A blinded, randomized clinical trial comparing the efficacy and safety of oclacitinib and ciclosporin for the control of atopic dermatitis in client-owned dogs

Peter R. Little*, Vickie L. King†, Kylie R. Davis*, Sallie B. Cosgrove† and Michael R. Stegemann‡

*Veterinary Medicine Research and Development, Zoetis, 45 Poplar Road, Parkville, VIC, 3052, Australia
†Veterinary Medicine Research and Development, Zoetis, 333 Portage Street, Kalamazoo, MI, 49007, USA
‡Veterinary Medicine Research and Development, Zoetis, Mercuriusstraat 20, 1930, Zaventem, Belgium

Correspondence: Peter R. Little, Veterinary Medicine Research and Development, Zoetis, 45 Poplar Road, Parkville, VIC 3052, Australia.
E-mail: peter.little@zoetis.com

Background – Ciclosporin is approved for the treatment of atopic dermatitis (AD) in dogs and has been shown to be safe and effective. Placebo-controlled studies suggest that oclacitinib is a safe and effective alternative therapy.

Hypothesis/Objectives – To evaluate the efficacy and safety of oclacitinib, in comparison to ciclosporin, for the control of AD in a blinded, randomized clinical trial, incorporating a noninferiority test at day 28.

Animals – A total of 226 client-owned dogs with a history of AD from eight sites were enrolled.

Methods – Enrolled animals were randomized to receive oral oclacitinib (0.4–0.6 mg/kg twice daily for 14 days, then once daily) or oral ciclosporin (3.2–6.6 mg/kg once daily) for 12 weeks. Owners assessed pruritus using an enhanced visual analog scale (VAS), and veterinarians assessed dermatitis using the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-02.

Results – On days 1, 2, 7, 14, 28, 56 and 84, the percentage reduction from baseline for owner-assessed pruritus changed from 25.6 to 61.0% in the oclacitinib group compared with 6.5 to 61.5% in the ciclosporin group; differences were significant at all time points up to day 28. On day 56, ciclosporin-treated dogs showed a similar decrease in pruritus to oclacitinib-treated dogs. On day 14, the percentage reduction from baseline CADESI-02 was significantly greater in the oclacitinib group (58.7%) than in the ciclosporin group (43.0%). Three times as many adverse events attributed to gastrointestinal signs were reported in the ciclosporin group compared with the oclacitinib group.

Conclusions and clinical importance – In this study of treatment for canine AD, oclacitinib had a faster onset of action and a lower frequency of gastrointestinal side effects compared with ciclosporin.

Introduction

Atopic dermatitis (AD) is a common chronic allergic skin disease in dogs that involves environmental allergens; pruritus associated with canine AD is a frequent presenting complaint in general and referral veterinary practice. Canine AD is a multifactorial condition that involves cutaneous dendritic cells, T lymphocytes, a multiplicity of other cells and an altered skin barrier function at the centre of the disease process. Environmental allergens that penetrate the cutaneous barrier trigger a complex immunological reaction involving the release of many different cytokines that drive the process, resulting in cutaneous inflammation and neuronal mechanisms that initiate the never-ending cycle of pruritus.

Guidelines for the management of canine AD have been produced by the International Committee for Allergic Diseases of Animals (ICADA). The most effective treatments based on systematic reviews are as follows: anti-inflammatory agents, including topical and oral glucocorticoids, oral ciclosporin and topical tacrolimus; antimicrobial therapy to manage secondary bacterial or fungal infections; bathing with nonirritating shampoos; and allergen-specific immunotherapy. There is no universal treatment protocol, and the management of canine AD needs to be tailored to the individual case based on response to therapy, potential for adverse effects, owner compliance and medication costs.

Ciclosporin (Atopica®, Novartis Animal Health Australasia Pty Ltd, North Ryde, NSW, Australia) is approved for the treatment of canine AD at a daily dose of 5 mg/kg p.o. (range 3.1–6.7 mg/kg p.o.). There is good evidence for the efficacy of oral ciclosporin and it may take 4–6 weeks to achieve satisfactory clinical improve-
ment. Gastrointestinal side effects may be observed; in a systematic review of clinical trials involving ciclosporin, vomiting and diarrhoea were reported with an overall prevalence of 25 and 15%, respectively.\textsuperscript{7,8} The Janus kinase (JAK) inhibitor, oclacitinib (Apoquel\textsuperscript{9}), Zoetis Inc., Florham Park, NJ, USA), is approved in a number of countries for the control/treatment of pruritus associated with allergic dermatitis and the control/treatment of AD in dogs >12 months of age.\textsuperscript{9,10} Oclacitinib is a targeted therapy that selectively inhibits key pathways that lead to itch stimulation and cutaneous inflammation, particularly through the inhibition of JAK-1 signalling of interleukin-31, a cytokine shown to induce pruritus in dogs.\textsuperscript{11–13} The efficacy and safety of oclacitinib have been demonstrated in placebo-controlled, randomized clinical trials in client-owned dogs.\textsuperscript{14,15} The present study was conducted to investigate the efficacy and safety of oclacitinib in comparison to ciclosporin for the control of AD in dogs, in a randomized clinical trial.

