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A blinded, randomized, placebo-controlled, dose determination trial of lokivetmab (ZTS-00103289), a caninized, anti-canine IL-31 monoclonal antibody in client owned dogs with atopic dermatitis

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Background – Pruritus is the hallmark clinical sign of atopic dermatitis (AD) in dogs. Lokivetmab, a caninized anti-canine IL-31 monoclonal antibody, reduced pruritus and associated inflammatory skin lesions in a proof-of-concept study in dogs with AD.

Hypothesis/Objectives – The objective was to describe lokivetmab dose response in a randomized, double blind, placebo-controlled trial.

Animals – Clinicians at 15 referral clinics enrolled 211 client owned dogs with a history of chronic AD.

Methods – Dogs were randomized to treatment with lokivetmab (0.125, 0.5 or 2.0 mg/kg) or placebo administered subcutaneously once on Day 0. Dog owners assessed visual analog scale (VAS) scores of pruritus on days 0, 1, 2, 3, 7, 14, 21, 28, 35, 42, 49 and 56. Clinicians assessed Canine AD Extent and Severity Index (CADESI-03) scores on days 0, 7, 14, 28, 42 and 56.

Results – Treatment with lokivetmab (2 mg/kg) resulted in a greater percentage reduction from baseline in owner assessed pruritus (days 1–49) and clinician assessed CADESI-03 scores (days 7–56) compared to placebo ($P < 0.05$); differences were achieved in lower dose groups but at later time points and for shorter duration for both owner assessed pruritus (0.5 mg/kg, days 2–35; 0.125 mg/kg, days 7–21) and clinician assessed CADESI-03 scores (0.5 mg/kg and 0.125 mg/kg, Day 14).

Conclusions and clinical importance – Lokivetmab (0.5, 2.0 mg/kg) reduced pruritus compared to placebo for at least 1 month. Level and duration of response increased with increasing dose. Further studies are needed to better understand variability in individual responses across a broader population of dogs with AD.

Introduction

Pruritus is the most prominent clinical sign of canine atopic dermatitis (AD), a genetically predisposed inflammatory allergic skin disease with characteristic clinical features.[1–3] Interleukin-31 (IL-31) has been implicated as a critical cytokine involved in pruritus associated with AD in several species, including humans and dogs.[4–10] Some of the most commonly used systemic treatments for AD in dogs, including corticosteroids, ciclosporin and oclacitinib, decrease IL-31 or its effects in dogs, rodents or humans.[6,11–21] These data provide encouraging evidence that targeted neutralization of IL-31 with a monoclonal antibody (mAb) will provide relief from AD-related pruritus and inflammation, with the possibility of improved safety over less targeted therapies.

Lokivetmab (ZTS-00103289) is a caninized, anti-canine IL-31 mAb that binds specifically to circulating IL-31, thereby inhibiting its binding to the IL-31 receptor.[22] Neutralization of IL-31 following subcutaneous (s.c.) administration of lokivetmab resulted in dose-related reduction in canine IL-31-induced pruritus in dogs for up to 8 weeks following a single dose.[23] An exploratory clinical trial in dogs with AD showed that s.c. administration of two doses of lokivetmab (2.0 mg/kg) at a 14 day interval reduced pruritus and skin lesion scores compared to placebo.[24] These results demonstrated for the first time that IL-31 is a key cytokine driving clinical signs of pruritus and inflammation in dogs with AD. The current randomized, placebo-controlled trial in client owned dogs with AD was designed to evaluate efficacy and safety, as assessed by veterinary clinicians and pet owners, of a single s.c. administration of three different doses of lokivetmab for 56 days. The specific aim of the study was to identify a lokivetmab dose that provided robust efficacy in reducing pruritus and the Canine Atopic Dermatitis Extent and Severity Index v3 (CADESI-03),[25] scores for at least 1 month.

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Conflict of Interest: All authors are employees of Zoetis Inc.

Materials and methods

Overview

The study was conducted in support of product registration by the United States Department of Agriculture. The protocol was approved by the relevant Institutional Animal Care and Use Committees in clinics situated within academic institutions. The protocol was reviewed and approved before study initiation by the Sponsor Ethical Review Board. The owners gave written informed consent for each dog to participate in the study.

Inclusion criteria

Dogs with AD were recruited from 15 referral clinics throughout the USA. Dogs were client owned, 12 months of age or older and in overall good health, apart from the AD, based on the initial (Day 0) physical examination, and weighed between 2 and 80 kg. Dogs were initially assessed for entry into the study by the owners based on a Visual Analog Scale (VAS) score of pruritus of at least 3 cm (10 cm scale) and by clinicians based on having a CADESI-03 score of at least 30 out of a possible 1240 points.

All dogs had a documented history of chronic, nonseasonal AD, based on established criteria.[3] Establishment of the diagnosis was made based upon compatible history and clinical signs, and exclusion of other diagnoses. Dogs underwent a diagnostic regimen, as determined by the clinician, sufficient to eliminate cutaneous adverse food reactions (CAFR), flea allergy dermatitis, bacterial or fungal dermatitis and/or otitis, internal and external parasitism, metabolic disease and other conditions as appropriate.

Dogs with concurrent conditions that required treatment could be enrolled if the treatment remained the same for at least the 6 weeks before the study and no change in medication was anticipated for the duration of the study. Dogs were flea-free at the time of the Day 0 visit and appropriate flea control/prevention was used throughout the study. Dogs being fed a hypoallergenic diet to manage previously diagnosed CAFR had to have been fed that diet for at least 6 weeks before Day 0, must have remained on the same diet during the study, avoided potential food allergen sources identified during dietary restriction testing and the CAFR must have been controlled by the hypoallergenic diet. All dogs (regardless of food allergy status) were fed their same diet for the duration of the study. If an intradermal allergen test had been conducted, it must have been completed at least 8 weeks before the start of the study. Concomitant allergen specific immunotherapy (ASIT) had to have been ongoing for at least 8 months before enrolment and the protocol must have been maintained throughout the study. If ASIT was discontinued, it must have been discontinued at least 8 weeks before enrolment.

Prohibited and conditionally allowed medications and therapies

Withdrawal times for prohibited medications were as follows: oclacitinib (Apoquel®; Zoetis Inc., Kalamazoo, MI, USA), 8 weeks; long acting injectable corticosteroids, 6 weeks; oral corticosteroids, cyclosporin, long acting injectable antimicrobial agents and miscellaneous compounds with known antipruritic activity [including Staphage Lysate (SPL®, Delmont Laboratories Inc.; Swarthmore, PA, USA), gabapentin, monoamine oxidase inhibitor and tacrolimus], 4 weeks; topical nonsteroidal anti-inflammatory drugs and topical glucocorticoids, 3 weeks; antihistamines, 2 weeks; and oral antibacterial/antifungal agents and topical anaesthetics, 1 week. Other medications and therapies were conditionally allowed, assuming that the owners, clinicians and other study personnel adhered to all minimal use and frequency of use guidelines for the concomitant medication (Table S1).

Exclusion criteria

Exclusion criteria included dogs with evidence of malignant neoplasia, evidence of demodicosis within the past year, evidence of immune suppression such as hyperadrenocorticism, dogs that should have been receiving systemic antimicrobial therapy for bacterial or fungal skin infections, and lactating bitches or dogs (male or female) intended for use as breeding animals.

Randomization and masking

Enrolled dogs were randomized to one of four treatment groups (placebo or lokivetmab at a dose of 0.125, 0.5 or 2.0 mg/kg) at an equal ratio at each clinic using the random uniform function (RANUNI) of SAS v9.2 (SAS Institute Inc.; Cary, NC, USA). Blocking was based on order of enrolment within clinic such that the first four dogs enrolled at a given clinic formed the first block at that clinic. Dog was the experimental unit. Clinicians and all site personnel, with the exception of the treatment dispenser, were masked to the treatment group assignments, as were owners and the laboratory personnel. Placebo and lokivetmab were stored refrigerated (2–8°C) before use. The treatment dispenser utilized a treatment randomization file that was unique to the site to determine the treatment group assignment and then drew up the correct dose of treatment into a syringe and provided it to the clinician for administration.

Treatment administration

Lokivetmab was provided in ready to use one mL single use vials that contained no preservative. The placebo was identical in appearance to lokivetmab and contained all of the same excipients except for lokivetmab.

Study schedule and variables measured

Following randomization, dogs were assigned to receive either placebo or lokivetmab at a dose of 0.125, 0.5 or 2.0 mg/kg. Dogs with worsening pruritus and/or AD could be withdrawn from the study to start conventional treatment as prescribed by the clinician.

