SAFETY AND EFFECTIVENESS OF SYNOVETIN OA®:

Results of three randomized trials evaluating treatment of naturally occurring canine elbow osteoarthritis

John M. Donecker, VMD, MS
Exubrion Therapeutics, Inc.

Steven M. Fox, MS, DVM, MBA, PhD
Senior Veterinary Consultant

Definitions

Note: First usages of the following definitions in the text are indicated by **bold** type.

colloid: A mixture of insoluble particles that remain distributed in a suspension without precipitating or settling to the bottom; nontoxic colloids are used for binding radionuclides to prevent them from escaping the intra-articular space into systemic distribution.

conversion electron: A low-energy electron released from an atomic shell as a result of radionuclide decay.

radionuclide: An unstable isotope of an atom that emits energy from the atomic nucleus. Some radionuclides exist naturally, but those with research and therapeutic applications are usually produced artificially; a radioisotope.

radiosynoviorthesis (RSO): A procedure where a radionuclide is injected into the synovial space to treat joint inflammation and mitigate chondromalacia, especially when systemic or other traditional therapies have failed to produce a satisfactory response; the effect of RSO is reduction of pain and synovial hypertrophy caused by traumatic injury, osteoarthritis, and other arthritides.

Synovetin OA®: A commercially available veterinary device consisting of tin-117m (also designated ^{117m}Sn) indicated for use in veterinary medicine as a synoviorthesis agent. Synovetin OA® contains the radionuclide tin-117m suspended in a colloid for intra-articular administration to treat synovial inflammation.

synoviorthesis: A medical therapy using intra-articular injection of a compound that diminishes the degree of synovial hypertrophy, thereby reducing the pain and inflammation that are early manifestations of degenerative joint disease; treatment of the synovium; can be performed by chemical synoviorthesis or radiosynoviorthesis, with the latter being preferred when a suitable radionuclide is available.

tin-117m: A radionuclide of tin with medical applications for localized treatment and imaging. Tin-117m has a half-life of 14 days. Two principal forms of the energy emitted are (1) conversion electrons that have a short penetration range in tissue (~300 μm), and (2) imageable gamma radiation, which enables monitoring of local distribution in tissue. Tin-117m is metastable, indicated by the "m" suffix, meaning that it is a radioisotope with an energetic nucleus and a relatively long half-life.

Key Points

- Synovitis, the initial lesion in degenerative joint disease (DJD), initiates expression of pro-inflammatory mediators, chondrodestructive enzymes, and synovial neovascularization, leading to DJD and its osteoarthritis (OA) end stage.
- Synovetin OA®, a homogeneous colloid of the novel radionuclide tin-117m, is a veterinary device indicated for intra-articular administration to treat synovial inflammation and elbow OA pain in dogs.
- Synovetin OA® emits low-energy electrons that cause targeted elimination of inflamed synovial cells.
- Three clinical trials were conducted by independent investigators at separate institutional locations to evaluate the safety and effectiveness of Synovetin OA® in dogs with radiographic OA of the elbow, a joint that is often poorly responsive to traditional treatment modalities.
- Effectiveness was evaluated using three metrics: the validated Canine Brief Pain Inventory, clinician assessments of lameness, and force plate gait analysis.
- Treatment success was determined by reduction in pain severity and pain interference of activity, corroborated by clinician assessments of lameness and increases in force plate vertical force and vertical impulse values.
- Trial 1 dogs (n=44) with Grade 1 or 2 elbow OA had a treatment success rate of 88.2% in the per-protocol (PP) population.
- Trial 2 dogs (n=15) with Grade 3 OA had a treatment success rate of 71.4% in the PP population.
- Trial 3 dogs (n=10) retreated with Synovetin OA® one year after an initial dose had a 66.7% treatment success rate in the PP population.
- Clinical chemistry, CBC, and urinalysis values remained within normal ranges for all dogs for up to 12 months following treatment. Joint fluid analysis revealed no treatment-related or clinically significant abnormalities, and scintigraphy results indicated that the tin-117m radionuclide was retained within the synovium of all dogs following intra-articular injection.
- Trial results indicated that Synovetin OA®, in a single dose, consistently provided reduction in pain and lameness and improved quality of life for up to one full year in dogs with clinical OA.

