12 June 2025
EMA/206767/2025
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Numelvi (EMEA/V/C/006480/0000)

INN: Atinvicitinib

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

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Introduction

The applicant Intervet International B.V. submitted on 24 June 2024 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Numelvi, through the centralised procedure under Article 42(2)c of Regulation (EU) 2019/6 (mandatory scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 19 February 2024 as Numelvi contains an active substance which has not been authorised as a veterinary medicinal product within the Union at the date of the submission of the application (Article 42(2)(c)).

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

Treatment of pruritus, inflammation and clinical manifestations associated with allergic dermatitis including atopic dermatitis in dogs.

The active substance of Numelvi is atinvicitinib, a selective Janus kinase (JAK) inhibitor, highly selective for JAK1. It inhibits the function of a variety of cytokines involved in itch and inflammation, as well as cytokines involved in allergy, that are dependent on JAK1 enzyme activity. The target species is dog.

Numelvi tablets contain 4.8 mg, 7.2 mg, 21.6 mg and 31.6 mg of atinvicitinib and are presented in packs containing 30 tablets and 90 tablets.

The rapporteur appointed is Rory Breathnach and the co-rapporteur is Cristina Muñoz Madero.

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

On 12 June 2025, the CVMP adopted an opinion and CVMP assessment report.

On 24 July 2025, the European Commission adopted a Commission Decision granting the marketing authorisation for Numelvi.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

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

The CVMP considers that the Pharmacovigilance system fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281.

Manufacturing authorisations and inspection status

Active substance

Manufacture the active substance Atinvicitinib takes place outside the EEA. A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration is based on an on-site audit by the manufacturing site responsible for batch release.

Finished product

Batch release of the finished product take place at Intervet Ges.m.b.H., Siemensstrasse 107, 1210 Vienna, Austria.
The site has a manufacturing authorisation issued on 13th September 2023 by the Austrian competent authority. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the activities indicated above, has been provided.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file was considered to be 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

The finished product is an immediate release, uncoated oral tablet containing the active substance atinvicitinib. The tablets are manufactured in four different strengths designated "S", "M", "L" and "XL" containing 4.8 mg, 7.2 mg, 21.6 mg and 31.6 mg of the active substance per tablet, respectively, to support treatment of dogs that range in body weight from 2.0 kg to 79.0 kg. Other ingredients in the formulation are microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, tocofersolan, hydroxypropylcellulose, colloidal anhydrous silica and magnesium stearate. The composition of the different strength tablets is qualitatively identical and quantitatively proportional.

Containers and closure system

The tablets are packaged in either a high-density polyethylene bottle or an aluminium/PVC/ polychlorotrifluoroethylene blister.

The bottles are made from high-density polyethylene (HDPE). The child resistant screw caps with a tamper evident ring are made from polypropylene (PP). Both bottles and caps comply with Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food. The bottles contain either 30 or 90 tablets and are packaged into a cardboard box as secondary packaging.

The blisters also comply with Regulation (EC) No 1935/2004. The blister strips contain 30 tablets and are packed in an outer cardboard box containing either 1 or 3 blister strips equivalent to 30 or 90 tablets.

The pack sizes are consistent with the dosage regimen and duration of use.

Product development

A common formulation blend with drug load of 3.00% w/w was selected in order to ensure that all tablet sizes could be easily manufactured and split. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or USP standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.

Dissolution method development included evaluation of apparatus I (basket) and II (paddle) and rotation speed, buffer type and surfactant concentration. The dissolution method was demonstrated to be discriminatory.

Manufacturing process development is described from lab-scale to GMP pilot scale batches to investigate the impact of scale up on the key parameters identified from the lab studies. All batches manufactured in the process range exhibited good blend uniformity, low segregation potential and good flowability. The blends were tableted, showing good content uniformity and comparable dissolution profiles with good similarity factors. The tablets include a functional break line in order to deliver fractional doses and testing was performed on half tablets which demonstrated compliance with Ph. Eur. 2.9.40 'Uniformity of dosage units' requirements and the requirements for 'Subdivision of tablets' in the Ph. Eur. general monograph for 'Tablets'. Friability, dissolution and loss of mass testing on half tablets was also demonstrated to be acceptable and comparable to that for whole tablets.

Description of the manufacturing method

All 4 tablet strengths are compressed from a common blend. The proposed batch size can be used for compressing tablets of one strength or for compressing tablets of two strengths. The manufacturing process involves manufacture of the formulation blend via granulation process. The manufacturing process is well described and is considered to be a standard process. In process controls (IPCs) are detailed. The dossier also describes 'critical process parameters' (CPPs) for this manufacturing process with specified values or ranges which are based on a quality risk assessment performed.

Hold times are proposed for the granulation solution, final blend and the bulk tablets and are supported, where necessary. Confirmation has been provided, that the start of shelf-life for the products will comply with the requirements of the 'Note for Guidance on start of shelf-life of the finished dosage form' EMEA/CVMP/453/01.

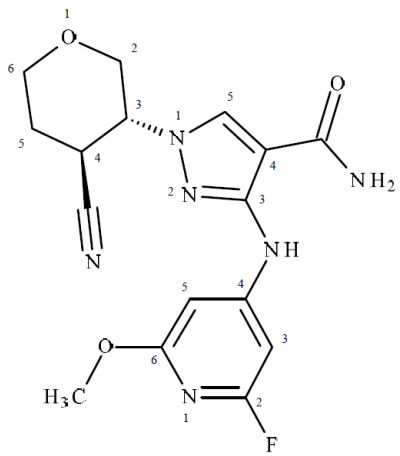
Manufacturing process validation of the tablets at the commercial batch size will be conducted prior to commercialisation. A satisfactory 'Process Validation Scheme' for full scale commercial manufacture is included in the dossier and includes the information described in Annex I of the *Guideline on process validation for finished products – information and data to be provided in regulatory submissions.* The absence of process validation data in the dossier can be accepted based on the standard nature of the manufacturing process and the data provided in the manufacturing process development section which is considered the sufficient to fulfil the requirement to provide 'experimental studies validating the manufacturing process'. The process validation data should be available at the manufacturing site for inspection.

Control of starting materials

Active substance

The active substance, atinvicitinib, is a small molecule JAK inhibitor. The active substance is not monographed in the Ph. Eur. The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

The active substance has the following structure:



IUPAC name: 1-[(3*R*,4*S*)-4-Cyanooxan-3-yl]-3-[(2-fluoro-6-methoxypyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide

CAS number: 2169273-59-8

Molecular formula: $C_{16}H_{17}FN_6O_3$

Molecular weight: 360.35

Atinvicitinib is a white to pale yellow powder. It exhibits stereo isomerism due to the presence of two chiral centres, with four stereoisomers possible.

Atinvicitinib is synthesised in stages, followed by purification and drying. Process flow diagrams are provided along with a brief description of the process. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF. The characterisation of the active substance and its impurities are generally in accordance with the Guideline on the chemistry of active substances for veterinary medicinal products (EMA/CVMP/QWP/707366/2017-Rev.1). Satisfactory information has been provided for mutagenic impurities, organic impurities, residual solvents, elemental impurities and nitrosamines.

The active substance specification includes tests for appearance, identification, water content, related substances, assay, chiral purity, residual solvents, elemental impurities, microbial quality, crystal form, specific optical rotation, colour of solution and particle size distribution. The specification is considered to be acceptable. The test methods are well described and considered to be acceptable. The method validation provided is in accordance with the VICH guidelines VICH GL 1 and VICH GL2 and so is acceptable. Compliant comparative batch analysis data is provided for batches of the active substance for all tests in the specification. Satisfactory information has been provided regarding the reference standards.

The active substance is packaged in transparent low-density polyethylene bags in a polyethylene drum. Acceptable specifications have been provided for the packaging, and declarations of the compliance of the immediate packaging contact material with the current requirements of EU Regulation No 10/2011 and with Ph. Eur.

Stability data are provided for production scale batches of the active substance at long-term and accelerated conditions. All results are within specification. An acceptable post-approval stability commitment was also provided.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or USP standards. Reference to USP is acceptable in the absence of a Ph. Eur. Monograph. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.

The dossier indicates that the excipients microcrystalline cellulose, lactose monohydrate, magnesium stearate and sodium starch glycolate are to be controlled in line with Ph. Eur. monographs and for additional parameters. Where additional relevant functionality-related characteristics have been omitted from excipient specifications, suitable justification has been provided.

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

A TSE declaration is provided by the manufacturer of the active substance and of the finished product manufacturer declaring compliance with the "Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via Human and Veterinary Medicinal Products (EMA/410/01 Rev 03)".

Control tests on the finished product

The specifications proposed at release are generally considered appropriate to control the quality of the finished product. The finished product specification includes tests for appearance, active substance identification, uniformity of dosage units assay, degradation products, water content, dissolution and microbiological quality.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Quality control testing is conducted and validation for each of these sites is provided. Satisfactory information regarding the reference standards used for assay is provided.

Batch analysis results are provided for numerous batches. The batches were tested according to the development specification in place at the time of testing. The results are within the proposed specifications and are comparable between batches of the same strengths. Certificates of Analysis are also provided.

An elemental impurities risk assessment was carried out in line with ICH Q3D and the reflection paper on risk management requirements for elemental impurities in veterinary medicinal products. All relevant elements were considered, and the total potential amount of each element is less than 30% of the PDE's.

Stability

The specification parameters proposed at the end of shelf-life are appropriate to control the quality of the finished product.

The finished product has been placed on stability under VICH long-term (30°C/65%RH) and accelerated (40°C/75%RH) conditions in both bottles and blisters. For the batches packaged in bottles, 36 months long-term (30°C/65%RH) data is available for pilot scale batches.

For the batches packaged in blisters, 36 months long-term (30°C/65%RH) data is available for pilot scale batches. 12 months data under accelerated (40°C/75%RH) conditions is available for these batches.

The product has been demonstrated not to be sensitive to light in a photostability study. In-use studies show no relevant changes and as such no in-use shelf-life is required.

The applicant has proposed a shelf-life of the finished product as packaged for sale of 3 years with no storage precautions which is supported. Advice that any remining half tablets should be placed back into the opened blister or bottle is included in the SPC.

New active substance (NAS) status

The applicant requested the active substance, atinvicitinib, contained in Numelvi to be considered a new active substance as it is not hitherto authorised in a veterinary medicinal product in the European Union.

The documentation to be provided by the applicant to support the request is described in Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance (NAS) status of chemical substances (EMA/CVMP/QWP/3629/2016-Rev.1).

Substantiation of the NAS claim in line with the Reflection paper has been provided. Based on the review of the data provided, the CVMP considered that the active substance atinvicitinib contained in the veterinary medicinal product Numelvi is a new active substance and does not expose patients to

a therapeutic moiety already authorised in the European Union.

Overall conclusions on quality

The products are immediate release, uncoated oral tablets containing either 4.8 mg, 7.2 mg, 21.6 mg or 31.6 mg of the active substance atinvicitinib. The tablets are packaged in either a high-density polyethylene bottle or an aluminium/PVC/polychlorotrifluoroethylene blister. The bottles are closed by a polypropylene child resistant screw cap with a tamper evident ring and contain either 30 or 90 tablets. The aluminium/PVC/polychlorotrifluoroethylene blister strips contain 30 tablets and each outer cardboard box contains either 1 or 3 blister strips equivalent to 30 or 90 tablets.

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

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way.

Part 3 – Safety documentation (safety tests)

The active substance of Numelvi is atinvicitinib, a selective Janus kinase (JAK) inhibitor, highly selective for JAK1. It inhibits the function of a variety of cytokines involved in itch and inflammation, as well as cytokines involved in allergy, that are dependent on JAK1 enzyme activity.

Atinvicitinib is a new active substance, which has not been authorised for a veterinary medicinal product in the EU at the date of submission of the application.

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

Safety tests

Pharmacology

Pharmacodynamics

For information on primary pharmacodynamics see part 4. The major pharmacodynamic properties of atinvicitinib are those associated with its Janus kinase-inhibiting activity.

Atinvicitinib has been demonstrated to be a potent and highly selective inhibitor of JAK1, with lesser potency against JAK2, JAK3 and tyrosine kinase (TYK) 2. The JAK1-selectivity of atinvicitinib was demonstrated in *in vitro* biochemical assays of human JAK family enzymes, displaying IC_{50} values of 0.43, 5.89, 1129.97 and 13.02 nM for JAK1, JAK2, JAK3, and TYK2, respectively.

Pharmacokinetics

For information on pharmacokinetics in the target species see part 4.

Atinvicitinib showed moderate plasma protein binding (range 81.2–88.7%) *in vitro*. Results were comparable for all species tested (dog, mouse, rabbit, rat).

Toxicokinetics were assessed in several of the toxicity studies. In rats orally administered atinvicitinib, mean concentrations of atinvicitinib increased with the increase in dose. However, increases in C_{max} and AUC_{0-24} values were less than dose-proportional in the 2- and 4-week studies at doses of 100 to 1000 mg/kg /day and 1 to 30 mg/kg /day. In the 13-week rat oral toxicity study, increases in C_{max} and AUC_{0-24} values were approximately dose-proportional at doses from 0.2 to 5 mg/kg/day. Accumulation ratio values ranged from 0.735 to 0.968 for C_{max} and from 0.810 to 2.03 for AUC_{0-24}. Generally, sex differences in atinvicitinib C_{max} and AUC_{0-24} values were less than 2-fold.

In a 4-week rat dermal toxicity study, the increases in C_{max} and AUC_{0-24} values were generally less than dose-proportional over the dose range of 3 to 10 mg/kg /day, and generally dose-proportional over the dose range of 10 to 100 mg/kg /day. Similar observations were made in the 13-week rat dermal toxicity study, with increases in C_{max} and AUC_{0-24} values generally less than dose-proportional from 12 to 300 mg/kg /day. No accumulation of atinvicitinib was observed after multiple doses in either study.

For rabbits, after administration via oral gavage, mean concentrations of atinvicitinib increased with the increase in dose. The increases in mean C_{max} and AUC_{0-24} values were generally less than dose-proportional at dose rates from 2 to 250 mg/kg /day. No accumulation of atinvicitinib was observed after multiple doses to pregnant rabbits.

Dermal absorption

An *in vitro* skin absorption test using human and rat skin was conducted. The overall absorption of atinvicitinib by human skin was 0.05% or 0.06% at dose levels of 60 g/l (600 µg/cm^2) and 10 g/l (100 µg/cm^2), respectively. In the case of rat skin, overall absorption of atinvicitinib was 0.28% or 0.43%, at dose levels of 60 g/l (600 µg/cm^2) and 10 g/l (100 µg/cm^2), respectively.

Toxicology

The safety of atinvicitinib was evaluated in a range of toxicity studies, i.e. acute oral and dermal toxicity studies in rats, repeat-dose oral and dermal toxicity studies in rats, developmental toxicity studies in rats and rabbits, and *in vitro* and in vivo studies to evaluate genotoxic potential. All main non-clinical toxicology studies were conducted in compliance with GLP.

Single-dose toxicity

Acute oral and dermal LD_{50} values for atinvicitinib of > 2000 mg/kg bw were estimated. An extended acute oral toxicity study in rats was conducted for the determination of an acute reference dose (ARfD). The approach used was largely in accordance with VICH GL54. Male and female rats were administered atinvicitinib by gavage at doses of 0, 225, 450, 900 and 1800 mg/kg bw on a single occasion. Plasma concentrations of atinvicitinib generally increased with the increase in dose level from 225 mg/kg bw to 1,800 mg/kg bw. Chin rubbing was observed in one male and one female in the 1,800 mg/kg bw group and in one female in the 900 mg/kg bw group shortly after dosing. The affected male also exhibited post-salivation staining of the lower jaw at 0.5 hours and 24 hours post dose. No atinvicitinib-related effects on food intake, bodyweight or bodyweight gain, macroscopic or microscopic changes were reported. Statistically significantly high lymphocyte and large unstained cell counts in males at all dose levels and in females ≥ 450 mg/kg bw when compared to controls were observed. Activated partial thromboplastin time was higher than controls in females treated at any dose level but was not observed in males. A number of other minor inter-group haematological differences from control were limited to one sex or lacked a dose-response relationship and are considered incidental. In males dosed with 450 mg/kg bw or above, low lactate dehydrogenase and high creatinine kinase activities were seen. Other effects on blood chemistry were considered minor, as they lacked a dose-response relationship or were confined to one sex. Regarding organ weights, statistically significant changes were observed in animals receiving 1800 mg/kg bw, with increases in weight-adjusted testes and heart weights in males, and increased weight-adjusted liver weight in females. Normal progression of the spermatogenic cycle, and the expected cell associations and proportions in the various stages of spermatogenesis were present. In the absence of macro- or microscopic changes in tissue structure, the changes in organ weights and biochemical parameters are considered non-adverse. The CVMP accepts that other changes observed are minor and can be considered incidental on the basis of inconsistency and/or lack of a dose-response relationship. An oral NOAEL for rats of 1800 mg/kg/day can be accepted. When an uncertainty factor of 100 is applied, an acute reference dose of 18 mg/kg bw is calculated. For the evaluation of short-term user exposure, the use of an acute toxicological reference value (TRV) is considered to be appropriate and consistent with guidance.

