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Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for CYTOPOINT (EMA/V/C/003939/0000)

International non-proprietary name: lokivetmab

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



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Introduction

On 28 January 2016 the applicant Zoetis Belgium SA submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for CYTOPOINT, through the centralised procedure falling within Article 3(1) and point 1 of the Annex of Regulation (EC) No 726/2004 (product developed by means of a biotechnological process).

The eligibility to the centralised procedure was agreed upon by the CVMP on 14-16 January 2014 as CYTOPOINT is developed by means of a biotechnological process (monoclonal antibody methods). CYTOPOINT is a caninised monoclonal antibody (mAb) specifically targeting canine interleukin-31. The mAb is referred to as lokivetmab.

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

The applicant applied for the following indication: Treatment of clinical manifestations of atopic dermatitis in dogs.

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

On 16 February 2017, the CVMP adopted an opinion and CVMP assessment report.

On 25 April 2017, the European Commission adopted a Commission Decision granting the marketing authorisation for CYTOPOINT.

Scientific advice

The applicant received scientific advice from the CVMP on 10-12 September 2013 (EMA/V/SA/156/13/I/EMA/CVMP/SAWP/331254/2013). The scientific advice pertained to clinical aspects of the dossier. Comments are raised in the relevant section of the CVMP Assessment Report Part 3 concerning compliance with the scientific advice given.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated 18 March 2015) which fulfils the requirements of Directive 2001/82/EC. 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

Lokivetmab active substance is manufactured at the following sites:

Syngene International Limited, Bangalore, India

Or

Zoetis Inc, Lincoln, Nebraska, USA.

The active substance is then shipped to Europe for finished product manufacturing, secondary packaging and batch release at:

Zoetis Belgium SA, Louvain-la-Neuve, Belgium.

An EU Good Manufacturing Practices (GMP) certificate for Syngene International Ltd. site was issued by the Veterinary Medicines directorate (VMD) (UK) on 14 December 2016 following an inspection of the relevant manufacturing and associated areas / laboratories used for lokivetmab production on 12 – 16 September 2016.

A GMP certificate issued by the Veterinary Medicines directorate (VMD) (UK) on 26 February 2015 is available for Zoetis Inc. Lincoln, USA following an inspection of the premises from 17 – 21 November 2014. Prior to this the site was covered by an EU GMP certificate issued on 8 July 2013 following an inspection by the VMD on 16 – 20 April 2012. The GMP status of the Lincoln site at the time of manufacture of the lokivetmab batches for which data are provided in the application (e.g. stability batches manufactured between October–December 2013), is considered satisfactory.

A GMP certificate issued on 5 December 2015 by AFMPS (Belgium) is available for Zoetis Belgium SA (Louvain-la-Nueve). This covers activities related to aseptically prepared large and small volume liquids as well as testing and batch certification activities and is considered acceptable. A copy of Manufacturing Authorisation No. 419V issued by AFMPS, Belgium on 12 October 2015 for the Zoetis site is also provided.

Overall conclusions on administrative particulars

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

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

Part 2 – Quality Composition

CYTOPOINT is a solution for injection containing the active substance lokivetmab which is a caninised monoclonal antibody (mAb) presented in four strengths (10, 20, 30 and 40 mg/ml) for administration to dogs of varying bodyweight. Excipients include L-histidine, histidine HCl monohydrate, trehalose dihydrate, disodium EDTA dihydrate, L-methionine, polysorbate 80 and water for injections.

Trehalose dihydrate, isotonicity agent, disodium EDTA dehydrate, L-methionine and Polysorbate 80 are added as excipients.

The final formulation does not contain preservative; it is a single dose vial.

Container

CYTOPOINT is presented in single dose Type I glass vials. The vial is closed with fluorobutyl rubber

stopper sealed with aluminium cap. The container is considered acceptable and meets relevant Ph. Eur. requirements.

Development pharmaceuticals

The proposed mechanism of action is that lokivetmab binds to IL-31 with a view to inhibiting the binding of IL-31 to its receptor. A summary of the screening processes and testing for the selection of the anti IL-31 mAb has been provided.

Lokivetmab is a fully caninised IgG mAb of the IgG class, with a subtype matching human IgG4. The characterisation of lokivetmab is described and the physical and chemical properties identified are provided. The batch to batch consistency and equivalence between sites has been adequately demonstrated. Details on the test methods used and the level of validation of these tests to determine product and process related impurities have been provided.

Analytical testing for developmental and release testing was based on VICH GL40 and on scientific advice (EMA/CVMP/SAWP/237792/2012) sought for a different proposed mAb by Zoetis. Justifications for inclusion or omission of testing have been provided.

CYTOPOINT is formulated at four different strengths of 10, 20, 30, 40 mg/ml in histidine buffer with trehalose dihydrate, polysorbate, disodium EDTA dehydrate and methionine. The final formulation does not contain preservative; it is a single dose vial. The selection of the excipients and the robustness of the formulation were well discussed and justified. The excipients are considered acceptable.

The container used for the finished product is Type I colourless glass vial, closed with pharmaceutical grade butyl rubber stopper with fluoropolymer coating and sealed with aluminium cap. The choice of container is based on well-established use of this type of container for injectable veterinary immunological products. The coated butyl rubber stoppers were chosen as the fluoropolymer film as an effective barrier against organic and inorganic extractables, for example, by excipients such as polysorbate 80. The container and stoppers meet Ph. Eur. requirements.

Method of manufacture

The active substance can be manufactured at 2 different sites , Zoetis Inc., Lincoln (US) and Syngene International Ltd., Bangalore (India) being then shipped to the Zoetis site in Belgium (Zoetis Belgium S.A., Louvain-la-Neuve) where the formulation and release testing is performed. An appropriate process flow was provided for both stages of manufacture; active substance (lokivetmab) and finished product (CYTOPOINT).

The active substance manufacture includes 8 steps (seed scale up, production culture, harvest, clarification, chromatography, pH adjustment, concentration and storage) before the bulk product formulation and filling.

Lokivetmab is produced using genetically engineered Chinese Hamster Ovary (CHO) cells and standard cell culture procedures at manufacturing scale. The cell line is handled according to a two-tiered cell-banking system (master cell bank and working cell bank), and these cell banks have been appropriately qualified according to Ph. Eur. and relevant EMA guidelines.

The description of the manufacturing process for the active substance contain sufficient details, has been adequately validated and appropriate in-process controls are in place.

The results of the development batches from the two sites showed consistency of the process but,

given the limited number of batches manufactured at one of the sites, a continued monitoring for trends in manufacture will be performed on the first 10 commercial lots of active substance. This is considered acceptable.

Control of starting materials

Starting materials listed in a Pharmacopoeia

Starting materials included are in line with the Ph. Eur. and comply with their respective monographs. Appropriate certificates of analysis for each starting material listed in a pharmacopoeia have been provided.

Starting materials not listed in a Pharmacopoeia

Starting materials of biological origin

Active substance

Lokivetmab is expressed in a genetically engineered CHO cell line.

The plasmid expressing the DNA sequences for the canine anti-IL-31 heavy and light chains were constructed at the facilities of Zoetis Inc. in Kalamazoo, MI, USA.

The expression plasmid was then used to transfect the CHO cell line. Individual transfectants were evaluated for antibody expression. The final candidate cell line was sub-cloned at the Kalamazoo facility to generate the pre-MCS which was then used to prepare the master cell seed (MCS) and working cell seed (WCS).

The details given on the individual plasmids and the component parts of the final plasmid construct (e.g. origins of replication, antibiotic resistance genes, promoters, enhancers etc.) are satisfactory and in line with the requirements of guideline ICH Q5B: 'Analysis of the expression construct in cell lines used for production of rDNA derived protein products'.

The mechanism of transfection of the expression plasmid into the CHO cell line including details of the nucleotide-sequence analysis of the cloned gene and the flanking control regions of the expression vector is described as required by Ph. Eur. 784 'Products of recombinant DNA technology'. The genetic stability of the cloned gene in the seed material and at the limit of *in vitro* cell age proposed for production is adequately described. The production and qualification of the lokivetmab MCS and WCS materials is well described.

In accordance with Ph. Eur. 5.2.4 'Cell cultures for the production of veterinary vaccines', the MCS and WCS have been tested for general microscopy, bacteria and fungi, mycoplasma, extraneous agents and karyotype. Cell line identity is based on the karyotype results as well as using a DNA assay. The MCS/WCS has not been tested for tumorigenicity. This is acceptable as CHO cells are widely approved for production of human monoclonal antibodies and therefore it is considered unlikely that the MCS/WCS are tumorigenic.

The MCS and WCS were tested in compliance with Ph. Eur. 2.6.1 'Sterility' and 2.6.7 'Mycoplasmas' testing requirements respectively.

The MCS and WCS have been tested for freedom from a range of canine extraneous agents on swine, canine, feline and bovine cells. In general, the agents listed in Guideline 7BIm10a which was in force at the time of preparation and testing of the seed materials have been taken into consideration. Many of the recommended canine agents listed in the CVMP 'Guideline on the production and control of veterinary vaccines' (EMA/CVMP/IWP/206555/2010-Rev.1), which was published after testing of the MCS and WCS, have also been considered (e.g. canine oral papilloma virus).

In accordance with the requirements for rodent cell lines in guideline ICH Q5A (R1) 'Viral safety assessment of biotechnology products derived from cell lines of human or animal origin', the MCS has been tested using hamster, mouse and rat antibody production tests as well as the absence of murine minute virus (by PCR) and encephalomyocarditis virus (EMCV) (by PCR). The MCS has also been tested for freedom from retroviruses. The MCS has not been subjected to *in vivo* testing although this is also recommended in ICH Q5A (R1) for rodent cell lines. This is considered acceptable on the basis that *in vivo* testing is not a requirement of Ph. Eur. 5.2.4 and taking into account that safety and efficacy data are available for CYTOPOINT in the target species.

Cells at the limit of *in vitro* cell age have also been tested for the absence of retroviruses in accordance with the requirements of Ph. Eur. 2031 'Monoclonal antibodies for human use' and recommended in ICH guideline Q5A (R1).

To support the viral clearance capacity of the lokivetmab production process, viral clearance data from a scaled down process for a related canine monoclonal antibody product are provided. The related product and lokivetmab have the same constant regions and have similar pI's and molecular weights and their production processes are similar. The viral clearance data for the related product is considered relevant to the lokivetmab process and sufficient. A satisfactory viral safety risk assessment has been provided in accordance with Ph. Eur. 5.1.7 'Viral safety' which supports a negligible risk of viral contamination for lokivetmab.

To support the proposed 3 year shelf life of lokivetmab at ≤ -40 °C, batches have been entered into a 36 months stability study. The study is complete for batches manufactured at one of the active substance manufacturing site (i.e. 36 months data available) while 18 months data are available for the batches from the other manufacturing site. No apparent trends were detected in the data supporting the 3 years shelf life at ≤ -40 °C. To further support the 3 years shelf life at ≤ -40 °C for lokivetmab, 3 further large scale size batches manufactured at one manufacturing site have been placed in a long term stability study.

The applicant is recommended to complete the stability evaluation up to 36 months of all batches in the current stability program.

Other starting materials of biological origin

In addition to the CHO cells, there is only one other biological origin starting material used in production. Sufficient data are presented to support its use and safety.

Non-biological origin starting materials

The starting materials of non-biological origin are listed.

The in-house preparation of all media and solutions is well described and is satisfactory.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

An assessment of TSE risk has been provided, consistent with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 Rev-3).

The TSE risk is considered negligible as the only material of animal origin used are CHO cells which originated from the USA.

Control tests during production

Active substance test methods are well described and validated.

The following tests are proposed for release of lokivetmab active substance: appearance; identification and specific activity; protein content; purity; product related impurities; pH(Ph. Eur.); endotoxin (Ph. Eur.); mycoplasma (Ph. Eur.) and sterility (Ph. Eur.).

The test used as a measure of the functional binding of lokivetmab to IL-31 has been appropriately validated and the criteria for monitoring of reagents used in the test and selecting replacement reagents are satisfactory.

The limits proposed for product related impurities measured in impurity test on active substance batches are considered acceptable.

Consistency data are provided for 8 batches of active substance. The data are supportive of the consistency of lokivetmab production at each site and between the two sites.

Control tests on the finished product

The following tests are proposed for release of filled vials of lokivetmab: appearance (Ph. Eur.); identification and specific activity; protein content; purity; product related impurities; pH (Ph. Eur.); endotoxin (Ph. Eur.); free methionine, osmolality and sterility (Ph. Eur.).

A test for extractable volume (Ph. Eur. 2.9.17) is not done. Instead regular in-process fill weigh checks are performed to confirm filling of the correct volume into the vials. Methionine content is tested in accordance with CPMP/QWP/486/95 "Note for guidance on manufacture of the finished dosage form".