Synovetin OA®—
A Unique Treatment Option for Osteoarthritis

Synovetin OA® is a homogeneous colloid suspension of the patented radionuclide tin-117m. The following combination of features enables Synovetin OA® to provide clinicians with a unique synoviorthesis treatment option for canine osteoarthritis (OA):

- **Single-dose treatment:** Has a convenience advantage versus daily or multi-dose OA therapies and eliminates concern over treatment compliance.
- **Extended duration of effect:** Therapeutic activity lasts up to a year following initial treatment.
- **Minimally invasive:** Non-surgical, clinician-administered, intra-articular procedure for chronic OA pain.
- **No systemic distribution or side effects:** Activity is confined locally to the intra-articular synovium, avoiding side effects associated with long-term exposure to systemic NSAIDs or other agents that bind to prostaglandin receptors as a mode of action.
- **Safety:** Laboratory evaluations indicated no significant effect on obligatory renal, gastrointestinal, hepatic, or immune functions.
- **Treatment flexibility:** Can be effectively and safely used either individually or as co-therapy in a multimodal regimen.
- **Annual retreatment:** Repeat doses can be safely given at one-year retreatment intervals.

Introduction

The conventional approach to treating osteoarthritis (OA) in companion animals is anti-inflammatory or analgesic therapy following clinically acute or radiographic diagnosis. First-line OA treatment typically includes nonsteroidal anti-inflammatory drugs (NSAIDs), hyaluronic acid injection, piprants, nutraceuticals, glucocorticoids, and regenerative therapies (e.g., stem cells, platelet-rich plasma). **Synovetin OA®**, a homogeneous **colloid** suspension of the **radionuclide tin-117m**, offers an alternative approach with therapeutic precision and safety. By targeting tissue critical to the genesis of the OA pathway, Synovetin OA® has significant advantages over other modalities that treat OA. As an intra-articular, single-dose, clinician-administered device, Synovetin OA® avoids systemic side effects and offers safety, convenience, and improved compliance versus agents such as NSAIDs that are given daily as chronic therapy by the pet owner.

Synovetin OA® is a novel preparation of the radionuclide tin-117m embedded in a homogeneous colloid. It is designed for intra-articular administration to treat synovial inflammation and mitigate OA as the end stage of degenerative joint disease (DJD) in dogs. Tin-117m emits **conversion electrons**, low-energy electrons released from the shell of the isotope as a result of radionuclide decay. Tin-117m conversion electrons have a short penetration range of approximately 300 µm (0.3 mm) in tissue and a half-life ($t_{1/2}$) of 14 days. These properties give tin-117m a limited and precise range of activity that avoids exposing adjacent, non-target tissues to radiation, as well as a duration of effect spanning several half-lives (approximately 42–70 days)[1-3] which enables sustained therapeutic activity. Although the energy activity depletes relatively quickly, the therapeutic effect lasts for up to one full year. No other radionuclide, or other treatment for canine OA pain and inflammation, has the properties of tin-117m.

The mode of action of Synovetin OA® is known as **synoviorthesis** (literally, restoration of the synovium), a medical therapy that reduces synovial hypertrophy, thus mitigating the joint inflammation and pain of OA. **Radiosynoviorthesis** refers to the use of radiation of sufficient duration and intensity to achieve elimination of inflamed synoviocytes. Following intra-articular injection, the tin-117m radionuclide particles in Synovetin OA® are selectively phagocytized by synovial macrophages and synoviocytes and retained in situ.[4] While the colloid particles embedded with tin-117m are small enough (2–20 µm) to be phagocytized by synovial macrophages, they are too large to escape the confines of the joint.[4] Studies in laboratory animals have confirmed exceptionally high joint retention (>99%) of the homogeneous colloid containing tin-117m.[2] The energy emitted by tin-117m conversion electrons results in apoptosis of the activated synoviocytes and macrophages. A recent study in normal dogs confirmed that the limited penetration of tin-117m leaves adjacent non-synovial tissues unexposed, thus preserving the integrity and functionality of non-target tissues such as bone, cartilage, tendons, and ligaments.[3]

Synovitis is the initial lesion in DJD and is instrumental in the progression to OA.[5-7] Synovial hyperplasia, permeability, and associated joint swelling cause acute pain and loss of joint mobility as the earliest signs of DJD. More significantly, acute or chronic synovitis can trigger a pernicious inflammatory process leading to cartilage degradation and loss.[8-11] For example, the Multicenter Osteoarthritis Study (MOST) found that human subjects with MRI-detected effusion synovitis (Grade ≥2, range 0–3) of the knee at baseline had a 2.7-fold greater risk (p=0.002) of cartilage loss 30 months later compared to individuals without synovitis.[12] The pathophysiology of joint inflammation includes marked intra-articular overexpression of pro-inflammatory mediators and cytokines, production of chondrodestructive enzymes, synovial neovascularization, and increased C-reactive protein, a biomarker of inflammation.[5,8,9,11] This inflammatory cascade activates neurons in synovial tissue as nociceptive transduction, resulting in a pain response. Given its primal role in DJD, synovitis becomes an inviting target for therapeutic intervention and a potential locus for disease modification.