Baseline data (demographic, physical examination, assessments of pruritus and dermatitis) were collected on enrolment at Day 0. A VAS score, consisting of a 10 cm line with word descriptors at 2 cm intervals, was used by dog owners to assess the severity of the 'itch'. Owners were instructed to place a mark on the VAS line at the location that best represented their dog's pruritus. The distance (in centimetres) from the bottom of the line ('normal dog') to the owner's mark on the line was recorded. Owners performed a VAS assessment on days 0, 1, 2, 3, 7, 14, 21, 28, 35, 42, 49 and 56. CADESI-03 scores were used by the clinicians to assess dermatitis and physical examinations were performed on days 0, 7, 14, 28, 42 and 56. Dogs were observed in the clinic for 30 min following each dose for signs of immediate hypersensitivity-like reactions (e.g. wheals, vomiting). Clinicians recorded adverse events reported by owners or identified on physical examination throughout the study.

On the final day of study (day 56 $\pm$ 3 days, or earlier for dogs withdrawn before Day 56), owners and clinicians assessed the dog's overall response to treatment (RTT). Improvement was assessed using a 10 cm VAS line, with a descriptor on one end of the line for 'no improvement' and a descriptor at the other end of the line for 'excellent results'. Owners and clinicians were instructed to place a mark on the VAS line at the location that best represented the effect of treatment on the dog's skin condition.[16] Blood samples [complete blood count, serum chemistry, anti-drug antibodies (ADAs) and lokivetmab concentrations] and urine samples for urinalysis and protein creatinine ratio were collected on Day 0 (before dosing) and on days 28 and 56. In addition to these time points, blood samples were collected for measurement of ADAs and lokivetmab concentrations on days 7, 14 and 42. Blood samples collected on Day 0 were also evaluated for free IL-31 serum concentrations. Blood and urine were collected again at the discretion of the clinician if the dog presented for an adverse event. All samples for haematology (complete blood count), serum chemistry, urinalysis and urine protein creatinine ratio were sent to one laboratory (Heska Corp.; Loveland, CO, USA). Predose serum samples were analysed for IL-31[6] and serum samples at each time point were analysed for lokivetmab and ADAs using validated methods by Zoetis Inc. (Kalamazoo, MI, USA).[23]

Sample size justification

Based on power calculations that accounted for randomized blocked study design and repeated measurements over time,[26] a minimum of 48 cases per treatment group was required to detect a significant difference at the 0.05 level of significance using a two-sided test with

at least 80% power. This assumed a 5% treatment success rate for the placebo group and a 50% treatment success rate for the lokivetmab group for treatment success for Owner Pruritus VAS, with 5% treatment success rate for the placebo group and at least 40% treatment success rate for the lokivetmab group for treatment success for CADESI-03.

Efficacy outcome measures

The effectiveness variables assessed were as follows: (i) treatment success, based on the Owner Pruritus VAS assessment and the clinician's CADESI-03 assessment; (ii) CADESI-03 score at each clinician assessment; (iii) VAS score at each owner assessment; and (iv) owner and clinician RTT VAS.

Treatment success was defined, using the Owner Pruritus VAS score and clinician's CADESI-03 score, as a 50% or greater score reduction in either score from baseline at Day 0, compared with the day of assessment. Dogs that were withdrawn from the study on or before each day of assessment due to worsening signs of AD (lack of efficacy) or for an adverse event believed to be related to the study treatment were considered to be treatment failures for both the Owner Pruritus VAS and clinician's CADESI scores. For continuous variables (including owner pruritus VAS, RTT VAS and clinician's CADESI-03 scores), dogs withdrawn from the study on or before each day of assessment due to worsening signs of AD (lack of efficacy) or for an adverse event believed to be related to the study drug were not included past the withdrawal time point.

In order to be included in the effectiveness analysis, dogs must have received placebo or lokivetmab (0.125, 0.5 or 2.0 mg/kg) on Day 0. No more than 40% of the total cases were permitted to enrol from any one site. To ensure that all treatments were replicated at each site and to ensure that blinding was maintained at all sites, clinics with less than one evaluable case in each treatment group were excluded from the effectiveness analyses. Those dogs with a protocol deviation that affected the collection or integrity of their efficacy data were also excluded from the analyses. Every effort was made to ensure that the same owner or clinician who performed the Day 0 assessment performed all subsequent VAS and CADESI-03 assessments.

Data analysis

Data were analysed using SAS v9.2 (SAS Institute). The level of significance was set at $P < 0.05$. Generalized mixed linear models described below were fit using PROC GLIMMIX. Mixed linear models described below were fit using PROC MIXED.

Treatment success variables were analysed using a generalized linear mixed effects model for repeated measures for a binomial distribution with logit link. The model included the fixed effect of treatment, time point and the treatment by time point interaction. The random effects included clinic, block within clinic, the interaction between clinic and treatment, animal within clinic, block and treatment, and the interaction between clinic, treatment and time. The proportion of success with 95% confidence interval for each treatment and the odds ratios with 95% confidence intervals comparing the treatments were reported at each time point. The covariance structure for the repeated measures for each response variable was selected based on the smallest AICC among the following structures: CS, AR(1), CSH, ARH(1), UN and SP(POW)(Time).

The Owner Pruritus VAS scores and clinician's CADESI-03 scores (continuous variables) were analysed using a mixed linear model for repeated measures. The model included the fixed effects of treatment, time point, the treatment by time point interaction and baseline covariate (centred Day 0 response). The random effects included clinic, block within clinic, the interaction between clinic and treatment, animal within clinic, block and treatment, the interaction between clinic, treatment and time, and error.

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

Frequency distributions by treatment groups were calculated regarding whether or not a dog was normal by CADESI-03 (obtained a score ≤ 15)[27] at least once post-treatment and regarding whether or not a dog achieved a level of pruritus ranging from "normal to very mild" by Owner Pruritus VAS (obtained a score of <3.5 cm).[28] Percentages of animals normal by CADESI or normal to mild by Owner Pruritus VAS were compared using a generalized linear mixed effects model for a binomial distribution with logit link. The model included the fixed effect of treatment and random effects for clinic, block within clinic, and the interaction between clinic and treatment. To be included in the efficacy analysis, clinics had to have at least one evaluable case in each treatment group.

Safety outcome measures

All enrolled dogs that were administered treatment were included in the safety summaries. For each continuous haematology and serum chemistry measure, summary statistics (mean, median, standard deviation, minimum and maximum) were calculated by treatment and time point. Frequencies of dogs reported to experience at least one adverse event were displayed by clinical sign for all unique terms. Frequencies of dogs receiving each concomitant medication over the course of the study were summarized.

Results

Demographics

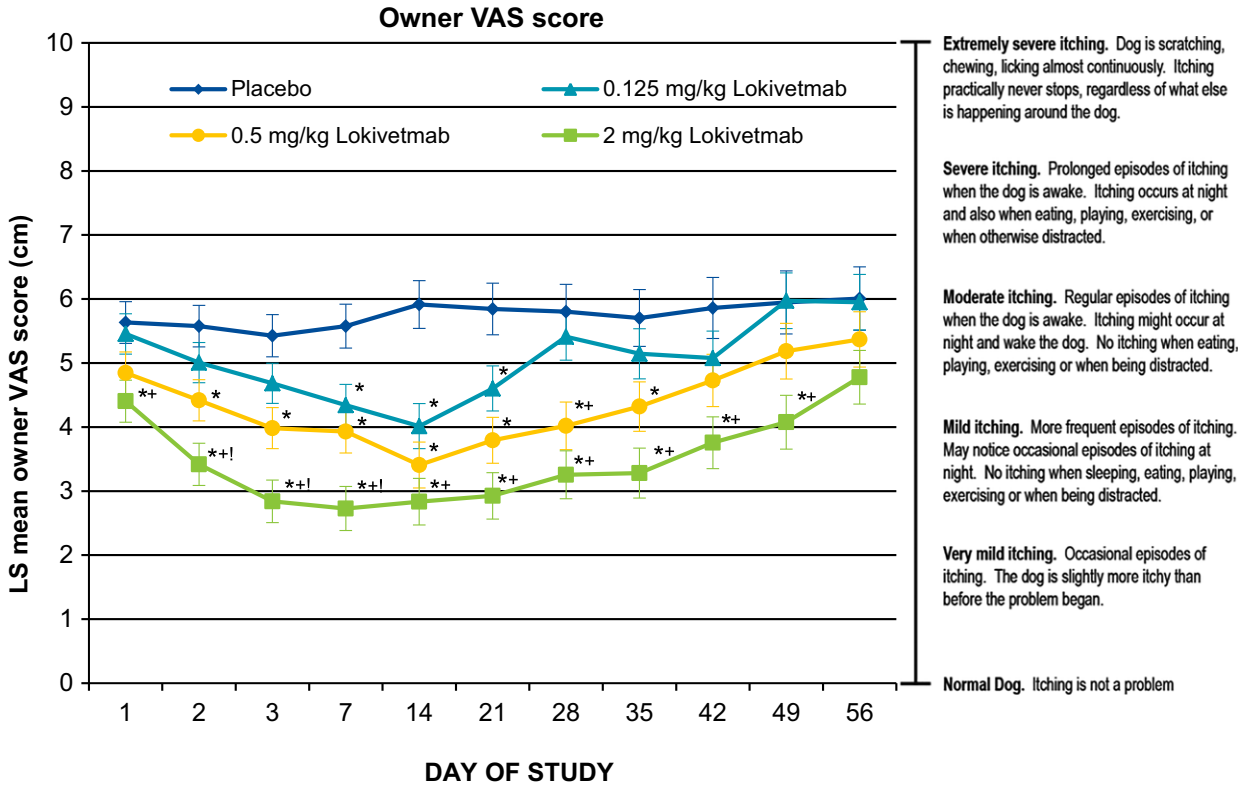
A total of 211 dogs were enrolled (Table S2). The breeds most commonly listed were Labrador retriever (20 purebred, 12 crossbred) followed by German shepherd (12 purebred, 4 crossbred), golden retriever (11 purebred, 2 crossbred) and shih tzu (12 purebred).

