12 June 2025
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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Zenrelia (EMEA/V/C/006332/0000)

INN: Ilunocitinib

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

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Introduction

The applicant Elanco GmbH submitted on 1 December 2023 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Zenrelia, 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 13 July 2023 as Zenrelia 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 indications:

Treatment of pruritus associated with allergic dermatitis in dogs.
Treatment of clinical manifestations of atopic dermatitis in dogs.

The active substance of Zenrelia is ilunocitinib, a Janus kinase (JAK) inhibitor, which inhibits the function of a variety of pruritogenic and pro-inflammatory cytokines, as well as cytokines involved in allergy which are dependent on JAK enzyme activity. The target species is dog.

Zenrelia film-coated tablets contain 4.8 mg, 6.4 mg, 8.5 mg and 15 mg of ilunocitinib and are presented in packs containing 10 tablets, 30 tablets and 90 tablets.

The rapporteur appointed is Rory Breathnach and the co-rapporteur is Marcin Glanda.

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 Zenrelia.

Scientific advice

The applicant received scientific advice from the CVMP on 12 May 2022. The scientific advice pertained to quality issues related to the development of the active substance. This was preceded by another scientific advice from the CVMP,, received on 20 May 2019 which also related to the development and quality of the active substance. In most respects, the scientific advice provided by the CVMP has been followed by the applicant.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

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

Manufacturing authorisations and inspection status

Active substance

Manufacture, quality control, and packaging of the active substance ilunocitinib takes place within the EEA. A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the proposed EU dosage form manufacturing and batch release site, Elanco France S.A.S. The declaration was based on an onsite audit by the manufacturing site responsible for batch release.

Finished product

Batch release of the finished product takes place at Elanco France S.A.S., Huningue, France. The site has a manufacturing authorisation issued on 22nd April, 1987 by the French competent authority. GMP certification, which confirms the date of the last inspection and shows that the site is authorised activities indicated above, is available in EudraGMDP.

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 presented as film-coated, immediate-release tablets for oral administration containing either 4.8 mg, 6.4 mg, 8.5 mg or 15 mg of ilunocitinib as active substance. The other ingredients are: microcrystalline cellulose calcium hydrogen phosphate dihydrate, pregelatinized starch, povidone, magnesium stearate and Opadry Yellow. The tablets are yellow, oblong, coated, immediate release tablets, scored on both sides.

The product is packaged in unit-dose aluminium/ aluminium blisters (each strip containing 10 film-coated tablets) packed into an outer cardboard box. Pack sizes of 10, 30 or 90 tablets. The pack sizes are consistent with the dosage regimen and duration of use.

Containers and closure system

The primary packaging is an aluminium/ aluminium blister consisting of a forming foil of polyamide/aluminium/polyvinyl chloride and a lidding foil of paper/polyethylene terephthalate/aluminium/heat-seal lacquer. Declarations have been provided confirming compliance of the forming foils and lidding foils with EU Regulation No 10/2011 on plastic materials and articles intended to come into contact with food. The forming foils also comply with Ph. Eur. 3.1.11 'Materials based on non-plasticised poly(vinyl chloride) for containers for solid oral dosage forms for oral administration'. The blister card was developed to be child resistant, in compliance with ISO 14375, as

assessed in section 3.A.6.3.

Product development

The active substance ilunocitinib exhibits polymorphism, and the anhydrous Form II was chosen for commercialization based on its ease of preparation, thermal stability, and low hygroscopicity.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards, with the exception of the film coating, which is controlled by an in-house method. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.

All tablet strengths were used in the clinical trials and so no comparative dissolution profiles were required to demonstrate the similarity/comparability of the tablet strengths. As such, the dissolution method is only used for the control of the finished product to ensure batch-to-batch consistency, and, ideally, signal potential problems with in vivo bioavailability with respect to those of the pivotal clinical trial batches.

The dissolution method was developed generally in line with the principles of Ph. Eur. 2.9.3 and 5.17.1, The dissolution test and its specification have been demonstrated to be discriminatory.

The final formulation used for Clinical Trial Material manufacturing, and for the Primary Stability/ Clinical Trial Material manufacturing is as per the proposed commercial formulation, with yellow coated, oblong, scored 4.8 mg, 6.4 mg, 8.5 mg, and 15 mg tablets. In general, satisfactory information has been provided regarding selection and optimisation of the product formulation. No overages are used for the products.

The dossier includes an extensive report on manufacturing process development detailing results of design of experiment studies covering all areas of manufacture development including laboratory scale, pilot scale development and optimisation, manufacture of clinical batches, stability batch manufacture, scale up and optimisation at commercial scale and development of the commercial scale control strategy. Evaluation and optimisation of each unit operation is described, and process understanding elaborated through design of experiment studies. The report is comprehensive and generally supports the manufacture and control strategy described in 3.2.P.3.

Data is provided to demonstrate the compliance of the registration batches of each strength with the requirements of the test for "Subdivision of tablets" of the Ph. Eur. dosage form monograph for "Tablets".

Description of the manufacturing method

The manufacturing process consists of sieving, blending, direct compression into tablets and film-coating the tablets before packaging. Purified water is used as a processing aid and is removed during manufacture. The process is considered to be a standard manufacturing process. The manufacturing process description includes detail of the equipment for different batch sizes.

The in-process parameter controls are generally adequate for this type of manufacturing process and pharmaceutical form.

A holding time was established and the packaging used to hold the bulk product is complaint with EU Regulation No. 10/2011 for plastic materials and articles intended to come into contact with food.

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.

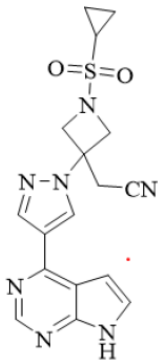
It is accepted that process validation on full scale batches will be performed post-authorisation. The process validation data on at least 3 commercial scale batches will be available at the manufacturing site for inspection. A process validation protocol for future commercial scale batches was provided and is acceptable. Hold times for the bulk blend and uncoated tablets are supported by the data. Compliance with the 'Note for Guidance on start of shelf-life of the finished dosage form' EMEA/CVMP/453/01 has been confirmed.

Control of starting materials

Active substance

The active substance, ilunocitinib, is a small molecule JAK inhibitor. The active substance is not monographed in the Ph. Eur. Data on the active substance is provided in the dossier.

The active substance has the following structure:



IUPAC name:	2-[1-cyclopropylsulfonyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]azetidin-3-yl]acetonitrile
CAS number:	1187594-14-4
Molecular formula:	$C_{17}H_{17}N_7O_2S$
Molecular weight:	383.43

Ilunocitinib is a white or off-white to beige or brownish solid. It is non-hygroscopic and achiral, and has low aqueous solubility. The active substance exhibits polymorphism, with two anhydrous forms and a metastable anhydrous form, a dihydrate form and at least three solvates. The anhydrous Form II is chosen for commercialization based on its ease of preparation, thermal stability, and low hygroscopicity, and is controlled in the active substance specification with an x-ray powder diffraction identification test.

Ilunocitinib is synthesised in three synthetic steps, followed by purification, drying, milling and packaging. Detailed descriptions of the process were provided, along with flow-charts and a synthetic pathway. The suitability of starting materials and their specifications, has been demonstrated in line with the Scientific Advice provided to the applicant. Adequate specifications have been provided for the remaining raw materials. Adequate in-process controls are applied during the synthesis. The specifications provided for the intermediates are considered to be acceptable.

The process will be validated with a minimum of 3 consecutive, commercial-scale batches at the proposed manufacturing sites, prior to commercialisation of the finished product. The characterisation of the active substance is in accordance with the Guideline on the chemistry of active substances for

veterinary medicinal products (EMA/CVMP/QWP/707366/2017-Rev.1). Potential and actual impurities were well discussed with regards to their origin, fate and control.

The active substance specification includes tests for appearance, identification (including polymorphic form), assay, related substances, residual solvents, water content, residual palladium, residue on ignition (Ph. Eur.), particle size distribution and microbial quality (Ph. Eur.), and is considered to be adequate. A residual solvent present at levels higher than the VICH GL18 limit was qualified by toxicological data and appropriate specifications have been set. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the VICH guidelines VICH GL1 and 2.

Batch analysis data on six pilot-scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Stability data on pilot-scale batches of active substance from the proposed manufacturers stored in the packaging proposed for commercial batches, were provided for 24 months under long term conditions at 25 ºC/60% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH guidelines. Results on stress conditions (heat, humidity and light in solid state; acid, base, light and oxidation in solution) were also provided for one batch, in order to generate and characterise the degradation products found.

The parameters tested during stability are the relevant stability indicating parameters in the active substance specification. The analytical methods used were the same as for the active substance specification and were stability indicating. All tested parameters were within specification and no trending was apparent. The stability results indicate that the active substance manufactured by the proposed manufacturers is sufficiently stable and justify the proposed retest period.

Excipients

Microcrystalline cellulose 302, pregelatinized starch, calcium hydrogen phosphate dihydrate, povidone K30 and magnesium stearate are well known pharmaceutical ingredients and their quality is compliant with their Ph. Eur. monographs, and with the microbiological requirements of Ph. Eur. 5.1.4 for non-sterile substances for pharmaceutical use. Additional functionality related characteristic limits are included for microcrystalline cellulose, povidone and magnesium stearate, and justification is provided for any other functionality related characteristics that are referenced in the relevant Ph. Eur. monographs but not included in the excipient specifications. In addition, a reference to compliance with its Ph. Eur. monograph has also been included for purified water used in the preparation of the coating suspension.

The non-pharmacopoeial excipient, Opadry Yellow, is controlled by an in-house specification which includes tests and limits for colour and appearance, identification, ash, dispersion and microbial quality (Ph. Eur.), and is considered to be acceptable. Satisfactory analytical methods have been provided, along with method validation. In line with the requirements of the 'Guideline on excipients in the dossier for application for marketing authorisation for veterinary medicinal products' EMA/CVMP/QWP/307647/2023, the qualitative and quantitative composition of the Opadry Yellow coating has been provided, along with reference to compliance with pharmacopoeial or Commission Regulation requirements for food additives.

No novel excipients are used in the manufacture of the product.

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

No materials of human or animal origin are used in the manufacture of the proposed product. The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev 3).

Control tests on isolated intermediates

Not applicable.

Control tests on the finished product

The specifications proposed at release are appropriate to control the quality of the finished product. The finished product specification includes tests for appearance, active substance identification, tablet dimensions and weight, assay, degradation products, uniformity of dosage units, dissolution and microbial quality. The specification presented is acceptable

The analytical methods used have been adequately described and are appropriately validated in accordance with the VICH GL1: *Validation of analytical procedures: definition and terminology* and VICH GL2: *Validation of analytical procedures: methodology*.

Batch analysis results are provided for commercial-scale batches of all tablet strengths and confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

All of the batches placed on stability were manufactured at pilot scale at the proposed manufacturing site. Batches were stored under long term conditions for 18 months at 25 ºC/60% RH, intermediate conditions for 18 months at 30 °C/75% RH, and accelerated conditions for 6 months 40 ºC/75% RH in accordance with the VICH guideline GL3. Additional tests include storage at 5 °C for 12 months, storage at 50 °C for one month.

The specifications proposed at the end of shelf-life are the same as those proposed at release except for the deletion of tablet weight and dimensions, and uniformity of dosage units testing.

The analytical procedures for appearance, water content, active substance assay, degradation products, dissolution, and microbial quality used are stability indicating. No significant changes have been observed.

In addition, a single batch of the 4.8 mg tablets was exposed to light as defined in the VICH guideline GL5 on photostability testing of new veterinary drug substances and medicinal products. The results demonstrate that light has no adverse effect on the quality of the finished product. Freeze-thaw testing was also conducted on a single batch of the 4.8 mg and 15 mg tablets packaged in the primary Alu/Alu blisters. All results are within specification and no significant changes are observed. No storage precaution is therefore considered necessary.

Data from in-use stability testing on halved tablets from a single batch of the 4.8 mg and 15 mg tablets placed in commercial blisters stored for 20 days at long-term and intermediate conditions have been provided. No significant changes are observed. The results of the testing demonstrate stability

over the 20 days however, an-use period is not required for stable tablets and is therefore not included on the SPC.

Based on the available stability data, the proposed shelf-life of 24 months as stated in the SPC is acceptable.

Regional Information

Not applicable.

New active substance (NAS) status

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

The documentation provided by the applicant to support the request is described in Reflection paper on the chemical structure and properties criteria 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 ilunocitinib contained in the veterinary medicinal product Zenrelia 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 finished products are film-coated, immediate-release tablets containing either 4.8 mg, 6.4 mg, 8.5 mg or 15 mg of ilunocitinib as active substance.

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

Physicochemical aspects relevant to the performance of the product have been investigated. Within the product development section, an evaluation of the active substance and excipients is provided, along with a summary of the formulation work performed and the development of the manufacturing process.

