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# Efficacy and Field Safety of Ilunocitinib for the Control of Allergic Dermatitis in Client-Owned Dogs: A Multicenter, Double-Masked, Randomised, Placebo-Controlled Clinical Trial

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## ABSTRACT

**Background:** Inhibition of the Janus kinase pathway is an established treatment for allergic dermatitis.

**Objective:** To evaluate the efficacy and safety of ilunocitinib for control of pruritus in dogs with allergic dermatitis in a randomised, double-masked clinical trial.

**Animals:** Three-hundred-and-six dogs at 15 veterinary clinics.

**Materials and Methods:** Enrolled client-owned dogs with severe pruritus and a presumptive diagnosis of allergic dermatitis were randomised to receive either ilunocitinib ($n = 206$; 0.6–0.8 mg/kg) or placebo ($n = 100$; 0 mg/kg) once daily for 28 days. Pruritus was assessed by owners using a pruritus Visual Analog Scale (PVAS). Treatment success was defined as ≥ 50% reduction from baseline PVAS on at least five of seven initial treatment days. Clinical remission from pruritus was considered achieved when PVAS < 2. Safety assessments were conducted over 112 days.

**Results:** On Day (D)7, 25.4% of ilunocitinib-treated dogs achieved treatment success compared to 7.7% of placebo dogs ($p = 0.006$). Starting on D3, the proportion of dogs with a ≥ 50% reduction from baseline PVAS was significantly higher in the ilunocitinib group ($p < 0.01$) and by D28, a significantly higher percentage of ilunocitinib-treated dogs (51.8%) achieved clinical remission compared to placebo dogs (12.7%; $p < 0.05$). Signs of dermatitis improved within 7 days. The 112-day ilunocitinib treatment was well-tolerated.

**Conclusions and Clinical Relevance:** Ilunocitinib administered once a day was well tolerated and effective at rapidly reducing pruritus, with steady and continuous improvement over time. Clinical remission of pruritus was achieved by 51.8% of ilunocitinib-treated dogs by D28, regardless of allergic aetiology.

## 1 | Introduction

Canine allergic dermatitis is characterised by intense pruritus, manifesting as scratching, rubbing, licking, chewing and overall discomfort [1, 2]. Potential aetiologies in dogs include flea allergy dermatitis (FAD), contact allergy, cutaneous adverse food reactions, and canine atopic dermatitis (cAD) [3–6]. The treatment of acute allergic dermatitis typically focuses on quickly reducing pruritus and skin inflammation while trying to identify and eliminate the underlying cause if possible [5–8]. Common options to systemically treat allergic dermatitis are oral immunomodulators such as glucocorticoids and

Janus kinase inhibitors (JAKi), or injectable anti-interleukin (IL)-31 monoclonal antibodies (mAB). Supportive therapy includes antihistamines, nonirritating shampoos and oral essential fatty acids, along with antibiotics to treat secondary bacterial infections [5, 9–14]. Even though a majority of dogs suffering from allergic dermatitis can be managed well with the aforementioned treatment options, there are still many cases, which either do not satisfactorily respond to any of the medications or where undesired adverse effects limit long-term use of a product such as glucocorticoids [13, 15–17]. Therefore, there is a need to develop alternative therapies for the management of pruritus associated with canine allergic dermatitis.

Molecular pathways involved in the development of allergic pruritus offer a number of potential targets for therapeutic drugs. Regardless of the allergic trigger, the Janus kinase-signal transducer and activator of transcription (JAK–STAT) pathway plays an important role in the signalling process of several proinflammatory and pruritogenic cytokines, such as IL-2, IL-4, IL-6, IL-8, IL-13 and IL-31, which are involved in the pathogenesis of allergic dermatitis to various degrees [5, 18–23]. Hence, targeting the JAK–STAT pathway with small molecules such as JAKi modulates T-helper-2 cell-mediated inflammation, epidermal barrier dysfunction and pruritus signalling [24–30]. Ilunocitinib is an approved non-selective JAKi (Zenrelia; Elanco Animal Health) which inhibits the function of a variety of pruritogenic, pro-inflammatory and allergy-related cytokines that are dependent on JAK enzymes. Ilunocitinib has a high potency for JAK1, JAK2 and tyrosine kinase 2 (TYK2) inhibition (unpublished data). While both oclacitinib (Apoquel; Zoetis) and ilunocitinib provide rapid relief of pruritus, in a recent cAD clinical trial, a once-a-day administration of ilunocitinib offered significantly better long-term control of pruritus and skin lesions compared to twice-a-day for 14 days, then once-a-day thereafter oclacitinib administration, with more dogs achieving clinical remission of pruritus from D28 to D112 [31]. Fast reduction of pruritus (within the first week of treatment) is an important benefit of JAKis as it prevents self-trauma by intense scratching, mitigating further damage to the skin barrier and subsequent worsening of clinical signs, such as secondary bacterial and fungal infections [32–34].

