Date of Approval: May 14, 2013

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-345

APOQUEL

Oclacitinib Tablet

Dogs

Control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age

Sponsored by:

Zoetis Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-345

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

APOQUEL

D. Established Name

Oclacitinib tablet

E. Pharmacological Category

Immunosuppressant

F. Dosage Form

Tablet

G. Amount of Active Ingredient

3.6, 5.4, or 16 mg of oclacitinib as oclacitinib maleate per tablet

H. How Supplied

APOQUEL tablets contain 3.6 mg, 5.4 mg, or 16 mg of oclacitinib as oclacitinib maleate per tablet. Each strength tablets are packaged in 20 and 100 count bottles. Each tablet is scored and marked with AQ and either an S, M, or L that correspond to the different tablet strengths on both sides.

I. Dispensing Status

Rx

J. Dosage Regimen

The dose of APOQUEL (oclacitinib maleate) tablets is 0.18 to 0.27 mg oclacitinib/lb (0.4 to 0.6 mg oclacitinib/kg) body weight, administered orally, twice daily for up to 14 days, and then administered once daily for maintenance therapy.

K. Route of Administration

Oral

L. Species

Dogs

M. Indication

Control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age.

II. EFFECTIVENESS

A. Dosage Characterization

1. Pharmacokinetics

Oclacitinib maleate has been shown to have low plasma clearance (CL_{total}) and a steady-state volume of distribution (V_{dss}) that is consistent with drug distribution being limited to total body fluids. The absolute bioavailability of oclacitinib maleate was found to be 89%. The oclacitinib protein binding was low with 66.3-69.7% bound in fortified canine plasma at nominal concentrations ranging from 10-1000 ng/mL. Inhibition of canine cytochrome P450 enzymes by oclacitinib is minimal with IC_{50s} that are 50 fold greater than the observed maximum plasma oclacitinib concentrations at the proposed use dose. The major clearance mechanism for oclacitinib is metabolism. The formulation and polymorphic form of oclacitinib did not appear to have an effect on the absorption kinetics of oclacitinib. A bioequivalence study was conducted which demonstrated that the Form B active pharmaceutical ingredient (API) tablets, the intended final market formulation, are bioequivalent to the Form C API tablets. The Form C tablets were used in the field studies (Study numbers 1962C-60-09-930, 1962C-60-10-A16, and 1962C-60-10-A17) and the margin of safety study (Study number 1462N-60-10-A29).

Table 1: Pharmacokinetic parameters reflecting total drug concentrations in plasma (mean and confidence interval) following a 0.282 mg/kg intravenous dose of oclacitinib in dogs

Parameter	Least Square Mean (95% Confidence Interval)
Area under the plasma concentration-time curve from 0 and extrapolated to infinity ($AUC_{0-\infty}$), ng·hr/mL	953 (713, 1275)
Terminal Plasma elimination half-life ($T_{1/2}$), hours	3.45 (2.21, 4.68)
CL_{total}, mL/h/kg	316 (237, 396)
V_{dss}, mL/kg	942 (870, 1014)

Table 2: Pharmacokinetic parameters reflecting total drug concentrations in plasma (mean and confidence interval) following a 0.18 to 0.27 mg/lb (0.4 to 0.6 mg/kg) oral dose of oclacitinib in dogs

Parameter	Least Square Mean (95% Confidence Interval)
Maximum concentration normalized to 0.4 mg/kg, (C_{max}), ng/mL	259 (189, 355)
Time of maximum concentration (T_{max}), hours	0.9 (0.46, 1.34)
$AUC_{0-\infty}$ normalized to 0.4 mg/kg, ng·hr/mL	1206 (909, 1599)
$T_{1/2}$, hours	4.13 (3.08, 5.19)
Bioavailability	89% (85%, 94%)

2. Dose Selection

In a canine flea allergic dermatitis model, oclacitinib produced sustained and reproducible anti-pruritic effects at dosages as low as 0.25 mg/kg twice daily (BID). The onset of anti-pruritic activity was rapid (within 1.5 hrs) after a single oral dose of oclacitinib administered at 0.4 mg/kg. Doses of 0.4 mg/kg BID or higher improved skin lesions and erythema in as little as seven days.

In a one-month long study conducted in 56 client-owned dogs with atopic dermatitis, oclacitinib administered at 0.2 to 0.4 mg/kg BID reduced skin lesion scores from baseline compared with dogs administered a placebo.

A dose of 0.4 to 0.6 mg oclacitinib/kg BID was initially proposed for chronic use. However, a margin of safety could not be established for chronic use of 0.6 mg oclacitinib/kg BID in six-month-old dogs. That safety study was discontinued after four months because clinical evidence of immunosuppression, including bacterial pneumonia and generalized demodex mange infections, was observed in the high dose (3X and 5X) treatment groups (1.8 and 3.0 mg/kg BID).

Subsequently, three alternate dosing regimens were evaluated for safety and effectiveness in a study conducted in 220 client-owned dogs with atopic dermatitis that were at least one year of age. A dose of 0.4 mg to 0.6 mg oclacitinib/kg administered BID for 14 days followed by once daily administration for maintenance provided the best continuing control of atopic dermatitis and was selected for further development.

B. Substantial Evidence

1. Field Study for Control of Pruritus Associated with Allergic Dermatitis

Study Title: Efficacy and Field Safety of Oclacitinib Maleate for the Control of Pruritus Associated with Allergic Dermatitis in the Dog.
Study Number: 1962C-60-09-930 (Study 930)

a. Type of Study: Field safety and effectiveness study

The study had two phases: Study Phase (8 days) and Continuation Phase (up to 21 additional days).

b. Study Dates: August 17, 2009 to November 30, 2009

c. Investigators and Locations:

Table 3: Investigators and Locations (Study 930)

Brett Berryhill, DVM Baton Rouge, LA	Glen Burkett, BVSc, DACVD Estero, FL
Jay Butan, DVM Lake Worth, FL	Randall Carpenter, DVM Grand Rapids, MI
Terry Clekis, DVM Bradenton, FL	Jeffrey Dizik, DVM Lincoln Park, MI
Sam Geller, DVM Quakertown, PA	Mary Grabow, DVM Indianapolis, IN
Robert Jackson, DVM Caledonia, MI	Mark Lelli, DVM Muskegon, MI
Marc Leven, DVM Wyoming, MI	David Lukof, DVM Harleysville, PA
Patrick McSweeney, DVM Metairie, LA	Kathleen Neuhoff, DVM Mishawaka, IN
Karan Oberhansley, DVM Whitehouse Station, NJ	Greg Paplawsky, DVM Grand Rapids, MI
Andrew Pickering, DVM Terre Haute, IN	Jeffrey Pinkston, DVM Swartz Creek, MI
Dean Rund, DVM Springfield, MO	Jason St. Romain, DVM Zachary, LA
Roger Sifferman, DVM Springfield, MO	Kathy Tater, DVM, DACVD Boston, MA
Bradford Theodoroff, DVM Rochester Hills, MI	Philip VanVranken, DVM Battle Creek, MI
Philip Waguespack, DVM Baton Rouge, LA	Melissa Wiest, DVM O'Fallon, MO

d. Study Design:

Study 930 was a masked, multi-site, well-controlled study that evaluated the effectiveness and safety of oclacitinib maleate, dosed orally twice daily (BID) at 0.4 to 0.6 mg oclacitinib/kg for the control of pruritus associated with allergic dermatitis. Determination of effectiveness was based on improvement in Owner-assessed pruritus visual analog scale (VAS) scores in the Study Phase (Days 0-7). The Study Phase was followed by a Continuation Phase that lasted up to Day 28 (+2).

