Veterinary Dermatology

Vet Dermatol 2016 DOI: 10.1111/vde.12364

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

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Background – Lokivetmab (ZTS-00103289) is a caninized anti-canine IL-31 monoclonal antibody that has demonstrated efficacy in reducing pruritus associated with atopic dermatitis (AD) in dogs in field trials.

Hypothesis/Objectives – This study evaluated the safety of lokivetmab in a randomized, double blind, placebo-controlled trial in client owned dogs with AD with minimal restrictions on concomitant medications and co-morbidities.

Animals – Clinicians at 14 veterinary clinics enrolled client owned dogs (n = 245) with chronic AD.

Methods – Dogs were randomized at a 2:1 ratio to receive either lokivetmab (1.0–3.3 mg/kg) or placebo administered subcutaneously on days 0 and 28. Clinicians examined dogs, and collected blood and urine for assessment of clinical pathology and immunogenicity (days 0, 28 and 42).

Results – There were no immediate hypersensitivity reactions (e.g. wheals, vomiting). Discomfort at administration occurred in 5.1% of dogs and was similar in frequency and severity between lokivetmab- and placebo-treated groups. Pruritus was reported as an adverse event during the study less frequently in the lokivetmab-treated group (4.9% and 19.3%, respectively); otherwise, adverse events occurred at a similar frequency between treatment groups. There were no clinically important differences between groups in clinical pathology results. Treatment-induced immunogenicity was found in 2.5% of lokivetmab treated dogs. A wide variety of concomitant medications were used with no clinically apparent adverse interactions.

Conclusions and clinical importance – Among a diverse population of 162 client owned dogs with a clinical diagnosis of AD, treatment with two monthly doses of lokivetmab was safe, based on observed adverse events and clinical pathology results over a 42 day period.

Introduction

Lokivetmab is a caninized anti-canine interleukin-31 (IL-31) monoclonal antibody (mAb) that binds to and neutralizes the soluble inflammatory mediator IL-31 in dogs.[1,2] Field and laboratory studies show IL-31 is a critical cytokine involved in pruritus in dogs with atopic dermatitis (AD).[1] The current report details results of a randomized clinical trial that evaluated the safety of lokivetmab in dogs with AD under field conditions where there were minimal restrictions on co-morbidities and no restrictions on concomitant medications.

Materials and methods

The study was conducted in support of product registration by the United States Department of Agriculture. The protocol was reviewed by and approved before study initiation by the Zoetis Ethical Review Board. The owners gave written informed consent for each dog to participate in the study.

Dogs were client-owned of any age and body weight, overall healthy, apart from AD, based on the initial (Day 0) physical examination and were diagnosed with AD based on clinical signs and compatible history, according to the veterinarian. Exclusion criteria included dogs with evidence of malignant neoplasia or immune suppression (e.g. hyperadrenocorticism) and lactating bitches or dogs intended for use as breeding animals.

Enrolled dogs were randomized to treatment with lokivetmab or placebo in a 2:1 ratio at each clinic using SAS v9.3 (SAS Institute Inc.; Cary, NC, USA). Blocking was based on order of enrolment within clinic. Dog was the experimental unit. Dog owners, laboratory personnel, clinicians and all site personnel, with the exception of the treatment dispenser, were masked to treatment group assignments. The treatment dispenser utilized a treatment randomization file that was unique to the site to determine the treatment group assignment, drew up the correct dose of treatment into a syringe and then provided it to study personnel for administration.

Lokivetmab was provided in ready-to-use one mL single-use (no preservative) vials containing 10, 20, 30 or 40 mg/mL in a histidine buffer. Dogs in the placebo group were given the same volume as dogs in the lokivetmab group; the placebo was identical in appearance to the lokivetmab and contained all of the same excipients except for lokivetmab. Placebo and lokivetmab were stored refrigerated (2–8°C) before use. Following randomization, dogs were

Accepted 17 June 2016
Source of Funding: This study was initiated and funded by Zoetis Inc, Florham Park, NJ, USA.
Conflict of Interest: All authors are employees of Zoetis Inc.

assigned to receive either placebo or lokivetmab (1.0–3.3 mg/kg) subcutaneously on days 0 and 28 (±3 days). A dose of 1.0 mg/kg represented a nominal dose.

