

## A blinded, randomized clinical trial evaluating the efficacy and safety of lokivetmab compared to ciclosporin in client-owned dogs with atopic dermatitis

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**Background** – Lokivetmab is an injectable anti-canine-IL-31 monoclonal antibody to treat clinical manifestations of atopic dermatitis (AD) in dogs.

**Hypothesis/Objectives** – To characterize the efficacy and safety of lokivetmab, and to demonstrate its noninferiority to ciclosporin under field conditions.

**Animals** – Dogs with chronic AD ( $n = 274$ ) were enrolled from 40 practices in Belgium, The Netherlands, France and Germany.

**Methods** – Animals were randomized (1:1) to oral ciclosporin (5 mg/kg/once daily) or monthly injectable lokivetmab (1–3.3 mg/kg) for three months. Eighty one animals that successfully completed the comparative phase were enrolled in a continuation phase receiving lokivetmab for an additional six months. Owners assessed pruritus on a Visual Analog Scale, skin lesions were assessed by veterinary investigators with a Canine AD Extent and Severity Index (CADESI-03) scale.

**Results** – Lokivetmab was noninferior to ciclosporin for pruritus reduction on Day 28 (51.90% versus 43.72%). For Day 28 CADESI-03 percentage reduction, noninferiority of lokivetmab (54.17) versus ciclosporin (56.86%) was not achieved. At none of the time points were mean CADESI-03 scores significantly different between groups. Continued efficacy towards pruritus and lesions was demonstrated in the continuation phase where 76.3% of animals ( $n = 45$ ) were assessed as 'normal' for pruritus at study end. No abnormal health events associated with lokivetmab were observed during the initial three month phase (142 dogs) or during the subsequent six month phase (81 dogs).

**Conclusions and clinical importance** – Lokivetmab at a minimum monthly dose of 1 mg/kg provided quick onset (within one day) of a lasting effect in reducing pruritus and skin lesions with a good safety profile.

### Introduction

Atopic dermatitis (AD) is estimated to affect 10–15% of the total canine population.<sup>1</sup> It is a chronic condition, necessitating life-long treatment.<sup>2</sup> Glucocorticoids have long been the treatment of choice for both short- and long-term management of skin disease although adverse effects are reported in 30–80% of treated dogs.<sup>3</sup> Ciclosporin is also used for the treatment of canine AD (cAD);

gastrointestinal effects, including vomiting, diarrhoea and anorexia, have been reported for some dogs.<sup>3–6</sup> Other treatment options for cAD include oclacitinib.<sup>7</sup>

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.<sup>8</sup> 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 eight weeks following a single dose.<sup>9</sup> A blinded, placebo-controlled trial revealed greater reduction in pruritus for at least one month compared to placebo, and the level and duration of the response were shown to increase with increased dose.<sup>10</sup> An exploratory clinical trial in dogs with AD showed that a repeated administration of lokivetmab (2.0 mg/kg) s.c. at a 14 day interval reduced pruritus and skin lesion scores compared to placebo.<sup>11</sup> These results support the view that IL-31 is a key cytokine driving clinical signs of pruritus and inflammation in dogs with AD.

The objective of this study was to characterize the efficacy and safety of lokivetmab; and to demonstrate

**Abbreviations:** AD, atopic dermatitis; ADAs, Anti-drug antibodies; AHE, abnormal health event; CADESI, Canine AD Extent and Severity Index; DMSO, dimethylsulfoxide; NSAIDs, non-steroidal anti-inflammatory drugs; RTT, response to treatment; VAS, Visual Analog Scale.

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**Conflict of interest:** All authors are employees of Zoetis Inc.

noninferiority to ciclosporin for the treatment of the clinical manifestations of cAD in client-owned atopic dogs under field conditions in Europe.

## Materials and methods

### Overview

The study consisted of two phases. A double-blinded, ciclosporin-controlled comparative phase for the first three months, followed by a six month, open label continuation phase for a subset of lokivetmab-treated animals.

All data were collected in compliance with the principles of the International Cooperation on Harmonisation for Veterinary Medicines (VICH) Good Clinical Practice (GCP) Guideline 9.<sup>12</sup> The protocol was reviewed and approved prior to study initiation by the Sponsor Ethical Review Board, as well as FAGG-AFMPs (Brussels, Belgium; authorization no. 00001008-00001570), the Medicines Evaluations Board (Utrecht, The Netherlands; authorization no. BC/2014/407779/p), ANSES (Fougères, France; authorization no. EC-00704). As per national requirements at the time, Paul Ehrlich Institute (Langen, Germany) and all local competent authorities of the involved states in Germany were notified before the start of the study. The owners gave written informed consent for their dog to be included in the study.

Dogs with AD were recruited from 40 different veterinary practices in Belgium ( $n = 5$ ), The Netherlands ( $n = 3$ ), France ( $n = 21$ ) and Germany ( $n = 11$ ). The main procedures for the study, which was similar to previous studies on oclacitinib, are summarized below and presented in Table S1.<sup>13,14</sup> Sample size estimates were derived from power calculations based on variance and effect sizes observed in unpublished data from a multi-centre noninferiority field study with ciclosporin as the control product with the aim to achieve at least 80% power at the one-sided 0.025 significance level for a 15% equivalence margin. Estimates used were similar to those previously reported.<sup>14</sup>

### Inclusion criteria

Dogs were client-owned, six months of age or older, weighed between 3 and 80 kg and in overall good health, apart from a documented history of chronic, nonseasonal AD, based on published criteria.<sup>15</sup> All dogs were investigated with a diagnostic regimen, as determined by the investigator, sufficient to eliminate food allergy (elimination diets were pursued at the investigator's discretion), flea allergy dermatitis, sarcoptic mange, bacterial or fungal dermatitis, internal and external parasitism, and metabolic disease. To be enrolled in the study, the owners had to assess their dog as having at least mild itching on a categorical assessment form and the investigator had to assess the skin lesions with a minimum score of 60 on the Canine AD Extent and Severity Index, 3<sup>rd</sup> iteration (CADESI-03)<sup>16</sup> on the initial (Day 0) physical examination.

Continued use of a flea insecticidal treatment during the study period was mandatory. Dogs that had previously been diagnosed with cutaneous adverse reactions to food (with concurrent AD) that were consuming a hypoallergenic diet were provided with the diet for at least six weeks prior to Day 0 and remained on the same diet during the study. Regardless of food allergy status, all dogs had to remain on the same diet for the entire duration of the study. Prior or current desensitization immunotherapy was allowed if the dog had been on therapy for at least eight months before Day 0, or if the unsuccessful treatment had been discontinued for at least eight weeks before Day 0.

### Prohibited and conditionally allowed medications and therapies

Withdrawal times for prohibited medications were long-acting injectable corticosteroids and amantadine, six weeks; oral corticosteroids, ciclosporin, topical tacrolimus, long-acting injectable antibacterial agents and miscellaneous compounds with known antipruritic activity, four weeks; topical steroids, topical NSAIDs and DMSO, three weeks; oclacitinib, antihistamines, systemic azole antifungals and live vaccines, two weeks; and oral antibacterial agents and topical anaesthetics, one week. Other medications and therapies were

conditionally allowed, assuming that the owners, investigators and other study personnel adhered to all minimal use and frequency of use guidelines for the concomitant medication (Table S2).

### Exclusion criteria

Exclusion criteria were signs of uncontrolled ill health unrelated to AD on Day 0, evidence of immune suppression such as hyperadrenocorticism or generalized demodicosis, and lactating bitches; or dogs (male or female) intended for use as breeding animals. As per contraindications on the Atopica® (Eli Lilly and Company; Indianapolis, IN, USA) Summary of Product Characteristics, dogs with a history of malignant disorders or progressive malignant disorders and dogs vaccinated with a live vaccine within a two week interval before treatment were excluded.<sup>5</sup>

### Randomization and blinding

The first (comparative) phase of this study was a randomized complete block design with one-way treatment structure replicated in multiple sites. Blocks were generally complete blocks (one animal per treatment group per block), but incomplete blocks were also allowed. Blocking was based on order of enrolment by the dispenser. The animal was the experimental unit for treatment. Each animal was randomly allocated to either daily oral ciclosporin (T01) or monthly injectable lokivetmab (T02) in a 1:1 ratio on Day 0. Investigators and all site personnel, with the exception of the treatment dispenser, were blinded to the treatment group assignments, as were owners and the laboratory personnel. The treatment dispenser drew up the correct dose of injectable treatment (lokivetmab or saline, with identical appearance) into a syringe and provided it to the investigator for administration. Owners were provided with blinded boxes that contained blisters with either placebo or ciclosporin capsules (Atopica®; Eli Lilly and Company).