(1) Purpose of Study:

To demonstrate the effectiveness and safety of oclacitinib maleate for the control of pruritus associated with allergic dermatitis in dogs.

(2) Study Animals:

The study enrolled 436 client-owned dogs, 217 females and 219 males. There were 135 mixed-breed and 301 pure-bred dogs. At enrollment, dogs were 6 months to 18 years of age and weighed 3.0 kg to 61.7 kg.

Dogs could have more than one of the following presumptive diagnoses for allergic dermatitis, including atopic dermatitis, contact dermatitis, flea allergy dermatitis, food hypersensitivity, or other. To be enrolled, owners had to document "moderate" pruritus (the minimum level of pruritus to be enrolled in the study), with or without dermatitis, and the dog had to be otherwise healthy.

Specifically excluded from enrollment were pregnant or lactating bitches, dogs with malignant neoplasia, dogs with evidence of immune suppression, and dogs with demodectic mange, bacterial folliculitis, or fungal dermatitis.

Prior to study entry, dogs were withdrawn from drugs that might have interfered with the assessment of effectiveness. A flea prevention program was implemented on enrollment for dogs that had evidence of fleas.

Commonly represented breeds enrolled in the study included Labrador Retrievers (10.3%), Golden Retrievers (5.5%), Shih Tzu (5.7%), Jack Russell Terriers (3.2%), Beagles (2.8%), and Yorkshire Terriers (2.8%).

(3) Treatment Groups:

Table 4: Treatment Groups (Study 930)

Group	Dosage of Oclacitinib	Dosage Schedule for Oclacitinib Maleate and Placebo Oral Tablets	Number of Dogs Enrolled
Oclacitinib Maleate	0.4 to 0.6 mg/kg	BID for 7 to 28 (+2) days	216
Placebo [a]	0 mg/kg	BID for 7 to 28 (+2) days	220

[a] The placebo was a vehicle control.

See Table 5, below, for the presumptive diagnoses at enrollment (Day 0) for each treatment group.

Table 5: Presumptive Diagnoses at Enrollment (Study 930)

Presumptive Diagnoses [a] for Pruritus and Allergic Dermatitis	Oclacitinib Maleate Group Number (%) of Dogs n = 216	Placebo Group Number (%) of Dogs n = 220
Flea Allergy Dermatitis	72 (33.3)	70 (31.8)
Food Allergy Dermatitis	48 (22.2)	51 (23.2)
Contact Allergy Dermatitis	24 (11.1)	23 (10.5)
Atopic Dermatitis [b]	175 (81.0)	179 (81.4)
Other [c]	12 (5.6)	10 (4.5)

[a] Each dog may have had more than one presumptive diagnosis for its pruritus and allergic dermatitis.

[b] 41.5% of the dogs had a presumptive diagnosis of atopic dermatitis alone.

[c] All of the cases with presumptive diagnoses of "other" also had atopic dermatitis, except for one oclacitinib maleate group dog with the "other" diagnosis of "unspecified allergic dermatitis." Pyoderma

or bacterial dermatitis was the most common "other" diagnosis (in 15 of the 22 dogs), but lick granuloma, otitis, and anal gland irritation were reported in one to two cases in each treatment group.

(4) Randomization and Masking:

Drug Administration: Dogs in the oclacitinib maleate group were administered oclacitinib maleate tablets orally at 0.4 to 0.6 mg oclacitinib/kg BID for 7 to 28 (+2) days. The scored tablets were provided in three strengths containing 3.6 mg, 5.4 mg, and 16 mg of oclacitinib. The placebo group dogs were administered tablets that were identical in appearance to oclacitinib maleate tablets and contained all of the same pharmacological ingredients except oclacitinib maleate. Owners administered study drug ideally every 12 hours (± 2 hours) daily, beginning on Day 0.

(5) Study Schedule and Variables Measured:

The Study Phase was Day 0 through Day 7 (+3). Baseline data (demographic, physical examination, assessments of pruritus and dermatitis, complete blood count (CBC), serum chemistry, urinalysis, and whether flea control was initiated on Day 0) were collected on enrollment at Day 0.

Owners filled out the Owner Assessment of Pruritus form (for the primary variable, based on a 10 cm enhanced visual analog scale [VAS]) at baseline on Day 0 and then once daily at home on Days 1 through 7. The enhanced VAS had the notations "normal dog", "very mild itching", "mild itching", "moderate itching", "severe itching", and "extremely severe itching" adjacent to 0, 2, 4, 6, 8, and 10 cm along the VAS line.

Dogs were scheduled to return to the Investigator on Day 7 (+3). The Investigator rated the severity of dermatitis on a VAS at the Day 0 and Day 7 (+3) visits as a secondary variable. Physical examination, CBC, serum chemistry, concurrent treatment, dosing compliance (owner dosing forms and tablet reconciliation), and adverse event data were collected at Day 7 (+3).

If, in the Investigator's clinical judgment, the pruritic condition resolved or improved to a point that no additional therapy was indicated, the Investigator regarded Day 7 (+3) as the Final Study Day. If the Investigator determined that the dog would benefit from a continuation of therapy beyond Day 7 (+3), the dog entered into the Continuation Phase of the Study.

The Continuation Phase was Day 8 through Day 28 (+2). Owners did not assess pruritus in the Continuation Phase. The Investigator could elect to schedule between one and three Continuation Phase visits. At each visit, the Investigator rated the severity of dermatitis (VAS) and performed safety assessments. A dog could be discontinued from study at any time during the Continuation Phase of the study. The

Investigator determined which Continuation Phase visit was the Final Study Day based on clinical judgment. CBC and serum chemistry were repeated on the Final Study Day of the Continuation Phase. Concurrent treatment, dosing compliance, and adverse event data were also collected in the Continuation Phase.

Certain concurrent treatments not permitted on Days 0-7 could be added on or after Day 8 (e.g. systemic antimicrobial drugs). Steroids, antihistamines, cyclosporine, or other immunosuppressive drugs were not permitted during either phase of the study.

(6) Statistical Methods:

The primary analysis for effectiveness was a comparison of the proportions of treatment success in each group using a generalized linear mixed model (GLMM) (GLIMMIX procedure in SAS). The statistical model included treatment as a fixed effect, and site and the site by treatment interaction as random effects. The model employed the binomial distribution with logit link. The experimental unit was the individual dog. The difference between treatment groups was evaluated at a 2-sided α=0.05 for owner-assessed pruritus VAS success rates. Estimated success rates and confidence intervals were back-transformed from the GLMM least squares estimates.

e. Results for the Field Study for Control of Pruritus Associated with Allergic Dermatitis (Study 930)

(1) Primary Effectiveness Analysis at Day 7:

Owners assessed the dog's pruritus over the previous 24 hours, using the VAS forms, in the clinic on Day 0, and at home on Days 1, 2, 3, 4, 5, 6, and 7, ideally after the second daily dose of study drug.

The criterion for success/failure was the proportion of dogs that were treatment successes based on the Owner-assessed pruritus VAS scores on Days 1 through 7. Treatment success for a dog was defined as at least a 2 cm decrease from baseline on the 10 cm Owner-assessed pruritus VAS on at least 70% of Days 1-7 (at least 5 of 7 days).