Assessment of effectiveness

The effectiveness dataset for treatment success at Day 28 comprised 185 dogs in the Owner Pruritus VAS dataset (47 for placebo and 50, 44 and 44 in the 0.125, 0.5 and 2.0 mg/kg lokivetmab-treated groups, respectively) and 193 dogs in the clinician's CADESI-03 dataset (49 for placebo and 51, 48 and 45 in the 0.125, 0.5 and 2.0 mg/kg lokivetmab-treated groups, respectively). The median number of evaluable cases per clinic was 12 (range 6–48). The datasets for all variables assessed changed at each time point as a result of errors in compliance with the trial and data collection protocols.

Owner Pruritus VAS

The clinic, the clinic-by-treatment interaction and the clinic-by-treatment-by-time interaction combined, accounted for no more than 3.4% of the total variation at any time point for the logit-transformed binomial response, strongly indicating the homogeneity of treatment effect across clinics (Table S3). A greater proportion of dogs administered lokivetmab achieved treatment success compared to those administered placebo at the following time points by treatment group ($P < 0.05$; range, $P < 0.0001$–0.0465): days 7–14 (0.125 mg/kg), days 2–28 (0.5 mg/kg), days 1–56 (2.0 mg/kg). At Day 28, the percentage of dogs with treatment success was 21% for 0.125 mg/kg, 32% for 0.5 mg/kg and 57% for 2 mg/kg lokivetmab-treated groups compared to 14% for the placebo-treated group ($P = 0.4171$, $P = 0.0450$, $P < 0.0001$, respectively). The 95% confidence intervals were 7–27%, 12–34%, 20–47% 42–71% for the placebo and 0.125, 0.5 and 2.0 mg/kg lokivetmab-treated groups, respectively; odds ratios for treatment differences



Lokivetmab (mg/kg)	Day 1	Day 2	Day 3	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56
	Number of dogs on study per treatment group										
0	48	48	44	44	39	26	28	22	23	22	20
0.125	50	49	50	51	46	46	42	31	31	27	28
0.5	46	47	48	49	44	43	41	36	35	26	28
2.0	46	46	44	45	45	44	42	35	38	32	33

Figure 1. Least squares mean Owner Pruritus Visual Analog Scale (VAS) scores (±SE) following subcutaneous administration of placebo or lokivetmab once on Day 0. * significantly different from placebo ($P < 0.05$; range, <0.0001–0.0192). + significantly different from 0.125 mg/kg lokivetmab ($P < 0.05$; range, <0.0001–0.0227). ! significantly different from 0.5 mg/kg lokivetmab ($P < 0.05$; range, 0.0111–0.0276). LS Mean, least squares mean; Day 0 arithmetic mean values by treatment group were 7.3 (placebo), 6.8 (0.125 mg/kg), 7.3 (0.5 mg/kg) and 7.0 (2.0 mg/kg).

compared to placebo were 1.541, 2.807 and 7.926, respectively.

Owner Pruritus VAS scores and percentage reduction from baseline

The mean Day 0 Owner Pruritus VAS scores were 7.3, 6.8, 7.3 and 7.0 cm for the placebo, 0.125, 0.5 and 2.0 mg/kg lokivetmab-treated dogs, respectively, corresponding to 'severe itching' on the enhanced Owner Pruritus VAS score (Figure 1). Percentage reduction from baseline in Owner Pruritus VAS scores is presented in Figure 2 by treatment group.

Percentage of dogs categorized as normal–very mild (<3.5 cm) for Owner Pruritus VAS scores for at least one time point post-treatment were greater for all lokivetmab-treated groups [0.125 mg/kg, $n = 30$ (56.6%) $P = 0.0222$; 0.5 mg/kg, $n = 31$ (62.0%) $P = 0.0088$; 2.0 mg/kg, $n = 40$ (85.1%) $P < 0.0001$] than for the placebo-treated group [$n = 15$ (30.6%)] (Table S4).

Clinician's CADESI-03

The clinic, the clinic-by-treatment interaction and the clinic-by-treatment-by-time interaction, accounted for 25.7%, 7.5% and 5.8% of the total variation, respectively, at any time point for the logit-transformed binomial response (Table S3). The lower percentages (<10%) for the clinic-by-treatment associated interactions support the relative homogeneity of treatment effect across clinics.

At Day 28, 46% of 2.0 mg/kg lokivetmab-treated dogs were considered to be a treatment success compared with 9% of placebo-treated dogs ($P = 0.0013$); 13% of 0.125 mg/kg and 22% of 0.5 mg/kg lokivetmab-treated dogs were a treatment success ($P > 0.05$). The 95% confidence intervals were 3–26%, 4–32%, 8–47% and 21–72% for placebo, 0.125, 0.5 and 2.0 mg/kg lokivetmab, respectively; odds ratios for treatment differences compared to placebo were 1.454, 2.823 and 8.321, respectively. A greater percentage of dogs achieved treatment success in the 2.0 mg/kg group compared to placebo

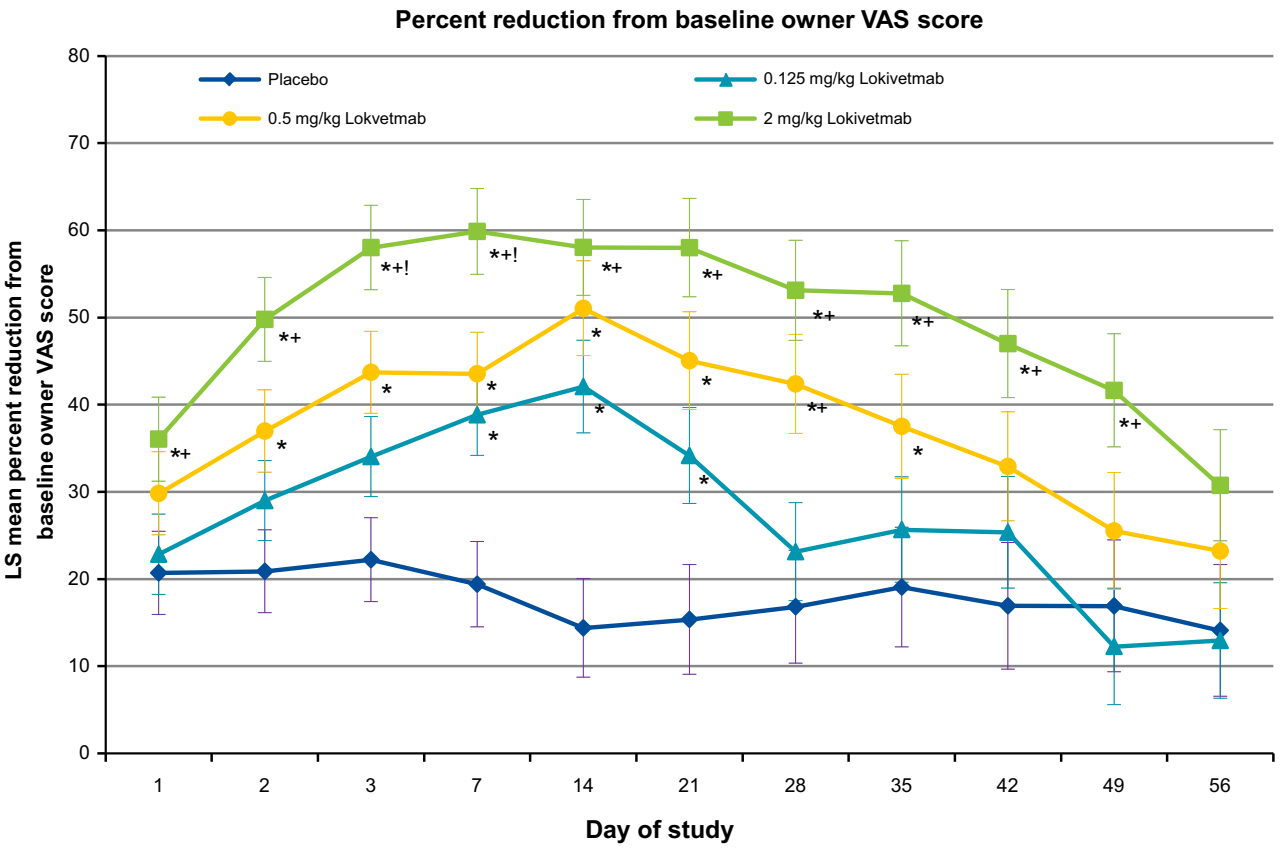


Figure 2. Percentage reduction from baseline Owner Pruritus Visual Analog Scale (VAS) score (±SE) following subcutaneous administration of placebo or lokivetmab once on Day 0. See Figure 1 for number of dogs on study per treatment group at each day of study. * significantly different from placebo ($P < 0.05$; range, <0.0001–0.0426); + significantly different from 0.125 mg/kg lokivetmab ($P < 0.05$; range, 0.0002–0.0467); ! significantly different from 0.5 mg/kg lokivetmab ($P<0.05$; range, 0.0167–0.0333).

from days 14–56 ($P < 0.05$; range, $P < 0.0013$–0.0301). There were no significant differences detected between placebo and the remaining dose groups.

