In November 2021, a panel of experts convened to discuss how to successfully control itch and inflammation when treating acute flares of allergic and atopic dermatitis in dogs. They reviewed recent scientific discoveries and the published data from clinical field studies in client-owned dogs to provide evidence-based guidance on key points, selection of therapies, and management of canine allergic dermatitis.

They concluded that the anti-inflammatory and antipruritic effects of Apoquel® (oclacitinib tablet) make this immunomodulator an exceptional first-line treatment choice for acutely flaring, pruritic, and inflamed allergic and atopic dogs, regardless of disease severity. Published clinical studies indicate that Apoquel controlled pruritus (itch) and inflammation due to allergic and atopic dermatitis as effectively as steroids or cyclosporine.1-5 These proceedings will present supporting evidence and expert opinions to give practitioners confidence in their treatment approach and recommendations.

**The Importance of Controlling Itch & Inflammation**

Until about a decade ago, we had to rely on steroids for rapid and effective control of canine allergic and atopic dermatitis. We have come a long way in a short period of time. We now have targeted therapies specifically designed to treat allergic/atopic dermatitis. What does the evidence say about treating allergic pruritus and inflammation? Are steroids still the best option, or do targeted therapies perform as well?

“In general, I do not use steroids as the primary means to control my allergic and/or atopic patients,” said Dr. Lindsay McKay. “There is always going to be a place for steroids in the management of atopic dermatitis and allergic disease in dogs. The key uses for me are going to be managing severe otitis and severe pododermatitis.”

Allergic skin disease continues to be challenging to manage. One basic principle remains true: We must ensure that our management plan for allergic and
atopic dermatitis is grounded in current scientific evidence provided by randomized controlled clinical studies, where it exists.

Where Do We Start?
The presenting problem for most owners of allergic/atopic dogs is pruritus. They are frustrated, worried, and stressed, and they want their pet to get back to normal. Choosing the right medication to treat these dogs can help build owner confidence in our recommendations.

“When people typically come to see me, it is because the animal is itchy and destroying itself,” said Dr. Rosanna Marsella. “Controlling the itch is the most critical thing to the owner. That returns patient quality of life and gives a break to the owners who live with that pet so they can all get a good night’s sleep.”

“Itch is what drives my clients in. Successfully controlling the dog’s pruritus is the quickest way to earn their trust so they’ll actually listen to and follow our recommendations,” Dr. McKay said.

The experts were asked to participate in a poll during the roundtable. Responses were consistent and aligned with clinical experience. They agreed that, when selecting a treatment, their decision is based on how well it works. The factor they ranked most essential to success was speed of resolution of pruritus, closely followed by speed of resolution of inflammation and improvement of skin lesions (Figure 1). At the bottom end of the scale were cost of treatment and “broad” anti-inflammatory effect. Both received the lowest scores, with most experts feeling they are “not essential.”

Can We Do More?
Although itch may be what causes pets to be presented to the clinic, we know that inflammation plays a major

| Factors in Managing Acutely Pruritic Allergic Patients, Ranked by the Experts |
|---------------------------------|------------------|
|                                | Essential to success |
| Speed of onset of anti-inflammatory effect | 1.1 |
| Effective at improving inflammatory skin lesions whether mild or severe | 3.8 |
| Speed of onset of anti-pruritic effect | 4.7 |
| Low cost to pet owner | 2.4 |
| Treatment is systemic (versus topical) | 3.1 |
| Treatment is broad in its anti-inflammatory effect | 3.6 |
| Treatment is specifically targeted in its anti-inflammatory effect | 3.4 |
| One product can be used throughout the treatment period | 3.2 |

*FIGURE 1* In this poll, responses ranged from 1 to 5, with 1 being “nice to have but not essential” and 5 being “essential to success.”
Controlling inflammation in dogs with allergic/atopic dermatitis is important to:
- Prevent disease progression
- Decrease the likelihood of secondary infections of the skin and ears
- Prevent recurrence of pruritus
- Provide a long-term solution

“Atopic dermatitis has been described as a relentlessly progressive disease, and that’s because of inflammation,” Dr. McKay said.

