fracture; with history of injury resulting in neurologic deficits or intervertebral disc disease (if interference with efficacy assessment expected); administered prohibited medication (Table S1). Use of conditionally allowed medication was subject to specified conditions for minimal use and frequency of use (Table S1); dogs could be enrolled if specified withdrawal times or minimal use and frequency of use were followed. One dog could be enrolled from a household at a time.

Randomization and blinding

Enrolled dogs were randomized 1:1 to placebo (saline) or bedinvetmab (Librela™ (bedinvetmab injection); Zoetis Inc., Kalamazoo, MI, USA) according to a randomized complete block design with one-way treatment structure replicated in multiple clinics. Randomization was done using SAS Release 9.4 (SAS Institute, Cary, NC, USA). Dogs were randomly assigned to groups based on order of entry into study at the clinic and according to the randomization provided by the statistician. Within each site, blocks of two dogs were formed based on order of enrollment. Within each block, dogs were

allocated at random to saline or bedinvetmab. The randomization was uploaded into an electronic system and accessible only to the dispenser. Day 0 was the day a dog was first dosed. Owners and clinic study personnel, except the dispenser, were blinded to treatment allocation and block size, and remained blinded at the end of study. Dispensers prepared the correct test article (bedinvetmab or saline; identical appearance) and were not involved in data collection. The veterinarian or their designee administered the test article.

Treatment administration

A dosage chart ensured bedinvetmab dosage between 0.5 and 1.0 mg kg^{-1} using a ready-to-use formulation in single-use 1 mL vials (vial strengths: 5, 10, 15, 20 or 30 mg mL^{-1}). Dogs randomized to placebo were administered an equivalent volume of saline. Test article was administered subcutaneously.

Study schedule

A screening visit occurred 2−21 days before day 0. Baseline data collection occurred on day 0, before enrolment. There were six clinic visits after day 0, including monthly visits (days 28, 56, 84) where test article was administered and visits on days 7, 14, and 42. Veterinary examination and sample collection occurred at all visits.

At each visit, owners blinded to their prior assessments completed the CBPI and veterinarians completed physical examination and documented adverse events (AEs) or medications, if any. Serum samples were prepared at each visit for measurement of bedinvetmab and total NGF concentrations and evaluation for anti-drug antibodies (ADAs). Blood was collected for hematology (day 7 and monthly) and serum chemistry (monthly), and urine was collected (monthly) for urinalysis and measurement of protein creatinine ratio.

Escape clause and use of rescue and prohibited therapies

A dog could be withdrawn from study by the veterinarian or owner at any time. Prohibited or conditionally allowed medications could be administered before withdrawal, if necessary, for animal welfare reasons. 'Rescue' treatment for an OA-related reason [e.g. lack of efficacy (LOE)] was a prohibited treatment. A 'prohibited' treatment that was not rescue treatment was one that could interfere with efficacy assessments and was used for a reason unrelated to OA.

Efficacy outcome measures

Dogs from clinics with fewer than two evaluable cases per treatment group, and dogs having a protocol deviation impacting integrity or collection of data were excluded from effectiveness analyses. Use of prohibited treatment following enrollment resulted in exclusion of efficacy data at all subsequent assessments except for dogs administered rescue treatment (or withdrawn for LOE), which were treated as failures in the CBPI TS analysis beginning on day of rescue (or withdrawal) and continuing through all subsequent assessments (see Fig. 1).

Data were statistically analyzed for days 7 (−0/+2), 14 (±3), 28 (±5), 42 (±5), 56 (±7) and 84 (±7). Day 28 CBPI TS was the primary efficacy end point. TS required PSS (0−10) decrease $\geq$ 1 and PIS (0−10) decrease $\geq$ 2 as recommended by Brown et al. (2013).

Secondary end points were CBPI TS at all other time points, CBPI PSS, PIS and QoL, the proportion of dogs categorized as having 'very good' or 'excellent' QoL and the proportion of dogs with improvement in QoL. Success/failure rates were used *post hoc* to calculate values for number needed to treat (NNT) (Cook & Sackett 1995). Standardized effect size (ES) for change in PSS and PIS were calculated *post hoc* (Sullivan & Feinn 2012).

Safety outcome measures and analysis

Safety assessments included all animals. Frequencies of dogs with AEs were summarized by preferred term and organ class term for each clinical sign using Veterinary Dictionary for Drug Related Affairs coding (Committee for Veterinary Medicinal Products 2023). Clinical pathology data were summarized using shift tables showing the number of dogs with results above, within or below the laboratory reference range by time point.

Pharmacokinetics and immunogenicity assessment

Bedinvetmab concentrations and ADAs in serum were analyzed at each time point, while a subset of 25 animals (placebo and bedinvetmab-treated animals with and without immunogenicity) had samples assayed for total NGF (free NGF + NGF bound to bedinvetmab; lower limit of quantitation, 0.05 ng mL^{-1}), using validated bioanalytical methods. Bedinvetmab concentrations were used to calculate pharmacokinetic variables and assess ADA results for treatment-emergent immunogenicity. The ADA data were integrated with bedinvetmab and total NGF concentration data to assess clinical importance of immunogenicity data. These data were evaluated with safety and efficacy data using a by animal assessment of impact of treatment-emergent immunogenicity on CBPI TS. AEs were assessed for relationship to treatment-emergent immunogenicity.

Statistical analysis

Data analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). The CBPI PSS and PIS were analyzed separately using a general linear mixed model for repeated measures. Pre-treatment (day 0) scores were used as covariates in the model. The model included fixed effects of treatment, day of study and interaction between treatment and day of study.