The manufacturing process consists of blending, direct compression, and film-coating, and is considered to be a standard manufacturing process. Adequate process parameter and in-process controls are provided, along with satisfactory information on intermediates. The compliance of the products with the 'Note for Guidance on start of shelf-life of the finished dosage form' EMEA/CVMP/453/01 has been confirmed.

Information on the control of starting materials has been provided. The active substances ilunocitinib is not monographed in a pharmacopoeia, and data on the active substance is provided in the dossier. Adequate specifications are provided for the raw materials. The control of the critical steps and intermediates is acceptable. The active substance specification, analytical methods and validation are acceptable. The supporting documentation on the container closure system is satisfactory. Stability data has been provided to justify the proposed retest period.

The excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. monographs as relevant, and acceptable data has been provided for the non-monographed coating. Data has been presented to give reassurance on TSE safety.

The finished product specification presented is acceptable, controlling the relevant parameters for the product. An acceptable elemental impurities risk assessment for the products has been provided.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Satisfactory stability studies have been carried out under long-term and accelerated conditions support a shelf life of 24 months.

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 and residues tests)

The active substance of Zenrelia is ilunocitinib, a Janus kinase (JAK) inhibitor, which inhibits the function of a variety of pruritogenic and pro-inflammatory cytokines as well as JAK activity-dependent cytokines involved in allergy.

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

Ilunocitinib is a non-selective JAK inhibitor. It is principally an inhibitor of JAK1 and JAK2, has high potency against TYK2 activity, and very little potency against JAK3. Ilunocitinib was highly specific in the kinase screen for the JAKs, with minimal activity for other kinases (e.g. CaMKI, DRAK1, Mnk2, MSK2, p70S6K, and PKA) at maximal concentrations.

The effects of ilunocitinib on inhibition of cytokines involved in inflammation (IL-2 and IL-6), allergy (IL-4 and IL-13), haematopoiesis (GM-CSF) and the innate immune response (IL-12 and IFNγ) have been examined, with ilunocitinib displaying potent, minimally selective inhibitionof all cytokines tested. Ilunocitinib had an inhibitory effect (IC_{50} = 0.05038 µM) on the stimulatory action of IL-31 on canine macrophages. IL-31 has been previously identified as the key component of the pruritus response.

Pharmacokinetics

See part 4.

Toxicology

The safety of ilunocitinib was evaluated in a comprehensive battery of toxicity studies: acute oral toxicity studies in rats, repeat-dose oral toxicity studies in rats and dogs, exploratory repeat-dose oral toxicity studies and margin-of-safety target animal safety studies in dogs, 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 GLP-compliant.

Single-dose toxicity

A GLP-compliant acute toxicity study of ilunocitinib was carried out in rats by oral gavage, in accordance with OECD test guideline (TG) No. 420.

After oral exposure in rats, the acute toxicity of the test substance was low, as no apparent toxicity was observed at up to 2000 mg/kg bodyweight (bw). At 2000 mg/kg bw, skin redness was observed at day 1. Given the short duration of this observation, and apparent absence of other effects, such a change is regarded as a potential first point of departure from the normal physiological state.

Repeat-dose toxicity

The toxicity of repeated daily oral doses of ilunocitinib was evaluated in rats and dogs. The studies provided include a non-GLP-compliant dose-range finding study and two GLP-compliant studies.

In a 28-day oral toxicity study, male rats were given ilunocitinib by gavage at doses of 0, 50, 125 or 300 mg/kg bw/day, while female rats were dosed with 0, 75, 150 or 400 mg/kg bw/day. This was a GLP-compliant study, conducted in accordance with the OECD TG No. 407. Thymus, spleen and adrenal organ weights were reduced in all treatment groups. Effects on lymph nodes, spleen, thymus, stomach, liver, skin and prostate comparable to those of the high dose groups were observed in the low and intermediate dose groups. Skin lesions (scabs on the neck, in the scapular region and/or on the mouth) were reported in all female dose groups, including the low dose (75 mg/kg bw) group. It was also noted that in the male low dose groups, significantly lower mean bodyweights were observed in the 50 mg/kg bw/day (males) from day 20, while statistically significant decreases in bodyweight appeared from day 17 to 18, from day 21 to 22 and from day 25 to 27 at 75 mg/kg bw/day in female rats.

It is accepted that the primary target organs/systems for ilunocitinib are the haematopoietic (bone marrow) and lymphoid systems and organs (thymus, bone marrow, spleen, mesenteric and mandibular lymph nodes, GALT and BALT), stomach, duodenum, skin and bone. Effects on these tissues have been observed at all doses. The applicant suggests that the low dose (50 mg/kg bw in males and 75 mg/kg bw in females) can be considered the NOAELs. However, as the effects seen on haematopoietic and lymphatic systems at the low doses are similar to those seen at higher doses

(although less severe), the proposed NOAEL for this study is not accepted. Further, the applicant suggests that effects at the low doses are related to pharmacological activity of the active substance. While technically this may be the case (effects related to JAK inhibition), the effect is manifested in tissues that are not the target and, in the CVMP's view, such effects should be viewed as toxicity.

A 90-day study in rodents was not performed and instead is replaced by a repeated dose study conducted in the target species (the pivotal target animal safety study). Based on the findings of this study, the applicant concluded that the highest tested dose 4 mg/kg was considered a NOAEL because the effects observed can be attributed to the pharmacological (immunomodulatory) effects of the active substance. While the CVMP can accept that the treatment-related effects seen can be explained by the immunomodulatory effect of the substance, a number of the effects observed should be considered adverse. Indeed, while the 0.8 mg/kg dose was generally well tolerated, effects (albeit mild) that may be considered treatment-related were detected in the 0.8 mg/kg bw dose group (consistent with other studies). The proposed NOAEL of 4 mg/kg bw for dogs based on this study is therefore not accepted. The pivotal TAS study is summarised and commented on in detail in part 4.

Tolerance in the target species

See part 4.

Reproductive toxicity, including developmental toxicity

Study of the effect on reproduction

No studies on the effects on reproduction have been provided. This is acceptable since the product is not intended for use in breeding animals or animals intended to be used for breeding. Adequate warnings are included in the SPC.

Study of developmental toxicity

A prenatal developmental toxicity study was conducted in rabbits at doses (oral gavage) of 0, 1, 3 or 10 mg/kg bw/day. No maternal or foetal toxicity was observed at doses up to 10 mg/kg bw/day. In the absence of any maternal or foetal developmental effects, an oral NOAEL for rabbits of 10 mg/kg bw/day is accepted.

Another prenatal developmental toxicity study was conducted in rats at doses (oral gavage) of 0, 1, 10 or 50 mg/kg bw/day. A significant decrease in food consumption was observed in the highest dose group from day 15 post coitum. A significantly lower bodyweight gain was observed at day 6–8 of pregnancy at 10 mg/kg bw/day and at 50 mg/kg bw/day between days 6–11 and 18–19 of pregnancy, respectively. Skeletal abnormalities were observed in a dose-dependent manner in the 1, 10 and 50 mg/kg bw/day groups, i.e. bent *scapulae* and short, thickened and bent femora, *tibiae*, *ulnae*, *radii* and *humeri*. A delay in foetal development such as medially thickened/kinked ribs, a delay in ossification of cranial centres, *sternebrae* and thoracic *vertebrae* as well as variations in lens shape were also observed in the 10 and 50 mg/kg bw/day groups. As foetal abnormalities were observed at the lowest dose of 1 mg/kg bw/day, no NOAEL could be determined for foetal development in the rat. A maternal NOAEL of 1 mg/kg bw/day can be accepted based on reduced bodyweight gain.

To define a point of departure (POD), a benchmark dose lower 95% confidence limit (BMDL) was calculated using the U.S. Environmental Protection Agency's (EPA) BMD software, version 3.3.2. Based on the results of the modelling, the most conservative average BMDL was selected as POD for an

exposure calculation for ilunocitinib. The selected POD is 0.86 mg/kg bw/day for major developmental abnormalities in rats.

The following text is proposed for inclusion in section 3.7 of the SPC:

"*Pregnancy and lactation:*
The use is not recommended during pregnancy and lactation.
Laboratory studies in rats have shown evidence of teratogenic and foetotoxic effects.

Fertility:
The use is not recommended in breeding animals."

In the absence of studies evaluating the effect on reproduction in the target species, and noting the developmental findings in rats, the proposed wording is considered appropriate.

Genotoxicity

The potential genotoxic effects of the phosphate salt of ilunocitinib have been investigated in three in vitro tests for mutagenicity and clastogenic potential in *S. typhimurium* and one in vivo test (micronucleus test in bone marrow cells of the mouse). In addition, an in vitro micronucleus assay using human lymphocyte cultures (in accordance with OECD TG No. 487) and an in vivo mouse micronucleus test (in accordance with OECD TG No. 474) investigating the genotoxic effects of ilunocitinib were also provided. The phosphate salt of ilunocitinib was negative in both the bacterial reverse mutation assay and an in vitro chromosome aberration assay in human lymphocytes. The phosphate salt of ilunocitinib was concluded to be negative for the induction of micronuclei in the presence of S9 and equivocal for the induction of micronuclei in the absence of S9 in a non-GLP-compliant in vitro micronucleus screening test. In the in vivo mammalian erythrocyte micronucleus test, the phosphate salt of ilunocitinib was administered to mice at doses of 0, 500, 1000, or 2000 mg/kg bw/day. The 500 and 2000 mg/kg bw/day treatment groups exhibited statistically significant increases in the frequency of mean micronucleated polychromatic erythrocytes (PCEs) compared to the negative control. While the mean micronucleated PCEs were within the historical negative control range and no clear dose-related increase was observed, all criteria for classifying a test substance as clearly negative were not fulfilled (that is, statistically significant increases in the frequency of micronucleated immature erythrocytes were noted in some groups compared with the concurrent negative control). Therefore, the results were equivocal.

As the free base rather than the phosphate salt is being used for therapeutic use, ilunocitinib was additionally investigated in an in vitro mammalian micronucleus test in human peripheral blood lymphocytes. Ilunocitinib induced micronuclei in the absence or presence of metabolic activation. Additional mechanistic analysis determined that the observed increase was the result of aneugenic events.

Based on the findings of the new in vitro study, the applicant concluded as follows:

- ilunocitinib induced micronuclei (MN) in vitro in cultured human lymphocytes;
- additional mechanistic analysis determined that the observed increase was the result of predominantly aneugenic events;
- the pattern of in vitro results (no induction of gene mutations or chromosomal aberrations, but induction of MN via an aneugenic mode of action) is consistent with the therapeutic mode of action as a kinase inhibitor;
- since aneugens primarily affect non-DNA targets they are accepted as exhibiting a threshold, and exposures below the threshold would not be expected to induce genotoxic effects.

In the second bone marrow in vivo micronucleus test in mice using the free base, a statistically significant increase in micronucleated PCEs compared to the vehicle control following treatment with ilunocitinib at 2000 mg/kg bw/day were observed. No increase was observed at any of the other doses. It is concluded, therefore, that ilunocitinib was positive in the in vivo micronucleus test in mice. In this study, no genotoxic responses were seen at doses up to 1000 mg/kg/day. Taking into account the aneugenic mode of action, it is argued that there would be a threshold below which there would be no genotoxic risk, and the 1000 mg/kg/day dose can be considered to be a no-effect dose. The mean C_{max} at this dose in mice was 9.65 µg/ml. In contrast, the mean C_{max} for ilunocitinib from the pharmacokinetic study in dogs administered a therapeutic dose of 0.8 mg/kg bw was 0.3 µg/ml. The C_{max} in dogs administered the maximum recommended dose is over 30 times lower than the plasma exposure at the no-effect dose for MN induction. Since the mode of action is aneugenic, and therefore exhibits a threshold, the applicant concludes that there would be no genotoxic risk at therapeutic exposures.

Based on the results of the genotoxicity tests, it can be concluded that ilunocitinib is an aneugen and therefore has genotoxic potential. Further, noting the aneugenic mode of action, a threshold for such effects is expected and, indeed, the results of the second in vivo micronucleus test suggest that there is a practical threshold for this genotoxic effect. While the original bone marrow in vivo micronucleus test detected statistically significant increases in the frequency of mean MN PCEs compared to the negative control in the lowest treatment group, i.e. 500 mg/kg bw/day, the result was not considered to be biologically relevant as the increase was minor and fell within the historical negative control range. Noting also that no statistically significant increase in MN PCE frequency was seen at the mid-dose (1000 mg/kg/day), and that this was consistent with the observation in the second in vivo mouse micronucleus test using the free base, where no genotoxic responses were seen at doses up to 1000 mg/kg bw/day, a no observed genotoxicity effect level (NOGEL) of 1000 mg/kg bw/day for an aneugenic effect is accepted. When calculating an MOE based on dose administered, a NOGEL of 1000 mg/kg bw compared against the maximum recommended dose of 0.8 mg/kg bw results in a safety margin of 1250 for the target animal. Noting that aneugens act primarily on proteins involved in cell division in a concentration-dependent manner, it is considered that an adequate margin of safety between the observed aneugenic threshold for ilunocitinib and the therapeutic dose administered to the target species on a long-term daily basis exists. The potential risk for the user due to the aneugenic effect is discussed under 'user safety' below.