Only animals from the lokivetmab group that completed the first three months of treatment and for which lokivetmab was considered efficacious by the owner and the investigator (i.e. their clinical manifestations of AD responded to treatment) were allowed to be enrolled on the open label continuation phase where they received lokivetmab for an additional six months. Specific Visual Analog Scale (VAS) or CADESI-03 cut-off criteria to qualify for enrolment were not determined because the judgement of a satisfactory response depended on Day 0 baseline scores and varied between individual expectations from owners and investigators.

The demographic dataset on Day 0 was not analysed statistically because animals were blocked on order of enrolment within a study site and treatment groups were assigned randomly. Any potential differences for demographics on Day 0 between treatment groups could occur by chance and would mimic normal field conditions.

### Treatment administration

Lokivetmab was provided as a ready-to-use formulation in single-use vial containing 1 mL that contained no preservative. Vials provided contained solution in one of four concentrations (10, 20, 30 and 40 mg/mL). A dosing chart was provided to ensure the actual dose of lokivetmab administered to each dog was between 1 and 3.3 mg/kg depending upon the dog's body weight. Dogs in T01 were treated with ciclosporin capsules once daily at 5 mg/kg starting on Day 0 and continuing until Day 28. From Day 28 the dosage regimen could be adjusted as previously described.<sup>17</sup>

### Study schedule and variables measured

Baseline data (demographic, physical examination, initial assessment of pruritus and adherence to inclusion criteria) were collected at enrolment on Day 0. A VAS was used by dog owners to assess the severity of the 'itch'.<sup>18</sup> Owners performed a pruritus VAS assessment on days 0, 1, 2, 7, 14, 21 and 28, and monthly thereafter. CADESI-03 scores were used by the investigators to assess skin lesions and combined with a general physical examination; these were performed on days 0, 14, 28 and monthly thereafter.<sup>16</sup> Dogs were observed in the clinic for 30 min following each administration for signs of immediate adverse reactions. Investigators recorded

abnormal health events (AHEs) and/or concomitant treatment reported by owners or identified on physical examination throughout the study.

On the final day of study (Day 84 in the comparative phase and for a subset on Day 252 in the continuation phase, or earlier for dogs withdrawn prior to Day 84 or 252), owners and investigators assessed the dog's overall response to treatment (RTT) by drawing a vertical line on a horizontal 10 cm scale ranging from 'no improvement' to 'excellent results'.

Blood samples were collected for evaluation of haematological parameters, serum chemistry and anti-drug antibodies (ADAs) on a monthly basis, and urine samples were taken for urinalysis and evaluation of protein creatinine ratio every three months. Blood and urine were collected again at the discretion of the investigator if the dog presented for an AHE. All samples were sent to the same laboratory except a fraction of the serum samples at each time point, which were analysed for ADAs using validated methods at the authors' laboratory.<sup>9</sup>

In cases of suspected secondary bacterial infections, it was recommended to collect a swab sample for standard bacteriological investigation at the same clinical pathology laboratory, including antibiogram, through standard veterinary procedures.

### Efficacy outcome measures

The primary efficacy end-points were defined as the reduction from baseline in the owner-assessed pruritus as measured by VAS, and the reduction from baseline of investigator-assessed by CADESI-03 on Day 28. Data were summarized for days 0, 1, 2, 7 ( $\pm 1$ ), 14 ( $\pm 3$ ), 21 ( $\pm 1$ ), 28 ( $\pm 5$ ), 56 ( $\pm 5$ ) and 84 ( $\pm 5$ ). Data from animals that fell outside of these permitted visit windows were excluded from efficacy analysis. For the continuation phase, a seven day range on the 28 day interval between clinic visits was allowed.

Secondary efficacy end-points included VAS and CADESI-03 score at each time point, percentage of dogs achieving 'a normal range' on the pruritus VAS and CADESI-03 score on each of the study time points, and assessment of overall RTT from the owner and the investigator at study completion or withdrawal. Using the VAS, a score of 0–1.9 cm was presumed to be the best approximation of a 'normal range'.<sup>19</sup> For CADESI-03 scores, the interval 0–15 was presumed to represent 'in remission'.<sup>20</sup> The efficacy data set excludes those dogs that were considered to have had a protocol deviation that affected the collection or integrity of their data, or had a dosing compliance below 80% over the study period preceding an efficacy assessment for ciclosporin-treated animals. In case of withdrawal, all available efficacy data (except if impacted by a protocol deviation) were included in the analyses.

### Safety outcome measures and analysis

The dataset used for the assessment of safety included all data from all animals that were administered at least one dose of study drug (ciclosporin or lokivetmab). Frequencies of dogs reported to show at least one AHE were summarized by clinical sign and frequencies of dogs receiving concomitant medication over the course of the study were summarized by functional use term.

For each haematological, serum chemistry and quantitative urinalysis value, summary statistics (mean, median, standard deviation, minimum, maximum) were calculated by treatment and intended day of sampling. Haematological and serum chemistry values are summarized reporting the number of dogs that fell below, within or above the normal range (provided by the laboratory) at each day of sampling. In addition, shift tables provided the number of dogs that had an increased or decreased shift compared to baseline at each day of sampling.

### Data analysis

Data analysis was performed using SAS v9.3 (SAS Institute; Cary, NC, USA) as described previously,<sup>13</sup> with the exception of the primary efficacy end-points where results for dogs treated with lokivetmab were compared with results for dogs treated with ciclosporin with a 15% noninferiority margin.<sup>21</sup> This margin was set following statistical

Guideline EMA/CVMP/EWP/81976/2010 recommendations and based on previously generated clinical data comparing lokivetmab to a negative control.<sup>10</sup> Mixed linear models were fitted using PROC MIXED. Where appropriate, transformations were applied to end-points prior to statistical analysis as a remedial measure to address violations in the assumptions for the statistical models. The level of significance was set at  $\alpha = 0.05$  (two-sided).

## Results

### Demographic data

A total of 274 dogs were enrolled in the comparative phase of which the demographic details are summarized in Table 1. Bulldogs were the most common dominant breed, comprising 20.5% of the study population (French bulldog 15.7%, English bulldog 4.4% and American bulldog 0.4%). Other dominant breeds that made up >2% of the study population were Labrador retriever (11.7%), German shepherd dog (5.1%), Jack Russell terrier (5.1%), West Highland white terrier (5.1%), Yorkshire terrier (3.3%), shih tzu (2.6%), American Staffordshire terrier (2.2%) and boxer (2.2%).

### Treatment administration

On Day 0 of the comparative phase, the actual lokivetmab dose was 1.0–2.8 mg/kg (mean = 1.3 mg/kg and median = 1.2 mg/kg). At enrolment in the open label continuation phase (day 84), the actual lokivetmab dose was 1.0–1.9 mg/kg (mean = 1.2 mg/kg and median = 1.2 mg/kg).

### Assessment of effectiveness

The primary effectiveness dataset at Day 28 comprised 234 dogs in the owner pruritus VAS dataset (117 ciclosporin-treated and 117 lokivetmab-treated) and 234 dogs in the veterinary investigator's CADESI-03 dataset (116 ciclosporin-treated and 118 lokivetmab-treated). In all figures and tables, assessments for lokivetmab-treated animals up to and including Day 84 reflect the animals enrolled in the comparative phase (142 at the beginning of the study), whereas the subsequent assessments (as from Day 112) reflect the subset of animals that continued monthly treatment for an additional six months (81 at initiation of the continuation phase). The datasets for both variables changed at each time point as a result of missed assessments or errors in compliance with the trial and data collection protocols, in both phases of the study.