Dr. Jeanne Budgin agreed that managing inflammation to prevent pruritus from returning is also vital. “While it is case-dependent, I think it’s about more than just providing itch relief, because we know that atopic dermatitis/allergic skin disease does tend to be chronic and relapsing,” she said, “so addressing the underlying inflammatory component is really important when it comes to preventing recurrence and providing long-term relief.”

“We really need to control both itch and inflammation,” said Dr. Amelia White. “When we don’t, then not only is the quality of life for the pet and the owner quite poor, but now we’re going to have to deal with other complicating factors like infection.”

Clearly, product efficacy is most important. In terms of how the products work, the experts’ rankings in the poll tended to cluster toward a treatment that is targeted in its anti-inflammatory effect as being more essential to success.

The experts also noted that having a treatment that is systemic (rather than topical) and being able to use a single therapy throughout the treatment period were of moderate importance.

The Value of Systemic, Targeted Therapy

When allergens enter the body of an allergic patient, an exaggerated immune response that involves a wide variety of cell types is initiated, producing proteins such as cytokines, chemokines, and other inflammatory mediators.

Recent research has indicated that cytokines play a central role in most stages of the immune response, triggering and driving inflammation associated with allergic dermatitis. Many of the cytokines that are integral to atopic dermatitis amplify the inflammatory response through the Janus kinase 1 (JAK1) signaling pathway.

Along with our evolving understanding of the pathomechanisms of allergic/atopic dermatitis, there is another critically important concept we need to understand (see How Can a Targeted Therapy Have a Broad Effect?, next page). Previously, we thought of the inflammatory response as being a linear process or directional cascade. Although that may still be true at the beginning of sensitization, we now know that these cytokines interact in a complex, interconnected inflammatory network, affecting many components in a multidirectional manner once clinical signs appear and the disease is established.

What Does This New Knowledge Mean for Our Patients?

Using a specific therapy that targets these cytokines, rather than broadly inhibiting the immune system, is a good choice for our allergic and atopic patients.

“At the beginning, when everything’s on fire, you do need to inhibit a lot of cytokines. But you can do that with a more targeted therapy like Apoquel, compared to something less targeted like steroids,” Dr. White said. “We need a drug that is going to rapidly, effectively, and safely reduce inflammation and pruritus simultaneously, and I think we all agree that the best way to do that is by targeting multiple cytokines, since allergy is cytokine-mediated and there are usually many cytokines involved” (see Figure 2, next page).

“If we knew there was a broad treatment that was super safe and didn’t have side effects, then it might not be as much of a concern,” said Dr. Bourgeois. “With targeted treatment, we assume there are fewer side effects, so it makes pet owners (and us as doctors) feel more comfortable” (see Steroid Use in Allergic Dermatitis: There Are Costs for the Patient & the Pet Owner, page 5).

With the JAK1 signaling pathway being so important in the activation of cells involved in the allergic inflammatory network, targeting JAK1 specifically will have broad effects for canine patients with allergic or atopic dermatitis.

How Do We Decide Which Drug to Use?

We now understand many of the mechanisms involved in allergic and atopic dermatitis, but there is still much to learn. However, examining a treatment’s mechanism of action and its effect on the cytokine network and hypothesizing on its clinical effects, while important and helpful, does have limitations. We also need to consider the literature to look at real-world results with patients in practice.

“We have to have some general idea of how treatments compare to each other in larger groups,” Dr. Marsella said. “One way is to run a study… and see if there are any statistically significant differences between treatments, with the understanding that you’re comparing 2 groups. Having said that, that does not equate to there being a cookie-cutter approach to this—that whatever treatment
With targeted treatment, we assume there are fewer side effects, so it makes pet owners (and us as doctors) feel more comfortable.

—Dr. Ashley Bourgeois

**HOW CAN A TARGETED THERAPY HAVE A BROAD EFFECT?**

**A Complex, Multidirectional Network**

We know that canine allergic/atopic dermatitis is a cytokine-driven disease, but rather than the old model of a unidirectional, linear cascade—the idea that if you interfere with one component, only what is directly downstream may be affected—the updated thinking is that cytokines interact with inflammatory cells within an interconnected and multidirectional network (see *Figure 2*). This means that affecting one component does not only affect what is happening downstream but also potentially alongside and upstream.


