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A blinded, randomized, placebo-controlled trial of the efficacy and safety of the Janus kinase inhibitor oclacitinib (Apoquel®) in client-owned dogs with atopic dermatitis

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Background – Pruritus is the hallmark clinical sign of atopic dermatitis (AD) in dogs. Preliminary study results suggest that oclacitinib, a selective Janus kinase inhibitor, could reduce pruritus and associated inflammatory skin lesions in dogs with AD.

Hypothesis/Objectives – The objective was to evaluate efficacy and safety of oclacitinib (Apoquel®) for the control of AD in a randomized, double-blind, placebo-controlled trial.

Animals – Clinicians at 18 specialty clinics enrolled client-owned dogs (n = 299) with a history of chronic AD.

Methods – Dogs were randomized to receive either oclacitinib (0.4–0.6 mg/kg twice daily for 14 days and then once daily for up to 112 days) or an excipient-matched placebo. Owners assessed visual analog scale (VAS) scores of pruritus on days 0, 1, 2, 7, 14, 28, 56, 84 and 112. Clinicians assessed Canine AD Extent and Severity Index (CADESI-02) scores on days 0, 14, 28, 56, 84 and 112.

Results – On days 1, 2, 7, 14 and 28, oclacitinib-treated dogs had a 29.5, 42.3, 61.5, 66.7 and 47.4% reduction from baseline in owner-assessed pruritus scores, respectively, compared with a 6.5, 9.1, 6.5, 3.9 and 10.4% reduction in placebo-treated dogs. On days 14 and 28, dermatologists recorded a 48.4% reduction in CADESI-02 scores in oclacitinib-treated dogs compared with a 1.7% reduction and a 3.6% increase in placebo-treated dogs. After day 28, >86% of all placebo-treated dogs had moved to an open-label study, making between-group comparisons biased. Differences were significant at all time points assessed ($P < 0.0001$).

Conclusions and clinical importance – Oclacitinib provided rapid, effective and safe control of AD, with substantial improvement in VAS and CADESI-02 scores.

Introduction

The diagnosis and management of skin disease is a major component of small animal practice.[1] Canine atopic dermatitis (AD) is one of the most common dermatoses diagnosed by veterinarians. The exact prevalence is not known, but one study reported a diagnosis of AD in 8.7% of >31,000 dogs seen in 52 veterinary practices in the USA.[2] Atopic dermatitis has been defined as 'a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed against environmental allergens'.[3]

The diagnosis of AD is typically based on a compatible history, clinical signs and exclusion of other pruritic dermatoses, in that a definitive diagnostic test to confirm the diagnosis of AD is currently not available. The American College of Veterinary Dermatology (ACVD) Task Force (now the International Committee for Allergic Diseases of Animals; ICADA) summarized the clinical manifestations of AD.[4] There is consensus that dogs with AD typically develop pruritus, often at a young age, possibly seasonally, with lesions most commonly involving the face, extremities, axillae or ventrum.

The current hypothesis of the pathogenesis of canine AD proposes that pro-inflammatory cytokines, neuronal itch stimuli and the animal's pruritic behaviours establish a vicious cycle of itch that perpetuates and potentially exacerbates the skin lesions and defects in the skin barrier function.[5] The ICADA has released guidelines for the management of AD in clinical practice.[6] Acute flares of AD should be treated with a combination of nonirritating baths and topical glucocorticoids after attempts have been made to remove suspected causes of the flare; oral glucocorticoids and antimicrobials should be added on an as-needed basis. For the treatment of chronic AD, the following combination of interventions should be

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considered: avoidance of factors that trigger flares of AD; improving the skin barrier by bathing with nonirritating shampoos; dietary supplementation with essential fatty acids; allergen-specific immunotherapy; and administration of anti-inflammatory medications with evidence of good efficacy, including topical and oral glucocorticoids, oral ciclosporin and topical tacrolimus.[6] The dose and frequency of these medications should be tailored to each individual dog, considering the efficacy, adverse effects and costs of the medication and the ability of the owner to comply with application/administration of the prescribed treatment regimen.

One of the key therapeutic goals when treating AD is to stop the itch quickly and reliably to prevent further damage to the skin and improve the quality of life of the dog and the owner.[7] Glucocorticoids are the most commonly prescribed medication for treatment of this condition, and they are highly effective.[8] The high frequency of adverse effects, including polyuria, polydipsia and polyphagia, may result in decreased owner compliance. Moreover, long-term administration of glucocorticoids may result in serious health conditions, including pancreatitis, gastrointestinal ulceration, lipidaemia, diabetes mellitus, muscle wasting and iatrogenic hyperadrenocorticism.[9–11]

Ciclosporin is approved for use for the control of AD in dogs; the time to onset of action may limit its usefulness for the immediate relief of pruritus and in managing acute flares of AD.[6] The use of oral and topical essential fatty acids can improve the skin barrier function and potentially impede the cutaneous absorption of allergens associated with AD and contact dermatitis; again, the time to onset of action may make this an impractical therapy for the treatment of acute pruritus.[6] As a topically applied product, glucocorticoids appear to be of most value in the treatment of localized disease.[6,8,12] There is, therefore, an unmet need for a safe and rapidly effective treatment for pruritus and skin lesions.

Oclacitinib is a novel Janus kinase inhibitor, recently approved in the USA and EU, for the control/treatment of pruritus associated with allergic dermatitis and the control/treatment of AD in dogs. It was selected for its rapid onset of action as well as its activity against JAK1-dependent cytokines and its minimal activity against JAK2-dependent cytokines in cellular assays.[13] Janus kinases play a central role in cytokine signalling and are involved in signal transduction of many pro-inflammatory, pro-allergic and pruritogenic cytokines.[14,15] They are involved in the signalling of interleukin (IL)-31, a recently identified cytokine that induces pruritus in dogs.[16] Oclacitinib has been shown to inhibit IL-31 cytokine function, and it also significantly reduces IL-31-induced pruritus in dogs.[17] The activity of oclacitinib is not restricted to antipruritic effects, because it may also possess pronounced anti-inflammatory properties, as determined by its ability to inhibit the function of pro-inflammatory and pro-allergic cytokines, such as IL-2, IL-4, IL-6 and IL-13.[13]

The efficacy and safety of oclacitinib has been demonstrated in a randomized, placebo-controlled trial in client-owned dogs with pruritus associated with allergic dermatitis, as assessed primarily by general practitioners.[18] The present study was designed to evaluate efficacy and safety of oclacitinib in a randomized, placebo-controlled trial in client-owned dogs with AD, as assessed by veterinary dermatologists. The two studies have been used to support the approval of oclacitinib for two separate label indications, namely the control of pruritus associated with allergic dermatitis and the control of AD in dogs 12 months of age or older.[19]

Materials and methods

Overview

The study was conducted in support of new drug registration in the USA and in accordance with Good Clinical Practice, No. 85.[20] In clinics sited within academic institutions, the protocol was approved by the relevant Institutional Animal Care and Use Committee. The protocol was reviewed by and approved prior to study initiation by the Zoetis Ethical Review Board. The owners gave written informed consent for each dog to participate in the study.

Inclusion criteria

Dogs with AD were recruited from 18 clinics throughout the USA; all 18 participating clinicians were diplomates of the ACVD. All dogs were client owned, 12 months of age or older and in overall good health, apart from the AD, based on the initial (day 0) physical examination. Dogs weighed between 3 and 80 kg. Dogs were initially assessed for entry into the study by their owners as having moderate to severe itching (pruritus), using a categorical scale, and by clinicians as having a minimal CADESI-02 score of 25 out of a possible 360 points.[21–23]

All dogs had to have a documented history of chronic, nonseasonal AD, based on Prélaud's criteria.[24,25] Establishment of the diagnosis was made based upon compatible history and clinical signs and exclusion of other diagnoses. Dogs underwent a diagnostic regimen, as determined by the clinician, sufficient to eliminate differential diagnoses for AD including cutaneous adverse food reactions, flea-allergy dermatitis, bacterial or fungal dermatitis and/or otitis, internal and external parasitism, metabolic disease and other conditions as appropriate.

Dogs with concurrent conditions that required 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 had to be flea free at the time of the day 0 visit, and appropriate flea control/prevention was used throughout 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, must have remained on the same diet during the study and avoided potential food allergen sources identified during dietary restriction testing. All dogs (regardless of food allergy status) remained on their same diet for the duration of 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 1 year prior to enrolment, and the protocol must have been maintained throughout the study. If allergen-specific immunotherapy was discontinued, it had to be discontinued at least 8 weeks prior to enrolment.