The justification for not providing testing for the in-process related impurities, as either an in-process control or a release test is acceptable.

The same test to measure functional binding is used for release of active substance and filled vials. The specific activity limit for batches to date has demonstrated that the limit does not represent a concern for clinical efficacy.

Data from 12 batches of filled vials manufactured at Zoetis's Louvain-La-Neuve, Belgium site containing active substance produced at either the Syngene or Lincoln sites are provided to support consistency of production. On the basis of the data from these consistency batches, many of the originally proposed acceptance limits for the release tests have been tightened and are now considered acceptable.

Stability

The 12 consistency batches of filled vials have been entered into a stability program to support the proposed 24 months shelf life when stored at 2 °C – 8 °C. Details are given in the stability protocol.

A maximum of 12 months data are available to date from these 12 batches. To support the requested 24 months shelf life for filled vials at 2 °C – 8 °C, additional data from development batches are provided. It has been confirmed that these batches were manufactured using the proposed production process. From a combination of data from the real time and development studies it can be accepted that there is no evidence of significant changes or trends in the results for the appearance, pH, specific activity, protein content or methionine tests over the proposed 24 months storage period. Similarly the data do not suggest an increase over time for aggregates.

On the basis of these data the proposed 24 months shelf life is considered acceptable.

Overall conclusions on quality

The screening process for anti-IL-31 mAb involved the generation of anti IL-31 mAbs in mice and evaluation of their affinity to IL-31 and testing for their ability to inhibit IL-31 mediated signalling in cells. A lead molecule was identified and then caninised. This molecule was named lokivetmab.

Lokivetmab was tested for structural and physicochemical properties to characterise it and demonstrate consistent manufacture. The glycosylation profile provided is sufficient. Characterisation and quantitative data provided for product and process related impurities ensure adequate control of the drug substance and drug product. Analytical testing included in the developmental and release testing was based on VICH GL40 and on scientific advice (EMA/CVMP/SAWP/237792/2012) for another mAb from Zoetis. Based on the data provided and the ability to show the binding capacity for the target it is considered that a single impurity test is sufficient for release. However, due to the limited number of batches manufactured at one of the active substance manufacturing sites, isoelectric focusing (IEF) will be monitored for trending of manufacture for the first 10 commercial lots of active substance and any out of trend results will be notified to the authorities.

The formulation has been well described.

The containers and closures have been described adequately.

Overall the description of the manufacturing process is sufficient. Mycoplasma testing takes place on the active substance. The process validation included three batches each manufacturing site. The batches tested met the required specifications but there were some differences in important parameters between the active ingredient produced at Lincoln and Syngene. Further data has been therefore provided to determine consistency of production and the equivalence of production between the two sites. The data overall indicates consistency in production and equivalence between the two sites. Appropriate information has been provided on starting materials listed in the pharmacopoeia.

The information provided on the construction of the expression plasmid, its transfection into the CHO cell line and the genetic stability of the cloned gene is satisfactory.

The production of the lokivetmab MCS and WCS materials is well described.

The MCS and WCS have been tested for general microscopy, bacteria and fungi, mycoplasma and karyotype in accordance with Ph. Eur. 5.2.4.

In general, the MCS and WCS have been tested for freedom from the relevant extraneous agents listed in Guideline 7Blm10a which was current at the time the seeds were laid down. In addition, many of the recommended canine agents listed in the CVMP 'Guideline on the production and control of veterinary vaccines' (EMA/CVMP/IWP/206555/2010-Rev.1), which was published after preparation and testing of the seed materials, have also been considered (e.g. canine oral papilloma virus). The MCS has been tested using antibody production tests and also for freedom from retroviruses using both co-cultivation infectivity assays and a validated QFPERT as recommended by ICH Q5A.

Cells at the limit of *in vitro* cell age have also been satisfactorily tested for freedom from retroviruses as required by Ph. Eur. 5.2.4. A viral safety risk assessment in accordance with Ph. Eur. 5.1.7 is provided which supports a negligible risk for lokivetmab.

The proposed 36 months shelf life for lokivetmab active substance stored at ≤ -40 °C is supported by stability data for both Lincoln and Syngene manufactured batches.

The preparation of media and solutions are well described.

The TSE risk is considered negligible as the only animal origin materials are CHO cells which originated from the USA.

For the active substance release tests, the limits are acceptable based on data from the consistency and clinical batches. Other than mycoplasma testing (which is only done on the active substance), the same tests are proposed for release of active substance and filled vials with additional tests for osmolality and free methionine on the filled vials. The test used to measure the functional binding of IL-31 by lokivetmab is considered acceptable and the revised specific activity limit is supportive of clinical efficacy of the product.

Twelve months real time stability data are available for the filled vials with additional 24 month data from development batches. The shelf life limits are supported.

Based on the review of the data on quality, the manufacture and control of CYTOPOINT are considered approvable with the following conditions:

- Endotoxin: The endotoxin results for the first 20 batches released onto the EU market should be provided and the specification revised if justified. Data to be provided within 12 months of the granting of the marketing authorisation.
- Active substance stability: The applicant should complete the ongoing lokivetmab stability evaluation up to 36 months at the different batch sizes. These final reports should be provided by April 2018 and November 2019, for the ongoing 300 L and 2000 L stability studies, respectively.
- Capillary Isoelectric Focusing (cIEF). The applicant should additionally test for cIEF for a limited number of lokivetmab batches manufactured at the alternative site. The cIEF test should be done on the first 10 commercial lots of active substance and any out-of-trend data should be notified to the EMA. The data should be provided within 24 months of the granting of the marketing authorisation.
- Specific Activity (SA): The applicant should continue monitoring the specific activity results for the first 10 commercial lots of lokivetmab active substance manufactured at the alternative site to ensure that it is consistent and within trend. Any out-of-trend data should be notified to the EMA. The data should be provided within 24 months of the granting of the marketing authorisation.

Part 3 – Safety

The safety data presented for CYTOPOINT was generated using a non-standard approach, that is, it did not fall under the scope of the requirements for either an immunological or a pharmaceutical veterinary medicinal product. Therefore, the approach to safety testing was developed using a focused, science-based approach taking into account the characteristics of the mAb, with consideration given to potential unwanted target effects. It is noted no off-target effects were identified. Lokivetmab is highly specific for IL-31, a soluble protein which belongs to the IL-6 family of cytokines of which members have low sequence homology. The CVMP considers that the approach taken is acceptable. While the number of studies presented was not large, each study comprised a comprehensive set of measurements.

The following information is relevant for the evaluation of safety:

- Lokivetmab is a fully caninised IgG mAb of the IgG class, with a subtype matching human IgG4. The heavy chain of lokivetmab is 93% identical to a published native canine IgG sequence with the divergence shown to be in the complementarity determining regions (CDRs) only. Therefore, the only sequences that are not endogenous to dogs are the CDRs, consisting of 31 amino acids derived from a mouse anti-IL-31 mAb (following immunisation of mice with a canine IL-31 immunogen).
- Lokivetmab is a mAb which binds canine interleukin 31 (IL-31), a T-cell derived pro-inflammatory cytokine of the IL-6 family of cytokines. IL-31 is a secreted protein that signals through a unique receptor complex; the heterodimeric IL-31 receptor composed of the IL-31 receptor alpha (IL-31RA) subunit and the oncostatin M receptor (OSMR). Binding to the IL-31 receptor results in activation of the STAT signalling cascade via Janus kinase phosphorylation, and leads to upregulation of target genes. IL-31 is mainly produced by T_H2 cells, and functions in innate and adaptive immunity in tissues that are in close contact with the environment, i.e. the skin, the airways and the lung. However, IL-31 is associated with a number of diseases, including atopic dermatitis (AD), characterised by deregulation of cells of both the innate immune system, including mast cells and eosinophils, and the adaptive immune system.

The risks that may potentially be associated with the use of lokivetmab in the dog, and how these risks have been evaluated, are summarised by the applicant in the dossier, supported by published literature.

The following points were discussed within the evaluation of potential toxic responses:

Target-related effects, off-target and biological activation:

IL-31 is a soluble, 141 amino acid protein belonging to the IL-6 cytokine family. To date, in literature, there has been no clinical disease attributed to absence of IL-31 signalling. Cells and tissues expressing IL-31 and its receptor have been identified in various species (Cornelissen et al, 2012):

- Cells that produce IL-31 include T-cells (CD4+, CD8+, TH1, TH2, Cutaneous lymphocyte-associated antigen [CLA]+), macrophages, dendritic cells, mast cells, keratinocytes, and fibroblasts, but predominantly TH2 cells. These cell types generally link IL-31 to several mechanisms associated with pruritus and AD.
- Cells that express the IL-31 receptor include monocytes, eosinophils, mast cells, dendritic cells, keratinocytes, human dermal microvascular endothelial cells, primary cells of bronchial epithelia,

pulmonary macrophages, colonic subepithelial myofibroblasts, and neurons of the dorsal root ganglia.

The potential for mAb binding to unintended target epitopes is considered to be low; lokivetmab has been designed to bind to a single specific epitope on IL-31, thereby sterically hindering the binding of IL-31 to its receptor. It is not considered that there is potential for CYTOPOINT to bind to unintended target epitopes due to the highly targeted nature of mAbs or that lokivetmab would bind to other interleukins of the IL-6 cytokine family (members of which show very low sequence homology) or any other endogenous canine protein. This is concluded by the applicant on the basis that attempts to identify IL-31 paralogs in the published boxer genome using multiple low-stringency approaches failed to identify any predicted amino acid sequence with an E-value better than threshold, suggesting that murine and human IL-31 are more closely related to canine IL-31 than any other protein in the canine proteome.

As a caninised mAb, CYTOPOINT becomes part of the circulating pool of endogenous-origin antibodies and is eventually catabolised similarly to any protein.

Immunogenicity:

The potential effects of lokivetmab immunogenicity are an increase in clearance of the mAb or interference with binding of the mAb to its target epitope, both of which would shorten the observed duration of clinical effectiveness. The potential for other adverse consequences is low, because CYTOPOINT is not identical to any endogenous peptide that would produce a clinical deficiency syndrome and mAb: IL-31 complexes remain soluble, making effector function unlikely.

Idiosyncratic responses:

In humans, the most common adverse effects observed following administration of mAbs in patients, at an incidence of 5–10% and greater than placebo, were headache, pain, fatigue, nausea and rhinitis/nasopharyngitis. The similarity of these minor events across the mAbs suggests that they have little relationship with the pharmacology of the mAb itself (Martin and Bugelski, 2012).

Overall, the CVMP considers that the applicant has prepared a comprehensive overview of the potential risks that may be associated with the use of CYTOPOINT. The design of the safety program has been given detailed consideration and the potential risks associated with the mAb have been discussed taking into account the available information on IL-31 function.

Safety documentation

Laboratory tests

Safety of the repeated administration of one dose

- An early exploratory, margin of safety study was conducted in normal beagle dogs. The study was a randomised, placebo-controlled study in which dogs were dosed with placebo (T01) or 1 mg/kg (T02), 3 mg/kg (T03), or 9 mg/kg (T04) lokivetmab subcutaneously (n=6/group), with dogs receiving three doses administered at two week intervals (dosing on days 0, 14 and 28 (that is, the test item was administered by the recommended route at the minimum recommended treatment dose and multiples (~1x, ~3x) of the maximum recommended treatment dose, with a between treatment interval less than proposed). Safety parameters were evaluated and animals were

euthanised and necropsy performed on day 31. Serum lokivetmab was quantified and potential immunogenicity was assessed using an anti-drug antibody assay.

Results indicated that administration was well-tolerated, with a shorter dosing interval than proposed for recommended use. There were no mortalities or test-article related findings for clinical observations, body weight, serum chemistry or urinalysis parameters. There were no anti-drug antibodies (ADAs) detected in any animal during the study. The pharmacokinetic analysis, while based on relatively few sampling points, suggest that there is low between animal variability in serum lokivetmab concentrations, that serum lokivetmab concentrations increase in dose-dependent manner, and that the elimination half-life is approximately 9 days with the potential for accumulation following repeated treatments (with the highest serum concentration recorded at day 31 of the study, 3 days following administration of the final dose). Overall, based on the findings of this exploratory study, it was accepted that the test item was well tolerated at 3x the maximum recommended treatment dose.