Owner-assessed enhanced pruritus Visual Analog Scale (PVAS) scoring, a validated measure [7, 35, 36], and previously used yet nonvalidated [9] veterinary surgeon-assessed dermatitis VAS (DVAS) scoring using a 10 cm line with word descriptors are considered acceptable tools to assess the severity of pruritus and dermatitis before and during the administration of novel therapeutic agents in canine clinical trials [7, 9, 10, 35, 36]. Historically, treatment success is defined by a numerical reduction from baseline, either of 2 units or by ≥ 50% in PVAS score. However, in recent years, the International Committee of Allergic Diseases of Animals (ICADA) introduced a Core Outcome Set for Canine Atopic Dermatitis (COSCAD'18) to emphasise the importance of achieving a level below a certain threshold of pruritus [7, 37]. Based on this outcome set, clinical remission from pruritus is defined as a PVAS score of < 2, which is comparable to the pruritus level of 'normal', nonallergic dogs [35].

The objective of this study was to evaluate the efficacy and safety of ilunocitinib, a new JAKi, administered to dogs with allergic dermatitis as a once-daily oral tablet to control pruritus based on the owner-assessed PVAS scoring. Additionally, this study assessed the proportion of dogs achieving clinical remission from pruritus (PVAS < 2).

## 2 | Materials and Methods

### 2.1 | 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.

### 2.2 | Study Design

This double-masked, randomised, placebo-controlled, multicentre clinical trial was conducted at 15 veterinary clinics across the USA. Dogs meeting all inclusion criteria, with a presumptive diagnosis of allergic dermatitis, were randomised in a 2:1 ratio to receive once daily an oral dose of either ilunocitinib or placebo tablets for ≤ 28 days. Approximately 6 months after first case inclusion, the study protocol was amended to include an optional Continuation Phase to collect additional data on the long-term efficacy and safety of ilunocitinib. Dogs that completed the 28-day period had the option to enrol in the masked Continuation Phase for another 12 weeks, maintaining the previously assigned treatment. Owners were free to withdraw their dog at any time.

A sample size estimate of 240 evaluable subjects (160 ilunocitinib; 80 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 30% (ilunocitinib) and 7.5% (placebo) success rates based on unpublished data from a previous pilot field study.

### 2.3 | Inclusion and Exclusion Criteria

Client-owned dogs, of any breed, sex, ≥ 12 months of age and weighing ≥ 3.0 kg, were eligible for enrolment. Dogs were in good health as per physical examination (including haematological and serum biochemical parameters) at enrolment (D0), and free of serious or systemic diseases that could potentially interfere with study objectives. They were, however, either newly diagnosed or had a history of at least one of the following presumptive diagnoses: cAD, contact dermatitis, FAD, sarcoptic mange, food hypersensitivity or other allergic dermatitis. Enrolment also required a minimum PVAS score of 6 of 10 (corresponding to severe itching) as assessed by owners. No minimum DVAS was required for enrolment.

Dogs with conditions requiring continuous medications could be enrolled so long as the treatment remained consistent before and throughout the study (e.g., nonsteroidal anti-inflammatory

drugs [NSAIDs], antiseizure or thyroid medications, ophthalmic tacrolimus/ciclosporin) and/or the medication was not likely to interfere with evaluations (e.g., parasiticides and/or vaccinations). Specific washout periods for prohibited medications (e.g., JAKi, glucocorticoids, local anaesthetics, antimicrobials, systemic ciclosporin and anti-IL-31 mAB) or those which were conditionally allowed (e.g., allergen specific immunotherapy) were strictly followed (see Table S1). Flea treatment/prevention was given monthly (or every 3 months) beginning at, and continuing after, enrolment for the duration of the study.

Pregnant or lactating dogs, 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.

### 2.4 | Randomisation and Masking

Dogs meeting all inclusion criteria were blocked and randomised in a 2:1 allocation ratio using SAS v9.4 (SAS Institute) based on order of enrolment at each clinic to receive once daily oral administrations of ilunocitinib or placebo tablets. To ensure adequate masking, ilunocitinib and placebo tablets were identical in size and appearance. All study personnel and owners remained masked throughout the study. At each site, the treatment dispenser (unmasked) designated by the investigator provided assigned tablets (ilunocitinib or placebo) to owners.

### 2.5 | Treatment Administration

Dogs in the ilunocitinib group received ilunocitinib tablets at a dose of 0.6–0.8 mg/kg body weight once daily from study D0 to D28. The dosage of ilunocitinib or placebo given to each dog from D0 to D28 was determined based on their body weight at baseline. For dogs in the Continuation Phase, their body weight at subsequent clinic visits was used to calculate the dosage. Tablets were administered with or without food, and at approximately the same time each day by the owner.

### 2.6 | Study Activities

Baseline data (clinical history, concomitant medications/therapies, body weight, results from physical examinations [including the presence or absence of fleas], blood for haematological and serum biochemical profile, PVAS and DVAS scores) were collected for each dog at enrolment (D0). Follow-up clinic visits were carried out on D7 (±1) and D28 (±2), with additional visits on D56 (±3), D84 (±3) and D112 (±3) if participating in the optional Continuation Phase. At each of these visits, a physical examination (including body weight measurement), blood collection (for haematological and serum biochemical profile), owner-assessed PVAS scoring (right before the clinic visit) and investigator-assessed DVAS scoring were performed. Urine samples were collected for urinalysis on D28 and D112, only for dogs participating in the Continuation Phase. All blood and urine samples were sent to a central laboratory (IDEXX Bioanalytics). Owners kept a daily log of feeding, dosing and observations including any possible adverse events (AEs).