Materials and methods

Overview

Seven study investigators enrolled a total of 226 client-owned dogs with a history of chronic, nonseasonal AD in an 84 day study. The study was conducted in compliance with applicable animal welfare regulations relating to the care and use of animals for scientific purposes, and the study protocol was approved by the relevant institutional Animal Ethics Committee. The study was conducted in accordance with good clinical practice guidelines,\textsuperscript{16} and written informed consent was obtained from the owner of each participating dog. Many of the methods used in this study, particularly inclusion criteria, exclusion criteria and excluded and conditionally allowed concurrent medications (including drug withdrawal times), were as previously reported;\textsuperscript{15} a summary of methods and key differences are provided here.

Study design and sample size estimation

This study was conducted as a positively controlled, single-blinded clinical trial with a randomized complete block design, replicated at eight study sites in Australia. The individual animal was the experimental unit, and blocking was based on the order of enrolment at each clinic. The intended period of study for each enrolled dog was 84 ± 2 days. Ciclosporin was used as the positive control drug. The primary measures of efficacy were the percentage reduction from baseline for both owner-assessed pruritus and investigator-assessed Canine Atopic Dermatitis Extent and Severity Index (CADESI)-02, each incorporating a noninferiority test at day 28. Using a noninferiority margin of 15% and a one-sided significance level of 0.05, a sample size of 99 animals per treatment was required to show noninferiority of oclacitinib compared with ciclosporin for CADESI-02, with 80% power.

Inclusion and exclusion criteria

All dogs enrolled were to be >12 months of age, weigh between 3 and 80 kg, have moderate to severe pruritus (owner assessed) using a categorical scale and a minimum CADESI-02 score (investigator assessed) of 25 of a possible 360 points. Systemic azole antifungals (e.g. ketoconazole) were prohibited in this study in order to avoid any potential influence on the pharmacokinetics of ciclosporin.

Randomization and blinding

Dogs meeting the inclusion criteria and relevant drug withdrawal times for excluded treatments were randomized in a 1:1 ratio to receive either oclacitinib or ciclosporin. A randomization file was produced for each study site using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). One or more nonblinded treatment dispensers at each study site allocated enrolled dogs to treatment groups, dispensed the trial medication and provided instructions to owners regarding the requirements for drug administration. Treatment dispensers and owners were instructed not to discuss the description of the trial drug or dosing regimen with the investigator. Due to the different dosing regimens of the two trial drugs, as well as the label requirement for the Atopica\textsuperscript{16} capsules to be kept in their foil blister packaging until required for use, dog owners were not blinded in this study.

Drug administration

Oclacitinib was administered at a dose rate of 0.4–0.6 mg/kg p.o. twice daily for 14 ± 2 days, then once daily up to day 84 ± 2, with or without food. Ciclosporin was administered at a dose rate of 3.2–6.6 mg/kg p.o. once daily for the duration of the study. Owners of dogs in the ciclosporin group were instructed not to administer the trial drug within 2 h before or after feeding, according to the label directions. Day 0 of the study was defined as the first day of treatment for each enrolled dog.

Study schedule and variables measured

Baseline data (signalment, clinical history, concurrent medications, body weight, physical examination and assessments of pruritus and atopic dermatitis) were recorded for each dog enrolled in the study. Pruritus (assessed by the owner) and dermatitis (assessed by the veterinarian) were subsequently assessed at scheduled clinic visits on days 1 ± 2, 28 ± 2, 56 ± 2 and 84 ± 2; pruritus was also assessed by the owner at home on days 1, 2 and 7 ± 1. Pruritus was scored using an enhanced visual analog scale (VAS) consisting of a 10 cm line with text descriptors of severity and behaviour placed at 2 cm intervals.\textsuperscript{17} The extent and severity of skin lesions were scored using the CADESI-02. On the final study day, the overall response to treatment (RTT) was assessed by both the owner and the veterinary investigator (not necessarily independently of each other) using a 10 cm VAS line, with a descriptor of ‘no improvement’ at 0 cm and ‘excellent results’ at 10 cm.

Owners and/or veterinarians were free to withdraw their dog from the study at any time due to an adverse event, worsening of clinical signs of AD or for any other reason; the reason for early withdrawal (or late completion) was recorded. Blood samples for haematology and serum chemistry were collected at enrolment (baseline) and on days 14, 29, 56 and 84; urine samples for general urinalysis were also collected at enrolment and on days 28 and 84. There was no specific requirement regarding the method of urine collection. Blood and urine samples were sent to a central veterinary diagnostic laboratory (Gribbles Veterinary Pathology, Clayton, Victoria, Australia). At scheduled and unscheduled clinic visits, a physical examination was performed and the dog’s body weight recorded. Any abnormal clinical signs reported by the owner or identified by the examining veterinarian, as well as concurrent treatments, were recorded. Abnormal clinical signs were classified by the veterinary investigator at the time of observation as mild, moderate or severe, based on their clinical judgement.

Efficacy outcome measures

The primary efficacy measures assessed in this study were the percentage reduction from baseline score at each time point for both pruritus VAS and CADESI-02. Secondary efficacy variables included the following: (i) the absolute score at each time point for pruritus VAS and CADESI-02; (ii) the achievement of a ≥50% reduction from baseline score at each time point for pruritus VAS and CADESI-02; and (iii) owner and investigator RTT VAS on the final study day.