- The safety of the test article when administered subcutaneously at 1x and 3x the highest proposed label dose, once monthly for 7 consecutive monthly doses, to normal healthy beagle dogs was evaluated in the pivotal target animal safety study. This was a good quality, GLP standard, randomised, placebo-controlled, blinded study. Animals were randomly allocated to the placebo group (n=12), 3.3 mg/kg dose group (1x maximum label dose, n=12) or 10 mg/kg dose group (3x maximum label dose, n=12). The study included an adequate number of test animals to allow for meaningful analysis (indeed, the number of test animals/group exceeds guideline recommendations). Parameters measured within this study included body weight, food consumption, ophthalmic examinations, daily health observations, veterinary clinical observations, haematology, serum chemistry, urinalysis, quantitation of serum lokivetmab for PK analysis, analysis of ADAs, and necropsy at study end including an enhanced histopathology for evaluation of lymphoid organs to screen for potential immunomodulatory effects.

Results demonstrate that administration of CYTOPOINT at 1X and 3X the maximum recommended treatment dose at monthly intervals for 7 consecutive months was well-tolerated and resulted in no local or systemic adverse effects in treated animals. No mortalities were reported, and there were no test-article related findings for clinical observations, body weight, food consumption, clinical pathology parameters, ophthalmic findings, urinalysis, or general health observations. Examination of tissues at necropsy did not reveal any adverse effects of the repeated administration of CYTOPOINT in the 1X or 3X dose groups. The enhanced histopathology showed no immune organ lesions that would indicate adverse immunological effects.

It was noted that the study deviated from CVMP Scientific advice regarding the design of the study, notably with respect to the use of normal dogs vs atopic dogs. However, the applicant justified the use of normal dogs, in particular on the basis that test-article related findings would be difficult to distinguish from disease-related changes and that safety of the product would be evaluated in the context of field safety data in AD dogs. The CVMP accepted the applicant's justification for deviation from the advice given.

ADAs were not detected in any of the animals in the 1x or 3x treatment groups.

- An exploratory toxicity study of the histidine buffer (i.e. test product without the active substance) was presented, in which vocalisation (pain at injection) was reported in higher dose groups following subcutaneous administration. The dose of polysorbate 80 in the final product formulation is lower than the quantity that induced vocalisation or aggressive responses in dogs in this study.

Neither, it was noted that vocalisation or aggressive responses during administration were noted in the other safety studies presented.

Examination of reproductive performance

No studies were conducted to determine if there are any adverse effects on reproductive performance. The SPC carries a warning that the product is not recommended for use in reproducing animals. This is considered acceptable.

Examination of immunological functions

The examination of immunological functions was undertaken in a laboratory study using the T-cell Dependent Antibody Response Test (TDAR) as a method to determine if immune function was impaired following treatment with lokivetmab. The TDAR test measures a) the antibody response following immunisation with the model antigen KLH (by ELISA) and b) T-cell functional assays; by measurement of IL-2 production and lymphoproliferation in response to stimulation with KLH (by IL-2 ELISpot for cytokine production and ³H-thymidine uptake for proliferation of peripheral blood mononuclear cells). Two groups of dogs were treated with 10 mg/kg lokivetmab (T03 and T04) on day 0 and 21 or two groups of dogs were included as placebo (T01 and T02). Immunising doses of KLH antigen were administered to all study dogs on days 5 and 26, with a lower dose of KLH (0.1 mg) administered to T01 and T02, and a higher dose of KLH (10 mg) administered to T03 and T04.

Results demonstrated that the administration of 10 mg/kg lokivetmab twice, with an interval of 3 weeks did not impair the immune response to KLH antigen; the anti-KLH antibody kinetic profiles were similar in test article or placebo groups, the only difference being that higher titres were achieved in test and placebo group that were immunised with the higher dose of 10 mg KLH. Treatment with lokivetmab had no effect on the anti-KLH antibody response at either level of KLH immunisation. Similarly, IL-2 cytokine production was similar in treatment groups; one week after the 2nd KLH dose (at doses of 0.1 mg and 1 mg), half or more of dogs in each group had acquired T-cell specific recall responses as measured by IL-2 ELISpot. Treatment of dogs with lokivetmab failed to inhibit this response; neither lokivetmab-treated group had fewer responding dogs or lower ranges of response compared to their corresponding controls. Treatment with test article did not reduce the number of dogs with a positive proliferation response, or the range of responses, at either level of KLH immunisation.

While the TDAR test is considered an acceptable method for the evaluation of possible immune impairment following test article treatment given that it is a functional assay dependent on complex interactions of multiple components of the immune system, it was considered a shortcoming that these results were unable to address whether immunosuppression could develop in dogs that undergo long-term treatment with lokivetmab. However, it was noted that the examination of immunological function was also evaluated within the context of the pivotal TAS study in which the enhanced immunohistopathology analysis supported that there were no adverse effects (manifesting as changes in lymphoid organs) in normal healthy beagle dogs following monthly dosing for six consecutive months. Furthermore, it was acknowledged that the data from the US and EU field studies were also relevant to the examination of immunological functions. The applicant was requested to address the potential for development of immunosuppression in dogs with AD when treated as recommended (i.e. no limit on duration of use), in particular considering that there was a concern raised over the frequency of use of systemic antibacterials in animals treated with CYTOPOINT in the pivotal EU field study. The issue was addressed satisfactorily; given the narrower anti-inflammatory effect of

CYTOPOINT (that is, compared to the positive control group treated with cyclosporine), it is proposed that there is a period during the initial weeks of treatment prior to the resolution of skin lesions associated with AD during which time the cutaneous microenvironment facilitates bacterial infections due to pre-existing dysbiosis (imbalances in the residing cutaneous bacteria). A suitable warning was added to the SPC to draw attention to the need to monitor for bacterial infections, especially in the first weeks of treatment with CYTOPOINT. In addition, data from a continuation therapy study was provided, in which dogs in the test group from the pivotal EU field study continued on treatment for a maximum of six additional monthly doses. No indications of development of treatment-related immunosuppression emerged from this study. While it is emphasised that animals for which CYTOPOINT is considered an efficacious therapy will likely be on treatment for significantly longer durations than nine months, the absence of identified risks with the data presented to date, in addition to the mechanism of action of the anti-IL-31 mAb provides sufficient reassurance that the risk of treatment-related immunosuppression can be considered negligible.

Overall, it is concluded that use of the product, as recommended, is not expected to have an adverse effect on immunological function.

Interactions

Specific studies to investigate the interaction of CYTOPOINT with other veterinary medicinal products have not been performed. However, during the field studies, numerous veterinary medicinal products that would typically be encountered during treatment of dogs with AD were administered concurrently and no specific drug interactions were reported.

Field studies

Three field studies are presented, one positively-controlled safety and efficacy study in the EU, a single-arm, unblinded continuation therapy study following this pivotal EU field study and one placebo-controlled safety only study in the US. All studies were conducted in client-owned AD dogs and the animals included were considered representative of the intended target population.

- In the US field study, 162 dogs received two treatments of the test article at the proposed dose of 1 mg/kg, with an interval of one month between treatments, while the control group (n=83) were treated with histidine buffer with polysorbate 80 (vehicle). Follow-up was 14 days after the second dose.
- In the EU field study, 142 client-owned dogs with AD were treated with CYTOPOINT at the proposed dose of 1 mg/kg once monthly for three consecutive months, with follow-up to one month after the final dose. The positive control group (n=132) received Atopica (cyclosporine) in accordance with label recommendations.
- In the continuation therapy study 81 client-owned dogs from the test group in the previous study for which lokivetmab had been evaluated as an efficacious treatment during the initial three months of treatment. The continuation study allowed dogs to continue on treatment for an additional six monthly consecutive doses, with final follow-up at one month after the last dose.

Overall, the data from the EU field study demonstrate that administration of test article was well-tolerated, there were no mortalities or adverse events considered related to test-article treatment. In the EU field study, gastrointestinal signs (vomiting and diarrhoea) were reported very commonly, affecting 26.1% of dogs treated with CYTOPOINT; however, the incidence was less than that observed

for the positive control group (55.3%). Systemic effects (lethargy, anorexia) were commonly reported, with a similar incidence in both the test and control groups. Many of the adverse events reported during the study were related to clinical manifestations of AD in dogs; e.g. dermatitis, eczema, pruritus, erythema, alopecia, otitis externa, other external ear disorders/pain. Bacterial skin infections (7.0%) were commonly reported in dogs treated with CYTOPOINT. Injection site pain was reported in one animal only in lokivetmab-treated dogs in this study. Data from the continuation therapy study demonstrated that the incidence of gastrointestinal signs decreased to 19%, and systemic disorders decreased to 8% (compared to an incidence of 19% in the initial three months of treatment in the test group).

The CVMP accepts that the abnormal clinical observations do not represent test-article related adverse events; skin and appendages disorders are complicating factors related to the disease, while vomiting and diarrhoea (observed at a frequency of 10% and 8%, respectively, in the continuation study), and lethargy (5%) and anorexia (4%) can be accepted as non-treatment related, based on a) the unlikely relationship of these signs to the subcutaneous administration of a purified monoclonal Ab, b) based on the highly targeted mechanism of action of the anti-IL-31 mAb, c) considering that literature exists that supports that such clinical observations would be reported in a population of dogs with AD (albeit undergoing treatment with a different veterinary medicinal product), and d) that such signs were observed at similar frequencies in the placebo group in the US field study.

ADAs were reported in three dogs in the EU field study in the CYTOPOINT treatment group, and the presence of ADAs was correlated with reduced efficacy in at least one dog. During the continuation therapy study, ADAs did not develop in any of the dogs treated for an additional six months. A warning is included in the SPC to describe that treatment may induce transient or persistent ADAs which may reduce efficacy.

The data from the US field study also demonstrate that administration of test article under field conditions was relatively well-tolerated. It is noted that during this study, there were no restrictions on the administration of concomitant medications and a wide range of other veterinary medicinal products were administered during the study, including antiparasitics, antibacterials, antifungals, corticosteroids, vaccines, immunotherapy, antihistamines and other agents used for the management of AD/allergic skin disease, such as oclacitinib and cyclosporine. Adverse events observed up to two weeks after the administration of the second dose in the test group included dermatitis and eczema (10%), bacterial skin infection (9%), pruritus (5%), alopecia (3%), otitis externa (13%), however these clinical signs were reported also in the placebo group at either similar or slightly higher frequencies and were presumably disease-related. Lethargy (6%), anorexia (6%), emesis (7%) and diarrhoea (4%) were observed in both treatment groups.

User safety

A user safety assessment compliant with the CVMP 'Guideline on user safety for immunological veterinary medicinal products' (EMA/CVMP/IWP/54533/2006) was provided.

The risk to the person administering the veterinary medicinal product is associated with the potential for accidental self-injection and the potential development of an immune response to the product. The potential for immediate hypersensitivity reactions to develop and the possibility that the risk of hypersensitivity could increase with repeated self-administration have been evaluated; additional wording in the SPC is proposed to reflect this risk which is considered acceptable. There are no other potential concerns arising from accidental self-injection given that it has been demonstrated that lokivetmab cannot bind human IL-31 and a target-related effect is therefore not expected. Thus,

while the user may develop an immune response to lokivetmab following accidental self-injection, from a user safety point of view this risk would be no different to developing an immune response following accidental self-injection of a conventional veterinary vaccine.

Environmental risk assessment

An environmental risk assessment has been provided in accordance with the Note for Guidance on the environmental risk assessment of immunological veterinary medicinal products (EMA/CVMP/074/95). The veterinary medicinal product will only be used in non-food animals. Based on the data provided, CYTOPOINT is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Overall, the available safety data support that the use of lokivetmab in accordance with the recommended conditions of use can be considered to be safe for the target species, the user of the veterinary medicinal product and the environment. The safety profile has been demonstrated to be favourable in the target species following nine consecutive months of CYTOPOINT treatment.

The product does not pose an unacceptable risk to the user when used in accordance with the SPC. The appropriate warnings for the user have been included in the product literature.

The product is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Introduction and general requirements

CYTOPOINT (INN: lokivetmab) is a mAb which binds canine interleukin 31 (IL-31) and is proposed for use for the treatment of clinical manifestations of canine AD. The product is presented in four strengths; 10, 20, 30 and 40 mg/ml to be administered by subcutaneous injection on a monthly basis. The proposed minimum dose is 1 mg/kg, with dosing on a weight banding basis that results in dogs receiving 1 – 3.3 mg/kg based on its location within the dose weight band. There is no limit specified for the duration of treatment.

Canine AD is defined as a 'genetically predisposed inflammatory and pruritic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed to environmental allergens' (Halliwell 2006). AD is a common condition, estimated to affect 10-15% of the total canine population. Many dogs with this condition require life-long therapy to manage their clinical signs and to maintain an acceptable quality of life. Currently there is no single product which is effective at both treating the underlying cause(s) of the disease and resolving the varied clinical signs. The drugs most commonly prescribed for the treatment of canine AD are glucocorticoids, oclacitinib, cyclosporine, antihistamines, essential fatty acids, and various non-steroidal anti-inflammatory agents (Saridomichelakis and Olivry, 2015). When underlying bacteria or fungal disease are present, a variety of antimicrobials may also be prescribed.