Repeat-dose toxicity

The toxicity of repeated daily doses of atinvicitinib was evaluated in rats following oral and dermal administration. The GLP-compliant studies investigated toxicity following oral administration of atinvicitinib over 2, 4 and 13 weeks, with 4 and 12-week study durations for the dermal route.

Oral

In a 14-day oral toxicity study, atinvicitinib was administered by oral gavage to rats at doses of 0, 100, 300, or 1000 mg/kg/day. These doses were based on an escalating dose phase where chin rubbing and paddling of forepaws was seen after dosing of 1000 mg/kg on day 3 for males and females. Treatment-related reduction in lymphocyte counts and reduced basophil counts were recorded for all groups, with mean reticulocyte counts being lowered in all female groups and reduced large unstained cell counts observed in males. Mean cell haemoglobin and mean corpuscular volume were higher than controls for males receiving 300 or 1000 mg/kg/day. Eosinophil counts were low for males receiving 1000 mg/kg/day. Changes in clinical chemistry were observed at all dose levels, with decreases in alanine amino-transferase activity and bile acids, elevated acetylcholine esterase activity in plasma in males and high glutamate dehydrogenase activity and slight reduction of plasma phosphorus concentrations in females. High lactate dehydrogenase was recorded in males and females, although statistical significance was only observed in the 100 and 300 mg/kg/day groups. Lower sodium and chloride concentrations were recorded for males receiving 1000 mg/kg/day and plasma phosphorus concentrations were reduced in all treated female groups. At 300 and 1000 mg/kg/day, bile acids and creatinine were reduced in females. Thymus and spleen bodyweight-adjusted weights were reduced in all treatment groups, with bodyweight-adjusted testicular weights being statistically significantly increased in males given 300 or 1000 mg/kg/day. Treatment-related microscopic findings were noted in the thymus, with minimal to marked decreased cellularity seen in both sexes in all treatment groups. Minimal decreased cellularity was also observed in the spleen, bone (sternum including marrow and femur including joint), mesenteric lymph node and Peyer's Patches/GALT, varying between doses and sexes. As significant changes in the thymus associated with decreased cellularity were observed at all doses, in addition to changes in haematological parameters, a NOAEL could not be established. The CVMP agrees with the overall conclusions of the study.

In a 4-week oral toxicity study, atinvicitinib was administered to rats by gavage at doses of 0, 1, 3, 10 or 30 mg/kg/day. At 30 mg/kg/day, haematological examination identified treatment-related statistically significant decreases in reticulocytes and eosinophil counts in females, and reductions in lymphocyte and monocyte counts, total white blood cell count, and platelet counts in males. Significant changes in clinical chemistry were observed at doses of 30 mg/kg/day, with total cholesterol, high-density lipoprotein concentrations and total protein increased in females. In males, triglyceride concentrations were reduced at 30 mg/kg/day, with reduced alpha-2-globulin concentrations observed at 10 and 30 mg/kg/day. Bodyweight-adjusted spleen weights were statistically significantly low in females when compared to control at all doses, whereas significantly lower absolute spleen weight was observed at 30 mg/kg/day in males. Thymus bodyweight-adjusted weights were significantly reduced at 10 and 30 mg/kg/day groups in males and females. Histopathological changes, namely decreased cellularity and/or increased apoptosis in the thymus and decreased cellularity in the spleen and peripheral lymph nodes, including the mesenteric and/or axillary lymph nodes, were observed at 10 and 30 mg/kg/day in both sexes. At 3, 10 and 30 mg/kg/day, significant treatment-related decreases in testicular spermatid count and testicular total spermatid count occurred. No adverse effects were observed in sperm morphology or during histopathological examination of the testes. Based on the available data, the applicant proposes a NOAEL of 1 mg/kg/day, despite a significant decrease in bodyweight-adjusted spleen weights observed in females administered 1 mg/kg/day. It is accepted that the absence of histopathological changes in the spleen as well as haematological changes at 1 mg/kg/day indicates that the observation is non-adverse. An oral NOAEL for rats of 1 mg/kg/day can be accepted.

In a 13-week oral toxicity study, rats were given atinvicitinib by gavage at doses of 0, 0.2, 1 or 5 mg/kg /day. This was a GLP-compliant study, conducted in accordance with the OECD Test

Guideline (TG) No. 408. An increase in neutrophil count in females was observed at a dose of 5 mg/kg bw/day with a decrease in lymphocyte counts in females at 1 and 5 mg/kg/day. Lactate dehydrogenase concentrations were high in females receiving 5 mg/kg/day. There were no treatment-related effects on histopathology at any dose. Bodyweight-adjusted spleen, testes and epididymides weights were lower in males administered 5 mg/kg/day. Testicular spermatid count and total spermatid count decreased significantly at all dose levels. However, no dose-response relationship was observed, and only the 1 mg/kg/day group had a mean total spermatid count below the historical control data (HCD). Overall sperm motility and motion were unaffected by treatment. The applicant does not consider any of the findings to be adverse effects and proposes an oral NOAEL of 5 mg/kg/day over 13 weeks. While significant effects on testicular spermatid counts (a recognised effect of treatment based on previous studies) were observed at all treatment doses, the CVMP accepts that this effect is non-adverse, noting that values for the atinvicitinib-treated groups were generally within the historical control range, with values for the control group above the historical control range, together with no treatment-related effects on testicular macro- and histopathology. A 13-week oral NOAEL of 5 mg/kg/day can be accepted. However, as there appeared to be a treatment-related effect on male reproductive function, and acknowledging CVMP concerns, the applicant has used a LOEL of 5 mg/kg/day for user risk assessment purposes.

Dermal

A 4-week dermal toxicity study (6 hours semi-occlusive) was conducted in rats, with atinvicitinib administered at doses of 0, 3, 10, 30 or 100 mg/kg/day. This was a GLP-compliant study, conducted in accordance with OECD TG No. 410. No treatment-related changes in clinical chemistry were reported. While several changes in haematological parameters were observed, the applicant considered these to be due to biological variation. In females, decreases in total white blood cell count and monocytes were observed at doses of 10, 30 and 100 mg/kg/day, with decreases in counts of lymphocytes at 30 and 100 mg/kg/day and neutrophils at 100 mg/kg/day, respectively. In males, a decrease in monocyte counts was noted at all treatment doses as well as a reduction in lymphocytes at 100 mg/kg/day. These changes are comparable to those observed in the oral toxicity studies. At 100 mg/kg/day, bodyweight-adjusted spleen weights were lower in males and females. In the absence of macroscopic or microscopic changes, the reduction in spleen weights is considered to be non-adverse. A decrease in testicular spermatid count which was within HCD range, along with a non-significant increase in testis weight at 100 mg/kg/day was observed. As the spermatid counts were within the historical control range and histopathological analysis of the testes confirmed normal progression of the spermatogenic cycle, the changes observed were considered by the applicant to be non-adverse. Given that testicular or epididymal effects may affect reproductive function without histopathological changes it is not possible to conclude if this effect is non-adverse. Notwithstanding the fact that there were changes in haematological parameters, there is no consistent response across studies and no correlation with (histo)pathological or clinical effects. Based on the findings of this study, the applicant concluded that the highest tested dose of 100 mg/kg/day can be considered a NOAEL because the effects observed were non-adverse. The proposed NOAEL for atinvicitinib in this 4-week dermal toxicity study of 100 mg/kg/day can be accepted for general systemic effects. In the case of male reproductive function a LOEL of 100 mg/kg/day can be accepted.

In a 13-week dermal toxicity study in rats, atinvicitinib was administered at dose rates of 0, 12, 60 and 300 mg/kg/day. This was a GLP-compliant study, conducted in accordance with the OECD TG No. 411. In males, at 60 and 300 mg/kg/day, a decrease in neutrophils was observed, while reductions in lymphocytes, eosinophils, monocytes and total leucocyte count were observed at 300 mg/kg/day. Reductions in reticulocytes were observed at all doses in males. No treatment-related haematological changes were observed in females. At 300 mg/kg/day, cholesterol, high-density lipoprotein and

phospholipid levels were increased in males, while in females, alkaline phosphatase and phosphorous levels were increased. In addition, triglyceride levels were increased in females at all dose levels, although these effects were not considered to be treatment-related. At 60 and 300 mg/kg/day absolute bodyweight and/or brain-relative mean spleen weights were lower in males and females. Lower absolute and relative weights of the thymus were observed in males at all dose levels and in females at 60 and 300 mg/kg/day, although these decreases were not statistically significant and there were no associated microscopic findings. A decrease in percentage rapid sperm and an increase in percentage slow sperm were observed at 60 and 300 mg/kg/day, with significant decreases in some sperm velocity parameters at all treatment levels. Although motility was within the HCD range, this suggests a treatment-related effect. In addition, non-significant decreases in sperm counts were observed in all treatment groups. However, there were no associated changes in testicular weights or reproductive histopathology. While significant decreases in some sperm velocity parameters were noted, there was no statistically significant difference in overall motility, and there were no associated changes in testicular weights or reproductive histopathology in the 12 mg/kg/day group compared to control. Therefore, the CVMP accepts that the changes are not adverse. Treatment-related microscopic findings were observed at 60 and 300 mg/kg/day in males and at 300 mg/kg/day in females in the spleen (decreased cellularity of the white pulp), and at 300 mg/kg/day in males in the bone marrow of the femur and sternum (decreased cellularity) as well as in the axillary lymph node (decreased cellularity). Based on the findings of this study, the applicant proposed a NOAEL of 12 mg/kg/day. However, as there appeared to be a treatment-related effect in several male reproductive parameters, and acknowledging CVMP concerns, the applicant treats this as a LOEL for user risk assessment purposes. The CVMP considers this approach to be appropriate.

The potential systemic effects following subchronic and chronic exposure (oral and dermal) have been extensively investigated in the rat. The studies provided were compliant with GLP principles and relevant OECD TGs. Based on the findings of those studies, the spleen and thymus are the primary target organs for atinvicitinib. Decreased weight of these organs correlated with decreased cellularity at higher doses. In the absence of changes in macro- and histopathology, these reductions in weight could be considered non-adverse at lower doses. Decreased cellularity was also observed in bone (sternum including marrow and femur including joint), varying between sexes at high doses, and in Peyer's Patches/GALT at oral doses of 300 mg/kg/day as well as in peripheral lymph nodes, including the mesenteric and/or axillary lymph nodes, at 10 and 30 mg/kg/day in both sexes. Reductions in white blood cell counts, namely lymphocytes, monocytes, basophils, neutrophils and/or eosinophils have also been reported, although it is noted that there was variability in response between sexes and from study to study. Atinvicitinib-related effects on the male reproductive system were observed, with decreases in sperm count and motility noted. Although no changes in macro- and histopathological parameters were observed, adverse effects on reproductive potential are still possible e.g. a significant reduction in sperm motility is associated with infertility. That said, the TRVs determined from these studies for user risk assessment purposes are considered appropriate.

A number of biochemical changes were observed during the oral and dermal studies. However, the absence of a dose-response relationship in many cases and lack of repeatability between studies makes it difficult to draw associations with atinvicitinib treatment. Changes in blood chemistry were observed at oral doses of 30 mg/kg/day with total cholesterol and high-density lipoprotein concentrations increased, which can be linked to the role that Janus kinases play in lipid metabolism.

For the purpose of user safety, 13-week oral and dermal toxicity LOELs of 5 and 12 mg/kg/day have been selected for assessment of the risk of adult oral and dermal exposure, respectively.

Tolerance in the target species

See part 4.

Reproductive toxicity, including developmental toxicity

Study of the effect on reproduction

Conventional reproductive toxicity studies have not been conducted. However, the effects of atinvicitinib on reproduction were evaluated as part of the 4-week and 13-week oral and dermal repeat-dose toxicity studies in rats. In those studies, no effects on oestrus behaviour or female reproductive tissue were detected. However, in males, effects on sperm count and mobility were noted for longer periods of exposure, although no correlating macro- or histopathological findings were observed. It is noted that testicular or epididymal effects may affect reproductive function without histopathological changes. Consequently, for effects on sperm, 13-week oral and dermal toxicity LOELs of 5 and 12 mg/kg/day should be considered.

Section 3.7 of the SPC thus includes the following statements:

"*The safety of the veterinary medicinal product has not been established during pregnancy and lactation or in breeding dogs.*

Fertility:
The use is not recommended in breeding animals.
Laboratory studies in male rats showed an effect on sperm counts and sperm motility."

The first sentence is a statement of fact, while the recommendation against use in breeding animals is appropriate, given the known effects on sperm numbers/motility in rats and noting that reproductive safety specifically has not been evaluated in the target species.

Study of developmental toxicity

The potential toxic effects of atinvicitinib on pregnant females and embryo-foetal development were investigated orally in one dose-finding and two pivotal studies in rodents (rats) as well as one dose-range finding and two pivotal studies in non-rodents (rabbits). These studies were conducted in accordance with GLP principles and OECD TG No. 414.

A dose range-finding prenatal developmental toxicity study was conducted in rats. Atinvicitinib was administered by oral gavage at doses of 0, 1, 5, 25 or 125 mg/kg/day between days 5 to 20 after mating. A low incidence of minor skeletal abnormalities was observed at all doses: the abnormalities were generally within the HCD range and were not associated with a dose-response relationship. As this was a preliminary study conducted with a low number of animals, no clear conclusion on the effect of atinvicitinib on embryo-foetal development could be made. The NOEL for maternal toxicity, growth and survival was 125 mg/kg/day.

A prenatal developmental toxicity study was conducted in rats. Atinvicitinib was administered by oral gavage at doses of 0, 62.5, 250, 1000 mg/kg/day between 5 to 20 days after mating. Ano-genital distance of male and female foetuses was reduced in the 250 and 1000 mg/kg/day groups. A low incidence of foetal abnormalities occurred in all treatment groups. At 1000 mg/kg bw/day, additional abnormalities were observed. A dose-related increase in incidence of medially thickened/kinked ribs, which was outside of the HCD range was observed at 1000 mg/kg/day. The NOAEL for maternal toxicity, embryo-foetal growth and survival was 1000 mg/kg/day. Due to the presence of foetal-abnormalities in all treatment groups, a NOAEL for embryo-foetal development

could not be established.

A prenatal developmental toxicity study was conducted in rats. Doses of atinvicitinib were administered by oral gavage at doses of 0, 10, 30 or 90 mg/kg/day between 5 to 20 days after mating. At 90 mg/kg/day, there was an increase in incidence of medially thickened/kinked ribs, which was outside of the HCD range. The applicant considered these changes unrelated to treatment, noting that the occurrences of medially thickened/kinked ribs at 10 and 30 mg/kg/day were within the HCD. However, noting that these changes occurred in a dose-related fashion in the previous study, the CVMP is of the opinion that the increased incidence of these minor skeletal abnormalities observed at 90 mg/kg/day could be related to treatment. While a NOEL of atinvicitinib of 90 mg/kg/day can be accepted for maternal toxicity, embryo-foetal survival and growth, a NOAEL of 30 mg/kg/day for embryo-foetal development is considered to be more appropriate.

