02 February 2021
EMA/69127/2021
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Solensia (EMEA/V/C/005179/0000)

Common name: frunevetmab

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Introduction

On 10 December 2020, the CVMP adopted an opinion and CVMP assessment report.

On 17 February 2021, the European Commission adopted a Commission Decision granting the marketing authorisation for Solensia.

The applicant Zoetis Belgium SA submitted on 21 June 2019 an application for a marketing authorisation to the European Medicines Agency (the Agency) for Solensia, through the centralised procedure under Article 3(1) of Regulation (EC) No 726/2004 (mandatory scope).

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

At the time of submission, the applicant applied for the following indication: For the treatment of pain associated with osteoarthritis in cats.

The active substance of Solensia is frunevetmab, a felinised anti-Nerve Growth Factor (NGF) monoclonal antibody (mAb) expressed through recombinant techniques in Chinese hamster ovary (CHO) cells, which inhibits NGF-mediated cell signalling to provide relief from pain associated with osteoarthritis. The target species is cats. The product is intended for administration by subcutaneous use.

Furthermore, the CVMP considers that frunevetmab is a new active substance, as claimed by Zoetis Belgium SA. Taking into consideration the position paper EMA/CVMP/IWP/029/97, the CVMP's opinion is that frunevetmab can be considered a new active substance. The CVMP's opinion is based on the following: The antibody affects a physiological response in the target animal through a particular mode of action (alleviation of pain via binding to NGF).

Solensia 7 mg solution for injection for cats contains 7 mg/ml frunevetmab and is presented in packs containing 1, 2 or 6 vials of 1 ml each.

The rapporteur appointed is Rory Breathnach and the co-rapporteur is Gerrit Johan Schefferlie.

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

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system (version 2, dated 28 May 2018) which fulfils the requirements of Directive 2001/82/EC was provided. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Manufacture of the final product takes place at Corden Pharma Caponago S.p.A, Italy. This site holds a valid GMP certificate.

Manufacture and batch release of the final product within the EU takes place at Zoetis Belgium S.A., Rue Laid Burniat 1, Belgium. This site holds a valid GMP certificate.

An additional site for batch release of the final product within the EU is at Zoetis Belgium SA – Tullamore, Ireland. The manufacturing site at Zoetis Belgium SA – Tullamore, Ireland holds a valid GMP certificate.

The biological active substance manufacturing site at Zoetis Belgium SA – Tullamore, Ireland was inspected by a National competent authority of the EEA and the Manufacturing and Importation Authorisation (MIA) provided covers the relevant activities for which the site is registered.

Overall conclusions on administrative particulars

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

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

Part 2 – Quality

Chemical, pharmaceutical and biological/microbiological information (quality)

Qualitative and quantitative particulars of the constituents

Qualitative and quantitative particulars

Solensia is a sterile solution for injection for use in cats, containing frunevetmab (Active substance) at 7 mg/ml and excipients (L-histidine monohydrochloride, sorbitol, polysorbate and water for injections). All excipients meet Ph. Eur. standards.

Container and closure

The final product is filled into borosilicate type 1 clear glass vials and sealed with rubber stoppers and aluminium overseals. The container and stoppers meet Ph. Eur. 3.2.1 and 3.2.9 requirements and are acceptable for solutions for injection.

Product development

Manufacturing development

The applicant presented a detailed manufacturing process development, including a flow diagram. The Zoetis Tullamore facilities are the intended commercial manufacturing site for the active substance (frunevetmab).

Characterisation of frunevetmab

Characterisation and elucidation of frunevetmab has in general been acceptably performed. An extensive characterisation package has been presented. Primary, secondary and higher order structures of the mAb have been acceptably elucidated. Post-translational modifications have been adequately described.

The reference standard is considered suitable.

Genetic stability of frunevetmab has been demonstrated.

Potency

The binding of frunevetmab to NGF infers a potential biological activity which can be supported with satisfactory efficacy data.

The NGF-binding ELISA test method used to demonstrate potency of the finished product is acceptably validated.

Impurities

The reducing and non-reducing Capillary Electrophoresis - Sodium Dodecyl Sulphate (CE-SDS) and Size Exclusion High Performance Liquid Chromatography (SE-HPLC) were used to analyse potential product-related impurities.

Host cell protein (HCP) levels were provided from different batches of the drug substance. Results were found to be within the proposed acceptance criteria, The HCP assay for the applicant's manufacturing process is in line with Ph. Eur. requirements and the test is retained for the unprocessed bulk to monitor the levels of HCP that may change due to foreseen changes to the manufacturing process.

A justification of the acceptance criteria set for the host cell DNA is provided and is in line with the WHO guidelines.

The report for downstream process impurity clearance is provided.

A validated ELISA kit is used to determine Protein A. A justification for the acceptance criteria and a validation report are provided.

Proposed DS release tests

The tests to be included in DS release are: visible particles, opalescence, colour, pH, total protein concentration, potency, purity, osmolality, bioburden and residual CHO host cell proteins (HCP). Satisfactory validation of the proposed test methods for in-process and finished product testing is provided.

The bioburden limit is justified based on the Ph. Eur. 5.1.4.

The reference standard used for testing is considered suitable.

Description of the manufacturing method

Drug Substance

An appropriate description of the upstream processing is provided, including a process flow diagram. Validation for any hold times is provided.

Cell-free medium containing Frunevetmab is further processed through a series of purification steps. An adequate description of the downstream processing has been provided, including a process flow diagram. Appropriate details, parameters and justification for hold times and filter integrity testing described during the downstream and upstream processes are provided.

The active substance is packaged into bio-containers tested in accordance with Ph. Eur. 3.1.5 and a validation report is provided. Overall information provided on the container closure system and bio-container bags is adequate.

Drug Product

The drug product formulation is a dilution step to bring the monoclonal antibodies concentration to the appropriate concentration, followed by filtration and final filling. An appropriate process flow diagram is provided. The DS formulation steps are adequately described. The final bulk hold time and the hold time during the filling processes are validated. The results of filter integrity testing for filters used during the final filtration have been provided. Validation was performed in different batches. All batches met the proposed finished product release specifications.

Production and control of starting materials

Starting materials listed in pharmacopoeias

Appropriate certificates of analysis of starting materials to Ph. Eur. are provided.

Specific materials not listed in a pharmacopoeia

Starting materials of biological origin

The source and history of the CHO parental cell line are provided in accordance with Ph. Eur. 0784: 'Products of recombinant DNA technology'.

Frunevetmab is based on the rat anti-mouse nerve growth factor (NGF) monoclonal antibody. A detailed report on the generation of frunevetmab antibody-encoding vector is provided. The applicant described the origin of the nucleotide sequence coding for the antibody. The report includes the maps of all the plasmids used for the generation of the final vector - TSE risk assessment. Satisfactory details of the preparation of the media used in the upstream processing were provided by the applicant and by the media components' supplier.

A detailed description of the MCB generation, including the type of banking system used, the container and closure system used, the methods used for preparation of the cell bank(s) including the aseptic techniques, cryoprotectants and storage and maintenance of the cell bank are provided.

Satisfactory details were provided of the system for storage and maintenance of the MCB, including details of the GMP certification. The MCB was tested for viability using an adequate in-house protocol and specifications; details of the test and CoA are provided.

Extraneous agents testing on the MCB showed that the cells were clear of adventitious viruses in accordance with EMA guidance EMA/CVMP/IWP/206555/2010. With respect to retroviruses, a validated Q-PERT was performed to confirm the absence of reverse transcriptase activity in the MCB cells.

The WCB was satisfactorily tested for the same range of viral contaminants as MCB in line with Ph. Eur. 5.2.4 requirement, including retrovirus testing by Q-PERT.

Viral clearance studies were conducted as part of the process validation studies. The viral reduction capacity of the manufacturing process has been sufficiently demonstrated.

The applicant presented data confirming the homology of the MCB and end of process-derived sequences.

Appropriate details for the protein A resin or the column used were provided.

The TSE risk can be considered negligible. The source and subsequent handing of the CHO cell line used in the manufacture of Frunevetmab is provided and the CHO cell line is widely used in the production of monoclonal antibodies for human use.

Starting materials of non-biological origin

Overall the information provided is satisfactory.

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

The qualitative and quantitative compositions of the culture media are provided in the dossier.

Packaging material

The container and stoppers meet Ph. Eur. requirements and are acceptable for solutions for injection.

Control tests during the manufacturing process

The following tests are performed on Solensia drug substance; appearance, opalescence, colour, pH, osmolality, SE-HPLC, NGF-binding ELISA, total protein, CE-SDS, endotoxin, bioburden and residual HCP. Testing for absence of mycoplasma will be carried out routinely on the bulk harvest.

The endotoxin limit for the DS is in accordance with Ph. Eur. 5.1.10.

Appearance, opalescence and colour tests are carried out according to Ph. Eur. 2.9.20, 2.2.1 and 2.2.2, respectively.

The NGF-binding ELISA is performed as an identity test in accordance with VICH.

The applicant proposed both the NGF-binding activity ELISA in combination with the pI by iCIEF method for identification of frunevetmab.

pH is tested in line with the Ph. Eur. 2.2.3.

Sufficient data to set specifications for osmolality has been provided.

The proposed range for the % monomer of drug substance is considered sufficient, based on the data provided.

The CE-SDS non-reduced procedure is proposed to form part of the in-process controls and finished product testing. Specifications set are considered acceptable based on the data provided.

The endotoxin test is carried out in accordance with Ph. Eur. 2.6.14 and the acceptance criteria set are justified, based on the data provided.

The bioburden testing was carried out in accordance with Ph. Eur. 2.6.12.

The method to determine residual protein A in the drug substance is satisfactory, based on the data provided.

Residual host cell protein concentration is determined by ELISA. A validation report and a test method protocol have been provided. Testing and the replacement of reagents are described in accordance with Ph. Eur. 2.6.34.

The applicant provided an adequate protocol for the determination of residual host cell DNA by PCR based on data provided.

Mycoplasma testing is carried out according to Ph. Eur. 2.6.7.

Potency – NGF-binding ELISA and TF-1 proliferation assay

The NGF-binding assay is used to determine the relative potency to the reference standard.

A protocol which gives details on the testing and acceptance criteria for replacement reagents has been provided, including details of the assessment/revalidation and criteria proposed in advance of proposed changes.

A protocol for the replacement of the reference standard for the NGF-binding ELISA is provided.

The proposed acceptance criterion for the DS release specifications are acceptable.

Control tests on the finished product

The description of the methods used for the control of the finished product (appearance, pH, osmolality, SE-HPLC, identity, total protein, CE-SDS, sterility and endotoxin and the specifications were provided.

The appearance test is carried out according to Ph. Eur. 2.9.20.

