

## Efficacy of oclacitinib (Apoquel®) compared with prednisolone for the control of pruritus and clinical signs associated with allergic dermatitis in client-owned dogs in Australia

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**Background** – Oral glucocorticoids are widely used to reduce pruritus and dermatitis associated with allergic dermatitis. Data suggest that oclacitinib, a Janus kinase inhibitor, is a safe and effective alternative.

**Hypothesis/Objectives** – To evaluate the efficacy and safety of oclacitinib compared with prednisolone for the control of pruritus associated with allergic dermatitis in a single-masked, controlled clinical trial with a randomized complete block design.

**Animals** – Client-owned dogs ( $n = 123$ ) with a presumptive diagnosis of allergic dermatitis and moderate to severe pruritus as assessed by the pet owner were enrolled.

**Methods** – Dogs were randomized to treatment with either oclacitinib (0.4–0.6 mg/kg orally twice daily for 14 days, then once daily) or prednisolone (0.5–1.0 mg/kg once daily for 6 days, then every other day) for 28 days. An enhanced visual analog scale (VAS) was used by owners to assess pruritus and by veterinarians to assess dermatitis, at all time points assessed.

**Results** – Both treatments produced a rapid onset of efficacy within 4 h. The mean reductions in pruritus and dermatitis scores were not significantly different between the treatments except on day 14, when reductions were more pronounced for oclacitinib than prednisolone ( $P = 0.0193$  for owner pruritus scores;  $P = 0.0252$  for veterinarian dermatitis scores). Adverse events were reported with similar frequency in both groups.

**Conclusion and clinical importance** – In this study, both oclacitinib and prednisolone provided rapid, effective and safe control of pruritus associated with allergic dermatitis, with substantial improvement in pruritus, reported by owners, and dermatitis, reported by veterinarians.

### Introduction

Pruritus is the most common clinical sign of many canine allergic skin diseases, including flea allergy dermatitis, atopic dermatitis (AD), food allergy and, rarely, contact allergy.<sup>1</sup> Glucocorticoids are often used to provide relief of pruritus because they are highly effective and have a rapid speed of onset; however, short-term and chronic adverse events are common.<sup>2</sup>

Oclacitinib (Apoquel®; Zoetis Inc., Florham Park, NJ, USA) selectively inhibits key pathways involved in itch and inflammation associated with allergies in dogs.<sup>3</sup> It is approved for the control/treatment of pruritus associated with allergic dermatitis and the control/treatment

of atopic dermatitis in dogs.<sup>4,5</sup> It inhibits a number of cytokines that are pro-inflammatory or have a role in allergic responses, including pruritus.<sup>3,6</sup> Results from field efficacy studies have demonstrated the efficacy, speed of onset and safety of oclacitinib in the control/treatment of pruritus associated with allergic dermatitis and atopic dermatitis.<sup>7–9</sup> No results have been published illustrating field efficacy and safety of oclacitinib compared with other registered treatments, including glucocorticoids.

In spite of the widespread usage of oral glucocorticoids to treat pruritus and skin lesions of dogs with allergic dermatitis, there are no published studies reporting the efficacy of glucocorticoids in dogs suffering from presumptive allergic dermatitis (not limited to atopic dermatitis). The dosage regimen and treatment duration of glucocorticoids used clinically in allergic dermatitis is variable. The International Task Force on Canine Atopic Dermatitis recommends prednisolone be dosed at 0.5 mg/kg once or twice daily until clinical remission occurs in cases of acute episodes of atopic dermatitis.<sup>10</sup>

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**Conflict of Interest:** All authors are current employees of Zoetis Inc. (formerly Pfizer Animal Health).

The aim of this study was to evaluate the efficacy and safety of oclacitinib compared with prednisolone for the control of pruritus and clinical signs associated with allergic dermatitis in client-owned dogs.

## Materials and methods

The materials and methods used for this study were largely identical to those described previously.<sup>8</sup>

### Study design

This study was conducted as a single-masked, positively prednisolone-controlled clinical trial, with a randomized complete block design. The study design was replicated at 12 veterinary clinics in three states of Australia (Queensland, New South Wales and Victoria). All participating veterinarians were general practitioners with an interest in dermatology.

### Overview

Prior to initiation, the study protocol was approved by the Director General's Animal Care and Ethics Committee, New South Wales Department of Primary Industries. The study was conducted in compliance with national animal welfare regulations relating to the care and use of animals for scientific purposes and the international standards of good clinical practice.<sup>11</sup> Written informed consent was obtained from the owner of each dog.

### Inclusion criteria

All dogs were client-owned, 12 months of age or older and in overall good health based on the initial physical examination (day 0). Dogs were assessed by their owners as having moderate to severe itching (pruritus), using a categorical scale.<sup>12</sup> A presumptive diagnosis of allergic dermatitis was established based on the dog's history and clinical signs. Veterinarians attributed the dog's pruritic condition to one or more of the following presumptive diagnoses: AD, flea allergy dermatitis, food allergy dermatitis or contact dermatitis. Appropriate ectoparasite treatment was implemented where evidence of ectoparasite infestation was confirmed or suspected. All dogs were maintained on appropriate flea prevention for the duration of the study.