Carcinogenicity

No carcinogenicity data have been provided. Although ilunocitinib was confirmed as having an aneugenic effect, this effect is concentration dependent. The observed aneugenic threshold for ilunocitinib greatly exceeds the therapeutic dose administered to the target species. In the absence of structural alerts for carcinogenicity, together with the absence of proliferative changes in the repeat-dose toxicity studies and as there was no evidence of mutagenic potential in a standard battery of genotoxicity studies, the absence of carcinogenicity data can be accepted.

Other requirements

Special studies

Based on the results of the in vitro and in vivo GLP-compliant studies provided, it can be accepted that neither ilunocitinib nor the final formulation of Zenrelia are anticipated to cause irritation to the skin or eyes. As the results of the in vitro skin sensitisation tests were inconclusive an in vivo skin

sensitisation test (local lymph node assay) in the mouse was performed. The results of the study indicate that ilunocitinib is not a sensitiser.

Although it is noted that no skin sensitisation studies have been conducted with the final formulation, it is considered that the data provided indicate that the candidate VMP is highly unlikely to cause local irritation or skin sensitivity. The tablets are film-coated, which will limit dermal contact with the active substance and most of the excipients. The applicant has also provided data which demonstrate that expected loss/friability due to breaking (where split tablet dosing is required) is minimal.

Observations in humans

No human data are available for ilunocitinib.

However, JAK inhibitors are commonly used in human medicine, which differ with regards to selectivity to various JAKs. JAK inhibitors developed for human therapeutic indications are devoid of genotoxicity and carcinogenicity, and the effects observed in developmental toxicity studies are considered as an expected consequence of the pharmacological activity. Toxicity profiles in rodents and in non-rodent species are driven by the pharmacological potential of the distinct type(s) of on-target (JAK) inhibition.

Excipients

The excipients included in the final formulation are commonly used in veterinary as well as in human medicinal products and are not considered to represent any risk for human safety. Skin and ocular irritation tests using the final formulation of Zenrelia showed no evidence of irritation to the skin or eyes. The applicant has stated that all of the excipients and coating materials are known to be non-sensitising. Considering that the excipients are of limited toxicological potential, the substance of interest regarding user safety is the active ingredient, ilunocitinib.

User safety

A user safety assessment has been provided, in accordance with the CVMP 'Guideline on user safety for pharmaceutical veterinary medicinal products' (EMA/CVMP/543/03-Rev.1).

It is accepted that the excipients included in the proposed final tablet formulation are widely used in approved and marketed veterinary and human pharmaceutical products, and none are anticipated to be a human user safety concern. Therefore, the substance of interest regarding user safety is the active ingredient, ilunocitinib.

With regards to the quantitative risk assessment, three 15 mg tablets (i.e. a total dose of 45 mg ilunocitinib) was considered appropriate for use in worst-case scenario calculations. In addition, the potential risk of accidental ingestion of unused divided tablets by children was also considered.

In the rat developmental toxicity study, a LOEL of 1 mg ilunocitinib/kg bw was determined for skeleton malformations. A BMDL of 0.86 mg/kg bw/day for major developmental abnormalities in rats was used as a point of departure (POD). The BMDL POD was chosen as toxicological reference value (TRV) to address all user safety-related risks.

Using the suggested worst-case scenario involving accidental ingestion of three 15 mg tablets (intended for a very large dog weighing 62.5–74.9 kg), and the BMDL POD of 0.86 mg/kg bw as the TRV, the margins of exposure (MOE) for a 60 kg adult and 10 kg child were calculated. The resulting MOEs for oral exposure were below or around 1 (0.19–1.15), thus indicating a potential risk to users and/or children.

The potential risk of accidental ingestion of unused divided tablets by children or adults has also been considered. Assuming accidental ingestion of half a 15 mg tablet, and 0.86 mg/kg bw as the TRV, MOEs below the acceptable threshold of 100 are calculated, i.e. 1.15 for a child and 6.88 for adults. This indicates a potential risk to users and/or children. For this scenario, it should be noted that, in relation to the potential for aneugenic effects, a threshold of 1000 mg/kg bw as a TRV would result in an MOE of 1333 for a child and 8,000 for adults, indicating an acceptable risk.

The MOEs determined for dermal exposure are all well above the margin of 100, and therefore no risk is identified for this scenario.

Adverse effects have been observed in humans after long-term exposure to other JAK inhibitors (e.g. blood and lymphatic system disorders, viral, fungal, and bacterial infections, gastrointestinal disorders, thrombosis, pulmonary embolism). As it is unknown to what extent these adverse effects could also occur after short-term exposure of children to ilunocitinib, and in order to reflect the very low margin of exposure following accidental ingestion, appropriate wording has been included in section 3.5 of the SPC:

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

Notwithstanding the low MOEs, the risk for accidental ingestion of the VMP (ilunocitinib) by an adult user (including a pregnant woman) is considered highly unlikely. In addition, noting that the product is presented as a film-coated tablet, hand-to-mouth exposure may be considered negligible where elementary personal hygiene measures are maintained (e.g. washing hands after use).

With regards to accidental ingestion by a child, the risk from tablets will be partly mitigated by the presentation of Zenrelia tablets in a child-resistant packaging. Indeed, the applicant has provided certification that the blister packaging conforms to ISO 14375. Nonetheless, the following additional warning in section 3.5 of the SPC is included:

"*Keep tablets and unused half tablet in the original packaging until next administration, in order to prevent children from getting direct access to the veterinary medicinal product.*"

Regarding divided tablets, the SPC states that tablets can be divided in half to reach the recommended dose for the dog. The proposed warning further mitigates against children obtaining direct access to the unused half tablet.

Environmental risk assessment

The applicant has conducted an environmental risk assessment in accordance with the CVMP 'Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38' (EMA/CVMP/ERA/418282/2005-Rev.1- Corr.1) and VICH GL6. The assessment can stop at Question 3 of Phase I, as the candidate VMP is intended only for use in non-food-producing animals, i.e. dogs.

No specific environmental warnings are considered necessary, and the standard text relating to disposal of unused product is proposed for inclusion in the SPC of the candidate product and this is considered acceptable. Adverse environmental events are not anticipated when the instructions included in the proposed SPC are followed.

Overall conclusions on the safety documentation:

Pharmacology:

Pharmacodynamics and pharmacokinetics are addressed in part 4.

Toxicology:

- The acute oral LD_{50} for ilunocitinib in rats was estimated to be > 2000 mg/kg bw.
- The potential systemic effects following sub-chronic and chronic oral exposure to ilunocitinib have been comprehensively investigated in the rat and dog. The studies conducted were GLP-compliant, conducted in accordance with OECD TG No. 407 (rat) and VICH GL43 (dog). Pharmacological effects of ilunocitinib started at low doses, with clear effects on the haematopoietic and lymphatic system. Clinical signs such as bodyweight reduction, bone marrow toxicity, erosions and ulcerations in the gastrointestinal glands and skin lesions were interpreted as "exaggerated pharmacological effects" by the applicant and considered adverse in severity. The applicant suggests that effects at the low doses are related to pharmacological activity of the active substance and therefore may be considered non-adverse. While technically this may be the case (effects related to JAK inhibition), the effect is manifest in tissues that are not the target of interest and, in the CVMP's view, such effects should be viewed as toxicity.
- Target animal safety is addressed in part 4.
- In the developmental toxicity study in rats, foetal skeletal malformations were seen at 1 mg/kg bw and above. Low numbers of visceral abnormalities were found in the low and mid-dose groups, but not in the high dose group. In contrast to the skeletal abnormalities, these findings were not dose-dependent, very rare and were therefore seen as spontaneous findings. A BMDL of 0.86 mg/kg bw/day for major developmental abnormalities in rats was proposed as a point of departure. In rabbits, no malformations were detected. Section 3.7 of the proposed SPC therefore includes a clear statement that reproductive safety of ilunocitinib has not been studied and that use in such breeding/pregnant dogs or those intended for breeding is not recommended. In addition to that statement, information advising of the developmental findings in rats is included in section 3.7 of the SPC.
- The potential genotoxic effects of the phosphate salt of ilunocitinib have been investigated in three in vitro tests for mutagenicity and clastogenic potential in *S. typhimurium* and one in vivo test (micronucleus test in bone marrow cells of the mouse). In addition, an in vitro micronucleus assay using human lymphocyte cultures and an in vivo mouse micronucleus test investigating the genotoxic effects of ilunocitinib were also provided. Based on the results of the genotoxicity tests, it can be concluded that ilunocitinib is not mutagenic or clastogenic, but an aneugen and therefore has genotoxic potential. However, noting the aneugenic mode of action and in the absence of mutagenic or clastogenic effects, a threshold for such genotoxic effects is expected.
- Studies on carcinogenicity were not conducted for ilunocitinib. This is justified based on the absence of structural alerts for carcinogenicity in the compound; no evidence of mutagenicity in the battery of tests conducted; a threshold for aneugenic effects and the absence of proliferative changes in the repeated target animal safety in dogs.
- Ilunocitinib (including the final tablet formulation) was non-irritating in in vivo ocular and dermal irritation studies. A skin sensitisation test (local lymph node assay) in the mouse was performed to investigate the skin sensitisation potential of ilunocitinib. It was concluded that the active substance does not have sensitisation potential.

User safety:

A user safety assessment has been provided in accordance with the CVMP 'Guideline on user safety for pharmaceutical veterinary medicinal products' (EMA/CVMP/543/03-Rev.1).

It is accepted that the excipients included in the proposed final tablet formulation are widely used in approved veterinary and human marketed pharmaceutical products, and none are anticipated to be a human user safety concern. Therefore, the substance of interest regarding user safety is the active ingredient, ilunocitinib.

The MOEs determined for dermal exposure are all well above the margin of 100, and therefore no risk is identified for this scenario. The worst-case scenario for user safety is accidental ingestion of three tablets by a child, with an estimated MOE of 0.19. A risk to the user following accidental ingestion of half tablets was also identified. Regarding the potential for aneugenic effects, the MOE is 1,333 for a child indicating an acceptable risk. The product is presented in child-resistant blisters and appropriate safety advice/warning statements are included in the SPC to mitigate the risks.

The CVMP concludes that the product is not expected to pose a risk to the user when used in accordance with the SPC.

Environmental safety:

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.

Part 4 – Efficacy

Pre-clinical studies

Zenrelia is presented as film-coated tablets containing 4.8, 6.4, 8.5 or 15 mg ilunocitinib, a novel Janus kinase inhibitor. Zenrelia is intended for use in dogs for the treatment of pruritus associated with allergic dermatitis and clinical manifestations of atopic dermatitis. The proposed dose is 0.6-0.8 mg/kg bw by once daily oral administration.

Ilunocitinib 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.

Animal welfare concerns were noted in a number of pre-clinical studies, some of these being deviations from the relevant Directive 2010/63/EU. While these studies were compliant with local welfare regulations, studies presented in support of applications for marketing authorisation in the European Union should be conducted as detailed in Annex II to Regulation (EU) 2019/6, Section I.1.7: "*All experiments in animals shall be conducted taking into account the principles laid down in Directive 2010/63/EU, notwithstanding the place of conduct of the experiments*". Deviations from Directive 2010/63/EU noted by the CVMP include inadequate cage sizes, individual housing in US conducted studies and one in Australia, and the use of inappropriately-sized gavage equipment leading to reflux/aspiration and ultimately unscheduled death of three animals in the non-GLP pilot TAS study conducted in the EU.

Pharmacology

Pharmacodynamics

Ilunocitinib 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 JAK 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. To date, only one JAKi, oclacitinib, has been approved in veterinary therapeutics.

In vitro kinase tests compared ilunocitinib with oclacitinib and determined its JAK selectivity. Similar to oclacitinib, ilunocitinib was found to be non-selective. The below table shows the IC50 values of ilunocitinib for JAK1, 2, 3 and TYK2. The same study indicated that ilunocitinib was not a significant inhibitor of other protein or lipid kinases.

Estimated IC_{50} values (nM)

Kinase	JAK1	JAK2	JAK3	TYK2
Ilunocitinib	1	1	16	4
Oclacitinib	7	67	110	67

The effects of ilunocitinib on cytokines involved in innate and acquired immunity were also examined *in vitro*. Ilunocitinib showed potent, minimally selective inhibition of all cytokines tested.

Both ilunocitinib and oclacitinib had similar functional impacts on JAK signalling; however, ilunocitinib was found to be of higher potency.