Of the 436 (216 oclacitinib maleate and 220 placebo) enrolled dogs, 203 oclacitinib maleate and 204 placebo group dogs were included in the assessment of treatment success. Cases that were excluded from the effectiveness assessments received < 80% of intended doses, had major dosing errors, received disallowed concurrent medication, had < 5 days of evaluable Owner VAS results, or withdrew before Day 5.

The proportion of dogs that were treatment successes in the oclacitinib maleate group was significantly different from ($p<0.05$) and greater than the placebo group for Owner-assessed pruritus. See Table 6, below.

Table 6: Owner-Assessed Pruritus VAS Treatment Success (Study 930)

Treatment Group	Number of Dogs with Treatment Success	Proportion [a] of Dogs [Treatment Success]	95% Confidence Interval (CI)
Placebo n = 204	60	0.29	0.23 to 0.36
Oclacitinib Maleate n = 203	135	0.67 [b]	0.59 to 0.73

[a] Estimated proportion of dogs based on back-transformed least squares means.
[b] Placebo vs. oclacitinib maleate $p<0.0001$.

After one week of treatment, 86.4% of oclacitinib maleate group dogs compared with 42.5% of placebo group dogs had achieved a 2 cm reduction on the 10 cm Owner-assessed pruritus VAS.

The study also evaluated the effect of flea treatment on treatment success. Flea treatment was initiated on Day 0 for 13% and 19% of the dogs in the placebo and oclacitinib maleate treatment groups, respectively. Within the placebo group, flea treatment initiated on Day 0 doubled the percentage of dogs that were treatment successes. Within the oclacitinib maleate group, the percentage of dogs that were treatment successes was similar regardless of whether they received or did not receive flea treatment on Day 0.

(2) Secondary Effectiveness Variable Owner-Assessed Pruritus VAS by Day:

At Day 0, the arithmetic mean Owner-assessed pruritus VAS score was 7.4 cm and 7.6 cm for the oclacitinib maleate and placebo groups, respectively. Over the following 7 days, the estimated mean Owner-assessed pruritus VAS scores decreased for the oclacitinib maleate group and were significantly different from the placebo group each day (Table 7). At Day 7, the estimated mean Owner-assessed pruritus VAS score had decreased to 2.6 cm (a 4.9 cm reduction) and 5.5 cm (a 1.9 cm reduction) for the oclacitinib maleate and placebo groups, respectively.

Table 7: Owner-Assessed Pruritus VAS Scores by Day (Study 930)

Study Day	Oclacitinib Maleate Group Mean [a]	Placebo Group Mean [a]
0	7.4 cm	7.6 cm
1	5.3 cm [b]	6.5 cm
2	4.5 cm [b]	6.2 cm
3	3.8 cm [b]	6.0 cm
4	3.4 cm [b]	5.8 cm
5	3.0 cm [b]	5.6 cm
6	2.8 cm [b]	5.6 cm
7	2.6 cm [b]	5.5 cm

[a] The Day 0 values are the arithmetic mean Owner-assessed pruritus VAS, and the Day 1-7 values are estimated mean Owner-assessed pruritus VAS scores.

[b] Significant difference between the oclacitinib maleate and placebo groups at $p<0.0001$.

(3) Secondary Effectiveness Variable Investigator-Assessed Dermatitis VAS Scores:

The arithmetic mean Day 0 baseline Investigator-assessed dermatitis VAS score was similar for each treatment group, 6.2 cm for the oclacitinib maleate group and 6.2 cm the placebo group. At Day 7, the estimated mean Investigator-assessed dermatitis VAS score for the oclacitinib maleate group (2.2 cm) was significantly ($p\leq0.0001$) different (improved) compared to the placebo group (4.9 cm). For those dogs that continued oclacitinib maleate treatment past Day 7, the mean Investigator-assessed dermatitis VAS score continued to improve through Day 30.

(4) Adverse Reactions:

All 436 (216 oclacitinib maleate and 220 placebo) of the enrolled dogs received at least one dose of study drug, and were evaluated for safety. During the 30-day study, there were no fatalities and no adverse reactions requiring hospital care. Because the majority of dogs in the placebo group withdrew after the 8-day Study Phase, the incidence of adverse reactions is provided for the Study Phase. See Table 8, below. In most of these cases, signs spontaneously resolved with continued dosing.

Table 8: Study Phase (Days 0-7) Adverse Reactions (Study 930)

Adverse reactions that began during the Study Phase (Days 0-7)	Oclacitinib Maleate Group Number (%) of Dogs n = 216	Placebo Group Number (%) of Dogs n = 220
Diarrhea	5 (2.3)	2 (0.9)
Vomiting	5 (2.3)	4 (1.8)
Lethargy	4 (1.8)	3 (1.4)
Anorexia	3 (1.4)	0 (0.0)
Polydipsia	3 (1.4)	0 (0.0)

One oclacitinib maleate group dog was removed at the end of the masked Study Phase because of darkening areas of skin and fur.

The masked Continuation Phase (Days 8-30) was three times longer than the Study Phase and contained approximately 2.5 times more oclacitinib maleate (179) than placebo (73) group dogs. Six dogs (four oclacitinib maleate and two placebo) were withdrawn from the study during the Continuation Phase for adverse reactions. The four oclacitinib maleate group dogs were removed for the following reasons: diarrhea (1 dog); fever, lethargy, and cystitis (1 dog); an inflamed footpad and vomiting (1 dog); and diarrhea, vomiting, and lethargy (1 dog). One placebo group dog was removed because of acute cholangiohepatitis; the other was removed for evaluation of abnormal hepatic enzyme activity. Diarrhea occurred in three additional oclacitinib maleate group dogs. Vomiting occurred in four additional

oclacitinib maleate group dogs and one placebo group dog. Lethargy occurred in two additional oclacitinib maleate group dogs.

(5) Clinical Pathology:

Over the course of the 30-day study, dogs in the oclacitinib maleate group had a slight decrease in mean white blood cell counts (neutrophil, eosinophil, and monocyte counts) that remained within the normal reference range. Mean lymphocyte counts for dogs in the oclacitinib maleate group increased at Day 7, but returned to pretreatment levels by study end without a break in oclacitinib maleate administration. Serum cholesterol increased in 25% of oclacitinib maleate group dogs, but mean cholesterol remained within the reference range. Elevated liver enzymes (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase) occurred with similar incidence rates in dogs in the oclacitinib maleate and placebo groups during the study.

(6) Concurrent Medications:

Oclacitinib maleate was used in conjunction with various medications, including antiparasitics, nutritional supplements, and topical skin and otic cleansers that did not contain glucococorticoids. Systemic and topical glucocorticoids, cyclosporine, and antihistamines were prohibited. Over the entire study, products to control ectoparasites were used in 48.6% (105/216) and 45.9% (101/220) of oclacitinib maleate and placebo group dogs, respectively. Products to control endoparasites were used in 67.1% (145/216) and 68.2% (150/220) of oclacitinib maleate and placebo group dogs, respectively. Flea control products were included in the ectoparasite and endoparasite control product categories. Systemic antibacterial products were only permitted during the Continuation Phase of the study, where they were used in 9.5% (17/179) of the oclacitinib maleate group dogs and 15.1% (11/73) of the placebo group dogs.

f. Conclusions for the Field Study for Control of Pruritus Associated with Allergic Dermatitis (Study 930):

Study 930 demonstrated that oclacitinib maleate, administered at doses of 0.4 to 0.6 mg oclacitinib/kg twice daily for one week, was effective for the control of pruritus associated with allergic dermatitis in client-owned dogs. The study assessed safety through Day 30, and there were no serious adverse reactions.

