The Use of ^{117m}Sn (Tin) Colloid for Treatment of Naturally Occurring Grade 3 Elbow Osteoarthritis in Client Dogs

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Abstract

Background

The pathology associated with elbow dysplasia is progressive and irreversible and long-term prognosis is poor. Evidence has revealed the important role synovitis plays in the pathophysiology of osteoarthritis. The use of radiosynoviothesis has been proposed as an alternative in early therapeutic intervention to prevent, delay or limit joint disease progression. The aim of this study was to evaluate the effect and duration of improvement following intra-articular injection of ^{117m}Sn colloid on naturally occurring Grade 3 elbow osteoarthritis in dogs. Dog elbows (15 dogs/27 elbows) were injected with ^{117m}Sn colloid and cohorts followed check point assessments on Days 90, 180, 270 and 365 post treatment. Effectiveness was evaluated using: 1) Canine Brief Pain Inventory (CBPI) assessed by the caretaker, and 2) clinician-assessed lameness. Complete blood count, chemistry panel, joint fluid analysis and urinalysis were assessed for safety.

Results

At least half the dogs showed success at each study time check point (Days 90, 180, 270 and 365) compared with baseline, using the validated CBPI User Guide criteria. Day 270 provided the largest percentage (70%) of successes when compared with baseline. These CBPI findings were corroborated by statistical agreement with success of clinician-assessed lameness. The mean Pain Severity Score (PSS) improved significantly at Days 90, 270 and 365 compared to baseline, while the mean Pain Interference Score (PIS) improved significantly at Day 270 compared to baseline. Safety assessments did not reveal concerns for the study duration.

Conclusions

Dogs diagnosed with Grade 3 osteoarthritis in at least one elbow benefited by either not worsening or improving over 365 days after treatment with ^{117m}Sn colloid. No ^{117m}Sn colloid-related safety concerns were observed.

Background

It has been suggested that as many as 20% of dogs over 1 year of age are afflicted with osteoarthritis (OA).[1] Canine elbow OA occurs most commonly as a sequela to elbow dysplasia.[2] Elbow dysplasia has been shown to occur more frequently in medium and large sized dogs, such as the German shepherd, Labrador retriever and Rottweiler.[3,4] The current approach to treatment of elbow OA is multimodal, consisting of a combination of weight management, non-steroidal anti-inflammatory drugs (NSAIDs), nutraceuticals, nutrition, intra-articular therapies, and surgical treatment.[5] Because the pathology associated with elbow dysplasia is progressive and irreversible, long-term prognosis is poor and treating the resulting OA is aimed at the management of pain and alleviation of associated clinical signs.[4,5,6,7]

Mounting evidence has revealed the important role synovitis plays in the pathophysiology of OA.[8,9] Catabolic and proinflammatory mediators produced by inflammation of the synovial membrane are associated with OA pathogenesis.[1,10,11] The Multicenter Osteoarthritis Study (MOST) following 514 human subjects with magnetic resonance imaging (MRI)-detected effusion synovitis of the knee over 30 months found that subjects had a 2.7-fold greater risk ($p = 0.002$) of cartilage loss compared with individuals without synovitis.[12] In addition, low-grade synovitis appears to persist long term following surgical treatments of joints, predisposing the patient to insidious progression of OA.[13] A number of conservative therapies currently used to treat OA, including NSAIDs and corticosteroids, are thought to work by reducing synovitis in those joints.[8,14,15,16]

Elevation of cytokines in early human OA patients suggests activation of the immune response in the synovial membrane.[11] It has been proposed that early therapeutic intervention targeting the synovium may alleviate clinical signs of joint disease and may even prevent, delay or limit progression.[10,11] One such alternative is the use of radiosynoviorthesis, using a low-energy ionizing radiation (conversion electrons) emitted by a radiotherapeutic radionuclide to penetrate the synovial membrane. The ionizing radiation emission causes macrophage apoptosis and ablation of inflammatory cytokines and growth factors within the joint lining synovium.[17] Studies of both human and canid subjects diagnosed with chronic synovitis (human)[18] or OA (canine)[19] revealed that radiation therapy is an effective therapy and was associated with a favorable clinical outcome over a period of one year.