A preliminary prenatal developmental toxicity study was conducted in rabbits. Atinvicitinib was administered by oral gavage at doses of 0, 2, 10, 50 or 250 mg/kg/day between 6 to 28 days post coitus. No maternal toxicity was observed. At 250 mg/kg/day, the number of resorptions and post-implantation losses was high. Major abnormalities of multiple thoracic vertebral/rib abnormalities outside of HCD range were reported in the 50 and 250 mg/kg/day groups. However, as an incident of thoracic hemivertebra also occurred in the control group, it cannot be reliably concluded if this was related to treatment. Given that this was a preliminary study conducted with a low number of animals and litters, and considering the uncertainties related to the major foetal abnormalities observed, a LOEL of 50 mg/kg bw for embryo-foetal development can be accepted. The NOEL for growth or survival was 50 mg/kg/day and the NOEL for maternal toxicity was 250 mg/kg/day.

A prenatal developmental toxicity study was conducted in rabbits. Atinvicitinib was administered by oral gavage at doses of 0, 10, 50 or 250 mg/kg/day between days 6 to 28 post coitum. No treatment-related effects on females administered up to 250 mg/kg/day were observed. At 250 mg/kg/day, post implantation losses were high, with the total number of late resorptions outside the historical control range. Major skeletal abnormalities at 250 mg/kg/day such as spinal meningocele, sacral spina bifida, flattened cranium and the inability to straighten hindlimbs were observed, with thoracic/lumbar vertebral and rib abnormalities, as well as several minor structural abnormalities affecting the thoracic vertebrae, ribs, costal cartilage and sternebrae present at both 50 and 250 mg/kg/day. At 50 and 250 mg/kg/day, a minor visceral abnormality bi-lobed gall bladder was recorded. As a single foetus with similar major rib and vertebral abnormalities was observed at 10 mg/kg/day, a NOAEL for foetal development was not established. A maternal oral NOAEL of 250 mg/kg/day and a NOAEL for embryo-foetal survival and growth of 50 mg/kg/day were established. A subsequent study was conducted in order to investigate embryo-foetal toxicity further. The NOEL/NOAELs proposed based on the findings of this study are accepted.

A prenatal developmental toxicity study was conducted in rabbits. Atinvicitinib was administered by oral gavage at doses of 0, 2, 10 or 50 mg/kg/day between 6 to 28 days post coitus. This was a GLP-compliant study, conducted in accordance with the OECD TG No. 414. In order to increase statistical power, each group consisted of 48 females, instead of the recommended 24. Red discharge/staining in the vaginal/perigenital area was seen in two females receiving 2 mg/kg/day, one female receiving 10 mg/kg/day and two females receiving 50 mg/kg/day. In addition, convulsion was observed in one animal in the 50 mg/kg/day group. As suspected abortion and convulsion were consistent with HCD, these effects were not considered to be treatment-related. While the number of late and total resorptions were high relative to control in the 50 mg/kg/day group, statistical significance was not reached and values were within the HCD range. The incidence of major skeletal abnormalities thoracic/cervical hemivertebra, brachyury, partially fused/misshapen/disorganised caudal vertebra(e) was increased at 50 mg/kg/day. Minor thoracic vertebral element abnormalities were

also observed at this dose but were within HCD range. In addition, misaligned costal cartilage and sternebrae-misaligned hemi-centres were observed at 10 and 50 mg/kg/day. However, the applicant argues that the litter and foetal incidence of these minor skeletal abnormalities observed at 10 mg/kg/day were within the HCD range when the double-sized study was accounted for. In addition, a dose-response relationship in litter incidences of minor skeletal abnormalities was not observed. Consequently, the minor skeletal abnormalities at 10 mg/kg/day were not considered to be related to treatment. While the applicant's approach to adjusting the HCD is questionable (doubling the historical control range for 'double-sized' studies), based on all available information, the CVMP accepts the overall conclusion. A maternal oral NOAEL of 250 mg/kg/day and NOAEL for embryo-foetal survival and growth of 50 mg/kg/day were established. Based on the skeletal abnormality observations at 50 mg/kg per day and as a relationship to treatment could not be ruled out, it was concluded that a foetal developmental NOEL of 10 mg/kg per day was appropriate.

The following text is therefore included in section 3.7 of the SPC:

"*Pregnancy and lactation:*

The use is not recommended during pregnancy and lactation.
Laboratory studies in rats and rabbits have shown effects on prenatal development, inherent to the class of JAK inhibitors."

In the absence of comprehensive studies evaluating the effect on reproduction in the target species, the proposed wording is appropriate. Additionally, information advising of the developmental findings in rabbits and rats, as well as observations on sperm numbers/motility in rats is included.

Genotoxicity

The potential genotoxic effects of atinvicitinib have been investigated in two *in vitro* tests (bacterial reverse mutation assay, mammalian cell micronucleus test in human peripheral blood lymphocytes) and one *in vivo* test (mouse micronucleus test).

The potential of atinvicitinib to induce gene mutations was investigated in *S. typhimurium* (strains TA98, TA100, TA1535 and TA1537) and *E. coli* (strains WP2 uvrA pKM101) in the presence or absence of metabolic activation. The study was performed in accordance with OECD TG No. 471. No increase in revertant colony numbers was observed. Atinvicitinib may thus be considered negative in the bacterial reverse mutation assay.

In an *in vitro* mammalian cell micronucleus test in human peripheral blood lymphocytes, atinvicitinib did not induce micronuclei in the absence or presence of metabolic activation. The study was performed in accordance with OECD TG No. 487.

A bone marrow *in vivo* micronucleus test in mice was conducted in accordance with OECD TG No. 474. Mice were administered dose rates of 500, 1000 and 2000 mg/kg/day. Systemic exposure to atinvicitinib was confirmed. There were no significant increases in micronucleus formations compared to the vehicle control following treatment with atinvicitinib. It was concluded that atinvicitinib was negative in the *in vivo* micronucleus test in male mice.

Based on the negative results in a standard battery of genotoxicity tests, it can be concluded that atinvicitinib does not have genotoxic potential.

Carcinogenicity

No carcinogenicity data have been provided. As there was no evidence of genotoxic potential in a standard battery of genotoxicity studies, and in the absence of treatment related pre-neoplastic

lesions in the repeat-dose toxicity studies, the absence of carcinogenicity data for atinvicitinib can be accepted.

Other requirements

Special studies

In vitro studies to investigate the potential for dermal and ocular irritation were conducted, reflecting the 3Rs principles laid down in Directive 2010/63/EU. The dermal irritation potential of atinvicitinib was evaluated in an *in vitro* skin irritation assay performed. The substance was found to be non-irritant. Skin corrosion was also investigated in an *in vitro* skin corrosion test performed in accordance with OECD TG No. 431 using a human skin model. The results indicated that atinvicitinib is non-corrosive.

The potential for ocular irritation was evaluated in two *in vitro* models. Atinvicitinib was found to be non-irritant to eyes.

In a local lymph node assay in mice conducted in accordance with, atinvicitinib tested at concentrations up to 25% w/w did not show any skin sensitisation potential.

No signs of neurotoxicity were observed in repeat dose toxicity studies. Therefore, no specific studies were performed. This can be accepted.

Observations in humans

No human data are available for atinvicitinib.

However, JAK inhibitors in general have been used in human medicine for decades where they are mainly used or are undergoing final trials for the treatment of atopic dermatitis, psoriasis and other types of immune system-related skin diseases, spondylitis, rheumatoid arthritis and other forms of joint inflammation, ulcerative colitis, as well as neoplastic diseases such as B-cell lymphoma, leukaemia, myelofibrosis and other certain myeloproliferative neoplasms.

Depending on the particular JAK inhibitor, reported side effects include changes in haematological test results such as thrombocytopenia, leukopenia, neutropenia, anaemia or myelosuppression, biochemical changes in laboratory test results such as increasing plasma concentrations of liver enzymes, lipoproteins (total, low- and high-density), cholesterol and blood creatine phosphokinase, as well as a higher risk of infectious diseases primarily of the respiratory tract followed by recurrent, treatment-emergent infections. These side effects depend on the selectivity profile of the specific JAK inhibitor regarding the types of Janus kinases inhibited.

Development of resistance and related risk in humans

Not applicable.

Excipients

With the exception of tocofersolan, the excipients in the product are currently used in veterinary medicines and do not raise any toxicological concern. Regarding tocofersolan, after absorption to enterocytes, vitamin E and polyethylene glycol (PEG) are metabolically separated by hydrolysis and, subsequently, subjected to separate metabolism. Noting that vitamin E is an essential vitamin and PEG is currently used as an excipient in veterinary medicines, tocofersolan does not raise any toxicological concerns.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP 'Guideline on user safety for pharmaceutical veterinary medicinal products' (EMA/CVMP/543/03-Rev.1).

The product is presented in aluminium/PVC/polychlorotrifluoroethylene blisters (each strip containing 30 tablets) or HDPE plastic bottles with child resistant closure. The maximum strength tablet contains 31.6 mg atinvicitinib, which can be divided into two equal halves. The product is to be administered once daily.

The user may be exposed to the veterinary medicinal product (VMP) including the active ingredient atinvicitinib and all excipients, with the main exposure scenarios being dermal contact and accidental oral ingestion by children. It is not expected that any of the excipients have the potential for adverse local or systemic effects, therefore the substance of interest regarding user safety is the active ingredient, i.e. atinvicitinib.

Regarding dermal exposure, a 13-week rat dermal LOEL of 12 mg/kg/day has been used as a toxicological reference value (TRV) to characterise the risk. To account for the use of a LOEL, a safety factor of 5 has been used, resulting in an exposure limit of 2.4 mg/kg/day for margin of exposure (MOE) calculation. Data from an *in vitro* skin penetration study with human and rat skin reported absorption rates of atinvicitinib of 0.05% and 0.28%, respectively. To take into account the difference in dermal penetration, a ratio of 5.6 was applied to the dermal TRV of 2.4 mg/kg/day to give 13.44 mg/kg/day. Following administration of two tablets containing 31.6 mg atinvicitinib to dogs, it is estimated that a dermal exposure of 0.065 mg/kg bw could occur in an adult weighing 60 kg. The resulting margin of exposure (MOE) of 207 indicates that dermal exposure will not pose a risk to an adult user.

When characterising the risk for adult oral hand-to-mouth exposure, the applicant has used a LOEL of 5 mg/kg/day from a sub-chronic (rat) 13 weeks repeat-dose toxicity study. To account for the use of a LOEL, a safety factor of 5 has been used resulting in an exposure limit of 1 mg/kg/day for MOE calculation. Assuming poor hygiene practices, it is considered that maximum exposure volumes during eating, drinking or smoking may be up to 10% of the amount contained in a tablet on contaminated hands. Therefore, maximum oral exposure would be a single dose of 0.0065 mg atinvicitinib/kg bw. A MOE for adult oral hand-to-mouth exposure of 154 has been calculated (1/0.0065).

Based on the physical properties of the tablet, the applicant has chosen a loss of 0.2% of material when handling two whole XL tablets. Each XL tablet contains 31.6 mg atinvicitinib, resulting in an abrasion of 0.0632 mg atinvicitinib per tablet (31.6 mg atinvicitinib/tablet x 0.002) and a potential dermal user exposure when administering two of those tablets of 0.1264 mg per person (2 x 0.0632 mg). This equates to an exposure of 0.0021 mg/kg for dermal or 0.00021 mg/kg for oral hand-to-mouth, respectively. When compared against the above-mentioned LOELs, this results in MOEs of 6400 and 4761 for adult dermal and oral hand-to-mouth exposure, respectively. The approach is considered to be suitably conservative for full tablets, acknowledging that abrasion from fingertips will be insignificant. Noting also that the dermal repeat dose toxicity studies were conducted with a daily exposure of 6 hours (semi-occlusive), as compared to a brief daily exposure during administration, the risk to the user from dermal exposure can be considered minimal.

The CVMP accepts that the risk for hand-to-mouth exposure may be considered negligible where basic personal hygiene measures are maintained (e.g. washing hands after use). Despite the absence of a risk, advice to wash hands thoroughly after use is included in the SPC.

In the case of accidental oral ingestion by a child, an ARfD of 18 mg/kg bw (NOAEL of 1800 mg/kg/day) is an appropriate short-term (acute) TRV based on the results of the extended single-dose oral study in rats. For a 12.5 kg child, the ingestion of one tablet containing 31.6 mg atinvicitinib would equate to 2.5 mg atinvicitinib/kg bw, resulting in a MOE of 7.2. As this value is greater than 1 (given that an uncertainty factor of 100 has already been accounted for when calculating the ARfD), no risk to children from accidental ingestion is expected.

As part of the user risk assessment, the risks from potential mutagenic impurities to the user were evaluated. It can be concluded that the identified potential mutagenic impurities will not pose a risk to the user (adult or child) when controlled as proposed.

The CVMP generally agrees with the overall conclusion that the veterinary medicinal product (VMP) poses a low user health risk. The inclusion of advice to "wash hands thoroughly with soap and water immediately after use of the veterinary medicinal product" is considered appropriate. Although no risk was identified for hand-to-mouth or hand-to-eye transfer, this proposed advice will serve to further minimise exposure.

In relation to accidental oral ingestion by children, the calculated margin of exposure does not indicate a risk for this scenario. As the risk of accidental ingestion by children is acceptable, the absence of child-resistant blisters does not pose a concern (although not confirmed child-resistant, it is accepted that blister packs require some dexterity to open and this will have some effect on limiting child access to the product). It is noted that the HDPE plastic bottle presentation has a child-resistant closure conforming to ISO 8317, minimising the risk of accidental ingestion. While it is noted that tablets can be divided into two equal halves, in the absence of a risk to children, advice on precautions to be taken with any unused divided tablets is not required.

It can be accepted that the risk to the user is acceptable when the product is used, stored and handled as directed in the SPC.

Environmental risk assessment

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food-producing species.

Overall conclusions on the safety documentation: safety tests

Pharmacology:

Pharmacodynamics and pharmacokinetics are addressed in part 4.

An *in vitro* skin absorption test using human and rat skin was conducted. The overall absorption of atinvicitinib for human skin was 0.05% or 0.06%. In the case of rat skin, overall absorption of atinvicitinib was 0.28% or 0.43%.

Toxicology:

Acute oral and dermal LD_{50} values for atinvicitinib of >2000 mg/kg bw were estimated. An extended acute oral toxicity study in rats was conducted for the determination of an Acute Reference Dose (ARfD). Based on an oral NOAEL for rats of 1800 mg/kg/day and an uncertainty factor of 100, an ARfD of 18 mg/kg bw was derived.

The potential systemic effects following subchronic and chronic exposure (oral and dermal) have been extensively investigated in the rat. The studies provided were compliant with GLP principles and OECD TGs. From the studies provided, the spleen and thymus are primary target organs for

atinvicitinib. Decreased weight of these organs correlated with decreased cellularity at higher doses. In the absence of changes in macro- and histopathology, these reductions in weight could be considered non-adverse at lower doses. Decreased cellularity was also observed in bone (sternum including marrow and femur including joint) varying between sexes at high doses, in Peyer's Patches/GALT at oral doses of 300 mg/kg/day and in peripheral lymph nodes, including the mesenteric and/or axillary lymph nodes at 10 and 30 mg/kg/day in both sexes. Reductions in white blood cell counts, namely lymphocytes, monocytes, basophils, neutrophils and/or eosinophils have also been reported at doses of ≥10 mg/kg/day (oral) and at 300 mg/kg/day (dermal). Although it is noted that there was a variability in response between sexes from study to study. Atinvicitinib-related effects on the male reproductive system were observed, with decreases in sperm count and motility noted, although no changes in macro- and histopathological parameters were observed.

A number of biochemical changes were observed during the oral and dermal studies, albeit the absence of a dose-response relationship in many cases and the lack of repeatability between studies makes it difficult to draw associations with atinvicitinib treatment. Changes in blood chemistry were observed at oral doses of 30 mg/kg/day with total cholesterol and high-density lipoprotein concentrations increased, which can be linked to the role that Janus kinases play in lipid metabolism.

For the purpose of user safety, 13-week oral and dermal toxicity LOELs of 5 and 12 mg/kg/day, based on the effects on male reproductive function, have been selected for assessment of the risk of adult oral and dermal exposure, respectively.

Target animal safety is addressed in part 4.

Conventional reproductive toxicity studies have not been conducted. However, the effects of atinvicitinib on reproduction were evaluated as part of the 4-week and 13-week oral and dermal repeat-dose toxicity studies in rats. In those studies, no effects on oestrus behaviour or female reproductive tissue were detected. However, in males, effects on sperm count and mobility were noted for longer periods of exposure, although no correlating macro- or histopathological findings were observed. For effects on sperm, 13-week oral and dermal toxicity LOELs of 5 and 12 mg/kg/day are considered appropriate. Section 3.7 of the proposed SPC includes relevant precautionary statements, see below.

