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Safety and Efficacy of Cefovecin (Convenia®) as an Adjunctive Treatment of Periodontal Disease in Dogs

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ABSTRACT

This study was designed to determine the safety and efficacy of cefovecin (Convenia®; Pfizer Animal Health) when compared to clindamycin (Antirobe®; Pfizer Animal Health) as an adjunctive therapy to periodontal scaling or surgery for severe periodontal disease in dogs. A multi-centre, double-masked, randomised study was conducted in 299 dogs with severe periodontal disease. Clindamycin, administered once daily at 11 mg/kg bodyweight orally for 10 days following dental surgery was compared with a single, subcutaneous injection of cefovecin (8 mg/kg bodyweight) administered at the time of dental surgery. The primary efficacy parameter assessed was percentage of tooth-root sites bleeding when probed (an indicator of gingival inflammation) 42 days after surgery. Two-hundred and ninety-one (291) dogs were included in the efficacy assessments. Cefovecin was shown to be non-inferior to clindamycin. The percentage of sites bleeding on probing was reduced from 54.3% to 20.3% for the cefovecin group (53.1% reduced to 17.4% for the clindamycin group). There were no suspected adverse drug experiences attributed to treatment with cefovecin or clindamycin. Cefovecin was shown to be as effective and safe adjunctive treatment for severe periodontal disease in dogs undergoing periodontal scaling and surgery as clindamycin.

Keywords: Canine; Antibiotics; Dentistry; *Porphyromonas gulae*; *Prevotella intermedia*

1. Introduction

Periodontal disease is the most common dental infection in dogs [1]. It is caused by the accumulation of plaque and an associated change in periodontal bacterial flora (from commensal aerobic to pathogenic anaerobic bacteria such as *Porphyromonas* spp. and *Prevotella* spp) [2-5]. Periodontal disease is a collective term for a number of inflammatory conditions affecting the periodontium around the tooth (attached gingiva, periodontal ligament, cementum of the root and alveolar bone). It progresses from reversible gingivitis, characterised by inflamed and often bleeding gingiva, to periodontitis with the associated inflammatory tissue damage, the formation of deep periodontal pockets or gingival recession, loss of epithelial attachment and bone resorption. The end result of periodontitis is loss of the tooth due to progressive destruction of its periodontium [6].

As periodontal disease disturbs the integrity of mucous membranes, periodontal pathogens can be exported via the blood stream. In severe periodontal disease, bacteraemia may even occur during minimal mechanical disturbance, such as normal mastication, without any professional tooth cleaning or surgery [7,8]. Periodontal disease is associated with myocardial infarction and stroke in humans [9] and with abscesses in organs, endocarditis and glomerulonephritis in dogs [10,11].

In dogs, prevention of periodontal disease by home applied hygiene as in humans is rarely possible and the effect of poor plaque control is often only managed by periodontal treatment (e.g. debridement, scaling, polishing). However, mechanical periodontal therapy alone will not adequately reduce the periodontopathogen load [12,13]. In severe and progressive cases adjunctive antibiotic treatment is justified to augment a reduction in periodontopathogens and physiological bacterial flora, thereby facilitating detoxification of the periodontium from detrimental bacterial toxins and aiding gingival healing [13-16]. Results from clinical studies in dogs support this notion, as systemic treatment with clindamycin in periodontal disease significantly decreased plaque scores, gingivitis and pocket depths compared to placebo when used as adjunctive therapy to ultrasonic scaling, root planing and polishing [17-19].

Neither in human nor in veterinary dentistry is there a consensus in the choice of antimicrobial agent or in the minimum duration required to successfully treat perio-

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dontal infections [13]. Here we show that in a large clinical study, a single subcutaneous administration of cefovecin at 8 mg/kg effectively aided healing of the periodontal tissues after professional periodontal treatment and surgery in dogs.

Cefovecin is an extended-spectrum cephalosporin, approved for veterinary use in dogs and cats. It is formulated as an injectable solution containing 80 mg/ml cefovecin sodium. Following subcutaneous administration in dogs, cefovecin has a long elimination half-life (5.5 days), low clearance (0.76 ml/hour/kg) and therapeutic tissue concentrations are maintained for approximately 14 days [20]. As a consequence, prolonged therapeutic efficacy can be maintained through injections administered at 14-day intervals. Cefovecin, administered as a subcutaneous injection at 14-day intervals, was highly effective in the treatment of both superficial and deep canine pyoderma [21,22] and also of wounds and abscesses in both cats [23,24] and dogs [21,22]. Furthermore, cefovecin was demonstrated to be an effective and safe treatment for urinary tract infections in dogs [25] and cats [26].