Overall, ilunocitinib has been demonstrated to have similar inhibition pathways as many registered JAKi, including oclacitinib. It has been shown to have equipotent inhibition on JAK1 and 2, high potency against TYK2 and little inhibitive effects on JAK3.

The CVMP notes that the pharmacological action of ilunocitinib also includes effects on other cytokines not related to allergic/pruritogenic mechanisms (for example, those involved in host defence or haematopoiesis), which may have the potential for unwanted effects. The text in section 4.2 of the SPC (Pharmacodynamics) includes the following statement regarding the potential risks to the target animal resulting from the immunomodulatory and haematopoietic effects of ilunocitinib:

"*Ilunocitinib may also exert effects on other cytokines (for example, those involved in immune defences or haematopoiesis), which may have the potential for unwanted effects.*"

Pharmacokinetics

The applicant has conducted a battery of *in vitro* and *in vivo* studies to characterise the pharmacokinetic properties of ilunocitinib. Parameters including absorption, distribution, metabolism and excretion of the active substance were evaluated 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. Pharmacokinetic parameters were also compared between formulations, at different stomach pH levels, and fed vs. fasted conditions in the target species.

Ilunocitinib showed weak plasma protein binding (approx. 50%) in vitro. Results were comparable for all species tested (dog, cat, rabbit and rat).

Intestinal permeability was shown to be moderate to high and while ilunocitinib is a substrate of gastrointestinal efflux transporter, p-glycoprotein activity does not appear to impact ilunocitinib absorption due to its high permeability and high oral bioavailability.

After IV administration of 0.8 mg/kg bw to dogs, ilunocitinib had a low plasma CL of 437 ml/h/kg. The volume of distribution was 1.58 L/kg and terminal half-life was 4.4 hours.

After oral administration of 0.8 mg/kg bw ilunocitinib using the final tablet formulation in fasted dogs, the absolute bioavailability was 58%. The elimination half-life was 5.4 hours. In fed dogs, oral bioavailability increased up to 80%, showing a similar elimination half-life as observed in fasted dogs (5.0 hours).

In general, T_{max} generally occurred between 1 and 4 hours.

After oral administration of 0.4, 0.8, 1.6, 2.4, and 4.0 mg ilunocitinib/kg bw as the final tablet formulation to fasted dogs, a less than dose proportional increase of exposure (C_{max} and AUC) was observed from 0.4 to 2.4 mg/kg bw dose and an approximately proportional increase of exposure from 2.4 to 4.0 mg/kg bw dose. Following daily administration of 0.8 mg ilunocitinib/kg bw as final formulation to fasted dogs over 10 days, no significant change in exposure of ilunocitinib was observed. This indicates that significant accumulation is not anticipated at the recommended therapeutic dose (RTD). However, it is noted that for one individual, significant accumulation was observed (5.66 for dose-normalised (DN) C_{max} and 3.39 for DN AUC_{0-24}). However, given that accumulation ratios based on C_{max} and AUC_{0-24} values were below 1.6 for all other dogs in study and also considering the results of the pivotal TAS study, the CVMP can accept that the high accumulation ratio observed for this dog can be considered an isolated incident and is not expected to impact target animal safety.

After oral administration of 0.8, 2.4, and 4 mg/kg bw with the final tablet formulation to fed dogs, also a less than dose proportional increase of exposure (C_{max} and AUC) was observed from 0.8 to 4.0 mg/kg bw dose. After oral administration of 0.8, 1.6, 2.4 and 4.0 mg/kg bw in the pivotal TAS study (final formulation tablets administered in fed conditions), exposure increased with dose and the deviation from dose proportionality was small.

Following oral administration daily for 10 days of 0.8 mg/kg bw as the final formulation to fasted dogs, no relevant change in exposure of ilunocitinib was observed, indicating absence of significant accumulation. Indeed, given the short terminal half-life of approximately 5 hours, no significant accumulation was expected under this proposed dosing regimen. These findings were further verified in the pivotal TAS study, where the final tablet formulations were administered daily in fed conditions for 182 days.

No relevant sex-or age-dependent differences in exposure of dogs were observed.

Inter- as well as intraindividual variability between animals was high after oral administration to fasted dogs with reduced variability observed in fed conditions.

Assessment of *in vivo* organ distribution after oral administration of 0.8 mg/kg bw [^{14}C]-ilunocitinib to Beagle dogs showed that the radioactivity was rapidly and widely distributed from blood to tissues/organs. Blood-brain-barrier penetration was low. High amounts of radioactivity were found in

the bile, liver and kidney. At 120 hours after oral administration, most of the radioactivity was eliminated from the body. [^{14}C]-ilunocitinib related radioactivity was excreted in dogs via the biliary/faecal route, with approximatively 50% eliminated within 48 hours. Excretion of radioactivity into urine amounted to approximately 30% of the entire clearance of drug related material. In urine and faeces, parent drug was the main component. Di-hydroxylation in combination with reduction led to several minor metabolites. Radioactivity present in dog plasma was mainly covered by parent drug (about 71% of AUC).

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

Dose determination and confirmation

Dose justification

A dosage of 0.6-0.8 mg ilunocitinib/kg bw by once daily oral administration was selected based on the results of laboratory efficacy studies and a pilot field study conducted with varying dosages of ilunocitinib (0.1-0.8 mg/kg bw) given daily to dogs. All studies showed superior efficacy by improvement in lesion and pruritus scores in the dosage range of 0.6-0.8 mg ilunocitinib/kg bw daily compared to other ranges (0.1-0.6 mg/kg bw) and compared to a placebo.

Dose determination studies

The applicant has conducted a thorough and appropriate dose determination program, which assessed efficacy of a range of doses (0.1–1.2 mg/kg bw ilunocitinib) in different models and naturally occurring disease. Overall, the studies were considered to have been well-conducted.

In a 28 day GCP-compliant dose determination study conducted under field conditions, once daily ilunocitinib was tested at three different dosages (0.25 - 0.4 mg/kg bw, 0.4 - 0.6 mg/kg bw and 0.6 - 0.8 mg/kg bw) using a close to final tablet formulation compared to placebo. The study was conducted in the US in 173 client-owned dogs with allergic pruritus. To be included in the study, dogs were to have a pruritus score of $\geq$6 on a validated visual analogue scale (PVAS) with scoring ranging from 0 (normal dog) to 10 (extremely severe itching). A total of 173 dogs were included (43 placebo, 44 low dosage, and 43 each in the medium and high dosage groups).

The efficacy was assessed by owners using PVAS and a Response to Treatment (RTT) visual analogue scale which ranged from 0 to 10 and by the recruiting veterinarian using CADESI-4 (a scale for assessing skin lesions) and a RTT scale.

The primary endpoint was the improvement of the pruritus based on owner assessment and success was defined as a reduction of 2 points on the PVAS on at least 70% of the first seven assessment days (i.e. at least five of the first seven assessment days).

For the primary efficacy variable, there was a clear dose/effect response with treatment success increasing with increasing dose of ilunocitinib. Of the dogs in the high dose (0.6-0.8 mg/kg bw) group, 71.9% were defined as successfully treated (reduction of 2 units in PVAS on 5 of the first 7 days) which was significantly higher than the placebo group (29.4%; p=0.0006). The difference from placebo to the medium dosage group was also significant, however there was an overlap of confidence intervals between this and the placebo group, suggesting that this dose may be inadequate for reduction in pruritus.

The high dose group was the only group associated with an at least 50% improvement in pruritus in more than 50% of the treated dogs. According to published literature (Olivry et al., 2018), this outcome measure is usually considered more significant than a two-unit reduction of the pruritus score.

For investigator assessment of skin lesions based on CADESI-4, a statistically significant improvement in lesion score relative to the placebo was demonstrated for all treatment groups. Indeed, the improvement of this parameter in the medium and higher dosage groups were similar at 76 and 77%, respectively ($p<0.0001$). That is, the findings of this study would suggest that a dose of 0.4-0.6 mg/kg bw is as effective as a dose of 0.6-0.8 mg/kg bw for improvement in skin lesions (based on investigator assessment). Similarly, overall response to treatment, as assessed separately by the owner and the investigator, indicated significant improvement for all ilunocitinib treatment groups, relative to placebo, with comparable improvements noted for the 0.4-0.6 mg/kg bw and 0.6-0.8 mg/kg bw dose groups.

It is agreed that the oral dose rate of 0.6-0.8 mg/kg bw ilunocitinib administered once daily is likely to be an effective dose for the treatment of canine pruritus. Noting the results for the primary efficacy parameter, selection of 0.6-0.8 mg/kg bw as the dose for the pivotal studies can be followed. However, as noted above, for the other efficacy parameters evaluated, ilunocitinib at a dose of 0.4-0.6 mg/kg bw was found to be as effective as ilunocitinib at a dose of 0.6-0.8 mg/kg bw.

Regarding the proposed once daily treatment, available data suggest that a dose less than that proposed may not be effective for the full 24 hours. In one house dust mite model study, the data suggest that the effect of the 0.4 mg/kg bw dose was wearing off by 20-22 hours post-dosing. That is, these data suggest that a dose of >0.4 mg/kg bw is required to maintain effect up to 24 hours.

The RTD has been justified and the selected dose range of 0.6-0.8 mg/kg bw ilunocitinib is suitable for further evaluation in subsequent TAS and clinical field studies to confirm safety and efficacy under clinical conditions.

Dose confirmation studies

Based on the conclusions of the dose determination studies, the applicant selected a dose of 0.6 – 0.8 mg/kg bw ilunocitinib administered orally once daily for the treatment of pruritus associated with allergic dermatitis and treatment of clinical manifestations of atopic dermatitis to be progressed for continued development and for use in the three clinical trials which also served as dose confirmation studies. See Part 4B for assessment of these studies.

Tolerance in the target animal species

The tolerance of ilunocitinib was tested in three pre-clinical TAS studies and in an additional study addressing the potential effect on vaccination.

In both the pivotal and pilot tolerance studies, pharmacokinetic analyses indicated that all animals were exposed to ilunocitinib.

Study 1

The objective of this non-GLP-compliant pilot TAS study was to provide information on the target species tolerance of ilunocitinib (suspension, non-final formulation) when given orally by gavage for 6 months to fasted Beagle dogs (9-months old). Dogs received either the maximum recommended dose of 0.8 mg/kg bw (1X, group 2) and multiples thereof, 2.4 mg/kg bw (3X, group 3) and 3.6 mg/kg bw

(4.5X, group 4) or vehicle (0X, group 1). On Day 64, the dose of group 4 was decreased from 3.6 to 1.6 mg/kg bw (2X) due to poor general health conditions in this group.

The following endpoints were evaluated: faeces, body weight, food consumption, ophthalmology, electrocardiography, body temperature, clinical pathology, Coombs test, immunophenotyping, acute phase protein (CRP), pharmacokinetic, gross necropsy and histopathology, as well as organ weights.

Three dogs (two males treated at 2.4 mg/kg bw/day and one female treated at 3.6 mg/kg bw/day) were euthanised during the study because of rapid decline in health which manifested as weight loss, apathy, breathing difficulties, increased body temperature and changes in clinical pathology suggestive of inflammation. Necropsies were carried out in each case and revealed very similar changes of acute lung inflammation. In two animals, there was evidence of foreign material and/or bacteria suggesting the possibility that the test item was aspirated or reflux from the stomach had occurred. The ante- and post-mortem findings, including histopathology, are consistent with gavage error. Reported observations such as lethargy, pyrexia, shallow breathing, tachypnoea, and mucosal pallor are all suggestive of pathological processes in the respiratory system. Microscopic examination revealed acute and severe inflammatory changes in lung tissue, with foreign material and bacterial colonies present. The applicant has also cited published literature to support their argumentation that pulmonary lesions such as bronchopneumonia with or without foreign material present can commonly be seen in toxicity studies where gavage administration is used.

It is therefore accepted that the 3 unscheduled deaths in this pilot TAS study were related to gavage error, rather than a direct toxicological effect of ilunocitinib.

In the remaining animals, minor clinical signs were observed, such as a thin appearance (without effect on the body weight), discoloured or dry gums or ears and vomiting. Some minor faecal changes were also reported. Red blood cell parameters as well as proportion of lymphoid cells were decreased in some dogs in all ilunocitinib treated groups. Decreased ALT and cholesterol were also sometimes noted. Histological examination revealed an increased incidence of and severity of erythropoiesis in the spleen. There was no clear dose-relationship for many of these changes, and variability between individuals was high.

While the 1X RTD of 0.8 mg/kg bw appeared generally well tolerated, treatment-related effects (although mild) were observed at that dose: these included vomiting, effects on RBC parameters, T-cytotoxic cells and abnormalities of the spleen. These findings were similar to those observed during toxicity studies in laboratory animals and pharmacokinetic studies in the target species.