The potential effects of atinvicitinib on development have been investigated in oral prenatal developmental toxicity studies. One dose-finding and two pivotal studies in rats as well as one dose-range finding and two pivotal studies in rabbits were conducted. A maternal oral NOAEL of 250 mg/kg/day and NOAEL for embryo-foetal survival and growth of 50 mg/kg/day were established in rabbits. Based on skeletal abnormality observations and as a relationship to treatment could not be ruled out, a foetal developmental NOEL of 10 mg/kg/day in rabbits was accepted.

In the case of rats, in the absence of adverse effects related to treatment at the highest dose tested, an oral NOAEL of 1000 mg/kg/day was established for maternal toxicity, embryo-foetal growth and survival. However, noting that the occurrences of medially thickened/kinked ribs were observed across the studies, a NOAEL of 30 mg/kg/day for embryo-foetal development is considered by the CVMP to be appropriate.

The following text is included in section 3.7 of the SPC:

" *The safety of the veterinary medicinal product has not been established during pregnancy and lactation or in breeding dogs.*

Pregnancy and lactation:
The use is not recommended during pregnancy and lactation.

Laboratory studies in rats and rabbits have shown effects on prenatal development, inherent to the class of JAK inhibitors.

Fertility:
The use is not recommended in breeding animals.
Laboratory studies in male rats showed an effect on sperm counts and sperm motility."

In the absence of comprehensive studies evaluating the effect on reproduction in the target species, the proposed wording is appropriate. Information advising of the developmental findings in rabbits and rats, as well as observations on sperm numbers/motility in rats is also included.

The potential genotoxic effects of atinvicitinib have been investigated in two *in vitro* tests (bacterial reverse mutation assay, mammalian cell micronucleus test in human peripheral blood lymphocytes) and one *in vivo* test (mouse micronucleus test). All studies were GLP-compliant and were conducted in accordance with relevant OECD guidance. Atinvicitinib did not induce mutations either directly or with metabolic activation in *Salmonella typhimurium* or *Escherichia coli* strains at any dose tested in the bacterial reverse mutation assay. Atinvicitinib did not induce micronuclei in the absence or presence of metabolic activation in the *in vitro* mammalian cell micronucleus test in human peripheral blood lymphocytes. In addition, in the *in vivo* micronucleus test atinvicitinib did not show an increase in micronucleus formation. Based on the negative results in a standard battery of genotoxicity tests, it can be concluded that atinvicitinib does not have genotoxic potential.

No carcinogenicity data have been provided. As there was no evidence of genotoxic potential in a standard battery of genotoxicity studies, and in the absence of treatment related pre-neoplastic lesions in the repeat-dose toxicity studies, the absence of carcinogenicity data for atinvicitinib can be accepted.

Atinvicitinib was non-irritating in *in vitro* ocular and dermal irritation studies. It is not considered a sensitiser based on the results of a mouse local lymph node assay. No effects on the nervous system have been reported for atinvicitinib in the toxicity tests provided.

User safety

A user safety assessment in line with the relevant guidance document has been presented. The risk from dermal exposure is considered low and acceptable when the candidate product is used in accordance with the SPC. When characterising the risk for adult oral hand-to-mouth exposure, the applicant has used a LOEL of 5 mg/kg/day from a sub-chronic (rat) 13 weeks repeat-dose toxicity study. This results in an estimated margin of exposure of 4,761. In relation to accidental oral ingestion by children, ingestion of one tablet by a child results in an estimated margin of exposure of 720.

It can be accepted that the risk to the user is acceptable when the product is used, stored and handled as directed in the SPC.

Environmental safety:

An appropriate environmental risk assessment was provided. Based on the data provided, the ERA can stop at Phase I, as none of the Phase II criteria are met. The product is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Numelvi is presented as tablets containing 4.8, 7.2, 21.6 or 31.6 mg atinvicitinib, a novel Janus kinase inhibitor. Numelvi is intended for use in dogs for the treatment of pruritus associated with allergic dermatitis including atopic dermatitis, and for the treatment of clinical manifestations of atopic dermatitis. The proposed dose is 0.8 - 1.2 mg/kg bw by once daily oral administration.

Atinvicitinib is a new active substance, which has not been authorised for a veterinary medicinal product in the EU at the date of submission of the application.

Pharmacology

Pharmacodynamics

Atinvicitinib is a new immunomodulatory compound of the Janus kinase inhibitor (JAKi) class, which inhibits the function of a variety of pruritogenic and pro-inflammatory cytokines, as well as cytokines involved in allergy which are dependent on JAK1 enzyme activity.

JAK enzymes (JAK1, JAK2, JAK3 and TYK2) have been demonstrated to play critical roles in both innate and adaptive immune responses. Therefore, JAK inhibitors for immune modulation were developed based on knowledge of specific JAK enzyme mutations which characterised specific immunodeficiency syndromes. A broad range of JAKi are marketed in human therapeutics.

The applicant has presented several studies evaluating the pharmacodynamic properties of atinvicitinib.

An *in vitro* kinase test determined IC_{50} values for atinvicitinib against JAK1, JAK2, JAK3, and TYK2 to be 0.43 nM, 5.89 nM, 1129.97 nM, and 13 nM, respectively. These results demonstrate that atinvicitinib elicits a 14-, 2628-, and 30-fold JAK1 selectivity over JAK2, JAK3, and TYK2, respectively. For comparison, the same assays were conducted for oclacitinib, which demonstrated IC_{50} values against JAK1, JAK2, JAK3, and TYK2 of 3.47, 7.57, 31.09, and 21.31 nM, respectively. These results indicate that oclacitinib displayed a 2-, 9- and 6-fold JAK1 selectivity over JAK2, JAK3, and TYK2. These data suggest that atinvicitinib shows greater selectivity and potency against JAK1 than oclacitinib.

The *in vitro* potency of atinvicitinib as an inhibitor of JAK1 and JAK2 activity was also evaluated in a cell-based signalling pathway engagement assay. The assay used a cell-based transcriptional reporter technology that is responsive to interleukin-6 (IL-6) for inhibition of JAK1 and JAK2, and to erythropoietin (EPO) for inhibition of JAK2. The IC_{50} values obtained for atinvicitinib show much greater inhibition of IL-6 signalling pathways compared to those associated with EPO. As IL-6 signals through JAK1 and JAK2 while EPO signals solely through JAK2, it may be concluded that the IC_{50} against IL-6 can largely be attributed to the inhibition of JAK1 and not JAK2, thus confirming the high JAK1 selectivity of atinvicitinib. Additionally, the JAK1 selectivity profile over JAK2 for atinvicitinib in the cell pathway engagement assay supports the selectivity observed in the enzyme binding assay. In comparison to oclacitinib, atinvicitinib displayed greater selectivity and potency in inhibiting the IL-6 signalling pathway: the IC_{50} value for atinvicitinib against IL-6 (41.5 nM) was significantly lower than that for oclacitinib (255.8 nM), with approximately 11-fold greater selectivity for IL-6 vs. EPO for atinvicitinib compared to 2-fold selectivity for JAK1 over JAK2 for oclacitinib.

In conclusion, atinvicitinib has been demonstrated to have similar inhibition pathways as other approved JAKi, although with greater JAK1 selectivity and potency than oclacitinib.

This JAK1 inhibitory effect was also confirmed in *in vivo* studies with a cIL-31 induced pruritus model. The administration of atinvicitinib at doses of 0.5 and 1 mg/kg bw resulted in a significant reduction in pruritus score compared to placebo dogs when the VMP was administered 2 hours before cIL-31 challenge.

The CVMP is of the opinion that the basic pharmacodynamic properties of atinvicitinib have been adequately described and are appropriately summarised in section 4.2 of the SPC.

Pharmacokinetics

The applicant has conducted a battery of *in vitro* and *in vivo* studies to characterise the pharmacokinetic properties of atinvicitinib. Parameters including absorption, distribution, metabolism and excretion of the active substance were evaluated in the target species across a range of GLP and non-GLP studies. The applicant developed and validated a bioanalytical method (LC/MS-MS) for the determination of PK parameters; validation reports were provided. Pharmacokinetics were also compared between clinical trial materials, and in fed vs. fasted conditions in the target species.

Atinvicitinib showed moderate plasma protein binding *in vitro* (range 81.2-88.7%). Results were comparable for all species tested (dog, mouse, rabbit, rat).

After IV administration of 0.3 mg/kg bw to dogs, atinvicitinib had a low plasma clearance of 1074 ml/h/kg. The volume of distribution was 1651 ml/kg and elimination half-life was 2 hours.

After oral administration of 1.2 mg/kg bw atinvicitinib using the final tablet formulation, systemic exposure to atinvicitinib in terms of AUC_{last} was on average more than twice as high in animals in a fed state compared to animals in a fasted state. $C_{max,}$ reached at 1 h after administration, was more than four times higher in fed animals than in fasted animals.

After multiple oral administrations to dogs (once daily administration for four consecutive days), exposure to atinvicitinib in terms of C_{max} and AUC_{last} generally increased proportionally in dose groups (0.5X to 2X, i.e. 0.6 to 2.4 mg/kg/dose), with an approximately 1.5-fold increase between dose rates (0.5X, 1X and 2X). At 0.5 mg atinvicitinib/kg, mean C_{max} was 115 ± 35.1 and 97.3 ± 38.1 ng/mL and mean AUC_{last} was 375 ±163 and 311± 140 h*ng/mL after the 1st and 4th dose, respectively, with a harmonic mean $t_{½}$ of 3.43 h after the 1st dose. Following multiple oral administrations at the recommended therapeutic dose (RTD) (1.2 mg/kg), mean C_{max} was 182 ± 45.2 and 190 ± 35.3 ng/mL, mean AUC_{last} was 606 ± 240 and 679 ± 224 h*ng/mL, and harmonic mean $t_{½}$ was 1.71 h and 2.00 h after the 1st and 4th dose, respectively. Following 2X multiple oral administrations, mean C_{max} was 278 ± 57.1 and 311 ± 66.2 ng/mL, mean AUC_{last} was 1178 ± 350 and 1368 ± 513 h*ng/mL, and harmonic mean $t_{½}$ was 2.40 and 2.29 h after the 1st and 4th dose, respectively. Median T_{max} was at 1 h for all doses.

No accumulation of atinvicitinib was observed after multiple once daily doses in dogs over 4 days. In the pivotal TAS study, where the VMP was administered once daily for 182 days, limited accumulation was observed (Week 26-27/Study Day 1-2 mean R_{AUC} values ranged from 1.17 to 1.49 across dose rates and sexes). The applicant has included a statement to this end in SPC section 4.3.

No relevant sex-dependent differences in exposure were observed when atinvicitinib was administered at the proposed maximum recommended therapeutic dose (RTD) of 1.2 mg/kg/day.

Assessment of *in vivo* organ distribution after oral administration of 2.4 mg/kg [^{14}C]-atinvicitinib to Beagle dogs showed that, in total, 52.84% and 53.45% of the total dose administered could be recovered in the male and the female dog. Radioactivity was predominantly excreted in the faeces and represented about 41% of total dose administered. Urinary elimination was a minor route of

excretion and represented about 3% of the total dose administered. The radioactivity recovered from selected tissues (bile, liver, kidney, gastrointestinal tract walls and subsamples of renal fat and muscle) at 2 h post last dose accounted for approximately 6% and 8% total dose. Due to the loss of the radiolabelled methyl group following demethylation, it was not possible to determine the complete route of atinvicitinib biotransformation quantitatively.

The data package presented is accepted by the CVMP as adequate to characterise the pharmacokinetic profile of atinvicitinib in the dog. The text proposed for inclusion in section 4.3 of the SPC (Pharmacokinetics) is appropriate.

Dose determination and confirmation

Dose justification

The proposed dose and dosing regimen for atinvicitinib was established using qualitative pharmacokinetic modelling and selected doses were tested *in vivo* in a relevant pruritus model. The first-generation JAK inhibitor oclacitinib was used for comparison in these studies. The derived dose and dosing regimen combinations were evaluated in a clinical trial resulting in the recommended clinical dose and dosing regimen of 0.8-1.2 mg atinvicitinib/kg bw once daily.

The studies supporting the selected dosage include:

1) the determination of selectivity and potency of atinvicitinib and oclacitinib in JAK-family enzyme binding and cell pathway engagement assays (*in vitro*, non-GLP),
2) qualitative modelling using the pharmacokinetic (PK) profile of oclacitinib (Collard *et al.* 2013) at the dose approved for the targeted indications (allergic dermatitis and atopic dermatitis in dogs) and the relationship to its JAK1 IC_{50} in a cell pathway engagement assay to establish the target exposure of atinvicitinib (*in vivo*, non-GLP),
3) determination of the inhibition of JAK1 signalling *in vivo* at selected doses of atinvicitinib derived from the PK modelling using a cIL-31-induced pruritus model in healthy Beagle dogs (*in vivo*, non-GLP), and
4) evaluation of the selected dosing regimens of atinvicitinib in a GCP-compliant clinical trial.

Dose determination studies

In vitro pharmacodynamic studies

The ability of atinvicitinib to inhibit the catalytic activity of JAK1, JAK2, JAK3, and TYK2 using a recombinant purified glutathione S-transferase-tagged catalytic domain for each enzyme in a homogenous time resolved fluorescence (HTRF) format biochemical assay, as well its ability to inhibit JAK1 and JAK2 activity in intact cells using CellSensor transcriptional reporter technology, was evaluated in comparison with the authorised active substance oclacitinib.

In vitro kinase tests IC_{50} values for atinvicitinib against JAK1, JAK2, JAK3, and TYK2 were determined to be 0.43 nM, 5.89 nM, 1129.97 nM, and 13 nM, respectively. For comparison, IC_{50} values for oclacitinib against JAK1, JAK2, JAK3, and TYK2 were 3.47, 7.57, 31.09, and 21.31 nM, respectively. These data suggest that atinvicitinib shows greater selectivity and potency against JAK1 than oclacitinib. Based on the findings of the cell-based signalling pathway engagement assays, the high JAK1 selectivity of atinvicitinib was confirmed. In comparison to oclacitinib, atinvicitinib displayed greater selectivity and potency in inhibiting the IL-6 signalling pathway: the IC_{50} value for atinvicitinib against IL-6 (41.5 nM) was significantly lower than that for oclacitinib (255.8 nM). The

IC_{50} values derived from the cell-based assays were used by the applicant in the qualitative PK modelling (see below).

At the time of initial dose determination, the T_{max} and $T_{1/2}$ of atinvicitinib (based on the pharmacokinetics of exploratory formulations) and oclacitinib (based on published data, Collard et al., 2013) were sufficiently similar after oral administration to perform qualitative modelling to estimate the dose of atinvicitinib expected to provide clinical effectiveness.

The hypothesis proposed by the applicant assumes that the *in vivo* inhibition of JAK1 by atinvicitinib at $[plasma]_{free}$ near its JAK1 IC_{50} will be similar to that of oclacitinib at $[plasma]_{free}$ near its JAK1 IC_{50}. In addition, the applicant assumes that a dose of atinvicitinib that results in $[plasma]_{free}$ that are sustained at levels greater than the JAK1 IC_{50} for a longer period of time (that is, dosing at 1 mg atinvicitinib/kg bw to achieve a C_{max} greater than JAK1 IC_{50}) will be associated with a greater duration of effect and require less frequent dosing (e.g. once daily (SID) vs. twice daily (BID) dosing).

To confirm this hypothesis *in vivo*, a series of studies using a cIL-31-induced pruritus model in healthy Beagle dogs was conducted.

In vivo pharmacodynamic studies

To demonstrate the ability of atinvicitinib to inhibit JAK1 activity *in vivo* and to inform dose determination, four studies using a canine interleukin (cIL)-31-induced pruritus model were conducted evaluating several doses of atinvicitinib, compared to the reference substance oclacitinib (administered at 0.4 – 0.6 mg oclacitinib/kg bw). In all studies, cIL-31 was administered intravenously to healthy Beagle dogs at a dose of 1.75 or 5 mg/kg bw. Following a 5-minute rest period post cIL-31 dosing, animals were observed over 2 h for displays of pruritic behaviour. A categorical "yes/no" decision was made at discrete 1-minute intervals with regard to whether at least one pruritic behaviour was displayed. The number of discrete minutes categorized as "yes" was summed to generate a pruritus score. The minimum score possible was 0 (indicating no pruritic behaviours), while the maximum was 120 (representing pruritic behaviours during all discrete 1-minute-observations over the 2-h-period).

