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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Librela (EMEA/V/C/005180/0000)

Vaccine common name: bedinvetmab

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted

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Introduction

The applicant Zoetis Belgium SA submitted on 5 September 2019 an application for a marketing authorisation to the European Medicines Agency (the Agency) for Librela, through the centralised procedure under Article 3(1) of Regulation (EC) No 726/2004 (mandatory scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 11 October 2018 as Librela has been developed by means of a biotechnological process (monoclonal antibody methods).

The indication is: For the alleviation of pain associated with osteoarthritis in dogs.

The active substance of Librela is bedinvetmab, a canine monoclonal antibody targeting nerve growth factor (NGF), expressed through recombinant techniques in Chinese hamster ovary (CHO) cells, which inhibits NGF-mediated cell signalling to provide relief from pain associated with osteoarthritis. The target species is dog. The product is intended for administration by subcutaneous use.

Librela solution for injection contains 5 mg/ml, 10 mg/ml, 15 mg/ml, 20 mg/ml or 30 mg/ml bedinvetmab and is presented in packs containing 1, 2 or 6 vials of 1 ml each.

The rapporteur appointed is Frida Hasslung Wikström and the co-rapporteur is Gerrit Johan Schefferlie.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC – full application.

Marketing authorisation under exceptional circumstances

Not applicable.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system (dated 28 May 2018) which fulfils the requirements of Directive 2001/82/EC was provided. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Manufacture of the final product takes place at Zoetis Belgium. This site holds a valid GMP certificate.

GMP declaration for the active substance manufacturing site Zoetis Lincoln, USA was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by the manufacturing site responsible for batch release.

New active substance status

Bedinvetmab (INN) is a canine immunoglobulin G2 (IgG2) monoclonal antibody that binds to canine nerve growth factor (NGF), preventing NGF binding to its cellular receptor TrkA, and therefore reducing pain. This is the main mode of action. Bedinvetmab is intended for the alleviation of pain associated with osteoarthritis in dogs.

Bedinvetmab is produced in CHO cells by recombinant DNA technology.

Bedinvetmab is a biologically active substance not previously authorised as a medicinal product in the European Union. There is no essentially similar medicinal product authorised in the community, or has not been a previously authorised medicinal product, which is comparable in the manufacturing and safety to Librela.

Based on the review of the data the Rapporteurs consider that the active substance bedinvetmab contained in the medicinal product Librela is to be qualified as a new active substance.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of the active substance and of the finished product manufacturing site have been satisfactorily established and are in line with legal requirements.

It can be concluded that bedinvetmab contained in the medicinal product Librela is a new biological molecule that has never been authorised in the European Union, and that bedinvetmab is to be qualified as a new active substance.

Part 2 – Quality

Chemical, pharmaceutical and biological/microbiological information (quality)

Qualitative and quantitative particulars of the constituents

Qualitative and quantitative particulars

Librela is a sterile solution for injection for use in dogs, containing bedinvetmab (the active substance) at five different strengths (5, 10, 15, 20 and 30 mg/ml) and excipients (L-histidine, histidine hydrochloride monohydrate, trehalose dihydrate, disodium EDTA dihydrate, L-methionine, Poloxamer 188 Bio and water for injections). All excipients are of Ph. Eur. standards.

Container closure

Drug product

The drug product (DP) is presented in single dose type I glass, 4 ml vials closed with rubber stoppers and aluminium caps. Both the vial and stopper are of Ph. Eur. quality; the vials are compliant with Ph. Eur. 3.2.1, the rubber stoppers to Ph. Eur. 3.2.9, and their sterilisation is adequate.

The stability data on drug product have been generated with this container/closure system.

The provided information on container/closure for the drug product is found acceptable.

Formulated drug substance

Bedinvetmab formulated drug substance (FDS) is stored in disposable, sterile, ready-to-use bioprocess bags. The bags are sterilised by gamma irradiation.

Certificates of release have been provided for all bag sizes, declaring compliance with compendial requirement. Further, certificates of irradiation are provided.

Qualification testing has been conducted by the supplier and Zoetis. Compendial requirements for plastics, extractable/leachable materials, manufacturing, sterilisation process have been completed as part of the qualification of the container. In general, the information provided in this section is considered acceptable.

Characterisation and elucidation of structure

Bedinvetmab (ZTS-00508841) is an immunoglobulin G2 (IgG2) monoclonal antibody (mAb) produced in mammalian cell culture. Bedinvetmab is intended for the alleviation of pain associated with osteoarthritis in dogs. The antibody binds to canine nerve growth factor (NGF), preventing NGF binding to its cellular receptor TrkA, and therefore reducing pain. This is the main mode of action.

The molecule has been engineered to eliminate antibody effector functions (antibody-dependent cell-mediated cytotoxicity [ADCC] and complement-dependent cytotoxicity [CDC]). Effector functions have therefore not been investigated.

Characterisation and elucidation of bedinvetmab has in general been acceptably performed. An extensive characterisation package has been presented. Primary, secondary and higher order structures have been elucidated demonstrating a typical mAb structure, including two heavy and two light chains connected by disulphide bonds. Post-translational modifications include glycosylation and deamidation.

Biological activity has been characterised by two analytical methods, and correlation between the two methods has been successfully shown.

Process-related impurities are briefly discussed on a qualitative basis and no quantitative results are provided. This is acceptable, since results demonstrating sufficient clearance are presented during process validation studies.

Product development

Formulated drug substance

The process development is in general well described. Both design of experiment (DOE) and one factor at a time (OFAT) experiments have been executed and the results for each step are described briefly.

The downstream process characterisation is described with sufficient amount of detail. Each step is described separately, with information on DOE/OFAT studies, results and conclusions. The conclusions, the criticality designation and proposed acceptable ranges (PARs) are in general supported. The applicant has narrowed the ranges tested in characterisation for the parameters with significant impact on a quality attribute. This is endorsed. These parameters are in most cases classified as key process parameters (KPPs).

Drug product

Comprehensive studies were performed on formulation development, targeted to develop a ready-to-use sterile solution for use in dogs. These studies included pre-formulation characterisation and formulation development and optimisation, in which the composition of the final formulation was justified. This final formulation has been used when manufacturing of the drug product used in the field studies.

Description of the manufacturing method

Formulated drug substance

The Zoetis Lincoln, USA, site is the intended commercial production site for bedinvetmab FDS. The information provided on the manufacturer of bedinvetmab FDS is found sufficient.

The bedinvetmab FDS is expressed in Chinese hamster ovary (CHO) cells. The process is initiated by thawing of one vial of the working cell bank (WCB). The cells are then expanded by successive cultivation in shake flasks and stirred tank bioreactors until sufficient cells are available to seed the production bioreactor. The product, bedinvetmab, is secreted into the culture medium. At harvest, the culture supernatant is separated from the cells and cell debris by continuous flow disc-stack centrifugation followed by a series of filtration steps to isolate product in a cell-free medium.

Cell-free medium containing bedinvetmab is further processed through a series of purification steps. No reprocessing is described, and thus not allowed.

In general, the FDS process description is acceptable.

Drug product

The bedinvetmab DP is manufactured at Zoetis Belgium. The same site is responsible for quality control (QC) testing and for QP release. The information provided on manufacturer of bedinvetmab DP is found sufficient. A flow diagram describing the proposed commercial scale operations involved in the manufacturing process has been provided, as well as a description of the manufacturing process and controls and batch formula.

The manufacturing process is acceptably described.

No reprocessing is claimed by the applicant.

Control of critical steps and intermediates

Critical and key process parameters (CPPs and KPPs) are together with key process attributes (KPAs) listed in the dossier.

Process validation

Validation of the FDS process has been acceptably demonstrated. It is agreed upon that the data provided support the claim of consistent FDS production at the Zoetis Lincoln site.

All validation results complied with the acceptance criteria in the DP specification and are in support for a consistent performance of the manufacturing process.

Virus clearance validation

Virus clearance has been sufficiently established.

Starting materials

Starting materials listed in pharmacopoeias

Certificates of analysis (CoA) have been provided and all conform to specifications in the Ph. Eur.

Starting materials not listed in a pharmacopoeia

No starting materials of animal or human origin, beside the cell bank, are used during the production of bedinvetmab. The applicant has provided an example CoA for each starting material, including materials used during cell banking. The results show that the starting materials are tested in line with the Ph. Eur. requirements. Further, certificates of non-animal origin/TSE-BSE statements are also provided for the raw materials.

Starting materials of biological origin

Bedinvetmab is expressed in a CHO cell line. The source, history and generation of the cell substrate is described in sufficient detail. The applicant has adequately described the host cell, design and construction of the plasmid DNA, the transfection procedure, screening for anti-NGF antibodies in pools, and finally selection of a single clone, which was later used in the production of the master cell bank (MCB) and the working cell bank (WCB).

The manufacturing process of MCB/WCB has been sufficiently described. The extraneous agents testing, and characterisation of the MCB/WCB/EOP cells have been executed in most cases in accordance to ICH Q5A, Ph. Eur. 5.2.4 and EMA/CVMP/IWP/206555/2010 (Guideline on requirements for the production and control of immunological veterinary medicinal products, Annex 2). All methods used and results obtained during characterisation have been described in the dossier, including references to pharmacopoeia monographs, when relevant. In general, the extended testing and characterisation of MCB/WCB/EOP is acceptably performed.

During the development of the cell banks, material of animal origin was used. The origin of the raw material has been stated and a TSE/BSE risk assessment demonstrated that the risk is negligible. Extraneous agents specific for hamster (cell origin) and canine (intended species) have been tested on both MCB and WCB. The level of tests performed is considered in accordance with guidelines.

Genetic stability testing has been executed.

Starting materials of non-biological origin

Chromatography resins; certificates of analysis have been provided.

