RESEARCH PAPER

A prospective, randomized, blinded, placebo-controlled multisite clinical study of bedinvetmab, a canine monoclonal antibody targeting nerve growth factor, in dogs with osteoarthritis

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Abstract

Objective Bedinvetmab is a canine monoclonal antibody targeting nerve growth factor. This study evaluated the efficacy and safety of bedinvetmab for alleviation of pain associated with osteoarthritis in dogs.

Study design Double-blind, randomized, multicentre, placebo-controlled study.

Animals Client-owned dogs ($n = 287$) with osteoarthritis.

Methods Dogs were randomized (1:1) to subcutaneous injection with placebo (saline, $n = 146$) or bedinvetmab (0.5–1.0 mg kg^{-1}, $n = 141$) administered monthly. After 3 months, 89 bedinvetmab-treated dogs that responded positively based on owner and veterinarian assessments were administered up to six additional doses of bedinvetmab in a single-armed open-label continuation phase. The primary efficacy end point was treatment success based on the owner-assessed canine brief pain inventory (CBPI) on day 28. Treatment success was defined as ≥ 1 reduction in pain severity score (0–10) and ≥ 2 in pain interference score (0–10).

Results Percentage treatment success was significantly greater in the bedinvetmab group than in the placebo group from day 7 through all assessed time points ($p \leq 0.0025$). On day 28, 43.5% of dogs achieved treatment success with bedinvetmab compared with placebo (16.9%) ($p = 0.0017$). Treatment success continued through days 56 (50.8%) and 84 (48.2%) in the bedinvetmab group and was < 25% in the placebo group at all time points. Sustained efficacy was demonstrated in the continuation phase. Adverse health events occurred at similar frequencies in both groups. They were considered typical for a population of dogs with osteoarthritis and not related to study treatment. Treatment with bedinvetmab demonstrated a significant effect on all three components of CBPI—pain interference, pain severity, quality of life.

Conclusions and clinical relevance This study demonstrated the effectiveness and safety of bedinvetmab administered monthly for up to 9 months at 0.5–1.0 mg kg^{-1} for alleviation of pain associated with canine osteoarthritis.

Keywords analgesia, canine osteoarthritis, degenerative joint disease, monoclonal antibody, pain, pain management.

Introduction

Canine osteoarthritis (OA) is a degenerative disease that leads to chronic pain, loss of joint function and impaired mobility. It is estimated that 20–37% of dogs aged > 1 year are affected (Johnston 1997; Wright et al. 2019; Anderson et al. 2020). To date, no single drug is effective for treating the underlying cause(s) of OA and resolving clinical signs of pain. The goal of available therapies is to relieve joint pain, delay the progression of the disease and restore mobility, with the final objective to improve the overall quality of life (QoL) (Singh 2003).

Non-steroidal anti-inflammatory drugs (NSAIDs) are currently the standard therapy for management of pain in dogs. NSAIDs have been associated with class-related side effects in some dogs (Lascelles et al. 2005; Sanderson et al. 2009; Enomoto et al. 2019). In many cases, pain reduction is inadequate when NSAIDs are used as monotherapy (Lascelles et al. 2005; Belshaw et al. 2016). OA-related pain management remains challenging and is a frequent cause of euthanasia in dogs (Moore et al. 2001; Moreau et al. 2003). Thus, there is a need for new effective and safe therapeutic alternatives. Bedinvetmab is a fully canine monoclonal

antibody (mAb), administered subcutaneously (SC) at monthly intervals, targeting nerve growth factor (NGF) which plays an important role in pain signalling in mammals (Hefti et al. 2006; Abdiche et al. 2008; Chang et al. 2016; Enomoto et al. 2019) and is elevated in osteoarthritic joints of dogs (Isola et al. 2011). Bedinvetmab binds to NGF preventing interaction with its receptor, tropomyosin receptor kinase A (TrkA), and consequently interrupting the NGF/TrkA signalling and decreasing the hyperalgesic response associated with OA (Enomoto et al. 2019).

Once bedinvetmab had shown efficacy in various laboratory models (data not shown), this study was designed to evaluate the efficacy and safety of bedinvetmab for the alleviation of pain associated with OA in client-owned dogs using the canine brief pain inventory (CBPI).

Materials and methods

Study design

The study consisted of two phases: first a 3 month, randomized, double-blind, placebo-controlled phase, the comparative phase, followed by a 6 month, single-armed open-label continuation phase. All data were collected in compliance with the principles of the Veterinary International Conference on Harmonization (VICH) and Good Clinical Practice (GCP) Guideline [European Medicines Agency (EMEA) VICH Topic GL9 (GCP), 2000]. The protocol was reviewed and approved prior to study initiation by the Sponsor Ethical Review Board, and authorization from the country regulatory authorities (Ireland no. CT22006/002; Hungary no. 02.2/1586-2/2018; and Portugal no. 55/ECVPT/2018). Following national requirements at the time, all local competent authorities of the involved states in Germany were notified before the start of the study. Informed consent was obtained from all owners.

Sample size estimates ($\geq$120 evaluable cases per group) were derived from power calculations based on variance and effect sizes observed in unpublished data from a propriety placebo-controlled field study (proportions of CBPI treatment successes were assumed at 0.309 and 0.532 for placebo and bedinvetmab, respectively) with the aim to achieve at least 80% power at $\alpha = 0.05$ (two-sided).

Study population

Client-owned dogs of any breed, sex and body weight could enrol in the study. Specific eligibility criteria ensured inclusion of dogs with OA that had no other uncontrolled concurrent disease or concomitant treatments that could confound the evaluation of bedinvetmab efficacy and safety.

For the comparative phase, dogs ($n = 287$) were enrolled from 26 veterinary practices in Hungary ($n = 8$), Ireland ($n = 6$), Germany ($n = 3$) and Portugal ($n = 9$). A subset of bedinvetmab-treated dogs that responded positively during the comparative phase of the study were treated for up to an additional 6 months in the single-armed continuation phase. Enrolment in this continuation phase included 89 dogs at 14 study sites in Portugal ($n = 5$), Hungary ($n = 4$) and Ireland ($n = 5$). Enrolment in the continuation phase was closed once the predefined target number of cases was achieved.

Inclusion criteria

Dogs were aged $\geq$ 12 months at enrolment. Clinical evidence of OA was confirmed during orthopaedic examination in at least one joint of the pelvic or thoracic limbs and dogs had radiographic evidence of OA. At least one of the three components of the veterinarian categorical assessment (VCA), lameness/weight-bearing, pain on palpation/manipulation of joint(s) and general musculoskeletal condition, was moderately affected. Each VCA component was classified by the veterinarians with a severity grade: 'clinically normal', 'mild', 'moderate', 'severe' or 'nearly incapacitating'.

