Received: 15 November 2024 | Accepted: 1 April 2025

DOI: 10.1111/vde.13344

Veterinary Dermatology

ORIGINAL ARTICLE

Efficacy and field safety of ilunocitinib for the control of atopic dermatitis in client-owned dogs: A multicentre, double-masked, randomised, placebo-controlled clinical trial

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Funding information
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Abstract

Background: Inhibition of the Janus kinase (JAK) pathway is a well-established option for canine atopic dermatitis (cAD).

Objective: To evaluate the efficacy and safety of ilunocitinib, a novel JAK inhibitor for the control of pruritus and skin lesions in client-owned dogs with cAD.

Animals: Two hundred sixty-eight dogs at 25 veterinary clinics.

Materials and Methods: In this randomised, double-masked, clinical trial, dogs received either ilunocitinib (n=181; 0.6–0.8 mg/kg) or placebo (n=87; 0.0 mg/kg) tablets once daily for 112 days. Pruritus was assessed by owners using a pruritus Visual Analog Scale (PVAS), while skin lesions were assessed by Investigators using the cAD Extent and Severity Index, 4th iteration (CADESI-04). Treatment success was defined as ≥50% reduction from baseline PVAS or CADESI-04 score on Day (D)28. Proportions of dogs achieving clinical remission from pruritus (PVAS<2) or skin lesions (CADESI-04<10) also were assessed.

Results: At D28, 83% of ilunocitinib-treated dogs achieved treatment success compared to 31% of placebo-treated dogs (p<0.001). A significantly higher proportion of ilunocitinib-treated dogs achieved ≥50% reduction in CADESI-04 scores at all time points (p<0.001). The proportion of dogs achieving clinical remission PVAS or CADESI-04 scores was significantly higher in the ilunocitinib group starting on D7 and D14, respectively (p<0.05). The 112-day ilunocitinib treatment was well tolerated.

Conclusions and Clinical Relevance: Once daily ilunocitinib was well-tolerated and effective at rapidly reducing pruritus and resolving cAD-associated skin lesions. Clinical remission was achieved by two-thirds of dogs after 4 months of treatment. Ilunocitinib is safe and effective for managing clinical signs associated with cAD.

KEYWORDS
canine atopic dermatitis, clinical remission, ilunocitinib, JAK inhibitor, pruritus, skin lesions

INTRODUCTION

Canine atopic dermatitis (cAD) is a chronic inflammatory skin disease, with pruritus being the primary clinical sign. Skin lesions are either primary (erythema, erythematous macular or papular eruptions) or secondary to pruritic manifestations (excoriations, self-induced alopecia and lichenification).[1] Secondary complications such as bacterial or fungal colonisation and infections are common.[2] The pathogenesis of cAD is complex and multifactorial involving genetic and environmental factors, as well as a defective skin barrier.[3] Diagnosis is based on history, clinical features and exclusion of other pruritic skin diseases, including flea and/or food allergies in nonseasonal patterns.[4] It is therefore critical to control pruritus and

skin lesions with interventions to allow the skin to heal and prevent chronic inflammatory changes and secondary infections.[5]

A multitude of cytokines secreted by T-helper and other immune cells are mediators of pruritus and inflammation associated with cAD.[6–10] Many of these cytokines signal via the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway.[6–10] The JAK–STAT pathway plays a crucial role in transmitting signals from cell membrane receptors to the nucleus, thus activating cells to produce additional inflammatory mediators.[11,12] JAK inhibitors (JAKi) are a class of therapeutic agents, indicated in humans for a variety of chronic inflammatory conditions, that principally inhibit JAK1 yet may also inhibit JAK2, JAK3 and/or tyrosine kinase 2 (TYK2).[13] A systematic review and meta-analysis of JAKi for the treatment of atopic dermatitis (AD) in humans found them to be safe and effective.[14] Oclacitinib, a veterinary JAKi, has been demonstrated to be effective in the treatment of cAD. However, up to one-third of dogs may be non- or minimally responsive to the treatment, leaving room for further treatment options.[15–17]

Ilunocitinib is a novel veterinary JAKi with a half-life of approximately 5 h. It has a high in vitro potency for inhibition of JAK1, JAK2 and tyrosine kinase 2 (TYK2) (unpublished data). Exploratory studies (unpublished data) demonstrated the ability of ilunocitinib to control pruritus and reduce skin lesions in laboratory dogs sensitised to house dust mites, and in naturally occurring cAD in a small number of client-owned dogs. Owner-assessed pruritus Visual Analog Scale (PVAS) and veterinary surgeon-assessed skin lesions using the Canine Atopic Dermatitis Extent And Severity Index, 4th iteration (CADESI-04) are tools validated to assess the severity of pruritus and skin lesions in clinical trials evaluating therapeutics for cAD.[15–23] The main objective of this randomised, placebo-controlled clinical trial was to evaluate the safety and efficacy of ilunocitinib in the management of cAD in client-owned dogs. Remission from clinical signs of cAD, defined as normal PVAS <2 and CADESI-04 <10 scores, also was evaluated based on the International Committee of Allergic Diseases of Animals (ICADA)'s Core Outcome Set for Canine Atopic Dermatitis (COSCAD'18).[18,19]

MATERIALS AND METHODS

Ethics

Study procedures were reviewed and approved by the Animal Care and Use Committee *at Elanco Animal Health* and by participating site investigators. Owners signed an informed written consent before enrolment.

Study design

This double-masked, randomised, placebo-controlled, multicentre clinical trial was conducted at 25 veterinary clinics in the United States (US) (n=24) and Canada (n=1). Participating veterinary surgeons included 11 board-certified first-line and 14 general practitioners. Dogs meeting all inclusion criteria, with a confirmed diagnosis of cAD, were randomised in a 2:1 ratio to receive once-daily oral doses of either ilunocitinib or placebo tablets for up to 112 days. A sample size estimate of 210 evaluable subjects (140 ilunocitinib; 70 placebo) was calculated to be sufficient to detect a significant difference in the primary efficacy outcome variable between groups, with a power of 90% at a 5% significance level. Calculations assumed 50% (ilunocitinib) and 27% (placebo) success rates, respectively, based on unpublished data from a previous pilot field study.

Inclusion and exclusion criteria

Client-owned dogs of any breed, sex, >12 months of age and weighing ≥3 kg were eligible for enrolment. Dogs diagnosed with cAD needed to be physically healthy (based on complete physical examination, haematological and serum chemical analysis and urinalysis) and free of serious or systemic diseases that could potentially interfere with study objectives. cAD was diagnosed based on history, clinical signs, exclusion of other pruritic conditions and fulfilment of at least six of the eight Favrot criteria from set 1.[4,22] Dogs could have either seasonal or nonseasonal cAD. Additionally, dogs needed to score an owner-assessed PVAS of ≥6.0 corresponding to moderate-to-severe itching, and an investigator-assessed CADESI-04 of ≥25. Dogs had no evidence of flea infestation at enrolment, and continuous use of flea control throughout the study was mandatory.

