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Attached is an Abstract of a Zoetis Presentation at the

EUROPEAN SOCIETY OF VETERINARY DERMATOLOGY, 2013

TITLE: SELECTION OF AN EFFICACIOUS DOSING REGIMEN OF OCLACITINIB (APOQUEL®, ZOETIS) FOR THE CONTROL OF ATOPIC DERMATITIS IN CLIENT-OWNED DOGS USING VISUAL ANALOG SCALE AND CADESI SCORES

SELECTION OF AN EFFICACIOUS DOSING REGIMEN OF OCLACITINIB (APOQUEL®, ZOETIS) FOR THE CONTROL OF ATOPIC DERMATITIS IN CLIENT-OWNED DOGS USING VISUAL ANALOG SCALE AND CADESI SCORES

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ABSTRACT: Oclacitinib inhibits the function of multiple pro-inflammatory and pruritogenic cytokines that are dependent on Janus kinase (JAK) enzyme activation. Oclacitinib preferentially inhibits JAK1 dependent cytokines. The efficacy of three doses and regimens of oclacitinib for the control of canine atopic dermatitis compared to placebo was evaluated. Fourteen dermatologists enrolled 220 dogs with a history of chronic nonseasonal AD. Dogs were randomly allocated to one of four treatment groups: (T01) placebo, (T02) oclacitinib 0.4-0.6 mg/kg twice daily from Day 0-14 followed by once daily until Day 112, (T03) oclacitinib 0.4-0.6 mg/kg once daily from Day 0-112, and (T04) oclacitinib 0.2-0.3 mg/kg once daily from Day 0-112. Treatment success (TS) was defined as a ≥2 cm reduction from baseline for owner VAS score for pruritus or by a ≥50% reduction from baseline CADESI-02 scores. For pruritus assessments on Days 28, 56, 84 and 112, the three oclacitinib-treated groups showed a larger percentage of TS than the placebo-treated controls. Within the oclacitinib-treated groups, T02 had a larger percentage of TS (85%, 76%, 66%, 69%) than T03 (70%, 68%, 54%, 56%) and T04 (42%, 36%, 35%, 28%). Treatment success for the placebo-treated group was ≤5% at all timepoints. CADESI-02 assessments mirrored these findings: T02 had a larger percentage of TS (58%, 59%, 61%, 59%) than T03 (47%, 47%, 42%, 50%) and T04 (24%, 26%, 31%, 28%). Treatment success for the placebo-treated group was ≤7% at all time points. The twice-daily/once-daily dosing regimen (T02) was selected for later clinical trials.

FUNDING: Pfizer Animal Health

CONFLICT OF INTEREST: All authors are current or former employees of Zoetis, Inc., formerly Pfizer Animal Health.

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OCLACITINIB (APOQUEL®, ZOETIS) IS A NOVEL JANUS KINASE INHIBITOR THAT HAS ACTIVITY AGAINST CANINE PRO-ALLERGIC AND PRO-INFLAMMATORY CYTOKINES

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ABSTRACT: Cytokine dysregulation can orchestrate a variety of cellular and molecular changes that lead to chronic conditions including allergy in dogs. Many cytokines thought to trigger such changes bind receptors that activate Janus kinase (JAK) enzymes. The objective of this study was to determine if the novel JAK inhibitor oclacitinib could reduce the activity of a variety of cytokines thought to induce many of the clinical signs associated with allergic conditions in dogs. Using isolated enzyme systems and in vitro human or canine cell models, the potency and selectivity of oclacitinib was evaluated against individual JAK family members as well as cytokines dependent on JAK activation. Oclacitinib inhibited JAK family members by 50% at concentrations (IC50) ranging from 10-99nM and did not inhibit a panel of 38 other non-JAK kinases (IC50's > 1000nM). Oclacitinib was most effective at inhibiting JAK1 (IC50 = 10nM). Oclacitinib also inhibited the function of JAK1-dependent cytokines involved in allergy and inflammation (IL-2, IL-4, IL-6, and IL-13), as well as those that cause pruritus (IL-31) at IC50 ranging from 36-240nM. Oclacitinib had minimal activity against JAK2-dependent cytokines involved in hematopoisis (erythropoietin and GM-CSF; IC50 > 1000nM), and it did not inhibit other JAK2-dependent cytokines involved in innate immune responses (IL-12, IL-23; IC50 >3000nM). These results demonstrate that oclacitinib selectively inhibits JAK1-dependent cytokines involved in allergy, inflammation and pruritus. As a result of this widespread yet role-specific anti-cytokine activity, oclacitinib is likely to be effective to treat clinical signs of allergic diseases in dogs.

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ABSTRACT: Oclacitinib inhibits the function of a variety of pro-allergic, pro-inflammatory and pruritogenic cytokines that are dependent on Janus kinase (JAK) enzyme activity. Four hundred and seven client-owned dogs with moderate-to-severe owner-assessed pruritus and a presumptive diagnosis of allergic dermatitis were enrolled. Dogs were randomized to receive either oclacitinib at 0.4 to 0.6 mg/kg orally twice daily or an excipient-matched placebo. A 10.0 cm long visual analog scale (VAS) was used by owners to assess pruritus severity from Days 0 to 7. Treatment Success (TS) was defined as achieving a >2 cm reduction from baseline VAS score on at least 70% of the study treatment days assessed (i.e. Day 1 to Day 7). Treatment success at Day 7 was compared between dogs receiving flea control or not on Day 0, but,regardless of whether fleas were present at that time. Sixty-five of 407 dogs (16.0%), 27 (13.2%) placebo-treated and 38 (18.7%) oclacitinib-treated, received flea products on Day 0. On Day 7, the percentage of TS for oclacitinib-treated dogs was approximately the same whether or not they were treated for fleas (63.2% vs 67.7%). By contrast, initiating flea treatment in placebo-treated dogs on Day 0 doubled the percentage of TS (52%) compared to dogs not treated for fleas (26%). In summary, adding flea treatment on Day 0 did not appear to impact the efficacy of oclacitinib for pruritus control in dogs with allergic dermatitis, but it could explain as much as 50% of the pruritus reduction observed in placebo-treated dogs.

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