The OA-related pain was evaluated by the owner unaware of group assignment using the validated CBPI questionnaire (Brown et al. 2013, 2014). CBPI consists of three domains: the pain severity score (PSS, 0−10), the pain interference score (PIS, 0−10) and the overall impression of the QoL. To be eligible for the study, initial PSS $\geq$ 2 and PIS $\geq$ 2 were required. Users adhered to all instructions in the CBPI User Guide (http://www.vet.upenn.edu/docs/default-source/VCIC/canine-bpi-user%27s-guide-2017-07). Animals were confirmed to be in good general health based on a physical examination and any concurrent disease was well controlled. Dogs were confirmed suitable when blood and urine clinicopathological results were satisfactory.

Exclusion criteria

Main exclusion criteria were: dog had been enrolled in a clinical trial of any type $\leq$ 30 days prior to day 0 or had previously been treated with an anti-NGF mAb; dog was pregnant, lactating or intended for use as a breeding animal; dog had a condition for which surgical intervention was anticipated during the study; dog had started a physical therapy or a weight loss program < 8 weeks before day 0; dog had lameness known to be related to neoplasia, primary neurologic or immunologic disorder, infection, recent joint trauma or non-healed fracture; dog had history of intervertebral disc disease or evidence of injury resulting in neurologic deficits; and dogs being administered any of the prohibited medications (Table S1). Conditionally allowed medications were permitted if the withdrawal times, minimal use and frequency were respected. Dogs could be enrolled following completion of the respective withdrawal times, and/or respecting minimal use and frequency.

Randomization and blinding

Eligible dogs were randomly allocated to placebo (saline) or bedinvetmab (0.5−1.0 mg kg^{-1}; Librela; Zoetis Inc., MI, USA) group in an intended 1:1 ratio for the initial comparative phase. Animals were randomized according to a randomized complete block design with one-way treatment structure replicated in multiple clinics. Dogs were randomly assigned to groups based on order of entry into the study at the clinic and according to the randomization provided by the statistician. The dispenser used the electronic data capture system to randomize the animals. Within each site, blocks of two animals were formed based on order of enrolment. Within each block, dogs were allocated at random to groups. Day 0 was defined as the day a dog was dosed for the first time. Owners, veterinarians and all site personnel, with the exception of the treatment dispenser, were blinded. Dispensers were responsible for the preparation and administration of study treatment.

Treatment administration

Bedinvetmab was provided as a ready-to-use formulation in single-use 1 mL vial (without preservative). A dosing chart was provided to ensure a dosage between 0.5 and 1.0 mg kg^{-1} was administered depending on body weight. Dogs in the placebo group were administered the same volume of saline as required for bedinvetmab. Monthly treatments were administered SC for a maximum of 9 months.

Study schedule

Baseline data were collected at enrolment. Following treatment administration on day 0, each dog was expected to complete seven visits (days 0, 7, 14, 28, 42, 56 and 84) to the veterinary clinic in the initial comparative phase for clinical examination and sample collection. Dosing occurred on days 0, 28 and 56. Bedinvetmab-treated dogs enrolled in the single-armed continuation phase were expected to complete seven additional monthly visits over 6 months. Monthly bedinvetmab dosing occurred a maximum of six times during this phase.

At every visit, owners completed the CBPI and the veterinarian performed a physical examination, completed a VCA, and ensured all adverse health events (AHEs) and concomitant medications were documented. Blood samples were collected for evaluation of haematological variables, serum chemistry, bedinvetmab, total NGF serum concentration and anti-drug antibodies (ADAs) on a monthly basis. Urine was collected for urinalysis and evaluation of protein creatinine ratio every 3 months.

Escape clause, rescue and prohibited therapies

At any time, the owner or the veterinarian could withdraw the dog at their discretion. If for animal welfare reasons, prior to study completion, the veterinarian considered necessary the use of a prohibited or conditionally allowed treatment(s), this was permitted. After exiting the study, dogs could resume conventional OA treatment. A 'rescue treatment' was defined as the use of a prohibited treatment for which the indication was considered to be OA-related, that is, for worsening of clinical signs of OA or perceived lack of efficacy (LOE). A 'prohibited treatment' was a therapy that could interfere with the assessment of pain for which the indication was not considered OA-related, such as postsurgical analgesia.

Efficacy outcome measures

The efficacy data set excluded dogs that had a protocol deviation affecting the collection or integrity of the data (Fig. 1a & b). Dogs administered rescue treatment and/or withdrawn for worsening of clinical signs of OA or perceived LOE were considered as treatment failures starting on the day of rescue or withdrawal, respectively. Use of a prohibited treatment following day 0 resulted in exclusion of efficacy data at all subsequent time point(s).

Data of the comparative phase were statistically analysed for days 7 (−0/+2), 14 (±3), 28 (±3), 42 (±5), 56 (±5) and 84 (±5). For the continuation phase, a 5 day range on the 28 day interval between visits was allowed and data were summarized for each visit. The primary efficacy end point was treatment success at day 28 based on owner assessment of pain using CBPI. Treatment success was defined as a reduction ≥ 1 in PSS (0−10; 0 no pain, 10 extreme pain) and ≥ 2 in PIS (0−10; 0 no pain, 10 extreme pain) following the CBPI author recommendation (Brown et al. 2013, 2014) compared with pretreatment (baseline).

Secondary efficacy end points included CBPI-based treatment success for all other assessed time points, the owner-assessed PSS and PIS scores (CBPI), the overall impression of QoL (CBPI) and the percentage of dogs classified as having a 'very good' or 'excellent' QoL at each time point. The overall improvement of VCA across the three components was defined as: 1) improved in at least one component and scores in the other two were not worse, or 2) improved scores in at least two components and the other score was worse or unchanged. An animal was defined as not having improved if neither of the two conditions applied, or if the animal had been withdrawn because of perceived LOE (including animals administered rescue treatment).

