

# Long-term compassionate use of oclacitinib in dogs with atopic and allergic skin disease: safety, efficacy and quality of life

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**Background** – Oclacitinib is safe and effective for treating dogs with pruritus associated with allergic and atopic dermatitis, based on randomized clinical trials of up to 4 months duration.

**Hypothesis/Objectives** – This study assessed long-term safety, efficacy and quality of life of oclacitinib-treated dogs enrolled in a compassionate use programme.

**Animals** – Two hundred and forty-seven client-owned dogs with allergic skin disease that had previously benefited from oclacitinib therapy.

**Methods** – Dogs were enrolled in an open-label study at 26 veterinary clinics. Dogs received 0.4–0.6 mg/kg oclacitinib twice a day for 14 days, then once a day for up to 630 days. Assessments were performed at ~90 day intervals. Owners completed a quality-of-life survey and assessed pruritus using a Visual Analog Scale (VAS) at each clinic visit. Veterinarians assessed dermatitis using a similar VAS. Abnormal health events, concomitant medication and clinical pathology results were summarized.

**Results** – Visual Analog Scale scores showed improvement from baseline at all time points. The percentage of dogs showing  $\geq 50\%$  reduction from baseline on day 90 was 63.9% for pruritus and 66.4% for dermatitis. Owners saw a positive impact on quality of life in  $>91\%$  of all dogs. Urinary tract infection/cystitis, vomiting, otitis, pyoderma and diarrhoea were the most frequently reported ( $>5\%$  of dogs) abnormal clinical signs. Haematology and serum chemistry means remained within the normal reference ranges. Concomitant medications were well tolerated.

**Conclusions and clinical importance** – Results indicated that oclacitinib was safe and efficacious for long-term use and improved the quality of life for dogs in this study.

## Introduction

Oclacitinib is a novel Janus kinase (JAK) inhibitor, approved in the USA, Canada and the EU (as Apoquel<sup>®</sup>) for the control/treatment of pruritus associated with allergic dermatitis and the control/treatment of atopic dermatitis (AD) in dogs 12 months of age or older.<sup>1–4</sup> In the USA, there were ~1300 dogs enrolled in one or more blinded, randomized, placebo-controlled clinical trials<sup>5–8</sup> conducted in support of the registration of oclacitinib. Following the completion of these studies, owners and veterinarians requested continued access to the drug, outside of the clinical trials, for dogs that had benefited from its use.

In human medicine, the US Food and Drug Administration (FDA) regulations allow, access to investigational drugs to treat patients with a serious or immediately life-

threatening disease or condition for which no comparable or satisfactory alternative treatment exists.<sup>9</sup> Recognizing the impact of allergic skin disease in dogs, the drug manufacturer, in consultation with the FDA's Center for Veterinary Medicine, established a programme for dogs that met strict enrolment criteria. The programme, designed as a single-arm study, enabled dogs to receive oclacitinib until the product became commercially available for purchase. This use of a drug before it is available is also termed 'compassionate use' (by the FDA and the European Medicines Agency).

A wide variety of topical and systemic therapies have been used for both short- and long-term management of allergic skin disease in dogs, and a series of systematic reviews has provided a detailed assessment of the efficacy of each of these therapies; the majority of the studies are of  $<60$  days duration, and no studies have extended beyond 1 year.<sup>10,11</sup>

As the role of cytokine dysregulation in disease has become more apparent, therapeutic drugs that inhibit cytokine activity have entered human and veterinary medicine. JAK inhibitors, such as oclacitinib, can inhibit cytokine function and have been approved for use, but much

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still remains to be learned about the long-term effects of inhibiting these pathways.<sup>12</sup> The efficacy, safety and quality-of-life (QL) variables evaluated in this study contribute to a more thorough understanding of the effects of prolonged administration of oclacitinib.

## Materials and methods

### Overview

The study was conducted in support of drug registration in the USA and in accordance with Good Clinical Practice, VICH GL9.<sup>13</sup> In clinics sited within academic institutions, the protocol was reviewed by the relevant institutional Animal Care and Use Committee. The protocol was reviewed by and approved prior to study initiation by the Sponsor's Ethical Review Board. The owners gave written informed consent for each dog to participate in the study.

### Inclusion criteria

Dogs had previously participated in one or more oclacitinib studies<sup>5–8</sup> and met the enrolment criteria specified for those studies. Dogs had been diagnosed with either atopic dermatitis or pruritus associated with allergic dermatitis and had a documented history of having failed to respond to, or having been unable to tolerate, conventional therapy used for the treatment of their atopic dermatitis or allergic skin disease. Dogs were enrolled from 26 clinics throughout the USA. All dogs were 12 months of age or older and weighed between 3 and 80 kg.

### Prohibited and conditionally allowed medications and therapies

Dogs requiring treatment with systemic glucocorticoids or ciclosporin were either removed from study or given an oclacitinib drug holiday. Dogs were permitted to receive antimicrobial therapy while receiving treatment with oclacitinib.

### Exclusion criteria

Breeding animals and lactating bitches were not eligible. Dogs with evidence of malignant neoplasia, demodicosis, conditions that could have affected immune function (hypothyroidism, rickettsial disease, idiopathic thrombocytopenia or Von Willebrand's disease) and dogs with clinically relevant abnormalities in their pretreatment complete blood count, serum chemistry or urinalysis were not eligible for enrolment until the underlying condition had been controlled.

