White Paper on:

Efficacy and Safety of an Oral Nutraceutical in Dogs with Osteoarthritis: A Double Blind Placebo Controlled Study

Analysis done by: Kevin Callender, Eli Data Consulting, LLC

Compilation and summarization by: Dr. Ihor Basko

EXECUTIVE SUMMARY

History of product need:

Background and Justification: Nutraceuticals have showed mixed efficacy as a treatment for osteoarthritis, a disease that affects up to 20% of dogs over one year of age. However, past efficacy studies have relied primarily on subjective outcome assessments, providing equivocal evidence of the supplement's therapeutic utility. A randomized, blinded, placebo-controlled clinical trial was conducted on seventy otherwise-healthy dogs with clinical osteoarthritic symptoms, in order to more rigorously assess the efficacy of nutraceuticals on secondary osteoarthritic symptoms. This brief report focuses on abridged analyses on two key outcomes, activity level and pain, measured using objective movement accelerometers an objective assessment tool and validated owner surveys, respectively.

Study Design: This was a randomized, blinded, placebo-controlled clinical trial. Seventy (70) healthy client-owned dogs with clinical symptoms secondary to osteoarthritis were studied. Inclusion criteria included overall good health, lameness and/or disability from arthritis, joint pain on orthopedic exam, arthritis confirmed by radiographs, and informed owner consent. Prior to enrollment dogs had a complete blood count and chemistry screen. They were not treated with steroids for 30 days, NSAIDs for 7 days, analgesic medications for 7 days, and other glucosamine and/or chondroitin products (including Hills J/D or Purina J/M diets) for 14 days. Dogs remained off these products for the duration of the study. A complete history and physical exam were completed including body condition score, body weight, and severity of disability (none, mild, moderate, severe, critical). Owners completed a Canine Brief Pain Inventory (CBPI) addressing the dog arthritis prior to enrollment in the study. After enrollment, each dog was fitted with an accelerometer (activity monitor) collar and an accelerometer was dispensed with operating instructions. Patient activity was monitored every 60-seconds for the duration of the study period. The accelerometer protocol used in this study was previously validated for the use of monitoring activity in dogs with arthritis. After 7 days of monitoring normal patient activity each patient was randomized to the treatment or placebo group. In addition, owners completed a validated osteoarthritis questionnaire (Canine Brief Pain Inventory) at each reexamination. Patient exams and owner questionnaires were completed on day 0±3, 7±3, 28±5, and 49±7 of the study.

The Investigator, all other study personnel involved in patient observations, and the pet owners were masked to the coding and dosage of treatment (placebo or supplement) given to each dog. A staff member was designated as dispenser and maintained the treatment assignment and randomization schedules in confidence at the study site until the completion of data collection. The dispenser stored all forms and other documents related to treatment administration in a secured location to maintain masking.

The first 7 days of the study period was used to measure the patient's regular activity. This time period was used for comparison to the treatment period. A 2-tailed $\chi 2$ test was used to compare the frequency of an increase in mean group activity, mean individual activity, and median individual activity. An evaluation was done for days 0-24, 25-50, and 0-50.

METHODOLOGY OVERVIEW

Statistical Approach

Activity data were collected every 60-seconds using an accelerometer collar for the duration of the study period. Baseline values were estimated per dog by averaging activity data collected for 12 days prior to the start of the trial. Activity data for days 1 to 24 were averaged per dog to estimate 1st Period values. Finally, activity data for days 25 to 50 were averaged per dog to estimate 2nd Period values. Average Baseline values were subtracted from average First and Second Period values per dog, resulting in a difference score. Positive numbers indicated increase in activity relative to baseline, and were recoded to equal "1." Negative scores indicated a decrease in activity relative to baseline, and were recoded to equal "0." Binary logistic regressions were conducted to test for the effect of treatment on activity change for each of the two time periods.

Owners reported the pain of their dogs on a scale from 0 to 10, with 10 indicating most severe pain and 0 indicate no pain at all. Owners separately reported the worst pain, least pain, average pain, and current pain of their dogs at four different time points: Baseline (roughly 7 days prior to the trial), T0 (first day of trial), T1 (28th day of trial), and T2 (48th day of trial). A series of random-intercepts mixed models with unstructured covariance structures was conducted to assess the fixed effects of time points, treatment group (Supplement vs. Placebo), and their interaction on the owners' reports of their dogs pain. Intercepts at the individual (dog) level were left freely vary to account for differences in their baseline.

