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EXPERIENCE FROM VETERINARIANS' CLINICAL USE IN EUROPE

Technical Bulletin

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INTRODUCTION

Osteoarthritis (OA) is a highly prevalent disease in dogs, and the chronic pain associated with OA negatively impacts many areas of a dog's health, including mobility, cognitive function, affect, and relationships—both human and animal.[1] Although highly prevalent, OA remains underdiagnosed. As a progressive and currently incurable disease, early diagnosis and management can help reduce pain, improve mobility, and improve a dog's quality of life. Current pain treatment options are effective but may have some limitations.[1-6] Although nonsteroidal anti-inflammatory drugs (NSAIDs) have been the mainstay for OA treatment, these medications are not always sufficiently effective when used as monotherapy,[7] not all dogs will respond to NSAID therapy, and some will not tolerate it.[3,4] Compliance with daily medications can be difficult for some pet owners and some stop treatment altogether.[8] These challenges led Zoetis to search for new solutions to help veterinarians manage OA pain.

The launch of new anti-nerve growth factor (NGF) antibody therapies, such as Librela, to control OA pain is an exciting development and represents the first new pain medication class outside the prostaglandin pain pathway in more than 20 years. Following approval, Librela was launched in Europe in February 2021. In the US, Librela was approved in May 2023 and is indicated for the control of OA pain in dogs; it is administered by a veterinary professional as a monthly subcutaneous injection.[9]

The goal of this bulletin is to review the challenges in OA diagnosis and pain treatment and illustrate how Librela could help to address these challenges. This bulletin provides veterinary professionals with a broad overview of the use of Librela in clinical practice, including patient selection, real-world efficacy, perceptions of cost, a look at safety, and veterinarian and pet owner satisfaction.

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THE CHALLENGES OF IDENTIFYING OA PAIN

Osteoarthritis is caused by many factors, including developmental issues, injury, and obesity. The impact of joint conformation is such a major driver of disease that the development of OA can begin much earlier in a dog's life than what is often expected. Conformational changes impact both large (hip dysplasia) and small dogs (patellar luxation), so dogs of any size should be screened for OA. Signs of pain exhibited by dogs are often misinterpreted or missed entirely by pet owners. Dogs may hide signs of discomfort, and owners may attribute signs to "old age," only recognizing them very late in the disease when the signs are obvious and dramatic.[6]

OA Is Highly Prevalent, and Proactive Screening Protocols Could Help Identify More Dogs in Pain

Arthritis is more common than previously reported.[5,10,11] Exam time is limited and often needs to cover multiple medical goals, signs of arthritis can be hard to distinguish (especially in early to moderate OA), and dogs are good at hiding signs of discomfort—all of which may lead to missed or delayed diagnoses.

The prevalence of osteoarthritis in dogs can vary in literature, with reported numbers ranging from 2.5%[12] to 6.6%[13] in primary care practices in the UK, to up to 20% in a study of dogs seen by referral hospitals in the US.[10]

The true prevalence of the disease, however, is likely to be higher when unreported cases and the discrepancies in recording systems are taken into consideration.[14] Prevalence based on record review, as in the studies cited above, is likely to be much lower than prevalence based on proactive screening. In a recent study using an owner-completed canine OA screening checklist to help identify previously undiagnosed OA cases that have clinical signs, close to 40% of dogs proactively screened had clinical signs of OA. This indicates the potential to increase diagnosis rates by proactively helping to identify cases for further evaluation that could otherwise remain undiagnosed.[11,15]

2.5%-20%

RETROSPECTIVE PREVALENCE

~40%

PROSPECTIVE PREVALENCE

When asked in market research, veterinarians estimate the prevalence of OA pain in dogs to be between 30% and 40%, with approximately half of those cases being diagnosed and half being suspected to have OA based on clinical signs of pain.[5] This group of dogs suspected to have OA represents an unmet need.

While there is no cure for the disease, early diagnosis and a multimodal management plan, including pain control, appropriate exercise, and weight management may improve the quality of life of dogs with chronic pain.[16]

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Pet Owners' Role in Identifying OA Pain

An important first step to improving diagnosis rates is for pet owners to recognize changes in their dog's behavior and bring them to a veterinarian for diagnosis. This can be challenging, however, as owners may dismiss signs of OA pain as a natural part of their dog's aging process and may not mention them to their veterinarian. Some pet owners may believe they know the signs of OA pain but are looking for obvious signs of discomfort that dogs don't exhibit very often, like vocalization or limping.[6] Roughly 2 in 3 dog owners are not aware that weight gain or obesity are associated with arthritis; 30% are not aware that aging is also associated with arthritis.[17]

The age of the dog can also impact diagnosis. Owners may not always notice the early signs of OA, particularly in younger dogs. Mobility changes can be subtle, including slowness in rising and hesitating when getting in or out of the car or climbing stairs. Persistent and worsening signs trigger a visit and discussions with the veterinarian. Dogs who visit the veterinarian specifically for signs of OA pain, rather than a wellness visit, were more likely to receive an OA diagnosis and tended to be older (8.7 years) than the suspected dogs (5.5 years). Zoetis market research showed that at these visits, nearly half of dogs received an OA diagnosis; in the dogs that did not receive a diagnosis of OA, the veterinarian nonetheless mentioned it as a possibility.[6]

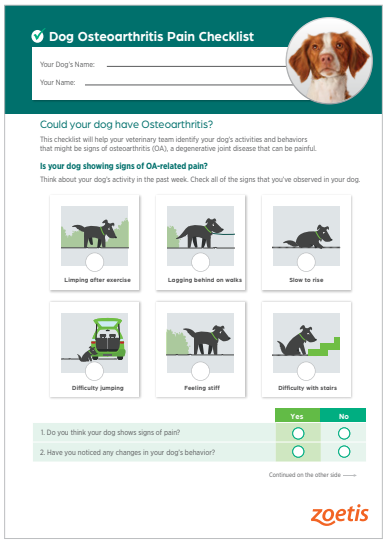
Reasons for not confirming a diagnosis of canine OA include[6]:

- Age of the dog
- Severity of signs (too mild or too severe)
- Owner's inability to afford testing
- Owner not seeing it as necessary

Officially confirming a diagnosis could be very helpful to the pet owner. Pet owners follow the veterinarian's lead, and having a clear sign that there is a medical condition (and the ability to improve quality of life) will help them in making care decisions. For example, diagnosed dogs are far more likely to be treated and more likely to be treated with prescription medications.[6]

Owners associate pain with obvious signs of discomfort that dogs don't exhibit very often, like vocalization or limping

Use of a screening checklist can help to increase owner awareness of early signs of OA pain and the likelihood of mentioning them at their annual exam.[11,15] Including the OA checklist as a standard part of the annual exam would ensure more dogs with OA pain are identified. A checklist (shown below) is easy to implement in the clinic when the entire team understands the benefit to the owner and dog and uses it consistently with all clients. Pet owners may feel guilt or sadness upon a diagnosis of OA; however, the veterinary team can keep the conversation positive by focusing on what may be done to help the dog.



