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Laboratory safety evaluation of bedinvetmab, a canine anti-nerve growth factor monoclonal antibody, in dogs

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ABSTRACT

Nerve growth factor (NGF), a critical mediator of nociception, is a novel analgesic therapeutic target. Bedinvetmab, a canine monoclonal antibody (mAb), binds NGF and inhibits its interaction with tropomyosin receptor kinase A (trkA) and p75 neurotrophin receptor ($p75^{NTR}$) receptors. The objective of three integrated laboratory studies was to demonstrate the safety of bedinvetmab in adult laboratory Beagle dogs. Daily health, veterinary, clinical pathology, systemic exposure, and anti-drug antibody evaluations were performed. Study 1 additionally included electrocardiography, neurologic, and ophthalmic assessments, and radiographic monitoring of joints of the appendicular skeleton. Study 2 evaluated T-lymphocyte-dependent immune function. Study 3 evaluated the safety of short-term concurrent administration of carprofen, a nonsteroidal anti-inflammatory drug (NSAID), with bedinvetmab. Studies 1 and 3 included terminal pathology and histopathology evaluations. Study designs and procedures included directed complementary morphologic and functional evaluations of a literature- and in vitro-based list of potential safety issues related to the NGF signaling pathway and characteristics engineered into this mAb. Screening-level general procedures evaluated effects associated with mAbs that target and inhibit soluble agonist cytokines.

There were no treatment-related adverse changes in clinical evaluations, clinical neurological and ophthalmic examinations, joints, immune morphology or function, and no effects of short-term concurrent NSAID usage. Treatment-emergent immunogenicity was not observed. Bedinvetmab (1 mg/kg SC monthly; 3× and 10× dose multiples) was well tolerated in normal laboratory Beagle dogs for 6 months and with 2 weeks' concurrent NSAID administration.

Introduction

Osteoarthritis (OA) affects approximately 20% of dogs ≥1 year old and 90% of dogs >5 years old (Anderson et al., 2020; Johnston, 1997). NSAIDs are commonly used to control OA pain in dogs but are not always effective when used as monotherapy and are associated with safety and tolerability concerns pertaining to their GI, renal, and hepatotoxicity (Lascelles et al., 2005; Papich, 2008; Enomoto et al., 2019; Watson et al., 2008).

Nerve growth factor (NGF) has developmental roles in the nervous system (Levi-Montalcini and Booker, 1960) and is a mediator of nociception in adults. In animal models of acute and chronic pain states, demonstration of analgesia via selective antagonism of NGF (Woolf et al., 1994; McMahon et al., 1995) has occurred with few adverse effects (Hefti et al., 2006; Zorbas et al., 2011). NGF antagonists offer an effective option for clinical pain relief in OA without the adverse effects of traditional analgesic drugs (Hefti et al., 2006; Tive et al., 2019). In humans, a worsening of osteoarthritis (rapidly progressive osteoarthritis (RPOA): joint space narrowing >1 mm/year) that occurs at background rate in a small percentage of patients (Wise et al., 2021), has slightly increased incidence with anti-NGF mAbs and more markedly increased incidence when NSAIDs are co-administered. There are no agreed mitigation strategies addressing concerns that long-term use of anti-NGF mAbs or uncontrolled concurrent self-medication with NSAIDs might

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increase the incidence of RPOA unacceptably over time.[1,2] Rapidly progressive osteoarthritis has not been recognized in veterinary medicine.

Bedinvetmab, an NGF antagonist mAb, is a native canine IgGB designed for use against the pain of osteoarthritis in dogs. Bedinvetmab has been modified to eliminate Ig effector functions (Bergeron et al., 2014). Following SC administration, bedinvetmab is absorbed and becomes part of the endogenous pool of circulating antibodies. Bedinvetmab's terminal elimination half-life (9.5 ± 1.8 days) is due to antibody recycling via the FcRn receptor. Terminal elimination is via endogenous proteases (Ryman and Meibohm, 2017; Liu, 2018); amino acids are reused for biosynthesis or undergo metabolic oxidation. Bedinvetmab binds to NGF, forming a complex of one or two mAbs bound to a single NGF dimer (Jonsson et al., 2016). Bedinvetmab:NGF complexes have pharmacokinetics and elimination similar to unbound bedinvetmab. Immunogenicity cannot be predicted or prospectively evaluated.

This manuscript describes the laboratory safety evaluation of bedinvetmab. The safety evaluation of bedinvetmab factored in its properties and pharmacology (Table 1). The evaluation considered the following: targeting and inhibiting NGF binding to trkA and $p75^{NTR}$ receptors in peripheral tissues/organs; cross-reactivity/unintended binding to possible homologs; processing/elimination of mAb:target complexes; general effects of mAbs that target and inhibit soluble agonist cytokines (Martin and Bugelski, 2012); screening for in vivo evidence of effector function; injection site tolerance; immunogenicity; anaphylactoid and idiosyncratic reactions; biology of OA; and canine medicine and concurrent diseases. Safety evaluations, including screening-level and directed morphologic and functional evaluations of peripheral nervous, immune, and bone/joint systems were incorporated into three integrated laboratory studies.

Study 1, a long-term safety study, was designed with general and directed evaluations and adapted according to human biopharmaceutical pre-clinical safety evaluations.[3] The study included directed clinical neurologic and musculoskeletal evaluations and extended gross and microscopic pathology evaluations of peripheral nerve (including ganglia), immune tissues, and joint tissues of the appendicular skeleton (Gropp et al., 2018). The maximum intended label dose, 1 mg/kg, and 3X and 10X dose multiples, evaluated the therapeutic dose and "super-saturating" overdoses. Pathology tissue sampling included capillary beds, where bedinvetmab:NGF or anti-drug antibody (ADA) complexes might initiate local inflammatory responses. The surrogate for tissue cross-reactivity and unexpected Fc effector functions (Martin and Bugelski, 2012) was the pathology evaluation of a complete set of tissues.[4]

Study 2 evaluated the functional immune response of bedinvetmab to keyhole limpet hemocyanin (KLH), a T-cell dependent model antigen (Lebrec et al., 2014). Study 3 evaluated adverse effects in joints of the appendicular skeleton or organs with 2 weeks' concurrent administration of bedinvetmab and a NSAID (carprofen).

Table 1
Binding properties of bedinvetmab.

Property[a]	Control mAb[b]	Bedinvetmab	Implication of positive binding/function
Affinity[c] for βNGF (KD)	NB	51 pM	Intended: binding to target
Specificity[d]: affinity for other neurotrophins (KD)			Cross-reactivity with potentially similar molecules, leading to unintended adverse effects
BDNF	10.8 nM	NB	
NT-3	2.3 pM	NB	
NT-4	1.06 nM	NB	
IC50	NA	0.09 nM	Neutralization of target signaling (canine NGF-induced TF1 cell proliferation)
Affinity[c] for FcγRI	5 nM	NB (>10 μM)	ADCC
Affinity[c] for FcγRIII	500 nM	NB (>10 μM)	ADCC
Affinity[c] for hC1q	10 nM	580 nM	Complement activation
Affinity[c] for FcRn	331 nM	360 nM	In vivo half-life

ADCC, antibody-dependent cell-mediated cytotoxicity; IC50, concentration producing 50% inhibition; KD, equilibrium dissociation constant; μM, micromolar; NA, not applicable; NB, no binding observed; nM, nanomolar; pM, picomolar.