Safety outcome measures and analysis

All animals were included in the safety assessment. Frequencies of dogs with at least one AHE were summarized by clinical sign. The AHEs were clustered in organ classes following the Veterinary Dictionary for Drug Related Affairs (VeDDRA) coding (https://www.ema.europa.eu/en/

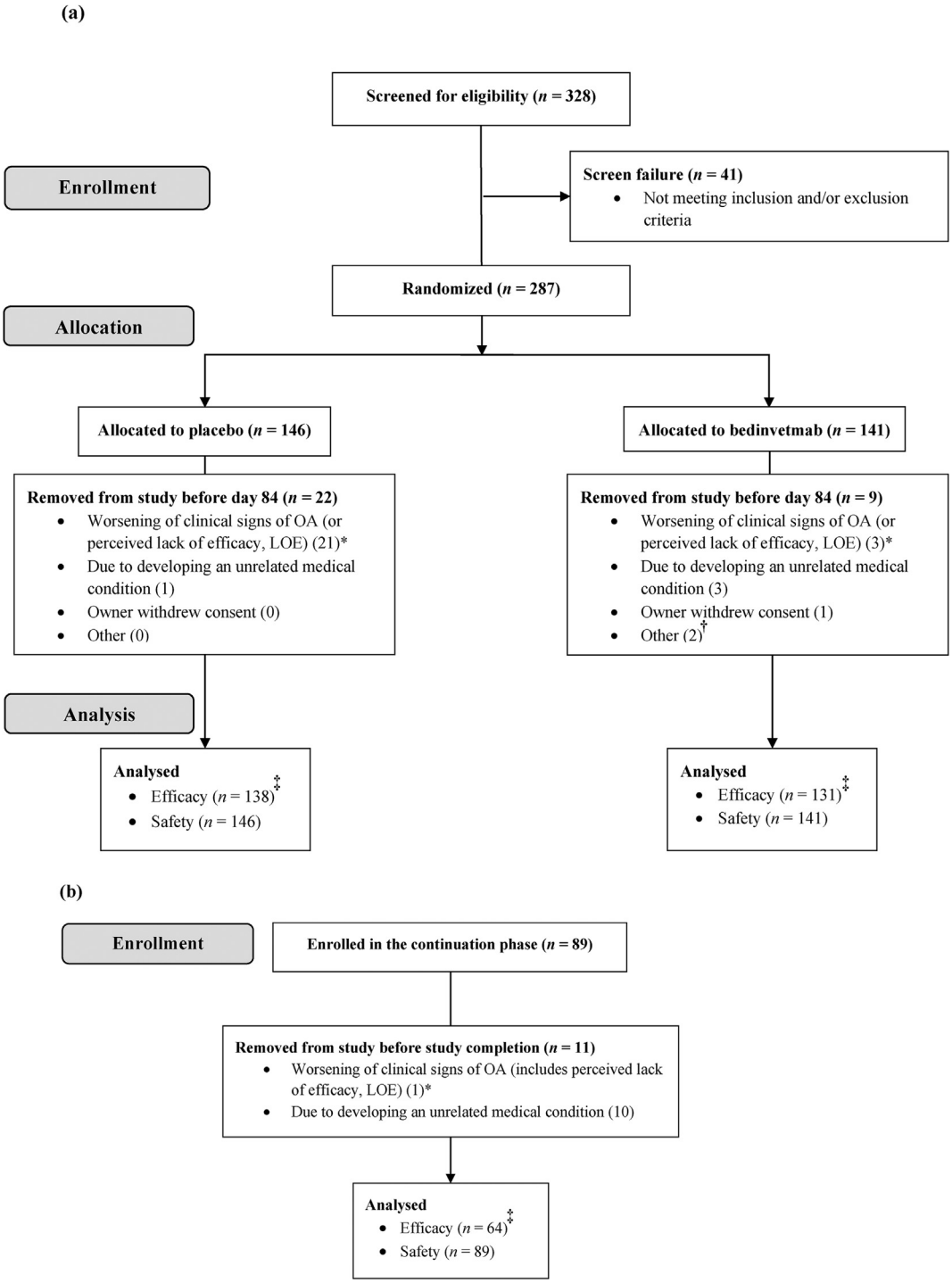

Figure 1 Flow diagrams for participants in (a) 3 month comparative phase and (b) 6 month single-armed continuation phase. *n*, number; OA, osteoarthritis. *Animals administered rescue treatment during the study or were withdrawn because of worsening of clinical signs of OA (or perceived lack of efficacy) were considered treatment failures as from the day of rescue or withdrawal, respectively, and were included in the analysis. †Two animals were withdrawn for reasons related to misdosing. ‡Data excluded due to protocol deviations (visits out of the allowed window, different owner making the assessments, animals that were misdosed), or administration of prohibited treatments explains the cases excluded from the efficacy analysis. All animals were included in the safety data analysis.

documents/regulatory-procedural-guideline/combined-veterinary-dictionary-drug-regulatory-activities-veddra-list-clinical-terms-reporting_en.pdf). Concomitant medications were coded using the Anatomical Therapeutic Chemical Classification System for veterinary medicinal products (ATCvet; https://www.whocc.no/atc_ddd_index/).

For each intended day of sampling, haematological, serum chemistry and urinalysis values were summarized reporting the number of dogs below, within or above the normal range (provided by the central laboratory). Shift tables provided the number of dogs that had an increased or decreased shift compared with baseline. Treatment-emergent immunogenicity was evaluated throughout the study. Serum bedinvetmab concentrations were summarized, and simple statistics were used to calculate means and standard deviations. The significance of the immunogenicity data was evaluated by integrating the ADA data with bedinvetmab and total NGF concentrations.

Statistical analysis

Data analysis was performed using SAS Version 9.4 (SAS Institute, NC, USA). The CBPI PSS and PIS were analysed separately using a general linear mixed model for repeated measures. The pretreatment (day 0) scores were used as covariates in the model. The model included the fixed effects of treatment, day of study and the interaction between treatment and day of study. The random effects of the model included site, block within site, the interaction between site and treatment, the interaction between site, treatment and day of study, and error. Treatment success and any binary data (i.e., Yes/No) were analysed, separately by day of study, using generalized linear mixed models with binomial distribution and logit link. The model included fixed effect of treatment and random effects of site, block within site, and interaction between site and treatment. The level of significance was set at $\alpha = 0.05$ (two-sided).

Results

Demographic data

A total of 328 dogs were screened for the study, of which 41 dogs did not meet eligibility criteria; therefore, 287 dogs were enrolled (Table 1).

Efficacy assessment

In the comparative phase, a total of 146 and 141 dogs were assigned to placebo and bedinvetmab groups, respectively. Animals withdrawn from the comparative phase included 22 from the placebo group and nine from the bedinvetmab group (Table 2). The main reason for withdrawal was worsening of clinical signs of OA. A total of 22/287 animals required rescue treatment, 19 in the placebo group and three in the bedinvetmab group. Protocol deviations resulting in exclusion of data included visits out of the allowed window for a given visit, different owner completing the assessment, animals administered an incomplete dose or being misdosed or administration of prohibited treatments.