2. Field Studies for Control of Atopic Dermatitis

Study Titles and Numbers:
Dose Confirmation: Field Safety and Efficacy of PF-03394197 Compared to Placebo for the Control of Atopic Dermatitis in Client-Owned Dogs
Study Number: 1962C-60-10-A16 (Study A16)
Dose Confirmation: Replacement Therapy for Dogs Removed from Field Safety and Efficacy of PF-03394197 Compared to Placebo for the Control of Atopic Dermatitis in Client-Owned Dogs
Study Number: 1962C-60-10-A17 (Study A17)

a. Type of Studies: Field safety and effectiveness studies

b. Study Dates: July 30, 2010 to April 26, 2011 for Study A16/A17

c. Investigators and Locations for Study A16/A17

All Investigators were board certified veterinary dermatologists (Diplomate of the American College of Veterinary Dermatology, DACVD)

Table 9: Investigators and Locations (Study A16/A17)

Glen Burkett, BVSc, DACVD Estero, FL	Sarah Colombini Osborn, MS, DVM, DACVD Houston, TX
Kimberly Coyner, DVM, DACVD Las Vegas, NV	Karen Farver, DVM, DACVD Valley Forge, PA
Dunbar Gram, DVM, DACVD Virginia Beach, VA	Terry L. Grieshaber, DVM, DACVD Carmel, IN
Craig E. Griffin, DVM, DACVD San Diego, CA	Carolyn Kidney, DVM, MS, DACVD Bloomfield Hills, MI
Allison Kirby, DVM, DACVD Marina Del Rey, CA	Thomas P. Lewis, DVM, PC, DACVD Gilbert, AZ
Lindsay McKay, DVM, MS, DACVD Aurora, IL	Colleen L. Mendelsohn, DVM, DACVD Tustin, CA
Linda Messinger, DVM, DACVD Englewood, CO	Sandra J. Sargent, DVM, DACVD Pittsburgh, PA
Amy K. Shumaker, DVM, DACVD Tucson, AZ	Mitchell Song, DVM, DACVD Phoenix, AZ
Laura B. Stokking, PhD, DVM, DACVD San Diego, CA	Sheila M. F. Torres, DVM, MS, PhD, DACVD St. Paul, MN

d. Study Design

Study A16 was a masked, multi-site, well-controlled, 112-day study that evaluated the effectiveness and safety of oclacitinib maleate, dosed at 0.4 to 0.6 mg oclacitinib/kg twice daily (BID) for 14 days followed by once daily dosing (SID), for the control of atopic dermatitis. Determination of effectiveness was based on improvement in Owner-assessed pruritus visual analog scale (VAS) scores and improvement in Investigator-assessed CADESI-02[1] scores between Day 0 and Day 28 (± 2).

[1] CADESI-02 is the Canine Atopic Dermatitis Extent and Severity Index, version 2.

Dogs that completed at least 14 (± 2) days of Study A16 could withdraw and enter Study A17. Study A17 was an unmasked study where all dogs received oclacitinib maleate at a dose of 0.4 to 0.6 mg oclacitinib/kg body weight once daily until Day 112 (± 2), based on Day 0 of Study A16.

(1) Purpose of Study:

To demonstrate the effectiveness and safety of oclacitinib maleate for the control of atopic dermatitis (AD) in dogs.

(2) Study Animals:

Study A16 enrolled 299 client-owned dogs, 162 males and 137 females. There were 80 mixed-breed and 219 pure-bred dogs with chronic, non-seasonal AD. At enrollment, dogs were 1 to 13 years of age and weighed 3.4 kg to 77.2 kg. Commonly represented breeds enrolled included Labrador Retrievers (15.7%), Golden Retrievers (7.7%), German Shepherd Dogs (4.0%), Shih Tzu (4.0%), West Highland White Terriers (3.7%), Maltese (3.3%), Pugs (3.3%), French Bulldogs (3.0%), Boxers (2.7%), and English Bulldogs (2.7%).
To be enrolled, dogs had to have a minimum of "moderate" pruritus (documented by Owners), a minimum CADESI-02 Score of 25 out of a possible 360 points (scored by Investigators), and the dog had to be in good health apart from their atopic dermatitis. Other causes of allergic dermatitis were ruled out.

Specifically excluded from enrollment were dogs intended for use as breeding animals, dogs with malignant neoplasia, dogs with evidence of immune suppression, dogs with evidence of fleas, and dogs receiving systemic antimicrobial therapy for treatment of bacterial or fungal skin infections. Dogs on antimicrobial therapy could enroll in Study A16 following resolution of infections and after protocol-prescribed drug withdrawal intervals. Dogs on drugs that might have interfered with the assessment of effectiveness (e.g., glucocorticoids, cyclosporine, and antihistamines) could enroll in Study A16 after protocol-prescribed drug withdrawal intervals. Flea control/prevention was required during the study.

Study A17 only enrolled dogs that completed at least 14 (± 2) days in Study A16.

(3) Treatment Groups:

Table 10: Treatment Groups (Study A16/A17)

Study and Group	Dosage of Oclacitinib	Dosage Schedule for Oclacitinib Maleate and Placebo Oral Tablets [a]	Number of Dogs Enrolled [b]
Study A16 Placebo	0 mg/kg	BID on Days 0 to 14 (±2 days) SID on Days 14 to 112 (±2 days)	147
Study A16 Oclacitinib Maleate	0.4 to 0.6 mg/kg	BID on Days 0 to 14 (±2 days) SID on Days 14 to 112 (±2 days)	152
Study A17 Oclacitinib Maleate	0.4 to 0.6 mg/kg	SID from entry in Study A17 to Day 112 (±2 days) based on Day 0 of Study A16	158 [c]

[a] The placebo was a vehicle control.
[b] The A16/A17 study enrolled a total of 299 dogs.
[c] All dogs in Study A17 came from the placebo (128 dogs) or oclacitinib maleate (30 dogs) groups in Study A16.

(4) Randomization and Masking:

In Study A16, dogs were randomized 1:1 within each location to receive oclacitinib maleate or placebo. For Study A16, each site had an unmasked treatment dispenser, but the Investigator, all other site personnel, the Owner, and the clinical pathology laboratory were masked. For Study A16, dogs were not unmasked on the Final Study Day nor were they unmasked due to early removal, or if moved to Study A17. Study A17 was not masked and all dogs were administered oclacitinib maleate.

(5) Drug Administration:

In Study A16, dogs were administered oclacitinib maleate or placebo tablets at 0.4 to 0.6 mg oclacitinib/kg (or equivalent size for placebo) per dose, BID for 14 (±2) days, ideally every 12 (±2) hours, beginning on Day 0, and then once daily at approximately the same time each day. The oclacitinib maleate tablets were scored and provided in three strengths containing 3.6 mg, 5.4 mg, and 16 mg of oclacitinib. The placebo group dogs were administered tablets that were identical in appearance to oclacitinib maleate tablets and contained all of the same pharmacological ingredients except oclacitinib maleate. In Study A17, dogs were administered oclacitinib maleate tablets at 0.4 to 0.6 mg oclacitinib/kg once daily at approximately the same time each day. Tablets were administered without respect to when dogs were fed.