[a] All methods used to measure Fc receptor binding affinity and C1q binding have been reported previously (Bergeron et al., 2014).

[b] Control mAb used for NGF binding, IC50 data, C1q binding, and Fc receptor binding is a canine IgGB wild-type isotype control lacking affinity to NGF. Control mAbs used to measure affinity to non-NGF neurotrophins consisted of three individual mAbs known to bind to BDNF, NT-3, and NT-4, respectively.

[c] Binding affinity is a function of the KD; the lower the KD shown, the tighter the binding affinity.

[d] The neurotrophins shown here have sequences or other features most closely related to the site on βNGF where bedinvetmab binds. Data shown indicates binding affinity of mAbs to human BDNF (97% sequence identity to canine), human NT-3 (95% sequence identity to canine), and canine NT-4.

Materials and methods

Animals and care

All three studies were GLP-compliant[5] and conducted in accordance with local, state, national, and international animal welfare legislation after ethical review. Animal welfare protocols are described in a Supplementary file (see Appendix: Supplementary material). The protocols for studies 1 and 3 were approved by the Charles River Ashland Institutional Animal Care and Use Committee (Study numbers 344158 and 344163, respectively; Dates of approval 21 March 2018 and 22 August 2018, respectively). The protocol for study 2 was approved by the Kalamazoo Institutional Animal Care and Use Committee (Approval number AUP: KZ-3187e-2016-09-arb; Date of approval, 6 September 2016). Environmental conditions were managed and monitored via automated facility systems. Dogs were housed in one room individually in stainless steel cages that were cleaned daily. Municipal water was provided ad libitum. Food was provided for at least 2 h each day.

Dogs were purpose-bred adult laboratory Beagles (widely used species and breed for which significant historical control data are available), 10–12 months old and 5.1–12.7 kg, healthy (veterinary physical

[1] See: Bell, J. March 26, 2021. Pfizer and Lilly's pain drug hits setback in negative committee vote. In BioPharma Dive; Industry Dive, publisher. https://www.biopharmadive.com/news/pfizer-lilly-tanezumab-advisory-committee-vote/597397/ (Accessed 9 August 2021).

[2] See: Weintraub, K. March 25, 2021. FDA panels reject tanezumab to treat arthritis pain, finds limited effectiveness makes rare side effect not worth the risk. USA Today. Gannett Co., Inc., publisher. https://www.usatoday.com/story/news/health/2021/03/25/tanezumab-fda-panels-reject-drug-treat-arthritis-pain-citing-risks/6998417002/ (Accessed 9 August 2021).

[3] See FDA S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals (Accessed 9 August 2021).

[4] See: Guidance for Industry. Target Animal Safety for Veterinary Pharmaceutical Products. VIGH GL43. https://www.fda.gov/files/animal%20%26%20veterinary/published/CVM-GFI–185-%28VICH-GL43%29-Target-Animal-Safety-for-Veterinary-Pharmaceutical-Products.pdf (Accessed 9 August 2021).

[5] See: United States Code of Federal Regulations Title 21, part 58. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58 (accessed United States Code of Federal Regulations Title 21, part 58). (Accessed 9 August 2021)

examinations and clinical pathology evaluations normal; stable body-weight and food intake; behaviorally normal; subsidence of minor background findings typical under conditions of the studies), sexually intact, and previously immunized against standard canine pathogens. Dogs in studies 1 and 3 had no significant radiographic evidence of pre-existing joint disease. Dogs were acclimated for approximately 1 month prior to dosing. At the conclusion of the studies, dogs were released to the stock colony (study 2) or humanely euthanized using IV sodium pentobarbital (Socumb, Henry Schein) prior to necropsy (studies 1 and 3).

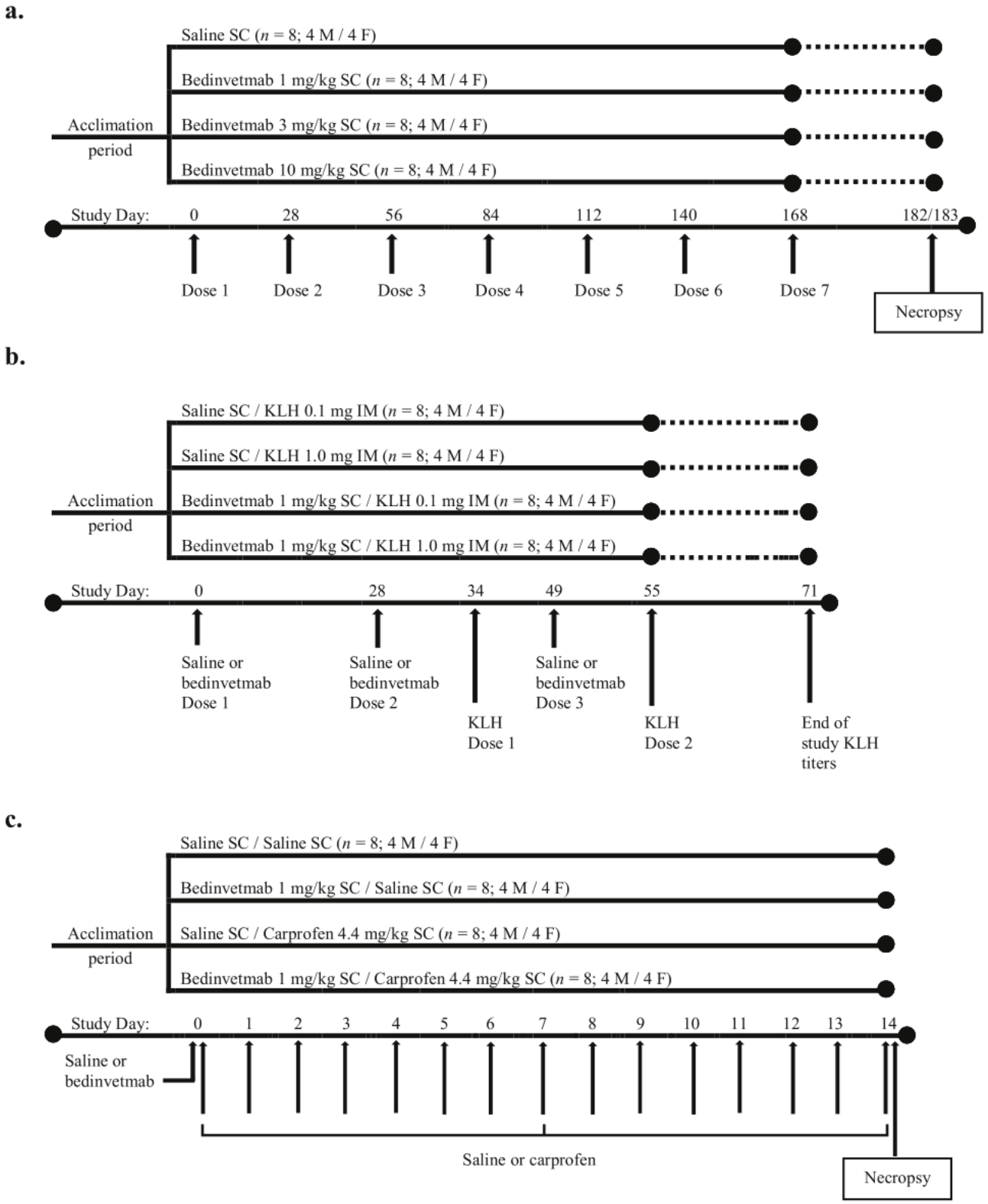

Fig. 1. Study designs for treatment administration: a., Study 1; b., Study 2; c., Study 3. In each study, dogs were randomized to pens and treatment groups during the acclimation period (prior to study day 0). All treatments were administered once on the study days indicated.
F, female; KLH, keyhole limpet hemocyanin; M, male.