Some animals were excluded from the efficacy data set at specific time points due to dosing noncompliance, incorrect dose dispensed, administration of prohibited drugs, or if an efficacy assessment was performed outside the prescribed assessment window. Dogs with one or more major protocol deviations that affected the collection or integrity of their efficacy data were also excluded from the analysis.

© 2014 Zoetis Australia Research & Manufacturing Pty Ltd, Veterinary Dermatology, 26, 23–e8.
Safety outcome measures
All dogs that received at least one dose of oclacitinib or ciclosporin were included in the safety summaries. For each continuous haematology, serum chemistry and urinalysis measure, summary statistics (mean, median, standard deviation, minimum and maximum) were calculated by treatment and time point. Haematology and serum chemistry values were summarized, reporting the number of dogs that fell below, within or above the normal reference range, as well as the number and percentage of dogs that had an increased shift (from below or within the reference range at baseline to above the reference range) or a decreased shift (from above or within the reference range at baseline to below the reference range) at each time point.

Frequency of dogs reported to experience at least one abnormal health event were calculated by preferred adverse event term, based on the Veterinary Dictionary for Drug Related Affairs (VeDDRA) standard term list.18 Descriptive statistics (mean, median, standard deviation, minimum and maximum) for body weight and percentage change from baseline body weight were calculated by treatment and time point. Frequencies of dogs receiving each concurrent medication recorded during the study were calculated.

Data analysis
Efficacy data were analysed using SAS version 9.2. Noninferiority tests of the percentage reduction from baseline of pruritus VAS scores and CADESI-02 scores on day 28 were performed at the one-sided 0.05 significance level with a delta of 15%; all other hypothesis tests were performed at the two-sided 0.05 significance level. For the percentage reduction and binomial analyses, the last time point data available were used as the day 28 values for dogs that were withdrawn from the study before day 28 due to worsening signs of atopic dermatitis or for an adverse event possibly related to the study drug.

The percentage reduction from baseline, for both pruritus VAS and CADESI-02, was analysed using a general linear mixed model for repeated measures, with the centred baseline value as a covariate. The fixed effects in the model were clinic, block within clinic, clinic-by-treatment term) and residual.

Pruritus VAS scores and CADESI-02 scores were analysed using a general linear mixed model for repeated measures. The achievement of a ≥50% reduction from baseline score at each time point, for both pruritus VAS and CADESI-02, was analysed using a generalized linear mixed model for repeated measures with a logit link and binomial distribution, with the least-squares means being estimated proportions. The models were the same as for the percentage reduction variables without the covariates. Least-squares means investigator- and owner-assessed RTT VAS scores were analysed using a general linear mixed model. The fixed effect in the model was treatment and the random effects were clinic, block within clinic and residual.

An intention-to-treat analysis for the primary efficacy measures is available as Supporting Information (Tables S1 and S2).

Results

Baseline characteristics of the study population
A total of 226 dogs were enrolled in the study and received at least one dose of drug (Table 1). The most frequently represented breeds, either as a purebred dog or the predominant breed in a cross-bred dog, were as follows: Labrador retriever (12.4%), Staffordshire bull terrier (7.5%), Maltese (7.5%), beagle (5.3%), West Highland white terrier (4.9%) and miniature poodle (4.4%). Fewer than 15% of animals in each group were sexually intact.

Study completion
A total of 176 of 226 (77.9%) animals completed the study as scheduled on day 84 ± 2; 19 animals in each group were withdrawn early (prior to day 82); five in each group completed the study late (after day 86); and two animals, both in the oclacitinib group, did not present for the final clinic visit. Table 2 summarizes the number of animals completing the study by period, as well as the reasons for early withdrawal or late completion.

Assessment of efficacy
The data set for the assessment of efficacy included >60 animals per treatment group at each time point for all variables measured and >100 animals per group for both primary outcome measures at day 28.

Owner-assessed pruritus VAS score
Oclacitinib had a significantly higher mean percentage reduction compared with ciclosporin on days 1, 2, 7, 14 and 28 (Table 3). Mean pruritus VAS scores at each time point are shown in Figure 1. There was a rapid reduction in mean pruritus score in the oclacitinib group from day 1 (5.6 cm) to day 14 (2.8 cm) and then a slight increase to 3.7 cm at day 28. On day 84, the mean score was below 3 cm for each treatment.

The estimated proportion of animals achieving a ≥50% reduction from baseline pruritus score at each time point is shown in Table 3; the proportion was significantly higher in the oclacitinib group at all time points up to day 28.