Clinician CADESI-03 scores and percentage reduction from baseline

The mean Day 0 Clinician CADESI-03 scores were 145, 141, 168, and 163 for the placebo and 0.125, 0.5 and 2.0 mg/kg lokivetmab-treated dogs, respectively, corresponding to the 'severe' CADESI-03 category (Figure 3).[27] Percentage reduction from baseline in CADESI-03 scores for placebo-treated and lokivetmab-treated dogs is presented in Figure 4.

The clinic, the clinic-by-treatment interaction and the clinic-by-treatment-by-time interaction, accounted for no more than 14.5%, 4.3% and 0.24% of the total variation, respectively, at any time point (Table S3). The low percentages (<5%) for the clinic-by-treatment associated interactions support the relative homogeneity of treatment effect across clinics. There were no differences among treatment groups for the percentage of dogs categorized as normal (≤15 of a possible score of 1240) for CADESI-03 scores post treatment ($P > 0.05$).

Free serum IL-31

Day 0 serum IL-31 concentrations were above the lower limit of quantitation (LLOQ; 0.020 ng/mL) in 17.5% (37/211) of dogs. Of these, the mean IL-31 concentration was 0.27 ng/mL (median, 0.06 ng/mL; range, 0.020–3.1 ng/mL); serum IL-31 concentrations were >1.0 ng/mL in two of the 37 dogs. Serum IL-31 concentrations following lokivetmab administration were not measured due to limitations of assay sensitivity and specificity.

Pharmacokinetic data and immunogenicity

Following a 2.0 mg/kg dose of lokivetmab, the mean peak serum concentration, 10 μg/mL, was observed at a mean of 9.8 days following administration. The mean terminal elimination half-life was 16 days. Covariates for weight, age, sex, purebred (yes, no) and food allergy (yes, no) were not found to affect exposure in a clinically meaningful way.

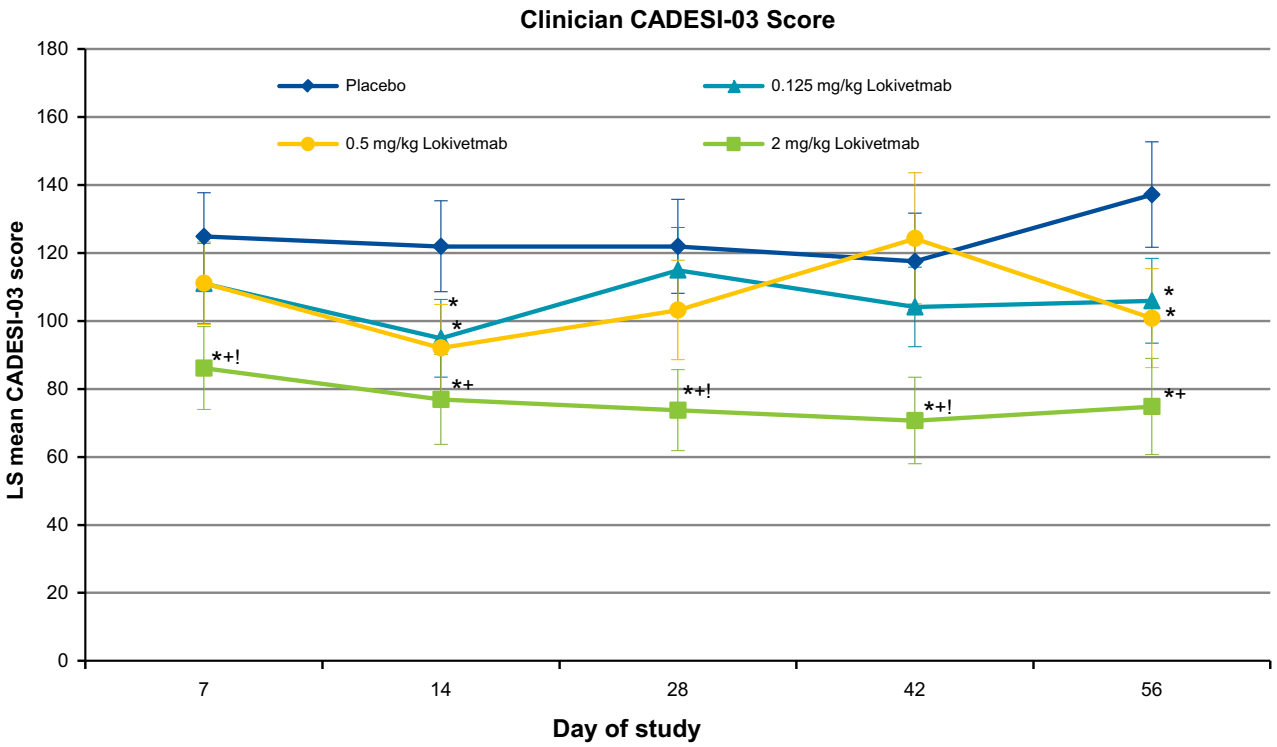
No dogs were found to have developed treatment-induced immunogenicity.

Response to treatment (RTT)

The mean Owner RTT VAS scores and Clinician RTT VAS scores at the end of the study were improved ($P \leq 0.0185$) following treatment with lokivetmab at all dose levels compared with placebo (Table 1).

Safety assessment

The safety assessment comprised a summary of the adverse events, clinical pathology results and change in body weight from Day 0 to Day 56. All 211 dogs enrolled in the study were included in the summaries. Table 2 shows the number of dogs enrolled, the number of dogs



Lokivetmab (mg/kg)	Day 7	Day 14	Day 28	Day 42	Day 56
	Number of dogs on study per treatment group				
0	49	41	30	24	23
0.125	53	47	43	30	29
0.5	50	47	45	35	30
2.0	47	45	43	40	34

Figure 3. Clinician Canine Atopic Dermatitis Extent and Severity Index v3 (CADESI-03) scores (±SE) following subcutaneous administration of placebo or lokivetmab once on Day 0. * significantly different from placebo ($P < 0.05$; range, $P < 0.0001$–0.0184). + significantly different from 0.125 mg/kg lokivetmab ($P < 0.05$; range, $P < 0.0001$–0.0497). ! significantly different from 0.5 mg/kg lokivetmab ($P < 0.05$; range, 0.0027–0112). LS Mean, least squares mean; Day 0 arithmetic mean values by treatment group were 145 (placebo), 141 (0.125 mg/kg), 168 (0.5 mg/kg) and 163 (2.0 mg/kg).

withdrawn before completion and the reason for withdrawal.

Adverse events

All 211 dogs were included in the safety assessments. There was an inverse relationship between dose level of lokivetmab and the proportion of dogs in each treatment group that remained on study at each visit (Table 2), thus confounding a between-group comparison of adverse events (Table 3). Despite the dose-related difference in time on study, Table 3 provides a direct comparison of adverse events that occurred in >2% of dogs in any treatment group. The vomiting, diarrhoea, lethargy, anorexia and anxiety resolved spontaneously in 87% of cases, with the remaining cases responsive to supportive care. All reports of pyoderma, dermatitis and otitis externa were classified by the clinicians as "mild" or "moderate" in severity; collection of follow-up data until resolution post-study, when dogs were permitted treatment with, for example, systemic antibiotics or glucocorticoids, was not conducted as part of this study.

