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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Portela (EMEA/V/C/005890/0000)

INN: relfovetmab

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 submitted on 23 July 2024 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Portela, through the centralised procedure under Article 42(2)(a) of Regulation (EU) 2019/6 (mandatory scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 14 July 2022 as Portela has been developed by means of a biotechnological process, i.e. using hybridoma and monoclonal antibody methods (Article 42(2)(a)(iii)).

At the time of submission, the applicant applied for the following indication:

"For the alleviation of pain associated with osteoarthritis (OA) in cats."

The target species is cat. The active substance of Portela is relfovetmab, a felinised monoclonal antibody against 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 product is intended for administration by subcutaneous use.

Portela solution for injection contains 2.5 mg/mL or 6.4 mg/mL relfovetmab and is presented in cardboard boxes containing 1, 2 or 6 vials of 1 mL each.

The rapporteur appointed was Manuela Leitner and the co-rapporteur was Keith Baptiste.

The dossier has been submitted in line with the requirements for submissions under Article 8 of Regulation (EU) 2019/6 – full application.

On 10 September 2025, the CVMP adopted an opinion and CVMP assessment report.

On 27 October 2025, the European Commission adopted a Commission Decision granting the marketing authorisation for Portela.

Scientific advice

Not applicable.

Limited market status

Not applicable.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF), has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

All sites involved on the different steps of the manufacturing of the drug substance hold a valid GMP certificate.

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site Zoetis Belgium in Ottignies-Louvain-la-Neuve (LLN). The declaration was based on an on-site audit by the manufacturing site responsible for batch release in 04/2023.

Finished product

The batch release of the finished product takes place at Zoetis Belgium LLN site, which holds a valid GMP certificate.
A manufacturing and import authorisation (MIA) for Zoetis Belgium is available, confirming compliance with GMP principles.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file is considered to be in line with legal requirements.

The GMP status of the active substance(s) and of the finished product manufacturing sites has been satisfactorily established and is in line with legal requirements.

The new GMP certificate of the testing site SGS Lab Simon has been provided.

Part 2 - Quality

Quality documentation (physico-chemical, biological, and microbiological information)

Qualitative and quantitative composition

Portela is a solution for injection available in two strengths (2.5 and 6.4 mg/mL), each packaged in a 1 mL single dose presentation. The active substance's recommended INN is relfovetmab, a felinised monoclonal antibody expressed through recombinant techniques in Chinese hamster ovary (CHO) cells. Other ingredients (including their functions) are following compendial grade excipients: sodium acetate trihydrate and acetic acid glacial (pH buffer agents), sucrose (stabiliser, isotonicity), disodium EDTA dihydrate (metal chelator), L-methionine (antioxidant), Poloxamer 188 (surfactant, stabiliser) and water for injections (vehicle). No intentional overage is added during the manufacturing process of relfovetmab drug product.

The drug product is filled in 4 ml glass type I vials closed with a fluorobutyl rubber stopper and aluminium crimp seal with flip-off cap. The product is packed in a cardboard box containing 1, 2 or 6 vials.

The drug product should be stored in the original container at 2 – 8 °C protected from light. The proposed shelf life is 36 months.

Container and closure system

Relfovetmab formulated drug substance is stored in disposable, sterile, ready-to-use and single-use bioprocess bags in sizes of 30 mL, 6 L and 12 L. Technical drawings and certificates of analysis have been provided and conformity with Ph. Eur. requirements has been confirmed. The information provided is comprehensible and can be considered acceptable.

Glass type I vials, in which relfovetmab drug product is filled, are compliant with Ph. Eur. 3.2.1. The closure system, i.e. fluorobutyl rubber stoppers, is compliant with Ph. Eur. 3.2.9. All product contact components of the container closure system are suitable for pharmaceutical or "in contact with food" use. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Specifications for drug product packaging components (glass vial, rubber stopper, aluminium cap) are provided, including sterilisation description for vials and stoppers as well as representative drawings. Examples of certificates of analysis are provided for vials and rubber stoppers, confirming their Ph. Eur. compliance.

Following an extractable study performed by the supplier of the stopper, a safety assessment of the extractable results (and potential worst-case leachables) was performed by Zoetis, wherein results were considered to *not* represent a safety concern in conjunction with the intended administration to cats. Based on this, no additional leachable studies were deemed necessary to be performed.

Overall, the documentation on the drug product's container closure system including the results and interpretation of performed extractable studies is considered comprehensive, traceable and thus acceptable.

Product development

Drug substance

The drug substance manufacturing process was initially developed at a CMO in small scale and later transferred to the final drug substance manufacturing plant where further development and process upscale took place.

The upstream manufacturing process of relfovetmab uses standard bioreactor techniques, starting with cell vial thaw, proceeding through a standard seed train including passaging every 3-5 days, followed by cell growth in single use bioreactors, cell harvest and clarification, which is conducted by continuous flow disc-stack centrifugation followed by a series of filtration steps.

A design of experiments was chosen for the upstream development performed at the CMO. Based on the development at the CMO, further manufacturing process scale-up has been performed by Zoetis where the bioreactor process has been scaled-up. Process parameters and culture media have been evaluated and adapted throughout development up to the final process in order to achieve an optimal product quality and yield. Cell count and viability, as well as other biochemical parameters, have been investigated on an appropriate number of batches.

The downstream process consists mainly of purification steps. The process finishes with product concentration and buffer exchange, followed by the addition of excipients to the active substance. The development of the downstream process is based on the applicant's previous development experience with feline and canine monoclonal antibodies.

A FMEA (Failure Modes & Effects Analysis) was applied to the manufacturing process in order to evaluate each step for its criticality and potential critical process parameters. An extensive investigation of each manufacturing step was conducted to identify critical process parameters. Comparative tables listing the process parameters of the commercial manufacturing scale vs. lab scale have been provided. Process parameters were classified as scale-dependent and scale-independent and scale-down factors for each manufacturing step were presented.
The process characterisation program presented is well-structured and explained in detail.

Drug product

Pharmaceutical development was performed based on an initial Quality Target Product Profile, which was further translated into concrete quality attributes comprising appearance, identity, assay, impurities, sterility, endotoxins, pH, particulate matter, extractable volume, oxygen in headspace, container/closure integrity, osmolality.

Relfovetmab is manufactured from the formulated drug substance, whereas the same buffer system is used for the drug substance and for the final drug product. Both strengths of finished drug product are manufactured from the identical formulated drug substance by dilution in the formulation step. The development of further formulation buffer components was based on extensive knowledge on buffer formulations for monoclonal antibodies in general. Beyond that, studies were performed to investigate the antibody's potential aggregation under differing buffer conditions. Overall, the formulation is of a standard design and typical of that used in human and animal health monoclonal antibodies (mAbs).

The same formulation, as proposed for drug substance and for drug product, was used for pivotal studies and for the manufacturing of commercial registration batches.

A detailed explanatory calculation has been provided on how the respective amounts of the pH

buffer agents are obtained in the two drug product strengths, 2.5 mg/mL and 6.4 mg/mL. In particular, the respective concentration of each of the buffer agents in the underlying formulated drug substance (FDS) was clearly elucidated.

The originally developed drug product manufacturing process starts with thawing of the frozen formulated drug substance, followed by dilution with formulation buffer to the final concentration. The blend is filtered in a ”low bioburden” holding tank (with optional holding time at room temperature). The blend is then aseptically filtered into vials.

An alternative modified process is proposed for drug product manufacturing, where bioburden reduction is performed *after* the optional holding time – immediately prior to final sterile filtration.

Different manufacturing scales are applied correspond to pilot scale batches, and “laboratory scale” batches.

Characterisation

Elucidation of structure and other characteristics

An in-depth characterisation of relfovetmab has been conducted, including the determination of primary, secondary and higher-order structure, post-translational modifications (such as glycoforms and heavy chain C-terminal lysine removal), biological activity and purity. The test methods applied are appropriate and considered state of the art.

Amino acid sequence (primary structure) was determined by HPLC, peptide mapping and mass spectrometry. Higher order structure of relfovetmab was investigated by LC-MS/MS, scanning calorimetry and spectroscopy.

With regard to post-translational modifications, the glycan pattern has been investigated by capillary electrophoresis under reducing conditions.

Fc functions may have impact on pharmacokinetics, safety and efficacy. Surface plasmon resonance (SPR) was used on the FDS VICH registration batches, commercial batches and on a clinical batch to investigate the kinetics and binding affinity of relfovetmab to FcRn. All batches were tested at different concentrations and showed a similar binding affinity to NGF and FcRn in the SPR sensograms, irrespective of the manufacturing scale. Furthermore, safety and efficacy of relfovetmab have been evaluated in safety and efficacy trials where the same batches were used as those included in the comparative SPR testing.

Charge variants were elucidated by isoelectric focussing (IEF).

Formation of aggregates was determined by chromatography and analytical ultracentrifugation.

For specificity/potency determination, two orthogonal methods were used. Intact and degraded relfovetmab samples in drug product formulation were tested with both methods and the results were compared. The results showed comparability between the methods on intact and degraded samples, and therefore the applicant proposes to use the ELISA as routine test method. According to guideline ICH Q6B, a ligand or receptor binding assay may be used instead of a biological assay when sufficiently justified. As this is the case for relfovetmab, this approach is acceptable. Comparability of reference standards was assessed.

Impurities

The product- and process-related impurities have been listed in the dossier and are divided into product related impurities and process-related impurities mainly originating from the Chinese hamster ovary (CHO) cells. The information provided is comprehensible and clear, the possible origins of process-related impurities and the analytical procedures used for verification have been explained and justified. For the majority of the impurities listed, appropriate specifications have been set, and testing is part of the release criteria.

Description of the manufacturing method

Drug substance

The manufacturing process consists of upstream processing (USP) starting from WCB thaw, followed by sequential expansion in culture media. Relfovetmab production until harvest takes place in bioreactors. The bulk harvest is obtained by centrifugation followed by a series of filtration steps. The supernatant containing the harvest is clarified.
The downstream process consists of chromatography to reduce process-related impurities, followed by virus inactivation and chromatography. Nanofiltration is established as second dedicated virus safety step, followed by ultrafiltration for product concentration and buffer exchange. Finally, the product solution is filtered for bioburden reduction and the volume adjusted to achieve a target concentration. The drug substance is filled into bioprocess bags (BPC) and stored.

A manufacturing flow chart is provided, including each manufacturing step, key process parameters (KPP), key process attributes (KPA), as well as critical process parameters (CPP), all with their respective limits/ranges. In-process controls have been defined and listed at each manufacturing step with their respective limits/ranges.

A hold time/in-process stability study has been conducted by taking samples from each process intermediate.
A study evaluating potential microbial growth during prolonged hold time at different temperatures has been conducted. No microbial growth has been observed after any of the hold times, irrespective of the hold time temperature. Additional sampling and testing for microbial contaminants is conducted when limits are exceeded.

Drug product

As briefly outlined under process development, the manufacturing process of relfovetmab drug product consists of a dilution step of the formulated drug substance with the formulation buffer, followed by sterile filtration prior to filling in final containers.

Commercial batch formula for both drug product strengths, i.e. 2.5 mg/mL and 6.4 mg/mL, is listed for representative batch sizes.

The manufacturing process can be performed via two different processes. Flow chart, graphical representation and detailed narrative description have been provided for each of the proposed processes.

Moreover, a detailed comparison of both processes has been provided, including assessment of the potential impact of the differences.

No overage to account for losses during the drug product manufacturing process is performed. However, a small "overfill" is included in each vial to ensure that the volume delivered is acceptable. It is acknowledged that the drug product manufacturing process does not comprise critical steps or intermediates.

Process validation and / or evaluation

Drug substance

Downscale of virus safety steps: downscaled process models were used. Comparative quality and process attribute results were presented showing that the downscaled model was adequately chosen compared to the commercial scale manufacturing process.

Virus validation: Two dedicated viral safety steps are included in the relfovetmab manufacturing process. The validation studies were conducted using downscaled models, which is in line with EMA guideline CPMP/BWP/268/95 (*Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses*). Detailed descriptions of the validation of the downscaling have been provided.

The model viruses used in the validation studies are deemed appropriate, as they represent a broad range of different physicochemical properties, which are relevant in the course of virus validation. Virus-spiked preparations of defined product samples were used to determine the reduction/inactivation capacity of each virus safety step. Duplicate runs per each step were conducted with each model virus. Cytotoxicity and interference studies were performed as well – no cytotoxicity or interference was observed.

Virus validation has been conducted appropriately, following current guidance and under adequately down-scaled conditions.

Drug product

Process validation was performed for the proposed drug product manufacturing processes. It included, for both processes, the holding time at room temperature. Process validation parameters included routine in-process control, in-process monitoring and filter integrity testing. In addition, formulation homogeneity was investigated and confirmed for the blended formulation and during the filling procedure. All in-process validation results fulfilled specified acceptance criteria. Final filled vials were tested according to the proposed drug product release specification and fulfilled all specified release criteria.