Test and control articles; model vaccine antigen

The test article was bedinvetmab (Librela, Zoetis) 15 mg/mL or 30 mg/mL (refrigerated, 2 °C–8 °C), administered SC (route intended for clinical administration). The control article was 0.9% sterile saline solution for injection (Hospira, Inc.), administered SC at volume equivalent to the 10 mg/kg dose volume. Injections were administered at marked locations on the lateral neck. The KLH in study 2 was an unadjuvanted subunit, GMP grade KLH (Stellar Biotechnologies), endotoxin-free (0 EU/mg of protein), formulated in 10 mM phosphate-buffered saline at potencies of 0.1 or 1 mg/mL/dose, and administered IM into the hindquarter within 24 h of formulation.

Study designs

Personnel conducting subjective treatment-phase observations were blinded to group assignments. In each study, 32 dogs were randomly selected and assigned to pens and one of four treatments ($n = 8$; 4 males, 4 females per treatment) in pen order. Randomizations to pens, treatments, and procedures were generated using SAS Release 9.4 (SAS Institute). The experimental unit was the dog.

In study 1, there were three bedinvetmab dose groups (1 mg/kg, 3 mg/kg, 10 mg/kg) and a saline group. Treatment was administered SC every 28 days for seven doses (Fig. 1a). The 10 mg/kg dose was chosen to facilitate mAb penetration of tissues and detection of mAb binding to

Table 2
Schedule of animal observations/measurements.

Procedure	Frequency of evaluation
General health observations	All 3 studies: at least once daily during acclimation; at least twice daily (>5 h apart) during the dosing phases; in study 2, additionally, on dosing days, observations were pre-dose and approximately 2 and 10 h (±30 min) after the first dog was dosed.
Veterinary clinical observations (evaluations of the injection site, overall condition, general attitude, cognition, and the presence of emesis, abnormal urine, or feces)	Study 1: Once each on Days −3 and −2; on dosing days, once pre-dose and 2 h (±30 min) post-dose; once on each of the 2 days following dosing, and on day 181. Injection sites were evaluated immediately post-dose, then at 30 min, 8 h, and the 3rd through 6th days following dosing. Study 2: Days −2 and 71; on dosing days, once pre-dose, then 6 and 24 h post-dose Study 3: Day −1; on dosing days, once pre-dose, then 2 and 8 h (±30 min) post-dosing, and on Days 2, 8, and 14.
Veterinary physical examinations (evaluation of the ocular, musculoskeletal, cardiovascular, respiratory, nervous, integumentary, lymphatic, genitourinary, and gastrointestinal systems as well as the general behavior and gait of the animal)	Study 1: day of animal arrival (day −27), Days −8, 30, and 90, and on Day 182 or 183 Study 2: Days −2 and 71 Study 3: Days −14 and 14
Veterinary neurologic examinations	Study 1 only: Day −8 or −7; Days 91 or 92; and Days 178 or 180
Bodyweight	Study 1: once weekly during acclimation; Day −1; then weekly (±2 days) during the study period; the day prior to and the day of the scheduled necropsy. Study 2: days −14, −7, −2, 5, 12, 19, 26, 34 (predose), 41, 48, 55 (predose), 62, and 71 Study 3: once weekly during acclimation; Days 0 (predose), 7 (±2 days), 13, and 14
Body temperature	Study 1 (BDMS Microchip): Days −3, and −2; on dosing days, once predose, then 2 h (±30 min), 24 h, and 48 h post-dosing; and on day 181 Study 2 (rectal): pre-bedinvetmab or saline: predose, then the 1st and 2nd days post-dose. Pre-KLH: days 34 (predose), 35, 36, 55 (predose), 56, 57; day 71 (rectal) Study 3 (BMDS microchip): Day −1; on Day 0, once at predose, 2 and 8 h (±30 min) post-dosing; Days 2, 8, and 14.
Food consumption	Study 1: daily starting on day −14; continued throughout the study Study 2: NA Study 3: daily starting on day −7 and continued throughout the study
Ophthalmic examinations	Study 1 only: once during acclimation (day −22), once after the last dose (day 170)
Radiography of both the right and left femorotibial joints, hips, scapulohumeral joints, and elbows	Study 1: once during acclimation and once after the last dose (day 170) Study 2: NA Study 3: once during acclimation
Electrocardiography	Study 1 only: once during the acclimation period (day −16/−14) and on days 30/34, 89/93, and 174/176
Blood pressure and respiration rate	Study 1 only: once during the acclimation period and on Days 29, 106, and 181
Clinical pathology sampling[a] (see table footnote below for clinical pathology analytes)	Study 1: day −12, predose on days 0, 28, 56, 84, 112, 140, 168, and on days 182/183 Study 2: days −9 and 71; (not including urine or SDMA) Study 3: days −10/−9, 7, 14
Toxicokinetic and anti-bedinvetmab antibody sampling[b]	Study 1: trough concentrations predose on Days 0, 28, 56, 84, 112, 140, and 168; profile sampling on Days 7, 14, and 21, Days 147, 154, and 161; and Days 175, and 182. Study 2: Trough concentrations predose on days 0, 28, and 49; and on Day 71 Study 3 (not including ADA): Day 0 (predose) and 7 only.
Blood collection for immune function assays (anti-KLH antibody titers)	Study 2 only: on days −2, 34 (predose), 41, 48, 55 (predose), 58, 62, 71
Anatomic pathology evaluation with standard full set of tissues for histopathology (see tissue list in Table 7).	Study 1: yes Study 2: NA Study 3: yes
Clinical chemistry: albumin, total protein, globulin (by calculation), A/G (by calculation), TBIL, urea nitrogen, creatinine, SDMA, ALP, ALT, AST, GGT, glucose, total cholesterol, calcium, chloride, phosphorus, potassium, sodium, sorbitol dehydrogenase, triglycerides, CK, LDH, bicarbonate	
Hematology: WBCs, RBCs, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, reticulocyte count, neutrophils, lymphocyte, monocytes, eosinophils, basophils, large unstained cells, red cell distribution width, red cell morphology, absolute reticulocytes, MPV	
Coagulation: aPTT, PTT, fibrinogen	
Urinalysis: specific gravity, pH, total volume, color, clarity, protein, glucose, ketones, bilirubin, occult blood, protein:creatinine ratio (calculated)	

ADA, anti-drug antibody; A/G, albumin to globulin ratio; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil counts, aPTT, activated partial thromboplastin time; prothrombin time; AST, aspartate aminotransferase; BMDS, bio medic data systems; CK, creatine kinase; GGT, gamma glutamyltransferase; KLH, keyhole limpet hemocyanin; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; NA, not applicable; RBC, red blood cell, SDMA, symmetric dimethyl arginine; TBIL, total bilirubin; WBC, white blood cell count.