Dogs with other conditions that required concomitant treatment could be enrolled if the treatment remained the same for at least the 6 weeks prior to the study and no change in medication was anticipated during the study. Dogs that were receiving a hypoallergenic diet to manage previously diagnosed adverse food reactions had to have been on that diet for at least 6 weeks prior to day 0 and must have remained on the same diet during the study. Intradermal allergen tests had to have been conducted at least 8 weeks prior to the start of the study. Concomitant allergen-specific immunotherapy had to have been ongoing for at least 6 months prior to enrolment, and the protocol had to be maintained throughout the study. If allergen-specific immunotherapy was stopped, it had to have been stopped at least 8 weeks prior to enrolment.

### Exclusion criteria

Exclusion criteria included the following: dogs with evidence of malignant neoplasia, severe infections, demodicosis, scabies or immune suppression, such as hyperadrenocorticism; dogs that were receiving or should have been receiving antimicrobial/fungal therapy for bacterial folliculitis or fungal dermatitis; and lactating bitches or dogs (male or female) intended for use as breeding animals.

### Prohibited and conditionally allowed medications and therapies

Systemic and topical antibacterial and antifungal treatment were prohibited at enrolment, but were allowed to commence from day 6 onwards.

### Randomization and blinding

Dogs were randomized to one of the two treatment groups, oclacitinib or prednisolone, in a 1:1 ratio. Blocking and randomization were based on order of enrolment within clinic, and the individual dog was the experimental unit.

At each study site, an unblinded treatment dispenser was responsible for dispensing the appropriate treatment to the owner, labelled as Treatment A for prednisolone and Treatment B for oclacitinib. Upon each dog's enrolment in the study on day 0, the treatment dispenser allocated the dog to the appropriate group according to the site randomization list. Treatment dispensers and dog owners were instructed not to discuss the description, administration or dosing regimen with the examining veterinarian at any clinic visits. Owners were not aware of treatment group assignment and drug name. Investigators as well as laboratory staff conducting blood and urine tests were blinded to treatment group assignment. As owners could potentially unmask themselves by finding out the treatment group based on the different dosing regimen, the study was considered to be a single-masked study.

### Drug administration

Dogs were given oclacitinib tablets orally at a dose of 0.4–0.6 mg/kg twice daily (as close to a 12 h interval as possible) for 14 days, followed by the same dose once daily until the conclusion of the study. Dogs in the other treatment group were given prednisolone 5 mg tablets (Delta-Cortef Corticosteroid Tablets for Dogs; Zoetis, Sydney, NSW, Australia) orally at a dose of 0.5–1.0 mg/kg once daily (in the morning if possible) for 6 ± 1 days, followed by the same dose every other day until the conclusion of the study. The first dose was administered by the dispenser or dog owner at the clinic; owners were instructed to give the second dose (for dogs in the oclacitinib group) that evening before going to bed, regardless of the time of day of the first clinic visit. Owners administered both test treatments with or without food.

### Study schedule and variables measured

Following enrolment on day 0, clinic visits for physical examination and assessment of pruritus and dermatitis were scheduled on days 6 ± 1, 14 ± 2 and 28 ± 2. Dogs were withdrawn from the study at study visits on day 6 or 14 if the veterinarian felt that the dog's pruritus and/or dermatitis required treatment with a prohibited medication or if there was no improvement in pruritus and/or dermatitis observed. Additionally, owners were free to withdraw their dog at any point during the study for any reason, such as perceived lack of efficacy or intolerable adverse effects.

Owners performed a pruritus visual analog scale (VAS) assessment twice on day 0 (pre-enrolment and 4 ± 2 h following the first treatment), then on days 1, 6 ± 1, 14 ± 2 and 28 ± 2 (or the final study day if the dog was withdrawn early). Veterinarians performed a dermatitis VAS assessment on day 0 and at subsequent clinic visits.<sup>8</sup> On the final day of study (day 28 ± 2), or earlier if the dog was withdrawn from the study, owners and veterinarians assessed the dog's response to treatment (RTT). Improvement was assessed using a 10 cm VAS line with a descriptor on one end of the line for 'no improvement' and a descriptor on the other end of the line for 'excellent results'. Owners and veterinarians were instructed to place a mark on the VAS line at the location that best represented the effect of treatment on the dog's skin condition. At the end of the study, the distance (in centimetres) from the 'no improvement' descriptor to the owner's or veterinarian's mark on the line was measured and recorded.

Blood and urine samples (for complete blood count and serum chemistry to investigate liver and renal function and urinalysis) were collected, if possible, on day 0 (prior to dosing) and day 28 ± 2 (or the final study day if before day 28 ± 2). All samples were sent to one veterinary diagnostic laboratory (Gribbles Veterinary Pathology, Clayton, Victoria, Australia) for analysis.