Several studies were performed to assess the sterile filters used in the commercial drug product manufacturing process. Overall, performed studies to assess the suitability of sterile filters for their intended use are considered traceable and comprehensive.

A representative certificate of the filter has been provided. Filter validation studies were performed for the sterile filtration step, which is considered a "worst case" use of filters. Thus, these studies are also considered valid for the preceding bioburden reduction filtration step.

Production and control of starting materials

Starting materials listed in pharmacopoeias

Generally, the materials used for manufacturing of relfovetmab are common materials for use in manufacturing of immunological / biological / biotechnological products for human and veterinary use.

The materials used have been listed, respective CoAs and TSE certificates are provided, and conformity with Ph. Eur. requirements has been shown.

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin

The applicant has chosen a CHO (Chinese hamster ovary) cell line for the production of relfovetmab. CHO cells are widely used and well established in mAb manufacturing in the human and veterinary area. Information regarding the source of the cell line has been provided in line with the requirements of Ph. Eur. 0784 "Products of recombinant DNA technology".

According to the requirements of ICH GL Q5B "Analysis of the expression construct in cell lines used for production of rDNA derived protein products", a detailed description on the generation of the relfovetmab encoding vector is provided in the dossier.

Generally, the source of the cell line and also the expression vector construction are adequately described.

Cell bank system:

The applicant presented detailed information regarding preparation and maintenance of master cell bank (MCB), working cell bank (WCB) and end of production (EOP) cells. Furthermore, a detailed MCB and WCB analytical report has been provided in the Annex of CTD section 3.2.S.2.3.

Storage and maintenance of MCB and WCB

MCB and WCB are stored in cryogenic vials in the vapour phase of a liquid nitrogen freezer. DMSO is added as a cryoprotectant. No additional materials are added to the MCB or WCB and no materials of animal origin are used. Preparation and maintenance of the cell seeds are performed in standard procedures for cell banks for manufacturing of medicinal products. The passage history for MCB, WCB and EOP cells has been presented in tabular form. The information provided is generally in line with the requirements of Ph. Eur. 5.2.4.

Appropriate information regarding container materials used for MCB and WCB has been presented. The media composition has been described and the applicant confirmed that no material of animal origin is used for their preparation. It is stated that the MCB is secured by several parameters, like monitoring of storage parameters, emergency power supply, safety measures against unauthorised access, and a second MCB is stored at another place in case the measures chosen are not sufficient in a case of emergency.

Testing

CoAs for MCB, WCB and EOP cells are provided in the dossier.

General microscopy, identity testing, testing on purity and mycoplasma detection have been

performed according to the requirements of Ph. Eur. 5.2.4, 2.6.1 and 2.6.7. All results obtained were in line with the current requirements. Detailed method descriptions and the results have been provided.

Karyotyping has been performed. All results were compliant with the requirements of Ph. Eur. 5.2.4. Tumorigenicity.

Tumorigenicity testing has not been performed (in line with GL ICHQ5D, where it is stated that testing is not necessary when appropriate limits for impurities are shown to be consistently met by either process validation studies or by lot release testing).

This approach is acceptable.

Extraneous agents testing

Extraneous agents testing is focused on the species of cell origin (hamster) and the target species for the product (cat), since no further materials of animal origin are introduced in the cell banks. Nevertheless, the applicant also performed testing for canine, bovine, porcine and equine extraneous agents as part of a global registration strategy.

Also testing on retroviruses has been performed on MCB, WCB and EOP cells. This approach is in line with the requirements of Ph. Eur. 5.2.4.

Extraneous agents testing (hamster, feline, canine, bovine, porcine, equine species) has been performed on MCB, WCB and EOP cells level. According to the documents provided, the tests are in line with Ph. Eur. requirements). All relevant pathogens listed in Ph. Eur. 5.2.5 and GL have been taken into consideration, and the cells can be considered free from the relevant extraneous agents.

A TSE risk statement is provided for the master and working cell bank and the FDS, stating that bovine serum albumin has been used during the construction of the expression vector, prior to transfection of the expression vector into the CHO parent cell line. Routine production of relfovetmab is performed without reagents of animal or human origin.

Genetic stability testing

Genetic stability was investigated by evaluation of protein product expression and the integrated recombinant DNA sequence beyond the typical passage utilised at commercial scale. Protein quality alterations could not be found.

WCB testing in routine production will be reduced according to Ph. Eur. 5.2.4. The following parameters can be omitted for WCB's: karyotyping, identity, endogenous retroviruses and tumorigenicity, also the tests for certain hamster and feline viruses will be omitted in future WCB production. The justification thereof is provided in a comprehensive risk assessment and can be accepted.

Starting materials of non-biological origin

Certificates of analysis are provided for the materials used during manufacturing processes. This is acceptable.

No novel excipients are used in the manufacture of relfovetmab.

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

The in-house preparation of media and feeds are described in the dossier.

Media, feed and auxiliary materials used in the upstream manufacture process of relfovetmab FDS are listed in the dossier. A qualitative composition of media components has been provided. The applicant is enrolled in a change notification program with the vendors of the media, to be notified of any changes in media compositions.

It is mentioned in the dossier that the media are undergoing sterile filtration before use. Storage conditions for the media preparations are taken over from the supplier's proposals.

Control tests during the manufacturing process

Drug substance

The quality of the drug substance is controlled at the final formulated drug substance (FDS).

All in-house methods have been validated in line with the requirements of VICH GL1 and GL2. For Ph. Eur. methods, feasibility investigations have been conducted.

Protein content is determined by spectrometry; two methods have been validated and based on the results provided, both methods are appropriate to be used.

For purity two methods were validated, i.e. chromatography and electrophoresis. Both methods are appropriate to determine product-related fragments as well as high and low molecular mass species potentially present in the FDS.

Specific activity/potency: an ELISA has been validated to determine the potency of relfovetmab drug substance and drug product that bind specifically to NGF.

A commercially available ELISA was validated to determine the HCP concentration in FDS samples. All validated parameters were well within their acceptance criteria, and the method is considered appropriate for its intended use.

A real-time PCR method has been validated as alternative method to Ph. Eur. 2.6.7. Specificity, LOD and robustness were evaluated, and it was demonstrated that PCR is a suitable method to detect mycoplasma species that might be potentially present in relfovetmab. Omission of avian mycoplasma species testing has been sufficiently explained and justified.

All test parameters of the drug substance specification have been appropriately validated.

Drug product

In the frame of drug product manufacturing process, in-process monitoring of bioburden is performed on the formulated blend prior to sterile filtration. Further, filling volume (by weight) is controlled as in-process control during filling of the sterile filtered blend into vials.

Control tests on the finished product

For specific activity (ELISA) and monomers and LMMS (both determined by chromatography) release as well as end-of-shelf-life specifications are defined, which is acceptable. Osmolality, bacterial endotoxins, subvisible particles and Poloxamer content are only determined at release. The testing panel for the drug product is considered appropriate to determine relevant product quality attributes at release.

Bacterial endotoxins are tested according to Ph. Eur. 2.6.14. chromogenic kinetic method. A

feasibility study has been conducted and is acceptable. Maximum valid dilution (MVD), interference and recovery have been tested, and the results reveal that all predefined acceptance criteria have been met. The stability of detectable endotoxin was demonstrated during shelf life, thus justifying the suitability of the method for release testing without a defined time limit.

Sterility is tested according to Ph. Eur. 2.6.1. membrane filtration method. Also, for this parameter a feasibility study has been performed. The growth of standard test microorganisms in the presence and absence of relfovetmab FDS was investigated under two different temperature conditions in two different media (depending on test organisms). The results show a similar growth of the test organisms with and without product and the method can therefore be considered validated.

Free methionine and Poloxamer content are determined by chromatography. The test methods have been validated appropriately in line with VICH GL 1 and GL2.

Additionally, in support of the 3Rs principles the applicant is asked to consider changing the current chromogenic test to the recombinant factor G reagent test according to Ph. Eur. 2.6.32.

Reference standards

One reference standard was qualified primarily for system suitability testing of physicochemical test methods, while another reference standard was qualified for the potency ELISA of the FDS. Both of them were used for release and stability testing of the batches used in the pivotal safety and efficacy studies as well as for the registration batches. Furthermore, one of them was used to show correlation between clinical efficacy and reference batch performance.

Extensive comparability testing has been conducted to compare all reference materials with each other. Comparative testing of the reference standards showed that the small differences do not have any impact and have been sufficiently discussed and justified. Furthermore, a list of all reference standards used for relfovetmab quality testing has been submitted.

A requalification protocol for future reference standard preparations has been provided, including bioburden and endotoxin testing at release but not at retest. The qualification strategy as presented is accepted.

Batch-to-batch consistency

Drug substance

Batch-to-batch consistency

Batch analysis data are provided for registration batches, commercial batches, one engineering batch and one that was used in the EU clinical program. The test methods applied are those that are performed for routine release testing of the FDS and the test results are all well within their acceptance criteria. Additionally, results from characterisation were presented as well.

Justification of specification

Establishment of FDS specifications is based on historical data, product characterisation, toxicological and clinical evaluation, stability data from the commercial process as well as validation data.
The justifications provided for the FDS specifications are plausible and are based on consistent monitoring of the different parameters throughout development, manufacture and stability. The FDS specification parameters chosen are considered acceptable to determine adequate FDS quality. The

applicant also presented other parameters and tests that are not included in the FDS specification and provided respective explanations/justifications for their omission. Based on these justifications the omission of these testing is accepted. The contents of Poloxamer and free methionine are monitored during manufacture of the FDS which is acknowledged, as these parameters are tested at the final drug product.

Drug product

Batch-to-batch-consistency

Consistency DP batches of both formulation strengths (2.5 and 6.4 mg/mL) have been manufactured according to one of the processes. Two of these DP consistency batches were processed from FDS that had undergone different freeze-thaw cycles prior to be processed to DP. Another six DP batches were manufactured according to the other process with an increased batch size. Batch analysis data from the DP batches used in clinical trials were provided as well.

Based on batch analysis data the specification range of the protein concentration is considered adequate.

Justification of specification

The quality acceptance criteria of the drug product are based on historical data, product characterisation, toxicological and clinical evaluation, stability data from the commercial process and validation data.
The justifications provided for the DP specifications are plausible and are based on consistent monitoring of the different parameters throughout development, manufacture and stability. Comments are outlined below on certain parameters.

Based on the data provided the omission of osmolality and Poloxamer testing at the end of shelf life is acceptable.

For the specific activity, an ELISA method has been developed, and it is the same method for FDS as well as DP testing. Differing release and end-of-shelf-life specifications are defined for the drug product, which can be accepted, as the specific activity may change during storage due to product degradation.

For NR-CGE method for %monomer and %LMMS, different specifications for release and end of shelf-life are defined - based on the stability data provided, the acceptance criterion is considered appropriate.

Bacterial endotoxins are only tested at DP release but not at the end of shelf life, which is in accordance with EMA questions and answers on the quality of medicines (Quality of medicines questions and answers: Part 2 | European Medicines Agency (EMA)).

Subvisible particles are tested in line with Ph. Eur. 2.9.19 at release and end of shelf life for ongoing stability studies. Additionally, subvisible particles will also be tested in the stability studies following post-approval changes of the manufacturing process unless otherwise justified, based on a risk assessment.

Stability

Drug Substance

Different batches of relfovetmab active substance were followed in stability program, to support a 36-month shelf life. Different batches were at commercial scale were stored at +2 °C to +8 °C for up to 6 months (accelerated stability study).

In addition, a stressed study was also initiated on one consistency batch of relfovetmab FDS.

The results obtained from the primary and the supportive stability studies show no trends or deviations in any of the measured parameters when stored at ≤-40 °C or at 5±3 °C for the intervals submitted. The same applied to storage at accelerated conditions for the FDS (this condition is also the selected real-time condition for the finished product, which is a lower concentration of the formulated drug substance. The stability data support a shelf-life period for the active substance of 36 months when stored at a targeted temperature of ≤ -40 °C.

The post-approval stability program is well justified and considered acceptable.

Characterisation stability results have been included, which are not part of the release criteria; the parameters have been only included for better characterization and understanding of the product and monitoring purposes. No trends have been observed, the data presented in the dossier can therefore be considered acceptable. The tests will not be part of future stability programs but will be conducted in the case of significant changes in the manufacturing process to ensure consistent product quality.

The applicant is asked to perform a real-time study on a batch at commercial scale and to inform the competent authority immediately in case any trends or OOS results are observed. This request is considered a PAM (post authorisation measure).

Drug Product

VICH-compliant stability studies were performed under long term conditions [36 months at 5 ± 3 °C, ambient relative humidity (RH)] and under accelerated conditions (6 months at 25 ± 2 °C / 60 ± 5% RH) with drug product batches of both strengths (2.5 and 6.4 mg/mL). Different batches were produced at pilot scale; one batch was manufactured at a final commercial batch size. All batches were manufactured according to the manufacturing process Batches were filled in containers intended for commercial batches. Batches were stored in upright and inverted position to demonstrate the suitability of used stoppers.