Investigator-assessed CADESI-02 score
Oclacitinib was significantly better than ciclosporin on day 14, with a mean reduction of 58.7% for oclacitinib compared with 43.0% for ciclosporin (P < 0.0001). On days 28, 56 and 84, the mean percentage reductions were similar in both treatment groups (Table 4); oclacitinib passed the statistical test of noninferiority for this variable on day 28. Mean CADESI-02 scores at each time point are shown in Figure 2; the scores decreased in both groups by day 14, with mean scores of 24.5 in the oclacitinib group and 31.2 in the ciclosporin group (not

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of the study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Purebred status</td>
</tr>
<tr>
<td>[n(%)]</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Sex distribution</td>
</tr>
<tr>
<td>[n(%)]</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Mean(range) age (years)</td>
</tr>
<tr>
<td>Mean(range) weight (kg)</td>
</tr>
<tr>
<td>Mean(range) pruritus VAS (cm)</td>
</tr>
<tr>
<td>Mean(range) CADESI-02 score</td>
</tr>
</tbody>
</table>

© 2014 Zoetis Australia Research & Manufacturing Pty Ltd, Veterinary Dermatology, 26, 23–e8. 25
significant, \( P = 0.0763 \). On day 84, the mean CADESI-02 score was below 20 for both treatments.

On day 14, there was a significantly higher proportion of animals in the oclacitinib group achieving a \( \geq 50\% \) reduction from baseline CADESI-02 compared with the ciclosporin group; proportions were similar in both treatment groups at subsequent time points (Table 4).

### Overall response to treatment

The owner- and investigator-assessed RTT VAS scores were similar in both groups at the end of the study. For owner-assessed RTT, the mean scores were 7.1 cm for ciclosporin and 7.4 cm for oclacitinib (\( P = 0.5053 \)); for investigator-assessed RTT, the mean scores were 7.3 cm for ciclosporin and 7.7 cm for oclacitinib (\( P = 0.3494 \)).

### Assessment of safety

#### Abnormal health events

The frequency of abnormal clinical signs occurring in two or more dogs in either treatment group, calculated on a per animal basis and excluding pre-existing conditions, is presented in the Supporting Information (Table S3).

Six animals in the ciclosporin group were withdrawn from the study due to vomiting (with or without diarrhoea), with four of these before day 7, and one animal from the oclacitinib group. New raised or nodular skin lesions (including lesions variously recorded as lump, mass, nodule, swelling, plaque, histiocytoma, papilloma or tumour) were found in 12 dogs (10.7%) in the ciclosporin group and in 12 dogs (10.5%) in the oclacitinib group; these skin lesions were biopsied in three ciclosporin-treated dogs and four oclacitinib-treated dogs. In the ciclosporin group, histopathological findings included the following: a melanocytic naevus (typically benign); changes consistent with but not clearly diagnostic of papilloma viral infection or an excessive lichenoid reaction to bacterial pyoderma; a sebaceous gland adenoma (benign); and a grade 1 mast cell tumour. In the oclacitinib group, histopathological findings were as follows: histiocytoma; follicular dilatation/orthokeratosis; suspect histiocytoma, and nonspecific inflammatory changes; and chronic hyperplastic and ulcerative pododermatitis with fibroadnexal dysplasia.

Adverse events were classified by the veterinary investigator as severe in 17 animals (15.2%) in the ciclosporin group and 14 animals (12.3%) in the oclacitinib group. The majority of severe adverse events in both treatment groups were due to pre-existing conditions and/or concurrent disease, and many of these were due to potential complications of atopic dermatitis, such as bacterial pyoderma, fungal (yeast) skin infection and/or otitis externa. Severe adverse events not related to a pre-existing condition or concurrent disease occurred in six dogs in each treatment group. In the ciclosporin group, two animals developed severe vomiting following the first one or two doses and were withdrawn from the study; one animal had a severe flare in itch and was very distressed after two doses, and was withdrawn from the study; one animal developed numerous grey plaques on the trunk and limbs as well as an alopecic mass on a hindlimb; one animal developed severe diarrhoea on day 24, which resolved by day 28; and one animal developed severe anorexia and lethargy on day 47, which resolved by day 54. In the oclacitinib group, one animal experienced a chemical burn to the cornea on day 22; a mammary nodule was identified in one animal on day 60, which was subsequently biopsied and found to be a lipoma or normal mammary tissue; one animal developed elevated liver enzymes (alkaline phosphatase and alanine aminotransferase) on day 14, which increased further on day 21, so the animal was removed on day 25 for treatment of suspected bacterial cholangiohepatitis; and one animal had a firm swelling on the toe identified on day 56, which did not respond to antibiotics and continued to enlarge, so a biopsy was taken with a finding of chronic hyperplastic and ulcerative pododermatitis with fibroadnexal dysplasia.

Two animals in the oclacitinib group were diagnosed with long-bodied Demodex (Demodex injai) infestation in skin scrapings taken from the dorsal trunk, one on day 28 and one on day 56. Both dogs were male West Highland white terriers, aged 4 and 7 years, with presenting clinical signs including dorsal erythema, scaly skin and/or a greasy hair coat. At the time of enrolment, each of these dogs was receiving oclacitinib for treatment of suspected bacterial cholangiohepatitis; and one animal had a firm swelling on the toe identified on day 56, which did not respond to antibiotics and continued to enlarge, so a biopsy was taken with a finding of chronic hyperplastic and ulcerative pododermatitis with fibroadnexal dysplasia.