Rodent experimental models evaluating the use of ^{117m}Sn colloid in the treatment of OA were used in pre-canine studies conducted by J Simón et al.[20,21] During this sequential staged investigational process, no significant safety concerns were observed. Such findings led the authors to conduct this canine study on the intended target species, i.e., dogs with naturally occurring elbow OA. The Nuclear

Regulatory Commission has released a technical evaluation report regarding the use of ^{117m}Sn colloid to treat dogs with OA. (https://adams.nrc.gov/wba/ Oct 30, 2020, Exubrion Technical Evaluation Report; ML20269A274).

The purpose of this study was to determine both the change and duration of change in visual lameness and Canine Brief Pain Inventory (CBPI) score[22,23] following intra-articular injection of ^{117m}Sn (tin) colloid (Synovetin OA®, Exubrion Therapeutics, Buford, GA) on naturally occurring canine Grade 3 elbow OA.

Results

Fifteen dogs were enrolled in the study and a total of 27 elbows were treated via intra-articular injection of ^{117m}Sn colloid. Mean age of the dogs was 8.47 years (range 1.5–12.9 years). Mean baseline weight of the dogs was 31.57 kg (range 19.8–45.7 kg). Of the 15 dogs enrolled, 8 dogs were male (two intact) and seven dogs were spayed females. All 15 dogs (27 elbows) were analyzed with respect to the intent-to-treat (ITT) criteria, defined as all dogs originally entered into the study. One dog was excluded from the per protocol (PP) analysis, defined as those dogs that completed the treatment originally intended, as the injected dose was >20% under the intended dose. An overall treatment success of 93.3% (14/15) and 92.9% (13/14) was calculated for the ITT and PP study populations, respectively.

Effectiveness data were analyzed using the PP population. Using the criterion of CPBI success, at least 50% of the dogs showed success at all timepoints compared with baseline. Day 270 provided the largest percentage (70%) of successes when compared with baseline. Success was not generally seen when compared with the previous visit (e.g., Day 270 vs Day 365) (**Table 1**). Both PSS and PIS showed improvement of ³ 1 or ³ 2 integers, consecutively, in at least 57% of the dogs from baseline to all time-points (**Table 2**). The average improvement in PSS was significantly ($p<0.05$) greater at Days 90, 270 and 365, when compared to baseline. The average improvement in PIS was significantly ($p<0.05$) greater at Day 270 compared to baseline.

Clinician-assessed lameness was used to evaluate dogs at a walk, trot and for the greater lameness at walk or trot (worst lameness score) (**Table 3**). Dogs were walked by a trained handler in a consistent manner. The CBPI findings were corroborated with statistical agreement between clinician-assessed lameness success and CBPI success (**Table 4**).

Of the 25 PP population elbows, 19 had follow-up radiographs at Day 365. Radiographic imaging of a majority (78.9%) of the 19 elbows radiographed at Day 365 showed a progression (worsening) of the conditions ($p<0.01$). Computed tomography (CT) results for the categorical variables (**Table 5**) showed no significant differences between baseline scores and scores at Day 365. Most scores for other CT variables did not change from baseline to Day 365.

MRI of the cranial joint pouch width showed least square mean values at both Days 180 and 365 were significantly lower than the mean at baseline (**Tables 6 and 7**). There were no significant differences for any other continuous or categorical variables between time points.

When comparing clinical success and change seen in radiographs, there was significant ($p<0.01$) lack of agreement between the two variables. More dogs exhibited clinical success and radiologic failure than showed clinical failure and radiologic success. When comparing other imaging variables (CT success, MRI Day 180 success and MRI Day 365 success), there was apparent agreement between clinical success and each of the imaging variables ($p>0.05$), using McNemar's test of agreement.

Safety assessments were performed on the ITT population (15 dogs/27 elbows). Independent laboratory assessments of joint fluid, urinalysis, and bloodwork did not reveal any safety concerns over the 365-day study duration. No adverse device events (ADEs) were related to ^{117m}Sn colloid.