Baseline data (demographic, physical examination) were collected on enrolment at Day 0. Owners returned dogs to the clinic on days 28(±3) and 42(±3) for physical examination. Clinicians recorded adverse events[3] reported by owners or identified on physical examination throughout the study.

Blood samples [complete blood count, serum chemistry, anti-drug antibodies (ADAs) and lokivetmab concentrations] and urine samples for urinalysis and urine protein creatinine ratio were collected on days 0 and 28 (before dosing) and Day 42. The samples were sent to one laboratory (Heska Corp.; Loveland, CO, USA). Serum samples at each time point were analysed for lokivetmab and ADAs using validated methods at Zoetis Inc., Kalamazoo, MI, USA.

Data were summarized using SAS v9.3 (SAS Institute). No hypothesis testing was conducted.

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

Results

Two hundred and forty five dogs were enrolled from 14 veterinary clinics (Table 1). All enrolled dogs were included in the summaries. The same percentage (1.2%) of cases in both treatment groups were withdrawn from study or lost to follow-up before Day 42.

Table 2 provides a comparison of adverse events that occurred in >2% of lokivetmab-treated dogs. A similar proportion of vomiting, anorexia, lethargy and diarrhoea adverse events in both groups resolved spontaneously or with supportive care. Adverse events involving skin infection (e.g. pyoderma) were followed post-study until resolution or considered by the clinician to be a chronic condition. Discomfort associated with injection persisting beyond the immediate post-injection period was reported once and involved scratching at the site of lokivetmab administration for 15 min following the first dose only. 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). The remaining adverse events occurred in <2.0% of the lokivetmab-treated group. Arithmetic mean values for all clinical pathology analytes in both treatment groups fell within the laboratory's normal reference ranges at all visits (days 0, 28 and 42) except serum alkaline phosphatase (placebo group) which was slightly above reference range throughout the study.

Table 1. Demographics of enrolled dogs at Day 0

Variable	Lokivetmab *N* = 162 % (*n*)	Placebo *N* = 83 % (*n*)
Breed distribution		
Purebred	72.8 (118)	72.3 (60)
Mixed breed	27.2 (44)	27.7 (23)
Sex distribution		
Male	51.9 (84)	59.0 (49)
Female	48.1 (78)	41.0 (34)
Age at study onset, years (range)	6.8 (1.0–14.5)	6.2 (0.8–13.0)
Weight at study onset, kg (range)	26.0 (2.4–88.6)	20.7 (4.6–63.6)

Table 2. Adverse events occurring at least once in > 2% of lokivetmab-treated group over the course of the 42 day study

Adverse Reactions*	Lokivetmab *N* = 162 % (*n*)	Placebo *N* = 83 % (*n*)
Otitis externa	13.0 (21)	12.0 (10)
Dermatitis	9.9 (16)	13.3 (11)
Bacterial skin infection	9.3 (15)	12.0 (10)
Erythema	8.0 (13)	4.8 (4)
Vomiting	7.4 (12)	10.8 (9)
Anorexia	6.2 (10)	4.8 (4)
Lethargy	5.6 (9)	6.0 (5)
Pruritus	4.9 (8)	19.3 (16)
Diarrhoea	3.7 (6)	4.8 (4)
Alopecia	2.5 (4)	7.2 (6)
Fleas	2.5 (4)	2.4 (2)

*Adverse reactions were tabulated per animal.

Two dogs in each treatment group showed serious adverse events. The first case was a 4-year-old neutered female English cocker spaniel; significant findings on Day 0 before treatment with lokivetmab included fever (39.8°C), mild regenerative anaemia, slight polychromasia and three nucleated red blood cells per 100 white blood cells; platelets were clumped and an accurate count was, therefore, unavailable. Treatment with cefpodoxime proxetil was initiated (Day 8) to treat a cough associated with tracheobronchitis of one day duration. Immune-mediated haemolytic anaemia and immune-mediated thrombocytopaenia were diagnosed (Day 12); remission was achieved by Day 43 with immunosuppressive treatment. Serious adverse events in the remaining three dogs included a placebo-treated dog diagnosed with diabetes mellitus after initiating a corticosteroid and two dogs, one placebo-treated and one lokivetmab-treated, that had pre-existing conditions (well-controlled hypoadrenocorticism and moderate regenerative anaemia, respectively) and were diagnosed with lymphoma while on study.