(6) Study Schedule and Variables Measured:

Study A16:
Baseline data (demographic, physical examination, assessments of pruritus and dermatitis, complete blood count (CBC), serum chemistry, and urinalysis) were collected on enrollment at Day 0.

Owners filled out the Owner Assessment of Pruritus form (based on a 10 cm enhanced visual analog scale [VAS]) at baseline on Day 0, once

daily at home on Days 1, 2, and 7, and at clinic study visits on Days 14 (±2), 28 (±2), 56 (±2), 84 (±2), and 112 (±2) or Final Study Day. The enhanced VAS had the notations "normal dog", "very mild itching", "mild itching", "moderate itching", "severe itching", and "extremely severe itching" adjacent to 0, 2, 4, 6, 8, and 10 cm along the VAS line. Owners also filled out medication dosing records each day and a VAS for Response to Treatment at the Final Study Day.

Investigators filled out a CADESI-02 Scoring Form to quantitatively describe the skin condition of dogs enrolled in this study (lesion score) at baseline on Day 0 and at clinic study visits on Days 14 (±2), 28 (±2), 56 (±2), 84 (±2), and 112 (±2) or Final Study Day. The form was used to separately score forty areas of the dog's body for erythema, lichenification, and excoriation. Investigators also filled out a VAS for AD Severity at each clinic visit, and a VAS for Response to Treatment and a Study Completion form at the Final Study Day for Study A16.

Physical examinations, hematology, and serum chemistry were performed at clinic study visits on Days 0, 14 (±2), 28 (±2), 56 (±2), 84 (±2), and 112 (±2) or Final Study Day. Assessment of adverse events, and dosing compliance were performed at all clinic study visits after Day 0. Urinalyses were collected on Days 0, 28 (±2), and 112 (±2) or Final Study Day.

Study A17:
Study A17 followed the same schedule as Study A16. Day 0 for the placebo group dogs from Study A16 was based on the first day of oclacitinib maleate treatment in Study A17. Day 0 for the oclacitinib maleate group dogs from Study A16 remained as Day 0 of Study A16.

Certain concurrent treatments not permitted on Days 0-28 (±2) in Study A16 (e.g. systemic antimicrobial drugs) could be added on or after Day 28 in Study A16 or A17. Steroids, antihistamines, cyclosporine, or other immunosuppressive drugs were not permitted during Study A16 or A17.

(7) Determination of Effectiveness for the Control of Atopic Dermatitis:

Substantial evidence of an effect of treatment was established if the proportion of dogs that were treatment successes in the oclacitinib maleate group was significantly ($p<0.05$) different and greater than for the placebo group for both Owner-assessed pruritus VAS and Investigator-assessed CADESI-02 scores.

A treatment success for each case for Owner-assessed pruritus VAS was defined as at least a 2 cm decrease from baseline at Day 28 (±2) on the 10 cm Owner-assessed pruritus VAS.

A treatment success for each case for Investigator-assessed CADESI-02 was defined as a 50% score decrease from Day 0 at Day 28 (±2).

Dogs that failed to meet these criteria were considered treatment failures for the relevant effectiveness variable. Success for Investigator-assessed CADESI-02 was not tied to success for Owner-assessed pruritus VAS.

Dogs that withdrew from the study on or before Day 28 (±2) due to worsening signs of AD (lack of effectiveness) or for an adverse event believed to be related to the study drug were considered treatment failures for both variables for statistical analysis.

(8) Statistical Methods:

The primary analysis for effectiveness was a comparison of the proportions of treatment success in each group using a generalized linear mixed model (GLMM) (GLIMMIX procedure in SAS). The statistical model included treatment as a fixed effect, and site and the site by treatment interaction as random effects. The model employed the binomial distribution with logit link. The experimental unit was the individual dog. The difference between treatment groups was evaluated at a 2-sided α=0.05 separately for both VAS and CADESI success rates. Estimated success rates and confidence intervals were back-transformed from the GLMM least squares estimates.

e. Results for the Field Studies for Control of Atopic Dermatitis (Study A16/A17)

(1) Primary Effectiveness at Day 28 (±2), Study A16:

The proportion of dogs that were treatment successes in the oclacitinib maleate group was significantly different from ($p<0.05$) and greater than for the placebo group for both Owner-assessed pruritus VAS and Investigator-assessed CADESI-02 scores at the two-sided 0.05 significance level. See Tables 11 and 12, below.

Table 11: Owner-Assessed Pruritus VAS Treatment Success

Study A16 Treatment Group	Number of Dogs with Treatment Success	Proportion [a] of Dogs [Treatment Success]	95% Confidence Interval (CI)
Placebo n = 133	5	0.04	0.01 to 0.09
Oclacitinib Maleate n = 131	86	0.66 [b]	0.54 to 0.76

[a] Estimated proportion of dogs based on back-transformed least squares means.
[b] Placebo vs. oclacitinib maleate $p<0.0001$.

Table 12: Investigator-Assessed CADESI-02 Treatment Success

Study A16 Treatment Group	Number of Dogs with Treatment Success	Proportion [a] of Dogs [Treatment Success]	95% confidence Interval (CI)
Placebo n = 134	7	0.04	0.01 to 0.11
Oclacitinib Maleate n = 134	67	0.49 [b]	0.32 to 0.66

[a] Estimated proportion of dogs based on back-transformed least squares means.
[b] Placebo vs. oclacitinib maleate $p<0.0001$.

(2) Study Withdrawals for Worsening of Clinical Signs:

By Day 30 of Study A16, 86% (127/147) of the placebo group dogs and 15% (23/152) of the oclacitinib maleate group dogs withdrew for worsening of clinical signs. After Day 30, there were not enough dogs remaining in the placebo group of Study A16 for a reasonable comparison of Owner-assessed pruritus VAS scores, Investigator-assessed CADESI-02 scores, or the effect of systemic antimicrobial drugs on effectiveness between the oclacitinib maleate and placebo groups. Systemic antimicrobial drugs were not permitted until Day 28 (±2) in Studies A16 and A17.

(3) Secondary Effectiveness Variable Owner Assessed Pruritus VAS by Day:

At Day 0, the arithmetic mean Owner assessed pruritus VAS score was 7.8 cm and 7.7 cm for the oclacitinib maleate and placebo groups, respectively. On Days 1, 2, 7, and 14 the estimated mean Owner-assessed pruritus VAS scores decreased for the oclacitinib maleate group and were significantly different from the placebo group each day (Table 13). At Day 14, the estimated mean Owner-assessed pruritus VAS score had decreased to 2.6 cm (a 5.2 cm reduction) and 7.4 cm (a 0.3 cm reduction) for the oclacitinib maleate and placebo groups, respectively.

Table 13: Owner-Assessed Pruritus VAS Scores by Day (Study A16)

Day	Oclacitinib Maleate Group Mean [a]	Placebo Group Mean [a]
0	7.8 cm (n = 147)	7.7 cm (n = 139)
1	5.5 cm [b] (n = 142)	7.2 cm (n = 134)
2	4.5 cm [b] (n = 135)	7.0 cm (n = 130)
7 (±1)	3.0 cm [b] (n = 131)	7.2 cm (n = 131)
14 (±2)	2.6 cm [b] (n = 131)	7.4 cm (n = 105)
28 (±2)	4.1 cm (n = 117)	6.9 cm (n = 27)

[a] The Day 0 values are the arithmetic mean Owner-assessed pruritus VAS scores, and the Day 1-14 values are estimated least squares mean Owner-assessed pruritus VAS scores.
[b] Significant difference between the oclacitinib maleate and placebo groups at $p<0.0001$.