2. Materials and Methods

2.1. General Study Design

This multi-centre study was conducted in compliance with VICH guidelines for Good Clinical Practice [27] (International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Medical Products) in veterinary practices in Belgium (n = 5) and France (n = 15). At each site one veterinarian, experienced in veterinary dentistry made all the observations, who received training in the procedures before study start. Approval was obtained from the appropriate regulatory authorities and the study conformed to local animal welfare standards. Informed consent was obtained from the owners of all dogs participating in the study. Dogs were randomised in a 1:1 ratio to treatment with either cefovecin or clindamycin in a double-masked study.

2.2. Selection of Animals

Only dogs, which were assessed by the veterinarian to have advanced severe periodontal disease requiring systemic antimicrobial therapy for at least 10 days as an adjunct to professional periodontal treatment, were considered for the study. Inclusion also required that dogs had at least one tooth site of gingival bleeding in addition to either a gingival pocket of at least 4.0 mm deep and/or a gingival recession of at least 1.0 mm. Pocket depth was defined as the distance (mm) between the margin of the gingiva and the bottom of the deepest pocket at that site. Gingival recession was defined as the distance (mm) from the gingival margin to the associated tooth's apical cemento-enamel junction.

Dogs that had been treated with local or systemic antimicrobial agents or long acting corticosteroids within the previous 4 weeks, with short acting corticosteroids within the previous week, and dogs being treated with an oral antiseptic or an anti-plaque agent were excluded. Concomitant administration of local or systemic antimicrobials or corticosteroids was not permitted.

2.3. Clinical Examination and Parameter Measurements

Prior to treatment (day 0) and at study completion (day 42) all dogs were subjected to a detailed mouth examination under general anaesthesia. First halitosis and general oral health were assessed on a visual analogue scale (VAS, healthy to extremely unhealthy). Then before any invasive procedures, any two most severely affected teeth (*i.e.* not necessarily the same teeth on day 0 and 42) were selected for subgingival bacteriological sampling using sterile paper points (Nº. 40, Roeko, Dentsply Belgium). The 2 samples from the same dog were pooled and later analyzed together.

Following sampling, the Gingival Bleeding Index (GBI) was assessed whilst probing the tooth-root sites with a pressure sensitive probe (Florida Probe, Florida Probe Corporation, Gainesville, Florida) to measure the gingival pocket depth and to identify any evidence of gingival recession. For each site, normal gingiva was given a GBI score of 0, mild inflammation without bleeding was scored 1, moderate inflammation with bleeding within 30 seconds was scored 2, whilst severely inflamed gingiva which spontaneously bled on probing scored 3. All measurements were undertaken at 50 pre-determined tooth-root sites, which are reported to be most frequently and most severely affected in dogs [6]. This included all labial roots (both mesial and distal of multiple-rooted teeth) of all investigated teeth and both labial and palatal side of the upper canine teeth. No root-sites were considered for any of the first premolar, the second molar and the third molar teeth. In addition, the height of the upper canine tooth (mm) was recorded to allow adjustments of the total mouth periodontal scores for periodontitis (TMPS-P) for the size of the animal [28].

After all measurements taken on day 0, dental procedures were completed as necessary, including ultrasonic supragingival scale, subgingival debridement, dental polish and extraction. Further VAS assessments of halitosis and general oral health were recorded on day 14 on unanaesthetized animals. Veterinarians and owners were requested to report all suspected adverse events for all treated dogs.

2.4. Laboratory Examination

A single laboratory in Belgium (Katholieke Universiteit Leuven, Leuven) was used to evaluate bacteriological samples. These were transported by courier in a cool box to the laboratory. Upon arrival, the samples were plated on agar plates and incubated for growth. After incubation, total aerobic colony forming units (cfu) and total anaerobic cfu were counted. In addition, within the anaerobic strains, the black pigmented strains were identified morphologically, and the *Porphyromonas gulae* and *Prevotella intermedia* were identified via enzymatic tests. All strain identification was performed by the same laboratory technician.