#### Owner pruritus VAS

Lokivetmab was demonstrated to be noninferior to ciclosporin with respect to the Day 28 percentage reduction from baseline for owner pruritus VAS [43.72% (37.61–49.83%) in ciclosporin-treated animals versus 51.90% (45.94–57.87%) in lokivetmab-treated animals], as the test value for noninferiority (0.3%) was less than the 15% noninferiority margin set per protocol. Mean percentage reductions on days 1, 2, 7, 14, 21, 28, 56 and 84 were 8.26, 15.21, 24.92, 33.46, 38.08, 43.72, 44.35 and 53.01%, respectively, in the ciclosporin-treated animals versus 21.79, 33.66, 43.80, 52.45, 51.01, 51.90, 56.81 and 59.68%, respectively, in the lokivetmab treatment group. On days 1, 2, 7, 14 ( $P < 0.0001$ ), 21 ( $P = 0.0014$ )

**Table 1.** Demographics of enrolled dogs on the lokivetmab/ciclosporin trial at Day 0

	Ciclosporin <i>n</i> = 132 [% ( <i>n</i> )]	Lokivetmab <i>n</i> = 142 [% ( <i>n</i> )]	Total <i>n</i> = 274 [% ( <i>n</i> )]
<b>Breed distribution</b>			
Pure-bred	82.6% (109)	78.9% (112)	80.7% (221)
Mixed breed	17.4% (23)	21.1% (30)	19.3% (53)
<b>Sex distribution</b>			
Male	40.9% (54)	47.9% (68)	44.5% (122)
Female	59.1% (78)	52.1% (74)	55.5% (152)
Neutered/spayed	49.2% (65)	52.8% (75)	51.1% (140)
Mean age at study start, years (range)	5.4 (1.0–12.0)	5.3 (0.5–14.0)	5.4 (0.5–14.0)
Mean weight at study start, kg (range)	20.2 (3.0–53.4)	22.2 (3.6–68.0)	21.2 (3.0–68.0)
Median owner VAS, mm (range)	67.0 (30.0–100.0)	75.0 (33.0–100.0)	70.0 (30.0–100.0)
Median CADESI-03 (range)	141.0 (62.0–773.0)	152.0 (61.0–635.0)	146.0 (61.0–773.0)

*n* number of animals (all animals enrolled, irrespective of whether they were excluded from the analysis due to protocol deviations), VAS Visual Analog Scale, CADESI-03 Canine Atopic Dermatitis Extent and Severity Index, 3<sup>rd</sup> iteration.

and 56 ( $P = 0.0115$ ), the difference between treatment groups was statistically significant.

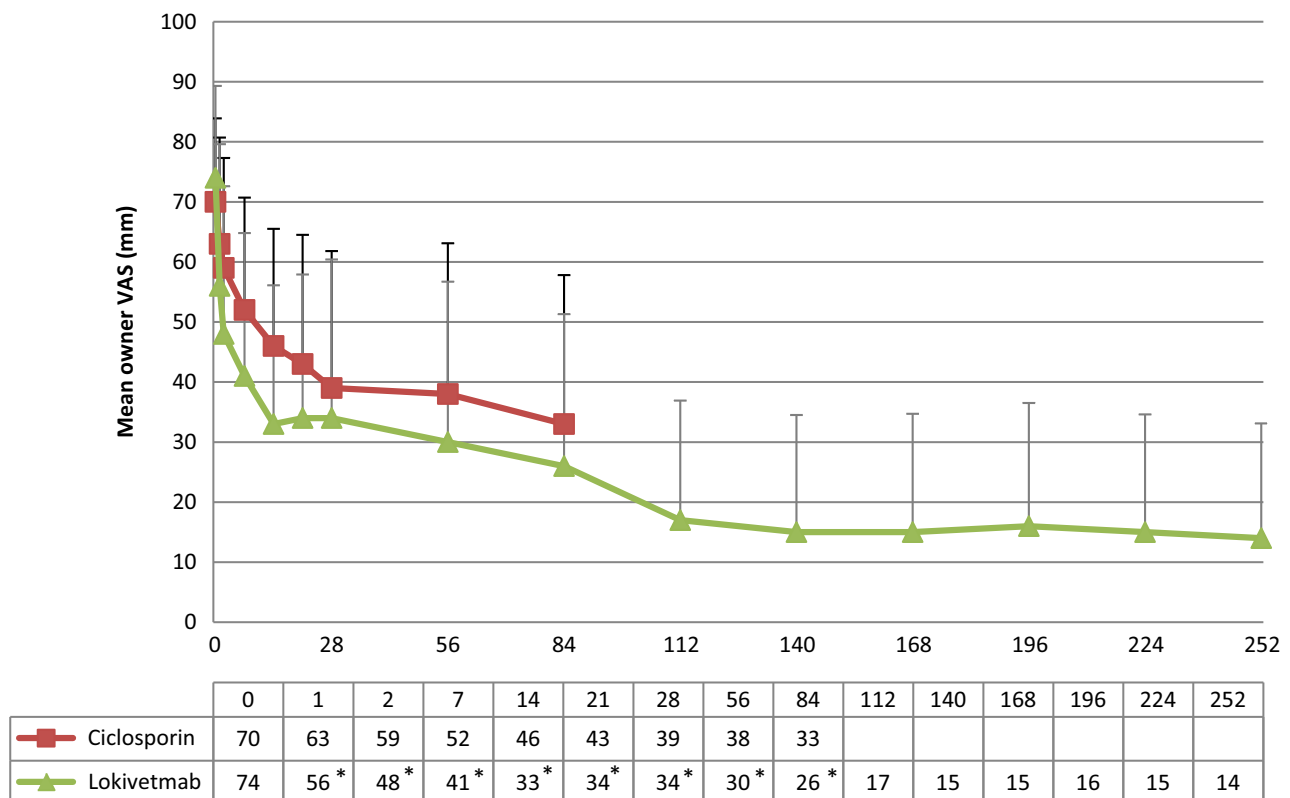
At every study time point after Day 0, the owner-assessed pruritus VAS means were significantly lower in the group of animals treated with lokivetmab versus the group of animals treated with ciclosporin (Figure 1). The mean owner VAS of the subset of animals that were enrolled in the continuation phase (days 84–252) decreased to a minimum of 14 on Day 252.

On all time points after Day 0, the percentage of animals achieving a 'normal' VAS score was numerically higher in the lokivetmab treatment group compared to the group of animals receiving ciclosporin. By Day 84, 38.0% of the ciclosporin-treated animals were scored as