There were no hypersensitivity-related reactions (e.g. wheals, vomiting) reported immediately post-dosing. One dog (2.0 mg/kg lokivetmab), a 4-year-old male dachshund mixed breed dog that had been on weekly ASIT for the past year, had a possible injection site reaction comprising two subcutaneous nodules near the site of injection beginning on Day 5 that resolved spontaneously by Day 42 without treatment; causality was confounded by concomitant use of SC ASIT that was discontinued at the time of the reaction. The remaining reported adverse events occurred in no more than one dog per group; of these, there were two events considered by the clinician to be severe. The first dog (0.5 mg/kg lokivetmab) had haemorrhage associated with iatrogenic laceration of a body wall vessel following cystocentesis at the Day 56 visit and recovered with hospitalization and treatment. The second dog (0.5 mg/kg lokivetmab) had pre-existing

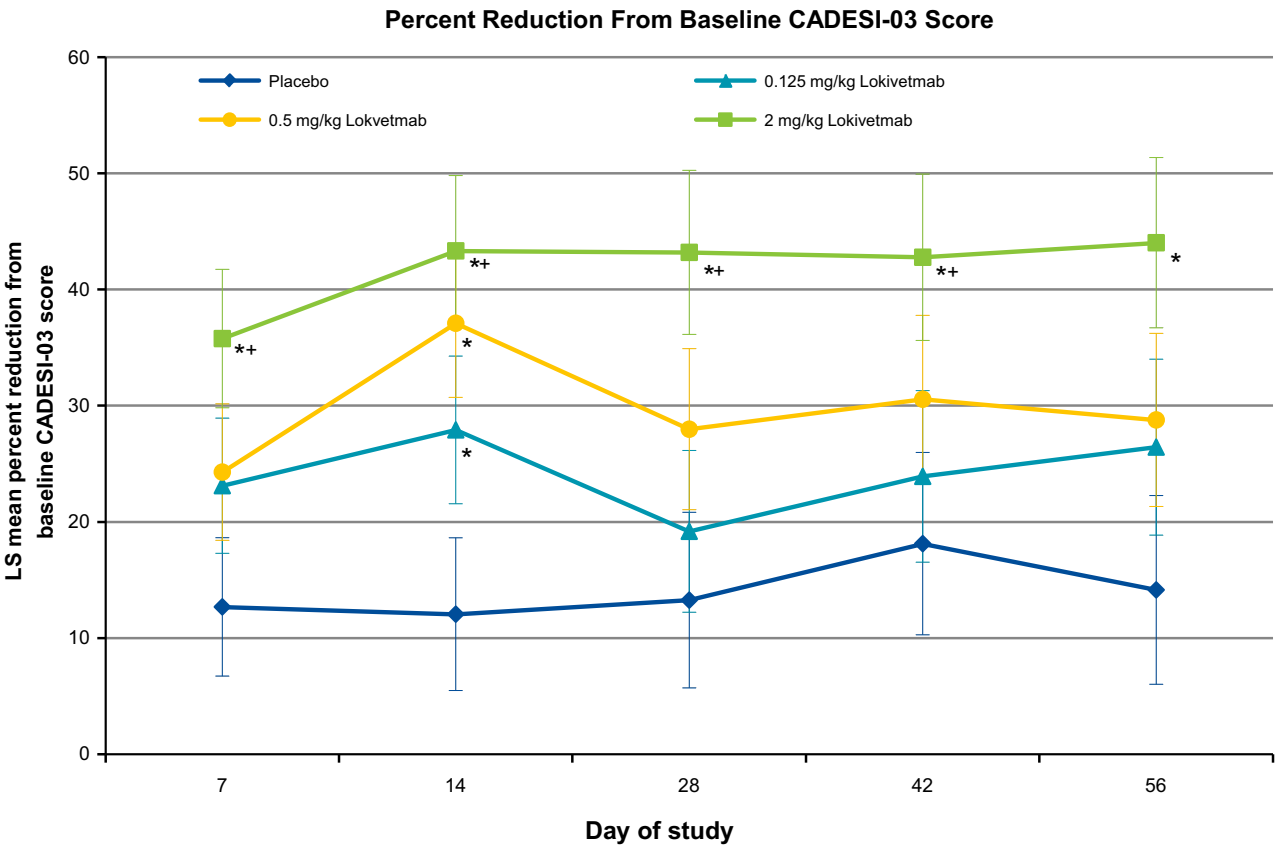


Figure 4. Percentage reduction from baseline clinician Canine Atopic Dermatitis Extent and Severity Index, v3 (CADESI-03) scores (±SE) following subcutaneous administration of placebo or lokivetmab once on Day 0. See Figure 3 for number of dogs on study per treatment group at each day of study. * significantly different from placebo ($P < 0.05$; range, <0.0001–0.0307); + significantly different from 0.125 mg/kg lokivetmab ($P < 0.05$; range, 0.0040–0.0438).

Table 1. Response of dogs to treatment with placebo or lokivetmab in terms of Visual Analog Scores (VAS) at the end of the study (or earlier if withdrawn before Day 56)

	Owner's RTT VAS [cm; mean ± SE (*n*)]	*P*-value*	Clinicians RTT VAS [cm; mean ± SE (*n*)]	*P*-value
Placebo†	2.4 ± 0.49 (49)	–	2.6 ± 0.55 (50)	–
Lokivetmab†				
0.125 mg/kg	4.3 ± 0.49 (49)	0.0082	4.1 ± 0.55 (49)	0.0185
0.5 mg/kg	5.4 ± 0.49 (49)	<0.0001	4.4 ± 0.55 (48)	0.0059
2.0 mg/kg	7.4 ± 0.51 (46)	<0.0001	6.5 ± 0.56 (46)	<0.0001

RTT, response to treatment.
*Difference compared to placebo.
†Least squares means ± SE.

bilateral pinnal irritation and otitis externa but the severity for right pinna irritation became severe on Day 24; the dog was withdrawn in order to administer medications not permitted by the study.

Reasons for withdrawal before Day 56 are provided in Table 2. No cases were withdrawn due to abnormal clinical pathology results or for adverse events considered by the clinician to be related to drug treatment. Two cases were withdrawn early for an unrelated medical condition. Of these, one had worsening clinical signs of a pre-existing urinary tract infection on Day 26 and was withdrawn so that oral antibiotics could be initiated. The second dog had moderate cellulitis involving one digit on Day 18. Oral antibiotics and topical antiseptic were initiated on Day 25; the dog was withdrawn at the Day 28 visit and cellulitis was reported to have resolved 2 weeks later. Four cases were withdrawn due to owner noncompliance and three were withdrawn at the Day 7 visit because they were inadvertently administered 0.5 mg/kg lokivetmab instead of placebo ($n = 2$) or 0.5 mg/kg lokivetmab instead of 2.0 mg/kg lokivetmab ($n = 1$). Any adverse events that occurred before withdrawal were included in the summaries for the actual dose level administered. There was a tendency towards a slight increase in body weight with increasing dose of lokivetmab.

Haematology, serum chemistry, urinalysis and urine protein:creatinine ratio

Arithmetic mean values for all haematology, serum chemistry analytes and urine protein:creatinine ratio in all treatment groups fell within the laboratory's normal reference range for that analyte at all visits (days 0, 28 and 56).

Concomitant medications

A wide variety of concomitant medications were used in this study. The most frequently used concomitant medications (i.e. ≥6% of any lokivetmab-treated group) are summarized by drug class and treatment group in Table S5. There were no clinically apparent adverse

Table 2. Study completion and reasons for early withdrawal

Treatment Group	Total *N* (%)	Completed 56 day study [*n* (%)]	Withdrawn from study before Day 56 [*n* (%)]		
			On or before Day 17	Day 18–31	Day 32–56
Placebo	52 (100.0)	25 (48.1)	18 (34.6)	6 (11.5)	3 (5.8)
Lokivetmab					
0.125 mg/kg	55 (100.0)	31 (56.4)	6 (10.9)	12 (21.8)	6 (10.9)
0.5 mg/kg	54 (100.0)	32 (59.3)	6 (11.1)	8 (14.8)	8 (14.8)
2.0 mg/kg	50 (100.0)	36 (72.0)	2 (4.0)	6 (12.0)	6 (12.0)

Treatment group	Reason for withdrawal from study before Day 56 [*n* (%)]			
	Worsening signs of AD	Unrelated medical condition	Owner noncompliance	Other
Placebo	27 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lokivetmab				
0.125 mg/kg	22 (91.7)	0 (0.0)	2 (8.3)	0 (0.0)
0.5 mg/kg	17 (77.3)	2 (9.1)	1 (4.5)	2 (9.1)
2.0 mg/kg	12 (85.7)	0 (0.0)	1 (7.1)	1 (7.1)

Table 3. Adverse events occurring at least once and in greater than 2% of any treatment group over the course of the 56 day study

Adverse events observed during days 0–56*	Placebo (*n* = 52) [*n* (%)]	Lokivetmab (mg/kg)		
		0.125 (*n* = 55) [*n* (%)]	0.5 (*n* = 54) [*n* (%)]	2.0 (*n* = 50) [*n* (%)]
Vomiting	1 (1.9)	3 (5.5)	2 (3.7)	4 (8.0)
Diarrhoea	0 (0.0)	1 (1.8)	2 (3.7)	3 (6.0)
Pyoderma	2 (3.8)	4 (7.3)	3 (5.6)	2 (4.0)
Lethargy	0 (0.0)	1 (1.8)	0 (0.0)	2 (4.0)
Anorexia	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)
Dermatitis	2 (3.8)	0 (0.0)	4 (7.4)	1 (2.0)
Otitis externa	2 (3.8)	1 (1.8)	3 (5.6)	1 (2.0)
Anxiety	0 (0.0)	0 (0.0)	2 (3.7)	0 (0.0)
Aural haematoma	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)

*Adverse events were tabulated per animal.

interactions with administered concomitant medications and lokivetmab.