Batches were tested according to the shelf-life specification. Overall, stored consistency batches all fulfilled specified acceptance criteria under long-term and accelerated conditions. In line with the requirements laid down in VICH GL3 and VICH GL17, the amount of investigated batches representative for the commercial scale manufacturing process is considered sufficient.

Real time storage for up to 36 months of consistency batches – supported by results from accelerated studies currently support the proposed shelf life of 36 months at 2 – 8 °C for batches manufactured according to the two-tanks process.

Available results from storage for up to 12 months at long-term (+2 °C to +8 ºC) and up to 6 months at accelerated (25 ± 2 °C/60 ± 5% RH) conditions were provided for several commercial scale batches manufactured according to the manufacturing process. Vials were stored in upright or inverted position. All results fulfilled specified acceptance criteria. Overall, so far obtained

stability results support the intended shelf life of 36 months at 5 ± 3 °C for batches manufactured according to the "one-tank" process.

In addition, supportive stability studies were performed with batches manufactured according to the commercial manufacturing process – albeit in a smaller scale – and further investigated in pivotal clinical trials. Obtained results from storage of three clinical batches at long term and accelerated conditions essentially were within specified acceptance criteria. Supportive stability studies essentially confirm the proposed shelf-life claim of 36 months at 2 – 8 °C.

Further on, a freeze-thaw study was performed, which showed that the drug product's stability is not impaired by the freeze-thawing cycles. Finally, a photostability study was performed with two consistency batches. "Unprotected" drug product vials without secondary packaging, drug product vials packed in secondary packaging intended for commercial batches, and vials protected with aluminium foil were exposed to artificial daylight. Based on obtained results, the proposed secondary packaging was shown to provide adequate protections from light.

The applicant committed himself to fulfil the following post-authorisation measures, which are overall supported: in order to confirm the current proposed shelf life, at least one commercial drug product batch of each strength will be placed on stability at 2-8 °C for a minimum of 36 months and at 25 °C for up to 6 months. Beyond that, one production batch of (rotating) strength will be placed on stability at 2-8 °C for a minimum of 36 months on a yearly basis.

New active substance

The applicant requested the active substance relfovetmab contained in Portela to be considered a new active substance as it is novel and not hitherto authorised in a veterinary medicinal product in the European Union.

The applicant has submitted a document to justify the applicability of relfovetmab as a new active substance. Additional information has been provided with regard to substantial differences in the primary structure (amino acid sequence) of the active substance compared to other monoclonal antibodies authorised in the EU with the same clinical indication. For this purpose, the Union Product Database (UPD) was searched for other, already approved monoclonal antibodies with the same indication and target species.

Based on the review of the data provided, the CVMP considers that the active substance relfovetmab contained in the medicinal product Portela is to be qualified as a new active substance considering quality and chemical structure.

Overall conclusions on quality

Overall, the quality documentation on the veterinary medicinal product "Portela 2.5 mg [or 6.4 mg] solution for injection for cats" is presented in accordance with requirements as laid down in Annex II to Regulation (EU) 2019/6 (as amended). Relevant scientific guidelines relating to quality of veterinary medicinal products as well as relevant monographs of the European Pharmacopoeia were taken into account for the compilation of the submitted quality documentation.

Information has been provided on the development, characterisation, manufacture and control of the active substance and was presented in a satisfying way. A few minor concerns related to GMP, manufacture and testing were answered satisfactorily.

The qualitative and quantitative composition of the medicinal product is adequately drawn up. The container closure system used is suitable for the dosage form. The choice of drug product

constituents as well as the development of the final formulation buffer are adequately described. As explained in detail, the drug product is manufactured according to alternative processes. Further, comprehensive information is overall provided on the [development of the] commercial manufacturing process, and on the manufacturing scales applied.

The drug product as well as the drug substance control strategy are considered appropriate, quality-relevant parameters are identified and all in-house test methods are validated. Respective specifications are set.

Additionally, in support of 3Rs principles the applicant confirms to consider a post-authorisation measure to change a current test to a different test according to Ph. Eur. 2.6.32.

As a post authorisation measure it is confirmed that a real-time-stability study will be conducted on an additional drug substance commercial batch and that the Agency will be notified on any occurring trends or OOS results.

VICH-compliant stability studies currently support the proposed drug product shelf life of 36 months (when stored at 2 – 8 °C) for batches manufactured according to the approved manufacturing process. Beyond that, available stability data have been provided, which support the intended shelf life of 36 months at 5 ± 3 °C for batches manufactured.

Taken together, from a quality perspective, the veterinary medicinal product "Portela 2.5 mg [or 6.4 mg] solution for injection for cats" is considered approvable.

Recommendations:

1. Endotoxin testing: The applicant confirms that a post-approval variation will be submitted to replace a method to a different test according to Ph. Eur. 2.6.32 once the feasibility of the transition has been assessed at Zoetis and the method developed and validated.

2. Stability of the drug product: In order to confirm the current proposed shelf life, at least one commercial drug product batch of each strength will be placed on stability at 2-8 °C for a minimum of 36 months and at 25 °C for up to 6 months. Beyond that, one production batch of (rotating) strength will be placed on stability at 2-8 °C for a minimum of 36 months on a yearly basis. In case any trends or OOS results are observed, the applicant will notify the competent authority immediately.

Part 3 – Safety documentation (safety and residues tests)

General requirements

The active substance of Portela is relfovetmab, a felinised monoclonal antibody against nerve growth factor (NGF), which inhibits NGF-mediated cell signalling to provide relief from pain associated with osteoarthritis in the proposed target species, cats. The recommended dose is 0.5–1.25 mg relfovetmab/kg body weight (bw), once every three months, to be administered by subcutaneous route.

Relfovetmab is presented as a new active substance by the applicant, which has not been authorised for a veterinary medicinal product in the EU at the date of submission of the application. However, applicant has experience from other anti-NGF mAbs used for treatment of osteoarthritis in dogs and cats (bedinvetmab and frunevetmab). Reference to those other mAbs is made by the applicant in the dossier.

A full safety file in accordance with Article 8(1)(b) of Regulation (EU) 2019/6 has been provided.

Safety tests

Pharmacology

Pharmacodynamics

The studies submitted in support of the mode of action and pharmacodynamic properties of relfovetmab are summarised in Part 4.

Pharmacokinetics

The specific pharmacokinetic studies provided for relfovetmab and performed in cats are summarised in Part 4.

Six pharmacokinetic studies in rodents were provided but were considered supportive only. A detailed assessment of these studies was not deemed necessary, given the pharmacokinetic studies carried out in the target species, the cat, with the claimed dosage regimen.

Toxicology

The toxicological studies with relfovetmab were conducted in the target species, i.e. cat.

Single-dose toxicity

A single dose subcutaneous toxicity study was performed at 5 times the maximal claimed dose, to compare the toxicity profile of three different batches of relfovetmab. Assessment of single subcutaneous dose toxicity also included the first dose in the three safety studies, one exploratory laboratory safety study up to 28.8X the maximal claimed dose, one non-pivotal GLP TAS study up to 23X the maximal claimed dose, and one pivotal GLP TAS study up to 5X the maximal claimed dose.

See Part 4 for details.

Repeat-dose toxicity

The safety profile of repeated doses of relfovetmab was assessed in safety studies conducted in the target species. This was assessed as the doses administered after the first dose in the three safety studies mentioned under single-dose toxicity and in a study where two administrations of the maximal claimed dose were given two weeks apart. Adverse events were reported at the recommended dose and/or at overdose, see Part 4 for details. The most common adverse reactions were pain at injection, dermatitis and various skin lesions. The frequency of skin lesions was dose dependent. Those adverse events are mentioned in the corresponding sections (3.6 or 3.10) of SPC.

Injection site reactions (swelling and hair loss) were also reported uncommonly at the recommended dose. The CVMP agrees that this is related to the administration procedure, as they were noted in groups administered with the recommended dose and in placebo animals. These findings are stated in the SPC, section 3.6, with an uncommon frequency of occurrence in order to inform the veterinarian.

Tolerance in the target species

See Part 4.

Reproductive toxicity, including developmental toxicity

NGF has well established roles during development, and NGF-inhibiting monoclonal antibodies for use in humans have shown developmental toxicity when tested in non-human primates. These findings are expected to be representative of a class effect of inhibition of NGF.

No studies on the effects on reproduction have been provided. This is acceptable since the product is not intended for use in breeding animals or animals intended to be used for breeding. Based on information that relfovetmab may affect neonatal development, the product is contraindicated in animals intended for breeding or in pregnant or lactating animals. Adequate warnings are included in the SPC.

Genotoxicity

Since relfovetmab is a monoclonal antibody, no interaction with DNA or direct/indirect genotoxicity is expected. No studies on genotoxicity have been conducted with relfovetmab, which is in line with ICH S6(R1).

Carcinogenicity

Carcinogenicity studies have not been conducted with relfovetmab. Relfovetmab is not expected to stimulate cell proliferation, induce cancer, increase its incidence or cause any other cellular changes that would be expected to be carcinogenic by other means. In a T-cell immune response study, relfovetmab had no immunosuppressive effect (see below). The justification for the absence of carcinogenicity studies is considered acceptable.

Other requirements

Special studies

Immunotoxicity

Due to the immune functions of NGF, there is potential for an immunomodulatory effect of relfovetmab. The applicant has addressed this issue with reference to EMA's scientific guideline on "Immunotoxicity studies for human pharmaceuticals" (ICH S8) and the CVMP Q & A document on monoclonal antibodies (EMA/CVMP/ADVENT/307606/2017).

Immunotoxicity was specifically assessed in cats in a GLP-compliant 70-day T cell-dependent antibody response study (TDAR), following injection of keyhole limpet haemocyanin (KLH). TDAR assessment after administration of the clinical dose of relfovetmab was also included in the pivotal GLP TAS study (see Part 4).

Naïve domestic shorthair cats aged from 10 to 11 months were divided in 4 groups of 8 each and were subcutaneously administered with relfovetmab at doses of 0 and 4.8 mg/kg bw on days 1, 29 and 50, while 0.1 mg adjuvanted and non-adjuvanted KLH was administered on days 34 and 55. The test article was not the final formulation intended for marketing. The dose was not the recommended dose either. It is accepted that the TDAR test is a suitable test for the evaluation of potential immunosuppression. There were no significant differences between the anti-KLH immunoglobulin (Ig) titre response when comparing saline-treated and relfovetmab-treated groups, with adjuvanted or unadjuvanted KLH administration. It can be accepted that, under the conditions of the study, there was no evidence of immunosuppression.

No signs of immunotoxicity were apparently observed in the other tolerance studies provided.

Anti-drug antibodies (ADAs) were assayed using a validated method to assess the immunogenicity of relfovetmab. No pre-existing reactivity or treatment-emergent immunogenicity to relfovetmab was observed.

The safety of the product was followed during the study. Safety parameters evaluated were similar to those observed during the pivotal target animal safety (TAS) study.

In this study, no treatment-related mortality, clinical observations or changes in clinical pathological parameters were observed.

Skin biopsies were sampled in the case of skin lesions identified in 3 male cats (one cat in the control group on day 71, one in the relfovetmab group (unadjuvanted KLH) on days 50 and 71 and in one cat in the relfovetmab group (adjuvanted KLH) on day 70. Microscopic findings consisted of mild-to-moderate ulceration with inflammation characterised predominantly by infiltrates of neutrophils and mast cells. These observations were not correlated with an auto-immune disease.

Immunogenicity

Immunogenicity has been tested in the cats participating in the TDAR test (see section 'Immunotoxicity' for details). No ADAs were detected after relfovetmab administration in this study. Additionally, immunogenicity has been tested in 10 other studies (laboratory or field studies) and was reported in 8 out of these 10 studies (see Part 4 for details).

Reversibility

Reversibility of the effects of relfovetmab was only shown in an *in vitro* experiment using feline NGF, in which an artificial effect from the procedure cannot be ruled out. This has not been checked *in vivo* in the target species and, as such, reversibility cannot be claimed.

Observations in humans

Currently, there are no anti-NGF mAbs that are registered for human use. Tanezumab (Raylumis) was submitted for registration for human use with an intended indication for the treatment of osteoarthritis pain, but the benefit-risk profile was not favourable, primarily due to the risk of worsening arthritis that the drug can cause in some people. The greatest concern with tanezumab was its association with increased propensity to develop rapidly progressive osteoarthritis (RPOA).

Phase 3 OA studies on tanezumab included 9732 patients that received at least one dose of tanezumab (2.5–20 mg). In general, adverse events (AEs) that occurred more commonly in tanezumab-treated patients when compared to placebo groups included joint damage (RPOA, arthralgia, osteoarthritis and joint swelling) and neurological signs (hypoesthesia, paraesthesia, burning sensation and carpal tunnel syndrome). A subgroup analysis did not indicate increased risks for these AEs in special populations.

A higher rate of mortality due to a major cardiac event (MACE) was also observed in the tanezumab-treated population, and, after post-hoc adjudication by a group of cardiology experts, a signal could not be excluded. There was no cardiovascular risk factor that existed at baseline which stratified with MACE while on tanezumab.