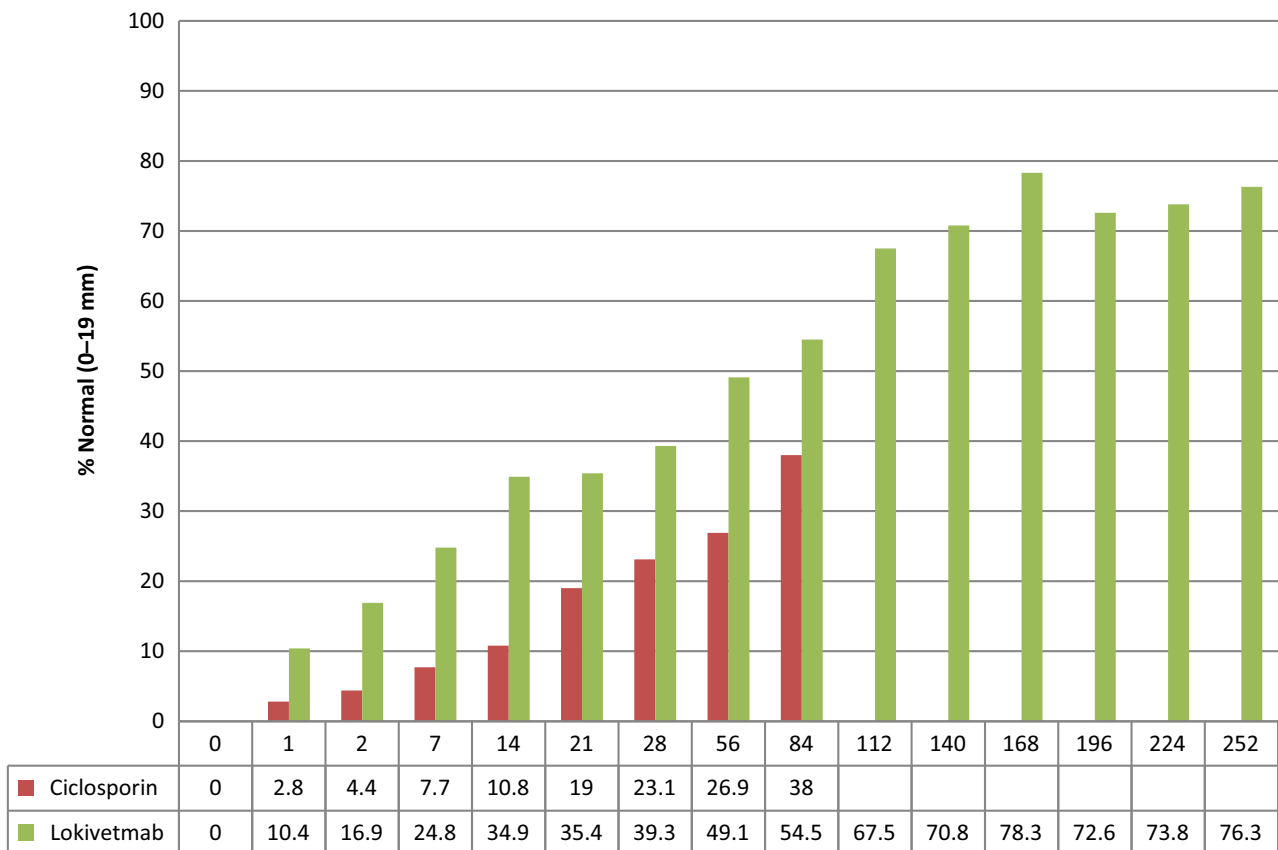
'normal' in terms of level of pruritus versus 54.5% of the lokivetmab-treated animals (Figure 2). At the end of the continuation phase up to 76.3% of the animals were assessed as 'normal' for pruritus. A frequency distribution of additional owner VAS categories at each time point for both treatment groups is presented in Figure S1.

#### Investigator CADESI-03

For the Day 28 percentage reduction from baseline for CADESI-03, the test value for noninferiority (18.0%) was 3% points larger than the 15% margin, and thus noninferiority of lokivetmab [54.17% (47.42–60.93%)] versus ciclosporin [56.86% (50.47–63.25%)] was not achieved. Mean percentage reductions on days 14, 28, 56 and 84



**Figure 1.** Plot of mean owner assessment of pruritus Visual Analog Scale (VAS) (with one side standard deviation) by treatment on each evaluation day. \*Statistically significant difference between the mean owner VAS value for ciclosporin and lokivetmab,  $P < 0.05$ .



**Figure 2.** Plot of percentage of dogs receiving either ciclosporin or lokivetmab, with pruritus Visual Analog Scale (VAS) in 'normal' range (0–19) by treatment on each evaluation day.

were 42.25, 56.86, 67.38 and 74.26%, respectively, in the ciclosporin-treated animals versus 44.30, 54.17, 62.27 and 62.04%, respectively, in the lokivetmab treatment group. On Day 84, the difference between treatment groups was statistically significant ( $P = 0.0200$ ). Five animals were identified in the lokivetmab treatment group that showed <10% reduction compared to baseline for CADESI-03 on Day 28, as well as on days 56 and 84. Similar cases were not observed in the group of animals treated with ciclosporin.

Mean CADESI-03 decreased from 165 on Day 0 to 46 on Day 84 in the control group. In the lokivetmab-treated group, the mean CADESI-03 score reduced from 184 on Day 0 to 57 on Day 84. At none of the time points was the mean score significantly different between the treatment groups (Figure 3). For the subset of animals that received six additional monthly injections, the score further reduced to 32 on Day 252.

At all time points after Day 0, the percentage of animals 'in remission' on the CADESI-03 scale (0–15) was numerically higher in the lokivetmab treatment group compared to the group of animals receiving ciclosporin. By Day 84, 27.6% of the ciclosporin-treated animals were scored as 'in remission' with regards to the skin lesions versus 36.6% of the lokivetmab-treated animals (Figure 4). Of the animals in the continuation phase, 59.3% were scored as 'in remission' on Day 252. A frequency distribution of additional CADESI-03 categories at each time point for both treatment groups is presented in Figure S2.

### Response to treatment (RTT)

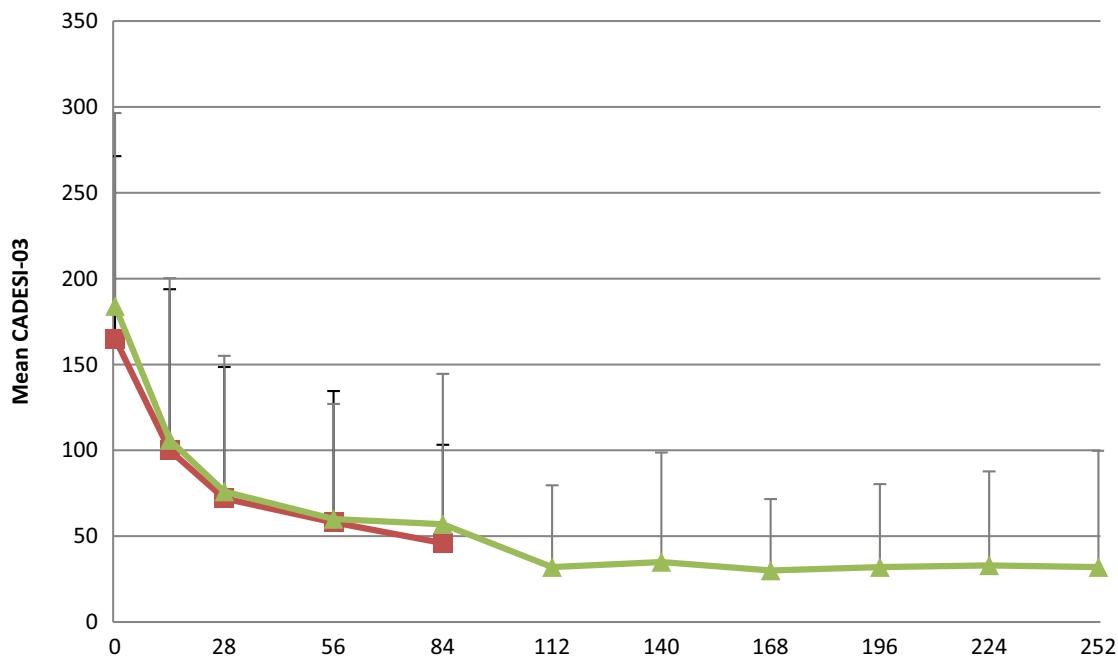
The observed differences in mean RTT scores between both treatment groups were not significant: 69.5 in the ciclosporin-treated group versus 72.5 in the lokivetmab-treated group for owner RTT and 74.07 versus 72.86 for investigator RTT. At the end of the continuation phase (or earlier in case of withdrawal) the remaining lokivetmab-treated animals had a mean owner RTT and investigator RTT of 84.