Osmolality testing is in line with Ph. Eur. 2.2.35.

The validation report for the NGF-binding ELISA, determination of total protein, SE-HPLC and non-reduced CE-SDS are the same for both the drug product and drug substance.

Tests for opalescence, colour and pH are carried out according to the Ph. Eur. 2.2.1, 2.2.2 and 2.2.3, respectively.

The acceptance criteria proposed for the NGF-binding assay for release of the DP are considered acceptable based on the data presented in the validation report.

The applicant has justified the proposed finished product release criteria based on the data provided.

An acceptable fill volume for the drug product has been provided.

Endotoxin testing of the drug product is based on the levels detected in the different batches. Testing will be retained in the DP release.

The omission of testing for protein A and host cell DNA is considered acceptable based on the consistency data provided. The omission of HCP testing for the DP is considered acceptable as HCP testing is included for the DS.

Sterility testing is in accordance with the Ph. Eur. 2.6.1.

Potency

The NGF-binding assay is proposed to determine the potency of the DP. The ability of frunevetmab to bind to NGF, albeit to murine NGF in the ELISA, is considered to be demonstrated acceptably (data provided has shown frunevetmab binds to feline and murine NGF with an equivalent capacity).

Batch-to-batch consistency

Analytical release data from frunevetmab FDS batches manufactured at the Zoetis Tullamore facility are provided, including appropriate CoAs. Appropriate test descriptions and the limits of acceptance were presented. CVMP Note for Guidance EMEA/CVMP/598/99 states that where product is produced using aseptic processing, data on at least three consecutive batches at production scale aseptic techniques must be provided prior to approval.

From the data obtained for the batches presented, appearance, opalescence, colour, pH and osmolality are all within the required specifications.

Results of SE-HPLC are presented as % monomer, and all DP batches are above the proposed specification for monomer content and the HMWS are below the specification proposed.

Results for iCIEF displayed consistency among all of the batches tested.

The results of the release tests for consistency data for DP batches conform to the proposed specifications and support validation of the manufacturing process at the LNN and Corden sites.

Stability

Drug substance:

The stability of the drug substance for 2 years at the recommended storage conditions is supported.

Drug product:

The stability data provided indicate that the product is stable for 24 months at the recommended storage conditions.

For preservative efficacy:

N/A

In-use stability:

N/A

Use immediately.

Overall conclusions on quality

Sufficient information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner.

Biological and physicochemical aspects relevant to the performance of Solensia have been investigated and satisfactory information is provided.

Information has been presented to give reassurance on EA and TSE safety.

Overall, based on the review of the data on quality, the manufacture and control of Solensia are considered acceptable.

The manufacturing process, including appropriate in-process controls and quality controls on the finished product, is described in sufficient detail to give confidence that the manufacture will yield a consistent product. Mycoplasma testing is retained for the bulk harvest. HCP testing is retained for DS in line with Ph. Eur. 2.6.34 and EMA/CVMP/ADVENT/307606/2017. Endotoxin testing is retained for DS and DP in line with data provided in accordance with Ph. Eur. 5.1.10.

The manufacturing method is a relatively straightforward process and is overall well described and satisfactory validation data on DS batches were provided. Data from DS batches and DP batches give reassurance as to the batch-to-batch consistency of the manufacturing process at the LNN site. Consistency DP data support the consistency of the manufacturing at the proposed manufacturing scale (for the Corden site).

The stability data at the recommended storage conditions for the drug substance and to shelf life at the recommended storage conditions for the drug product can be accepted.

Part 3 – Safety

Introduction and general requirements

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

Solensia (frunetvetmab) is a felinised monoclonal antibody for use in cats for the alleviation of pain associated with osteoarthritis (OA). The product is proposed to be administered as a single subcutaneous injection on a monthly basis, at a minimum dose of 1 mg/kg bodyweight (bw). A single-strength injection (7 mg/ml) will be packaged in 1 ml vials. The proposed injection volumes and consequently, the number of vials to be used, vary with bodyweight, resulting in an effective dose range of 1 mg/kg – 2.8 mg/kg bodyweight. The product is intended for use in cats of 2.5 – 14.0 kg bodyweight. There is no proposed limit on the duration of use.

Solensia has been classified by the EMA as an immunological veterinary medicinal product (IVMP), however since the product is not intended to provide active or passive immunity following administration to the target species, not all of the requirements for safety testing for immunological veterinary medicinal products as outlined in Annex I of Directive 2001/82/EC, as amended, are relevant. The applicant has highlighted the limited guidance available for this type of product with respect to the data requirements, albeit reference is made to the 'Questions and Answers on monoclonal antibodies for veterinary use' (EMA/CVMP/ADVENT/307606/2017), and the principle that safety testing should therefore be considered on a case-by-case basis taking into account the properties of the mAb and the target(s) of the mAb.

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

- NGF effects have typically been evaluated in terms of the interaction with the trkA receptor and p75NTR, but NGF signalling is more complex. NGF, trkA, or p75NTR, singly or in combination, can produce effects via interactions with other receptors such as sortilin, integrin α9β1 receptor, and NRH2. NGF and its pro-peptide form pro-NGF bind with and interact with multiple receptors along with or independently of trkA. NGF and its receptors are expressed widely.
- NGF is well recognised for its role in the pain response, including osteoarthritis pain. However, NGF signalling is a factor in many adaptive responses other than pain, some of which could be adversely affected by inhibition of NGF signalling.
- NGF is crucial to normal development and maturation; in adults, NGF has a role in maintaining normal neuronal differentiation, including control of sensory neurotransmitter and neuropeptide synthesis, and expression of tyrosine hydroxylase in adrenergic nerves. In skeletal muscle, NGF is involved in inflammation and repair, including following strenuous exertion. In heart, NGF has a crucial role in maintaining sensory nerve supply and in contributing to a proper sympathetic: parasympathetic innervation balance; disruptions in sensory or adrenergic function are known factors underlying sudden cardiac death in specific disease states. In peripheral vasculature, innervation contributes to vasomotor control, including via norepinephrine and neuropeptides. NGF, in concert with vascular endothelial growth factor (VEGF), is a factor in wound healing responses. In the kidney and bladder, in the respiratory system, and the gastrointestinal (GI) system, NGF is a component of both beneficial and adverse processes. NGF has modulating roles in endocrine functions including pancreatic, adrenomedullary, and pituitary, and in immune function.
- Inference from specific NGF literature to potential risks in veterinary patients is aided by considering that NGF-mediated effects on sensory and sympathetic nerve encompass autonomic nervous system

function. Autonomic regulation of body functions is based on specific neuronal pathways in the periphery and a specific organization of neural circuits connected to these pathways in the central nervous system (CNS). Central centres continuously receive sensory neural, hormonal and humoral monitoring signals reflecting the mechanical, thermal, metabolic and chemical states of the tissues, including monitoring of gut microbiota, external infection pressure, and others (Janig 2014). This information is relayed via nerve to various peripheral nervous system (PNS) and CNS levels, up to and including brain. At any or all levels, a reflex efferent response may be triggered.

Potential impact:

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

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

Safety documentation

Eight safety studies were conducted to investigate the safety of the product and included five laboratory studies and three field trials.

Study title	Route of administration
Evaluation of the Safety of frunevetmab Given by Rapid IV injection to Cats (non-GLP)	Intravenous
Pilot study to investigate pharmacokinetics and safety of frunevetmab when administered at 1x, 3x and 5x of the maximum intended dose in cats	Subcutaneous
Pilot study to determine the preliminary pharmacokinetic profile and safety of frunevetmab (feline mAb), when administered twice, intravenously or subcutaneously, to cats.	Intravenous or Subcutaneous
Target Animal Safety Study of frunevetmab in Cats	Subcutaneous
T-Cell Dependent Immune Responses in Cats Treated with frunevetmab	Subcutaneous
Multi-centre Study to Evaluate the Effectiveness and Field Safety of frunevetmab for the Control of Pain Associated with Osteoarthritis (OA) in Cats.	Subcutaneous
Pilot proof of principle: Evaluation of the pain alleviating effects of subcutaneously delivered NV-02 in cats suffering from degenerative joint disease (DJD) associated pain.	Subcutaneous
A Multi-centre Exploratory Study to Evaluate the Effectiveness and Field Safety of frunevetmab for the Control of Pain and Improvement in Mobility in Cats with Osteoarthritis (OA).	Intravenous and subcutaneous or subcutaneous

Laboratory tests

Three pilot laboratory safety studies and one pivotal target animal safety (TAS) study were conducted which investigated the safety of the administration of one dose, an overdose and the repeated administration of one dose. In addition, one laboratory safety study was conducted to investigate the effect of treatment on immunological function. In the three pilot laboratory studies, different formulations of frunevetmab were administered using different administration routes, intravenous (IV) and subcutaneous (SC). These studies were originally designed to characterise the safety of the IV route of administration, but the finally proposed route of administration that was pursued in the pivotal studies was the SC route. Note that the studies are discussed under sections 'Safety of one administration of an overdose' or 'Safety of the repeated administration of one dose' given that the studies also involved the administration of an overdose or repeated administration of a dose.

Safety of the administration of one dose

Refer to 'Safety of one administration of an overdose' and 'Safety of the repeated administration of one dose'.

Safety of one administration of an overdose

Safety of an administration of an overdose of Solensia was examined in two exploratory studies and in the pivotal target animal safety study.

Evaluation of the Safety of Solensia Given by Rapid IV injection to Cats

In this non- good laboratory practice (GLP) compliant, unmasked pilot safety study, the safety of a single dose of test item (final formulation) administered by rapid IV injection (3 ml [21 mg]) bolus dose was investigated. Twelve (12) healthy male cats were randomised to one of two dose groups; Group T0: four cats were dosed with 3.0 ml of vehicle via IV injection; Group T1: eight cats were dosed with 3.0 ml of frunevetmab (7 mg/mL solution in vehicle) via IV injection in 15 seconds or less. The average weight of cats in the treatment group T1 was 4.2 kg (range 3.2 to 4.7 kg), therefore the average dose administered in this study by the IV route was 21 mg frunevetmab/4.2 kg bodyweight, or 5 mg/kg bodyweight, which is approximately 1.8X the maximum recommended treatment dose (1 – 2.8 mg/kg bw). Follow-up for 7 days post-dosing included the evaluation of clinical signs, physical examinations including injection site evaluations, rectal temperature, haematology, and clinical chemistry.

Results demonstrated that there were no adverse test-article related effects, as determined by clinical and physical examinations, haematology, and clinical chemistry in the 7 days post-dosing follow-up period. While the findings of this study are noted, given that the test article was not administered using the proposed subcutaneous route of administration, the relevance of the findings from this study are limited. However, it would appear that the rapid IV injection of an (approximately) 1.8X overdose of the maximum recommended treatment dose on a single occasion did not result in adverse test article-related effects. While the applicant claims that in the pharmacokinetic (PK)/bioavailability studies, it was demonstrated that bioavailability following SC administration was 100%, therefore almost identical to that of IV, it is not accepted that bioavailability is identical for both routes of administration (refer to comments in Part 4).