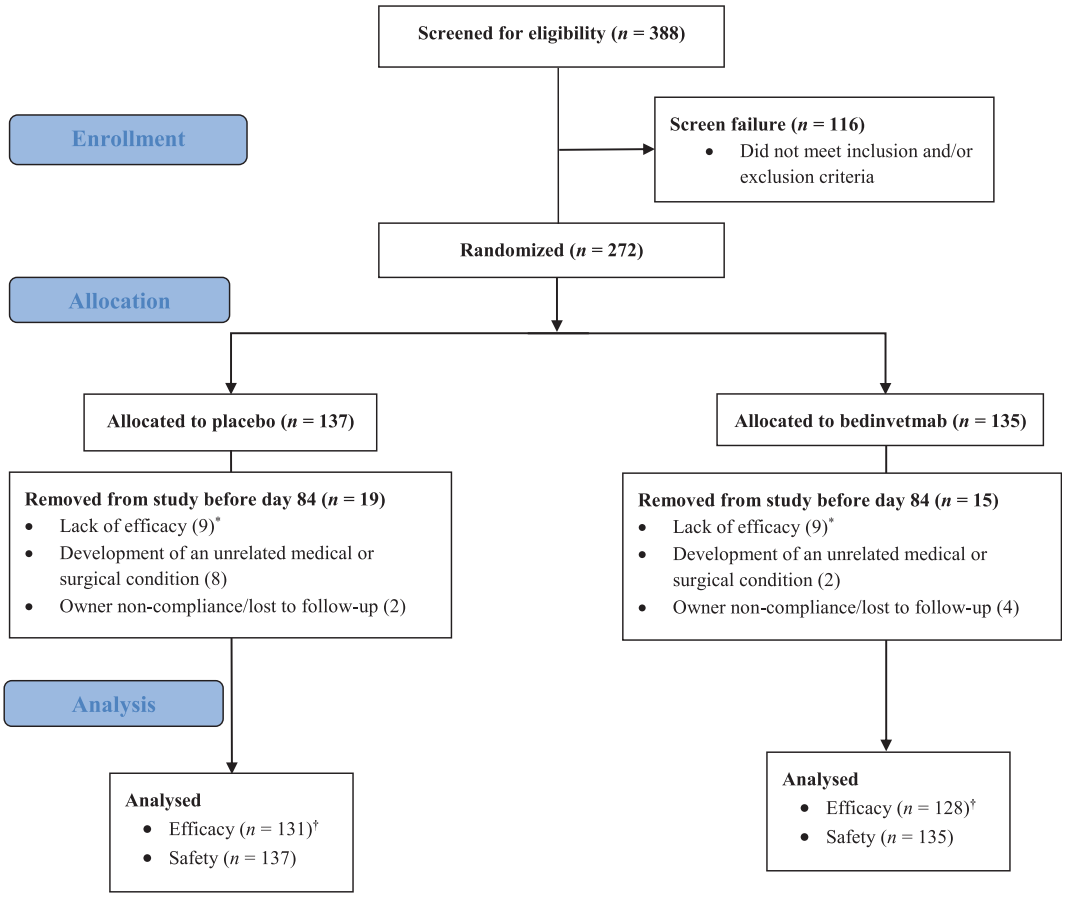


Figure 1 CONSORT flow diagram describing all cases recruited for the 3 month study. *n*, number; OA, osteoarthritis. *Animals administered rescue treatment during the study or that were withdrawn because of lack of efficacy were considered treatment failures beginning on the day of rescue or withdrawal, respectively, and were included in the analysis for treatment success. †Data excluded due to protocol deviations [i.e. eligibility criteria not met, owner did not complete the Canine Brief Pain Inventory assessment at the clinic visit (completed over the phone)], site did not meet enrolment criterion of two or more evaluable cases per treatment group, animal withdrawn for developing an unrelated medical or surgical condition, owner non-compliance/lost to follow-up, or administration of prohibited treatments explains the cases excluded from the efficacy analysis. All animals were included in the safety data analysis.

Random effects of the model included site, interaction between site and treatment, interaction between site, treatment and day of study, animal within site and treatment, and error. TS and any binary data (i.e. yes/no) were analyzed, separately by day of study, using generalized linear mixed models with binomial distribution and logit link. The NOBOUND option in PROC GLIMMIX was used in the analysis of TS (Stroup et al. 2018). The model included fixed effect of treatment and random effects of site, and interaction between site and treatment. The level of significance was set at $\alpha = 0.05$ (two-sided).

Results

Demographic data

Eligibility criteria were not met for 116 of 388 dogs screened; thus, 272 dogs (placebo, $n = 137$; bedinvetmab, $n = 135$) were randomized and administered a test article (Table 1).

Efficacy assessment

Of enrolled dogs, 34 were withdrawn (placebo, $n = 19$; bedinvetmab, $n = 15$) (Table 2). Twenty-two dogs (11/group) were counted as failures, for withdrawal for LOE (9/group) and/or administration of rescue treatment (placebo, $n = 8$; bedinvetmab, $n = 7$). Ten animals were withdrawn for a medical or surgical condition unrelated to test article and six were withdrawn for owner non-compliance or lost to follow-up. Exclusion of data occurred for protocol deviations for visits outside of the permitted window, different owner *versus* day 0 completed assessment or owner completed assessment over phone *versus* in-clinic, animal mis-dosed, administration of prohibited treatment or failure to meet eligibility criteria.

Table 1 Demographics of enrolled dogs with osteoarthritis at day 0. Bedinvetmab group: subcutaneous administration of bedinvetmab monthly; placebo group: equivalent volume of saline. Data are presented as *n* (%) or mean ± standard deviation (range). *n*, number of animals (all animals enrolled, including animals with protocol deviations excluded from analysis).