If present and identified, one strain per pre-treatment sample of *P. gulae* and *P. intermedia* was tested for antimicrobial sensitivity using agar dilution minimum inhibitory concentration (MIC) methodology (supplemented Brucella Blood agar) in accordance with CLSI guidelines M31-A3 and M11-A8. Antimicrobials tested were cefovecin, clindamycin, metronidazole and amoxicillin/clavulanate 2 to 1 ratio.

2.5. Investigational Treatment Administration

As 10 days of antimicrobial treatment was required, dogs randomised to receive cefovecin received a single subcutaneous injection of cefovecin (8 mg/kg bodyweight; Convenia®, Pfizer Animal Health) followed by 10 days of oral placebo capsules. Dogs randomised to receive clindamycin capsules received a placebo subcutaneous injection followed by 10 days of oral clindamycin capsules (11 mg/kg bodyweight; Antirobe®, Pfizer Animal Health). The veterinarian administered the subcutaneous injections to dogs after periodontal treatment on day 0 and the owners administered the capsules once daily. Owners kept a diary in which capsule administration was recorded and compliance with treatment could then be determined.

2.6. Assessment Criteria

The primary efficacy criterion was the percentage of tooth sites which bled when probed (GBI > 1). This was measured using a clear and reproducible, GBI scoring system, validated for veterinary use [28]. Clinically, bleeding on probing is a well accepted and objective measure of active gingivitis and current periodontal pocket inflammation. Statistically, because each dog is assessed at numerous sites to generate an overall percentage, the power for comparison is superior to a variable such as clinical success or bacteriological cure. Further, the good reproducibility of the score between dogs and clinics ensures that high quality data is generated, permitting robust statistical comparison between treatment groups. Therefore, for both clinical and statistical reasons, percentage of bleeding on probing was considered the most suitable parameter for a primary efficacy endpoint.

Gingival pocket depth, total mouth periodontal scores (TMPS), the presence of pathogens before and after treatment, halitosis and general oral health at each examination were considered as secondary efficacy endpoints.

TMPS for gingivitis (TMPS-G) was calculated according Harvey *et al*. [28] and was a composite of all the GBI scores for a particular dog, weighted according to the circumference of the cemento-enamel junction at each site, giving a final individual score for each dog of between 0 and 3. TMPS-P was a composite of all the pocket depth measurements for a particular dog, weighted according to the root surface area at each site and normalised according to the length of the upper canine. This allowed comparison of periodontitis in dogs of different sizes.

2.7. Statistical Analysis

For each assessment criterion, two analyses were conducted. One analysis included all treated dogs which completed the study on day 42 (Intent to Treat analysis: ITT). A second analysis (Per Protocol analysis: PP) excluded all animals for which procedures (including treatment administration and efficacy measurements) were not conducted to a sufficient standard to enable a fair comparison. Results are presented for the PP analysis only unless otherwise stated.

As recommended by EMEA guidelines [29] a non-inferiority approach to compare cefovecin with clindamycin was selected for the primary efficacy criterion. For each animal, the percentage of tooth sites with a GBI > 1 was calculated for both day 0 and 42. Data were analysed using a mixed linear model using the day 0 results as a covariate. For the non-inferiority test, the difference in the mean percentage between the two treatments (cefovecin minus clindamycin) on day 42 was calculated together with a 95 percent two-sided confidence interval. Thus, if the upper confidence bound on the difference was less than 10 percentage points, then cefovecin was considered non-inferior to clindamycin. The 10% margin was justified based on pilot data which indicated that 4 weeks after adjunctive treatment with cefovecin, the percentage of bleeding on probing was reduced by a further 14% than for surgery alone (data not shown). Thus it was reasoned that to be clinically relevant, the non-inferiority margin should exclude the effect of surgery alone; *i.e*. to be less than 14%. Power calculations based on preliminary data indicated that a minimum of 50 dogs per treatment group were needed to

demonstrate non-inferiority with at least 90% power.

All secondary parameters were assessed via the calculation of the treatment difference and 95% confidence intervals.