[a] Animals were fasted overnight prior to blood and urine collection in all 3 studies.

[b] Serum was obtained and stored frozen at ≤ −10 °C until assayed for bedinvetmab concentrations (range of quantitation 0.09−64 µg/mL).

Table 3
Bodyweights by treatment group and sex: study 1.[a]

Study day	Bodyweight (grams)[b]							
	Saline		Bedinvetmab					
			1 mg/kg		3 mg/kg		10 mg/kg	
	LSM (90% CI)		LSM (90% CI)		LSM (90% CI)		LSM (90% CI)	
	Female $n = 4$	Male $n = 4$	Female $n = 4$	Male $n = 4$	Female $n = 4$	Male $n = 4$	Female $n = 4$	Male $n = 4$
−1 (pre-treatment)	7058.3 (992.0)	9471.3 (939.6)	6945.5 (979.9)	9408.3 (1556.3)	6671.0 (780.1)	9533.8 (576.7)	6834.0 (1116.2)	10616.0 (158.6)
27 (week 4)	8507.7 (8186.6, 8828.8)	8702.4 (8385.5, 9019.3)	8789 (8463.1, 9114.9)	8634.3 (8319.8, 8948.9)	8623.2 (8284.1, 8962.2)	8664.2 (8344.8, 8983.5)	8458.8 (8127.8, 8789.8)	8861.2 (8484.2, 9238.2)
55 (week 8)	8626.2 (8305.1, 8947.3)	8633.4 (8316.5, 8950.3)	8674.5 (8348.6, 9000.4)	8756.3 (8441.8, 9070.9)	8584.2 (8245.1, 8923.2)	8927.7 (8608.3, 9247.0)	8543.3 (8212.3, 8874.3)	8849.7 (8472.7, 9226.7)
83 (week 12)	8912.5 (8591.4, 9233.5)	8794.1 (8477.2, 9111.0)	8921 (8595.1, 9246.9)	8768.1 (8453.6, 9082.6)	8673.7 (8334.6, 9012.7)	9199.7 (8880.3, 9519.0)	8849.6 (8518.5, 9180.6)	9102.7 (8725.7, 9479.7)
111 (week 16)	8964.5 (8643.4, 9285.5)	8740.9 (8424.0, 9057.8)	8670.3 (8344.4, 8996.2)	8761.8 (8447.3, 9076.4)	8787.4 (8448.4, 9126.4)	9034.4 (8715.1, 9353.8)	8909.1 (8578.0, 9240.1)	9092.7 (8715.7, 9469.7)
118 (week 17)	9193.0 (8871.9, 9514.0)	8965.1 (8648.2, 9282.0)	8777.0 (8451.1, 9102.9)[c]	9081.3 (8766.8, 9395.9)	8729.4 (8390.4, 9068.4)[c]	9202.9 (8883.6, 9522.3)	8960.6 (8629.5, 9291.6)	9181.4 (8804.4, 9558.4)
125 (week 18)	9477.2 (9156.1, 9798.3)	9114.4 (8797.5, 9431.3)	8941.8 (8615.9, 9267.7)[c]	9378.3 (9063.8, 9692.9)	8995.4 (8656.4, 9334.4)[c]	9267.9 (8948.6, 9587.3)	9333.6 (9002.5, 9664.6)	9307.7 (8930.7, 9684.7)
132 (week 19)	9288.5 (8967.4, 9609.5)	9268.4 (8951.5, 9585.3)	8881.0 (8555.1, 9206.9)	9260.6 (8946.1, 9575.1)	8802.2 (8463.1, 9141.2)[c]	9377.4 (9058.1, 9696.8)	9391.6 (9060.5, 9722.6)	9388.9 (9011.9, 9765.9)
139 (week 20)	8964.5 (8643.4, 9285.5)	8740.9 (8424.0, 9057.8)	8670.3 (8344.4, 8996.2)	8761.8 (8447.3, 9076.4)	8787.4 (8448.4, 9126.4)	9034.4 (8715.1, 9353.8)	8909.1 (8578.0, 9240.1)	9092.7 (8715.7, 9469.7)
167 (week 24)	9141.5 (8820.4, 9462.5)	9063.4 (8746.5, 9380.3)	9231.5 (8905.6, 9557.4)	9171.8 (8857.3, 9486.4)	8934.2 (8595.1, 9273.2)	9411.2 (9091.8, 9730.5)	9215.1 (8884.0, 9546.1)	9459.4 (9082.4, 9836.4)
174 (week 25)	9130.7 (8809.6, 9451.8)	8904.9 (8588.0, 9221.8)	9150.8 (8824.9, 9476.7)	9208.1 (8893.6, 9522.6)	8891.2 (8552.1, 9230.2)	9559.9 (9240.6, 9879.3)[c]	9359.6 (9028.5, 9690.6)	9411.7 (9034.7, 9788.7)[c]
181 (pre-terminal)	9086.7 (8765.6, 9407.8)	8968.4 (8651.5, 9285.3)	9059 (8733.1, 9384.9)	9105.6 (8791.1, 9420.1)	8951.2 (8612.1, 9290.2)	9290.4 (8971.1, 9609.8)	9188.8 (8857.8, 9519.8)	9329.2 (8952.2, 9706.2)

90% CI, 90% confidence interval; LSM, least squares mean.

[a] No statistically significant differences in bodyweights were reported in studies 2 and 3.

[b] Day −1 bodyweights were used as a covariate in statistical analyses; therefore, LSM (90% CI) was not calculated. The Day −1 values provided as a reference in this table are means (standard deviations).

[c] Significantly different ($P < 0.10$) compared to the same-sex saline group on that day.

Table 4
Radiography findings evident pre-treatment and pre-terminal: study 1.[a]

Treatment Sex	Pre-treatment assessment	Pre-terminal assessment
Saline		
Male	Osteophyte right acetabulum	No progression of findings
Female	Osteophyte left acetabulum, minimal bilateral femoral neck enthesophyte	No progression of findings
Female	No finding evident	Osteophyte right acetabulum, minimal right femoral neck enthesophyte suggesting the presence of minimal DJD at the right hip
Bedinvetmab 1 mg/kg		
Male	Minimal right acetabulum remodeling	No progression of findings
Female	Minimal left acetabulum remodeling and mild left femoral neck enthesophyte	No progression of findings
Female	Osteophyte left acetabulum, minimal left femoral neck enthesophyte	No progression of findings
Female	Minimal left acetabulum remodeling	No progression of findings
Female	Osteophyte right acetabulum	No progression of findings
Bedinvetmab 3 mg/kg		
Male	Osteophyte left acetabulum	No progression of findings
Male	Minimal left femoral neck enthesophyte	Minimal left femoral neck enesthophyte and osteophyte, left acetabulum[b]
Female	Osteophyte left femoral head, left femoral neck enthesophyte	No progression of findings
Female	Minimal bilateral DJD; mild bilateral femoral neck enthesophyte	Moderate left DJD; osteophyte left acetabulum, mild left acetabulum remodeling and severe left femoral neck enthesophyte
Bedinvetmab 10 mg/kg		
Male	Bilateral acetabulum osteophyte, mild bilateral femoral neck enthesophyte	No progression of findings
Female	Minimal left acetabulum remodeling and minimal left femoral neck enthesophyte	No progression of findings

DJD, degenerative joint disease; NA, not applicable.
[a] Radiography not performed in study 2; pre-treatment radiographs were performed for animal selection in study 3 (data not shown).
[b] Despite detection of a new radiographic finding, the overall severity of the DJD did not progress compared to pre-treatment.