### 2.7 | Efficacy Assessment

Pruritus was assessed by owners using the PVAS at D0 (enrolment), D1–7, D14 and D28, considering observations over the previous 24 h. Investigators assessed dermatitis at D0 (enrolment), D14 and D28, using an enhanced DVAS with text descriptors ranging from 0 (no dermatitis) to 10 (extremely severe dermatitis) as described previously [9]. For dogs participating in the Continuation Phase, PVAS and DVAS scoring also was performed on D56, D84 and D112.

Treatment success was defined as ≥ 50% reduction from baseline PVAS scores on ≥ 70% of study D1–7—thus, five of seven days immediately after initiation of treatment. Further efficacy assessments included (i) reduction from baseline and mean PVAS score by day (D1–7, D14 and D28), (ii) proportion of dogs with ≥ 50% reduction from baseline in PVAS score (D1–7, D14 and D28), (iii) reduction from baseline and mean DVAS score (D7 and D28) and (iv) frequency of dogs with evidence of clinical remission from pruritus (PVAS < 2) [7, 36].

### 2.8 | 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 weight measurements, clinical pathological results (haematological and serum biochemical) and urinalysis (for dogs in Continuation Phase only) results. An abnormal clinical sign occurring at any time during the study after dosing on D0 was reported as an AE, whether or not it was considered to be treatment related.

### 2.9 | Statistical Analysis

All statistical analyses were conducted using SAS FOR WINDOWS (v9.4; SAS Institute). All assessments were evaluated at a two-tailed 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 (GLMM; GLIMMIX procedure in SAS). The model used a binomial distribution and a logit link and included treatment as a fixed effect; 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. To evaluate the effect of the presence of fleas at D0 on the efficacy of ilunocitinib against pruritus, treatment success was stratified by flea presence/absence, and the proportion of treatment success was calculated for each stratum.

Investigator-assessed DVAS and owner-assessed PVAS scores were analysed using a linear mixed model for repeated measures

(LMMRM). Baseline scores were included in each model as covariates. Data collected during the Continuation Phase were analysed using summary statistics by study group for each time point.

Frequency tables with counts and proportions of dogs with normal PVAS scores for each treatment were created for each time point (i.e., D1–7, D14, D28, D56, D84 and D112). The proportion of dogs withdrawn for perceived lack of efficacy was summarised per study group using descriptive statistics at each time point.

For safety, summaries of descriptive statistics (mean, median, standard deviation [SD], minimum and maximum) were performed for physical examination findings, haematological and serum biochemical and urinalysis results by study group for each relevant time point. Frequencies of dogs reported to experience at least one AE were summarised by preferred terms (PT) based on Veterinary Dictionary for Drug Regulatory Activities (VeDDRA). Frequencies of dogs receiving each concomitant medication recorded during the study also were summarised.

## 3 | Results

### 3.1 | Baseline Demographic Characteristics

A total of 306 dogs were enrolled and received either ilunocitinib ($n = 206$) or placebo ($n = 100$) (Table 1). The mean age at enrolment was 6.2 years (range 1.0–15.0 years) and mean body weight was 22.3 kg (range 3.0–83.3 kg). Approximately half of the dogs (50.3%) were pure-bred, with the most common breeds being Labrador retriever and shih tzu (11.0% each), followed by American pit bull terriers (8.4%) and Golden retrievers (6.5%). The ilunocitinib group included a slightly higher percentage of female dogs (53.9% ilunocitinib, 49.0% placebo), and had higher percentages of intact males (21.1% ilunocitinib, 7.8% placebo) and females (13.5% ilunocitinib, 8.2% placebo).

Presumptive diagnoses were similar between groups. Over 90% of dogs in each group had a presumptive diagnosis of cAD, with only 45% and 39% having cAD as the sole diagnosis in the ilunocitinib and placebo groups, respectively. Other diagnoses included contact dermatitis (23.3% ilunocitinib, 26.0% placebo), FAD (15.5% ilunocitinib, 19.0% placebo), food hypersensitivity (24.3% ilunocitinib, 27.0% placebo) and other allergic hypersensitivity (3.4% ilunocitinib, 5.0% placebo). There were no enrolled dogs with suspected sarcoptic mange.

Of 306 dogs enrolled, 17 dogs (10 ilunocitinib, seven placebo) were excluded owing to insufficient site enrolment (i.e., minimum of six evaluable cases/site) (four ilunocitinib), owner noncompliance/inadequate dosing (four ilunocitinib, six placebo), reported AE (one placebo) and prohibited therapy/enrolled in error (two ilunocitinib). As a consequence of inadequate dosing (three ilunocitinib and one placebo) and administration of prohibited therapy (one placebo), five more dogs were excluded from the primary efficacy analysis, leaving 284 dogs (193 ilunocitinib, 91 placebo) assessed for treatment success on D7. Additionally, 289 dogs (196 ilunocitinib, 93 placebo) were evaluated for at least one secondary efficacy outcome variable.

By D28, 2% and 27% of ilunocitinib-treated and placebo dogs, respectively, had been withdrawn from the study owing to lack of efficacy. As the optional continuation phase was introduced several months after the study start, not all dogs had the opportunity to stay in the study beyond D28. Consequently, a total of 143 dogs entered the continuation phase (123 ilunocitinib, 20 placebo). Of these, a total of 120 dogs (104 ilunocitinib, 16 placebo) completed 112 days of treatment.