3. Results

3.1. Evaluation and Completion of Dogs

In total 308 dogs were evaluated for inclusion in the study. Four dogs were excluded before dental treatment as they were unsuitable for anaesthesia (n = 2) or their owners did not want to proceed (n = 2). After periodontal treatment and bacteriological sampling, 5 dogs did not continue (2 did not meet inclusion criteria, the probe failed in 2 and 1 dog did not recover from anaesthesia).

Following periodontal treatment, 150 dogs received cefovecin and 149 clindamycin. One dog did not complete the study due to owner non-compliance (clindamycin group) and one other dog was excluded because of concomitant antimicrobial therapy for a non-study related adverse event (cefovecin group). Hence 297 dogs completed the study on day 42 and were included for the ITT analyses. Six further dogs were excluded from all PP analyses; four dogs were underdosed during the study (1 in cefovecin and 3 in clindamycin group), one dog received an unauthorised concomitant therapy, whilst data was missing for another (both clindamycin group). A further 25 dogs (14 in cefovecin and 11 in clindamycin group) were excluded from PP analyses of pocket depth and TMPS-P due to incorrect probe usage.

Of the 299 dogs enrolled into the study, 240 were purebred (wide range of small, medium and larger breeds) and the remaining were crossbred. The ages of the dogs in both groups ranged from 2 to 17 years (mean: 9.3 and 9.2 years for the cefovecin and clindamycin group, respectively). The mean body-weights were 11.6 kg and 11.0 kg for the cefovecin and clindamycin group, respectively. There were 161 female dogs (81 intact and 80 neutered) and 138 male dogs (99 intact and 39 neutered). In Belgium, 72 dogs were enrolled from 5 practices, and in France, 227 dogs were enrolled from 15 practices.

3.2. Gingival Bleeding Index

The mean percentages of the GBI scores per animal are summarized on **Figure 1**. Before treatment more than half of the sites bled when probed, and less than 20% of the sites were considered normal. More than 20% of all sites had the highest GBI score of 3 in both groups. On day 42, the number of sites with normal gingiva had more than doubled in both treatment groups, whilst the number of most severely affected sites (GBI = 3) was reduced by more than 75%. Overall, there was a reduction in the number of bleeding sites in both treatment groups with no significant difference between cefovecin and clindamycin (**Table 1**). Therefore, cefovecin successfully achieved non-inferiority to clindamycin.

3.3. Gingival Pocket Depth

Before treatment, the mean gingival pocket depth was 2.48 mm (cefovecin group) and 2.39 mm (clindamycin group). Of the total number of tooth root sites measured, 19% had a pocket depth between 3 - 5 mm in both groups and the proportion of pocket depth larger than 5 mm was 5.3% and 3.9% in the cefovecin and clindamycin group

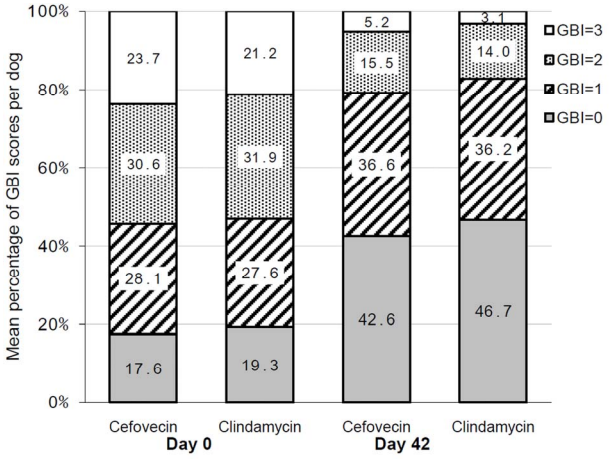

Figure 1. Mean percentage of 0, 1, 2 or 3 Gingival Bleeding Index (GBI) scores per animal in each treatment group before treatment (day 0) and at the end of the study (day 42).

Table 1. Summary of percentage of sites bleeding on probing before treatment (day 0) and after treatment (day 42).