Pilot study to investigate pharmacokinetics and safety of frunevetmab when administered at 1x, 3x and 5x of the maximum intended dose in cats

Reference to 1x, 3x and 5x the maximum recommended therapeutic dose (RTD) of 5.6 mg/kg body weight (bw) is made in the study report. It is therefore assumed that a different (higher) recommended treatment dose was originally proposed for this product during the clinical development programme. Currently, 2.8 mg/kg bw is considered the maximum recommended therapeutic dose and, therefore, 2x, 6x and 10x are the actual overdoses used in the study.

In this non-GLP compliant, pilot safety study, the pharmacokinetics and the safety of the subcutaneous administration of either 5.6, 16.8 or 28 mg/kg bw frunevetmab on a single occasion was evaluated. Six (6) healthy cats were randomised to one of the three dose groups (n=2 cats per group (1 male and 1 female); the test item (not the final formulation) was administered by the recommended route at multiples (2x, 6x, 10x) of the maximum recommended treatment dose (2.8 mg/kg bw). General health observations, clinical assessments including injection site evaluation, rectal temperature, bodyweight, plasma concentrations of frunevetmab, haematology, and clinical chemistry were evaluated within the 43 days follow-up period post-dosing.

Notwithstanding the use of an earlier product formulation and the low number of animals included (2 cats/dose level), the results suggest that single administration of a 2x, 6x and 10x overdose of the proposed maximum RTD was well-tolerated. There did not appear to be any test-article related effects on clinical observations, body weight, haematology, clinical chemistry or urinalysis parameters.

The PK analysis, albeit based on limited numbers of animals, showed a dose proportional increase in C_{max} (at the 5.6 mg dose level, C_{max} was 50 and 34 µg/ml, at 16.8 mg/kg bw was 141 and 153 µg/ml, and at

28 mg/kg bw was 199 and 231 µg/ml in the two cats studied), with T_{max} at 1.0 to 2.78 days for 5/6 cats, and 4.28 days for 1 cat (in 5.68 mg/kg bw dose group).

Overall, while this small scale pilot study is considered supportive only (given the number of animals included and the use of different formulation than that proposed for marketing), it does suggest that the product was well-tolerated following the administration of a single 2x, 6x or 10x overdose of the proposed maximum RTD of 2.8 mg/kg bw using the proposed route of administration.

Safety of the repeated administration of one dose

Pilot study to determine the preliminary pharmacokinetic profile and safety of frunevetmab, when administered twice, intravenously or subcutaneously, to cats.

In this non-GLP, pilot safety study the safety of the administration of a 2 mg/kg bw dose of frunevetmab (intermediate dose, based on the proposed dose bands of 1 – 2.8 mg/kg bw), when administered twice with a between treatment interval of 28 days (as recommended), by the subcutaneous route in two healthy cats and the intravenous route in two healthy cats was evaluated. The test article was not the final formulation (concentration of 2 mg/ml frunevetmab formulated in phosphate buffered saline) intended for marketing. General health, body weight, clinical observations including body temperature and injection site evaluation, plasma concentrations of frunevetmab, haematology, and clinical chemistry were evaluated within the 42 days follow-up period post-dosing.

It is considered that little can be concluded from this study due to the limited number of animals included. While it is noted that no treatment-related adverse events (AE) were reported to occur, 1 of 4 cats developed a skin lesion with an unknown relationship to test-article treatment. Concerning clinical chemistry and haematology parameters, many results were above or below the normal reference ranges, however potential relationship to test-article administration is not possible to determine in this small pilot study. It would appear that no notable differences in the safety profile were observed depending on test article administration route, i.e. intravenous or subcutaneous.

It is noted that while plasma samples post-treatment were obtained for PK analysis, the results are not presented in the report of the study. A PK summary was provided in Part 4 of the dossier. Little can be concluded regarding the PK summary based on the limited number of animals included, however it is noted that whilst the applicant states that SC bioavailability is 100%, the individual SC bioavailability for each of the two cats was 50% and 154% and which differs to the findings from another study where absolute bioavailability in cats with OA was determined to be 60.3% following subcutaneous administration using the candidate formulation.

Target Animal Safety Study of Solensia in Cats

This study was the pivotal, randomised, blinded, GLP-compliant target animal safety study which investigated the effects of 6 consecutive monthly subcutaneous doses of Solensia at 1x (2.8 mg/kg bw), 3x (8.4 mg/kg bw) and 5x (14.0 mg/kg bw) the maximum recommended therapeutic dose (2.8 mg/kg bw) in healthy cats, compared to a placebo (vehicle) control group (8 cats per group, 4 male, 4 female). This was a comprehensive study which included safety evaluation in accordance with VICH GL43 (clinical observations, physical examination, temperature, injection site evaluations, body weight, food consumption, clinical pathology, gross necropsy and histopathology and additional targeted analyses (neurological examination, flow cytometry, evaluation of plasma frunevetmab, evaluation of development of anti-drug antibodies). The follow-up period concluded at 7 or 8 days after the final dose.

The results demonstrated that doses of 1x, 3x and 5x the maximum RTD at monthly intervals for 6 consecutive months were well-tolerated; no mortalities or serious adverse events occurred. It is accepted that there were no test-article related changes for neurological examinations, body weight, food

consumption, clinical pathology parameters, necropsy and histopathological examination, lymphocyte populations. The applicant considers that there were no test-article related findings on the basis that findings were noted with similar incidence in the control group, were limited to single animals, were not noted in a dose-related manner, and/or were common findings for laboratory cats (skin and hair coat abnormalities; alopecia, erythema, induration/scale, abrasions/scratches/scabs, mouth and oral cavity abnormalities; lip erythema, lip induration, lip scabbing, and vomiting). However, while the clinical observations in this study were considered to be non-test article related, findings from the field clinical trials suggest that the occurrence of skin lesions (alopecia, dermatitis, pruritus) are associated with test article administration.

Whilst Solensia is classed as an IVMP, it is considered appropriate that the study was conducted in accordance with VICH GL43 (Guideline on target animal safety for veterinary pharmaceutical products). With the exception of pain on injection, there was no noticeable worsening of the safety profile in animals that received 3x or 5x the maximum RTD for 6 monthly doses. Confirmed treatment-induced anti-drug antibodies were not detected in any of the animals treated with Solensia, however given the detection of confirmed anti-drug-antibodies (ADAs) in 3/8 cats in the vehicle control group, there are concerns raised over the specificity of the method to detect 'true' frunevetmab-induced immunogenicity, in addition to the potential for the mAb to bind non-NGF endogenous feline proteins. The applicant was requested to comment on the suitability/specificity of the test method to detect feline ADAs given the high prevalence of ADAs in the control group (3/8 cats confirmed positive) and 3/24 cats in the frunevetmab groups with ADA confirmed positive in the pre-dosing time point, that is, in the absence of frunevetmab administration.

In response to a question concerning the positive results in the control group that were claimed to be due to 'pre-existing immunogenicity', the applicant acknowledged that non-specific interactions are possible. However, regardless of the underlying cause of the interactions, they are not important as long as the pre-existing reactivity is not boosted following mAb administration: it is only when the response increases significantly after drug administration that one can be certain that an immune response is developing. The applicant concludes that the pre-existing reactivity that was observed in this target animal safety study does not raise safety or efficacy concerns since the responses were not boosted. In the frunevetmab field studies, there were 19 animals with pre-existing immunogenicity that was not boosted after drug administration and only 1 animal with treatment-boosted immunogenicity.

With regard to the possibility that the test article interferes with the ADA analysis, the applicant acknowledges that frunevetmab in the plasma samples does interfere with the detection of ADAs (frunevetmab present in sample decreases the sensitivity of the assay) and advises that part of the validation process is to determine the 'drug tolerance' of the assay. On this point, it was noted that frunevetmab concentrations in the high dose group (14 mg/kg bw) in this study were so high that even the trough plasma samples exceeded the drug tolerance level of the assay and thus all of the post-dose samples from that group were 'ADA-inconclusive'. However, drug tolerance was not an issue in the pilot and pivotal field studies: since trough samples were collected and the concentrations were approximately 5 µg/mL, this was well within the drug tolerance of the assay.

In conclusion, it is accepted that the assay is suitable for its intended purpose noting that pre-existing reactivity only rarely resulted in treatment-boosted immunogenicity following mAb administration.

The PK analysis from the pivotal TAS study compared PK parameters prior to and within the 28 days after the 1st and 5th dose administrations. Findings demonstrated that all treated animals are systemically exposed to the active substance, C_{max} and area under the curve AUC_{0-28} increased in an approximately dose-dependent manner across the 1x, 3x and 5x RTD groups, but was slightly less than dose proportional; elimination is relatively slow, with an average elimination half-life of 10.4 ± 3.6 days. For repeat dosing at intervals of 28 days, there is some evidence of accumulation: AUC_{0-28} days was

170 µg-d/ml per mg/kg bw after the first dose, while it was 213 µg-d/ml per mg/kg bw after the 5th dose, representing an increase of approximately 25% (which is somewhat higher than the 18% estimated by the applicant).

Regarding the potential for accumulation, the applicant advises that some accumulation is expected as not all drug is eliminated during the dosing interval. Using a standard equation for accumulation, a 17% increase in AUC from the first dose to steady-state is estimated, based on terminal elimination half-life of 10.1 days and a dosing interval of 28 days. Since the standard equation is most accurate for AUC data based on IV bolus administration, the applicant developed a PK model to support the discussion on the potential for accumulation of frunevetmab after monthly SC administration. The model developed predicted very little accumulation beyond the 3rd dose, with a theoretical accumulation ratio of 23%. Given that TAS data were generated based on six administrations of the test item at monthly intervals and the pivotal field safety data relates to three administrations of the test item at monthly intervals, the observed accumulation is not considered a concern given that safety has been evaluated at steady-state.

Examination of reproductive performance

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

The absence of studies to demonstrate safety in breeding animals and in pregnant or lactating queens can be accepted given that the applicant proposes to contraindicate use of Solensia in such animals, and that it is known from available literature in non-target species that the absence of NGF (arising from the proposed mechanism of action of neutralisation of NGF's effects by frunevetmab binding) would be associated with reproductive toxicity.

In the pivotal target animal safety study, there were no effects on reproductive tracts or gonads of either males or females. However, the product may present a risk if used in reproducing females given that antibodies are actively transported across the placenta in cats and consequently, use of an anti-NGF mAb in a pregnant queen may result in abnormal neuronal development in the developing foetuses (as reported in other species). Solensia is therefore contraindicated in pregnant or lactating animals and in animals intended for breeding.