On Days 56, 84, and 112, Study A16 oclacitinib maleate group estimated mean Owner-assessed pruritus VAS scores were 3.5, 3.6, and 3.2 cm, respectively.

In Study A17, where all dogs were on oclacitinib maleate, arithmetic mean Owner-assessed pruritus VAS scores were 4.4, 3.6, 3.5, and 3.6 cm in Months 1, 2, 3, and 4, respectively.

(4) Secondary Effectiveness Variable Investigator-Assessed CADESI-02 by Day:

At Day 0, the arithmetic mean Investigator-assessed CADESI-02 score was 62 and 58 for the oclacitinib maleate and placebo groups, respectively. The Day 14 and Day 28 estimated mean Investigator-assessed CADESI-02 scores for the oclacitinib maleate group were significantly different from the placebo group. See Table 14, below.

Table 14: Investigator-Assessed CADESI-02 Scores (Study A16)

Day	Oclacitinib Maleate Group Mean [a]	Placebo Group Mean [a]
0	62 (n = 147)	58 (n = 139)
14 (±2)	32 [b] (n = 144)	57 (n = 135)
28 (±2)	32 [b] (n = 123)	61 (n = 28)

[a] The Day 0 values are the arithmetic mean Investigator-assessed CADESI-02 scores, and the Day 14 and Day 28 values are estimated least squares mean Investigator-assessed CADESI-02 scores.
[b] Significant difference between the oclacitinib maleate and placebo groups at $p<0.0001$.

On Days 56, 84, and 112, Study A16 oclacitinib maleate group estimated mean Investigator-assessed CADESI-02 scores were 29, 27, and 26, respectively.

In Study A17, where all dogs were on oclacitinib maleate, arithmetic mean Investigator-assessed CADESI-02 scores were 34, 25, 24, and 21 in Months 1, 2, 3, and 4, respectively.

(5) Secondary Effectiveness Variables Investigator-Assessed and Owner-Assessed Responses to Treatment:

At the Final Study Day of Study A16, Investigators and Owners each recorded a Response to Treatment (RTT) score on a 10 cm VAS, where 0 was labeled "No improvement" and 10 cm was labeled "Excellent results." The estimated mean Investigator-assessed and Owner-assessed RTT VAS scores for the oclacitinib maleate group were significantly different from the placebo group. See Table 15, below.

Table 15: Response to Treatment (RTT) VAS Scores (Study A16)

Parameter	Oclacitinib Maleate Group Mean [a]	Placebo Group Mean [a]
Investigator-Assessed RTT	6.4 [b] (n = 139)	1.0 (n = 132)
Owner-Assessed RTT	6.8 [b] (n = 139)	0.7 (n = 131)

[a] The group means are estimated least squares mean RTT VAS scores.
[b] Significant difference between the oclacitinib maleate and placebo groups at $p<0.0001$.

In Study A17, where all dogs were on oclacitinib maleate, arithmetic mean Investigator and Owner assessed RTT VAS scores were 7.5 and 7.4, respectively.

(6) Adverse Reactions:

All 299 (152 oclacitinib maleate and 147 placebo) of the enrolled dogs received at least one dose of masked study drug, and were evaluated for safety. Because the majority of dogs in the placebo group withdrew by Day 14 (±2), the incidence of adverse reactions is provided for Days 0-16. In Study A16, 108 of the 147 placebo group dogs withdrew before Day 17, compared to 13 of the 152 oclacitinib maleate group dogs. See adverse reactions in Table 16, below.

Table 16: Study A16 Adverse Reactions, Days 0-16

Adverse Reactions that began during Days 0-16 of Study A16 [a]	Oclacitinib Maleate Group Number (%) of Dogs n = 152	Placebo Group Number (%) of Dogs n = 147
Diarrhea	7 (4.6)	5 (3.4)
Vomiting	6 (3.9)	6 (4.1)
Anorexia	4 (2.6)	0
New Dermal, Epidermal, or Subcutaneous Lump [b]	4 (2.6)	4 (2.7)
Lethargy	3 (2.0)	2 (1.4)

[a] Adverse reactions were tabulated per animal; animals with pre-existing conditions are not listed.
[b] Lumps included papillomas in two placebo group dogs and a histiocytoma in one oclacitinib maleate group dog. The other lumps did not have specific diagnoses.

In most cases, diarrhea, vomiting, anorexia, and lethargy spontaneously resolved with continued dosing.

There were 283 dogs that received at least one dose of oclacitinib maleate in Study A16 and/or A17 (maximum of 114 days of dosing). Of these 283 dogs, two dogs were withdrawn from study due to suspected treatment-related adverse reactions: one dog that had an intense flare-up of dermatitis and severe secondary pyoderma after 19 days of oclacitinib maleate administration, and one dog that developed generalized demodicosis after 28 days of oclacitinib maleate administration. Two other dogs on oclacitinib maleate were withdrawn from study due to suspected or confirmed malignant neoplasia and

subsequently euthanized, including one dog that developed signs associated with a heart base mass after 21 days of oclacitinib maleate administration, and one dog that developed a Grade III mast cell tumor after 60 days of oclacitinib maleate administration. One of the 147 dogs in the placebo group developed a Grade I mast cell tumor and was withdrawn from the masked study. Additional dogs receiving oclacitinib maleate were hospitalized for diagnosis and treatment of pneumonia (one dog), transient bloody vomiting and stool (one dog), and cystitis with urolithiasis (one dog).

In the 283 dogs that received at least one dose of oclacitinib maleate in Study A16 and A17, the following clinical signs were reported after beginning oclacitinib maleate (percentage of dogs with at least one report of the clinical sign as a non-pre-existing finding): pyoderma (12.0%), non-specified dermal lumps (12.0%), otitis (9.9%), vomiting (9.2%), diarrhea (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). On average, dogs gained 4% body weight on oclacitinib maleate in Study A16 and A17.

(7) Clinical Pathology:

Dogs on oclacitinib maleate had decreased leukocytes and serum globulin, and increased cholesterol and lipase compared to the placebo group. The oclacitinib maleate group mean white blood cell (WBC), neutrophil, eosinophil, and monocyte counts decreased to Day 14 (neutrophils and monocytes) or Day 28 (WBC and eosinophils) and then remained stable. Although mean values remained within the normal range, individual dogs developed leukopenia due primarily to neutropenia. Mean lymphocyte count increased at Day 14 and then returned to baseline level. 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 oclacitinib maleate administration.

(8) Concurrent Treatment:

Dogs that were diagnosed as food allergic (with concurrent atopic dermatitis) had to have been on their hypoallergenic diet for at least 6 weeks prior to enrollment. All dogs had to remain on the same diet for the duration of the study. In Study A16, diet formulations for food allergies were fed to 60% and 64% of the oclacitinib maleate and placebo group dogs, respectively.