Discussion

Elbow dysplasia typically results in progressive OA,[24] clinically characterized by signs of pain and lameness.[1,5] Signs of pain and lameness may be difficult to see in dogs with bilaterally symmetrical disease necessitating additional diagnostic techniques. Accordingly, dogs that clinically improve following a given treatment are considered favorable outcomes from that treatment.

It is conventionally accepted that elbow dysplasia is most commonly a bilateral condition.[6]

Twelve of the 15 client-owned dogs enrolled were treated bilaterally for naturally occurring Grade 3 elbow OA (27 elbows) and followed over a 12-month period. In this study CBPI was used to assess effectiveness using the combined criteria (≥1 integer improvement for PSS and ≥2 integers improvement for PIS) for the successful treatment of an individual patient. Using these criteria, success was

achieved in at least half of the dogs at Days 90, 180, 270 and 365 (compared with baseline), with Day 270 identified as the time of highest success (70%) within the year following a treatment.

Two factors in the intended use of CBPI as a subjective measurement of a dog's pain differed from its use in this study. CBPI is typically used for the validation of systemic treatment modalities and this study was a one-time local treatment of either one or two elbows.[25,26,27] The use of CBPI to assess the effect of treatment in individual dogs typically requires, and has been used for, a much larger sample size than was used in this smaller study of a novel treatment. [25,26,27] Based on these considerations and the fact that CBPI was developed as a scale analogous to that used in human chronic pain studies to capture an owner's perception of both pain severity and how pain interfered with daily life,[23] we examined the PSS and PIS individually from baseline to each time-point (Table 2). PSS significantly improved at all time points, except for Day 180, which although not significant compared to baseline, was still improved compared with baseline. PIS significantly improved at Day 270, however, although not significant, there was improvement in PIS scores at all other timepoints compared to baseline. Using the individual criteria for successful treatment, the highest rate of improvement in PSS (72.7%) was measured at Day 365 and in PIS (90%) at Day 270, compared with baseline.

Statistical assessment by McNemar's test of agreement between the CBPI and clinician-assessed lameness yielded p-values ≥ 0.05 for many comparisons from baseline to each visit, indicating agreement. Although the two assessments were conducted by different sets of individuals (dog caregivers and clinical investigators) using different assessment parameters, both of the assessments are focused toward measurement of compromised activity or movement. Corroboration of these assessed parameters and their statistical agreement validate the results of treatment success. The high degree of agreement between the two assessments indicates that both the dogs' caregivers and clinicians were able to evaluate consistent improvement in the treated dogs' lameness. Smaller incremental improvements in the dogs' lameness over the study period (12 months) were evident by the caretakers' ability to document them using the CBPI survey.

Various imaging modalities were used over the 12-month study period. Clinical success was defined by whether the dog improved or showed no change when compared with CBPI baseline assessments. The poor correlation (as high as 69% incidence of false-negative radiographic diagnosis) between radiographic and clinical findings of dogs with osteoarthritis is well recognized.[28] In this study, regardless the CBPI outcome, radiographic indices worsened over the course of the study, resulting in a lack of correlation between radiographic results and treatment outcome assessments.

Magnetic resonance imaging showed statistically significant changes in the cranial joint pouch width (JPW) when comparing Day 180 and Day 365 images to baseline. The statistically significant reduction in cranial JPW from baseline over time to Day 180 and Day 365 follow-up time points is consistent with a reduction in joint effusion. In general, the cranial JPW MRI variable tends to be smaller in magnitude than the caudal JPW, explaining why small changes in magnitude for this variable may have been more easily detected.

There was agreement, based on McNemar's test of agreement, between CT (all time points) and MRI (Day 180 and Day 365) imagining variables and clinical success ($p > 0.05$). Given that the total number of dogs with both clinical and imaging variables was very small (10 to 12 dogs), it is possible that lack of agreement may have been shown if the sample size was larger.

Favorable results seen across all laboratory safety assessments demonstrate the lack of clinically significant safety concerns related to the use of ^{117m}Sn colloid over the duration of the 12-month study period. Therefore, a good safety profile was demonstrated for ^{117m}Sn colloid under the prescribed conditions for use.