Using a cross-over design with 8 dogs, atinvicitinib (1 mg/kg bw), oclacitinib (0.4 – 0.6 mg/kg bw) or placebo tablets were administered on a single occasion 2 h prior to cIL-31 challenge. Administration of atinvicitinib at a dose of 1 mg/kg bw resulted in a pruritus score (24.6 ± 15.6) that was significantly lower than that of the placebo (51.5 ± 22.17) group and numerically lower than that observed in dogs treated with oclacitinib (36.6 ± 18.8). A negative relationship was observed between plasma atinvicitinib as well as oclacitinib concentrations and the pruritus scores.

In a second cross-over study, efficacy of atinvicitinib at doses of 0.5, 0.1 or 0.05 mg/kg bw versus oclacitinib at 0.4 – 0.6 mg/kg bw and placebo was evaluated. The study was designed initially with five sessions separated by a 1-week washout period that involved dosing drug followed by the cIL-31 challenge (N = 2 dogs/group in each session; a total of 10 dogs were used). There was, however, an increase in both pruritus scores and intensity of the pruritus after cIL-31 challenge over the three first sessions and consequently a 14-day washout was instituted for the 4^{th} and 5^{th} sessions. A statistical analysis of the data using a model incorporating sequence, test item, and dose session as variables demonstrated a significant session effect. Therefore, the data from session 1 are the only results free of this period effect (N = 2/treatment group) and they demonstrate that 0.5 mg atinvicitinib/kg bw and 0.4 – 0.6 mg oclacitinib/kg bw treated dogs had the lowest average pruritus scores (29 and 31, respectively), whereas the dogs treated with placebo, 0.05 or 0.1 mg atinvicitinib/kg bw had similarly high average pruritus scores (104, 71, and 82, respectively). Similar to the previous study, there was a negative relationship between plasma atinvicitinib concentrations and pruritus scores across all test sessions. This is a very limited dataset, but it does provide some

evidence of efficacy in the cIL-31 challenge model at a dose of 0.5 mg atinvicitinib/kg bw and no/limited effect at lower doses.

A third study was performed to evaluate the duration of pruritus inhibition after a single dose of atinvicitinib or oclacitinib. In this parallel-design study using 8 dogs/group, administration of placebo, atinvicitinib (1 mg/kg bw), or oclacitinib (0.4 – 0.6 mg/kg bw) 12 h prior to the cIL-31 challenge was performed and the impact of each treatment was compared to that of drug or placebo administered 2 h prior to cIL-31 challenge after a 12- to 14-day washout period. Administration of atinvicitinib or oclacitinib 2 h prior to cIL-31 challenge resulted in pruritus scores of 22.1 ± 13.2 and 33.5 ± 29.5, respectively. For atinvicitinib, the pruritus score was significantly lower than the score for placebo treated dogs (56.8 ± 22). Administration of atinvicitinib or oclacitinib 12 h prior to cIL-31 challenge, however, resulted in pruritus scores (46.1 ± 22.3 and 46.9 ± 33.2 for atinvicitinib or oclacitinib, respectively) that were only modestly lower than placebo treated dogs (57.0 ± 21.5 - no statistical difference relative to placebo). As noted by the applicant, these findings are in contrast to a published study in which oclacitinib was administered (0.4 mg/kg bw in a gel capsule) 6, 11, or 16 h prior to a cIL-31 challenge and a sustained reduction in pruritus scores was observed at all 3 pre-challenge times (Gonzales *et al*. 2016). The absence of a significant effect on pruritus score 12 hours after treatment raises questions about sustained efficacy at a dose of 1 mg/kg bw and the applicant's decision to select a once daily treatment schedule rather than a twice daily treatment schedule.

A further study was performed to evaluate the duration of pruritus inhibition after atinvicitinib administration. Test animals (8 dogs/group) were administered either placebo or atinvicitinib (0.5 mg/kg/day) for three consecutive days with the final dose administered 14 h prior to the cIL-31 challenge. The effect of this dose regimen on pruritus scores was compared to that of a single dose of atinvicitinib (0.5 mg/kg bw) administered 2 h prior to challenge. A single administration of atinvicitinib 2 h prior to cIL-31 challenge resulted in pruritus scores that were significantly lower (47.9 ± 18.9) than in placebo treated dogs (82.5 ± 19.4), whereas the same dose of atinvicitinib administered for three consecutive days with the final dose administered 14 h prior to cIL-31 challenge resulted in a low inhibition of cIL-31 induced pruritus (pruritus score = 61.9 ± 22.3). Again, in the absence of a significant effect on pruritus score 14 hours after treatment, this study provides no support for the applicant's decision to select a once daily treatment schedule. However, it is noted that the dose of test product administered was 0.5 mg/kg bw and not the RTD of 1 mg/kg bw.

Overall, several studies demonstrated that doses of 0.5 and 1 mg atinvicitinib/kg bw resulted in a significant reduction in pruritus scores compared to placebo controls when administered 2 hours before cIL-31 challenge. The CVMP accepts that this confirms effective *in vivo* inhibition of JAK1 in the target species. The reduction of pruritus scores when atinvicitinib was administered ≥12 h before cIL-31 challenge, or when atinvicitinib was administered at doses <0.5 mg/kg bw, were similar to or modestly lower than those of the placebo groups. The absence of effect in these scenarios is attributed to the negative relationship between plasma drug concentrations and pruritus scores (available data suggest a correlation between plasma atinvicitinib concentration and antipruritic effect).

The applicant argues that the comparability of the magnitude of pruritus inhibition between atinvicitinib and oclacitinib, as well as the plasma drug concentration and pruritus score relationship for both substances, were sufficient for hypothesis generation and testing in a clinical field trial. Based on the totality of the pharmacodynamic data presented, it is accepted that there is adequate support to evaluate doses of 0.5 and 1 mg atinvicitinib/kg bw in the clinical setting. However, the *in vivo* data generated up to this point provide no support for the proposed once daily treatment schedule – that is, they do not confirm the applicant's hypothesis that dosing at 1 mg atinvicitinib/kg

bw to achieve a C_{max} > JAK1 IC_{50} will be associated with a greater duration of effect and require less frequent dosing (e.g.: once daily (SID) vs. twice daily (BID) dosing). While the *in vivo* data summarised above do not support the proposed once daily dosing schedule, efficacy of the proposed posology was evaluated in a clinical trial in client-owned dogs compared with a twice daily dose scheme in which changes associated with allergen sensitisation occur naturally and chronic changes such as skin lesions could be evaluated clinically. The dose was further confirmed in the allergic dermatitis clinical trial which also included atopic dogs but with a focus on reduction of pruritus as the main endpoint. See below.

Dose confirmation studies

The applicant concluded based on study data that a dose of ≥0.5 mg atinvicitinib/kg bw or a dose of 0.4 – 0.6 mg oclacitinib/kg bw, at which the $[plasma]_{free}$ of each compound at C_{max} is approximately equal to their JAK1 IC_{50}, suppresses cIL-31 induced pruritus due to JAK1 inhibition. Based on the data, the applicant hypothesised that:

- A dose of atinvicitinib that results in a $[plasma]_{free}$ at C_{max} that is approximately equal to its JAK1 IC_{50} will be effective for the treatment of allergic dermatitis and atopic dermatitis in dogs. Furthermore, they expected that atinvicitinib at this dose would be at least as effective as oclacitinib when dosed at the same frequency.
- A dose of atinvicitinib that results in $[plasma]_{free}$ that are sustained at levels greater than the JAK1 IC_{50} for a longer period of time (e.g. dosing to achieve a C_{max} greater than JAK1 IC_{50}) will require less frequent dosing (e.g. once daily (SID) vs. twice daily (BID) dosing).

No dedicated dose confirmation study was conducted. However, the applicant tested these hypotheses in a US-based pilot clinical trial which evaluated two dosing regimens of atinvicitinib in client-owned dogs with atopic dermatitis. In this pilot clinical trial, efficacy of the proposed RTD of 1 mg atinvicitinib/kg bw once daily in the treatment of pruritus and clinical manifestations of atopic dermatitis was evaluated against twice daily dosing at 0.5 mg/kg bw for 14 days, followed by once daily for the next 14 days at the same dose and compared to a placebo control group. Detailed assessment of this study is presented in section 'Clinical trial(s)' below.

Tolerance in the target animal species

The safety of the VMP in target animals was demonstrated in three specifically designed margin of safety studies, all conducted using orally administered atinvicitinib.

Additionally, atinvicitinib, based on its potential immunosuppressive properties, was evaluated in a GLP-compliant safety study using specific pathogen free (SPF) young dogs, for any impact on response to primary vaccinations when given daily for 84 days (at 3X the maximum RTD).

In all tolerance studies, pharmacokinetic analyses indicated that all animals were exposed to the VMP.

First pilot TAS study

This was a well-designed, GLP-compliant pilot study, conducted to assess the safety of atinvicitinib in adult Beagle dogs. However, the doses/dosing regimens evaluated are not fully in line with those proposed for the candidate VMP (i.e. 0.8-1.2 mg atinvicitinib/kg bw, SID) and the test item was a non-final formulation. Nonetheless, the observations reported in the study may be considered as supportive data.

Atinvicitinib was administered orally in tablet form, at a target dose rate of 0.5 mg/kg bw (1X BID), 1.5 mg/kg bw (3X BID), or 2.5 mg/kg bw (5X BID), or once daily (SID) at a dose rate of 5 mg/kg bw

(5X SID) for 6 weeks (42 days). A control group received placebo tablets twice daily for the same period. Atinvicitinib was administered to animals in the fed state (noting that systemic exposure is greater in the fed state compared to the fasted state).

The following parameters and endpoints were assessed: mortality, faecal observations, body weights, food consumption, physical examinations (vital signs), blood pressure, ophthalmic observations, electrocardiographic (ECG) measurements, clinical observations, clinical pathology (haematology, coagulation, clinical chemistry, urinalysis, faecal evaluation tests), organ weights and macroscopic and microscopic observations. Blood samples were collected for toxicokinetic evaluation.

One male dog administered 2.5 mg atinvicitinib/kg bw BID presented with an interdigital cyst on Day 39 of the study. Interdigital cysts are a known adverse event which have been associated with other molecules in the JAKi family. Following treatment consisting of an NSAID (carprofen) and antibiotic (sulfadimethoxine/ormetoprim), the cyst in animal D0301 resolved and by necropsy on Day 42 was no longer apparent. On the basis of satisfactory resolution, the finding was considered by the applicant as not adverse. An interdigital cyst was also reported in a female dog administered 3X BID on Day 4 but was considered unrelated to test article given its very early onset after dosing initiation. The cyst in this animal was apparently in the process of resolving when first observed, and no treatment was deemed necessary. While the CVMP can accept that the interdigital cyst observed in female dog at Day 4 is less likely to have been treatment related, it is not possible to exclude an association between the occurrence of the lesion recorded in male dog and atinvicitinib administration.

No unscheduled deaths occurred during this study, and no treatment effects were reported in relation to bodyweights, food consumption, physical examination parameters, blood pressure, ophthalmology, or cardiology. Other clinical observations during the study included non-formed faeces, liquid faeces, vomitus, excessive salivation, red conjunctiva, and discharge from the eyes. For these, there was no clear dose relationship, the findings were transient and/or also occurred at a comparable incidence in the control group.

Minor haematological effects were observed in dogs administered 5X BID or 5X SID. These included minimal to mild decreases in red blood cell count [RBC], haemoglobin concentration, and/or haematocrit on single assessments. Additionally, a minimal decrease in absolute reticulocyte count was observed on Day 36 in females administered 5X SID. It is noted that no clinical or microscopic correlates were identified for the minor changes of the haematology parameters. Furthermore, a minimally decreased red cell mass observed on Day 36 in females administered 1X BID was not considered by the applicant as test item related, due to the absence of a dose-response and occurrence in only one animal (group 2, 1X BID) on Day 36), with a haematocrit value slightly lower than the historical reference range. Mean group values for red blood cell count [RBC], haemoglobin concentration, and/or haematocrit were generally within the historical reference ranges, with only some individual animals having values slightly outside those ranges. All haematological changes were considered non-adverse based on their small magnitude and absence of correlating clinical or histopathological findings.

Exposure to atinvicitinib, in terms of mean C_{max} and AUC_{last} values, increased with the increase in dose from 0.5 to 2.5 mg/kg bw/dose following twice daily administration (1.0 to 5.0 mg/kg/day). The increases in atinvicitinib mean C_{max} and AUC_{last} values were generally dose proportional following twice daily administration. While the mean C_{max} and AUC in each treated group was generally higher after 6 weeks of dosing than after the first dose, the difference is small and suggests limited accumulation of atinvicitinib after multiple twice daily or once daily doses. Exposure was generally similar when comparing once daily administration to twice daily administration approximately 12 h apart at the same daily dose.

Second pilot TAS study

This non-GLP pilot margin-of-safety study evaluated the safety of atinvicitinib in 8-month-old Beagle dogs, when administered 1X, 3X, and 5X the maximum recommended clinical dose (1.2 mg/kg/day). The test article was administered orally as the final formulation blend, filled into gelatin capsules. Animals were administered a loading dose of 1X, 3X, and 5X the maximum recommended clinical dose per day, which was split and administered twice daily (BID), for 6 weeks (Day 1 to Day 42). Thereafter, doses of 0.5X, 1.5X and 2.5X the recommended treatment dose were administered once daily (SID) for additional 10 weeks (Day 43 to Day 112/113). Additionally, a group of dogs was administered 5X the maximum recommended clinical dose (5 X 1.2 mg/kg bw/day) once daily (SID) for 16 weeks (Day 1 to Day 112/113). A control group (0X) was included and administered empty gelatin capsules for 16 weeks. Test and control articles were administered to dogs in the fed state (noting that systemic exposure is greater in the fed state compared to the fasted state).

The following parameters were assessed: mortality, clinical observations, bodyweights, food consumption, veterinary physical examinations, ophthalmic examinations, ECG, blood pressure, clinical pathology parameters (haematology, coagulation, clinical chemistry, C-reactive protein [CRP]), faecal analysis, urinalysis, and toxicokinetic evaluation. Gross necropsy, organ weights and histopathological examinations were conducted on Day 113/114.

No unscheduled deaths occurred during this study, and no changes were reported in relation to bodyweight, food consumption, ophthalmic examinations, ECG or blood pressure which were considered as treatment-related.

In the 1X group, abnormal faeces were observed on single occasions; however, these occurrences were sporadic and transient in nature and considered not related to treatment as similar observations were recorded in the control group.

In the other 3X BID/SID animals, abnormal faeces were observed only sporadically. However, in male dogs administered 3.0 mg/kg/dose BID (5X) and 6.0 mg/kg/dose SID (5X) abnormal faeces were generally noted throughout treatment at a greater severity and number of observations compared to control animals. Some of these instances were related to *Giardia*, *Campylobacter* or *Clostridium* species infections, which also resolved under veterinary treatment.

Furthermore, several animals in the 5X groups had findings of interdigital cysts in one or multiple paws over the course of the study. Sporadic incidences of conjunctivitis and gingivitis were also reported in the 5X group, which resolved with veterinary treatment.

In one (5X BID/SID) animal, a large firm non-painful swelling on the right side of mandible (caudal edge) was observed on Day 11. The swelling resolved with treatment by Day 15.

There were no atinvicitinib related findings for the coagulation, haematology, clinical chemistry, CRP, urinalysis, and parasitic faecal screening. All other dogs had negative counts for coccidia, and all dogs had negative counts for nematode ova.

Grossly at necropsy, the left and right foot pads of the hind limb paws in two animals (5X BID/SID and 5X SID, respectively) were recorded as "swollen"; however, there were no histopathological correlates and no evidence of any inflammatory lesions; the foot pads were just thicker.

