

## Masitinib decreases signs of canine atopic dermatitis: a multicentre, randomized, double-blind, placebo-controlled phase 3 trial

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### Conflict of Interest

Masitinib is under clinical development by the study sponsor, AB Science, SA, Paris, France. The sponsor was involved in the study design, data interpretation, manuscript preparation and submission. A.M. is an employee and shareholder of the study sponsor. O.H. and

P.D. are consultants and shareholders of the study sponsor. E.B. is the recipient of a research grant from AB Science. No other conflicts of interest have been declared.

### Abstract

This study investigated the efficacy and safety of masitinib, a selective tyrosine kinase inhibitor capable of downregulating mast cell functions, for treatment of canine atopic dermatitis (CAD). Dogs with confirmed CAD received masitinib at 12.5 mg/kg/day ( $n = 202$ ) or control ( $n = 104$ ) for 12 weeks. A reduction in CAD Extent and Severity Index (CADESI-02) score of  $\geq 50\%$  at week 12 was observed in 61% of masitinib-treated dogs versus 35% of control dogs ( $P < 0.001$ ), according to the modified intent-to-treat population. For dogs resistant to ciclosporin and/or corticosteroids (60% of the study population), CADESI-02 response rates were 60 versus 31%, respectively ( $P = 0.004$ ). The mean reduction in pruritus score of severely pruritic dogs was 46 versus 29%, respectively ( $P = 0.045$ ). Furthermore, 65% of owners with severely pruritic dogs assessed masitinib efficacy as good/excellent versus 35% control ( $P = 0.05$ ). Overall, 63% of investigators assessed masitinib efficacy as good/excellent versus 35% control ( $P < 0.001$ ). Premature discontinuations from the modified intent-to-treat population (28.2% masitinib versus 26.0% control) were mainly due to adverse events (13.4 versus 4.8%, respectively) or lack of efficacy (12.4 versus 18.3%, respectively). In total, 13.2% dogs presented with severe adverse events (16.0% masitinib versus 7.7% control). Masitinib showed a risk of reversible protein loss, although regular surveillance of blood albumin and proteinuria allowed for discontinuation of treatment while the dog was still clinically asymptomatic. Masitinib proved to be an effective and mostly well-tolerated treatment of CAD, including severe and refractory cases, with medically manageable adverse effects.

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### Introduction

Atopic dermatitis is a chronic, pruritic inflammatory skin disease. Its severity can range from an annoyance in the form of mild itching through to debilitating extensive lesion coverage that has a profoundly negative impact on the quality of life. The prevalence of canine atopic derma-

titis (CAD) is poorly defined, but it is well recognized that dogs suffering from this condition will be regularly presented to veterinary practitioners.<sup>1</sup> The condition usually manifests itself before 3 years of age and is likely to be a life-long condition, necessitating a long-term treatment regimen aimed at keeping an animal in remission rather than intermittently managing exacerbations.<sup>2</sup> Despite this fact, therapeutic options for treating generalized CAD are limited. In a review of randomized clinical trials investigating various interventions for CAD and practical guidance on its treatment,<sup>3,4</sup> evidence of high efficacy in decreasing pruritus and/or skin lesions was found for oral glucocorticoid steroids and calcineurin inhibitors, such as oral ciclosporin.<sup>5,6</sup> However, glucocorticoids are associated with numerous detrimental adverse effects, especially with prolonged exposure, making their long-term use questionable, while ciclosporin, although generally better tolerated, is associated with the adverse effects of vomiting, diarrhoea and anorexia, among others.<sup>2,4</sup>

Given that CAD has a complex pathogenesis with varied pathology, no single therapeutic approach is likely to be beneficial for all cases, i.e. certain dogs will be responsive to one therapy but unresponsive to another. This diverse nature of CAD necessitates that a patient's treatment is individually and continuously tailored for effective management. Another aspect currently lacking from CAD treatment is that therapies are rarely curative, with a rapid return towards baseline values commonly occurring upon treatment cessation; for example, 87 and 62% of dogs treated respectively with methylprednisolone and ciclosporin relapsed within 2 months.<sup>7</sup> Thus, beyond the already-developed therapeutic strategies, there exists an unmet medical need to identify alternative treatments for CAD that can demonstrate high efficacy over time in monotherapy, that exploit novel therapeutic targets for more effective combination therapies or treatment of dogs resistant to current therapies, and that minimize long-term toxicity and are ideally curative. One such approach involves blocking intracellular proinflammatory messages, represented presently by the strategy of selective protein tyrosine kinase inhibition.

There is a growing body of evidence implicating the involvement of mast cells in the pathogenesis of CAD.<sup>8–10</sup> These cells release large amounts of various mediators that sustain the inflammatory network, which in turn is responsible for many of the clinical manifestations of the disease. Molecules that are able to inhibit the survival and/or activation of mast cells may therefore be valuable tools for the treatment of CAD. Stem cell factor, the ligand of the c-Kit receptor, is a critical growth factor for mast cells;<sup>11</sup> hence, there exists a strong connection between c-Kit and the pathogenesis of CAD.

Masitinib is a tyrosine kinase inhibitor that potently and selectively targets c-Kit, thereby exerting a direct antiproliferative and proapoptotic action on mast cells through disruption of the stem cell factor–mast cell c-Kit pathway.<sup>12</sup> Previously, a phase 3 study showed oral masitinib at 12.5 mg/kg/day to be safe and effective for the treatment of canine mast cell tumours.<sup>13,14</sup> Masitinib (Masivet<sup>®</sup>; AB Science, Paris, France) has subsequently been approved by the European Medicines Agency and has received conditional approval (as Kinavet CA-1<sup>®</sup>) from

the US Food and Drug Administration. In addition to its antiproliferative properties, masitinib can also regulate the activation of mast cells through its targeting of Lyn and Fyn, key components of the transduction pathway leading to IgE-induced degranulation.<sup>15</sup> This can be observed in the inhibition of the high-affinity IgE receptor (FcεRI)-mediated degranulation of human cord-blood-derived mast cells.<sup>12</sup>

The purpose of this study was to evaluate the efficacy and safety of masitinib in the treatment of dogs with atopic dermatitis.

## Methods

### Study design

This was a 12 week, prospective, multicentre, randomized, double-blind, placebo-controlled, pivotal phase 3 study to compare efficacy and safety of masitinib at 12.5 mg/kg/day with a control, in the treatment of CAD. An open-ended extension phase was possible for those dogs experiencing improvement. Dogs stayed with their owners throughout the study, in their usual conditions, and the owner signed an informed consent form. Before initiation of the study, the protocol was reviewed and approved by the US Food and Drug Administration and by the European Agency for the Evaluation of Medicinal Products. The study was conducted in compliance with the Procedures and Principles of Good Clinical Practice. A study flow-chart detailing typical visit and assessment schedules is presented in Table S1 (see Document S1 in Supporting Information).