Demographic		Groups		Total ($n = 272$)
		Placebo ($n = 137$)	Bedinvetmab ($n = 135$)	
Breed distribution				
	Pure-bred*	89 (65.0)	82 (60.7)	171 (62.9)
	Mixed breed	48 (35.0)	53 (39.3)	101 (37.1)
Sex distribution				
	Male	57 (41.6)	60 (44.4)	117 (43.0)
	Female	80 (58.4)	75 (55.6)	155 (57.0)
Neutered/ovariohysterectomized		133 (97.1)	127 (94.1)	260 (95.6)
Age (years)		9.6 ± 3.0 (2.0–17.0)	9.4 ± 2.8 (1.0–15.0)	9.5 ± 2.9 (1.0–17.0)
Weight (kg)		28.8 ± 13.4 (1.8–62.4)	27.7 ± 13.8 (2.9–62.7)	28.3 ± 13.6 (1.8–62.7)
History of ruptured cranial cruciate ligament >6 months prior to enrolment†		22 (16.1)	21 (15.6)	43 (15.8)
Pre-treatment day 0 CBPI PIS (0–10)		6.01 ± 1.87 (2.33–9.67)	5.92 ± 1.86 (2.17–9.67)	5.97 ± 1.86 (2.17–9.67)
Pre-treatment day 0 CBPI PSS (0–10)		5.38 ± 1.68 (2.00–10.00)	5.10 ± 1.63 (2.00–9.00)	5.24 ± 1.66 (2.00–10.00)
VCA general musculoskeletal condition, moderate or worse at study start		124 (90.5)	122 (90.4)	246 (90.4)

CBPI, Canine Brief Pain Inventory; CBPI PIS, pain interference score; CBPI PSS, pain severity score; VCA, veterinary categorical assessment.
*Labrador Retriever was the predominant breed ($n = 33$; 12.1%), then Golden Retriever ($n = 16$; 5.9%) and German Shepherd ($n = 9$; 3.3%). No other individual pure-bred comprised ≥ 3% of the total. †Veterinarian responded (yes/no) to 'Does the dog have a history of ruptured cruciate ligament?' A similar number in both groups were reported to have undergone surgical stabilization (almost exclusively extracapsular stabilization).

Five dogs (placebo, $n = 2$; bedinvetmab, $n = 3$) were administered prohibited medication. Data for four dogs at two sites were excluded for sites not having at least two evaluable cases per treatment group.

Owner assessment (CBPI)

Frequency of CBPI TS was numerically greater in bedinvetmab than in placebo group at all visits; between-group difference was significant at day 28 (47.4% *versus* 36.6%; $p = 0.0410$), day 42 (55.9% *versus* 39.8%; $p = 0.0143$), day 56 (58.0% *versus* 41.7%; $p = 0.0193$) and day 84 (57.4% *versus* 34.2%; $p = 0.0026$), but not day 7 (30.0% *versus* 24.9%; $p = 0.372$) or day 14 (41.4% *versus* 30.5%; $p = 0.128$) (Table 3). TS in both groups increased after second dose, plateaued in bedinvetmab group beginning day 42 and did not decrease in placebo group until day 84. The NNT calculated from data at each visit decreased after each dose: 19.6 (day 7), 9.2 (day 14), 9.3 (day 28), 6.2 (day 42), 6.1 (day 56), 4.3 (day 84).

Mean PSS and PIS were numerically lower in bedinvetmab than in placebo group at all visits after enrolment; between-group differences for PSS and PIS were significant on days 28, 42, 56 and 84 ($p \leq 0.0223$) but not day 7 ($p = 0.0567$) or 14 ($p = 0.121$) (Fig. 2a & Table S2) and days 14, 28, 42, 56 and 84 ($p \leq 0.0279$) but not day 7 ($p = 0.0596$) (Fig. 2b & Table S3), respectively. Standardized ES for PSS and PIS, respectively, increased through day 42: day 7 (0.2, 0.2), 14 (0.2, 0.2), 28 (0.3, 0.3), 42 (0.4, 0.5), 56 (0.4, 0.4) and 84 (0.4, 0.5).

There was a numerically higher proportion of bedinvetmab-treated dogs with improvement in CBPI QoL at all visits *versus* placebo (Table S4). The proportion of animals with 'excellent' or 'very good' QoL is shown (Fig. 3).

Safety assessment

Adverse events and concomitant medications

At least one AE was reported for 86 and 79 dogs in placebo and bedinvetmab groups, respectively (Tables 4 and 5). Most frequently reported AEs were 'skin and appendages disorder' (including 'bacterial skin infection', 'dermatitis') and 'renal and urinary disorders' (including 'urinary tract infection', 'inappropriate urination'). AEs occurred at an overall similar frequency in both groups, although some occurred at higher frequency in one group or the other. Inspection of AEs supports that differences between groups in individual AE frequencies (by preferred term or organ class) were incidental occurrences not related to administration of bedinvetmab (frequently associated with coexisting morbidities). Interestingly, cranial cruciate ligament (CCL) rupture during study occurred in three placebo-treated and no bedinvetmab-treated dogs; one bedinvetmab-treated dog with stifle effusion and lameness at day 84 was diagnosed 1 month later with CCL rupture.

Table 2 Overview of dogs with osteoarthritis administered either saline (placebo group) or bedinvetmab by monthly subcutaneous injection (bedinvetmab group) for 3 months that were withdrawn from the study prior to the day 84 visit. Data were excluded from the efficacy analysis for cases with protocol deviations. All animals were included in the safety analysis.