Prohibited and conditionally allowed medications and therapies

Withdrawal times for prohibited medications were as follows: long-acting injectable glucocorticoids, 6 weeks; oral glucocorticoids, ciclosporin, long-acting injectable antimicrobial agents and miscellaneous compounds with known antipruritic activity [e.g. Staphage Lysate[26] (SPL®; Delmont Laboratories Inc., Swarthmore, PA, USA), gabapentin, monoamine oxidase inhibitors and tacrolimus], 4 weeks; topical nonsteroidal anti-inflammatory drugs and topical glucocorticoids, 3 weeks; antihistamines, 2 weeks; and oral antibacterial/antifungal agents, 1 week. Other medications and therapies were conditionally allowed, assuming that the owners, veterinarians and other study personnel adhered to all minimal use and frequency of use guidelines

for the concomitant medication (Table 1). Following the day 28 assessments, dogs were permitted to receive antimicrobial therapy.

Exclusion criteria

Exclusion criteria included dogs with evidence of malignant neoplasia, demodicosis, conditions that could have affected immune function (hypothyroidism, rickettsial disease, idiopathic thrombocytopenia, Von Willebrand's disease), dogs that were receiving, or should have been receiving, systemic antimicrobial therapy for bacterial folliculitis or fungal dermatitis, and lactating bitches or dogs (male or female) intended for use as breeding animals. Dogs with clinically relevant abnormalities in their pretreatment complete blood count, serum chemistry or urinalysis tests were withdrawn from the study.

Randomization and masking

The enrolled dogs were randomized to one of two treatment groups (i.e. oclacitinib or placebo) in a 1:1 ratio at each clinic using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). Blocking was based on order of enrolment within clinic. The dog was the experimental unit. The clinician and all site personnel, with the exception of the treatment administrator, were masked to the treatment group assignments, as were the owner and the laboratory personnel. Placebo and oclacitinib tablets were packaged in a commercial Good Manufacturing Practices facility into high-density polyethylene bottles with induction-sealed caps. The bottles were labelled in a masked fashion, and each bottle was marked with a unique, nonsequential randomly assigned container identification number.

The treatment dispenser utilized a treatment randomization file that was unique to the site to determine the treatment group assignment and then a container randomization list that 'decoded' the identity of the treatment in each numbered container to ensure proper masked assignment. The appropriate treatment was then dispensed to the client in commercially available prescription tablet vials or tablet trays that gave no indication of treatment group assignment.

Drug administration

Dogs in the oclacitinib treatment group were given oclacitinib maleate tablets provided in three strengths containing 3.6, 5.4 and 16 mg of oclacitinib. Dogs in the placebo treatment group were given the same number of tablets, identical in appearance to oclacitinib maleate tablets and containing all of the same excipients except oclacitinib maleate. Owners administered the study drug at home, with or without food,[27] and were instructed to adhere to the appropriate interval between doses.

Study schedule and variables measured

Following randomization, the dogs were assigned to receive either the excipient placebo or oclacitinib at a dose of 0.4–0.6 mg/kg, per os (p.o.) twice daily from day 0 to day 14 and then once daily to day 112. A dose of 0.4 mg/kg represents a nominal dose. Based on the available tablet strengths, a dog received a minimum dose of 0.4 mg/kg and, depending on body weight and the corresponding tablet strength, a maximum dose of 0.6 mg/kg. Dogs with worsening pruritus and/or AD that had been on study to day 14 could be withdrawn and then enrolled in an open-label study, in which every dog received oclacitinib at a dose of 0.4–0.6 mg/kg once daily. Study personnel that were blind to treatment group assignments, including the owner and the clinician, were not permitted to be unblinded prior to a dog being withdrawn from the placebo-controlled study and transferred to the open-label study. Dogs that entered the open-label study continued with the same study schedule and clinic visits based on original day 0 (enrolment). The length of the two studies combined did not exceed 112 days. Alternatively, dogs could be withdrawn from the study to start conventional treatment as prescribed by the clinician.

Baseline data (demographic, physical examination, assessments of pruritus and dermatitis) were collected on enrolment at day 0. A visual analog scale (VAS) score, consisting of a 10 cm line with word descriptors at 2 cm intervals, was used by dog owners to assess the severity of the 'itch'. Owners were instructed to place a mark on the VAS line at the location that best represented the dog's pruritus. At completion of both the masked study and the open-label study, the distance (in centimetres) from the bottom of the line ('normal dog') to the owner's mark on the line was measured and recorded. Owners performed a VAS assessment on days 0, 1, 2, 7, 14, 28, 56, 84 and 112. CADESI-02 scores were used by the clinicians to assess dermatitis on days 0, 14, 28, 56, 84 and 112.

On the final day of study, owners and clinicians assessed the dog's overall 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 at the other end of the line for 'excellent results'. Owners and clinicians 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; the distance (in centimetres) from the 'no improvement' descriptor to the owner's or clinician's mark on the line was measured and recorded.

Blood samples (complete blood count and serum chemistry) were collected on day 0 (prior to dosing) and on days 14, 28, 56, 84 and 112. Samples for urinalysis were collected on days 0, 28 and 112. Blood and urine were collected again if the dog presented for an abnormal health event. All samples for haematology (complete blood count), serum chemistry and urinalysis were sent to a central laboratory (Heska Corp., Loveland, CO, USA).

Sample size estimation

A minimum of 50 cases per treatment group was required to show a significant difference at the 0.05 level of significance using a two-sided test, assuming a 25% treatment success rate for placebo

Table 1. Conditionally allowed medications and therapy

Medications and therapy	Withdrawal time (weeks)	Minimal use*(weeks immediately preceding study start)	Frequency of use*
Essential fatty acids	2	6	No change in established routine
Nutraceuticals	2	6	No change in established routine
Vitamins	2	6	No change in established routine
Anticonvulsants	Not applicable	6	No change in established routine
Systemic nonsteroidal anti inflammatory drugs	6	6	No change in established routine
Thyroid supplementation	Not applicable	6	No change in established routine
Medicated shampoos†(not containing steroids/antihistamines)	2	6	Not to exceed once a week
Topical antimicrobial agents†‡	2	6	Not to exceed every other day

*Owners and veterinarians were given the option either to withdraw from the medication or therapy or to adhere to the minimal use and frequency criteria.

†Use could be initiated after day 28.

‡Topical includes shampoos, creams, ointments, sprays, and otic and ophthalmic products.

animals and a 50% treatment success rate for oclacitinib to provide at least 80% power.

Efficacy outcome measures

The effectiveness variables assessed were as follows: (i) treatment success, based on the Owner Pruritus VAS assessment and the clinician's CADESI-02 assessment; (ii) CADESI-02 score at each clinician assessment; (iii) VAS score at each owner assessment; and (iv) owner and clinician RTT VAS.

A treatment success for Owner Pruritus VAS was defined as at least a 2 cm reduction from baseline at the day of assessment; a treatment success for clinician's CADESI-02 was defined as 50% or greater score reduction from baseline at the day of assessment (days 28, 56, 84 and 112). Dogs that failed to meet these criteria were considered to be treatment failures for the relevant efficacy variable. For the treatment success variables, dogs that were withdrawn from the study on or before each day of assessment due to worsening signs of AD (lack of efficacy) or for an adverse event believed to be related to the study drug were considered to be treatment failures for both variables. For all other variables, dogs that were withdrawn from the study on or before each day of assessment due to worsening signs of AD (lack of efficacy) or for an adverse event believed to be related to the study drug were not included past the withdrawal time point.

To be included in the effectiveness analyses, dogs had to have received a minimum of 80% of the intended doses from day 0 to day 28. Not >40% of the total cases were permitted to enrol from any one site. To ensure that both treatments were replicated at each site and to ensure that blinding was maintained at all sites, clinics with fewer than two evaluable cases in each treatment group were excluded from the effectiveness analyses. Those dogs with a protocol deviation that affected the collection or integrity of their efficacy data were also excluded from the analyses. For the analyses involving owner assessments, there was an additional requirement that dogs had been properly dosed in the 24 h prior to each assessment. Every effort was made to ensure that the same owner or clinician who performed the day 0 assessment performed all subsequent VAS and CADESI-02 assessments.

Data analysis

Data were analysed using SAS version 9.2 (SAS Institute). The level of significance was set at $P < 0.05$.

Treatment success on day 28 was analysed using a generalized linear mixed model with a logit link and binomial error. The model included the fixed effect of treatment, the random effects of clinic and treatment by clinic interaction. The proportion of success with 95% confidence interval for each treatment and the odds ratio with 95% confidence interval comparing the treatments was reported. Frequency distributions were calculated for treatment success beyond day 28.

The Owner Pruritus VAS scores and the clinician's CADESI-02 scores to day 28 were analysed with linear mixed models for repeated measures. The fixed effects in the model were treatment, time and treatment by time interaction. The random effects in the model were clinic, clinic by treatment interaction, clinic by treatment by time interaction and animal. Data from the oclacitinib treatment group from day 28 onwards were analysed with a linear mixed model for repeated measures. The fixed effect in the model was time. Random effects included clinic, the clinic by time interaction and animal. The Owner Pruritus VAS scores and the clinician's CADESI-02 score for the placebo treatment group from day 28 onwards were summarized by time, including the number of animals, mean, standard deviation, minimum and maximum.