Excipients

The excipients used in the final formulation of Portela, i.e. sucrose, sodium acetate trihydrate, Poloxamer 188, acetic acid glacial, L-methionine and disodium EDTA dihydrate, are widely used in approved veterinary or human pharmaceutical products and are not anticipated to be a safety concern at the levels used in the formulation.

User safety

The applicant has presented a user safety risk assessment (URA) with reference to the 'Guideline on user safety for pharmaceutical veterinary medicinal products' (EMEA/CVMP/543/03-FINAL rev.1).

The main potential routes of accidental contact with the product have been considered, and it was concluded that the most likely route is accidental self-injection. It is considered likely that adverse events will not occur as a result of dermal or ocular contact.

The veterinary medicinal product will be administered by a professional only (i.e. a veterinarian or a veterinarian’s assistant).

No studies on reproductive developmental toxicity, genotoxicity or carcinogenicity were conducted with relfovetmab, and this is considered acceptable. However, inhibition of NGF by tanezumab, a discontinued candidate mAb for human use, had adverse developmental effects in cynomolgus monkey offspring based on findings in two pre- and post-natal development studies. Based on this information, precautions to be taken by pregnant women are included in the SPC.

With regard to accidental self-injection, the applicant has not performed a quantitative risk characterisation establishing a margin of exposure (MOE) as required in the cited CVMP guideline. For the present family of substances (biological substance other than non-immunological), this omission is acceptable. Furthermore, the presented URA takes a worst-case approach to the potential hazards. Therefore, no further assessment is needed.

Immunogenicity/immunotoxicity were studied in pharmacokinetic studies, safety studies and in clinical trials.

There was no functional disruption of the immune response as investigated by the TDAR assay. There were no significant differences between the anti-KLH Ig titre response when comparing saline-treated and relfovetmab-treated groups. A such, there was no evidence of immunosuppression.

Immunogenicity was reported in several studies, and the impact on the efficacy of the candidate product cannot be excluded (please refer to Part 4 for details). There was no apparent impact on the safety of the product, but no definitive conclusion can be drawn for the impact on safety due to too sparse data.

However, there is a possibility of hypersensitivity, which could increase with repeated administration.

Predictions of binding of relfovetmab to human NGF in heart, synovial fluid and skin was used for assessment of biological effects in humans. For the URA, an NGF occupancy of ≥ 10% was considered the minimum threshold for measurable biological effect. With the highest dose of 1.28 mg (0.2 ml of the maximum relfovetmab strength), the NGF occupancy peaked at 41.8% in heart, 42.9% in skin and 71.6% in synovial fluid. The NGF occupancy was estimated to exceed the 10% threshold for 8.2, 11.2 and 13. 8 days in the respective tissue. For a needle stick injury containing a maximum of 0.32 mg relfovetmab, all tissues had an NGF occupancy above the 10% threshold, i.e. 15.3% in heart, 15.8% in skin and 38.7% in synovial fluid, with a duration of 3.3, 5.0 and 7.9 days, respectively. However, while basing the URA on relfovetmab binding affinity to human NGF is acceptable, this method is designed for a conservative first-in-humans (FIH) dose selection intended to reach a pharmacological response with minimal risk for adverse events. In addition, the NGF occupancy estimations in tissues are based on predictions using a mechanistic pharmacokinetics (PK) model, which is not considered properly validated from a human safety perspective. Nevertheless, the method can, to some extent, be considered helpful in the URA.

Margins to undesired pharmacological effects in humans may also be considered by comparing accidental self-injection with a volume of 0.2 mL (1.28 mg or 0.021 mg/kg) in relation to the pharmacological dose in cats (0.5-1.25 mg/kg). Due to the low margin between the two values (factor cca. 24), the potential for pharmacological effects after accidental self-injection is indicated (assuming a similar pharmacodynamic potential between species). Thus, regardless of the approach used, the margins to pharmacological effect in humans are low in the case of accidental self-injection. Therefore, the applicant’s proposal of an SPC warning concerning minor and reversible peripheral neurological symptoms (as noted in humans exposed to tanezumab after injection) is appropriate.

Warnings regarding special subpopulations (pregnant women, women trying to conceive, and breastfeeding women) as well as warnings for hypersensitivity reactions, including anaphylaxis reactions have been stated in the SPC (section 3.5 - 'Special precautions to be taken by the person administering the veterinary medicinal product to animals'). These warnings are appropriate and sufficient to ensure the safety of the user when the product is used as recommended.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided in accordance with VICH GL6. A Phase II ERA is not required, as the veterinary product will only be used in non-food producing species. Relfovetmab is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation: safety tests

Relfovetmab binds the neurotrophin NGF with high affinity, which is able to block NGF-induced functions.

The safety studies were all conducted in the target species (cat) and are summarised in Part 4 of this report, except for the specific TDAR test. No sign of immunotoxicity was reported in this GLP-compliant 70-day study.

No studies on reproductive developmental toxicity, genotoxicity or carcinogenicity were conducted with relfovetmab. This is considered acceptable for this kind of active substance.

A user risk assessment, overall performed in accordance with the CVMP 'Guideline on user safety for pharmaceutical veterinary medicinal products' (EMEA/CVMP/543/03-FINAL rev.1), has been provided. The veterinary medicinal product will be administered by a professional only (a veterinarian or a veterinarian's assistant) and exposure scenarios are well identified. The risk in the case of dermal and ocular contact is considered as being very low and does not raise any concern for the user. Relevant warnings are proposed for specialised populations (pregnant women, women trying to conceive, and breastfeeding women) and for hypersensitive individuals. With regard to accidental self-injection, the applicant has not performed a quantitative risk characterisation. This is considered acceptable for Portela. Relevant, appropriate and sufficient warnings have been proposed in the SPC.

No environmental risk is anticipated following the use of Portela in accordance with the SPC.

Part 4 – Efficacy

Pre-clinical studies

Method validations used in (pre-)clinical studies

For the quantitation of relfovetmab in cat serum, a chromatography and mass spectrometry method was developed and correctly validated. This method was only used for the pivotal clinical trial as a complement to the ligand binding assay. The other method used for the four main PK studies was a ligand-binding assay. The validation study for the quantification of relfovetmab in cat serum is considered acceptable, as it was conducted appropriately and in line with current guidance, and all predefined acceptance criteria were met. The reference standard was included in the *in vitro* characterisation program and was shown to be appropriate for its intended use as reference standard.

Anti-drug antibodies (ADAs) against relfovetmab in feline serum were determined using an electrochemiluminescence assay. A bridging assay was used, consisting of a screening and titre assay as well as a confirmatory assay. Detailed descriptions of the different assay procedures are provided. Relevant parameters were considered in the validation, mainly in line with guideline ICH M10. The validation as it has been conducted is acceptable, and the results of the experiments show that the acceptance criteria were met; where these were exceeded, respective explanations were given and retesting was performed, if applicable. It has been demonstrated that the electrochemiluminescence assay is capable to determine anti-drug antibodies (ADAs) against relfovetmab.

Neutralising anti-drug antibodies (ADAs) against relfovetmab in feline serum were detected using a competitive ligand binding electrochemiluminescence method. Overall, the validation of the study has been conducted appropriately.

Pharmacology

Pharmacodynamics

Several studies and references have been submitted in support of the mode of action and pharmacodynamic properties of relfovetmab.

Pharmacological characteristics determined by surface plasmon resonance (SPR) demonstrate that relfovetmab binds with high affinity to canine NGF (100% sequence identity), similar to other anti-NGF mAbs including bedinvetmab and izenivetmab. These data also demonstrate that relfovetmab selectively binds NGF and not the other neurotrophin family members.

In vitro potency of relfovetmab was assessed using cell-based assays. The results demonstrated that relfovetmab inhibited feline/canine NGF-induced neuronal cell proliferation, neurite outgrowth, and spontaneous neuronal firing.

In addition to studies concerning relfovetmab, the applicant has provided studies of izenivetmab and bedinvetmab for comparative reasons, and it can be concluded that relfovetmab and izenivetmab have a similar structure and functional activity.

In conclusion, the pharmacodynamics is well described, with results indicating that relfovetmab binding to NGF inhibits NGF-mediated cell signalling.

Pharmacokinetics

The ADME characteristics of relfovetmab in cats are expected to be similar to those of other monoclonal antibodies and thus specific ADME studies were deemed not necessary.

Pharmacokinetic (PK) data for relfovetmab in cats are available from a study: "Absolute Bioavailability and Pharmacokinetics of Relfovetmab in Cats with Naturally Occurring Osteoarthritis". The PK of relfovetmab was also studied in further studies of varying GLP status at higher doses and was quantified using various bioanalytical methods. However, only the studies that are considered pivotal in terms of PK are presented below.

In a non-GLP PK study of relfovetmab, cats (3.0-9.9 kg body weight) with naturally occurring OA were randomised into two sequences (A and B, n=6 per group) in a cross-over design to receive subcutaneous (s.c.) and intravenous (i.v.) injections at doses ranging from 0.5 to 1.17 mg/kg bw of the final formulation of relfovetmab at 49-day intervals. Blood samples were collected at 20 time points during the pre-dose and post-dose periods, covering 28 days after each administration.

Validated methods were used to quantify relfovetmab (ligand-binding assay method) and ADAs (multi-tier method) in feline serum.

Relfovetmab was quantifiable until day 28 post-dose for both routes of administration. PK parameters are presented below.

Clearance (CL) was 9.47 mL/kg/day and the volume of distribution was 52 mL/kg. Following s.c. dosing, the bioavailability was 41.8%, with a mean C_{max} of 2.95 µg/mL observed around 3 days post dose.

Table: Mean PK parameters following IV or SC dosing (overall, n=12)

Relfovetmab i.v.					
Parameter	**Units**	**Least Squares Mean**	**Standard Error**	**90% Confidence Limit**	**Range**
$t_{1/2}$	Days	5.06	0.439	4.25 to 5.86	3.21 to 7.16
$AUC_{0-\infty}$/Dose	µg*Days/mL/mg/kg	109	8.75	94.2 to 126	70.6 to 215
CL	mL/kg/Days	9.47	0.692	7.99 to 10.9	4.65 to 14.2
Vss	mL/kg	52.0	3.03	45.5 to 58.4	39.5 to 72.4
Relfovetmab s.c.					
C_{max}	µg/mL	2.95	0.282	2.41 to 3.62	1.76 to 4.36
C_{max}/Dose	µg/mL/mg/kg	4.08	0.209	3.66 to 4.55	3.25 to 5.9
T_{max}	Days	3.58	0.504	2.51 to 4.66	1 to 7
$t_{1/2}$	Days	5.42	0.439	4.62 to 6.23	3.57 to 8.58
$AUC_{0-\infty}$/Dose	µg*Days/mL/mg/kg	44.4	3.56	38.3 to 51.4	33.2 to 69.4
Bioavailability	(F*100) %	41.8	2.54	36.4 to 47.2	27.3 to 62

Despite the study not being GLP-compliant, its design, dosing regimen, sampling schedule, and analytical methods are appropriate and support the applicant's conclusions.

In a non-GLP pharmacokinetic study, five healthy cats received a single s.c. dose of 1.0 mg/kg bw of the final formulation of relfovetmab on day 0. Samples were collected up to day 112 to study the pharmacokinetics of relfovetmab over a longer period than the 28 days observed in the previous study. Samples were analysed using a validated ligand-binding assay method. The mAb was detected up to 42 days post dose.

In the GLP TAS study, the final formulation of relfovetmab was administered by subcutaneous injection to healthy domestic shorthair cats (3.5-7.2 kg body weight) at dose concentrations of 1.25, 3.75, and 6.25 mg/kg bw/dose on Days 1, 85, and 169. Samples were analysed using a validated ligand-binding assay method. Both maximum serum concentration (C_{max}) and the area-under-curve (AUC) (0-83 days) increased approximately in proportion to the dose and no accumulation was observed. This is adequately reflected in the SPC.

In the pivotal clinical trial, 307 client-owned cats with naturally occurring osteoarthritis (OA) were enrolled, with 153 receiving relfovetmab (0.5-1.25 mg/kg bw) and 154 receiving a placebo. Both treatments were administered subcutaneously at 90-day intervals for a total of three doses. Serum samples were collected at baseline, around 14 days after each dose (days 14, 104, and 194), before dosing on days 90 and 180, and at the end of the third dosing interval (day 270). A total of 153 subjects from the placebo group and 152 from the relfovetmab group were evaluable.

Relfovetmab concentrations were measured however, the number of quantifiable samples remained insufficient for accurate pharmacokinetic (PK) characterisation. This limitation affects the robustness of the PK conclusions, indicating that further refinement of the analytical methods or an increase in sample size is necessary to improve data reliability.

Additional PK studies are not deemed necessary in view of the nature of the molecule.

Dose determination and confirmation

Four pre-clinical non-GLP studies were presented and are summarised below. Several deviations and deficiencies in the conduct and reporting of these studies were highlighted. Two exploratory studies were conducted with a feline model using monoiodoacetate (MIA) to induce arthritis, while two other laboratory studies were carried out in cats with naturally occurring OA. The pivotal dose determination study is a GCP-compliant clinical trial conducted under field conditions with a similar study design as the pivotal clinical trial and using the recommended dose regimen (see section 'Clinical trials').