Dogs with conditions requiring continuous medications could be enrolled as long as the treatment remained consistent before and throughout the study (e.g. NSAIDs, antiseizure or thyroid medications; topical tacrolimus/ciclosporin), and/or the medication was not likely to interfere with evaluations (e.g. parasiticides and vaccinations). Specific washout periods for prohibited medications (e.g. JAKi, glucocorticoids, anti-interleukin [IL]-31 monoclonal antibodies, local anaesthetics, antimicrobials and systemic ciclosporin) or those which were conditionally allowed (e.g. allergen-specific immunotherapy) were strictly followed (Table S1). Following completion of the Day (D)28 evaluations, if required, dogs were able to receive systemic and topical otic antimicrobials.

Pregnant or lactating dogs or dogs intended to be used for breeding purposes, dogs diagnosed with malignant neoplasia, demodicosis or immune-altering conditions such as hyperadrenocorticism or dogs with a known sensitivity to JAKi were excluded.

Randomisation and masking

Included dogs were blocked and randomised in a 2:1 allocation ratio based on the order of enrolment at each clinic to receive daily oral administrations of ilunocitinib or placebo tablets using SAS v9.4 (SAS Institute., Cary, NC, USA).

In order to ensure adequate masking, each tablet strength was randomly assigned a unique colour

code used on study labels rather than the actual tablet strength. In addition, investigators, owners and any study personnel conducting physical examinations and/or efficacy/safety assessments remained masked throughout the study. At each site, the treatment dispenser designated by the investigator provided assigned tablets (ilunocitinib or placebo) to owners.

Treatment administration

Placebo tablets matched the qualitative formula in shape, colour and size of ilunocitinib tablets yet contained no active ingredient. Individual baseline and thereafter monthly body weights were used to calculate and adjust the dose of ilunocitinib (0.6–0.8 mg/kg) or placebo (0.0 mg/kg) administered to each dog, if needed. The first dose was administered in the clinic by the dispenser or owner under the supervision of the investigator. Thereafter, dogs were dosed orally by owners once daily at home, approximately the same time each day with or without food until withdrawal or study completion (D112).

Study activities

Baseline data (clinical history, concomitant medications/therapies, body weight, physical examinations, PVAS and CADESI-04) were collected for each dog on D0. Follow-up clinic visits were carried out on D14 (±2), D28 (±2), D56 (±3), D84 (±3) and at study exit on D112 (±3) (or earlier if premature study withdrawal). At each clinic visit, data from the physical examination (including body weight measurement), owner-assessed PVAS score, investigator-assessed CADESI-04 score and both the owner and investigator (independently recorded) overall response to treatment (RTT) were collected. RTT was assessed using a simple VAS scale graded from 'no improvement' at 0 cm to 'excellent improvement' at 10 cm, designated as ORTT-VAS and IRTT-VAS, respectively. Owners kept a daily log of feeding, dosing and observations including any possible adverse events (AEs).

Blood samples were collected for haematological and serum chemical analyses on D0 (before initiating treatment), D28, D56, D84 and D112. Urine samples were collected for urinalysis on D0, D28 and D112. All blood and urine samples were sent to a central laboratory (IDEXX Bioanalytics).

Efficacy assessment

Treatment success was defined as ≥50% reduction from baseline PVAS or CADESI-04 score on D28. Dogs that were withdrawn from the study owing to a perceived lack of efficacy on or before D28 were considered to be treatment failures. Further secondary efficacy assessments included evaluation of the (i) change in PVAS or CADESI-04 score over time, (ii) proportion of dogs with ≥50% decrease in PVAS or CADESI-04 score, (iii) frequency of dogs in remission of clinical signs of cAD and (iv) overall RTT from ORTT and IRTT scores. Additional categories of severity included very mild (2 to <4), mild (4 to <6) and moderate-to-severe (≥6) for PVAS and mild (10–34), moderate (35–59) and severe (>60) for CADESI-04.[18,21,23,24]

Owners assessed pruritus using PVAS scoring at enrolment (D0) and on D1–7, D14, D28, D56, D84 and D112, based on observations over the previous 24 h. Pruritus assessments were conducted at approximately the same time of day. On visit days, owners completed the PVAS scoring before meeting with the investigator. Investigators assessed skin lesions using CADESI-04 scoring at enrolment (D0) and again on D14, D28, D56, D84 and D112 during clinic visits.

Safety assessment

All study dogs receiving at least one dose of either ilunocitinib or placebo were included in the safety assessment. Clinical safety was based on reported AEs, physical examination findings, body weights and results from clinical pathological investigation (haematological and serum chemical analysis and urinalysis). An abnormal clinical sign occurring at any time during the study after dosing on D0 was reported as an AE.

Statistical analysis

All statistical analyses were conducted using SAS FOR WINDOWS (v9.4). All assessments were evaluated at a two-tailed $p < 0.05$ level of significance. The dog was the experimental unit.

The primary analysis for efficacy was a comparison of the proportions of treatment success in each group, using a generalised linear mixed model (GLIMMIX procedure in SAS). The model used a binomial distribution and a logit link and included treatment as a fixed effect, and site and site-by-treatment as random effects. Estimated success proportions and corresponding 95% confidence intervals (CI) were obtained by back-transformations from the GLMM least-square (LS) estimates. Secondary efficacy outcome variables with a binary response included the proportion of dogs with ≥50% reduction from baseline in CADESI-04 or ≥50% reduction from baseline PVAS analysed using a GLMM for repeated measures with a logit link and binomial error. Treatment, time and treatment-by-time were included as fixed effects while site, site-by-treatment interaction and site-by-treatment by time and dog were included as random effects. Model-derived estimates and corresponding 95% CI were obtained by using a back-transformation from log-scale for each treatment group.

Additionally, proportions of dogs achieving a clinical remission were analy**s**ed by treatment group for each time point as described above for a binary response and compared between groups. Model-derived estimates of proportions and 95% CI were calculated for each treatment group without making multiple comparison adjustments.

Continuous efficacy assessments for ORTT-VAS, IRTT-VAS, PVAS and CADESI-04 scores were analysed

using a linear mixed model for repeated measures with treatment, time and treatment-by-time interaction as fixed effects and site, site-by-treatment, site-by-time and site-by-treatment by time and animal as random effects. Baseline scores were included as covariates. Least-square (LS) means and SE as well as 95% CI were calculated by treatment group for each clinic visit.

The proportion of dogs withdrawn for perceived lack of efficacy (worsening of clinical signs of cAD) was summarised per group using descriptive statistics at each timepoint.

In order to analyse safety-related clinicopathological findings, summaries of descriptive statistics (mean, median, standard deviation [SD], minimum and maximum) were performed for haematological, serum chemical, urine pH and specific gravity (USG) results by treatment group for each time point. Findings from physical examinations (respiration and heart rates, rectal temperature, body weights) were summarised for each treatment group by visit. Descriptive statistics for body weight and percentage change from baseline were calculated by treatment and time point. Frequencies of dogs reported to experience at least one AE were summarised by preferred terms (PT) based on the Veterinary Dictionary for Drug Regulatory Activities (VeDDRA). Frequencies of dogs receiving each concomitant medication recorded during the study also were calculated.