### Eligibility criteria

Dogs of any breed or sex, diagnosed with CAD according to the standard clinical criteria<sup>16</sup> and having a CAD Extent and Severity Index (CADESI-02)<sup>17,18</sup> score  $\geq 25$ , were recruited from 45 veterinary clinics across Europe and the USA. No minimal pruritus score was defined. Dogs were required to show at least one positive reaction to either an *in vitro* or an intradermal test within 6 months prior to enrolment. Any dogs presenting with CAD that was exclusively seasonal, food related or due to flea allergy (as determined via testing) were excluded. Other exclusion criteria were as follows: dogs presenting with certain infections, including *Staphylococcus*, *Malassezia*, purulent otitis and dermatophytes; dogs younger than 12 months of age, weighing less than 3.5 kg, or used for breeding; dogs with inadequate organ function (as determined via blood tests); a life expectancy of less than 3 months; or a medical condition that could interfere with disease evaluation.

Use of the following treatments was prohibited during the study, with wash-out periods observed for the indicated duration prior to baseline: anti-inflammatory agents, including nonsteroidal anti-inflammatory drugs (2 weeks); corticosteroids (2–8 weeks); ciclosporin (4–8 weeks); tacrolimus (2 weeks); allergen-specific immunotherapy (4 weeks); antihistamines H1 (1 week); investigational treatments (4–12 weeks); vaccination for control of infectious disease or immunotherapy (4 weeks); and any change of intake for essential fatty acids (4 weeks) or vitamin E supplementation (8 weeks). The only authorized concomitant antibiotic or antifungal treatments were cefalexin or amoxicillin–clavulanate, and miconazole or ketoconazole, respectively. A weekly use of shampoo containing chlorhexidine, ethyl lactate or benzoyl peroxide was permitted for antiseptic treatment, while Epi-Otic<sup>®</sup> (Virbac, Carros, France) was allowed for auricular care.

### Experimental protocol

Masitinib was provided by AB Science in 50 or 150 mg nondivisible coated tablets, administered orally, once daily for 12 weeks. Composition and dispensing of the test drug and control treatment were identical except for omission of the active ingredient from the control. The initial masitinib dose of 12.5 mg/kg/day was selected based upon results from a pilot study,<sup>9</sup> as well as toxicity and bio-

availability studies in dogs and rats (Patrice Dubreuil, 2010; personal communication). Treatment interruption or changes to dose were permitted for dogs experiencing mild to moderate toxicity following predefined criteria: treatment could be temporarily interrupted and resumed at the same dose upon resolution; if toxicity was recurrent, dosage could be decreased by 2.5 mg/kg/day; and in the case of persistent toxicity following dose reduction, treatment was discontinued. Treatment was also discontinued for dogs experiencing disease progression, defined as a 25% increase in their CADESI-02 baseline value.

Dogs were randomized into one of two parallel groups, masitinib or control, with a ratio of 2:1, respectively. A restricted randomization schedule for packaging and labelling, based upon a minimization technique, was generated and held by a decentralized service (Cardinal Systems, Paris, France). At each inclusion, the randomization centre was contacted and treatment allocated depending on how best to reduce the difference between treatment groups (probabilistic weighting of 0.75). All participants and study personnel, including investigators, statisticians and data managers, were blinded to treatment allocation over the duration of the study. Treatment compliance was assessed via review of a questionnaire completed daily by the owner and by recording the number of tablets returned.

### Assessment of efficacy

For each dog, all efficacy parameters were recorded on the first day of treatment (baseline), then at weeks 4, 8 and 12, and every 4 weeks thereafter during the extension phase. Concomitant long-acting flea treatment was administered between 4 and 2 weeks prior to baseline, then every 4 weeks from baseline until week 12, and every 12 weeks thereafter (extension phase; see Table S1, Document S1 in Supporting Information).

Evaluation of efficacy was based upon response in two co-primary end-points, CADESI-02 and pruritus scores, after 12 weeks of masitinib treatment as compared with control. Analyses were conducted individually for each primary end-point and also for concurrent success in both co-primary end-points. Subpopulation analyses were conducted on each primary end-point to explore the efficacy of masitinib in those dogs identified by the investigator as being refractory to ciclosporin and/or corticosteroids.

Canine Atopic Dermatitis Extent and Severity Index score-02 is a composite index of three clinical symptoms associated with CAD (namely, erythema, lichenification and excoriations), with a decrease in score between two time points indicating clinical improvement.<sup>17,18</sup> Response was expressed as the mean difference in CADESI-02 at week 12 relative to baseline, and as the proportion of dogs achieving the *a priori* threshold of  $\geq 50\%$  improvement at week 12. Pruritus was classified using a visual analog scale (VAS) of pruritus, for which owners estimated the severity of pruritus during the 3 days preceding each visit by drawing a mark on a 200 mm vertical VAS. As no minimal pruritus score was specified within the eligibility criteria and so that improvement could be detected during the study, analyses were conducted on a subpopulation with severe pruritus at baseline using a threshold of the upper 15%, i.e. a pruritus score of 170–200 mm. Response was expressed as the proportion of dogs achieving the *a priori* threshold of  $\geq 20\%$  improvement, with a maximal value of 100 mm, at week 12. As a consequence of these dual criteria on pruritus response, responders from the severe baseline pruritus subpopulation must in fact achieve an improvement of  $>40\%$ .

Dogs resistant or intolerant to ciclosporin and/or corticosteroids (referred to generally hereafter as the 'resistant to ciclosporin and/or corticosteroids population') were dogs that: (i) received ciclosporin and/or corticosteroids according to the standard of care and experienced disease progression without an initial response (primary resistance or refractory); (ii) initially responded to treatment but then experienced disease progression (secondary resistance); and (iii) discontinued therapy due to occurrence of an adverse event (AE) during treatment, or because of risks associated with cumulative exposure to those treatments. Resistance or intolerance to ciclosporin and/or

corticosteroids was assigned by each investigator based upon prior treatment history.

Secondary end-points included both an investigator's and an owner's global assessment of efficacy at week 12, based upon their perception of treatment efficacy using a rating scale of none, poor, fair, good or excellent. The use of antibiotic, antifungal or antiseptic treatments over the 12 week study period was also analysed to explore their potential impact on pruritus response. Additionally, further subanalysis of improvement in CADESI-02 at week 12 relative to baseline was performed using several *a priori* ranges, and the time to response from date of randomization was evaluated based upon first documented response in CADESI-02.