Conclusion

From the results of this study we conclude that the use of ^{117m}Sn colloid has been proved advantageous for the treatment of dogs with Grade 3 osteoarthritis in the elbow. Dogs afflicted with this progressive degenerative disease benefited by either not worsening or improving over the 365-day study period. No device-related safety concerns were observed following treatment with ^{117m}Sn colloid over the study period, demonstrating a good safety profile for the device under the prescribed conditions for use.

Methods

Animals

Companion dogs treated in this study resided in their caretaker's household during and after completion of the study. Prior to any study-related procedure, caretakers signed a consent agreeing to participation, treatment and follow-up evaluations through month 12 post

treatment. Study-eligible dogs were at least 1 year of age and weighed 4.54 kg (10 lbs.) or more, exhibited clinically evident weight-bearing lameness of Grade +1 on a Lameness Scoring System,[29] regardless of NSAID therapy, located in one or both elbows, and had radiographic evidence of Grade 3 OA in at least one elbow. Ongoing NSAID therapy was acceptable, provided the dog was initially lame at baseline evaluation while being treated with an NSAID. Additional criteria included MRI or CT evidence of osseous osteoarthritis changes and a grade 3+ for both questions 1 and 5 of the CBPI survey. Dogs were excluded from the study if they had comorbidities likely to preclude a one-year survival post treatment, evidence of bone neoplasia, severe osteochondritis dissecans (OCD) lesions, septic arthritis, a recently ruptured synovial cyst that communicated with the articular cavity, were pregnant or lactating, or had a known hypersensitivity to the active substance or excipients. This study protocol was approved by the Louisiana State University Institutional Animal Care and Use Committee (IACUC Protocol #16-008) and all methods were carried out in accordance with relevant guidelines and regulations outlined here.

Dose Determination

Dogs were treated with a 1.75 mCi ^{117m}Sn colloid intra-articular dose, which was normalized by body weight based on a standard intra-articular dose for a 22.72 kg (50 lb) dog (**Table 8**). At the time of this study dose calibration standards for ^{117}Sn had not been determined by the National Institute of Standards and Technology. The amount of radionuclide delivered was determined by the manufacturer based on rate constants, the date of manufacture, and the date the dose was to be administered. Enrollments were assessed with respect to the delivered dose of ^{117m}Sn colloid in comparison to the intended dose. If the injected dose was >20% under or over the intended dose, the subject was excluded from the PP analysis.

Baseline Assessments

Baseline assessments were obtained within 30 days of treatment. A history and physical examination were performed at baseline and Days 1, 90, 180, 270 and 365. Blood was assessed by CBC and serum chemistry at baseline, Day 180 and Day 365. Urine was collected for urinalysis via free catch or ultrasound-guided cystocentesis at baseline, daily during the post-treatment hospitalization and on Days 180 and 365.

Imaging Procedures

Digital radiography, CT and MRI were each performed at baseline and Day 365. MRI was also performed at Day 180.

Standard Treatment Protocol

Dogs were anesthetized and placed into right or left lateral recumbency depending on the clinician's approach to the target elbow. Hair overlying the elbow joint was clipped and the skin was surgically prepared by scrubbing with povidone iodine or chlorhexidine, beginning at the injection site and spiraling outward. The elbow was covered with a sterile surgical drape. The procedure was performed using either a lateral or medial approach, depending on the surgeon's preference. For the lateral approach, with the elbow flexed at 90 degrees, a sterile 22G 1½-inch diamond-tipped spinal needle was inserted caudolaterally between the lateral condyle of the humerus and the triceps tendon, then directed distal and slightly medial along the cranio-lateral aspect of the ulnar anconeus into the supratrochlear foramen of the humerus. For a medial approach, the needle was inserted approximately 1 cm distal to the medial epicondyle and directed perpendicular into the joint. Following needle placement, 0.5 to 1.0 mL of joint fluid was aspirated into a sterile syringe. This syringe was removed and a different sterile syringe containing the ^{117m}Sn colloid was attached to the same positioned needle. The colloid was injected slowly into the joint, followed by approximately 0.3 mL of air to clear as much of the colloid from the syringe and needle as possible. The needle was removed from the joint and direct pressure was applied to the injection site for 2 minutes to prevent leaking of the radioisotope and encourage hemostasis.