RESULTS

Baseline demographic characteristics

A total of 268 dogs were enrolled and received either ilunocitinib (n=181) or placebo (n=87). The mean age of this population was 5.9±3.5 years and the mean body weight was 22.9±13.32 kg. The study population comprised 46.3% pure-bred dogs and 53.7% mixed-breed dogs (Table 1). Pure-bred dogs representing more than 5% of the population were German Shepherd dogs (9.7%), American Pit Bull Terriers (8.9%), Labrador Retrievers (8.1%), French Bulldogs (6.5%), Shih Tzus (6.5%) and Golden Retrievers (5.6%). There was no significant difference in mean PVAS or CADESI-04 scores between treatment groups on D0.

Of these 268 dogs, 13 (seven ilunocitinib, six placebo) dogs were excluded from the efficacy assessment owing to enrolment errors (four per group), administration of prohibited medications (two ilunocitinib, one placebo) and overdosing (one per group). The remaining 255 (174 ilunocitinib, 81 placebo) dogs were evaluated for all secondary efficacy outcome variables. The median prescribed dosage across all time points was 0.68 mg/kg. Dosing compliance was good through the primary efficacy assessment (D28 visit) with only six cases (two ilunocitinib, four placebo) excluded from the primary efficacy analysis as a consequence of dosing issues. This resulted in a total of 249 (172 ilunocitinib, 77 placebo) dogs for comparative purposes.

Efficacy analyses

Treatment success

On D28, the proportion of dogs achieving treatment success was significantly higher (p<0.001) in the ilunocitinib group (82.9±3.5%; 95% CI [74.1–89.2]) compared to the placebo group (30.9±8.0%; 95% CI [16.6–50.0]) (Figure 1).

Owner-assessed pruritus scores (PVAS)

Figure 2a represents LS mean (mean) PVAS scores over time, showing significantly lower mean PVAS

TABLE 1 Baseline demographic characteristics of study population on Day 0.

Characteristic	Statistics	Ilunocitinib (n=181)	Placebo (n=87)	Total (n=268)
Age (year)	Min, Max	1.0, 17.3	1.0, 14.7	1.0, 17.3
	Mean	5.69	6.34	5.90
	SD	3.38	3.71	3.50
Body weight (kg)	Min, Max	3.3, 67.3	3.1, 53.2	3.1, 67.3
	Mean	23.7	21.4	22.9
	SD	13.9	11.97	13.32
Sex	Female (intact)	81 (6)	40 (7)	121 (13)
	Male (intact)	100 (10)	47 (6)	147 (16)
Breed	Mixed-breed	98	46	144
	Pure-bred	83	41	124
PVAS (max score 10)	Min, Max	6, 10	6, 10	6, 10
	Mean	7.53	7.77	7.61
	SE	0.075	0.121	0.064
CADESI-04 (max score 180)	Min, Max	25, 156	25, 155	25, 156
	Mean	56.91	58.32	57.37
	SE	2.072	3.119	1.724

Abbreviations: CADESI-04, Canine Atopic Dermatitis Extent and Severity Index, 4th iteration; PVAS, pruritus Visual Analog Scale.

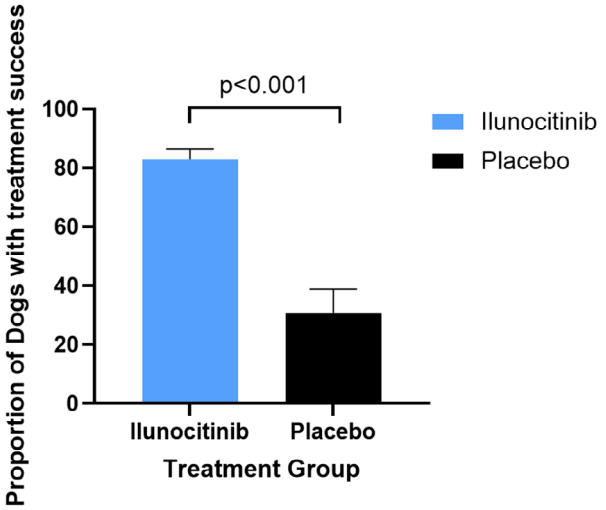

FIGURE 1 Proportions (%) of dogs with treatment success (defined as ≥50% reduction from baseline pruritus Visual Analog Scale [PVAS] or from baseline Canine Atopic Dermatitis Extent and Severity Index, 4th iteration [CADESI-04] score on Day 28) in the ilunocitinib-treated (n=172) and placebo (n=77) groups. Error bars represent standard errors (SE).

scores in the ilunocitinib group starting as early as D2 and steadily decreasing through to D112 compared to the placebo group (p<0.001). Arithmetic mean PVAS scores for both groups are presented in Table S2.

The proportion of dogs with ≥50% reduction in PVAS score was significantly higher in the ilunocitinib group (29%–85%) compared to the placebo group (6%–38%) from D3 to D84 (p<0.05), yet not on D112 (82% and 58%, respectively) (p=0.153) (Table S3).

A significantly higher proportion of dogs treated with ilunocitinib achieved PVAS scores <2 compared to dogs in the placebo group, starting from D7 until the end of the study (p<0.05) (Figure 3a). In ilunocitinib-treated dogs, the proportion continuously increased from 44% at D28 to 67% at D112, while in the same time period, the proportion in placebo dogs increased from 8% to 20%.

Investigator-assessed skin lesion scores (CADESI-04)

Figure 2b represents LS mean for CADESI-04 scores over time, showing a significant difference between groups from D14 (first evaluated time point) to D112 with lower CADESI-04 scores recorded for the ilunocitinib group compared to the placebo group (p<0.001). LS mean CADESI-04 scores decreased from moderate at baseline (57) to mild (27) as early as D14 in the ilunocitinib group, while in the placebo group scores remained moderate (38–59) until the end of the study. A significantly higher proportion of dogs in the ilunocitinib group (60%–90%) achieved ≥50% reduction in CADESI-04 scores compared to the placebo group (13%–60%) at all time points (p<0.001) (Table S4).

Skin lesions were reduced to normal (CADESI-04 < 10) in a significantly higher proportion of dogs treated with ilunocitinib compared to placebo dogs, starting on D14 (first assessed time point) until the end of the study on D112 (p<0.05) (Figure 3b). By D28, 33% of ilunocitinib-treated and 0% of placebo dogs achieved clinical remission from skin lesions, while 67% and 27% (respectively) had normal CADESI-04 scores on D112.

ORTT-VAS and IRTT-VAS scores

The LS means of ORTT-VAS scores were significantly higher in the ilunocitinib group compared to the placebo group at all time points (p<0.001) indicating a better clinical response as assessed by the owner (Table S5). Likewise, LS means of IRTT-VAS scores were significantly higher in the ilunocitinib group compared to the placebo group at all time points (p<0.001) also indicating a better clinical response as assessed by the veterinary surgeon (Table S5).

Perceived lack of efficacy

A total of 59 (14 ilunocitinib, 45 placebo) of 268 dogs (22%) exited before completion of the study owing to a perceived lack of efficacy (Table 2). Forty-eight (10 ilunocitinib, 38 placebo) dogs exited by D28 and the remainder (four ilunocitinib, seven placebo) exited by D84.

Safety analyses

Physical examinations

Means for heart rate, body temperature and respiration rate were similar between groups at baseline and remained stable over time. The mean percentage change in body weight on D112 compared to baseline was +4.9% for the ilunocitinib group and –1.5% for the placebo group.