Following study initiation, if a condition developed that had the potential to impact the immune system, such as the development of a malignant neoplasm, serious infection or infestation, owners and veterinarians were advised (not mandated) to withdraw the dog from study or to institute a drug holiday. Oclacitinib therapy could be re-initiated at any time assuming the dog again met all inclusion and exclusion criteria. The assessment and treatment of these conditions was left to the veterinarian's discretion; diagnostic tests for such conditions (e.g. cytology and histopathology) were not mandated.

### Randomization and masking

This was an open-label study.

### Drug administration and study schedule

Dogs received oclacitinib at a dose of 0.4–0.6 mg/kg, orally twice a day for the first 14 days of treatment and then once a day thereafter for maintenance. For the first year on study, clinic visits occurred at ~90 day intervals. After completing 1 year on study, owners and veterinarians were given the option to extend an individual dog's visit interval to 180 days. However, this option required that owners return for a dispensing visit on the alternate visit days. While the dog was not required to be present for the dispensing visit, owners were asked whether the dog had experienced any abnormal health events prior to an additional 90 day supply of oclacitinib being dispensed.

### Variables measured

An enhanced Visual Analog Scale (VAS) score, consisting of a 10 cm line with word descriptors at 2 cm intervals, was used by dog owners and veterinarians to measure the severity of the pruritus and dermatitis, respectively. In addition, owners were asked to complete a QL assessment based on earlier validated surveys for dogs with skin disease.<sup>14–17</sup>

Beginning on day 0, (first dose of oclacitinib), veterinarians performed a VAS assessment and owners performed a VAS and QL assessment; these assessments were repeated at ~90 day intervals for a minimum of 1 year. Beyond 1 year, VAS and QL assessments were performed at either 90 or 180 day intervals. The visit interval was determined by whether or not the dog was alternating clinic visits with dispensing visits. There was flexibility ( $\pm 14$  days) allowed with regard to the exact timing of the visit based on the owner's and veterinarian's availability, and observations were reported based on the targeted date of the assessment. All data available at any given time point (days 0, 90, 180, up to 630) were included in the data summaries. More dogs were included in the earlier assessments compared with the later assessments because the enrolment was dynamic and many dogs did not reach the later assessment time points.

A complete physical examination and sample collection for haematology, serum chemistry and urinalysis (free catch or cystocentesis) were performed prior to dosing on day 0 and at all subsequent clinic visits (including unplanned visits for adverse events), with the exception of the dispensing visits. Collected samples were sent to each veterinarian's local diagnostic laboratory, resulting in variable units and reference ranges being used for some tests.

### Efficacy outcome measures

The effectiveness variables summarized were as follows: (i) Owner Pruritus VAS score and Veterinarian Dermatitis VAS score at each owner and veterinarian assessment; (ii) percentage of dogs showing a  $\geq 50\%$  reduction from baseline score in Owner Pruritus and Veterinarian Dermatitis VAS scores; (iii) percentage of dogs assessed as 'normal' (VAS score 0–1.9 cm) at each owner and veterinarian assessment; and (iv) Owner QL scores at each assessment, categorized as strongly disagree (1), disagree (2), neither agree nor disagree (3), agree (4), strongly agree (5).

To be included in the effectiveness summaries, dogs had to have received a minimum of 80% of the intended doses prior to each assessment. The summaries excluded those dogs with a protocol deviation that affected the collection or integrity of their efficacy data. Every effort was made to ensure that the same owner or veterinarian who performed the day 0 baseline assessments also performed all subsequent VAS and QL assessments.

### Safety outcome measures

The safety variables summarized for all dogs included the following factors: (i) adverse events; (ii) laboratory results; (iii) body weight; and (iv) concomitant medications administered.

### Data analysis

Data were summarized using SAS version 9.2.2 (SAS Institute, Cary, NC, USA). No hypothesis tests were conducted.

### Efficacy outcome measures

Summary statistics [number of animals, mean, Standard Deviation (SD) and range] of Owner Pruritus VAS and Veterinarian Dermatitis VAS were calculated. The number and percentage of dogs with a  $\geq 50\%$  reduction from baseline of the Owner and Veterinarian VAS scores, with 'normal' Owner and Veterinarian VAS scores and Owner QL scores, were calculated for each assessment.

For ease of interpretation, prior to calculating the frequency distributions for the QL data, the scores of 'strongly disagree' and 'disagree' were combined into one category, while the scores of 'agree' and 'strongly agree' were combined into another category.

## Safety outcome measures

Frequencies (expressed as percentages) of all adverse events (number of dogs displaying abnormal clinical sign/total number of dogs on study) were calculated. All abnormal health events that resulted in euthanasia, regardless of the reason, were classified as serious adverse events. By definition, a serious adverse event includes events that were fatal or life threatening or which resulted in persistent or relevant disability, incapacity or a congenital anomaly or birth defect.<sup>18</sup> For each continuous haematology, serum chemistry and urinalysis measure, summary statistics (mean and SD) were calculated by time point.

All concomitant medications administered during the treatment period were coded using a standard coding dictionary of veterinary treatments. Summary statistics of body weight and percentage change from baseline were calculated for each assessment time.