Study 2

A GLP-compliant pilot TAS study was conducted to evaluate the safety of ilunocitinib when administered once daily orally, in fasted conditions, as tablets (preliminary formulation), to 12-month-old Beagle dogs for a minimum of 182 consecutive days. This was a well conducted and comprehensive safety study (according to VICH GL43). Eight dogs per group received 0X (sham dosed), or 1X, 3X, 4X or 5X the maximum recommended dose of 0.8 mg/kg bw ilunocitinib. Similar parameters as for the previous study were assessed.

During the study, 13 serious adverse events were reported. Most of these events were diagnosed as infected interdigital cysts requiring treatment with antibiotics. One such event occurred in an animal in the 1X dose group and occurred with higher frequency in higher dose groups. Three of the serious adverse reactions, namely two occurrences of gum infections and one of generalized demodicosis, relate to one dog in the 4X group (3.2 mg/kg bw). These side-effects should be considered drug-related because of the known pharmacological (immunosuppressive) effects of JAKi.

Other clinical observations observed in treated dogs included papillomas, skin papules, pododermatitis, swollen foot and lymph node enlargement. All of the above observations in males were considered treatment-related; however, in females only papillomas, pododermatitis and interdigital cysts were considered associated with treatment.

With regards to haematology parameters, decreased red blood cell counts, haematocrit and haemoglobin were seen, particularly in males in the 3X, 4X and 5X groups. The occurrence of infected skin lesions coincided with other changes such as increased fibrinogen, decreased albumin and increased C-reactive protein (parameters associated with inflammation). Most of the other abnormalities were not considered treatment-related, were minor and often present in only several individuals.

Although no clear dose response was observed, lower mean spleen weights, correlated microscopically with decreased lymphoid cellularity, was noted in all ilunocitinib-treated groups. Similar findings were noted in the previous study.

Based on the toxicokinetic data generated in this study, concentrations of ilunocitinib increased with increasing dose, but were generally less than proportional relative to dose. In addition, there was no apparent increase in systemic exposure on Day 182 relative to Day 1, indicating similar exposure (no accumulation) after 6 months of dosing.

Based on the results of this study, oral (tablet) administration of ilunocitinib to Beagle dogs at dosage levels of 0.8, 2.4, 3.2, and 4.0 mg/kg bw/day for 182 or 183 consecutive days resulted in clinical observations, effects on haematology, coagulation, and serum chemistry, gross findings, effects on spleen weights, and histologic findings for males and females at all dosage levels that were attributed to the immunosuppressive effects of ilunocitinib. While effects were generally mild in the 0.8 mg/kg bw group, there is the potential for clinically relevant effects: lesions such as papilloma and interdigital cysts did occur at that dose. In addition, it is noted that a case of generalised demodicosis was observed in one dog administered 3.2 mg/kg bw.

Study 3

This was a pivotal GLP-compliant TAS study, designed and conducted in accordance with VICH GL43 and OECD Guideline 417. The study was conducted in fed animals, as the PK studies demonstrated higher bioavailability of ilunocitinib in fed animals. The test article was the final formulation.

The study lasted approximately 6 months and was conducted in 11 to 12-month-old Beagle dogs. Dogs received 0X (sham dosed), 1X, 2X, 3X or 5X the maximum recommended dose of 0.8 mg ilunocitinib/kg bw once daily. Safety in the target species was assessed through the following parameters: mortality, clinical signs, physical and neurological examinations, body weights, body weight gains, food consumption, ophthalmology, clinical pathology parameters (haematology, coagulation, serum chemistry, urinalysis, and C-reactive protein), leukocyte analysis (peripheral blood immunophenotyping), toxicokinetic parameters, gross necropsy findings, organ weights, and histopathologic examinations.

No treatment-related effects were observed on ophthalmoscopic examination, physical and neurological examinations, urinalysis or leukocyte analysis (immunophenotyping). All animals survived to scheduled necropsy.

Ilunocitinib-related clinical findings observed in both males and females when the test item was administered at overdose included skin lesions, skin lesions with discharge, swollen paws, skin thickening, skin discoloration or scabbing of the feet (paws/digits). The frequency of clinical findings in animals in the 0.8 mg/kg bw group was low, increasing with increasing dose. Most foot lesions were diagnosed as interdigital cysts by the veterinarians. Interdigital cysts in most animals were resolved by

standard treatments, except for two animals. While this clinical condition may be observed in normal animals at lesser frequency, there is a clear treatment-related effect which is considered related to the pharmacologic effect (immunomodulation) of ilunocitinib.

Ilunocitinib-related effects on coagulation and clinical chemistry parameters included higher C-reactive protein (CRP), total protein and globulin concentrations; lower albumin:globulin ratios and higher fibrinogen and lower albumin concentration (with concomitantly lower calcium concentration) were not considered adverse and collectively indicative of an acute phase response.

Based on the findings of this study, the applicant concluded that the highest tested dose 4 mg/kg bw can be considered a NOAEL because the effects observed can be attributed to the pharmacological (immunomodulatory) effects of the active substance. While the CVMP can accept that the treatment related effects seen can be explained by the immunomodulatory effect of the substance, a number of the effects observed should be considered adverse. Indeed, while the 0.8 mg/kg bw dose was generally well tolerated, effects (albeit mild) that may be considered treatment-related were detected in the 0.8 mg/kg bw dose group (consistent with other studies). The proposed NOAEL of 4 mg/kg bw for dogs based on this study is not accepted.

Interestingly, it is noted that no histopathological findings relating to the spleen were reported in this study. Given that observations such as reduced spleen weight, decreased lymphoid cellularity, increased erythropoiesis, and pigmentation were recorded for all dose levels of ilunocitinib in both the non-GLP and GLP pilot TAS studies, this finding was unexpected. The applicant has stated that the histopathological findings for the spleen reported in both the non-GLP and GLP pilot TAS studies were limited to those studies and not repeated in the pivotal TAS study. It is also noted that histological changes in the spleen were highly variable in the pilot studies. The applicant has also cited published literature to support their position that splenic changes of a subtle nature, such as extramedullary haematopoiesis (EMH), are sparse in the dog. Indeed, it is claimed that EMH is not seen in dog spleens even in studies in which the spleen is a target organ and the applicant has questioned the relevance of such findings in the pilot studies (also considering that the majority of published data relate to rodents). References from published literature (Haley, 2017; Sato, 2012) support a lack of veracity for these findings in the dog, and the applicant suggests that the term may have been incorrectly inferred by pathologists more accustomed to evaluating rodent spleens (where EMH is an accepted finding). Based on the totality of evidence presented, the CVMP accepts that these histopathological findings lack repeatability, and no clear dose relationship was seen. As no pathological correlates to the splenic changes were observed across the TAS studies conducted, the CVMP agrees that the changes observed were not clinically relevant.

Also in one study, histopathology at necropsy revealed ten total instances of changes in the lung (encompassing eight animals) – these were all focal, minimal in scope, and noted across 0X, 1X, 3X and 5X groups. In two animals (5X, M and 5X, F), a single pale focus was noted grossly and correlated with a non-specific, minimal infiltrate of inflammatory cells. The applicant interpreted these findings as not being treatment-related, as such low levels of infiltrates can commonly be seen in normal populations. The applicant cited published literature indicating that focal, minor accumulations of mononuclear inflammatory cells are a recognised background lesion in Beagle dogs. It is noted that mononuclear cell infiltrates were reported in both control and ilunocitinib animals. While the incidence and scope of these specific lesions was consistent with background, a number of ilunocitinib dogs did present lesions which were not recorded in the control group. It is argued that the acute alveolar inflammation in six of the ilunocitinib-treated animals was in fact a precursor of the mononuclear cell infiltrates observed in both control and ilunocitinib-treated dogs (the incidence and scope of which were consistent with background levels reported in published literature). Considering that no clinically

relevant signs were noted in these animals which would indicate pulmonary compromise, the CVMP can accept that these findings may not be considered adverse.

Study 4

This GLP-compliant TAS study was conducted to evaluate the response to primary vaccination in 10-month-old vaccine naïve Beagle dogs (4/sex/group) administered 0 or 2.4 mg/kg bw (i.e. 3X the maximum recommended dose) of the final formulation of ilunocitinib tablets for 89 days. The enrolled animals were raised specifically for use in this study, and were confirmed as seronegative to CDV, CPV, CPiV, CAV-2, and rabies prior to the start of the study.

The results of this study were heavily confounded by infection with *Isospora canis,* the causative agent of coccidiosis, in all animals in the test article group (starting Day 26). Despite the poor clinical condition of the dogs in the test article group, the responses to primary vaccination for canine adenovirus (CAV-2), canine distemper virus (CDV), canine parainfluenza virus (CPiV), and canine parvovirus (CPV) were similar to responses in control dogs. However, a delayed response was observed to primary vaccination for rabies virus (RV) after ilunocitinib treatment. The applicant claims that no impact is expected on dogs treated with ilunocitinib according to the intended product recommendations. Additionally, ilunocitinib is only indicated for dogs aged 12-months or older, who have already received their required vaccine doses for primary immunisation prior to starting treatment with ilunocitinib.

The applicant has also conducted a GRP-compliant study to evaluate the response of ilunocitinib-treated dogs (at 1X and 3X the RTD) in comparison to untreated controls to booster vaccination with modified live CAV-2, CDV, CPV, and inactivated RV vaccines in 10-11 month-old Beagle dogs. There was no significant difference in the antibody titres between the control and both the ilunocitinib dose groups on study day 43, except for CPV titres which were higher in the 1X group compared to the controls. Serological responses in both groups met the non-inferiority criteria compared to the control group on study day 56. Therefore, it can be concluded that the primary and secondary outcomes for serological response were achieved with both ilunocitinib treated groups. The percentage of dogs with adequate immune response (cage average serum titre above threshold) in the ilunocitinib-treated groups was comparable to the control on study days 43 and 56.

Based on the original and supplementary data on primary vaccine and booster responses in treated dogs, section 3.8 of the SPC has been updated as follows:

"The effect of ilunocitinib administration on vaccination with canine parvovirus (CPV), canine distemper virus (CDV), canine adenovirus-2 (CAV-2), canine parainfluenza (CPiV) and inactivated rabies vaccine (RV), has been studied in 10-month-old vaccine naïve dogs, receiving 2.4 mg/kg (3X the maximum recommended label dose) for 89 days. Based on assessment of serological antibody titres, an adequate immune response to canine core Modified Live Vaccines (CAV-2, CDV, and CPV) was observed following primary vaccination on Day 28. Response to primary CPiV (non-core vaccine) vaccination in treated animals was 4 of 6 above threshold vs 6 of 8 controls above threshold following primary vaccination. A delayed or reduced response to RV was observed. The clinical relevance of these observed effects in animals vaccinated while being administered ilunocitinib in accordance with the recommended dosing regimen is unclear. The effect of ilunocitinib on response to booster vaccinations has been studied in 10-month-old previously vaccinated dogs receiving 1X or 3X the recommended label dose (0.6-0.8 or 1.8-2.4 mg/kg, respectively) for 56 days and showed no difference in booster vaccination response between control and 1X or 3X ilunocitinib treated groups."

As rabies vaccines are frequently given to dogs aged over 12 months (e.g. booster vaccines and/or to meet travel requirements), it is agreed that the prescribing veterinarian should be made aware of potential impacts on vaccine efficacy when given to dogs receiving concomitant treatment with

ilunocitinib. The proposed text is considered to be acceptable to the CVMP, noting that similar warnings have been included for oclacitinib.

Two unscheduled deaths occurred in the ilunocitinib-administered group during this vaccine response study. Clinical deterioration in the first animal was reported over the course of the study, starting on day 8 despite continuous therapeutic efforts with several concomitant medications administered at various periods. Post-mortem examination following unscheduled euthanasia at day 52 revealed a colonic intussusception. The applicant has claimed that the severe morbidity noted in this animal was likely due to this intussusception. While the CVMP acknowledges that colonic intussusceptions can be deemed idiopathic in some cases, the applicant's argumentation that a relationship to ilunocitinib administration can be excluded is not accepted. Gastrointestinal parasitism (e.g. coccidial infection) is also a known risk factor in the occurrence of intussusceptions in the target species. The clinical history provided support the possible presence of a low-grade, intermittent intussusception (with episodes of vomiting and diarrhoea, dehydration) which deteriorated dramatically prior to euthanasia.

Clinical signs observed in the second dog including vomiting and/or diarrhoea starting on day 14/21, with worsening of the general health conditions on day 24, and depression and dehydration on day 47. This animal received intensive care and medications until euthanasia on Day 54 for animal welfare reasons. Post-mortem histopathology findings included multifocal necrotising hepatitis with intranuclear hepatocellular inclusion bodies, consistent with lesions seen in Infectious Canine Hepatitis, a condition associated with Canine Adenovirus-1 (CAV-1).

In response to the query raised over a potential link between treatment with ilunocitinib and the risk of vaccine-induced disease following administration of a canine adenovirus vaccine, the applicant has presented a comprehensive body of evidence, including PCR data from the affected animal (811-495) to argue that the clinical signs observed were due to natural infection with CAV-1 rather than the vaccine strain of CAV-2.