Two exploratory studies investigated the analgesic efficacy of relfovetmab in cats that were injected with MIA in the right stifle 8 months to 3 years (first study) or 15 months (second study) prior to study inclusion. Both studies were designed similarly and were blinded, randomised, placebo-controlled and non-GLP-compliant.

A non-final formulation of IVP was used. The dose of relfovetmab injected subcutaneously was higher than that eventually selected (5 mg/kg bw instead of 0.5-1.25 mg/kg bw). The placebo group received the vehicle. A third group was included to test a different antibody candidate in the second study.

Ten or eleven relfovetmab-treated cats from each study received one or two subcutaneous injections 36 days apart (first study). The cats were 3-5 years old (first study) or 1-2 years old (second study). Cats weighed 3 to 8 kg.

A Tekscan mat was used to measure the pressure corresponding to the body weight being distributed through the right hind limb. MIA-injected cats which showed more than a 10% reduction (only pre-defined in the protocol of the first study) in standing body weight distribution to the right hind limb were included in the study. Following MIA injection, force on the Tekscan mat was measured initially at weekly intervals and later monthly to monitor each cat's decline in force, to determine if a cat met inclusion criteria for study. Baseline was calculated as a mean of day -11, -7, and -5 (first study) and day -8, -2, and 0 (second study). Mean right hind Tekscan (kg) was measured after treatment with relfovetmab at day 0, 3, 8, 15, 22, 29, 36, 43 and 57 (first study) and day 0, 7, 14, 28 and 35

(second study).

In the first study, there was a significant improvement ($p=0.10$) in weight-bearing on the affected limb compared to placebo at all time points except at day 15, and also a significant change from baseline ($p<0.1$) at all timepoints except at day 15 and 43. Eight cats showed injection reactions seemingly pain-related in connection with the second injection, although it is not clear whether they were injected with vehicle or relfovetmab.

In the second study, the severity of the lameness (non-weight bearing) was already too far advanced in the MIA-injected joint to enable the evaluation of efficacy, and no difference between relfovetmab and the placebo was seen. Thus, the MIA-model is considered a harsh model which is not appropriate and clinically relevant for the evaluation of the pain associated with osteoarthritis. Moreover, the 3Rs principles were not followed in this study, as it was not conduced in a manner consistent with acceptable animal welfare.

Two other laboratory studies were conducted in cats with naturally occurring OA. A non-final formulation of the IVP was used. Both studies were designed similarly and were non-GLP, blinded, randomised and placebo controlled. A non-final formulation was used. For the first study, 3 groups of 16 cats received one single subcutaneous injection of either relfovetmab at 0.5 mg/kg bw or at 3.0 mg/kg bw or placebo (vehicle). In the second study, 3 groups of 16 cats received one single injection of either relfovetmab at 3.0 mg/kg bw or frunevetmab at 3.0 mg/kg bw or placebo (vehicle). The efficacy endpoints were the same for both studies (actimetry-motor activity, response to mechanical temporal summation (RMTS), Short Form of the Montreal Instrument for Cat Arthritis Testing by a Veterinarian questionnaire, stairs assays and tactile sensitivity), with assessments both at pre-treatment and then every 2 weeks until 8 weeks (first study) or 12 weeks (second study) post-treatment.

There were no significant differences between groups but some within-group significant changes from baseline. Both studies conducted in naturally occurring OA were inconclusive.

Therefore, it was concluded that the dose-effect at 0.5, 3, 6 and 12 mg/kg bw had to be investigated in the field (see the dose determination clinical trial).

Tolerance in the target animal species

The applicant presented one GLP-compliant pivotal target animal safety study, one non-GLP-compliant 3-month exploratory target animal safety study, one GLP-compliant 6-month study of overdose, one non-GLP-compliant study for comparing three different batches of the final formulation, and one non-GLP-compliant safety evaluation study of two doses of the final formulation. A specific TDAR test has also been summarised in part 3.

In addition, target animal safety data were obtained from the pharmacokinetic studies, dose selection study and other clinical trials.

Considerations regarding animal welfare

In accordance with Regulation (EU) 2019/6, all animal experiments shall adhere to the principles outlined in Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. It is acknowledged that in several of the studies, cats were housed individually and in cages that did not fully meet the minimum requirements of Directive 2010/63/EU. However, those studies were performed before Regulation (EU) 2019/06 came into force. These studies were conducted outside the EU, in the US, and complied fully with all applicable local and national animal welfare regulations and standards at the respective

facilities.

Also, one study reported a single mortality due to restraint during blood collection, and in two studies, a total of five cats out of 64, were euthanized following diagnosis of feline urologic syndrome (FUS).

The applicant acknowledged that the early euthanasia and the sudden death during restraint could present possible welfare concerns and stated that corrective measures were implemented for future studies to avoid similar scenarios.

Animals diagnosed with urinary obstruction due to FUS were identified well before becoming moribund and from the time of diagnosis until euthanasia all cats with FUS received appropriate treatment. In alignment with the principles of the 3Rs (Replacement, Reduction, Refinement), affected animals were humanely euthanized to prevent further decline in health and ensure animal welfare.

While inappropriate diet or suboptimal environment can contribute to FUS, the cats in these studies were maintained on standard, nutritionally complete laboratory and therapeutic diets, minimizing dietary confounders.

Pivotal TAS study

This was a GLP-compliant pivotal TAS study investigating the safety of administration of Portela at 1X (1.25 mg relfovetmab/kg bw), 3X (3.75 mg relfovetmab/kg bw) and 5X (6.25 mg relfovetmab/kg bw) the maximum recommended dose to groups of eight healthy domestic shorthair cats aged 20-28 months (3.5-7.2 kg bw) compared to placebo (saline). A final formulation of Portela was administered subcutaneously three times on days 1, 85 and 169, *i.e.* approximately at the recommended treatment interval (3 months). The study was designed and conducted in accordance with VICH GL43, which is considered appropriate. It should be noted that doses were incorrectly calculated on day 85, since they were based on day 1 body weight, and the IVP groups were given 8.0% (1X), 6.5% (3X), and 6.1% (5X) mean percentages below the calculated correct dose levels at day 85. Furthermore, an undetermined amount of IVP was lost from the dose site following injection for one male cat in dose group 3.75 mg/kg bw (3X), resulting in the cat showing no detectable levels of IVP after the first dose. Immunotoxicity was assessed with a subcutaneous administration of 0.1 mg of KLH on days 90 and 111.

Parameters evaluated were clinical observations (including injection site and neurological examinations, ophthalmology, body temperature), body weight, food consumption, blood pressure, electrocardiography, clinical pathology, gross necropsy and histopathology (including all tissues known to express NGF and its receptor – including lymphatic organs/tissues, nervous system and joints), joint radiographs, relfovetmab concentrations, and immunogenicity (anti-drug antibodies – ADAs).

There was no product-related mortality. The results demonstrated that all doses were generally well tolerated. Clinical findings were of the types expected in laboratory cats and there was no clear difference in frequency of events between groups. Pain on injection was reported in all groups, including the control group. No clear dose-related incidence was noted. However, as this effect is reported in other studies, it is stated in the current SPC. This is considered acceptable.

Skin lesions were noted in all groups, with a higher incidence in the two highest dosed groups. However, these slight to moderate pruritic ventral cervical skin lesions were also observed at 1.25 mg/kg bw (the maximum recommended dose) in one female. The observed skin reactions are described in section 3.10. 'Symptoms of overdose (and where applicable, emergency procedures and

antidotes)' of the SPC. In addition, pruritus and consequent skin scabs are stated in section 3.6. 'Adverse events' of the SPC (with the frequency uncommon).

There were no differences in any clinical pathology parameters that were considered to be test article-related, except for triglycerides. Product-related minimally to mildly increased triglycerides were noted in males at 3.75 and 6.25 mg relfovetmab/kg bw when all time points were combined. This is due to a high increase in one male from each group, which had higher baseline values prior to the first dose administration. Consequently, this finding was probably not treatment related.

For other clinical parameters, occasional values outside the reference range showed no dose response relationship, and were considered incidental, and/or negligible in magnitude.

No test article-related macroscopic or microscopic findings were noted in the bone and joints evaluated. There were no test article-related macroscopic or microscopic changes in selected neurological organs, except for a moderate ventricular dilatation (or hydrocephalus) in one male dosed with 6.25 mg/kg bw. While an association with the test article cannot be completely ruled out, ventricular dilatation is considered a spontaneous, often congenital, finding in a number of domestic and laboratory species, including cats. Other findings were concluded to be not product related.

Anomalies noted in cardiovascular parameters and ECG were identified. A further assessment by an expert chosen by the applicant concluded that these findings were unrelated to the test product. However, a comparison of findings across studies shows exposure to relfovetmab is associated with a modest dose-dependent reduction in heart rate that ranged from 5 to 20 bpm (4-16%; approximately 5 bpm or 4% in the 1.25 mg/kg bw [1X group]). The magnitude of these changes was small and the occurrence was sporadic. Furthermore, they were not associated with clinical signs and values remained within physiological range, and no histopathological finding was observed in the heart or associated nerves.

There were no product-related changes in radiographic findings, especially in joints, in either males or females up to 6.25 mg/kg bw/dose.

Three animals out of 24, all in relfovetmab-treated groups (one cat dosed with 1.25 mg/kg bw and two cats dosed with 3.75 mg/kg bw) exhibited treatment-induced immunogenicity (12.5%).

Statistical analysis of T cell-dependent antibody response (TDAR) to adjuvanted KLH reactive titres from the 1.25 mg/kg bw/dose animals revealed no significant differences when compared to the control group. It is noted in the final report that the samples for the two other groups that received relfovetmab (3.75 and 6.25 mg/kg bw/dose) were not analysed and were discarded. The applicant justified this absence by the fact that immunotoxicity was assessed at overdoses in several other studies, and then they considered that these measures in the overdose groups in this study were unnecessary. This should have been the subject of an amendment of the study protocol.

3-month exploratory safety study

This was a non-GLP-compliant exploratory TAS study investigating the safety of administration of relfovetmab at 2.4X (3 mg relfovetmab/kg bw), 9.6X (12 mg relfovetmab/kg bw), and 28.8X (36 mg relfovetmab/kg bw) the maximum recommended dose to groups of eight healthy domestic shorthair cats aged approximately 11 months (2.82-7.02 kg bw), compared to placebo (saline). The doses were initially intended to represent 1X, 4X, or 12X multiples of the maximum recommended dose. This means the 24 treated animals in this experiment were exposed to unintended high dosage levels. A non-final formulation of the product was administered subcutaneously four times at monthly intervals. Parameters evaluated were similar to the pivotal TAS study.

It should be noted that one cat was prematurely euthanised due to deteriorating physical condition associated with feline urologic syndrome (FUS). This finding was probably not related to the test

product. However, as this finding was reported in another study, husbandry conditions, including monitoring of animals, are questionable. This observation raised further concerns on possible deficiencies in animal welfare. See the general considerations regarding animal welfare included above.

In terminal-necropsy animals, the most common treatment-related finding consisted of focal areas of skin discolouration (red) or alopecia (hairless) of the face/head/neck, recorded variously as "sore" or "lesion" or "focus". These areas were noted in 1 of 4 low- and high-dose males, and in 1, 2, and 3 (of 4 each) low-, mid-, and high-dose females (respectively). Microscopic examination revealed ulcers or areas of epidermal hyperplasia. The cause of these lesions and of the dose-related characteristic are undetermined. Those reactions are mentioned in the section 3.10. of the SPC.

There was no product-related mortality. Clinical findings were generally of the types expected in laboratory cats. Mild reactions at the injection site were noted at histopathology but may have been due to the injection rather than the test substance, as similar findings were observed in controls. There were no differences in clinical pathology parameters that were considered to be test article related. One cat in the 2.4X dose group was identified with bradycardia with sinus arrhythmia at day 97, but this observation was not considered test article related.

The incidence of treatment-induced immunogenicity in the study was 8.3% for the drug-treated animals (2/24). No sign of immunotoxicity was observed.

6-month safety study

This was a GLP-compliant TAS study investigating the safety of administration of relfovetmab at 3.8X (4.8 mg relfovetmab/kg bw), 11.5X (14.4 mg relfovetmab/kg bw) and 23X (28.8 mg relfovetmab/kg bw) the maximum recommended dose to groups of eight healthy domestic shorthair cats aged approximately 11 months (2.80-6.17 kg bw), compared to placebo (saline). The doses were initially intended to represent 1X, 4X, or 6X multiples of the maximum recommended dose. This means the 24 treated animals in this experiment were exposed to unintended high dosage levels. A non-final formulation of the product was administered subcutaneously once every 28 days for 7 treatments. Parameters evaluated were similar to the pivotal TAS study.