Table 5
Clinical pathology evaluations, incidental findings and effect of bedinvetmab: studies 1, 2, and 3.

Evaluation	Incidental findings	Effect of bedinvetmab
Clinical chemistry (albumin, total protein, globulin [by calculation], A/G [by calculation], TBIL, urea nitrogen, creatinine, SDMA, ALP, ALT, AST, GGT, glucose, total cholesterol, calcium, chloride, phosphorus, potassium, sodium, sorbitol dehydrogenase, triglycerides, CK, LDH, bicarbonate)	Study 1: increased LDH and CK (one 3 mg/kg female, days 0, 28, 56, 84, 112, 140, and 168, resolved on day 182); increased ALP (one 1 mg/kg male, days 84–182; no correlation with morphologic liver pathology); statistically significant changes compared to controls: decreased A/G not accompanied by substantial changes in albumin or globulins when categorized by sex (1 mg/kg and 3 mg/kg males and females, ≤4 timepoints; 10 mg/kg males, 3 timepoints); decreased albumin (1 mg/kg and 3 mg/kg males and females, ≤4 timepoints); increased globulin (1 mg/kg and 3 mg/kg males and females, 1 timepoint); decreased GGT (1 mg/kg, 3 mg/kg, 10 mg/kg males and females, ≤4 timepoints); decreased glucose (1 mg/kg males and females, 1 timepoint); increased glucose (10 mg/kg males and females, 1 timepoint); increased LDH (1 mg/kg and 3 mg/kg males and females, 1 timepoint); decreased TBIL (1 mg/kg, 3 mg/kg and 10 mg/kg dogs, ≤2 timepoints) Study 2: no changes reported Study 3: statistically significant decreased calcium compared to controls (bedinvetmab/saline and saline/carprofen males and bedinvetmab/carprofen females) attributed to biological variation	No effect
Hematology (WBCs, RBCs, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, reticulocyte count, neutrophils, lymphocyte, monocytes, eosinophils, basophils, large unstained cells, red cell distribution width, red cell morphology, absolute reticulocytes, MPV)	Study 1: statistically significant changes compared to controls: decreased absolute lymphocyte counts (1 mg/kg females, 3 mg/kg males, and 10 mg/kg females, 1 timepoint); increased absolute lymphocyte counts (1 mg/kg females, 1 timepoint); decreased MCV (1 mg/kg, 3 mg/kg, and 10 mg/kg males); increased MPV (1 mg/kg and 3 mg/kg females, 1 timepoint); increased WBC and ANC (3 mg/kg males and females, 1 timepoint) Study 2: no changes reported Study 3: minimal changes in eosinophils, lymphocytes, and MCV/MCH/MCHC	No effect
Coagulation (aPTT, PT, fibrinogen)	Studies 1, 2, 3: no changes reported	No effect
Urinalysis (specific gravity, pH, total volume, color, clarity, protein, glucose, ketones, bilirubin, occult blood, protein:creatinine ratio [calculated])	Study 1: statistically significantly increased urine pH (3 mg/kg and 10 mg/kg dogs) compared to controls consistent with biological variation Study 2: ND Study 3: no changes reported	No effect

A/G, albumin to globulin ratio; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil counts, aPTT, activated partial thromboplastin time; PT, prothrombin time; AST, aspartate aminotransferase; CK, creatine kinase; GGT, gamma glutamyltransferase; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; ND, not done; RBC, red blood cell; SDMA, symmetric dimethyl arginine; TBIL, total bilirubin; WBC, white blood cell count.

unintended targets if present,[1] and to provide increased exposure to residual traces of impurities or degradation products.

In study 2, two paired groups were allocated to receive 0.1 mg or 1 mg KLH IM; within each pair, one received bedinvetmab 1 mg/kg and the other received saline SC (Fig. 1b) on day 0. The first administration of KLH on day 34 was designed to occur after approximately 34 days' prior NGF inhibition in immune system tissues. The 3-week interval between first and second KLH administrations was the optimal post-priming dose interval; administration of bedinvetmab 5 days prior to each immunization was timed to coincide with approximate C_{max} systemic exposures to bedinvetmab.

In study 3, two groups received saline SC and two groups received bedinvetmab 1 mg/kg SC on day 0, followed by saline or carprofen (Rimadyl, Pfizer) 4.4 mg/kg SC daily for 14 days (Fig. 1c).

Study schedules

All observations and measurements are listed in Table 2.

Observations

In study 1, specialized evaluations included serial veterinary neurologic (Dewey et al., 2015) and ophthalmic examinations; pre-treatment and pre-terminal survey radiographs of the femorotibial and scapulohumeral joints, hips, and elbows; and serial 24-h electrocardiograms (ECGs) using jacketed external telemetry (JET). Ophthalmic examinations were performed after application of a mydriatic agent, using an indirect ophthalmoscope and slit-lamp biomicroscope to examine ocular structures. Neurologic, ophthalmic, and electrocardiographic evaluations were conducted by clinical veterinarians with board certification in the respective specialties. Radiograph interpretation was performed by a veterinarian specializing in radiology, imaging, bone biomarkers, and biomechanics from laboratory musculoskeletal research, toxicology, and osteoarthritis studies.

Clinical pathology sampling and assays

Blood and urine were collected and assayed on automated analyzers using validated methods overseen by technical experts.

Toxicokinetic, ADA sampling and anti-KLH antibody assays

Toxicokinetic evaluations were performed in all three studies. Toxicokinetic parameters were calculated from individual serum concentrations and summarized by sex, dosage level, and evaluation period. In study 1, the bedinvetmab concentration profile was assessed after doses one and six. ADA assays were performed in studies 1 and 2.

In study 2, immune function was evaluated by measuring anti-KLH IgG antibody titers using ELISA (Piccotti et al., 2005). Data were analyzed using the average of duplicate background-corrected optical density data having <25% coefficient of variation.

Terminal pathology

In studies 1 and 3, following humane euthanasia and a complete gross necropsy, a complete set of tissues, including intact hip, knee, elbow, and scapulohumeral joints, and standard weights were collected, and all tissues were placed in 10% neutral buffered formalin. Fixed tissues other than joints were processed to slides for microscopic evaluation. Joints (study 1 only) were transferred to ethanol and underwent a blinded, qualitative high-resolution radiography (Faxitron) evaluation before decalcification. The medial and lateral femoral condyles and the medial and lateral tibial plateaus were sectioned in 3 equidistant midsagittal planes, approximately 2–3 mm apart, and including the

Table 6
Pharmacokinetic profile of bedinvetmab: study 1.