These targeted analyses were designed to highlight some of the most potentially important health outcomes associated with osteoarthritic therapy.

RESULTS

Results from a binary logistic regression indicated that pets on the test supplement had 2.6 greater odds (90% CI: 1.15, 5.92) of showing an increase in activity after 25 days of treatment (relative to baseline activity), compared to pets on a placebo, p = .055. Using this approach, the supplement resulted in a statistically significant increase of activity at the .10 alpha levels. No significant effects of treatment were found within the 1st period of the trial, suggesting that the supplement may require a period of continuous use before showing some efficacy.

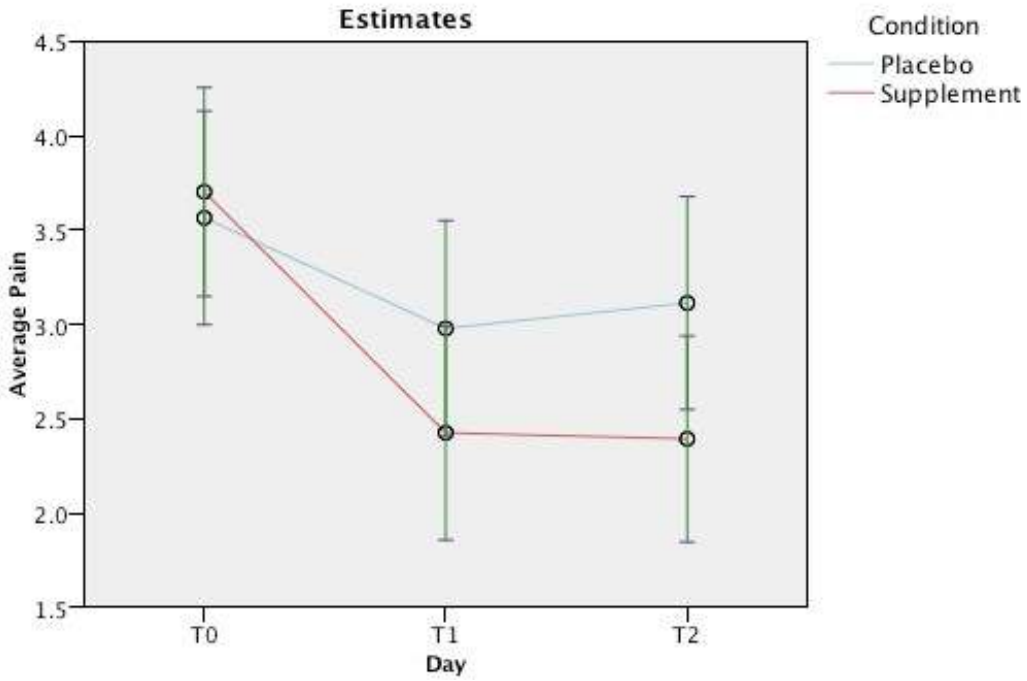
Table 1. Binary logistic regression: Effects of test supplement on change in activity

Time Period Relative to Baseline	Odds Ratio	90% CI Lower Bound	90% CI Upper Bound	*p*-value
1st Period (Days 0-24)	1.47	0.65	3.35	0.437
2nd Period (Days 25-40)	2.60	1.15	5.92	0.055

Results from a random-intercepts mixed model indicated that twenty eight days following the baseline period, pets on the test supplement (M = 2.399, SE = .332) showed a trending decrease in owner-reported average pain, compared to pets on the placebo (M = 2.936, SE = .329). This trend continued on day 48 (M = 2.297, SE = .353 on supplement vs. M = 3.033, SE = .368 on placebo). Similar patterns were found for owner-reported current level of their dog's pain, lowest level of their dog's pain, and worst level of their dog's pain.