Discussion

The current trial in client owned dogs with AD evaluated reduction in Owner Pruritus VAS and clinician assessed CADESI-03 scores for 56 days following administration of a single s.c. dose of lokivetmab at each of three dose levels compared to a placebo control. The results showed that the magnitude and duration of efficacy was dose-related up to 2.0 mg/kg, the highest dose studied. A reduction in pruritus scores compared to placebo for at least 1 month was achieved in the 0.5 mg/kg and 2.0 mg/kg groups ($P < 0.05$) but not in the 0.125 mg/kg group. Based on the observed results, s.c. administration of 2.0 mg/kg lokivetmab to dogs with AD resulted in decreased pruritus within 1 day, decreased CADESI-03 scores within 7 days and continued robust efficacy in most dogs for at least 1 month following a single dose.

Several studies in humans have reported a correlation between serum IL-31 levels and severity of AD,[7,29,30] although another study reported no correlation with either disease severity or itch intensity.[31] A study conducted to characterize the inflammatory transcriptome of experimental acute canine AD lesions demonstrated significant upregulation of genes encoding IL-31 along with a number of other cytokines.[32] The frequency of dogs with AD having serum IL-31 concentrations above the LLOQ in prior studies have ranged from 7%[24] to 57%.[6] Although IL-31 serum levels were below the LLOQ (20 pg/ml) in most dogs in the current study, the observed clinical improvement following lokivetmab therapy supports that IL-31 is an important cause of pruritus and exacerbation of skin lesions in dogs with AD. The authors believe that clinically meaningful levels of circulating IL-31 may be present in most dogs with AD but at concentrations below current limits of quantitation which warrants further work on more sensitive assays. Results of the current study lend promise that inhibition of IL-31 may be an effective treatment for other pruritic conditions in dogs that have not been reported to be associated with elevated serum IL-31, such as flea allergy dermatitis.[6]

The results of this study support a lack of cytokine redundancy for IL-31's role in pruritus in dogs with AD. Neutralization of IL-31 alone resulted in improved pruritus and CADESI-03 scores compared to placebo at the earliest time points measured (days 1 and 7, respectively) in the 2.0 mg/kg lokivetmab-treated group. Notably, CADESI-03 scores were improved compared to placebo at a lokivetmab dose as low as 0.125 mg/kg (Day 14). Administration of oclacitinib (Apoquel®), a JAK1 inhibitor possessing pronounced anti-inflammatory efficacy, to dogs with AD resulted in decreased pruritus and CADESI-02 scores within one and 14 days (the earliest time points measured), respectively.[16,33] The magnitude and rapid onset of effect of lokivetmab in reducing pruritus in the current study provide further confirmation that IL-31 is a critical pruritogenic cytokine in dogs with AD; likewise, the magnitude and rapid onset of effect in reducing CADESI-03 scores is consistent with suppression of pro-inflammatory effects of IL-31 and underscores the important role of IL-31 in canine AD.

As expected based on lokivetmab's high affinity and specificity for soluble IL-31,[34] there was no clinical evidence of interference with efficacy or adverse interactions when administered with other currently available therapeutic products.[24,35] Additional studies are needed

to determine if a combination of lokivetmab with other treatments that inhibit IL-31 function but require a tapering dose, such as corticosteroids, ciclosporin or oclacitinib, will result in an additive therapeutic effect.

The reported adverse events involving 159 dogs treated with lokivetmab do not indicate any specific safety concern associated with treatment. The proportion of dogs that discontinued the study before Day 56 was dose-related largely due to worsening signs of AD in the placebo- and 0.125 mg/kg lokivetmab-treated groups, as expected in a study designed to evaluate dose response and duration of efficacy (Table 2). A direct comparison of adverse event frequencies between groups in this study is difficult due to the low number of events and the bias in the placebo group due to early withdrawals. Although a hypersensitivity reaction (e.g. wheals, vomiting) following repeated injection of any protein is possible, none were observed in the current single dose study. In addition, no treatment-induced immunogenicity was observed and there was no apparent treatment-related effect on clinical pathology results. A subsequent study was conducted to evaluate the safety of lokivetmab compared to placebo.[35]

Neutralization of canine IL-31 by the therapeutic mAb, lokivetmab, represents a targeted treatment option for dogs with AD with the possibility of improved safety over therapies such as corticosteroids that are not as specifically targeted and can have negative impacts on multiple body systems. The level and duration of response varied among individuals across the dose levels tested, although a minimum dose of 0.5 mg/kg provided significant improvement in pruritus compared to placebo for at least 1 month in most dogs. Further studies are needed to better understand the variability in individual responses in a broader population of dogs with AD, and to evaluate safety and efficacy following repeat dosing in dogs with AD. The duration of effectiveness will likely vary in individual patients. The rapid onset of effect following s.c. administration and continued robust efficacy for at least 1 month in most dogs in the current study supports a dosing regimen that will encourage regular veterinary monitoring of dogs with chronic AD.

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References

1. Halliwell REW. Revised nomenclature for veterinary allergy. *Vet Immunol Immunopathol* 2006; 114: 207–208.
2. Bizikova P, Santoro D, Marsella R et al. Review: clinical and histological manifestations of canine atopic dermatitis. *Vet Dermatol* 2015; 26: 79–e24.
3. Favrot C, Steffan J, Seewald W et al. A prospective study on the clinical features of chronic canine atopic dermatitis and its diagnosis. *Vet Dermatol* 2010; 21: 23–31.
4. Cevikbas F, Kempkes C, Buhl T et al. Chapter 13. Role of Interleukin-31 and oncostatin M in itch and neuroimmune communication. In: Carstens E, Akiyama T, eds. *Itch: Mechanisms and Treatment*. Boca Raton, FL: CRC Press/Taylor & Francis, 2014. Available at http://www.ncbi.nlm.nih.gov/books/NBK200913/. Accessed June 22, 2016.
5. Cevikbas F, Wang X, Akiyama T et al. A sensory neuron-expressed IL-31 receptor mediates T helper cell-dependent itch: involvement of TRPV1 and TRPA1. *J Allergy Clin Immunol* 2014; 133: 448–460.
6. Gonzales AJ, Humphrey WR, Messamore JE et al. Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol* 2013; 24: 48–53, e11–2.
7. Raap U, Wichmann K, Bruder M et al. Correlation of IL-31 serum levels with severity of atopic dermatitis. *J Allergy Clin Immunol* 2008; 122: 421–423.
8. Rossbach K, Baumer W. PCR detects bands consistent with the expression of receptors associated with pruritus in canine dorsal root ganglia. *Vet Dermatol* 2014; 25: 9–e4.
9. Dillon SR, Sprecher C, Hammond A et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol* 2004; 5: 752–760.
10. Cornelissen C, Luscher-Firzlaff J, Baron JM et al. Signaling by IL-31 and functional consequences. *Eur J Cell Biol* 2012; 91: 552–566.
11. Fleck T, Humphrey W, Coscarelli E et al. Comparison of the janus kinase (JAK) inhibitor, oclacitinib, and prednisolone in canine models of pruritus. *Vet Dermatol* 2012; 23 (Suppl 1): 38. (Abstract).
12. Hwang JS, Kim GC, Park E et al. NFAT1 and JunB cooperatively regulate IL-31 gene expression in CD4 + T cells in health and disease. *J Immunol* 2015; 194: 1963–1974.
13. Otsuka A, Tanioka M, Nakagawa Y et al. Effects of cyclosporine on pruritus and serum IL-31 levels in patients with atopic dermatitis. *Eur J Dermatol* 2011; 21: 816–817.
14. Cohn L. The influence of corticosteroids on host defense mechanisms. *J Vet Intern Med* 1991; 5: 95–104.
15. Barnes PJ. Corticosteroids: the drugs to beat. *Eur J Pharmacol* 2006; 533: 2–14.
16. Cosgrove SB, Wren JA, Cleaver DM et al. A blinded, randomized, placebo-controlled trial of the efficacy and safety of the Janus kinase inhibitor oclacitinib (Apoquel®) in client-owned dogs with atopic dermatitis. *Vet Dermatol* 2013; 24: 587–597, e141–2
17. Cedeno-Laurent F, Singer EM, Wysocka M et al. Improved pruritus correlates with lower levels of IL-31 in CTCL patients under different therapeutic modalities. *Clin Immunol* 2015; 158: 1–7.
18. Vocca L, Di Sano C, Uasuf CG et al. IL-33/ST2 axis controls Th2/IL-31 and Th17 immune response in allergic airway diseases. *Immunobiology* 2015; 220: 954–963.
19. Kyoya M, Kawakami T, Soma Y. Serum thymus and activation-regulated chemokine (TARC) and interleukin-31 levels as biomarkers for monitoring in adult atopic dermatitis. *J Dermatol Sci* 2014; 75: 204–207.
20. Gonzales AJ, Bowman JW, Fici GJ et al. Oclacitinib (APOQUEL®) is a novel Janus kinase inhibitor with activity against cytokines involved in allergy. *J Vet Pharmacol Ther* 2014; 37: 317–324.
21. Olivry T, Bizikova P. A systematic review of randomized controlled trials for prevention or treatment of atopic dermatitis in dogs: 2008-2011 update. *Vet Dermatol* 2013; 24: 97–117, e25–6.
22. Fleck TJ, Bammert G, Shelly J et al. Identification and characterization of ZTS-00103289, a monoclonal antibody neutralizing IL-