In-house preparation of media and solutions consisting of several components

Information regarding the qualitative and quantitative composition of all culture media and their storage conditions is provided in the dossier.

Control tests during the manufacturing process

The proposed FDS release specification includes analyses of appearance, specific activity, identity, pH, total protein, purity, impurities and microbiology analyses. In general, the methods proposed for inclusion in the FDS release specification are found acceptable.

Justifications of the FDS specification have been summarised for all FDS release assays. The limits have been chosen based on release and stability results from VICH registration and clinical batches. The approach and the proposed limits are in general found to be acceptable and clinically qualified.

A few tests were proposed to be excluded in the FDS specification. The exclusion of the proposed tests is found acceptable.

The main part of the analytical methods included in the FDS specification is also included in the DP specification.

The analytical methods used for analysis of bedinvetmab include both product-specific as well as pharmacopoeial methods. The product-specific analytical methods have been provided for review while the compendium-based test methods have been stated to be in line with the respective Ph. Eur. monographs. The product-specific analytical procedures were satisfactorily validated in accordance with the guidance given in VICH GL2 and are found acceptable.

Identification/specific activity for bedinvetmab

An analytical method is used for identification as well as for determination of specific activity of bedinvetmab and the test is applicable to both FDS and DP. The description of the method has been provided. The method has been validated in line with VICH GL2. The method is linear within a suitable range, and specificity, accuracy, precision and robustness have been demonstrated. The description and validation of the method is acceptable.

Control tests on the finished product

The release specifications for the DP have been provided and relevant tests are included (visual appearance, specific activity, pH, total protein, % of monomer, % of fragments, osmolality, bacterial endotoxins, sterility, etc.). The justification for the specifications is found acceptable. The proposed acceptance criteria are based on VICH registration batches and their release and stability data and all batches met the proposed specifications. The proposed acceptance criteria are in general deemed acceptable and judged as clinically qualified. The end-of-shelf-life specification has been included in the dossier.

The section on drug product specifications is found acceptable.

Reference standard

Two reference standards are currently available for the Librela process. Although it is desirable to use the same reference standard for all relevant analysis, it is acceptable to use separate reference standards for the biological assay and for physicochemical testing.

Batch-to-batch consistency

Formulated drug substance

Analytical release data from bedinvetmab FDS batches are provided in the dossier, including results from the VICH registration batches and validation batches. Further, results on characterisation analyses not included in the proposed release specification are presented. This approach is endorsed and supports the claim to exclude analyses from the specification.

Comparison of quality attributes using material produced at the two FDS manufacturing sites demonstrates similar patterns with respect to FDS release specification analyses.

Drug product

Batch analyses data for Librela drug product lots have been provided.

All clinical EU batches are manufactured at a reduced scale. The applicant has also provided analytical results for US clinical batches.

All the batch analysis data presented comply with the limits in the proposed drug product release specifications and confirm product consistency. In conclusion, the provided batch data demonstrate in general a reproducible manufacturing of Librela drug product.

Stability

Formulated drug substance

The proposed shelf life for FDS is 24 months at the recommended storage conditions and this is considered acceptable.

Drug product

The proposed shelf-life of the drug product of 24 months at the recommended storage conditions at +2 to +8 °C is found acceptable. The results from the ongoing primary stability studies will be provided. The drug product should always be stored in the secondary package as described in the SPC.

Overall conclusions on quality

Bedinvetmab (ZTS-00508841) is an IgG2 monoclonal antibody produced in CHO cells. Librela, in which bedinvetmab is the active substance, is proposed to be used for the alleviation of pain associated with degenerative joint disease such as osteoarthritis in dogs. The antibody binds to canine nerve growth factor, preventing NGF binding to its cellular receptor TrkA, and therefore reducing pain. This is the main mode of action.

Librela is a sterile solution for injection for use in dogs; it contains bedinvetmab at five different strengths (5, 10, 15, 20 and 30 mg/ml) and excipients. The product is presented in single dose type I glass vials with a volume of 1 ml, and the vials are closed with rubber stoppers and aluminium caps.

Information on development, characterisation, manufacturing and control of the active substance and the drug product has been presented in a satisfactory manner. The proposed shelf life of the drug product of 24 months at the recommended storage conditions at +2 to +8 °C is found acceptable. However, the results from the ongoing primary stability studies should be provided post authorisation (recommendation).

Part 3 – Safety

Introduction and general requirements

The active substance of Librela, bedinvetmab, a monoclonal antibody (mAb), is a new active substance not authorised for a veterinary medicinal product in the EU before. A full safety file in accordance with Article 12(3)(j) has been provided.

Librela (bedinvetmab) is a canine mAb for use in dogs for the alleviation of pain associated with osteoarthritis (OA). The product is proposed to be administered monthly, at a minimum dose of 0.5 mg/kg body weight subcutaneously. There is no proposed limit of the duration of treatment. Vial presentations at various concentrations (5, 10, 15, 20, and 30 mg/ml) will be delivered at a fixed 1 ml injection volume. The vial concentration and the number of vials to be used vary with body weight, resulting in an effective dose range of 0.5 – 1 mg/kg body weight.

Librela is a biological product and has been classified by the EMA and submitted as an immunological veterinary medicinal product. However, since the product is not intended to provide active or passive immunity following administration to the target species, not all the requirements for safety testing for immunological veterinary medicinal products as outlined in Annex I of Directive 2001/82/EC, as amended, are relevant. The applicant has highlighted the limited guidance available for this type of product with respect to the data requirements, albeit reference is made to the 'Questions and Answers on monoclonal antibodies for veterinary use' (EMA/CVMP/ADVENT/307606/2017).

The applicant refers to Section 6 of the ADVENT Q&A document, which discusses safety evaluation topics specifically related to mAbs, emphasising *a priori* risk assessment and the principle that safety testing should therefore be considered on a case-by-case basis, taking into account, amongst other aspects, the properties of the mAb, the target of the mAb, the downstream effects of neutralising the target function, and the potential off-target effects.

The applicant presented an overview of the potential risk that may be associated with the use of Librela, summarised as follows:

- Nerve growth factor (NGF) effects have typically been evaluated in terms of the interaction with the TrkA receptor and p75NTR, but NGF signalling is more complex. NGF, TrkA, or p75NTR, alone or in combination, can produce effects via interactions with other receptors such as sortilin, integrin α9β1 receptor, and NRH2. NGF and its pro-peptide form, pro-NGF, bind with and interact with multiple receptors along with or independently of TrkA. NGF and its receptors are expressed widely.

- NGF is well recognised for its role in the pain response, including osteoarthritis pain. However, NGF signalling is a factor in many adaptive responses other than pain, some of which could be adversely affected by inhibition of NGF signalling.
- NGF is crucial to normal development and maturation; in adults, NGF has a role in maintaining normal neuronal differentiation, including control of sensory neurotransmitter and neuropeptide synthesis, and expression of tyrosine hydroxylase in adrenergic nerves. In skeletal muscle, NGF is involved in inflammation and repair, including following strenuous exertion. In heart, NGF has a crucial role in maintaining sensory nerve supply and in contributing to a proper sympathetic - parasympathetic innervation balance; disruptions in sensory or adrenergic function are known factors underlying sudden cardiac death in specific disease states. In peripheral vasculature, innervation contributes to vasomotor control, including via norepinephrine and neuropeptides. NGF, in concert with vascular endothelial growth factor (VEGF), is a factor in wound healing responses. In the kidney and bladder, in the respiratory system, and the gastrointestinal (GI) system, NGF is a component of both beneficial and adverse processes. NGF has modulating roles in endocrine functions including pancreatic, adrenomedullary, and pituitary, and in immune function.
- Inference from specific NGF literature to potential risks in veterinary patients is aided by considering that NGF-mediated effects on sensory and sympathetic nerve encompass autonomic nervous system function. Autonomic regulation of body functions is based on specific neuronal pathways in the periphery and a specific organisation of neural circuits connected to these pathways in the central nervous system (CNS). CNS continuously receives sensory neural, hormonal and humoral monitoring signals reflecting the mechanical, thermal, metabolic and chemical states of the tissues, including monitoring of gut microbiota, external infection pressure, and others. This information is relayed via nerves to various peripheral nervous system (PNS) and CNS levels, up to and including brain. At any or all levels, a reflex efferent response may be triggered.

Potential impact:

- The NGF dependency of the system of afferents and efferents, reflex arcs, and central oversight suggest a potential for disruption of a range of adaptive responses by interference with NGF-dependent elements. Systems potentially at risk include heart/cardiovascular, immune, inflammation response/control, intestine, kidney, endocrine (pancreatic islet cells, adrenal gland, pituitary gland), and energy allocation and metabolism, to name a few.
- In addition to the homeostatic mechanisms above, there are some NGF-dependent functions at local level that involve non-neural cell types. One example may be skin ulcers.

This review highlights the pleiotropic effects of NGF signalling, and that the potential for unwanted inhibition of NGF signalling, or off-target effects is reasonably high. The safety aspects specific to this product and their potential impact upon the target species are discussed in each of the studies below.

Safety documentation

Safety of the product was investigated in eight studies, including four laboratory studies and four field trials.