## Results

### Demographics

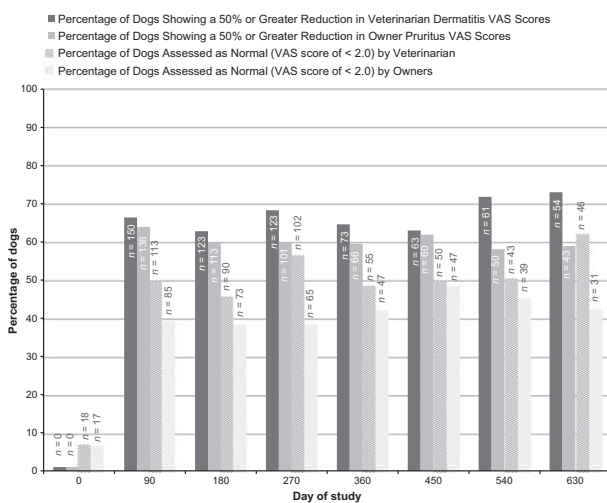
Of the 247 dogs enrolled in this study, 219 had been enrolled with a diagnosis of chronic AD.<sup>6–8</sup> For the remaining 28 dogs, 16 had a presumptive diagnosis of AD alone, two were diagnosed with allergic dermatitis alone and 10 had a diagnosis of AD in combination with additional presumptive diagnoses (including one or more of the following: flea allergy dermatitis, food allergy and contact allergy).<sup>5</sup> The study enrolled a largely middle-aged to older population of dogs (mean 6.8 years). Over 75% of the dogs were purebred, with males and females approximately equally represented.

### Treatment duration

The mean length of time on study was 401 days (15–672 days) and the median length of time on study was 356 days, with 52.3% of the dogs enrolled for <1 year and 47.7% of the dogs enrolled for >1 but <2 years (Figure 1).

### Effectiveness summary

The effectiveness data set for all variables assessed comprised 247 dogs on day 0. The data sets for all variables assessed decreased at each subsequent time point because of the following factors: (i) a dynamic enrolment



**Figure 1.** Percentage of normal dogs and percentage of dogs with a  $\geq 50\%$  reduction from baseline in Owner Pruritus Visual Analog Scale (VAS) scores and Veterinary Dermatitis VAS scores by day of study. *n* is the number of dogs (of total percentage).

over a 2 year time period, with dogs that were enrolled later not reaching all time points; (ii) protocol noncompliance (as outlined above under 'Efficacy outcome measures'); and (iii) dogs withdrawn from study (Table 1).

The mean day 0 Owner Pruritus VAS scores (7.1 cm) and Veterinarian Dermatitis VAS scores (5.4 cm) were reduced at the first post-treatment visit (day 90), and the reduction remained constant up to the final visit (day 630), when the mean Owner Pruritus VAS score was 3.0 cm and the mean Veterinarian Dermatitis VAS score was 1.7 cm.

The percentage of dogs showing a  $\geq 50\%$  reduction from their day 0 VAS score on day 90 was 63.9% based on Owner scores and 66.4% based on Veterinarian scores; this reduction remained relatively constant for all subsequent time points assessed up to day 630 (Figure 1).

A normal dog was defined as a dog with a VAS score <2 cm.<sup>19</sup> The percentage of dogs that achieved a normal Owner Pruritus VAS score ranged from 38.5 to 48.5%. The percentage of dogs that achieved a normal Veterinarian Dermatitis VAS score ranged from 45.9 to 62.2% (Figure 1).

### Quality of life

The frequency distributions relating to acceptance of the disease showed that  $\sim 90\%$  of the dog owners believed or strongly believed that they understood the disease and  $>96\%$  accepted that their dog would require life-long care. The frequency distributions relating to the available treatment options indicated that  $\geq 88\%$  of the dog owners were dissatisfied with the treatment options that were previously available to them with regard to resolution of skin disease and  $\geq 91\%$  were confident that treatment with oclacitinib was effective (Table 2).

### Safety assessment

All 247 enrolled dogs were included in the safety assessment.

### Abnormal clinical signs

The abnormal clinical signs reported most frequently (in  $\geq 5\%$  of the dogs) as a nonpre-existing finding were as follows: urinary tract infection/cystitis (11.3%), vomiting (10.1%), otitis (9.3%), pyoderma (9.3%) and diarrhoea (6.1%). Descriptive statistics showing the number of dogs that experienced each abnormal clinical sign and the frequency of occurrence as well as treatment and outcome are presented in Table 3.

### Serious adverse events

Of the 247 dogs, 21 dogs were withdrawn from the study and subsequently euthanized. Ten dogs were euthanized because of confirmed or suspected malignant neoplasms and eight dogs were euthanized as a result of conditions that were diagnosed prior to study start [AD (one), epilepsy (one), diabetes (one), cardiovascular disease (one), aggression (two) and arthritis (two)]. The remaining three dogs were euthanized as a result of a ruptured cruciate ligament, an undefined central nervous system disorder and for abdominal ascites with pleural effusion (one each). The mean age of the eutha-

**Table 1.** Dogs withdrawn from study and reasons for withdrawal

Reason for withdrawal	Number withdrawn (euthanized)	Percentage of dogs withdrawn	Specific diagnosis
Medical or surgical condition	26 (18)	39.4	Neoplasm or suspected neoplasm (12), arthritis† (2), abdominal ascites and pleural effusion (1), Cushing's disease* (1), cardiovascular disease† (1), central nervous system disorder (1), cruciate rupture (1), dermal pigmented viral plaques (1), decreased appetite (1), degenerative disc disease surgery* (1), demodectic mange* (1), diabetic ketoacidosis† (1), epilepsy† (1), musculoskeletal disorder (1)
Worsening clinical signs of atopic dermatitis	18 (1)	27.3	
Protocol noncompliance	7	10.6	
Owner no longer wished to participate	6	9.1	
Owner relocated (outside study area)	5	7.6	
Abnormal clinical pathology results	2	3.0	Increased alkaline phosphatase† (1), increased alanineaminotransferase*(1)
Other	2 (2)	3.0	Aggression†
Total	66	100	

\*Re-enrolled after medical or surgical condition was resolved or abnormal laboratory values resolved.