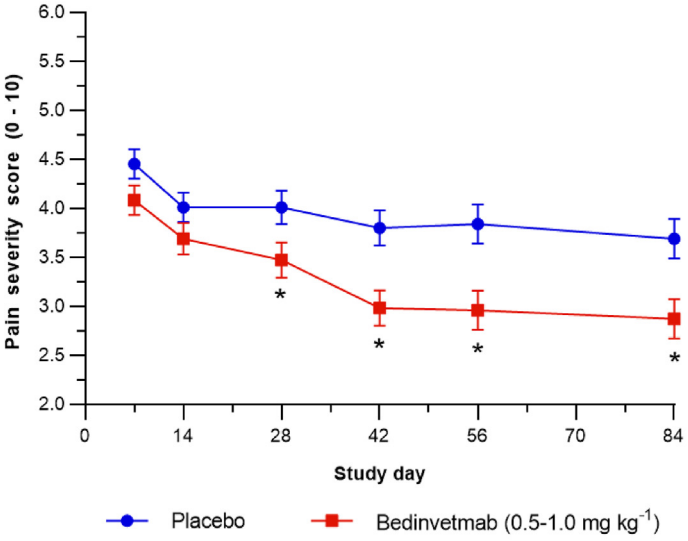
Study day	Group	
Study day 0 visit	**Placebo (137 dogs)**	**Bedinvetmab (135 dogs)**
	Cumulative total number of dogs withdrawn before day 28 visit = 2	**Cumulative total number of dogs withdrawn before day 28 visit = 2**
	Two cases were withdrawn because of developing an unrelated surgical condition (ureteroliths and jejunal mural sarcoma, respectively)	Two cases were withdrawn because of owner non-compliance/lost to follow-up
Study day 28 visit	**Placebo (135 dogs)**	**Bedinvetmab (133 dogs)**
	Cumulative total number of dogs withdrawn before day 56 visit = 13	**Cumulative total number of dogs withdrawn before day 56 visit = 13**
	Five cases were withdrawn because of lack of efficacy	Seven cases were withdrawn because of lack of efficacy
	Two cases were withdrawn because of developing an unrelated surgical condition (both with unilateral cranial cruciate ligament rupture)	One case was withdrawn because of developing an unrelated surgical condition (tooth root abscess)
	Two cases were withdrawn because of developing an unrelated medical condition (severe abdominal pain and unilateral temporalis muscle atrophy, respectively)	One case was withdrawn because of developing an unrelated medical condition (degenerative myelopathy in the rear limbs)
	Two cases were withdrawn because of owner non-compliance/lost to follow-up	Two cases were withdrawn because of owner non-compliance/lost to follow-up
Study day 56 visit	**Placebo (124 dogs)**	**Bedinvetmab (122 dogs)**
	Cumulative total number of dogs withdrawn before day 84 visit = 19	**Cumulative total number of dogs withdrawn before day 84 visit = 15**
	Four cases were withdrawn because of lack of efficacy	Two cases were withdrawn because of lack of efficacy
	Two cases were withdrawn because of developing an unrelated medical condition (pancreatic necrosis syndrome and worsening health due to suspected neoplasia, respectively)	
Study day 84 visit	**Placebo (118 dogs)**	**Bedinvetmab (120 dogs)**

Table 3 Primary efficacy variable: Canine Brief Pain Inventory (CBPI)-based treatment success of dogs with osteoarthritis assigned to treatment with monthly subcutaneous injections of bedinvetmab (bedinvetmab group, $n = 135$) or saline (placebo group, $n = 137$) by group and study day. Protocol deviations or administration of prohibited treatments result in exclusion of cases from the efficacy analysis so that the number of animals active in the study is affected and may fluctuate between time points, depending on the nature of the protocol deviation. Dogs withdrawn due to lack of efficacy or use of rescue treatment are counted as 'treatment failures' from the day of rescue or withdrawal, respectively, through all subsequent time points. Data are presented as proportion of dogs achieving treatment success (95% confidence interval; CI).

Study day	Group	Animals (*n*)	Treatment success Proportion of dogs* (95% CI)	Standard error	Odds ratio (95% CI)	*p*
7	Placebo	129	0.249 (0.163–0.362)	0.048	1.292 (0.720–2.317)	0.372
	Bedinvetmab	125	0.300 (0.204–0.419)	0.052		
14	Placebo	130	0.305 (0.214–0.415)	0.049	1.611 (0.861–3.013)	0.128
	Bedinvetmab	129	0.414 (0.309–0.528)	0.054		
28	Placebo	131	0.366 (0.270–0.473)	0.049	1.561 (1.020–2.387)	0.0410
	Bedinvetmab	128	0.474 (0.368–0.581)	0.052		
42	Placebo	127	0.398 (0.305–0.498)	0.047	1.922 (1.155–3.198)	0.0143
	Bedinvetmab	124	0.559 (0.458–0.656)	0.048		
56	Placebo	128	0.417 (0.320–0.520)	0.049	1.932 (1.125–3.317)	0.0193
	Bedinvetmab	125	0.580 (0.476–0.678)	0.049		
84	Placebo	122	0.342 (0.246–0.453)	0.051	2.592 (1.450–4.635)	0.0026
	Bedinvetmab	121	0.574 (0.460–0.680)	0.054		

*Back-transformed least squares mean proportion.

a. Plot of the CBPI Pain Severity Scores (PSS) by treatment group and study day



b. Plot of the CBPI Pain Interference Scores (PIS) by treatment group and study day

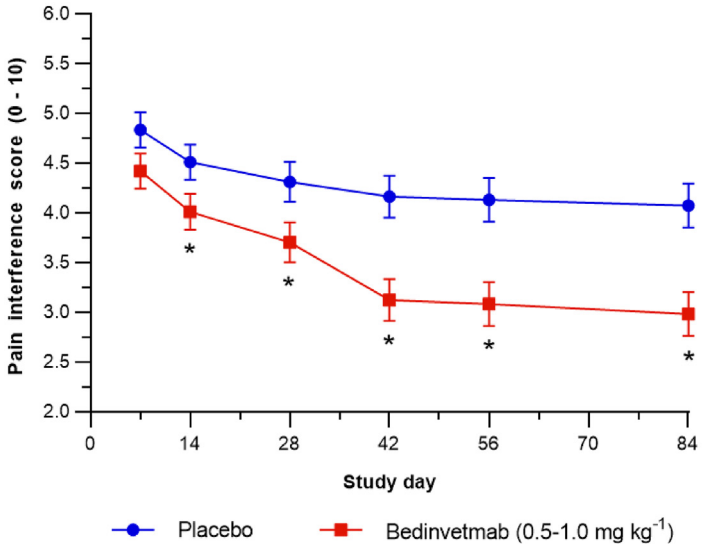


Figure 2 Canine Brief Pain Inventory (CBPI) (a) pain severity scores and (b) pain interference scores of dogs with osteoarthritis assigned to treatment with monthly subcutaneous injections of bedinvetmab (bedinvetmab group, squares; $n = 135$) or saline (placebo group, circles; $n = 137$) for 3 months. Data are presented as least squares mean ± standard error of the mean. The scale of the y-axis was chosen to increase the visibility of error bars. *n*, number of dogs. *Significant difference compared with placebo ($p < 0.05$).