“Everything influences everything around it, whether it’s the skin barrier, cytokines, or infections,” said Dr. Ashley Bourgeois. “We know that these cytokines influence one another. Why does it matter? Because we know that this is a chronic disease that we can get these roller coasters of acute flares with, and we need to deal with it in our treatment—not only for the short term but long term as well.”

**The Role of JAK1-Signaling Pathways in Allergic & Atopic Dermatitis**

We have known for years that many of the cytokines that are released during the complex inflammatory response are dependent on JAK1 for signaling and activating cells, but we now know that JAK1 is also involved in several other important, interconnected pathways in this inflammatory network. This is why inhibiting JAK1 produces a significant effect on controlling itch and inflammation associated with allergic and atopic dermatitis (see *Figure 2*).

“JAK1 signaling is an extremely important pathway in allergic inflammation and itch in many—maybe even most—allergic dogs,” Dr. Doug DeBoer said. “It’s not the only pathway, but it’s maybe the most important pathway in allergic itch and inflammation.”

Apoquel specifically modulates JAK1-dependent, pruritogenic, and proinflammatory cytokines that play a major role in inflammation of the skin. In this way, Apoquel controls both pruritus and inflammation due to allergic and atopic dermatitis.1-5

Cytopoint® (canine allergic dermatitis immunotherapeutic) binds to and neutralizes interleukin (IL)-31.6 IL-31 plays a major role in pruritus, but it also induces a variety of proinflammatory cytokines from macrophages, including IL-1β, IL-8, tumor necrosis factor-alpha (TNFα), and IL-6, that can trigger inflammation.7 Thus, we now know that Cytopoint also has both an antipruritic and anti-inflammatory effect.8

![FIGURE 2](image-url)

*This figure is intended to provide a clear and accurate framework of the concept without purporting to be a comprehensive and complete reflection of all events involved.*
works based on that paper necessarily applies to a specific patient. But we have to have a place to start.”

The experts agreed that they’ve learned to not make assumptions about which treatment will work for a specific case. “I tell my clients [the inflammatory response with allergy] is like a soup,” Dr. Jennifer Schissler explained. “Different dogs have different soups. They have different things going on [in that soup]—some worse, some better—but it’s really complicated.”

“It is [like] a soup,” Dr. Doug DeBoer agreed. “It’s complex and multifactorial and is all orchestrated by the cytokine network.”

The experts concurred that treatment recommendations need to be based on comparative, head-to-head studies, which is the core of evidence-based medicine. Randomized controlled studies can provide compelling evidence of the efficacy of a product and the likelihood for success in a certain population of affected dogs (compared with placebo or a previous standard of care), but they do not guarantee the outcome in every patient in the real world.

Dr. DeBoer affirmed that the results of these studies can be applied to most, but not all, dogs. The results of controlled trials can provide the confidence practitioners need to make a recommendation.

The Evidence for Using Targeted Therapy: Apoquel Reduces Allergic Pruritus & Skin Lesions2,5

A single-blinded, randomized study by Gadeyne and colleagues2 evaluated the efficacy and safety of oclacitinib compared with prednisolone in 123 client-owned dogs with allergic dermatitis and moderate to severe pruritus. In this controlled study, oclacitinib worked as fast and as well as steroids in reducing pruritus and was as effective as steroids in reducing dermatitis associated with allergic dermatitis in dogs at all time points in the study.

Another single-blinded, randomized study by Little et al.5 compared the efficacy and safety of oclacitinib and cyclosporine for the control of canine atopic dermatitis in 226 client-owned dogs. In this controlled clinical trial, oclacitinib controlled pruritus faster than cyclosporine and controlled dermatitis as well as cyclosporine in dogs with atopic dermatitis.

What Do the Experts Think?
The experts reviewed these published studies and agreed that Apoquel performed as well as prednisolone and cyclosporine in controlling pruritus and inflammation due to allergic and atopic dermatitis.

In addition, they were presented with further sub-analysis of the Apoquel and prednisolone comparative study, evaluating only dogs with dermatitis Visual Analogue Scale (VAS) scores indicating moderately severe to extremely severe dermatitis. The experts agreed that the findings support the original study conclusion that “Apoquel administered orally in the recommended dosing regimen reduced pruritus and clinical signs associated with allergic dermatitis to a level comparable to the efficacy of prednisolone administered at a dose of 0.5-1 mg/kg daily for 6 days,” even in dogs with more severe dermatitis.