A total of 89 dogs were enrolled in the continuation phase and 11 dogs were withdrawn before completing the study (Table 3). In 10 cases, the dogs developed unrelated medical conditions and one case was administered rescue treatment. Prohibited medication was administered to six and two dogs in

Table 1 Demographics of enrolled dogs with osteoarthritis at day 0 in the initial 3 month placebo-controlled comparative phase. Bedinvetmab group: subcutaneous administration of bedinvetmab monthly; placebo group: equivalent volume of saline. Data are presented as *n* (%) or mean ± standard error (range). *n*, number of animals (all animals enrolled, including animals with protocol deviations excluded from analysis); PIS, pain interference score; PSS, pain severity score

Demographic	Groups		Total ($n = 287$)
	Placebo ($n = 146$)	Bedinvetmab ($n = 141$)	
Breed distribution			
Pure-bred*	86 (58.9)	79 (56.0)	165 (57.5)
Mixed breed	60 (41.1)	62 (44.0)	122 (42.5)
Sex distribution			
Male	67 (45.9)	66 (46.8)	133 (46.3)
Female	79 (54.1)	75 (53.2)	154 (53.7)
Neutered/ovariohysterectomized	94 (64.4)	81 (57.4)	175 (61.0)
Age (years)	8.7 (1.5–16.0)	9.2 (1.0–17.5)	8.9 (1.0–17.5)
Weight at study start (kg)	27.2 (2.6–66.0)	26.1 (1.7–62.3)	26.7 (1.7–66.0)
Baseline PIS score at study start (0–10)	5.14 ± 0.15 (2.33–9.50)	5.65 ± 0.17 (2.00–9.67)	5.39 ± 0.11 (2.00–9.67)
Baseline PSS score at study start (0–10)	4.66 ± 0.13 (2.00–9.00)	4.83 ± 0.14 (2.00–8.75)	4.75 ± 0.10 (2.00–9.00)

*Labrador Retriever the predominant breed ($n = 54$; 18.8%) then Golden Retriever ($n = 18$; 6.3%) and German Shepherd ($n = 18$; 6.3%). No other individual purebred comprised ≥ 5% of the total.

Table 2 Overview of dogs with osteoarthritis (OA) administered either saline (placebo group) or bedinvetmab by monthly subcutaneous injection (bedinvetmab group) for 3 months (comparative phase of the study) that were withdrawn from the study during this time. Data were excluded from the efficacy analysis for cases with protocol deviations. All animals were included in the safety data analysis

Study day	Group	
Study day 0 visit	**Placebo (146 dogs)** **Cumulative total number of dogs withdrawn on or before day 28 visit = 12** 12 cases were withdrawn because of worsening of clinical signs of OA	**Bedinvetmab (141 dogs)** **Cumulative total number of dogs withdrawn on or before day 28 visit = 5** 3 cases were withdrawn because of worsening of clinical signs of OA 2 cases were withdrawn because of developing an unrelated medical condition (pyometra and cranial cruciate ligament rupture, respectively)
Study day 28 visit	**Placebo (134 dogs)** **Cumulative total number of dogs withdrawn on or before day 56 visit = 20** 7 cases were withdrawn because of worsening of clinical signs of OA 1 case was withdrawn because of developing an unrelated medical condition (lymphoma)	**Bedinvetmab (136 dogs)** **Cumulative total number of dogs withdrawn on or before day 56 visit = 8** 2 cases were withdrawn upon Sponsor's request for reasons related to misdosing (protocol deviation) 1 case was withdrawn because the owner withdrew the consent
Study day 56 visit	**Placebo (126 dogs)** **Cumulative total number of dogs withdrawn on or before day 84 visit = 22** 2 cases were withdrawn because of worsening of clinical signs of OA	**Bedinvetmab (133 dogs)** **Cumulative total number of dogs withdrawn on or before day 84 visit = 9** 1 case was withdrawn because of developing an unrelated medical condition (pancreatitis)
Study day 84 visit	**Placebo (124 dogs)**	**Bedinvetmab (132 dogs)**

placebo and bedinvetmab groups, respectively, during the comparative phase and 10 dogs during the continuation phase.

Owner assessment (CBPI)

During the comparative phase, a significantly greater proportion of dogs in bedinvetmab group (43.5%) achieved CBPI-based treatment success *versus* placebo group (16.9%) at day 28 ($p = 0.0017$). A significantly greater proportion of dogs in bedinvetmab group achieved treatment success *versus* placebo group at all other assessment days (Table 4). The maximum bedinvetmab treatment effect was observed on day 42 after the second dose was administered, with onset of efficacy as early as day 7. Treatment success in placebo group was < 25% throughout the study (Table 4). At enrolment in the continuation phase, treatment success was 62.8% ($n = 78$), subsequently ranging 73.3−82.2% ($n = 64$−75; Table 5).

The PSS and PIS variables were significantly different between bedinvetmab and placebo groups at every time point ($p \leq 0.0026$; Fig. 2a & b). Mean (range) PSS scores ≤ 2.4 (1.7−2.4) were maintained throughout the continuation phase. PIS scores ≤ 2.8 (1.9−2.8) were similar.

The percentage of dogs that demonstrated improvement in the CBPI overall impression of QoL was higher in bedinvetmab group than in placebo group at every visit during the comparative phase (data not shown), illustrated by animals categorized as having an 'excellent' or 'very good' QoL (Fig. 3). QoL is summarized for animals enrolled in the continuation phase over 9 months, showing that the owners' overall impression of QoL continued from day 28 onwards (Fig. 4).

Veterinarian Categorical Assessment

At enrolment, 86.12% of the animals were classified as having the general musculoskeletal condition moderately affected to nearly incapacitating (53.02% moderately affected, 29.54% severely affected, 3.56% nearly incapacitating). For each VCA assessment item, the improvement *versus* baseline in bedinvetmab group was significantly different than that in placebo group at all time points (data not shown; $p < 0.01$). From day 7, up to and including day 84, the overall improvement based on VCA was significantly different in bedinvetmab group *versus* placebo group ($p \leq 0.0002$). The percentage of overall improvement during the comparative phase was 69.2−91.4% in bedinvetmab group and ≤ 57.9% in placebo group (Fig. 5).