Haematological and serum chemical results

Although all means remained within physiological ranges, a slight treatment effect was observed at D28 for white blood cell counts (WBCs; absolute), notably a decrease in neutrophils and eosinophils (relative and absolute), and monocytes (absolute) and an increase in relative lymphocytes in the ilunocitinib-treated dogs. A treatment-by-time effect was observed on D112 as a mild increase in mean corpuscular volume (MCV) in the ilunocitinib group, albeit remaining in the physiological range. Mean serum chemistry variables were all within normal physiological ranges at all time points except for triglycerides which were slightly above the normal range (20–150 mg/dL) for the ilunocitinib group on D56 (164.9 mg/dL) and D84 (158.5 mg/dL), and for the placebo group on D112 (152.4 mg/dL). A treatment effect was observed, notably a slight increase in blood urea nitrogen (BUN), chloride, creatinine, potassium and cholesterol, and a mild decrease in globulin and total protein in the ilunocitinib-treated dogs although all means remained within physiological ranges. A

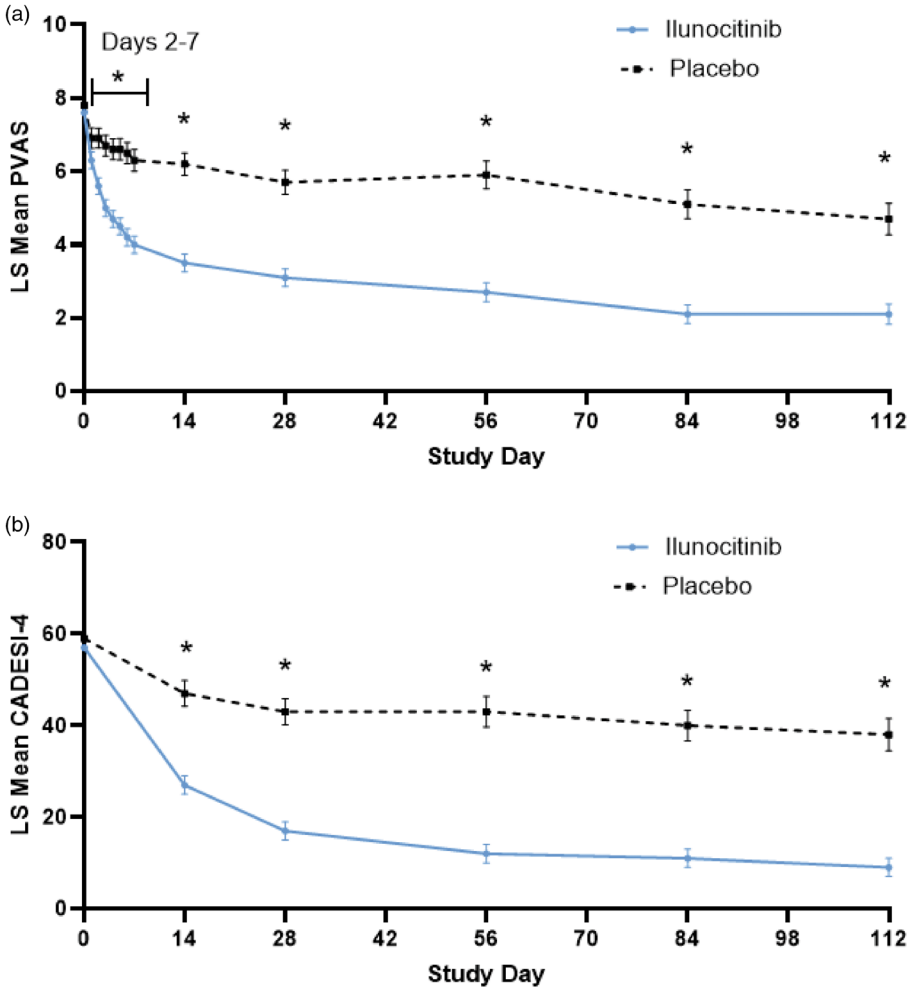

FIGURE 2 Least-square (LS) mean pruritus Visual Analog Scale (PVAS) scores (a) and LS mean Canine Atopic Dermatitis Extent and Severity Index, 4th iteration (CADESI-04) scores (b) over time in the ilunocitinib-treated and placebo groups. *n*, number of dogs. Error bars are standard errors (SE). *Indicates a significant difference ($p < 0.001$).

treatment-by-time effect was observed on D56, D84 and D112 as a mild increase in albumin in the ilunocitinib group (Table S6). Means for USG and urine pH were similar between groups at baseline and remained stable over time.

Adverse events

Because the number of mean days on study for the ilunocitinib group (97.8) was almost double that of the placebo group (55.6 days), with medians of 112 and 29 days, respectively, the lengthier involvement of more ilunocitinib-treated dogs generated a disproportionately higher volume of safety data over the course of the study. To address these disproportionate safety data and enable a more accurate comparison of AE frequencies between treatment groups, frequency data up to D28 were presented along with data up to D112 (Table 3). The percentage of dogs with one or more AEs up to D28 were similar between treatment groups (58.0% in the ilunocitinib group [*n*=181] vs. 66.7% in the placebo group [*n*=87]) and remained consistent up to D112 (82.3% in the ilunocitinib group vs. 79.3% in the placebo group). The most reported AEs were, in a descending order of frequency, skin and appendage disorders, digestive tract disorders, systemic disorders, and ear and labyrinth disorders.

Serious AEs (SAEs) were observed in five (three ilunocitinib, two placebo) dogs. One ilunocitinib-treated dog reported tendonitis on D111 from trauma, which eventually resulted in an amputation as a consequence of difficult aftercare of the fractious dog. Another ilunocitinib-treated dog experienced multiple SAEs owing to a ruptured abdominal hemangiosarcoma identified shortly after study exit. Although it completed the study, it was euthanised 1 month later. For the third ilunocitinib dog, a moderate neutropenia was discovered on D28. This dog had a pre-existing subclinical urinary tract infection based on the urine sample at enrolment, which had further progressed, and it exited the study on D35 to allow for antibiotic treatment. Post-exit rechecks for the next 2 months revealed cyclic neutropenia in this patient. The two SAEs in the placebo group involved the digestive and circulatory systems. None of the reported SAEs were considered to be treatment-related.