The applicant conducted post-mortem PCR testing on stored tissue samples obtained from the dog in question. The CAV-1 specific PCR technique used was non-GLP, however the applicant has provided validation reports which indicate that the assay was fit for purpose.

In brief, the diagnosis of CAV-1 in dog 811-495 was further confirmed following Sanger sequencing and Topoisomerase-based (TOPO) cloning of the CAV-1 PCR bands. The first replicate for dog 811-495 was 100% identical to the CAV-1 challenge strain and the second replicate only differed by a single nucleotide. This single nucleotide difference did not align to the CAV-2 Nobivac vaccine strain either. The CAV-2 Nobivac strain differed from the CAV-1 sequence from the test samples and the challenge strain at 26 nucleotides (27 nucleotides in 811-495 replicate 2). The applicant states that these sequencing results definitively confirm the presence of CAV-1 in the study dogs based on the 99-100% sequence alignment with the CAV-1 challenge strain and only 84% alignment with CAV-2 Nobivac vaccine strain.

Considering the disparate clinical signs associated with CAV-1 and CAV-2 serotypes respectively (i.e., CAV-2 infection generally precipitates mild respiratory symptoms, compared to the potentially severe clinical disease — including hepatic lesions, and peracute death — observed with CAV-1 infections in naïve dogs), the CVMP can accept that the findings for dog 811-495 were not related to the modified live vaccine strain of CAV-2. This is further supported by multiple references to published scientific literature.

It is noted that in September 2024, the US-FDA issued a "Dear Veterinarian" letter to veterinarians in the United States relating to the risk of vaccine-induced disease. However, the cited PCR analysis was conducted subsequent to the publication of this letter (January 2025) – therefore these data were not available to US authorities. On this basis, the CVMP is satisfied that, as argued by the applicant, it is

not necessary to include additional warning regarding risk of vaccine-induced disease in the EU product information for ilunocitinib.

Based on the argumentation provided by the applicant relating to the unscheduled deaths in one study, the immunomodulatory effects of ilunocitinib cannot be excluded as a significant factor in the precipitation of clinical coccidiosis. *I. canis* infection only occurred in animals receiving the ilunocitinib, despite being housed in the same room as the control animals. The CVMP is of the opinion that immunosuppression related to the ilunocitinib cannot be fully excluded as a factor in the clinical signs which pre-empted euthanasia in each case. Nonetheless, it is noted that the risk of opportunistic infections in the target species has been adequately mitigated by the inclusion of the following statement in section 3.5 of the SPC: "*Ilunocitinib modulates the immune system and may increase susceptibility to opportunistic infection. Dogs receiving the veterinary medicinal product should be monitored for the development of infections and neoplasia.*"

Clinical trials

The applicant conducted three multi-site GCP-compliant pivotal clinical trials to assess effectiveness and safety in the field, one in support of the claim for the treatment of pruritus associated with allergic dermatitis and two in support of the claim for the treatment of clinical manifestations of atopic dermatitis. The final tablet formulation was used in all three studies.

The first trial was conducted in the US, to support the claim for the treatment of pruritus associated with allergic dermatitis. The study was double-blinded, and 306 privately-owned dogs received either ilunocitinib at 0.6 - 0.8 mg/kg bw or a placebo orally once daily, either with or without food. The randomisation ratio was 2:1 with 206 dogs receiving ilunocitinib while 100 dogs received the placebo. Ilunocitinib was administered as the final formulation, and certificates of analysis were provided.

For inclusion, dogs had to have a pruritic condition presumed to be associated with allergic skin disease. Atopic dermatitis was the sole presumptive diagnosis in 42.8% of total cases (44.7% ilunocitinib, 39.0% placebo). Other diagnoses included contact dermatitis (23.3% ilunocitinib, 26.0% placebo), flea allergy dermatitis (15.5% ilunocitinib, 19.0% placebo), food hypersensitivity (24.3% ilunocitinib, 27.0% placebo) and other (3.4% ilunocitinib, 5.0% placebo). Diagnosis was made based on examination and medical history and, while there appears to have been limited diagnostic investigations to determine the precise cause of skin disease, the population evaluated in this study can be considered representative of the intended target population (dogs with allergic skin disease). Notwithstanding the fact that this study was conducted in the US, and that there may be some differences between the regions in terms of the frequency at which different allergic skin conditions are diagnosed, it is accepted that the findings can be extrapolated to the EU situation (allergic skin conditions and underlying pathophysiology is expected to be the same).

Pruritus intensity had to be at least 6 (moderate to severe) on a validated scale ranging from 0 to 10 (designated as PVAS=Pruritus Visual Analogue Scale). This is considered an appropriate inclusion criterion. Appropriate wash-out periods were implemented for concomitant medications. It is noted that pregnant or lactating dogs, or those intended for breeding purposes were excluded from the study. This can be accepted, as section 3.7 of the proposed SPC states that safety of ilunocitinib has not been evaluated in such animals, and that its use is therefore not recommended in those circumstances. In addition, reasons for exclusion included malignancy, evidence of immunosuppression (including demodicosis) and 'uncontrolled' systemic disease (e.g. epilepsy, diabetes mellitus, hypothyroidism, etc.). Section 3.5 of the SPC has therefore been appropriately amended to include the following precautions for safe use in the target species:

"*Do not use in dogs with evidence of malignant neoplasia, demodicosis or immune suppression such as hyperadrenocorticism, as the active substance has not been evaluated in these cases".*

"Ilunocitinib modulates the immune system and may increase susceptibility to opportunistic infection. Dogs receiving the veterinary medicinal product should be monitored for the development of infections and neoplasia."

A total of 300 dogs were targeted for enrolment to obtain 240 evaluable cases. A sample size of 240 animals had been estimated, based on a 2:1 allocation ratio of animals to treatment groups, to be sufficient to achieve at least 90% power for detecting a significant difference between the IVP and placebo (160 IVP to 80 placebo control) for the primary outcome variable at a 5% significance level. The calculations assumed 30% and 7.5% success rates on the primary outcome variable for the IVP and placebo groups, respectively. The assumptions for the treatment success rates were based on data from a pilot field study.

The study was conducted in two phases. All dogs first received either ilunocitinib or the placebo for 28 days. Owners were given the option to continue in the trial for an additional 12 weeks, with dogs remaining in the same treatment group as at initial randomisation. Dogs were evaluated by the study veterinarians after 7 and 28 days for the first phase with pruritus assessments performed by the owner from days 1 to 7 and days 14 and 28. In the continuation phase, dogs were rechecked at days 56, 84 and 112. Sampling for determination of plasma ilunocitinib concentration occurred at days 7 and 28.

The primary endpoint for efficacy was treatment success, defined for an individual dog, as at least a 50% reduction from baseline in owner assessed pruritus score (PVAS) on a minimum of 70% of the first seven days of treatment. Notwithstanding that the efficacy endpoint is owner-assessed, it is accepted as being relevant to the proposed indication. At day 7, 25.4% of the ilunocitinib-treated dogs (placebo 7.7%) had achieved at least a 50% reduction of the PVAS on at least 5 out of 7 days of treatment ($p=0.006$). While a significant improvement relative to placebo was detected, the success rate for the IVP group is slightly less than the assumed treatment success rate used in the power calculations. That said, further improvements were noted over time: at day 14, the percentages of dogs with at least 50% reduction were 69% for ilunocitinib-treated dogs and 23% for placebo treated dogs and at day 28, the percentages were 81% (ilunocitinib) and 37% (placebo). In both cases, the differences were statistically significant ($p<0.001$).

At day 28, 187 (out of 206) ilunocitinib-treated dogs (placebo 61 out of 100) were still in the study ($p<0.0001$). Following introduction of the optional continuation phase, 102/123 ilunocitinib-treated dogs (placebo, n:16/20) continued on study to day 112 ($p<0.0001$). When considering a 2-unit reduction in pruritus, by day 2, a statistically significant difference was observed between the groups ($p=0.035$), with 42.9% of dogs in the ilunocitinib group having achieved this improvement, increasing to 79.3% ($p<0.001$) by day 7, and 93.4% ($p<0.001$) at day 28. For the continuation phase, the proportion of ilunocitinib- treated dogs with a reduction of pruritus higher than 50% remained high (84.8% at day 56 and 91.1% at day 112). At day 112, pruritus returned to normal in 80 out of 101 ilunocitinib-treated dogs while only 8 out of 15 placebo-treated dogs remaining on study were considered normal by the owners ($p=0.04$, Fisher exact test).

All 306 dogs were included in the evaluation for safety. The results of haematology, urinalyses and chemistry were unremarkable, except certain WBC parameters decreasing and triglyceride concentrations increasing in the ilunocitinib treated dogs. The applicant has provided a detailed overview of blood triglyceride concentrations obtained from control and ilunocitinib-treated dogs across several studies, including pilot and pivotal TAS studies, and two clinical trials. Considering the totality of evidence presented and the absence of a statistically or biologically significant trend, the CVMP can accept the applicant's conclusion that the elevations observed in triglycerides were not likely to have

been treatment-related. Severe adverse events were rare throughout the study and were considered unlikely to be related to treatment. In the placebo group, skin and ear disorders remained more prevalent throughout the study, likely due to a lack of control of pre-existing dermatitis. Other adverse events were mainly gastrointestinal in nature, with no obvious differences between groups.

Concomitant medications administered during this study were considered to be generally typical of dogs with dermatitis or other co-morbidities present. The most common pharmaceuticals administered were endo- and ectoparasite preventatives, and vaccines. Other classes of concomitant therapies included antibacterial/antiseptic/antifungal medication and nutritional supplements/vitamins. No negative interactions between ilunocitinib and other medications were reported.

The second study was a well conducted GCP-compliant clinical trial, involving 25 veterinary clinics across the USA and Canada. Similar to the previous study, it was also double-blinded, placebo-controlled and the same dosage of ilunocitinib (0.6 - 0.8 mg/kg bw) was used. The test item was the final formulation proposed for marketing.

The study was conducted by a mix of board-certified dermatologists and general practitioners. All participating general practitioners underwent a training session conducted by a board-certified dermatologist to ensure that the clinical diagnoses were accurate.

A total of 240 dogs were targeted for enrolment to obtain at least 210 evaluable cases. A sample size of 210 animals had been estimated, based on a 2:1 allocation ratio of animals to treatment groups, to be sufficient to achieve at least 90% power for detecting a significant difference between the IVP and placebo (140 IVP to 70 placebo control) for the primary outcome variable at a 5% significance level. The calculations assumed 50% and 27% success rates on the primary outcome variable for the IVP and placebo groups, respectively. A total of 268 dogs were enrolled and randomly (ratio 2:1) assigned to the ilunocitinib (n: 181) and placebo groups (n: 87). Dogs were treated orally once daily for 112 days, either with or without food.

In this study, only dogs suffering from atopic dermatitis were included. The diagnosis of atopic dermatitis was made based on compatible history and clinical signs (based on Hensel's guidelines and at least six of eight of Favrot's criteria). The diagnostic regimen was to have been sufficient to exclude diseases resembling atopic dermatitis including food allergies, flea allergy dermatitis, primary bacterial or fungal dermatitis and/or otitis, internal and external parasitism, metabolic disease, and others, as appropriate. At enrolment, the dog was to have at least moderate pruritus (PVAS score $\geq$ 6.0, corresponding to moderate to severe itching as assessed by owners) and at least a mild skin lesion score ($\geq$ 25, based on CADESI-4 as assessed by the investigator).

Four different scores were used for efficacy assessment: PVAS for the assessment of the pruritus by the owners, CADESI-4 for the grading of skin lesions severity by the investigators, Owner and Investigator Response to Treatment (ORTT and IRTT, respectively). Pruritus was assessed daily from days 0 to 7, then on days 14, 28, 56, 84 and 112 while other parameters were assessed on days 0, 14, 28, 56, 84 and 112. In this study, efficacy was evaluated based on treatment success, whereby dogs had to achieve at least one of two defined endpoints at day 28: 50% reduction in PVAS or 50% reduction in CADESI-4. Whilst it is recognised that one of the primary endpoints, owner assessment, is subjective, it is noted that objective investigator assessment (based on CADESI-4) is captured as part of 'treatment success' and as a standalone measure is included as a secondary efficacy variable. For investigator assessment, every effort was made for the same assessor or examining veterinarian to make the lesion assessments at each time point.

For the primary endpoint, the proportion of dogs that were treatment successes in the ilunocitinib group was significantly greater at day 28 than the placebo group ($p<0.001$). At day 28, 82.9% of

ilunocitinib-treated dogs compared with 30.9% of placebo treated dogs had achieved treatment success.

At study completion, 141 out of 181 ilunocitinib-treated dogs remained in the study (77.9%) while only 33.3% (29 out of 87) of placebo-treated dogs were available for analysis ($p<0.0001$). This was considered likely a consequence of poor control of clinical signs of dermatitis in the placebo group.