### 3.2 | Efficacy Analyses

#### 3.2.1 | Treatment Success

On D7, the proportion of dogs achieving treatment success—≥ 50% reduction from baseline PVAS scores on at least five of the first 7 days of treatment—was significantly higher ($p = 0.006$) in the ilunocitinib group (25.4% ± 2.4%; 95% CI [20.6–30.9]) compared to the placebo group (7.7% ± 2.9%; 95% CI [3.2–17.2]). Because most dogs (> 90%) in both groups had no evidence of fleas on D0, stratification for fleas (presence/absence) did not change the proportion of dogs with treatment success in either group.

**TABLE 1** | Baseline demographic characteristics of enrolled study dogs.

| Variable | Ilunocitinib | Placebo | Total |
|---|---|---|---|
| Breed distribution: *n* (%) | | | |
| Mixed breed | 95 (46.1%) | 57 (57.0%) | 152 (49.7%) |
| Pure-bred | 111 (53.9%) | 43 (43.0%) | 154 (50.3%) |
| Sex distribution: *n* (%) | | | |
| Total female | 111 (53.9%) | 49 (49.0%) | 160 (52.3%) |
| Total male | 95 (46.1%) | 51 (51.0%) | 146 (47.7%) |
| Age at enrolment [years]: mean (range) | 6.1 (1.0–15.0) | 6.5 (1.0–14.7) | 6.2 (1.0–15.0) |
| Body weight at enrolment [kg]: mean (range) | 22.5 (3.0–83.3) | 21.9 (3.9–47.7) | 22.3 (3.0–83.3) |

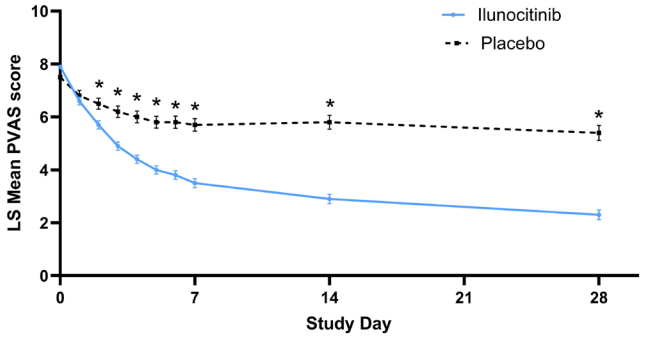


**FIGURE 1** | Least-square (LS) mean owner-assessed pruritus Visual Analog Scale (PVAS) scores over time in the ilunocitinib ($n=196$) and placebo ($n=93$) groups. Day (D)0, arithmetic mean; D1–28, LS mean ± standard error (SE). Ilunocitinib is significantly different from placebo at *$p \leq 0.001$.

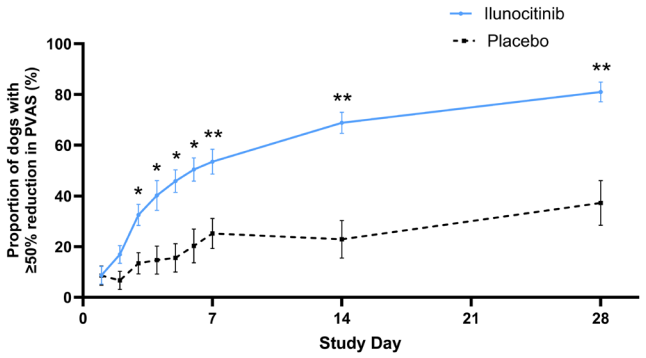


**FIGURE 2** | Proportions (%) of dogs with ≥ 50% reduction from baseline pruritus Visual Analog Scale (PVAS) over time in the ilunocitinib ($n=196$) and placebo ($n=93$) groups. Error bars represent standard errors (SE). Ilunocitinib is significantly different from placebo at *$p<0.01$ and **$p<0.001$.

### 3.2.2 | Owner-Assessed Pruritus Scores (PVAS)

Mean PVAS scores were similar on D0 for ilunocitinib (7.9) and placebo (7.5) groups. Figure 1 represents LS mean PVAS scores over time showing continuously decreasing PVAS scores in the ilunocitinib group, which were significantly lower compared to the placebo group as early as D2 ($p=0.001$ and $<0.001$ for all subsequent time points). Reductions of mean PVAS scores from baseline in the ilunocitinib group were consistently double that of the placebo group, reaching −5.6 and −2.4 for ilunocitinib and placebo, respectively, on D28.

The proportion of dogs with ≥ 50% reduction from baseline in PVAS scores was significantly higher in the ilunocitinib group (32.5%) from D3 ($p=0.004$) compared to the placebo group (13.4%), continuously increasing to 53.5% versus 25.2% by D7 and 81.0% versus 37.2% by D28 ($p<0.001$), respectively (Figure 2). Improvement continued for later time points during the Continuation Phase, with 84%–91% of ilunocitinib-treated dogs and 73%–75% of placebo dogs demonstrating ≥ 50% reduction from baseline on D56–112.