Possible mild, transient (resolved within 1 day) injection site reaction in one dog in each group after the first dose only was reported by owners at day 1 (placebo, swelling; bedinvetmab, minimal warmth) but not confirmed by veterinary examination. Of 762 doses, 0.8% (6/762) were associated with an adverse response (e.g. vocalization) immediately upon administration [bedinvetmab, 1.1% (4/378); placebo, 0.5% (2/384)]. Two dogs per group were euthanized (Table 2). The two placebo-treated dogs were euthanized on days 58 and 61, respectively, for acute pancreatic necrosis syndrome (confirmed on necropsy) and suspected malignancy (not confirmed). The two bedinvetmab-treated dogs were euthanized on days 24 and 83 (post-study). In one dog with severe OA, the owner felt the OA condition, although not worse, was not improving. This dog was withdrawn for LOE (day 24). The other dog was withdrawn (day 28), as per protocol due to

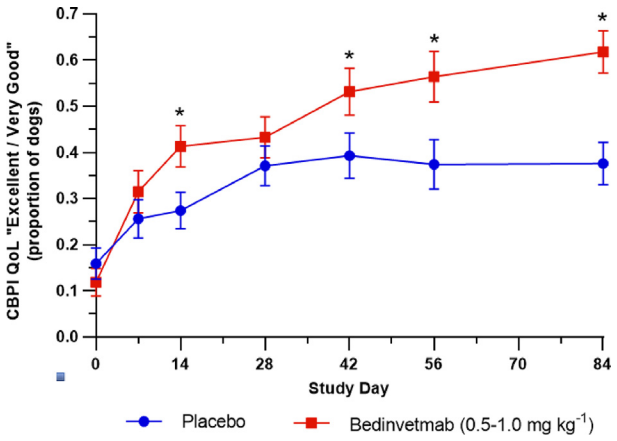


Figure 3 Proportion of dogs with osteoarthritis assigned to treatment with monthly subcutaneous injections of bedinvetmab (bedinvetmab group, squares; $n = 135$) or saline (placebo group, circles; $n = 137$) for 3 months and classified by the owners as having an 'excellent' or 'very good' overall impression of quality of life (QoL) on the CBPI assessment. Data are presented as least squares mean ± standard error of the mean. CBPI, Canine Brief Pain Inventory; *n*, number of dogs. *Significant difference compared with placebo ($p < 0.05$).

receiving rescue analgesia; degenerative myelopathy was suspected before withdrawal and progressed post-study. It was concluded that all AEs reported during the study were incidental and not unusual for a population of older dogs diagnosed with OA and having expected comorbidities.

Concomitant medications were administered to 124 and 114 dogs in placebo and bedinvetmab groups, respectively (Table 6). Summaries show no clear differences between groups. Overall, concomitant medications were well tolerated in the bedinvetmab group. All dogs met the minimum required 7 day withdrawal for NSAIDs before enrollment. Data review showed that 32.7% (89/272) and 2.9% (8/272) of dogs were administered an NSAID within 3 months and 1 month, respectively, before enrollment.

Clinical pathology

Mean and median values for all hematology and serum chemistry analytes in both groups fell within reference ranges for the measured analytes at all visits. Shift changes in clinical pathology results (increased or decreased *versus* pre-treatment) occurred throughout the study at low frequency in both groups and were not clinically significant. Mean results of quantitative urine measures within reference range pre-treatment remained within reference range.

Pharmacokinetic data and immunogenicity

Following the first dose of bedinvetmab, mean dose normalized $AUC_{0-\infty}$ was 172 μg d mL^{-1} per mg kg^{-1} and peak serum concentration, 5.01 μg mL^{-1} per mg kg^{-1}, was observed at a mean (±SD) of 9.3 (3.0) days. Arithmetic mean (±SD) terminal elimination half-life was 19.1 (8.3) days, while harmonic mean half-life was 15.8 days. Mean bedinvetmab trough concentrations on days 28, 56 and 84 were 1.56 (1.03), 2.03 (1.46) and 2.13 (1.58) μg mL^{-1}, respectively. Before the first dose, total NGF could not be quantitated in most serum samples.

Treatment-emergent ADAs occurred in one dog per group; those in the placebo-treated dog are considered false-positive results. For the bedinvetmab-treated dog, treatment-emergent ADAs appeared to be neutralizing or clearing based on corresponding decreased serum concentrations of bedinvetmab and total NGF. However, CBPI TS was achieved at all time points in this dog and, thus, there was no apparent impact on efficacy. ADA findings were not associated with AEs.

Table 4 Adverse events (AEs) in dogs with osteoarthritis with monthly subcutaneous injections of bedinvetmab (bedinvetmab group) or saline (placebo group) occurring at least once in > 2% of the bedinvetmab group. AEs are listed by frequency of clinical signs using the Veterinary Dictionary for Drug Regulatory Activities (VeDDRA) system organ class classification on a per-animal basis*. Data are presented as n (%); *n*, number of dogs (all animals enrolled).

System organ class clinical sign (VeDDRA)	Group	
	Placebo ($n = 137$)	Bedinvetmab ($n = 135$)
Any AE	86 (62.8)	79 (58.5)
Skin and appendages disorders (e.g. bacterial skin infection, dermatitis)	32 (23.4)	36 (26.7)
Renal and urinary disorders (e.g. urinary tract infection, dysuria)	22 (16.1)	19 (14.1)
Digestive tract disorders (e.g. diarrhea, emesis)	18 (13.1)	16 (11.9)
Ear and labyrinth disorders (i.e. otitis externa)	20 (14.6)	13 (9.6)
Systemic disorders (e.g. anorexia, lethargy)	20 (14.6)	12 (8.9)
Investigations† (e.g. elevated protein:creatinine ratio, neutrophilia)	15 (10.9)	11 (8.1)
Musculoskeletal disorders (e.g. lameness, joint pain)	13 (9.5)	10 (7.4)
Behavioral disorders (e.g. inappropriate urination, anxiety)	8 (5.8)	8 (5.9)
Respiratory tract disorders (e.g. cough, tachypnoea)	12 (8.8)	6 (4.4)
Eye disorders (e.g. conjunctivitis, ocular discharge)	5 (3.6)	6 (4.4)
Neurological disorders (e.g. muscle tremor, proprioception abnormality)	4 (2.9)	3 (2.2)

*Occurrence is calculated on a per-animal basis; no matter how many observations of the same AE was recorded for a dog, it only contributed a single observation to the occurrence calculation. †Investigation pertains to abnormal laboratory results.