Study title
A 3-months exploratory safety study (once every 4 weeks) of ZTS-00508841 by subcutaneous injection in adult beagle dogs
A 6-months study of ZTS-00508841 by subcutaneous injection in adult beagle dogs

Study title
A 2-week safety study of ZTS-00508841 when administered to beagle dogs receiving concurrent NSAID
T-cell dependent immune response in dogs treated with ZTS-00508841
A double-masked, randomized, negative-controlled, multicenter trial investigating four dose levels of (another anti-NGF mAb candidate), a caninized anti-canine-NGF monoclonal antibody, administered subcutaneously for the treatment of clinical signs of osteoarthritis in dogs
EU field study efficacy and safety of ZTS-00508841 compared to placebo for the treatment of pain associated with osteoarthritis in client-owned dogs
Field safety and efficacy of ZTS-00508841 compared to placebo for treatment of pain associated with osteoarthritis in dogs
Continuation therapy with ZTS-00508841 for the treatment of pain associated with osteoarthritis in client-owned dogs

Laboratory tests

One exploratory target animal safety (TAS) study and one pivotal TAS study were conducted, which investigated the safety of the administration of one dose, an overdose, and the repeated administration of one dose (note that the studies are discussed under section 'Safety of the repeated administration of an overdose'). In addition, one laboratory safety study was conducted to investigate the effect of treatment on immunological function, and one study was conducted to investigate the safety of Librela co-administered with non-steroidal anti-inflammatory drugs (NSAIDs).

Safety of the administration of one dose

Refer to 'Safety of the repeated administration of one dose'.

Safety of one administration of an overdose

Refer to 'Safety of the repeated administration of one dose'.

Safety of the repeated administration of one dose

Safety of the administration of one dose, an overdose and repeated administration of one dose was examined in one exploratory target animal safety (TAS) study and in one pivotal TAS study.

Exploratory TAS study

This was a non–GLP compliant, exploratory safety study, which investigated the safety of four consecutive monthly subcutaneous administrations of the veterinary medicinal product at 1X, 4X, and 12X the maximum recommended therapeutic dose (RTD) of bedinvetmab (1 mg/kg body weight) in groups of 8 healthy dogs compared to placebo. The product was not the final formulation and limited batch data are available.

The results demonstrated that all doses were generally well-tolerated. Perivascular mononuclear infiltrate at the injection site was observed at histopathology in the treated animals. However, these findings were minimal to mild and overall results showed that the product was well tolerated, with few injection site reactions reported in the field studies, at a similar frequency to injection with saline. No test article-related effects on clinical pathology parameters were demonstrated. One animal in the 4X RTD group was positive for anti-drug antibodies (ADAs) at one of several sampling time points, but this finding is

considered incidental since the titres were close to cut-off and concentrations of bedinvetmab and NGF in this animal did not suggest clearing or neutralising antibodies.

This study is considered supportive due to the non-GLP status and that a non-final formulation with limited batch data was used.

Pivotal TAS study

This was a GLP compliant, pivotal TAS study, which investigated the safety of seven consecutive monthly subcutaneous administrations of Librela at 1X, 3X, and 10X the maximum RTD of bedinvetmab (1 mg/kg body weight) in groups of eight healthy beagle dogs aged 11-12 months, compared to placebo (saline). The investigational veterinary medicinal product (IVMP) was the final formulation. This was a comprehensive study which included safety evaluation in accordance with VICH GL43 (target animal safety for veterinary pharmaceutical products). Parameters evaluated were clinical observations (including injection site and neurological examinations), clinical pathology, gross necropsy and histopathology (including all tissues known to express NFG and its receptor, evaluation of all lymphatic organs/tissues, and evaluations of joints), joint radiographs, evaluation of bedinvetmab concentrations, and development of anti-drug antibodies (ADAs). Animals were euthanised 14 or 15 days after the last dosing.

The results demonstrated that all doses were generally well tolerated. Focal granulomatous inflammation was observed in the superficial dermis at the injection sites in one animal in the 1X and in one animal in the 3X RTD group. Other local reactions, such as mild swelling and heat, were noted sporadically and at similar frequency in treated animals and controls.

A trend towards increased blood urea nitrogen (BUN) in treated animals compared to pre-treatment and to controls was observed. A similar trend was observed in two of the field studies. Although some of the test article-treated animals (stratified by sex) displayed statistically significant increase in BUN at some time points, decreased concentrations were also noted in some groups compared to controls. All the dogs had BUN concentrations within reference range. Hence, the present study did not raise any concerns about treatment-related effect on BUN concentrations.

One animal in the 3X RTD group had signs of mild degenerative joint disease (DJD) of the right hip pre-treatment and moderate DJD post-treatment. Severe hip dysplasia was the suspected cause. In addition, one animal in the 3X group and one animal in the control group showed deteriorating signs of DJD (although the signs were mild). These findings were considered incidental.

Two animals in the control group were positive for ADAs at occasional time points (2.9% of all screened samples). Considering that the titres were close to cut-off and that the assay was designed to have a false positive rate of 1%, the positive samples are not considered unexpected. No animals in test article-treated groups developed ADAs.

In conclusion, a possible Librela-related effect of mild inflammation at the injection site was noted and these findings are accurately reflected in the product information.

Examination of reproductive performance

No reproductive studies were provided. The applicant has proposed that the product is contraindicated for use in animals intended for breeding, in addition to pregnant or lactating animals.

The product may present a risk if used in pregnant bitches given that antibodies are actively transported across the placenta in dogs and consequently, use of an anti-NGF mAb in pregnant bitches may result in

abnormal neuronal development in the developing foetuses (as reported in other species). The absence of reproductive studies is acceptable as the use of Librela in pregnant or lactating animals is contraindicated (SPC section 4.7) in addition to a contraindication for use in animals intended for breeding (SPC section 4.3).

Examination of immunological functions

Possible effects on immunological functions were evaluated by enhanced immunopathology evaluation on immune tissues in the pivotal TAS study, monitoring of clinical health status in the field trials, and by the T-cell dependent antibody response test (TDAR). The TAS studies and the TDAR study did not give rise to any concerns regarding effects on immunological functions, but in two of the field studies the use of systemic antibacterial products was higher in the test article-treated dogs than in controls. Based on a summary of data from all the field studies and presented causes for treatment, overall 10.5% of test article-treated dogs were treated with systemic antibacterial products compared to 8.2% in control dogs. The antibacterial products were prescribed for a wide variety of indications and there were no signs of increased use over time. It was accepted that there were no other indications from the clinical studies that Librela would cause immunosuppression and that the small difference observed between test article-treated dogs and controls likely represented sporadic events.

Immunogenicity (development of anti-drug antibodies – ADAs) was evaluated in the laboratory trials and in the field studies. Samples for ADA detection were collected before treatment, and at various time points after treatment and analysed using a multi-tier strategy of screening, confirmatory, and titre determination with a fully validated method. Results demonstrated that immunogenicity was low. Treatment-induced immunogenicity was noted in 3/270 (1.1%) of Librela-treated animals in the field studies. In two of these animals decreased bedinvetmab and NGF concentrations suggested neutralising or clearing antibodies. The possibility of ADA induction is addressed through appropriate warnings in the SPC:

"This veterinary medicinal product may induce transient or persistent anti-drug antibodies. The induction of such antibodies is uncommon and may have no effect or may result in a decrease in efficacy in animals that responded to treatment previously."

<u>T-cell dependent antibody response test (TDAR) study</u>

The examination of immunological functions was undertaken in a GLP-compliant laboratory study using the T-cell dependent antibody response test (TDAR) as a method to determine if immune function was impaired following treatment with Librela. The immune response to a model antigen Keyhole limpet haemocyanin (KLH) was evaluated in dogs treated with Librela at the recommended dose (1 mg/kg bw), in comparison to dogs treated with placebo. KLH was administered without adjuvant at two dose levels; low dose (0.1 mg/dog) and high dose (1 mg/dog). Two groups of eight dogs were treated with 1 mg/kg bw bedinvetmab (T03 and T04) or placebo (T01 and T02), three times. The second dose was administered 28 days after the first administration, and the third dose 21 days after the previous administration (*i.e.* with a shorter interval than the proposed treatment interval of 28 days). KLH antigen was administered to all animals at day 34 and day 55. The primary endpoint was the T-cell antibody response (*i.e.* KLH antibody titres measured by ELISA) on days 62 and 71. Additional endpoint parameters were IL-2 production (IL-2 ELISpot) and lymphoproliferation. In addition to the TDAR, safety parameters, plasma bedinvetmab concentration, and ADAs were evaluated within the study until day 71 (3 weeks after the last test article administration).

The results demonstrated that on days 61 and 71, after the second administration of KLH, there was a clear response in antibody titres across all groups. The increase was slightly higher in dogs immunised with high dose KLH than with low dose KLH, but the titres were similar in test article-treated animals compared to controls.

The secondary parameters, IL-2 ELISpot and lymphoproliferation, did not provide robust results. This was accepted since the antibody response (primary endpoint) was considered the most relevant to evaluate the immune response.

The few abnormal clinical observations observed during the study appeared to be sporadic events and unrelated to treatment. In conclusion, administration with Librela three times at 1X the RTD of bedinvetmab was well tolerated and did not have an effect on the primary endpoint KLH antibody titres. It can be accepted that under the conditions of the study, there was no evidence of immunosuppression.

User safety

The Applicant has provided a user safety assessment in accordance with CVMP guideline EMEA/CVMP/IWP/54533/2006.