### Efficacy outcome measures

To be included in the efficacy analyses, dogs must have been in the study until at least day 6 ± 1. In addition, they must have received a

minimum of 80% of their intended doses prior to each assessment, as recorded in a daily log completed by the owner. Data were analysed using SAS version 9.2 (SAS Institute, Cary, NC, USA). The level of significance was set at  $P < 0.05$  (two-sided).

The primary efficacy variable was defined as the percentage reduction of owner-assessed pruritus from baseline at day 14 and was used to calculate sample size. Forty-eight animals per treatment group were necessary to detect a difference of 15% change from baseline in Owner Pruritus VAS at one time point using an  $\alpha$  of 0.05 (two-sided) and power of 80%.

Additional efficacy variables assessed were as follows: (i) Owner Pruritus VAS score at each assessment time; (ii) percentage change from baseline in pruritus score at each assessment time; (iii) dogs achieving a reduction of  $\geq 50\%$  compared with baseline in Owner Pruritus VAS scores at each assessment time; (iv) Veterinarian Dermatitis VAS score at each clinic visit; (v) percentage change from baseline in dermatitis score at each clinic visit; (vi) owner VAS score for overall RTT; and (vii) veterinarian VAS score for overall RTT.

The Owner Pruritus VAS score, Veterinarian Dermatitis VAS score, percentage change from baseline in pruritus and percentage change from baseline in dermatitis were each analysed with a general linear mixed model for repeated measures. The model included the fixed effects of treatment, time point and treatment by time point interaction, and the random effects of clinic, block within clinic, clinic by treatment interaction, treatment by block within clinic interaction and clinic by treatment by time point interaction. Contrasts were used to compare treatments at each time point. Treatment least-squares (LS) means, standard errors, 95% confidence intervals and minimums and maximums were calculated for each time point.

Achievement of a reduction of  $\geq 50\%$  in pruritus score was analysed using a generalized linear mixed model for repeated measures with a logit link function and binomial distribution. The terms in the model and comparisons were the same as those for the continuous repeated measures variables. The treatment LS means, standard errors and 95% confidence intervals were transformed to a proportion scale. Assessment of overall response by the owner and veterinarian was analysed with a general linear mixed model, including the fixed effect of treatment and the random effects of clinic, block within clinic and treatment by clinic interaction. Treatment LS means, standard errors, 95% confidence intervals and minimums and maximums were calculated. For all efficacy outcome measures, two different data sets were analysed, namely 'per protocol' and 'intention to treat'.

### Safety outcome measures

All dogs that were administered at least one dose of test drug were included in the safety analysis. For each continuous haematology and serum chemistry measure, summary statistics (mean, median, standard deviation, minimum and maximum) were calculated by treatment and time point. Frequencies of dogs reported to show at least one abnormal health event were displayed by clinical sign for all unique terms.

## Results

### Demographics

A total of 123 dogs were enrolled (Table 1). A total of 40.7% of dogs were purebred, with the Maltese (14.6%), Staffordshire bull terrier (7.3%), Jack Russell terrier (6.5%) and West Highland white terrier (4.9%) being the most frequently represented breeds. Greater than 90% of dogs in both treatment groups were neutered.

### Presumptive diagnoses

The presumptive diagnoses for dogs enrolled in the study are shown in Table 2. Veterinarians attributed the dog's pruritic condition to one or more possible cause of allergic dermatitis. More than 97% of dogs had a presumptive

**Table 1.** Baseline characteristics of 123 enrolled dogs

Variable		Prednisolone ( <i>n</i> = 62)	Oclacitinib ( <i>n</i> = 61)
Breed distribution [ <i>n</i> (%)]	Mixed breed	40 (64.5)	33 (54.1)
	Purebred	22 (35.5)	28 (45.9)
Sex distribution [ <i>n</i> (%)]	Female	34 (54.8)	33 (54.1)
	Male	28 (45.2)	28 (45.9)
Mean age at study onset [years (range)]		6.0 (1.0–13)	5.6 (1.0–12)
Mean weight at study onset [kg (range)]		13.1 (4.0–34.6)	16.2 (3.0–49.4)

**Table 2.** Presumptive diagnoses of 123 dogs at enrolment

Presumptive diagnosis*	Prednisolone <i>n</i> (%)	Oclacitinib <i>n</i> (%)
Atopic dermatitis	61 (98.4)	59 (96.7)
Contact dermatitis	26 (41.9)	29 (47.5)
Flea allergy dermatitis	25 (40.3)	20 (32.8)
Food allergy dermatitis	12 (19.4)	14 (23.0)

\*Each dog may have had more than one presumptive diagnosis for the pruritus.

diagnosis of atopic dermatitis, but only 26% had atopic dermatitis as a sole diagnosis. Contact dermatitis was presumed to be the cause of the allergic dermatitis in ~45% of dogs and flea allergy dermatitis in ~37% of dogs. A total of 21% of dogs were presumed to have food allergy dermatitis.