Table 5 Adverse events (AEs) in dogs with osteoarthritis with monthly subcutaneous injections of bedinvetmab (bedinvetmab group) or saline (placebo group) occurring at least once in > 2% of the bedinvetmab group. AEs are listed by frequency of clinical signs using the Veterinary Dictionary for Drug Regulatory Activities (VeDDRA) preferred term classification on a per-animal basis*. Data are presented as n (%); *n*, number of dogs (all animals enrolled).

Preferred term clinical sign (VeDDRA)	Group	
	Placebo ($n = 137$)	Bedinvetmab ($n = 135$)
Any AE	86 (62.8)	79 (58.5)
Urinary tract infection	11 (8.0)	15 (11.1)
Otitis externa	20 (14.6)	13 (9.6)
Bacterial skin infection	9 (6.6)	11 (8.1)
Dermatitis	8 (5.8)	10 (7.4)
Dermal mass	5 (3.6)	8 (5.9)
Diarrhea	11 (8.0)	7 (5.2)
Lameness	8 (5.8)	6 (4.4)
Erythema	5 (3.6)	6 (4.4)
Anorexia	7 (5.1)	4 (3.0)
Emesis	6 (4.4)	4 (3.0)
Pruritus	5 (3.6)	4 (3.0)
Alopecia local	4 (2.9)	4 (3.0)
External parasite (i.e. fleas or ticks)	3 (2.2)	4 (3.0)
Dermal cyst(s)	2 (1.5)	4 (3.0)
Inappropriate urination†	1 (0.7)	4 (3.0)
Lethargy	11 (8.0)	3 (2.2)
Cough	5 (3.6)	3 (2.2)
Skin lesion (e.g. abrasion, laceration)	3 (2.2)	3 (2.2)
Conjunctivitis	2 (1.5)	3 (2.2)
Tooth disorder (e.g. tartar, loose/broken tooth)	2 (1.5)	3 (2.2)
Dysuria (i.e. pollakiuria)	1 (0.7)	3 (2.2)
Histiocytoma	0 (0.0)	3 (2.2)

*Occurrence is calculated on a per-animal basis; no matter how many observations of the same AE was recorded for a dog, it only contributed a single observation to the occurrence calculation.
†Of these, two dogs treated with bedinvetmab were among those reported with a urinary tract infection.

Discussion

Efficacy and safety of bedinvetmab were demonstrated under field conditions based on CBPI assessments, lack of reported bedinvetmab-related AEs, low frequency of treatment-emergent immunogenicity and clinical pathology. These data corroborate bedinvetmab field safety and efficacy reported for the similarly designed placebo-controlled phase of a study conducted in Europe (Corral et al. 2021) and safety in laboratory dogs (Krautmann et al. 2021). The present study reported a bedinvetmab day 28 CBPI TS rate (47.4%) similar to that reported by Corral et al. (43.5%), but with a nearly 20% difference (36.6% and 16.9%, respectively) in the corresponding placebo group TS rates.

Consideration of veterinary care, husbandry, OA disease process and other aspects of veterinary practice indicate no reason to attribute between study differences in placebo response to regional differences. Most dogs enrolled in both bedinvetmab studies had moderate or worse OA based on the veterinary categorical assessments of general musculoskeletal condition. Linguistic validation of CBPI translations from English was completed (Wells et al. 2021) for the Corral et al. (2021) study and as required by CBPI User Guide copyright and terms of use Brown (2017). Demographics (breed, age, weight, sex) were similar between studies except there were more intact dogs in the Corral et al. (2021) population; however, no reports indicate that neuter status impacts canine OA pain response to treatment. Human neuropathic pain studies have shown a lower placebo effect in Europe than in the USA (Tuttle et al. 2015) although meta-analyses of human OA studies did not report on geographical differences in placebo effect (Zhang et al. 2008b; Wen et al. 2022). Published randomized, multicenter, placebo-controlled field studies that evaluated efficacy of a canine OA pain treatment, other than bedinvetmab, reported a wide range in placebo CBPI TS rates, ranging from 4.76% at day 7 (Salichs et al. 2022) to 53% at day 42 (Salichs et al. 2021) for European studies and from 16.0% at day 7 (Rausch-Derra et al. 2016) to 35% at day 14 (Robertson-Plouch et al. 2019) for USA studies (Table 7). No such studies conducted in the USA evaluated efficacy beyond day 28. Thus, placebo CBPI TS frequencies in both bedinvetmab studies are within the range reported in published randomized, blinded, placebo-controlled multicenter field studies conducted in the USA or Europe (Table 7). The placebo response frequency reached approximately 90% of maximum at 6 weeks in both bedinvetmab studies, consistent with time course of placebo response in human OA treatment (5–7 weeks) (Wen et al. 2022).