Owner and clinician RTT VAS scores were analysed using a general linear mixed model with the fixed effect of treatment and the random effects of clinic, clinic by treatment interaction and block.

Frequency distributions were calculated regarding whether or not an animal was normal by CASESI-02 (obtained a score of ≤15 at least once following day 0[28]) by treatment group and regarding whether or not an animal was normal by Owner Pruritus VAS (obtained a score of <2.0 cm at least once following day 0[29]).

For the open-label study, efficacy data were summarized by time point and previous treatment received on the placebo-controlled study, including the number of animals, mean, median, standard deviation, minimum and maximum.

Safety outcome measures

All enrolled dogs that were administered at least one dose of oclacitinib or placebo 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 experience at least one abnormal health event were displayed by clinical sign for all unique terms. Frequencies of dogs receiving each concomitant medication over the course of the study were summarized.

Results

Demographics

A total of 299 dogs were enrolled (Table 2). Retrievers and terriers were the most common dog breed groups, comprising 23.4% (Labrador retrievers, 15.7%; and golden retrievers, 7.7%) and 12.7% of the study population, respectively.

Assessment of effectiveness

The effectiveness data set for treatment success comprised 264 dogs in the Owner Pruritus VAS data set (133 placebo- and 131 oclacitinib-treated dogs) and 268 dogs in the clinician's CADESI-02 data set (134 placebo- and 134 oclacitinib-treated dogs). The data sets for other variables assessed changed at each subsequent time point as a result of errors in compliance with the trial and data collection protocols.

Treatment success: Owner Pruritus VAS

Defining treatment success as at least a 2 cm reduction from baseline at the day of assessment, at day 28 the majority of oclacitinib-treated dogs (66.0%) were considered to be a treatment success compared with 4.0% of the placebo-treated dogs ($P < 0.0001$). The 95% confidence interval was 54–76% for oclacitinib and 1–9% for placebo. After day 28, the percentage of cases that were a treatment success remained constant at 60.3% on day 56, 59.5% on day 84 and 61.3% on day 112 for the oclacitinib-treated group, compared with ≤2.3% of cases for the placebo-treated group.

Table 2. Demographics and baseline visual analog scale (VAS) data

Variable	Placebo group	Oclacitinib group
Breed distribution [*n* (%)]		
Purebred	107 (72.8%)	112 (73.7%)
Mixed breed	40 (27.2%)	40 (26.3%)
Sex distribution		
Male	78 (53.1%)	84 (55.3%)
Female	69 (46.9%)	68 (44.7%)
Age at study onset [years (range)]	5.5 (1.0–12.5)	5.8 (1.0–13.0)
Weight at study onset [kg (range)]	21.1 (3.8–58.0)	25.8 (3.4–77.2)

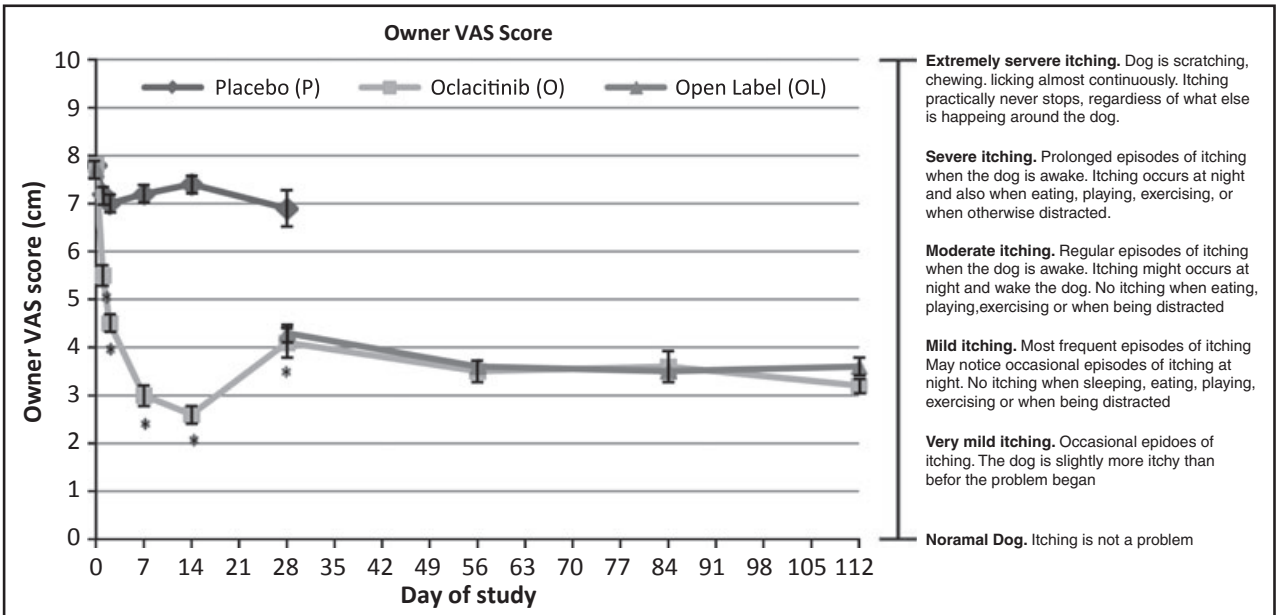
Treatment success: clinician's CADESI-02

At day 28, 49% of oclacitinib-treated dogs were considered to be a treatment success compared with 4.0% of the placebo-treated dogs ($P < 0.0001$). The 95% confidence interval was 32–66% for oclacitinib and 1–11% for placebo. After day 28, the percentage of cases that were a treatment success, over the remaining period, remained relatively constant at 55.6% on day 56, 50.4% on day 84 and 56.1% on day 112 for the oclacitinib-treated group, compared with ≤2.3% of cases for the placebo-treated group.

Owner Pruritus VAS scores by day of study

The mean day 0 Owner Pruritus VAS scores were very similar ($P = 0.7315$) between the treatment groups (7.8 and 7.7 cm for the oclacitinib-treated dogs and placebo-treated dogs, respectively; Figure 1), corresponding to 'severe itching' on the enhanced Owner Pruritus VAS score. After 1 day of treatment, there was a 2.3 cm reduction of the least squares means (mean) from the average baseline in the oclacitinib group, while the dogs receiving placebo treatment had a 0.5 cm reduction (Figure 1). By day 14, the mean Owner Pruritus VAS score for the oclacitinib-treated dogs had decreased to 2.6 cm (a 5.2 cm reduction from baseline). In contrast, the pruritus score for the placebo-treated dogs had decreased to 7.4 cm (a 0.3 cm deduction from baseline; Figure 1). At this time (day 14), 102 (76%) placebo-treated dogs withdrew for worsening of clinical condition associated with AD, with the majority (99%) moving to the open-label study, compared with nine (6%) oclacitinib-treated dogs, of which all (100%) moved to the open-label study. For six of the nine oclacitinib-treated dogs moved to the open-label study, a lack of clinical improvement was cited; two dogs were moved for protocol noncompliance and one dog was moved as a result of an unrelated medical or surgical condition. At day 28, the mean pruritus score for the oclacitinib-treated dogs was 4.1 cm (a 3.7 cm reduction from baseline), equating to 'mild itching'. In contrast, the mean pruritus score for the placebo-treated dogs was 6.9 cm, a 0.8 cm reduction from baseline (Figure 1). The Owner Pruritus VAS scores were significantly lower in the oclacitinib-treated dogs than in the placebo-treated dogs on each day of assessment, beginning with day 1, to day 28 ($P < 0.0001$).

The mean VAS scores for oclacitinib-treated dogs continued to improve from day 28 to day 112 to a score of 3.2 cm (a 4.6 cm reduction from baseline), although these changes were not significant. For the dogs that moved to the open-label study, the mean Owner Pruritus VAS score was 7.7 cm on the first day that the dog received oclacitinib, similar to the day 0 score for both of the treatment groups in the placebo-controlled study. Following treatment with oclacitinib, the mean pruritus scores were 4.5 cm by day 28 and 3.6 cm by study end at day 112.



Day 0	Day 1	Day 2	Day 7	Day 14	Day 28	Day 56	Day 84	Day 112
P:*n* = 139	P:*n* = 134	P:*n* = 130	P:*n* = 131	P:*n* = 105	P:*n* = 27			
O:*n* = 147	O:*n* = 142	O:*n* = 135	O:*n* = 131	O:*n* = 131	O:*n* = 117	O:*n* = 96	O:*n* = 84	O:*n* = 85
OL:*n* = 153					OL:*n* = 135	OL:*n* = 143	OL:*n* = 144	OL:*n* = 121

** = Oclacitinib is significantly different from Placebo (P < 0.0001)*

n = Number of dogs on study, P = Placebo-treated dogs enrolled in masked study, O = Oclacitinib-treated dogs enrolled in masked study, OL = Placebo- and Oclacitinib-treated dogs enrolled in open-label study

Figure 1. Owner Pruritus visual analog scale (VAS) scores by day of study (95% confidence interval).