### Assessment of safety

Blood albumin and urine protein checks were carried out every 2 weeks throughout the course of treatment, with clinical safety monitoring including haematology and biochemistry analyses performed every 4 weeks (See Table S1, Document S1 in Supporting Information). Toxicity was graded according to the Veterinary Cooperative Oncology Group common terminology criteria for AEs.<sup>19</sup> An AE was thus defined as any unfavourable or unintended sign (including an abnormal clinicopathological finding), clinical sign (e.g. loss of mobility or gastrointestinal, genitourinary or dermatological signs) or disease temporally associated with the use of the treatment that may or may not be related to the treatment. Safety assessment was via occurrence of AEs (subcategorized as mild, moderate or severe intensity) and serious AEs (including nonfatal serious AEs, deaths and euthanasia). All AEs, regardless of causality, were recorded during the study.

### Sample size

Response in CADESI-02 and pruritus clinical parameters, as well as withdrawal rate, was estimated from related or similarly designed CAD studies.<sup>9,17</sup> Based upon the estimates of active and control interventions respectively having a CADESI-02 response of 40 versus 8% and a pruritus score response of 20 versus 5%, it was calculated that a sample size of at least 300 dogs (randomized as 200 dogs in the masitinib group and 100 dogs in the control group) was required for a study power of at least 85% ( $\alpha = 0.025$ , two-sided Bonferroni multiple comparison for co-primary end-points).

### Statistical analyses

Evaluation of efficacy was based upon response in two co-primary end-points, CADESI-02 and pruritus scores, after 12 weeks of masitinib treatment as compared with control. The type I ( $\alpha$ ) error was 5% (two sided) for all analyses, with a confidence interval (CI) of 95%. To adjust for multiple testing of the two primary efficacy variables, a Bonferroni corrected significance level of 2.5% and CI of 97.5% were used. Response rates were calculated for each treatment group and compared between groups using the stratified Cochran–Mantel–Haenszel test with stratification on centre. Comparisons of change from baseline were made using a repeated analysis of covariance (ANCOVA) model with treatment, time and baseline value as factors. Kaplan–Meier estimates were plotted and the median calculated for time to response analyses (groups were compared using a stratified log-rank test with stratification on centre), with data from dogs reporting no response or lost to follow up being censored at the last date a dog was known not to be presenting a response. All data analyses and reporting procedures used SAS v9.1 (SAS Institute, Cary, NC, USA) in a Windows XP operating system environment.

Analyses were performed on a modified intent-to-treat (mITT) population and per protocol population. The intent-to-treat population was defined as all randomized dogs whether they had received study treatment or not. The mITT population included all randomized dogs except for those exiting the study prematurely due to well-documented, nontreatment-related causes.<sup>20</sup> The per protocol population was defined as a subgroup of the mITT population that in addition had presented no major protocol deviations. Analyses on each population were conducted according to three possible data sets: imputation of missing values according

to the last observation carried forward methodology; the absence of data imputation, i.e. the observed cases data set; and considering missing data as nonresponders, i.e. the missing data as failure data set.

## Results

### Baseline characteristics

Patient characteristics, including demographic profile, clinical baseline, disposition and drug exposure, are presented in Table 1. There were no statistically significant differences between treatment groups for any of the efficacy parameters tested (Table 1).

Between November 2006 and November 2009, a total of 367 dogs were screened, of which 316 were randomized (210 dogs into the masitinib group and 106 dogs

into the control group). The mITT population comprised 306 dogs (202 dogs in the masitinib group and 104 dogs in the control group), while the per protocol population consisted of 275 dogs (180 dogs in the masitinib group and 95 dogs in the control group). Overall median age, weight and CADESI-02 baseline score of dogs in the mITT population were 5.1 years, 25 kg and 42, respectively. The median baseline pruritus score, as measured on the 200 mm VAS, was 149 mm, with 86 of 306 dogs (28%) classified as having severe pruritus at baseline. A total of 190 of 306 dogs (62.1%) were classified as resistant to ciclosporin and/or corticosteroids, comprising 10 of 190 dogs (5%) treated previously with ciclosporin, 158 of 190 dogs (83%) treated previously with corticosteroids and 22 of 190 dogs (12%) previously treated with both.

**Table 1.** Baseline characteristics, overall disposition and dosing history, according to modified intent-to-treat population

Parameter	Masitinib (n = 202)	Control (n = 104)	All (n = 306)
<b>Demographic</b>			
Age (years)			
Mean ± SD	5.4 ± 2.6	5.0 ± 2.7	5.3 ± 2.6
[Min, Max]	[0.8, 12.8]	[1.0, 12.0]	[0.8, 12.8]
Weight (kg)			
Mean ± SD	23.0 ± 14.0	26.0 ± 14.6	24.0 ± 14.2
[Min, Max]	[4.0, 68.5]	[4.6, 81.8]	[4.0, 81.8]
Sex (n, %)			
Female	106 (52.5%)	52 (50.0%)	158 (51.6%)
Region (n, %)			
West European	93 (46.0%)	55 (52.9%)	148 (48.4%)
East European	13 (6.4%)	4 (3.8%)	17 (5.6%)
Guadeloupe	25 (12.4%)	11 (10.6%)	36 (11.8%)
Southern USA	42 (20.8%)	14 (13.5%)	56 (18.3%)
Western USA	10 (5.0%)	9 (8.7%)	19 (6.2%)
Centre/midwest USA	19 (9.4%)	11 (10.6%)	30 (9.8%)
<b>Clinical</b>			
CADESI-02			
Mean ± SD	50 ± 25	55 ± 37	52 ± 30
[Min, Max]	[25, 162]	[26, 265]	[25, 265]
Pruritus score			
Mean ± SD	138 ± 42	142 ± 41	140 ± 42
[Min, Max]	[11, 200]	[10, 200]	[10, 200]
Severe pruritus (n, %), ≥170	51 (25.2%)	35 (33.7%)	86 (28.1%)
Infection at baseline*, Yes	43 (21.3%)	31 (29.8%)	74 (24.2%)
Prior resistance†, Yes	121 (59.9%)	69 (66.3%)	190 (62.1%)
<b>Disposition</b>			
Discontinued before week 12 (n, %)			
Total	57 (28.2%)	27 (26.0%)	84 (27.5%)
Adverse event	27 (13.4%)	5 (4.8%)	32 (10.5%)
Lack of efficacy	25 (12.4%)	19 (18.3%)	44 (14.4%)
Consent withdrawn	2 (1.0%)	1 (1.0%)	3 (1.0%)
Other	3 (1.5%)	2 (1.9%)	5 (1.6%)
Entered extension (n, %)	60 (29.7%)	31 (29.8%)	91 (29.7%)
<b>Drug exposure</b>			
Initial dose (mg/kg/day), Mean ± SD	11.6 ± 1.5		
Treatment duration (weeks), Mean ± SD	17.2 ± 17.3		
Dose reduction (n, %)	20 (9.9%)		

Abbreviations: CADESI, Canine Atopic Dermatitis Extent and Severity Index; Min, minimum; Max, maximum; SD, standard deviation.