### Table 2. Study completion

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Completed on schedule ( \times n (% ) )</th>
<th>Withdrawn from study early or completed study late ( \times n (% ) )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1–12</td>
<td>Day 13–27</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>88 (78.6)</td>
<td>8 (7.1)</td>
</tr>
<tr>
<td>Oclacitinib</td>
<td>88 (77.2)</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for early withdrawal or late completion ( \times n (% ) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible adverse reaction</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Ciclosporin</td>
</tr>
<tr>
<td>Oclacitinib</td>
</tr>
</tbody>
</table>

\( ^{\dagger} \) Final study visit on day 84 ± 2.

\( ^{\ddagger} \) Owner noncompliance\( ^{\dagger} \) includes four dogs that completed the study late; ‘other’ includes six dogs that completed the study late and two that did not present for the final study visit.

© 2014 Zoetis Australia Research & Manufacturing Pty Ltd, Veterinary Dermatology, 26, 23–e8.
Table 3. Least-squares mean percentage reduction from baseline and estimated proportion of animals achieving ≥50% reduction from baseline (95% confidence intervals) for owner-assessed pruritus VAS score at each post-treatment time point

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment group</th>
<th>Day of study</th>
<th>Day 1 (%)</th>
<th>Day 2 (%)</th>
<th>Day 7 (%)</th>
<th>Day 14 (%)</th>
<th>Day 28 (%)</th>
<th>Day 56 (%)</th>
<th>Day 84 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases per group (n)</td>
<td>Ciclosporin</td>
<td>104</td>
<td>88</td>
<td>103</td>
<td>92</td>
<td>101</td>
<td>85</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oclacitinib</td>
<td>110</td>
<td>100</td>
<td>107</td>
<td>109</td>
<td>103</td>
<td>92</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Percentage reduction (%)</td>
<td>Ciclosporin</td>
<td>6.5 (2.3–10.7)</td>
<td>8.6 (4.5–12.7)</td>
<td>21.7 (16.6–26.8)</td>
<td>27.9 (22.0–33.8)</td>
<td>39.2 (33.2–45.2)</td>
<td>53.6 (46.7–60.4)</td>
<td>61.5 (54.4–68.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oclacitinib</td>
<td>25.6 (19.8–31.4)</td>
<td>41.4 (34.8–47.9)</td>
<td>56.6 (50.1–63.2)</td>
<td>63.2 (56.7–69.6)</td>
<td>50.9 (44.1–57.8)</td>
<td>53.5 (46.4–60.6)</td>
<td>61.0 (54.1–67.8)</td>
<td></td>
</tr>
<tr>
<td>Proportion ≥50% reduction</td>
<td>Ciclosporin</td>
<td>0.02 (0.01 to 0.05)</td>
<td>0.01 (-0.02 to 0.04)</td>
<td>0.10 (0.04-0.17)</td>
<td>0.24 (0.15-0.32)</td>
<td>0.37 (0.27-0.46)</td>
<td>0.60 (0.50-0.70)</td>
<td>0.71 (0.61-0.81)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oclacitinib</td>
<td>0.19 (0.11–0.27)</td>
<td>0.41 (0.31–0.51)</td>
<td>0.58 (0.48–0.67)</td>
<td>0.68 (0.58–0.77)</td>
<td>0.51 (0.41–0.61)</td>
<td>0.63 (0.53–0.73)</td>
<td>0.66 (0.55–0.77)</td>
<td></td>
</tr>
</tbody>
</table>

*pSignificant treatment difference at P < 0.05.
received antibacterials for systemic and dermatological use, as well as otologics.

**Discussion**

The results of this study indicated that the efficacy of oclacitinib for the control of canine AD is at least as good as that of oral ciclosporin and has a significantly faster onset of effect. The reduction in pruritus and skin lesions seen in the oclacitinib-treated dogs closely mirrored the results of a placebo-controlled study conducted in client-owned dogs in the USA, suggesting consistently high efficacy of oclacitinib in populations of dogs with AD in different regions of the world. The percentage reduction from baseline pruritus VAS score and the proportion of dogs achieving ≥50% reduction from baseline were significantly better in the oclacitinib group in comparison to the ciclosporin group on days 1, 2, 7, 14 and 28 following initiation of treatment. After day 28, the level of pruritus continued to improve in both groups. Although there were no scheduled owner assessments between days 28 and 66, it was not until 8 weeks of treatment were completed that a similar improvement in pruritus was achieved in the ciclosporin-treated dogs compared with the oclacitinib-treated dogs. A limitation of this study was that owners were not blinded to treatment group allocation, due to the different dosing regimens of the two trial drugs as well as the label requirement for Atopica capsules to be left in the blister packaging until required for use. This might have resulted in a degree of observation bias in assessments of pruritus, although the direction and extent of any bias would be difficult to quantify.

Improvement in skin lesions, as measured by the percentage reduction from baseline CADESI-02 score and the proportion of dogs achieving ≥50% reduction from baseline, was significantly better in the oclacitinib group on day 14. Oclacitinib passed the test of noninferiority on day 28, indicating that the efficacy of oclacitinib is at least as good as that of ciclosporin in terms of the percentage reduction from baseline CADESI-02 at that time point. By day 84, mean pruritus VAS scores in both groups were below 3 cm, corresponding to mild to very mild itching, and mean CADESI-02 scores were below 20. Only a small number of dogs were withdrawn early from this study due to worsening signs of AD; six in the oclacitinib group and three in the ciclosporin group. The dosage frequency of ciclosporin was not tapered in dogs that responded to treatment, largely due to the need to maintain blinding and the corresponding complexity of making decisions around clinical improvement and possible dose adjustment.