Clinician CADESI-02 scores by day of study

The mean day 0 Clinician CADESI-02 scores were similar ($P = 0.3909$) for the two treatment groups (62 and 58 for the oclacitinib- and placebo-treated dogs, respectively; Figure 2). At days 14 and 28, the mean CADESI-02 scores for the oclacitinib-treated group had decreased to 32 (a reduction of 30 from baseline), while the mean scores for the placebo-treated group were 57 (a decrease of 1 from baseline) on day 14 and 61 (an increase of 3 from baseline) on day 28 (Figure 2; $P < 0.0001$). The mean CADESI-02 score continued to improve from day 28 to day 112, with a final score of 26 (a reduction of 36 from baseline), although these changes were not significant. For the dogs that moved to the open-label study from both treatment groups, the mean Clinician CADESI-02 score was 58 on the first day that the dog received oclacitinib, similar to the day 0 CADESI-02 score for both of the treatment groups in the placebo-controlled study. Following treatment with oclacitinib, the mean CADESI-02 scores were 34 at day 28 and 21 by the end of the study at day 112.

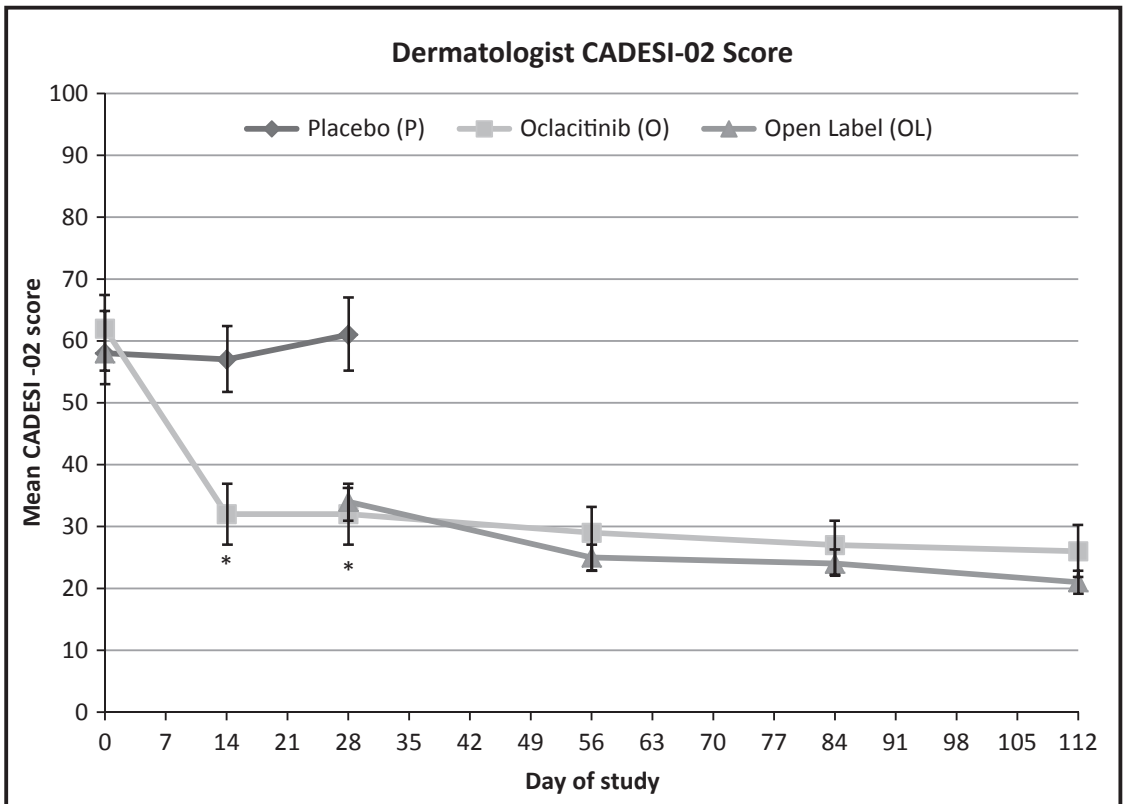
Table 3. Response-to-treatment VAS scores

	Owner's RTT VAS [cm; mean ± SD (*n*)]	Dermatologist's RTT VAS [cm; mean ± SD (*n*)]
Placebo*	0.7 ± 0.19 (131)	1.0 ± 0.26 (132)
Oclacitinib*	6.8 ± 0.30 (139)	6.4 ± 0.34 (139)
Open label†	7.4 ± 0.26 (148)	7.5 ± 0.24 (147)

Abbreviation: RTT, response to treatment.
*Least squares means ± SEM.
†Arithmetic means ± SD.

Response to treatment

The least squares means RTT VAS scores (Table 3) at the end of the study were significantly better following treatment with oclacitinib (owner's score, 6.8 cm; and clinician's score, 6.4 cm) compared with placebo (owner's score, 0.7 cm; and clinician's score, 1.0 cm; $P < 0.0001$). At the end of the open-label study, the mean owner's and clinician's scores were 7.4 and 7.5 cm, respectively.



Day 0	Day 14	Day 28	Day 56	Day 84	Day 112
P:*n* = 139	P:*n* = 135	P:*n* = 28	P:*n* = 7	P:*n* = 3	P:*n* = 4
O:*n* = 147	O:*n* = 144	O:*n* = 123	O:*n* = 101	O:*n* = 90	O:*n* = 91
OL:*n* = 154		OL:*n* = 136	OL:*n* = 143	OL:*n* = 145	OL:*n* = 121

** = Oclacitinib is significantly different from Placebo (P < 0.0001)*

n = Number of dogs on study, P = Placebo-treated dogs enrolled in masked study, O = Oclacitinib-treated dogs enrolled in masked study, OL = Placebo- and Oclacitinib-treated dogs enrolled in open-label-study

Figure 2. Clinician CADESI-02 scores by day of study (95% confidence interval).

Table 4. Study completion

Treatment group	Total [*n* (%)]	Completed placebo-controlled study [*n* (%)]	Withdrawn from placebo-controlled study [*n* (%)]					Transferred to open-label study [*n* (%)]	Completed open-label study* [*n* (%)]	Withdrawn from open-label study*† [*n* (%)]
			On or before day 14	Day 14–28	Day 28–56	Day 56–84	Day 84–112	Total [*n* (%)]		
Placebo	147 (100.0)	9 (6.1)	108 (73.5)	23 (15.6)	2 (1.4)	4 (2.7)	1 (0.68)	147 (100.0)	128 (87.1)	10 (9.8)
Oclacitinib	152 (100.0)	110 (72.4)	13 (8.6)	17 (11.2)	4 (2.6)	6 (3.9)	2 (1.3)	152 (100.0)	30 (19.7)	29 (96.7)	1 (3.3)

Treatment group	Reason for withdrawal from placebo-controlled study [*n* (%)]				
	Worsening signs of AD	Abnormal clinical pathology results	Unrelated medical or surgical condition	Possible adverse reaction to drug treatment	Owner noncompliance	Other
Placebo	131 (94.9)	3 (2.2)	0 (0.0)	0 (0.0)	3 (2.2)	1 (0.7)
Oclacitinib	30 (71.4)	0 (0.0)	2 (4.8)	3 (7.1)	4 (9.5)	3 (7.1)

*Treatment group refers to assignment in placebo-controlled study.
†Ten dogs previously assigned to the placebo group failed to completed the open-label study; three were removed for owner noncompliance, three were removed for worsening signs of atopic dermatitis (AD), two for possible adverse events, one for abnormal clinical pathology results and one for an unrelated medical or surgical condition. One dog previously assigned to the oclacitinib group that failed to complete the open-label study was removed for worsening signs of AD.

Table 5. Adverse reactions, day 0–16

Adverse reactions observed during days 0–16*	Oclacitinib (*n* = 152) [*n* (%)]	Placebo (*n* = 147) [*n* (%)]
Diarrhoea	7 (4.6)	5 (3.4)
Vomiting	6 (3.9)	6 (4.1)
Anorexia	4 (2.6)	0
New dermal, epidermal or subcutaneous mass†	4 (2.6)	4 (2.7)
Lethargy	3 (2.0)	2 (1.4)

*Adverse reactions were tabulated per animal; animals with pre-existing conditions are not listed.
†Masses included papillomas in two placebo-treated dogs and a histiocytoma in one oclacitinib-treated dog. The other masses did not have specific diagnoses.

Percentage of dogs with Owner Pruritus VAS and CADESI-02 scores in the range of normal dogs

The frequency distributions for dogs with normal CADESI-02 scores recorded at one or more time points post-treatment were better for oclacitinib-treated dogs [$n = 69$ (46.9%)] than for placebo-treated dogs [$n = 11$ (8.1%); $P < 0.0001$]. Likewise, the frequency distributions for dogs with normal Owner Pruritus VAS scores recorded at one or more time points post-treatment were better for oclacitinib-treated dogs [$n = 91$ (62.3%)] than for placebo-treated dogs [$n = 5$ (3.6%); $P < 0.0001$].