Table 3 Withdrawal information of dogs enrolled in bedinvetmab group, administered a single dose subcutaneously once a month for 3 months (comparative phase of the study) and then for 6 months (single-armed continuation phase). Data were excluded from the efficacy analysis for cases with protocol deviations. All animals were included in the safety data analysis

Visit	Bedinvetmab group withdrawal information
Study day 0 visit	**Bedinvetmab (89 dogs)**
	Total number of dogs withdrawn on or before day 28: 2 dogs
	1 case—Death—Necropsy revealed testicular tumour (Leydig cell tumour), lung metastasis and multiorgan failure
	1 case was withdrawn because of developing an unrelated medical condition: Neurological deficits of the pelvic quarters resulting from thoracic vertebrae 11−12 spinal collapse
Study day 28 visit	**Bedinvetmab (87 dogs)**
	Total number of dogs withdrawn between day 28 and before day 56: 3 dogs
	1 case was withdrawn due to worsening of clinical signs of OA: Pelvic limb paresis—Euthanasia—Owner declined necropsy—OA could not be ruled out as a contributing factor and the dog received 'rescue treatment' (rescued on day 48 and euthanized on day 49)
	2 cases were withdrawn because of developing an unrelated medical condition: 1) interdigital dermatitis and 2) coronoid process fracture
Study day 56 visit	**Bedinvetmab (84 dogs)**
	Total number of dogs withdrawn between day 56 and before day 84: 1 dog
	1 case was withdrawn due to developing an unrelated medical condition: 1) Testicular tumour—Leydig cell tumour
Study day 84 visit	**Bedinvetmab (83 dogs)**
	Total number of dogs withdrawn between day 84 and before day 112: 4 dogs
	4 cases were withdrawn due to developing an unrelated medical condition: 1) Leptospirosis—Euthanasia—Necropsy revealed acute anuric renal failure, pancreatitis and hepatic disease due to leptospirosis and a testicular tumour—Leydig cell tumour; 2) interdigital dermatitis and prohibited treatment administered; 3) upper respiratory tract infection; and 4) distal humeral condylar fracture
Study day 112 visit	**Bedinvetmab (79 dogs)**
	Total number of dogs withdrawn between day 112 and before day 140 (±5 days): 1 dog
	1 case was withdrawn, due to death—owner declined necropsy—age related according to investigator
Study day 140 visit	**Bedinvetmab (78 dogs)**
	Total number of dogs withdrawn between day 140 and before day 168 (±5 days): none
Study day 168 visit	**Bedinvetmab (78 dogs)**

During the continuation phase, the overall VCA improvement plateaued (range, 89.2−94.9%).

Safety assessment

Health events and concomitant medications

During the comparative phase, a total of 41 and 26 dogs in placebo and bedinvetmab groups, respectively, experienced an AHE (Table 6). The most frequently reported were 'musculoskeletal disorders', which included 'joint pain' and 'lameness'. Joint pain was reported in 22 (15.1%) dogs in placebo group and three (2.1%) dogs in bedinvetmab group. During the comparative study, two cases of cranial cruciate ligament rupture were reported (one case per group). The injuries were surgically repaired and were not considered to be treatment related. Whereas the incidence of AHEs was similar in both groups, in some VeDDRA system organ classes (digestive tract disorders, skin disorders, eye disorders), the AHE incidence was sometimes higher in placebo group (ear disorders, blood disorders) and sometimes higher in bedinvetmab group (systemic disorders, respiratory disorders, renal and urinary disorders). Review of all AHEs suggests that differences were incidental findings (often associated with comorbidities) and not related to bedinvetmab administration. During the continuation phase, 23 dogs experienced at least one AHE and the types of AHEs were similar in both phases, with no clear upward trend in any system organ class (Table 6).

A mild transient (resolved after 6−7 days) injection site reaction was observed in one dog in each group, and in both instances the diagnosis and resolution were complicated by underlying and pre-existing atopy. During the comparative phase, two dogs died; one dog in placebo group was euthanized on day 54 with severe clinical signs of malignant lymphoma and one dog in bedinvetmab group was euthanized on day 74 because of multiorgan failure from pancreatitis (Table 2). During the continuation phase, four deaths were reported (Table 3). None of the deaths were considered related to study treatment administration. Evaluation of all AHEs reported during the 9 months revealed that they were associated with incidental comorbidities and/or were typical for a population of often older dogs with OA.

Table 4 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, $n = 141$) or saline (placebo group, $n = 146$) during the comparative phase 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 perceived 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). *n*, number of dogs

Study day	Group	Number of animals	Treatment success Proportion of dogs* (95% CI)	Standard error	*p*
7	Placebo	135	0.038 (0.014–0.095)	0.017	0.0017
	Bedinvetmab	130	0.178 (0.102–0.293)	0.046	
14	Placebo	140	0.097 (0.053–0.171)	0.028	<0.0001
	Bedinvetmab	135	0.355 (0.252–0.473)	0.054	
28	Placebo	137	0.169 (0.101–0.270)	0.041	0.0017
	Bedinvetmab	133	0.435 (0.313–0.566)	0.063	
42	Placebo	140	0.211 (0.139–0.307)	0.041	0.0001
	Bedinvetmab	134	0.526 (0.414–0.636)	0.055	
56	Placebo	140	0.199 (0.120–0.313)	0.047	0.0002
	Bedinvetmab	135	0.508 (0.327–0.644)	0.068	
84	Placebo	138	0.235 (0.151–0.347)	0.047	0.0025
	Bedinvetmab	131	0.482 (0.358–0.608)	0.062	

*Back-transformed least squares means proportion.

Table 5 Summary of the canine brief pain inventory (CBPI)-based treatment success of dogs with osteoarthritis administered bedinvetmab (bedinvetmab group, $n = 89$) by subcutaneous monthly injection for 9 months, enrolled in the comparative and continuation phases of the study by study day. Treatment success defined as ≥ 1 reduction from baseline in CBPI pain severity score and ≥ 2 reduction from baseline in CBPI pain interference score. Baseline for this calculation corresponds to day 0 pretreatment data. A protocol deviation resulted in 11 of 89 dogs enrolled in the continuation phase being excluded from all efficacy assessments at all time points. Data excluded from the efficacy analysis due to protocol deviations (visits out of the allowed window, different owner completing the assessments), or administration of prohibited treatments explains the other cases excluded from the efficacy analysis. Dogs that were withdrawn due to perceived 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 number of dogs (%) or number of dogs

Study phase	Study day	Treatment success	
		Yes	Total
Comparative phase	7	17 (22.7)	75
	14	39 (50.0)	78
	28	49 (62.8)	78
	42	51 (65.4)	78
	56	53 (67.9)	78
Continuation phase	84	49 (62.8)	78
	112	55 (73.3)	75
	140	60 (82.2)	73
	168	58 (79.5)	73
	196	49 (75.4)	65
	224	49 (75.4)	65
	252	48 (75.0)	64

A total of 74 dogs (46 and 28 in placebo and bedinvetmab groups, respectively) were administered concomitant medications, predominantly for comorbidities (Table 7). Numerically, there were no clear differences between groups except for anti-inflammatories (17.1% placebo *versus* 7.8% bedinvetmab). Similar concomitant medications were administered during the continuation phase. Overall, concomitant treatments were well tolerated and not associated with any specific AHEs in bedinvetmab group.