The three clinical trials described in this report were multi-center studies conducted by independent investigators using multiple assessment methods to evaluate the safety and effectiveness of Synovetin OA® in canine patients. Each trial was conducted during a one-year post-treatment period, allowing assessment of treatment durability over time and an extended evaluation of safety. Trial 1 evaluated treatment response in dogs with mild to intermediate (Grade 1 and 2) elbow OA, Trial 2 evaluated dogs with severe (Grade 3) elbow OA, and Trial 3 evaluated dogs with Grade 1 and 2 OA that were reinjected with Synovetin OA® one year after initial treatment.

The principal inclusion criterion for enrollment was clinical, radiographically confirmed OA of the canine elbow. Elbow OA in the dog is a commonplace diagnosis in clinical practice and can be a challenging therapeutic model. While the canine stifle and hip are often responsive to conventional therapies including surgery, the elbow often defies standard approaches to treating OA. This is due to involvement of multiple etiologies affecting a joint with three articulating bones (radius, ulna, and humerus). At least three arthritic syndromes commonly affect the canine elbow, including in young dogs: fragmented coronoid process (FCP), osteochondrosis dessicans (OCD), and ununited anconeal process (UAP). Thus, obtaining a successful treatment response to radiographically confirmed canine elbow OA was a rigorous study end point.

METHODS

Study sites

The trials were conducted at three study sites: the College of Veterinary Medicine at the University of Missouri (MU), the School of Veterinary Medicine at Louisiana State University (LSU), and Gulf Coast Veterinary Specialists (GCVS), a veterinary referral practice in Houston, Texas. The primary investigator at each study site performed all diagnostic evaluations and was responsible for compliance with the study protocol.

Test animals

The study population consisted of companion animal dogs residing in their owners' homes. Dogs were ≥1 year of age (average 5.4, range 1–11) and weighed at least 8 kg (average 30.1, range 12.1–66.8). All dogs had radiographically diagnosed lameness in one or both elbow joints but no clinically significant OA in the shoulder or carpus. Radiographic findings revealed evidence of Grade 1 (mild), 2 (intermediate), or 3 (severe) OA. Dogs could be treated prior to enrollment with an NSAID but had to be lame at the baseline diagnosis. Dogs with bilateral elbow OA were treated in only one elbow joint in the Grade 1 and 2 elbow OA study. For the Grade 3 elbow OA and reinjection studies, both elbows were treated if there was bilateral elbow OA present.

Test article

The tin-117m colloid (Synovetin OA®, Exubrion Therapeutics) was supplied as a 2–4 mCi (74–148 MBq/mL) sterile suspension packaged in single-dose glass vials. For purposes of dose determination, three tin-117m potencies were evaluated for clinical response in the Grade 1 and 2 elbow OA study: a low (1.00 mCi), medium (1.75 mCi), and high (2.50 mCi) dose. For the Grade 3 elbow OA and retreatment studies, dogs were only treated with the medium (label) dose of 1.75 mCi. Individual doses were calculated based on the patient's body surface area adjusted relative to a 50 lb dog. Synovetin OA® was administered by intra-articular injection into the affected elbow joint(s). Dogs were injected while in lateral recumbency during general anesthesia.

Pain and lameness assessment

The Canine Brief Pain Inventory (CBPI), a survey instrument validated for canine OA and cancer,[13-15] was used for dog owners to subjectively score their pet's pain severity and its functional impact before and after treatment with Synovetin OA®. Owners completed the 11-item survey (see Appendix) at baseline (BL) and at various post-treatment intervals. The mean value of CBPI items 1–4 represented a pain severity score (PSS), and the mean value of CBPI items 5–10 represented a pain interference score (PIS). Item 11 was a Quality of Life (QOL) score.

Clinician assessment of lameness was performed on all enrolled dogs at BL and at various post-treatment intervals. Lameness assessments by the attending veterinarian at both a walk and trot were performed immediately before and after an orthopedic exam. Of the four lameness assessments (walk and trot before and after the exam), the worst value was used for purposes of scoring. Lameness was scored on the following scale:

Grade 0, walks normally, no lameness;

Grade 1, slight lameness;

Grade 2, obvious weight-bearing lameness;

Grade 3, severe weight-bearing lameness;

Grade 4, intermittent non–weight-bearing lameness;

Grade 5, continuous non–weight-bearing lameness.