Safety assessment

The safety assessment was comprised of a summary of the abnormal health events, clinical pathology results and changes in body weight from day 0 to day 112 for both the placebo-controlled and the open-label study. All 299 dogs (147 placebo-treated and 152 oclacitinib-treated), having received one or more doses of either placebo or oclacitinib, were included in the summaries. Table 4 shows the number of dogs enrolled in both the placebo-controlled and the open-label studies, the number of dogs withdrawn prior to completion and the reason for withdrawal.

Abnormal health events

For the safety assessment, three dogs assigned to placebo treatment that inadvertently received oclacitinib for 1 day or more were included in the oclacitinib-treated group safety summaries. One hundred and eight of the 147 placebo-treated dogs withdrew on or before day 16 (day 14 ± 2), compared with 13 of the 152 oclacitinib-treated dogs; by day 28, only 33 of the 147 placebo-treated dogs (22.4%) remained on study, compared with 148 of the 155 (95.5%) oclacitinib-treated dogs.

The majority of the placebo-treated dogs withdrawn prior to day 28 were removed for worsening clinical signs of AD, and most were then enrolled into the open-label study. At the time of the day 112 assessment, only nine placebo-treated dogs remained in the placebo-controlled study. The small number of placebo-treated dogs confounds a between-group comparison of the abnormal health events. Given that the majority of the placebo-treated dogs withdrew before day 16, Table 5 depicts only the direct comparison of adverse events observed in the two treatment groups up to day 16. The diarrhoea, vomit-

ing, anorexia and lethargy spontaneously resolved in 90% of the cases, with the remainder of the cases responsive to supportive care; dosing continued uninterrupted throughout the adverse event.

Between the placebo-controlled and the open-label study, 283 dogs received at least one dose of oclacitinib. The following clinical signs were reported after beginning oclacitinib (expressed as the percentage of dogs with at least one report of the clinical sign as a nonpre-existing finding): pyoderma, 12.0%; nonspecified dermal nodules, 12.0%; otitis, 9.9%; vomiting, 9.2%; diarrhoea, 6.0%; histiocytoma, 3.9%; cystitis, 3.5%; anorexia, 3.2%; lethargy, 2.8%; yeast skin infections, 2.5%; pododermatitis, 2.5%; lipoma, 2.1%; polydipsia, 1.4%; lymphadenopathy, 1.1%; nausea, 1.1%; increased appetite, 1.1%; aggression, 1.1%; and weight loss, 0.7%.

Of the 283 oclacitinib-treated dogs, two (0.7%) were withdrawn from study due to suspected or confirmed malignant neoplasia, including one dog (a 5.5-year-old Labrador retriever) that developed a heart-based mass after 21 days of treatment with oclacitinib, and one (an 11-year-old mixed breed) that developed a Grade III mast cell tumour after 60 days on oclacitinib. In the placebo group, one of 147 dogs developed a Grade I mast cell tumour and was withdrawn from the study. Two other dogs (0.7%) were withdrawn from the study due to suspected treatment-related adverse reactions, including one dog that had an intense flare-up of dermatitis and severe secondary pyoderma after 19 days of oclacitinib administration, and one dog that developed generalized demodicosis after 28 days of oclacitinib administration. Additional dogs were hospitalized for diagnosis and treatment of pneumonia (one dog), transient bloody vomiting and stool (one dog) and cystitis with urolithiasis (one dog). There were few changes in body weight. Placebo-treated dogs lost ~1% of their body weight in the first 28 days of the study, although the remaining placebo-treated dogs then showed a slight weight gain (2.5%) by day 112. Oclacitinib-treated dogs showed an overall weight gain compared with baseline [~4% (−14 to 29%)] by day 112.

Haematology, serum chemistry and urinalysis

The arithmetic mean ('mean') value for all of the haematology and serum chemistry analytes in both treatment groups fell within the laboratory's normal reference range for that analyte at all of the visits reported during both the placebo-controlled and the open-label studies. While still within the normal reference range, an increase in mean serum cholesterol and mean serum lipase levels and a decrease in mean serum globulin and leukocyte levels were observed. In the oclacitinib-treated group, mean white blood cell, neutrophil, eosinophil and monocyte counts decreased to day 14 (neutrophils and monocytes) or day 28 (white blood cells and eosinophils) and then remained stable. Although mean values remained within the normal range, individual dogs developed leukopenia, primarily due to neutropenia. The mean lymphocyte count increased at day 14 and then returned to baseline. In the oclacitinib-treated dogs, mean serum globulin decreased to day 56 and then remained stable, within the normal range; mean serum cholesterol increased by day 14 and then remained stable, within the normal range; mean serum lipase increased to day 56 and then remained stable, within the normal range. Mean liver enzymes were not affected by administration of oclacitinib maleate. There were no differences in urinalysis, and summaries showed no apparent differences between the placebo-treated dogs and the oclacitinib-treated dogs.

Concomitant medications

A wide variety of concomitant medications and therapies were used in conjunction with either placebo or oclacitinib treatment. The concomitant medications administered most often (i.e. in ≥7% of the oclacitinib-treated dogs) are summarized by drug class and treatment group in Table 6. There did not appear to be any drug–drug interactions associated with administration of oclacitinib.

Discussion

Results of the study provide evidence of the effectiveness of oclacitinib for the control of AD, with each of the efficacy variables assessed being significantly ($P \leq 0.0001$) better for the oclacitinib-treated dogs than for the placebo-treated dogs.

Owner Pruritus VAS treatment success was ~60% or higher for all assessment time points, and the Clinician CADESI-02 success rates were approximately 50% or higher, in contrast to the success rates for placebo.

The antipruritic effect was rapid, with owners reporting a mean 29.5% reduction in pruritus in oclacitinib-treated

Table 6. Concomitant medications and therapies

Functional use term	Placebo (n = 147) [n (%)]	Oclacitinib (n = 152) [n (%)]	Open label (n = 158) [n (%)]
Endectocides	99 (67.3)	102 (67.1)	115 (72.8)
Ectoparacitides, insecticides and repellents	111 (75.5)	100 (65.8)	118 (74.7)
Antimicrobials			
Systemic	4 (2.7)	70 (46.0)	102 (64.6)
Topical	57 (38.8)	91 (59.9)	102 (64.6)
Other dermatological preparations	55 (37.4)	52 (34.2)	62 (39.2)
Emollients and protectives	23 (15.6)	32 (21.1)	40 (25.3)
Canine vaccines	34 (23.1)	31 (20.4)	38 (24.1)
Otologicals	17 (11.6)	26 (17.1)	44 (27.8)
Omega 3 Fatty acids	22 (15.0)	19 (12.5)	23 (14.6)
Glucosamine (with and without chondroitin) and nonsteroidal anti-inflammatory products (carprofen and other coxib inhibitors)	9 (6.1)	11 (7.2)	13 (8.2)

dogs within 24 h compared with only a 6.5% reduction for placebo-treated dogs. By day 14, the reduction in pruritus was 67% with oclacitinib, compared with 3.9% in placebo-treated dogs. The improvement in lesion scores was also rapid, with a 48.4% reduction in CADESI-02 scores (compared with a 1.7% decrease in placebo-treated dogs) after only 14 days of treatment.

The improvements in pruritus and lesion scores were maintained for 112 days and replicated in dogs entered into the open-label study. These results are comparable to an earlier randomized placebo-controlled trial[18] that reported a 26% reduction in pruritus by 24 h following treatment with 0.4 mg/kg oclacitinib every 12 h. That trial followed dogs for only 14 days, after which there was a 68% reduction in pruritus scores and a 54% reduction in CADESI-02 scores.