Although the pathogenesis of AD is not fully understood, it is thought that sensitisation to environmental allergens occurs via cutaneous exposure through a defective skin barrier. Following sensitisation to allergens, subsequent exposure and cross-linking of the allergen with IgE on the

surface of dermal mast cells can lead to degranulation and immediate release of additional inflammatory and pruritogenic mediators such as histamine, cytokines, leukotrienes, and prostaglandins. Research has demonstrated the importance of cytokines, particularly IL-31, in the pathogenesis of both allergic dermatitis and AD in dogs (Olivry et al 1999; Nuttal et al 2002a; Marsella et al 2006; Schlotter et al 2011; Gonzales et al 2013; Olivry et al 2015). Thus, IL-31 is a pro-inflammatory cytokine which is thought to play a significant role in pruritus and AD in both dogs and humans. CYTOPOINT, an anti-IL-31 mAb, is proposed to have a highly targeted effect of treatment by binding canine IL-31, thereby preventing IL-31 from binding to the IL-31 receptor and exerting downstream pro-inflammatory and pruritic effects.

As previously discussed, although the product is classified as an immunological veterinary medicinal product, given the different mode of action compared to a live or inactivated vaccine, CYTOPOINT falls outside the scope of the data requirements for a veterinary vaccine. No regulatory guidance is currently available for the efficacy requirements for a mAb for veterinary use. However, the applicant has presented an efficacy data package which is tailored for the current product in accordance with the proposed indications for use. Data are provided from both laboratory and field studies throughout the development of the product.

Efficacy studies have been presented with batches that meet (exceed) the proposed limit for % purity of the mAb monomer and specific activity (ELISA) and the applicant has confirmed that the batches used throughout the studies were representative of the final formulation proposed for marketing, that all batches were derived from the same and final clone and that the manufacturing method used for the production of the batches used in the pivotal clinical studies was representative of the final proposed method for commercial supply.

Throughout the field efficacy studies presented in this marketing authorisation application, in which the efficacy of lokivetmab in client-owned dogs with AD was evaluated, the primary efficacy variable was similarly evaluated based on assessment of response to treatment by the owner and by the investigator.

- Owner-assessed pruritus: based on the percentage reduction from baseline using an enhanced Visual Analogue Scale (VAS [or owner VAS; OVAS]). This VAS is a continuous 10 cm long scale which combines behavioural features and severity-based information with a visual analogue scale (Hill *et al*, 2007). The owner draws a mark on the vertical line at the point at which they consider their dog's level of itching lies; six behavioural descriptors placed alongside the vertical line from the lowest point to the top of the scale comprise the following: 'normal dog –itching is not a problem', 'very mild itching/only occasional episodes', 'moderate itching/regular episodes', 'severe itching/prolonged episodes', 'extremely severe itching/almost continuous'. Each behavioural descriptor is accompanied by an example. After the mark is placed on the VAS, a transparent sheet containing graduated markings is overlaid on the VAS to measure the score (from 0 to 100 mm).
- Investigator-assessed response: based on the percentage reduction from baseline of skin lesions using the Canine Atopic Dermatitis Extent and Severity Index (CADESI) 02 and in more recent studies CADESI-03. CADESI-02 quantitatively describes the dog's skin condition, separately scoring forty areas of the dog's body for erythema, lichenification, and / or excoriation as 'Normal or absent' (0), 'Mild' (1), 'Moderate' (2), or 'Severe' (3). CADESI-03 differs from CADESI-02 in that it has an increased number of body sites (62), another clinical sign is added (self-induced alopecia) and each sign is graded in a wider scale (scale of 0 to 5). CADESI-03 is a validated tool for assessment of disease severity in clinical trials testing the efficacy of interventions in dogs with AD (Olivry *et al*, 2007). It is noted that CADESI-03 was used for the measurement of efficacy in a

previous marketing authorisation application for a veterinary medicinal product indicated for the treatment of clinical manifestations of AD in dogs (Apoquel).

Laboratory trials

Establishment of a challenge model

Due to the complexity of pathogenesis of AD, a laboratory model capable of reproducing the features of the disease is not available. The applicant has used an IL-31 'challenge' model using exogenous IL-31, which has been shown to induce rapid onset of pruritus in a laboratory setting in normal, healthy dogs (Gonzales *et al*, 2015). Although the IL-31 pruritic model may not be fully representative of the complexity of the disease, since the clinical signs of pruritus are IL-31-mediated, it is accepted that this is an appropriate model for the evaluation of the inhibitory effect of CYTOPOINT on the pruritic response.

All laboratory studies were conducted in normal beagle dogs as they were able to generate a consistent and measurable pruritic response to IL-31. In this model, recombinant canine IL-31 is administered intravenously and the pruritic response of the dogs is measured in one minute intervals over a two hour period. Categorical "yes/no" decisions are made at discrete 1 minute intervals with regard to whether at least "one pruritic behaviour" is displayed by the study animals. Displays of pruritic behaviour such as licking/chewing of paws, flank and/or anal regions, scratching of flanks or neck, floor pawing, head-shaking and scooting of their bottom across the cage flooring are registered with a "yes" response. The cumulative number of "yes" determinations made within each observation period provide the pruritus score. Following the intravenous dose, initial IL-31 concentrations are approximately 30 ng/ml and decrease to 0.4 ng/ml at the end of the two hour observation period. The applicant states that these circulating levels of IL-31 are higher than that observed in the majority of atopic dogs; quantitation of levels of serum IL-31 in atopic dogs showed that 90% had <0.4 ng/ml circulating IL-31 (Gonzales *et al*, 2013). Therefore, antibody levels sufficient to inhibit IL-31-mediated pruritus in this model are proposed to be adequate to inhibit IL-31-mediated disease in a clinical setting (Gonzales *et al*, 2015).

Determination of the dose

The applicant has justified the Recommended Therapeutic Dose (RTD) of 1 mg/kg, for administration by subcutaneous injection with a monthly dosing frequency on the basis of a combination of pharmacokinetic analyses, laboratory and field proof of concept studies, and laboratory and field dose titration studies.

Pharmacokinetic comparison of anti-IL-31 monoclonal antibody formulations in beagle dogs

This pharmacokinetic study evaluated the pharmacokinetics of two formulations of lokivetmab (with and without polysorbate 80) and two other potential mAb candidates. Two subcutaneous doses, separated by an interval of 3 weeks, followed by an intravenous dose 3 weeks later were administered to healthy beagle dogs (8 per treatment group) and pharmacokinetic analyses of serum mAb were conducted. lokivetmab exhibited a longer half-life and higher serum drug concentrations than the other two mAb candidates. There were no differences in pharmacokinetics when lokivetmab was administered with (treatment group 1) or without (treatment group 4) polysorbate 80. The data also showed that:

- lokivetmab is systemically available and bioavailability is almost complete following subcutaneous administration;

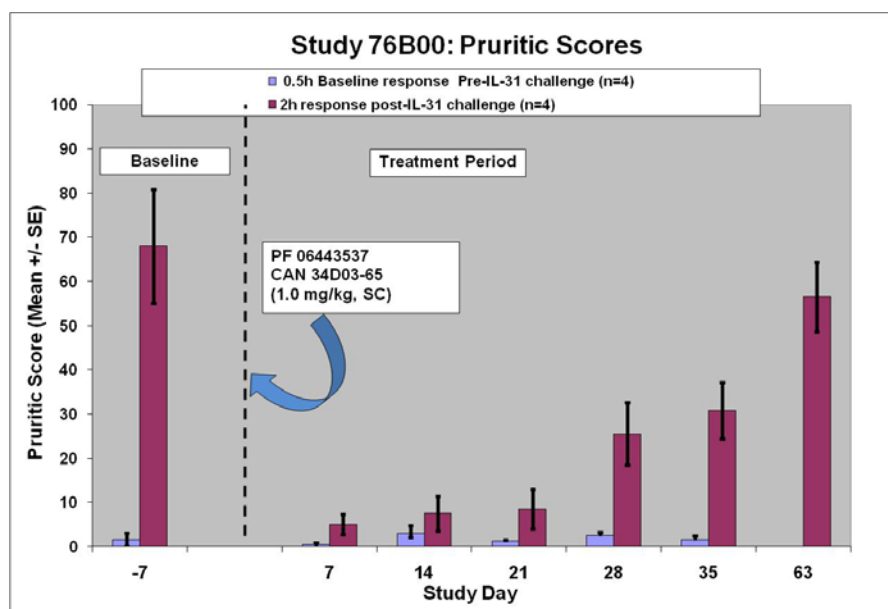
- Following peak concentrations, lokivetmab is eliminated with a relatively long half-life; and
- With a between dosing interval of 21 days, there is some potential for bioaccumulation.

From this study, bioavailability was calculated to be $89 \pm 30\%$. It is noted that the calculation of AUC following intravenous administration will likely have been influenced by some accumulation arising from previous subcutaneous treatments. Therefore, the calculated AUC following intravenous administration may have been overestimated to a small extent with the result that the estimated bioavailability may have been underestimated. That said, it is accepted, based on these data, that bioavailability following subcutaneous administration is very high (almost complete).

Proof of concept

Pilot study: Evaluation of the anti-pruritic effect of anti-IL-31 monoclonal antibody CAN34D03-65 in a canine model of IL-31 induced pruritus

A baseline pruritic response to canine IL-31 was established for 4 adult beagle dogs one week prior to administration of a single 1 mg/kg subcutaneous dose of lokivetmab. At 1, 2, 3, 4, 5 and 9 weeks after lokivetmab administration, IL-31 challenge was repeated (administration of canine recombinant IL-31 intravenously). Baseline (pre-IL-31 challenge) pruritic scores were minimal however one week prior to lokivetmab administration, the 2 hour pruritic scores induced by IL-31 challenge averaged 68 ± 13 . Following the administration of lokivetmab on day 0, the mean post-IL-31 challenge pruritic scores observed 1, 2 and 3 weeks post-administration had decreased to 5 ± 2 , 8 ± 4 , and 9 ± 5 , respectively (see figure on Pruritic Scores below).



The mean post-IL-31 pruritus scores gradually increased at 4, 5 and 9 weeks after treatment to 26 ± 7 , 31 ± 6 , and 57 ± 8 , respectively. This study demonstrated the ability of a single 1 mg/kg subcutaneous injection of lokivetmab to inhibit IL-31-induced pruritic behaviour in four beagle dogs in an experimental IL-31 challenge model with duration of effect of 3 weeks. In this study, the response to challenge was evaluated relative to baseline (pre-treatment) response (there was no contemporaneous untreated control group). That said, it is accepted that relative to baseline, the test article did appear to suppress pruritic response to IL-31 challenge (by 86-92% compared to pre-treatment scores) and that there was a clear time-related effect.

Proof of efficacy and safety of an anti-IL-31 monoclonal antibody (IL-31 mAb) for the treatment of AD in client-owned dogs

This was a good quality, non-GCP, placebo-controlled US field study conducted in client-owned dogs with AD which investigated the safety and efficacy of two doses of 2 mg/kg lokivetmab, administered subcutaneously two weeks apart. Animals included (placebo group, n=25, test group, n=53) had a documented history of non-seasonal AD for at least one year, had at least 'moderate' pruritus as assessed by the owner and a minimum CADESI-02 score of 25. AD diagnosis was based on Prelaud's modification of Willemse's criteria. The test population was considered representative of the target population. Efficacy was assessed on day 28 (two weeks after the second dose) and day 42 (one month after the second dose). The primary efficacy variables, evaluated at days 28 and 42 were:

- percent change from baseline for owner-assessed pruritus using the enhanced VAS.
- percent change from baseline for investigator-assessed CADESI-02.