Dr. Bourgeois specifically appreciated that the studies showed that Apoquel worked as well as steroids for severe flares of canine allergic dermatitis. “We can use Apoquel in severe disease and still reduce inflammation, still make these pets comfortable, and not have those panic calls 3 days later because the pet’s urinating all over the house,” she said.

The experts were also impressed by the data showing the rapid onset of effect of Apoquel as compared with glucocorticoids in the clinical studies. Dr. Budgin acknowledged that it has impacted the way she practices. “I had always just been reaching for steroids for acute pruritus, pyotraumatic dermatitis (hotspots), things like that. I found the data to be really exciting; that was what launched me into feeling far more comfortable with using Apoquel,” she said.

Others agreed that the additional analysis from the oclacitinib and prednisolone (Gadeyne) comparative study gave them more evidence to support using Apoquel for moderate...
to severe allergic dermatitis in their canine patients. “It’s nice
when the data show with numbers what we see clinically
happening,” said Dr. White. “For those with severe inflamma-
tion due to allergic and atopic dermatitis, the study results
showed that the dogs that received Apoquel performed as
well as the dogs that received steroids.”

“I think that most veterinarians want the evidence-based
data comparing the treatments head-to-head with our
standard of care,” said Dr. McKay. “I think that turns a lot of
people around in understanding why Apoquel is as good as
steroids and why antihistamines don’t work.”

“Most pet owners know steroids come with a compromise.
They’re not all that good; they affect every cell in the body,
and immunologically, it ties one paw behind their back.
We’re often dealing with infection at the same time, and with
steroids, the dogs aren’t able to fight infection as well as they
normally could;” Dr. Jay Crisman explained. “The Gadeyne
[oclacitinib and prednisolone] study really is a comparative
study that is conclusive and objective and answers those
questions. It helps us put doubts aside; we don’t have to
compromise like we used to with steroids when we see a dog
with itch and inflammation due to allergic dermatitis.”

Apoquel works as quickly and as effectively
for managing allergic pruritus and dermatitis as steroids.
—Dr. Lindsay McKay

Cytopoint Controls Allergic
Pruritus and Inflammation
Cytopoint has been shown to be effective in the treatment
of dogs against allergic dermatitis and atopic dermatitis.6
Cytopoint binds to and neutralizes IL-31, a key cytokine that
triggers activity within immune cells that leads to pruritus
and inflammation due to allergic and atopic dermatitis.6,7

In a blinded, randomized clinical trial, Moyaert and
colleagues6 evaluated the efficacy and safety of Cytopoint
compared with cyclosporine in 274 client-owned dogs
with chronic atopic dermatitis. Cytopoint provided rapid,
long-lasting relief of allergic pruritus and skin lesions simi-
lar to cyclosporine in this controlled study.

What Do the Experts Think?
The experts agreed that the results of this study can give
practitioners confidence in their choice of Cytopoint.
“It’s important to provide relief quickly for the animal,
as well as to have the owner buy into whatever plan we
are going to propose for the medium and long-term,”
Dr. Marsella said, “so I think that the speed of action [of
the chosen therapy] is very relevant.”

“If a dog favorably responds to Cytopoint, then we are
going to see a decrease in inflammation due to allergic der-
matitis, especially as it relates to self-induced excoriations,”
Dr. White concluded. “But I do think that we also see in
some dogs a decrease in inflammation beyond the itching
and scratching behavior.”

Additional Tips to Help You Succeed
Beyond following the evidence-based data from published
controlled studies and the science as it evolves, what else
can we do to set up ourselves and our allergic/atopic
dermatitis patients for success?

1. Set Client Expectations
The experts emphasized the importance of educating
clients about allergic dermatitis, including setting the expec-
tation early in the course of the disease that chronic man-
agement will be required. As Dr. DeBoer said, “I don’t think a
general practice veterinarian can say often enough and early
enough, ‘I think your dog is allergic. I can offer you a treat-
ment for that, but you need to understand that your dog’s
allergies are not going to go away. This is a chronic disease.’”