Oclacitinib maleate was used in conjunction with various medications, including antiparasitic drugs, shampoos and other topical skin and otic products that did not contain glucocorticoids, omega-three fatty acid supplements, hyposensitization allergen injections, and thyroid supplements. Systemic and topical glucocorticoids, cyclosporine, and

antihistamines were prohibited. Flea control was required by protocol. Systemic antibacterial and antifungal products, prohibited before Day 28 (±2), were unrestricted after Day 28 (±2) in Study A16/A17. In the open label Study A17, systemic antibacterial and antifungal products were used in 47% and 18% of dogs on oclacitinib maleate, respectively.

f. Conclusions for the Field Studies for Control of Atopic Dermatitis (Study A16/A17):

Study A16/A17 demonstrated that oclacitinib maleate, administered at doses of 0.4 to 0.6 mg oclacitinib/kg twice daily for two weeks followed by once daily administration, was effective for the control of atopic dermatitis in client-owned dogs. Oclacitinib maleate may increase the susceptibility to infection, demodex mange, and the development of neoplasia.

3. Continuation Therapy Field Study (Study A75)

Dogs that were previously enrolled in one of the U.S. field safety and effectiveness studies for oclacitinib maleate and had a history of inadequate response or intolerance of glucocorticoids and or cyclosporine were permitted to enroll in an unmasked (no placebo control) continuation study (Study A75) for an unrestricted period of time. At the time of enrollment, dogs were to be generally healthy, apart from their atopic or allergic dermatitis disease. Dogs receiving systemic glucocorticoids or cyclosporine were permitted on study after protocol-prescribed drug withdrawal intervals. The study enrolled 239 dogs. The mean age of dogs on study was 6.8 years (range 2.5 to 13 years) and the mean time on study was 372 days (range 1 to 610 days).

Of these 239 dogs, one dog developed demodicosis following 273 days of oclacitinib maleate administration. One dog developed dermal pigmented viral plaques following 266 days of oclacitinib maleate administration. One dog developed a moderately severe bronchopneumonia after 272 days of oclacitinib maleate administration; this infection resolved with antimicrobial treatment and temporary discontinuation of oclacitinib maleate administration. One dog was euthanized after developing abdominal ascites and pleural effusion of unknown etiology after 450 days of oclacitinib maleate administration. Six dogs were euthanized because of suspected malignant neoplasms: including one dog each with thoracic metastatic, abdominal metastatic, splenic, frontal sinus, and intracranial neoplasms, and transitional cell carcinoma after 17, 120, 175, 49, 141, and 286 days of oclacitinib maleate administration, respectively. Two dogs each developed a Grade II mast cell tumor after 52 and 91 days of oclacitinib maleate administration, respectively. One dog developed low grade B-cell lymphoma after 392 days of oclacitinib maleate administration. Two dogs each developed an apocrine gland adenocarcinoma (one dermal, one anal sac) after approximately 210 and 320 days of oclacitinib maleate administration, respectively. One dog developed a low grade oral spindle cell sarcoma after 320 days of oclacitinib maleate administration.

III. TARGET ANIMAL SAFETY

A. Margin of Safety

Title: Margin of Safety Study of PF-03394197 Administered for 26 Weeks to Adult Dogs. Study number 1462N-60-10-A29 (Study A29)

1. Type of Study: Laboratory study

2. Study Dates: September 16, 2010 to April 8, 2011

3. Investigator and Location:

   Phyllis B. Malpas, DVM, PhD, DABT
   Kalamazoo, MI

4. Study Design:

   a. Purpose of Study:

      To evaluate the margin of safety of oclacitinib maleate administered orally in dogs at 1, 3, and 5 times maximum exposure dose of 0.6 mg/kg oclacitinib twice daily (BID) for 6 weeks, then once daily (SID) for 20 weeks.

   b. Study Animals:

      Sixteen male and sixteen female Beagle dogs approximately 12 months of age weighing between 6.7 and 9.9 kg

   c. Treatment Groups and Drug Administration:

      Table 17: Treatment Groups (Study A29)

Group	Dosage of Oclacitinib and Dosage Schedule	Animals per Treatment
Placebo [a]	0 mg/kg orally for 6 weeks BID, then SID for 20 weeks	8 (4M/4F)
1X Oclacitinib maleate [b]	0.6 mg/kg orally for 6 weeks BID, then SID for 20 weeks	8 (4M/4F)
3X Oclacitinib maleate	1.8 mg/kg orally for 6 weeks BID, then SID for 20 weeks	8 (4M/4F)
5X Oclacitinib maleate	3 mg/kg orally for 6 weeks BID, then SID for 20 weeks	8 (4M/4F)

      [a] The placebo was an empty gelatin capsule.
      [b] The labeled dose is 0.4-0.6 mg/kg oclacitinib BID for two weeks followed by 0.4-0.6 mg/kg SID.

   d. Variables Measured:

      Clinical observations, physical examinations, ophthalmoscopic examinations, body weights, food consumption, hematology, serum

chemistry, coagulation, urinalysis, gross necropsy, histopathology, and plasma oclacitinib concentration measurements were performed on all animals.

e. Statistical Analyses Methodology:

In all analyses, the experimental unit was the individual animal. Variables measured once (organ weights) were analyzed for treatment effects by using a general linear mixed model. For continuous variables measured more than once (body weight, feed consumption, hematology, serum chemistry, coagulation, and urine), data were examined by using a general linear mixed model for repeated measures with a covariate.

5. Results for the Margin of Safety Study (Study A29):

a. Clinical Observations and Physical Examinations:

There were no deaths or serious adverse effects during the 6-month treatment period. Clinical observations that were considered likely to be related to oclacitinib maleate included a dose-dependent increase in the number and frequency of interdigital furunculosis (cysts) on one or more feet during the study. Additional clinical observations were primarily related to the interdigital furunculosis and included dermatitis (local alopecia, erythema, abrasions, scabbing/crusts, and edema of feet) and lymphadenopathy of peripheral nodes. Papillomas were also considered treatment related due to incidence in placebo 0X (no dogs), 1X (4 dogs), 3X (2 dogs), and 5X (4 dogs). Most of the papillomas resorbed spontaneously. Vomiting occurred in all groups. Mild diarrhea/soft stool occurred in the placebo group as well as the 3X and 5X groups.

b. Clinical Pathology:

Clinical pathology findings considered to be oclacitinib maleate-related included a mild, dose-dependent reduction in hematocrit, hemoglobin, and reticulocyte counts during the twice daily dosing period (the mean of the 5X group dropped below the lower limit of the reference range) with a decrease in leukocyte subsets of lymphocytes, eosinophils, and basophils. Total proteins were decreased during the twice daily dosing period primarily due to decreases in the albumin fraction.

c. Pathology:

Direct oclacitinib maleate-related microscopic findings included decreased cellularity (lymphoid) in Gut-Associated Lymphoid Tissue (GALT), spleen, thymus, and cervical and mesenteric lymph node; decreased cellularity of sternal and femoral bone marrow; sinus histiocytosis of cervical lymph nodes; chronic active inflammation of the interdigital area of forepaws and hindpaws (interdigital furunculosis); and chronic active inflammation and lymphoid hyperplasia of prescapular and popliteal lymph nodes draining forepaws and hindpaws with interdigital furunculosis. Five oclacitinib maleate-treated dogs had evidence of mild interstitial pneumonia on microscopic examination.

d. Pharmacokinetics:

There were no systematic male/female differences in pharmacokinetics parameters across all study days and doses. Plasma exposure of oclacitinib was consistent with drug accumulation following the administration of 0.6, 1.8, or 3.0 mg/kg BID, with higher C_{max} and AUC_{0-12} values on Day 21 in comparison to study Day 0. Following a dosing regimen change from BID to 0.6, 1.8, or 3.0 mg/kg SID administration, there was a numerical decrease in the steady state plasma exposure (AUC_{0-12}). This decrease is consistent with the expected change in drug accumulation associated with the switch in daily dose and dosing interval for this drug. Following SID dosing, plasma oclacitinib concentrations achieved steady-state between Day 53 and Day 168. On Day 168, the increase in AUC_{0-12} and C_{max} was dose proportional from 0.6 to 3.0 mg/kg.