†Pre-existing.

**Table 2.** Quality of life

	Strongly disagree or disagree (%)	Neither agree or disagree (%)	Strongly agree or agree (%)
<b>Acceptance of the disease</b>			
Dog will require life-long care	0.0–0.8	0.0–3.4	96.1–100.0
Have a clear understanding of the dog's skin disease	0.0–4.9	5.3–8.4	89.9–93.8
Constantly seeking new therapies for the skin disease	5.7–27.8	20.2–31.9	42.6–74.1
Will limit other expenses to pay for dog's treatment	7.7–14.2	17.6–24.4	62.5–70.3
<b>Treatment options</b>			
Previous treatments have not resolved my dog's condition and are time consuming	0.0–4.8	2.2–9.1	87.7–95.7
Confident that the current treatment (oclacitinib) is effective	0.0–3.4	1.7–7.1	91.2–97.2
<b>Quality of life before oclacitinib</b>			
The skin disease made my dog's behaviour worse	12.0–22.4	15.0–21.5	58.1–71.3
My dog was less playful	12.0–21.9	9.2–16.7	66.5–78.7
My dog woke up constantly to scratch, lick, bite or chew itself	0.0–5.3	1.9–6.7	89.1–98.1
My dog's scratching, licking biting or chewing woke me up at night	2.8–7.8	3.3–8.8	85.0–93.3
I had to limit other expenses in order to pay for my dog's treatment	15.1–28.7	20.0–30.1	49.8–60.0
I had to take my dog's collar off at night	13.9–29.5	18.3–24.0	47.5–67.7
My dog seemed more tired and had less energy	6.7–16.2	11.8–18.9	65.7–79.6
I was unhappy with the number of times I had to go to the veterinary clinic to treat this problem	7.5–17.4	13.9–19.4	65.8–76.9
<b>Quality of life after oclacitinib</b>			
My dog is happy and content	0.0–4.0	3.2–6.1	90.6–95.7
My dog is playful and active	0.0–2.9	4.9–7.5	90.6–94.0
My dog sleeps well	1.9–5.4	2.5–5.9	88.8–95.0
I sleep better	1.3–4.5	5.6–19.0	77.1–92.6

nized dogs was 9.8 years (range 5.0–14.5 years), and the mean number of days on oclacitinib was 279 days (range 17–646 days) (Table 4).

There were nine other abnormal health events (in eight dogs) that were considered to be serious but did not result in withdrawal from study and euthanasia (Table 5). One dog was diagnosed with demodicosis, two dogs were diagnosed with serious infections and six dogs presented for known or suspected neoplasms.

In addition to the known or suspected neoplasms, 47 dogs developed new dermal, epidermal or subcutaneous masses that did not have a specific diagnosis established.

### Haematology and serum chemistry

The arithmetic mean ('mean') value for all of the haematology and serum chemistry analytes fell within the laboratory normal laboratory reference ranges for that analyte at all of the visits.

While overall haematology and serum chemistry means remained within the normal reference range, individual dogs showed transient decreases in white blood cell, neutrophil, eosinophil, monocyte and platelet counts and transient increases in mean serum cholesterol and total protein levels. The transient increases and decreases did not result in drug holidays or withdrawal from study.

**Table 3.** Frequency distributions and summary statistics for the most commonly reported abnormal clinical signs

	Abnormal clinical signs*				
	UTI/cystitis	Vomiting	Otitis	Pyoderma	Diarrhoea
Frequency of occurrence† (%)	11.3	10.1	9.3	9.3	6.1
Number of dogs with sign	28	25	23	23	15
Number of unique occasions in which abnormal clinical sign was observed	37	30	29	32	16
Mean age in years (range)	7.4 (3.5–14.5)	7.2 (3.0–13.5)	7.1 (2.5–11.5)	7.5 (3.5–12.0)	8.0 (3.5–14.5)
Sex					
SF	19	12	9	11	7
F	0	0	0	0	1
CM	7	11	13	11	6
M	2	2	1	1	1
Treatment required‡	37/37	7/30	29/29	31/32	10/16
Treatment	Systemic antibiotics	Bland diet and/or gastro-protectants and/or anti-emetics	Topical and/or systemic anti-microbial agents	Topical and/or systemic anti- microbial agents	Diet change and/or anti-emetics and/or systemic antimicrobial agents
Required interruption in dosing‡	0/37	9/30	0/29	0/32	3/16
Length of interruption	NA	≤5 days	NA	NA	≤3 days
Required hospitalization	0	1/30	0	0	0
Diagnosis if hospitalized		Pancreatitis			
Classified as a serious adverse event (SAE)	0	1/30	0	0	0
Required removal from study	0	0	0	0	0

\*Occurring in 5% or more of the dogs on study.

†Frequency is the Number of dogs in which a clinical sign was reported/ total number of dogs on study × 100.

‡Denominator is the number of occasions.

Abbreviations: F, female; M, male; NA, not applicable; NM, neutered male; SF, spayed female.

Overall means for hepatic and renal analytes were not affected by administration of oclacitinib maleate. A small number of dogs were enrolled with creatinine (2%) or blood urea nitrogen (4.5%) values elevated outside of the normal range, which either remained stable or decreased over time. Twenty-one per cent of the dogs had an elevated alkaline phosphatase at the time of enrolment, which remained stable or decreased over time. Two dogs were withdrawn from study because of elevated laboratory values; one with pre-existing elevated alkaline phosphatase and the other with an elevated alanine aminotransferase. Approximately 14% of the enrolled dogs had total thyroxine (T<sub>4</sub>) levels below reference range at the time of enrolment.