Force plate gait analysis was performed to evaluate patients while walking and trotting at BL and following treatment at two of the sites (LSU and GCVS) and for the reinjection phase of testing at the third site (MU). All three sites used the same model force plate (OR6-WP-1000, Advanced Medical Technology, Newton, MA) and kinetic force analysis software (Acquire version 7.3, Sharon Software, Dewitt, MI). Mean vertical impulse (IMP) and peak vertical force (PF) during the step cycle were measured. Treatment success was defined as a ≥5% post-treatment improvement in PF or IMP compared to BL in the OA-affected limb(s).

Study design

The studies were prospective, randomized clinical trials involving intent-to-treat (ITT) and per-protocol (PP) populations. Dogs in the ITT population that received dosages ±20% of the recommended tin-117m dose or had other deviations from the study protocol were excluded from the PP population. Dogs with Grade 1 or 2 elbow OA (n=44) were assigned to Trial 1, dogs with Grade 3 elbow OA (n=15) were assigned to Trial 2, and Trial 3 dogs (n=10) assigned to a one-year reinjection study were obtained from the Trial 1 population.

For purposes of trial enrollment, radiographs of elbow joints with clinical OA were obtained under general anesthesia at BL and scored as follows:

- **Grade 0,** normal, no radiographic evidence of OA;
- **Grade 1,** minimal bone change (<2 mm) along anconeal process of ulna and subchondral bone changes (trochlear notch sclerosis);
- **Grade 2,** additional bone proliferation (2–5 mm) along anconeal process;
- **Grade 3,** well-developed degenerative joint disease with bone proliferation along anconeal process >5mm;
- **Grade 4,** radiographic evidence of a severely damaged elbow.

Treatment effectiveness was determined by CBPI scores reported by the dog owner and corroborated by statistical agreement with clinician-assessed lameness scores and force plate gait analysis when available. Treatment success compared to BL or prior post-treatment intervals determined by CBPI scoring was defined as a successful improvement when PSS was reduced by >1.0 and PIS was reduced by >2.0. This is the conventional definition for CBPI scoring to indicate a treatment success for the patient. If there was disagreement between the force plate results and the CBPI results, the force plate results took precedence.

For purposes of evaluating product safety, clinical chemistry testing, CBC, urinalysis, and joint fluid analysis were performed for diagnostic samples obtained at BL and at post-treatment intervals as noted in the individual trial descriptions below. Joint fluid aspiration of the treated joint was performed for all dogs to evaluate changes in intra-articular cellular populations. All testing of diagnostic samples was performed by an independent laboratory. Nuclear scintigraphy was performed for all treated joints to verify intra-articular injection of tin-117m.

Appropriate statistical evaluations were performed, which included the change from baseline, the baseline value, the dose group, and the month and dose group, including within-group analysis, over time. Within-group *p*-values were generated by the paired t-test or Wilcoxon Sign Rank Test depending on the distribution of the data.

Trial 1

Trial 1 was a multi-center study conducted at all three locations. The trial objective was twofold: (1) to evaluate the safety and effectiveness of Synovetin OA® following administration to dogs with Grade 1 and 2 elbow OA; and (2) to determine which of three tin-117m colloid dosages provided optimum effectiveness at the lowest dose in the study population (thus conforming to the radiotherapy principle of ALARA, "as low as reasonably achievable," to obtain the desired effect). The 44 dogs in Trial 1 were randomly assigned to either the low (n=14), medium (n=14), or high (n=16) tin-117m dosage groups. Using CBPI assessment criteria described above, treatment response in terms of pain severity and interference was assessed by dog owners at BL and at 1, 3, 6, 9, and 12 months following treatment. Concurrent with the CBPI assessments, a clinician assessment of lameness while patients were walking or trotting was performed. At BL and the same post-treatment intervals as the clinician assessment, a force plate gait analysis was performed on dogs at the LSU and GCVS sites. A composite of the CBPI data, clinician assessment values, and force plate gait results was used to determine which of the three tin-117m dosages provided optimum results.

Trial 2

Trial 2 was conducted at the GCVS and LSU sites. Its methods and objectives were similar to those used in Trial 1 except that (1) only the tin-117m medium intra-articular dose of 1.75 mCi for a 50 lb. dog, normalized by individual body weight, was used; (2) the patient population consisted exclusively of dogs with Grade 3 elbow OA; and (3) both elbows were treated if affected by OA. Treatment success was primarily determined by CBPI results reported by the participating dog owners and clinician lameness assessments. Assessments were made at BL and at 3, 6, 9, and 12 months following treatment. Blood, urine, and joint fluid samples were obtained at BL and at 6 and 12 months following treatment.