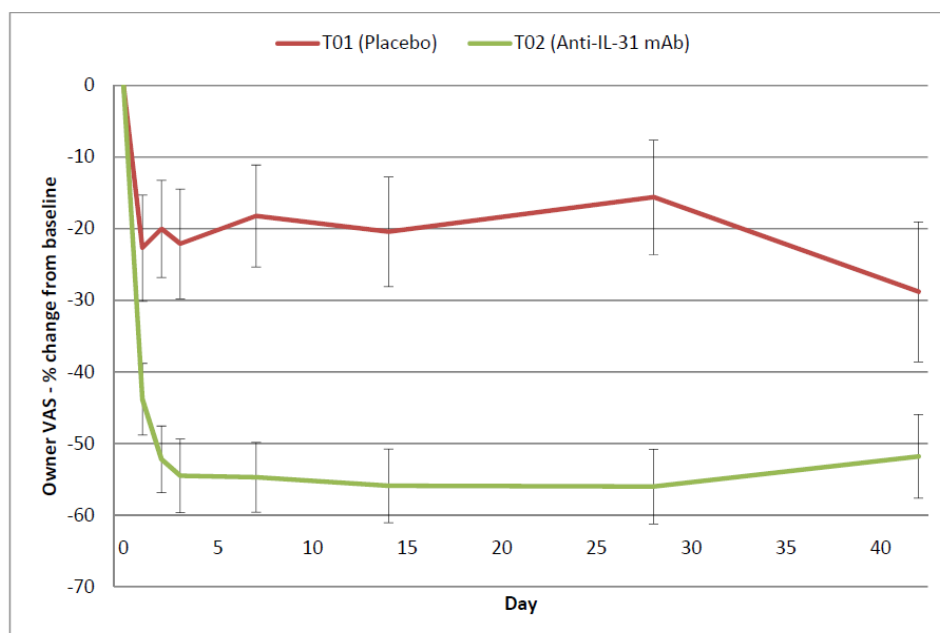
Secondary efficacy variables were also analysed during the study for investigator-assessed pruritus, response to treatment by the owner and the investigator, and overall treatment success.

Safety was also evaluated during the study (physical examination, haematology, serum chemistry, urinalysis, monitoring for hypersensitivity reactions in the immediate post-administration period) in addition to quantification of serum lokivetmab levels and ADA assays on selected samples.

Results demonstrated a significant reduction in owner-assessed pruritus scores on day 28 and 42, but a significant reduction in CADESI-02 was demonstrated only at day 28 (2 weeks after the second dose) and not at day 42 (4 weeks after the second dose):

- On day 28 and day 42, a significantly greater reduction from baseline in owner-assessed pruritus was demonstrated in lokivetmab-treated dogs relative to placebo dogs. A significantly greater reduction from baseline in owner VAS for pruritus for dogs in T02 (lokivetmab) compared to T01 was observed at all times up to and including day 42 (see figure 1 below).

Figure 1. Percent Change from Baseline Owner Assessed Pruritus VAS Plot of LS Means by Treatment Group



- On day 28, but not day 42, a significant reduction in CADESI-02 scores was demonstrated relative to placebo dogs. On day 28, the percent change from baseline in CADESI-02 scores was -4.6% in placebo dogs compared to -35.5% in lokivetmab-treated dogs. On day 42, the percent change from baseline in CADESI-02 scores was -4.2% in placebo dogs compared to -27.9 in lokivetmab-treated dogs.

Analysis of secondary efficacy variables demonstrated that:

- Investigator-assessed pruritus (VAS) was significantly reduced in T02 compared to T01 on days 14 and 28 but not on day 42.
- Response to treatment, evaluated using a horizontal VAS scale with response ranging from 'No Improvement' (0) to 'Excellent Results' (100) was significant when evaluated by the Owner (LSM VAS score of 70.5% in T02 compared to 33.7% in T01) but not when evaluated by the Investigator (LSM VAS score 60.8% in T02 compared to 33.1% in T01).
- By day 42, owner-assessed treatment success (at least a 2 cm reduction from the baseline pruritus VAS on day 28 and 42) was 84.2% in T02 and 55.6% in T01. Investigator-assessed treatment success (a 50% reduction in CADESI score from baseline on days 28 and 42) was 34.2% in T02 and 11.1% in T01.

Withdrawals due to worsening of clinical signs of AD were higher in the placebo group (44%, 11/25 dogs) compared to the lokivetmab group (19%, 10/53 dogs). There were no other withdrawals in T02 (in T01, 3 additional dogs withdrawn due to 'possible adverse reaction to treatment', 'abnormal clinical pathology results' or 'owner non-compliance').

Safety evaluation demonstrated that lokivetmab appears to have been well tolerated at a dose of 2 mg/kg; there were no mortalities or serious adverse events that were related to test-article administration. Vomiting and diarrhoea/soft stool were the most frequent AEs observed in lokivetmab-treated dogs, in 15.1% and 11.3% of animals, respectively. While the percentage of dogs with diarrhoea/loose stool was higher for the test item group compared to the placebo group, there was no clear association with treatment.

ADA screening and confirmatory assays performed on the pre-dose, day 14, and last day samples did not reveal any immunogenicity in the drug-treated animals.

Overall, the CVMP accepts that the results of this study demonstrated a favourable effect of treatment for the reduction of pruritus and a reduction in CADESI-02 scores in the target population. However, the dose administered was twice the recommended label dose (2 mg/kg vs 1 mg/kg) and the interval between doses was 14 days rather than the proposed monthly administration. Investigator-assessed CADESI-02 scores were significantly (at the 1% level) reduced in dogs treated with lokivetmab on days 14 and 28 compared to the placebo group. It is of note that evaluation of CADESI-02 between the placebo group and the test group at day 42 (four weeks after the second dose on day 14), with dogs treated with twice the recommended dose, did not lead to statistically significant differences between groups. Notwithstanding this point, in subsequent studies a single dose of 2 mg/kg was demonstrated to be efficacious with respect to CADESI-03 scores at one month post-treatment relative to placebo-treated dogs and a dose of 1 mg/kg was shown to reduce CADESI-03 scores over the course of treatment (EU field study). In addition, efficacy of the proposed minimum treatment dose (1 mg/kg) has been evaluated in two laboratory efficacy studies. Therefore it was not considered necessary to request comment on efficacy of the 2 mg/kg dose from this early proof of concept study given that any comment provided was unlikely to impact on the overall conclusions on efficacy.

In this study, significance was set at $p < 0.1$. In addition, it is noted that the statistical analysis did not include a correction for repeated analyses. Therefore, one could question the differences between study groups claimed as significant. That said, recognising that this is a proof of concept study in clinically diseased dogs, it is accepted that there is a numerical difference between groups with respect to withdrawals, pruritis score and CADESI score.

In summary, although the dosing interval was shorter than that proposed for recommended use, this first field efficacy study suggested that lokivetmab had a rapid onset of action (with differences in owner-assessed VAS scores on the day after the first dose).

Overall, it can be accepted that the laboratory and field proof of concept studies demonstrated that lokivetmab, when administered at the proposed RTD of 1 mg/kg, could have an effect on both experimentally induced pruritus, AD-associated pruritus and other clinical manifestation of AD.

Dose determination/dose justification

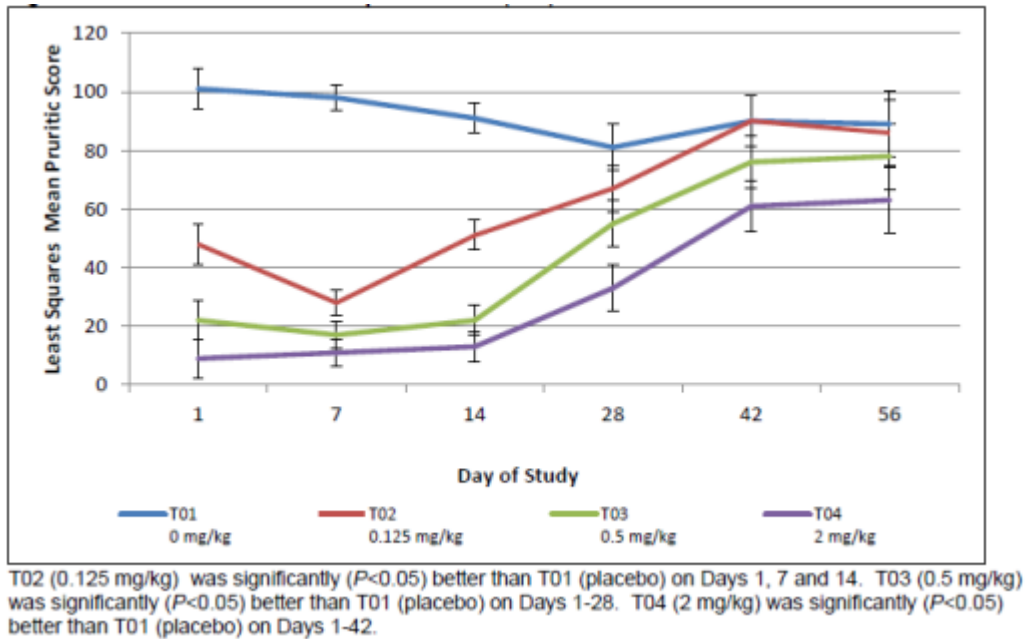
Two dose determination studies are presented, one conducted in a laboratory model of IL-31-induced pruritus, and one field dose titration study conducted in client-owned dogs with AD.

Evaluation of the anti-pruritic effect of lokivetmab, an anti-canine IL-31 monoclonal antibody in a canine laboratory model of IL-31-induced pruritus

The anti-pruritic effect of 0.125, 0.5 or 2.0 mg/kg lokivetmab administered once, subcutaneously to beagle dogs ($n=6$ /group) was evaluated by IL-31 challenge at up to 56 days post-dosing. A baseline pruritic response to canine IL-31 was established for 24 beagle dogs one week prior to administration of test or placebo treatment. At 1, 7, 14, 28, 42 and 56 days after administration, IL-31 challenge was repeated (administration of canine recombinant IL-31 intravenously). A clear dose dependent effect on the magnitude and duration of the anti-pruritic response was demonstrated, with the greatest decrease in pruritus scores relative to placebo and a longer duration of effect demonstrated in dogs in the 0.5 mg/kg and 2 mg/kg dose. The lowest pruritus scores were observed at the IL-31 challenge one day after treatment, with scores gradually increasing in all groups T02, T03 and T04 thereafter. The best response in terms of anti-pruritic effect was observed at the 2 mg/kg dose level, with the duration of effect persisting until 42 days after the single subcutaneous dose. Efficacy was lower at the 0.5 mg/kg dose, however there was still a significant reduction in pruritus scores relative to the placebo group at day 28 ($p=0.0288$) (but not at day 42).

- On day 1 and day 14, in all lokivetmab treatment groups, a significant reduction ($p < 0.05$) was observed in pruritus scores relative to placebo.
- On day 28, a significant reduction in pruritus scores relative to placebo was observed in the 0.5 mg/kg group (T03) and 2 mg/kg group (T04) only, with a LSM score of 55 and 33 in T03 and T04, respectively, compared to 81 in the placebo group.
- On day 42, only dogs in T04 (2 mg/kg) had a significant reduction in pruritus relative to placebo. Although the duration of effect was significantly different only in T04 dogs at this time point, there was no significant difference in mean scores between the 0.5 mg/kg and 2.0 mg/kg groups at any time point.
- By day 56, there were no significant differences between treatment groups (see figure 2 below).

Figure 2. Plot of Treatment Least Squares Means (\pm SE) for Pruritic Score



The PK analysis correlated with the dose-dependent effect observed for pruritus scores; Cmax and AUC were generally correlated with dose (Cmax of 1.30, 3.80 and 14.1 μ g/ml in the 0.125 mg/kg, 0.5 mg/kg and 2 mg/kg dose groups, respectively). The mean AUC0- ∞ was 511, 2110 and 7670 μ g-h/ml in T01, T03 and T04, respectively. The elimination half-life was similar at all dose levels, with half-life of 9.1, 11.2 and 12.0 days in the 0.125 mg/kg, 0.5 mg/kg and 2 mg/kg dose groups, respectively. PK/PD modelling estimated that at a dose of 1 mg/kg, 88% of animals are expected to be above the EC50 for 28 days, these data informed the applicant's decision to select 1 mg/kg as the RTD. However, while it may be questioned if serum concentrations intended to produce only half of the maximal effect (maximum reduction of pruritus scores from baseline) for 28 days would be a satisfactory level of efficacy; the CVMP is of the view that the approach taken is reasonable. Further it must be acknowledged that these are modelling data only and that the level of efficacy achieved at this dose was subsequently evaluated in specifically designed dose confirmation studies.

Anti-drug antibody assay: one dog in the 2 mg/kg dose group was positive in the confirmatory assay using the homogenous acid-dissociation ligand binding assay for ADAs on study days 1 and 7 only. There were no unusual changes in the serum lokivetmab concentrations for this dog which would suggest that the antibodies were neutralising.

Safety: no adverse events were recorded during the study.

Overall, while the proposed recommended dose of 1 mg/kg was not investigated in this laboratory study, the results demonstrated a clear dose-dependent effect on the magnitude and duration of response of a single subcutaneous injection of lokivetmab to inhibit IL-31-induced pruritic behaviour in beagle dogs in an IL-31 laboratory challenge model, with significant reduction in pruritus scores relative to placebo demonstrated to day 28 for the 0.5 mg/kg and 2 mg/kg dose groups, and to day 42 for the 2 mg/kg dose group.