Scan the QR code below to download the OA Pain Checklist

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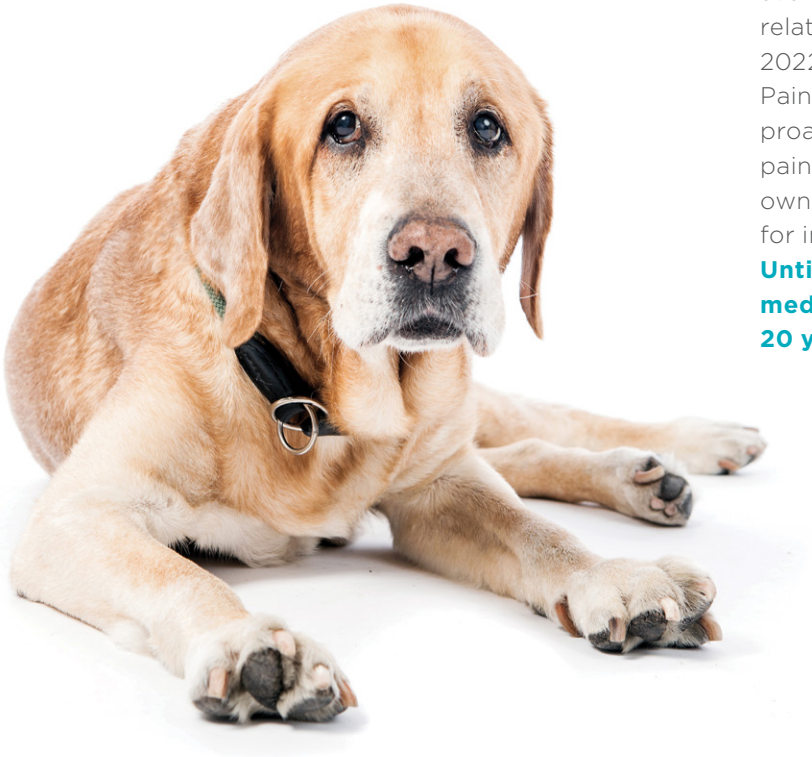
THE CHALLENGES OF CONTROLLING OA PAIN PRIOR TO THE LAUNCH OF LIBRELA

For more than 20 years, NSAIDs have been commonly used to help manage OA pain in addition to multimodal therapy.[7] Current options are effective, and veterinarians have been generally satisfied with NSAIDs.[5] However, they do have some limitations, including pet owner compliance.[1-6] Furthermore, NSAIDs are not always sufficiently effective when used as monotherapy, not all dogs will respond to NSAID therapy, and some will not tolerate it.[2-4,7,18]

Compliance with daily medications can be difficult for some pet owners. When asked why they had delivered fewer days of pain treatment than recommended by the veterinarian, the most common reasons were[5]:

- I didn't think my dog needed the treatment
- The treatment was ineffective
- I forgot to administer some of the treatment
- I found it difficult to administer the treatment to my dog
- Treatment was too expensive
- I was concerned with side effects
- My dog recovered before the treatment ended



In addition to missed or late doses, many owners who started giving their dog a prescribed pain treatment stopped administering it altogether.[6] The reasons that owners discontinued prescription treatment for OA pain in their dogs included:

- **Limited effectiveness:** Owners believe treatments are only somewhat effective and don't have a major impact on OA
- **Cost:** Owners choose to stop treatment because the cost is not worth the relatively modest benefit for the dog
- **Administration:** For some owners, giving their dog a daily pill or liquid is a hassle (eg, owner forgets, dog spits it out) and they stop when the difficulty outweighs the benefits
- **Lack of veterinarian proactivity:** Veterinarians don't typically recommend stopping treatment, but they rarely try to persuade owners to keep their dogs on, re-start once they've stopped, or help them find alternative treatments. If there is no follow-up, they may not realize the owner has stopped the treatment. This underscores the importance of the veterinarian's recommendation

Despite the high prevalence of OA and the availability of numerous treatment options, OA-related pain remains challenging to control. The 2022 AAHA pain guidelines and the 2022 Global Pain Council guidelines discuss how important proactive pain management is for managing chronic pain.[19,20] The role of the veterinarian in guiding pet owners to accept a treatment recommendation and for improved compliance is incredibly important. **Until now, there has been no new class of medication to manage OA pain in more than 20 years in either human or veterinary medicine.**

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LIBRELA – A NEW ERA IN OA PAIN MANAGEMENT

Librela is the first and only monthly injectable anti-NGF monoclonal antibody therapy developed to control canine OA pain. Librela contains bedinvetmab, a monoclonal antibody (mAb) that binds to nerve growth factor (NGF), a key player in OA pain. (For a review of NGF's role in OA pain, please refer to the open access review journal article by Enomoto et al.[18]) The inhibition of NGF-mediated cell signaling has been demonstrated to provide control of pain associated with OA.[9] Librela is administered once a month via subcutaneous injection for the control of pain associated with OA in dogs. For more details regarding Librela, contact your Zoetis representative or visit LibrelaVetTeam.com.

- Approved as safe and effective for controlling OA pain in dogs[9,21]
- Works differently from NSAIDs by reducing NGF effects, a key factor in OA pain[9,18,22,23]
- Functions like naturally occurring antibodies with minimal metabolism by the liver or kidneys[9,24,25]
- Puts OA pain treatment in your hands as a monthly injection delivered in clinic
- Dogs experienced decreased pain, which led to increased activity and improved quality of life[9,26-28]

"As a vet for nearly 30 years now and dog owner for even longer, I have seen many new veterinary products come into the market with varying results. I would like to congratulate and also thank the team at Zoetis for the production of Librela. It really is a godsend and we as a profession are seeing amazing results. As the owner of a 6-year-old retriever with severe elbow arthritis, I am also immensely grateful...since we started Librela he is happy and active again."

— Veterinarian, UK

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VETERINARIAN INSIGHTS FROM THE FIRST YEAR OF LIBRELA IN CLINICAL PRACTICE

Zoetis launched Librela in Europe in February 2021. At the end of its first year in market, February 28, 2022, 1.9 million doses had been shipped to veterinarians across Europe. Clinic re-order rates were high as an increasing number of canine OA patients started Librela therapy (Zoetis Data on File, 2022). Once Librela was commercially available, the rapid adoption and volume of doses shipped in the product's first year spoke to the fact that Librela was helping satisfy a strong existing unmet need.

To help understand veterinarians' usage and satisfaction with Librela, Zoetis conducted multiple market research studies to quantify veterinarian utilization, perceptions of efficacy, safety, and cost, compliance, and satisfaction.[5,29,30] Feedback on overall satisfaction and perceptions of cost was also sought from pet owners.[5] These studies provided valuable insights into veterinarians' use of Librela in practice and its application in various canine populations.

Although the majority of veterinarians stated that they do not use a standard method to stage dogs with OA,[30] they nonetheless apply pain treatment decisions by disease stages. To ensure consistency, veterinarians in these market research studies were shown definitions of various stages of OA to use when considering severity of disease (**see Stages of Canine OA Pain in the following chart**).