Despite nearly identical study designs and eligibility criteria for the two bedinvetmab studies, there may have been differences in study populations. Exclusion of dogs treated with an anti-NGF mAb in a previous study likely had a substantially different regional impact on the pool of potential study candidates, because two thirds of USA *versus* no European sites (personal communication) participated in an anti-NGF mAb study previously. Only dogs enrolled at sites with at least two evaluable cases per treatment group were included in the analysis population to meet USA regulatory requirements; implementation of this criterion to the Corral et al. (2021) study showed no impact on findings of statistically significant ($p < 0.05$) differences at each time point (personal communication). The low frequency of NSAID use within 1 month (2.9%) or 3 months (32.7%) before enrolment reported in this study is surprising given NSAIDs are the predominant prescribed treatment for canine OA pain (Johnston et al. 2008; Monteiro-Steagall et al. 2013). Placebo response in human OA

Table 6 Frequency of occurrence of administration of concurrent medications to > 2% of dogs with osteoarthritis assigned to bedinvetmab group (monthly subcutaneous injections) during the study. Data are presented as *n* (%) by 'drug name' as categorized by the ATCvet drug classification. ATCvet, Anatomical Therapeutic Chemical Classification System for veterinary medicinal products. *n*, number of dogs.

ATCvet drug classification	Group	
	Placebo ($n = 137$)	Bedinvetmab ($n = 135$)
Any drug	124 (90.5)	114 (84.4)
Other anthelmintic agents, optional classification (i.e. oral heartworm preventive)	57 (41.6)	62 (45.9)
Ectoparasiticides for systemic use (i.e. oral flea and/or tick treatments)	49 (35.8)	44 (32.6)
Other anti-inflammatory and antirheumatic agents, non-steroids (i.e. joint supplement such as glucosamine or chondroitin)[1]	28 (20.4)	24 (17.8)
Antibacterials for systemic use	24 (17.5)	22 (16.3)
Endectocides (e.g. topical selamectin)	23 (16.8)	20 (14.8)
Ectoparasiticides for topical use, including insecticides (e.g. fipronil)	14 (10.2)	12 (8.9)
Oclacitinib	13 (9.5)	12 (8.9)
Antiseptics and disinfectants (e.g. chlorhexidine)	12 (8.8)	10 (7.4)
Anti-inflammatory and antirheumatic products, non-steroids (i.e. non-steroidal anti-inflammatory drugs)	10 (7.3)	9 (6.7)
Anti-infectives and antiseptics, excluding combinations with corticosteroids (i.e. topical for ears)	14 (10.2)	8 (5.9)
Anti-infectives/antiseptics in combination with corticosteroids (i.e. topical for eyes or ears)	5 (3.6)	8 (5.9)
Moxidectin (i.e. extended-release injectable suspension)	8 (5.8)	6 (4.4)
Immunologicals for Canidae (i.e. vaccines)	7 (5.1)	6 (4.4)
Antihistamines for systemic use (e.g. diphenhydramine)	5 (3.6)	6 (4.4)
Tramadol	5 (3.6)	6 (4.4)
Diet formulations for skin health	8 (5.8)	5 (3.7)
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents (i.e. metronidazole)	7 (5.1)	5 (3.7)
Gabapentin*	7 (5.1)	5 (3.7)
Endocrine therapy (e.g. thyroxine)	5 (3.6)	5 (3.7)
Anti-infectives (i.e. topical for eyes)	3 (2.2)	5 (3.7)
Lokivetmab	4 (2.9)	4 (3.0)
Diet formulations for treatment of joint disease (i.e. veterinary prescription diet for joint health)*	1 (0.7)	4 (3.0)
Drugs for peptic ulcer and gastroesophageal reflux disease (e.g. omeprazole)	3 (2.2)	3 (2.2)
Opioids (e.g. sedation for radiographs)	2 (1.5)	3 (2.2)
Other hypnotics and sedatives (e.g. dexmedetomidine)	2 (1.5)	3 (2.2)
Probiotics	2 (1.5)	3 (2.2)
Anesthetics, general (e.g. isoflurane)	1 (0.7)	3 (2.2)
Ciclosporin (i.e. topical for eyes)	0 (0.0)	3 (2.2)
Local anesthetics (i.e. topical proparacaine)	0 (0.0)	3 (2.2)

*All dogs shown met conditional use requirements (Table S1) for 'Other anti-inflammatory and antirheumatic agents, non-steroids', (veterinary prescription) 'diet formulation for joint health', and gabapentin except for 'gabapentin' — three dogs in the placebo group and one dog in the bedinvetmab group met the conditional use requirements (the remainder were administered gabapentin as rescue treatment).

studies was higher when < 50% *versus* > 50% of patients reported previous NSAID use (Wen et al. 2022). Regardless of these considerations, application of an almost identical study design in two different groups of dogs with OA yielded corroborative efficacy and safety data.

A high placebo effect is often encountered in studies conducted to evaluate efficacy of products for control of pain associated with OA (Gruen et al. 2017; Wen et al. 2022). Caregiver placebo effect associated with subjective assessments, such as owner-assessed CBPI, further contributes to placebo response in veterinary OA studies (Conzemius & Evans 2012; Gruen et al. 2017). The NNT for the current study [4.3 at day 84 (12 weeks)] compares extremely favorably with that for NSAIDs for human OA pain (4.7−8.4 after 12 weeks of treatment; Cadet et al. 2021). ES for PSS and PIS for this study (range, 0.2−0.5) compares favorably with ES of approximately 0.3 reported in high-quality trials for NSAIDs in humans (Zhang et al. 2008a, 2010). No similar published studies in dogs involving a licensed product for canine OA pain provide NNT or ES calculations for comparison (i.e. Table 7).

These results support encouraging bedinvetmab safety data reported previously (Corral et al. 2021; Krautmann et al. 2021). Frequency of AEs in eight of the 11 System Organ Class categories, although lower in bedinvetmab group than in placebo group, were similar between groups. A more detailed review of AEs supports no apparent bedinvetmab safety concerns compared with placebo. Most dogs were administered at least one concurrent medication, largely attributable to antiparasitic products (e.g. heartworm, flea/tick) or comorbidities. There were no clinically relevant changes in clinical pathology summary statistics. Pharmacovigilance monitoring conducted post marketing will further inform safety and efficacy of bedinvetmab in a broader population.

Table 7 Placebo success rates using the Canine Brief Pain Inventory (CBPI) in prospective, randomized, blinded, placebo-controlled multicenter field studies involving dogs with osteoarthritis. Data are presented as *n* (%)*.