The main potential routes of accidental contact with the product have been considered and it is agreed that the main risk to the user is likely to be associated with accidental self-injection. Accidental subcutaneous injection of dose volumes up to 0.2 ml (6 mg) could occur very rarely and could produce systemic exposures and potential for pharmacodynamic responses for as long as 6 days. With respect to target effects, the applicant states that the binding epitope in canine NGF is similar to that in humans, and bedinvetmab has been shown to bind human NGF, thus there are potential mechanism of action-related risks associated with human parenteral exposure to bedinvetmab. An extended assessment was provided concluding that a single exposure of 6 mg of bedinvetmab is very unlikely to produce paraesthesia or other sensory effects, nor any significant negative effects on pre-existing peripheral neuropathy. Potential adverse events should be reversible and only impact a very small sub-population of users (OA patients with pre-existing neuropathies). Therefore, information in SPC section 4.5 is not considered necessary. More importantly, NGF is known to be important to normal growth and development of the embryo/foetus, and exposure of gestating monkeys to a human anti-NGF mAb produced increased stillbirths, increased infant mortality, and induced some degree of developmental neurotoxicity in the offspring. In addition, the contents of the vial are expected to be immunogenic with repeated parenteral exposure. The range of clinical signs associated with an acquired immune response, resulting from parenteral exposure to any foreign protein, could range anywhere from clinically silent to acute anaphylaxis-type responses. On the basis of the assessment conducted, the applicant has proposed the following statements for inclusion in section 4.5 of the SPC:

"Hypersensitivity reactions, including anaphylaxis, could potentially occur in the case of accidental self-injection. Repeated self-administration may increase the risk of hypersensitivity reactions.

The importance of Nerve Growth Factor in ensuring normal foetal nervous system development is well-established and laboratory studies conducted on non-human primates with human anti-NGF antibodies have shown evidence of reproductive and developmental toxicity. Pregnant women, women trying to conceive and breastfeeding women should take extreme care to avoid accidental self-injection.

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

In the event of accidental parenteral exposure, three main risks are considered to arise: (a) the potential risk for the developing embryo/foetus; (b) the potential development of an immunological response; c) a potential pharmacological response.

The person administering the product will be a trained professional and although the risk of accidental self-injection exists, the likelihood of this event occurring is not expected to be any greater than for any other injectable formulation.

The suggested text is considered adequate.

Interactions

A two-week NSAID co-administration study was performed to study potential interactions of Librela with NSAID. In addition, during the field trials, Librela was administered concurrently with several other veterinary medicinal products and no specific drug interactions were reported. The following text is included in section 4.8 of the SPC:

"No other laboratory studies on the safety of concomitant administration of this veterinary medicinal product with other veterinary medicinal products have been conducted. No interactions were observed in field studies where this veterinary medicinal product was administered concomitantly with veterinary medicinal products containing parasiticides, antimicrobials, topical antiseptics with or without corticosteroids, antihistamines and vaccines.

If a vaccine(s) is to be administered at the same time as treatment with this veterinary medicinal product, the vaccine(s) should be administered at a different site to that of Librela's administration, to reduce any potential impact on immunogenicity of the vaccine."

NSAID co-administration study

This was a GLP-compliant laboratory study evaluating the safety of the administration of one dose of Librela (final formulation) in conjunction with an injected nonsteroidal anti-inflammatory drug (NSAID) given once daily for 14 days in healthy dogs. Eight dogs were administered a single dose of Librela at 1X the maximum RTD (1 mg/kg bw) at day 1 and received daily 4.4 mg/kg bw carprofen (1X RDT) administered subcutaneously for 14 consecutive days. Three control groups (eight animals per group) were included (placebo/placebo, Librela/placebo, placebo/carprofen). Parameters evaluated were clinical signs, clinical pathology, evaluation of bedinvetmab concentrations, gross necropsy, and histopathology. The animals were euthanised on the last day of the NSAID dosing.

The results demonstrated that a single subcutaneous injection of Librela with and without concurrent treatment with carprofen for 14 days was well tolerated in healthy animals. Overall, the few abnormal findings observed in controls and Librela-treated animals were mild and were not considered test article-related. Although it is accepted that no interactions were observed under these circumstances, these conditions cannot be considered representative of the clinical situation. The animals included were healthy beagle dogs without signs of osteoarthritis. Moreover, the duration of the study was short, and the number of animals administered both treatments was limited. In human studies, a negative interaction of anti-NGF mAbs with NSAIDs has been reported; drug:drug interactions were identified when tanezumab was administered concurrently with NSAIDs. The major risk was associated with chronic use (more than 90 days) and related to the occurrence of rapidly progressive osteoarthritis (RPOA). This condition has been reported in human patients receiving anti-NGF monoclonal therapy, with and without concurrent use of NSAIDs. However, long term co-administration with NSAIDs appears to increase the risk. The findings from the NSAID co-administration study are not intended to support

conclusions regarding safety of long-term concurrent use of Librela and NSAIDs. In the two pivotal field studies only ten dogs treated with Librela received concomitantly NSAIDs and only for a limited time. No negative interactions were observed in these studies. To summarise, there is no safety data on concurrent long-term use of NSAIDs in dogs but there is currently no indication that intermittent short-term co-administration of NSAIDs and Librela in dogs should pose a significant additional risk. The following information is included in SPC section 4.8:

"In a laboratory study over a 2-week period in young, healthy dogs without osteoarthritis, this veterinary medicinal product had no adverse effect when concomitantly administered with a non-steroidal anti-inflammatory product (carprofen).

There are no safety data on the concurrent long-term use of NSAIDs and bedinvetmab in dogs. In clinical trials in humans, rapidly progressive osteoarthritis has been reported in patients receiving humanised anti-NGF monoclonal antibody therapy. The incidence of these events increased with high doses and in those human patients that received long-term (more than 90 days) non-steroidal anti-inflammatory drugs (NSAIDs) concomitantly with an anti-NGF monoclonal antibody.

Dogs have no reported equivalent of human rapidly progressive osteoarthritis."

Field studies

One dose determination study and two pivotal field studies (one conducted in EU and one in the USA) are presented by the applicant. In addition, the applicant submitted an open-label, uncontrolled field study in support of long-term safety. Studies were conducted in client-owned dogs with osteoarthritis. The applied inclusion and exclusion criteria were similar in all the field studies, but in the dose determination study the criteria were further defined. Dogs had to be in good general health and with satisfactory clinical pathology results to be included in the field trials. Osteoarthritis typically affects older dogs, implying that a substantial proportion of the target population will be elderly individuals which are likely to often suffer from different concomitant diseases. Inclusion/exclusion criteria applied in the clinical studies were stringent and the study population in the field studies accurately reflected the intended target population. Dogs with stable comorbidities were not disqualified from entering the studies, and the criteria were applied to ensure that participating subjects would have a good chance of completing the trials, and to avoid confounding factors interfering with the determination of the results. Based on data from the field studies, and from human studies with anti-NGF mAbs, it was concluded that risks of treatment would not be higher in older dogs with comorbidities such as kidney and liver disease. It was accepted that there were no signs from the field studies that dogs treated with Librela were at higher risk of kidney disease or liver disease compared to placebo, regardless of their kidney and liver status at enrolment. Furthermore, based on data from the field studies, there was no evidence that the potential risk of treatment is higher in dogs with advanced degenerative joint disease.

<u>Dose determination study</u>

For dose determination, the applicant extrapolated from another anti-NGF mAb candidate to bedinvetmab, both molecules being very similar and targeting the same epitope.

This was a dose determination study performed under field conditions evaluating the efficacy, duration of effect, and safety of four dose levels (0.25 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg) of another anti-NGF mAb candidate administered as a single dose compared to placebo. This study was carried out according to good scientific practices and principles but did not comply fully with all the requirement of GCP. Three hundred and forty-six client-owned dogs with osteoarthritis were randomly allocated to one of five treatment groups. This other anti-NGF mAb candidate targets the same antigen but differs in composition

and pharmacokinetic properties from bedinvetmab (see part 4).

Animals were examined weekly and follow-up extended up to 56(±5) days after the administered dose. The overall frequency of adverse events was slightly higher in test article-treated animals compared to placebo (48.6% vs 41.4%). Systemic disorders, such as lethargy and anorexia were more frequently reported in test article-treated animals (10.5% vs 7.1%) as well as hepatobiliary disorders (5.1% vs 1.4%). The frequency of dogs with decreased RBC and HCT (compared to pre-treatment and to reference ranges) were higher in test article-treated animals (4.0%) compared to controls (0%). The frequency of animals with increased blood urea nitrogen (BUN) were higher in test article-treated animals (4.3%) than in controls (2.9%). Based on a review of the data from all the clinical studies, it was concluded that Librela was well tolerated.

In total, seven (2.5%) of the 276 test article-treated dogs had cranial cruciate ligament (CCL) injuries compared to 0% of the controls. Of these, five (8.9%) occurred in the 2X dose group. The recruitment of dogs to this group was stopped early due to this observation. Dogs with pre-existing conditions of the stifle were included in the pivotal field studies and the incidence of CCL injuries in these studies was low. In total, only two cases of CCL rupture (one of these occurred post-study) were reported in the dogs treated with Librela in the clinical field trials compared to four cases in the controls. It was also noted that no CCL ruptures were reported in the 6-month continuation study that was submitted in support of long-term safety. Based on the information from all the field trials it was accepted that treatment with Librela did not appear to increase the risk of CCL injuries.

Over 80 concomitant medications were administered with the test article. Antibacterial products for systemic use were administered more frequently in test article-treated animals (10.1%) compared to controls (7.1%). Ten dogs (3.6%) were concomitantly treated with NSAIDs and test article.

Overall, the data from the study suggest that administration of this other anti-NGF mAb candidate up to 1X the maximum RTD of bedinvetmab demonstrated an acceptable level of tolerance.

EU field trial

This pivotal GCP-compliant field study was a multicentre, placebo-controlled, randomised, blinded study in which 287 client-owned dogs with osteoarthritis were treated with Librela (n=141) at the proposed dose of 0.5-1 mg/kg bw or placebo (n=146), once monthly for three consecutive months. Follow-up extended to four weeks after the last administration. Safety parameters measured included clinical signs and clinical pathology parameters (haematology, serum biochemistry, and urinalysis). All animals were tested for ADAs at multiple time points and concentrations of bedinvetmab were measured.