It should be noted that four male cats (2 from the control group, 1 dosed at 14.4 mg/kg bw and 1 dosed at 28.8 mg/kg bw) had to be prematurely euthanised due to deteriorating physical condition associated with feline urologic syndrome (FUS). This finding was probably not related to the test product. However, as a similar finding was reported in another study, husbandry conditions, including monitoring of animals, are questionable. Furthermore, a cat died due to restraint during blood collection. These observations raised further concerns on possible deficiencies in animal welfare. See the general considerations regarding animal welfare included above.

Anomalies in cardiovascular parameters and ECG were identified. A further assessment by an expert chosen by the applicant concluded that these findings were unrelated to the test product. However, a comparison of findings across studies shows that exposure to relfovetmab is associated with a modest dose-dependent reduction in heart rate that ranged from 5 to 20 bpm (4-16%; approximately 5 bpm or 4% in the 1.25 mg/kg bw [1X group]) (see pivotal TAS study). The magnitude of these changes was small and the occurrence was sporadic. Furthermore, they were not associated with clinical signs, and values remained within physiological range.

Also, an increase in creatinine in the 14.4 mg/kg bw (11.5X) group and a minimal increase in SDMA in the 4.8 and 14.4 mg/kg bw (3.8X and 11.5X) groups was identified but was regarded as a result of biological difference.

Minimal to focal lesions in bones and joints were observed in control and treated cats.

However, focal, unilateral and minimal cartilage degeneration and focal minimal bone cyst were reported from the 14.4 or 28.8 mg relfovetmab/kg bw groups and not reported in control animals. Additional findings such as osteophyte at the right acetabulum, indicating the presence of degenerative joint disease, and meniscal mineralisation in the right femorotibial joint, were observed in one male in the 4.8 and 14.4 mg/kg bw IVP groups, respectively. These findings were not present at pre-treatment. It was concluded that although some of these changes were not observed in concurrent controls, there were no patterns, trends, or correlating data to suggest that these changes were related to administration of relfovetmab based on incidence, nature, severity and distribution of changes.

Treatment-emergent immunogenicity was observed in 8.3% of the relfovetmab-treated animals (2/24). No signs of immunotoxicity were observed.

Safety evaluation study of a single 5X dose of three batches

This was a non-GLP-compliant study comparing the tolerance to different batches of the final formulation after a single subcutaneous administration of 5X the maximum recommended dose when administered to groups of ten healthy domestic shorthair cats older than 11 months of age (2.4-6.9 kg bw), compared to placebo (saline). Parameters evaluated were similar to the pivotal TAS study (except for the immunogenicity, which was not assessed in this study).

No product-related mortality was reported.

There was a visible trend indicating that test article administration resulted in more non-zero pain scores as compared to control article. Review of these data, however, did not indicate a batch-effect on pain or discomfort at the time of injection.

There were no treatment-related abnormal clinical observations. Most documented abnormalities were intermittent, non-specific, and were consistent with conditions commonly identified in colony felines at the test facility.

There was no batch-effect on assessed safety parameters.

Safety evaluation of two doses

This was a non-GLP-compliant study investigating the safety of administration of the final formulation at the maximum recommended dose (1.25 mg relfovetmab/kg bw) twice (on Days 0 and 14) to a group of 10 healthy domestic shorthair cats older than 11 months (3.0-5.7 kg bw), compared to placebo (saline).

Parameters evaluated were similar to the pivotal TAS study (except for the immunogenicity, which was not assessed in this study).

There was an observable trend indicating pain on test article administration compared to control article. Pain is included as an adverse event in section 3.6. of the SPC.

Polyuria was observed only in the treated group (2 cats). However, based on values of blood chemical parameters (BUN and creatinine), which remained in normal physiological ranges, and as no systemic signs were associated with observed polyuria, no systemic disease is suspected.

Before the administration of the product, one treated cat had several observations related to a linear abrasion on the left side of the nose. This cat subsequently developed two new skin lesions on days 17 and 23. Skin reactions occurred in two cats in the control group and two cats in the treatment group (1.25 mg/kg bw), which included the animal with the pre-existing lesions. Consequently, no relationship with the product can be established from the results of this study.

Other clinical observations were noted with the same frequency/incidence in the control and treated groups and were considered not to be product related. This included injection site reactions.

Clinical parameters showed occasional values outside the reference range and were considered incidental, and/or negligible in magnitude.

Safety evaluation in the PK studies

No mortality, adverse events, or hypersensitivity reactions were reported in those studies.

Safety evaluation in the dose selection study

The test product (non-final formulation) was subcutaneously administered on a single occasion at 0 (saline), 0.5, 3, 6 or 12 mg relfovetmab/kg bw to client-owned cats (older than 12 months of age) with osteoarthritis. On days 14, 42, 70, 98, 126 and 154 (±3 days each), the owners were contacted by blinded study personnel via phone. Adverse events were considered typical for the population of cats enrolled. Overall, the numbers and frequencies of abnormal health events were similar across all groups. Pain on injection was noted. This effect is stated in the SPC, section 3.6. 'Adverse events'.

Skin disorders were reported in 11 relfovetmab-treated cats. One cat presented such lesions at 0.5 mg/kg bw (the smallest claimed dose). Dermatitis and skin scabs are appropriately mentioned in section 3.6. 'Adverse events' of the SPC.

In the 0.5 mg/kg bw group, 4.4% of animals (3/68) developed treatment-emergent immunogenicity.

Safety evaluation in clinical trials

In a clinical trial, the test product (non-final formulation) was subcutaneously administered at 0 (saline) or 3 mg relfovetmab/kg bw to client-owned cats (aged from 3 to 20 years) with OA on days 0, 28 and 56. On days 14, 42, 70 as well as 2 and 8 weeks post study, the owners were contacted by blinded study personnel via phone. Adverse events were considered typical for a population of cats with OA and occurred at a similar frequency in both groups. An adverse response (e.g. vocalisation) immediately upon administration occurred in 5.6% of relfovetmab-treated cats (8 of 15 doses involving five cats) vs 1.1% of placebo-treated cats (1 of 3 doses involving one cat). A single vocalisation/a meow is the expression of pain and not an adverse reaction. Immediate pain upon injection (as a very common adverse event) is appropriately stated in SPC section 3.6. 'Adverse events'.

Also in this trial, a higher frequency of treatment-related AEs with a causality of musculoskeletal disorders occurring during the trial was reported in the IVP-treated cats (17.8%) compared to placebo-treated cats (9.6%). In the post-study follow-up, there were also more musculoskeletal adverse events in the IVP group (8.9%) versus 4.3% in the placebo group. However, based on the small number of affected cats and the absence of significant difference in the incidence between both groups, these findings can be considered as not product related.

Immunogenicity due to relfovetmab administration developed in 2.3% of evaluable cats but had no apparent impact on efficacy or safety.

In the pivotal clinical trial, client-owned cats with OA were subcutaneously administered the IVP (final formulation) at 0 (saline) or 0.5-1.25 mg relfovetmab/kg bw on days 0, 90 and 180. Owners were contacted by study site personnel via phone for safety follow-up on days 30, 60, 120, 150, 210, 240 and 284.

Adverse events were considered typical for a population of cats with OA and in general occurred at a similar frequency in both groups except for application site disorders (pain) that were observed in 3/154 (1.9%) cats in placebo group and in 17/153 (11.1%) cats in relfovetmab group. This effect is

currently stated in the SPC, section 3.6. 'Adverse events'. 3.92% of animals in the placebo group were detected with ADAs vs. 1.97% in the relfovetmab group. The applicant considered that the highest incidence in the placebo group can be considered false positive findings. Presence of ADAs before the administration of the product may result from previous exposure to similar or related proteins, but such antibodies are also found in treatment-naïve patients. Thus, it cannot be excluded that the immunogenicity observed after treatment in the untreated cats has another origin.

In this pivotal clinical trial, no cats with kidney disease IRIS stage >3 were included. The use of the product in such cases should be based on a benefit-risk assessment performed by the responsible veterinarian. A related warning has been added in section 3.5. 'Special precaution for use' of the SPC.

In addition, in order to strictly reflect the conditions of the pivotal clinical trial, the text "*In the clinical trials, joint radiographs were only taken at screening. Therefore, potential negative effects on the progression of the osteoarthritis have not been investigated."* has been included in SPC section 3.5 'Special precautions for safe use in the target species'.

Overall, the safety of the veterinary medicinal product was tested in cats weighing from 1.9 kg in the presented clinical trials.

Immunotoxicity

From all studies presented, it appears that immune function was not impacted by the test product.

Immunogenicity

Immunogenicity was assessed in 11 safety/pre-clinical/clinical studies.

Immunogenicity was not observed in 3 out of 11 studies. When observed, treatment-emergent immunogenicity varied from 2% to 12.5% in the different studies. This results in an average of 5%. However, the dose of relfovetmab applied was variable between studies, as well as the number of administrations and the formulation used. The applicant has considered whether there were any trends towards increased immunogenicity with repeated dosing; however, no such trends were noted. Anti-drug antibodies were either persistent or transient following repeated administrations. However, no information is available over a treatment period longer than 9 months.

Approximately 2% (1.97%) of immunogenicity was reported in pivotal clinical trial conducted with the final formulation administered three consecutive times at the recommended dose in cats suffering from osteoarthritis.

From the dose selection clinical trial, in the 0.5 mg/kg bw group 4.4% of animals (3/68) developed treatment-emergent immunogenicity.

Regarding the impact of immunogenicity on efficacy, reduction of efficacy cannot be excluded in cases with confirmed immunogenicity, as decrease of relfovetmab serum concentration and presence of neutralising antibodies have been reported. Impact on efficacy based on CSOM, owner assessment and VCA treatment success was unclear in the clinical trials. Regarding the impact of immunogenicity on safety, given the low number of cats with anti-drug antibodies, no conclusion can be drawn.

This is reflected in the SPC (section 3.4).

Clinical trials

Three clinical trials were conducted in client-owned cats to assess the efficacy and safety of the investigational veterinary product (IVP) containing relfovetmab for the alleviation of pain associated with OA. All trials were multi-centre, placebo-controlled, double-blinded, randomised and were

conducted according to the standards of the VICH GL9 on GCP.

Dose determination study

This dose determination clinical trial was multi-centre (10 sites in France, 12 sites in Spain and 18 sites in Italy) and compared the efficacy and safety of four different doses of relfovetmab used for the alleviation of pain associated with naturally occurring OA. Enrolled client-owned cats showed clinical signs of OA and pain upon orthopaedic examination in at least two joints or spinal segments, confirmed by radiographic evidence. Before enrolment, sufficient wash-out periods were applied for concomitant treatment providing pain relief for OA. Cats were allocated randomly to five treatment groups: placebo (T01) or relfovetmab at four different doses of 0.5 mg/kg bw (T02), 3 mg/kg bw (T03), 6 mg/kg bw (T04) or 12 mg/kg bw (T05). All treatments were administered once on day 0 (D0) as a subcutaneous injection. Initially the cats were to be followed up for 84 days after treatment, but the protocol was amended to extend the follow-up period to 168 days.

Owners evaluated the clinical condition of their cats related to OA using Client-Specific Outcome Measures (CSOM). The CSOM is based on the evaluation of physical activities that are difficult for the cat to perform as a result of OA, or activities that have changed as a result of OA. Three activities were identified by the owner for each cat individually before D0 and were assessed during the study by the owner by rating the degree of impairment on a five-grade scale (scores 1 to 5). All post-treatment assessments on D14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154 and 168 had to be done by the same owner who completed the assessment on D0. Owners also assessed the overall response to treatment (Owner Overall Assessment) on a four-grade scale, as 'Excellent', 'Good', 'Fair' or 'Poor'. The proportion of animals with either "Good" or "Excellent" treatment response and with only "Excellent" treatment response were analysed separately.

The examining veterinarian performed an orthopaedic examination on all joints of all limbs and on each segment of the spinal column at each monthly visit on D0, 28, 56, 84, 112, 140 and 168. Pain, crepitus, effusion and thickening were scored on all the limbs except for the hip where only pain and crepitus were scored and the spinal segments scored for pain only. Pain on palpation was scored on a five-grade scale. Crepitus, effusion and thickening were scored on a three-grade scale. In addition to the orthopaedic examination score (OES), the overall pain level of each cat was assessed on a five-grade scale (Veterinary Categorical Assessment, VCA). Treatment success for the VCA was defined as a decrease of ≥1 score compared to D0. An animal's pain score was deemed to have improved if the pain score of at least one joint or spinal segment was lower than the pain score on D0 and none of the joints or spinal segments had an increased pain score compared to D0.

The primary efficacy endpoint was the Total CSOM (TCSOM) score. Secondary endpoints included treatment success on CSOM, Owner Overall Assessment, the OES and VCA. Treatment success on CSOM was defined as an improvement (reduction) of the Total CSOM scores by ≥2 and with no increase in any individual CSOM activity score post-treatment compared to D0.

Cats were considered treatment failures if they were withdrawn for lack of efficacy or due to an adverse event (AE) possibly related to IVP treatment or administration of a rescue treatment.