Clinical pathology

Increasing and/or decreasing shifts in clinical pathology results compared with baseline were observed throughout the 9 months. The changes were not clinically significant and generally occurred in both groups during the comparative phase. Increased aspartate aminotransferase and blood urea nitrogen concentrations were higher in bedinvetmab group than in placebo group when compared with both baseline and reference ranges. More dogs in bedinvetmab group than in placebo group were identified with decreased haemoglobin and packed cell volume. Mean values of quantitative urine measurements that were within normal range on day 0 remained within range. There was no evidence that the AHEs were associated with bedinvetmab administration.

Immunogenicity

A total of four dogs developed treatment-emergent ADAs during the 9 month study; two in each study phase. Of these, two ADA-positive dogs presented a transient ADA response

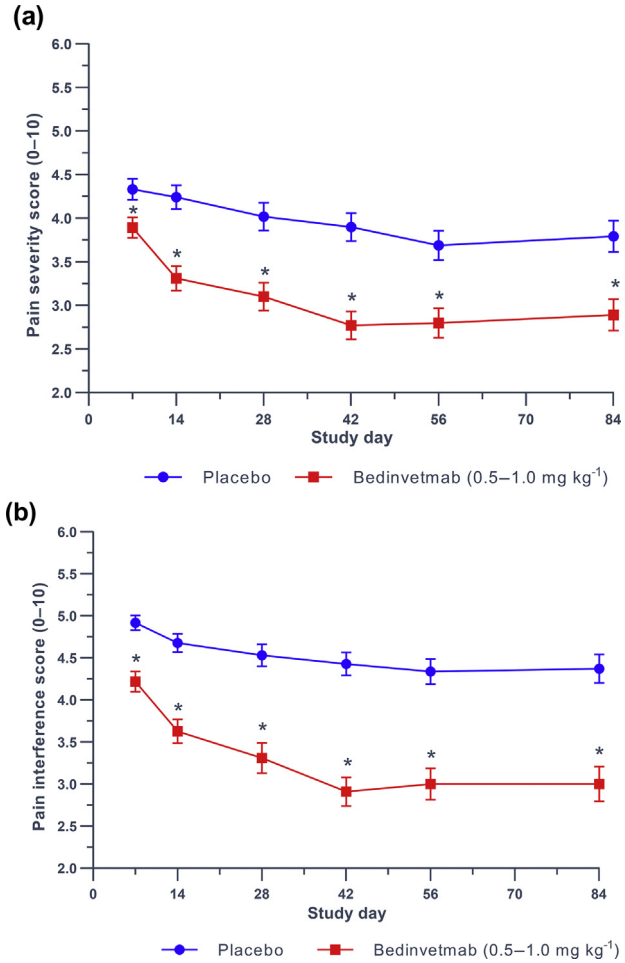

Figure 2 Canine brief pain inventory (CBPI) (a) pain severity score and (b) pain interference score of dogs with osteoarthritis assigned to treatment with monthly subcutaneous injections of bedinvetmab (bedinvetmab group, squares; $n = 141$) or saline (placebo group, circles; $n = 146$) for 3 months (comparative phase of the study). 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 animals. *Significant difference compared with placebo ($p < 0.05$).

that did not appear to be neutralizing or clearing based on bedinvetmab serum concentration, total NGF concentration and/or CBPI efficacy data. The two other ADA-positive dogs developed persistent ADAs; in one animal, the persistent ADAs seemed to have a neutralizing or clearing effect because CBPI treatment success was not achieved at most time points, and in the other dog, a neutralizing or clearing effect was only observed in the beginning of the study since CBPI-based treatment success was demonstrated at later time points. No AHEs were associated with ADA findings.

Discussion

Bedinvetmab was administered by monthly injections for up to 9 months to dogs with OA. Treatment efficacy and safety was confirmed by the owner-assessed CBPI, the physical and orthopaedic examinations (VCA) performed by trained clinicians and the absence of bedinvetmab-related AHEs during the study. The results indicated that bedinvetmab provides good long-term efficacy and safety profile under field conditions.

The owner-assessed CBPI questionnaire used in this study was developed for canine OA (Brown et al. 2013, 2014) and was successfully employed in the efficacy assessment of grapiprant and carprofen using almost identical treatment success definitions as primary end points (Brown et al. 2008; Rausch-Derra et al. 2016). The percentage of dogs achieving CBPI-based treatment success on day 28 after a single SC dose of bedinvetmab was 43.5% (*versus* 16.9% treated with placebo) which is comparable with those reported on day 28 after daily oral administration of grapiprant (2 mg kg^{-1}) 48.1% ($n = 63/131$) for the grapiprant-treated dogs and 31.3% ($n = 41/131$) for the placebo-treated dogs (Rausch-Derra et al. 2016). Using the same CBPI treatment success definition, Brown et al. (2013) reported success rates of 45.6% ($n = 26/57$) in the carprofen-treated dogs (4.4 mg kg^{-1}, orally, daily) and 14 of 59 (23.7%) placebo-treated dogs after 14 daily oral treatments. No further time points were assessed in these trials.