	Treatment				Treatment Comparison	
	Cefovecin		Clindamycin			
	Day 0*	Day 42*	Day 0*	Day 42*	Difference day 42 [95% CI]	Non-inferiority demonstrated?
PP[1]	54.3%	20.3%	53.1%	17.4%	2.91% [−0.65 to 6.48]	Yes (<10%)
ITT[2]	54.5%	20.5%	52.7%	17.4%	3.16% [−0.35 to 6.67]	Yes (<10%)

*Day 0 is presented as a Mean and day 42 as a Least Square (LS) Mean because day 0 datum is used as a covariate in the model to compare the results from day 42. [1]PP: per protocol analysis; Number of dogs in the cefovecin group: 148 and 143 in the clindamycin group. [2]ITT: intent to treat; Number of dogs in the cefovecin group: 149 and 148 in the clindamycin group.

respectively (**Figure 2**). On day 42, a reduction in pocket depth of 0.51 mm and 0.40 mm was observed for cefovecin and clindamycin, respectively. For the deepest pockets (≥5.0 mm) measured on day 0, there appeared to be a proportionally greater reattachment (approximately 30%) following treatment than for less severe pockets. There was no statistically significant difference in any subgroup analysis between treatment groups. Similar results were obtained for the ITT analysis.

3.4. Total Mouth Periodontal Scores

Dogs in both treatment groups exhibited a very similar mean score for both TMPS-G and TMPS-P at the beginning of the study (**Table 2**). The high mean pre-treatment scores corroborate that the study population had moderate to severe periodontal disease, as required by the inclusion criteria. On day 42, the TMPS-G score for both groups was approximately halved whilst the TMPS-P score for both groups was reduced by approximately 20%. The difference between treatments for both scores was not statistically significant.

3.5. General Oral Health and Halitosis

General oral health and halitosis improved by more than 80% after treatment for both the cefovecin and clindamycin groups. There was no statistically significant difference between treatments on days 14 and 42 ($p \geq 0.09$ at all time points). Similar results were found in the ITT population.

3.6. Bacteriology

From the 304 dogs assessed for inclusion, 301 bacterial strains were isolated. *Porphyromonas gulae* was identified in the majority of samples collected on day 0 (272 strains), with *Prevotella intermedia* being identified less frequently (29 strains). MIC_{90} values for these strains to various antimicrobials are presented in **Table 3**. The *P. gulae* strains were highly susceptible to cefovecin, with a slightly wider susceptibility range for *P. intermedia*.

After treatment, there was a reduced recovery of both bacterial species (see **Table 4**). For *P. gulae*, the odds ratio comparing the two treatments was 0.334, indicating that *P. gulae* was less likely to be isolated on day 42 from dogs treated with cefovecin than those treated with clindamycin ($p < 0.0001$). For *P. intermedia* this odds ratio was 0.379, indicating that this species was also less likely to be isolated on day 42 from dogs treated with cefovecin. This difference was not statistically significant ($p = 0.25$).

Aerobic and anaerobic bacteria were identified in all isolates. On day 0, anaerobic black pigmented bacteria were recorded in 145 out of 151 samples in the cefovecin and in 146 out of 150 in the clindamycin group. On day 42, this ratio was 110 out of 149 and 110 out of 145 samples, respectively.

3.7. Safety Assessments

All dogs that received medication were included in the

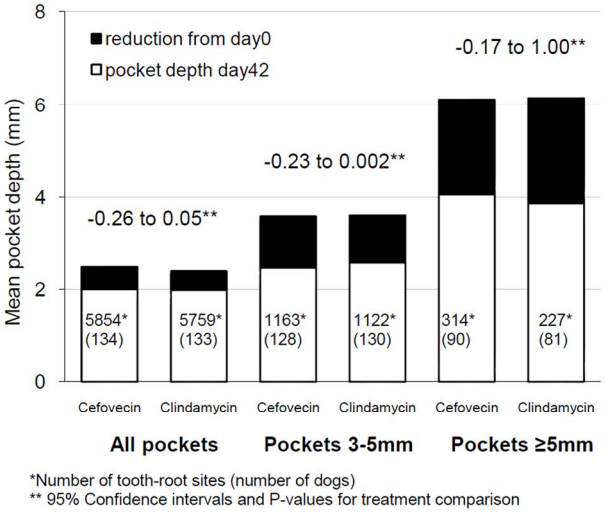

Figure 2. Changes in pocket depth during the study period in all pockets and in the most severely affected pockets. The top of the black bars shows the pocket depth on day 0, the top of the white bars shows the pocket depth after treatment on day 42. The black shaded area shows the reduction in the pocket depth between day 0 and 42.

Table 2. Summary of Total Mouth Periodontal Scores (TMPS) on day 0 and day 42.