Toxicokinetic results showed that exposure to atinvicitinib as assessed by mean C_{max} and AUC_{last} values increased in a generally dose proportional manner with increasing doses from 0.6 to 6.0 mg/kg/day). While C_{max} and AUC were slightly higher in group administered 0.6 mg atinvicitinib BID on Day 112 compared to Day 1, there is no evidence of accumulation of atinvicitinib in the other (higher) dose groups after multiple twice daily or multiple once daily dosing. For the 1X, 3X and 5X

BID/SID groups, exposure was generally similar within the groups following the first daily dose during the first six weeks with twice daily administration (BID) when compared to once daily (SID) administration of half the daily dose during the remaining study period.

The applicant considers that clinical observations relating to minor infections reported in treated dogs from this study (interdigital cysts, conjunctivitis, pododermatitis, swollen feet) can generally be a recurrent problem in large dog colonies (often associated with environmental pathogens). While it is accepted that available data indicate no risk for immunosuppression at the target dose, section 3.10 of the SPC includes a statement advising that, at overdoses, the veterinary medicinal product may lead to a higher susceptibility of dogs for the development of bacterial, fungal and/or parasitic skin disease. This is considered appropriate.

Pivotal TAS study

This is considered the pivotal target animal safety study. It was a well conducted, GLP-compliant study, designed and conducted in accordance with VICH GL43. The final formulation of the VMP produced according to GMP regulations at the commercial manufacturing site was used in this pivotal clinical trial.

The test article used is considered representative of the final formulation, and certificates of analysis were provided.

The study was conducted in 6-month-old Beagle dogs. Dogs received 0X (sham dosed – tap water), 1X, 3X or 5X the maximum recommended dose of 1.2 mg/kg bw once daily for 6 months. As the administration of atinvicitinib in a fed prandial state has been demonstrated to give the highest systemic exposure to the active substance, all dogs were fed shortly prior to treatment and food consumption was recorded.

Safety in the target species was assessed through the following parameters: mortality, pen/cage side observations, pre- and post-dose observations, detailed clinical observations, veterinary clinical observations, faecal evaluations/screening, vital signs, ophthalmology, body weights, food consumption, clinical pathology parameters (haematology, coagulation, clinical chemistry, CRP, urinalysis, bone marrow smear evaluations), pharmacokinetic evaluation, organ weights and macroscopic and histopathological examinations.

No atinvicitinib-related observations or changes in vital signs (body temperature, heart rate and respiratory rate), ophthalmology, bodyweight, or food consumption were reported. Furthermore, no atinvicitinib-related changes were noted at any dose rate for haematology, coagulation, clinical chemistry, urinalysis, CRP, and bone marrow. All differences observed in the parameters, regardless of statistical significance, were not considered to be atinvicitinib related based on their small magnitude, inconsistent direction, absence of a dose response, general overlap of individual values with the range of control and baseline values, and/or the fact that they were of a magnitude of change commonly observed in dogs under similar conditions.

Atinvicitinib plasma concentrations generally declined after T_{max} in a mono-phasic manner up until the last quantifiable concentration. However, ongoing concentration increases were observed in some animals between approximately 6- and 10-hours post-dose across dose groups, from where concentrations then declined up to the last quantifiable concentration. Exposure was variable within dose groups, with one animal in the 5X group exhibiting an approximately up to eight times higher exposure compared to other animals in the 5X dose group. Another animal in the 5X group tended to show two-fold the mean exposure of animals in the same group. One animal in the 1X group showed low exposure on Day 1. Considering individual variability, mean C_{max} and AUC_{tlast} values increased in a generally dose proportional manner from 1X to 5X in males and females across

sampling occasions. In more detail, C_{max} and AUC_{tlast} increased approximately 3.4 to 3.9-fold and 4.2 to 6.0-fold in males and females, respectively, for a 5-fold increase in dose for males and females combined.

No obvious trend in the time to peak concentration (median T_{max}) or mean $t_{1/2}$ was observed as the dose increased from 1X to 5X across sampling occasions. Following 26 weeks of repeated once daily dosing with the VMP, exposure to atinvicitinib was generally comparable to that following a single dose across the dose range in both sexes. Week 7/Day 1-2 mean R_{AUC} values ranged from 1.08 to 1.66 across dose rates and sexes, while Week 26-27/Study Day 1-2 mean R_{AUC} values ranged from 1.17 to 1.49 across dose rates and sexes. Systemic exposure to atinvicitinib was generally comparable between male and female dogs. The CVMP agrees, based on these results, that the safety of the VMP has been evaluated under steady state conditions.

Occasional abnormal faecal observations were noted in all treatment groups including the controls, which were not considered by the applicant to be treatment related. Faecal samples from each dog were collected and analysed to investigate the presence of endoparasites (*Giardia*, coccidial oocysts, and nematode eggs) prior to the first treatment and at the end of the study. *Giardia*, a common parasite, was identified in most dogs in all groups (including control dogs) during the faecal screenings prior to Day 1. After deworming and antiprotozoal treatment during acclimatisation, only two paired dogs in the control group tested positive for *Giardia* in week 1. In some dogs, coccidial oocysts were identified during acclimatisation. All dogs had coccidial oocyst counts of <50 oocysts/g except for 2 dogs in the control group, 4 dogs in the 1X group, 3 dogs in the 3X group, and 2 dogs in the 5X group, which had ≥50 coccidial oocysts/g. The coccidial oocysts were subsequently treated successfully during acclimatisation. Screening for parasites conducted on Day 183, however, revealed a recurrence of *Giardia* throughout all dose groups, including control dogs. No coccidial oocysts were detected at this point. The high number of *Giardia* positive dogs in this study was considered unusual, with the recurrence suggesting that *Giardia* may have been endemic in this dog colony. The CVMP can accept this rationale, given that the findings applied to all treatment groups (including the controls), and there was no clear dose relationship between atinvicitinib administration and apparent risk of infection.

Clinical observations reported during this study were generally considered unrelated to treatment with atinvicitinib as the findings were not dose-dependent, were also observed in the control group, and/or were transient in nature. However, regarding the clinical observations for one dog in the 5X group, a potential causal relationship with atinvicitinib treatment cannot be excluded. This dog was euthanised early on Day 175. On study Day 127, the dog began to develop bilateral interdigital cysts on both front paws between the third interdigital spaces and interdigital swellings. Despite treatment being administered, by Day 174, the dog's condition had deteriorated further (depressed behaviour, multiple areas of alopecia, dry and flaky skin). In addition, several pustules were observed at the border of the oral cavity and skin, and the paws appeared swollen, particularly around the previously noted interdigital cysts. The dog was treated with antibiotics, nonsteroidal anti-inflammatory drugs and bathed with antimicrobial/antimycotic solution at this point. Samples of hair, dermal/cyst swabs, and fine needle aspiration identified *Staphylococcus pseudintermedius*, *Streptococcus canis*, *Demodex* sp. and yeast species. These are generally commensal organisms but may also act as opportunist pathogens.

On Study Day 175, due to the clinical status and poor prognosis, the animal was determined unfit to be dosed with the test article. The dog was euthanised to acquire the most appropriate pathology data. Necropsy revealed thin hair in regions on the head, and right knee, and an interdigital swelling on each forelimb were recorded. These lesions correlated histologically with presence of mild to moderate demodicosis and were accompanied by minimal to marked foci of chronic or chronic-active

inflammation in the adjacent adnexa or dermis.

While exposure to atinvicitinib was variable within dose groups, this individual exhibited high exposure across all PK sampling timepoints. During the study, various haematological and clinical chemistry changes were observed in this animal and considered to be associated with the clinical condition of the animal. No definitive data is available which would explain the higher level of atinvicitinib exposure in this animal in the pivotal TAS study. However, it is proposed that one potential cause for the significantly increased exposure observed could be coprophagic activity by the animal in question. There was no other case of such a difference in exposure across the PK and TAS study program, which limits the possibility for most other potential (intrinsic) causes. It was agreed that the clinical observations reported for this animal could be related to the intrinsic properties of atinvicitinib on JAK receptors at a high overdose setting, compared to the other dogs in the same group which had lower plasma PK results.

Demodex mites are not typically associated with overt clinical disease unless there is compromise or modulation of the immune system in some way.

An interdigital cyst was also noted at necropsy in one animal dosed with 3.6 mg/kg/day (3X). However, due to the low incidence and the fact that interdigital cysts were considered by the applicant to be a recognised background finding, a solid relationship to treatment this case could not be established

Section 3.5 of the SPC includes warnings on use of the VMP in dogs with pre-existing bacterial, fungal or parasitic skin disease. In addition, section 3.10 of the SPC includes a statement advising that, at overdoses, the veterinary medicinal product may lead to a higher susceptibility of dogs for the development of bacterial, fungal and/or parasitic skin disease. This is considered appropriate.

Pivotal vaccine response study

This pivotal GLP-compliant vaccine response study was conducted to assess the effect of atinvicitinib on the immune response to vaccination in dogs and to monitor the general health of dogs following treatment with atinvicitinib and vaccination. The final formulation of the VMP produced according to GMP regulations at the commercial manufacturing site was used in this pivotal clinical trial.

Commercially available batches of US-produced Nobivac Canine 3-DAPv (Canine Adenovirus type-2 (CAV), Canine Distemper Virus (CDV), and Canine Parvovirus (CPV)) and Nobivac 3-Rabies (chemically inactivated rabies virus) were used in this study.

Six-month-old, specific pathogen free, vaccine-naive Beagle puppies were dosed once daily orally with control item (placebo tablets) or atinvicitinib at a target dose rate of 3.6 mg/kg bw (3X the maximum RTD) for 84 days. Following the last dosing day (Day 84), the dogs were observed for a post-treatment period of 12-weeks, during which no atinvicitinib treatment was administered. The entire in-life phase of this study lasted for a total of 168 days. Nobivac Canine 3-DAPv modified live vaccine was administered on Days 28 and 56. A single dose of Nobivac 3-Rabies was administered on Day 28. All study animals were confirmed to be clinically healthy and serologically negative for CAV, CDV, CPV and RV prior to study start.

The VMP and placebo were administered to dogs in the fed state, based on pharmacokinetic data which demonstrated greater atinvicitinib exposure following feeding compared to fasted dogs.

The following parameters were evaluated in this study: mortality, body weights, veterinary physical examinations, clinical observations, faecal screenings, clinical pathology (haematology, clinical chemistry, and urinalysis), plasma concentrations and serum antibody titres.

Clinical observations included a high incidence of lacrimation (slight watery ocular discharge) and

abnormal findings in the skin of the ears (redness of the pinnae and ear canal, presence of red spots, and/or less frequently, crust or ear discharge) present in both groups. The lacrimation was considered not clinically relevant and did not require veterinary treatment. The abnormal findings on the skin of the ears were generally mild and deemed not clinically relevant upon veterinary examination, with the exception of one dog in the treatment group, which was treated for otitis externa during the recovery phase. One dog in the control group was also treated for otitis externa during the study and had also treatment prescribed for the redness of the pinnae and ear canals. The underlying cause for the development of lacrimation and redness of the ears was not elicited. Considering the occurrence in both the control and treatment groups both during the treatment and recovery phase, the findings were not attributed to the treatment and were likely related to a reaction to environmental factors.

Additional occasional clinical observations included dental plaques, mild gingivitis, minor skin wounds/lesions, emesis and coughing. These clinical observations were considered unrelated to treatment with atinvicitinib since they were also present in the control group, and/or were transient in nature.

Cryptosporidium sp. was identified in faecal samples of dogs from both the treatment and the control group during pre-treatment screening for endoparasites. The dogs were then screened weekly for *Cryptosporidium* until the infection was considered self-resolved. The weekly faecal screenings were terminated on Day 70 as the two preceding weekly screens returned negative for *Cryptosporidium*. No clinical signs associated with cryptosporidiosis were observed throughout the study.

All haematological parameters were within the study non-treatment reference range at all time points, with the exception of a minor increase in values of lymphocytes and large unstained cells (LUC) for males in the treatment group on Day 56. The observed higher mean value on this day was considered of no clinical significance and not treatment related based on its small magnitude, transient nature, and absence in females. All clinical chemistry parameters were within the study control reference range at all time points, except for a minimal decrease of inorganic phosphate values for females in the treatment group on Day 168. The observed lower mean value on this day was not considered clinically significant or treatment-related based on its small magnitude and absence in males. Exposure to atinvicitinib was confirmed by pharmacokinetic analyses. The primary variable for immune response was the serum antibody titres on Day 84. The following titres were the minimum level necessary to conclude protective immunity: CDV VN50 ≥32, CAV VN50 ≥16, CPV HAI ≥80, and RV >0.5 IU/mL. All treated dogs achieved an adequate immune response (serum antibody titres for protective immunity) for each vaccine antigen on Day 84. However, one control animal was found to be seronegative for CAV-2 at all three timepoints, despite having mounted an adequate antibody response to CDV and CPV.

No CAV-2 serology results were reported for 4 control animals on Day 84. However, these animals demonstrated protective titres of antibodies against CAV-2 at the timepoints before (D56) and after (D168) and given the known kinetics of antibody response it may be presumed that these dogs would also have protective titres at D84.

Dogs treated with atinvicitinib had notably higher CAV-2 antibody titres than control dogs at D56, D84 and D168.

On Days 56 and 84, all animals were found to have protective levels of antibodies against rabies virus (>0.5 IU/mL). On Day 168, all animals except for one animal treated with atinvicitinib and two control animals were found to have protective levels of antibodies against rabies virus. The applicant states that the reported results were comparable with a study on the kinetics of rabies antibodies, in

which 99% of dogs achieved protective antibody titres against rabies at day 60 after vaccination, decreasing to 88.5% of dogs by day 180 after vaccination (with a booster shot 30 days after vaccination) (Babboni et al. 2014).

Based on the results reported from the above study, the CVMP can accept that the immune response mounted to Nobivac Canine 3-DAPv (Distemper-Hepatitis-Parvovirus) and Nobivac 3-Rabies vaccination was unaffected by administration of atinvicitinib at three times the maximum recommended dose for a period of 12 weeks. All treated dogs achieved antibody titres above those required for protective immunity for each vaccine antigen on Day 84. Additionally, the VMP was well tolerated by all treated dogs in this study.

Clinical trial(s)

The applicant conducted one pilot and one pivotal multisite GCP clinical trial to assess effectiveness and safety in the field. The pilot study evaluated the efficacy and safety of two dosing regimens (SID vs. BID oral administration) of atinvicitinib in the treatment of canine atopic dermatitis in client-owned dogs. The pivotal clinical trial was intended to support the safety and effectiveness of atinvicitinib administered at the RTD (0.8-1.2 bw mg/kg once daily) for the treatment of pruritus associated with allergic dermatitis, including atopic dermatitis, in dogs.

Both clinical trials were conducted in the USA. However, considering the mechanism of allergic dermatitis, including atopic dermatitis, and pharmacological action of atinvicitinib, the CVMP agrees that the findings of these studies can be extrapolated to the EU situation. Allergic dermatitis and atopic dermatitis are common conditions in dogs worldwide, and their clinical manifestations and response to treatment are consistent across different geographical regions. In particular, the mode of action of the active substance (i.e. inhibition of JAK1) is not expected to be influenced by the geographical location or the environmental condition of the dogs.

US atopic dermatitis study

This GCP-compliant pilot study was conducted in the USA, to evaluate the efficacy and safety of two dosing regimens of atinvicitinib against canine atopic dermatitis (cAD) in client-owned dogs under field conditions. Dogs were treated orally either once daily at the target dose of 1.0 mg/kg bw (dose range based on tablet sizes: 0.8 – 1.2 mg/kg bw, SID) for 28 days or twice daily at the target dose of 0.5 mg/kg bw (dose range based on tablet sizes: 0.4 – 0.6 mg/kg bw) for 14 days, followed by once daily for the next 14 days at the same dose (BID/SID). Another group of dogs served as comparison and was treated with an oral placebo control (CP) twice daily for 14 days, followed by once daily for 14 days. The test article used in this study was close to, but not identical to, the final formulation. This is considered acceptable to the CVMP, as the stated differences are minor in nature.

Animals were evenly distributed across the three treatment groups and were randomly allocated to treatment groups by order of enrolment at each study site. All dogs were evaluated for pruritus and skin lesions using the Pruritus Visual Analog Scale (PVAS – owner assessed) and the Canine Atopic Dermatitis Extent and Severity Index (CADESI-4 – investigator assessed) scoring tools. Considering the nature (e.g. chronicity, gross lesions, behavioural issues) of the conditions proposed for treatment with Numelvi, the applicant's approach in including an investigator assessed primary efficacy endpoint in combination with the targeted owner assessed PVAS as primary efficacy endpoint is accepted.