### Urinalysis

In addition to the dogs reported to have an abnormal health event of urinary tract infection/cystitis, urinalysis results showed 13 additional dogs with urine abnormalities, as follows: four dogs with proteinuria (two resolved, one not resolved until after study completion and one chronic), four dogs with haematuria (resolved), three dogs with bacteriuria (resolved), one dog with hyposthenuria (not resolved until after study completion) and one dog with microalbuminemia (resolved).

### Concomitant medications

There were >1000 unique concomitant medications and therapies from ~300 drug classes used in conjunction with oclacitinib treatment, all of which appeared to be well tolerated (see Table S1 in Supporting information). Antimicrobial agents were administered systemically to 64.8% and topically to 48.6% of enrolled dogs. A variety of vac-

cines, including rabies and multiple live vaccine combinations, were concomitantly administered to 44.9% of the enrolled dogs. There were no lack-of-efficacy reports associated with the administration of any vaccine.

Of the 247 dogs on study, 37 (15.0%) dogs received one or more types of systemic glucocorticoids (31 concurrent with oclacitinib and six while on an oclacitinib holiday) on 47 separate occasions. Per protocol, the use of glucocorticoids while on study was prohibited; a protocol deviation was written for any dog on study that received glucocorticoids. Glucocorticoids were administered for the treatment of seasonal atopic flares, presurgical and postsurgical procedures, infection, inflammatory bowel disease and other concurrent procedures (aural haematoma).

Of the 31 dogs that received glucocorticoids administered concurrently with oclacitinib, six dogs had abnormal health events reported. Of these six dogs, three dogs were reported to have vomited and one dog had diarrhoea and an interdigital nodule (attributed to a foreign body); all resolved without treatment and did not require that either glucocorticoids or oclacitinib be discontinued. One dog developed haematochezia/haematemesis, which resolved with treatment and did not require that either glucocorticoids or oclacitinib be discontinued. Another dog that entered the study with diabetes developed diabetic ketoacidosis and was euthanized.

### Body weight change

When compared with baseline day 0 values [mean = 26.29 kg (±16.1 SD)], body weights remained relatively constant until the final study day [mean = 28.93 kg (±17.1 SD)]. Anorexia with weight loss was reported in two (0.8%) dogs (confounded by serious adverse events),



**Table 4.** Serious adverse events resulting in euthanasia

Case no.	Age (years)*	Breed	Sex†	Diagnosis	Total days on prescription (in present study)
<b>Confirmed or suspected malignant neoplasms</b>					
1	11.5	Labrador retriever	M	Thoracic metastatic neoplasm	17
2	11.5	Golden retriever	F	Frontal sinus neoplasm	49
3	12	Golden retriever	F	Mast cell tumour, grade II	52
4	9.5	Mastiff cross-bred	M	Abdominal metastatic neoplasm	120
5	6	French bulldog	F	Intracranial neoplasm	141
6	13	Labrador retriever	F	Splenic neoplasm	175
7	8	West Highland white terrier	F	Transitional cell carcinoma	286
8	9	Newfoundland	F	Primary malignant bone neoplasia	308
9	9	Irish wolfhound	M	Thoracic mass (with megaesophagus, gastric volvulus and bronchopneumonia)	343
10	10.5	Golden retriever	F	Spindle cell sarcoma, low grade (resulting in cruciate rupture)	646
<b>Musculoskeletal</b>					
11	9	Setter	M	Arthritis‡	200
12	12	Beagle	M	Cruciate ligament rupture	361
13	12	German shepherd	M	Arthritis‡	400
<b>Behavioural disorders</b>					
14	11	German shepherd	M	Aggression‡	50
15	6.5	Boxer	F	Aggression‡	63
<b>Central nervous system disorders</b>					
16	8.5	Boston terrier	F	Status epilepticus‡	590
17	14.5	Labrador retriever cross-bred	M	Central nervous system disorder	592
<b>Skin and integument disorder</b>					
18	9	West Highland white terrier	M	Worsening of atopic dermatitis‡	33
<b>Pulmonary disease</b>					
19	5	Labrador retriever	M	Abdominal ascites and pleural effusion	450
<b>Cardiovascular disorder</b>					
20	11	Chihuahua	M	Cardiovascular disease‡	566
<b>Endocrine disorder</b>					
21	6	Labrador retriever	M	Diabetic ketoacidosis‡	432

\*At euthanasia.

†Spayed females (F) or castrated males (M).

‡Pre-existing.

anorexia alone was reported as an abnormal health event in seven dogs (2.8%) and weight loss alone in two dogs (0.8%). Increased appetite and polyphagia were each reported as an abnormal health event in one dog (0.4%).

## Discussion

Earlier studies evaluated the safety and efficacy of oclacitinib for 30 days for the control/treatment of pruritus associated with allergic dermatitis and for 112 days for the control/treatment of atopic dermatitis.<sup>5–8</sup> This compassionate use study afforded these dogs an opportunity to continue oclacitinib therapy and remain on the drug until commercial product became available.