A significantly higher proportion of dogs treated with ilunocitinib (19%) achieved clinical remission from pruritus (PVAS < 2) compared to dogs in the placebo group (2%), starting on D4 (Table 2). A steady increase in the proportion of ilunocitinib-treated dogs achieving clinical remission from pruritus was observed in 31.5% of dogs on D7, 51.8% on D28 and 79.2% on D112. Clinical remission was observed in 10.2%, 12.7% and 53.3% of placebo dogs for the same corresponding study days.

**TABLE 2** | Proportions (%) of dogs with owner-assessed pruritus Visual Analog Scale (PVAS) of < 2 considered in clinical remission from pruritus.

| Study day | Ilunocitinib: LS mean (SE) | Placebo: LS mean (SE) | *p* |
|---|---|---|---|
| 1 | 2.0 (1.4) | 4.8 (2.8) | 0.371 |
| 2 | 7.7 (2.5) | 3.4 (3.1) | 0.381 |
| 3 | 13.5 (3.6) | 1.1 (1.5) | 0.052 |
| 4 | 18.9 (4.1) | 2.3 (1.9) | **0.01** |
| 5 | 23.9 (4.5) | 2.3 (1.9) | **0.003** |
| 6 | 27.0 (5.3) | 5.6 (4.3) | **0.027** |
| 7 | 31.5 (5.5) | 10.2 (4.2) | **0.004** |
| 14 | 38.4 (5.3) | 8.6 (4.8) | **0.005** |
| 28 | 51.8 (5.4) | 12.7 (6.1) | **0.001** |

*Note:* Bold numbers are statistically significant.
Abbreviations: LS, least-square; SE, standard error.

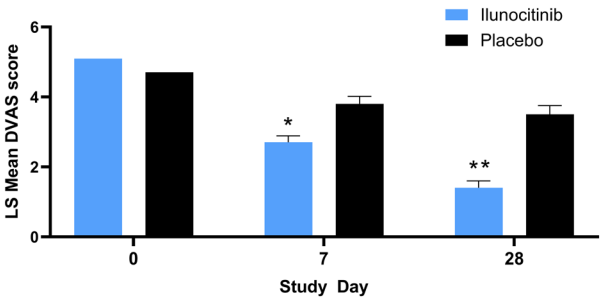


**FIGURE 3** | Least-square (LS) mean investigator-assessed dermatitis Visual Analog Scale (DVAS) scores over time in the ilunocitinib ($n=196$) and placebo ($n=93$) groups. Day (D)0, arithmetic mean; D7 and D28, LS mean ± standard error (SE). Ilunocitinib is significantly different from placebo at *$p<0.01$ and **$p<0.001$.

### 3.2.3 | Investigator-Assessed Dermatitis Scores (DVAS)

Mean DVAS scores were similar on D0 for ilunocitinib (5.1) and placebo (4.7) groups. Figure 3 shows LS Mean DVAS scores with significantly lower values in the ilunocitinib group on D7 ($p=0.003$) and D28 ($p<0.001$) compared to placebo. After 7 days of treatment, the DVAS score in the ilunocitinib-treated group was reduced from baseline by an average of −2.3, which was significantly different from the reduction observed in the placebo group (−1.2). By D28 the mean reduction from baseline in DVAS was −3.5 for ilunocitinib-treated dogs compared to −1.5 for placebo dogs ($p<0.001$).

### 3.3 | Safety Analyses

All 306 enrolled dogs (206 ilunocitinib, 100 placebo) were included in the safety assessment.

#### 3.3.1 | Physical Examinations

Means for heart rate, body temperature and respiration rate were similar between groups at baseline and remained stable over time. Mean percentage changes in body weight on D112 compared to baseline were similar, at +4.0% for the ilunocitinib group and + 3.7% for the placebo group.

#### 3.3.2 | Clinical Pathological Findings

Means for all standard haematological variables were within normal physiological ranges at all time points. In both groups, means for total leucocytes as well as some of the differential counts (eosinophils, monocytes, neutrophils) decreased by either D7 (ilunocitinib) or D28 (placebo) and remained lower through the study, although fluctuations did not appear to be clinically relevant and were well within normal ranges. Mean lymphocyte counts fluctuated slightly in both groups and were unremarkable. All serum biochemical variables remained within normal ranges throughout the study, except for triglycerides and cholesterol. Mean triglyceride means fluctuated in both study groups (137.1–218.6 mg/dL ilunocitinib; 110.8–141.3 mg/dL placebo; normal range 20–150 mg/dL). Likewise, cholesterol means, although within the normal range (131–345 mg/dL), varied in the placebo group and showed a slight increase over time in the ilunocitinib group (206.2–253.9 mg/dL ilunocitinib, 213.6–233.3 mg/dL placebo). Urinalysis was performed only for dogs participating in the Continuation Phase on D28 and D112, and revealed no clinically relevant abnormalities. Mean urine specific gravity and urine pH were within normal physiological ranges and similar between study groups at both time points.