### Assessment of efficacy

Of the 123 enrolled animals, 61 dogs were randomized to oclacitinib and 62 to prednisolone treatment. A total of seven prednisolone-treated and five oclacitinib-treated dogs were withdrawn prior to day 28. Among the prednisolone-treated group, in addition to being withdrawn due to owner noncompliance ( $n = 3$ ), dogs were withdrawn for worsening of clinical signs ( $n = 2$ ) or abnormal clinical pathological data ( $n = 2$ ). All five oclacitinib-treated dogs were withdrawn for owner noncompliance (being late for scheduled clinic visits). The data sets to assess efficacy were different at each time point owing to errors in compliance with the trial and data collection protocols.

### Owner Pruritus VAS

Pruritus scores (listed as LS means in Table 3) decreased rapidly in both treatment groups by 4 h post-treatment on day 0, with a 28.1% reduction in the prednisolone group and a 31.1% reduction in the oclacitinib group. In the oclacitinib group, the peak percentage reduction from baseline occurred on day 14, when it reached 67.5%, which coincided with the conclusion of twice-daily dosing in this treatment group; thereafter, the percentage reduction from baseline reduced to 52.5% by day 28. The reduction in Owner Pruritus VAS scores peaked for the prednisolone group on day 6 at 60.3%, coinciding with the conclusion of once-daily dosing; thereafter, the percentage reduction from baseline decreased to 52.2% on day 14 and 55.0% on day 28. A significant difference between the two treatment groups was observed only at day 14

**Table 3.** Owner Pruritus VAS (least-squares means and confidence intervals; per protocol analyses)

Study time	Prednisolone			Oclacitinib		
	VAS score (cm)	Percentage reduction from baseline	Percentage of dogs with ≥50% reduction	VAS score (cm)	Percentage reduction from baseline	Percentage of dogs with ≥50% reduction
0 h (62/60) <sup>†</sup>	7.17 [6.71–7.64] <sup>‡</sup>	–	–	7.31 [6.86–7.76]	–	–
4 h (61/60)	5.32 [4.55–6.09]	28.1 [18.5–37.6]	24	4.96 [4.23–5.68]	31.1 [21.3–40.9]	34
Day 1 (58/57)	4.24 [3.49–4.99]	43.1 [33.6–52.6]	41	4.22 [3.48–4.95]	41.3 [31.4–51.2]	40
Day 6 (57/57)	2.91 [2.29–3.53]	60.3 [51.5–69.0]	59	3.24 [2.65–3.83]	54.7 [46.3–63.0]	56
Day 14 (56/54)	3.45* [2.74–4.16]	52.2** [42.5–62.0]	47***	2.33* [1.73–2.92]	67.5** [59.0–76.0]	74***
Day 28 (53/51)	3.30 [2.57–4.02]	55.0 [45.4–64.5]	57	3.33 [2.62–4.05]	52.5 [42.3–62.7]	51

Abbreviations: LS, least squares; VAS, visual analog scale.

\**P* = 0.0087; \*\**P* = 0.0193; \*\*\**P* = 0.0132.

<sup>†</sup>Values in curved brackets in this column are the numbers of animals included in least-squares means analysis for VAS scores (prednisolone/oclacitinib).

<sup>‡</sup>Values in square brackets throughout the body of the table are 95% confidence intervals.

**Table 4.** Veterinarian Dermatitis VAS (least-squares means and confidence intervals; per protocol analyses)

Study time	Prednisolone		Oclacitinib	
	VAS score (cm)	Percentage reduction from baseline	VAS score (cm)	Percentage reduction from baseline
Day 0 (62/60) <sup>†</sup>	4.89 [4.18–5.60] <sup>‡</sup>	–	4.90 [4.18–5.62]	–
Day 6 (57/57)	2.34 [1.70–2.97]	54.0 [43.3–64.7]	2.03 [1.39–2.66]	58.9 [49.7–68.0]
Day 14 (56/54)	2.34* [1.71–2.97]	53.7** [43.9–63.5]	1.34* [0.71–1.97]	71.0** [59.6–82.4]
Day 28 (53/52)	2.30 [1.64–2.96]	53.8 [42.3–65.2]	1.63 [0.97–2.29]	64.3 [54.6–74.1]

\**P* = 0.0022; \*\**P* = 0.0252.

<sup>†</sup>Values in curved brackets in this column are the numbers of animals included in least-squares means analysis for VAS scores (prednisolone/oclacitinib).

<sup>‡</sup>Values in square brackets throughout the body of the table are 95% confidence interval.

(*P* = 0.0193), when the LS mean difference in percentage reduction between treatments was 15.3.

On day 1, ~40% of dogs in both treatment groups achieved a reduction of ≥50% from baseline in Owner Pruritus VAS scores (Table 3). On day 14, 74% of the oclacitinib-treated dogs and 47% of the prednisolone-treated dogs achieved a reduction of ≥50% from baseline in Owner Pruritus VAS scores (*P* = 0.0132).