Regarding reduction of pruritus (≥50%), the difference between groups was statistically significant at day 3 and remained so until day 84. At day 112, 81% of the treated dogs were still controlled but 58% of the placebo treated dogs were also deemed controlled. Given the attrition rate within the placebo group, due to lack of control of clinical signs, this is not considered relevant when population sizes are compared. When PVAS <2 is considered (return to normal), the ilunocitinib group performed substantially better than placebo at days 56, 84 and 112 (p values <0.0001, 0.0003 and 0.001, respectively, Fisher exact test).

With regard to the CADESI-4 scores, after 14 days, 60.1% of the ilunocitinib treated dogs achieved at least a 50% reduction of the score while only 13.4% of the placebo-treated dogs reached the same level of improvement. The difference was highly statistically significant and remained so during the whole study. 15.1%, 32.7%, 50.3%, 54.8% and 63.2% of the treated dogs were deemed normal (CADESI-4 <10) after 14, 28, 56, 84 and 112 days, respectively. These findings reflect the observations of the dose determination studies.

Both ORTT and IRTT were also statistically different at all time points.

Product safety was evaluated in terms of adverse events and results of physical examination and clinical pathology. Safety was not evaluated in pregnant or lactating dogs, nor those intended for breeding. This can be accepted by the CVMP, on the grounds that section 3.7 of the proposed SPC adequately communicates that use of ilunocitinib is not recommended in pregnancy, lactation or in dogs intended for breeding, in the absence of safety data. In addition, reasons for exclusion included malignancy, evidence of immunosuppression (including demodicosis) and 'uncontrolled' systemic disease (e.g. epilepsy, diabetes mellitus, hypothyroidism, etc.). Section 3.5 of the SPC has therefore been appropriately amended to include the following precautions for safe use in the target species:

"*Do not use in dogs with evidence of malignant neoplasia, demodicosis or immune suppression such as hyperadrenocorticism, as the active substance has not been evaluated in these cases".*

"Ilunocitinib modulates the immune system and may increase susceptibility to opportunistic infection. Dogs receiving the veterinary medicinal product should be monitored for the development of infections and neoplasia."

Vital parameters, haematology and serum chemistry parameters remained unremarkable throughout the study. Similar to a number of other studies, triglycerides were slightly elevated and certain WBC parameters decreased in the ilunocitinib-treated dogs. Considering the totality of evidence presented and the absence of a statistically or biologically significant trend, the CVMP can accept the applicant's conclusion that the elevations observed in triglycerides were not likely to have been treatment related.

The percentages of dogs with at least one Adverse Event (AE) were similar in both groups (58% ilunocitinib versus 66.7% placebo). Skin related AEs, which would constitute a lack of efficacy, were less frequently observed in the ilunocitinib-treated group (25.4% vs 41.4%), confirming the efficacy of ilunocitinib to control allergy associated skin changes.

Gastrointestinal signs occurred in both treatment and control groups with similar frequency and included diarrhoea and emesis. Severe AEs were rare in both groups, and it is accepted that they are unlikely to be drug-related. The concomitant medications and vaccines administered during this study

were generally typical of dogs with dermatitis or other co-morbidities present. The most common pharmaceuticals administered were endo- and ectoparasite preventatives, vaccines, and prescription diets. Other classes of concomitant therapies included antibacterial/antiseptic/antifungal medication, shampoos, and ear cleansers. No negative interactions between ilunocitinib and other medications were reported.

The results obtained indicate that ilunocitinib is effective when administered either with or without food for dogs with atopic dermatitis.

The third pivotal clinical trial was conducted in the EU and compared the efficacy of ilunocitinib to an authorised product containing oclacitinib in client-owned dogs with atopic dermatitis. This was a GCP-compliant study, conducted in accordance with local regulations in the respective member states (Germany, Hungary, Ireland and Portugal). The study was initially planned for 56 days, however during the in-life phase an optional continuation phase was introduced to extend the study up to 112 days.

The test item was ilunocitinib, which was administered as the final tablet formulation as intended for marketing. The positive control product is considered appropriate as it is authorised in the EU for the same indication as proposed for ilunocitinib.

It is noted that it was not possible to fully blind the IVP and control groups, as the control and test item tablets were of different appearance and had different dose regimens. Oclacitinib was administered orally at the standard dosage twice daily either with or without food for the first two weeks, as recommended by the manufacturer. Sufficient measures were taken to ensure that blinding of investigators assessing skin lesions and performing clinical examination was maintained.

A sample size total of at least 272 evaluable subjects (136 in each treatment arm) was estimated to be sufficient to demonstrate non-inferiority for ilunocitinib with a power of 85% and a non-inferiority margin of 20%, for each of the primary outcome variables. The study had 85% power to detect an upper limit of the 95% CI on the difference percentage change from baseline at Day 28 (control product (CP) group - ilunocitinib group) below 20% under above assumptions. Approximately 300 dogs were planned to be enrolled (150 per group) to obtain at least 272 evaluable cases.

The test population were client-owned dogs with atopic dermatitis. Diagnosis of atopic dermatitis was made through the dog having a compatible history and clinical signs. The diagnostic regimen was sufficient to exclude diseases resembling atopic dermatitis including food allergies, flea allergy dermatitis, primary bacterial or fungal dermatitis and/or otitis, internal and external parasitism, metabolic disease and others, as appropriate. For enrolment, the dog must have had at least moderate pruritus (PVAS score ≥6.0, corresponding to moderate itching as assessed by owners) and at least a moderate skin lesion score (≥35, based on CADESI-4 assessed by investigator). These inclusion criteria are considered appropriate. It is noted that the CADESI-4 score threshold for inclusion on this study is higher than that used in the US atopic dermatitis study (>25); the reason for this is not stated, but it is accepted that it does not impact on the interpretation or overall conclusions of the study.

A total of 338 dogs were randomised equally in both treatment groups (n=169). Inclusion and exclusion criteria were similar to those used in the previous studies. This is acceptable to the CVMP. Again, pregnant and lactating bitches, and those intended for breeding were excluded from the study. In addition, reasons for exclusion included malignancy, evidence of immunosuppression (including demodicosis) and 'uncontrolled' systemic disease (e.g., epilepsy, diabetes mellitus, hypothyroidism, etc.).

Section 3.5 of the SPC has therefore been appropriately amended to include the following precautions for safe use in the target species:

"*Do not use in dogs with evidence of malignant neoplasia, demodicosis or immune suppression such as hyperadrenocorticism, as the active substance has not been evaluated in these cases".*

Owners assessed pruritus was conducted using the same validated PVAS as previous studies at enrolment (Day 0) as well as on Days 1-7, 14, 28 and 56, based on observations over the previous 24 hours. For dogs participating in the continuation phase, owners also assessed pruritus on days 84 and 112. Investigators assessed skin lesion scores using CADESI-4 at enrolment (Day 0) and again on Days 14, 28 and 56. For dogs participating in the continuation phase, CADESI-4 was also conducted on days 84 and 112. As for previous studies, ORTT and IRTT were also assessed.

Two equal primary endpoints were evaluated for efficacy, namely the percentage reduction in PVAS and the percentage reduction in CADESI-4 at day 28, with the objective of showing non-inferiority to the control product, oclacitinib. The endpoints also demonstrated non-inferiority to oclacitinib and can be accepted. Indeed, with regards to PVAS, superiority was demonstrated, and regarding CADESI4, superiority was missed only narrowly. Both Intention to Treat (ITT) and Per Protocol (PP) analyses were performed, however as there were negligible differences between the two outputs, the below results describe the ITT population.

The majority of included dogs competed the study until day 56 (91.7%) and 154 dogs entered the continuation phase, of which 88.3% (n: 136) completed the whole study (to Day 112). The high retention rates for both ilunocitinib and control groups suggest that both drugs are likely to be effective.

The ilunocitinib-treated group had a significantly higher proportion of dogs with a reduction in CADESI-4 score ≥50% at day 28 and 56 when compared to oclacitinib (p-values 0.009 and 0.003, respectively). At day 14, no differences were observed, although the oclacitinib group was dosed in accordance with manufacturer's recommendation, twice daily during that period. These findings indicate that ilunocitinib is at least as efficacious as oclacitinib for the improvement of skin lesions.

For the first primary endpoint (percentage reduction in PVAS at day 28) not only non-inferiority, but superiority was shown since the two-sided 95% confidence interval of 1.589% to 14.782% did not include 0%. This was almost similar for the second primary endpoint (CADESI-4 at day 28), where superiority was missed only narrowly but non-inferiority was demonstrated clearly at a margin as small as -0.5% with a 95% confidence interval between -0.464% and 9.561%.

For the secondary endpoints (i.e. the proportion of dogs with 50% improvement in pruritus compared to baseline), both products worked equally well, and no statistically significant differences were observed at any time point. However, a rebound of the pruritus was observed at day 28 in oclacitinib-treated dogs with the proportion of dogs achieving a 50% reduction of this sign returned to day 14 values by day 56 in the oclacitinib group. This rebound effect, which has been documented in published literature (Cosgrove et al, 2013) was not observed in the ilunocitinib-treated group. On day 56, 62% of the ilunocitinib-treated dogs achieved a pruritus score below 2 (return to normal), while this proportion was 45% with the control drug (p=0.002). This return to normal levels of pruritus continued throughout the duration of the study such that on day 112 the proportion of dogs with pruritus <2 in the ilunocitinib group was 77.1% while it was 60.6% in the oclacitinib group (p=0.04).

It is noted that 91% of the ilunocitinib-treated dogs reached a pruritus improvement greater than 50% at day 56, compared to 77% of the oclacitinib-treated dogs (p=0.08).

When considering the CADESI-4 scores at each study day, the proportion of dogs achieving 50% reduction from baseline consistently improved throughout the duration of the study. By day 56, 97.5%

of ilunocitinib-treated dogs had achieved a 50% improvement in skin lesion scores. At all timepoints after day 28, a statistically significant difference was observed in favour of ilunocitinib, suggesting that it is able to provide a clinically meaningful improvement in signs of atopic dermatitis.

Considering that the conducted clinical trials evaluated the safety and efficacy of ilunocitinib under field conditions over a limited time period (112 days), section 3.9 of the SPC includes the following statement regarding the basis for extending treatment beyond 112 days: '*The requirement for long-term maintenance therapy should be based on an individual benefit-risk assessment by the responsible veterinarian.'* This is considered appropriate.

All 338 randomised animals, which received at least one dose of ilunocitinib or oclacitinib, were included in the safety evaluations. Vital parameters remained stable over the time in both groups. In this study, no significant differences in serum chemistry parameters were detected. For haematological parameters, similar to other studies, a treatment effect was observed for certain WBC and RBC parameters. The percentages of AEs were very similar in both groups (27.2% ilunocitinib and 24.3% control). The most observed AEs were digestive tract disorders (e.g. emesis and diarrhoea) with 13.6% and 10.7% in the ilunocitinib and oclacitinib group, respectively.

The concomitant medications and vaccines administered during this study were generally typical of dogs with dermatitis or other co-morbidities present. The most common pharmaceuticals administered were endo- and ectoparasite preventatives, vaccines, non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics. No negative interaction between ilunocitinib and other medications were reported.

All in all, the CVMP considers that the results indicate that ilunocitinib is not inferior to oclacitinib for the improvement of the clinical signs of canine atopic dermatitis.

In conclusion, the data obtained from these well conducted, GCP-compliant clinical trials are considered sufficient to support efficacy for the proposed indications for use in dogs at least 12 months of age when used in accordance with the proposed SPC.

Overall conclusions on efficacy

Pharmacology

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. Ilunocitinib has equipotent inhibition on JAK1 and 2, high potency against TYK2 and little inhibitive effects on JAK3. A broad range of JAKi are marketed in human therapeutics. To date, only oclacitinib has been approved in veterinary therapeutics.

Similar to oclacitinib, ilunocitinib was found to be non-selective, with IC_{50} values demonstrated for JAK1, 2, 3 and TYK2 of 1 nM, 1 nM, 16 nM and 4 nM respectively. The same in vitro study indicated that ilunocitinib was not a significant inhibitor of other protein or lipid kinases, indicating a low risk of off-target activity.

The effects of ilunocitinib on inhibition of cytokines involved in inflammation (IL2 and IL6), allergy (IL4 and IL13), haematopoiesis (GM-CSF) and the innate immune response (IL12 and IFNγ) were examined in vitro, and ilunocitinib displayed potent, minimally selective inhibition, but was most inhibitive on IL6. Ilunocitinib had an inhibitory effect (IC_{50} = 0.05038 µM) on the stimulatory action of IL31 (previously identified as the key component of the pruritus response) on canine macrophages.

The basic pharmacodynamic properties of ilunocitinib have been adequately characterised, and the text included in section 4.2 of the SPC is acceptable.