\*Infections not listed in the exclusion criteria, e.g. conjunctivitis, otitis media.

†Dogs resistant (primary or secondary) or intolerant to ciclosporin and/or corticosteroids.



**Participant flow**

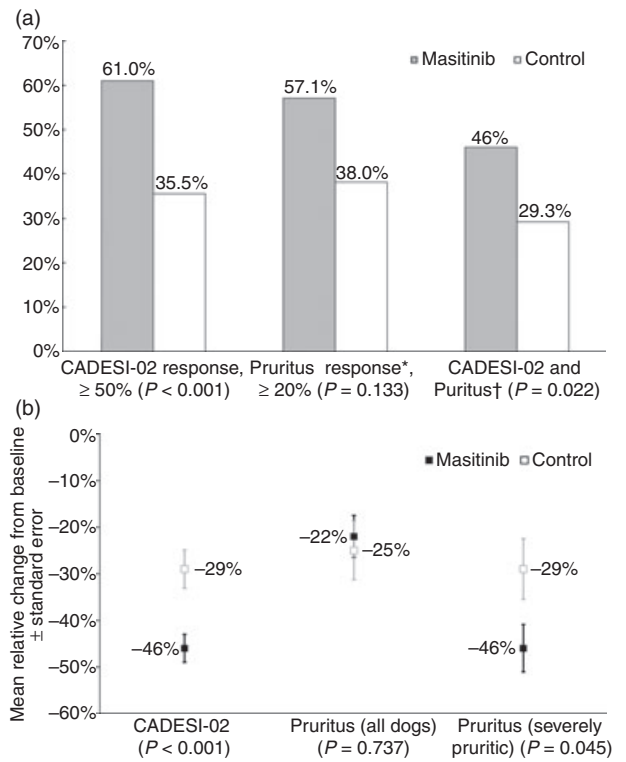
A total of 84 of 306 dogs (27.5%) withdrew prematurely prior to completion of the 12 week treatment period; 57 of 202 dogs (28.2%) and 27 of 104 dogs (26%) in the masitinib and control groups, respectively ( $P = 0.787$ ). The most frequently cited reasons were AEs (13.4 versus 4.8%, respectively) or lack of efficacy (12.4 versus 18.3%, respectively). The average study duration of dogs from each treatment group was similar at  $8.6 \pm 4.3$  versus  $9.5 \pm 5.5$  weeks, respectively. Ninety-one dogs from the mITT population (29.7%) entered the blinded extension phase upon completion of the 12 week study period, comprising 60 of 202 dogs (29.7%) and 31 of 104 dogs (29.8%) from the masitinib and control groups, respectively.

**Compliance**

Compliance records did not reveal any major overall deviation from the prescribed treatment. On average, the dose of masitinib received was 95% of the intended dose, with the doses received at randomization being  $11.6 \pm 1.5$  and  $11.9 \pm 1.4$  mg/kg/day in the masitinib and control groups, respectively. Dose intensity was <80% of the theoretical dose prescribed for 20 of 202 dogs (9.9%) in the masitinib group and four of 104 dogs (3.8%) in the control group. Lack of treatment compliance over the 12 week study led to study termination for two of 202 dogs (1.4%) from the masitinib group compared with none from the control group.

**Efficacy assessment**

Overall, evaluation of efficacy based upon the mITT population was well supported by their corresponding per protocol population analyses. Likewise, all analysed data sets showed similar improvement trends, with the mITT observed cases data set at 12 weeks presented hereafter unless stated otherwise. A summary of the primary end-point assessment for masitinib is presented in Table 2 (including analyses according to the missing data as



**Figure 1.** Primary end-point assessment according to modified intent-to-treat population, observed cases at week 12. (a) Response rates. (b) Relative mean change from baseline (least square means  $\pm$  SEM). \*Analysis for subpopulation of dogs with severe pruritus at baseline. †Analysis for all dogs regardless of pruritus at baseline.

failure data set, i.e. overall mITT) and Figure 1, while the secondary end-point assessment is presented in Table 3.

**Assessment of primary end-points**

Canine atopic dermatitis symptoms were significantly improved for masitinib-treated dogs according to the

**Table 2.** Summary of primary end-points at week 12 in the modified intent-to-treat (mITT) population according to the data sets of observed cases and missing data as failure\*

	Observed cases			Missing data as failure		
	Masitinib	Control	P-value	Masitinib	Control	P-value
CADESI-02 relative change from baseline†	-46% $\pm$ 3.0	-29% $\pm$ 4.1	<0.001	—	—	—
CADESI-02 response rate, $\geq 50\%$	86 of 141 (61.0%)	27 of 76 (35.5%)	<0.001	86 of 202 (42.6%)	27 of 104 (26.0%)	<0.001
Pruritus relative change from baseline	-22% $\pm$ 4.5	-25% $\pm$ 6.3	0.737	—	—	—
Pruritus relative change (severely pruritic)‡	-46% $\pm$ 5.1	-29% $\pm$ 6.5	0.045	—	—	—
Pruritus response rate, $\geq 20\%$ § (severely pruritic)	20 of 35 (57.1%)	8 of 21 (38.1%)	0.133	20 of 51 (39.2%)	8 of 35 (22.9%)	0.040
Pruritus and CADESI-02 response rate	64 of 139 (46.0%)	22 of 75 (29.3%)	0.022	64 of 202 (31.7%)	22 of 104 (21.2%)	0.038

\*The mITT population consisted of all randomized dogs except for those exiting the study prematurely due to well-documented, nontreatment-related causes. Analyses were conducted according to different data sets: the observed cases data set absence of data imputation, and the missing data as failure data set, i.e. considering missing data as nonresponders. For example, the mITT masitinib treatment group consisted of 202 dogs, of which 141 dogs were evaluable at week 12 for the CADESI-02 response rate.

†Least square means  $\pm$  SEM given for observed cases data set with an ANCOVA (repeated analysis of covariance model) adjusted on baseline value. All analyses are done with the same model.

‡Analysis for subpopulation of dogs with severe pruritus at baseline.

§Pruritus response was expressed as the proportion of dogs achieving the *a priori* threshold of  $\geq 20\%$  improvement, with a maximal value of 100 mm, at week 12. The implication of these dual criteria on pruritus response is that responders from the severe baseline pruritus subpopulation exhibited an improvement of  $\geq 40\%$ .