Field study investigating three dose levels of an anti-IL-31 monoclonal antibody for treatment of AD in dogs

This was a US field safety and efficacy dose-titration study which investigated the efficacy of dose levels of 0.125, 0.5 or 2.0 mg/kg, administered once, subcutaneously. Client-owned dogs with AD (n=211) were allocated to either placebo or one of the lokivetmab dose groups (50 – 55 dogs/group). Dogs included were representative of the intended target population; inclusion criteria included a documented history of non-seasonal AD for at least one year, at least 'mild itching' as assessed by the owner (OVAS), and a minimum score of 30 on the CADESI-03. AD diagnosis was based on criteria according to Favrot *et al*, 2010.

The primary efficacy variables were treatment success for days 28, 42 and 56 based on:

1. Owner-assessed pruritus score; treatment success: ≥ 2 cm decrease in pruritus score.
2. Investigator-assessed CADESI-03 scores; treatment success: $\geq 50\%$ decrease in scores.

Dogs that failed to meet these criteria were considered treatment failures for the relevant efficacy variable. In addition, dogs withdrawn from the study due to worsening signs of AD (lack of efficacy) were considered treatment failures for both variables.

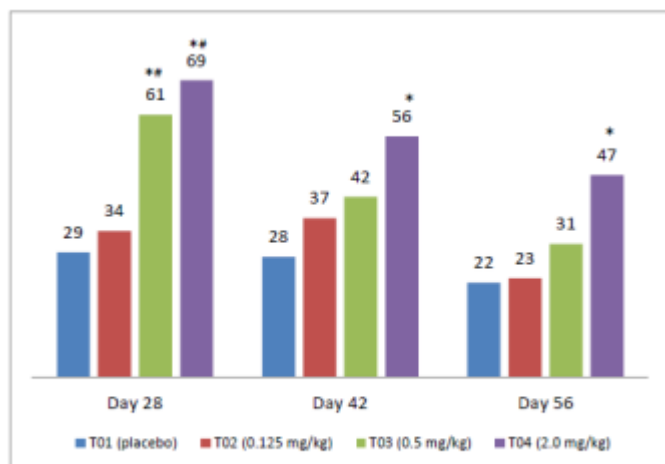
Secondary efficacy variables included treatment success (Yes/No) based on 50% reduction from baseline in OVAS, OVAS score, CADESI-03 score, % change from baseline for OVAS, % change from baseline for CADESI-03 score, % change from baseline for Investigator-assessed dermatitis severity (overall condition, assessment on a VAS line), Response to treatment by both owner and investigator (using a VAS line with the descriptors 'No improvement' and 'Excellent results' located at either end of the line).

In addition, the following additional parameters were measured during the study: physical examination (including body weight), collection of blood and urine samples for haematology, serum chemistry and urinalysis, observation for hypersensitivity reactions for at least 30 minutes post-administration, and occurrence of adverse events monitored throughout study. Serum samples pre-dose and on days 7, 14, 28, 42 and 56 for PK analysis. ADA assays performed on all samples to detect possible immunogenicity.

A clear dose-dependent effect was observed in this study for both Owner-assessed pruritus and Investigator-assessed CADESI-03:

- Owner-assessed pruritus: on day 28, the proportion of dogs achieving treatment success for pruritus (≥ 2 cm decrease in Owner-assessed pruritus score) was significantly greater in the 0.5 and 2 mg/kg dose groups compared to placebo dogs. A significant reduction in pruritus at day 42 and 56 was only observed in the 2 mg/kg dose group (see figure 3 below).

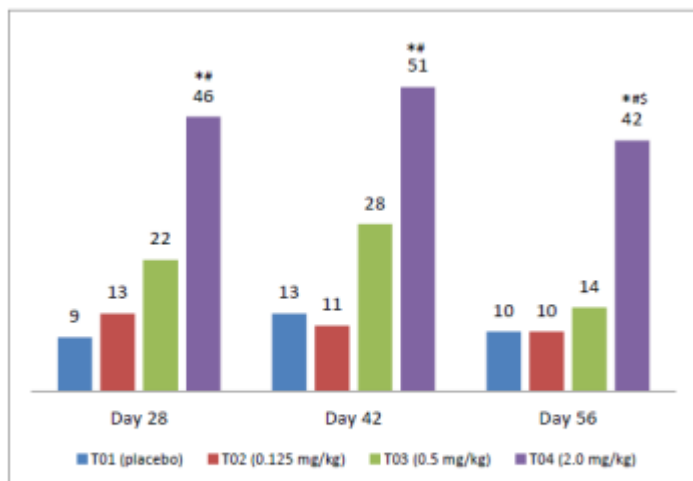
Figure 3. Primary Effectiveness: Back-Transformed LS Mean Percentage of Dogs with Treatment Success Based on Owner Pruritus VAS Scores for Each Treatment Group



*=significant difference compared to T01 (placebo) at the 0.05 level.
 #=significant difference compared to T02 (0.125 mg/kg) at the 0.05 level.

- On days 28, 42 and 56, treatment success as defined by the primary efficacy variable for CADESI-03 was not achieved for dogs in the 0.125 or 0.5 mg/kg dose groups. However, a significantly greater proportion of dogs in the 2 mg/kg group achieved treatment success ($\geq 50\%$ decrease in CADESI-03 score from baseline) compared to the placebo group at days 28, 42 and 56 (see figure 4 below).

Figure 4. Primary Effectiveness: Back-Transformed LS Mean Percentage of Dogs with Treatment Success Based on Investigator-assessed CADESI-03 for Each Treatment Group



*=significant difference compared to T01 (placebo) at the 0.05 level.
 #=significant difference compared to T02 (0.125 mg/kg) at the 0.05 level.
 \$=significant difference compared to T03 (0.5 mg/kg) at the 0.05 level.

Overall, it was demonstrated that the 0.5 mg/kg dose was significantly different from placebo for only one of the primary efficacy variables: Owner-assessed pruritus, at day 28 (but not day 42 or 56). Dogs in this dose group failed to achieve statistical significance relative to placebo for CADESI-03 scores at any time point. Dogs treated with 2 mg/kg were significantly different to placebo for the primary variables (both OVAS and CADESI-03 scores) on days 28, 42 and 56. While the clinical relevance of the definition of treatment success for owner-assessed pruritus (a ≥ 2 cm reduction in the VAS score

compared to baseline) may be questioned, the secondary efficacy variable comparing the proportion of dogs achieving a 50% reduction from baseline in VAS further support a significant reduction in owner-assessed pruritus; a significantly higher proportion of dogs in the 0.5 mg/kg dose group (0.32) and the 2 mg/kg dose group (0.57) had a 50% reduction of VAS scores at day 28 compared to placebo (0.14). Overall, the approach to efficacy assessment and the variables chosen can be considered appropriate. In this study, significance was set at $p < 0.05$. It is noted that the statistical analysis did not include a correction for repeated analyses; however, the findings will be accepted as reported noting that, where significance is claimed, this is typically with p values $<< 0.05$.

The results of the secondary efficacy variables generally reflected the results of the primary analysis; Owner-assessed pruritus scores were dose-dependent with significant differences compared to the placebo group at the 0.5 mg/kg dose group until 28 or 35 days. A significant difference in CADESI-03 scores relative to placebo, was observed at day 14 of the study in all lokivetmab treatment groups, and at day 56 for the 0.125 and 0.5 mg/kg groups, and at all study time points for the 2 mg/kg dose group. For CADESI, the greatest percentage reduction from baseline was approximately 40%; this level was achieved in the T04 (2 mg/kg, 43-44% reduction, days 14-56) and T03 (0.5 mg/kg, 37% reduction, Day 14) groups. It is notable that in the 0.5 mg/kg dose group, the investigator-assessed percentage reduction of dermatitis severity (on days 14 – 42) and the overall response to treatment at the end of the study, both measured on a VAS line, were significantly higher compared to the placebo group.

PK analysis in this study was consistent with that of previous studies, with peak serum concentrations almost dose-proportional (between the 0.5 and 2 mg/kg doses). PK modelling predicted that serum concentrations of 2.3 µg/ml were required to achieve 60% OVAS treatment success, with this serum concentration correlating to 35% success rate on the CADESI-03 scores. On this basis, the applicant considers that a 1 mg/kg dose would be expected to result in a geometric mean serum concentration of about 2.75 µg/ml at 28 days post dose.

Safety results were consistent with previous studies, demonstrating that the administration of one dose was well-tolerated (there were no adverse effects considered attributable to treatment).

ADA analysis revealed non-specific weak antibodies in animals in both the placebo and lokivetmab treatment groups however none of the data indicated a strong antibody response to lokivetmab.

Overall, this study demonstrated that in client-owned dogs with AD, there is a clear dose-dependent effect observable with respect to Owner-assessed pruritus and CADESI-03 scores following a single administration of test article, with greatest efficacy achieved in the 2 mg/kg dose group.

Throughout the various studies presented, serum concentrations of lokivetmab were measured. Although sampling timepoints were generally limited, the applicant conducted pharmacokinetic analysis (or descriptive statistics) on the data. Following administration of CYTOPOINT, serum concentrations increase in a dose-related manner, with the true C_{max} unknown but likely within 1 – 4 days post-dosing. The elimination half-life at the proposed dose is ~11 days, and steady state conditions are probably reached after 5 – 7 months of treatment. Whether steady state conditions were correctly evaluated (due to non-extensive sampling), it is noted that drug levels decline to the lowest serum concentrations in advance of each subsequent dose and therefore there is no concern raised with respect to accumulation.

Overall comments on dose determination:

The applicant has justified the recommended minimum treatment dose of 1 mg/kg taking into account the results of the two dose-determination studies, carried out in laboratory conditions using a canine

model of IL-31 induced pruritus in normal beagle dogs, and in dogs with AD under field conditions. In both studies, dose groups consisted of 0.125, 0.5 and 2 mg/kg, and therefore the dose of 1 mg/kg was chosen on the basis of pharmacodynamics/pharmacokinetic modelling as discussed in the two studies. Based on these data, the applicant considered that a dose of 1 mg/kg would be appropriate to test in the pivotal confirmatory efficacy and field studies. As the product is to be offered in four different strengths (10, 20, 30 and 40 mg/ml), individual dogs receive at each administration a dose of 1 – 3.3 mg/kg depending on the dog's bodyweight.

It is considered that the applicant has presented a relatively robust justification for the selected dose of 1 mg/kg, supported by pilot dose titration studies conducted under both laboratory and field settings, and analysis of serum lokivetmab concentrations. Based on the clear dose response effect observed, it can be accepted that a dose of 1 mg/kg will have an effect. The applicant proceeded with the 1 mg/kg dose level in the subsequent laboratory and field dose confirmation studies, and the efficacy data at the 1 mg/kg dose level will be presented in the following sections. In the dossier the applicant discusses that IL-31 is essentially up-regulating, therefore removal of IL-31 from circulation of AD dogs by treatment and maintenance of serum lokivetmab concentrations may be expected to not only neutralise IL-31 but to down-regulate IL-31 production, however, no investigations into potential dose reduction after reaching steady state conditions were conducted.

Dose confirmation

The efficacy of the proposed dose of 1 mg/kg was investigated in three studies; two laboratory studies conducted using the experimental IL-31 challenge model in normal beagle dogs, one of which investigated the onset of the effect of treatment and the second investigating the duration of effect. The third study is the pivotal EU field study which evaluated the efficacy of lokivetmab under recommended conditions of use in client-owned dogs with AD.

Laboratory onset of effectiveness study of canine AD immunotherapeutic in dogs compared to placebo in an induced-pruritus model following a single subcutaneous dose of anti-IL-31 monoclonal antibody at 1.0 mg/kg body weight

A baseline pruritic response to canine IL-31 was established for 12 beagle dogs one week prior to administration of test or placebo treatment. Dogs were allocated to test article (n=6) or placebo group (n=6) blocked by historical pruritus scores (e.g. the four dogs with the lowest scores form one block), with both treatment groups occurring twice within a block. At 8 hours after administration of test article or placebo, IL-31 challenge was repeated (administration of canine recombinant IL-31 intravenously). All dogs were administered IL-31 challenge within a 30 minute period, with order of IL-31 challenge conducted on a block by block basis (4 dogs per block). Recording of pruritic responses (scored at one minute intervals over a 2 hr period) began within 15 to 25 minutes after the last dog was challenged. Each scorer observed one block simultaneously with a real time image of each dog displayed on a single monitor. The observer of pruritic responses was blinded to treatment allocation.

The pruritus scores were significantly lower in dogs treated with 1 mg/kg LSM score for pruritus: 13) compared to dogs treated with placebo (LSM score: 84) at 8 hours post-dosing ($p < 0.0001$). Therefore, it can be accepted that this study demonstrated the onset of the anti-pruritic effect of a single 1 mg/kg dose, administered subcutaneously, at 8 hours post-administration in the experimental IL-31-induced pruritus model in normal beagle dogs.