Stages of Canine OA Pain

Mild (early stage) – Dog experiencing intermittent pain and showing intermittent signs of lameness that resolve after rest and that may be more apparent after sudden bouts of exercise

Moderate (mid-stage) – Dog experiencing chronic pain and becoming exercise intolerant; may hesitate or show difficulty jumping into car or going up stairs and more likely to lag behind during walks

Severe (late stage) - Dog experiencing chronic pain and losing ability to walk and muscle wasting in affected limbs

These studies were masked, meaning they were run by third-party market research vendors with the study sponsor (Zoetis) unknown to participants. Companion animal veterinarians in practice for at least 2 years, working no less than 20 hours per week in direct patient care, and seeing at least 40 canine patients per month were randomly selected and invited to participate in these studies.

"Librela injections makes the life of my dog pain free. It's an effective medicine to treat [osteo]arthritis. It's easy to administer."

— Dog owner, UK[5]

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LIBRELA PATIENT SELECTION

Post-launch, Librela is being used broadly in Europe as a first-line therapy for dogs with OA pain. This includes dogs of all ages, sizes, and breeds; dogs newly diagnosed and dogs with existing OA pain; and in dogs with mild, moderate, and severe OA disease.

Librela Is Being Used in Dogs of Many Ages and Sizes

In clinical studies conducted in Europe, dog ages ranged from 1.0 to 17.5 years with an average age of 9.2 years.[26] In a post-launch survey, veterinarians were asked to report case details on 5 to 7 of their average Librela cases. In this study ages ranged from 2 years to 20 years with an average age of 11 years (n=1,932 dogs) (**Figure 2**).[30]

FIGURE 2. IN A POST-LAUNCH MARKET RESEARCH SURVEY IN EUROPE,[30] AGES OF DOGS RECEIVING LIBRELA RANGED FROM 2 YEARS TO 20 YEARS WITH AN AVERAGE AGE OF 11 YEARS (N=1932 DOGS).

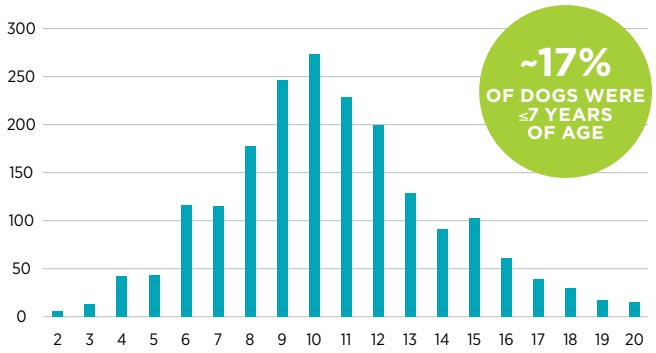
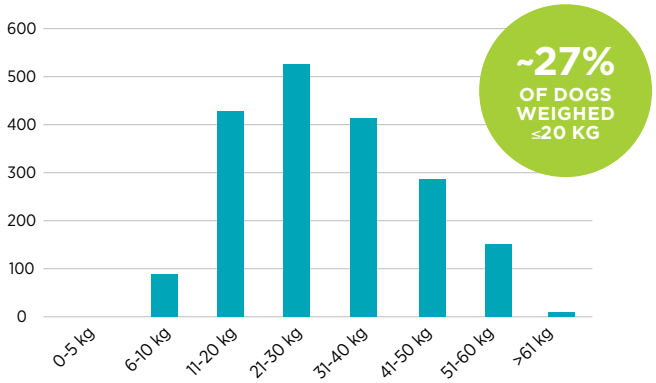


FIGURE 3. DISTRIBUTION OF DOGS RECEIVING LIBRELA BY WEIGHT IN A POST-LAUNCH MARKET RESEARCH STUDY (N=1932 DOGS).[30]



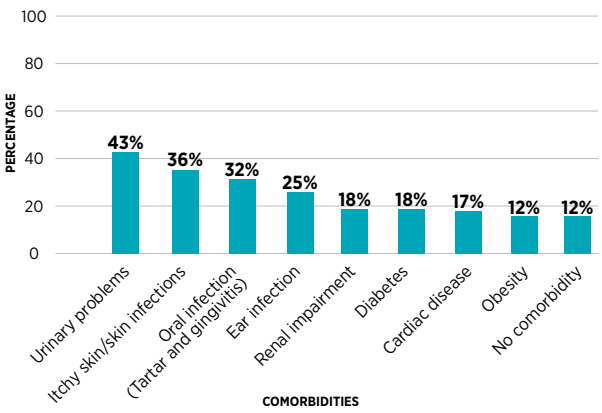
In pivotal clinical studies, dog body weights ranged from 1.7 kg to 62.3 kg with an average weight of 26.1 kg.[26] In the post-launch market research study, dog weights ranged from 6 kg to 72 kg with an average weight of 30 kg.[30] The distribution of dogs by weight is shown in (**Figure 3**). In this study, 27% of dogs (522/1932) were less than 20 kg.[30]

Dog breed was not captured in the post-launch market survey; however, in the clinical trials, the most common breeds were mixed breeds (n=122; 42.5%) followed by Labrador retrievers (n=54; 18.8%), golden retrievers (n=18; 6.3%), and German shepherds (n=18; 6.3%). No other individual purebred comprised more than 5% of the total.[26]

Comorbidities at the Start of Pain Treatment

In the post-launch market research study, older dogs had many existing comorbidities at the start of Librela treatment (**Figure 4**).[30] No significant differences were seen by gender. When it comes to severity level, urinary problems tend to be more frequent among moderate-severe OA patients than among the mild cases. Renal impairment, diabetes, cardiac disease and obesity tend to be more frequent among severe OA patients than among mild-moderate cases. Differences were seen among age groups: urinary problems and renal impairment are more frequent after 6 years old, cardiac disease tends to be more frequent among 16- to 21-year-old patients than among 0- to 5-, 6- to 10-, or 11- to 15-year-old patients, while diabetes is more frequent among patients over 11 years of age.

FIGURE 4. COMORBIDITIES OR ASSOCIATED CONDITIONS IN PATIENTS AT THE START OF LIBRELA TREATMENT IN EUROPE (N=1932 DOGS).[30]



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Disease Severity

In 2 other market research studies, veterinarians were asked what percent of patients by severity type they would recommend Librela to[29] or had used Librela in[30] (**Table 1**).