**Table 3.** Summary of secondary end-points at week 12 in the modified intent-to-treat population, according to observed cases data

	Masitinib	Control	<i>P</i> -value
Investigator's global assessment (good/excellent)	90 of 143 (62.9%)	26 of 74 (35.1%)	<0.001
Investigator's global assessment of severely pruritic dogs (good/excellent)	24 of 34 (71%)	8 of 20 (40%)	0.053
Owner's global assessment (good/excellent)	80 of 143 (55.9%)	31 of 74 (41.9%)	0.084
Owner's global assessment of severely pruritic dogs (good/excellent)	22 of 34 (65%)	7 of 20 (35%)	0.050
Concomitant antimicrobial medications	68 of 202 (33.7%)	47 of 104 (45.2%)	0.049
CADESI-02 response rate (subanalysis)*	<i>n</i> = 141	<i>n</i> = 76	0.002
Complete response (100% decrease)	2 (1.4%)	0 (0.0%)	
Good response ( $\geq 75$ and $< 100\%$ decrease)	40 (28.4%)	16 (21.1%)	
Partial response ( $\geq 50$ and $< 75\%$ decrease)	44 (31.2%)	11 (14.5%)	
Low response ( $\geq 25$ and $< 50\%$ decrease)	26 (18.4%)	26 (34.2%)	
No response ( $< 25\%$ decrease or increase)	27 (19.1%)	17 (22.4%)	
Aggravation ( $\geq 25\%$ increase)	2 (1.4%)	6 (7.9%)	

\*Improvement in CADESI-02 at week 12 relative to baseline with performance rated according to *a priori* ranges.

CADESI-02 response rate, with 86 of 141 dogs (61.0%) in the masitinib group showing a  $\geq 50\%$  reduction of their baseline CADESI-02 score at week 12, compared with 27 of 76 dogs (35.5%) in the control group ( $P < 0.001$ , according to observed cases data set; Table 2 and Figure 1). Change in CADESI-02 score relative to baseline also showed significant improvement, with a decrease in the least squares means value of  $-46\% \pm 3.0$  for the masitinib group compared with  $-29\% \pm 4.1$  for the control group ( $P < 0.001$ ). Similar improvements were observed for the subpopulation of dogs resistant to ciclosporin and/or corticosteroids, with CADESI-02 response rates of 49 of 82 dogs (59.8%) in the masitinib group compared with 16 of 52 dogs (30.87%) in the control group ( $P = 0.004$ ), and relative decreases in CADESI-02 least squares means values of  $-45\% \pm 3.9$  in the masitinib group compared with  $-22\% \pm 5.0$  in the control group ( $P < 0.001$ ). These improved response rates were corroborated by their associated missing data as failure data sets with comparable statistical significance (Table 2). Furthermore, significant improvement in change of CADESI-02 relative to baseline for masitinib-treated dogs was evident after 4 weeks of treatment compared with control ( $P = 0.021$ ), improving steadily through weeks 8–12. Likewise, CADESI-02 response rates were superior for masitinib-treated dogs at week 4, with 66 of 193 dogs (34.2%) showing a  $\geq 50\%$  reduction of their baseline CADESI-02 score compared with 24 of 100 dogs (24.0%) in the control group ( $P = 0.098$ ; see Table S2, Document S1 in Supporting Information).

Considering the mITT population with severe pruritus at baseline ( $n = 86$ ), a significant improvement in pruritus response rate was observed in the missing data as failure data set at week 12, with 20 of 51 dogs (39.2%) in the masitinib group achieving the response criteria (i.e. equivalent to a  $\geq 40\%$  reduction) compared with eight of 35 dogs (22.9%) in the control group ( $P = 0.04$ ; Table 2 and Figure 1). A significant improvement in pruritus response rate was also evident for those dogs resistant to ciclosporin and/or corticosteroids that also presented with severe pruritus at baseline, with 14 of 32 dogs (43.8%) from the

masitinib group meeting the response criteria compared with six of 24 dogs (25%) from the control group ( $P = 0.021$ ).

The number of dogs showing a positive response to both co-primary end-points (regardless of pruritus severity) was significantly higher for the masitinib group, with 64 of 139 dogs (46.0%) achieving concurrent response compared with 22 of 75 dogs (29.3%) in the control group ( $P = 0.022$ ; Table 2 and Figure 1). Likewise, analysis according to the missing data as failure data set revealed statistical significance, with 64 of 202 dogs (31.7%) achieving concurrent response in the masitinib group compared with 22 of 104 dogs (21.2%) in the control group ( $P = 0.038$ ).

#### Assessment of secondary end-points

Investigators rated the efficacy of masitinib in reducing the symptoms of CAD as significantly better than the control, with a rating of 'excellent' or 'good' being assigned to 90 of 143 dogs (62.9%) from the masitinib group compared with 26 of 74 dogs (35.1%) from the control group ( $P < 0.001$ ; Table 3). This significant change in global assessment of efficacy was apparent as early as weeks 4 and 8 ( $P = 0.027$  and  $0.032$ , respectively). Considering the subpopulation of dogs resistant to ciclosporin and/or corticosteroids, a rating of 'excellent' or 'good' was given at week 12 for 53 of 83 dogs (63.9%) from the masitinib group compared with 14 of 50 dogs (28.0%) from the control group ( $P = 0.001$ ). Owner-assigned global assessments of treatment efficacy likewise showed a favourable opinion towards masitinib.

Subanalysis of the CADESI-02 response rate was conducted with responses subcategorized from complete response (a 100% decrease from baseline) to aggravation ( $\geq 25\%$  increase from baseline; Table 3). Overall, two of 141 dogs (1.4%) from the masitinib group achieved a complete response compared with none from the control group. Conversely, the rate of dogs experiencing an aggravation in their condition was greater in the control group compared with the masitinib group; six of 76 dogs (7.9%) versus two of 141 dogs (1.4%), respectively. The evaluation of time to CADESI-02 first response, defined as the delay between the date of randomization and date

of documented first response, showed a median time of 1.9 weeks (95% CI 1.9–2.0) for masitinib-treated dogs, which was significantly shorter than the 3.4 weeks (95% CI 2.1–9.5) observed in the control group ( $P = 0.014$ ). Finally, assessment of concomitant antimicrobial or antiseptic treatment over the 12 week study period showed a higher frequency of use in the control group compared with the masitinib group; 47 of 104 dogs (45.2%) versus 68 of 202 dogs (33.7%), respectively ( $P = 0.049$ ; Table 3).