Examination of immunological functions

T-Cell Dependent Immune Responses in Cats Treated with frunevetmab

The examination of immunological functions was undertaken in a GLP-compliant laboratory study using the T-cell Dependent Antibody Response Test (TDAR) as a method to determine if immune function was impaired following treatment with Solensia. The TDAR test measures the antibody response following immunisation with the model antigen Keyhole limpet haemocyanin (KLH) (by ELISA). The test article was administered at 1x the maximum RTD, 3 times 21 days apart (i.e. with a shorter re-treatment interval than proposed (28 days). Two groups of cats were treated with 2.8 mg/kg bw frunevetmab (final formulation) (T03 and T04) or placebo (saline) (T01 and T02) on days 0, 21 and 42 (n=8/treatment group). Immunising doses of KLH antigen were administered to all study cats on days 26 and 47, with unadjuvanted KLH (0.1 mg) administered to T01 and T03, and adjuvanted KLH (0.1 mg) administered to T02 and T04. The antibody response to KLH was evaluated by ELISA on days -2, 26, 33, 40, 47, 50, 54 and 63. In addition to the TDAR test, safety parameters, plasma frunevetmab concentration and analysis of ADAs were evaluated within the study until day 63 (3 weeks after the last dose of test/control article).

The results demonstrated that all cats had low anti-KLH titers on Days -2 and 26, as expected. Animals immunised with unadjuvanted KLH (T01, T03) did not develop high titres following initial or boost immunisations. In the animals immunised with adjuvanted KLH (T02, T04), titres increased in 3/8

animals in T02 and 8/8 animals in T04 following initial KLH immunisation on Day 26, with increases in titres observed in all animals in T02 and T04 following boost KLH immunisation on Day 47. On Day 40, 47, 50, 54 and 63, titres from T04 (frunevetmab) were statistically significantly higher ($p < 0.0001$) than titres in T02 (saline) at the same time point.

Thus, following the administration of three SC doses of 2.8 mg/kg bw frunevetmab, at day 0, 21 and 42, the immune response to administration of adjuvanted KLH antigen on days 26 and 47 was higher compared to the vehicle control group. Therefore, it can be accepted that under the conditions of the study, there was no evidence of immunosuppression. While justification for the timing of KLH immunisation was not provided, with first administration at 5 days after the 2nd dose of Solensia, it is likely that this would have provided adequate time for any potential down-regulation of the immune response as a result of Solensia treatment to have occurred. The applicant suggests that the finding of a ≤10-fold higher titre in T04 (frunevetmab) compared to T02 (saline) may not be biologically meaningful, as the TDAR assay is not optimised to detect immune-stimulation. Further, there were no clinical or clinic-pathological findings suggestive of an inappropriately robust immune response or adverse effect.

Standard safety evaluation was also conducted during this study and results demonstrated that Solensia was generally well-tolerated at 1x the maximum likely clinical dose at the RTD; however, while there were no mortalities or test-article related clinical findings, vomiting was observed in the test groups in addition to the development of a skin lesion in one animal. While the applicant considered that the relationship of the skin lesion to treatment with frunevetmab is uncertain, it is noted from other studies with frunevetmab, an increased incidence of skin lesions (e.g. erosions and ulcers) on the head and neck of cats has been observed. While the clinical observations in this study were considered to be non-test article related, it was concluded that the findings from the field clinical trials also suggest that the occurrence of skin lesions (alopecia, dermatitis, pruritus) are associated with test article administration. A description of these adverse events is included in section 4.6 and section 6 of the SPC and package leaflet, respectively.

Analysis of plasma frunevetmab concentrations in animals in groups T03 and T04 (animals in both groups treated with test article on days 0, 21 and 42), demonstrated a general increase in mean plasma levels at each treatment time point suggestive of an accumulation of frunevetmab and which is consistent with the findings from other studies in which frunevetmab concentrations were measured.

The ADA analysis indicates that no ADAs to frunevetmab developed during the course of the study in either of the test article groups.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/IWP/54533/2006.

The main potential routes of accidental contact with the product have been considered and it is accepted that the main risk to the user is associated with accidental self-injection. The person administering the product will be a trained professional and although the risk of accidental self-injection exists, the likelihood of this event occurring is not expected to be any greater than for any other injectable formulation.

It is accepted that in the event of accidental parenteral exposure, there are two main risks which are considered to arise: (1) the potential for binding of the mAb to human NGF and associated on-target pharmacological effects; and (2) the potential development of an immunological response. It is expected that frunevetmab is capable of binding and inhibiting human NGF *in vivo*, thus there are potential mechanism of action-related risks associated with human parenteral exposure to frunevetmab. The subcutaneous administration of 1.4 mg of frunevetmab (0.2 ml injection of a 7 mg/ml formulation) was

selected as the worst-case scenario of accidental exposure in a human. The results of PK modeling of a 1.4 mg dose administered in humans are interpreted as very unlikely to produce paresthesias or other sensory effects, nor any significant negative effects on pre-existing peripheral neuropathy, based on available literature of pharmacologic effects with human anti-NGF mAbs. However, the only clearly vulnerable sub-population is the developing embryo/foetus and nursing infant; NGF is known to be important to normal growth and development of the embryo/foetus, and exposure of pregnant monkeys to a human anti-NGF mAb resulted in increased stillbirths, increased infant mortality, and induced some degree of developmental neurotoxicity in the offspring.

In view of the information provided (in particular, the experience with human anti-NGF in clinical trials), it is not expected that a single exposure to the product at a dose that could potentially be self-administered would be capable of any clinically noticeable interference with NGF signalling. The only possible exception to this is with maternal exposure, where embryos/foetuses or nursing infants might be more sensitive to even short periods of inhibition of NGF.

The risk of potential hypersensitivity reactions, including anaphylaxis, exists for this product (as for any foreign protein), in addition this risk would be heightened upon repeated accidental self-administration, therefore appropriate warnings are included in the product information.

Concerning the risk for pregnant women, women trying to conceive and breastfeeding women, the severity of the risk is adequately reflected in the product information. In the opinion of the CVMP, the recommendation that such women 'should take extreme care to avoid accidental self-injection' is considered to be a sufficient warning statement. Here, it is appropriate to highlight that the user population will be veterinary professionals and, once they have clear information on the risk of exposure, they will be equipped to decide whether or not it is appropriate for them to use the product and/or the steps that they need to take to avoid exposure to the product.

In summary, it can be accepted that the use of Solensia will not pose an undue risk to the person administering the veterinary medicinal product, when used in accordance with recommendations.

Interactions

Specific studies to investigate the interaction of Solensia with other veterinary medicinal products have not been performed. However, during the field studies, frunevetmab was administered concurrently with several veterinary medicinal products that would typically be encountered during treatment of cats with OA and no specific drug interactions were reported.

The applicant has included text in section 4.8 to specify that if a vaccine is to be administered at the same time as treatment with frunevetmab, the vaccine should be administered at a different site to that of frunevetmab administration, to mitigate potential recruitment of immunogenicity (formation of anti-drug antibodies) to the mAb.

In human studies, a negative interaction of anti-NGF mAbs with NSAIDs has been reported; drug:drug interactions were identified when a human anti-NGF mAb was administered concurrently with non-steroidal anti-inflammatory drugs (NSAIDs). The major risk was associated with chronic use (≥16 weeks) and related to the occurrence of rapidly progressive osteoarthritis (RPOA). In the pivotal field study, 14 cats (9 treated with Solensia and 5 treated with placebo control) also received treatment with a NSAID (robenacoxib or meloxicam). There were no reports of conditions similar to the RPOA that has been observed in human trials of anti-NGF mAbs (however it is noted that lameness was reported as an AE in 8/182 (4.4%) of test group animals compared to 2/93 (2.2%) animals in the control group).

In response to a question on this point, the applicant argues that the risk of adverse events with concurrent NSAID and anti-NGF mAb use - including frunevetmab - in veterinary patients is very low. This

is primarily based on safety data relating to concurrent administration of human anti-NGF mAbs and NSAIDs in human clinical trials. In human studies, a negative interaction of anti-NGF mAbs with NSAIDs has been reported; drug:drug interactions were identified when human anti-NGF mAbs was administered concurrently with NSAIDs. The major risk was associated with chronic use (more than 90 days) and related to the occurrence of rapidly progressive osteoarthritis (RPOA). This condition has been reported in human patients receiving anti-NGF monoclonal therapy, with and without concurrent use of NSAIDs. However, long term co-administration with NSAIDs appears to increase the risk. In light of these data and the fact that short-term NSAID co-administration in the feline clinical studies was not associated with any adverse events (albeit based on limited data), the CVMP is prepared to accept that intermittent short-term co-administration of an NSAID in cats on Solensia should not pose a significant additional risk. Information is included in the SPC to reflect that there are no safety data on the concurrent use of NSAIDs and frunevetmab in the cat, whilst noting the available information in clinical trials in humans. It is also stated that cats have no reported equivalent of human RPOA.

In conclusion, the text proposed for inclusion in section 4.8 of the SPC can be accepted.

Field studies

One pivotal safety and efficacy field study conducted in the US and two non-pivotal, exploratory field safety and efficacy studies conducted in the US are presented by the applicant. Studies were conducted in client-owned cats with osteoarthritis (OA) and are considered representative of the intended target population in the EU.

Multi-centre Study to Evaluate the Effectiveness and Field Safety of Solensia for the Control of Pain Associated with Osteoarthritis (OA) in Cats.

The pivotal good clinical practice (GCP)-compliant field study was a multi-centre, placebo-controlled, randomised, blinded GCP study, in which 182 client-owned cats with OA diagnosed by physical examination and radiography were treated with Solensia at the proposed dose band of 1.0 to 2.8 mg/kg bw once monthly for three consecutive months (day 0, 28, 56) (i.e. in accordance with recommendations). Ninety-three (93) client-owned cats were included in the placebo control group (vehicle control). Follow-up was one month after the third dose (day 84), with additional telephone contact with owners one month later. Safety parameters measured included haematology, serum chemistry, and urinalysis variables at screening and on day 84. All cats received comprehensive physical examinations (including injection site evaluations) at each clinic visit (screening, day 28, 56 and 84) and complete blood count (CBC) and clinical chemistry analyses at the screening and day 84 visits. Additional blood samples were also collected from all animals at the screening visit and prior to each dose on day 0, day 28, day 56 and at the end of the study (day 84) for the evaluation of plasma frunevetmab concentration and the presence of anti-drug-antibodies (ADAs).

