A RANDOMISED CONTROLLED MASKED CLINICAL TRIAL OF TWO TREATMENTS FOR OSTEOARTHRITIS IN DOGS.

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Key Words: Osteoarthritis, Dog, 4CYTE™ Canine
ABSTRACT

The product 4CYTE™ Canine (Interpath Pty Ltd., Ballarat, Victoria) contains four active ingredients: 3 marine-derived, plus Epiitalis® which is extracted from the plant Biota orientalis, Epiitalis®. Carprofen is a non-steroidal anti-inflammatory drug (NSAID) licensed for treatment of osteoarthritis in dogs and is the active ingredient in several licensed products. This study aimed to compare the efficacy of 4CYTE™ Canine with carprofen for treatment of pain from osteoarthritis.

The trial was a randomised, masked, parallel group trial in dogs with naturally occurring osteoarthritis. Sixty-nine (69) dogs between 10 and 50 kg of body weight were enrolled in the study of which 66/69 (95.7%) completed the study. The 4CYTE™ Canine was administered at 60 mg active/kg daily and carprofen at 2-4 mg/kg daily with a loading dose of up to 4 mg/kg on the first day. The trial duration was 28 days.

The primary outcome was defined as improvement in Owner Lameness Score at Day 28 compared to Day 0. Other outcomes measured included Veterinary Lameness Scores and the Owner Mobility Scores. At Day 28, 14/29 (48.3%) dogs which received 4CYTE™ Canine and 13/37 (35.1%) dogs which received carprofen had improved.

The 4CYTE™ Canine was found to be non-inferior to carprofen at Day 14 for the Owner Mobility Score, and at Day 28 for all three outcomes. This response pattern suggests that improvement in response to 4CYTE™ Canine continued between Day 14 and Day 28. These results support the conclusion that 4CYTE™ Canine is not inferior to carprofen by end-point clinical efficacy.

250 words
INTRODUCTION

Chronic osteoarthritis is a common disorder in dogs\(^1\) for which there is no cure. Treatment of osteoarthritis is aimed at managing the associated pain and inflammation, with the use of non-steroidal anti-inflammatory drugs (NSAIDs), centrally acting pain relief drugs and agents with claimed chondroprotective properties. Carprofen is an NSAID licensed in many products for the treatment of naturally occurring osteoarthritis in the dog.

The veterinary product 4CYTE™ Canine (Interpath Pty Ltd., Ballarat, Victoria, Australia) is registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA 69230). This product contains four ingredients: 3 marine-derived, plus Epiitalis®. This product is a second-generation nutraceutical product, a more purified derivative of commercial nutraceutical formulations (4CYTE Equine (SEQ™) APVMA 65276, also Sasha’s Blend Joint Health Powder (APVMA 54231, Interpath Pty Ltd., Ballarat, Victoria, Australia). The 4CYTE™ Canine formulation is aimed to prevent and treat cartilage damage in dogs at risk for or suffering from osteoarthritis and to provide relief from clinical signs of joint pain.

The anti-inflammatory and chondroprotective effects on articular cartilage of Epiitalis® presented as 4CYTE™ Equine (SEQ™) and as Sasha’s Blend (Interpath, Melbourne, Australia) has been investigated both \textit{in vitro}\(^2,3\) and \textit{in vivo}\.4 These studies demonstrated inhibitory effects of a simulated digest of SEQ™\(^3\) and/or its individual constituents\(^5\) on interleukin-1 (IL-1)-induced prostaglandin E2 (PGE2), glycosaminoglycan (GAG) and nitric oxide (NO) production by cartilage explants. Except for NO inhibition, these effects were also observed \textit{in vivo} in horses challenged with low-dose intra-articular injections of IL-1.4 A recent clinical study in dogs with naturally occurring osteoarthritis also demonstrated the efficacy of Epiitalis® for treatment of osteoarthritis in dogs.6 Collectively, these studies suggest that products containing Epiitalis® have potential for treating dogs with osteoarthritis.
The objective of this clinical trial was to compare the efficacy of 4CYTE™ Canine to the non-steroidal anti-inflammatory agent (NSAID) carprofen, for the treatment of naturally occurring osteoarthritis in the dog in support of the regulatory approval for the product.
MATERIALS AND METHODS