### Safety assessment

#### Health events and concomitant medications

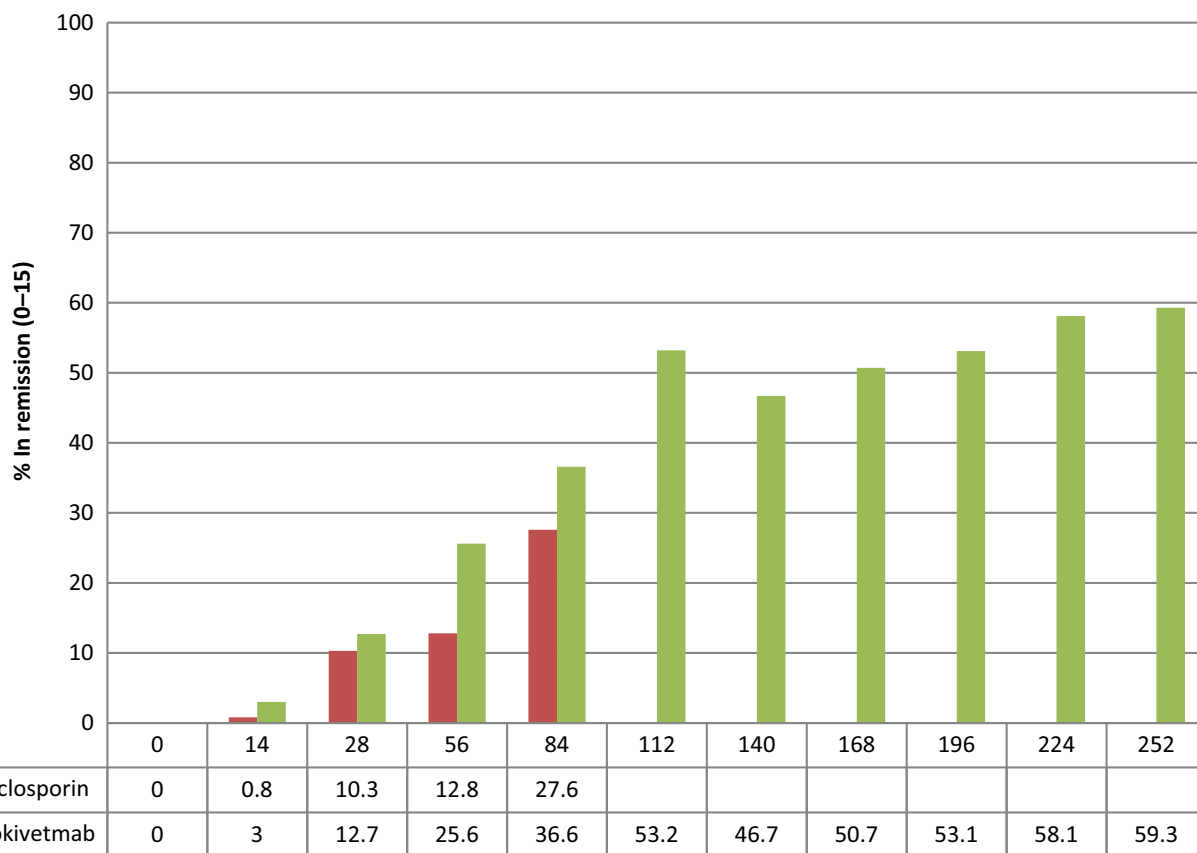
**Comparative phase.** Two lokivetmab-treated animals were enrolled with pre-existing uncontrolled underlying diseases violating the study inclusion and exclusion criteria. Because this information only became available in a retrospective manner, one case (G1313) completed the study up to and including Day 84. The other (G1317) was withdrawn on Day 71. The data for both cases were excluded from the efficacy analyses due to a violation of the inclusion criteria, but remained included in the safety analyses. Both animals ultimately had to be euthanized for nontreatment-related reasons.

In total, 27 cases were withdrawn during the comparative phase (nine ciclosporin-treated animals and 18 lokivetmab-treated animals; Table 2). Six animals from the ciclosporin-treated group were withdrawn due to possible adverse reactions to drug treatment: vomiting/diarrhoea (four cases) and the development of severe papillomatosis



	0	14	28	56	84	112	140	168	196	224	252
■ Ciclosporin	165	100	72	58	46						
▲ Lokivetmab	184	106	76	60	57	32	35	30	32	33	32

**Figure 3.** Plot of mean Canine Atopic Dermatitis Extent and Severity Index, 3<sup>rd</sup> iteration (CADESI-03) (with one side standard deviation) for dogs receiving either ciclosporin or lokivetmab.



**Figure 4.** Plot of percentage of dogs with Canine Atopic Dermatitis Extent and Severity Index, 3<sup>rd</sup> iteration (CADESI-03) in 'remission' (0–15) by treatment on each evaluation day.

**Table 2.** Summary of reasons for withdrawal from the lokivetmab/ciclosporin trial\*

	Possible adverse reaction to drug treatment [n (%)]	Unsatisfactory clinical efficacy [n (%)]	Secondary skin infection [n (%)]	Owner noncompliance [n (%)]	Other [n (%)]
Ciclosporin (n = 132)	6 (4.5%)	2 (1.5%)	3 (2.3%)	2 (1.5%)	0 (0.0%)
Lokivetmab (n = 142)	0 (0.0%)	8 (5.6%)	5 (3.5%)	4 (2.8%)	5 (3.5%)
Total (n = 274)	6 (2.2%)	10 (3.6%)	8 (2.9%)	6 (2.2%)	5 (1.8%)

\*As assessed by the study organizer. Note that for several animals there was a combination of different reasons leading to the withdrawal which is why the totals from the table above do not match with the total number of animals withdrawn.  
n number of animals.

(two cases). For eight animals in the lokivetmab treatment group, their withdrawal was related to unsatisfactory clinical efficacy, as perceived by owner or veterinary investigator; and in each of these cases reflected unsatisfactory VAS and/or CADESI-03 scores, versus two animals in the ciclosporin treatment group. The percentage of animals where withdrawal was related to a secondary skin infection was similar between both treatment groups (2.3% of animals treated with ciclosporin versus 3.5% of the lokivetmab-treated animals).

Frequency of AHEs occurring in >2% of the lokivetmab-treated group as from Day 0 is summarized in Table 3. The percentage of animals with digestive tract disorders was twice as high in the group of animals treated with ciclosporin versus the group of animals treated with lokivetmab. Vomiting and diarrhoea were the most frequently reported clinical signs. For lokivetmab-treated dogs, vomiting was reported in 22 animals (15.5%) and diarrhoea in 19 animals (13.4%).

The overall percentage of animals developing skin disorders during the comparative phase was similar between both treatment groups: 15.2% in ciclosporin-treated animals versus 18.3% in lokivetmab-treated animals.

A summary of concurrent treatments administered in >2% of the lokivetmab-treated animals during the comparative phase is shown in Table S3. The percentage of animals treated with systemic antibacterial drugs prior to Day 84 was numerically lower in the ciclosporin treatment group versus the lokivetmab treatment group (8.3 versus 19.0%). This observation is linked with the numerically higher number of skin, ear and eye disorders being reported in lokivetmab-treated animals versus ciclosporin-treated animals, although the percentage of animals sampled for bacteriology due to a suspected skin infection after Day 0 and up to Day 84 was comparable between both treatment groups (15.9% in the group of animals treated with ciclosporin versus 19.0% in the lokivetmab treatment group). Within the first dosing interval (days 0–31), two ciclosporin-treated dogs received their first systemic antibacterial treatment for bacterial skin or ear infections, followed by six additional cases during the second interval (days 32–59) and one remaining case during the third interval (days 60–83); the corresponding distribution for lokivetmab-treated dogs was nine, seven and two dogs.

*Continuation phase.* One animal was euthanized two days after enrolment in the continuation phase due to

nodules in the stomach wall, intestine and mesentery identified on laparotomic investigation. Histopathological evaluation postmortem resulted in a diagnosis of panniculitis. Another animal was euthanized at the owner's request on Day 167 after being hit by a car. The most frequently reported clinical signs during the continuation phase (CT in Table 3) were disorders associated with the skin, ears or eyes (22.2%), followed by digestive tract disorders (19.8%). Two animals were reported with a dermal mass during the study. For one, the nodule resolved spontaneously and was considered a granulomatous reaction to a pronounced papule in one of the facial folds. For the other, the hyperpigmented nodule in front of the dog's right ear was diagnosed as a benign angiokeratoma and was surgically removed. One animal was diagnosed with a mammary gland carcinoma, which was surgically removed with low risk of metastasis.

In total, ten animals were treated with systemic antibacterial drugs during the course of the continuation phase (12.4%). Five animals were sampled for bacterial culture and antimicrobial susceptibility testing, for four of these, antibacterial and/or topical antifungal treatment was prescribed.

During the entire nine month study, there were no hypersensitivity reactions (e.g. wheals, vomiting) immediately post-dosing and no reports of injection site reactions (e.g. injection site swelling or redness) apart from one animal that was reported with pain upon lokivetmab injection.