The results demonstrated that the most commonly reported adverse events were gastrointestinal disorders; emesis was reported in 13.2%, and diarrhoea in 6.6% of frunevetmab-treated cats. While it is noted that both of these GI symptoms were also observed in the vehicle control group, it was at a lower incidence. In addressing a question on this point, the applicant reviewed the gastrointestinal signs (i.e. emesis and diarrhoea) reported as AEs in the pivotal field study. Based on this analysis, the applicant concludes that there were 12 cats in the frunevetmab group and 9 cats in the placebo group in which the gastrointestinal events could not be explained with any underlying or pre-existing disease. Therefore, the frequency of unexplained gastrointestinal clinical signs was 6.59% (12/182) in the frunevetmab group and 9.68% (9/93) in the placebo group. It is accepted, based on this review, that the frequency of unexplained gastrointestinal clinical signs was not greater in the frunevetmab group compared to the placebo group.

Systemic effects (anorexia, lethargy, dehydration, weight loss) were commonly reported, and the incidence appears to have been slightly higher in the test compared to the control groups, e.g. anorexia 6.6% in test group vs 4.3% in control group, however no significant differences in body weight were reported in this study.

Injection site pain was reported at similar frequencies in the test (3.8%) and control (4.3%) groups as an adverse event. It is accepted that the incidence of 'pain on injection' is comparable to what has been observed following injection with saline and, therefore, is more likely to be associated with the act of injection itself rather than pain elicited by the product.

A higher incidence of skin and appendages disorders were observed in the test group compared to the control group. A description of these adverse events is included in section 4.6 and section 6 of the SPC and package leaflet, respectively, and are considered appropriate.

There did not appear to be any test article-related effects on haematological, serum chemistry or urinalysis parameters in this study.

The PK and ADA analysis presented indicated that 1/179 (0.6%) animals in the Solensia group developed ADAs over the course of the study, however this was not associated with PK data that would suggest faster clearance or neutralisation of the mAb.

Overall, there were no test-article related mortalities during the study and the safety data from the pivotal field trial would suggest that Solensia demonstrated an acceptable level of tolerance; the adverse reactions observed are considered to be adequately reflected in the product information.

Pilot proof of principle: Evaluation of the pain alleviating effects of subcutaneously delivered frunevetmab in cats suffering from degenerative joint disease (DJD) associated pain.

In this double-blind, placebo-controlled, randomised pilot, proof of concept study, the efficacy of a single subcutaneous administration of two different doses of frunevetmab (not the final formulation) was investigated in client-owned cats with naturally occurring degenerative joint disease; 0.4 mg/kg bw (n=11) and 0.8 mg/kg bw (n=12). The placebo control group (n=11) received sterile saline. Cats were followed up for 9 weeks after treatment administrations.

Abnormal health events were reported in 6 cats, one in the placebo group, two in the 0.4 mg/kg bw frunevetmab group and three in the 0.8 mg/kg bw frunevetmab group, however none of these events were considered related to treatment administration by the applicant.

This study can be considered supportive only given that the product was not administered in accordance with recommendations, a lower dose than proposed was administered on a single occasion only. Furthermore, the test article was not the final formulation intended for marketing (phosphate buffered saline vs histidine buffer).

A Multi-centre Exploratory Study to Evaluate the Effectiveness and Field Safety of frunevetmab (Solensia) for the Control of Pain and Improvement in Mobility in Cats with Osteoarthritis (OA).

This was a blinded, randomised, placebo-controlled, multi-centre, exploratory field study which investigated the safety and efficacy of two consecutive monthly doses of frunevetmab (final formulation) at the recommended dose (1.0 to 2.8 mg/kg bw) in client-owned cats. Frunevetmab was administered to two groups of cats either intravenously for the first dose (on Day 0) and subcutaneously 28 days later (Group T1, n=42) or subcutaneously on both occasions (Group T2, n=43). A total of 85 client-owned cats (>6 months of age, ≥2.5 kg bodyweight) with OA received two consecutive monthly doses of Solensia. The placebo control group (n=41) received the vehicle (histidine buffer) IV on day 0 and SC on day 28. Cats completed the study 56 days after the first treatment administration. Safety parameters measured

included physical examination, neurological examination (at screening), injection site evaluation, and clinical pathology analyses (haematology, serum chemistry and urinalysis).

While the safety of the administration of two consecutive doses was investigated, half of the test animals were administered the first dose of Solensia by the intravenous route with the second dose administered subcutaneously, while the other half of the test animals received the test article by the recommended route of administration, subcutaneous, for both doses. The results demonstrated that, while there were no test-article related mortalities, the most commonly reported adverse events were skin and appendages disorders, with dermatitis and eczema reported in a significant number of cats in the test group (10/42 [23.8%] in the IV/SC group and 6/43 [14.0%] in the SC/SC group) compared to the control group (1/41 [2.4%], in addition to alopecia (7.1% and 2.3% of the two test groups).

For three cats treated with frunevetmab IV/SC, the skin disorders in the neck region were classified as adverse events and led to the withdrawal of the animals from the study. Although the applicant claims that this was due to the neck collar worn with an activity monitor fitted for efficacy evaluation, cats in the placebo group also wore a neck collar, therefore, while the neck collar may have exacerbated the development of skin lesions around the neck region, it remains a fact that the incidence of such findings was reported to be higher in the frunevetmab groups and therefore, a relationship to treatment cannot be excluded.

Diarrhoea was observed commonly in the two test groups in this study (7.1% and 2.3%) but absent in the control group, while vomiting was observed commonly in all groups (with higher prevalence in the control group). Lethargy was reported at similar incidences in each study group (4.8% in the IV/SC group, 2.3% in the SC/SC group and 2.4% in the placebo group). Sneezing was more prevalent in the test groups (7.1%, 2.3%), however it is noted that this was reported at a low incidence in the test group in the pivotal field study (1.1%) and is not commented on further.

There were no test-article related findings of clinical relevance for any haematology or clinical chemistry parameters.

Overall, the safety data in this field study suggests that the administration of two doses of frunevetmab at the recommended dose, separated by an interval of one month, may be associated with skin lesions, such as dermatitis, pruritus and/or alopecia. It is noted that skin disorders were more severe in this study compared to the pivotal field study, however in this study a collar was worn, which may have exacerbated this adverse effect.

Environmental risk assessment

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

Overall conclusions on the safety documentation

Target animal safety

Three pilot laboratory safety studies and one pivotal TAS study were conducted which investigated the safety of the administration of one dose, an overdose and the repeated administration of one dose. Overall, the studies demonstrated that treatment was well-tolerated, with no mortalities or serious adverse events occurring. There did not appear to be any test-article related effects on clinical pathology parameters. In the pivotal TAS study, doses of 1x, 3x and 5x the maximum RTD at monthly intervals for 6 consecutive months were well-tolerated; no mortalities or serious adverse events occurred. It is

accepted that there were no test-article related changes for body weight, food consumption, clinical pathology parameters, necropsy and histopathological examination, lymphocyte populations. The applicant considers that there were no test-article related findings on the basis that findings were noted with similar incidence in the control group, were limited to single animals, were not noted in a dose-related manner, and/or were common findings for laboratory cats (skin and hair coat abnormalities; alopecia, erythema, induration/scale, abrasions/scratches/scabs, mouth and oral cavity abnormalities; lip erythema, lip induration, lip scabbing, and vomiting). However, while the clinical observations in this study were considered to be non-test article related, the findings from the field clinical trials suggest that the occurrence of skin lesions (alopecia, dermatitis, pruritus) are associated with test article administration. The adverse events are adequately described in the product information.

Reproduction safety

Reproduction safety was not investigated. The absence of studies to investigate the effect of frunevetmab on reproductive performance in the target species is considered acceptable, on the basis that the applicant proposes to contraindicate use of Solensia in animals intended for breeding, and in pregnant or lactating animals, and given that it is known from available literature in non-target species that the absence of NGF (arising from the proposed mechanism of action of neutralisation of NGF's effects by frunevetmab binding) would be associated with reproductive toxicity.

Immunological function

The impact of treatment on immunological function was investigated using the TDAR Test as a method to determine if immune function was impaired following treatment with Solensia. Following the administration of three SC doses of 2.8 mg/kg bw, at day 0, 21 and 42, the immune response to administration of adjuvanted KLH antigen on days 26 and 47 was higher in the test group compared to the vehicle control group [on days 40, 47, 50, 54 and 63, titres from T04 (frunevetmab) were statistically significantly higher ($p<0.0001$) than titres in T02 (saline)]. Therefore, it can be accepted that under the conditions of the study, there was no evidence of immunosuppression.

Interactions

Specific studies to investigate the interaction of Solensia with other veterinary medicinal products have not been performed. However, during the field studies, frunevetmab was administered concurrently with several veterinary medicinal products that would typically be encountered during treatment of cats with OA and no specific drug interactions were reported. Information is included in section 4.8 to specify that if a vaccine is to be administered at the same time as treatment with frunevetmab, the vaccine should be administered at a different site to that of frunevetmab administration, to mitigate potential recruitment of immunogenicity (formation of anti-drug antibodies) to the mAb.

Field studies

One pivotal safety and efficacy field study conducted in the US and two non-pivotal, exploratory field safety and efficacy studies were conducted. Overall, the safety data from the pivotal field trial would suggest that Solensia demonstrated an acceptable level of tolerance. There were no test-article related mortalities during the study. However, an association between treatment administration and adverse reactions such as skin and appendage disorders cannot be excluded. In addition, the exploratory multi-site field study suggests that the administration of two doses of frunevetmab at the recommended dose, separated by an interval of one month, may be associated with dermatitis, pruritus and/or alopecia. It is noted that skin disorders were more severe in this study compared to the pivotal field study, however in this study a collar was worn, which may have exacerbated this adverse effect.

User safety

A user safety assessment in line with the relevant guidance document has been presented. It is accepted that the main risk to the user is associated with accidental self-injection. In the event of accidental parenteral exposure, there are two main risks which are considered to arise: (1) the potential for binding of the mAb to human NGF and associated on-target pharmacological effects; and (2) the potential development of an immunological response. The user safety warnings included in the product information adequately highlight these risks. It is accepted that the use of the product will not present an unacceptable risk to the user, when used in accordance with recommendations.

Environmental safety

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

Part 4 – Efficacy

Introduction and general requirements

Solensia is an injectable solution of a felinised monoclonal antibody (mAb) (frunevetmab) intended for the alleviation of pain associated with osteoarthritis (OA) in cats.

Frunevetmab has been classified as an immunological by EMA/CVMP and as such overarching guidance on the efficacy testing of veterinary immunologicals is provided by Directive 2001/82/EC, Annex I, Title II (as amended). However, these requirements were written specifically with vaccines and immunosera in mind and so are not fully relevant for a monoclonal antibody.