Laboratory effectiveness study of an anti-IL-31 monoclonal antibody in dogs compared to a negative control in an induced-pruritus model following single subcutaneous dose

A baseline pruritic response to canine IL-31 was established for 36 beagle dogs one week prior to administration of test or placebo treatment. At 1, 28 and 56 days after administration, IL-31 challenge was repeated (administration of canine recombinant IL-31 intravenously). Dogs were allocated to test article (n=18) or placebo (n=18) groups blocked by historical pruritus scores (e.g. the two dogs with the lowest scores form one block), with both treatment groups occurring once within a block.

Characterisation of the IL-31-induced pruritic response was conducted for 70 dogs screened for this study, with animals with the highest historical pruritus scores selected for inclusion (with appropriate flexibility to ensure similar percentages of male and female dogs). On the days of challenge, all dogs were administered IL-31 challenge within a 30 minute period, with order of IL-31 challenge conducted on a block by block basis (2 dogs per block). Recording of pruritic responses for a 2 hr period began within 15 to 25 minutes after the last dog was challenged. Each scorer observed two blocks (four dogs) simultaneously with a real time image of each dog displayed on a single monitor. All study personnel collecting clinical assessment data and observing pruritic responses were blinded to treatment allocation.

The primary decision variable was the degree of pruritus on day 28. Treatment success was defined as the lower 95% confidence limit for the stratified mitigated fraction (stratification was on block) for treatment relative to placebo being above 40% for the Day 28 pruritus score. In addition, pruritus scores were analysed and least squares means were calculated and treatment differences within time point were assessed.

- The criteria for treatment success was met; the stratified mitigated fraction for treatment (T02) relative to placebo (T01) was 88.9% (95% CI: 66.7%, 100%) with lower 95% confidence limit of 66.7% > 40%, thus, satisfying the criteria for treatment success.
- The pruritus scores were significantly lower in dogs treated with 1 mg/kg lokivetmab (LSM score: 8) compared to dogs treated with placebo (LSM score: 70) at 1 day post-dosing, and at 28 days post dosing (LSM score of 17 and 62 in the 1 mg/kg and placebo groups, respectively).
- The pruritus scores were not significantly lower in dogs treated with 1 mg/kg lokivetmab (LSM score: 53) compared to dogs treated with placebo (LSM score: 67) at 56 days post-dosing.

Safety evaluation during this study demonstrated that there were no mortalities, adverse events or test-article related abnormal clinical signs during the study.

The pharmacokinetic analysis demonstrates that lokivetmab is absorbed and systemically available following subcutaneous administration, with an estimated Tmax of 3.9 days, and Cmax of 7.7 µg/ml. The half-life averaged 11.9 days. On day 28, when there is a significant difference in pruritus scores between T01 and T02, the average serum concentration is 2.27 ± 0.87 µg/ml, with a range of 0.367 – 3.62 µg/ml.

It is noted that one dog in the 1 mg/kg group was an outlier, both with respect to pruritic scores and serum lokivetmab levels on day 28; dog AVI-2 had a pruritus score of 86 and serum concentration of 0.367 µg/ml. These data support the proposed correlation between serum concentrations and efficacy. No ADA analysis was conducted during this study, therefore it is unknown if this dog developed neutralising antibodies following treatment however it is possible considering that serum lokivetmab levels were not notably low at days 1 (when pruritic score after IL-31 challenge was comparable to other lokivetmab-treated dogs) and 3 post-dosing but declined by day 7 and by day 14. Therefore,

overall it can be concluded that 1/18 (~6%) dogs did not respond satisfactorily to treatment, for unknown reasons but potentially linked to development of neutralising antibodies.

Overall, it is accepted that this study demonstrates a significant reduction in pruritus scores following a single subcutaneous dose of 1 mg/kg, with duration of effect of 28 days, in a canine IL-31-induced pruritic model in normal, healthy beagle dogs.

It is concluded that the two laboratory dose-confirmation studies significantly reduced an IL-31-induced pruritic response in dogs treated at the RTD of 1 mg/kg relative to placebo control dogs, with an onset and duration of effect of 8 hours and 28 days, respectively. However, it is noted that these data, although robust, do not reflect the spectrum of clinical signs associated with AD, and given the absence of laboratory studies in AD dogs, data from the EU field study are considered pivotal to support the proposed indications for use.

Efficacy and safety of lokivetmab compared to Atopica for the treatment of AD in dogs

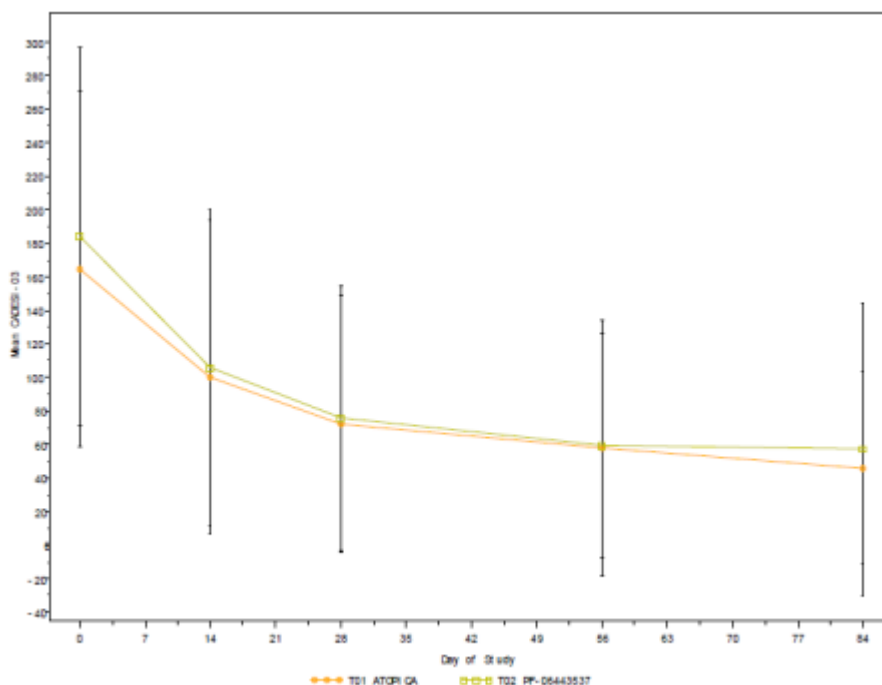
This was a good quality, GCP field study conducted at 43 sites over 4 EU Member States. Client-owned dogs with confirmed AD according to Favrot *et al*, 2010 were enrolled and randomly allocated to either test (lokivetmab) (n=142) or control (Atopica) (n=132) groups. Dogs in the test group received 1 mg/kg lokivetmab, monthly, by subcutaneous injection for three consecutive months, with placebo capsules administered orally. Dogs in the control group received cyclosporine (Atopica) in accordance with label recommendations, with monthly subcutaneous administrations of saline to maintain blinding during the study. Pruritus scores as evaluated by the Owner using an enhanced Visual Analogue Scale (OVAS) and skin lesion scores as evaluated by the Investigator using CADESI-03 were the primary efficacy variables. The study was designed to demonstrate non-inferiority of lokivetmab compared to the positive control, cyclosporine. The control product is authorised in the Community for the treatment of chronic manifestations of atopic dermatitis in dogs and the choice of positive control is therefore considered appropriate.

- The results of the first primary efficacy variable, owner-assessed pruritus, clearly demonstrated a significant treatment effect; pruritus scores decreased throughout the study from a mean score of 74 at baseline to a mean score of 26 at day 84 in lokivetmab-treated dogs. The test for non-inferiority at day 28 was met (test value for non-inferiority: 0.3%); the mean percentage reduction from baseline in pruritus at day 28 was 44% and 52% in the cyclosporine group and lokivetmab group, respectively. The results of the secondary efficacy variables for pruritus scores also supported a significant effect on the reduction of pruritus; OVAS scores were significantly lower in the test group compared to the control at each study time point and at the end of the study on Day 84, the percentage reduction in OVAS scores was 53% in T01 (cyclosporine) and 60% in T02 (lokivetmab). The proportion of dogs achieving 75% reduction in OVAS scores was significantly higher in the test group compared to the control group at days 14, 28, 56 and 84. The proportion of dogs achieving 75% reduction from baseline in OVAS scores at day 84 was 0.24 in T01 (cyclosporine) and 0.45 in T02 (lokivetmab). The applicant provided sufficient justification for using the time point of 28 days after initiation of treatment for the evaluation of the primary efficacy parameters, considering that this was selected in order to provide further support for the proposed monthly dosing interval. In addition, the applicant has discussed that while the SPC for Atopica states that treatment should be stopped if no response is obtained within the first 8 weeks, it also states that satisfactory clinical improvement will generally be seen within 4 weeks.
- The second primary efficacy variable, non-inferiority of CADESI-03 scores in T02 (lokivetmab) compared to T01 (cyclosporine) at day 28, was not met; the mean percentage reduction in

CADESI-03 scores was 57% in the cyclosporine group (T01) compared to 54% in the lokivetmab group (T02) (test value for non-inferiority: 18%, thus exceeding the 15% non-inferiority margin). It is noted that CADESI-03 thresholds for disease severity are as follows; 0 – 15: remission, 16 – 59: mild AD, 60 – 119: moderate AD and ≥ 120 : severe AD (Olivry *et al*, 2008). Therefore, prior to treatment the average CADESI-03 value in both groups was well above the score for severe AD, and it is noted that the mean value for dogs in the test group was higher than in the control group. By day 28, the mean score was reduced to within the 'moderate' AD threshold (72 and 76 in the T01 and T02 groups, respectively) by day 56 scores were 58 ('mild') and 60 ('moderate') in T01 and T02, respectively and, as already stated, on day 84 it was reduced to 46 in T01 and 57 in T02, both within the 'mild AD' category. In both treatment groups, at each study visit, the percentage of cases achieving a 75% reduction from baseline scores increased, and while there were no significant differences between treatment groups, this parameter was numerically higher in T02 (lokivetmab) compared to T01 (cyclosporine) on days 56 and 84. Therefore, while non-inferiority with the positive control product was not confirmed, the available data for CADESI-03 scores nevertheless appear to support a favourable effect of treatment. In addition, it is generally accepted in the treatment of canine atopic dermatitis that reductions in CADESI-03 scores of 50% or more represent a good response to treatment.

- It has been identified that a small number of dogs that responded notably poorly had a large impact on the statistical output (n=5) for non-inferiority of CADESI-03 scores, and while data excluding these animals are not considered valid in terms of concluding on the efficacy of treatment, this finding has led to the applicant's proposal to include a warning in the SPC to indicate that some animals will have a low response or will not respond to treatment.

Figure 5. Investigator-assessed CADESI-03 with Self-Induced Alopecia – Plot of treatment means and Standard Deviations



Eight dogs in the lokivetmab group were withdrawn due to lack of efficacy during the study, compared to two dogs in the positive control group. While the CVMP raised concerns regarding the manner in

which these dogs were included/excluded from the efficacy datasets at day 28, 56 and 84, the applicant provided appropriate clarification concerning the rationale for exclusion of data from the efficacy datasets. It is accepted that the statistical analyses were conducted in accordance with the pre-defined protocol. Concerning the animals withdrawn due to lack of efficacy, these animals were excluded from the efficacy dataset if the last measurement of VAS or CADESI-03 scores was outside of the protocol specified time window of ± 5 days of the study visit day 28, 56 or 84. Furthermore, due to missing data (VAS or CADESI-03 scores missing due to owner and/or investigator non-compliance or oversight), the number of animals in each efficacy dataset varied. While animals withdrawn due to lack of efficacy were not included in the primary efficacy variable analyses if there had been a protocol deviation (i.e. data unavailable or data outside of the day 28 ± 5 day window), these cases were included in the secondary variable analyses and were treated as failing to achieve 50% or 75% reduction from baseline for all subsequent time points after withdrawal for both VAS and CADESI-03 scores.