TABLE 1. VETERINARIAN PERCEPTION OF OA PAIN SEVERITY IN PATIENTS SELECTED FOR TREATMENT WITH LIBRELA IN TWO STUDIES.[29,30]

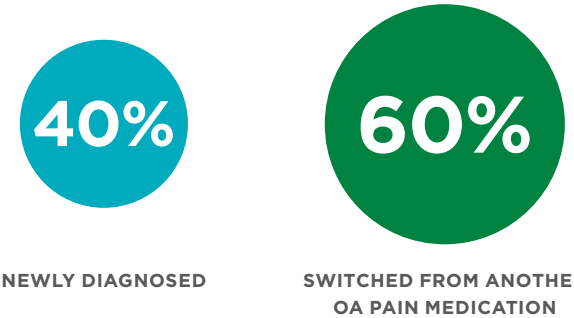
	MILD	MODERATE	SEVERE
Study 1—Vet Perception[29] (N=514)	13%	37%	50%
Study 2—Chart Pull[30] (N=1932 dogs)	36%	37%	27%

Actual usage of Librela was relatively equally spread across severity of disease. Use was greater in mild cases and less in severe cases than what was predicted.[29,30]

Use in Existing Patients With OA Pain and Newly Diagnosed OA Patients

Looking across multiple market research studies, Librela has been used in dogs both newly and previously diagnosed for OA pain.[29,30] In one study, 4 out of 10 dogs were newly identified as having OA pain and 6 out of 10 dogs prescribed Librela had previously received another OA pain treatment (**Figure 5**).[30] Of these dogs, 84% had been receiving an oral medication, 92% of which were NSAIDs.[30]

FIGURE 5. LIBRELA USE IN EUROPE (N=1932 DOGS).[30]



Top 3 Reasons Veterinarians Started Librela Treatment in Their Patients With OA[30]

- ***Lack of previous treatment efficacy (40%)***
- ***Desire to improve compliance (28%)***
- ***To decrease patient's number of medications (21%)***

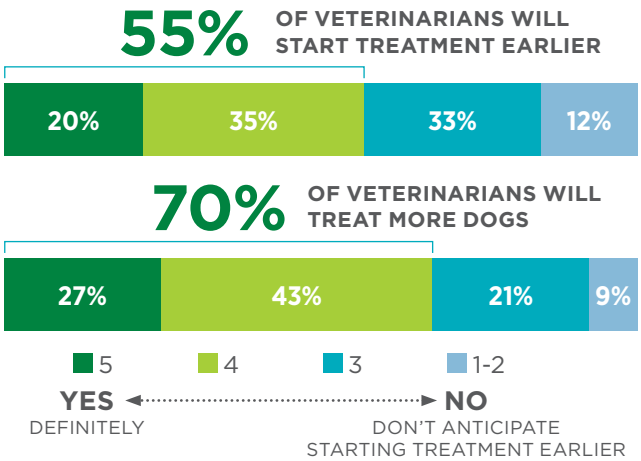
Dogs That Cannot Use NSAIDs

Experience from the early use of Librela also shows that it may help mitigate some of the gaps in current pain treatment options for OA. These gaps include dogs that do not tolerate or do not have an acceptable efficacy response to NSAIDs and owners that have difficulty administering oral medications to their dogs. Although there are possible safety and tolerability concerns with the use of NSAIDs in some dogs, other approved pharmacologic treatment options for the control of pain have been limited to date.[19] Librela offers an alternative to NSAIDs. As a monthly injectable, Librela provides a new option for patients that are hard to dose orally or where owners recognize compliance to be a daily challenge. When reviewing gaps such as these in current pain treatment regimens for OA, veterinarians said they would prescribe Librela to almost 75% of dogs that do not tolerate NSAIDs and to more than 50% of their patients with OA that are difficult to orally medicate.[5]

Expanding Treatment Populations for OA Pain

Now that Librela is available, veterinarians indicated they will increase treatment of canine OA (**Figure 6**).[29]

FIGURE 6. EARLIER INITIATION OF PAIN TREATMENT AND ESTIMATED INCREASE IN NUMBER OF DOGS RECEIVING OA PAIN TREATMENT IN EUROPE NOW THAT LIBRELA IS AVAILABLE (N=514).[29]



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SHIVA: MIXED BREED FEMALE, 12 YEARS OLD

- History of obesity and was not willing to move
- Despite weight reduction and going for walks, she showed worsening signs of lameness: could not stand up, took a long time to move
- Meloxicam plus prednisolone gave her only slight relief

Scan the QR codes to view video of Shiva before and after treatment with Librela

SHIVA BEFORE LIBRELA INJECTION

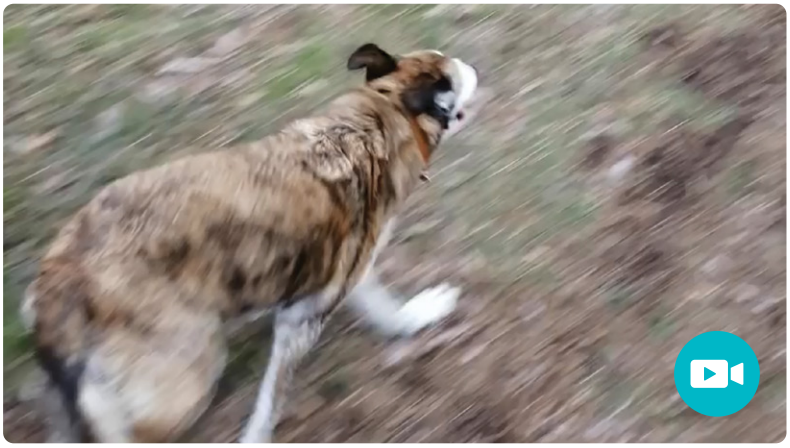
Scan the QR code or visit the link below to view video

https://bcove.video/3H0t7zr

SHIVA ONE WEEK AFTER FIRST LIBRELA INJECTION

Scan the QR code or visit the link below to view video

https://bcove.video/3XQsgqY



SHIVA AFTER SECOND LIBRELA INJECTION

Scan the QR code to view video

https://players.brightcove.net/1455209554001/default_default/index.html?videoId=6316620439112

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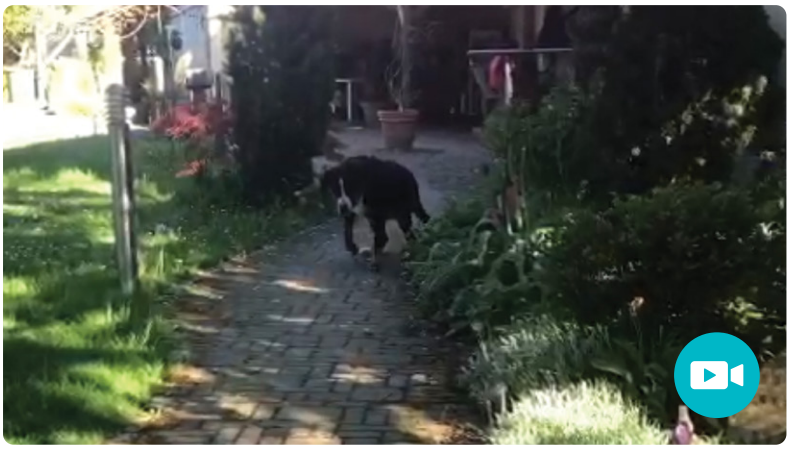
EMMA: GREATER SWISS MOUNTAIN FEMALE, 6 YEARS OLD

- Injured elbow 6 years ago; recently confirmed spondylosis/spondylarthrosis and history of forelimb OA
- Lameness for half a year: she was lying down a lot and unhappy
- NSAID therapy provided only slight improvement and resulted in nausea and weight loss