In total, 327 cats were enrolled, including 68 placebo-treated and 259 IVP-treated cats at the dose of 0.5 mg/kg bw (T02; n=68), 3.0 mg/kg bw (T03; n=62), 6.0 mg/kg bw (T04; n=64) or 12.0 mg/kg bw (T05; n=65). Ten animals completed the study prior to implementation of the study period extensions. From the remaining 317 animals, 58 cats did not complete the study on D168: 13, 11, 9, 13, and 12 cats in T01, T02, T03, T04 and T05 groups, respectively. These included 5 cats in T01 (placebo) and 17 in the IVP treated groups (5, 4, 4 and 4 cats in T02, T03, T04 and T05 groups, respectively) that were withdrawn due to lack of efficacy. Adverse events that resulted in death or euthanasia were reported for 16 cats: 5, 3, 3, 3 and 2 cats in T01, T02, T03, T04 and T05 groups,

respectively. Two abnormal health events were reported (1 in T02 and 1 in T04). In total, 259 cats completed the study on D168.

After D0, the TCSOM scores decreased in all groups, indicating improvement. Statistically significant differences in TCSOM scores between IVP-treated groups and placebo groups were seen at all timepoints except on D154 for T02. For the placebo-treated group, treatment success (TS) ranged between 30.8% on D14 and 50.8% on D56, while in the treated groups the highest TS was seen on D42 in T02 (77.8%), on D56 in T03 (82.8%), on D70 in T04 (82.5%) and T05 (73.3%). The difference in TCSOM scores TS between IVP-treated and placebo groups were statistically significant at all timepoints up to D140 (except on D140 in T03). On D154 and D168, the overall treatment effect was not significant. A significantly higher percentage of cats achieved Good/Excellent treatment response at the Owner Overall Assessment in T03, T04 and T05 IVP-treated groups until D98, compared to placebo (T02 group until D84). As of D126, the overall treatment effect was not significant. According to the veterinarians' assessments, before treatment (D0), more than 50% of the cats from each group (61.2% to 80%) had severe pain (scores 3 and 4) at the palpation/manipulation of their joints. Pain scores decreased in all groups following treatment. In the placebo group 61.2%, 41.5%, 36.8% and 38.3% of the cats had severe pain on D0, 28, 56 and 84, respectively. The proportion of cats with severe pain decreased in all IVP-treated groups over 84 days (in T02 from 79.1% to 25%, in T03 from 66.1% to 14.8%, in T04 from 73.4% to 14.5% and in T05 from 80% to 25%). The treatment success for the VCA was significantly higher ($p \leq 0.0086$) in all IVP-treated groups at all timepoints compared to placebo. Numerically, the maximum treatment response in T02 was seen on D56 (69.4%), in T03 on D28 (71.4%), in T04 on D56 (82.5%) and in T05 on D56 (76.8%).

Groupwise statistical comparison of the proportion of cats with improved pain scores on the orthopaedic examination showed significant difference between the IVP-treated groups and the placebo until D84, except on D28 for T03. From D112 onwards, the overall treatment effect was not significant and groupwise comparisons were not tested further.

Adverse events were considered typical for the population of geriatric cats enrolled. Overall, the numbers and frequencies of abnormal health events were similar across all groups, except for skin disorders that were reported in 11 IVP-treated cats (n=1 in T02; n=2 in T03; n=5 in T04; n=3 in T05) and in none of the placebo group. Immediate reactions to the injection such as pain were observed in 21 cats of all groups including the placebo.

In summary, the maximum treatment response was seen between Days 42 and 98 in the IVP-treated groups. Significant differences in all efficacy endpoints were seen between all IVP-treated groups vs placebo until at least D84 (except the orthopaedic examination pain score improvement on D28 in T03). Nevertheless, all hypothesis testing was conducted at the 10% level of significance ($p \leq 0.1$).

Statistically significant differences could not be consistently detected between any of the IVP-treated groups. In conclusion, a statistically significant difference in efficacy (TCSOM) was shown between all treated groups and the placebo group until Day 126. The duration of efficacy for the alleviation of pain associated with OA in cats treated at the relfovetmab dose of 0.5 mg/kg bw lasted for at least three months. Similar safety profiles were observed in all groups.

Pivotal clinical trial

This multi-centre pivotal clinical trial (12 sites in France, 15 sites in Italy, 4 sites in Hungary and 10 sites in Portugal) included two treatment groups (T01, placebo-treated cats and T02, IVP-treated cats). The efficacy and safety of the IVP for the treatment of pain associated with OA were assessed in client-owned cats receiving either relfovetmab at the proposed dose range (0.5 to 1.25 mg/kg bw) or placebo, administered subcutaneously every three months, on three occasions (D0, 90 and D180).

The same inclusion and exclusion criteria as for the other clinical trials were applied, except that cats had to weigh at least 1 kg in this trial. In total, 307 cats (154 placebo-treated; 153 IVP-treated) were included: 153 females and 154 males of various breeds including 14% purebred, 1 to 21 years old (mean age of 10.9 years), weighing 2.1 to 11.8 kg.

Efficacy assessments included owner-assessed CSOM, Owner Overall Assessment, actual quality of life, actual temperament, change in quality of life, temperament and happiness assessments by the owners and veterinary orthopaedic examination (OE) and Veterinary Categorical Assessment (VCA). Owners assessed the actual score and change from pre-treatment of quality of life and temperament and the change from pre-treatment of happiness on a five-grade scale. Assessments were performed on D3, 7, 14, 30, 60, 90, 104, 120, 150, 180, 194, 210, 240 and 270 and had to be done by the same owner who completed the assessment on D0. The orthopaedic examination with the OE scoring and the VCA was made on D0, 14, 90, 104, 180, 194 and 270.

The primary efficacy endpoint was the owner assessed treatment success on CSOM on D90. Treatment success on CSOM was defined as an improvement (reduction) of the Total CSOM scores by ≥2 and with no increase in any individual CSOM activity score post treatment compared to D0. Cats were considered treatment failures from the date of removal if they were withdrawn for lack of efficacy or for AEs possibly related to treatment or received rescue treatment.

Secondary endpoints included treatment success on CSOM (other than on D90), Total CSOM scores, Owner Overall Assessment, quality of life, temperament and happiness assessments by the owner, veterinary orthopaedic examination results and VCA. The proportion of animals that improved on the quality of life, temperament and happiness assessments were analysed separately by timepoint using the same method as for treatment success based on CSOM scores. Treatment success on VCA was defined as a decrease (improvement) of ≥1 score compared to D0. All hypothesis testing was conducted at the 2-sided 5% level of significance ($p \leq 0.05$).

45 cats (29.2%) in the placebo-treated group and 27 cats (17.6%) in the IVP-treated group were withdrawn from the study, thus 109 cats in T01 (70.8%) and 126 cats in T02 (82.4%) completed the study on day 270.

A significant difference in treatment success on CSOM scores between IVP-treated cats (72.9%) vs placebo (46.2%) was seen at day 90 ($p=0.0006$). Significant differences in treatment success on CSOM scores were found at all other timepoints. Already on day 3, 40.5% of the IVP-treated cats were considered treatment success based on CSOM versus 21.6% in the control group ($p=0.0025$). Treatment success of 72.9%, 78.9% and 79.3% of the IVP-treated cats and 46.2%, 41.4% and 41.8% of placebo-treated cats was seen at day 90, day 180 and day 270, i.e. 3 months after one, two and three treatments, respectively.

Mean pre-treatment Total CSOM scores (D0) were similar among the groups: 10.9 in T01 and 11.0 in T02 (out of the maximum score of 15), indicating moderate to severe mobility impairment. Mean Total CSOM scores were significantly lower in the IVP group at all timepoints ($p \leq 0.0007$). At Day 90, the mean CSOM score was 8.6 in the placebo group versus 7.2 in the Portela group ($P<0.0001$), indicating a moderate improvement in the mean CSOM score. The percentage of cats with "Good" or "Excellent" Owner Overall Assessment was significantly higher in the IVP group at all assessment points ($p \leq 0.0197$) and ranged between 24.5% on D3 and 81.9% on Day 194. Compared to the placebo group, a significantly higher proportion of IVP-treated cats were rated as 'Greatly Improved' or 'Slightly Improved' on the change in the quality-of-life assessment ($p \leq 0.0022$) and on the change in temperament assessment ($p \leq 0.0007$) and as 'Much Happier' or 'Slightly Happier' on the change in happiness assessment ($p \leq 0.0125$) at all timepoints.

The treatment success rate of T02 on the VCA was significantly higher at all time points (p≤0.0006). Treatment success rate in T01 ranged between 27.8% on D14 and 37.3% on D194 and in T02 between 60.6% on D90 and 79.8% on D194. Three months after each treatment, on D90, D180 and D270, treatment success rate was 35.5%, 33.1% and 31.9% in T01 and 60.6%, 72.2% and 71.4 % in T02, respectively. These figures have been included in sub-section Clinical trials of section 4.2 of SPC.

Adverse events were considered typical for a population of cats with OA and occurred at a similar frequency in both groups, except for disorders at administration site that were observed in 3/154 (1.9%) cats in the placebo group and 17/153 (11.1%) cats in the IVP-treated group. The disorders at administration site were mostly pain reactions to the injection, which was diagnosed in 11 IVP-treated cats (7.2%) and two placebo-treated cats (1.3%). Treatment-emergent immunogenicity developed in 3.92% (6/153) of the evaluable cases in the placebo group and 1.97% (3/152) of the evaluable cases in the IVP-treated group but had no apparent impact on efficacy or safety.

The study results demonstrated efficacy and safety of relfovetmab (0.5-1.25 mg/kg bw) administered by subcutaneous injection every three months to cats for the alleviation of pain associated with OA, with a rapid onset of efficacy as early as three days after first dose. The number needed to treat (NNT) calculated for the success rate on CSOM scores at day 90 (1/(0.462-0.729)) and NNT for the Veterinary Categorical Assessment (1/(0.355-0.606)) is 4.

Supportive (overdose) clinical trial

Another multi-centre (39 sites in USA and 2 sites in Canada) clinical trial investigated the efficacy and safety of three consecutive monthly subcutaneous administrations of relfovetmab at the dose of 3.0-4.8 mg/kg bw (overdose) in comparison to a placebo. One hundred and eighty-four client-owned cats were randomised into 2 treatment groups: placebo (saline, n=94) or relfovetmab (3 to 4.8 mg/kg bw, n=90). Enrolment was stopped earlier than planned because new results from a separate clinical trial indicated that relfovetmab was effective at a lower dose and for more than 1 month. On D0 (day of treatment), the cats were 3 to 20 years old (mean of 12.8 years) and weighed from 2.5 to 11.4 kg (mean of 5.4 kg).

The primary efficacy endpoint was treatment success (TS) at D28 based on owner assessment using the Client-Specific Outcome Measures (CSOM). Secondary endpoints were CSOM treatment success (D14, 56, 84), Total CSOM scores (TCSOM), Owner Global Assessment (OGA) (D14, 28, 56, 84) and Veterinary Categorical Assessment-OA Pain (VCA) (D28, 56, 84). CSOM TS was defined as a reduction of ≥2 in TCSOM with no increase in score for any individual CSOM activity versus baseline on D0. VCA TS was defined as a decrease in score ≥1 versus D0 baseline.

The D0 median TCSOM score was 11. Despite the early termination of enrolment, there was a statistically significant difference in treatment success between IVP-treated group and placebo-group at D14 (65.1% versus 42.3%; p=0.0059), at D28 (68.6% vs 48.9%, p=0.0129), at D56 (82.5% vs 64.6%; p=0.0133), but not at D84 (78.5% versus 67.1%). Mean TCSOM scores vs placebo were significantly lower at D14, 28, 56 and 84 (p≤0.0203). The percentage of cats with OGA of "Good" or "Excellent" was higher in relfovetmab versus placebo groups at all assessment points: D14 (30.9% vs 21.8%), D28 (45.9% vs 33.4%), D56 (67.5% versus 54.1%), D84 (73.5% versus 57.2%). A significant difference in VCA treatment success between IVP-treated group and placebo-group was seen at D56 (76.2% versus 54%, p=0.0048) and at D84 (77.9% versus 57.6%, p=0.0081), but not at D28.

The number and frequency of adverse events due to concomitant disease were similar in both treatment groups: 55 (58.5%) in the placebo group and 58 (64.4%) in the IVP group. Overall, none of the abnormal health events were considered to be related to the relfovetmab treatment. Pain at

injection occurred in 5.6% of IVP-treated cats (8 of 15 doses in five cats) versus 1.1% of placebo-treated cats (1 of 3 doses in one cat). Despite the early termination of enrolment, efficacy and safety for the treatment of pain associated with OA in cats were shown over three consecutive monthly treatments.

Overall conclusions on efficacy

Considerations regarding animal welfare

In accordance with Regulation (EU) 2019/6, all animal experiments shall adhere to the principles outlined in Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. It is acknowledged that in several of the studies, cats were housed individually and in cages that did not fully meet the minimum requirements of Directive 2010/63/EU. However, those studies were performed before Regulation (EU) 2019/06 was in force. These studies were conducted outside the EU, in the US, and complied fully with all applicable local and national animal welfare regulations and standards at the respective facilities.