Trial 3

Trial 3 was conducted at the MU and LSU sites. The trial objective was to evaluate the safety and effectiveness of a second (follow-up) dose of Synovetin OA® in dogs with Grade 1 and 2 elbow OA that had been given an initial treatment at least one year earlier. The tin-117m medium dose (1.75 mCi) was used as the follow-up treatment in all Trial 3 dogs. Both elbows of each dog were treated. Response to the second Synovetin OA® dose was evaluated in the PP population for a follow-up period of ≥12 months. Treatment success was determined by CBPI results, clinician assessment of lameness at walk and trot, and force plate gait analysis. Assessments using the CBPI were made at 3, 6, 9, and 12 months following treatment. Force plate gait analyses and clinician assessments of lameness were conducted at BL and at 3 and 6 months following treatment. Blood and urine samples and joint fluid were obtained at BL and at 180 days following treatment.

RESULTS

Safety

Intra-articular injection with tin-117m was well tolerated, and none of the participating dogs experienced clinically significant treatment-related adverse effects or other sequelae. In all three trials, some significant variation occurred between dosage groups in urinalysis, CBC, and clinical chemistry values at various post-treatment intervals. However, all values were within normal ranges. Joint fluid analysis revealed no treatment-related or clinically significant abnormalities. Scintigraphy results indicated that tin-117m was retained within the synovium of all study dogs following intra-articular injection.

TRIAL 1

Table 1. Statistically significant responses to the Canine Brief Pain Inventory (CBPI) in dogs with Grade 1 and 2 elbow osteoarthritis treated with low, medium, or high doses of Synovetin OA®

CBPI factor	Post-treatment interval (month[s])	Dosage group (no. dogs)*	Mean difference in CBPI score from BL (± SEM)†	Within dosage-group *p*-value
Pain severity	1	Medium (14)	-1.77 ± 0.59	0.0101
		High (11)	-1.73 ± 0.57	0.0132
	3	Medium (14)	-2.13 ± 0.65	0.0061
		High (11)	-1.48 ± 0.41	0.0046
	6	Medium (14)	-2.34 ± 0.81	0.0129
		High (9)	-1.67 ± 0.72	0.0491
	9	Medium (13)	-3.00 ± 0.70	0.0011
		High (10)	-2.23 ± 0.57	0.0038
	12	Low (10)	-1.35 ± 0.50	0.0239
		Medium (12)	-2.33 ± 0.76	0.0110
		High (11)	-2.39 ± 0.50	0.0067
Pain interference	1	Low (10)	-2.00 ± 0.57	0.0067
		Medium (14)	-1.73 ± 0.66	0.0207
	3	Low (10)	-2.15 ± 0.73	0.0168
		Medium (14)	-2.06 ± 0.65	0.0074
	9	Medium (14)	-2.95 ± 0.67	0.0009
	12	Medium (12)	-2.60 ± 0.96	0.0202
Quality of life	1	Low (10)	0.90 ± 0.31	0.0187
	9	Medium (13)	1.08 ± 0.40	0.0195
	12	Medium (12)	0.92 ± 0.40	0.0195

*Low dose = 1.00 mCi, medium dose = 1.75 mCi, high dose = 2.50 mCi.
†A negative change is an improvement in the lameness score.
BL = baseline; SEM = standard error of the mean.

Table 1 shows which tin-117m dosages resulted in significant improvements ($p<0.05$) from BL in clinical pain response (PSS and PIS) as determined by the CBPI assessment factors (Appendix). Significant PSS improvement from BL occurred at all post-treatment intervals for the medium (label) and high dosages. Significant PIS improvement from BL occurred at all post-treatment intervals for the medium dose. Significant QOL improvement from BL occurred at one month following treatment in dogs given the low dose and at 9 and 12 months in dogs given the medium dose.

Clinician assessments of lameness at BL and post-treatment intervals of each dog at a walk and a trot showed statistical agreement ($p \geq 0.05$) with the CBPI assessments for all dosage levels and for all comparisons between BL and each post-treatment interval. Test groups given any of the three tin-117m dosage levels had a mean reduction in lameness score from BL at each post-treatment level with four exceptions, all involving the high dose (Table 2). Dogs given the high dose showed either no improvement or an increase of ≤0.43 in mean lameness score at days 30 and 90.