Imaging Assessments

A radiographic osteoarthritis grade was assigned to each elbow joint, for each dog, as previously described.[30] Scoring at Day 365 was made as related to the initial score and the immediately previous examination. Scoring was: -1 (worsening), 0 (static) or +1 (improvement).

The CT scan for each patient was evaluated for specific continuous and categorical variables (**Table 5**). Categorical variables were assigned a grade of 0 to 3 based on subjective assessment for severity of changes, where 0 indicated an absence of the metric and 3 indicated the presence of severe changes. One and 2 indicated mild and moderate severity, respectively.

MRI studies were performed using different sequences at each site owing to the difference in equipment between sites. Each investigator followed a pre-determined quantitative morphometric protocol for MRI evaluation. Cranial and caudal JPW was measured on sagittal T2W sequences. The sagittal proton density (PD) was used to assess for the presence of hypointense synovial bodies surrounded by hyperintense synovial fluid. A positive change was considered when an increase in fluid over time and a decrease in the synovial body size occurred. The presence of synovial fluid heterogeneity that could be created by fibrin strands, was considered a negative change. Subchondral changes in bone intensity were assessed in sagittal and dorsal reformatted images using the 3D sequences optimized for each site. Sclerosis of the subchondral bone was assessed at the ulna at the base of the medial coronoid process and trochlear sulcus. Cartilage erosions were assessed by determining if the cartilage covered the joint uniformly and was assessed in the PD weighted sequences. The thickness of the joint capsule medial and lateral to the joint was measured on dorsal multiplanar reconstructed 3D scans. Images were evaluated by the radiologist investigator using eFilm viewing software (IBM Watson Health, Armonk, NY). The image for each patient was evaluated for specific continuous and categorical variables (**Table 9**).

Assessment Parameters

The CBPI was used at each visit to assess changes in pain and activity (www.caninebpi.com).[22,23] The pain severity score (PSS) was calculated as the mean of questions 1 through 4. The pain interference score (PIS) was calculated as the mean of questions 5 through 10. Improvement was assessed by comparing each visit with baseline and comparing each visit to the most recent visit. Success was defined, using the criteria for successful treatment of an individual patient[23], as the improvement of one or more full integer change for the PSS *and* improvement of two or more full integer changes for the PIS.

Clinician assessment was used to evaluate lameness during walk and trot based on a six-point scale with Grade 0 representing no lameness and Grade 5 representing continuous non-weight-bearing lameness. The worse value (highest) of the two assessments (walk or trot) at a follow-up visit was also collected and statistically analyzed.

Safety Data Analyses

A CBC, serum chemistry, urinalysis and joint fluid analysis at baseline and on Days 180 and 365 were performed by an independent laboratory. In addition, joint fluid parameters were reviewed with respect to safety-related considerations.

Statistical Analysis

Data analyses were performed with statistical analysis software (SAS, version 9.4, SAS Institute Inc, Cary, NC). For those variables that were assessed for each elbow, the elbow was the experimental unit. For those variables that could only be evaluated for the whole animal, the dog was the experimental unit. For effectiveness, tests of statistical significance were completed at a two-sided alpha level of 0.05. For the CBPI assessment, success was presented as the number and percentage of dogs meeting each criterion for baseline compared with Days 90, 180, 270 and 365, and for each visit compared with the most recent visit. For the clinician assessment of lameness, descriptive statistics (number of dogs, mean, standard error of the mean (SEM), minimum, 1^{st} quartile median, 3^{rd} quartile and maximum values) were compared with baseline and Days 90, 180, 270 and 365. The same descriptive statistics were also compared with change from baseline for each visit and for change from the previous visit to the current visit. Within group p-values were generated by the paired t-test or Wilcoxon signed rank test, depending on the distribution of the data, for clinical lameness assessments. The CBPI success criteria data was compared with the clinical lameness assessments of walk and trot for each dog. Lameness success was defined as an improvement from baseline of one or more integers. Two-by-two tables for success/failure were constructed for each visit. McNemar's test of agreement was applied to each metric. P-values ≥ 0.05 indicate agreement. Data for the categorical variables for both CT and MRI were analyzed using the Sign Test to compare baseline with post-treatment scores for each animal and treated elbow. The pre- and post-treatment MRI data for continuous variables were analyzed using repeated measures ANOVA with dog/leg as the replicate and time as the main effect. Least-squares means were calculated for each time point