Three systematic reviews of clinical trials of pharmacological interventions in canine AD concluded that there remains a lack of well-designed randomized clinical trials for the majority of products used in the treatment of AD.[8,12,30] The ICADA clinical practice treatment guidelines recommend, among other interventions, the use of glucocorticoids (orally and topically) and ciclosporin for the control of AD.[6] In two studies considered high quality,[22,31] prednisolone or methylprednisolone administered at recommended label doses resulted in a 45–69% reduction in CADESI scores and a 33–81% reduction in pruritus scores over 14–120 days. In nine randomized clinical trials with a total of 424 dogs,[12,30] ciclosporin administered at the recommended label dose resulted in a 39.9–67% reduction in CADESI scores and a 36–78% reduction in pruritus scores over 21–120 days. Additionally, 47–87.5% of dogs showed a ≥50% reduction in the CADESI scores. The efficacy of oclacitinib therefore appears to be at least as good as that for systemic glucocorticoids and ciclosporin. The efficacy end-points for ciclosporin were from day 21 onwards, which reflects the time needed to see clinical benefit for this drug. Given that there may be a period of time before the full clinical benefit from ciclosporin may be observed, it has been suggested that ciclosporin is co-administered with prednisolone at 1 mg/kg every other day for the first 14 days for dogs with AD.[32]

In this study, normal was defined as obtaining a CADESI-02 score of ≤15 and a pruritus VAS score of <2 cm. These definitions align with what has been proposed as normal by Olivry *et al.*[28] for CADESI-03 and by Rybnicek *et al.*[29] for the pruritus VAS. The percentage of dogs with lesions and pruritus scores in the range of normal was 46.9 and 62.3%, respectively, for oclacitinib-treated dogs compared with 8.1 and 3.6% for placebo-treated dogs. The most recent systematic review[12] summarized the results of three clinical trials, in which the percentage of dogs with lesions in the range of normal dogs and percentage of dogs with pruritus in the range of normal dogs was assessed. In one study,[33] hydrocortisone acetate administered topically once daily for 7 days and then every other day resulted in 30% of dogs with lesions in the range of normal dogs and 10% of dogs with pruritus in the range of normal dogs. In another study,[34] in which ciclosporin was administered orally at a dose 50–200 mg/day, 25% of dogs were reported with lesions in the range of normal dogs and pruritus was not reported. In a third study, when hydrocortisone acetate applied topically once daily was compared with ciclosporin administered orally once daily at an initial dose of 5 mg/kg, with the frequency decreased to either every other day or twice weekly if effective, hydrocortisone acetate resulted in 33% of dogs with lesions in the range of normal dogs and 42% of dogs with pruritus in the range of normal dogs, compared with 43 and 33%, respectively, for ciclosporin-treated dogs.[35] In comparison, in the present study, oclacitinib appears to be equivalent or better than either hydrocortisone acetate or ciclosporin in returning dogs with AD to a normal state. It should be reiterated that the present study was designed and the results analysed to support the registration of oclacitinib. While the selection of the variables to be assessed and the criteria used for the assessment met the rigid standards required to for product approval, they do not always allow for a direct comparison with other randomized clinical trials (e.g. number of dogs exhibiting a 50%/90% reduction of pruritus and CADESI scores).[8,9,30]

Oclacitinib appeared to be well tolerated, with few differences in the incidence of adverse events between oclacitinib-treated and placebo-treated dogs during the first 2 weeks of treatment. Many of the clinical signs reported here (otitis externa, pyoderma and pododermatitis) are secondary complications of AD and therefore not likely to be associated with oclacitinib administration.[36] Although anorexia was reported in four of 152 (2.6%) oclacitinib-treated dogs (and none of the placebo-treated dogs), the anorexia was transient and resolved without treatment. Of note, oclacitinib-treated dogs had a slight weight gain over the course of the study. No comparison between the two treatment groups was possible after 14 days, because most placebo-treated dogs were withdrawn from the study. However, by study end, a total of 283 (of 299) dogs had received at least one dose of oclacitinib, and the reported adverse events do not indicate any specific safety alert associated with oclacitinib treatment. Most of the frequently reported adverse events, such as pyoderma, nonspecific dermal masses, otitis, histiocytoma, yeast skin infections, pododermatitis and lipoma, were related to the skin. Many of these could be related to compromised skin and/or immune function in chronic AD, and it is unlikely that the frequency of adverse events that are directly related to the skin would be different with other AD treatments. A number of gastrointestinal disorders were observed; vomiting in 9.2% and diarrhoea in 6.0% of the 283 oclacitinib-treated dogs. The majority of these cases were of mild or moderate severity, and many resolved in a single day without treatment, with most dogs continuing on oclacitinib therapy for the duration of the study. In a 4 month study, 47% of ciclosporin-treated and 25% of methylprednisolone-treated dogs exhibited gastrointestinal disorders, suggesting that oclacitinib treatment could be better tolerated than both of these common treatments.[31]

Polydipsia was observed in only 1.4% (four of 283 dogs) of the oclacitinib-treated dogs, and polyuria and polyphagia were not observed at all. In another study of canine AD, 25% of methylprednisolone-treated dogs

(n = 59) exhibited polyuria/polydipsia, with 12% showing increased appetite and body weight.[31]

It is known that inhibiting JAK/STAT signal transduction can affect the activity of selected interleukins, which can interfere with the development, differentiation and function of some leukocyte populations.[37] For this reason, bacterial, fungal or parasitic infections were carefully monitored and recorded.

Infections and infestations that caused either withdrawal from the study or hospitalization were observed in four oclacitinib-treated dogs, as follows: withdrawal due to severe secondary pyoderma (after 19 days of treatment); withdrawal due to generalized demodicosis (after 28 days of treatment); hospitalization for diagnosis and treatment of pneumonia (after 91 days of treatment); and hospitalization for cystitis secondary to urolithiasis (after 80 days of treatment). All four animals recovered fully. Long-term administration of up to five times the recommended dose for 26 weeks (twice daily for 6 weeks and once daily for 20 weeks) was well tolerated in dogs of 1 year of age in laboratory safety studies, without any indication of secondary bacterial or parasitic infections.[38]

While the clinicians reported a number of nonspecified dermal nodules, virtually all were considered benign. Only two malignant skin tumours, both mast cell tumours, were diagnosed. Mast cell tumours are the most common cutaneous tumour in dogs and occur most frequently in mixed breeds, although Boston terriers have been noted to be at higher risk.[39] The equal frequency in the two treatment groups, the high incidence of canine mast cell tumours and the breed predilection suggest it is unlikely that these neoplasms were caused by oclacitinib treatment. The only other potential malignancy, a heart base mass suggestive of a haemangiosarcoma, was observed after only 21 days, and it is hypothesized that this neoplasm was present before oclacitinib treatment started. However, as with any other immunomodulator that may exacerbate neoplastic conditions, dogs treated with oclacitinib should be monitored for the development of neoplasia.[40]

In the study reported here, two sets of data were analysed; the per protocol data set was used for the assessment of efficacy and the intent-to-treat data set used for the assessment of safety. By definition, an intent-to-treat data set includes all animals that were randomized to study in their respective treatment groups.[41,42] In the present study, the intent-to-treat data set was not used for the assessment of efficacy, in that once a dog was withdrawn from study, there were no data available for the time points after the withdrawal. Thus, it was not possible to conduct an intent-to-treat efficacy analysis as has been performed in other randomized clinical trials for AD.[8]

Recent insight into the pathophysiology of AD, including the most clinically relevant inflammatory mediators and cytokines, suggests that more targeted therapies than those currently available could be developed.[4] Oclacitinib represents such a targeted treatment option, as described by Gonzales *et al.*[16] The dosage regimen, aimed for the long-term control of chronic AD, investigated in this study was designed both to maximize the beneficial effects, such as the inhibition of IL-31, and to minimize the T-cell inhibition to avoid any safety concerns, especially with chronic use. The efficacy and safety results of our study suggest that the oclacitinib regimen fulfils both criteria; twice daily dosing for the first 14 days rapidly breaks down the itch–cycle and, as hypothesized,[13,19] successfully downregulates some inflammatory, allergic and pruritogenic cytokine activity, and the subsequent once daily dosing, administered as maintenance therapy, provides a solid margin of safety while maintaining efficacy for chronic use, during the time period observed.

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References

1. VPI® Pet Insurance website. Top 10 pet medical conditions of 2010. Available at: http://press.petinsurance.com/pressroom/02222011Pet_Conditions_2010.aspx. Accessed Dec 28, 2012.
2. Lund EM, Armstrong PJ, Kirk CA *et al.* Health status and population characteristics of dogs and cats examined at private veterinary practices in the United States. *J Am Vet Med Assoc* 1999; 214: 1336–1341.
3. Halliwell R. Revised nomenclature for veterinary allergy. *Vet Immunol Immunopathol* 2006; 114: 207–208.
4. Griffin CE, DeBoer DJ. The ACVD task force on canine atopic dermatitis (XIV): clinical manifestations of canine atopic dermatitis. *Vet Immunol Immunopathol* 2001; 81: 255–269.
5. Marsella R, Sousa CA, Gonzales AJ *et al.* Current understanding of the pathophysiologic mechanisms of canine atopic dermatitis. *J Am Vet Med Assoc* 2012; 241: 194–207.
6. Olivry T, DeBoer DJ, Favrot C *et al.* Treatment of canine atopic dermatitis: 2010 clinical practice guidelines from the International Task Force on Canine Atopic Dermatitis. *Vet Dermatol* 2010; 21: 233–248.
7. Favrot C, Linke M, Mueller R. Development of a questionnaire to assess the impact of atopic dermatitis on health-related quality of life of affected dogs and their owners. *Vet Dermatol* 2010; 21: 64–70.
8. Olivry T, Mueller RS. Evidence-based veterinary dermatology: a systematic review of the pharmacotherapy of canine atopic dermatitis. *Vet Dermatol* 2003; 14: 121–146.
9. Scott DW, Griffin CE, Campbell KL. Dermatologic therapy. In: *Muller and Kirk's Small Animal Dermatology*. 7th ed. St Louis: Saunders Elsevier, 2013; 150–153.
10. Plumb DC. Glucocorticoid agents, general information. In: *Plumb's Veterinary Drug Handbook*. 4th ed. Ames: Blackwell Publishing, 2002; 387–389.