A single-arm study was required to ensure that all dogs received oclacitinib at label dose. This study design presented several limitations in that neither the owners nor the veterinarians were blinded to the treatment group assignment and there was no opportunity for comparison with either a placebo control or conventional therapies. However, this study used a subset of the veterinarians,

owners and many of the most severely affected dogs that had participated in earlier placebo-controlled studies. While the QL survey was a new tool, owners and veterinarians were previously trained on the use of the VAS score to assess efficacy. The VAS scores from the present study align with what has been reported previously and demonstrate continuing efficacy for up to 630 days.<sup>5–8</sup> Based on the response to the QL survey, for the dogs enrolled in this study, owners observed an improvement in their dog's overall quality of life when treated with oclacitinib that did not exist with earlier treatment options.

In this study, the long-term administration of oclacitinib appeared to be well tolerated. The abnormal clinical signs reported most frequently in this study (urinary tract infection/cystitis, vomiting, otitis, pyoderma and diarrhoea) resolved with either no treatment or symptomatic treatment and infrequent interruption in dosing, suggesting that these clinical signs are typical of what would occur in any population of dogs over an extended period of time. Middle-aged to older spayed female dogs appeared to be at a higher risk for developing urinary tract infection/

**Table 5.** Serious adverse events not resulting in euthanasia

Case no.	Age (years)	Breed	Sex†	Diagnosis	Days on prescription at time of diagnosis	Outcome	Days on prescription after treatment (if applicable)
<b>Infestations and infections</b>							
1	6	Scottish terrier	M	Demodicosis	273	Drug holiday; treated and re-enrolled	62
2	8*	Pug	M	Bronchopneumonia	272	Drug holiday; antibiotic therapy and re-enrolled	330
3	10	Mixed breed	F	Dermal pigmented viral plaques	266	Withdrawn from study	–
<b>Neoplasms</b>							
1	6	Pug	F	Mast cell tumour, grade I	623	Remained on study	14
2	8*	Pug	M	Mast cell tumour, grade II	91	Remained on study	521
3	12	Mixed breed	F	Apocrine gland adenocarcinoma	210	Remained on study	455
4	10	Cavalier King Charles spaniel	M	Apocrine gland adenocarcinoma	320	Remained on study	350
5	5	German shepherd mix	F	Anal sac adenocarcinoma (with concurrent cystitis)	33	Withdrawn from study	–
6	7	Poodle	M	Low-grade B-cell lymphoma	392	Withdrawn from study	–

\*Same case.

†Spayed females (F) or castrated males (M).

cystitis. This finding aligns with what has been reported in the literature.<sup>20</sup> No dogs were withdrawn from the study as a result of these abnormal clinical signs.

Oclacitinib modulates the immune system and may increase susceptibility to infection and infestation and exacerbate neoplastic conditions.<sup>1,2,4</sup> In the present study, infections and infestations that resulted in hospitalization or withdrawal from the study were observed in three dogs, and 16 dogs were diagnosed with either a confirmed or suspected neoplasm. Based on these results, the routine monitoring of oclacitinib-treated dogs for the development of these conditions, as stated on the product label,<sup>1,2,4</sup> would be recommended.

Of the 16 dogs diagnosed with either confirmed or suspected neoplasia, the average number of days on oclacitinib prior to the detection of the tumour was 238 (range 17–644 days) and the mean age was 9.3 years (range 5–13 years). Of the 10 dogs that were euthanized, eight were either large or giant breeds. Of the six noneuthanized dogs, four remained on study with no additional complications. Forty-seven dogs were observed to have skin masses which, based on the veterinarian's visual assessment, did not necessitate further diagnostics or removal. These masses were continually monitored throughout the study.

Mast cell tumours and adenocarcinomas were the most frequently diagnosed type of malignant tumour (three each). The other types of tumours were each reported with only one occurrence. Two of the dogs with mast cell tumours and two of the dogs with adenocarcinomas (one apocrine, one anal sac) remained on study following the diagnosis with no additional complications. Mast cell tumours are the most common cutaneous

tumour in dogs,<sup>21</sup> while adenocarcinomas are reported to represent only 2% of all cutaneous tumours in dogs.<sup>22,23</sup>

For the dogs enrolled in this study, age (middle-aged to older) and a history of allergic skin disease are key risk factors in the development of malignant neoplasia. Cancer is the leading cause of death in dogs, with tumours of the skin listed as the most frequently diagnosed type of tumour.<sup>24</sup> In one report, 45% of all dogs presented for postmortem examination that had lived to 10 years of age died of cancer; and with no age adjustment in the same study, 23% of patients died of cancer.<sup>25</sup> With these confounding factors, it is unknown whether the duration of oclacitinib therapy has any relevance to the development of, or exacerbation of, neoplasia in this population of dogs.

In the present study, there were few changes in any clinical pathology values that were considered to be clinically significant. Overall haematology and serum chemistry means remained within the normal reference range. Individual dogs showed transient decreases in white blood cell, neutrophil, eosinophil, monocyte and platelet counts and transient increases in mean serum cholesterol and total protein levels. Two dogs were removed from study because of abnormal laboratory values, one with an elevated alkaline phosphatase that was also elevated prior to study start and the other with an elevated alanine aminotransferase. Two additional dogs were given treatment holidays, one because of an elevated alkaline phosphatase and an elevated alanine aminotransferase and the other because of an elevated alkaline phosphatase; in both cases, the values were elevated prior to study start. There were no other transient increases or decreases observed in any other analytes, including red blood cells.