#### 3.3.3 | Adverse Events

Because mean days on study for the ilunocitinib group (73.5 days) was double that for the placebo group (36.9 days), with medians of 105.5 and 28 days for ilunocitinib-treated and placebo dogs, respectively, the lengthier time on study for ilunocitinib-treated dogs generated a disproportionately higher volume of safety data over the course of the study. To enable a more accurate comparison of AE frequencies between study groups, safety data up to D7 are presented along with data up to D28 (Table 3). The percentages of animals with one or more AEs were similar between study groups (ilunocitinib 29.1%, placebo 34.0%) up to D7. These findings were consistent up to D28 (ilunocitinib 47.6%, placebo 49.0%) and D112 (ilunocitinib 59.7%, placebo 53.0%). The most reported AEs, in descending order of frequency and in ≥ 5% of ilunocitinib-treated or placebo dogs up to D7, were systemic disorders (anorexia, lethargy), digestive tract disorders (vomiting or nausea, diarrhoea), skin and appendage disorders and ear and labyrinth disorders (Table 3). Overall, the greatest difference between groups for any individual observation during the study was dermatitis, with the ilunocitinib group reporting fewer cases up to D7 (4% difference between groups), up to D28 (5.1% difference) and for the entire study (7.1% difference).

**TABLE 3** | Summary of adverse events (AEs) reported during the study for ilunocitinib ($n = 206$) and placebo ($n = 100$) groups up to Day (D)7 and D28.

| | Study D0–7 | | Study D0–28 | |
|---|---|---|---|---|
| **Adverse event** | **Ilunocitinib *n* (%)** | **Placebo *n* (%)** | **Ilunocitinib *n* (%)** | **Placebo *n* (%)** |
| Any adverse event | 60 (29.1%) | 34 (34.0%) | 98 (47.6%) | 49 (49.0%) |
| Systemic | 23 (11.2%) | 11 (11.0%) | 35 (17.0%) | 14 (14.0%) |
| Digestive tract | 15 (7.3%) | 14 (14.0%) | 44 (21.4%) | 18 (18.0%) |
| Skin and appendages | 13 (6.3%) | 8 (8.0%) | 38 (18.4%) | 20 (20.0%) |
| Ear and labyrinth | 2 (1.0%) | 2 (2.0%) | 9 (4.4%) | 7 (7.0%) |
| Behavioural | 3 (1.5%) | 1 (1.0%) | 5 (2.4%) | 2 (2.0%) |
| Respiratory tract | 3 (1.5%) | 0 (0%) | 6 (2.9%) | 0 (0%) |
| Eye | 3 (1.5%) | 1 (1.0%) | 4 (1.9%) | 1 (1.0%) |
| Renal and urinary | 2 (1.0%) | 0 (0%) | 5 (2.4%) | 0 (0%) |
| Musculoskeletal | 1 (0.5%) | 0 (0%) | 3 (1.5%) | 0 (0%) |
| Neurological | 1 (0.5%) | 1 (1.0%) | 1 (0.5%) | 1 (1.0%) |
| Reproductive system | 1 (0.5%) | 0 (0%) | 1 (0.5%) | 1 (1.0%) |
| Blood and lymphatic system | 0 (0%) | 1 (1.0%) | 1 (0.5%) | 1 (1.0%) |
| Psychological | 0 (0%) | 0 (0%) | 1 (0.5%) | 0 (0%) |
| Cardiovascular system | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1.0%) |

Serious AEs (SAEs) were observed in four dogs (three ilunocitinib, one placebo) and not considered treatment-related. One ilunocitinib-treated dog was observed to be pawing at his face and then falling to the floor on D78, which was caused by its collar being too tight. Once loosened, it did not cause any further issues, and the dog completed the study without any further reported AEs. Another ilunocitinib-treated dog experienced acute renal dysfunction, vomiting, bloody diarrhoea and dehydration on D85, which was suspected to be the result of toxin ingestion or bacterial exposure as a nonstudy littermate in the household showed the same clinical signs. This dog recovered 9 days after exiting the study. The third ilunocitinib-treated dog presented with vomiting, dyspnea, depression, fever, abdominal discomfort, azotaemia and low urine specific gravity. It was withdrawn from the study on D4 as a consequence of having creatinine levels above the physiological range at D0 and radiographs revealing an enlarged irregularly shaped left kidney. This dog was lost to follow-up. The SAE in the placebo group involved multiple AEs caused by a ruptured splenic haemangiosarcoma, and the dog was euthanised owing to poor prognosis.

### 3.3.4 | Concomitant Medications

A variety of concomitant medications and therapies were administered to 205 (99.5%) and 99 (99%) of ilunocitinib-treated and placebo dogs, respectively, during the study period. Dogs may have received more than one concomitant treatment and/or received the same one multiple times. Concomitant therapies most administered in the ilunocitinib group were parasiticides

**TABLE 4** | Summary of the list and number of occasions concomitant medications and/or therapies were administered during the study in the ilunocitinib-treated ($n = 205$ of 206; 99.5%) and placebo ($n = 99$ of 100; 99%) dogs, in decreasing order of total number of occasions.