Animals, drugs and protocol

The study was conducted as a randomised, masked, positive controlled, parallel group, non-inferiority clinical trial. The trial was conducted with approval of the University of Melbourne Animal Ethics Committee (#1011929) and according to the Principals of Good Clinical Practice. All phases of the study were conducted at the Melbourne Veterinary School, 250 Princes Highway, Werribee, Vic between May 2011 and August 2012. Five veterinary practitioners conducted the in-life evaluations with approximately equal share of cases. Allocation of animals to treatment groups was sequential by enrolment, using tables of randomised sequence for Treatment Group A versus Treatment Group B, generated using Microsoft Excel “rand” function by a non-investigating author (TW). One sequential table was generated. As each dog was enrolled the next available Treatment Group in the sequence was assigned. The dispensary staff were masked to treatment identity and dispensed the treatments according to the assigned treatment group. The treatment products had previously been re-packed into identical outer packages labelled with the treatment group letter. Group A received the trial test product 4CYTE™ Canine and Group B received carprofen (Rimadyl®, Zoetis Inc, Parsippany, NJ).

Dogs were enrolled into the trial if they satisfied the inclusion criteria. Dogs must have been greater than 6 months old and presented to the University of Melbourne Veterinary Hospital with a presenting sign of lameness. The dogs’ body weight range initially was defined as between 13 and 50 kg but was altered after initiation of the trial to include animals from 10 to 50 kg. The dogs needed to be in general good health as determined by a physical examination. Enrolment required dogs to have no major haematological or clinical chemistry abnormalities on Day 0. Dogs must also have shown radiographic evidence of osteoarthritis as determined by a specialist veterinary radiologist (authors CB, MM, DT).
Otherwise eligible dogs were excluded from enrolment if they had been given any registered or unregistered veterinary medication for the treatment of osteoarthritis or lameness or pain or inflammation in the 14 days preceding enrolment; dimethyl sulfoxide, sodium hyaluronate, chondroitin sulphate, glucosamine, green lipped mussel extracts, pentosan polysulfate, (also known as calcium xylopyranose polysulfate), tiludronic acid and any nonsteroidal anti-inflammatory drug (NSAID). Other treatments such as vaccinations, worming medications, heartworm preventatives, flea/insect treatments, shampoos, topical treatments of antibiotics or antifungal drugs were permitted concurrently as these were thought to have little likelihood to impact outcomes of the study.

The 4CYTE™ Canine was administered once daily with the evening meal for 28 days according to the labelled dose (Table 1). The formulation was administered orally by adding the required amount of formulation to the meal or alternatively, directly to the animal, as preferred by the owner. The carprofen was administered within the dose range of 2 - 4 mg/kg daily with a loading dose of up to 4 mg/kg optionally divided on the first day as indicated on its approved label (Table 1). The formulation was administered orally directly over the base of the tongue or hidden in food, at the discretion of the owner.

**Outcomes**

As baseline assessments, each dog received a veterinary physical examination on its enrolment day (Day 0) and on Days 14 (± 2) and 28 (± 2). Clinical chemistry and haematology were assessed on Days 0 and 28. Radiographic images were acquired on each dog’s Day 0. Under general anaesthesia, plain radiographs were taken in two planes for the suspected osteoarthritic joints. The radiologists made a diagnosis of osteoarthritis “confirmed” or “not-confirmed.”

Three outcome measures, Owner Lameness Score (OL), Veterinary Lameness Score (VL) and Owner Mobility Score (OM) were established as minor modifications of the unidirectional ordinal ranking
scores recommended by regulatory authorities for evaluation of efficacy of NSAID drugs in the
treatment of osteoarthritis.⁸ Owners and veterinarians were instructed on the use of the scoring
systems. Dogs were each assessed and recorded on Days 0, 14 (± 2) and 28 (± 2) (Table 2). The
study’s primary outcome measure was declared a priori as binomial derivation from OL with 0 for
“not improved” or 1 for “improved”, calculated for Day 28 (Imp_28). Additional secondary outcome
measures were calculated: binomial variables were calculated similarly for each of Day 14 (Imp_14)
and of Day 14 or Day 28 (Imp_Any) to identify any improvement in each dog at any time point and
for improvement between Day 14 and 28 (Imp_14_28).