11. Olivry T, Sousa C. The ACVD task force on canine atopic dermatitis (XX): glucocorticoid pharmacotherapy. *Vet Immunol Immunopathol* 2001; 81: 317–322.
12. Olivry T, Bizikova P. A systematic review of randomized controlled trials for prevention or treatment of atopic dermatitis in dogs: 2008-2011 update. *Vet Dermatol* 2013; 24: 97–117, e26–e26.
13. Gonzales AJ, Bowman J, Fici G *et al.* Oclacitinib (Apoquel®; Zoetis) is a novel Janus kinase inhibitor that has activity against canine pro-allergic and pro-inflammatory cytokines. *Vet Dermatol* 2013; 24: 384–385. (abstract).
14. Carmi-Levy I, Homey B, Soumelis V. A modular view of cytokine networks in atopic dermatitis. *Clin Rev Allergy Immunol* 2011; 41: 245–253.
15. Ong PY, Leung DY. Immune dysregulation in atopic dermatitis. *Curr Allergy Asthma Rep* 2006; 6: 384–389.
16. Gonzales AJ, Humphrey WR, Messamore JE *et al.* Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol* 2013; 24: 48–53, e11–e12.
17. Fleck T, Humphrey W, Coscarelli E *et al.* Comparison of the janus kinase (JAK) inhibitor, oclacitinib, and prednisolone in canine models of pruritus. *Vet Dermatol* 2012; 23(Suppl 1): 38 (abstract).
18. Cosgrove S, Wren J, Cleaver D *et al.* Efficacy and safety of oclacitinib for the control of pruritus and associated skin lesions in dogs with canine allergic dermatitis. *Vet Dermatol* 2013; 24: 479–e114.
19. Apoquel® product label. Available at: https://online.zoetis.com/US/EN/Products/Documents/Apoquel_PI.pdf. Accessed Jul 16, 2013.
20. International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), Good Clinical Practice Website. Available at: http://www.vichsec.org/en/topics.htm. Accessed Dec 28, 2012.
21. Olivry T, Marsella R, Iwasaki T *et al.* Validation of CADESI-03, a severity scale for clinical trials enrolling dogs with atopic dermatitis. *Vet Dermatol* 2007; 18: 78–86.
22. Olivry T, Rivierre C, Jackson HA *et al.* Cyclosporine decreases skin lesions and pruritus in dogs with atopic dermatitis: a blinded randomized prednisolone-controlled trial. *Vet Dermatol* 2002; 13: 77–87.
23. Olivry T, Steffan J, Fisch RD *et al.* Randomized controlled trial of the efficacy of cyclosporine in the treatment of atopic dermatitis in dogs. *J Am Vet Med Assoc* 2002; 221: 370–377.
24. Prélaud P, Guaguère E, Alhaidari Z *et al.* Re-evaluation of diagnostic criteria of canine atopic dermatitis. *Rev Med Vet (Toulouse)* 1998; 149: 1057–1064.
25. Gross TL, Ihrke PJ, Walder EJ *et al.* Diseases of the dermis. *Skin Diseases of the Dog and Cat*, 2nd edition. Oxford: Blackwell Publishing, 2005: 200–206.
26. Epinette WW. Treatment of atopic eczema with staphylococcal toxoid. *J Am Med Assoc* 1988; 259: 2759–2760.
27. Collard WT, Hummel BD, Malpas PB *et al.* Single and multiple dose pharmacokinetics of oclacitinib maleate in the dog. In: *Proceedings of the American Academy of Veterinary Pharmacology and Therapeutics Biennial Meeting*. Potomac, MD, USA: 2013.
28. Olivry T, Mueller R, Nuttall T *et al.* Determination of CADESI-03 thresholds for increasing severity levels of canine atopic dermatitis. *Vet Dermatol* 2008; 19: 115–119.
29. Rybnicek J, Lau-Gillard P, Harvey R *et al.* Further validation of a pruritus severity scale for use in dogs. *Vet Dermatol* 2008; 20: 115–122.
30. Olivry T, Foster AP, Mueller RS *et al.* Interventions for atopic dermatitis in dogs: a systematic review of randomized controlled trials. *Vet Dermatol* 2010; 21: 4–22.
31. Steffan J, Alexander D, Brovedani F *et al.* Comparison of cyclosporine A with methylprednisolone for treatment of canine atopic dermatitis: a parallel, blinded, randomized controlled trial. *Vet Dermatol* 2003; 14: 11–22.
32. Dip R, Carmichael J, Letellier I *et al.* Concurrent short-term use of presnisolone with cyclosporine A accelerates pruritus reduction and improvement in clinical scoring in dogs with atopic dermatitis.*BMC Vet Res* 2013; 9: 173.
33. Bryden SL, Burrows AK, Rème C *et al.* Efficacy of a 0.0584% hydrocortisone acetate spray (Cortavance) for the management of pedal pruritus in atopic dogs; a pilot study. *Vet Dermatol* 2008; 19(Suppl 1): 40 (abstract).
34. Carlotti DN, Boulet M, Ducret J *et al.* The use of recombinant omega interferon therapy in canine atopic dermatitis; a double-blind controlled study. *Vet Dermatol* 2009; 20: 405–411.
35. Nuttall TJ, McEwan NA, Bensignor E *et al.* Comparable efficacy of a topical 0.0584% spray and oral ciclosporin in treating canine atopic dermatitis. *Vet Dermatol* 2012; 23: 4–10, e1–e2.
36. DeBoer DJ, Hillier A. The ACVD task force on canine atopic dermatitis (XV): fundamental concepts in clinical diagnosis. *Vet Immunol Immunopathol* 2001; 81: 271–276.
37. Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. *Immunol Rev* 2009; 228: 273–287.
38. Malpas PB, Franks RK, King VL *et al.* Margin of safety study of oclacitinib maleate administered to adult laboratory dogs for 26 weeks at multiples of the therapeutic dose. In: *Proceedings of the American Academy of Veterinary Pharmacology and Therapeutics Biennial Meeting*. Potomac, MD, USA: 2013.
39. Thamm D, Vail D. Chapter 16: Mast cell tumors. In: Withrow SJ, MacEwen EG, eds. *Saunders Small Animal Clinical Oncology*. 3rd edition. Philadelphia: W.B. Saunders Co., 2001; 261–282.
40. Novartis Animal Health website. Atopica [indications]. Available at: http://www.ah.novartis.com/products/en/atopica_dog.shtml. Accessed Jan 25, 2013.
41. Committee for Medicinal Products for Veterinary use (CVMP). Guidelines on statistical principles for veterinary clinical trials. EMA/CVMP/EWP 20 September 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/01/WC500120834.pdf. Accessed Sept 13, 2013.
42. Alshurafa M, Briel M, Akl EA *et al.* Inconsistent definitions for intention-to-treat in relation to missing outcome data: systematic review of the methods literature. *PLoS One*. website. Available at http://dx.doi.org/10.1371%2Fjournal.pone.0049163. Accessed Aug 20, 2013.

Résumé

Contexte – Le prurit est le signe clinique typique de la dermatite atopique (AD) chez le chien. Les résultats d'études préliminaires suggèrent que l'oclacitinib, un inhibiteur sélectif de Janus kinase, pourrait réduire le prurit et les lésions inflammatoires cutanées associées chez les chiens atteints d'AD.

Hypothèses/Objectifs – L'objectif était d'évaluer l'efficacité et l'innocuité de l'oclacitinib (Apoquel®) pour le contrôle de l'AD dans une étude randomisée, contrôlée contre placebo, en double aveugle.

Sujets – Les cliniciens de 18 cliniques spécialisées ont inclus des chiens de propriétaires (n = 299) atteints de dermatite atopique chronique.

Méthodes – Les chiens ont été randomisés pour recevoir soit de l'oclacitinib (0.4–0.6 mg/kg deux fois par jour pendant 14 jours puis une fois par jour pendant 112 jours) soit un placebo contenant l'excipient. Les propriétaires ont réalisé des échelles de prurit visuelles à jours 0, 1, 2, 7, 14, 28, 56, 84 et 112.Les cliniciens ont réalisé des scores CADESI-02 (Canine AD Extent and Severity Index) à jours 0, 14, 28, 56, 84 et 112.

Résultats – Aux jours 1, 2, 7, 14 et 28, les chiens ayant reçu de l'oclacitinib avaient respectivement 29.5, 42.3, 61.5, 66.7 et 47.4% de réduction de scores de prurit évalué par les propriétaires comparé à 6.5, 9.1, 6.5, 3.9 et 10.4% de diminution chez les chiens contrôles ayant reçu le placebo. A jours 14 et 28, les dermatologues ont enregistré une diminution de 48.4% des scores CADESI-02 chez les chiens recevant de l'oclacitinib comparé à une diminution de 1.7% et une augmentation de 3.6% chez les chiens recevant le placebo. Après le jour 28, plus de 86% des chiens recevant le placebo ont été transféré dans une étude ouverte faisant des biais de comparaison entre les groupes. Les différences étaient significatives à tous les points évalués ($P < 0.0001$).
Conclusions et importance clinique – L'oclacitinib a entrainé un contrôle rapide, efficace et sûr de l'AD, avec une amélioration substantielle des scores de l'échelle analogue visuelle et du CADESI-02.