Abbreviations

ADEs
Adverse device events
CBC
Complete blood count
CBPI
Canine Brief Pain Inventory

CT
Computed tomography
HTC
Homogenous tin colloid
ITT
Intent to treat
JPW
Joint pouch width
MOST
Multicenter osteoarthritis study
MRI
Magnetic resonance imaging
NSAIDs
Non-steroidal anti-inflammatory drugs
OA
Osteoarthritis
OCD
Osteochondritis dissecans
PD
Proton density
PIS
Pain interference score
PP
Per protocol
PSS
Pain severity score
SEM
Standard error of the mean

Declarations

Ethics approval and consent to participate

This study was approved by the Louisiana State University Institutional Animal Care and Use Committee, IACUC Protocol #16-008. Owners signed a written consent form following a detailed verbal explanation of the study protocol.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The primary author (J. Donecker) is an employee of Exubrion Therapeutics. Drs. Aulakh, Hudson and Fabiani are members of the Exubrion Therapeutics advisory board.

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Authors' contributions

MF and LG oversaw the safe use and administration of Synovetin OA®, which contains the radioisotope tin 117m. MF and KA recruited and evaluated dogs throughout the study. JMD oversaw the execution of this study. Dr. Karen Aiken of Embark Consulting Group provided technical writing assistance for this report.

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Tables

Table 1. Validated CBPI Criteria of Success: Improvement of PSS ³ 1 **and** PIS ³ 2

Comparison	Result	Outcome
Baseline to Day 90	Success	7/14 (50.00%)
	Failure	7/14 (50.00%)
Baseline to Day 180	Success	6/12 (50.00%)
	Failure	6/12 (50.00%)
Baseline to Day 270	Success	7/10 (70.00%)
	Failure	3/10 (30.00%)
Baseline to Day 365	Success	6/11 (54.55%)
	Failure	5/11 (45.45%)
Day 90 to Day 180	Success	1/12 (8.33%)
	Failure	11/12 (91.67%)
Day 180 to Day 270	Success	4/10 (40.00%)
	Failure	6/10 (60.00%)
Day 270 to Day 365	Success	0
	Failure	10/10 (100.00%)

Table 2. CBPI scores for 15 dogs with Grade 3 elbow OA at baseline and at each time-point post treatment. Values are presented as median (range).

CBPI item	Baseline	Day 90	Day 180	Day 270	Day 365
Worst pain last 7 days[a]	7.5 (5-9)	4.5 (0-9)	5.5 (0-8)	3 (0-8)	5 (0-8)
Least pain last 7 days[a]	4.5 (1-8)	2.5 (0-7)	2.5 (0-8)	1 (0-6)	2 (0-6)
Average pain last 7 days[a]	6 (2-8)	3.5 (0-8)	3.5 (0-7)	1.5 (0-7)	3 (0-7)
Current pain[a]	6 (0-8)	3 (0-8)	2.5 (0-7)	1 (0-7)	3 (0-8)
General activity[b]	7 (2-10)	3.5 (0-8)	4 (0-9)	1.5 (0-6)	3 (0-8)
Enjoyment of life[b]	6.5 (2-9)	2.5 (0-8)	4 (0-9)	1 (0-7)	3 (0-7)
Ability to rise from laying down[b]	7 (0-9)	3 (0-9)	5 (0-8)	1.5 (0-5)	3 (1-8)
Ability to walk[b]	6 (0-9)	2 (0-8)	3.5 (0-9)	2 (0-7)	2 (0-7)
Ability to run[b]	8 (1-10)	2.5 (0-9)	5.5 (0-10)	2.5 (0-7)	3 (0-9)
Ability to climb[b]	7.5 (1-10)	4.5 (0-9)	3.5 (0-10)	2 (0-7)	2 (0-9)
PSS (average Q1 -1 Q4)	**5.82 (2.00-8.00)**	**3.46* (0.00-7.25)**	**3.54 (0.00-6.50)**	**2.33* (0.00-7.00)**	**3.25* (0.00-6.25)**
Improve ³1 integer since baseline[c]		10/14 (71.4%)	8/12 (66.7%)	7/10 (70.0%)	8/11 (72.7%)
PIS (average Q5 – Q10)	**6.42 (1.17-8.83)**	**3.48 (0.17-8.33)**	**4.04 (0.17-7.17)**	**2.20** (0.00-6.50)**	**3.14 (0.17-8.00)**
Improve ³2 integers since baseline[c]		8/14 (57.1%)	7/12 (58.3%)	9/10 (90%)	7/11 (63.6%)