	TMPS——Gingivitis		TMPS——Periodontitis	
	Cefovecin	Clindamycin	Cefovecin	Clindamycin
Number of animals	148	143	133	133
Mean day 0*	1.65 ± 0.57	1.61 ± 0.60	1.99 ± 0.87	1.96 ± 0.71
LS Mean day 42	0.83	0.77	1.54	1.60
% reduction	49.7%	52.2%	22.6%	18.4%
Treatment comparison (CI, p-value)	0.065 (–0.02 to 0.15, p = 0.12)		–0.056 (–0.15 to 0.04, p = 0.22)	

*± standard deviation.

Table 3. Summary of activity of antimicrobials against the strains isolated in dogs with periodontal disease, before antimicrobial treatment.

Bacterial species (number of strains)	Summary MIC parameters	Value (μg/ml) for each antimicrobial agent			
		Cefovecin	Clindamycin	Metronidazole	Amoxicillin/Clavulanate 2 to 1 ratio
Porphyromonas gulae (272)	MIC range	≤0.008 to 1	≤0.008 to >128	≤0.008 to >128	≤0.008 to 2
	MIC_{50}	0.031	≤ 0.008	0.031	0.125
	MIC_{90}	0.062	≤ 0.008	0.062	0.25
	Geo. Mean	0.029	0.011	0.027	0.088
Prevotella intermedia (29)	MIC range	≤0.008 to 4	≤0.008 to >128	0.016 to 1	≤0.008 to 2
	MIC_{50}	0.125	≤ 0.008	0.5	0.062
	MIC_{90}	1	>128	1	0.5
	Geo. Mean	0.15	0.053	0.30	0.083
Total (301)	MIC range	≤0.008 to 4	≤0.008 to >128	≤0.008 to >128	≤0.008 to 2
	MIC_{50}	0.031	≤0.008	0.031	0.125
	MIC_{90}	0.125	≤0.008	0.25	0.25
	Geo. Mean	0.034	0.013	0.035	0.087

Table 4. Summary of the number and percentage of samples where *Porphyromonas gulae* or *Prevotella intermedia* were identified before treatment on day 0 and at the end of the study on day 42.

	Treatment				Treatment comparison		
	Cefovecin*		Clindamycin**		95% confidence interval		
	Day 0 (%)	Day 42 (%)	Day 0 (%)	Day 42 (%)	Odds ratio (p-value)	Lower	Upper
Porphyromonas gulae	126 (83.4%)	32 (21.5%)	117 (78.0%)	65 (44.8%)	0.334 (p < 0.0001)	0.20	0.56
Prevotella intermedia	10 (6.6%)	2 (1.3%)	13 (8.7%)	5 (3.5%)	0.379 (p = 0.25)	0.07	2.01

*total number of samples on day 0 = 151; on day 42 = 149; **total number of samples on day 0 = 150; on day 42 = 145.

safety assessments. One dog (clindamycin group) died before antimicrobial therapy due to post-anaesthetic complications. There were no abnormal injection sites reported in any dogs administered either active cefovecin or placebo. There was no notable difference in the incidence of adverse events between the two treatment groups. Two dogs in the cefovecin group vomited during the study period, on a total of 3 occasions; one dog showed inappetence in the clindamycin group and one dog was lethargic and had modified feces on one occasion in the cefovecin group. None of these events was considered to be related to the administration of the medications by the veterinarians.

4. Discussion

Periodontal disease is a very common and potentially serious infectious dental disease in dogs [1]. Here we investigated the efficacy and safety of the only veterinary approved long-acting injectable antimicrobial, cefovecin in the adjunctive treatment of severe periodontal disease in dogs.

It has to be noted that the assessment of antimicrobial efficacy for periodontal treatment is hampered by the complexity of the disease. While the primary treatment is professional periodontal therapy, the inclusion of such therapy could be considered a confounding factor for antimicrobial treatment comparisons. Nevertheless, application of antimicrobials alone is not recommended [16]. Further, EMEA guidelines recommend that when assessing a new compound for treatment of a potentially serious condition, a non-inferiority approach comparing to a reference product is preferable to a conventional hypothesis test for superiority using a placebo [29]. Essentially this is designed to demonstrate that the new compound is "at least as good as" the reference product by a predefined margin. Here clindamycin (Antirobe® capsules) was selected as reference product, because it has been shown to effectively reduce the signs of periodontal disease, including gingivitis and pocket depths compared to placebo, when used adjunctive to professional periodontal treatment in dogs [17-19]. It was used at the recommended European dosage of 11 mg/kg bodyweight orally once a day for at least 10 days.