The majority of clinical trials assessing the long-term use of NSAIDs have a duration of 1−2 months in dogs (Innes et al. 2010), including a recent trial evaluating a new piprant-class NSAID, grapiprant (Rausch-Derra et al. 2016). Innes

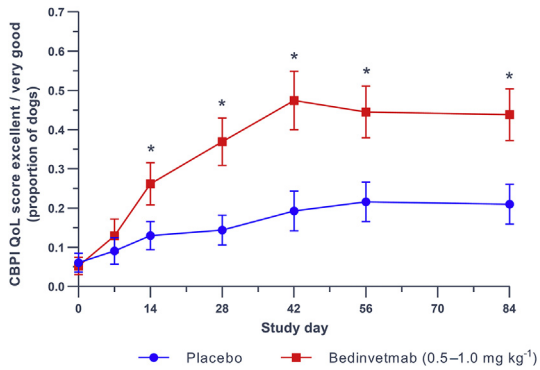

Figure 3 Proportion of dogs with osteoarthritis assigned to treatment with monthly subcutaneous injections of bedinvetmab (bedinvetmab group, squares; $n = 141$) or saline (placebo group, circles; $n = 146$) for 3 months (comparative phase of the study) and classified by the owners as having an 'excellent' 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 ($p < 0.05$).

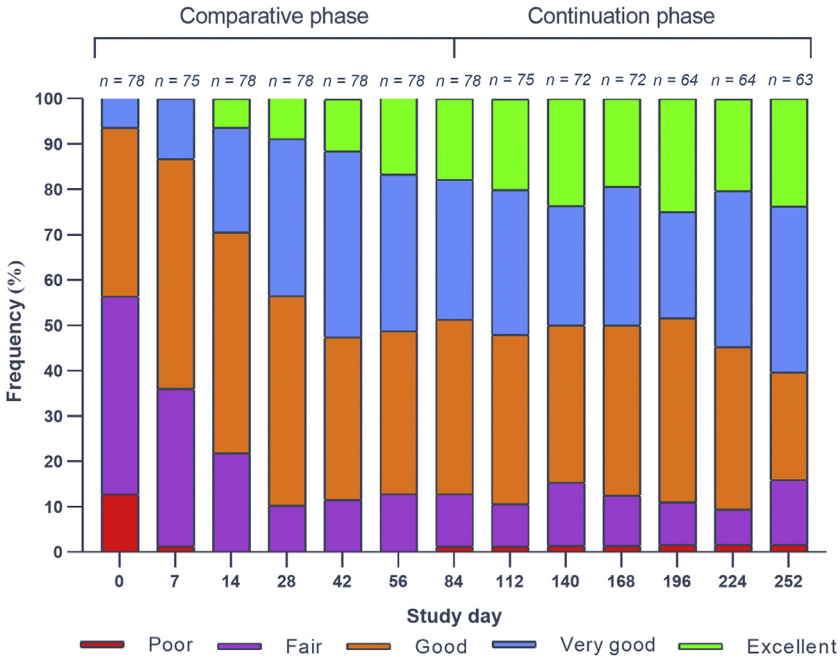

Figure 4 Percentage of dogs with osteoarthritis administered bedinvetmab (bedinvetmab group, $n = 89$) by subcutaneous monthly injection for 9 months, enrolled in the comparative and continuation phases of the study, and were classified by the owners as having a 'poor', 'fair', 'good', 'very good' or 'excellent' overall impression of quality of life (QoL) on the CBPI assessment. A protocol deviation resulted in exclusion of 11 dogs enrolled in the continuation phase from all efficacy assessments at all time points. Data excluded from the efficacy analysis due to protocol deviations (visits out of the allowed window, different owner completing the assessments) or administration of prohibited treatments explains the cases excluded from the efficacy analysis. Data are presented as percentage of dogs (%) for each QoL category. CBPI, canine brief pain inventory; *n*, number of dogs.

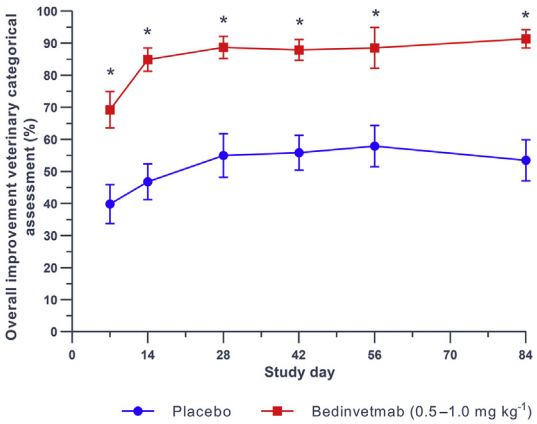

Figure 5 Percentage of dogs with osteoarthritis administered either saline (placebo group, circles; $n = 146$) or bedinvetmab by subcutaneous monthly injection (bedinvetmab group, squares; $n = 141$) for 3 months (comparative phase of the study) achieving veterinary categorical assessment (VCA)-overall improvement. Data are presented as least squares mean ± standard error of the mean. *n*, number of dogs. *Significant difference compared with placebo ($p < 0.05$).

et al. (2010) highlight that for a chronic disease such as canine OA, clinical cases under field conditions may require extended treatments > 28 days, thereby emphasizing the limitations of the current available literature. The present study design included a 6 month single-armed continuation phase ($n = 89$) providing long-term data following an initial 3 month placebo-controlled phase. The authors acknowledge that the inclusion of a negative control in the continuation phase would have been of scientific value. However, long-term placebo treatment for a painful condition such as OA would be unethical and contrary to good animal welfare. The sustained effectiveness of monthly SC bedinvetmab administration for the alleviation of pain in client-owned dogs with OA was observed in this trial for up to 9 months in the population studied.

The CBPI is a relatively new tool that was not available or validated at the time other studies were conducted (Aragon et al. 2007). The VCA, although not considered completely validated, was included as a secondary end point. The overall VCA improvement for bedinvetmab-treated dogs was 88.7% (day 28) and 87.9% (day 42) and was maintained thereafter in the continuation phase (range 89.2–94.9%). These percentages are comparable to day 44 overall VCA improvement

Table 6 Adverse health events (AHEs) in dogs with osteoarthritis with monthly subcutaneous injections of bedinvetmab (bedinvetmab group) or saline (placebo group) occurring at least once in > 2% of the group during the comparative (days 0–84) and continuation (days 84–252) phases. AHEs 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 as from day 0*. Data are presented as *n* (%). *n*, number of animals (all animals enrolled)