Parameter		n[a]	Bedinvetmab		
			1 mg/kg Mean (SD)	3 mg/kg	10 mg/kg
C_{max} (μg/mL)					
	Day 0 (dose 1)	8	5.98 (1.13)	16.4 (3.3)	58.9 (9.1)
	Day 140 (dose 6)	8	6.95 (2.53)	17.3 (7.2)	70.1 (17.3)
	Day 168 (dose 7)	8	6.93 (2.39)	16.2 (5.3)	74.1 (18.8)
$t_{1/2}$ (days)[b]					
	Day 0 (dose 1)	8	10.0 (2.3)	9.30 (2.18)	9.45 (1.17)
	Day 140 (dose 6)	8	10.0 (2.4)	8.80 (1.04)	9.33 (1.34)
$AUC_{0-28\ days}$ (μg-d/mL)[a]					
	Day 0 (dose 1)	8	89 (23)	239 (59)	870 (148)
	Day 140 (dose 6)	8	111 (53)	257 (113)	1060 (267)

$AUC_{0-28\ days}$, area under the plasma concentration versus time curve over the 28-day dosing interval; C_{max}, maximum plasma concentration; SD, standard deviation; $t_{1/2}$, half-life.
Time of C_{max} (t_{max}) was 7 days in all animals after all doses.
[a] Four animals per sex.
[b] Not measured for day 168 due to partial pharmacokinetic sampling after dose 7.

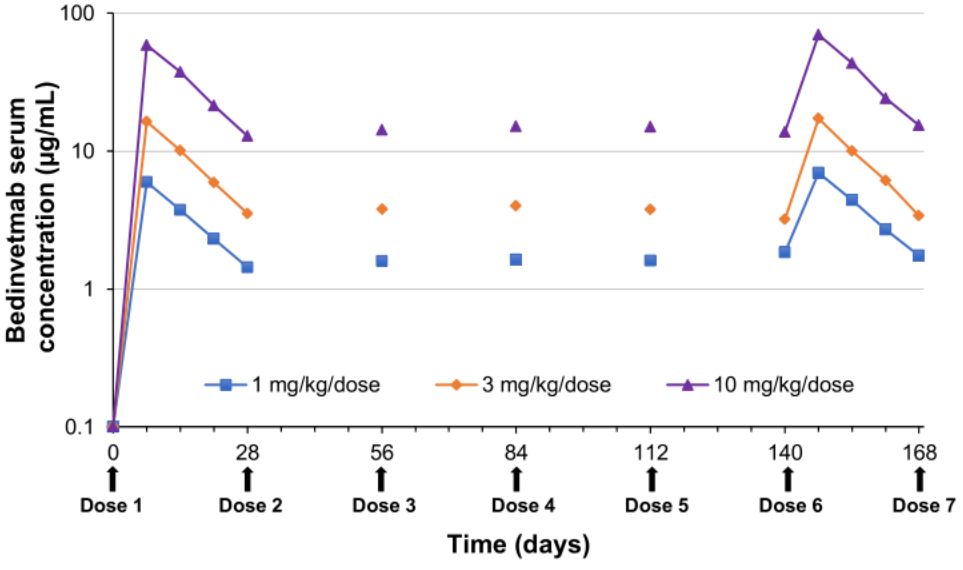

Fig. 2. Mean bedinvetmab serum concentrations (μg/mL) in adult dogs treated with bedinvetmab, on the days indicated, at three dose levels (1 mg/kg, 3 mg/kg or 10 mg/kg, SC; n = 8 per dose group), study 1. Weekly serum samples were obtained for 4 weeks after the first (day 0) and sixth (day 140) bedinvetmab doses. Serum samples obtained on days 28, 56, 84, 112, 140, and 168 were collected prior to bedinvetmab injection, and represent trough concentrations at these timepoints. Serum bedinvetmab levels prior to dosing on day 0 (all dogs) were below the lower limit of assay detection (<0.0878 μg/mL) and were arbitrarily set at 0.1 μg/mL for presentation in this graph.

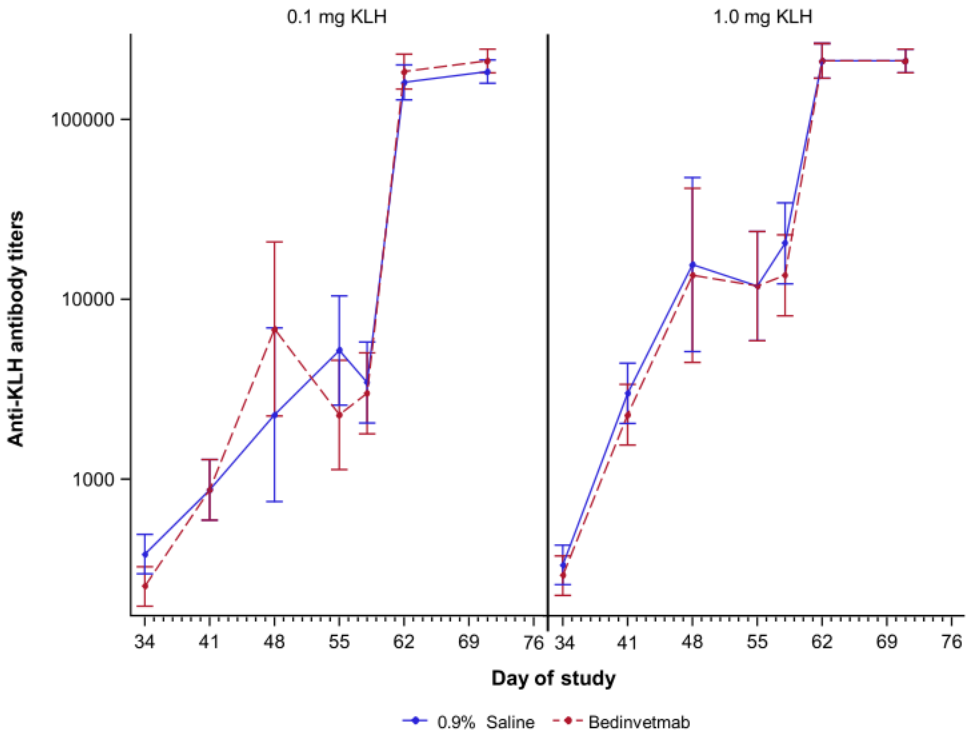

Fig. 3. Least squares mean (±standard error) anti-KLH antibody titers after immunization at two KLH antigen doses in adult dogs treated with saline (solid blue line, $n = 8$) or bedinvetmab (dashed red line, $n = 8$), study 2. Left panel, KLH dose = 0.1 mg; right panel, KLH dose = 1.0 mg. KLH, keyhole limpet hemocyanin.

midsagittal plane (3 slabs/site to cover the weightbearing surface of the condyle or plateau). The proximal femur, proximal humerus, proximal radius, and proximal ulna were bisected midsagittally (one slab/site). The distal humerus was sectioned in a coronal plane to include the central, weightbearing aspect of both the medial (trochlea) and lateral (capitulum and sagittal ridge) aspect. A single transverse section was taken from the acetabulum, going through the attachment of the round ligament and the dorsal acetabular rim. A single midsagittal section was taken through the glenoid cavity, perpendicular to the spine of the scapula and through the center of the scapular tuberosity. After decalcification, two serial sections from each block, were cut at 5–7 microns and stained with hematoxylin and eosin, and toluidine blue.