Scan the QR codes to view video of Emma before and after treatment with Librela



EMMA BEFORE LIBRELA INJECTION

Scan the QR code or visit the link below to view video

https://bcove.video/3B8cnlZ

EMMA AFTER LIBRELA INJECTION

Scan the QR code or visit the link below to view video

https://bcove.video/3Vnw1T8

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EFFICACY

Pivotal Trial

The efficacy of Librela was evaluated in two 3-month double-blind, randomized, multicenter, placebo-controlled studies, one conducted in the EU and one in the US. In the EU study, 287 client-owned dogs with OA were administered either saline (n=146) or Librela (n=141) once monthly for 3 months, followed by a 6-month continuation study (n=89).[9,21,26]

The US study had a similar study design, in which 272 dogs with OA were enrolled and administered Librela (n=135) or saline (n=137). Efficacy was measured using the Canine Brief Pain Inventory. Effectiveness was seen after the first injection of Librela in the EU study and after the second injection of Librela in the US study. In the EU study, Librela demonstrated a significant effect compared with the control group beginning at Day 7 after the first injection and increased through the first 2 months, then was maintained. In the US study, efficacy was not seen until after the second injection, but the percentage of dogs that were deemed treatment successes were higher than the control group for every assessment. A reduction in pain, increase in activity, and improved quality of life was demonstrated.[9,21,26]

For the 89 dogs from the EU study that continued on for an additional 6 months of treatment, efficacy was maintained through the entire study.[26]

Although efficacy may not be seen until after the second injection of Librela, some dogs may experience a reduction in pain as soon as 7 days after the first injection.[9]

Librela Can Improve Compliance by Extending Days of Therapy for Dogs in Pain

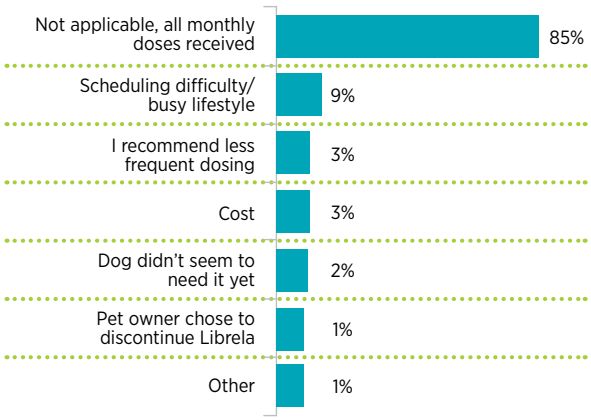
Efficacy is reliant on the dog receiving the medication. Compliance is a key issue in the successful treatment of any disease and OA pain is no exception.[8] Compliance with orally administered pain medications is often an issue with pet owners not recognizing signs of pain and/or remembering to administer the medication.[8] A monthly injection administered by the veterinarian takes the responsibility for compliance out of the pet owner's hands. Real-world data on compliance with monthly Librela dosing is high, with the average treatment duration of 8 months seen in a market research study (**Figure 7**).[30,31]

FIGURE 7. AVERAGE TREATMENT DURATION FOR LIBRELA AND NSAIDs IN MARKET RESEARCH STUDY.[30,31*]

*Different protocols per study.
†Longest average duration among all NSAIDs.

In the market research study, veterinarians recalled that doses were not skipped in 85% of cases and the reasons why patients did not receive the monthly dose are shown in (**Figure 8**).[30]

FIGURE 8. ALTHOUGH MONTHLY DOSES WERE NOT SKIPPED IN 85% OF CASES (N=1932), VETERINARIANS RECALLED SEVERAL REASONS FOR THOSE CASES THAT DID MISS A DOSE.[30]



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Short-Term Use With NSAIDs

In a 2-week laboratory safety study, 8 dogs concurrently received 1 subcutaneous injection of Librela and 14 days of an injectable NSAID. Although there are no significant findings, this limited study did not provide sufficient data to support a conclusion on the safety of concurrent use of Librela and NSAIDs.[9,21]

In clinical trials in humans, rapidly progressive OA has been reported in patients receiving humanized anti-NGF monoclonal antibody therapy. The incidence of these events increased with high doses and in those human patients who received long-term (more than 90 days) NSAIDs concomitantly with an anti-NGF monoclonal antibody. Rapidly progressing osteoarthritis (RPOA) has never been diagnosed in veterinary medicine, and there is no long-term safety data on the co-use of bedinvetmab and NSAIDs in dogs.

Librela Performance on Top OA Pain Product Attributes

Veterinarians' top reasons for selection of an OA pain product are, "improves dog's quality of life," "improves patient mobility," "effectively reduces OA pain," and "has few side effects." (**Table 2**)[5,29]

TABLE 2. ATTRIBUTE IMPORTANCE FOR ANY OA PAIN MEDICATION.

1.	Improves the quality of life for dogs with OA
2.	Improves patient mobility
3.	Effectively reduces OA pain
4.	Has few side effects
5.	Consistent supply
6.	Reduces inflammation
7.	Advances my care of OA patients
8.	Starts to work fast
9.	Improves my relationship with my clients
10.	Long acting
11.	Is cost effective for my clients
12.	Reduces central sensitization
13.	Route of administration (injection, tablet, liquid)
14.	Provides an innovative solution
15.	Mode of action (targets PGE2, EP4, NGF)
16.	Monoclonal antibody
17.	Injectable dose delivered in clinic
18.	Is the most profitable for my clinic

Veterinarian satisfaction level increased from one Librela dose to the next.[30]

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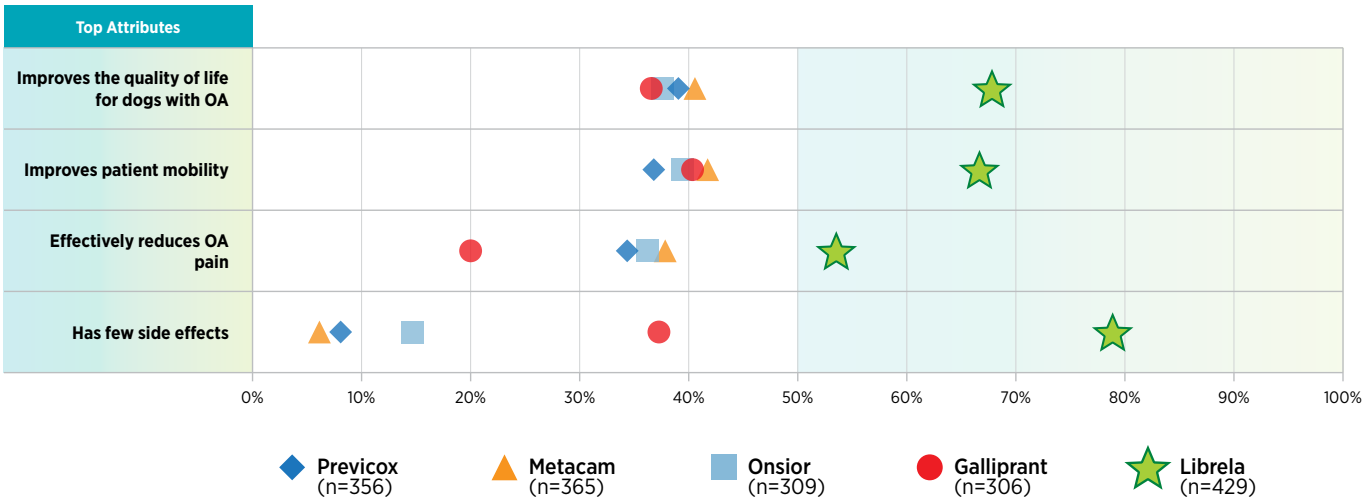
Librela Performance on Top OA Pain Medication Attributes