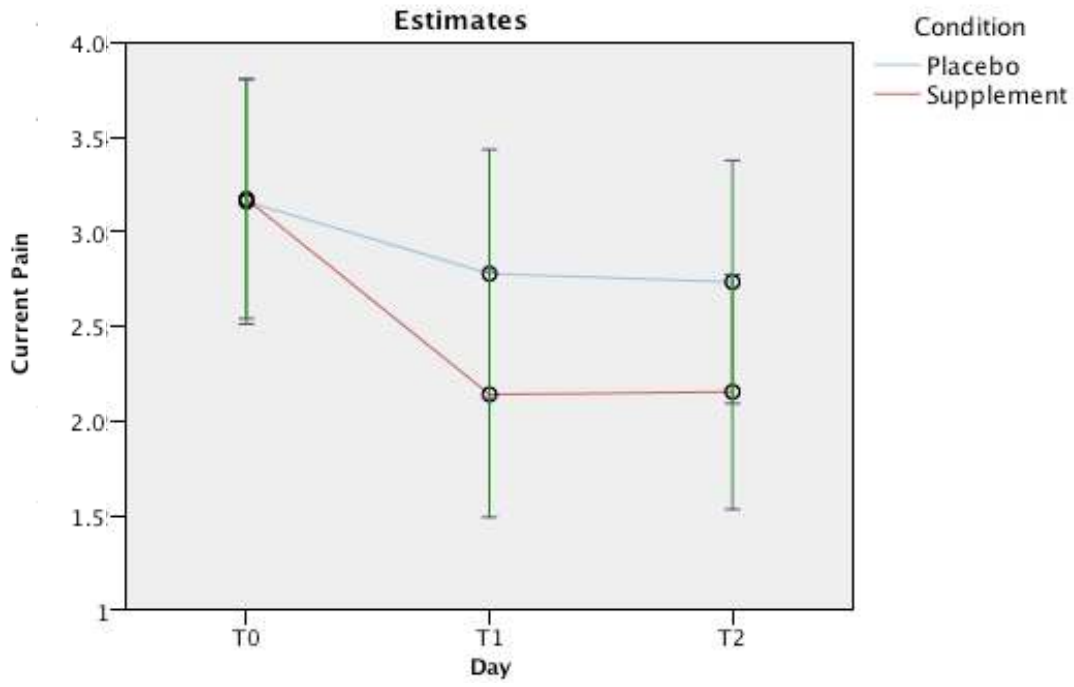
The graphs in the following pages more comprehensively illustrate the trending patterns of effects found from the analyses.

Figure 1. Average Pain of Dogs by Condition and Time Point



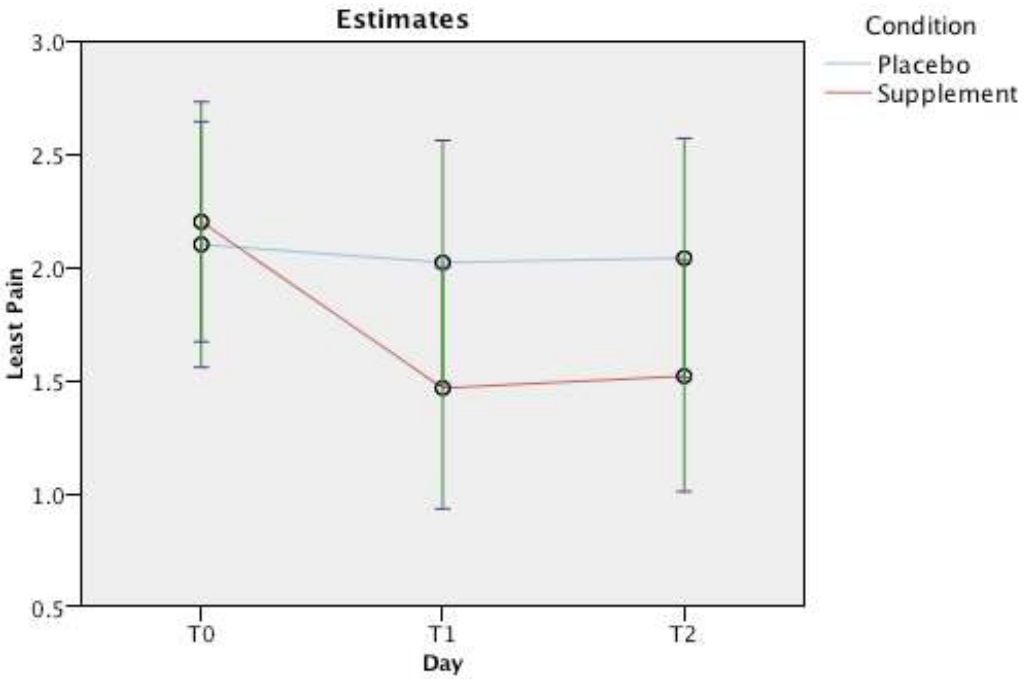
Note. T0 represents first day of trial, T1 represents 28th day of trial, and T2 represents 48th day of trial. Error bars indicate a group's 90% confidence interval of the estimated average pain at a particular time point.