The antipruritic effect of oclacitinib was rapid, with mean reductions in pruritus of 25.6% on day 1, 41.4% on day 2 and 63.2% on day 14. In contrast, the control of pruritus in the ciclosporin group was slower, with mean reductions of 6.5, 8.6 and 27.9% on the same study days. Most dog owners are likely to be satisfied with the prescribed treatment for AD once their dog experiences a ≥50% improvement in the level of pruritus compared with baseline, and this threshold has been used as a standard of efficacy in subsequent studies. In the present study, there was a rapid increase in the number of oclacitinib-treated dogs achieving ≥50% reduction in pruritus score, with 19% of dogs on day 1 and 68% on day 14 reaching this threshold, compared with 2 and 24% of dogs, respectively, in the ciclosporin group. By day 84, pruritus scores in the oclacitinib group had returned to levels similar to those seen at the end of the twice-daily dosing period, indicating that once-daily therapy with oclacitinib is suitable for maintenance once the acute itch has been brought under control.

The rapid onset of effect of oclacitinib was consistent with that seen for prednisolone in a positive-controlled randomized clinical trial in client-owned dogs with allergic dermatitis. In that study, both oclacitinib and prednisolone administered orally reduced pruritus levels substan-

---

**Table 4. Least-squares mean percentage reduction from baseline and estimated proportion of animals achieving ≥50% reduction from baseline (95% confidence intervals) for investigator-assessed CADESI-02 at each post-treatment time point**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment group</th>
<th>Day 14</th>
<th>Day 28</th>
<th>Day 56</th>
<th>Day 84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases per group (n)</td>
<td>Ciclosporin</td>
<td>93</td>
<td>101</td>
<td>85</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Oclacitinib</td>
<td>109</td>
<td>102</td>
<td>92</td>
<td>83</td>
</tr>
<tr>
<td>Percentage reduction</td>
<td>Ciclosporin</td>
<td>43.0 (36.5–49.5)</td>
<td>54.4 (47.7–61.1)</td>
<td>61.8 (64.9–68.8)</td>
<td>65.4 (58.3–72.5)</td>
</tr>
<tr>
<td>from baseline (%)</td>
<td>Oclacitinib</td>
<td>58.7 (62.3–65.0)</td>
<td>58.3 (51.6–65.1)</td>
<td>63.8 (66.9–70.8)</td>
<td>66.9 (59.7–74.0)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>0.2799</td>
<td>0.6011</td>
<td>0.7065</td>
<td></td>
</tr>
<tr>
<td>Proportion ≥50% reduction</td>
<td>Ciclosporin</td>
<td>0.42 (0.30–0.53)</td>
<td>0.69 (0.57–0.80)</td>
<td>0.76 (0.65–0.87)</td>
<td>0.78 (0.68–0.89)</td>
</tr>
<tr>
<td>from baseline</td>
<td>Oclacitinib</td>
<td>0.71 (0.60–0.82)</td>
<td>0.65 (0.54–0.77)</td>
<td>0.77 (0.66–0.88)</td>
<td>0.82 (0.72–0.93)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>0.6122</td>
<td>0.8816</td>
<td>0.5002</td>
<td></td>
</tr>
</tbody>
</table>

*Significant treatment difference at P < 0.05.
matosis, hypertrichosis and lichenoid dermatosis,5,23,24 receiving ciclosporin therapy include cutaneous papillomas. Skin lesions previously reported in dogs developed a nodular skin lesion revealed most to consist of inflammatory, dysplastic or benign changes; a mast cell tumour (grade 1) was identified in one dog in the ciclosporin group. In all cases, maropitant citrate (Cerena; Zoetis Australia Pty Ltd, West Ryde, NSW, Australia) was used.

Skin biopsies taken in a proportion of animals that developed a nodular skin lesion revealed most to consist of inflammatory, dysplastic or benign changes; a mast cell tumour (grade 1) was identified in one dog in the ciclosporin group. Skin lesions previously reported in dogs receiving ciclosporin therapy include cutaneous papillomas, hypertrichosis and lichenoid dermatosis,5,23,24 while in dogs receiving oclacitinib, unspecified dermal lesions, histiocytomas and papillomas have been reported.9,10,15 In a placebo-controlled study, one dog developed a grade 3 mast cell tumour after 60 days of oclacitinib treatment, while one placebo-treated dog developed a grade 1 mast cell tumour.18

In the present study, two dogs in the oclacitinib group were diagnosed with long-bodied Demodex (D. injai) infestation. Both animals were adult West Highland white terriers and had characteristic clinical signs of dorsal erythema, scaly skin and/or a greasy hair coat. Interestingly, both cases (but none of the other nine West Highland white terriers enrolled) had severe erythema of the dorsal thorax on day 0, so the possibility of D. injai being present in these two dogs at the time of enrolment cannot be ruled out. Previous reports of long-bodied Demodex infestation indicate that terriers are over-represented and that West Highland white terriers may be particularly susceptible.25–27 It is plausible that concomitant disease, particularly atopic dermatitis, together with a subclinical sebaceous gland hyperplasia, may predispose dogs to infestation with D. injai.27 Terrier breeds might therefore be more susceptible to this form of demodicosis because of their predisposition to develop AD.27 It has been suggested that prior treatment with immunomodulatory or immunosuppressive drugs, such as prednisolone, dexa-methasone, azathioprine or ciclosporin, could be a potential risk factor for D. injai infestation in terriers,26 however, these drug therapies are also used for the treatment of AD, and a causal relationship has not been established.