Table 2. Clinician assessment of lameness in dogs with Grade 1 and 2 elbow osteoarthritis treated with low, medium, or high doses of Synovetin OA®

Parameter	Test interval (month[s])	Dosage group	Mean change in lameness score from BL (± SEM)*
Lameness at walk	1	Low	-0.67 ± 0.21
		Medium	-0.22 ± 0.32
		High	0.29 ± 0.47
	3	Low	-0.60 ± 0.24
		Medium	-0.29 ± 0.29
		High	0.00 ± 0.26
	6	Low	-0.75 ± 0.48
		Medium	-0.44 ± 0.34
		High	-0.50 ± 0.22
	9	Low	-0.33 ± 0.33
		Medium	-0.78 ± 0.28
		High	-0.83 ± 0.31
	12	Low	-1.00 ± 0.37
		Medium	-0.75 ± 0.37
		High	-1.14 ± 0.26
Lameness at trot	1	Low	-0.50 ± 0.22
		Medium	-0.33 ± 0.37
		High	0.43 ± 0.43
	3	Low	-0.40 ± 0.24
		Medium	-0.43 ± 0.30
		High	0.00 ± 0.26
	6	Low	-0.75 ± 0.48
		Medium	-0.33 ± 0.29
		High	-0.50 ± 0.22
	9	Low	-0.17 ± 0.40
		Medium	-0.78 ± 0.32
		High	-0.83 ± 0.31
	12	Low	-0.83 ± 0.40
		Medium	-0.63 ± 0.38
		High	-1.00 ± 0.38

*A negative change is an improvement in the lameness score.
BL = baseline; SEM = standard error of the mean.

Based on a composite of force plate results, CBPI results, and clinician assessments of lameness, the individual treatment success (TS) rate by study site is shown in Figure 1. In the PP population, one treatment failure (TF) occurred in both the LSU and GCVS trials, and two treatment failures occurred at the MU site. The treatment failures occurred in a dog at the LSU site given the low tin-117m dose, a dog at the GCVS site given the medium dose, and two dogs at the MU site, one given the low dose and one the high dose. The overall TS rate was 88.2% in the PP population, with 80% success (8/10) in the low-dose dogs, 92% (12/13) for medium-dose dogs, and 90.9% (10/11) for high-dose dogs. The ITT population had a 75.0% (33/44) treatment success rate.