### Veterinarian Dermatitis VAS

Investigator-assessed dermatitis scores were identical between treatment groups at the start of the study (Table 4). They decreased rapidly in both treatment groups by day 6, with a 54.0% reduction in the prednisolone group and a 58.9% reduction in the oclacitinib group. The percentage reduction from baseline did not vary greatly thereafter for the prednisolone group, averaging 53.7% on day 14 and 53.8% on day 28. In contrast, for the oclacitinib group the percentage reduction from baseline continued to increase to day 14, when it reached 71.0% (coinciding with the conclusion of twice-daily dosing in this treatment group). By day 28, the percentage reduction from baseline was 64.3%. Analysis of treatment contrasts indicated a significant difference between the two groups at day 14 (*P* = 0.0252), when the LS mean difference in percentage reduction between the prednisolone group and the oclacitinib group was 17.3.

### Response to treatment

There was no significant difference (*P* = 0.1665) in the owner-assessed response to treatment between oclacitinib and prednisolone at the end of the study (7.2 and

6.5 cm, respectively). In contrast, investigator RTT scores demonstrated that treatment with oclacitinib produced a significantly (*P* = 0.0109) better least-squares mean RTT score of 7.3 cm for the oclacitinib-treated dogs compared with 6.0 cm for the prednisolone-treated dogs.

### Per protocol versus intention-to-treat analyses

In the sections above, the results for the ‘per protocol’ analyses are provided. No major differences between the ‘per protocol’ and ‘intention-to-treat’ analyses were observed (see Tables S1 and S2 in Supporting information).

### Abnormal health events

Only one serious adverse event was reported during the study in an animal treated with oclacitinib. The dog was a 3.5-year-old cross-bred and had a cruciate ligament injury on day 15, requiring treatment with a prohibited drug (nonsteroidal anti-inflammatory drug) and surgery. The dog was not withdrawn from the study early; however, subsequent time points (i.e. after day 14) were excluded from the efficacy analysis. The incidence of abnormal clinical signs was similar for both groups (see Table 5).

### Clinical pathology

The most common change in biochemistry values in the prednisolone-treated dogs was elevation of alkaline phosphatase, for which means increased to above the normal reference range. More animals in the prednisolone group (*n* = 8, 16%) had a shift to values above the reference range after treatment with prednisolone compared with oclacitinib-treated dogs (*n* = 2, 4.3%). Individual values

**Table 5.** Abnormal clinical signs, excluding pre-existing conditions\*

Abnormal clinical sign	Prednisolone-treated dogs [ <i>n</i> = 62; <i>n</i> (%)] <sup>†,‡</sup>	Oclacitinib-treated dogs [ <i>n</i> = 61; <i>n</i> (%)] <sup>†,‡</sup>
Pyoderma, including folliculitis	6 (9.7)	6 (9.8)
Dermatitis	3 (4.8)	2 (3.3)
Dermatomycosis	0 (0.0)	2 (3.3)
Otitis externa	1 (1.6)	2 (3.3)
Haematuria	0 (0.0)	2 (3.3)
Emesis	2 (3.2)	2 (3.3)
Lameness	0 (0.0)	2 (3.3)
Diarrhoea	2 (3.2)	1 (1.6)
Lethargy	3 (4.8)	1 (1.6)
Pinnal irritation	2 (3.2)	0 (0.0)

\*Observed in at least two dogs in one of the two treatment groups.

<sup>†</sup>Numbers and percentages are given on a per animal basis.

<sup>‡</sup>Reported in decreasing order of frequency in the oclacitinib treatment group.

for alkaline phosphatase increased up to 25 times the upper reference range limit in prednisolone-treated animals, whereas values did not exceed 2× the upper limit of the reference range in oclacitinib-treated dogs. Mean values for albumin increased to above the reference range after prednisolone treatment (from 37.49 g/L at day 0 to 40.20 g/L at day 28; reference range, 24–38 g/L). Serum cholesterol levels increased in both treatment groups, but levels remained within the reference range (from 6.36 and 5.73 mmol/L at day 0 to 7.59 and 6.41 mmol/L at day 28 for prednisolone- and oclacitinib-treated animals, respectively; reference range, 3.9–7.8 mmol/L). More animals in the prednisolone-treated group had a cholesterol value above the reference range at day 28 compared with day 0 (*n* = 11, 21.2% and *n* = 5, 8.9% for prednisolone- and oclacitinib-treated dogs, respectively). There were no major changes from reference ranges in the results of the complete blood counts for all dogs.

### Concurrent medications

A wide variety of concomitant medications were used in both groups in similar numbers and percentages of dogs. The following drug classes were administered to >2% of the oclacitinib-treated animals: ectoparasiticides (including repellents), endectocides, canine vaccines, shampoos (medicated and nonmedicated), anthelmintics, antifungals for the treatment of *Malassezia* infection, systemic antibacterials, anti-inflammatory products, otologicals and antiseptics/disinfectants. A variety of other medications were administered in <2% of animals, including analgesics, anaesthetics, antimycotics for systemic use, ophthalmologicals, skin emollients and skin protectants, vitamins and psychoanalgesics. No untoward effects resulting from the administration of concomitant medications were observed during the study.