Dr. Schissler makes sure her clients understand that as well,
both during visits and on the discharge instructions. She
explains that “allergic dermatitis is a lifelong condition that
will require lifelong treatment and may require treatment
adjustments.”

Dr. Natalie Marks conveys that allergic dermatitis is an
inflammatory disease that requires more than a one-and-
done approach. “Hopefully we can set the expectation that
this is a journey,” she said. “It’s an inflammatory disease.
That way, our clients get a sense of the weight of the disease
so they understand the compliance aspect.”

2. Provide a Long-Term Plan
Addressing both itch and inflammation due to allergic and
atopic dermatitis correctly is a good start. But that’s not
enough. The experts all felt that there is a need for a long-
term plan.
“We need to be more proactive in managing patients with allergic and atopic dermatitis,” said Dr. McKay. “We need to have a long-term strategy for our patients for the management to be successful.”

Dr. Phil Thompson also reminds his clients that the plan for managing canine allergic dermatitis is a living thing. “That plan will change based on what the patient’s needs are and what’s going on in that moment,” he said.

3. Refer Early
“Early referral to a veterinary dermatologist who will work in conjunction with the client’s primary care veterinarian can be beneficial in helping to manage secondary infections as well,” Dr. Budgin said. She suggested educating clients that referral is not a sign that their veterinarian has given up but rather wants to provide their pet with the best possible management for this chronic disease.

Dr. Bourgeois would certainly like to see these cases a bit sooner, “so we can help with that plan through the use of medications like Apoquel and Cytopoint, instead of allergy testing them when they’re 8 years old and we’re starting to already see the progression of that disease.”

4. Know When to Perform a Diagnostic Workup
The experts pointed out that every time a patient flares, a diagnostic workup needs to be top of mind (Figure 3). Flares are periods of worsening of disease. Continuing the anchor therapy during the workup is essential to keep the dog comfortable and to improve owner compliance with diagnostic trials.

“We can’t say too often in evaluating flares of atopic dermatitis: Make certain that parasite control and infection control are under way,” said Dr. DeBoer.

“And make sure you identify if it’s a food flare as well,” Dr. McKay noted, “That diagnostic workup that we do in the beginning needs to be running through our mind every time patients have a flare. Is it parasites? Is it infection? Is it food?”

When a patient is presented with a flare, Dr. Mike Canfield suggested that the practitioner should investigate possible causes, such as lack of compliance with topical therapy or an unresolved methicillin-resistant Staphylococcus infection.

5. Recognize That Flares Happen
Allergic/atopic dermatitis is not curable, and dogs with the disease are predisposed to flaring. “We know that even nonlesional skin in atopic dogs is abnormal. The components of a flare are always there waiting to develop; [the patients are] always on the verge of a flare,” said Dr. McKay.

“We know there will be flares…atopic dermatitis is a flare disease,” Dr. Thompson said. “Setting the expectation— that client communication part that’s so important for all of dermatology—makes these cases easier to handle.”

“Just because we have that little thing that gets ahead of us—whatever it is—life gets in the way and [the client] forgot flea control, for instance, we give up on a therapy,” Dr. Bourgeois said. “Plenty of pets flare even if they’re on chronic steroids.”

The important point is not to give up on a therapy; you may just need a little extra help for a while.

Key Takeaways
Veterinarians Need to Be Able to Rely on Clinical Evidence
The experts agreed that the data from the controlled studies, along with our new understanding of the inflammatory cytokine network being interconnected and multidirectional, support the choice of Apoquel to treat even a moderate to severe flare of canine allergic and atopic dermatitis.2,5,9

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**The Allergic Dermatitis Workup**

STOP PRURITUS

RULE OUT PARASITES

TREAT SKIN INFECTION

CONDUCT FOOD TRIAL

CONFIRM ATOPIC DERMATITIS

▲ FIGURE 3
By managing inflammation, we control pruritus, and we can control future infection as well.

—Dr. Amelia White

“We want to be as targeted as we can but also as broad as we need to be. We have something that is targeted specifically to interleukin-31, which would be Cytopoint, and it works very well for [particular] patients. [If] I need something that works a little more broadly, [that] would be Apoquel,” said Dr. Thompson. “Whether it’s Cytopoint, Apoquel, or allergen-specific immunotherapy, any of those 3 [therapies] are significantly more targeted than corticosteroids.”