Of the >200 concomitant medications administered during this study, those most frequently used (i.e. ≥6% of lokivetmab-treated group) are summarized in Supplementary Table 1.

Four (2.5%) of the lokivetmab-treated dogs were categorized as having treatment-induced immunogenicity; anti-lokivetmab titres in these dogs were <10 at Day 0, remained low on Day 28 (<10 to 10) and increased on Day 42 (32–315). Average day 28 and 42 serum lokivetmab concentrations were ~90% lower than the remaining treated animals.

Discussion

The lack of restrictions on concomitant medications in the current trial likely contributed to a similar proportion of placebo- and lokivetmab-treated dogs completing the study, thus allowing a direct comparison of adverse event frequencies. The cases with serious adverse events reported would not have been eligible to enrol in a traditionally designed field efficacy study with restrictions on concomitant conditions at enrolment, and where corticosteroids and systemic antibiotics are not permitted during study or shortly before enrolment.

There were no clinically apparent adverse interactions between lokivetmab and any of the concomitantly administered medications, although this study was not designed specifically to detect such interactions. Xenobiotic metabolizing enzymes, such as cytochrome P450 enzymes, are not involved in elimination of mAbs; therefore, metabolic drug–drug interactions, caused by inhibition or induction of cytochrome P450 enzymes, are not expected.[4] However, other types of interactions are possible**,** notably cytokine-mediated changes in expression of drug-metabolizing enzymes.[5] In chronic inflammatory diseases, elevated levels of cytokines such as IL-6 and TNFα lead to downregulation of cytochrome P450 enzymes.[5,6] Treatment with a mAb that blocks the action of pro-inflammatory cytokines can result in normalization of cytochrome P450 levels and thus affect the levels of other concomitantly administered small molecule drugs.[7] If pro-inflammatory cytokines downregulate cytochrome P450 enzymes in dogs with AD, a decrease in these cytokines following administration of a therapeutic mAb could be expected to lead to a decrease in circulating concentrations of concomitantly administered CYP450-metabolized drugs (e.g. ciclosporin), although such an effect is most relevant for drugs with a narrow therapeutic range (e.g. antineoplastic drugs).

Lokivetmab is a "caninized" monoclonal antibody;[2] such speciation decreases immunogenicity in the target species,[8] even though all therapeutic mAbs remain immunogenic to some extent.[9] ADAs may bind to therapeutic mAbs leading to neutralization or increased clearance and potentially result in decreased efficacy.[9,10] ADAs have been associated with a higher risk of hypersensitivity reactions[10] although such reactions have not been observed in dogs treated with lokivetmab in laboratory or clinical field trials thus far.

The current study was not designed to compare safety of doses within the range administered (e.g. 1.0 mg/kg compared to 3.3 mg/kg). However, laboratory dog studies identified no treatment-related adverse effects following repeat administration of lokivetmab at the highest dose tested (10 mg/kg) (data on file).

Results of this study demonstrated that under field conditions two consecutive monthly doses of lokivetmab (1.0–3.3 mg/kg) were safe in a diverse population of 162 client-owned dogs, diagnosed with AD, based on observed adverse events and clinical pathology results. Further studies are needed to evaluate the safety of lokivetmab following long-term use in dogs with AD.

Acknowledgements

We would like to thank the following veterinarians who enrolled dogs in this study and performed the clinical investigations: Ryan Carpenter, Terry Clekis, Karen Farver, Sam Geller, Robert Jackson, Carolyn Kidney, Thomas Lewis, Andrew Pickering, Chris Reeder, Jason St. Romain, Kristi Rowland, Jay Schweizer, Roger Sifferman and Timothy Strauss. The test article (lokivetmab or placebo) was provided at no cost to the clinic and clinicians were compensated for the costs associated with each dog's clinic visits. We thank the following current and former Zoetis colleagues for their contributions: Aniket Badkar, Patrick Birkholz, Joseph F. Boucher, Anne E. Daniels, Clifford Ferree, Matthew Krautmann, David Garcia-Tapia, Mary Pat Gorman, Jessica Harfst, Nicole Honsberger, Ben Hummel, Cari LaGrow, Sunil Narisetty, Candace Sousa and Rostyslav Tsapyak.