Concomitant medications

A variety of concomitant medications and therapies were administered to 180 (99.4%) and 87 (100%) of

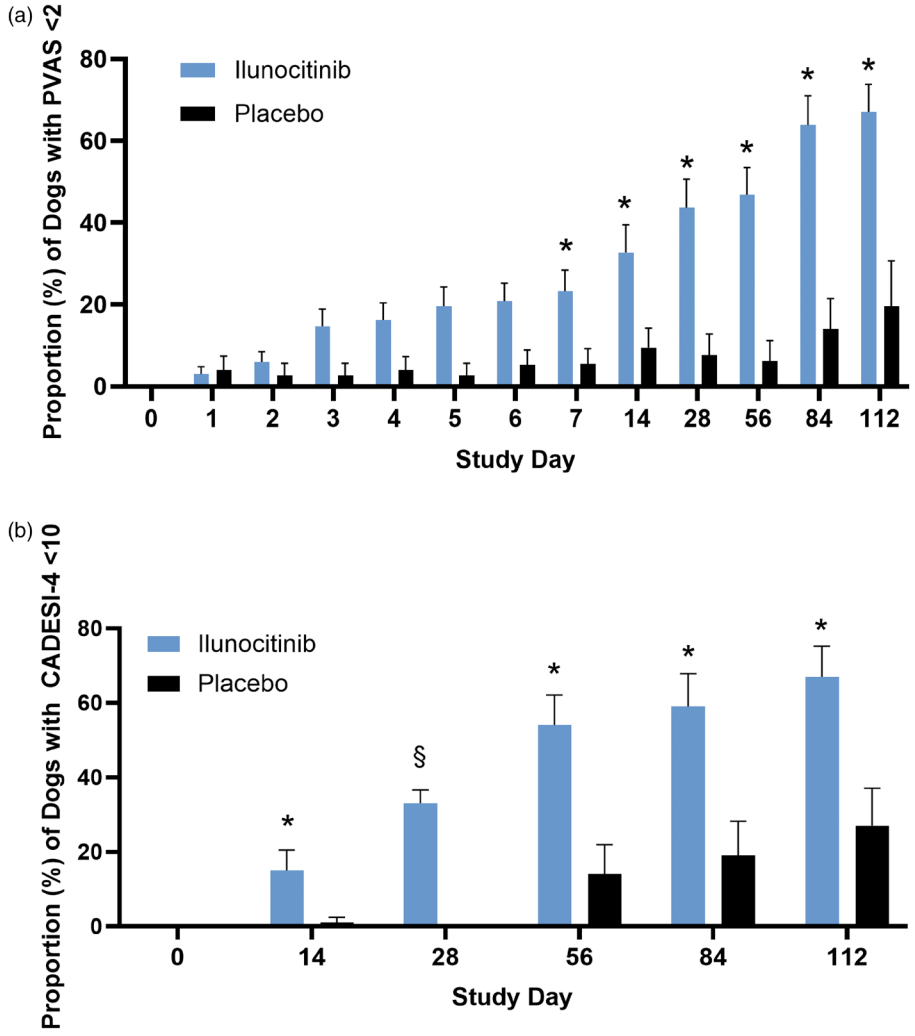

FIGURE 3 Proportions (%) of dogs achieving normal pruritus Visual Analog Scale (PVAS) scores (<2) (a) and normal Canine Atopic Dermatitis Extent and Severity Index, 4th iteration (CADESI-04) scores (<10) (b) in the ilunocitinib-treated and placebo groups, thereby achieving clinical remission from pruritus and skin lesions, respectively. *n*, number of dogs. Error bars are standard errors (SE). *Indicates significant difference ($p<0.05$); §No placebo cases had CADESI-04 < 10 on Day 28.

TABLE 2 Cumulative proportion of dogs ($n=268$) exiting before completion of the study owing to a perceived lack of efficacy per group and time point (D, day).

	Cumulative values *n* (%)	
Time period withdrawn	**Ilunocitinib (*n* = 181)**	**Placebo (*n* = 87)**
By D14	4 (2.2)	22 (25.3)
By D28	10 (5.5)	38 (43.7)
By D56	14 (7.7)	43 (49.4)
By D84	14 (7.7)	45 (51.7)
By D112	14 (7.7)	45 (51.7)

ilunocitinib-treated and placebo dogs, respectively, during the study period. However, systemic and topical otic antimicrobials were restricted during the first 4 weeks. Dogs may have received more than one concomitant treatment and/or received the same medication multiple times (Table S7). Most commonly (>20% of dogs) administered concomitant medications were ectoparasiticides, skin/otic topical preparations/cleansers containing antibacterial/antiseptic/antifungal agents and vaccines.

DISCUSSION

This study evaluated the efficacy and safety of ilunocitinib, a novel JAKi, following once-daily oral administration for the control of pruritus and skin lesions associated with cAD under field conditions. Dogs were enrolled from geographically diverse sites with a broad representation of ages, breeds, pre-existing medical conditions and concomitant medications. Results demonstrated that once-daily oral administration of ilunocitinib was effective at controlling clinical signs associated with cAD and was well tolerated in these client-owned dogs. The treatment success rate was significantly higher in the ilunocitinib group (83%) compared to the placebo group (31%) after 28 days of therapy. Furthermore, by D28, only a small number of dogs (5.5%) in the ilunocitinib group exited the study for perceived lack of efficacy compared to 44% of placebo dogs, further supporting the clinical efficacy of ilunocitinib.

Daily administration of ilunocitinib induced a rapid and significant decline in the mean PVAS score evident as early as after the first administration. A clinically relevant (≥50%) decrease in the pruritic

TABLE 3 Summary of adverse events (AEs) reported during the study for ilunocitinib (n=181) and placebo (n=87) groups up to study Day (D)28 and D112.

	D0–D28		D0–D112	
	Ilunocitinib	Placebo	Ilunocitinib	Placebo
AE[a]	*n* (%)[b]	*n* (%)[b]	*n* (%)[b]	*n* (%)[b]
Any AE	105 (58.0)	58 (66.7)	149 (82.3)	69 (79.3)
Skin and appendage disorders	46 (25.4)	36 (41.4)	80 (44.2)	45 (51.7)
Digestive tract disorders	40 (22.1)	16 (18.4)	77 (42.5)	23 (26.4)
Systemic disorders	31 (17.1)	18 (20.7)	59 (32.6)	22 (25.3)
Ear and labyrinth disorders	20 (11.0)	20 (23.0)	31 (17.1)	26 (29.9)
Eye disorders	5 (2.8)	9 (10.3)	18 (9.9)	11 (12.6)
Respiratory tract disorders	6 (3.3)	1 (1.1)	18 (9.9)	2 (2.3)
Renal and urinary disorders	8 (4.4)	1 (1.1)	14 (7.7)	2 (2.3)
Musculoskeletal disorders	2 (1.1)	2 (2.3)	10 (5.5)	3 (3.4)
Behavioural disorders	5 (2.8)	4 (4.6)	9 (5.0)	5 (5.7)
Neurological disorders	4 (2.2)	3 (3.4)	7 (3.9)	3 (3.4)
Psychological disorders	3 (1.7)	0 (0)	6 (3.3)	0 (0)
Blood and lymphatic system disorders	2 (1.1)	1 (1.1)	3 (1.7)	1 (1.1)
Hepato-biliary disorders	0 (0)	0 (0)	2 (1.1)	0 (0)
Mammary gland disorders	2 (1.1)	1 (1.1)	2 (1.1)	1 (1.1)
Reproductive system disorders	1 (0.6)	2 (2.3)	2 (1.1)	3 (3.4)
Application site disorders	0 (0)	0 (0)	1 (0.6)	0 (0)
Immune system disorders	0 (0)	3 (3.4)	1 (0.6)	4 (4.6)
Cardiovascular system disorders	0 (0)	0 (0)	0 (0)	1 (1.1)

[a]All related or unrelated AEs were included in this summary table; each reported clinical sign was coded with VeDDRA (Veterinary Dictionary for Drug Related Affairs) by preferred terms (PT).