Considerations by the applicant:

The applicant notes that there are currently no specific efficacy regulatory guidelines at European level for monoclonal antibodies for veterinary use.

Clinical signs of feline OA are known to be subtle and non-specific and it is reported rare for veterinarians to detect OA based on their physical examination alone (Klinck et al., 2012). Unlike in dogs, in the cat clinical signs of OA do not generally include lameness or gait disturbances. Arthritic joints in cats are often not particularly enlarged, making it a difficult feature to appreciate, and a reduced range of motion is rare (Clarke and Bennett, 2006). In addition to this, removing the cat from its home territory and taking it to the veterinary practice subjects the cat to stress that affects physiological parameters (Quimby et al., 2011; Belew et al., 1999). The stress response is likely to add to the difficulties in recognising clinical manifestations of chronic pain, making the accurate detection of OA pain in cats a major challenge for the veterinarians.

In light of the above, the applicant suggests that as the behavioural changes associated with chronic pain may develop gradually and may be subtle, these may be most easily detected by the animal owner. Altered behaviour in the home environment may therefore be the best way to assess musculoskeletal pain e.g. lack of socialising, lack of jumping, decreased height of jumping, reduced grooming, hiding, and grumpiness (Lascelles et al., 2010a). Several studies confirmed that owners are able to recognise these changed behaviours in their cats that are associated with chronic musculoskeletal pain (Clarke and Bennett, 2006; Lascelles et al., 2007, Bennett and Morton, 2009) and that the World Small Animal Veterinary Association (WSAVA) expert panel on pain concluded that the owner assessments are the mainstay of the assessment of chronic pain in cats (WSAVA, 2014).

NGF has been found to be elevated in the synovial fluid of animal models of induced arthritis (Orita et al., 2011), in human OA patients (Aloe et al., 1992) and in dogs with chronic OA. Locally produced NGF can contribute to joint pathology, and the key role of NGF in inflammatory pain is exemplified by its release

from damaged cells including synovial cells, chondrocytes, and a host of inflammatory cells including eosinophils, lymphocytes, macrophages, and mast cells (Mantyh et al., 2011 and Enomoto et al., 2018).

Monoclonal antibodies targeting NGF have demonstrated preclinical and clinical efficacy across multiple species. Together these points suggest NGF may be a major factor orchestrating many of the diverse changes driving clinical signs of pain associated with osteoarthritis and neutralising NGF can produce analgesia.

The applicant provided a succinct summary of the prevalence of osteoarthritis in cats, the current modalities for treatment and the difficulties associated with diagnosing OA and assessing pain in cats. In addition, the applicant has cited a number of studies (including WSAVA expert panel) that suggest that animal owners are best placed to assess chronic pain in cats.

Efficacy documentation

Six studies were conducted to investigate the efficacy of the product and included three laboratory studies and three field trials. Laboratory studies were non-GLP or non-GCP compliant, and two were considered exploratory studies. Two of the field studies were non-GCP and pilot / exploratory in nature. One pivotal, GCP-compliant field study was carried out in target animals, using a batch formulated in accordance with the final formulation proposed for marketing.

Study title	Route of administration
Absolute bioavailability and pharmacokinetics of frunevetmab (NV-02) in cats with naturally occurring osteoarthritis. (non-GLP)	Subcutaneous and intravenous
Exploratory study investigating the efficacy of frunevetmab feline anti-NGF monoclonal antibody, when administered once, intravenously or subcutaneously, compared with Meloxicam administered daily per os, to cats in a kaolin-induced model of inflammation, pain and fever. (non-GCP)	Subcutaneous or intravenous
Comparison of efficacy with 3 different dose levels of frunevetmab in a kaolin-induced model of pain and inflammation in cats (non-GCP)	Subcutaneous
Pilot proof of principle: Evaluation of the pain alleviating effects of subcutaneously delivered frunevetmab in cats suffering from degenerative joint disease (DJD) associated pain. (non-GCP)	Subcutaneous
A Multi-Centre Exploratory Study to Evaluate the Effectiveness and Field Safety of frunevetmab for the Control of Pain and Improvement in Mobility in Cats with Osteoarthritis (OA) (non-GCP)	Subcutaneous
Multi-center Study to Evaluate the Effectiveness and Field Safety of Frunevetmab for the Control of Pain Associated with Osteoarthritis (OA) in Cats.	Subcutaneous

Laboratory trials

Dose determination

In support of the proposed posology (1 – 2.8 mg/kg bw, by the subcutaneous route, once a month), a number of pre-clinical studies were presented.

In the first study, the absolute bioavailability and PK of Solensia (final formulation) in 10 cats with naturally occurring OA was investigated, at a dose rate of 3 mg/kg bw, when administered by IV or SC injection. This was a non-GLP compliant, non-blinded study, in which cats were randomised to receive injections of frunevetmab (3.0 mg/kg bw) SC and IV at 28-day intervals, in a cross-over design, followed by a 28-day follow-up. The dose of frunevetmab administered (3 mg/kg bw) is higher than the proposed minimum dose (1 mg/kg bw) but is only marginally higher than the maximum dose that may be administered based upon the proposed bodyweight range for each vial (2.8 mg/kg bw). Given that the elimination phase of the concentration-time profile for frunevetmab was found to be linear, the applicant has estimated the concentrations of frunevetmab of the clinical dose range (between 1.0 to 2.8 mg/kg bw).

By comparison of systemic bioavailability of frunevetmab following subcutaneous injection with intravenous administration (administered at 3.0 mg/kg bw), the applicant has estimated absolute bioavailability to be 60.3% following subcutaneous administration. However, it is noted from the final study report that the wash-out period (28 days) between treatment periods was inadequate and as a result, the applicant has subtracted the 'tail' of the first dose from the profile of the second dose. Further, it is noted that AUC values have been dose normalised.

Whilst the justification for using such an approach is understood and the approach is not 'standard', given the cross-over design of this study, it can be accepted that this study provides supportive information that quantifies systemic bioavailability following subcutaneous administration in cats with OA (the intended target population), albeit when administered at a slightly higher dose than the maximum likely under field conditions of use and following manipulation of data.

Whilst frunevetmab concentrations were high enough during the first week after dosing to cause some drug interference in the ADA assay, results suggest that none of the ten cats in this study had treatment-emergent immunogenicity (as measured by anti-drug antibodies).

Although the applicant suggests that the long half-life (10.2 days following IV administration) supports once per month dosing, it is considered that the half-life of frunevetmab on its own is insufficient to justify the proposed monthly interval between repeated treatment administration as this would need to be further supported by means of clinical efficacy parameters.

A second study was a non-GLP, exploratory dose selection study which investigated the efficacy of a single administration of three different IV doses (0.02, 0.2 and 2 mg/kg bw) and one SC dose (0.2 mg/kg bw) of frunevetmab (non-final formulation) administered to healthy cats when compared to a negative (PBS) and positive (Metacam) control, in a kaolin-induced pain model (n=5/treatment group). The proposed SC dose rate (1 mg/kg bw) was not investigated in this study. A kaolin-induced inflammatory pain model was used to investigate effect of frunevetmab in alleviating pain (as measured by lameness score). In this study, inflammation was induced 24 hours prior to frunevetmab administration. Efficacy parameters measured included rectal temperature, paw circumference and lameness score.

The results demonstrated that kaolin was successful at inducing inflammation in the paw as animals assigned to all study groups had a lameness score of 0 (a score of 0 indicated that the cat could walk fully weight bearing) prior to kaolin administration and had a score of 2-3 following administration (a score of 2-3 indicated that the cat had moderate to severe lameness, and was able to bear either slight weight or

none at all). The mean lameness scores were better (lower) in cats administered meloxicam followed by frunevetmab 2 mg/kg bw IV. The lower doses of frunevetmab 0.02 and 0.2 mg/kg bw did not seem to have overt efficacy. Results suggest little difference between 0.2 mg/kg bw frunevetmab administered subcutaneously or intravenously. Results did not show any effect of frunevetmab on rectal temperature or paw circumference.

Overall, little can be concluded from this study other than the fact that frunevetmab showed no evidence of anti-inflammatory activity and that lameness reduction over the 7 days follow-up period assessed in this study appears to have been less than that observed for meloxicam. Given the route of administration primarily investigated (IV), the dose rates studied, the estimated absolute bioavailability (60.3%) following SC administration (as reported in OA cats in the first study above) and the duration of follow-up, no conclusions are considered possible in terms of the proposed posology, i.e. route of administration, dose rate or re-treatment interval.

The third study was a non-GLP compliant, dose finding study which investigated the efficacy of 3 different dose levels of Solensia: 0.2 mg/kg bw, 0.6 mg/kg bw and 2.0 mg/kg bw (non-final formulation) when administered once by the SC route, in a kaolin-induced pain model compared to a negative control (PBS) in healthy cats (n=15/group). The proposed SC dose rate (1 mg/kg bw) was not investigated in this study. Four days after treatment (when plasma concentrations were expected to be highest), inflammation was induced in the right hind paw. Rectal temperature, paw circumference and lameness score were evaluated up to 7 days after kaolin injection.

The experimental model was successful in inducing inflammation and pain in the right hind paw of study animals (all injected animals having a lameness score of 1 or 2 following injection), however it is apparent that the level of inflammation and pain induced in this study was less than that induced in the previous study, given the lower mean lameness scores reported following kaolin injection in this study.

The results demonstrated that in the 2.0 mg/kg bw group, lameness scores were statistically significantly different (lower) for all study days except for study Day 1 compared to the negative control group, however there were no statistically significant differences to placebo for either the 0.2 mg/kg bw or the 0.6 mg/kg bw group. There was no statistically significant difference in the mean rectal temperature between the negative control group and the animals treated with the test item at 0.2, 0.6 and 2.0 mg/kg bw. Animals in the test item groups had a larger paw circumference than animals in the negative control group from study Day 3 to study Day 7.

Overall, results of this study suggest that a single SC administration of 2.0 mg/kg bw of frunevetmab to cats with kaolin-induced paw inflammation and pain results in a reduction of pain (as measured by lameness score) between 2 to 7 days following induction of inflammation and pain, but not at 0.6 or 0.2 mg/kg bw. Given that the proposed dose rate is 1 mg/kg bw and no effect was reported at 0.6 mg/kg bw but only at twice the proposed dose rate (2 mg/kg bw), the relevance of the findings from this study in terms of supporting a dose rate of 1 mg/kg bw is unclear.

Field studies

Two pilot/exploratory, non-pivotal field trials and one pivotal, GCP-compliant field trial were conducted to evaluate the safety and efficacy of Solensia. These studies were conducted in the USA, however CVMP accepted that the study populations could be considered representative of the intended target species and indication in the EU. One of the pilot studies is discussed under 'Dose determination' while the two remaining studies are discussed under 'Dose confirmation'.