The dogs included in this study represented a diverse population encompassing many breeds and a wide age range. The mean bodyweight suggested that there was a tendency towards smaller dogs. Indeed, small breed dogs

are considered to be particularly susceptible to naturally occurring periodontal disease. It has been reported that by the age of 3 years more than 85% of the small dog population has alterations in their vital organs due to periodontitis-associated recurrent bacteraemia [11]. As inclusion in this study required that the dogs had severe periodontal disease, it is likely that many also had systemic consequences of their periodontal disease. There is consensus amongst veterinary and human dentists that antimicrobial treatment as an adjunct to periodontal therapy for severe conditions and in patients with systemic diseases is fully justified [13-16]. Not only does this help to restore the non-pathogenic flora and promote gingival healing, but also minimises any associated bacteraemia.

The primary efficacy endpoint was percentage of pre-defined tooth-root sites bleeding on probing six weeks after the initial surgery. At the end of the study the percentage of sites bleeding on probing was more than halved in both treatment groups. Further, cefovecin successfully met the stringent *a priori* criteria and efficacy can be claimed.

Periodontal pocket depth was also considered as a clinically relevant endpoint for the efficacy analysis, however, assessment of depth using a probe is by nature prone to large error and individual variation thereby reducing the power of the study. Further, pocket depth does not specifically assess current active inflammation, but rather measures the extent of established damage historically caused by ongoing periodontal disease. Therefore, pocket depth was included as a secondary efficacy criterion. Subset analysis of the pocket depth data revealed that whilst there were no significant treatment differences, there was proportionally a larger reduction in pocket measurement in the deepest pockets, with a trend in favour of cefovecin. This might be due to creating a more favourable environment for re-attachment of the periodontal membrane by maintaining low supragingival bacterial flora following periodontal therapy.

The bacterial species identified during this study were typical of those associated with canine periodontal disease [3-5]. There was a high recovery of pathogens before treatment, with *P. gulae* being the most frequently isolated species. After periodontal and antimicrobial treatment, dogs treated with cefovecin were less likely to be infected than those treated with clindamycin, although for both groups there was a reduction in recovery of pathogens. All *P. gulae* isolates tested were susceptible to cefovecin. Whilst fewer *P. intermedia* strains were collected, cefovecin still exhibited good *in vitro* activity although a few isolates were resistant as defined in the existing summary of product characteristics (sensitive ≤2 μg/mL).

There is always the potential for the development of resistance when using antimicrobial drugs. The susceptibility to cefovecin of pathogens isolated in this study was very similar to previous results [30]. This indicates that despite exposure of periodontal pathogens to cefovecin since its approval in 2006, no MIC shift has occurred. Therefore, it is likely that the risk of resistance development of *Porphyromonas* spp. and *Prevotella* spp. through the use of cefovecin as an adjunctive treatment to periodontal therapy is minimal. Although clindamycin, metronidazol and amoxicillin/clavulanic acid have been used for a longer period against periodonthopathogens, the susceptibility of the tested strains to these drugs does not seem to have changed when compared to previous reports [31,32].

Other secondary parameters included the total mouth periodontal scores. The scores for gingivitis were approximately halved after treatment, with no significant difference between groups. The scores for periodontitis (TMPS-P) were also reduced after treatment, with no significant difference between groups. Similarly, general oral health and halitosis, improved after treatment for both the cefovecin and clindamycin groups.

Importantly, there were no adverse events reported due to treatment for either group. While owner diaries documented a few adverse events, including gastrointestinal symptoms, these were unrelated to treatment according to the observing veterinarians. There was no injection-site reaction reported.

In conclusion, cefovecin at a dose of 8 mg/kg bodyweight administered once subcutaneously was safe and efficacious in the adjunctive treatment of severe periodontal disease in dogs presented as veterinary patients. As the only veterinary approved long-acting injectable antimicrobial, cefovecin enables reliable treatment, especially in dogs where oral administration may be difficult following periodontal surgery.

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