The results showed that administration of Librela was generally well-tolerated. Systemic disorders such as lethargy and anorexia were more frequently reported in Librela-treated animals (5.1%) compared to controls (1.4%). Based on a summary of cases of lethargy and anorexia from all the field studies, the incidence was not significantly higher in dogs treated with Librela compared to controls, and it was accepted that no test article-related effect with respect to lethargy and anorexia was demonstrated.

Two cases of mild injection site reactions were reported, one in a control dog and one in a Librela-treated animal. Although the frequency of injection site reactions was low, observations only extended until approximately 30 min post administration and the next follow-up was 7 days after the administration. It is therefore possible that some local reactions at the injection site (which were noted in some of the laboratory studies) passed unnoticed. The present study did not raise any concern regarding possible adverse reactions related to CCL injury at the recommended treatment dose.

Results from clinical pathology demonstrated that the frequency of dogs with increased ALT, AST, and BUN concentrations (compared to both pre-treatment values and to reference ranges) were higher in the

Librela-treated group than in placebo. For RBC, Hb and PCV, the number of dogs with decreased values was slightly higher in the test article-treated group compared to controls. Based on a summary of these parameters from all clinical trials it was noted that the overall percentage of dogs with increased shift of ALT was similar in dogs treated with Librela compared to controls, and that no signs of hepatotoxic effects were seen. Regarding potential test article-related increase of BUN concentrations, the overall percentage of dogs with increased shift in BUN concentrations was slightly higher in dogs treated with Librela compared to controls. However, these appeared to be transient and sporadic events and they were not associated with increased creatinine concentration or with any clinical signs. Data were presented on all adverse events of anaemia (Librela=9 cases=1.8%, controls=1 case=0.3%). If excluding dogs with conditions that could explain the anaemia, the remaining cases of anaemia were mild or transient and the frequency was low and similar in dogs treated with Librela and controls (<1%). Based on the data presented, it was accepted that administration of Librela was not associated with any adverse events.

Several different medicinal products were administered concomitantly with Librela. Two dogs treated with Librela received vaccines. No apparent negative effect of concomitant administration with NSAIDs was observed but only five dogs received NSAIDs in combination with Librela. Systemic antimicrobial products were used at a higher frequency in Librela-treated animals (5.7%) than in controls (0%). As discussed previously, it was accepted that this difference represented sporadic events which were not related to treatment.

Anti-drug antibodies were detected at low frequencies before treatment (2.1% in controls, 0% in test article-treated group). Given that the assay was designed to have a 1% false positive rate, the incidental finding of positive animals both before treatment, and in placebo-treated animals, is not unexpected. Treatment-induced immunogenicity was detected in 0% of controls and in 2/138 (1.4%) of animals in test article-treated group, of which one also had low bedinvetmab concentrations. Appropriate warnings are included in the SPC.

Overall, the data suggest that tolerance of Librela was acceptable. The duration of the study was three months. Given the expectation that the product may be used as a lifelong treatment, the applicant presented data from a one-armed field study evaluating the safety of 9-month treatment with Librela.

Continuation therapy study

In this GCP-compliant multicentre field study a subset (n=89) of animals that participated in the 3-month EU field trial (study C866C-XC-17-194) were selected for continuing treatment with Librela for an additional six-month duration (total treatment time nine months). This was an open-label and uncontrolled study. Of 89 included dogs, 78 completed the study. Eleven dogs experienced severe adverse events including four deaths, but these were not considered to be related to treatment. The frequency of adverse events was similar to that in the preceding study. There were no signs that the frequency or severity of adverse events increased over time. Although the lack of a negative control group precluded definite conclusions, results from the study did not raise any concerns regarding long-term use of Librela.

It was furthermore concluded that the laboratory and field studies were performed over a period extending past steady-state and data from these studies support that Librela is well tolerated. The overall data provided were considered sufficient to conclude that safety of long-term use of Librela is acceptable.

USA field trial

This GCP-compliant field study was a multicentre, placebo-controlled, randomised, blinded study in which 272 client-owned dogs with osteoarthritis were treated with Librela (n=135) at the proposed dose of 0.5-

1 mg/kg bw or placebo (n=137), once monthly for three consecutive months. This study was performed in the USA during 2018 in parallel with the pivotal EU field study and basically follows the same design.

Results demonstrated that administration of Librela was well-tolerated. There were no Librela-related clinical findings or effects on clinical pathology parameters (including ALT, AST, BUN, and RBC). There were two owner reports of local reactions at the injection site, one in the placebo and one in the Librela-treated group. The present study does not raise any concern regarding possible adverse reactions related to CCL injury at the recommended treatment dose.

Two dogs (one control and one test article-treated animal) were classified as having treatment-induced immunogenicity of which the Librela-treated animal also had decreased bedinvetmab and NGF concentrations.

No apparent negative effect of concomitant administration with NSAIDs was observed, but only five dogs received NSAIDs in combination with Librela for an average of 11.6 days. Five dogs administered Librela received vaccinations during the study. The vaccines were administered > 7 days from the last Librela administration. Systemic antimicrobial products were used at similar frequency in treated animals and controls.

Overall, the data from this study suggest that Librela was well-tolerated with no apparent adverse effects.

Environmental risk assessment

An appropriate environmental risk assessment was provided. The veterinary medicinal product will only be used in non-food producing animals. Based on the data provided, Librela is not expected to pose an unacceptable risk for the environment when stored, handled, used and disposed of in accordance with the recommendations included in the proposed SPC.

Overall conclusions on the safety documentation

Eight studies were conducted to investigate the safety of Librela which included four laboratory studies and four field trials. Safety of the administration of one dose, an overdose, and repeated administration of one dose was examined in an exploratory target animal safety (TAS) study and in a pivotal TAS study. Overall, the results demonstrated that treatment was well-tolerated. In the pivotal TAS study, doses of 1X, 3X, and 10X the maximum RTD at monthly intervals for 6 consecutive months were well-tolerated in healthy dogs.

Reproductive safety was not investigated. The absence of studies to investigate the effect of bedinvetmab on reproductive performance in the target species is considered acceptable, on the basis that the applicant proposes to contraindicate use of Librela in animals intended for breeding (in section 4.3 of the SPC), and in pregnant or lactating animals (in section 4.7 of the SPC), and given that it is known from available literature in non-target species that the reduced levels of NGF are associated with negative effects on developing foetuses.

Immunological function was investigated using the TDAR test as a method to determine if immune function was impaired following treatment with Librela. Following the administration of three subcutaneous doses of 1 mg/kg bw at D0, D28 and D49, there was a clear response in antibody titres across treatment groups after the second administration of the KLH antigen. The antibody response was similar in test article-treated and control groups and the results support that under the conditions of the study, Librela is not related to impairment of immunological function.

A two-week NSAID co-administration study was performed to study potential interactions of Librela with NSAIDs but the relevance of the findings from this study is considered limited. No other specific studies of interactions were performed. During the field studies, Librela was administered concurrently with several veterinary medicinal products and no drug interactions were observed.

One dose determination field study, two pivotal field studies and one uncontrolled field study were conducted. Overall, the field safety data suggest that tolerance of Librela is acceptable. Mild reactions such as swelling and heat at the injection site may uncommonly be observed.

A user safety assessment in line with the relevant guidance document has been presented. It is accepted that the main risk to the user is associated with accidental self-injection. In the event of accidental parenteral exposure, there are two main risks which are considered to arise: (a) the potential risk for the developing embryo/foetus (b) the potential development of an immunological response. The applicant has proposed adequate user safety warnings relating to potential hypersensitivity reactions following exposure, and that accidental self-injection by a pregnant or lactating woman may present a risk to the unborn child or nursed neonate.

An appropriate environmental risk assessment was provided. Librela is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Introduction and general requirements

Librela contains the active substance bedinvetmab which is a canine monoclonal antibody (mAb) specifically targeting nerve growth factor (NGF). It is intended for the alleviation of pain associated with osteoarthritis in dogs.

Bedinvetmab has been classified as an immunological by EMA and as such overarching guidance on the efficacy testing of veterinary immunologicals is provided by Directive 2001/82, Annex I, Title II (as amended). However, these requirements were written specifically with vaccines and immunosera in mind and so are not fully relevant for a monoclonal antibody. The applicant notes that there are currently no specific efficacy regulatory guidelines at European level for monoclonal antibodies for veterinary use.

Canine osteoarthritis (OA) or degenerative joint disease (DJD) is a slowly progressing, degenerative disease of the joint that can lead to chronic pain via whole-joint structural changes including articular cartilage, synovium, and the subchondral bone. Multiple factors contribute in the development of the disease, including genetics, diet, environment, obesity, and age. The disease is currently incurable, and in addition to the negative pain consequences, it affects the mobility and, ultimately, the quality of life of dogs. Furthermore, the ongoing nociceptive input into the central nervous system leads to central sensitisation, which enhances the perception of pain. One of the main peripheral mechanisms attributable to joint pain is the activation and sensitisation of peripheral nociceptors by inflammatory and hyperalgesic mediators in response to noxious stimuli such as cytokines, including tumour necrosis factor alpha (TNFα) and interleukin-1 beta (IL-1β), as well as neurotrophins, such as NGF. NGF is implicated as a leading factor in the sprouting of sensory and sympathetic nerve fibres in response to tissue and/or nerve injury. NGF signalling also leads to transcriptional changes that result in the increased expression of pronociceptive neurotransmitters, thereby leading to central sensitisation.

According to the applicant, anti-NGF antibody therapies have shown efficacy both in preclinical models of pain as well as in the human clinical setting. Canine NGF and its receptor TrkA are closely homologous to other species, and both NGF and TrkA are expressed in similar tissues in dog and man, have similar functions, and appear to be under similar control mechanisms.