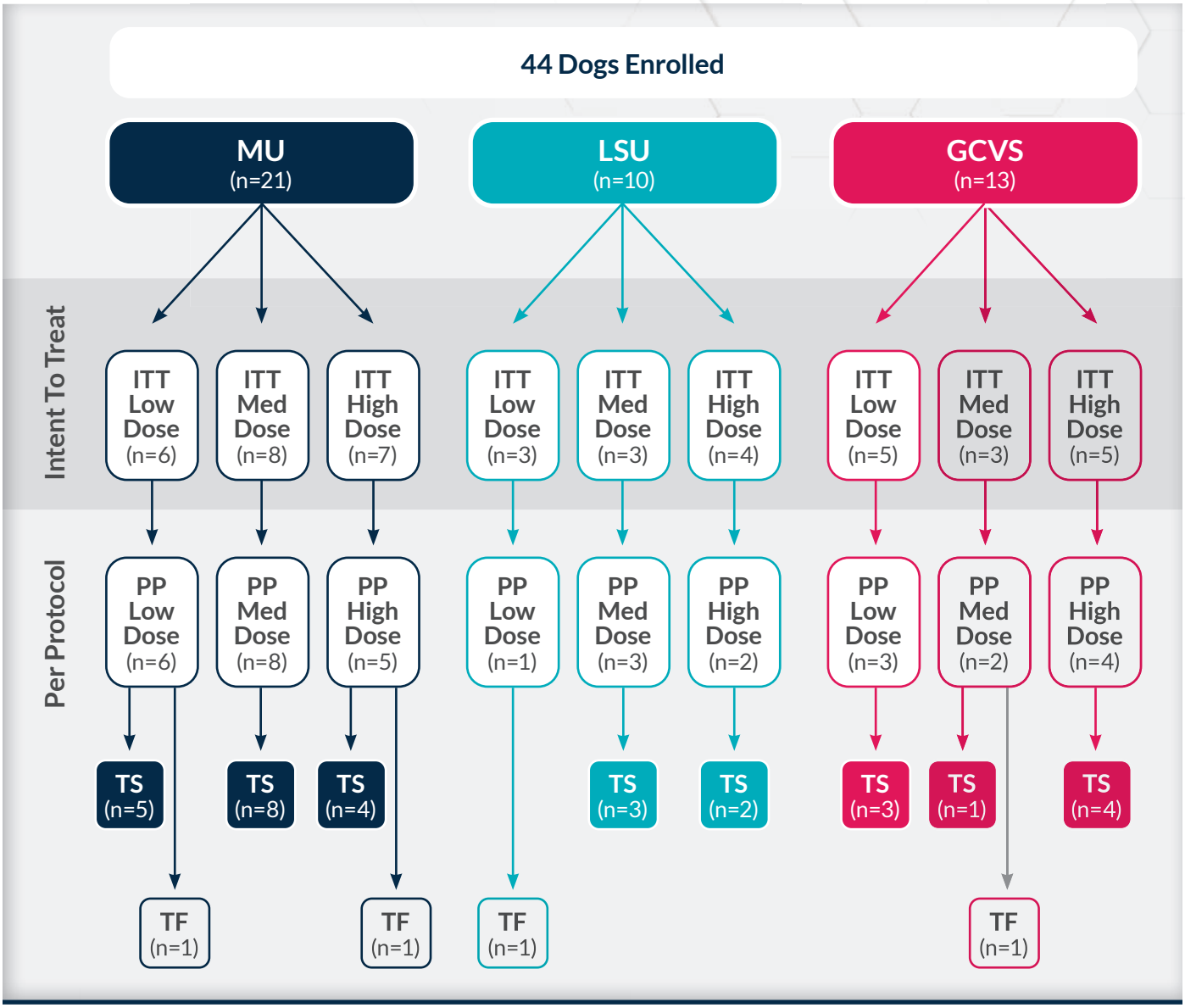


Figure 1. The Synovetin OA® treatment response rate is shown for the Grade 1 and 2 elbow osteoarthritis trial conducted at three study sites: the University of Missouri (MU), Louisiana State University (LSU), and Gulf Coast Veterinary Specialists (GCVS). The per-protocol (PP) population (n=34) had an 88.2% (30/34) overall treatment success (TS) rate. Treatment failure (TF) occurred in two dogs receiving the low dose, one each at the LSU and MU sites; 1 dog receiving the medium dose at the GCVS site; and 1 dog receiving the high dose at the MU site. The intent-to-treat population (n=44) had a 75.0% (33/44) overall treatment success rate.

Force plate gait analyses conducted for 22 dogs at the LSU and GCVS sites showed an overall treatment success rate of 81.8% (18/22, p=0.0022). Treatment success was 71.3% (5/7) in low-dose dogs, 83.3% (5/6) in medium-dose dogs, and 88.9% (8/9) in high-dose dogs (Table 3). A significant (p<0.05) improvement in mean PF values from BL occurred at 1, 3, 6, and 9 months after treatment. Figure 2 shows the treatment response in two representative dogs as determined by force plate data.

Table 3. Force plate improvement rate in dogs with Grade 1 and 2 elbow osteoarthritis treated with low, medium, or high doses of Synovetin OA®

Dosage	% (no.) dogs with treatment success	% (no.) dogs with treatment failure
Low	71.3 (5)	28.6 (2)
Medium	83.3 (5)	16.7 (1)
High	88.9 (8)	11.1 (1)
Overall	**81.8 (18)**	**18.1 (4)**

A combination of CBPI data and clinician assessment of lameness results was used for dose determination, i.e., the tin-117m dosage that provided optimum improvement in the OA-affected limb at the lowest therapeutic dose (the ALARA principle). Compared to dogs given the low dose, the medium-dose group had consistently better mean PSS, PIS, and QOL scores and a higher force plate success rate. Compared to the medium-dose group, dogs given the high dose had no significant improvement in PSS, PIS, or QOL and a marginally better force plate success rate. Based on these outcomes, the medium tin-117m dosage (1.75 mCi) was considered the optimum therapeutic dose.

Figure 2. The graph shows force plate testing results in two Trial 1 dogs with Grade 1 and 2 elbow osteoarthritis at five post-treatment intervals following intra-articular injection of Synovetin OA® at baseline (BL). The dashed gray line denotes mean BL peak force (PF) values, while the continuous gray line denotes a 5% increase from BL, the threshold for treatment success. The asterisk (*) denotes a significant difference in PF ($p<0.05$) from BL values, indicating that an improvement in joint function occurred after treatment. Force plate results showed that Dog A, evaluated at the GCVS site, showed significant improvement from BL in the treated limb at all time points up to 12 months after Synovetin OA® injection. The contralateral control limb in Dog A showed marked improvement as well, suggesting that a therapeutic response in the OA-affected limb resulted in gait normalization that improved functionality in both forelimbs. Dog B, treated at the LSU site, showed significant improvement from BL at 1, 3, 6, and 12 months. Force plate data showing significant improvement from baseline lasting 12 months in the treated limbs of both dogs provided an objective measure of treatment durability following a single dose.