A wide variety of concomitant medications, including vaccines, antiparasitics, antimicrobial agents, nonsteroidal anti-inflammatory agents, glucocorticoids and topical dermatological preparations, were well tolerated by dogs on this study. This finding corroborates the results of earlier clinical trials.<sup>5,6</sup> These clinical results are also supported by the oclacitinib *in vitro* canine cytochrome P450 enzyme inhibition data. The inhibitory concentrations (IC<sub>50</sub> values) are 50-fold higher than the therapeutic plasma concentrations, indicating that a drug–drug interaction due to oclacitinib inhibition of cytochrome P450 enzymes is unlikely.<sup>1</sup>

The results of this study support the efficacy and safety of chronic use of oclacitinib for up to 630 days and suggest an improved quality of life for the dog and the dog owner.

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## Supporting Information

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

**Table S1.** Concomitant medications.

### Résumé

**Contexte** – L’oclacitinib est sûre et efficace pour le traitement de chiens atteints de prurit lié à une dermatite allergique et atopique d’après des études cliniques randomisées d’une durée de 4 mois.

**Hypothèses/Objectifs** – Cette étude montre une sécurité, une efficacité et une qualité de vie au long cours des chiens traités à l’oclacitinib dans un programme d’usage compassionnel.

**Sujets** – Deux cent quarante-sept chiens de propriétaires atteints d’allergie cutanée ayant précédemment déjà bénéficiés de l’oclacitinib.

**Méthodes** – Les chiens ont été enrôlés dans une étude ouverte sur 26 cliniques vétérinaires. Les chiens ont reçu 0.4–0.6 mg/kg d’oclacitinib deux fois par jour pendant 14 jours puis une fois par jour pendant 630 jours. L’évaluation a été réalisée tous les 90 jours. Les propriétaires ont complétés une étude de qualité de vie et une évaluation du prurit à l’aide d’une échelle visuelle analogue (VAS) à chaque visite clinique. Les vétérinaires ont évalué la dermatite à l’aide d’une échelle équivalente. Les événements de santé anormale, les traitements concomitants et les résultats cliniques ont été résumés.

**Résultats** – Les scores de VAS ont montré une amélioration à tous les points. Le pourcentage de chiens montrant une réduction  $\geq 50\%$  au jour 90 était de 63.9% pour le prurit et de 66.4% pour les lésions. Les propriétaires rapportent un impact positif sur la qualité de vie pour plus de 91% de tous les chiens. Les signes cliniques anormaux les plus fréquemment rapportés étaient : infection urinaire, cystite, otite, pyodermite et diarrhée ( $>5\%$  des chiens). L’hématologie et la biochimie sont restées dans les valeurs usuelles. Les traitements concomitants ont été bien tolérés.

**Conclusions et importance clinique** – Les résultats indiquent que l’oclacitinib est sûre et efficace pour l’utilisation au long cours et améliore la qualité de vie des chiens de cette étude.

### Resumen

**Introducción** – el oclacitinib es un fármaco efectivo y seguro para el tratamiento del prurito en perros asociado con dermatitis alérgica y atopia basado en pruebas clínicas al azar de hasta cuatro meses de duración.

**Hipótesis/Objetivos** – este estudio evalúa la seguridad a largo plazo, la eficacia y la calidad de vida de los perros tratados con oclacitinib incluidos en un programa de uso por compasión.

**Animales** – 227 perros de propietarios privados con dermatitis alérgica que había sido previamente tratada con oclacitinib con resultados beneficiosos.

**Métodos** – los perros se incluyeron en un estudio abierto de 26 clínicas veterinarias. Los perros recibieron de 0,4 a 0,6 mg/kg de oclacitinib dos veces al día durante 14 días, y después una vez al día hasta 630 días. Las evaluaciones se realizan aproximadamente a intervalos de 90 días. Los propietarios completaron un cuestionario de calidad de vida y valoración del prurito utilizando una escala visual análoga (VAS) en cada visita clínica. Los veterinarios valoraron la dermatitis utilizando una escala similar VAS. Se anotaron los eventos adversos en la salud, medicaciones concomitantes, y los resultados de la patología clínica.

**Resultados** – los valores de la escala visual análoga mostraron una mejora del nivel basal en todos los tiempos tomados. El porcentaje de perros mostrando  $\geq 50\%$  de reducción del nivel basal en el día 90 fue del 63,9% para el prurito y 66,4% para la dermatitis. Los propietarios vieron un impacto positivo en la calidad de vida en más del 91% de los perros. Infecciones urinarias/cistitis, vómitos, otitis, pioderma y diarrea fueron los eventos adversos clínicos más frecuentemente observados (más del 5% de los perros). La hematología y la bioquímica de suero permanecieron normales. Las medicaciones concomitantes fueron bien toleradas.

**Conclusiones e importancia clínica** – los resultados indican que oclacitinib es un fármaco eficaz y seguro para el tratamiento a largo plazo y que mejora la calidad de vida de los perros en este estudio.

### Zusammenfassung

**Hintergrund** – Oclacitinib ist sicher und effektiv für die Behandlung von Hunden mit Juckreiz, der auf allergische und atopische Dermatitis zurückzuführen ist, was durch randomisierte klinische Studien von bis zu 4 Monaten Dauer gezeigt wurde.

**Hypothese/Ziele** – Diese Studie untersuchte die Langzeit-Sicherheit, Wirksamkeit und Lebensqualität von Hunden, die im Rahmen eines „Compassionate Use“ Programms (Anwendung von noch nicht zugelassenen Medikamenten bei Patienten mit besonderer schwerer Krankheit) mit Oclacitinib behandelt wurden.

**Tiere** – Zweihundertsiebenundvierzig private Hunde mit allergischer Hauterkrankung, bei denen sich schon zuvor eine Behandlung mit Oclacitinib günstig ausgewirkt hatte.