In summary, according to the applicant, NGF has been linked to pro-inflammatory processes, changes in both peripheral and central neuronal plasticity, nerve sprouting in response to tissue and/or nerve injury, and the activation and sensitisation of peripheral nociceptors, suggesting NGF may be a major factor orchestrating many of the diverse changes driving clinical signs of pain associated with osteoarthritis. For these reasons, NGF was chosen as a potential target for therapeutic antibodies to alleviate pain associated with osteoarthritis.

In the field efficacy program, the primary parameter for evaluation of efficacy of treatment was based on owner assessments of the severity of pain measured by the CBPI (Canine Brief Pain Inventory) tool. The CBPI is a validated and publicly available tool designed to quantify the severity of chronic pain and its impact on routine activities in companion dogs. It contains 11 questions in total: 4 questions pertaining to the severity of pain evident in a dog (the responses for these questions can be used to calculate a mean value that provides the pain severity score - PSS) and 6 questions pertaining to how the pain interferes with the dog's typical activities (the responses to these questions can be used to calculate a mean value that provides the pain interference score - PIS). Treatment success at a given time point is defined as a reduction ≥1 in PSS and ≥2 in PIS compared to baseline. In the final question, the owner is assessing the dog’s overall quality of life. For all but the final question, the assessment pertains to the condition of the dog during the past 7 days. In the pivotal field trial in the EU, veterinary categorical assessment (VCA) was included as a secondary parameter for evaluation of efficacy. In the VCA, the veterinarian categorised “lameness/weight-bearing”, “pain on palpation/manipulation of joint(s)” and “general musculoskeletal condition” as “clinically normal”, “mild”, “moderate”, “severe” or “nearly incapacitating” that best described the dog’s OA condition at the time of each study visit.

Efficacy documentation

Eight studies were conducted to investigate the efficacy of the product and included four laboratory studies and four field trials. Two of the field studies were compliant with VICH GL9 on good clinical practices (GCP), whereas the field dose determination study did not comply fully with all the requirements of GCP but was carried out according to good scientific practices and principles. In the dose determination field study, another anti-NGF mAb candidate was used. In the two pivotal field studies bedinvetmab (ZTS-00508841) of a batch formulated in accordance with the final formulation proposed for marketing was used. In addition, the applicant submitted an open-label, uncontrolled, field study in support of long-term safety and efficacy.

Study title
A Non-GLP Study of the Efficacy of Caninized Anti-NGF Monoclonal Antibodies (other anti-NGF mAb candidate) and ZTS-00508841 in the MIA Model of Osteoarthritis Pain in the Rat (non-GLP)
Pharmacokinetics of Anti-NGF Monoclonal Antibodies ZTS-00508841, ZTS-00508842, ABT-406, and ZTS-00509001 in Dogs (non-GLP)
Dose Proportionality of Anti-NGF Monoclonal Antibody ZTS-00508841 in Dogs (non-GLP)
ZTS-00508841: Intravenous (IV) and Subcutaneous (SC) Dose Pharmacokinetic and Immunogenicity Study in Dogs (GLP)

Study title
A Double-Masked, Randomized, Negative-Controlled, Multicenter Trial Investigating Four Dose Levels of (other anti-NGF mAb candidate), a Caninized Anti-Canine-NGF Monoclonal Antibody, Administered Subcutaneously for the Treatment of Clinical Signs of Osteoarthritis in Dogs (non-GCP)
EU Field Study Efficacy and Safety of ZTS-00508841 Compared to Placebo for the Treatment of Pain Associated with Osteoarthritis in Client-Owned Dogs (GCP)
Field Safety and Efficacy of ZTS-00508841 Compared to Placebo for the Treatment of Pain Associated with Osteoarthritis in Dogs (GCP)
Continuation therapy with ZTS-00508841 for the treatment of pain associated with osteoarthritis in client-owned dogs.

Laboratory trials

Pharmacodynamics

This was a non-GLP laboratory study, investigating the analgesic effect of two proprietary monoclonal antibodies, another anti-NGF mAb candidate (three different formulations) and ZTS-00508841 (=bedinvetmab), on monosodium iodoacetate (MIA)-induced osteoarthritis pain in the rat. Test articles were administered once at doses of 0.1 mg/kg bw, 0.5 mg/kg bw, and 2.0 mg/kg bw. Positive controls were administered morphine prior to testing, and vehicle was administered once to negative controls. Hind limb weight-bearing changes were assessed using the weight-bearing test method. This other anti-NGF mAb candidate produced significant increases in percent weight-bearing scores (WBS) compared to vehicle-treated animals, on D3, D14, and D21 when dosed at 2 mg/kg bw, and on D14 and D29 when dosed at 0.5 mg/kg bw. Bedinvetmab produced significant increases in %WBS compared to vehicle-treated controls on D3, D14 and D21 for all dose groups. On D29, also the 0.5 mg/kg bw dose group had significant increases in %WBS.

Overall, the results from this study showed that in rats a single administration of either mAb (bedinvetmab or the other anti-NGF mAb candidate) produced significant increases in weight-bearing scores compared to a negative control, at multiple time points and with dose levels of bedinvetmab ranging from 0.5 to 2.0 mg/kg bw. The results from this laboratory rodent model of MIA-induced OA in rats support the claim that bedinvetmab has analgesic effects.

Pharmacokinetics

The first pharmacokinetics study was a non-randomised, open-label non-GLP study where one group of 4 healthy beagle dogs was dosed twice subcutaneously (SC) and once intravenously (IV) at 28-day intervals with bedinvetmab at 2 mg/kg bw. The active substance given here was generated from another cell line and given as a different formulation compared to the final formulation. Bioanalysis of bedinvetmab was performed using a non-qualified method. Pharmacokinetics was analysed using non-compartmental analysis after exclusion of one ADA positive dog.

Clearance of bedinvetmab was 3.32 ml/d/kg bw and its half-life (arithmetic mean) was 13.0 ± 4.1 days after IV administration. After SC administration, peak serum concentrations of 21.2 µg/ml were observed at 7 days and the bioavailability was 96% ± 13%. Immunogenicity was not investigated.

Total NGF was measured as an indicator of NGF binding *in vivo*. Measured concentrations ranged from <10 pg/ml prior to dosing to 4380 pg/ml after dosing.

The second pharmacokinetics study was a non-randomised, open-label non-GLP study where 8 male and 4 female healthy beagle dogs were given a SC single dose of bedinvetmab at 0.2, 0.5 or 1.5 mg/kg bw.

The active substance given here is from an early batch that differs from the final substance. The formulation is however similar to the final product. Bioanalysis of bedinvetmab was performed using a non-qualified method. Pharmacokinetics was analysed using non-compartmental analysis after exclusion of an ADA positive dog. C_{max} of bedinvetmab ranged from 3.02 ± 0.07 µg/ml at 0.2 mg/kg bw to 23.9 ± 4.2 µg/ml at 1.5 mg/kg bw with peak concentrations observed at 3 or 7 days after dosing. Dose proportionality was demonstrated for AUC and C_{max}. Immunogenicity was not investigated.

Total NGF was measured as an indicator of NGF binding *in vivo*. Measured concentrations ranged up to 4020 pg/ml after dosing.

Issues with the documentation of early batches were revealed for non-GLP studies C461W-US-15-124 and C461W-US-17-165. Since the data is considered supportive only and is not included in the support for dose finding, the lack of comparability of the drug substance/product is acceptable from a PK point of view. Since PK parameters were, however, determined based on a non-validated bioanalytical method, inter-study comparisons should not be made. Since only one method for the quantification of total NGF was used, total NGF data may, however, be compared.

The third pharmacokinetics study was a randomised, crossover (intravenous/subcutaneous), open-label GLP study where healthy beagle dogs were given two doses of bedinvetmab. The target dose range of 0.5 to 1.0 mg/kg bw (achieved doses were 0.57 to 0.87 mg/kg bw) by intravenous or subcutaneous injection in a crossover design on study days 0 and 42. Study groups consisted of 2 dogs/sex/group. The final product formulation was given. Bioanalysis of bedinvetmab was performed using a validated method.

The bedinvetmab half-life was 12.2 days (harmonic mean, 12.4 ± 1.8 arithmetic mean) and 12.3 days (harmonic mean, 12.6 ± 1.9 arithmetic mean) after subcutaneous and intravenous administration, respectively, and $AUC_{0-\infty}$ was 141 ± 32 and 171 ± 35 µg x d/ml, respectively. Following subcutaneous dosing, the mean C_{max} was 6.10 ± 1.68 µg/ml, T_{max} was 5.6 days (range 2-7 days), and the bedinvetmab SC bioavailability was 83.5 ± 15.8%.

Treatment-emergent immunogenicity due to bedinvetmab administration was not observed in any of the animals.

Total NGF was measured as an indicator of NGF binding *in vivo*. The maximum Total NGF concentrations averaged 4.30 ± 1.60 ng/ml (intravenous) and 3.53 ± 1.23 ng/ml (subcutaneous).

Environmental antigens are not expected to interfere with ADAs or with bedinvetmab. There is at present no link between environmental antigens and diminished efficacy.

Based on pharmacokinetic studies in ADA positive and ADA negative dogs in the USA field study, it is concluded that pharmacokinetics is not significantly different in dogs with pre-existing ADAs. It is acceptable to report the data for all ADA negative patients.

Dose determination

Dose justification:

The choice of the proposed dose for bedinvetmab was based on its binding affinity to the nerve growth factor (NGF), taking into account PK and safety data. The applicant extrapolated from another anti-NGF mAb candidate to bedinvetmab, both molecules being very similar and targeting the same epitope.