31-mediated pruritus, in beagle dogs. *Vet Dermatol* 2015; 26: 147. (Abstract).
23. Walters RR, Boucher JP, Paquette JA et al. Laboratory dose titration efficacy study of ZTS-00103289, a caninized anti-IL-31 monoclonal antibody, in a canine model of IL-31-induced pruritus. *Vet Dermatol* 2015; 26: 145. (Abstract).
24. Michels GM, Ramsey DS, Mahabir S et al. Proof of concept efficacy and safety study of an anti-IL-31 monoclonal antibody for the treatment of atopic dermatitis in client-owned dogs. *Vet Dermatol* 2015; 26: 138. (Abstract).
25. Olivry T, Marsella R, Iwasaki T et al. Validation of CADESI-03, a severity scale for clinical trials enrolling dogs with atopic dermatitis. *Vet Dermatol* 2007; 18: 78–86.
26. Stroup WW. Mixed model procedures to assess power, precision, and sample size in the design of experiments. Muncie, IN: Midwest Biopharmaceutical Statistics Workshop, 1999; 15–24. Available at http://citeseerx.ist.psu.edu/viewdoc/download?-doi=10.1.1.546.1468&rep=rep1&type=pdf. Accessed June 22, 2016.
27. Olivry T, Mueller R, Nuttall T et al. Determination of CADESI-03 thresholds for increasing severity levels of canine atopic dermatitis. *Vet Dermatol* 2008; 19: 115–119.
28. Rybnicek J, Lau-Gillard P, Harvey R et al. Further validation of a pruritus severity scale for use in dogs. *Vet Dermatol* 2009; 20: 115–122.
29. Ezzat MH, Hasan ZE, Shaheen KY. Serum measurement of interleukin-31 (IL-31) in paediatric atopic dermatitis: elevated levels correlate with severity scoring. *J Eur Acad Dermatol Venereol* 2011; 25: 334–339.
30. Raap U, Weiβmantel S, Gehring M et al. IL-31 significantly correlates with disease activity and Th2 cytokine levels in children with atopic dermatitis. *Pediatr Allergy Immunol* 2012; 23: 285–288.
31. Siniewicz-Luzenczyk K, Stanczyk-Przyluska A, Zeman K. Correlation between serum interleukin-31 level and the severity of disease in children with atopic dermatitis. *Postepy Dermatol Alergol* 2013; 30: 282–285.
32. Olivry T, Paps JS, Linder KE et al. Characterization of the pro-inflammatory transcriptome in experimental canine acute atopic skin lesions. *Vet Dermatol* 2015; 26: 298. (Abstract).
33. Apoquel [Package insert]. Kalamazoo, MI, USA: Zoetis Inc.; 2013. https://www.zoetisus.com/apoquel-pet-owner/pdfs/apoquel_pi.pdf. Accessed July 18, 2016.
34. Ehrenmann F, Kaas Q, Lefranc M-P. IMGT/3Dstructure-DB and IMGT/DomainGapAlign: a database and a tool for immunoglobulins or antibodies, T cell receptors, MHC, IgSF and MhcSF. *Nucleic Acids Res* 2010; 38 (Database issue): D301–D307.
35. Michels GM, Walsh KF, Kryda K et al. A blinded, randomized, placebo-controlled trial of the safety of lokivetmab (ZTS-00103289), a caninized anti-canine IL-31 monoclonal antibody, in client owned dogs with atopic dermatitis. *Vet Dermatol* 2016. DOI: 10.1111/vde.12364 [Epub ahead of print].

Supporting Information

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

Table S1. Conditionally allowed medications and therapy.

Table S2. Demographics of enrolled dogs at day 0.

Table S3. Variance estimates of the random effects for the mixed effects repeated measures models.

Table S4. Percentage of dogs with normal to very mild owner pruritus VAS scores (0–3.4 cm/10 cm) by treatment group following subcutaneous administration of placebo or lokivetmab once on Day 0.

Table S5. Concomitant medications and therapies administered at least once in at least 6% of any lokivetmab group over the course of the 56 day study.

Résumé

Contexte – Le prurit est le signe clinique majeur de la dermatite atopique (AD) chez le chien. Le lokivetmab, un anticorps monoclonal anti IL-31 canin, réduit le prurit et les lésions inflammatoires cutanées associées dans une étude POC (proof of concept) chez le chien atopique.

Hypothèse/Objectifs – L'objectif était de décrire la réponse dose dépendante au lokivetmab dans une étude contrôlée contre placebo, en double aveugle, randomisée.

Sujets – Les cliniciens de 15 cliniques de référé ont enrôlés 211 c-chiens de propriétaires ayant des antécédents de AD chronique.

Méthodes – Les chiens ont été randomisés au traitement au lokivetmab (0.125, 0.5 ou 2.0 mg/kg) ou placebo administré en sous cutané une fois à jour 0. Les propriétaires ont évalués un score de prurit sur une VAS (échelle visuelle analogue à jours 0, 1, 2, 3, 7, 14, 21, 28, 35, 42, 49 et 56. Les cliniciens ont évalués un CADESI-03 (Canine AD Extent and Severity Index) à jours 0, 7, 14, 28, 42 et 56.

Résultats – Le traitement au lokivetmab (2 mg/kg) résultait en une meilleure réduction du pourcentage de la baseline dans le prurit évalué par le propriétaire (jours 1-49) et les scores de CADESI-03 évalués par le cliniciens (jours 7-56) comparé au placebo ($P < 0.05$); les différences ont été atteintes dans des groupes de plus petite dose mais avec des temps plus tardifs et pour une plus courte durée à la fois pour les prurit évalué par les propriétaires (0.5 mg/kg, jours 2–35; 0.125 mg/kg, jours 7–21) et les scores CADESI-03 évalués par les cliniciens (0.5 mg/kg and 0.125 mg/kg, jour 14).

Conclusions et importance clinique – Le lokivetmab (0.5, 2.0 mg/kg) réduit le prurit comparé au placebo pour au moins 1 mois. Le niveau et la durée de la réponse augmente avec l'augmentation de la dose. D'autres études sont nécessaires pour mieux comprendre la variabilité des réponses individuelles dans une population plus large de chiens atopiques.

Resumen

Introducción – El prurito es el síntoma clínico más distintivo de la dermatitis atópica (AD) en perros. Lokivetmab, un anticuerpo monoclonal anti-IL-31 canina canonizado, redujo el prurito y las lesiones cutáneas inflamatorias asociadas en un estudio de prueba de concepto en perros con AD.

Hipótesis/Objetivos – El objetivo fue describir la dosis de respuesta de lokivetmab en un estudio doble ciego, al azar, controlado con placebo.

Animales – veterinarios clínicos en 15 clínicas de referencia inscribieron 211 perros de clientes privados con una historia de AD crónica.
Métodos – Los perros fueron asignados al azar a tratamiento con lokivetmab (0,125, 0,5 o 2,0 mg/kg) o placebo administrado por vía subcutánea una vez en el día 0. Los dueños de los perros evaluaron los valores de prurito con una escala análoga visual (VAS) de prurito en los días 0, 1, 2, 3, 7, 14, 21, 28, 35, 42, 49 y 56. Los clínicos evaluaron el prurito según el índice de extensión y severidad de AD (CADESI-03) en los días 0, 7, 14, 28, 42 y 56.
Resultados – El tratamiento con lokivetmab (2 mg/kg) produjo la mayor reducción porcentual respecto al valor basal en la evaluación del prurito por los dueños (días 1-49) y el valor de CADESI-03 según los clínicos (días 7-56) en comparación con el placebo (P <0,05) ; se lograron diferencias en los grupos de dosis más bajas, pero en puntos de tiempo posteriores y de duración más corta tanto para el prurito evaluado por los propietarios (0,5 mg / kg, días 2-35; 0,125 mg/kg, días 7-21) y los valores de CADESI-03 evaluado por los clínicos (0,5 mg / kg y 0.125 mg/kg, el día 14).
Conclusiones e importancia clínica – Lokivetmab (0,5; 2,0 mg/kg) redujo el prurito en comparación con el placebo durante al menos 1 mes. El nivel y la duración de la respuesta aumentó con el aumento de la dosis. Se necesitan más estudios para comprender mejor la variabilidad en las respuestas individuales en una población más amplia y variada de perros con AD.