Pharmacokinetics

After IV administration of 0.8 mg/kg bw, ilunocitinib had a low plasma CL of 437 ml/h/kg. The volume of distribution was 1.58 L/kg and terminal half-life was 4.4 hours.

After oral administration of 0.8 mg/kg bw ilunocitinib using the final tablet formulation in fasted dogs, the absolute bioavailability was 58%. The elimination half-life was 5.4 hours. In fed dogs, oral bioavailability increased up to 80%, showing a similar elimination half-life as observed in fasted dogs (5.0 hours).

In general, T_{max} generally occurred between 1 and 4 hours.

After oral administration of the final tablet formulation to fasted dogs, a less than dose proportional increase of exposure (C_{max} and AUC) was observed from 0.4 to 2.4 mg/kg bw and a roughly proportional increase of exposure from 2.4 to 4.0 mg/kg bw dose. After oral administration of 0.8, 2.4, and 4 mg/kg bw with the final tablet formulation to fed dogs, a less than dose proportional increase of exposure (C_{max} and AUC) was observed from 0.8 to 4.0 mg/kg bw dose. After oral administration of 0.8, 1.6, 2.4 and 4.0 mg/kg bw in the pivotal TAS study (final formulation tablets administered in fed conditions), exposure increased with dose and the deviation from dose proportionality was small.

Following oral administration daily for 10 days of 0.8 mg/kg bw as the final formulation to fasted dogs, no relevant change in exposure of ilunocitinib was observed, indicating absence of significant accumulation. It is noted that for one animal, significant accumulation was observed (5.66 for dose-normalised (DN) C_{max} and 3.39 for DN AUC_{0-24}). However, based on the overall evidence presented by the applicant regarding this individual, the CVMP accepts that the high accumulation ratio observed for D0102 can be considered an isolated incident and thus is not anticipated to impact target animal safety.

No relevant sex-or age-dependent differences in exposure of dogs were observed.

Inter- as well as intraindividual variability between animals was high after oral administration to fasted dogs with reduced variability observed in fed conditions.

The data package presented adequately characterises the pharmacokinetic profile of ilunocitinib in the dog. The text included in section 4.3 of the SPC (Pharmacokinetics) is appropriate.

Dose determination

Considering all the studies performed for dose determination, a range of doses from 0.1–1.2 mg/kg bw ilunocitinib have been evaluated in different models and under clinical field conditions. It is accepted that the applicant has conducted a thorough and appropriate dose determination program, which assessed a range of doses in different models and naturally occurring disease. Overall, the studies were generally considered by the CVMP to have been well-conducted.

Based on the data provided, the rationale for selecting 0.6-0.8 mg/kg as the dose for evaluation in the pivotal safety and efficacy studies can be followed. Regarding the proposed once daily treatment, available data suggest that a dose less than that proposed may not be effective for the full 24 hours. In study ELA1700243, the data suggest that the effect of the 0.4 mg/kg bw dose was wearing off by 20-22 hours post-dosing. That is, these data suggest that a dose of >0.4 mg/kg bw is required to maintain effect up to 24 hours.

The RTD has been justified and the selected dose range of 0.6-0.8 mg/kg bw ilunocitinib administered once daily was suitable for further evaluation in subsequent TAS and clinical trials to confirm safety and efficacy under clinical conditions.

Tolerance in the target animal species

The tolerance of ilunocitinib was tested in three pre-clinical TAS studies and in an additional study assessing the potential effect on vaccination.

While safety in the target species has been comprehensively investigated, the applicant's conclusion that 4 mg/kg bw can be considered a NOAEL is not accepted. In the various studies conducted, oral (tablet) administration of ilunocitinib to Beagle dogs at dosage levels of 0.8, 2.4, 3.2, and 4.0 mg/kg bw/day for 182 or 183 consecutive days resulted in clinical observations, effects on haematology, coagulation, and serum chemistry, gross findings, effects on spleen weights, and histologic findings for males and females at all dosage levels. In the main target animal safety study, the observed effects were attributed to the immunosuppressive effects of ilunocitinib (effects on haematopoietic and lymphatic systems). While effects were generally mild in the 0.8 mg/kg bw group, there is the potential for clinically relevant effects: for example, lesions such as papilloma and interdigital cysts did occur at that dose. In other studies, severe infectious disease (generalised demodicosis and coccidiosis) was diagnosed in some dogs treated at overdose. Five unscheduled deaths were recorded across the non-GLP TAS studies, with 3 noted in the pilot TAS study and 2 in the vaccine response study. The 3 deaths which occurred in the non-GLP pilot TAS study, based on ante- and post-mortem findings, including histopathology, are in general consistent with gavage error. However, with respect to the 2 unscheduled deaths in the vaccine response study, the applicant did not consider the immunomodulatory effects of ilunocitinib. The role of ilunocitinib in the precipitation of clinical disease - coccidiosis (*I. canis*) in one dog cannot definitively be excluded. A second dog, which was euthanised on Day 54 was diagnosed with infectious canine hepatitis (Canine adenovirus 1 – subsequently demonstrated by post-mortem PCR analysis as wild-type rather than vaccine-induced). However, the CVMP remains of the opinion that immunosuppression related to the administration of ilunocitinib, albeit at 3X the recommended therapeutic dose, may have been a key determinant in the precipitation of opportunistic infections.

Furthermore, although it is accepted that at the recommended dose, limited incidence for the above findings was reported, the CVMP considered that lesions such as lethargy, interdigital cysts, papillomas and demodicosis are clinically relevant and may be a cause for concern for owners, with a potential requirement for reactive treatment. While it is noted that none of these effects were seen in the three clinical trials, these trials were of a significantly shorter duration than the TAS studies (112 days vs. 183 days, respectively). As such, section 3.6 of the SPC was updated to include the observed AEs of lethargy, papilloma, and interdigital cysts with frequency descriptors determined as appropriate from available TAS and clinical trial data.

Additionally, the applicant has included the following sentence in SPC section 3.5, which is considered appropriate:
"*Ilunocitinib modulates the immune system and may increase susceptibility to opportunistic infection. Dogs receiving the veterinary medicinal product should be monitored for the development of infections and neoplasia*".

Clinical trials

Efficacy

At the time of submission, the applicant proposed the following indications for Zenrelia tablets:

1. Treatment of pruritus associated with allergic dermatitis in dogs ("pruritus claim").
2. Treatment of clinical manifestations of atopic dermatitis in dogs ("atopic dermatitis claim").

To support the pruritus claim, the applicant conducted one US multi-site clinical trial. This study involved the once-daily oral administration of ilunocitinib for treatment of allergic dermatitis in client-owned dogs over a 28-day period, extended for up to four months for dogs in the optional continuation

phase. The dogs enrolled enabled data collection in a variety of clinical settings in dogs exposed to a wide range of environmental allergens. A broad range of ages, breeds, pre-existing medical conditions, and concomitant medications were represented.

To support the atopic dermatitis claim, two clinical trials (conducted in the US and EU, respectively) were conducted.

The US multi-site pivotal clinical trial of once-daily oral administration of ilunocitinib given with or without food at a dose of 0.6-0.8 mg/kg bw for control of atopic dermatitis in client-owned dogs over 112 days provided an extensive evaluation of product safety and efficacy data. Dogs were enrolled across a geographically diverse range of sites providing a study population exposed to a wide range of environmental allergens. Demographically, enrolled dogs provided a broad representation of ages, breeds, pre-existing medical conditions, and concomitant medications. Gender, age, and body weight were well balanced between treatment groups.

The European clinical trial demonstrated efficacy and safety of ilunocitinib, and additionally non-inferiority when compared to oclacitinib in client-owned dogs. Dogs were enrolled from 25 sites in Germany, Hungary, Ireland and Portugal; an adequate representation of the EU. Zenrelia tablets were administered with or without food at a dose of 0.6-0.8 mg/kg bw over 112 days. No drug interactions were observed with the concomitantly used veterinary medicinal products (vaccines, anti-parasitics and antibiotics).

The data obtained from these well conducted, GCP-compliant clinical trials are considered sufficient to support efficacy for the proposed indications for use in dogs at least 12 months of age when used in accordance with the proposed SPC.

Safety:

The proposed text for section 3.6 of the SPC has been based primarily on the results of the clinical trials. These studies were chosen as the most relevant for the SPC discussion because they used the final marketed tablet formulation and included over 550 ilunocitinib-treated dogs.

In the pivotal clinical trials, emesis, pruritus, diarrhoea, lethargy, otitis externa, anorexia, dermatitis and eczema were the most frequently reported abnormal clinical signs in the ilunocitinib treatment groups. However, it was noted that only "*emesis*" and "*diarrhoea*" were initially included under section 3.6 of the proposed SPC. Considering the above findings, and also observations from the pre-clinical studies conducted with ilunocitinib in which observations such as interdigital cysts and skin papules/papillomas were reported, the applicant reviewed and updated the product information further to include the adverse events "*lethargy*", "*papilloma*" and "*interdigital cyst*". Frequency descriptors for these additional AEs were based on available study data, and appropriately communicate the potential risks associated with administration of ilunocitinib at the RTD to prescribing veterinarians and animal owners.

Overall, the CVMP considers that the safety and efficacy of the product when used as intended has been demonstrated.

Part 5 – Benefit-risk assessment

Introduction

Zenrelia is available as a film coated tablets containing 4.8 mg, 6.4 mg, 8.5 mg or 15 mg of ilunocitinib and are presented in packs containing 10 tablets, 30 tablets and 90 tablets.

The active substance, ilunocitinib, is a Janus kinase (JAK) inhibitor. It inhibits the function of a variety of pruritogenic and pro-inflammatory cytokines, as well as cytokines involved in allergy which are dependent on JAK enzyme activity. The product is intended for use in dogs for the treatment of pruritus associated with allergic dermatitis and treatment of clinical manifestations of atopic dermatitis. The proposed dose of 0.6 to 0.8 mg/kg bw ilunocitinib/bodyweight, administered once daily, has been confirmed.

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

Benefit assessment

Direct benefit

The benefit of Zenrelia is its efficacy in the "*Treatment of pruritus associated with allergic dermatitis in dogs*" and "*Treatment of clinical manifestations of atopic dermatitis in dogs*". Three well designed clinical trials conducted in accordance with GCP have demonstrated that the product is efficacious for both indications at a dose of 0.6 to 0.8 mg/kg ilunocitinib/bodyweight, administered once daily.

The direct benefit for the treated animal is improved welfare as a result of reduced pruritus in cases of allergic dermatitis, and reduced pruritus and skin lesions in the case of atopic dermatitis.

Additional benefits

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

Risk assessment

Quality

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

Safety

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

Risks for the target animal

Administration of Zenrelia 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. Developmental findings in rats, namely teratogenic and foetotoxic effects, have been observed following treatment.

Ilunocitinib is not mutagenic or clastogenic, but an aneugen and therefore has genotoxic potential. In the absence of mutagenic or clastogenic effects, the available results suggest that there is a practical threshold for this genotoxic effect. Noting that aneugens act primarily on proteins involved in cell division in a concentration-dependent manner, it is considered that a sufficient margin of safety between the observed aneugenic threshold for ilunocitinib and the therapeutic dose administered to the target species on a long-term daily basis exists.

Risk for the user

The most severe risk is accidental ingestion by a child. Appropriate warnings are included in the SPC and the product is intended to be marketed in child-resistant packages.

Risk for the environment

Zenrelia 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, papillomas and interdigital cysts are included as adverse events in section 3.6 of the SPC. Section 3.10 of the SPC also notes that, at overdose, treatment with the veterinary medicinal product may lead to a higher susceptibility of dogs to development of lesions such as interdigital cysts, with or without discharge, swollen and/or scabs on the paws and paw thickening and/or discoloration. Additionally, and more commonly in males, a mild reduction in red blood cell mass was noted in some animals at 3X dose after 8 weeks of use. This reduction was self-limiting, with gradual recovery to pre-treatment measurements.

Section 3.5 of the SPC includes text advising that dogs receiving the veterinary medicinal product should be monitored for the development of infections and neoplasia. Additionally, it is communicated that the safety of ilunocitinib in dogs with evidence of malignant neoplasia, demodicosis or immune suppression such as hyperadrenocorticism, has not been evaluated and thus the VMP is not to be used in such cases.

Section 3.8 includes appropriate text on the potential for interactions.

Use of the VMP is not recommended during pregnancy, lactation, or in breeding dogs.

User safety

User safety risks have been identified, mainly the risks associated with exposure in children. These risks are mitigated by the presentation of the product in child-resistant packaging, and appropriate warnings relating to storage of the product and unused half tablets.

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 indications:

"*Treatment of pruritus associated with allergic dermatitis in dogs.*
Treatment of clinical manifestations of atopic dermatitis in dogs."

The product has been shown to be efficacious for these indications, and the CVMP accepted the indications as proposed by the applicant.

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

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 Zenrelia 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 medicinal product.

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