| Functional use term (drug class) | Ilunocitinib no. of occasions | Placebo no. of occasions | Total no. of occasions |
|---|---|---|---|
| Parasiticides (insecticides and repellents) | 279 | 130 | 409 |
| Canine vaccines | 53 | 21 | 74 |
| Systemic antimicrobial agents | 21 | 8 | 29 |
| Skin/otic topical preparations | 15 | 9 | 24 |
| Topical antifungal agents (± antimicrobial) | 13 | 6 | 19 |
| Digestive support | 11 | 2 | 13 |
| Nonsteroidal anti-inflammatory drugs (NSAIDs) | 7 | 4 | 11 |
| Anti-emetic agent | 9 | 1 | 10 |
| Joint support/glucosamine and enhancers | 6 | 3 | 9 |
| Antidepressant/anxiolytic agents | 7 | 1 | 8 |
| Fluids | 4 | 2 | 6 |
| Antiseizure medication | 3 | 1 | 4 |
| Opioids | 3 | 1 | 4 |
| Canine prescription diets | 2 | 1 | 3 |
| Ophthalmic agent | 3 | 0 | 3 |
| Vitamin supplements | 2 | 1 | 3 |
| Steroid-sparing immunosuppressant | 2 | 0 | 2 |
| Pre-anaesthetic agent | 2 | 0 | 2 |
| Systemic antifungal agents | 2 | 0 | 2 |
| Cardiovascular agents | 2 | 0 | 2 |
| Antihistamines | 1 | 1 | 2 |
| Antacids | 1 | 0 | 1 |
| Diuretic agent | 1 | 0 | 1 |
| Endocrine agent | 1 | 0 | 1 |
| Prokinetic agent | 0 | 1 | 1 |
| Others | 0 | 3 | 3 |

(e.g., afoxolaner, parasiticide combination products, fluralaner, heartworm preventatives) and vaccines (Table 4).

## 4 | Discussion

This study provides evidence of the efficacy of ilunocitinib in the rapid control of pruritus associated with allergic dermatitis in dogs, regardless of the aetiology. The primary outcome revealed that a significantly higher proportion of dogs achieved treatment success at D7 (25.4% vs. 7.7%) when treated once a day with ilunocitinib compared to placebo, with owners noting a rapid and substantial improvement in pruritus.

Treatment with ilunocitinib resulted in a visible reduction of the owner-assessed mean PVAS score already at D1, and pruritus was reduced by more than half in 53.5% of dogs within the first week of treatment, steadily increasing further until D28, at which time, 81.0% of dogs treated with ilunocitinib had ≥ 50% reduction in their pruritus. Significantly lower mean PVAS scores compared to placebo were achieved as early as D2. Efficacy of ilunocitinib was confirmed by investigator-assessed DVAS scores, also steadily decreasing after treatment initiation and showing a reduction of 72.5% by D28. DVAS values already started to be significantly lower compared to the placebo group at the first assessment time point (D7) after initiation of treatment.

When comparing results of this study to a similar evaluation of the efficacy of oclacitinib in dogs with allergic dermatitis, two important differences between the studies need to be taken into consideration: first, the different treatment regimen of the investigated drugs and second, the different definition of treatment success [9]. Regarding treatment regimen, ilunocitinib was administered once daily from the start throughout the course of the trial, while oclacitinib, in line with its label, was administered twice daily for the initial 14 days of treatment, followed by a once daily administration thereafter [9]. Ilunocitinib's continuous, once daily dosing regimen has several benefits: it reduces the caregiver burden by a lower number of administrations; it avoids dosing errors resulting from change in administration frequency; and finally, it prevents the rebound phenomenon in pruritus as observed previously with oclacitinib therapy when transitioned from twice to once daily dosing [10, 32, 38, 39]. The second key distinction between the two studies lies in the definition of treatment success. In the study evaluating oclacitinib, treatment success was defined as achieving a ≥ 2 cm (unit) reduction from baseline PVAS score on D7 observed on at least five of the first seven study days [9, 32]. By contrast, in the current study, treatment success was defined as a ≥ 50% reduction from baseline PVAS score observed on at least five of the first seven study days, which is a much higher hurdle to achieve and explains the apparent discrepancy in treatment success rates on D7 between studies (25.4% for ilunocitinib vs. 67% for oclacitinib). A 25.4% treatment success in the current study means that a quarter of the dogs treated with ilunocitinib experienced an improvement of their pruritus level by ≥ 50% by D3 at the latest. A recently published placebo-controlled study demonstrated the significant efficacy of ilunocitinib in treating clinical signs of cAD (pruritus and skin lesions) [40]. Another study, a direct comparison with oclacitinib, showed noninferiority for both pruritus and skin lesions. In the same study, ilunocitinib achieved a significantly greater mean PVAS reduction from baseline (68.2% vs. 59.4% for oclacitinib) at D28 ($p = 0.003$) [31].

The normal range for pruritic behaviour in nonallergic dogs, as measured by the owner-assessed PVAS, is between 0 and 1.9 [7, 37] and allergic dogs achieving PVAS scores < 2 are considered to be in clinical remission from pruritus [7, 37]. Using this newly established clinical target, the current study showed an increasing number of ilunocitinib-treated dogs achieving clinical remission from pruritus as the study progressed. One week after the study started, 31.5% of dogs treated with ilunocitinib were in clinical remission from pruritus (versus 10.2% for placebo), and this proportion continued to increase throughout the study, reaching 79.2% at D112 (53.3% for placebo). These results underline the efficacy of ilunocitinib in providing sustained relief from pruritus in allergic dogs.