Dose determination

Following on from the two pain-induced models, a proof-of-concept study was conducted in cats with naturally occurring degenerative joint disease.

The first study was a pilot, proof of principle, non-GCP, randomised, blinded study which investigated the pain alleviating effects of 2 dose levels of frunevetmab (not the final formulation) (0.4 mg/kg bw, n=11, 0.8 mg/kg bw, n=12) administered once by SC injection in client-owned cats suffering from degenerative joint disease (DJD)-associated pain compared to a placebo control group (n=11). The proposed SC dose rate (1 mg/kg bw) was not investigated in this study. (Note: according to the applicant, the two dose rates to be administered were 1.0 and 2.0 mg/kg bw, administered SC, however the discrepancy between planned dose vs administered dose arose from a different concentration of test article being used in the study). Cats were treated on day 14 of the study, with efficacy assessments conducted on days 0, 14, 35 (3 weeks), 56 (6 weeks) and 77 (9 weeks). The primary efficacy parameters consisted of owner assessment [client-specific outcome measures (CSOM) scores on a scale of 0 - 12 and feline musculoskeletal pain index (FMPI)] and activity using accelerometer counts; secondary outcomes were quality of life (QoL), temperament and happiness scales, dispositional optimism of owners and its effect on the placebo response.

Results showed that significant difference in total CSOM scores at 3 weeks post-treatment relative to placebo were observed in the 0.4 mg/kg bw group (p=0.003), but not for the 0.8 mg/kg bw group (p=0.07), however a statistically significant difference was observed for both treatment groups combined vs placebo at 3 weeks post-treatment (p=0.006). At this time point, median CSOM scores were 8.5 in each of the treatment groups, and 6 in the placebo group (in this study, larger CSOM numbers represent less activity impairment). While a statistically significant difference in change in CSOM scores from baseline was observed in both treatment groups at days 35, 56 and 77, a statistically significant difference was also observed in the placebo group at days 35 and 56.

Compared to placebo, the change in CSOM scores was significant only when combining the two test groups, and for one-time interval (D35-D14) only (p=0.035).

Concerning accelerometry measurements, the post-treatment activity in the placebo group seemed to decline compared to the pre-treatment baseline period, while in both test groups there was an increase in activity post-treatment for 6 weeks. Whilst it is noted that statistically significant differences between treated and control animals were reported for activity (as measured by accelerometry) from week 2 to 6 after treatment, this finding relates to the combined treatment groups. However, a statistically significant difference between individual treatment groups and placebo was only reported for the 0.8 mg/kg bw group at 2 and 5 weeks after treatment (not in between) and for the 0.4 mg/kg bw treatment group at 4 weeks after treatment. Whilst it is understood why measurement of activity might be used as a surrogate for analgesic effect, no information on the device used or whether it has been suitably validated for the intended purpose has been provided and consequently, little can be concluded from the results provided. It is noted that no statistically significant differences between any of the groups were reported for the FMPI questionnaire scores or for the quality of life, temperament or happiness scales.

It is accepted that the study has incorporated both objective (accelerometer measurements) and subjective (CSOM & FMPI scores) approaches to measuring efficacy of frunevetmab. However, it is noted that comparisons have been made using median scores as opposed to arithmetic or geometric mean scores. In the absence of a study protocol or statistical analysis plan, the justification/appropriateness of such an approach cannot be verified. However, given the pilot nature of this study, this point was not pursued.

Although the applicant suggests that the CSOM score is the most suitable of the two subjective scoring systems to use and claims that a statistically significant difference compared to placebo was observed in

cats administered frunevetmab, whilst this is factually correct, it should be noted that a statistically significant difference was only reported at one time point (D35 – 3 weeks after treatment) when comparing the combined treatment group (all animals administered frunevetmab) with placebo and animals administered 0.4 mg/kg bw frunevetmab with placebo. However, a statistically significant difference was not reported for the cats administered the highest dose (0.8 mg/kg bw) when compared with those receiving placebo.

Overall, in the absence of a study protocol or a statistical analysis plan and given the extensive and repeated statistical comparisons that have been reported, little can be definitively concluded from this study. However, given the pilot nature of this study, and the fact that the dose rates administered in this study (0.4 and 0.8 mg/kg bw) are lower than that proposed (1 mg/kg bw), responses to the identified deficiencies were not requested.

Dose justification:

The applicant has presented argumentation to support the rationale for the decision to proceed with the selected dose of 1 mg/kg bw (with a dose range based on bodyweight of 1.0 – 2.8 mg/kg bw) and the treatment interval of one month in the pivotal field trial. The once per month dosing regimen can be justified based on pharmacokinetic considerations.

It is suggested that for a mAb with low toxicity which acts as an antagonist, it is typical to have a dosing interval in the range of 2-3X the half-life; therefore, given the calculated half-life of 10 days, a one-month dosing interval is appropriate for frunevetmab.

For a mAb that acts as an antagonist, it is desirable to antagonize the target for the entire dosing period. Therefore, the plasma concentration at the end of the intended dosing interval is of most interest. The applicant conducted a series of analyses to support an argument that in spite of the variability in the dose (1-2.8 mg/kg bw), pharmacokinetics and drug exposure, the efficacy, as assessed using CSOM treatment success as a function of frunevetmab trough concentrations, was not substantially affected by the variability of these parameters. It is suggested by the applicant that efficacy is not overly sensitive to the dose of active substance concentrations in plasma.

The CVMP notes the analyses conducted and, while it appears to lend support to the selection of 1 mg/kg bw as the minimum RTD, the CVMP is not convinced of the validity of the analyses presented and would be cautious about over-interpreting these data. In particular, the additional analyses are descriptive only (not supported by statistical analyses). That said, the CVMP does acknowledge an apparent treatment-related effect in the first laboratory efficacy study: in the kaolin model, frunevetmab was effective in improving lameness scores when administered intravenously at 2 mg/kg bw (which would have been equivalent to approximately 3.3 mg/kg bw SC with regard to drug exposure), while the lower doses 0.02 and 0.2 mg/kg bw (equivalent to approximately 0.03 and 0.3 mg/kg bw SC) did not have overt efficacy. Further, in a second laboratory study, frunevetmab was effective in improving the lameness score of cats in a kaolin-induced model of pain and inflammation when administered once subcutaneously at 2.0 mg/kg bw but not at 0.2 or 0.6 mg/kg bw. In the pilot dose determination field study, several efficacy endpoints were measured in cats following SC doses of 0.4 or 0.8 mg/kg bw. While this study showed some statistically significant effects, these effects did not exhibit convincing time- or dose-dependencies. Thus, these 3 studies taken together indicate that frunevetmab doses of at least 2 mg/kg bw appear to be efficacious (in a laboratory model), while doses of 0.4-0.8 mg/kg bw had marginal efficacy and doses of 0.3 mg/kg bw or less were not efficacious.

Based on the argumentation presented, it appears reasonable that a dose of 1.0 mg/kg bw was selected as the minimum therapeutic dose for evaluation in pivotal clinical studies.

In conclusion, the CVMP accepted the approach to dose selection based on the pharmacokinetic arguments and the findings of the laboratory efficacy studies. However, it is noted that the pivotal data in support of the minimum therapeutic dose of 1.0 mg/kg bw is the pivotal field trial.

Dose confirmation

In order to confirm the suitability of the proposed minimum dose rate (1 mg/kg bw), an exploratory, multi-site field study is presented, discussed below, in addition to the pivotal field trial, (discussed under 'Field trials').

The dose confirmation study, was a non-GCP compliant, exploratory, dose confirmation, multi-site study in which the efficacy of two doses (1 mg/kg bw) of Solensia (final formulation) was evaluated in client-owned cats with OA. Cats diagnosed with OA and which had a CSOM score of ≥7 (on a scale of 0-15) were enrolled and therefore, the study population can be accepted as being sufficiently representative of the target population. The test article was administered to one test group (n=42) by the IV route on day 0, followed by the SC route on day 28, while the other test group received both doses by the SC route on day 0 and 28 (n=43). The vehicle (histidine buffer) was administered to the placebo control group (n=41). At least 8 days before day 0 each cat was fitted with an activity monitor (AM) attached to a collar or harness that measured activity. Data was downloaded as activity counts per minute for each minute of the study duration. Effectiveness was measured by owner's assessment using CSOM (treatment success defined as a reduction of at least 2 in the total CSOM score at day 14, day 28, day 42 and day 56 when compared to CSOM score at Day 0), owners' global assessment score (treatment success defined as good or excellent for day 28 and 56), and the FMPI questionnaire at screening and on day 0, day 14, day 28, day 42 and day 56. Orthopaedic examination was conducted at screening and on day 28 and day 56.

- Initial statistical analyses showed no meaningful difference between the two frunevetmab treated groups and placebo for any of the outcome parameters and they were then combined for analyses of all efficacy variables.
- Statistically significant differences were found between the combined frunevetmab-treated group and placebo at day 42 (p=0.0479) and day 56 (p=0.0033) for treatment success; 76.1% vs 55.3% of cats were considered treatment success at day 42 in test and placebo group, respectively and 80.3% vs 44.7% in test and placebo group, respectively at day 56.
- Statistically significant differences were found between the combined frunevetmab-treated group and placebo at day 28 (p=0.0134) and day 56 (p=0.0030) for owners' global assessment score.
- Concerning the more objective parameters measured, weekly activity monitoring data showed that while the average value for the frunevetmab group was always higher than for the placebo group after baseline, no statistically significant difference between treated and placebo cats was observed for increases in activity compared to baseline of ≥9% or ≥5%.
- Based on orthopaedic examination, there were no statistically significant differences between treatment groups for the total pain score or the total joint debility score.

This study has been described by the applicant as an exploratory study. It can be accepted that the study, whilst not conducted to GCP, has been reliably conducted and reported (that is, conducted in accordance with satisfactory quality standards for a study of this type).

Regarding the findings of the study, it is a concern that there were no statistically or clinically significant differences between the test group receiving Solensia as proposed (i.e., by SC injection only), compared to the placebo control. While a statistically significant difference in success (based on CSOM scores) when combining the two frunevetmab-treated groups is reported, it should be noted that in one of those groups, cats were administered the first dose of frunevetmab intravenously. According to the findings

from a pharmacokinetic study, absolute bioavailability of frunevetmab is approximately 60% following subcutaneous administration when compared with intravenous administration. Consequently, it is therefore assumed that by including data from cats that were administered frunevetmab intravenously the efficacy of the product in the combined group of animals is likely to have been impacted upon by a greater systemic exposure (approximately 40% greater) in half of the animals and as a consequence, efficacy may have been over estimated.