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Supporting Information

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

Table S1. Concomitant medications and therapies administered at least once to at least 6% of lokivetmab-treated group over the course of the 42 day study.

Résumé

Contexte – Le lokivetmab (ZTS-00103289) est un anticorps monoclonal anti-IL-31 canin qui a montré son efficacité dans la réduction du prurit associé à la dermatite atopique (AD) chez le chien dans les essais de terrain.

Hypothèses/Objectifs – Cette étude évalue l'innocuité du lokivetmab dans un essai contrôlé contre placebo, randomisé, en double aveugle, chez des chiens de propriétaires atteints de dermatite atopique avec des restrictions minimales sur les traitements concomitants et les comorbidités.
Sujets – Les cliniciens de 14 cliniques vétérinaires ont enrôlés des chiens de propriétaires (n = 245) atteints d'AD chronique.
Méthodes – Les chiens ont été randomisés au ratio 2:1 pour recevoir soit du lokivetmab (1.0–3.3 mg/kg) ou un placebo par voie sous cutanée à jours 0 et 28. Les cliniciens ont examiné les chiens, collectés du sang et de l'urine pour l'évaluation de pathologies cliniques et de l'immunogénicité (jours 0, 28 et 42).
Résultats – Il n'y a eu aucune réaction d'hypersensibilité immédiate (e.g. plaques, vomissements). Un inconfort à l'administration était rapporté dans 5.1% des chiens et était similaire en fréquence et intensité entre les groupes traités au lokivetmab et le groupe placebo. Le prurit a été rapporté comme effet indésirable moins souvent pour le groupe traité au lokivetmab (4.9% et 19.3% respectivement); cependant les effets indésirables ont été rapportés à la même fréquence entre les groupes. Il n'y avait aucune différence clinique importante entre les groupes dans les résultats pathologiques cliniques. L'immunogénicité induite par le traitement était identifiée dans 2.5% des chiens traités au lokivetmab. Une large variété de traitements concomitants a été utilisée sans interaction indésirable décelable cliniquement.
Conclusions et importance clinique – Parmi la population de 162 chiens de propriétaires atteins de AD, le traitement de deux doses à un mois d'intervalle de lokivetmab a été sûr, basé sur les effets indésirables observés et les résultats de pathologie clinique sur une période de 42 jours.

Resumen
Introducción – Lokivetmab (ZTS-00103289) es un anticuerpo monoclonal anti-canino caninizado frente a IL-31 que ha demostrado eficacia en la reducción del prurito asociado con la dermatitis atópica (AD) en perros en pruebas de campo.
Hipótesis/Objetivos – Este estudio evaluó la seguridad de lokivetmab en un estudio doble ciego, al azar, controlado con placebo en perros de propietarios privados con AD con restricciones mínimas acerca de medicamentos concomitantes y otras enfermedades conjuntas.
Animales – Los médicos veterinarios en 14 clínicas veterinarias admitieron perros de propietarios privados (n = 245) con AD crónica.
Métodos – Los perros fueron asignados al azar en una proporción de 2: 1 para recibir lokivetmab (1,0 a 3,3 mg / kg) por vía subcutánea o placebo administrado en los días 0 y 28. Los veterinarios examinaron los perros, la sangre y la orina recogidos para la evaluación de la patología clínica y la inmunogenicidad (días 0, 28 y 42).
Resultados – No hubo reacciones de hipersensibilidad inmediata (por ejemplo, ronchas, vómitos). Se observó malestar tras la administración en un 5,1% de los perros que fue similar en frecuencia y gravedad entre lokivetmab y los grupos tratados con placebo. Prurito fue reportado como un efecto adverso durante el estudio con menor frecuencia en el grupo tratado con lokivetmab (4,9% y 19,3%, respectivamente). Aparte de esto, los efectos adversos se produjeron con una frecuencia similar entre los grupos de tratamiento. No hubo diferencias clínicamente importantes entre los grupos en los resultados de patología clínica. Inmunogenicidad inducida por el tratamiento se encontró en 2,5% de los perros tratados con lokivetmab. Una amplia variedad de medicamentos concomitantes fueron utilizados durante el estudio sin interacciones adversas clínicamente aparentes.
Conclusiones e importancia clínica – En una población diversa de 162 perros de propietarios privados con un diagnóstico clínico de la AD, el tratamiento con dos dosis mensuales de lokivetmab fue seguro, basado en los eventos adversos observados y los resultados de patología clínica durante un periodo de 42 días.