#### Safety and tolerability of masitinib

The safety population was defined as all dogs enrolled in the study that received at least one treatment dose, comprising 206 of 310 dogs (66.5%) in the masitinib group and 104 of 310 dogs (33.5%) in the control group. A summary of AEs over the first 12 weeks of treatment is presented in Table 4. The incidence of dogs experiencing at least one AE over the 12 week study period was similar between treatment groups, with 121 of 206 dogs (58.7%) in the masitinib group and 54 of 104 dogs (51.9%) in the control group. However, the frequency of severe AEs and nonfatal serious AEs was higher in the masitinib group compared with the control group: 33 of 206 dogs (16.0%) versus eight of 104 dogs (7.7%); and 15 of 206 dogs (7.3%) versus none, respectively. Dogs resistant to ciclosporin and/or corticosteroids showed a similar safety profile to the overall population. Frequency of deaths over the 12 week study period was two of 206 dogs (1.0%) from the masitinib group and two of 104 dogs (1.9%) from the control group. Both dogs from the control group died from cardiac failure. In the masitinib group, one death was suspected as being related to the study drug, with the dog experiencing liver function test abnormalities and hypoalbuminaemia prior to death, while the other was not assessable. In addition, two of 206 dogs (1.0%) from the masitinib group were euthanized over the 12 week study period compared with none from the control group. One of these euthanized dogs

experienced complications related to nephropathy suspected to be related to masitinib, although this dog had a pre-existing chronic kidney failure at the time of study enrolment, which could have been aggravated by treatment. The reason for euthanasia of the other dog was unrelated to the study drug.

The majority of AEs were of mild to moderate intensity, with four AEs (according to all intensities) occurring more often in the masitinib group compared with the control group, i.e. a difference of >5%. These were protein loss, comprising proteinuria in 33 of 206 dogs (16.0%) versus nine of 104 dogs (8.7%), respectively; hypoalbuminaemia in 14 of 206 dogs (6.8%) versus one of 104 dogs (1.0%), respectively; anorexia in 22 of 206 dogs (10.7%) versus five of 104 dogs (4.8%), respectively; transaminases increased in 18 of 206 dogs (8.7%) versus three of 104 dogs (2.9%), respectively; and leukopenia in 11 of 206 dogs (5.3%) versus none, respectively. Considering the subcategory of severe AEs, only proteinuria in 12 of 206 dogs (5.8%) and hypoalbuminaemia in five of 206 dogs (2.4%) were reported at an incidence of >2% higher in the masitinib treatment group. Consistent with the known safety profile of tyrosine kinase inhibitors, masitinib was better tolerated after approximately 3 months of treatment, with a decrease in the frequency of AEs, severe AEs and nonfatal serious AEs reported during the extension phase compared with the first 12 weeks; (32 versus 59%; 7 versus 16% and 3 versus 7%, respectively). Furthermore, study discontinuation was similar between the masitinib and control groups during the extension phase (3.3 versus 3.2%, respectively); however, possible bias in withdrawal of intolerant dogs prior to the extension phase may be partly responsible for these observations.

## Discussion

Canine atopic dermatitis is the first nononcological veterinary application for the tyrosine kinase inhibitor, masitinib, although its potential in chronic inflammatory disorders has been demonstrated by numerous human clinical trials.<sup>21–23</sup> In fact, it is a common misnomer to describe masitinib, and similar tyrosine kinase inhibitors, as a chemotherapeutic agent because unlike cytotoxic chemotherapies that kill all dividing cells, including healthy cells, masitinib is a targeted therapy. The association of masitinib as an anticancer treatment is therefore more a consequence of its chronological development rather than any mechanistic basis. Depending on which kinases are targeted, tyrosine kinase inhibitors are equally well suited for the treatment of nononcological diseases.

Masitinib showed an equivalent level of efficacy when compared with available treatments, such as ciclosporin at 5 mg/kg and methylprednisolone at 0.75 mg/kg.<sup>17,24</sup> Specifically, the mean reduction in CADESI was 46% for masitinib, 52% for ciclosporin and 45% for methylprednisolone. The CADESI response rate was 61% for masitinib (43% according to the missing data as failure data set), 66% for ciclosporin and 58% for methylprednisolone. The investigator's global assessment of efficacy was 63% responses good/excellent for masitinib (45%

**Table 4.** Summary of adverse event frequency according to intent-to-treat population, ( $n = 310$ ) over the first 12 weeks of treatment

Number (%) of dogs with at least one	Masitinib ( $n = 206$ )	Control ( $n = 104$ )
Adverse event	121 (58.7%)	54 (51.9%)
Severe adverse event	33 (16.0%)	8 (7.7%)
Nonfatal serious adverse event	15 (7.3%)	0 (0.0%)
Death	2 (1.0%)	2 (1.9%)
Euthanasia	2 (1.0%)	0 (0.0%)
Discontinuation for safety reasons (total)	51 (24.8%)	6 (5.8%)
Prevention rules*	27 (13.1%)	4 (3.8%)
Adverse event related†	24 (11.7%)	2 (1.9%)

Note: 'severe' is not synonymous with 'serious', the former being used to describe the intensity of a specific event, although the event itself may be of relatively minor medical significance. Seriousness of an adverse event is based on patient/event outcome or action criteria, e.g. hospitalization, and serves as a guide for defining regulatory reporting obligations.

\*Discontinuations due to protein-loss prevention safety rules.

†Discontinuations due to adverse events, including renal adverse event.

according to the missing data as failure data set), 75% for ciclosporin and 63% for methylprednisolone. As masitinib is a registered anticancer treatment being used for a nononcological pathology, the relatively high patient withdrawal rate observed can be partly attributed to an understandably cautious response to AEs. For populations with such patient attrition, some degree of positive or negative bias is inevitable depending on which data set methodology is used, with the true value likely to be found between that of the observed cases and missing data as failure data set results.

The majority of masitinib-related AEs were of mild to moderate intensity, with a lower proportion of dogs reporting at least one AE compared with ciclosporin and methylprednisolone; 59% for masitinib versus 81% for both ciclosporin (5 mg/kg) and methylprednisolone (0.75 mg/kg).<sup>24</sup> However, masitinib did show a risk of protein loss and greater incidence of severe AEs. Protein loss was observed to occur almost uniquely during the first 3 months of treatment, with dogs recovering quickly and without relapse after discontinuation of masitinib.<sup>25</sup> Indeed, once identified, the development of a protein-loss management plan greatly mitigated this risk, with only one case reported following its implementation. Briefly, assessment of several biological markers of renal function led to the conclusion that albuminaemia was the best parameter with which to monitor the risk of masitinib-induced protein loss, using a threshold of 0.75 times the lower limit of normal. Thus, surveillance of albumin and proteinuria every other week allows for the discontinuation of masitinib whilst the dog is still clinically asymptomatic. Moreover, the reversibility of hypoalbuminaemia upon treatment discontinuation supports a temporary rather than permanent interruption in treatment.