The high placebo response is likely to stem from the substantial drop-out rate in this group selecting toward dogs with milder disease remaining in study, as well as caregiver optimism, natural disease fluctuations and trial-related care enhancements. Subjective PVAS scoring, influenced by expectation bias, may overestimate improvement, while the inherent variability of allergic dermatitis and regression to the mean contribute to perceived placebo efficacy. Structured ancillary care (e.g., medicated baths, flea control) and reduced environmental stressors during trials further mitigate clinical signs independently. Owner reassurance and behavioural adjustments also may indirectly reduce scratching. Ideally, such placebo effects (29%–79% in prior veterinary trials) would be balanced by objective biomarkers to complement subjective measures. However, at this time, PVAS is the most widely accepted tool to evaluate pruritus in client-owned dogs. A pronounced placebo effect in canine clinical trials is not uncommon, as similar findings have been reported in studies of various canine medical conditions, such as epilepsy and osteoarthritis [41, 42]. In these cases, nonpharmacological factors also contributed to high placebo effects observed.

Investigator-assessed DVAS scores were consistent with owner-assessed PVAS scores, indicating a positive effect of ilunocitinib on skin lesions associated with allergic dermatitis. By D7, there was a shift to more ilunocitinib cases with significantly lower DVAS scores (2.7 vs. 3.8) with an increasing difference observed by D28 (1.4 vs. 3.5). Results therefore show that ilunocitinib demonstrated significant efficacy in alleviating both pruritus and dermatitis, facilitating improvement of skin conditions regardless of the underlying allergic cause.

Concerning safety, ilunocitinib was well-tolerated for the duration of the study also when administered concomitantly with other classes of medications and vaccines. Results of physical examinations during the study were unremarkable and/or similar between groups. It is important to keep in mind that ilunocitinib-treated dogs were on study longer than placebo dogs, owing to on average earlier and higher rates of withdrawal of dogs from the placebo group, which resulted in a disproportionately higher volume of safety data generated for the ilunocitinib group. Despite this disparity, the placebo group experienced similar common AEs (vomiting or nausea,

diarrhoea, lethargy and anorexia) at comparable incidence rates. The longer observation time also needs to be considered when interpreting concomitant medication use. Although it initially appeared higher in the ilunocitinib group, this difference disappeared after accounting for the 2:1 enrolment ratio. The safety profile observed in this study is consistent with other ilunocitinib studies in dogs with AD [31, 40], and with a recently published margin of safety study, where ilunocitinib was well-tolerated by dogs treated with up to a five-fold greater therapeutic dose (0.8 mg/kg) [43]. Results of these studies also are in line with the safety profile of oclacitinib as reported in the literature [9, 10, 13, 32].

Overall, clinical pathological parameters stayed within physiological ranges in both study groups. Means for total leucocyte count as well as some differential counts (eosinophils, monocytes, neutrophils) decreased by either D7 (ilunocitinib) or D28 (placebo) and remained lower throughout the study. Transient decreases in leucocytes have been noticed in dogs and human patients on JAKi, with counts returning to pre-treatment values after withdrawal of the drug [9, 44, 45]. Safety concerns with JAK inhibition include suppression of erythropoiesis and myelopoiesis [44–48]. In this study, fluctuations in haematological parameters did not appear to be clinically relevant and were well within physiological ranges. Mean cholesterol concentrations, while within the normal range, were increased in the ilunocitinib-treated group without clinical relevance. Increase in cholesterol is a known adverse effect of treatment with JAKi in dogs [9, 13, 32] and are likely to be a result of the role of the JAK–STAT pathway in the synthesis of cholesterol [49]. However, elevated lipid levels generally have little to no clinical relevance, and no health risks have been identified previously in humans [49].

A limitation of this study was the disparity in the sample size ratio progressively increasing toward the end of the study as a consequence of the placebo dogs exiting the study before completion, because of no improvement or even deterioration of their clinical signs over time. The quickly decreasing number of placebo dogs in the current study is likely to have caused (i) a reduction in the difference between the ilunocitinib and placebo group, as less severe or self-resolving placebo cases continued the study, and (ii) an imbalance in the analysis of AEs for the study duration of 28 days and even more for the Continuation Phase (112 days). A second study limitation lies in the analysis of secondary end-points not being adjusted for multiple testing, resulting in the potential for inflating Type I statistical error. The interpretation of the results for secondary endpoints should take this into consideration.

## 5 | Conclusions

Ilunocitinib administered once daily was well-tolerated and rapidly alleviated pruritus in dogs with allergic dermatitis, reaching clinical remission from pruritus (PVAS < 2) in more than half of dogs within 28 days of treatment. Signs of dermatitis evaluated by veterinary surgeons improved within 7 days after treatment onset. This novel JAKi provides a safe and effective alternative for the management of allergic dermatitis in dogs, regardless of aetiology.

### Author Contributions

**Sophie Forster:** conceptualisation; writing – original draft and editing. **Simona Despa:** statistical analysis; writing – review and editing. **Candace M. Trout:** conceptualisation; writing – review and editing. **Annette Boegel:** writing – review and editing. **Darren Berger:** writing – review and editing. **Stephen King:** writing – review and editing.

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### Conflicts of Interest

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. **Data S1:** vde70009-sup-0001-Supinfo.docx.