**Methoden** – Die Hunde wurden in 26 Tierkliniken in Form einer offenen Studie registriert. Die Hunde erhielten 0,4–0,6 mg/kg Oclacitinib zweimal täglich für 14 Tage, danach einmal täglich für bis zu 630 Tage. Untersuchungen wurden in Intervallen von etwa 90 Tagen durchgeführt. Die BesitzerInnen füllten einen Fragebogen bezüglich der Lebensqualität aus und beurteilten den Juckreiz mittels Visual Analog Skala (VAS) bei jedem Klinikbesuch. Die Tierärzte beurteilten den Juckreiz mit einer ähnlichen VAS. Außergewöhnliche Veränderungen in Bezug auf die Gesundheit, begleitende Medikation und die Ergebnisse der klinischen Pathologie wurden zusammengefasst.

**Ergebnisse** – Die Visuelle Analog Skala zeigte vom Ausgangspunkt zu allen beurteilten Zeitpunkten eine Verbesserung. Der Prozentsatz der Hunde, die vom Ausgangswert eine  $\geq 50\%$  ige Reduktion am Tag 90 aufwiesen betrug 63,9% für den Juckreiz und 66,4% für die Dermatitis. Die BesitzerInnen sahen eine positive Veränderung auf die Lebensqualität bei  $> 91\%$  aller Hunde. Die am häufigsten beschriebenen abnormalen klinischen Zeichen ( $>5\%$  der Hunde) waren die von Harnwegsinfektionen/Zystitiden, Erbrechen, Otitis, Pyodermie und Durchfall. Hämatologische und blutbiochemische Untersuchungen blieben innerhalb der normalen Referenzwerte. Begleitende Medikamente wurden gut toleriert.

**Schlussfolgerungen und klinische Bedeutung** – Die Ergebnisse wiesen darauf hin, dass Oclacitinib sicher und wirksam für eine Langzeitbehandlung ist und die Lebensqualität der Hunde dieser Studie verbessert hatte.

## 要約

**背景** – 4ヶ月間までの持続期間におけるランダム化臨床試験に基づく、オクラシチニブはアレルギーやアトピー性皮膚炎に関連した痒みを示すイヌの治療に安全で効果的である。

**仮説/目的** – この研究ではオクラシチニブで治療した例外的使用プログラムに組み入れられたイヌにおいて長期的な安全性、効果ならびに生活の質を評価した。

**供与動物** – オクラシチニブの治療で今までに効果の得られたアレルギー性皮膚炎に罹患した247頭の飼い犬。

**方法** – 26の獣医診療所のイヌが非盲検試験に組み入れられた。イヌは0.4–0.6mg/kgのオクラシチニブを1日2回、14日間投与し、その後1日1回で630日まで投与を行った。評価は90日以内の間隔で行った。飼い主は病院を訪れるたびに、生活の質調査に記入し、ビジュアルアナログスケール(VAS)を用いて痒みの評価を行った。獣医師は類似のVASを用いて皮膚炎の評価を行った。健康上の異常な出来事、併用薬、ならびに臨床病理学的結果がまとめられた。

**結果** – ビジュアルアナログスケールスコアはすべての時点において基準値より改善を示した。90日目に痒みに対して、基準値より $\geq 50\%$ 減少を示したイヌの割合は63.9%で、皮膚炎に対しては66.4%であった。飼い主らはすべてのイヌのうち $>91\%$ で生活の質に肯定的な効果があると考えた。尿路感染/膀胱炎、嘔吐、耳炎、膿皮症ならびに下痢はもっとも頻度が高く報告された( $>5\%$ のイヌ)異常な臨床症状であった。血液学および血清生化学は正常な参照範囲以内にとどまっていたことを示していた。併用する薬剤はよく許容されていた。

**結論および臨床的な重要性** – 結果ではオクラシチニブは長期間の使用に安全で効果的であり、この調査におけるイヌにおいて生活の質を改善することを示唆していた。

## 摘要

**背景** – 在治疗犬过敏症和异位性皮炎相关的瘙痒症上, oclacitinib是安全且有效的药物, 这结论基于4个月以上的随机临床实验。

**假设/目的** – 该实验评估长期使用oclacitinib的安全性、有效性, 以及参与体恤计划的犬, oclacitinib治疗后的生活质量。

**动物** – 247只来自动物主人的过敏性皮肤病患犬, 曾获益于oclacitinib治疗。

**方法** – 参与这个开放性实验的患犬来自26家兽医诊所。一天两次给予oclacitinib 0.4–0.6 mg/kg, 连续14天, 然后改为一日一次连用630天。每隔90天评估一次。动物主人填写生活质量调查问卷, 并在每次复诊时用视觉模拟评分法(VAS)评估瘙痒程度。兽医同样用VAS评估皮炎。总结不良反应、联合用药和临床病理学结果。

**结果** – 视觉模拟评分法分数显示, 所有时间节点评分均有所改进。90天时, 瘙痒缓解率 $\geq 50\%$ 的为63.9%, 皮炎缓解率 $\geq 50\%$ 的为66.4%。主人所见生活质量改善的犬只所占比例 $>90\%$ 。尿道感染/膀胱炎、呕吐、耳炎、脓皮病和腹泻是最常见的( $>5\%$ 患犬)不良反应。血液学和血清生化检查显示指标均在正常参考范围内。同时药物耐受性良好。

**总结与临床意义** – 本次研究结果显示, 长期使用oclacitinib安全且有效, 并且能改善患犬的生活质量。