For dogs with severe pruritus at baseline, a significant improvement in pruritus response was observed in masitinib-treated dogs compared with those receiving control. This was not the case for analysis of the overall mITT population, i.e. no minimal pruritus score, a discrepancy possibly due to use of concomitant antimicrobial and/or antiseptic medications having a confounding effect on the owner-assessed pruritus scores for dogs presenting with nonsevere pruritus at baseline.<sup>17,26</sup> Further exploration of the potential impact from concomitant treatments in this study confirms this theory (see Document S1 in Supporting Information, including Tables S3 and S4, and Figures S1 and S2). For example, when dogs from the control group did not receive concomitant treatments, pruritus response rate was independent of baseline pruritus severity; however, when concomitant treatments were used then pruritus response rate was significantly higher for dogs presenting with mild to moderate pruritus at baseline compared with severe pruritus ( $P = 0.006$ ). Furthermore, because the pruritus score is subjective it can suffer from possible bias and high variability; effects which were more apparent in dogs with mild to moderate pruritus at baseline compared with those with severe pruritus (see Figures S1 and S2, and Table S4, Document S1 in Supporting Information). Hence, data on pruritus in the absence of minimal baseline criteria must be interpreted with caution. These findings support imposition of a minimal pruritus

threshold, in particular, restricting pruritus analyses to those dogs presenting with severe pruritus at baseline. Ideally, pruritus data should be considered in the context of complimentary parameters, such as CADESI response. Indeed, when considering concurrent response rates in CASESI-02 and pruritus criteria, then significant efficacy was shown for masitinib treatment compared with control, irrespective of pruritus baseline severity.

The present randomized controlled trial was one of the largest CAD cohorts tested to date,<sup>4</sup> in which concurrent and complicating diseases had been ruled out. Results provide strong evidence that daily administration of oral masitinib achieved significant reduction in the symptoms of CAD and could therefore be an effective treatment option. Given the selective targeting of mast cells by masitinib, these findings also provide further clinically relevant evidence of the involvement of this cell in CAD. Moreover, as CAD has a varied pathogenesis and because the mechanism of action of masitinib differs from those treatments already available, it is possible that masitinib might represent the optimal treatment option for a certain subpopulation of dogs. The proportion of masitinib responders from the ciclosporin and/or corticosteroid refractory subpopulation helps to support this hypothesis. Further evidence of such mechanistic subpopulations is also found from various ciclosporin or corticosteroids trials, in which 33–50% of dogs were reported as nonresponders,<sup>4</sup> and also that some dogs may be unresponsive to one of these drugs but respond well to the other, and *vice versa*. Further study is required to identify the bases of such subpopulations and, moreover, to identify which dogs will respond optimally to a given therapeutic approach.

In summary, a positive CAD response to masitinib was evident for treatment-naïve dogs, dogs resistant to ciclosporin and/or corticosteroids and dogs with severe pruritus, the latter two groups representing populations with high unmet medical need. Masitinib therefore provides an important new tool in the veterinarian's armamentarium for effective treatment of CAD.

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## Supporting Information

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

**Document S1.** Masitinib in canine atopic dermatitis.

**Table S1.** Study flow chart.

**Table S2.** Evolution of CADESI-02 response in the mITT population over a 12-week treatment period, according to data sets of observed cases and missing data as failure.

**Table S3.** Distribution of dogs according to their pruritus score at baseline.

**Table S4.** Pruritus response rate in the control group at week 12 according to concomitant use of antibiotic, antifungal or antiseptic treatments and baseline pruritus – mITT population.

**Figure S1.** Representation of the variability of severity perception among pet owners (Bland and Altman method).

**Figure S2.** Representation of the variability of perception of changes among pet owners (Bland and Altman method).

### Discussion on the bias in pruritus scoring.

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**Résumé** Cette étude porte sur l'efficacité et l'innocuité du masitinib, un inhibiteur sélectif de la tyrosine kinase, capable de diminuer les fonctions des mastocytes dans le traitement de la dermatite atopique canine (DAC). Des chiens atopiques ont reçu du masitinib à 12.5 mg/kg/jour ( $N = 202$ ) ou un traitement contrôle ( $N = 104$ ) pendant 12 semaines. Une réduction  $\geq 50\%$  du CADESI-02 à la semaine 12 a été observée pour 61% des chiens traités contre 35% des chiens contrôlés; ( $P < 0.001$ ); selon la

population ITT (intention to treat population) et l'ensemble de données des cas observés (cité ci-après sauf indication contraire). Les résultats correspondant obtenus en considérant que les cas manquants étaient des échecs étaient respectivement 43% contre 26% ( $P < 0.001$ ). Pour les chiens résistants à la ciclosporine et/ou aux corticostéroïdes (60% de la population de l'étude), les taux de réponse du CADESI-02 étaient respectivement de 60% contre 31% ( $P = 0.004$ ). La diminution moyenne du score de prurit des chiens sévèrement prurigineux était respectivement de 46% contre 29% ( $P = 0.045$ ). En outre, 65% des propriétaires de chiens sévèrement prurigineux ont évalué l'efficacité du masitinib comme bon/excellent contre 35% chez les propriétaires des chiens du groupe contrôle ( $P = 0.05$ ). De plus, 63% des investigateurs ont évalué l'efficacité du masitinib comme bon/excellent contre 35% chez les chiens contrôles ( $P < 0.001$ ). Les arrêts prématurés de la population mITT (28.2% masitinib contre 26.0% contrôle) ont été dus principalement aux effets indésirables (respectivement 13.4% contre 4.8%) ou au manque d'efficacité (respectivement 12.4% contre 18.3%). Au total, 13.2% des chiens ont présenté des effets indésirables sévères (16.0% masitinib contre 7.7% contrôle). Le masitinib a montré un risque réversible de fuite protéique bien qu'une surveillance régulière de l'albuminurie et de la protéinurie a permis un arrêt du traitement alors que l'animal était encore cliniquement asymptomatique. Le masitinib a prouvé son efficacité et a été plutôt bien toléré dans le traitement de la DAC, y compris pour des cas sévères et réfractaires avec des effets indésirables médicalement gérables.