**Data Analysis and Statistics**

An initial sample size estimate was for 40 animals per group or 80 animals for the two-group study.
The sample size calculation was made assuming a non-inferiority comparison of two groups on a
binomial variable (“not improved” or “improved”): where the control product was previously
determined to achieve approximately 80% responders ⁹ and with a desired Power of 80% and
probability of Type 1 error of 0.05, the test product must not be more than 10% worse than the
control product, with confidence of 90%. We also assumed up to 20% animals enrolled might be
excluded or lost to follow up or might be lost due to misadventure or other illness. Therefore, the
total number of animals targeted for recruitment was 100.

The blinding code for the treatment groups was held during the trial by one author (TW) and was
broken only after completion of the statistical analyses. No owner or other investigator was aware of
the assignment of treatment identities.

For each binomial outcome (Imp_14, Imp_28, Imp_14_28 and Imp_Any), with respect to each
outcome measure (OL, VL and OM), if the lower limit of the 90% confidence interval of the
difference in proportion improving between 4CYTETM Canine and carprofen was not less than -10% it
was concluded that the 4CYTETM Canine product would be non-inferior to carprofen for that
outcome. The calculation of the 90% confidence interval of the difference between two independent proportions (4CYTE™ Canine – carprofen) used method 10 of Newcombe (1998), as implemented by the –rdci- (v1.2) command of Stata for Windows v12.1 (StataCorp, College Station, TX). The Hodges-Lehmann estimate of the median of the pairwise differences was calculated using Stata for Windows v12.1 (StataCorp, College Station, TX).

Contingency tables and bar plots were generated for the outcome variables using IBM SPSS Statistics (v20) and Microsoft Excel.
RESULTS

Sixty-nine (69) dogs were recruited to the study. Of these dogs, 17 were crossbreeds, 8 were Labradors, 5 were Retrievers, 4 were Border Collies and the remainder were from sixteen other pure breeds. All dogs enrolled were deemed healthy although some baseline biochemistry and haematology values were outside of the reference ranges. Given reference ranges represent 95% of the normal population; it is expected for every 100 tests 5 will fall outside the reference range. Outlier values were assessed considering the animal’s history and clinical findings. The Day 0 lameness scores for the two groups were similar. The minimum, median and maximum scores for the primary response variable (OL) were Group A: 2, 1 and 4 for and Group B: 2, 1 and 3, respectively.

Data from 66/69 (95.7%) completed animals contributed to the conclusions of the study. Three (3/69 4.3%) dogs were excluded from the study after enrolment; one dog because it had been erroneously enrolled although its body weight exceeded the upper limit of enrolment criteria, one dog because it was diagnosed after enrolment with rhabdomyosarcoma and one dog because it required emergency intervention for severe acute onset of pain after the initial diagnostic work-up but before trial-treatment had begun. At the conclusion of the trial, no enrolled dogs had died or been euthanized during the study. No clinically relevant changes in haematology or biochemistry were observed at Day 28.

Two adverse events were reported. Dog 1 from Group B (carprofen) suffered acute vomiting on day 15 of the study, was admitted to the Veterinary Hospital and was treated symptomatically. Dog 58 from Group B was reported by the owner to have blood in its stools between enrolment and commencing dosing. Dosing was delayed until the stools had returned to normal and then the dog’s treatment trial was initiated.
The owner of one Group A dog reported that the dog avoided eating the medication and that different foods were needed to tempt the dog to eat the dose. This was the only report of issues with palatability of either product.

**Owner Lameness Score (OL)**

Improvement at Day 28 in OL compared to Day 0 had been declared *a priori* as the primary response outcome. At Day 28, 14/29 (48.3%) dogs which received 4CYTE™ Canine and 13/37 (35.1%) dogs which received carprofen had improved (Figure 1). The lower 90% confidence interval for the difference between proportions was -6.6% showing non-inferiority in efficacy of 4CYTE™ Canine compared to carprofen for this primary response variable.