“When I think about a therapy, I want it to be safe, but I want it to broadly cover those cytokines,” Dr. White explained. “To reduce inflammation and reduce itch at the same time and be safe to the patient, but also have few side effects, would be ideal.”

“When Apoquel first came out, it was so terrific to have a product that stopped the allergic [pruritus] so fast and effectively,” said Dr. Thompson. “With time, we saw that it really has great anti-inflammatory effects, and that was understandable as we learned more about the pathways involved in allergic dermatitis. It’s the same with Cytopoint, launched on the basis of providing great pruritus relief—which it does—but with use and observation, we see a decrease in inflammation as well, and the new science helps make sense of that.”

The Data Do Not Support the Need to Use Steroids for Most Flares

Current data show that, in many cases, regardless of the degree of disease severity—whether it’s a mild or moderate to severe flare—Apoquel works just as well as steroids as a first-line treatment to reduce itch and inflammation due to allergic and atopic dermatitis in dogs.2,9

“In a study, Apoquel worked as quickly and as effectively for managing pruritus and dermatitis as steroids,” said Dr. McKay. “Apoquel provided the antipruritic and anti-inflammatory benefits that you’re looking for, and we can get away from the side effects of steroids that we don’t like and we know are very distasteful to our clients” (see Steroid Use in Allergic Dermatitis: There Are Costs for the Patient & the Pet Owner, page 5).

“Apoquel and Cytopoint are some of the best tools that we have for controlling flares of allergic/atopic dermatitis in our canine patients,” Dr. Marsella agreed.

References

Immunomodulator

For oral use in dogs only

Caution: APOQUEL (oclacitinib maleate) is a synthetic Janus kinase (JAK) inhibitor. The chemical composition of APOQUEL is N-methyl[trans-4-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino) cyclohexyl]methanesulfonamide (2Z)-2-butenedioate.

The chemical structure of oclacitinib maleate is:

![Chemical structure]

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

Dosage and Administration: The dose of APOQUEL (oclacitinib maleate) tablets is 0.18 to 0.27 mg oclacitinib/kg (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. APOQUEL may be administered with or without food.

Dosing Chart

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Adverse Reactions:

Control of Atopic Dermatitis

In a masked field study to assess the effectiveness and safety of oclacitinib for the control of atopic dermatitis in dogs, 152 dogs treated with APOQUEL and 147 dogs treated with placebo (vehicle control) were evaluated for safety. The majority of dogs in the placebo group withdrew from the 112-day study by Day 16. Adverse reactions reported (and percent of dogs affected) during Days 0-16 included diarrhea (4.6% APOQUEL, 3.4% placebo), vomiting (3.9% APOQUEL, 4.1% placebo), anorexia (2.6% APOQUEL, 0% placebo), new cutaneous or subcutaneous lump (2.6% APOQUEL, 2.7% placebo), and lethargy (2.5% APOQUEL, 0% placebo). In most cases, diarrhea, vomiting, anorexia, and lethargy spontaneously resolved with continued dosing. Dogs on APOQUEL had decreased leukocytes (neutrophil, eosinophil, and monocyte counts) and serum globulin, and increased cholesterol and lipase compared to the placebo group but group means remained within the normal range. Mean lymphocyte counts were transiently increased at Day 14 in the APOQUEL group.

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Clinical Pharmacology:

Mechanism of Action

Oclacitinib inhibits the function of a variety of pruritogenic cytokines and pro-inflammatory cytokines, as well as cytokines involved in allergy that are dependent on JAK1 or JAK3 enzyme activity. It has little effect on cytokines involved in hematopoiesis that are dependent on JAK2.

Oclacitinib is not a corticosteroid or an antihistamine.

Pharmacokinetics

In dogs, oclacitinib maleate is rapidly and well absorbed following oral administration, with mean time to peak plasma concentrations (T_{max}) of less than 1 hour. Following oral administration of 0.4-0.6 mg oclacitinib/kg to 24 dogs, the mean (90% confidence limits [CL]) maximum concentration (C_{max}) was 3.3 (2.81, 3.72) ng/mL, and the mean area under the plasma concentration-time curve from 0 and extrapolated to infinity (AUC_{0-\infty}) was 1890 (1690, 2110) ng·hr/mL. The prandial state of dogs does not significantly affect the rate or extent of absorption. The absolute bioavailability of oclacitinib maleate was 89%.