Statistical analyses

Commercial statistical software (SAS version 9.4, SAS Institute, Cary, NC) was used for analyses. Hypothesis tests were conducted at the unadjusted 10% significance level. Continuous variables were analyzed with general linear mixed models. Pairwise comparisons were performed for all significant treatment interactions or main effects. ECG data were summarized separately by the board-certified cardiologist. General, bone/joint, and clinical pathology, and toxicokinetics/ADA data were summarized by respective experts unblinded to other study findings. Studies 1 and 3 enrolled the minimum number of dogs required to yield scientifically meaningful data for target animal safety studies consistent with VICH GL43.[2] Study 2 enrolled the minimum number of dogs required to detect a difference in mean log KLH titers of 2 or 4 with 80% power at 0.1 alpha level.

An interdisciplinary approach was used to interpret study findings. The phases of studies were reported by subject matter experts with access to all study findings. To minimize ambiguity, all reasonable differential explanations were considered on a weight-of-evidence basis. Interpretations drew upon comparison with control group findings, historical records of background/baseline findings, typical veterinary clinical correlations and complementary evaluations, relevant literature and textbooks, and statistical outcomes.

Results

Animal disposition

Disposition of animals is described in a Supplementary file (see Appendix: Supplementary material).

Clinical observations

The only noteworthy finding in all three studies was intermittent instances of slight injection site swelling, heat or redness. The most common of abnormal observations was swelling, noted almost always at 2 h post-injection, involving a few of the dogs that received the higher dose volumes of bedinvetmab or saline (which was dosed at a volume equivalent to 10 mg/kg bedinvetmab); thus, injection site observations were attributed to the injection procedure rather than bedinvetmab. No abnormal findings were identified in ophthalmic examinations, food consumption, body temperature, electrocardiography, or blood pressure. Isolated statistical differences in bodyweights did not have trends related to bedinvetmab (Table 3). Clinical neurology deficits, including conscious proprioception, hopping, perineal, cutaneous trunci, and flexor reflexes, were common pre-existing findings unchanged by treatment. Incidental observations (clear ocular discharge, abnormal stools, lameness/cracked pads/interdigital cysts, estrus) are common findings for laboratory dogs of this origin, age and breed. No meaningful treatment-related changes were identified between pre-treatment and pre-terminal survey radiographs of major joints (study 1; Table 4).

Clinical pathology

No treatment-related effects were identified in clinical pathology parameters. Incidental abnormal findings were minor, without morphologic pathology correlates, and consistent with biological

Table 7
Terminal pathology evaluations, incidental findings and effect of bedinvetmab: studies 1 and 3.

Evaluation	Incidental findings	Effect of bedinvetmab
Organ weights and organ to bodyweight ratios (adrenal glands, brain, epididymites, heart, kidneys, liver, ovaries, pituitary, prostate, spleen, testes, thymus, thyroid with parathyroids, uterus with cervix)	Study 1: spleen weight: 10 mg/kg males > controls (also significant when indexed to bodyweight and brain weight); heart weight: 10 mg/kg > controls (but no differences when indexed to body or brain weight); kidney weight: 3 mg/kg and 10 mg/kg males > controls (no differences when indexed to body or brain weight); lower pituitary weight relative to brain weight (1 mg/kg males and females) Study 3: ND	No effect
Complete gross pathology evaluation. Microscopic pathology evaluation of a complete set of tissues (adrenal glands, aorta, bone with marrow, femur sternum, bone marrow smear [from rib], brain, cervix, cranial cervical ganglion, dorsal root ganglia [cervical, lumbar], elbow joint, epididymides, eyes with optic nerves, femorotibial joint including menisci, cruciate ligaments, and synovial membrane, gallbladder, hip joint including acetabulum and round ligament, scapulohumeral joint, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, heart, injection sites, kidneys, liver)	Study 1: Gross pathology: dark red areas in the duodenum (3 mg/kg and 10 mg/kg males) and stomach (1 mg/kg female); misshapen epididymides (3 mg/kg); ovarian cyst (3 mg/kg); enlarged spleen (3 mg/kg female); gray discoloration of the prescapular lymph node (1 mg/kg male); enlarged prescapular lymph nodes (10 mg/kg males); vaginal cyst (10 mg/kg); dark red area of injection sites (3 mg/kg male, 10 mg/kg female) Microscopic pathology: focal granulomatous inflammation in the superficial dermis at the injection sites (1 mg/kg and 3 mg/kg females); mononuclear cell infiltrate in the brain (1 mg/kg male) and thyroid (10 mg/kg male); renal dysplasia (10 mg/kg males). Other findings: congestion in the duodenum, cecum, and colon; hemorrhage in the colon; sinus erythrocytosis of the axillary, mesenteric, and/or popliteal lymph nodes; mononuclear cell infiltrates in the prostate, esophagus, liver, salivary glands, and kidneys; tubular degeneration of the testes; hypoplasia of the testes; cellular debris in the epididymis were observed in males (across dose groups, including the control group) and were considered secondary to the peripubertal age of the animals at the time of necropsy Joints histopathology (tibia, distal femur, scapula, acetabulum): minimal focal or multifocal bilateral cartilage degeneration and proteoglycan depletion (some to most dogs, all groups); one 3 mg/kg female had mild to moderate cartilage degeneration, erosion, proteoglycan depletion of left head of femur and acetabulum (both hips had similar early radiographic abnormalities pre-treatment; right hip showed no progression); ulna: minimal to mild cartilage degeneration, clones, erosion, necrosis, ±proteoglycan depletion (13 dogs, all groups) Study 3: Gross pathology: estrus-associated findings (11 females); small thymus[a] (3 females,); pituitary cyst[a] (2 males and 1 female); accessory spleen (2 males and 1 female); misshapen spleen[a] (1 male); misshapen adrenal glands (1 female). Other individual findings in treated groups: yellow duodenal mucosa; white area in the liver and spleen[a]; depressed area in kidney[a]; skin scabbing[a]; green precipitate gall bladder contents; dark red area in spleen[a]; malpositioned vena cava; skin mass[a] Microscopic pathology: tubulointerstitial inflammation and fibrosis; minimal to mild duodenal or cecal glandular dilation; rectal inflammation; kidney tubule dilation; adrenal gland zona glomerulosa vacuolation; liver pigment; mesenteric or axillary lymph node sinus erythrocytosis; skin mononuclear cell infiltrate; focal meningeal fibrosis; focal perivascular mononuclear infiltrate in the brain and spinal cord; axillary lymph node histiocytic infiltrate; mandibular lymph node pigment; mammary gland hemorrhage; mononuclear cell infiltrate in the rectum and tongue; mixed cell inflammation and hyperkeratosis in the skin of the paw; focal gliosis in the spinal cord; parathyroid cyst; neutrophilic inflammation and ulceration in the skin; pituitary cyst; siderotic plaque in the spleen; thymic involution	No effect

ND, not done.
[a] Correlated with microscopic pathology.

variation (Table 5).

Toxicokinetic and ADA analyses

Serum bedinvetmab concentrations are shown in Fig. 2 (study 1). Mean ± standard deviation $t_{1/2}$ (all dogs, all doses) was 9.5 ± 1.8 days; T_{max} was 7 days after each dose; C_{max} and $AUC_{0–28\ days}$ increased approximately in proportion to dose (Table 6), and ≤25% drug accumulation occurred. In studies 2 and 3, all bedinvetmab-treated dogs showed measurable systemic bedinvetmab exposures (data not shown) except one dog (study 3; unidentifiable reason). In studies 1 and 2, no ADAs were detected. Bedinvetmab concentrations and toxicokinetics indicated that clearing or neutralizing ADAs were not induced.