Librela satisfaction for the top 4 OA pain medication attributes was higher than any other established OA pain prescription medication (**Figure 10**).[29]

FIGURE 10. LIBRELA PERFORMANCE AND VETERINARIAN SATISFACTION IN ATTRIBUTES OF TOP PRODUCTS IN ORDER OF IMPORTANCE.[29]



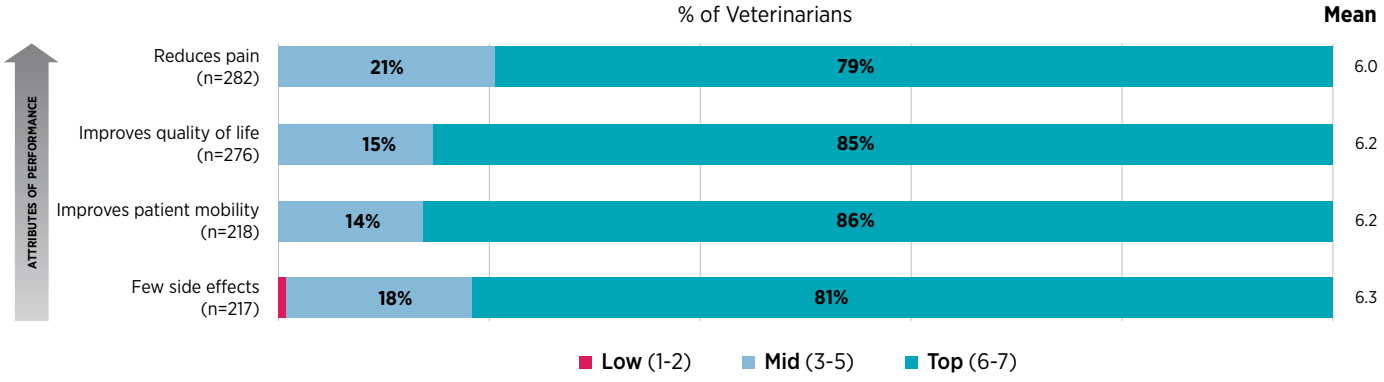
Veterinarian Perception of Onset of Activity

Veterinarians were also asked how Librela rated on top product attributes such as "Starts to work fast." Veterinarians who had used Librela and other OA pain products rated Librela similar in "Starts to work fast" to Metacam and Onsior.[29]

Veterinarian Satisfaction Confirmed in a Separate Study

Librela was rated in the top 2 boxes by 79% of veterinarians for OA pain reduction (**Figure 11**).[5]

FIGURE 11. LIBRELA ATTRIBUTE PERFORMANCE AND SATISFACTION: GLOBALLY, VETERINARIANS ARE VERY SATISFIED WITH LIBRELA AND RATED IT HIGHLY ON ALL 4 OF THE TOP ATTRIBUTES (N=75).[5]



Librela (bedinvetmab injection)

Librela Use Reduced the Number of Medications Needed

Before they were started on Librela, dogs across all stages of OA received an average of 1.9 drugs, including oral and injectable drugs and nutraceuticals. After starting on Librela, the average number of drugs given with Librela dropped to 1.3 (**Figure 12**). Librela was shown to reduce the number of other medications administered to dogs with mild, moderate, and severe OA (**Figure 13**). In dogs with severe OA, that number dropped from 2.2 drugs prior to Librela to 1.4 drugs after Librela. In more than 7 out of 10 cases, Librela was the main OA pain treatment, with no other treatments being required.[30]

FIGURE 12. AVERAGE NUMBER OF DRUGS GIVEN FOR OA BEFORE AND AFTER LIBRELA IN EUROPE (N=1199).[30] LIBRELA ACHIEVED THE OBJECTIVE OF REDUCING THE NUMBER OF MEDICATIONS.

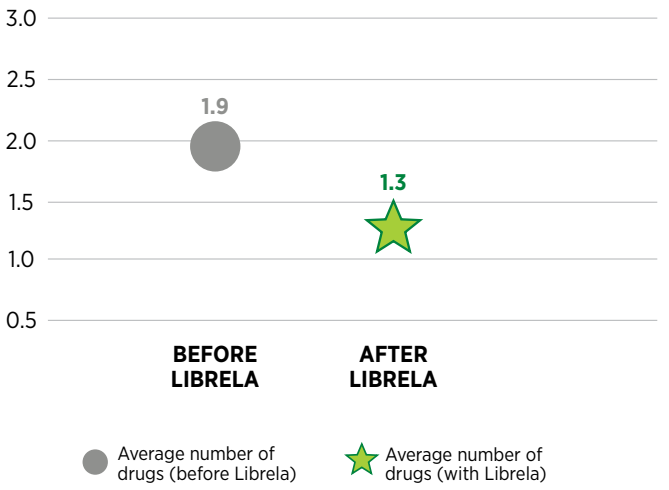
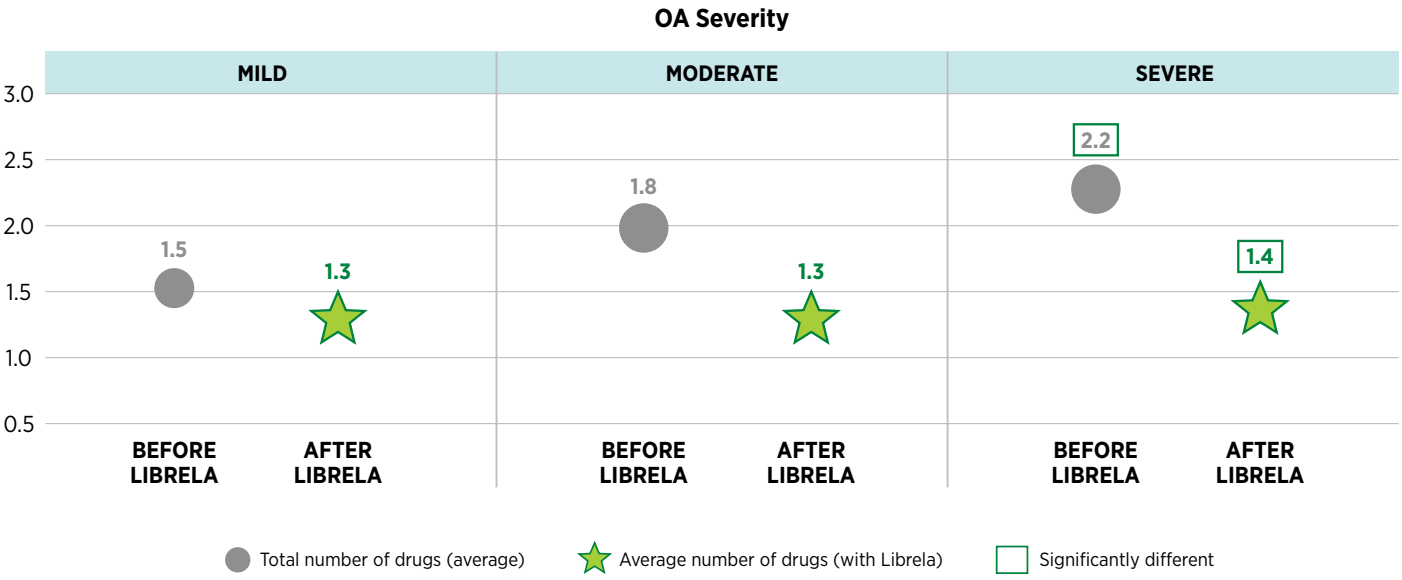