6. Conclusions for the Margin of Safety Study (Study A29):

Oral administration of oclacitinib maleate twice daily for 6 weeks, followed by once daily for 20 weeks at 1, 3, and 5 times the maximum recommended dose of 0.6 mg/kg oclacitinib, was associated with interdigital furunculosis, cysts and pododermatitis with associated lymphadenopathy, papillomas, and histopathologic evidence of mild interstitial pneumonia. This study supports the safety of oclacitinib maleate when used according to label directions.

B. Vaccine Response Study

Title: The Effect of Oral PF-03394197 on the Response to Primary Vaccination in Dogs. Study number 1462N-60-09-927 (Study 927)

1. Type of Study: Laboratory study

2. Study Dates: August 21, 2009 to December 17, 2009

3. Investigator and Location:

Jody A. Wren, DVM, PhD
Kalamazoo, MI

4. Study Design

a. Purpose of Study:

To evaluate the safety and effect of oclacitinib maleate on vaccine titers when administered orally, twice daily (BID), in vaccine naïve Beagle puppies, prior to and following primary vaccination, at 3 times the maximum exposure dose of 0.6 mg/kg oclacitinib for 12 weeks (3 months).

b. Study Animals:

Sixteen male and female vaccine-naïve Beagle dogs approximately 4 months of age and weighing at least 3 kg

c. Treatment groups:

Table 18: Treatment Groups (Study 927)

Group	Dosage of Oclacitinib and Dosage Schedule	Animals per Treatment
Placebo [a]	0 mg/kg orally BID for 12 weeks	8
3X Oclacitinib maleate [b]	1.8 mg/kg orally BID for 12 weeks	8

[a] The placebo was a vehicle control.
[b] The labeled dose is 0.4-0.6 mg/kg oclacitinib BID for two weeks followed by 0.4-0.6 mg/kg SID.

The 12-week vaccine response study was followed by no drug administration in the 3-month (81-day) recovery study.

d. Vaccines:

Multivalent modified live vaccine (MLV) containing canine distemper virus (CDV), canine parvovirus (CPV), canine adenovirus (CAV), and canine parainfluenza virus (CPI) was administered on Days 28 and 56 (following 4 and 8 weeks, respectively, of oclacitinib maleate treatment). A single dose of killed rabies virus (RV) vaccine was administered on Day 56.

e. Variables Measured:

Clinical observations, physical examinations, body weights, and food consumption were measured throughout the study. Blood samples for lymphocyte immunophenotyping were collected on Days -14, -7, and 84; contingency samples were collected on Day 60. Hematology, coagulation, and serum chemistry were analyzed on Days -14, -7, and 84. Vaccine titers were measured on Days -20, -3, and 84, except for one dog that died on Day 74. Titers for this dog were measured on Day 70.

5. Results for the Vaccine Response Study (Study 927):

a. Clinical Observations and Physical Examinations:

Enlarged lymph nodes and dermatological lesions were observed more frequently and in more oclacitinib-treated than placebo dogs. Enlarged lymph nodes were observed from Days 40 to 54 and interdigital furunculosis, cysts and mild to severe pododermatitis were observed concurrently (Days 36 to 68), in 5 of 8 oclacitinib maleate-treated dogs. One oclacitinib maleate-treated dog was euthanized on Day 74 for lethargy, elevated body temperature, bloody diarrhea, and an abdominal mass. At necropsy, the mass was determined to be an enlarged mesenteric lymph node adhered to the intestinal wall. The definitive pathological diagnosis for this dog was pneumonia of short duration and chronic lymphadenitis of mesenteric lymph nodes.

During the 3-month recovery study, one dog was euthanized on Day 28 due to clinical signs which included enlarged prescapular lymph nodes, bilateral epiphora, lethargy, mild dyspnea, and a rectal temperature of

103.5°F. The dog showed an elevated white blood cell (WBC) count. Necropsy revealed lesions consistent with sepsis secondary to immunosuppression, including lymphadenitis and lymphoid depletion. Bone marrow hyperplasia was consistent with response to sepsis.

b. Clinical Pathology:

There was a decrease in mean red blood cell (RBC) count, hemoglobin concentration, hematocrit, mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) in oclacitinib maleate-treated dogs compared to placebo dogs. There was an increase in the mean white blood cell (WBC) and neutrophil counts, and a decrease in mean eosinophil and basophil counts, in oclacitinib maleate-treated dogs compared to placebo dogs. Mean serum albumin concentration in the oclacitinib maleate-treated dogs was decreased and the mean was slightly below the normal reference range.

c. Antibody Titer Analyses:

Dogs were classified as having an adequate immune response if they were at or above an adequate titer, or had at least a 2-dilution increase in antibody titer from Day -3 to Day 84 for each antigen.
An adequate immune response (serology) to killed rabies (RV), modified live canine distemper virus (CDV), and modified live canine parvovirus (CPV) vaccination was achieved in all eight 16-week old vaccine naïve puppies while they were administered oclacitinib maleate at 1.8 mg/kg oclacitinib (3X maximum exposure dose) twice daily for 84 days. For modified live canine parainfluenza virus (CPI), <80% (6 of 8) of the dogs achieved adequate serologic response. Canine adenovirus (CAV) was not analyzed because all dogs had seroconverted to CAV-2 by Day -20, indicating pre-study exposure.

d. Quantification of B-lymphocytes (CD21+), T-lymphocyte (CD3+), T-helper lymphocytes (CD3+CD4+), and T-cytotoxic lymphocytes (CD3+CD8+):

Large variability in the lymphocyte phenotype results were observed for both the placebo and oclacitinib maleate-treated dogs. The day-over-day variance in the total numbers of the T lymphocytes (CD3+), T helper lymphocytes (CD4+), T cytotoxic lymphocytes (CD8+), and B lymphocytes showed no substantial differences.

6. Conclusions for the Vaccine Response Study (Study 927):

An adequate serological immune response to killed rabies, CDV, and CPV vaccination was achieved while dogs were administered oclacitinib maleate at 1.8 mg/kg (3X the maximum recommended dose) twice daily for 84 days. Administration of oclacitinib maleate was associated with moderate to severe pododermatitis with associated lymphadenopathy. Infection secondary to immunosuppression resulted in two deaths, including one death that occurred 28 days after discontinuation of oclacitinib maleate.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require

data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to APOQUEL:

> This product is not for human use. Keep this and all drugs out of reach of children. For use in dogs only. Wash hands immediately after handling the tablets. In case of accidental eye contact, flush immediately with water or saline for at least 15 minutes and then seek medical attention. In case of accidental ingestion, seek medical attention immediately.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that APOQUEL, when used according to the label, is safe and effective for control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to rule out other diseases in the diagnosis of allergic and atopic dermatitis, and to monitor the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

C. Patent Information

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.