Oclacitinib has low protein binding with 66.3-69.7% bound in fortified canine plasma at nominal concentrations ranging from 10-1000 ng/mL. The apparent mean (95% CL) volume of distribution at steady-state was 942 (870, 1014) mL/kg body weight. Oclacitinib is metabolized in the dog to multiple metabolites and one major oxidative metabolite was identified in plasma and urine. Overall the major clearance route is metabolism with minor contributions from renal and biliary elimination. Inhibition of canine cytochrome P450 enzymes by oclacitinib is minimal; the inhibitory concentrations (IC_{50}) are 50 fold greater than the observed T_{max} values at use dose.

Mean (95% CL) total body oclacitinib clearance from plasma was low – 316 (237, 396) mL/h/kg body weight (3.3 mL/min/kg body weight). Following IV and PO administration, the terminal t_{1/2} appeared similar with mean values of 3.5 (2.2, 4.7) and 4.1 (3.1, 5.2) hours, respectively.

Effectiveness:

Control of Atopic Dermatitis

A double-masked, 112-day, controlled study was conducted at 18 U.S. veterinary hospitals. The study enrolled 999 client-owned dogs with atopic dermatitis. Dogs were randomized to treatment with APOQUEL (152 dogs: tablets administered at a dose of 0.4-0.6 mg/kg per dose twice daily for 14 days and then once daily) or placebo (147 dogs: vehicle control, tablets administered at the same schedule). During the study, dogs could not be treated with other drugs that could affect the assessment of effectiveness, such as corticosteroids, anti-histamines, or cyclosporine. Treatment success for pruritus for each dog was defined as at least a 2 cm decrease from baseline on a 10 cm visual analog scale (VAS) in pruritus, assessed by the Owner, on Day 28. Treatment success for skin lesions was defined as a 50% decrease from the baseline Canine Atopic Dermatitis Extent and Severity Index (CADESI) score, assessed by the Veterinarian, on Day 28. The estimated proportion of dogs with Treatment Success in Owner-assessed pruritus VAS score and in Veterinarian-assessed CADESI score was greater and significantly different for the APOQUEL group compared to the placebo group.

Effectiveness Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APOQUEL (n = 203)</th>
<th>Placebo (n = 204)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Owner-Assessed Pruritus VAS</td>
<td>0.66 (n = 131)</td>
<td>0.04 (n = 133)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Veterinary-Assessed CADESI</td>
<td>0.49 (n = 134)</td>
<td>0.04 (n = 134)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Compared to the placebo group, mean Owner-assessed pruritus VAS scores (on Days 1, 2, 7, 14, and 28) and Veterinarian-assessed CADESI scores (on Days 14 and 28) were lower (improved) in dogs in the APOQUEL group. By Day 30, 86% (127/147) of the placebo group dogs and 15% (23/152) of the oclacitinib maleate-treated dogs withdrew from the masked study because of worsening clinical signs, and had the option to enroll in an unmasked study and receive APOQUEL. For dogs that continued APOQUEL treatment beyond one month, the mean Owner-assessed pruritus VAS scores and Veterinarian-assessed CADESI scores continued to improve through study end at Day 112.

Control of Pruritus Associated with Allergic Dermatitis

A double-masked, 30-day, controlled study was conducted at 26 U.S. veterinary hospitals. The study enrolled 436 client-owned dogs with a history of allergic dermatitis attributed to one or more of the following conditions: atopic dermatitis, flea allergy, food allergy, contact allergy, and/or unspecified allergic dermatitis. Dogs were randomized to treatment with APOQUEL (216 dogs: tablets administered at a dose of 0.4-0.6 mg/kg twice daily) or placebo (220 dogs: vehicle control, tablets administered twice daily). During the study, dogs could not be treated with other drugs that could affect the assessment of pruritus or dermal inflammation such as corticosteroids, anti-histamines, or cyclosporine. Treatment success for each dog was defined as at least a 2 cm decrease from baseline on a 10 cm visual analog scale (VAS) in pruritus, assessed by the Owner, on at least 5 of the 7 evaluation days. The estimated proportion of dogs with Treatment Success was greater and significantly different for the APOQUEL group compared to the placebo group.