[b]Number of percentage of animals (among population) that had at least one event of the indicated type.

behaviour of a significant proportion of ilunocitinib-treated dogs (29%) was detected as early as 3 days of treatment. This proportion of dogs continued to progressively increase over time to 82% by D112. Results at this last time point were not significantly different between groups, which is very likely to be the consequence of a skewed treatment population. As anticipated, many dogs from the placebo group were withdrawn from the study owing to a perceived lack of efficacy, leading to only 29 dogs in the placebo group remaining in the study at D112, compared to 141 dogs in the ilunocitinib group. Unsurprisingly, the placebo group dogs staying on study had relatively mild clinical signs, reducing the potential for statistical significance by D112.

The rapid onset of the ameliorative effect on pruritus can have an immediate and direct impact on quality of life of both dog and owner, yet it is also crucial in preventing exacerbation of skin lesions resulting from self-trauma and secondary infections.[2,20,25]

Clinical success in controlling skin lesions has been based on demonstrating a clinically relevant (≥50%) decrease in CADESI scoring schemes.[15–18,25] In this study, the mean CADESI-04 score in the ilunocitinib group significantly reduced by more than half from baseline after 2 weeks of daily administrations. Recently, the definition of treatment success has evolved through the development of COSCAD'18 to include the demonstration of clinical remission.[19] This remission state is more specifically quantified by PVAS and CADESI-04, correlating to scores of <2 and <10, respectively.[18,19,21,23,25] Considering this, results from this study demonstrate that clinical remission was achieved by a significant proportion of ilunocitinib-treated dogs by 1 week for pruritus (23%) and 2 weeks for skin lesions (15%), reaching 67% by the end of the study for both clinical scores versus 20%–30% in placebo dogs. To the best of the authors' knowledge, this is the first time that these normal benchmark thresholds have been used in the assessment of the efficacy of a JAKi. Independently assessed responses to treatment (ORTT-VAS and IRTT-VAS) further confirmed the efficacy of ilunocitinib perceived by both owners and veterinary surgeons.

Commonly used therapeutic agents such as glucocorticoids often cause undesirable adverse effects, especially with long-term use, whereas ciclosporin, an approved drug for the treatment of cAD, has a delayed onset of 4–6 weeks before a beneficial clinical effect can be detected.[5,26] It is difficult to compare the efficacy of ilunocitinib directly with these treatments, owing to major differences in target population, mode-of-action and efficacy measures. However, a comparison with oclacitinib, the currently marketed veterinary JAKi, may be possible. In a placebo-controlled study evaluating oclacitinib

treatment for cAD, the twice-daily administration of that JAKi resulted in a rapid decline in pruritus within 24 h based on owner LS mean PVAS scores.[16] Similar results were observed in this study using ilunocitinib, yet with only once-daily administration. In one study, owner-assessed pruritus scores decreased from moderate to severe at baseline to very mild after 14 days of twice-daily oclacitinib treatment.[16] Following this, the mean PVAS score rebounded from 2.6 to 4.1 by D28 when the dosing regimen was changed to once-daily administration and stayed above a mean PVAS score of 3 until D112.[16] By contrast, Owner-assessed PVAS decreased from moderate to severe at baseline to very mild after a 14 days of once-daily ilunocitinib treatment and continued to steadily decrease, eventually reaching normal (PVAS < 2) in two-thirds of the dogs by D112. Results from this study therefore show that once-daily administration of ilunocitinib may provide similar rapid efficacy to twice-daily administration of oclacitinib without evidence of the pruritus rebound reported for oclacitinib when transitioning from twice-daily to once-daily administration.[16,27–29] A direct comparative study, however, is needed to confirm these conclusions.

Safety data produced from these dogs who received daily treatment administration for 112 consecutive days revealed that ilunocitinib was well-tolerated even when administered concomitantly with other classes of medications for a variety of therapeutic reasons. The mild weight gain observed in ilunocitinib-treated dogs may have been secondary to improvement in the dog's pruritic condition and skin lesions, resulting in a more comfortable dog with lower daily calorific needs, as reported for oclacitinib.[16] Overall, means for haematological, serum chemical and urinalysis results were within normal limits during the current study in both treatment groups, with most parameter means remaining within physiological ranges. However, at D28, a decrease in neutrophils and eosinophils (relative and absolute) and monocytes (absolute), and an increase in relative lymphocytes were observed in the ilunocitinib-treated dogs. At D112, a mild increase in MCV was observed in the ilunocitinib group, albeit remaining in the physiological range. Mild decreases in serum globulin and WBCs (eosinophils, neutrophils and monocytes), and mild increases in cholesterol were reported previously with the administration of oclacitinib.[29] JAKi as a class also are known to cause mild elevations of lipid concentrations, as seen in this study, owing to the role of the JAK–STAT pathway in cholesterol synthesis.[24,30] However, these elevated lipid concentrations generally have little to no clinical relevance, and no health risks have been identified previously in humans.[31,32]

As expected from a clinical trial in dogs with cAD, skin and otic-related disorders were among the most reported AEs, yet in this study, they were reported less often in the ilunocitinib group compared to the placebo group. Most AEs were generally higher in placebo dogs, presumably as a consequence of inadequate control of clinical signs associated with AD. Adverse events considered 'probable' related to the treatment administered were infrequent in both groups (2.2% ilunocitinib vs. 2.3% placebo) and were nonserious, resolving spontaneously or following appropriate treatment. These results are in line with previous studies reporting the safety of JAKi.[16,17,25,33] The three SAEs reported for the ilunocitinib group were not considered related to JAKi administration.

A major limitation of this study was the resulting sample size ratio of approximately 5:1 between groups (rather than 2:1) at the end of the study. This occurred owing to progressive removal or exit before study completion for many placebo dogs as a consequence of the deterioration of their cAD symptoms over time. A quickly decreasing number of placebo dogs in this type of study may cause (1) the reduction in the difference between the treatment and placebo group as less severe placebo cases continued the study, and these dogs may have further improved their cAD owing to seasonal fluctuations, and (2) the imbalance in the analysis of AEs for the full study duration (112 days). Nevertheless, the beneficial effect of ilunocitinib on pruritus and skin lesions associated with cAD in the study population was clearly demonstrated. Additionally, the primary effectiveness variable successfully met statistical significance at D28 ($p < 0.001$). However, secondary end-point analyses were not adjusted for multiple testing, resulting in the potential for inflating the Type I error. The treatment effect interpretation for the secondary end-points should take this into consideration.

CONCLUSIONS

Ilunocitinib conveniently administered once daily was well tolerated and effective in rapidly reducing pruritus and resolving skin lesions associated with cAD. There was a steady and substantial improvement in both pruritus and skin lesions over time, with clinical remission achieved in two-thirds of atopic dogs after 4 months of treatment. Ilunocitinib represents a safe and effective alternative for managing clinical signs associated with cAD in dogs.

AUTHOR CONTRIBUTIONS

Sophie Forster: Writing – original draft; writing – review and editing; methodology; supervision; conceptualization. **Candace M. Trout:** Writing – review and editing; project administration. **Simona Despa:** Formal analysis. **Annette Boegel:** Writing – review and editing. **Darren Berger:** Writing – review and editing. **Stephen King:** Writing – review and editing.