Zusammenfassung
Hintergrund – Juckreiz ist ein Kardinalsymptom der klinischen Veränderungen bei atopischer Dermatitis (AD) bei Hunden. Lokivetmab, ein canonisierter anti-caniner IL-31 monoklonaler Antikörper reduzierte den Juckreiz und die damit einhergehende entzündliche Reaktion der Haut in einer Proof-of-Concept Studie bei Hunden mit AD.
Hypothese/Ziele – Das Ziel war die Beschreibung einer Reaktion auf die jeweilige Dosis von Lokivetmab in einer randomisierten, doppelgeblindeten, Plazebo-kontrollierten Studie.
Tiere – KlinikerInnen in Überweisungspraxen nahmen 211 Hunde in Privatbesitz mit der Anamnese einer chronischen AD in die Studie auf.
Methoden – Die Hunde wurde zufällig verteilt, um mit Lokivetmab (0,125; 0,5 oder 2,0 mg/kg) oder mit Plazebo einmal täglich am Tag 0 subcutan verabreicht, behandelt zu werden. Die HundebesitzerInnen beurteilten mittels Visual Analog Scale (VAS) den Juckreiz an den Tagen 0, 1, 2, 3, 7, 14, 28, 35, 42, 49 und 59. Die KlinikerInnen erfassten den Canine AD Extent und Severity Index (CADESI-03) Wert an den Tagen 0, 7, 14, 28, 42 und 56.
Ergebnisse – Die Behandlung mit Lokivetmab (2mg/kg) ergab eine höhere Reduzierung von der Ausgangsbasis beim durch die BesitzerInnen beurteilten Juckreiz (Tage 1-49) und den durch die KlinikerInnen beurteilten CADESI-03 Werten (Tage 7-56) im Vergleich zu Plazebo (P<0,05); die Unterschiede wurden in den Gruppen mit niedrigerer Dosierung erzielt, allerdings zu späteren Zeitpunkten und für eine kürzere Dauer sowohl für den durch BesitzerInnen beurteilten Juckreiz (0,5mg/kg, Tage 2-35; 0,125 mg/kg, Tage 7-21) wie auch für die durch KlinkerInnen beurteilten CADSI-03 Werte (0,5 mg/kg und 0,125 mg/kg, Tag 14).
Schlussfolgerungen und klinische Bedeutung – Lokivetmab (0,5; 2,0 mg/kg) reduzierte den Juckreiz im Vergleich zu Plazebo für mindestens 1 Monat. Die Werte und die Dauer der Verbesserung nahmen mit zunehmender Dosis zu. Es sind weitere Studien nötig, um die Variabilität der individuellen Reaktionen über eine breitere Population von Hunden mit AD zu verstehen.

要約
背景 — 掻痒は、犬のアトピー性皮膚炎(AD)の特徴的な臨床症状である。イヌ化抗イヌIL-31モノクローナル抗体であるlokivetmabは、AD犬を用いた実証実験において、掻痒とそれに関連する皮膚の炎症性病変を減少させた。
仮説/目的 — 本研究の目的は、無作為化・二重盲検法・プラセボ対象試験におけるlokivetmabの用量反応性を報告することである。
動物 — 15の二次診療施設より組み入れた慢性ADの病歴を持つ211頭の飼い犬。
方法 — 犬は無作為に各群に振り分けられ、Day 0に、lokivetmab(0.125, 0.5 あるいは 2.0 mg/kg)もしくはプラセボを皮下に1回投与された。 飼い主は痒みのvisual analog scale (VAS)スコア を投与日 (day 0)、投与1, 2, 3, 7, 14, 21, 28, 35, 42, 49, 56日後に評価した。獣医師は、犬アトピー性皮膚炎の範囲と重症度指数 (CADESI-03) スコアを投与日(day 0)と投与7, 14, 28, 42, 56日後に評価した.
結果 — Lokivetmab (2 mg/kg)投与群は投与前と比較して、飼い主が評価した痒みスコアが大幅に減少し(投与1–49日後)、また、プラセボと比較して、獣医師が評価したCADESI-03スコア(投与7–56日後)の大幅な減少が認められた(P < 0.05)。Lokivetmab低用量投与群でも、飼い主が評価した痒みスコア(0.5 mg/kg群, 投与2–35日後; 0.125 mg/kg群, 投与7–21日後)およびCADESI-03スコア(0.5 mg/kg群と0.125 mg/kg群, どちらも投与14日後)がともに減少したが、達成するまでの期間が長く、また効果も短かった。
結果および臨床的な重要性 — Lokivetmabの投与(0.5, 2.0 mg/kg)はプラセボと比べて、少なくとも1ヶ月はかゆみを減少させた。Lokivetmabの用量の増加に伴い、効果と反応期間は増大した。より多様な犬のアトピー性皮膚炎症例を組み入れた際の、個々の症例におけるlokivetmabへの反応性の違いをより良く理解するために、さらなる研究が必要である。

摘要

背景 — 瘙痒是犬异位性皮炎(AD)标志性的临床症状。Lokivetmab,一种备受推崇的抗犬IL-31单克隆抗体,在犬AD概念验证实验中,可减轻瘙痒和其相关的炎性皮肤病变。

假设/目的 — 目的为在随机、双盲、安慰剂对照的实验中,描述lokivetmab的有效剂量。

动物 — 15家转诊医院的临床兽医所接诊的、且具有慢性AD病史的211只家养犬。

方法 — 第0天,犬只通过随机皮下注射lokivetmab (0.125,0.5 或2.0 mg/kg)或安慰剂一次进行治疗。动物主人使用直观类比标度(VAS)瘙痒评分系统,在第0,1, 2, 3, 7, 14, 21, 28, 35, 42, 49和56日对犬进行评分。临床医生在第0, 7, 14, 28, 42和56日对犬AD程度和严重性指数(CADESI-03)进行评分。

结果 — 相较于安慰剂(P< 0.05),使用lokivetmab (2 mg/kg)治疗的病例,其动物主人瘙痒评估(1–49日)和CADESI-03评估(7–56日)分数明显下降;不同的是,通过动物主人对瘙痒(0.5 mg/kg, 第2–35日; 0.125 mg/kg, 第7–21日)的评分和临床医生对CADESI-03分数(0.5 mg/kg和0.125 mg/kg,第14日)的评估可得知,低剂量组起效时间晚,并且作用时间短。

总结和临床意义 — Lokivetmab (0.5, 2.0 mg/kg)和安慰剂相比,其减轻瘙痒作用至少持续一个月。减轻程度、持续时间与浓度成正比。为了更好的理解个体反应的差异性,仍需对大量的犬AD病例作进一步研究。

Resumo

Contexto – Prurido é o sinal clínico mais marcante na dermatite atópica (DA) em cães. Lokivetmab, um anticorpo monoclonal caninizado anti-IL-31 canina, reduziu o prurido e as lesões cutâneas inflamatórias associadas em um estudo de prova do conceito em cães com DA.

Hipóteses/Objetivos – Descrever a resposta de doses de lokivetmab em um ensaio clínico duplo cego, controlado e randomizado.

Animais – Veterinários de 15 clínicas de referência selecionaram 211 cães com histórico de DA crônica.

Métodos – Os cães foram randomizados para o tratamento com lokivetmab (0,125; 0,5 ou 2,0 mg/kg) ou placebo administrados por via subcutânea em dose única no dia 0. Os proprietários avaliaram os escores da escala analógica visual de prurido (VAS) nos dias 0, 1, 2, 3, 7, 14, 21, 28, 35, 42, 49 e 56. Os clínicos avaliaram os cães pelo CADESI-03 (*Canine Atopic Dermatitis Extent and Severity Index)* nos dias 0, 7, 14, 28, 42 e 56.

Resultados – O tratamento com lokivetmab (2mg/kg) resultou em uma porcentagem maior de redução do prurido basal, de acordo com a avaliação de pruido na VAS pelo proprietário (dias 1-49) e na avaliação do CADESI-03 pelos clínicos (dias 7-56), comparado ao placebo ($P < 0,05$); diferenças foram alcançadas nos grupos de dosagens mais baixas, mas mais tardiamente e com menor duração tanto na avaliação de prurido na VAS pelos proprietários (0,5 mg/kg, dias 2-35; 0,125 mg/kg, dias 7-21) quanto na avaliação do CADESI-03 pelos clínicos (0,5 mg/kg e 0,125mg/kg, dia 14).

Conclusões e importância clínica – Lokivetmab (0,5 e 2,0 mg/kg) reduziu o prurido por ao menos um mês, comparado ao placebo. O nível e a duração da resposta aumentaram com a elevação da dose. São necessários mais estudos para se compreender as variações individuais de resposta em uma população maior de cães com DA.