System organ class clinical sign (VeDDRA)	Group		
	Placebo Comparative phase ($n = 146$)	**Bedinvetmab** Comparative phase ($n = 141$)	**Bedinvetmab** Continuation phase ($n = 89$)
Any AHE	41 (28.1)	26 (18.4)	23 (25.8)
Investigations† (e.g., increased blood urea nitrogen, neutrophilia)	4 (2.7)	9 (6.4)	7 (7.9)
Digestive tract disorders (e.g., emesis, diarrhoea)	5 (3.4)	7 (5.0)	3 (3.4)
Systemic disorders (e.g., lethargy, anorexia)	2 (1.4)	7 (5.0)	10 (11.2)
Skin and appendages disorders (e.g., alopecia, pruritus)	5 (3.4)	6 (4.3)	4 (4.5)
Musculoskeletal disorders (e.g., joint pain, lameness)	23 (5.8)	5 (3.5)	5 (5.6)
Respiratory tract disorders (e.g., cough, tachypnoea)	1 (0.7)	4 (2.8)	0 (0.0)
Behavioural disorders (e.g., anxiety)	0 (0.0)	4 (2.8)	0 (0.0)
Eye disorders (e.g., cataract, conjunctivitis)	2 (1.4)	3 (2.1)	0 (0.0)
Renal and urinary disorders (e.g., polyuria, urinary incontinence)	0 (0.0)	3 (2.1)	1 (1.1)
Ear and labyrinth disorders (e.g., otitis externa)	4 (2.7)	0 (0.0)	4 (4.5)
Blood and lymphatic system disorders (e.g., lymphadenopathy)	2 (1.4)	0 (0.0)	2 (2.2)
Neurological disorders (e.g., proprioception abnormality, paresis)	0 (0.0)	0 (0.0)	4 (4.5)

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

results obtained for mavacoxib (93.4%) and carprofen (89.1%) (Payne-Johnson et al. 2015).

Whereas effectiveness has been demonstrated for NSAIDs in the treatment of pain associated with OA in dogs (Sanderson et al. 2009; Rausch-Derra et al. 2016), current treatment options may have limitations. Compliance may be impaired by owners who find oral daily administration challenging and, consequently, negatively impacting pain management and the overall QoL of the dog. In addition, senior dogs may have other chronic concurrent pathologies that require simultaneous administration of multiple medications. This may contribute to pet owner burden, particularly if orally administered.

It has been reported that not all dogs tolerate long-term NSAID therapy and veterinarians are required to closely monitor dogs under NSAID treatment through follow-up visits and laboratory tests. Overall, the incidence of AHEs in the present study was low and none were considered related to bedinvetmab administration. No obvious upward trends in any AHE category were observed during the continuation phase indicating that bedinvetmab was well-tolerated in the population studied; supported by the clinical pathology summary statistics that revealed no changes considered clinically relevant. Based on the present study results, and the available data from human studies with anti-NGF mAbs (Tive et al. 2019), the authors concluded that safety risks of treatment would not be higher in older dogs with comorbidities. Based on the number of digestive tract disorders in the current study and the very different mode of action, bedinvetmab probably has a considerably better gastrointestinal tolerability than NSAIDs (Lascelles et al. 2005; Belshaw et al. 2016). During the human clinical trials for tanezumab, chronic NSAID and mAb co-administration was linked to an increase in the incidence of rapidly progressive osteoarthritis (RPOA). RPOA has not been recognized in dogs (Enomoto et al. 2019), but owing to the likelihood that co-administration of an NSAID in a bedinvetmab animal will occur, such as for management of an unrelated medical or surgical condition, in case of an OA flare or when transitioning from one medication to another, the potential for a short-term adverse interaction effect on joints of dogs was evaluated in young, healthy dogs without OA in a laboratory study (Krautmann et al. 2021). In that study, bedinvetmab co-administered with carprofen (4.4 mg kg^{-1}) SC daily for 2 weeks

Table 7 Frequency of occurrence of administration of concomitant medications to > 2% of dogs with osteoarthritis assigned to bedinvetmab group (monthly subcutaneous injections) or placebo group (injected with saline) during the comparative phase (days 0–84). Data are presented as *n* (%) by 'drug functional use' 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 Comparative phase ($n = 146$)	**Bedinvetmab** Comparative phase ($n = 141$)
Any drug	46 (31.5)	28 (19.9)
Anti-inflammatory and antirheumatic products	25 (17.1)	11 (7.8)
Antibacterials for systemic use	0 (0.0)	8 (5.7)
Analgesics	3 (2.1)	6 (4.3)
General nutrients	4 (2.7)	4 (2.8)
Ectoparasiticides, insecticides and repellents	3 (2.1)	4 (2.8)
Antiemetics and antinauseants	0 (0.0)	4 (2.8)
Psycholeptics	2 (1.4)	3 (2.1)
Anaesthetics	1 (0.7)	3 (2.1)
Antiseptics and disinfectants	1 (0.7)	3 (2.1)
Other dermatological preparations	0 (0.0)	3 (2.1)

had no adverse effects on joint structures (bone, ligament, cartilage, synovium). There are no safety data on the concurrent long-term use of NSAIDs and bedinvetmab in dogs.

Bedinvetmab is the second mAb approved for use in veterinary medicine. Bedinvetmab and lokivetmab (Cytopoint; Zoetis Inc.) results seem to support that mAbs are a safe chronic treatment option for animals (Moyaert et al. 2017; Souza et al. 2018). The encouraging efficacy and safety data will have to be confirmed via the postmarketing pharmacovigilance system.

During the development of mAbs, special emphasis is paid to immunogenicity, as it may impact efficacy and/or safety (Doevendans & Schellekens 2019). Overall, in the present study the incidence of ADAs was low and in only one of two dogs with persistent ADAs a decrease/impact on efficacy was observed; an impact on safety was not observed in any ADA-positive animals. The low incidence of ADAs may be because bedinvetmab was constructed as a fully canine mAb rather than a caninized mAb that contains some percentages of noncanine sequences.

The development of a monthly injectable product may be preferred by some pet owners. Monthly injectable therapy could help maintain treatment compliance for certain OA dogs and their owners compared with daily oral administration of current pain treatments.

Conclusion

The results of this study conducted across four European countries in dogs administered monthly SC injections of bedinvetmab (0.5–1.0 mg kg^{-1}) for up to 9 months suggest that bedinvetmab is safe and efficacious for the alleviation of pain associated with OA in dogs as assessed by owners, veterinarians and laboratory clinical pathology.

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Authors' contributions

MJC and HM: study design, study monitor, data validation and interpretation, preparation of manuscript. TF: study monitor, data verification, data validation, manuscript review. ME: study design, regulatory permits, manuscript review. JKST: study design, statistical analyses, manuscript review. RRW: study design, analytical testing, data interpretation, manuscript review. MRS: sponsor representative, study design, data interpretation, preparation of manuscript. All authors read and approved the final version of the manuscript.

Conflict of interest statement

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

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaa.2021.08.001.

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