Study†	Region (USA, EU)	Day 7	Day 14	Day 28	Day 42
Brown et al. (2013)	USA	Not done	59 (23.7)	Not applicable	Not applicable
Rausch-Derra et al. (2016)	USA	131 (16.0)	131 (28.2)	131 (31.3)	Not applicable
Robertson-Plouch et al. (2019)	USA	Not done	43 (35.0)	Not applicable	Not applicable
Corral et al. (2021)	EU	135 (3.8)	140 (9.7)	137 (16.9)	140 (21.1)
Salichs et al. (2021) ‡	EU	53 (26)	53 (36)	53 (40)	53 (53)
Salichs et al. (2022) ‡	EU	21 (4.76)	21 (28.57)	21 (42.86)	21 (42.86)

*'Not applicable' because study duration was 14 days [Brown et al. (2013); Robertson-Plouch et al. (2019)] or 28 days [Rausch-Derra et al. (2016)]. 'Not done' because 'success' data were not reported at this time point.
†Data shown are as reported in each respective study. All studies used CBPI treatment success definition of improvement (PSS $\geq$ 1 and PIS $\geq$ 2) and required minimum PIS and PSS scores of $\geq$ 2 at enrollment for inclusion in CBPI treatment success efficacy data set.
‡Studies were positively and negatively controlled (Salichs et al. 2021, 2022).

Bedinvetmab pharmacokinetic data for this study support monthly dosing. Bedinvetmab harmonic mean half-life (15.8 days) was somewhat longer than in healthy laboratory dogs (Krautmann et al. 2021); this difference is likely due, at least in part, to higher variability observed in a clinical field study compared with laboratory Beagles. Based on mean trough serum bedinvetmab concentrations (days 28, 56 and 84), steady state was achieved after two doses.

Treatment-emergent immunogenicity was low, consistent with reports by Corral et al. (2021) and Krautmann et al. (2021). Bedinvetmab's particularly low immunogenicity may be due to its construction as a 'fully' canine mAb [analogous to fully human mAbs (Beck et al. 2010; Nelson et al. 2010) and containing 100% canine sequence] (Corral et al. 2021; Krautmann et al. 2021). However, currently marketed veterinary mAbs, lokivetmab, a caninized [analogous to humanized mAbs (Beck et al. 2010)] anti-IL-31 mAb, and frunevetmab, a felinized anti-NGF mAb (Gearing et al. 2016), are also reported with low immunogenicity (Michels et al. 2016a,b; Moyaert et al. 2017; Walters et al. 2021).

Conclusion

The results of owner and veterinary assessments, as well as clinical pathology assessments, reported in this study conducted in the USA further corroborate the safety and efficacy of bedinvetmab administered monthly to dogs for the control of pain associated with OA.

Acknowledgements

The authors thank the veterinary clinicians who enrolled dogs in this study and performed the clinical investigations. Additional thanks to Argenta for project support and their dedication to this project. We thank Zoetis Inc. colleagues for their contributions: Maria Corral, Flavia De Toni, Kelly Doty, Matthew Krautmann, Olivier Martinon, Hilde Moyaert, Michael Stegemann, Gordon Sture, Stacey VandenBerg and Kelly Walsh. This study was fully funded by Zoetis Inc.

Authors' contributions

GMM: study design, study monitor, data validation and interpretation, preparation of manuscript. NAH: study monitor, data verification, data validation and manuscript review. DMC: study design, regulatory correspondence and manuscript review. JKST: study design, randomization, statistical analyses and manuscript review. RRW: study design, analytical testing, data interpretation and manuscript review. All authors read and approved the final version of the manuscript.

Conflict of interest statement

All authors were Zoetis Inc. employees while engaged in this research.

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Received 6 February 2023; accepted 13 June 2023.

Available online 19 June 2023

Supporting Information.

Additional Supporting Information may be found in the online version of this article: https://doi.org/10.1016/j.vaa.2023.06.003.

Table S1. Prohibited and conditionally allowed medications during the study including corresponding withdrawal times and minimum frequency of use.

Table S2. Secondary efficacy variable: Canine Brief Pain Inventory (CBPI) pain severity scores (PSS) of dogs with osteoarthritis assigned to treatment with monthly subcutaneous injections of bedinvetmab (bedinvetmab group, $n = 135$) or saline (placebo group, $n = 137$) by group and study day. Protocol deviations and administration of prohibited treatments result in exclusion of cases from the efficacy analysis so that the number of animals active in the study is affected and may fluctuate between time points, depending on the nature of the protocol deviation. Dogs withdrawn from the study, regardless of reason, do not contribute PSS data following withdrawal. Data are presented as mean PSS (95% confidence interval; CI).

Table S3. Secondary efficacy variable: Canine Brief Pain Inventory (CBPI) pain interference scores (PIS) of dogs with osteoarthritis assigned to treatment with monthly subcutaneous injections of bedinvetmab (bedinvetmab group, $n = 135$) or saline (placebo group, $n = 137$) by group and study day. Protocol deviations and administration of prohibited treatments result in exclusion of cases from the efficacy analysis so that the number of animals active in the study is affected and may fluctuate between time points, depending on the nature of the protocol deviation. Dogs withdrawn from the study, regardless of reason, do not contribute PIS data following withdrawal. Data are presented as mean PIS (95% confidence interval; CI).

Table S4. Secondary efficacy variable: Canine Brief Pain Inventory (CBPI) overall impression of quality of life (QoL) improvement-proportion of dogs with osteoarthritis assigned to treatment with monthly subcutaneous injections of bedinvetmab (bedinvetmab group, $n = 135$) or saline (placebo group, $n = 137$) with 'improvement' in overall impression of QoL by group and study day. Protocol deviations and administration of prohibited treatments result in exclusion of cases from the efficacy analysis so that the number of animals active in the study is affected and may fluctuate between time points, depending on the nature of the protocol deviation. Dogs withdrawn from the study, regardless of reason, do not contribute QoL improvement data following withdrawal. Data are presented as proportion of dogs with improvement in QoL (95% confidence interval; CI).