ACKNOWLEDGEMENTS

We would like to thank all of the dog owners and the following who enrolled dogs in this study: Susan Baker, Karin Beale, Becka Byrd, Loren Candito, Sheila Carpenter, August Claybrook, Kimberly Coyner, Darin Dell, Natalie Dyson, Samuel Geller, David Genovese, Angela Gossom, Laura Gray, Chessie Green, Mochel

Choi Kat, Thomas Lewis, Rachel Lurvey, Joel Manley, Leigh O'Brien, Bill Oxford, Christine Rees, Sandra Sargent, Mitchell Song, Tim Strauss, Meliss Wiest, Stephanie Wolf and Danielle Wyatt. We thank the following current and former Elanco colleagues for their contributions: Jane Owens, Kelly Doucette and Shilpa Rani.

FUNDING INFORMATION

The study was initiated and funded by Elanco Animal Health, Inc., Greenfield, IN, USA.

CONFLICT OF INTEREST STATEMENT

All authors are current or former employees of Elanco Animal Health.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Forster S, Trout CM, Despa S, Boegel A, Berger D, King S. Efficacy and field safety of ilunocitinib for the control of atopic dermatitis in client-owned dogs: A multicentre, double-masked, randomised, placebo-controlled clinical trial. Vet Dermatol. 2025;00:1–13. https://doi.org/10.1111/vde.13344

Zusammenfassung

Hintergrund: Die Inhibition des Januskinase Zyklus (JAK) Zyklus ist eine gut begründete Behandlungsoption bei der caninen atopischen Dermatitis (cAD).
Ziel: Die Evaluierung der Wirksamkeit und der Sicherheit von Ilunocitinib, einem neuen JAK-Inhibitor zur Kontrolle von Juckreiz und Hautveränderungen bei Hunden mit cAD in Privatbesitz.
Tiere: Zweihundertachtundsechzig Hunde aus 25 Veterinärkliniken.
Materialien und Methoden: In dieser randomisierten, doppelblinden klinischen Studie erhielten die Hunde entweder Ilunocitinib (n=181; 0,6-0,8 mg/kg) oder Plazebo (n=87; 0,0 mg/kg) Tabletten einmal täglich für 112 Tage. Der Juckreiz wurde von den BesitzerInnen mittels Pruritus Visual Analog Scale (PVAS) beurteilt, während die Hautläsionen durch UntersucherInnen mittels cAD Extent und Severity Index, 4te Ausgabe (CADESI-01) erfasst wurden. Ein Behandlungserfolg wurde definiert als ≥50% Reduzierung vom Ausgangswert des PVAS oder CADESI-04 Wertes am Tag (D)28. Es wurde ebenfalls der Anteil der Hunde erfasst, die eine klinische Remission vom Juckreiz (PVAS <2) oder der Hautläsionen (CADESI-04 <10) erzielten.
Ergebnisse: Am D28 erzielten 83% der mit Ilunocitinib-behandelten Hunde einen Behandlungserfolg im Vergleich zu 31% der Plazebo-behandelten Hunde (p <0,001). Eine signifikant höhere Anzahl von Hunden, die mit Ilunocitinib-behandelt wurden, erzielten eine ≥50%ige Reduzierung des CADESI-04 Wertes zu allen Zeitpunkten (p <0,001). Beim Anteil der Hunde, die eine klinische Remission erzielten, waren PVAS oder CADESO-04 Werte in der Ilunocitinib Gruppe signifikant höher, was am D7 bzw D14 deutlich wurde (p <0,05). Die Ilunocitinib Behandlung über eine Dauer von 112 Tagen wurde gut toleriert.
Schlussfolgerungen und klinische Bedeutung: Eine einmal tägliche Verabreichung von Ilunocitinib wurde gut toleriert und war effektiv, um Juckreiz rasch zu reduzieren und Hautveränderungen im Zusammenhang mit cAD zu heilen. Eine klinische Remission wurde von zwei Drittel der Hunde nach einer 4-monatigen Behandlung erzielt. Ilunocitinib ist sicher und wirksam beim Management der klinischen Zeichen im Zusammenhang mit cAD.

摘要

背景: 抑制 Janus 激酶 (JAK) 通路是治疗犬特应性皮炎 (cAD) 的可靠选择。
目的: 评估伊洛西替尼(一种新型 JAK 抑制剂)在控制患有 cAD 的犬的瘙痒和皮肤病变方面的疗效和安全性。
动物: 25 家兽医诊所的 268 只犬。
材料和方法: 在这项随机、双盲临床试验中,犬每天服用一次伊诺西替尼(n=181;0.6-0.8 mg/kg)或安慰剂(n=87;0.0 mg/kg)片剂,持续 112 天。主人使用瘙痒视觉模拟量表 (PVAS) 评估瘙痒,而研究人员使用 cAD 范围和严重程度指数第 4 次迭代 (CADESI-04) 评估皮肤病变。治疗成功定义为第 28 天 (D) 的 PVAS 或 CADESI-04 评分较基线降低≥50%。还评估了临床缓解瘙痒 (PVAS <2) 或皮肤病变 (CADESI-04 <10) 的犬的比例。
结果: 在第 28 天,伊诺西替尼治疗组有 83% 的犬达到治疗成功,而安慰剂组仅有 31%(p <0.001)。在所有时间点,伊诺西替尼治疗组中达到 CADESI-04 评分降低 ≥50% 的犬比例显著更高(p <0.001)。从第 7 天和第 14 天的PVAS 或 CADESI-04 评分开始,伊诺西替尼治疗组达到临床缓解的犬比例显著更高(p <0.05)。为期 112 天的伊诺西替尼治疗耐受性良好。
结论和临床相关性: 每日一次的伊诺西替尼耐受性良好,可有效快速减少瘙痒并解决 cAD 相关皮肤病变。三分之二的犬在治疗 4 个月后达到临床缓解。伊诺西替尼对于管理与 cAD 相关的临床症状是安全有效的。

Résumé

Contexte: L'inhibition de la voie Janus kinase (JAK) est une option bien établie pour la dermatite atopique canine (DAC).
Objectif: Évaluer l'efficacité et l'innocuité de l'ilunocitinib, un nouvel inhibiteur de JAK, pour le contrôle du prurit et des lésions cutanées chez les chiens atteints de DAC.
Animaux: Deux cent soixante-huit chiens dans 25 cliniques vétérinaires.
Matériels et méthodes: Dans cet essai clinique randomisé, en double aveugle, les chiens ont reçu soit des comprimés d'ilunocitinib (n=181 ; 0,6-0,8 mg/kg), soit un placebo (n=87 ; 0,0 mg/kg) une fois par jour pendant 112 jours. Le prurit a été évalué par les propriétaires à l'aide d'une échelle visuelle analogique du prurit (PVAS),

tandis que les lésions cutanées ont été évaluées par les investigateurs à l'aide du cAD Extent and Severity Index, 4th iteration (CADESI-04). Le succès du traitement a été défini comme une réduction ≥50% du score PVAS ou CADESI-04 au jour (J)28. Les proportions de chiens ayant obtenu une rémission clinique du prurit (PVAS <2) ou des lésions cutanées (CADESI-04 <10) ont également été évaluées.
Résultats: À J28, 83 % des chiens traités par ilunocitinib ont réussi le traitement, contre 31 % des chiens traités par placebo (p <0,001). Une proportion significativement plus élevée de chiens traités par ilunocitinib a obtenu une réduction ≥50 % des scores CADESI-04 à tous les moments (p <0,001). La proportion de chiens ayant obtenu une rémission clinique des scores PVAS ou CADESI-04 était significativement plus élevée dans le groupe ilunocitinib à partir de J7 et J14, respectivement (p <0,05*)*. Le traitement de 112 jours par l'ilunocitinib a été bien toléré.
Conclusions et pertinence clinique: L'ilunocitinib administré une fois par jour a été bien toléré et efficace pour réduire rapidement le prurit et résoudre les lésions cutanées associées à DAC. Une rémission clinique a été obtenue chez deux tiers des chiens après 4 mois de traitement. L'ilunocitinib est sûr et efficace pour la prise en charge des signes cliniques associés à la DAC.