Immune function assays

In study 2, the antibody response to KLH was unaffected by exposure to bedinvetmab (Fig. 3).

Radiography

In study 1, abnormal pre-study survey radiography findings were present in acetabula of a number of animals (Table 4) and were interpreted as minimal degenerative joint disease (DJD). During treatment, the severity of DJD did not progress except in one control female (development of minimal DJD in a previously unaffected joint) and one bedinvetmab 3 mg/kg female (pre-treatment bilateral minimal hip DJD progressed to moderate DJD on one side only). Growth plate assessments were normal. All abnormal findings were considered incidental.

Terminal pathology

In studies 1 and 3, no gross lesions, alterations in organ weights, or microscopic pathology findings were attributed to bedinvetmab (Table 7). Statistical differences in absolute and/or relative organ weights had no microscopic correlates and were attributed to individual animals. Microscopic findings at injection sites (mononuclear cell infiltrates, muscle degeneration, hemorrhage) were common in all groups, and were attributed to the SC injection. In study 3, gross and microscopic pathology findings in all tissues, including major joints, were incidental and unrelated to bedinvetmab or NSAID.

Histopathology of joints from study 1 revealed findings consistent with early DJD, without relationship to treatment. One bedinvetmab 3 mg/kg female with pre-treatment bilateral DJD showed unilateral progression on histopathology. The profile, distribution, and severity of DJD findings, including the case of unilateral progression, were considered unrelated to treatment. In study 3, all joints, ligaments, menisci, bone, and marrow were unremarkable.

Discussion

For small molecules, including NSAIDs, side effects that complicate or preclude their use against pain in veterinary patients are easy to elicit under laboratory conditions. With mAbs, unless the target is available for binding and conditions support the expression of mAb Fc effector functions, the mAb becomes a small, silent component of the endogenous pool of immunoglobulins, with the same pharmacokinetics, metabolism and elimination characteristics. To evaluate overt and subtle effects of a novel mAb, and to demonstrate its pharmacology, an understanding of its targeted pathways, properties, and functions was used to design these three laboratory safety studies. To avoid the potential of comorbidities confounding results, healthy adult dogs were utilized. Systems possibly sensitive to disrupted basal NGF signaling (peripheral nervous, immune, musculoskeletal) were evaluated morphologically and functionally. The studies showed that bedinvetmab was well-tolerated in healthy dogs. The results align with findings in other species. Use of a humanized IgG_2 mAb in adult cynomolgus monkeys produced no toxicity (Zorbas et al., 2011). In human clinical trials, including sub-groups in which NSAIDs have safety limitations or are ineffective (diabetes mellitus, >65 years, severe OA), the humanized anti-NGF mAb tanezumab demonstrated safety and pain control similar to the overall population (Tive et al., 2019).

Rapidly progressive osteoarthritis (RPOA), an uncommon destructive arthropathy in humans, with unknown etiology and no distinguishing pathophysiology,[6] is diagnosed based on rate of clinical progression. In human clinical trials with anti-NGFs, the incidence of RPOA increased somewhat with increased doses, and markedly with chronic (≥4 months) co-administration of NSAIDs.[4] Post-hoc analysis suggested that concurrent mAb/NSAID usage totaling <90 days per year would be tolerated.[4] A follow-up clinical trial with tanezumab confirmed a dose-dependent increase in joint safety events compared to continuation of NSAIDs (Hochberg et al., 2021). RPOA has not been recognized in dogs. However, similarity in bone biology, OA pathophysiology, NGF signaling, and NSAID pharmacology across species suggest some inferred but unknown risk in dogs. Study 3 showed that dogs on bedinvetmab are not markedly sensitive to intermittent, short-term concurrent NSAID administration. These results suggest a washout period between NSAID and bedinvetmab administration is not needed and that intermittent short-term supplemental pain control via NSAIDs is possible. The results do not suggest that RPOA occurs in dogs or that dogs tolerate long-term concurrent administration of NSAIDs and bedinvetmab.

The T-cell dependent antibody response results showed no clinically meaningful immunomodulation. Unlike a typical vaccine, where the antigen is formulated with adjuvants to induce high and durable immunity in all recipients, KLH was dosed without adjuvant, at levels supporting detection of up- or down-regulation of the immune response. The antibody titer response to KLH is known to indicate intact cellular and humoral immune functions. The absence of morphologic or functional effects of bedinvetmab in study 2 suggest that dogs will demonstrate a robust immune response to vaccination with or without bedinvetmab treatment.

In adults, NGF signal alterations, including but not limited to neurons, generally appear to be adaptive in nature. One example is the inflammation of OA, where NGF signal in the joint is increased. Other examples include stress, inflammatory/immune responses, and diverse metabolic compensations in diseases of respiratory, cardiovascular, hepatic, urinary, or endocrine systems. With the latter examples, under conditions of concurrent primary disease, inhibition of NGF modulation of the overall adaptive response could affect the clinical manifestation of the primary disease. One example in humans receiving tanezumab may be unilateral peripheral neuropathy, which occurred mostly in association with carpal tunnel syndrome (Tive et al., 2019). In veterinary patients, which typically have a range of comorbidities, a study of 141 dogs treated with bedinvetmab for 3 months showed no differences in frequency or severity of concurrent diseases compared to controls (Corral et al., 2020).

Immunogenicity and anaphylactoid reactions are known hazards with veterinary medicines and vaccines. With few exceptions, the tools to query or predict these reactions in vivo in laboratory studies are not available. Thus, safety evaluation of the selection methods, engineering, point-mutations in silico and other techniques used to produce the bedinvetmab molecule was confined to monitoring ADAs across large numbers of dogs. ADA monitoring identified a 1.4% (2/138 evaluable cases) incidence of bedinvetmab-associated immunogenicity in a field study (Corral et al., 2020). Of the two ADA-positive cases, the only clinical manifestation was reduced efficacy, observed only in 1 of the 2 dogs. Anaphylactoid reactions were not observed, suggesting that such reactions will be less common than ADAs. In human biopharmaceuticals medicine, nonspecific "idiosyncratic" reactions tend to be common to all mAbs irrespective of their mode of action (Martin and Bugelski, 2012). In field studies, nonspecific reactions (lethargy, anorexia) were identified in eight of 138 dogs treated with bedinvetmab for 3 months compared to zero of 143 placebo dogs, and in five of 89 dogs receiving bedinvetmab for an additional 6 months (Corral et al., unpublished data).

Conclusions

Three integrated safety studies factoring for inhibition of NGF/trkA/p75 receptor signaling in adult dogs and for the specific properties engineered into bedinvetmab provided a systematic, complete set of screening-level and targeted safety evaluations showing that bedinvetmab administered monthly was well tolerated in healthy laboratory dogs. The laboratory results, as well as field safety results reported elsewhere, align well with those of anti-NGF mAbs in humans.

Conflict of interest statement

These studies were sponsored by Zoetis, Parsippany, NJ, USA. All co-authors are employees of Zoetis, Parsippany, NJ, USA or Charles River Laboratories Montreal, ULC, Senneville, Quebec, Canada.

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[6] See Tanezumab Arthritis Advisory Committee Briefing Document – FDA. https://authorzilla.com/ardDv/tanezumab-arthritis-advisory-committee-briefing-document-fda.html (accessed 9 August 2021).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.tvjl.2021.105733.

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