### Discussion

The findings of the study demonstrated that oclacitinib reduces pruritus in dogs suffering from allergic dermatitis as well as does prednisolone. The fact that the dose of

prednisolone was tapered after 6 days of treatment, while oclacitinib was not tapered until after 14 days, could explain the statistical differences in favour of oclacitinib on day 14. In keeping with a previous study, veterinarians were asked to make only a presumptive diagnosis, with the possibility of identifying several causes at the same time.<sup>8</sup> Although participating veterinarians had an interest in dermatology and were thoroughly trained to ensure that dogs suffering from pruritus with a nonallergic cause were not enrolled, a precise diagnosis supported by further testing would have been beneficial. Establishing a precise diagnosis would probably have reduced the number of animals enrolled with contact dermatitis. The percentage of ~45%, based on a presumptive diagnosis, has to be considered too high and is four times as high as reported recently when using a similar study design.<sup>8</sup>

In addition to assessing the antipruritic activity of the treatments by using a validated tool, the skin condition was assessed by a veterinarian-assessed dermatitis VAS, as previously described.<sup>8,12</sup> This scale has not been validated. It was felt that the assessment of skin using the Canine Atopic Dermatitis Extent and Severity Index (CAD-ESI) might be too time consuming for this study and, while this method is thoroughly validated, it is specifically limited to atopic dermatitis.<sup>13</sup> Not surprisingly, the results of the Clinician Dermatitis VAS scores mirror the findings of the Owner Pruritus VAS scores.

The 55% reduction from baseline in Owner Pruritus VAS on day 6 agrees well with results reported from a similar population (i.e. allergic dermatitis; presumptive diagnosis only);<sup>8</sup> results for other days are identical (day 14) or very similar (day 28) to reductions in pruritus reported when treating with oclacitinib animals that had been diagnosed with atopic dermatitis.<sup>7,9</sup>

In a systematic review of the pharmacotherapy of canine atopic dermatitis, the authors found three reports in which the trial design was of sufficient quality to provide evidence of the effectiveness of glucocorticoid therapy.<sup>14</sup> The reported mean reduction in pruritus scores in those studies ranged from 33 to 81%, as follows: 81% with 0.5 mg prednisolone/kg once daily; with prednisone, 67% (0.5 mg/kg) or 58% (0.25 mg/kg) reduction when administered first twice daily followed by once daily and then every other day; and 33% with methylprednisolone at 0.5–1.0 mg/kg once daily followed by every other day dosing and tapered by clinical response.<sup>15–17</sup> Different final assessment times ranging from 4 to 16 weeks after the start of treatment, as well as treatment of a different population of animals (i.e. only atopic dogs) complicate the comparison of the results reported here with the results of any of these previously published studies. In general, however, it seems that the reductions in pruritus scores reported here for prednisolone of 60% (day 6), 52% (day 14) and 55% (day 28) are within the range of reductions reported in previous studies.

A 50% reduction of pruritus scores from baseline represents a clinically relevant threshold above which owners are satisfied with treatment.<sup>18</sup> This percentage has been used subsequently as a standard for assessing the efficacy of treatments for pruritus.<sup>14,19,20</sup> By this measure, both of the treatments used in the study reported

here were effective; by day 28, >50% of dogs in both treatment groups achieved a reduction of  $\geq 50\%$  in Owner Pruritus VAS scores.

Speed of onset is a crucial element in the treatment of pruritus associated with allergic dermatitis.<sup>21</sup> The results of the study reported here, where prednisolone was initially administered at a dose of 0.5–1 mg/kg, suggest a comparable speed of onset between prednisolone and oclacitinib within 4 h of administration of the first dose. The lack of significant difference in speed of onset between prednisolone and oclacitinib in this field study compared with previously reported laboratory studies could be explained by the tools used to measure pruritus in these different models.<sup>22</sup> The laboratory studies used videotaping of the animals and counting the number of minutes spent exhibiting pruritic behaviour, whereas this field study used an enhanced Owner VAS scale. It could be speculated that the objective measurement of minutes spent on pruritic behaviour is much more sensitive in detecting changes compared with the more subjective Owner VAS scoring system.

Both prednisolone and oclacitinib were well tolerated during the 28 day study; adverse effects were in line with previously published reports.<sup>7–9,16</sup> The most commonly observed abnormal health event in the oclacitinib-treated animals was pyoderma. These cases were assessed as mostly mild in nature by the masked veterinarian and were treated with oral antibiotics or medicated shampoos. The incidence of pyoderma in both treatment groups is not surprising given that allergic dogs are prone to secondary skin infections,<sup>23</sup> given that both prednisolone and oclacitinib may increase susceptibility to infections, a possible drug effect cannot be completely excluded in either treatment group.

In conclusion, this study provides evidence that oclacitinib administered orally in the recommended dosing regimen reduces pruritus and clinical signs associated with allergic dermatitis to a level comparable to the efficacy of prednisolone administered at a dose of 0.5–1.0 mg/kg daily for 6 days followed by the same dose every other day.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article.

**Table S1.** Owner Pruritus VAS (least-squares means and confidence intervals; intention-to-treat analyses).

**Table S2.** Veterinarian Dermatitis VAS (least-squares means and confidence intervals; intention-to-treat analyses).

### Résumé

**Contexte** – Les corticoïdes oraux sont largement utilisés pour diminuer le prurit et les lésions associées aux dermatites allergiques. Les données suggèrent que l'oclacitinib, un inhibiteur de Janus Kinase, est une alternative sûre et efficace.