Bioanalytical methods

The methods used for the quantitation of relfovetmab in cat serum, the determination of anti-drug antibodies (ADAs) and neutralising anti-drug antibodies (ADAs) against relfovetmab in cat serum were confirmed to be appropriate and satisfactorily validated.

Pharmacodynamics

Pharmacodynamics is well described, with results indicating that relfovetmab binding to NGF inhibits NGF-mediated cell signalling. The pharmacodynamic properties are adequately outlined in section 4.2 of the SPC.

Pharmacokinetics

The pharmacokinetics of relfovetmab in cats has been well studied and characterised in 17 studies. Four of these studies used the final formulation with a validated assay method and were performed after subcutaneous administration of the recommended dose as indicated in the SPC.

Section 4.3 of the SPC was adequately documented, based on pharmacokinetic parameters from pivotal studies.

Dose determination and confirmation

Four pre-clinical exploratory studies (non-GLP compliant) were conducted using a non-final formulation of the product.

In the mono-iodoacetate induced arthritis model used in two studies, the dose rate of relfovetmab used was 5 mg/kg bw, while the recommended dose is 0.5-1.25 mg/kg bw. In the first study, there was a significant improvement ($p=0.10$) in weight bearing on the affected limb compared to placebo at all time points except at D15 and also a significant change from baseline ($P<0.1$) at all timepoints except at D15 and D43. In the second study, the severity of the lameness was already too far advanced to enable the evaluation of efficacy and no difference between relfovetmab and the placebo was seen.

The other two laboratory studies carried out in cats with naturally occurring OA and treated at the relfovetmab dose rate of 0.5 or 3 mg/kg bw were not conclusive as no significant differences between groups were observed, but only some within-group significant changes from baseline. Therefore, it

was concluded that the dose-effect relationship had to be investigated in the field (see the dose determination clinical trial).

Tolerance in the target animal species

In the pivotal TAS study conducted with Portela, no serious adverse events were reported with up to 5 times the maximum recommended dose. The same observation was made in two other studies, one conducted at 5X the maximum recommended dose and the other at the maximum (1X) recommended dose. However, possible treatment-related skin reactions at the recommended dose (reported also in other safety studies with a non-final formulation) were noted.

Based on the occurrence of dermatitis, pruritus and skin scabs in the clinical trials, those adverse events have been included in section 3.6 of the SPC 'Adverse events'.

No serious adverse events were reported in either field studies, which were conducted at the recommended doses. Treatment-related effect - injection site pain - was noted and is included in the SPC. Injection site reactions at the recommended dose (swelling and hair loss) are also included in the SPC.

From all studies presented, it appears that immune function was not impacted by the test product.

In the pivotal clinical trial conducted with the final formulation of Portela, the immunogenicity at the recommended dosage administered 3 consecutive times was approximately 2% (3 out of 152 cats). In the dose selection clinical trial, 4.4% of animals (3/68) treated once at a dose of 0.5 mg relfovetmab/kg bw group, developed treatment-emergent immunogenicity.

Regarding impact of immunogenicity on efficacy and safety, no clear conclusion can be drawn. This has been reflected in the SPC (section 3.4).

Clinical trials

Three clinical trials were conducted in client-owned cats to assess the efficacy and safety of the IVP containing relfovetmab for the alleviation of pain associated with osteoarthritis (OA) in cats. All trials were multicentre, placebo-controlled, double blinded, randomised and were conducted according to the standards of the VICH GCP. A non-final formulation was used in the dose determination clinical trial and in the supportive overdose clinical trial.

One clinical trial conducted in US and Canada investigated the efficacy of relfovetmab at a dose range of 3.0-4.8 mg/kg bw instead of the recommended dose range (0.5 to 1.25 mg/kg bw). Despite the early termination of enrolment, efficacy and safety for the alleviation of pain associated with OA in cats were shown over three consecutive monthly administrations of the overdose of 3.0-4.8 mg/kg bw.

The dose determination clinical trial tested the efficacy and safety of a single subcutaneous injection of four relfovetmab dose levels (0.5, 3, 6 or 12 mg/kg bw) compared to a placebo. At all dose levels, significant and clinically meaningful efficacy for the treatment for the pain associated with OA in cats lasted for at least three months. Similar safety profiles were observed in all groups.

The findings of the pivotal clinical trial confirmed the efficacy of the IVP administered 3 times subcutaneously at 3-monthly intervals at a relfovetmab dose range of 0.5 to 1.25 mg/kg bw (recommended dose).

The efficacy at the recommended dose was tested in cats weighing between 2.5 and 13.7 kg in the clinical trials. This is correctly reflected in the dosing chart in section 3.9 of SPC.

Adverse events were considered typical for a population of cats with OA and occurred at a similar frequency in both treated and placebo groups, except for disorders at administration site that were

observed in 3/154 (1.9%) cats in the placebo group and in 17/153 (11.1%) cats in the IVP-treated group. The number needed to treat (NNT) calculated for the success rate on CSOM scores at day 90 and NNT for the Veterinary Categorical Assessment is 4.

Part 5 – Benefit-risk assessment

Introduction

Portela solution for injection contains 2.5 mg or 6.4 mg of relfovetmab in 1 ml of solution. The product is intended for administration by subcutaneous use, and the target species is cat. The active substance of Portela is relfovetmab, a felinised monoclonal antibody against 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 recommended dose is 0.5-1.25 mg/kg body weight, once every three months.

Portela solution for injection for cats is presented in cardboard boxes containing 1, 2 or 6 vials of 1 mL each.

The applicant applied for a new active substance status for relfovetmab.

The application has been submitted in accordance with Article 8 of Regulation (EU) 2019/6 (full application).

Benefit assessment

Direct benefit

Portela administered subcutaneously at the dose of 0.5-1.25 mg relfovetmab/kg body weight every 3 months for 3 doses showed clear evidence of efficacy under field conditions. The results indicate that relfovetmab significantly improved scores as assessed by cat owners using client-specific outcome measures (CSOM), and reduced pain as assessed by veterinarians using a categorical pain assessment. These improvements were consistent over a 270-day period.

Additional benefits

Portela increases the range of available treatment possibilities against osteoarthritis in cats.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Satisfactory answers have been provided by the applicant to allow for a positive CVMP opinion regarding quality.

Risks for the target animal

Administration of Portela in accordance with SPC recommendations did not result in serious adverse events. The main reported adverse event at the recommended dose was pain upon injection, and skin lesions were reported at recommended dose and at overdose. Injection site reactions (*i.e.* swelling and hair loss) have also been stated as adverse events.

Immunogenicity appears to have been appropriately assessed and is overall well reflected in the

SPC.

Text relating to the rapidly progressive osteoarthritis observed in human patients receiving anti-NGF monoclonal antibodies has been added in SPC section 3.8, even if such event was not evidenced from the studies provided with relfovetmab in cats. An additional precaution has been included in SPC section 3.5.

As no cats with kidney disease IRIS stage >3 were enrolled in the clinical trials, a precaution has been added in SPC section 3.5.

Risk for the user

The main risk is considered to be accidental self-injection. Information regarding anticipated biological effects in human has been satisfactory presented.

Risk for the environment

Portela is not expected to pose a risk for the environment when used according to the SPC recommendations.

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.

User safety

Risk management or mitigation measures are considered appropriate.

Environmental safety

No environmental risk is anticipated following the use in accordance with the SPC. Standard advice on waste disposal is included in the SPC.

Target animal safety

Appropriate and sufficient risk management or mitigation measures are stated in the product information of Portela.

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status):

The veterinary medicinal product is subject to a veterinary prescription.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication: "For the alleviation of pain associated with osteoarthritis (OA) in cats."

The product has been shown to be efficacious for this indication and the CVMP accepted the indication as proposed by the applicant.

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.

Possible deficiencies in animal welfare have been noted and are included in this assessment report.

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 Veterinary Medicinal Products (CVMP) considers that the application for Portela is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) No 2019/6).

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.

In addition, based on the review of data on the quality-related properties of the active substance relfovetmab, the CVMP considers that relfovetmab is to be qualified as a new active substance considering quality and chemical structure.

Divergent position on a CVMP opinion on the granting of a marketing authorisation

Portela (EMEA/V/C/005890/0000)

The undersigned have a divergent position to the CVMP opinion on relfovetmab (Portela) for cats (EMEA/V/C/005890/0000), for the reasons outlined below:

CVMP The active substance of Portela is relfovetmab, a felinised monoclonal antibody against nerve growth factor (NGF), expressed through recombinant techniques, which inhibits NGF-mediated cell signalling to provide relief from pain. The product is intended "For the alleviation of pain associated with osteoarthritis in cats.". The dossier was submitted in line with the requirements for submissions under Article 8 of Regulation (EU) 2019/6 – full application as a new active substance.

An important premise is that by blocking NGF is specific for joints and osteoarthritic pain. However, NGF occurs throughout the body performing a variety of important functions, including neuronal survival and growth, neurite outgrowth and plasticity, pain modulation, promoting bone healing, maintaining tissue health, and influencing chondrocytes and vessel growth. Thus, general blocking NGF can have other implications for the body beyond pain modulation.

To prove the proposed indication of the product, the applicant conducted a pivotal clinical trial relying on a primary endpoint known as Client-Specific Outcome Measures score (CSOM) as assessed by cat owners. CSOM is an assessment of an individual cat's response to pain treatment, as assessed by performance of physical activities, and sociability. However, CSOM is not a standardised questionnaire, but tailored to each cat owner and thus the primary endpoint is not evaluated proportionately among all cat owners involved in the clinical trial. The published protocol for CSOM involves several components:

- Identifying the problematic activities: Owners are interviewed by a trained individual to identify at least three activities that his/her cat does not do as well anymore OR has recently stopped doing.
- Constructing the description of the activity to be followed: question/s are constructed to rate/score how much difficulty their cat has had with each activity.
- Specifying the time and place of the activity
- Review of the activities in the context of the veterinary exam: The activities chosen should be reviewed in the context of the location of osteoarthritis or degenerative joint disease. If for example the chosen activities are all related to jumping down, which emphasises forelimb function, and the OA/DJD is in the hind limbs only, the chosen activities for the CSOM should be considered questionable.

When the applicant was requested to confirm that they followed the full published CSOM protocol, an unsatisfactory response was given on the point of whether there was a review of the activities in the context of the veterinary exam and location of the osteoarthritis. This is important since several of the chosen CSOM activities were not directly related to osteoarthritic pain. Other validated published clinical metrology instruments are available for assessing pain in cats, with standardised

assessments, but were not utilised for this application. Since pain cannot be directly measured, then an objective surrogate measure is recommended alongside these subjective clinical metrology instruments, which are available for cat studies. No objective surrogate measures were included for the clinical trials for Portela.

Veterinary examinations/assessments were also included for the clinical trial as secondary endpoints. The veterinarian makes the diagnosis of osteoarthritis as well as a rather limited assessment of joint pain in a standardised format, called the Veterinary Categorical Assessment (VCA). Joints were not examined for gait assessment, deformity/alignment, muscle wasting, joint fluid analysis, follow-up x-rays or other imaging diagnostics. Also, the veterinarian was less involved in the follow-up during the treatment periods.

The primary efficacy endpoint (CSOM) was the owner's perception of their cat's pain manifested as three activities that his/her cat does not do as well anymore. The secondary endpoints by the veterinarian were related to osteoarthritis and joint issues. The veterinarian was never in a position to confirm/comment on the owner's chosen CSOM activities, as the full CSOM protocol does not appear to have been followed. Thus, it is unclear if the primary efficacy endpoint is based on a validated study protocol.

The indication for the product is "For the alleviation of pain associated with osteoarthritis in cats." Therefore, the pain assessed with the primary efficacy endpoint needed to be associated with osteoarthritis diagnosed in the cat. When the applicant was requested to demonstrate a correlation between the primary and secondary efficacy endpoints, an unsatisfactory response was given that did not identify a clinically relevant correlation between the relevant endpoints. Although the CSOM and VCA are recorded on different scales (CSOM scores range from 3-15 and the VCA on a 5-point scale), both endpoints utilise an ordinal scale, since decreases/increases in score are only possible for an ordinal scale and impossible for a nominal scale. Both CSOM and VCA assess pain severity ranging from clinically normal to nearly incapacitated for the same cat. Well established statistical methods exist to determine a correlation of two ordinal measures. More complex statistical models considering the repeated-measures component (i.e. visit) are also possible. The fact that variables have different scale ranges does not preclude the calculation of a correlation.

The undersigned do not agree that the indication for the product, Portela, has been proven to support a positive benefit-risk balance for a new active substance. It is acknowledged that cats are a challenging animal species to work with, in terms of understanding their behavioural changes specific to pain assessments. Therefore, it required a well-designed clinical trial that proved the efficacy of the product for a clinically relevant pain reduction specific to the diagnosis and location of the osteoarthritis.

Amsterdam, 5 September 2025

Keith Baptiste