### Haematological investigation, serum chemistry and urinalysis

For all serum chemistry parameters, the mean values remained within reference ranges on all study time points from Day 0 onwards, except for the lactate dehydrogenase mean in the ciclosporin treatment group on Day 56 (mean value 183.34 units/L; reference range <159 units/L) and on Day 224 (mean value 180.02 units/L; reference range <159 units/L). Increasing and/or decreasing shifts were observed throughout the entire nine month programme, but these were not clinically significant and generally occurring in both treatment groups during the comparative phase.

Increasing and/or decreasing shifts were equally observed in both treatment groups for haematological parameters. Overall, mean values did not appear to change during the entire phase for either treatment.

Mean values of quantitative urine measures remained within reference ranges with the exception of total

**Table 3.** Adverse health events occurring at least once in >2% of the lokivetmab-treated group during the comparative phase: summary table by frequency of occurrence of clinical sign on a per-animal basis as from Day 0 (D0)

Study period	Ciclosporin ( <i>n</i> = 132) [ <i>n</i> (%)] D0–D84	Lokivetmab ( <i>n</i> = 142) [ <i>n</i> (%)] D0–D84	Lokivetmab CT** ( <i>n</i> = 81) [ <i>n</i> (%)] D84–D252
<b>Digestive tract disorders</b> (55.3% versus 26.1% versus 19.8%)*			
Vomiting	49 (37.1)	22 (15.5)	8 (9.9)
Diarrhoea	47 (35.6)	19 (13.4)	7 (8.6)
<b>Systemic disorders</b> (12.9% versus 19.0% versus 8.6%)*			
Lethargy	11 (8.3)	14 (9.9)	4 (4.9)
Anorexia	5 (3.8)	7 (4.9)	3 (3.7)
Hyperthermia	0 (0.0)	3 (2.1)	1 (1.2)
<b>Skin and appendage disorders</b> (15.2% versus 18.3% versus 22.2%)*			
Bacterial skin infection	1 (0.8)	10 (7.0)	5 (6.2)
Dermatitis and eczema	6 (4.5)	8 (5.6)	8 (9.9)
Pruritus	9 (6.8)	6 (4.2)	3 (3.7)
Erythema	1 (0.8)	4 (2.8)	4 (4.9)
Alopecia	0 (0.0)	3 (2.1)	0 (0.0)
<b>Ear and labyrinth disorders</b> (8.3% versus 12.7% versus 12.4%)*			
Otitis externa	4 (3.0)	8 (5.6)	7 (8.6)
External ear disorder NOS	1 (0.8)	4 (2.8)	1 (1.2)
Otitis NOS	5 (3.8)	4 (2.8)	1 (1.2)
<b>Musculoskeletal disorders</b> (0.8% versus 2.8% versus 3.7%)*			
Lameness	1 (0.8)	3 (2.1)	3 (3.7)

\*For each functional/organ class, the total percentages for ciclosporin versus lokivetmab versus lokivetmab CT are put in between brackets (calculated irrespective of the 2% cut off).

\*\*Lokivetmab CT reflects the animals that were included in the continuation phase.

*n* number of animals, NOS not otherwise specified.

protein on Day 84 where the mean value was above the reference range (>530) in both treatment groups (554.47 in the ciclosporin treatment group and 557.67 in the group of animals treated with lokivetmab) and on Day 168 of the extended study (781.6) for the subset of lokivetmab-treated animals.

### Immunogenicity

Treatment-induced immunogenicity (increase in anti-drug antibody titre  $\geq 10$ -fold compared to pre-dose titre) was observed in three of 142 animals in the lokivetmab group (2.1%) during the first three months of treatment; none thereafter. There appeared to be no impact of immunogenicity on efficacy in two of the three cases and a possible impact in one case as the initial improvement in VAS score diminished. None of the observed AHEs in these three animals were considered to be related to treatment-induced immunogenicity.

### Discussion

The reductions in pruritus VAS and CADESI-03 score data presented here provide further evidence that neutralization of IL-31 has both an antipruritic and anti-inflammatory effect in cAD, a disease associated with IL-31 dysregulation.<sup>22</sup> Lokivetmab treatment demonstrated not only to be noninferior to ciclosporin treatment for control of pruritus (percentage reduction from baseline), but mean pruritus scores were also significantly lower compared to ciclosporin treatment. Although noninferiority of lokivetmab was not established in comparison to ciclosporin for skin lesions (percentage reduction of CADESI scores from baseline) a continuous improvement of these scores was observed over time (see Figures 3 and 4), and a significant difference of mean CADESI scores between the

two treatment groups could not be detected. Comparison of both pruritus and CADESI scores after repeated lokivetmab administration reported here with those reported earlier after a single administration indicate the benefit of repeated longer term administration of lokivetmab.<sup>10</sup>

When reviewing the CADESI-03 data at the individual animal level in an attempt to better understand the observed difference in percentage reduction between treatment groups especially on Day 84, five animals were identified in the lokivetmab treatment group that showed <10% reduction compared to baseline for CADESI-03 on Day 28, as well as on days 56 and 84. Similar cases were not observed in the group of animals treated with ciclosporin. No general rationale could be identified as to why these animals did not seem to respond to treatment with lokivetmab. Due to the complexity and multifactorial nature of AD, it is well accepted that one single treatment will likely not satisfactorily control the disease.<sup>23</sup> Thus, in some dogs, the targeted interference with IL-31-dependent pathways might on occasions not be as effective compared to products with a broader target. Alternatively, in AD cases that may be closely linked to IL-31 signalling alone, effectiveness of lokivetmab may be superior to less targeted therapy, thereby reducing the need for concurrent therapy in those cases. Breed-dependent differences in the clinical AD phenotypes of dogs have been reported.<sup>24</sup> These may be influenced by factors such as genetic background and environment, and they could also potentially impact the level of treatment effectiveness. The observation of partial or full lack of responsiveness to monoclonal antibody (mAb) treatment has previously been observed in trials in humans also, confirming the rare observation of reduced responsiveness in a small subset of the population for these targeted therapies.<sup>25–28</sup> It should be noted, however, that lack of



response to treatment was also reported previously for other available therapies with a broader mode of action, including methylprednisolone and ciclosporin.<sup>17</sup>

Overall the reductions in skin lesion scores after ciclosporin treatment were in line with what has been reported previously.<sup>14,29,30</sup> The relatively slow onset of efficacy of ciclosporin in controlling pruritus, as observed in this study, has been described in the past. The combination of ciclosporin with prednisolone treatment during the first weeks of therapy in order to control pruritus faster and more effectively has been reported.<sup>31,32</sup>

It would have been interesting to assess time-to-remission in a Kaplan–Meier approach to exclude potential bias because of lokivetmab-treated animals dropping out at higher rates due to insufficient treatment effect, but this could not be accurately determined based on the scheduled clinic visits where CADESI-03 was evaluated.

With regards to AHEs reported in the current study, the overall percentages of vomiting and diarrhoea reported for the ciclosporin-treated animals are slightly higher than the findings from a longitudinal study conducted in healthy dogs.<sup>33</sup> Considering that both the veterinary investigators and the owners were aware of the 50% chance of the animal being on ciclosporin treatment, and given that the gastrointestinal adverse effects are well known by prescribers and users, this could have introduced some bias and might have resulted in an over-reporting of gastrointestinal upset in both groups. Not surprisingly, some ciclosporin-treated dogs had to be withdrawn from treatment due to AHEs especially related to the gastrointestinal tract; a similar observation was made in a controlled study.<sup>14</sup>

Haematological and serum chemistry data support lokivetmab's safety over the 252 days when administered alone or in combination with a wide variety of medicines and vaccines commonly used in canine veterinary medicine. Because the study was designed and powered to demonstrate noninferiority for owner pruritus VAS and CADESI-03 at Day 28, retrospective statistical comparison of AHEs, blood and urine parameters between the two treatment groups would have been underpowered and was therefore not done. As with any new therapy, continued monitoring will occur via the tools of pharmacovigilance once lokivetmab is commercialized to further substantiate these observations.