At Day 14, 10/29 (34.5%) dogs which received 4CYTE™ Canine and 13/37 (35.1%) dogs which received carprofen had improved. The lower 90% confidence interval for the difference between proportions was -19.1%. Between Day 14 and Day 28 improvement in OL was found in 7/29 (24.1%) dogs which received 4CYTE™ Canine and 4/37 (10.8%) dogs which received carprofen. The lower 90% confidence interval for the difference between these proportions was -2.0% showing non-inferiority in efficacy of 4CYTE™ Canine compared to carprofen. For the change in OL between Day 0 and any other time-point, 15/29 (51.7%) dogs which received 4CYTE™ Canine and 16/37 (43.2%) dogs which received carprofen improved. The lower 90% confidence interval for the difference between proportions was -11.4%.

The difference between the median ordinal scores for OL, for each of the three time periods, equalled 0. Therefore, the lower and upper 90% confidence intervals’ boundaries also each equalled 0, allowing the conclusion that there was no difference detected between the median improvement in scores for the two products.

**Veterinary Lameness Score (VL)**
For their VL at Day 14, 10/29 (34.5%) dogs which received 4CYTE™ Canine and 15/37 (40.5%) dogs which received carprofen had improved. The lower 90% confidence interval for the difference between proportions was -24.5%. In contrast, at Day 28, 17/29 (58.6%) dogs which received 4CYTE™ Canine and 15/37 (40.5%) dogs which received carprofen had improved. The lower 90% confidence interval for the difference between these proportions was -2.2%. For the change in VL between Day 14 and Day 28, 9/29 (31.0%) dogs which received 4CYTE™ Canine and 6/37 (16.2%) dogs which received carprofen had improved. The lower 90% confidence interval for the difference between proportions was -2.3%. For the change in VL between Day 0 and any time-point, 18/29 (62.1%) dogs which received 4CYTE™ Canine and 20/37 (54.1%) dogs which received carprofen improved. The lower 90% confidence interval for the difference between proportions was -11.8%.

The 90% confidence interval of the percentile difference between the median ordinal scores for VL at each of the three time points ranged from 0 to 0, allowing the conclusion that there was no difference detected between the median improvement in scores for the two products.

**Owner Mobility Score (OM)**

For their OM at Day 14, 10/29 (34.5%) dogs which received 4CYTE™ Canine and 8/37 (21.6%) dogs which received carprofen had improved. The lower 90% confidence interval for the difference between proportions was -5.2%. At Day 28, almost twice the proportion of 4CYTE™ treated dogs, 12/29 (41.4%), had improved compared those that had received carprofen where only 8/37 (21.6%) dogs had improved since Day 0. The lower 90% confidence interval for the difference between proportions was -1.0%. For the change between Day 14 and Day 28, 4/29 (13.8%) dogs which received 4CYTE™ Canine and 4/37 (10.8%) dogs which received carprofen had improved. The lower 90% confidence interval for the difference between proportions was -10.5%. For the change between Day 0 and any other time-point, 14/29 (48.3%) dogs which received 4CYTE™ Canine and 11/37 (29.7%) dogs which received carprofen showed improvement. The lower 90% confidence interval for the difference between proportions was -1.2%.
The 90% confidence interval of the difference in proportion of dogs with improving scores calculated as 4CYTE™ Canine minus carprofen is shown in Figure 3. The 90% confidence interval of the percentile difference between the median ordinal scores for OM at each of the three time points ranged from 0 to 0 or 1, allowing the conclusion that there was no difference detected between the median improvement in scores for the two products.

A summary of the conclusions from the statistical evaluations is presented in Table 3.
DISCUSSION

This study was stopped before full enrolment had been achieved because storm damage to the hospital facility and resulting building renovations impeded work-flows. It was recognised that this raised the likelihood of an inconclusive result. Neither stopping rules nor interim analyses had been planned for this study. No interim analysis was conducted. Fortunately, the effect size was sufficient to allow conclusions to be drawn based on the \textit{a priori} chosen outcome despite the lower than planned number of trial animals.