Figure 2. Current Pain of Dogs by Condition and Time Point



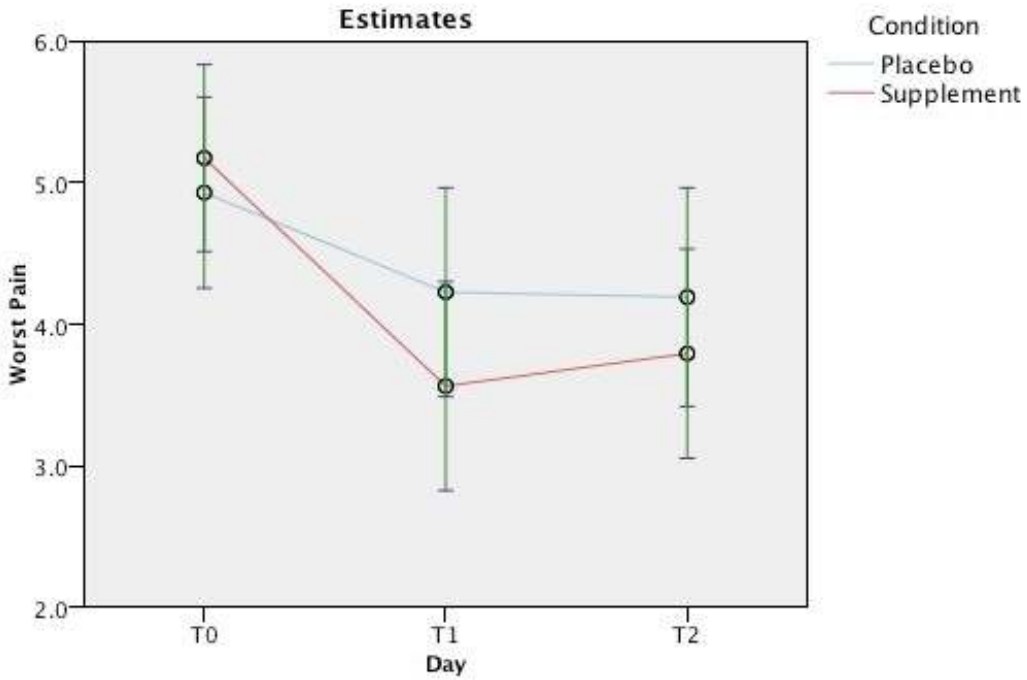
Note. T0 represents first day of trial, T1 represents 28th day of trial, and T2 represents 48th day of trial. Error bars indicate a group's 90% confidence interval of the estimated average pain at a particular time point.

Figure 3. Least Pain of Dogs by Condition and Time Point



Note. T0 represents first day of trial, T1 represents 28th day of trial, and T2 represents 48th day of trial. Error bars indicate a group's 90% confidence interval of the estimated average pain at a particular time point.

Figure 4. Worst Pain of Dogs by Condition and Time Point



Note. T0 represents first day of trial, T1 represents 28th day of trial, and T2 represents 48th day of trial. Error bars indicate a group's 90% confidence interval of the estimated average pain at a particular time point.

Main Findings

1. Pets on the test supplement had 2.6 greater odds of showing an increase in activity after 25 days of treatment (relative to baseline activity), compared to pets on a placebo.

2. Twenty eight days following the baseline period, pets on the test supplement showed a trending decrease in owner-reported average pain, compared to pets on the placebo. This trend continued on day 48. Similar patterns were found for owner-reported current level of their dog's pain, lowest level of their dog's pain, and highest level of their dog's pain.

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Daniel Uebelhart, M.D. Clinic of Rehabilitation, Department of Clinical Neurosciences and Dermatology University Hospital of Geneva 26 Avenue de Beau-Sejour 1211 Geneva 14, Switzerland 011 41 22 382 3612 / 011 41 22 382 3644 FAX
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