Zusammenfassung
Hintergrund – Lokivetmab (ZTS-00103289) ist ein caninisierter anti-Hunde IL-31 monoklonaler Antikörper, der bei der Reduzierung des Juckreizes, der durch eine atopische Dermatitis (AD) bei Hunden in Feldstudien bedingt war, Wirksamkeit gezeigt hat.
Hypothese/Ziele – Diese Studie evaluierte die Sicherheit von Lokivetmab in einer randomisierten, doppelblinden, Plazebo-kontrollierten Studie mit Hunden in Privatbesitz mit AD mit minimalen Einschränkungen von begleitenden Medikamenten und Begleiterkrankungen.
Tiere – KlinikerInnen in 14 Veterinärkliniken nahmen Privathunde (n = 245) mit chronischer AD in die Studie auf.
Methoden – Die Hunde wurden zufällig im Verhältnis 2:1 eingeteilt, um entweder Lokivetmab (1,0-3,3 mg/kg) oder Plazebo, welches subkutan verabreicht wurde, an den Tagen 0 und 28 zu erhalten. Die KlinikerInnen untersuchten die Hunde und nahmen Blut- und Urinproben, um die klinische Pathologie und die Immunogenität (an den Tagem 0, 28 und 42) zu erfassen.
Ergebnisse – Es bestanden keine Immunreaktionen vom Soforttyp (z.B. Blasen, Vomitus). Bei 5,1% der Hunde bestand ein Unbehagen bei der Verabreichung, welches ähnlich in Frequenz und Schweregrad in

der Lokivetmab- und in der Plazebo-Gruppe war. Juckreiz wurde während der Studie als Nebenwirkung weniger häufig in der Lokivetmab-behandelten Gruppe (4,9% bzw 19,3%) beschrieben; ansonsten traten Nebenwirkungen in einer ähnlichen Frequenz zwischen den Behandlungsgruppen auf. Es bestanden keine klinisch wichtigen Unterschiede zwischen den Gruppen in Bezug auf die Ergebnisse der klinischen Pathologie. Eine durch die Behandlung induzierte Immunogenität wurde bei 2,5% der mit Lokivetmab behandelten Hunde festgestellt. Es wurde eine große Breite an begleitenden Medikamenten verwendet, ohne offensichtliche klinische Nebenwirkungsreaktionen.

Schlussfolgerungen und klinische Bedeutung – In einer sehr unterschiedlichen Population von 162 Privathunden mit einer klinischen Diagnose von AD, war die Behandlung mit Lokivetmab bei einer Dosierung zweimal pro Monat sicher, was man aufgrund der beobachteten Nebenwirkungen und der Ergebnisse der klinischen Pathologie über einen Zeitraum von 42 Tagen feststellen konnte.

要約

背景 — Lokivetmab(ZTS-00103289)はイヌ化抗イヌIL-31モノクローナル抗体であり、臨床治験において、犬のアトピー性皮膚炎による痒みを減少させることが証明されている。

仮説/目的 — アトピー性皮膚炎の飼い犬を対象に、無作為抽出、二重盲検、プラセボ対象試験を実施し、lokivetmabの安全性を評価すること。患者を選出する際の併用薬および併発疾患に対する制限は最小限にとどめた。

供与動物 — 慢性のADに罹患した飼い犬(n=245)を14の動物病院の臨床獣医師によって選出した。

方法 — 患者は2:1の割合で、無作為にlokivetmab群(1.0–3.3 mg/kg)あるいはプラセボ群に組み入れられ、day0およびday28にそれぞれいずれかの薬剤を皮下投与された。患者は臨床獣医師による身体検査を受け、採取された血液および尿の臨床病理学的および免疫原性検査が実施された(day0, 28, 42)。