**Resumen** Este estudio investigó la eficacia y la seguridad del masitinib, un inhibidor selectivo de tirosin-quinasa capaz de disminuir las funciones del mastocito, para el tratamiento de la dermatitis atópica canina (CAD). Los perros con CAD confirmado recibieron masitinib a una dosis de 12,5 mg/kg/día ( $N = 202$ ) o control ( $N = 104$ ) durante 12 semanas. Se observó una reducción en CADESI-02  $\geq 50\%$  en la semana 12 en un 61% de perros tratados con masitinib frente a control que fue del 35% ( $P < 0,001$ ); de acuerdo con la población en intención de tratamiento, casos observados en el grupo de datos (mencionado de aquí en adelante a menos que esté indicado de otra manera). El resultado correspondiente según el grupo de datos considerando la ausencia como fallo fue del 43% frente a un 26%, respectivamente ( $P < 0,001$ ). Para los perros resistentes a ciclosporin y/o a corticoesteroides (el 60% de la población del estudio), los índices de respuesta CADESI-02 fueron de 60% frente a un 31%, respectivamente ( $P = 0,004$ ). La reducción media en prurito de perros severamente pruríticos fue del 46% frente a un 29%, respectivamente ( $P = 0,045$ ). Además, el 65% de dueños con perros severamente pruríticos determinaron eficacia del masitinib como buena/excelente frente a un 35% en perros control ( $P = 0,05$ ). En conjunto, el 63% de investigadores determinaron eficacia del masitinib como buena/excelente frente a perros control de un 35% ( $P < 0,001$ ). La interrupción prematura del tratamiento en la población del mITT (masitinib 28,2% frente a control 26,0%) fue principalmente debido a los efectos adversos (13,4% contra 4,8%, respectivamente) o falta de eficacia (12,4% frente a 18,3%, respectivamente). En total, 13,2% perros presentaron efectos adversos severos (masitinib 16,0% frente a control 7,7%). Masitinib demostró un riesgo reversible de pérdida de proteínas, aunque el control regular de la albúmina y de la proteinuria permitió la interrupción del tratamiento cuando el perro seguía siendo clínicamente asintomático. Masitinib demostró ser eficaz y sobre todo un tratamiento bien tolerado en la CAD, incluyendo casos severos y refractarios, con efectos secundarios médicamente manejables.

**Zusammenfassung** In dieser Studie wurde die Wirksamkeit und die Sicherheit von Masitinib, einem selektiven Tyrosinkinasehemmer, der imstande ist Mastzellfunktionen zu drosseln, für die Behandlung der caninen atopischen Dermatitis (CAD) untersucht. Hunde mit bestätigter CAD erhielten Masitinib in einer Dosierung von 12,5mg/kg/Tag ( $N = 202$ ) 12 Wochen, ebenso die Kontrollgruppe, die aus 104 Hunden bestand. Eine Reduzierung des CADESI-02 von  $\geq 50\%$  in der 12. Woche wurde bei 61% der mit Masitinib behandelten Hunde im Vergleich zu nur 35% der Kontrolltiere beobachtet ( $P < 0,001$ ); dies wurde mit einer modifizierten Intention-to-treat Gruppe (mITT) ermittelt. Bei Hunden, die resistent waren auf Cyclosporin und/oder Kortikosteroide (60% der Studienpopulation), betrugen die CADESI-02 Verbesserungsraten 60% bzw. 31% ( $P = 0,004$ ). Die durchschnittliche Verminderung des Juckreiz-Wertes von hochgradig juckenden Hunden betrug 46% bzw. 29% ( $P = 0,045$ ). Weiters beurteilten 65% der BesitzerInnen von hochgradig juckenden Hunden die Wirksamkeit von Masitinib als gut/exzellente im Vergleich zu 35% der BesitzerInnen der Kontrolltiere ( $P < 0,001$ ). Ein frühzeitiges Absetzen der mITT Population (28,2% Masitinib versus 26% der Kontrollen) war hauptsächlich auf Nebenwirkungen zurückzuführen (13,4% bzw. 4,8%) oder aufgrund fehlender Wirksamkeit (12,4% bzw. 18,3%). Insgesamt zeigten 13,2% der Hunde starke Nebenwirkungen (16% Masitinib bzw. 7,7% der Kontrolltiere). Bei der Behandlung mit Masitinib konnte ein reversibler Proteinverlust auftreten, obwohl eine regelmäßige Überwachung von Albumin und einer auftretenden Proteinurie den Abbruch der Behandlung noch während der Hund klinisch symptomlos war, ermöglichten. Masitinib zeigte sich als wirksame und weitgehend gut verträgliche Behandlung von CAD, auch bei schweren und hartnäckigen Fällen, mit Nebenwirkungen die medizinisch kontrollierbar waren.

**要約** この研究では、肥満細胞の機能をダウンレギュレートする選択性チロシンキナーゼ阻害薬であるマスチニブの、犬のアトピー性皮膚炎 (CAD) の治療に対する有効性と安全性を評価した。CAD と確定診断した群 ( $N = 202$ ) と対照群 ( $N = 104$ ) に  $12.5 \text{ mg/kg/日}$  のマスチニブを、12 週間投与した。12 週での CADESI-02 スコアの 50% 改善率は、マスチニブ投与群で 61% であったのに対して対照群では 35% であった ( $P < 0.001$ )。Intent-to-treat (ITT, 訳者註: 試験に割りつけた患者をすべての分析する) 群の解析によっても、症例データが存在した (別に記載されている場合をのぞき、今後引用する)。不完全なデータと考えられ、除外した症例でも、結果はそれぞれ 43% に対して 26% と同様であった ( $P < 0.001$ )。シクロスポリンおよび/またはコルチコステロイドに抵抗性の犬 (試験群の 60%) において、CADESI-02 改善率は 60% と 31% であった ( $P = 0.004$ )。重度のそう痒を示す犬のそう痒スコアの平均減少値はそれぞれ 46% と 29% であった。さらに、重度のそう痒を示した犬の飼い主の 65% がマスチニブの効果を良好/優れていると評価したのに対して、対照群では 35% であった。全体的に、調査者の 63% がマスチニブの効果を良好/優れていると評価した ( $P < 0.001$ )。mITT 群の早期の脱落症例 (28.2% マスチニブ群 vs 26.0% 対照群) は主に有害事象 (それぞれ 13.4% vs. 4.8%)、または無効 (それぞれ 12.4% vs. 18.3%) を原因としていた。全体で、13.2% の犬に重度の有害事象が認められた (16.0% マスチニブ群 vs. 7.7% 対照群)。マスチニブは可逆性のタンパク質の喪失のリスクを示したが、通常のアブミンとタンパク尿の検査で治療が中断されたが犬は臨床的に無症状であった。マスチニブは重症で難治性の症例を含む CAD の治療として有効であり、ほとんどの場合、医療的に対応可能な副作用はあるものの投与によく耐える。