Overall, it is accepted that the statistical analyses conducted were appropriate and that there was no bias introduced intentionally to lessen the impact of animals withdrawn due to unsatisfactory clinical efficacy. It is noted that bacterial skin infections were commonly reported in dogs treated with CYTOPOINT (7.0%), and the use of systemic antibacterials in this treatment group during the study was more than twice that of the positive control group (19.0% in lokivetmab-treated dogs vs 8.3% in cyclosporine -treated dogs). However, it is also noted that in the US field (safety only) study, the frequency of use of antibacterials was also similarly high as in the current study and was the same in placebo-treated animals (27%) and lokivetmab-treated animals (25%). While it was considered that this may be indicative of the expected frequency of use generally of antibiotics in the target population, the applicant was requested to comment on the use of systemic antibacterials in the lokivetmab group, with respect to a) whether this could indicate inadequate control of disease symptoms and establishment of secondary infections and b) whether this may indicate a negative impact on immune function in lokivetmab-treated dogs, and details of the time at which antibacterials were administered was requested, e.g. whether this occurred mainly close to the commencement of treatment or whether use of antibacterials was varied throughout the study. There was no apparent relationship between time of treatment and the use of systemic antibacterials, however the number of animals requiring systemic antibacterials gradually decreased with study progression and it appears that the main difference between the two treatment groups relating to systemic antibacterial treatment for bacterial skin/ear infections is observed during the first treatment interval. The applicant attributed the difference in the use of systemic antibacterials between the test and control group, and the difference in the incidence of skin infection between groups, particularly in the first dosing interval, to the difference in the anti-inflammatory effect exerted by cyclosporine (broader spectrum anti-inflammatory response) compared to lokivetmab (narrower spectrum anti-inflammatory response). The applicant provided satisfactory justification that the role of immunosuppression as a potential reason for the observed difference could be excluded; while other treatments currently used for immunosuppression of the inappropriately up-regulated immune response in atopic dermatitis are described, it is highlighted that lokivetmab-mediated inactivation of IL-31 is less capable/incapable of resulting in adverse immunosuppression, compared to conventional therapeutics such as corticosteroids or cyclosporine. As previously mentioned in Part 3, due to the mechanism of action of CYTOPOINT and the narrower anti-inflammatory effect compared to other therapeutics for treatment of AD, it is considered prudent to more closely monitor for bacterial infections during the first few weeks of treatment while skin lesions are healing. An appropriate warning is included in the SPC.

The development of ADAs was detected in three animals treated with lokivetmab, and the presence of ADAs was correlated with reduced efficacy in at least one dog. No safety issues specifically associated

with the presence of ADAs were documented. During the continuation study (see below), treatment-induced immunogenicity did not develop in any of the 81 dogs that received test article for up to nine consecutive months. A suitable warning is included in the SPC to describe that the product may induce transient or persistent ADAs, but that this is uncommon and may have no effect (transient ADAs) or may result in a noticeable decrease in efficacy (persistent ADAs).

Continuation therapy with lokivetmab for the treatment of AD in dogs.

This study was a GCP-standard, unblinded, single-arm, continuation therapy study following on from the pivotal EU field study, which enrolled 81 animals from the test group in the previous study for which lokivetmab had been evaluated as an efficacious treatment during the initial three months of treatment. The continuation study allowed dogs to continue on treatment for an additional six monthly consecutive doses, with final follow-up at one month after the last dose. Noting that 142 animals were enrolled in the test group in the preceding pivotal EU field study, the continuation of 81 animals into the extended study represented ~57% of the initial cohort in the test group. Safety was evaluated by monitoring of AEs, laboratory parameters, and treatment-induced immunogenicity (ADAs) and efficacy was evaluated using pruritus scores evaluated by the owner (VAS scores), skin lesion scores evaluated by the investigator (CADESI-03 scores) and the overall response to treatment (RTT) evaluated independently by both the owner and the investigator.

With respect to safety, there were no mortalities or test-article related adverse events or changes in haematology, serum chemistry or urinalysis variables; the main adverse events reported in the continuation therapy study were skin and appendages disorders (22%), digestive tract disorders (19%) and ear and labyrinth disorders (12%). Systemic signs such as lethargy (5%) and anorexia (4%) were also reported. As discussed in Part 3, the CVMP can accept the applicant's view that the AEs observed were unrelated to treatment. Compared to the preceding study, in which systemic antibacterials were used at a frequency of 19%, systemic antibacterials were used in ten animals (12%) for miscellaneous indications. However, over the course of the continuation study, while five animals (6%) were sampled for bacteriology due to a suspected skin or outer ear infection, only one of these sampled cases was considered to require systemic antibiotic treatment. During the course of the continuation therapy study, no animals developed ADA against lokivetmab.

Overall, while it is a weakness of the continuation therapy study that this arm of the study was not controlled, it is considered that there is sufficient safety data to alleviate concerns that chronic use could lead to immunosuppression, increased use of antibacterial medication, or that long-term treatment would give rise to treatment-induced immunogenicity. In fact, it would appear that any treatment-induced immunogenicity with consequent development of antibodies against lokivetmab would tend to occur relatively soon after treatment commences (i.e. within the first three months of treatment, given that 3/142 animals in the test group developed either transient or persistent ADAs in the preceding study [these three dogs were not subsequently enrolled in the continuation therapy study]).

Efficacy:

- Owner VAS data demonstrated that extended treatment with lokivetmab remained efficacious in the control of pruritus; the mean score available for 79 dogs at time of entering the continuation study (day 0, i.e. day 84/last visit of previous study) was 18, which reduced very marginally to a mean score of 14 at one month after the final dose of this study.
- Investigator-assessed CADESI-03 scores also demonstrated a beneficial effect of longer term treatment on the skin lesions associated with AD. At the final visit of the preceding study the mean CADESI-03 score for the test group (n=112) was 57, with a mean score of 37 for the subset of

dogs entering the continuation therapy study (n=80). By the end of the continuation therapy study, the mean CADESI-03 score was 32 (based on available scores from 59 animals). Thus, while there was no positive control group included in this study, it can be accepted that there is a beneficial effect of treatment on the control of skin lesions associated with AD.

- At the end of the study, the mean owner and investigator RTT scores were both 84 at study completion or withdrawal, which demonstrated that animals continued to respond very well during the continuation study. Not unexpectedly, the RTT is higher in the continuation study compared to the overall cohort of lokivetmab-treated animals in study, for which the owner and investigator assessed response to treatment were both ~73.

Overall, it is considered that the efficacy data presented in this single-arm study are supportive of a beneficial effect of treatment on the clinical signs (pruritus and skin lesions) associated with atopic dermatitis. While it is noted that the continuation therapy study was selective for dogs for which treatment had already been deemed efficacious, the data support that treatment at the proposed dose of 1 mg/kg, once monthly, remains an efficacious treatment in dogs that initially respond well to treatment.

In summary, efficacy data in dogs with atopic dermatitis at the proposed 1 mg/kg dose, treated according to the recommended schedule, are available from the pivotal positively-controlled EU field study for three months of treatment, and from the single arm, unblinded continuation therapy study which enabled a subset of dogs in the test group of the preceding field study to receive a further six months consecutive treatment. It is considered that the data are sufficient to conclude on the safety and efficacy of lokivetmab when used under recommended conditions of use, that is, no limit on the duration of treatment. Although a nine month treatment duration may still not be fully representative of the expected safety and efficacy for chronic treatment, there are no safety signals or indications of decreasing efficacy which would call into question that the results are not representative of longer-term use. In the pivotal EU field study, it was concluded that the first of the primary efficacy variables (pruritus) clearly showed a significant benefit of treatment. However while point of principle issues were raised regarding the fact that the second primary efficacy variable (CADESI-03) did not meet non-inferiority criteria at day 28, overall it is considered that a beneficial effect of treatment with respect to a reduction in CADESI-03 scores has been demonstrated, and therefore the data provided are considered sufficient to support the proposed claim 'treatment of clinical manifestations of atopic dermatitis in dogs'. However, due to the highly targeted nature of the anti-IL-31 mAb, and due to a complex pathogenesis of canine atopic dermatitis, for which presumably the role of IL-31 in the disease is not as strongly implicated, a small number of dogs will likely respond poorly to treatment. A suitable warning has been included in the SPC to reflect this point.

Field trials

See above.

In summary, the data from two supportive field studies; proof of concept study and dose titration study have been previously discussed. These studies are considered supportive only as dogs were not treated at the proposed dose of 1 mg/kg:

- In the field proof of concept study, dogs were treated twice with a dose of 2 mg/kg with an interval between doses of 2 weeks, and evaluation at 2 and 4 weeks after the second dose. The study demonstrated a favourable effect of treatment with respect to a reduction in owner-assessed pruritus scores but investigator-assessed CADESI-02 scores at 4 weeks after the second dose, while reduced, were not significantly different from placebo.

- In the field dose titration study, dogs were treated once with a dose of 0.125, 0.5 or 2 mg/kg, and it was demonstrated that the 2 mg/kg dose was efficacious in terms of owner-assessed pruritus scores and CADESI-03 scores at 28 days post-dosing, but a dose of 0.5 mg/kg was only efficacious (significantly different to placebo) in terms of OVAS scores.

The pivotal EU field trial and continuation therapy study have been conducted to investigate efficacy at the proposed dose of 1 mg/kg under field conditions in client-owned dogs with AD. These studies are discussed under 'Dose confirmation'.

Overall conclusion on efficacy

Under conditions of recommended use (a dose of 1 mg/kg, administered monthly by subcutaneous injection) in dogs with AD, it is concluded that a clear benefit of treatment with CYTOPOINT for the reduction of pruritus has been demonstrated, and it is noted that this is in accordance with the proposed highly targeted mode of action of an anti-IL-31 mAb for binding and neutralising the effector functions of IL-31. In laboratory studies in an experimental IL-31-induced model of pruritus, a single 1 mg/kg dose was shown to have an onset of effect of 8 hours, with duration of effect extending to 28 days. In addition, the data provided support that treatment at the proposed RTD had a beneficial effect on the reduction of disease severity as evaluated by CADESI-03 scores. Therefore, the CVMP considers that the claim for the 'treatment of clinical manifestations of AD in dogs' is supported by the data provided and a clear benefit of treatment has been demonstrated. Overall, it is concluded that treatment with CYTOPOINT for the claimed indications is efficacious.

Part 5 – Benefit-risk assessment

Introduction

CYTOPOINT is a solution for injection containing the new active substance lokivetmab which is a mAb specifically targeting canine interleukin-31 (IL-31). CYTOPOINT is presented in four strengths (10, 20, 30, 40 mg/ml) and indicated for the treatment of clinical manifestations of AD in dogs.

The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full dossier).

Benefit assessment

Direct therapeutic benefit

The benefit of CYTOPOINT is its efficacy in the treatment of clinical manifestations of AD in dogs which was evaluated in a number of laboratory and field studies. Well conducted controlled laboratory and clinical trials demonstrated that the product is efficacious in treatment of canine AD. At the proposed dose of 1 mg/kg, the efficacy data in the target species demonstrated a significant benefit of treatment for a reduction in pruritus, and a beneficial effect of treatment for the reduction of disease severity.

Additional benefit

CYTOPOINT has a rapid onset of action (8 hrs) and long lasting effect (28 days). CYTOPOINT increases the range of available veterinary medicines for treatment of AD in dogs.

Risk assessment

Main potential risks have been identified as follows:

Quality:

Information on development, manufacture and control of active substance and finished product of CYTOPOINT are presented satisfactorily. 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.

Based on the review of the data on quality, the manufacture and control of CYTOPOINT are considered approvable with the following conditions:

- Endotoxin: The endotoxin results for the first 20 batches released onto the EU market should be provided and the specification revised if justified. Data to be provided within 12 months of the granting of the marketing authorisation.
- Active substance stability: The applicant should complete the ongoing lokivetmab stability evaluation up to 36 months at the different batch sizes. These final reports should be provided by April 2018 and November 2019, for the ongoing 300 L and 2000 L stability studies, respectively.
- Capillary Isoelectric Focusing (cIEF). The applicant should additionally test for cIEF for a limited number of lokivetmab batches manufactured at the alternative site. The cIEF test should be done on the first 10 commercial lots of active substance and any out-of-trend data should be notified to the EMA. The data should be provided within 24 months of the granting of the marketing authorisation
- Specific Activity (SA): The applicant should continue monitoring the specific activity results for the first 10 commercial lots of lokivetmab active substance manufactured at the alternative site to ensure that it is consistent and within trend. Any out-of-trend data should be notified to the EMA. The data should be provided within 24 months of the granting of the marketing authorisation.

For the target animal:

The safety data presented to date have indicated that the product is well-tolerated, while the absence of long-term safety data (i.e. extending beyond nine months of treatment) in the intended target population of dogs with AD is noted, this is not considered a concern, given that the data provided to date have supported a favourable safety profile and there are no concerns that have emerged following nine consecutive months of treatment that may be expected to be exacerbated under longer term conditions of use. Use of CYTOPOINT is not expected to have any negative effects on immunological function in treated dogs due to the highly targeted mechanism of action.

However, a small proportion of treated animals may develop neutralising antibodies against CYTOPOINT which may lead to reduced efficacy.

For the user:

The CVMP concluded that user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

For the environment:

The product is not expected to pose a risk for the environment when used according to the SPC.

Risk management or mitigation measures

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

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for the treatment of clinical manifestations of AD in dogs.

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

Conclusion

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

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