結果 — 急性の過敏反応(膨疹、嘔吐など)は認められなかった。投与時の不快感が5.1%の患者で認められたが、lokivetmab群およびプラセボ群で共に同程度の頻度および重症度であった。治験中の有害事象としての痒みは、lokivetmab群でより低頻度に認められた(それぞれ4.9%および19.3%)が、それ以外の有害事象の発生は治療群間で同程度の頻度であった。臨床病理学的検査において、2群間に臨床的意義のある差は認められなかった。治療による免疫原性の誘導がlokivetmab群の2.5%に認められた。様々な併用薬が使用されたが、臨床的に明らかな有害な薬剤相互作用は認められなかった。

結論および臨床的な重要性 — アトピー性皮膚炎と臨床診断された多種多様な飼い犬162頭を対象に行ったlokivetmabの一月毎計2回の治療は安全であることが、42日間の観察可能期間中における有害事象および臨床病理学的検査の結果に基づいて示された。

摘要

背景 — Lokivetmab (ZTS-00103289)是一种抗犬IL-31单克隆抗体,临床试验显示其对犬异位性皮炎(AD)引起的瘙痒有效。

假设/目的 — 在一项随机、双盲且有安慰剂对照的试验中,实验动物为家养AD患犬,且患病动物最低程度的使用联合用药,并严格控制并发疾病,实验动物使用lokivetmab,并评估药物安全性。

动物 — 收集自14家兽医诊所,被临床医生记录为慢性AD的家养犬(n = 245)。

方法 — 从第0–28天,犬只以2:1的比例随机分组,分别皮下注射lokivetmab (1.0–3.3 mg/kg)或安慰剂。兽医检查犬只,并收集血液和尿液,并对犬的临床病理学和免疫原性进行评估(第0, 28和42天)。

结果 — 未出现速发型过敏反应(比如风疹、呕吐)。犬出现不适的比例为5.1%,Lokivetmab治疗组和安慰剂治疗组发生频率和严重程度相似。据报道,瘙痒作为不良反应的一种,很少出现在lokivetmab治疗组(两组分别为4.9%和19.3%);另外,治疗组间不良反应出现的频率相似。两组间临床病理学结果在临床上没有明显不同。lokivetmab组治疗的犬只中,2.5%的犬出现治疗诱导的免疫原性。多种联合药物未出现明显的交叉反应。

总结和临床意义 — 根据连续42天的不良反应和临床病理学记录,临床诊断为AD的162只犬,每月一次使用lokivetmab,连续2个月是安全的。

Resumo

Contexto – Lokivetmab (ZTS-00103289) é um anticorpo monoclonal caninizado anti-IL-31 canina que tem demonstrado eficácia na redução do prurido associado com dermatite atópica (DA) em cães, em pesquisas de campo.

Hipótese/Objetivos – Este estudo avaliou a segurança de lokivetmab em um ensaio clínico randomizado, duplo cego, placebo controlado em cães com DA, pertencentes a clientes, e com mínimas restrições em relação a medicações concomitantes e comorbidades.

Animais – Veterinários de 14 clínicas selecionaram cães atendidos com DA crônica (*n* = 245).

Métodos – Os cães foram randomizados em uma razão de 2:1 para receber lokivetmab (1,0 – 3,3 mg/kg) ou placebo administrados por via subcutânea nos dias 0 e 28. Os clínicos examinaram os animais e coletaram sangue e urina para avaliação clínico-patológica e de imunogenicidade (dias 0, 28 e 42).

Resultados – Não houve nenhuma reação de hipersensibilidade imediata (pápulas, vômito). Desconforto na administração ocorreu em 5,1% dos cães e foi similar em frequência e gravidade em ambos os grupos lokivetmab e placebo. Prurido foi menos frequentemente reportado como uma reação adversa no grupo tratado com lokivetmab que no placebo (4,9% e 19,3%, respectivamente); entretanto, efeitos adversos

ocorreram em frequência similar entre os dois grupos. Não houve nenhuma alteração significativa entre os grupos nos resultados de patologia clínica. Imunogenicidade induzida pelo tratamento foi encontrada em 2,5% dos cães tratados com lokivetmab. Um ampla variedade de medicações concomitantes foi usada sem interações adversas aparentes.

Conclusões e importância clínica – O tratamento com lokivetmab em duas aplicações mensais em 162 cães com DA crônica clinicamente diagnosticada foi seguro, baseado em reações adversas e análises clínicas, em um período de 42 dias.