Because lokivetmab is a caninized mAb, there is a decreased risk of immunogenicity in the target species, even though all therapeutic mAbs remain immunogenic to some extent.<sup>34,35</sup> ADAs may bind to therapeutic monoclonal antibodies leading to neutralization or increased clearance and potentially result in decreased efficacy.<sup>35,36</sup> ADAs also have been associated with a higher risk of hypersensitivity reactions.<sup>36</sup> Such reactions have not been observed in dogs treated with lokivetmab in laboratory or clinical field trials thus far and were also not observed in the current field study. Furthermore, treatment-induced immunogenicity was observed only in three of the lokivetmab-treated animals (2.1%) in the current trial and in a total of seven animals in the entire development programme (1.2%; data not shown). The degree of apparent immunogenicity of lokivetmab might be due to the high level of speciation with >92% of the protein

being identical to a naturally occurring antibody in the dog, thus minimizing the risk for the dog's immune system to trigger production of ADAs.<sup>37</sup>

Antibacterial treatment is a well-described concomitant intervention in the treatment of the atopic dog<sup>23</sup>. One study reported 64.8% of AD-diagnosed dogs ( $n = 247$ ) treated with oclacitinib for up to 630 days required systemic antibacterial treatment.<sup>38</sup> Although the overall percentage of animals being treated with systemic antibacterial drugs was low in the present study, it is noticeable that more lokivetmab-treated dogs (19%) required such treatment than ciclosporin-treated dogs (8.3%) in the comparative phase. Given that the percentage of animals sampled for bacteriology due to a suspected skin infection during the comparative phase was comparable between both treatment groups, it is unlikely that the higher incidence of treatment with systemic antibacterial drugs in the lokivetmab treatment group was caused by a higher incidence of secondary infections. Whilst there is no apparent relationship between the time point of lokivetmab administration and the need for systemic antibacterial drugs during the following month, the number of animals requiring systemic antibacterial therapy was gradually decreasing with study progression. It appears that the main difference of systemic antibacterial treatment for bacterial skin/ear infections between the two treatment groups is observed during the first treatment interval (i.e. two cases in the ciclosporin treatment group versus nine cases in the lokivetmab treatment group). This could potentially be linked to the mechanism of action of both treatments: the broader anti-inflammatory effect of ciclosporin might result in a faster improvement of skin lesions compared with the more targeted effect of lokivetmab. The latter might result in lokivetmab-treated dogs remaining slightly longer dysbiotic which could eventually lead to a slower reduction of skin infections at the beginning of treatment.<sup>39,40</sup> During longer treatment periods with lokivetmab (i.e. continuation phase) only three additional animals required systemic antibacterial treatment for a skin-related health event, suggesting that continued treatment with lokivetmab might eventually reduce the overall need for concomitant antibacterial use in atopic dogs.

This study demonstrated that lokivetmab at a minimum dose of 1 mg/kg s.c. and repeated at monthly intervals provided onset of effect in reducing pruritus within one day and continued efficacy (i.e. activity against pruritus and skin lesions) for one month. Lokivetmab's antipruritic efficacy was more pronounced than the one observed with ciclosporin; however, the effect of both treatments on skin lesions seemed comparable. The safety data demonstrated a favourable safety profile of lokivetmab. The ability to dose lokivetmab once monthly via s.c. injection may help maintain treatment compliance for certain AD dogs and their owners, and will potentially enable regular monitoring of dogs with chronic AD at the veterinary clinic when they present for re-administration of the treatment.

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## Résumé

**Contexte** – Le lokivetmab est un anticorps anti-IL-31 canin injectable pour traiter les manifestations cliniques de la dermatite atopique du chien (AD).

**Hypothèses/Objectifs** – Caractériser l'efficacité et l'innocuité du lokivetmab et de démontrer sa non-infériorité à la ciclosporine sous certaines conditions.

**Sujets** – Les chiens atteints de AD chronique ( $n = 274$ ) ont été inclus par 40 cliniques en Belgique, Hollande, France et Allemagne.

**Méthodes** – Les animaux ont été randomisés (1 :1) pour la ciclosporine orale (5 mg/kg/une fois par jour) ou le lokivetmab injectable une fois par mois (1-3.3 mg/kg) pendant trois mois. Quarante animaux ayant complété l'étude comparative, ont ensuite été inclus dans une phase de continuation en recevant du lokivetmab pendant six mois supplémentaires. Les propriétaires ont évalué le prurit sur une échelle visuelle analogue, les lésions cutanées ont été évaluées par les vétérinaires à l'aide d'un CADESI-03 (Canine AD Extent and Severity Index).

**Résultats** – Le lokivetmab était non-inférieur à la ciclosporine pour la diminution du prurit à jour 28 (51.90% contre 42.72%). Pour le jour 28, le pourcentage de réduction du CADESI-03, la non-infériorité du lokivetmab (54.17) contre la ciclosporine (56.86%) n'a pas été fini. A aucun moment les scores de CADESI-03 moyen n'étaient significativement différents entre les groupes. L'efficacité continue vis à vis du prurit et des lésions a été démontrée dans la phase de continuation où 76.3% des animaux ( $n = 45$ ) ont été évalué comme « normal » pour le prurit à la fin de l'étude. Aucun effet indésirable n'a été associé au lokivetmab au cours de la phase initiale des trois mois (142 chiens) ou au cours de la phase suivante de six mois (81 chiens).

**Conclusions et importance clinique** – Le lokivetmab à une dose minimale de 1mg/kg par mois, a entraîné une baisse rapide (en un jour) d'un effet de réduction du prurit et des lésions cutanées avec un bon profil d'innocuité.

## RESUMEN

**Introducción** – Lokivetmab es un anticuerpo monoclonal inyectable anti-IL-31-canina para tratar las manifestaciones clínicas de la dermatitis atópica (AD) en perros.

**Hipótesis / Objetivos** – Caracterizar la eficacia y seguridad de lokivetmab y demostrar que no es inferior a la ciclosporina en condiciones de campo.

**Animales** – Perros con AD crónica ( $n = 274$ ) fueron incluidos en 40 clínicas de Bélgica, Holanda, Francia y Alemania.

**Métodos** – Los animales fueron distribuidos al azar (1: 1) para ser tratados con ciclosporina oral (5 mg/kg / una vez al día) o lokivetmab inyectable mensual (1-3,3 mg /kg) durante tres meses. Ochenta y un animales que completaron con éxito la fase comparativa fueron incluidos en una fase de continuación que recibía lokivetmab durante otros seis meses. Los propietarios evaluaron el prurito en una escala análoga visual, las lesiones cutáneas fueron evaluadas por investigadores veterinarios mediante el de índice de extensión y severidad de la dermatitis atópica canina (CADESI-03).

**Resultados** – Lokivetmab fue comparable a la ciclosporina para la reducción del prurito en el día 28 (51,90% frente a 43,72%). En el día 28 el porcentaje de reducción de CADESI-03 para la no-inferioridad de

## Supporting Information

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

**Figure S1.** Frequency distribution (%) of owner pruritus VAS categories at each time point for ciclosporin and lokivetmab.

**Figure S2.** Frequency distribution (%) of CADESI-03 categories at each time point for ciclosporin and lokivetmab.

**Table S1.** Study procedures.

**Table S2.** Conditionally allowed medications and therapy.

**Table S3.** Concomitant medications - frequency of occurrence per functional use term for concurrent treatments administered in >2% of the lokivetmab-treated animals during the comparative phase.

lokivetmab (54,17) con ciclosporina (56,86%) no se logró. En ninguno de los puntos de tiempo hubo diferencia significativas en los valores medios de CADESI-03 entre los grupos. La eficacia continuada en el control del prurito y las lesiones se demostró en la fase de continuación donde un 76,3% de los animales (n = 45) fueron evaluados como 'normales' para prurito al final del estudio. No se observaron reacciones adversas asociadas con la administración de lokivetmab durante la fase inicial de tres meses (142 perros) o durante la fase subsiguiente de seis meses (81 perros).

**Conclusiones e importancia clínica** – Lokivetmab a una dosis mensual mínima de 1 mg /kg proporcionó un control rápido (en el primer día) y un efecto duradero en la reducción de prurito y lesiones cutáneas con un buen perfil de seguridad.

## Zusammenfassung

**Hintergrund** – Lokivetmab ist ein anti-caniner-IL-31 monoklonaler Antikörper zur Behandlung klinischer Manifestationen von atopischer Dermatitis (AD) des Hundes.