At enrolment (Day 0 prior to treatment), the owner assessed the severity of their dog's pruritus using an enhanced PVAS scoring system by placing a mark on a 10 cm long vertical line with a short horizontal line at the point they felt most closely matched their perception of their dog's pruritus

over the preceding 24 hours. Each owner also completed the PVAS evaluations at home daily on study Days 1 to 7, and then on Days 14 and 28.

To investigate the effect of treatment on the clinical manifestation of cAD, the veterinary examiner also assessed the severity of skin lesions including erythema, lichenification, and excoriations and/or alopecia in various regions according to the CADESI-4 scoring tool at the beginning of the study (Day 0 prior to treatment) and upon study completion (Day 28).

The owner-assessed PVAS scoring and investigator-assessed CADESI-4 scoring were carried out independently of each other to avoid the owner being influenced by the examiner's assessment and vice-versa. For each study animal, the PVAS score was assigned by the same animal owner/designee throughout the study. Similarly, for CADESI-4 evaluation, the same examiner assessed it for a specific animal throughout the trial.

Dogs of at least 12 months of age, with a clinical diagnosis of cAD and a PVAS baseline score of equal or greater than 6 (scale 0–10) were enrolled in the study. Initially, a minimum CADESI-4 score of 35 was required (scale 0–180). However, this minimum CADESI-4 requirement was later removed through a protocol amendment in order to increase enrolment to the study, which had been impacted by the COVID-19 pandemic. In addition to PVAS and CADESI-4, the clinical diagnosis of atopic dermatitis had to meet six or more clinical criteria as proposed by Favrot et al., 2010. These criteria included an age at onset of <3 years old, living primarily indoors, corticosteroid-responsive pruritus, chronic or recurrent yeast infections, involvement of front feet and ear pinnae, unaffected ear margins, and non-affected dorsal lumbar area. Other pruritic skin diseases were excluded through the use of standard diagnostic criteria or therapeutic methods. The CVMP can support the diagnostic basis on which dogs were assigned a diagnosis of atopic dermatitis, considering that the criteria proposed by Favrot et al. are well recognised and accepted internationally.

Dogs remained in their home environment under the care of their owners and were fed their usual diets during the study. Dogs could not have evidence of ectoparasite infestation (study dogs received ectoparasiticides throughout the study) and must have complied with a washout period for selected medications that might have an effect on the signs of atopic dermatitis, such as antihistamines, JAK inhibitors, monoclonal antibodies, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antimicrobials, among others.

The 61 dogs which met the inclusion criteria ranged from 1.4 to 16.3 years of age, weighed between 3.8 and 60.2 kg (average: 23.3 kg), and had average baseline PVAS and CADESI-4 scores of 7.1 (range: 4.5 – 9.7) and 44.2 (range: 0 – 119), respectively. Dogs were male and female, intact and neutered, with mixed breed dogs being most represented, followed by Shih Tzu, Chihuahua, and German Shepherd dogs. The CVMP agrees that the range of dogs included in the study population can be considered representative of the proposed target population.

Evaluation of effectiveness was based on improvement of CADESI-4 or PVAS scores during the study. The primary variable of effectiveness was a reduction of at least 50% in PVAS or CADESI-4 score on Day 28 as compared to baseline on Day 0.

Based on the results presented, treatment success rates were 87.5% and 73.3% in the SID and BID/SID groups, respectively, while a success rate of 23.1% was observed in the CP group. The difference in success rates was significant for both atinvicitinib-treated groups compared to the CP group, with p values of 0.0110 and 0.0327 for SID and BID/SID, respectively. In response to a request from CVMP, the primary parameters were re-assessed by the applicant combining both criteria, i.e. using "AND" instead of "OR" (50% reduction of CADESI-4 and PVAS from Day 0 to 28).

Based on this analysis, a clinically significant difference was observed for the SID group compared to CP (p=0.0305): 11/15 SID dogs (73.3%) achieved treatment success vs. 2/12 CP dogs (16.7%).

The secondary variables of effectiveness further support SID dosing over BID/SID dosing. While evaluating the results for '*at least 2 cm reduction for PVAS (Day 28 compared to Day 0)*', higher treatment success rates were observed in both atinvicitinib-treated groups compared to the CP group, with a statistically significant improvement observed in the SID group (80.0% treatment success) compared to CP (16.7% treatment success) (p=0.0417). The endpoint of reduction in PVAS scores by 2 cm is considered an appropriate and clinically relevant response to treatment. Additionally, in relation to PVAS scores on Days 0-7, 14, and 28, a steeper decreasing pattern for both atinvicitinib-treated groups was observed, compared to the CP. The difference was statistically significant compared to CP for both SID and BID/SID groups with p-values of 0.0029 and 0.0013, respectively. For CADESI-4, only the SID group showed a significant difference from CP (p=0.0462).

Further analysis was conducted using the smaller study population (n=30) that did not include animals with a baseline CADESI-4 below 35. The percent treatment success rate of a >50% reduction in CADESI-4 or PVAS scores after removing the dogs with baseline CADESI-4 below 35 was higher in the IVP-treated groups (91.7% and 80.0% for IVP SID and IVP BID/SID, respectively), compared to that of the CP group (37.5%). However, statistical significance was not reached for either IVP group (assumed to be due to the small sample size and/or the relatively high success in the placebo group).

In terms of safety assessments, thirty-six adverse events (AEs) were reported in 23 animals during the study. Eight of the AEs (6 dogs) were in the CP group, 14 AEs (10 animals) were in the BID/SID group, and the remaining 14 AEs (7 animals) were recorded in the SID group. Most of the AEs (22) were classified as digestive tract disorders, followed by 8 AEs classified as systemic disorders (anorexia, lethargy, and polydipsia). Investigators assessed all AEs to be non-serious and either unrelated to study treatment (25 of 36 AEs, 69%) or of unknown relation to study treatments (11 of 36 AEs, 31%). It is noted that all AEs resolved prior to the end of the study, with exception of 3 animals: one animal (CP) presented with polydipsia on Day 6, another animal (SID) presented inappropriate urination on Day 7, and another animal (BID/SID) presented with itching on Day 15. These AEs were listed as unresolved when the dogs completed the study on Day 28.

It is noted that dogs with underlying disease such as progressive malignant neoplasia, immunosuppressive conditions, or hyperadrenocorticism were excluded from the study. The rationale for such exclusion criteria can be accepted, given the known pharmacodynamic properties of atinvicitinib and other JAKi molecules. The product information includes text reflecting that safety has not been evaluated in such animals. In terms of adverse events, the applicant has included the following in section 3.6 of the SPC: emesis, diarrhoea, lethargy and anorexia as common adverse events observed during the clinical trials. The text proposed for SPC section 3.6 is considered acceptable to CVMP.

It is accepted that the test item was generally well tolerated by treated dogs during this study.

Concomitant medications administered during this study were considered to be generally typical of dogs with dermatitis or other co-morbidities present. A total of 42 concurrent medications and vaccinations were administered to 17 dogs in the study, equally distributed across study groups. The most commonly reported medications were for ectoparasite control and heartworm prevention. No negative interactions between atinvicitinib and other medications were reported during the course of this study. Appropriate text on the potential for interactions is included in SPC section 3.8.

Plasma concentrations of atinvicitinib were variable, trending numerically higher in the IVP SID group, compared to the IVP BID/SID group, most notably on Day 28. For the IVP BID/SID group,

average concentrations remained similar throughout the study ranging from 103.34 ng/mL (Day 14) to 111.96 ng/mL (Day 0), while average concentrations of atinvicitinib steadily increased in the IVP SID group, averaging 125.97, 163.93 and 191.69 on Days 0, 14, and 28, respectively.

Under the conditions of this clinical trial, the IVP was effective in the treatment of pruritus and clinical manifestations associated with atopic dermatitis when administered to client-owned dogs.

US allergic dermatitis study

The GCP-compliant pivotal clinical trial was conducted in the US to evaluate the safety and effectiveness of the VMP administered once daily at a dose of 0.8 – 1.2 mg atinvicitinib/kg bw for the treatment of pruritus associated with allergic dermatitis, in client-owned dogs under field conditions. The study included a control group of dogs, which were administered placebo tablets.

The final formulation of the VMP produced according to GMP regulations at the commercial manufacturing was used in this pivotal clinical trial.

The trial was conducted in two phases: Part I was the study phase through Day 7 (+3), and Part II was the optional continuation of therapy phase through Day 28 (± 3).

289 dogs (145 VMP, 144 CP) were enrolled in this trial, at 26 sites in 17 different states in the US. No site contributed more than 40% of treated animals and no more than 50% of dogs had atopic dermatitis as the sole diagnosis of the cause of pruritus. Age and weight ranges at enrolment were similar between the VMP and CP groups. Mixed breed dogs were most commonly represented, followed by American Pit Bull Terriers, Golden Retrievers, and Labrador Retrievers.

The study included dogs that were at least 6 months old, weighing at least 2 kg, receiving an approved flea preventative, and in good overall health. There were no breed or sex restrictions, but dogs that were pregnant, lactating, or intended for use in breeding were not eligible for enrolment. Dogs were required to have a diagnosis of allergic dermatitis and at least moderate pruritus on the owner's assessment on the PVAS (equal or greater than 6). Dogs were excluded from the study if they had evidence of overt superficial or deep microbial skin infection, evidence of impaired immune function, or recently had intradermal skin testing completed. Study dogs received ectoparasiticides throughout the study.

Inclusion and exclusion criteria were generally similar to those used in the previous pilot study, although the minimum age was 6 months old for this pivotal clinical trial. This in line with the proposed SPC. Additional reasons for exclusion included malignancy, and 'uncontrolled' systemic disease (e.g. hypothyroidism, rickettsial disease) which could affect immune function. Noting that safety has not been investigated in such animals, the product information (section 3.5 of the SPC) includes text to reflect that fact.

At enrolment, each case was evaluated by the examiner based on documented medical history, presenting clinical signs, diagnostics performed, and owner reporting to determine a diagnosis of pruritus associated with allergic dermatitis. The examiner assessed the most likely cause(s) of the dog's pruritus among the study population including atopic dermatitis, flea allergy dermatitis, food allergy dermatitis, contact dermatitis, sarcoptic mange, or other unspecified allergic dermatitis. Atopic dermatitis was the most common diagnosis for the cause of pruritus. It is accepted that the dogs enrolled in the study were an appropriate representation of the target population.

The owner assessed and documented the severity of their dog's itching (PVAS) at home on Days 1, 2, 3, 4, 5, 6, and 7. The same individual performed the PVAS assessment throughout the study for a particular case at approximately the same time each day.

All enrolled study dogs returned to the study site for visit 2 on Day 7 (+3). This was the final study

day for Phase I of the study. At this visit, the examiner performed a physical examination and a dermatitis VAS assessment and collected blood and urine (if possible). After completing Phase 1, owners/dogs had the option to remain on study (within respective treatment group). All remaining enrolled study dogs returned to the study site for visit 3 on Day 28. At this visit, the examiner performed a physical examination and a dermatitis VAS assessment and collected blood and urine (if possible).

The primary efficacy variable was defined as treatment success based on ≥50% reduction from baseline in owner-assessed PVAS score on at least 70% of Days 1 to 7 (the evaluation was performed on Day 7). The average PVAS at enrolment in the VMP group was 7.4 (± 0.96) centimetres, and the average PVAS in the CP group was 7.6 (± 1.01) centimetres.

At Day 7, 11 of 126 (8.7%) dogs in the CP group were treatment successes, and in the VMP group 31 of 128 (24.2%) dogs were treatment successes. The incidence of treatment success was statistically significantly higher in the VMP group in comparison to the CP group ($p = 0.0109$). While it is accepted that treatment success for the primary variable was statistically significantly higher in the IVP-treated dogs, it is a concern that greater than 75% of treated animals did not achieve the efficacy threshold for success. Further, on review of the PVAS scores on each assessment day, it appears that animals in the placebo group showed a greater reduction in pruritus score over the seven-day evaluation period than would be anticipated for dogs with allergic dermatitis and receiving no treatment. For example, by Day 7, 81.8% of IVP-treated dogs had achieved a 2 cm or more reduction in PVAS compared to 46.5% of the CP dogs. This finding supports the concern relating to the diagnostic criteria used in the selection of cases for inclusion in the trial.

Severity of the dermatitis was also assessed by the examiner using a dermatitis Visual Analog Scale (VAS) (Cosgrove et al., 2013). The examiner placed a mark on a 10 cm vertical line at the point that most closely matched their assessment of the severity of the dog's dermatitis (scale 0 to 10, with 0 being "Normal Dog. Dermatitis is not a problem." and 10 being "Extremely severe dermatitis. Extensive evidence of chronic lesion and/or active infections/excoriations."). While it is noted that this assessment method is not a validated approach, it is acknowledged that validated assessment tools, such as the Canine Atopic Dermatitis and Severity Index (CADESI-4), are limited to specific dermatitis, such as atopic dermatitis, and would not have been suitable to assess the variety of skin conditions seen in this study.

The mean change in dermatitis VAS scores in comparison to baseline was higher in the VMP group on Day 7 (2.45 cm) and on Day 28 (3.58 cm) in comparison to the CP group on Day 7 (1.33 cm) and Day 28 (3.07 cm). The difference between groups was statistically significant on Day 7, but not on Day 28.

The CVMP accepts that the approach to primary efficacy evaluation (based on owners -assessed pruritus) is appropriate to the disease condition under study. However, the period of evaluation is relatively short – firm conclusions on efficacy can only be made up to Day 7 given that the second phase was optional. The reduction in DVAS scores from Day 0 to Day 7 suggests potential efficacy for the VMP against pruritus and dermatitis as clinical manifestations of allergic dermatitis. However, this study does not confirm a sustained effect of treatment in this population of dogs beyond Day 7. Notably, the evaluation consisted of comparing DVAS scores on d 7 and d 28 as compared to the baseline. A statistically significant difference between groups was only observed on Day 7, but not on Day 28. Additionally, there is no definition of success, so the clinical significance of the results observed is not clear.

Whilst statistical significance was achieved vs. the placebo group with regard to PVAS scoring, the proportion of treated dogs that achieved the threshold for treatment success appears modest (in the

VMP group 31 of 128 (24.2%) dogs were treatment successes). Responding to this concern, the applicant argued that the criteria for treatment success are a strict definition of at least 50% reduction in PVAS on at least 70% of study days 1 to 7 (i.e. at least 5 of 7 days) and, despite this strict success criterion, atinvicitinib-treated dogs achieved statistically significant success compared to placebo. The applicant has related the numerically low efficacy percentages (24.2%) in the IVP group, compared to 8% success in the placebo group, to the stringency of the primary efficacy criterion. The secondary efficacy criteria results are also supportive of treatment success. When using the endpoint of 'at least 2 cm reduction from baseline PVAS at day 7', the success rates achieved were atinvicitinib 81.8% vs CP 46.5%.

Regarding the duration of the study (period of evaluation), the study was designed using guidance from published peer-reviewed data based on studies evaluating the efficacy of similar products for the treatment of canine pruritus due to allergic dermatitis. The applicant states that study durations were aligned with the allergic dermatitis trial of the EU-authorised JAKi oclacitinib, where the validated PVAS system was also used as the primary assessment of efficacy (Cosgrove et al., 2013a). A 7-day study duration was chosen for assessment of primary efficacy criteria for these studies because many causes of allergy can resolve with short-term management, and rescue therapy for control group cases could be quickly initiated.