After initiation of the trial it was realised that the external validity of the study would be enhanced by allowing enrolment of smaller body weight animals. Therefore, the protocol was amended to include smaller body weight dogs of over 10 kg rather than the initial 13 kg lower limit.

In this study the attempts to control bias included: separation of roles in the study design, conduct and analysis; masking of investigators; masking of owners; randomisation of assignation to study groups. Both the experimental formulation and the control formulation were repacked into identical outer packs to improve masking of owners and investigators. The impact of any possible loss of masking on the study outcome measures is unknown.

The interpretation of results of clinical trials can be biased by imprecise outcome measurements, preconceptions of investigators and readers, small effect sizes, and low numbers of independent studies.\textsuperscript{13} Objective lameness measures such as those from force plate measurement ideally reduce both imprecision and investigator bias, and should increase the likelihood of detecting responses to analgesia.\textsuperscript{14,15} However, for identification of clinically relevant improvement of lameness in response to treatment of osteoarthritis, both the sensitivity and accuracy of owner-dependent ordinal scoring has been higher than such objective measures.\textsuperscript{9,16} In this study, investigator observation using an ordinal “Lameness Score for Dogs” recommended by The European Agency for the Evaluation of Medicinal Products Veterinary Medicines and Inspections, for evaluation of non-steroid anti-
inflammatory drugs (NSAIDs) was used with minor changes to the wording to suit the geographical
use of language at the study site. In addition, because of the increased sensitivity if owner scoring is
used, the owner lameness score was chosen as the primary response outcome. Finally, since the
positive control drug, carprofen, was registered using an owner lameness score as an efficacy
outcome in its clinical efficacy trials, a similar scoring system was likely to result in similar effect-size
and variability; these parameters were the basis of the sample size calculation. As this study was
designed to support the application for regulatory approval of the product, use of a recommended
lameness score for dogs as the outcome measure was deemed appropriate.

In an earlier study, large number of separate outcome variables was used within a single trial, to
assess response to therapy for osteoarthritis. However, using large numbers of outcome measures
renders it more likely to form incorrect study conclusions. In the current study, only three ordinal
outcome measures were evaluated and one (OL) was a priori designated as the primary outcome.
From each ordinal outcome measure we derived binomial variables to identify improvement in
lameness scores at Day 14, Day 28, between Day 14 and 28, and finally improvement from baseline
at any time point. The primary response variable for conclusion of non-inferiority was defined a
priori as the calculated response for improvement at Day 28 versus Day 0 as determined by the
Owner Lameness Score (OL). This variable was chosen as it is thought to be the most relevant to
market acceptance of the proposed new product.

The 4CYTETM Canine was found to be statistically non-inferior to the carprofen at Day 14 for the
Owner Mobility Score, and at Day 28 for all three outcomes. These data suggest that, in contrast to
the response to carprofen, the improvement in lameness in response to 4CYTETM Canine continued
between Day 14 and Day 28. This finding aligns with expected response times based on the
proposed mechanism of action as an anti-inflammatory agent whose effect gradually accumulates. If
the inhibitory effects of the active agent on interleukin-1-induced prostaglandin E2 (PGE2),
glycosaminoglycan (GAG) and nitric oxide (NO) occur in dogs as has been demonstrated in the
In this study, carprofen failed to provide continuing improvement after Day 14. This finding contrasted with previous work where continued improvement occurred for up to 84 days.\textsuperscript{17} It is possible that the between-study differences in outcome measures, duration of therapy, population characteristics or management of dog pets that occur between geographical areas may have contributed to this contrast. It is also possible that the 11 outcome measures used in the earlier study increased the likelihood of an incorrect conclusion being made when compared to the current study with only 3 measures.\textsuperscript{13}

These results support the conclusion that the formulation 4CYTE\textsuperscript{TM} Canine is not inferior to the positive control carprofen when measured by lameness scoring after 14 days of therapy. Further, this study provides preliminary evidence that the formulation provided for further improvement with treatment until Day 28. This potential for continued improvement warrants further study.