**Hypothese/Ziele** – Die Charakterisierung der Wirksamkeit und Sicherheit von Lokivetmab und eine Darstellung der Tatsache, dass es Ciclosporin unter Feldbedingungen nicht unterlegen ist.

**Tiere** – Hunde mit chronischer AD (n = 274) aus 40 Praxen in Belgien, Holland, Frankreich und Deutschland wurden in die Studie aufgenommen.

**Methoden** – Die Tiere wurden zufällig (1:1) zu Ciclosporin *per os* (5mg/kg/einmal täglich) oder monatlichem Lokivetmab zur Injektion (1-3,3 mg/kg) für drei Monate zugeteilt. Einundachtzig Tiere, die die Vergleichsphase erfolgreich beendet hatten, gelangten in die weiterführende Phase, wo sie Lokivetmab für weitere sechs Monate erhielten. Die BesitzerInnen beurteilten den Juckreiz nach einer Visual Analog Skala, die Hautveränderungen wurden von tierärztlichen Untersuchern mittels Canine AD Extent and Severity Index (CADESI-03) Skala beurteilt.

**Ergebnisse** – Lokivetmab war Ciclosporin in Bezug auf die Reduzierung des Juckreizes am Tag 28 (51,90% versus 43,72%) nicht unterlegen. Für Tag 28 wurde keine prozentuelle CADESI-03 Reduktion erreicht bzw keine Unterlegenheit von Lokivetmab (54,17) versus Ciclosporin (56,86%) festgestellt. Zu keinem der Zeitpunkte waren die durchschnittlichen CADESI-03 Werte zwischen den Gruppen signifikant unterschiedlich. Eine fortgesetzte Wirksamkeit gegenüber dem Juckreiz und den Veränderungen wurde in der Folgephase gezeigt, worin 76,3% der Tiere (n=45) zu Studienende als „normal“ in Bezug auf den Juckreiz beurteilt wurden. Es wurden keine Nebenwirkungen für die Gesundheit mit Lokivetmab während der Einstiegsphase von drei Monaten (142 Hunde) oder während der Folgephase von sechs Monaten (81 Hunde) gesehen.

**Schlussfolgerungen und klinische Bedeutung** – Lokivetmab bewirkte bei einer minimalen monatlichen Dosis von 1 mg/kg eine rasche (innerhalb eines Tages) Reduktion des Pruritus sowie der Hautveränderungen, die eine anhaltende Wirkung bei gutem Sicherheitsprofil zeigte.

## 要約

**背景** – Lokivetmabは、犬アトピー性皮膚炎(AD)の臨床症状の治療のための注射用抗イヌIL-31モノクローナル抗体である。

**仮説/目的** – Lokivetmabの有効性と安全性を評価すること、および、臨床現場においてシクロスポリンに劣らない効果があることを実証すること。

**供与動物** – ベルギー、オランダ、フランス、ドイツの40の病院より組み入れられた慢性ADの犬(n = 274)。

**方法** – 患者は、経口シクロスポリン(5 mg/kg、1日1回)群または月一回のLokivetmab注射(1~3.3mg / kg)群に無作為(1:1)に振り分けられ、3ヶ月間治療を受けた。比較試験を完遂した81頭は、さらに6ヶ月間のLokivetmab継続試験に組み入れられた。飼い主は視覚的アナログスケール(Visual Analog Scale)を用いて痒みを評価し、皮膚病変は犬のADの範囲および重症度指数(CADESI-03)スケールを用いて、獣医師による評価が行われた。

**結果** – 28日目におけるLokivetmabの痒み軽減率は、シクロスポリンと比べて劣っていなかった(51.90%対43.72%)。28日目におけるCADESI-03の減少率については、シクロスポリン(56.86%)に対するLokivetmab(54.17)の非劣性は得られなかった。いずれの評価時点においても、2群間に平均CADESI-03スコアの有意差は認められなかった。継続試験において、76.3%の患者が(n = 45)試験終了時に痒みレベルが「正常」と評価され、痒みおよび病変に対する継続的な有効性が実証された。最初の3ヶ月間(142頭)またはその後の6ヶ月間(81頭)に、Lokivetmabに関連する有害事象は観察されなかった。

**結論および臨床的な重要性** – Lokivetmabを少なくとも1mg/kgの用量で毎月投与すると、安全に迅速で(1日以内)持続的な痒みおよび皮膚病変の軽減効果を示す。

## 摘要

**背景** – Lokivetmab是一种注射型抗犬IL-31的单克隆抗体,用于治疗犬异位性皮炎(AD)的临床症状。

**假设/目的** – 评估Lokivetmab的功效和安全性,并证明其临床效果不亚于环孢菌素。

**动物** – 来自比利时、荷兰、法国和德国40个试验点的慢性AD患犬(n=274)。

**方法** – 将动物随机分配(1:1)为口服环孢菌素组(5mg/kg,每日一次)或每月注射Lokivetmab组(1-3.3mg/

kg),连续使用3个月。81只动物在成功完成对比阶段的治疗之后,进入到持续治疗期,即额外接受6个月Lokivetmab治疗。宠主根据视觉模拟量表对瘙痒进行评估,皮肤病变则由兽医调查员根据犬AD程度和严重性指数(CADESI-03)量表进行评估。

**结果** — 在第28天,Lokivetmab的止痒效果并不亚于环孢菌素(51.9% VS 43.72%),同时,CADESI-03减少百分比,lokivetmab(54.17%)与环孢菌素(56.86%)并无明显差异。在任何时间点,组间CADESI-03评分均未显示显著差异。在继续治疗阶段,证实lokivetmab对瘙痒和病变具有持续性功效,其中76.3%的动物(n=45)在研究结束时瘙痒评估为正常。在初始治疗的三个月期间(142只犬)或随后的六个月期间(81只犬),均未观察到有与lokivetmab相关的不良反应事件。

**结论和临床意义** — Lokivetmab以每月1mg/kg的最低剂量即可快速起效(一天内),并具有持久减轻瘙痒和皮肤病变的效果,具有良好的安全性。

## Resumo

**Contexto** — O Lokivetmab é um anticorpo monoclonal anti-IL-31-canino para tratar as manifestações clínicas da dermatite atópica (DA) em cães.

**Hipótese/Objetivos** — Caracterizar a eficácia e segurança de lokivetmab, e demonstrar a sua não inferioridade à ciclosporina em condições de campo.

**Animais** — Foram selecionados 274 cães com DA de 40 clínicas da Bélgica, Holanda, França e Alemanha.

**Métodos** — Os animais foram randomizados (1:1) para ciclosporina oral (5 mg/kg/uma vez ao dia) ou aplicação mensal de lokivetmab (1–3.3 mg/kg) por três meses. Oitenta e um animais que completaram satisfatoriamente a fase comparativa foram incluídos em uma fase de continuação recebendo lokivetmab por seis meses adicionais. O prurido foi avaliado pelos proprietários através de uma escala de prurido analógica visual, as lesões cutâneas foram avaliadas pelos veterinários pesquisadores utilizando a escala *Canine AD Extent and Severity Index* (CADESI-03).

**Resultados** — O lokivetmab não foi considerado inferior à ciclosporina para a redução do prurido no Dia 28 (51.90% versus 43.72%). Para o Dia 28, a não inferioridade do lokivetmab (54.17) em relação à ciclosporina (56.86%) para a porcentagem de redução no CADESI-03 não foi alcançada. As médias de escore do CADESI-03 não foram significativamente diferentes entre os grupos em nenhum dos tempos. A eficácia contínua na redução do prurido e lesões cutâneas foi demonstrada na fase de continuação, em que 76,3% dos animais (n = 45) foram considerados como normais em relação ao prurido no fim do estudo. Não foram observadas ocorrências clínicas anormais associados ao lokivetmab durante a fase dos três meses iniciais (142 cães) ou durante a fase de continuação nos seis meses subsequentes (81 cães).

**Conclusões e importância clínica** — O lokivetmab na dose mensal mínima de 1mg/kg proporcionou um efeito rápido (em um dia) e duradouro de redução do prurido e lesões cutâneas com um perfil de segurança adequado.