要約
背景: ヤヌスキナーゼ(JAK)経路の阻害は、犬アトピー性皮膚炎(cAD)に対して確立された選択肢である。
目的: 本研究の目的は、新規のJAK阻害剤であるイルノシチニブの、オーナー所有犬cADにおける掻痒および皮膚病変の制御に対する有効性および安全性を評価することであった。
対象動物: 25の動物病院における268頭の犬。
材料と方法: この無作為化二重盲検臨床試験では、犬はイルノシチニブ(n=181、0.6~0.8mg/kg)またはプラセボ錠剤(n=87、0.0mg/kg)を1日1回、112日間投与された。掻痒はオーナーが痒みのVisual Analog Scale(PVAS)を用いて評価し、皮膚病変は治験責任医師がcAD Extent and Severity Index, 4th iteration(CADESI-04)を用いて評価した。治療成功は投与28日目にベースラインのPVASまたはCADESI-04スコアから50%以上減少したことと定義した。また、痒み(PVAS<2)または皮膚病変(CADESI-04<10)の臨床的寛解を達成した犬の割合も評価した。
結果: 試験開始28日目の時点で、イルノシチニブ投与犬の83%が治療成功を達成したのに対し、プラセボ投与犬では31%であった(p<0.001)。イルノシチニブ投与群では、すべての時点でCADESI-04スコアが50%以上低下した犬の割合が有意に高かった(p<0.001)。PVASまたはCADESI-04スコアの臨床的寛解を達成した犬の割合は、それぞれ試験開始7日目および14日目からイルノシチニブ群で有意に高かった(p<0.05)。112日間のイルノシチニブ治療は良好な忍容性を示した。
結論と臨床的意義: イルノシチニブは1日1回投与で忍容性が高く、掻痒を速やかに軽減し、cADに伴う皮膚病変を消失させる効果があった。治療4ヵ月後に3分の2の犬で臨床的寛解が達成された。イルノシチニブはcADに伴う臨床症状の管理に安全かつ有効である。

RESUMO
Contexto: A inibição da via da Janus quinase (JAK) é uma opção bem estabelecida para o tratamento da dermatite atópica canina (DAC).
Objetivo: Avaliar a eficácia e a segurança do ilunocitinib, um novo inibidor da JAK, para o controle do prurido e das lesões cutâneas em cães com DAC, de proprietários de cães.
Animais: Duzentos e sessenta e oito cães em 25 clínicas veterinárias.
Materiais e Métodos: Neste ensaio clínico randomizado, duplo-cego, os cães receberam comprimidos de ilunocitinib (n=181; 0,6–0,8 mg/kg) ou placebo (n=87; 0,0 mg/kg) uma vez ao dia durante 112 dias. O prurido foi avaliado pelos tutores utilizando a Escala Visual Analógica de Prurido (PVAS), enquanto as lesões cutâneas foram avaliadas pelos pesquisadores utilizando o Índice de Extensão e Gravidade da DAC, 4ª iteração (CADESI-04). O sucesso do tratamento foi definido como uma redução ≥50% no escore inicial de PVAS ou CADESI-04 no Dia (D)28. As proporções de cães que alcançaram remissão clínica do prurido (PVAS <2) ou lesões cutâneas (CADESI-04 <10) também foram avaliadas.
Resultados: No D28, 83% dos cães tratados com ilunocitinib alcançaram sucesso no tratamento, em comparação com 31% dos cães tratados com placebo (p <0,001). Uma proporção significativamente maior de cães tratados com ilunocitinib alcançou uma redução ≥50% na pontuação de CADESI-04 em todos os momentos (p <0,001). A proporção de cães que alcançaram remissão clínica na pontuação de PVAS ou CADESI-04 foi significativamente maior no grupo ilunocitinib a partir do D7 e D14, respectivamente (p <0,05). O tratamento de 112 dias com ilunocitinib foi bem tolerado.
Conclusões e Relevância Clínica: O ilunocitinib administrado uma vez ao dia foi bem tolerado e eficaz na rápida redução do prurido e na resolução das lesões cutâneas associadas à DAC. A remissão clínica foi alcançada em dois terços dos cães após 4 meses de tratamento. O ilunocitinib é seguro e eficaz no tratamento dos sinais clínicos associados à DAC.

RESUMEN
Introducción: La inhibición de la vía de la quinasa Janus (JAK) es una opción bien establecida para el control de la dermatitis atópica canina (cAD).
Objetivo: Evaluar la eficacia y seguridad de ilunocitinib, un nuevo inhibidor de JAK, para el control del prurito y las lesiones cutáneas en perros con cADA de propietarios particulares.
Animales: Doscientos sesenta y ocho perros de 25 clínicas veterinarias.
Materiales y métodos: En este ensayo clínico al azar, doble ciego, los perros recibieron comprimidos de ilunocitinib (n=181; 0,6-0,8 mg/kg) o placebo (n=87; 0,0 mg/kg) una vez al día durante 112 días. El prurito fue evaluado

por los propietarios mediante la Escala Visual Análoga de Prurito (EVAP), mientras que las lesiones cutáneas fueron evaluadas por los investigadores mediante el Índice de Extensión y Gravedad de la cAD, 4.ª revision (CADESI-04). El éxito del tratamiento se definió como una reducción ≥50% con respecto a la puntuación inicial en la escala PVAS o CADESI-04 el día 28. También se evaluó la proporción de perros que lograron remisión clínica del prurito (PVAS <2) o de las lesiones cutáneas (CADESI-04 <10).

Resultados: El día 28, el 83% de los perros tratados con ilunocitinib lograron éxito del tratamiento, en comparación con el 31% de los perros tratados con placebo (p <0,001). Una proporción significativamente mayor de perros tratados con ilunocitinib logró una reducción ≥50% en las puntuaciones CADESI-04 en todos los puntos temporales (p <0,001). La proporción de perros que lograron remisión clínica en las puntuaciones PVAS o CADESI-04 fue significativamente mayor en el grupo de ilunocitinib, comenzando el día 7 y el día 14, respectivamente (p <0,05). El tratamiento con ilunocitinib, de 112 días de duración, fue bien tolerado.

Conclusiones y relevancia clínica: El ilunocitinib administrado una vez al día fue bien tolerado y eficaz para reducir rápidamente el prurito y resolver las lesiones cutáneas asociadas a la cAD. Dos tercios de los perros alcanzaron la remisión clínica tras 4 meses de tratamiento. El ilunocitinib es seguro y eficaz para el manejo de los signos clínicos asociados a la cAD.