The binding affinity of the other anti-NGF mAb candidate and bedinvetmab for NGF are strong as measured by Biacore, with a stronger binding affinity of bedinvetmab (approximately 10-fold, although the difference may be overestimated due to the very slow dissociation rate). The activity in two *in vitro*

assays is in the same range for both antibodies. PK of the two antibodies differs, with half-lives of 10-13 days for bedinvetmab and 8-10 days for the other anti-NGF mAb candidate in laboratory studies. AUC was higher for bedinvetmab, and subcutaneous bioavailability was similar. Bedinvetmab is expected to have efficacy equal to or slightly better than the other anti-NGF mAb candidate at equal doses. The selected dose range was not intended to achieve maximal possible NGF blockade; rather, it was intended to achieve efficacy.

The choice of the optimal dose range for the other anti-NGF mAb candidate (0.5-1 mg/kg bw) was based on targeting an intermediate level of NGF binding of approximately 50% binding as extrapolated from total NGF levels, taking into account the safety data. A similar approach as for the other anti-NGF mAb candidate has been pursued for bedinvetmab, using total NGF levels from the laboratory pharmacokinetic study (C461W-US-17-165). Since bedinvetmab has a slightly longer half-life, total NGF is expected to accumulate to increased levels. However, this does not mean that more NGF is being captured, only that more accumulates in the serum.

The applicant did not explicitly address how/if total NGF correlates with clinical efficacy and did not comment whether total NGF in healthy animals can be a surrogate for target engagement in the target population. When bedinvetmab was administered in the field studies, a similar total NGF level was achieved after the first dose in the USA field study, but a higher C_{trough} was demonstrated in the EU field study. As aimed for, an intermediate level of target engagement seems to have been reached. As efficacy at the selected dose was demonstrated in clinical trials, and bedinvetmab administered at the selected dose was well-tolerated, the issue was not further pursued.

The study was a randomised, blinded, multicentre, clinical trial investigating the efficacy and duration of effect of the other anti-NGF mAb candidate compared to a negative control for the treatment of clinical signs of osteoarthritis (OA) in client-owned dogs. This study did not comply fully with all the requirements of GCP but has been accepted as it was performed according to good scientific practices and principles. The other anti-NGF mAb candidate is a different mAb from bedinvetmab, which is included in the final formulation of Librela, and comparability between the two mAbs has not been sufficiently demonstrated to allow extrapolation of data. The test article was administered once by subcutaneous injection at four different dose levels (0.25 mg/kg bw, n=74; 0.5 mg/kg bw, n=73; 1.0 mg/kg bw, n=73, 2.0 mg/kg bw, n=56). Saline was administered to negative controls (n=70). The primary efficacy endpoint was a modified owner-assessed CBPI on days 28, 42 and 56 after administration. The CBPI scoring was modified to allow evaluation of treatment success at earlier time points after dosing than what is used in the validated CBPI scoring. Most dogs were enrolled primarily for osteoarthritis of the hip (47.7%) or stifle (38.7%). This differs somewhat from the pivotal EU field study, where dogs had primarily osteoarthritis of the hip (48.1%) or elbow (26.7%), and fewer with osteoarthritis of the stifle (17.6%).

Results showed that a significantly greater proportion of the other anti-NGF mAb candidate -treated dogs achieved treatment success compared to the control group at the following time points by treatment group: day 14 for the 0.5 mg/kg bw group, day 28 for all four dose groups, and day 42 for the 0.5 mg/kg bw and the 1.0 mg/kg bw groups.

Field trials

The dose determination field study was assessed and commented on in the previous section ‘Dose determination’.

Three field studies were conducted to evaluate the efficacy and safety of Librela, two conducted in the EU and one in the USA.

EU field study

The EU field study is considered to be the pivotal field study for this application.

EU Field Study Efficacy and Safety of ZTS-00508841 Compared to Placebo for the Treatment of Pain Associated with Osteoarthritis in Client-Owned Dogs	
Objectives	To demonstrate the efficacy and safety of bedinvetmab (Librela) when administered for three months at a monthly minimum dose of 0.5 mg/kg by subcutaneous injection for the treatment of pain associated with naturally occurring osteoarthritis (OA) in client-owned dogs compared to a negative control.
Study design	Randomised, double-blinded, placebo-controlled clinical field study
Study sites	26 veterinary practices located in Portugal, Hungary, Ireland, and Germany
Compliance with regulatory guidelines	GCP
Animals	287 client-owned dogs, of which 57.5% purebred and 42.5% mixed breed, 46.3% male and 53.7% female. Labrador retriever was the most predominant breed (32.7%) followed by golden retriever (10.9%), German shepherd dog (10.9%), and collie (4.2%). Mean age was 8.9 years. Mean body weight was 26.7 kg. Dogs had OA in the hip (48.1%), elbow (26.7%), stifle (17.6%), carpus (5.3%), shoulder (1.3%), or tarsus (0.9%). Dogs were randomly allocated to Librela (n=141) or placebo group (n=146).
Eligibility criteria	Client-owned dogs (>12 months old) in good general health with clinical evidence of osteoarthritis in at least one joint of the pelvic or thoracic limbs confirmed by orthopaedic examinations and by radiographic evidence. A pain severity score (PSS) and a pain interference score (PIS) ≥2 on the CBPI completed by the owner. An assessment of "moderately affected", "severely affected" or "nearly incapacitated" for at least one of the veterinary categorical assessments (VCA) during orthopaedic examinations by the examining veterinarian in at least one joint of the pelvic (hip, stifle, tarsus) or thoracic (shoulder, elbow, carpus) limbs on day 0.
Test article	Bedinvetmab, final formulation. Dosing was based on a nominal minimum dose of 0.5 mg/kg bw with dosing on a weight banding basis such that each dog received 0.5−1.0 mg/kg bw based on its location within a dose weight band.
Placebo	Sterile saline (0.9% sodium chloride)
Methods	Dosing of test article or placebo on days 0, 28 and 56. Physical examination and veterinary categorical assessment (VCA) and owner CBPI assessment and owner categorical assessment (OCA) on days 7 (-0/+2), 14 (±3), 28 (±3), 42 (±5), 56 (±5), and 84 (±5).

Efficacy parameters	Primary efficacy endpoint was treatment success at D28 based on owner assessment of pain measured on the CBPI. The following was calculated for the CBPI: • CBPI pain severity score (PSS): average of questions 1 through 4 • CBPI pain interference score (PIS): average of questions 5 through 10 Treatment success was defined as a reduction ≥1 in PSS and ≥2 in PIS as per the validated official recommendations. Dogs that required rescue treatment or were withdrawn for lack of efficacy prior to the day 28 visit were considered treatment failures at day 28. Secondary efficacy endpoints were treatment success for CBPI as described for the primary efficacy endpoint at other timepoints (day 7, 14, 42, 56 and 84). Moreover, PSS and PIS results were analysed separately as secondary efficacy variables. Veterinary categorical assessments (VCA): the veterinarian categorised "lameness/weight-bearing", "pain on palpation/manipulation of joint(s)" and "general musculoskeletal condition" as "clinically normal", "mild", "moderate", "severe" or "nearly incapacitating" that best described the dog's OA condition at the time of each study visit. VCA data were analysed *post hoc* and the analysis included two types of assessments; 1) improvement versus baseline within each assessment type and 2) overall improvement across all assessment types.
Statistical method	Treatment success (yes/no) was analysed as a binary response using a generalised linear mixed model for binomial distribution with logit link. The model included the fixed effect of treatment. The random effects included site, block within site and the interaction between site and treatment. Back-transformed least square means were used as estimates of the treatment proportions and corresponding 95% confidence intervals were constructed. Treatment comparison was evaluated using log-odds ratios using a two-sided test at the 5% level of significance ($p<0.05$). Odds ratios and corresponding 95% confidence intervals were also constructed.
Results	
Efficacy parameters	Primary efficacy parameter: A significantly greater proportion of Librela-treated dogs (43.5%) achieved treatment success versus placebo (16.9%) on day 28 (P=0.0017). Secondary efficacy parameters: A nominally significantly greater proportion of Librela-treated dogs achieved treatment success versus placebo, at all assessment days: day 7 (17.8% vs 3.8%; P=0.0017), 14 (35.5% vs 9.7%; P≤0.0001), 42 (52.6% vs 21.1%; P=0.0001), 56 (50.8% vs 19.9%; P=0.0002) and 84 (48.2% vs 23.5%; P=0.0025). Mean PSS and PIS scores analysed separately were nominally significantly lower in the Librela-treated group versus placebo at all

	timepoints evaluated during the study (i.e. days 7, 14, 28, 42, 56 and 84). For the VCA the results showed that on each of the assessment time points the improvement compared to baseline (regardless of the applied definition/approach) was significantly better in the Librela-treated group compared to the placebo group. Moreover, the results showed that on each of the assessment time points the improvement compared to baseline across all assessment types based on the VCA was also significantly better in the Librela-treated group compared to the placebo group. The proportion of animals that required rescue treatment and was subsequently withdrawn from the study was 13.0% (n=19) in the placebo group versus 2.1% (n=3) in the Librela group.
Discussion	
Discussion/conclusions further to assessment	In this pivotal field study, efficacy of treatment was demonstrated for the primary efficacy parameter and the secondary parameters based on the CBPI assessment performed by animal owners and veterinary categorical assessments. Treatment success was achieved for the primary endpoint as well as across the secondary CBPI endpoints. VCA data were analysed in two ways; improvement versus baseline within each assessment type and overall improvement across assessment types. The results showed that the improvement was significantly better in the Librela-treated animals compared to the placebo group on each of the assessment time points. A marked placebo effect was demonstrated in this study, the treatment success based on CBPI in the placebo group was 16.9% compared to 43.5% in the Librela group. In the USA field trial (see below), this placebo effect was even more pronounced (36.6%). There is no apparent explanation for this discrepancy, and the applicant speculates whether this may be due to cultural differences leading to differences in interpretation of questions by animal owners.