Resumen
Introducción – el prurito es la signo clínico mas relevante de la dermatitis atópica (AD). Estudios preliminares sugieren que oclacinitib, un inhibidor selectivo de la quinasa Janus, puede reducir el prurito y las lesiones cutáneas inflamatorias asociadas a perros con AD.
Hipótesis/Objetivos – el objetivo fue evaluar la eficacia y seguridad de oclacinitib (Apoquel®) para el control de la dermatitis atópica en un a prueba doble ciega al azar controlada con placebo.
Animales – veterinarios clínicos de 18 hospitales especializados reclutaron perros de propietarios particulares (n = 299) con historia de AD crónica.
Métodos – los perros fueron distribuidos al azar para recibir bien oclacitinib (0,4- 0,6 mg/kg dos veces al día durante 14 días y después una vez al día hasta por 112 días) o un placebo con el mismo excipiente. Los propiertarios valoraron en la escala análoga visual el índice de prurito en los días 0, 1, 2, 7, 14, 28, 56, 84 y 112. Los clínicos hicieron lo mismo siguiendo el índice canino de extensión y severidad del prurito (CADESI-02) en los días 0, 14, 28, 56, 84 y 112.
Resultados – en los días 1, 2, 7, 14 y 28 los perros tratados con oclacinitib tuvieron una reducción del 29,5; 42,3; 61,5; 66,7 y 47,4% con respecto a los valores iniciales en la escala de prurito evaluada por los propietarios, respectivamente. Esto estuvo en contraste con la reducción en los perros tratados con placebo que fue de 6,5; 9,1; 6,5; 3,9 y 10,4%, respectivamente. En los días 14 y 28 los dermatólogos notaron una reducción del 48,4% en los valores de CADESI-02 en los perros tratados con oclacitinib comparado con una reducción de 1,7% y un aumento de 3,6% en perros tratados con placebo. Después del día 28, >86% de los perros tratados con placebo se pasaron a un estudio abierto, desviando la comparación entre grupos. Las diferencias fueron significativas en todos los puntos estudiados ($P = 0,0001$).
Conclusiones e importancia clínica – oclacitinib produjo un control rápido, efectivo y seguro de la AD con mejora sustancial en la escala visual análoga y los valores CADESI-02.

Zusammenfassung
Hintergrund – Juckreiz ist bei Hunden das Kardinalsymptom der atopischen Dermatitis (AD). Vorläufige Studienergebnisse zeigen, dass Oclacitinib, ein selektiver Janus Kirasehemmer, den Juckreiz und damit verbundene entzündliche Hautreaktionen bei Hunden mit AD reduzieren konnte.
Hypothese/Ziele – Das Ziel dieser Studie war es, die Wirksamkeit und Sicherheit von Oclacitinib (Apoquel®) zur Kontrolle von AD in einer randomisierten, doppelblinden, Plazebo-kontrollierten Studie zu evaluieren.
Tiere – KlinikerInnen aus 18 Spezialkliniken nahmen Hunde im Besitz von KundInnen (n = 299) mit der Anamnese einer chronischen AD in die Studie auf.
Methoden – Die Hunde erhielten zufällig entweder Oclacitinib (0,4-0,6 mg/kg zweimal täglich für 14 Tage und dann einmal täglich für bis zu 112 Tage) oder ein dem Trägermedium angepasstes Plazebo. Die BesitzerInnen beurteilten die Juckreiz Werte mittels visueller Analogskala an den Tagen 0, 1, 2, 7, 14, 28, 84 und 112. Die KlinikerInnen beurteilten die Canine AD Extent and Severity Index Werte (CADESI-02) an den Tagen 0, 14, 28, 56, 84 und 112.
Ergebnisse – An den Tagen 1, 2, 7, 14 und 28 zeigten die mit Oclacitinib behandelten Hunde eine 29,5; 42,3; 61,5 bzw 47,4%ige Reduktion der von den BesitzerInnen beurteilten Juckreizwerte im Vergleich zu 6,5; 9,1; 6,5; 3,9 und 10,4%igen Reduktion bei den mit Plazebo behandelten Hunden. An den Tagen 14 und 28 beschrieben die DermatologInnen eine 48,4%ige Reduktion der CADESI-02 Werte bei den mit Oclacitinib behandelten Hunde im Vergleich zu einer 1,7%igen Reduktion und einem 3,6%igen Anstieg bei den mit Plazebo behandelten Hunde. Nach dem Tag 28 waren >86% aller Plazebo-behandelten Hunde in einer offenen Studie, was die Vergleiche zwischen den Gruppen polarisiert. Die Unterschiede waren zu allen Zeitpunkten signifikant verschieden (P<0,0001).
Schlussfolgerungen und klinische Bedeutung – Oclacitinib stellte eine rasche, wirksame und sichere Kontrolle von AD mit einer deutlichen Verbesserung der Werte der visuellen Analogskala und der CADESI-02 Werte dar.

要約

背景 – そう痒はイヌにおけるアトピー性皮膚炎(AD)の代表的な臨床症状である。予備研究では、選択的なヤヌスキナーゼ阻害物質であるオクラシチニブはADを呈するイヌにおけるそう痒および関連する炎症性皮膚病変を減少させる可能性があることを示していた。

仮説/目的 – ADのコントロールにおけるオクラシチニブ（Apoquel®）の効果と安全性をランダム化した、二重盲検、プラセボ対照試験にて評価することを目的とした。

供与動物 – 18の専門病院の臨床家が慢性ADの病歴を持つ飼い犬(n = 299)を研究に組み入れた。

方法 – イヌはオクラシチニブ(0.4–0.6 mg/kg1日2回で14日間、その後1日1回で112日まで)、あるいは賦形剤対応対照をランダムに投与された。飼い主は0、1、2、7、14、28、56、84、112日目にそう痒をビジュアルアナログスケールで評価した。臨床家は Canine AD Extent and Severity Index (CADESI-02) スコアを0、14、28、56、84、112日目に評価した。

結果 – 1、2、7、14、28日目で、オクラシチニブを投与しているイヌはオーナーの評価したそう痒スコアにおいて、プラセボを投与しているイヌが基準値から6.5, 9.1, 6.5, 3.9 および 10.4% の減少であったのと比較しそれぞれ29.5, 42.3, 61.5, 66.7 および 47.4% の減少がみられた。14日目と28 日目において、プラセボを投与しているイヌにおいて皮膚科医がCADESI-02 スコアで1.7% の減少および3.6%の増加と比較し、オクラシチニブを投与しているイヌにおいて48.4%の減少を記録した。28日目以降、プラセボを投与しているイヌの86%以上がグループ間の比較の際、偏りを作ったため、非盲検試験に移行した。差は評価したすべての時点で有意であった(P < 0.0001)。

結論および臨床的な重要性 – オクラシチニブはビジュアルアナログスケールやCADESI-02スコアにおいて十分な改善を伴い、急速で、効果的ならびに安全なADのコントロールをもたらす。

摘要

背景 – 瘙痒是犬异位性皮炎（AD）的标志性临床症状。初步的研究结果显示，oclacitinib，一种选择性Janus激酶抑制剂，能减少瘙痒，以及犬异位性皮炎引起的皮肤炎症。

假设/目的 – 目的是通过随机、双盲、安慰剂对照试验，评估oclacitinib (Apoquel®)用于控制异位性皮炎的效果和安全性。

动物 – 18个专科诊所的临床医生所登记的有慢性异位性皮炎病史的就诊犬（n = 299）。

方法 – 犬被随机分配接受oclacitinib（0.4-0.6 mg/kg，连续14天每日两次，之后112天每日一次）或赋形剂相同的安慰剂。主人在0、1、2、7、14、28、56、84和112日时，评估瘙痒视觉模拟评分。临床医生在0、14、28、56、84和112日时，对犬异位性皮炎程度和严重指数（CADESI-02）进行评估。

结果 – 1、2、7、14日时，oclacitinib治疗犬的主人瘙痒评分分别从基线下降29.5、42.3、61.5、66.7 和47.4%，与安慰剂治疗的犬相比下降6.5、9.1、6.5、3.9、和10.4%。14和28日时，皮肤科医生记录oclacitinib治疗犬的CADESI-2评分分别下降了48.4%，而安慰剂治疗犬分别下降了1.7%，增加了3.6%。28日后，>86% 的安慰剂治疗犬移至开放实验室进行研究， 进行组间偏差比较。 所有时间点的评估差异显著（P <0.0001）.

结论和临床价值 – oclacitinib可快速、有效并安全的控制异位性皮炎，明显改善视觉模拟评分和CADESI-02评分。