**Hypothèses/Objectifs** – Déterminer l'efficacité et la sûreté de l'oclacitinib en comparaison avec la prednisolone pour le contrôle du prurit associé avec une dermatite allergique dans une étude clinique contrôlée en aveugle avec une structure complète randomisée en bloc.

**Sujets** – Des chiens de propriétaires ( $n = 123$ ) avec un diagnostic de dermatite allergique et un prurit modéré à sévère évalué par le propriétaire à l'inclusion.

**Méthodes** – Les chiens ont été randomisés au traitement oclacitinib (0.4–0.6 mg/kg per os deux fois par jour pendant 14 jours, puis une fois par jour) ou prednisolone (0.5–1.0 mg/kg une fois par jour pendant 6 jours, puis un jour sur deux) pendant 28 jours. Une échelle visuelle analogue (VAS) a été soumise aux propriétaires afin d'évaluer le prurit et aux vétérinaires pour évaluer les dermatites à tous les suivis de l'étude.

**Résultats** – Les deux traitements ont permis une réponse rapide en 4h. Les réductions moyennes du prurit et des scores cliniques n'étaient pas significativement différents entre les traitements sauf au jour 14 puis les réductions étaient plus prononcées pour l'oclacitinib que pour la prednisolone ( $P = 0.0193$  pour les scores de prurit par les propriétaires;  $P = 0.0252$  pour les scores cliniques des vétérinaires). Les effets secondaires étaient aussi fréquents dans les deux groupes.

**Conclusions et importance clinique** – Dans cette étude, l'oclacitinib et la prednisolone permettent un contrôle du prurit rapide, sûr et efficace dans les dermatites allergiques avec une amélioration substantielle du prurit rapportée par les propriétaires et des scores cliniques rapportés par les vétérinaires.

### Resumen

**Introducción** – los glucocorticoides orales son ampliamente utilizados para reducir el prurito y la inflamación asociada con la dermatitis alérgica. Los datos indican que oclacitinib, un inhibidor de la quinasa Janus, es una alternativa segura y eficaz.

**Hipótesis/Objetivos** – evaluar la eficacia y la seguridad de oclacitinib comparado con prednisolona para el control del prurito asociado con la dermatitis alérgica en una prueba clínica controlada y enmascarada, con un diseño completo al azar en bloques.

**Animales** – se incluyeron perros de propietarios privados ( $n = 123$ ) con un diagnóstico presuntivo de dermatitis alérgica y prurito moderado a severo según estaba indicado por el propietario.

**Métodos** – los perros se distribuyeron al azar para el tratamiento con oclacitinib (0,4-0,6 mg/kilo por vía oral dos veces al día durante 14 días, y después una vez al día) o prednisolona (0,5-1 mg/kilo una vez al día durante seis días, y después en días alternos) durante 28 días. Se utilizó una escala mejorada visual por los propietarios para evaluar el prurito y por los veterinarios para evaluar la dermatitis en todos los tiempos seleccionados.

**Resultados** – ambos tratamientos produjeron mejora rápida en cuatro horas. La reducción media de los de los valores de prurito y dermatitis no fue significativamente diferente entre los tratamientos, con excepción del día 14, cuando la reducción fue más pronunciada para el oclacitinib que la prednisolona ( $P = 0,0193$  para los valores de prurito evaluados por el propietario; y  $P = 0,0252$  para los valores de dermatitis indicados por los veterinarios). Se mencionaron efectos adversos con similar frecuencia en ambos grupos.

**Conclusiones e importancia clínica** – en este estudio tanto el oclacitinib como la prednisolona aportan un control rápido, efectivo y seguro del prurito que se asocia con la dermatitis alérgica, con una mejora sustancial del prurito indicado por los propietarios, y de la dermatitis indicada por los veterinarios.

### Zusammenfassung

**Hintergrund** – Glukokortikoide *per os* sind weitverbreitet im Einsatz, um Pruritus und Dermatitis, die durch eine allergische Dermatitis entstehen, zu reduzieren. Bisherige Daten weisen darauf hin, dass Oclacitinib, ein Janus Kinase Inhibitor, eine sichere und effektive Alternative darstellt.

**Hypothese/Ziele** – Eine Evaluierung der Wirksamkeit und Sicherheit von Oclacitinib im Vergleich zu Prednisolon zur Juckreizkontrolle im Zusammenhang mit allergischer Dermatitis in einer einseitig geblindeten, kontrollierten klinischen Studie mit einem randomisierten kompletten Block Design.

**Tiere** – Hunde von Kunden ( $n=123$ ) mit der mutmaßlichen Diagnose einer allergischen Dermatitis und moderatem bis hochgradigem Juckreiz, der durch die teilnehmenden PatientenbesitzerInnen beurteilt wurde.