Furthermore, for the primary efficacy parameter CSOM success/failure, a reduction of ≥2 was required for an animal to be considered a success. Given that the CSOM scale is based upon the scoring for three activities and is recorded on an overall scale of 3-15, the clinical significance of a change of 2 on such a scale was questioned. The applicant's efficacy expert has highlighted that as the median CSOM score was 10 in each group, a reduction in a score of 2 represents a 29% reduction in disability which is clinically relevant.

Notwithstanding the above, based on analysis comparing all animals administered frunevetmab with those administered placebo, it is evident that a statistically significant difference in success (based upon CSOM scores) was only observed on study days 42 and 56, i.e. 14 days and 28 days after administration of the second dose, but not before. However, based upon mean CSOM scores at day 42, it is evident that a difference of only 1.35 existed between frunevetmab treated animals and placebo treated animals, which is less than the cut-off value (2) selected by the applicant as denoting treatment success.

Field trials

One pivotal, GCP-compliant, blinded, randomised field study is presented, in which the safety and efficacy of 3 consecutive monthly doses of Solensia in client-owned cats with OA was evaluated. Cats with clinical signs of OA noted by the owner and confirmed by veterinarian's physical and orthopaedic examination in at least two joints or spinal segments, with radiographic evidence of OA in at least two of the joints or spinal segments that showed pain, and minimum total CSOM score of ≥7 (on a scale of 0 – 15) were enrolled in the study. A total of 182 animals were enrolled in the Solensia treatment group; the product was administered in accordance with recommendations (1 - 2.8 mg/kg bw SC at 28-day intervals, i.e. day 0, 28 and 56), with 93 animals included in the vehicle control group. The study was conducted in the USA; however, it is accepted that the animals included were representative of the target species intended for treatment. Clinical follow-up extended to 1 month after the last dose. The primary efficacy endpoint (based on the animal owner's observation) was evaluated at 56 days and compared the difference in 'treatment success', a reduction of the CSOM score by 2 or more between day 0 and day 56, between test and placebo groups.

Secondary efficacy endpoints included evaluation of treatment success at day 28 and at day 84, and the Owner's Global Assessment, a comparison of total CSOM scores, and a veterinary orthopaedic examination at day 28, day 56 and day 84.

The results as presented show that the percentage of treatment success was statistically significantly different between groups (p=0.0306), with 75.91% success for frunevetmab treated-treated cats and 64.65% for placebo-treated cats. However, while a statistically significant difference for the primary efficacy parameter between groups was reported, the CVMP raised concerns regarding the relevance of the statistically significant p-value cited in support of the claim of effectiveness of treatment for the following reasons:

- The high percentage of treatment success (76%) in the treated animals would suggest a beneficial effect of treatment, however it was noted that the placebo effect was also high, with 65% of animals in the placebo group considered by their owners to be a treatment success (≥2 point reduction in CSOM score between days 0 and 56). This high placebo effect is consistent with the findings in the

dose confirmation study, where the percentage of treatment successes was 60% at 14 days post-treatment administration. The CVMP questioned the clinical significance of a decrease of 2 on the CSOM scale and given the high percentage of treatment successes in the placebo group, it would appear that only an absolute difference of 11% between treated and control animals was observed in this study at day 56. In response to this concern, the applicant justified that the assessment of pain in cats is well established as being notoriously difficult, and that when any positive effects significantly greater than the placebo response rate are observed, they are considered highly clinically relevant. The CVMP accepted the challenges presented in assessing responses aimed at reducing pain in cats and accepted that a multi-dimensional approach including owner assessment of pain (as opposed to assessment in the veterinary clinic) is an established and widely reported approach to pain assessment in cats. The applicant chose to only use a subjective measurement tool for the primary efficacy parameter (CSOM score), with each cat owner responsible for evaluating their own cat's response to treatment. The CSOM score, a subjective measurement by the owner of the cat with respect to three parameters that they have chosen for their pet in order to evaluate changes in activity during the study, was similar between test and control groups at study start; mean scores were 11.0 and 11.4, respectively. On a score ranging from 3 – 15, this is stated to represent modest to severe mobility impairment and this can be accepted. The use of an owner-derived measurement tool for the primary efficacy parameter was further justified and was considered acceptable, given the target species and the nature of the parameter that was intended to be measured.

- It was questioned that at day 56, when a significant treatment effect is claimed in accordance with the primary efficacy parameter, the mean CSOM scores in the test and control groups were 7.08 and 7.93, respectively (difference=0.85), that is, there appeared to be little differences in mean scores between groups. At day 84, the mean CSOM scores in the test and control groups were 6.76 and 7.47, respectively (difference=0.71). However, the applicant justified that the mean change from baseline (i.e., the dynamic measurement) between groups, rather than a comparison of mean scores at each timepoint, is the more relevant aspect to take into consideration, providing an explanation as to why a statistically significant difference between groups was reported at day 56 when a comparison of mean scores did not seem notable between groups (since the pre-treatment scores CSOM scores were included in the statistical model as covariates).

Whilst a statistically significant difference in treatment success between groups was reported at study day 28 (p=0.0176) following a single treatment administration, it was noted that this was not the case at day 84 (p=0.082) following three monthly treatment administrations (at day 84, treatment success rates were 76.47% and 68.09% in the test and control groups, respectively, with mean CSOM scores of 6.67 and 7.47 in the test and control groups, respectively). However, the applicant argued that despite the lack of statistically significant differences between groups at this timepoint, that this finding did not represent a diminishing of efficacy, but that due to the nature of the parameter evaluated the improvement may not be equal at all time points. It was stated by the applicant that at day 84 in the pivotal study, 76.47% of the cats were considered a treatment success on CSOM. Additionally, 64.63% of the owners rated the overall treatment effect of Solensia as 'excellent' or 'good', the mean improvement in the cats' disability was 54.3% according to the change in Total CSOM scores and similarly, a 50.0% improvement was demonstrated on the veterinary pain scale.

Furthermore, in justifying the clinically relevant effect of treatment, the applicant presented a 'composite outcome summary'; a comparison of the number and percentage of cats in each group that met all of the following criteria; treatment success on CSOM, 'excellent' or 'good' response on the Global Owner Assessment and at least a 50% improvement on the total Veterinary Pain Scores. The results showed that in the frunevetmab group, 24.65%, 40.12% and 41.95% of the cats met all these criteria on day 28, 56 and 84, respectively, compared to 11.43%. 19.99% and 30.85% of the cats in the placebo group.

Overall, the CVMP concluded that sufficient reassurances of the clinical relevance of the statistically significant difference between groups for the primary efficacy parameter had been adequately demonstrated. Thus, it was concluded that this study supported the proposed indication 'for the alleviation of pain associated with osteoarthritis in cats' when used in accordance with recommendations, and that these data provided sufficient support for the benefit of treatment with Solensia.

Overall conclusion on efficacy

Dose determination

The proposed minimum dose of 1 mg/kg bw, administered by the subcutaneous route, was established based on a number of pre-clinical studies. The CVMP accepted the approach to dose selection based on the pharmacokinetic arguments and the findings of the laboratory efficacy studies. However, it is noted that the pivotal data in support of the minimum therapeutic dose of 1.0 mg/kg bw is generated in the pivotal field trial.

Dose-confirmation

Two dose-confirmation studies are provided in which the efficacy of the proposed minimum dose of 1 mg/kg bw, administered by the subcutaneous route at intervals of 28 days was investigated in client-owned cats with OA.

One of these two field studies was a non-GCP compliant, exploratory study in which two groups of frunevetmab-treated cats were included that received two doses of Solensia at the proposed dose of 1 mg/kg bw, 28 days apart, however one of the two groups received the first dose by the IV route. In the absence of statistically significant differences between each of the two test groups alone compared to the placebo group, results of both frunevetmab-treated groups were combined. Given that SC bioavailability is approximately 60% (relative to administration by the IV route), a treatment effect may have been overestimated by combining groups. This study can be considered supportive only.

Field trial

In the pivotal, GCP-compliant field trial, in which Solensia was administered at the proposed minimum dose rate of 1 mg/kg bw by the subcutaneous route for 3 consecutive months of treatment, a statistically significant difference in the test group compared to a placebo control group was demonstrated for the primary efficacy parameter, 'treatment success' (reduction of ≥2 for CSOM scores between day 0 and day 56 of the study) (p=0.0306), whereby the percentage of animals considered a treatment success was 75.91% (133/176) in the test group and 64.65% (59/91) in the placebo group. Despite the high placebo effect reported in this study, the applicant provided sufficient reassurances of the clinical relevance of the statistically significant difference between groups, and therefore these data were considered adequate to support the claim for the alleviation of pain associated with osteoarthritis.

Part 5 – Benefit-risk assessment

Introduction

Solensia 7 mg solution for injection for cats contains 7 mg/ml frunevetmab a felinised anti-Nerve Growth Factor (NGF) monoclonal antibody expressed through recombinant techniques in Chinese hamster ovary (CHO) cells.

The target species is cats. The product is intended for administration by subcutaneous use at monthly intervals, and it is claimed to inhibit NGF mediated cell signalling to provide relief from pain associated with osteoarthritis.

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

Benefit assessment

Direct therapeutic benefit

The benefit of Solensia is its efficacy for the alleviation of pain associated with osteoarthritis in cats, when administered in accordance with recommendations, i.e. at a dose rate of 1 – 2.8 mg/kg bw by the subcutaneous route at intervals of 28 days.

Additional benefits

Solensia would increase the range of available treatment possibilities for 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.

Safety:

Risks for the target animal:

Administration of Solensia in accordance with SPC recommendations is generally well tolerated. However, product administration is associated with skin related adverse reactions (pruritus, alopecia, dermatitis).

Risk for the user:

The main risk to the user is associated with accidental self-injection. The person administering the product will be a trained professional and although the risk of accidental self-injection exists, the likelihood of this event occurring is expected to be low. It is accepted that in the event of accidental parenteral exposure, there are two main risks which are considered to arise: (1) the potential for binding of the mAb to human NGF and associated on-target pharmacological effects; and (2) the potential development of an immunological response. Adequate precautions are included in the product information to mitigate against the risks for the user. Therefore, it can be considered that Solensia is not expected to pose a risk for the user when used according to the SPC recommendations.

Risk for the environment:

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

Risk management or mitigation measures

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

Evaluation of the benefit-risk balance

The applicant applied for the following indication: 'For the treatment of pain associated with osteoarthritis in cats'. The product has been shown to be efficacious for alleviating pain in cats with osteoarthritis, and as pain is only a clinical sign of osteoarthritis and thus cannot be 'treated' with the product, the CVMP agreed to the following indication: 'For the alleviation of pain associated with osteoarthritis in cats'. Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information. Based on the data presented, the overall benefit-risk is considered positive.

Conclusion

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

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