[a] Rank associated with rating of dog's pain on scale 0 (no pain) to 10 (extreme pain).

[b] Rank associated with how pain has interfered on scale 0 (does not interfere) to 10 (completely interferes).

[c] Number improved out of total measured at timepoint (% improvement).

*Average improvement significantly ($p<0.05$) greater than 1 unit compared to Day 1.

**Average improvement significantly ($p<0.05$) greater than 2 units compared to Day 1.

Table 3. Clinician-Assessed Lameness at Walk, Trot or Worse of the Scored Parameter

Parameter	Time point		n	Mean	SEM	Within Group P-value*
Lameness at Walk	Baseline	Baseline	14	2.14	0.18	
	Day 90	Value	14	1.29	0.30	
		Change	14	-0.86	0.27	0.0081
	Day 180	Value	12	1.58	0.36	
		Change[1]	12	-0.5	0.34	0.1661
		Change[2]	12	0.33	0.19	0.1039
	Day 270	Value	10	1.6	0.34	
		Change[1]	10	-0.4	0.34	0.2695
		Change[2]	10	0.3	0.21	0.1934
	Day 365	Value	11	2.18	0.26	
		Change[1]	11	0.18	0.30	0.5527
		Change[2]	10	0.6	0.34	0.1114
Lameness at Trot	Baseline	Baseline	13	2.15	0.15	
	Day 90	Value	13	1.31	0.31	
		Change	13	-0.85	0.25	0.0053
	Day 180	Value	11	1.91	0.28	
		Change[1]	11	-0.18	0.18	0.3409
		Change[2]	11	0.73	0.24	0.0119
	Day 270	Value	10	1.90	0.35	
		Change[1]	10	-0.2	0.33	0.5554
		Change[2]	10	0/0	0.26	1.0000
	Day 365	Value	11	2.36	0.24	
		Change[1]	11	0.27	0.19	0.1921
		Change[2]	10	0.50	0.27	0.0957
Worse Score	Baseline	Baseline	14	2.29	0.16	
	Day 90	Value	14	1.5	0.29	
		Change	14	-0.78	0.21	0.0028
	Day 180	Value	12	2.08	0.31	
		Change[1]	12	-0.17	0.21	0.4382
		Change[2]	12	0.67	0.22	0.0128
	Day 270	Value	10	2	0.33	
		Change[1]	10	-0.20	0.29	0.5086
		Change[2]	10	0.10	0.23	0.6783
	Day 365	Value	11	2.45	0.21	

	Change[1]	11	0.27	0.19	0.3750
	Change[2]	10	0.50	0.27	0.0957

*Within group p-values were generated by the paired t-test.

[1] Change from baseline

[2] Change from previous visit

Table 4. Agreement Between the CBPI Assessment and the Clinician-Assessed Lameness evaluations.