The CVMP can accept that efficacy has been satisfactorily demonstrated as regards treatment of pruritus associated with allergic dermatitis. However, having considered the original and complementary data provided, the CVMP does not agree that efficacy in treatment of clinical manifestations in dogs with allergic dermatitis in the study has been appropriately demonstrated. The following deficiencies, in particular, have been identified:

- No primary endpoint was established to measure efficacy for the treatment of clinical manifestations for allergic dermatitis cases. Treatment of clinical manifestations was defined as a secondary endpoint as follows: Dermatitis VAS scores on Visit 2 Day 7 (+ 3 days) and Visit 3 Day 28 (± 3 days) as compared to baseline.
- Although the Dermatitis Visual Analog Scale (DVAS - Cosgrove et al., 2013a) could be accepted for the assessment of skin lesions in the study, the CVMP notes that success and failure were not defined.
- The only condition for measuring efficacy of treatment of clinical manifestations of allergic dermatitis was based on statistically significant differences between Day 7 and baseline, and between Day 28 and baseline. Notably, statistically significant differences were only observed on Day 7, but not Day 28; therefore, the criteria were not met. On this point, it is important to highlight that the reduction of clinical signs/skin lesions likely requires more time than the reduction of causative pruritus, making the measurement on Day 28 especially relevant.
- Finally, despite DVAS having been used for the assessment of skin lesions in other similar clinical trials for similar products (oclacitinib and ilunocitinib), this endpoint was a secondary criterium and none of the products have authorised the indication for the treatment of skin lesions associated to allergic dermatitis.

Taking into account these deficiencies, the CVMP considers that the claim for the treatment of clinical manifestations associated with allergic dermatitis has not been appropriately demonstrated in the clinical studies. On this basis, the proposed indication has been amended as follows:

"*For the treatment of pruritus associated with allergic dermatitis including atopic dermatitis in dogs. For the treatment of clinical manifestations of atopic dermatitis in dogs.*"

All 298 randomised animals, which received at least one dose of VMP or CP, were included in the safety evaluations. Review of urinalysis and serum chemistry results did not reveal notable

differences between VMP and CP dogs and also did not indicate any trends or changes from baseline throughout the study. The VMP-treated dogs showed a decrease in white blood cell parameters indicative of allergies (i.e. eosinophil counts), or inflammation in general (i.e. WBC, neutrophil counts), while remaining within the normal ranges. There were no other notable differences between VMP and CP treated dogs, including no impact on the red blood cell counts.

There were 279 total AEs reported, with 138 in the VMP group (49.5%) and 141 in the CP group (50.5%), representing a roughly equal proportion in both treatment groups. The proportion of non-serious AEs was equal for both treatment groups. Erythema, otitis externa, emesis, and pruritus were reported in 5% or more of the VMP-treated dogs. Dermatitis and eczema, diarrhoea, pruritus, bacterial skin infection, and otitis externa were reported in 5% or more of the CP-treated dogs.

The concomitant medications administered to dogs enrolled in the study were generally typical of products administered to the general canine population that were allowed by the protocol. The most commonly reported medications administered to dogs enrolled in the study for each treatment group included isoxazolines, milbemycins, avermectins, pyrethrins and pyrethroids (administered to 5% or more of VMP-treated dogs). The VMP was used concurrently with other medications such as antimicrobials (including topicals), analgesics, anaesthetics, nutritional supplements, topical skin and otic cleansers that did not contain glucocorticoids, and medicated shampoos.

No adverse reactions were observed from the concurrent use of the VMP with other medications under these study conditions. Information on the potential for interactions is adequately captured in SPC section 3.8.

Considering the often prolonged and perhaps lifelong nature of allergic conditions such as atopic dermatitis, the applicant was requested to justify the 28-day duration of both clinical trials for determining the safety of longer term treatment with Numelvi. In its response, the applicant explained that potential adverse effects in client-owned animals with allergic dermatitis, including atopic dermatitis, can be adequately observed and assessed within 28 days, noting in particular:

- The toxicity profile of atinvicitinib in all species, including target animals, is defined by the JAK receptor interaction at higher doses and an early onset of effects.
- No significant accumulation is expected over a treatment course of 28 days or more.
- JAKs are highly conserved throughout mammalian species therefore no differences in potential adverse effects of treatment is expected between dog breeds – that is, the findings of the target animal safety studies (of 4- and 6-months duration) conducted in Beagles can be extrapolated to dogs of other breeds. Based on the TAS studies (up to 6 months in duration), atinvicitinib when administered at the recommended treatment dose was demonstrated to have an acceptable safety profile, with an acceptable margin of safety.
- The clinical trials were performed according to current quality standards VICH GL9 ("Good Clinical Practice") and the study populations reflect the target population for atinvicitinib.
- Potential adverse effects of atinvicitinib are related to the mode of action of atinvicitinib – inhibition of JAK1. Therefore, the potential for these adverse effects is the same in dogs suffering from atopic dermatitis or any other type of allergic dermatitis. The clinical trials, in general, evaluated safety for all indications.

The argumentation provided is accepted by CVMP. In addition, recognising that long-term safety has not been evaluated in client-owned dogs, the applicant proposed to include the following statement in the SPC to provide further guidance to veterinarians: "*The intensity and duration of signs of allergic dermatitis including atopic dermatitis are variable. The need for long-term treatment should be based on an individual benefit-risk assessment.*" The inclusion of such a statement is also considered appropriate.

Overall conclusions on efficacy

Pharmacodynamics

Atinvicitinib is a new immunomodulatory compound of the Janus kinase inhibitor (JAKi) class, which inhibits the function of a variety of pruritogenic and pro-inflammatory cytokines, as well as cytokines involved in allergy, which are dependent on the JAK1 enzyme activity.

A broad range of JAKi are marketed in human therapeutics. The applicant has presented several studies evaluating the pharmacodynamic properties of atinvicitinib, which has been demonstrated to have similar inhibition pathways as approved JAKi, although with greater JAK1 selectivity and potency than oclacitinib.

The CVMP is of the opinion that the basic pharmacodynamic properties of atinvicitinib have been adequately described and that the text proposed for inclusion in section 4.2 of the SPC (Pharmacodynamics) is acceptable.

Pharmacokinetics

The pharmacokinetic properties of atinvicitinib have been evaluated in a series of *in vitro* and *in vivo* studies.

Atinvicitinib showed moderate plasma protein binding (range 81.2-88.7%) *in vitro*. Results were comparable for all species tested (dog, mouse, rabbit, rat).

After IV administration of 0.3 mg/kg bw to dogs, atinvicitinib had a low plasma clearance of 1074 ml/h/kg. The volume of distribution was 1651 ml/kg and elimination half-life was 2 hours.

After oral administration of 1.2 mg/kg bw atinvicitinib, systemic exposure to atinvicitinib in terms of AUC_{last} was on average more than twice as high in animals in a fed state compared to animals in a fasted state. C_{max} reached at 1 h after atinvicitinib administration in fed animals was more than four times higher than in fasted animals.

After multiple oral administrations to dogs (once daily administration for four consecutive days), exposure to atinvicitinib in terms of C_{max} and AUC_{last} generally increased proportionally in dose groups (0.5X to 2X, i.e. 0.6 to 2.4 mg/kg/dose), with an approximately 1.5-fold increase between dose rates (0.5X, 1X and 2X).

However, in the pivotal TAS study where the VMP was administered once daily for 182 days, mild accumulation was observed (Week 26-27/Study Day 1-2 mean R_{AUC} values ranged from 1.17 to 1.49 across dose rates and sexes). A statement regarding accumulation is included in SPC section 4.3.

The data package presented is accepted by the CVMP as adequate to characterise the pharmacokinetic profile of atinvicitinib in the dog. The text proposed for inclusion in section 4.3 of the SPC (Pharmacokinetics) is appropriate.

Dose determination and confirmation

To demonstrate the ability of atinvicitinib to inhibit JAK1 activity *in vivo* and to inform on dose determination, four studies using a canine interleukin (cIL)-31-induced pruritus model were conducted, evaluating several doses of atinvicitinib, as well as the reference substance oclacitinib. Overall, several studies demonstrated that doses of 0.5 and 1 mg atinvicitinib/kg bw resulted in a significant reduction in pruritus scores compared to placebo controls when administered 2 hours before cIL-31 challenge. It is accepted that this confirms effective *in vivo* inhibition of JAK1 in the target species. The reduction of pruritus scores when atinvicitinib was administered ≥12 h before

cIL-31 challenge, or when atinvicitinib was administered at doses <0.5 mg/kg bw, were similar to or modestly higher than those of the placebo groups.

While the *in vivo* data summarised above do support an effective dose of ≥0.5mg/kg bw, the data does not support the proposed once daily dosing schedule. Thus efficacy of the proposed posology was evaluated in a clinical trial in client-owned dogs with atopic dermatitis compared with a twice daily treatment scheme. The dose was further confirmed in the allergic dermatitis clinical trial.

Tolerance in the target animal species

The tolerance of atinvicitinib was evaluated in three (one pivotal and two pilot) pre-clinical margin-of-safety studies and in an additional study addressing the potential effect on vaccination.

The results of these studies indicate that treatment of Beagle dogs with atinvicitinib at doses of up to 5X the maximum recommended clinical dose was generally well tolerated.

Interdigital cysts were observed at doses greater than those recommended for therapy. In this regard, section 3.10 of the SPC includes a statement advising that, at significant overdoses, the veterinary medicinal product may lead to a higher susceptibility of dogs for the development of bacterial, fungal and/or parasitic skin disease.

The clinical pathology parameters in the pivotal margin-of-safety study confirmed the high specificity of atinvicitinib for JAK1, significantly limiting off-target inhibition of other JAKs at multiples of the maximum recommended therapeutic dose.

The results of the vaccine response study indicate that treatment with atinvicitinib in dogs as young as 6 months did not inhibit the development of a suitable immune response to the vaccinations evaluated (CDV, CAV, CPV and RV). Therefore, the CVMP can accept that treatment of dogs with atinvicitinib is not expected to interfere with mounting of an immune response to routine vaccinations.

Overall, it is accepted that the test item is well tolerated based on the target animal safety data generated. Further, it is accepted that the text proposed for inclusion in SPC sections 3.6 and 3.10 is appropriate.

Clinical trials

Efficacy:

At the time of submission, the applicant proposed the following indication for Numelvi:

"*For the treatment of pruritus, inflammation and clinical manifestations associated with allergic dermatitis including atopic dermatitis in dogs*"

To support the proposed therapeutic claims, the applicant conducted two (one pilot and one pivotal) multi-centre US clinical trials. Both studies were conducted in client owned animals.

The pilot study evaluated the efficacy and safety of two dosing regimens of atinvicitinib in client owned dogs with atopic dermatitis under field conditions in the US. Dogs were treated orally with the VMP either once daily at a dose of 0.8 – 1.2 mg/kg bw for 28 days or twice daily at a dose of 0.4 – 0.6 mg/kg bw for 14 days, followed by once daily at the same dose for the next 14 days. Another group of dogs served as comparison and was treated with an oral placebo control (CP) twice daily for 14 days, followed by once daily for 14 days.

Evaluation of effectiveness was based on improvement of CADESI-4 or PVAS scores during the study. The primary variable of effectiveness was a reduction of at least 50% in PVAS or CADESI-4 score on Day 28 as compared to baseline on Day 0. Treatment success rates were 87.5% and 73.3% in the

SID and BID/SID groups, respectively, while a success rate of 23.1% was observed in the CP group. When comparing the two dosing regimens, atinvicitinib administered once a day at 0.8 – 1.2 mg/kg bw (SID) performed better in the efficacy parameters evaluated and consequently was chosen as final dosage.

The pivotal study evaluated the efficacy and safety of oral atinvicitinib for the treatment of pruritus associated with allergic dermatitis, in client-owned dogs under field conditions in the US. The VMP was administered once daily at a dose of 0.8 – 1.2 mg atinvicitinib/kg bw (with food) for 28 days.

At Day 7, 11 of 126 (8.7%) dogs in the CP group were treatment successes, and in the VMP group 31 of 128 (24.2%) dogs were treatment successes. The incidence of treatment success was statistically significantly higher in the VMP group in comparison to the CP group ($p = 0.0109$). The secondary efficacy criteria results are also supportive of treatment success: when using the endpoint of 'at least 2 cm reduction from baseline PVAS at Day 7', the success rates achieved were atinvicitinib 81.8% vs CP 46.5%.

The CVMP concludes that a claim for 'atopic dermatitis' can be accepted for the product when administered at the proposed dose regimen (0.8 – 1.2 mg atinvicitinib/kg bw SID).

The CVMP can also accept that efficacy has been satisfactorily demonstrated as regards pruritus associated with allergic dermatitis. However, having considered the original and complementary data provided, the CVMP does not agree that efficacy in treatment of clinical manifestations in dogs with allergic dermatitis in the pivotal clinical trial has been appropriately demonstrated.

On this basis, the indication has been amended as follows:

"For the treatment of pruritus associated with allergic dermatitis including atopic dermatitis in dogs. For the treatment of clinical manifestations of atopic dermatitis in dogs."

Finally, regarding the originally proposed claim for "*reduction of inflammation*" (defined as a decrease in the mean values of blood parameters indicative for a reduction of allergy mediated inflammation, i.e. absolute eosinophil count, absolute neutrophil count, and white blood cell count), the applicant has acknowledged that no distinct efficacy endpoints were included in either clinical trial to support that claim. Therefore, the word "*inflammation*" has been deleted from the proposed indication section.

Safety:

The proposed text for section 3.6 of the SPC has been based primarily on the results of the clinical trials.

The product was generally well tolerated, and most common adverse events reported during the clinical trials were emesis (10/259 dogs), diarrhoea (5/259 dogs), as well as lethargy (7/259 dogs) and anorexia (3/259 dogs). These have been adequately captured in section 3.6 of the SPC, with an appropriate frequency descriptor of "*Common (1 to 10 animals / 100 animals treated)*".

Part 5 – Benefit-risk assessment

Introduction

Numelvi is available as tablets containing 4.8 mg, 7.2 mg, 21.6 mg and 31.6 mg of atinvicitinib and are presented in packs containing 30 tablets and 90 tablets.

The active substance of Numelvi is atinvicitinib, a selective Janus kinase (JAK) inhibitor, highly selective for JAK1. It inhibits the function of a variety of cytokines involved in itch and inflammation, as well as cytokines involved in allergy, that are dependent on JAK1 enzyme activity.

The medicinal product is intended for use in dogs for the treatment of pruritus associated with allergic dermatitis including atopic dermatitis, and the treatment of clinical manifestations of atopic dermatitis.

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

Benefit assessment

Direct benefit

The benefit of Numelvi is its efficacy in the treatment of pruritus associated with allergic dermatitis including atopic dermatitis and treatment of clinical manifestations of atopic dermatitis, which was investigated in two GCP-compliant clinical trials.

Additional benefits

The product increases the range of treatments available in dogs for pruritus associated with allergic dermatitis including atopic dermatitis, and clinical manifestations of atopic dermatitis.

Atinvicitinib is at least 10 times more selective for JAK1 compared to the other JAK family members (JAK2, JAK3, Tyrosine Kinase (TYK)2). Thus, it has very little to no effect on cytokines involved in haematopoiesis or host defense that are dependent on JAK2 or the other JAK family members.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has generally been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics.

Safety

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal

Administration of Numelvi in accordance with SPC recommendations is generally well tolerated.

In the absence of data, use in pregnant and lactating bitches as well as in breeding animals is not recommended.

Risk for the user

The user safety for this product is acceptable when used according to the SPC recommendations.

Risk for the environment

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

Risk management or mitigation measures

Target animal safety

Emesis, diarrhoea, lethargy, and anorexia are included as adverse events in the proposed SPC. Section 3.10 of the SPC notes that, at significant overdose, treatment with the veterinary medicinal product may lead to a higher susceptibility of dogs for the development of bacterial, fungal and/or parasitic disease.

Section 3.5 of the SPC includes text advising that safety has not been investigated in dogs with has not been investigated in dogs with evidence of immune suppression, such as uncontrolled primary hypothyroidism or rickettsial disease, or with evidence of progressive malignant neoplasia.

Section 3.8 includes appropriate text on the potential for interactions.

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

The veterinary medicinal product is subject to a veterinary prescription.

Evaluation of the benefit-risk balance

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

"*For the treatment of pruritus, inflammation and clinical manifestations associated with allergic dermatitis including atopic dermatitis in dogs*".

However, the CVMP considers that the claim for the treatment of clinical manifestations associated with allergic dermatitis has not been appropriately demonstrated in the clinical studies. On this basis, the indication was further amended as follows:

"For the treatment of pruritus associated with allergic dermatitis including atopic dermatitis in dogs. For the treatment of clinical manifestations of atopic dermatitis in dogs."

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

The product information has been reviewed and is considered to be satisfactory and in line with the assessment.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Numelvi is approvable, since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6).

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

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