Effectiveness Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APOQUEL (n = 203)</th>
<th>Placebo (n = 204)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated Proportion of Dogs with Treatment Success</td>
<td>0.67</td>
<td>0.29</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

After one week of treatment, 86.4% of APOQUEL group dogs compared with 42.5% of placebo group dogs had achieved a 2 cm reduction on the 10 cm Owner-assessed pruritus VAS. On each of the 7 days, mean Owner-assessed pruritus VAS scores were lower in dogs in the APOQUEL group (See Figure 1). Veterinarians used a 10 cm VAS scale to assess each dog’s dermatitis. After one week of treatment, the mean Veterinarian-assessed VAS dermatitis score for the dogs in the APOQUEL group was lower at 2.2 cm (improved from a baseline value of 6.2 cm) compared with the placebo group mean score of 4.9 cm (from a baseline value of 6.2 cm). For dogs that continued APOQUEL treatment beyond one week, the Veterinarian-assessed dermatitis scores continued to improve through study end at Day 30.

Animal Safety:

Margin of Safety in 12 Month Old Dogs

Clinical monitoring was administered to healthy, one-year-old Beagle dogs twice daily for 6 weeks, followed by once daily for 20 weeks, at 0.6 mg/kg (1X maximum exposure dose, 8 dogs), 1.8 mg/kg (3X, 8 dogs), and 3.0 mg/kg (6X, 8 dogs) oclacitinib for 26 weeks. Eight dogs received placebo (empty gelatin capsule) at the same dosage schedule. Clinical observations that were considered likely to be related to oclacitinib maleate included papillomas and a dose-dependent increase in the number and frequency of interdigital furunculosis (cyts) 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. Microscopic findings considered to be oclacitinib maleate-related included decreased cellularity (lymphoid) in Gut-Associated Lymphoid Tissue (GALT), spleen, thymus, cervical and mesenteric lymph node; and decreased cellularity of sternal and femoral bone marrow. Lymphoid hyperplasia and chronic active inflammation was seen in lymph nodes draining feet affected with interdigital furunculosis. Five oclacitinib maleate-treated dogs had microscopic evidence of mild interstitial pneumonia. Clinical pathology findings considered to be oclacitinib maleate-related included mild, dose-dependent reduction in hemoglobin, hematocrit, and reticulocyte counts during the twice daily dosing period with decreases in the leucocyte subsets of lymphocytes, eosinophils, and basophils. Total proteins were decreased over time primarily due to the albumin fraction.

Vaccine Response Study

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 eight 16-week-old vaccine naïve puppies that 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. Clinical observations that were considered likely to be related to oclacitinib maleate treatment included enlarged lymph nodes, interdigital furunculosis, cyts, and pododermatitis. One oclacitinib maleate-treated dog (26-weeks-old) was euthanized on Day 74 after physical examination revealed the dog to be febrile, lethargic, with pale mucous membranes and frank blood in stool. Necropsy revealed a pneumonia of short duration and evidence of chronic lymphadenitis of mesenteric lymph nodes. During the three month recovery phase to this study, one oclacitinib maleate-treated dog (32-weeks old) was euthanized on Day 28 due to clinical signs which included enlarged prescapular lymph nodes, bilateral epiphora, lethargy, mild dyspnea, and fever. The dog showed an elevated white blood cell (WBC) count. Necropsy revealed lesions consistent with sepsis secondary to immunosuppression. Bone marrow hyperplasia was consistent with response to sepsis.

Margin of Safety in 6 Month Old Dogs

A margin of safety study in 6-month-old dogs was discontinued after four months due to the development of bacterial pneumonia and generalized demodex mange infections in dogs in the high dose (3X and 5X) treatment groups, dosed at 1.8 and 3.0 mg/kg oclacitinib twice daily, for the entire study.

Storage Conditions:

APOQUEL should be stored at controlled room temperature between 20° to 25°C (68° to 77°F) with excursions between 15° to 40°C (59° to 104°F).

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 100 and 250 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.

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