Oclacitinib is a targeted treatment for the control of canine AD, with a rapid onset of action and a good safety profile. Based on the results of this study, oclacitinib has a faster onset of action and a lower frequency of gastrointestinal side effects than orally-administered ciclosporin.

**Acknowledgements**

The authors wish to thank the clinical investigators: Amanda Burrows, Greg Burton, Andrew Carter, Peter Hill, Beth McDonald, Michael Shipstone and Linda Vogelnest. We also thank the following Zoetis colleagues for their contributions: Candace Sousa, Mary Pat Gorman, Caroline Gadeyne and Nigel Edwards.

**References**

Résumé

Contexte – La ciclosporine est un traitement validé, sûr et efficace de la dermatite atopique (AD) chez le chien. Les études contrôlées contre placebo suggèrent que l’oclacitinib est une alternative thérapeutique sûre et efficace.

Hypothèses/Objectifs – Évaluer l’efficacité et la sureté clinique de l’oclacitinib en comparaison avec la ciclosporine pour le contrôle de la dermatite atopique, par une étude clinique randomisée en aveugle, incluant un test de non-inériorité à jour 28.

Sujets – Un total de 226 chiens de propriétaires ayant une anamnèse d’atopie, issus de huit sites, ont été inclus.

Méthodes – Les sujets enrôlés ont été randomisés pour recevoir de l’oclacitinib orale (0,4–0,6 mg/kg deux fois par jour pendant 14 jours, puis une fois par jour) ou la ciclosporine orale (3,2–6,6 mg/kg une fois par jour) pendant 12 semaines. Les propriétaires ont évalué le prurit à l’aide d’une échelle visuelle analogue (VAS) et les vétérinaires ont évalué les lésions par un CADESI-02 (Canine Atopic Dermatitis Extent and Severity Index).

Résultats – A jours 1, 2, 7, 14, 28, 56 et 84, le pourcentage de réduction du prurit évalué par les propriétaires s’élevait de 25,6 à 61,0% dans le groupe oclacitinib comparé à 6,5 à 61,5% dans le groupe ciclosporine; les différences étaient significatives à tous les contrôle jusqu’au jour 28. Au jour 56, les chiens traités à la ciclosporine montraient une diminution du prurit identique aux chiens recevant de l’oclacitinib. A jour 14, le pourcentage de réduction du CADESI-02 était significativement meilleur dans le groupe oclacitinib (58,7%) que dans le groupe ciclosporine (43,0%). Trois fois plus d’effets indésirables gastro-intestinaux étaient rapportés dans le groupe ciclosporine comparé au groupe oclacitinib.

Conclusions et importance clinique – Dans cette étude, l’oclacitinib montre une meilleure rapidité d’action et une plus faible fréquence d’effets indésirables gastro-intestinaux que la ciclosporine dans le traitement de l’AD canine.

Supporting Information

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

Table S1. Intention-to-treatment: Least-squares mean (95% confidence interval) percentage reduction from baseline for owner-assessed pruritus VAS score at each time point.

Table S2. Intention-to-treatment: Least-squares mean (95% confidence interval) percentage reduction from baseline for investigator-assessed CADESI-02 score at each time point.

Table S3. Abnormal clinical signs occurring in two or more dogs in either treatment group, excluding pre-existing conditions.

Table S4. Concurrent medications and therapies used in ≥5% of animals in either treatment group.
Resumen

Introducción – La ciclosporina es un fármaco aprobado para el tratamiento de la dermatitis atópica (AD) en perros y ha demostrado ser segura y efectiva. Los estudios controlados con placebo sugieren que oclacitinib es una terapia alternativa segura y efectiva.

Hipothesis/Objetivos – Evaluar la eficacia y seguridad de oclacitinib, en comparación con ciclosporina, al tratamiento y control de la dermatitis atópica en un ensayo clínico al azar, ciego e incorporando una prueba de no inferioridad en el día 28.

Animales – Se incorporaron al estudio un total de 226 perros de propietarios privados con historia de dermatitis atópica de ocho localizaciones distintas.

Métodos – Los animales incluidos en el estudio se distribuyeron al azar para recibir oclacitinib (0,4 a 0,6 mg/kg dos veces al día durante 14 días, y después una vez al día) o ciclosporina oral (3,2–6,6 mg/kg una vez al día) durante 12 semanas. Los propietarios evaluaron el prurito utilizando una escala visual análoga reforzada (VAS), y los veterinarios valoraron la dermatitis utilizando el índice de extensión y severidad de la dermatitis atópica canina (CADESI)-02.