**Methoden** – Die Hunde wurden zufällig eingeteilt, um entweder mit Oclacitinib (0,4-0,6mg/kg zweimal täglich *per os* 14 Tage lang, danach einmal täglich) oder mit Prednisolon (0,5-1,0mg/kg einmal täglich für 6 Tage, dann jeden zweiten Tag) 28 Tage lang behandelt zu werden. Eine verstärkte Visuelle Analogskala (VAS) wurden von den BesitzerInnen verwendet, um den Juckreiz zu beurteilen und von den TierärztInnen, um die Dermatitis zu allen untersuchten Zeitpunkten zu beurteilen.

**Ergebnisse** – Beide Behandlungen zeigten innerhalb von 4h einen raschen Wirkungseintritt. Die durchschnittliche Abnahme des Pruritus und der Dermatitis Werte waren zwischen den Behandlungen nicht signifikant verschieden außer am Tag 14, wo die Abnahme für Oclacitinib deutlicher als für Prednisolon war ( $P=0,0193$  für Pruritus Werte durch die BesitzerInnen;  $P=0,0252$  für Dermatitis Werte durch die TierärztInnen). Nebenwirkungen wurden in beiden Gruppen in einer ähnlichen Frequenz festgestellt.

**Schlussfolgerungen und klinische Bedeutung** – In dieser Studie ergab die Verabreichung von sowohl Oclacitinib als auch Prednisolon eine schnelle, wirksame und sichere Juckreizkontrolle bei Juckreiz, der mit allergischer Dermatitis auftrat, wobei eine deutliche Verbesserung des Juckreizes, beurteilt durch die BesitzerInnen und der Dermatitis, beschrieben von der TierärztInnen, der Fall war.

## 要約

**背景** – 経口グルココルチコイドは、アレルギー性皮膚炎に関連した痒みと皮膚炎を軽減するために広く使用されている。データからヤヌスキナーゼ阻害剤であるオクラシチニブは、安全で効果的な代替薬であると示唆されている。

**仮説/目的** – 完全乱塊法を用いて、単盲検化された、比較臨床試験にてアレルギー性皮膚炎に関連する痒みのコントロールに対するプレドニゾロンと比較した、オクラシチニブの効果および安全性を評価すること。

**供与動物** – アレルギー性皮膚炎と推定診断され、中等度から重度の痒みがあると飼い主に評価された家庭犬 ( $n=123$ ) が組み入れられた。

**方法** – イヌをオクラシチニブ (0.4-0.6mg/kg経口投与1日2回で14日間、その後1日1回)あるいはプレドニゾロン (0.5-1mg/kg1日1回で6日間、その後1日おきに1回)での8日間の治療に無作為に分けた。評価したすべての時点において、改良されたビジュアルアナログスケール (VAS) を飼い主による痒みの評価を、獣医師による皮膚炎の評価に用いた。

**結果** – 両方の治療は4時間以内に迅速な効果の開始がみられた。痒みと皮膚スコアの減少の平均は平均的な低下は、プレドニゾロンよりもオクラシチニブの低下がより強調されていた14日目を除き、(飼い主の掻痒スコアは  $P = 0.0193$  で、獣医師の皮膚炎スコアは  $P = 0.0252$ ) 治療間で有意な差は認められなかった。有害事象は両方の群で同等の頻度で報告された。

**結論および臨床的な重要性** – この研究では飼い主の報告による痒みと、獣医師の報告による皮膚炎に対して十分な改善を認め、オクラシチニブとプレドニゾロンの両方がアレルギー性皮膚炎に関連する急速で効果的、かつ安全な痒みのコントロールをもたらした。

## 摘要

**背景** – 口服糖皮质激素被广泛用于减少过敏性皮炎的瘙痒与炎症反应。数据表明oclacitinib, 一种Janus激酶抑制剂, 是一种安全、有效的选择。

**假设/目标** – 通过与泼尼松龙比较控制过敏性皮炎引起的瘙痒, 评估oclacitinib的有效性和安全性, 用控制随机完全区组设计进行单盲对照临床试验。

**动物** – 将疑似过敏性皮炎并被宠物主人评价为中度到重度瘙痒患犬 ( $n = 123$ ) 作为研究对象。

**方法** – 狗随机分配用oclacitinib (0.4 – 0.6毫克/公斤, 每天两次口服14天, 然后每天一次) 或泼尼松龙 (0.5 – 1.0毫克/公斤6天, 每天一次, 然后隔天一次) 治疗28天。给主人和兽医同时提供一个加强版直观评分表 (VAS), 用以随时评估瘙痒程度及评估皮炎的轻重程度。

**结果** – 两种治疗方法均在4小时内产生疗效。除了第十四天, 两者在平均减少瘙痒、炎症严重程度的得分上没有显著不同。第十四天时, 比起泼尼松龙, oclacitinib 的效果更为明显。 ( $P = 0.0193$  为畜主瘙痒评分;  $P = 0.0252$  为兽医皮炎评分)。两组不良反应报告频率相似。

**结论及临床重要性** – 在这项研究中, 根据畜主的反馈及兽医的诊断评估, 我们可以得出以下结论: oclacitinib与泼尼松龙均可快速、有效和安全的控制过敏性皮炎引起的瘙痒, 并有明显改善。