3156 Words excluding Abstract
ACKNOWLEDGMENTS

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REFERENCES


Table 1. Doses of 4CYTE™ Canine and the control drug carprofen were administered by body weight category. Each carprofen tablet contained 50 mg carprofen. One dosing scoop equalled approximately 0.3 g active constituent Epiitalis®.

<table>
<thead>
<tr>
<th>Weight Block</th>
<th>Carprofen</th>
<th>4CYTE™ Canine</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Day 1 (Loading Dose)</td>
<td>Day 2 - 28</td>
</tr>
<tr>
<td>10 - &lt;13 kg</td>
<td>½ tab once</td>
<td>½ tab daily</td>
</tr>
<tr>
<td>13 - 20 kg</td>
<td>1 tab once</td>
<td>1 tab daily</td>
</tr>
<tr>
<td>&gt;20 - 25 kg</td>
<td>1 tab am then ½ tab pm</td>
<td>1 tab daily</td>
</tr>
<tr>
<td>&gt;25 - 30 kg</td>
<td>1 tab twice</td>
<td>1½ tab daily</td>
</tr>
<tr>
<td>&gt;30 - 38 kg</td>
<td>1½ tab am then 1 tab pm</td>
<td>1½ tab daily</td>
</tr>
<tr>
<td>&gt;38 - 50</td>
<td>2 tab am then 1 tab pm</td>
<td>2 tab daily</td>
</tr>
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</table>
Table 2. Ordinal scoring scales for outcome measure of Owner Lameness Score (OL), Veterinary Lameness Score (VL) and Owner Mobility Score (OM).

<table>
<thead>
<tr>
<th>Owner Mobility Score</th>
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<tbody>
<tr>
<td>Score</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
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<table>
<thead>
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<th>Owner Lameness Score and Veterinary Lameness Score</th>
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</thead>
<tbody>
<tr>
<td>Score</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>
Table 3. Summary of statistical conclusions from analysis of outcome measures at Days 14, and 28 after daily treatment with either 4CYTETM Canine or carprofen at labelled doses, evaluating both the non-inferiority of 4CYTETM Canine compared to carprofen and evaluating the median ordinal difference between the two treatments. The primary outcome measure is highlighted.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Owner Lameness Score</th>
<th>Veterinary Lameness Score</th>
<th>Owner Mobility Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-inferiority</td>
<td>Median Ordinal Difference</td>
<td>Non-inferiority</td>
</tr>
<tr>
<td>Imp_14</td>
<td>-</td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>Imp_28</td>
<td>NI</td>
<td>ND</td>
<td>NI</td>
</tr>
<tr>
<td>Imp_14-28</td>
<td>NI</td>
<td>ND</td>
<td>NI</td>
</tr>
<tr>
<td>Imp_Any</td>
<td>-</td>
<td>*</td>
<td>-</td>
</tr>
</tbody>
</table>

ND Not Different by Hodges-Lehmann estimate of the median of the pairwise differences

NI Not Inferior by Newcombe 90% confidence interval of the difference between two independent proportions (4CYTETM Canine – carprofen)

* Not calculated

- No statistical conclusion possible.
Legends to Figures

Figure 1. The percent of dogs that showed no improvement (black) or improvement (striped) in their Owner Lameness Score after (A) 14 or (B) 28 days, (C) between 14 and 28 days, and (D) at any time point, with daily oral treatment of either 4CYTE™ Canine or carprofen at labelled doses. Panel B displays the primary response outcome.

Figure 2. The percent of dogs that showed no improvement (black) or improvement (striped) in their Owner Mobility Score after (A) 14 or (B) 28 days, (C) between 14 and 28 days, and (D) at any time point, with daily oral treatment of either 4CYTE™ Canine or carprofen at labelled doses.

Figure 3. The 90% confidence intervals are shown for the difference between groups in their response to treatment, calculated as (the proportion of dogs which responded to 4CYTE™ Canine) minus (the proportion of dogs which responded to carprofen); Owner Lameness Scores (OL, solid bars), Veterinary Lameness Scores (VL, dotted bars), Owner Mobility Scores (OM, hatched bars) and at each measured time period (_days).

* OL Imp_28 is the a priori primary response outcome.
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