EU Continuation therapy study

This study was a GCP compliant, open-label, single-armed, multicentre, clinical field study where a subset (n=89) of animals that participated in the EU field trial were selected for continuing treatment with Librela for an additional six months duration (total treatment time nine months). Out of 89 dogs included, 78 completed the study. Treatment success was defined as a reduction ≥1 in PSS and ≥2 in PIS compared to Day 0 pre-treatment CBPI (D-84) assessment for the pivotal EU field study. The percentage of treatment success from the CBPI assessments in the continuation study was 62.8% on D0 and ranged from 73.3-82.2% during the study. From D28 onwards the percentage of treatment success was >70%, and this was maintained throughout the study until D168 (75.0%). Because of the lack of a control group, no definitive conclusions on efficacy can be drawn from this study. However, the results indicate sustained efficacy of treatment.

USA field study

This study was a GCP compliant, randomised, double-masked, multicentre, clinical field trial investigating the efficacy and field safety of Librela when administered at a dose of 0.5−1.0 mg/kg bw monthly for three months by subcutaneous injection for the treatment of pain associated with naturally occurring osteoarthritis in client-owned dogs under field conditions compared to a negative control (saline). Librela (n=135) was administered on days 0, 28 and 56. Saline was administered to negative controls (n=137). Eligibility criteria and methods in this study were similar to the EU pivotal field study described above. The primary efficacy endpoint was treatment success at day 28 based on owner assessment of pain measured by the CBPI. Secondary efficacy endpoints were treatment success for CBPI at other timepoints (day 7, 14, 42, 56 and 84). Moreover, PSS and PIS results were analysed separately as secondary efficacy variables. Treatment success was defined as a reduction ≥1 in PSS and ≥2 in PIS as per the validated official recommendations. Dogs that required rescue treatment or were withdrawn for LOE prior to the D28 visit were considered treatment failures at D28.

Results showed that a significantly greater proportion of Librela-treated dogs (47.4%) achieved treatment success versus placebo (36.6%) at day 28 (P=0.0410). A nominally significantly greater proportion of Librela-treated dogs also achieved treatment success versus placebo at days 42 (55.9% vs 39.8%; P=0.0143), 56 (58.0% vs 41.7%; P=0.0193) and 84 (57.4% vs 34.2%; P=0.0026). Mean PIS and PSS scores were nominally significantly lower in the Librela-treated group versus placebo, beginning at day 14 and day 28, respectively, throughout day 84.

There are no data from veterinary evaluations after treatment that could support the owner-based assessments in this study.

Treatment-induced immunogenicity with development of ADAs was seen in 2/138 and 1/132 of Librela-treated animals in the EU and the USA field studies, respectively. In two of these animals the decreased bedinvetmab and total NGF concentrations suggested neutralising or clearing antibodies. The possibility of ADA induction is addressed in the SPC section 4.4 Special warnings for each target species: "*This veterinary medicinal product may induce transient or persistent anti-drug antibodies. The induction of such antibodies is uncommon and may have no effect or may result in a decrease in efficacy in animals that responded to treatment previously.*" This information is considered sufficient.

Overall conclusion on efficacy

Pharmacodynamics

The results obtained from one laboratory study using a model of MIA-induced osteoarthritis in rats support the claim that bedinvetmab has analgesic effects.

The applicant thoroughly discussed the significance of the accumulation of total NGF in the blood. It is agreed that the accumulation of antibody-target complexes is common, with the complex typically exhibiting similar PK characteristics as the antibody. The complex is considered inactive and did not have any impact on the safety of bedinvetmab, as demonstrated in the TAS and field studies.

Different physiological conditions are not expected to result in spikes of free NGF. ADAs may lead to an increase in NGF, which is expected to be rapidly cleared, following its short half-life and rapid turnover. The affinity of bedinvetmab for NGF is stronger than the affinity of NGF for TrkA, resulting in bedinvetmab out-competing TrkA for NGF. The data does not indicate any retro-active increase in NGF or feedback on NGF synthesis.

Pharmacokinetics

Bioanalytical methods used for the GLP studies (bedinvetmab, immunogenicity and total NGF) were adequately validated. The non-GLP studies were analysed using a non-qualified assay for bedinvetmab. This is acceptable as long as no intra-study comparisons are necessary and given that the studies are not pivotal. The use of two reference standards in the qualification and the validation of the assay for bedinvetmab is deemed to have no impact, as the qualification was a pre-validation exercise and was not used for clinical sample measurement.

Overall, the pharmacokinetics of bedinvetmab is well described, with no apparent target-mediated drug disposition. No accumulation was seen upon multiple dosing, suggesting the dosing interval may be appropriate. Linearity of AUC and C_{max} was demonstrated for doses from 0.2 to 1.5 mg/kg bw. Immunogenicity was low. Target engagement was demonstrated with measurements of total NGF.

Although only sparse sampling results are available for the field studies, pharmacokinetics in the target population does not seem to differ significantly from that of healthy dogs.

The pharmacokinetic particulars of bedinvetmab have been included in section 5 of the SPC.

Dose determination

The applicant discussed the dose finding based on two studies using another anti-NGF mAb candidate, which is an antibody different than bedinvetmab, , and total NGF, as a measure of target engagement. Binding affinity of this other anti-NGF mAb candidate and bedinvetmab for NGF and the activity in two *in vitro* assays was in the same range for both antibodies. PK of the two antibodies differed, with bedinvetmab showing better PK characteristics than the other anti-NGF mAb candidate. It was concluded that bedinvetmab should have efficacy equal to or slightly better than the other anti-NGF mAb candidate at equal doses.

The applicant did not explicitly address how/if total NGF correlates with clinical efficacy and did not comment if total NGF in healthy animals can be a surrogate for target engagement in the target population. When bedinvetmab was given in the field studies, a similar total NGF level was achieved after the first dose in the US field study, but a higher C_{trough} was achieved in the EU field study. It is unclear whether a higher level of NGF should have been reached, but as aimed for, an intermediate level of target engagement was reached. As efficacy at the selected dose was demonstrated in clinical trials, and bedinvetmab administered at the selected dose was well-tolerated, the issue was not further pursued.

A field dose determination study investigated the efficacy and duration of effect of four different dose levels of the other anti-NGF mAb candidate compared to a negative control for the treatment of clinical signs of OA in client-owned dogs.

Dose confirmation and field efficacy

Two GCP-compliant field studies investigated the efficacy of Librela at the proposed dosing regimen in treatment of pain associated with osteoarthritis (OA) in dogs under field conditions. The field efficacy studies were conducted in the EU and the USA and were similar in design and conduct. As primary efficacy parameter, treatment success as determined by owner assessment using CBPI scoring on day 28 after first administration of Librela was used. Secondary efficacy endpoints were treatment success based on the CBPI for other timepoints, and an analysis of the PSS and PIS results separately. Veterinary evaluations (VCA) were performed in the pivotal EU field study, and these data were analysed by the applicant *post hoc* as requested by the CVMP. Results confirmed an improvement in the Librela-treated group that was significantly better compared to the placebo group.

The proportion of dogs achieving treatment success was similar between the EU field study (43.5%) and the USA field study (47.4%). However, the effect in the control group was larger in the USA study

(36.6%) than in the EU field study (16.9%). There is no apparent explanation for this discrepancy. The possibility of ADA induction is adequately addressed in the SPC.

Part 5 – Benefit-risk assessment

Introduction

Librela is a solution for injection containing the active substance bedinvetmab which is a canine monoclonal antibody specifically targeting nerve growth factor (NGF). Bedinvetmab is expressed through recombinant techniques in Chinese hamster ovary (CHO) cells.

The product is intended for the alleviation of pain associated with osteoarthritis in dogs and it is claimed to inhibit NGF-mediated cell signalling to provide pain relief. The suggested nominal minimum dose of bedinvetmab is 0.5 mg/kg bw, with dosing on a weight band basis such that a dog would receive 0.5−1.0 mg/kg bw based on its location within the dose weight band. Librela is intended to be administered on a monthly basis as a single 1 ml subcutaneous injection.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC – full application.

Benefit assessment

Direct therapeutic benefit

The proposed benefit of Librela is its efficacy in alleviation of pain associated with osteoarthritis in dogs, which was established in two well-designed placebo-controlled field studies conducted in accordance with GCP. It is concluded that administration of Librela at the recommended dose of 0.5-1.0 mg/kg bw once a month resulted in clinically relevant improvements in owner assessment scores of pain severity, pain interference and life quality in dogs with mild to moderate osteoarthritis. The results were confirmed by a veterinary assessment using a veterinary categorical assessment of lameness/weight-bearing, pain on palpation/manipulation of joint(s) and general musculoskeletal condition.

Additional benefits

Librela will increase the range of available treatment possibilities for osteoarthritis in dogs.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Results from the ongoing primary stability studies (for both FDS and DP) should be provided post authorisation (recommendation).

Safety:

Risk for the target animal:

Administration of Librela in accordance with SPC recommendations is generally well-tolerated. Mild reactions at the injection site, such as swelling and heat, may uncommonly be observed.

Risk for the user:

A risk for hypersensitivity reactions and a risk for the developing embryo/foetus following accidental self-injection of Librela were identified.

Risk for the environment:

Librela is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user and the environment and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

The applicant applied for the following indication: "For the treatment of pain associated with osteoarthritis in dogs". The product has been shown to be efficacious in dogs with osteoarthritis, however as pain is only a clinical sign of osteoarthritis and thus cannot be 'treated' with the product, the CVMP agreed to the following indication: "For the alleviation of pain associated with osteoarthritis in dogs".

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users and the environment, when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Based on the data presented, the overall benefit-risk is considered positive.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Librela is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above-mentioned medicinal product.