Resultados – En los días 1, 2, 7, 14, 28, 56 y 84, el porcentaje de reducción del valor basal en el prurito evaluado por los propietarios cambió de un 25,6 a un 61% para el grupo tratado con oclacitinib, comparado con un 6,5 a un 61,5% para el grupo tratado con ciclosporina; las diferencias fueron significativas en todos los tiempos hasta el día 28. En el día 56, los perros tratados con ciclosporina mostraron una disminución similar en el prurito a los perros tratados con oclacitinib. En el día 14, el porcentaje de reducción del valor basal en el CADESI-02 fue significativamente mayor en el grupo tratado con oclacitinib (58,7%) que en el grupo tratado con ciclosporina (43%). Se observan tres veces más efectos adversos gastrointestinal en el grupo tratado con ciclosporina.

Conclusiones e importancia clínica – En este estudio del tratamiento de la dermatitis atópica, el oclacitinib demostró una acción más rápida y con menor número de efectos gastrointestinales adversos comparado con la ciclosporina.

Zusammenfassung

Hintergrund – Ciclosporin ist für die Behandlung der atopischen Dermatitis (AD) der Hunde zugelassen und es hat sich als sicher und effektiv erwiesen.


Tiere – Es wurden 226 private Hunde mit einer Anamnese von AD an acht Kliniken aufgenommen.

Methoden – Die Tiere wurden zufällig zur Verabreichung von Oclacitinib (0,4-0,6 mg/kg zweimal täglich für 14 Tage, dann einmal täglich) oder von Ciclosporin (3,2-6,6 mg/kg einmal täglich) für einen Zeitraum von 12 Wochen eingeschlossen. Die BesitzerInnen beurteilten den Juckreiz mittels analoger Visualkala (VAS) und die TierärztInnen erfassten die Dermatitis mittels Canine Atopic Dermatitis Extent und Severity Index (CADESI)-02.

Ergebnisse – An den Tagen 1, 2, 7, 14, 28, 56 und 84 reduzierte sich der durch die BesitzerInnen beurteilte Juckreiz um 25,6 bis 61% vom Ausgangswert in der Oclacitinib Gruppe im Vergleich zu 6,5 bis 61,5% in der Ciclosporin Gruppe; die Unterschiede waren zu allen Zeitpunkten bis zum Tag 28 signifikant verschieden. Am Tag 56 zeigten die mit Ciclosporin behandelten Hunde eine ähnliche Juckreiz Verminderung wie die mit Oclacitinib behandelten Hunde. Am Tag 14 war die prozentuelle Verminderung vom Ausgangswert des CADESI-02 signifikant höher in der Oclacitinib Gruppe (58,7%) als in der Ciclosporin Gruppe (43%). Dreimal so viele Nebenwirkungen in Form von gastrointestinalen Symptomen wurden in der Ciclosporin Gruppe im Vergleich zur Oclacitinib Gruppe beschrieben.

Schlussfolgerungen und klinische Bedeutung – In dieser Studie über die Behandlung der AD des Hunes zeigte Oclacitinib im Vergleich zu Ciclosporin einen rascheren Wirkungseintritt und eine niedrigere Frequenz von gastrointestinalen Nebenwirkungen.
されたビジョカルナログスクール（VAS）でそう痒を評価し，猟医師はCanine Atopic Dermatitis Extent and Severity Index（CADESI）-02を用いて皮膚炎を評価した。

**結果** - 1, 2, 7, 14, 28, 56ならびに84日目に，飼い主が評価したそう痒のベースラインからの減少の割合は6.5%から61.5%に変化した。オクラシチニブ群では25.6%から61.5%に変化した。その差は28日までの全ての時点で有意であった。56日目において，シクロスポリンで治療されたイヌはオクラシチニブで治療したイヌと同等のそう痒の減少を示した。14日目において，CADESI-02のベースラインからの減少の割合は，シクロスポリン群（43.0%）に対して，オクラシチニブ群（58.7%）が有意に大きかった。オクラシチニブ群と比較し，シクロスポリン群では胃腸症状に起因する有害事象が3倍多く報告された。

**結論および臨床的な重要性** - チヌADの治療においてこの研究にて，オクラシチニブはシクロスポリンと比較し，効果が早く見られ，胃腸への副作用の頻度が少なかった。

**摘要**

**背景** - 病療素を批准された犬異位性皮炎の治療後，既に皮膚病と類似した現象を支持する研究として，オクラシチニブの有効性を証明する研究が行われた。

**仮説/目的** - 皮膚病と類似した現象を支持する研究として，オクラシチニブの有効性を証明する研究が行われた。

**動物** - 226頭の犬，異位性皮炎の例，それぞれ8つの機関から提供された。

**方法** - 226頭の犬は28日間，オクラシチニブ（0.4–0.6 mg/kg）を2日1回，14日目からは1日1回，これを用いて治療された。

**結果** - 28日目の評価で，オクラシチニブ群は25.6%から61.5%に改善した。

**総括と臨床意義** - 本研究では，オクラシチニブの有効性を証明する研究が行われた。