			Lameness at Walk			Lameness at Trot		
Improvement of:	**Comparison**	**CBPI Success/ Failure**	**Success**	**Failure**	**p-value***	**Success**	**Failure**	**p-value***
PSS≥1 **and** PIS≥2	Baseline to Day 90	Success	7/15(46.67%)	1/15(6.67%)	0.1025	6/14(42.86%)	2/14(14.29%)	0.4142
		Failure	5/15(33.33%)	2/15(13.33%)		4/14(28.57%)	2/14(14.29%)	
	Baseline to Day 180	Success	3/13(23.08%)	3/13(23.08%)	0.7055	2/12(16.67%)	3/12(25.00%)	0.3173
		Failure	4/13(30.77%)	3/13(23.08%)		1/12(8.33%)	6/12(50.00%)	
	Baseline to Day 270	Success	3/11(27.27%)	4/11(36.36%)	0.7055	4/11(36.36%)	3/11(27.27%)	0.3173
		Failure	3/11(27.27%)	1/11(9.09%)		1/11(9.09%)	3/11(27.27%)	
	Baseline to Day 365	Success	4/12(33.33%)	3/12(25.00%)	0.0833	2/12(16.67%)	5/12(41.67%)	0.0253
		Failure		5/12(41.67%)			5/12(41.67%)	
	Day 90 to Day 180	Success		1/13(7.69%)	1.0000		1/12(8.33%)	-
		Failure	1/13(7.69%)	11/13(84.62%)			11/12(91.67%)	
	Day 180 to Day 270	Success	1/11(9.09%)	4/11(36.36%)	0.1797	2/11(18.18%)	3/11(27.27%)	0.6547
		Failure	1/11(9.09%)	5/11(45.45%)		2/11(18.18%)	4/11(36.36%)	
	Day 270 to Day 365	Success		1/11(9.09%)	0.5637		1/11(9.09%)	1.0000
		Failure	2/11(18.18%)	8/11(72.73%)		1/11(9.09%)	9/11(81.82%)	

*P-values derived by McNemar's test for agreement. P-values≥0.05 indicate agreement.

Table 5. CT Imaging Variables Analyzed

Continuous Variables	Categorical Variables
Width of the humeral ulnar joint*	Presence/absence of medial coronoid process fragment(s)
Width of the humeral radial joint*	Presence/absence of erosion of ulnar side of the radial ulnar joint at level of medial coronoid process
Disease progression	Erosion of ulnar side of the radial ulnar joint at level of the medial coronoid process
	Degree of sclerosis of the semilunar notch
	Presence of bony fragments other than medial coronoid process
	Presence/absence of periarticular osteophytes

*Serial axial images were reformatted to generate sagittal and dorsal plain views of the elbow joint. Measurements of the humeral ulnar and humeral radial joints were made from specific panels based on a previous study.

Table 6. Least Square Means of Cranial Joint Pouch Width

Time	Least Square Means
Baseline	0.936
Day 180	0.811
Day 365	0.840

Table 7. Analysis of Variance for Cranial Joint Pouch Width

Cranial Joint Pouch Width ANOVA	Mean Square	p-value
Baseline vs. Day 180	0.1563	0.0017
Baseline vs. Day 365	0.0848	0.0172
Day 180 vs. Day 365	0.0079	0.4519

Table 8. Treatment Dose

Dog Weight (lbs.)	Dog Weight (kg.)	^{117}Sn Colloid Dose (mCi)
10 – 19	4.54 – 8.62	0.60 ± 10%
20 – 29	9.07 – 13.15	0.95 ± 10%
30 – 39	13.61 – 17.69	1.24 ± 10%
40 – 49	18.14 – 22.23	1.51 ± 10%
50 – 59	22.68 – 26.76	1.75 ± 10%
60 – 69	27.22 – 31.30	1.97 ± 10%
70 – 79	31.75 – 35.83	2.19 ± 10%
80 – 89	36.29 – 40.37	2.39 ± 10%
90 – 99	40.82 – 44.91	2.59 ± 10%
100 – 109	45.36 – 49.44	2.78 ± 10%
110 – 119	49.90 – 53.98	2.97 ± 10%
120 – 129	54.43 – 58.51	3.13 ± 10%
130 – 139	58.97 – 63.05	3.31 ± 10%
140 or greater*	63.50 or greater*	3.50 ± 10%

*Dose was capped at 3.5 mCi/joint (elbow) when weight exceeded 140 lbs. (63.50 kg) with the total body dose not exceeding 7.0 mCi (two elbows).

Table 9. MR Imaging Variables Analyzed

Continuous Variables	Categorical Variables
Cranial joint pouch width	Medial coronoid process fragmentation presence
Caudal joint pouch width	Radial ulnar subchondral joint erosion
Cranial synovial body width	Progression rating (from baseline)
Caudal synovial body width	Progression rating (from previous visit)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- caninebpiSupplementaryfile.docx