FIGURE 13. AVERAGE NUMBER OF DRUGS GIVEN FOR OA IN EUROPE BEFORE AND AFTER LIBRELA IN DOGS WITH MILD, MODERATE, AND SEVERE OA (N=1199).[30]



Librela (bedinvetmab injection)

A LOOK AT SAFETY

Safety Summary

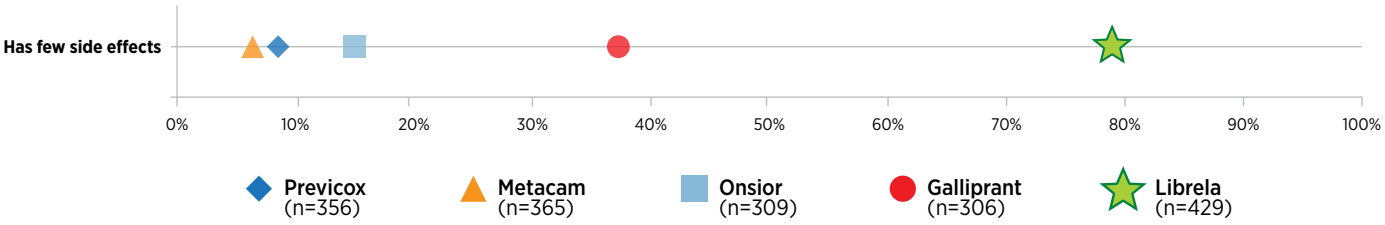
As a monoclonal antibody, Librela is very different from classical small molecule drugs. It functions more like naturally occurring antibodies and is eliminated via normal protein degradation pathways.[9,24,25] The metabolism of Librela has minimal involvement of the liver and kidneys, and safety studies showed little impact on the GI tract.[9,24,25] During the pivotal clinical trials, no interactions with other medications were identified. In these trials, Librela was administered together with other commonly used medications, including parasiticides and antibiotics.[32-34]

In the US study, the most common adverse events were urinary tract infection, bacterial skin infection, and dermatitis. These were reported at a similar incidence as the control group. In the EU study, the most common adverse event was increased blood urea nitrogen (BUN); for the vast majority of dogs with an elevated BUN, there were no clinical signs or elevations of other renal parameters. Other adverse events reported at a low rate included lethargy, emesis, and anorexia. Adverse events reported were similar to what would be expected for this population of dogs with OA.[9,21,26,35]

Veterinarian Perception of Safety in Market Research Studies

When veterinarians who have used Librela were surveyed, satisfaction with safety rated very highly and often much higher than for NSAIDs (**Figure 14**).[29]

FIGURE 14. VETERINARIANS REPORTED THAT LIBRELA HAS FEW SIDE EFFECTS COMPARED WITH OTHER TREATMENTS.[29]



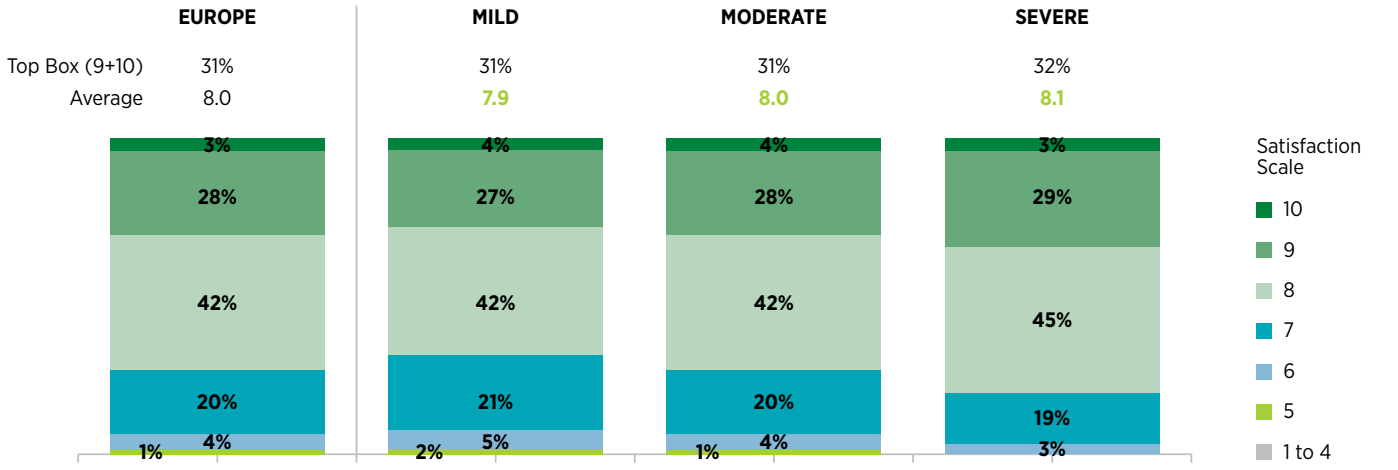
Librela (bedinvetmab injection)

VETERINARIAN SATISFACTION

Satisfaction with Librela among veterinarians across Europe has been extremely high. When asked to rate satisfaction on a scale from 1 to 10, with 1 = not satisfied at all and 10 = fully satisfied, 31% rated their satisfaction with Librela at 9 or 10, 42% at 8, 20% at 7, with only 4% at 6 or below (**Figure 15**).[30]

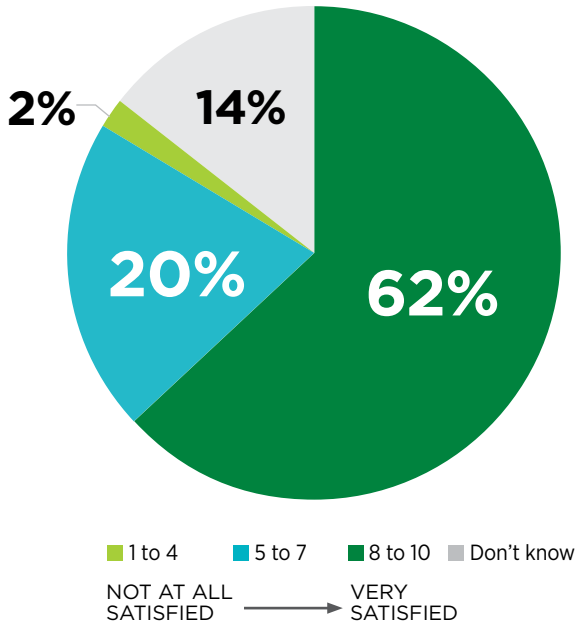
Similar satisfaction levels were reported in patient cases that received a previous OA pain treatment before Librela (8.1) and the ones that didn't (7.9).[26] Satisfaction level increased from one Librela dose to the next, especially after 5 to 6 doses. Furthermore, Librela satisfaction levels remained similar for all OA severity stages (**Figure 15**).[30]

FIGURE 15. LIBRELA SATISFACTION LEVELS AMONG VETERINARIANS IN EUROPE ON A SCALE OF 1-10 (N=1932 DOGS).[30]



This high level of satisfaction was also seen in a separate market research study with 580 veterinarians across Europe; 62% were very satisfied with Librela, giving it a rating of 8-10 on a scale of 1 to 10, with an overall average rating of 8 out of 10 (**Figure 16**).[29]

FIGURE 16. OVERALL VETERINARIAN SATISFACTION WITH LIBRELA IN EUROPE ON A SCALE OF 1-10 (N=580).[29]

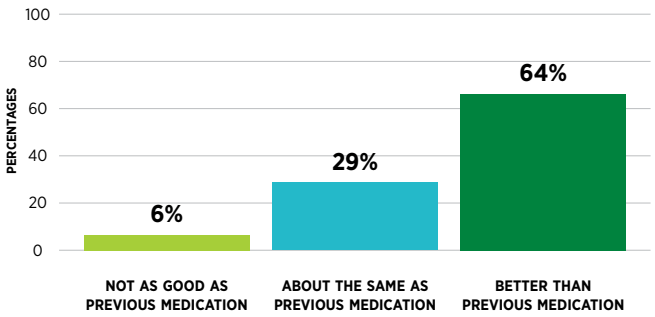


Librela (bedinvetmab injection)

PET OWNER SATISFACTION

Librela was rated better than previous medications by approximately two-thirds of dog owners (**Figure 17**).[5] Owner satisfaction with the effectiveness of Librela in reducing their dog's OA pain compared with other OA pain medications was 64%.

FIGURE 17. OWNER SATISFACTION WITH LIBRELA COMPARED WITH OTHER PAIN MEDICATIONS TO ALLEVIATE OA PAIN.[5] LIBRELA WAS RATED BETTER THAN PREVIOUS MEDICATIONS BY ~2/3 OF OWNERS (N=143).

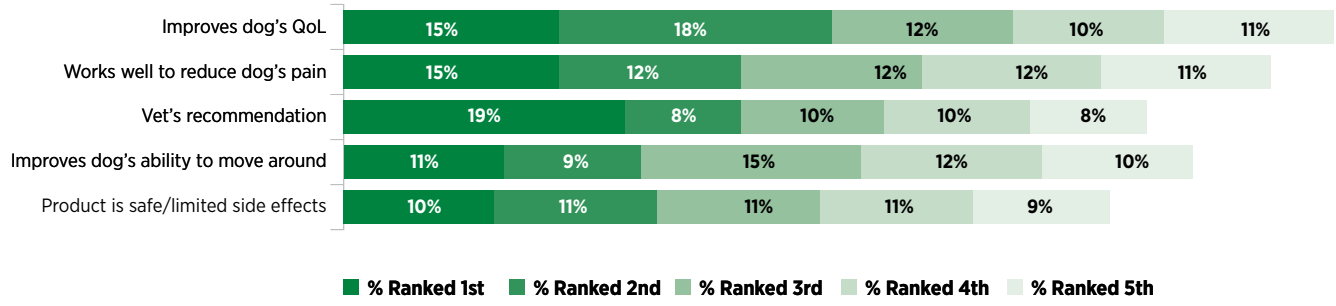


"The dog was much better after a short time, no more panting and quieter nights. He has also become more active."

– Dog owner, Germany[5]

The top 2 reasons that motivated pet owners to select a certain product for their dog with OA mirrored those of their veterinarians, including "improving their dog's quality of life" and "works well to reduce dog's pain" (**Figure 18**).[5] The third most important reason for OA product selection was their veterinarian's recommendation.

FIGURE 18. TOP ATTRIBUTES FOR OA PRODUCT SELECTION ON A 5-POINT SCALE ACCORDING TO PET OWNERS (N=143).[5]



Veterinarians prescribing Librela can anticipate a strong level of dog owner satisfaction

Librela™ (bedinvetmab injection)

PERCEPTIONS OF COST

An online survey completed by 375 veterinarians and 500 pet owners showed that veterinarians and pet owners have differing perceptions on the treatment cost with Librela.[5] When considering the benefits of Librela, the majority of veterinarians perceived Librela to be expensive but reasonable, while the majority of dog owners rated Librela as a good value product (**Table 3**).

TABLE 3. VETERINARIAN COST PERCEPTION OF CANINE OA PAIN TREATMENT WITH LIBRELA (N=375).[5]

	Veterinarians	Pet Owners
Inexpensive		**7%**
Good value	10%	**44%**
Expensive but reasonable	**59%**	**37%**
Very expensive	29%	10%
Too expensive	2%	1%

88%

believed cost to be inexpensive, a good value, or expensive but reasonable

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Librela™
(bedinvetmab injection)

LIBRELA: A NEW ERA IN OA PAIN MANAGEMENT

Canine OA is highly prevalent but challenging to diagnose and treat

- Chronic pain negatively impacts mobility, cognitive function, affect, and relationships[1]
- Diagnosis increases the likelihood of treatment with proven medications; however, OA remains underdiagnosed[5,11,15]
- Current treatments are effective but have limitations[1-6]

Librela offers a new option for the management of OA pain

- First injectable monthly antibody developed to control canine OA pain
- One subcutaneous injection, delivered in clinic, controls OA pain for 1 month[9]

Veterinarians report broad, first-line use of Librela for dogs with OA pain[5,29,30]

- More than 4.6 million doses experienced since launch in EU (as of November 2022)
- Dogs of all ages and sizes, with mild, moderate, and severe disease[29,30]
- Dogs newly and previously diagnosed with OA pain, many with comorbidities at the start of treatment

Clinical trial experience[9,21,26]

- Significant effects on pain interference, pain severity, and quality of life as soon as Day 7; efficacy maintained through the full 9 months
- Librela was well tolerated with few GI side effects; the most common adverse events were urinary tract infection, bacterial skin infection, dermatitis, and elevated BUN*

Highly rated by veterinarians in real-world clinical practice

- High levels of satisfaction for pain reduction, improved mobility, improved quality of life, and safety/tolerability across all stages of OA[5,29]
- High rates of compliance[30]

High level of pet owner satisfaction

- Rated better than previous medications by approximately two-thirds (64%) of dog owners[5]
- Cost rated as inexpensive, a good value, or expensive but reasonable by 88% of dog owners[5]

*For the vast majority of dogs with elevated BUN, there were no associated clinical signs or changes in other renal parameters.

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

zoetis

Librela™
(bedinvetmab injection)

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

Single-Use Vial

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

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

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

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

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

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

Table 1. Dosing Table

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

REFERENCES

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

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

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