Trial 2

Using a composite of CBPI results and clinician assessments of lameness, a TS rate of 71.4% (10/14) was reported for the Grade 3 OA-affected elbows in the PP population (Figure 3), based primarily on CBPI results. Three PP dogs at the GCVS site and one at the LSU site experienced TF. Dogs in the ITT population had a 73.3% (11/15) TS rate.

Clinician assessments showed mean reductions in lameness scores at each post-treatment interval except at 12 months (Table 4). The dog-owner CBPI assessments of TS in the PP population were statistically validated by the clinician assessments of TS based on lameness scoring. The two assessment methods were in statistical agreement (p>0.05) using McNemar's test of agreement.

Trial 3

Based on CBPI results, force plate analysis, and clinician assessments of lameness, dogs in the PP population had a 66.7% (6/9) TS rate. One dog at the MU site and two dogs at the LSU site had treatment failures (Figure 4). The ITT success rate was 60% (6/10). The comparison of the CBPI success criteria with the clinician-assessed success using McNemar's test of agreement based on lameness scores for dogs at a walk or trot yielded p-values >0.05, indicating agreement between the two measures.

The force plate analyses performed at 3 and 6 months after treatment revealed a ≥5% PF or IMP improvement from BL occurred in either elbow at either visit for 6/9 (66.7%) PP dogs. At 3 months, 5/9 (55.6%) dogs were improved and at 6 months, 6/9 (66.7%) dogs were improved.

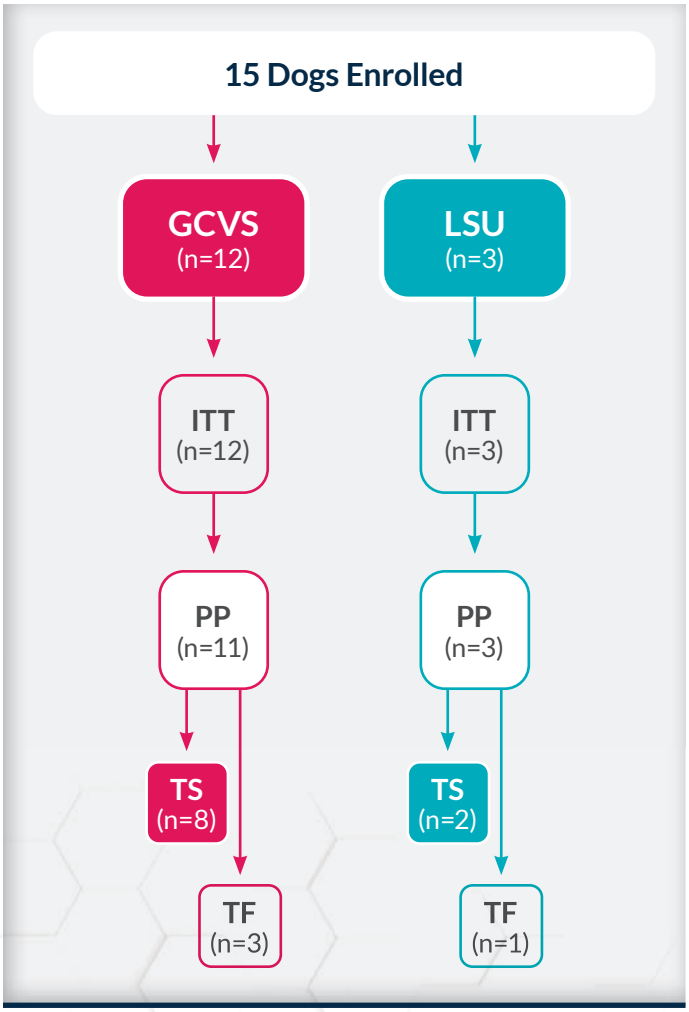


Figure 3. The Synovetin OA® treatment response rate is shown for the Grade 3 elbow osteoarthritis trial conducted at two study sites, Gulf Coast Veterinary Specialists (GCVS) and Louisiana State University (LSU). The per-protocol (PP) population (n=14) had a 71.4% (10/14) overall treatment success (TS) rate. The intent-to-treat (ITT) population had a 73.3% (11/15) TS rate.

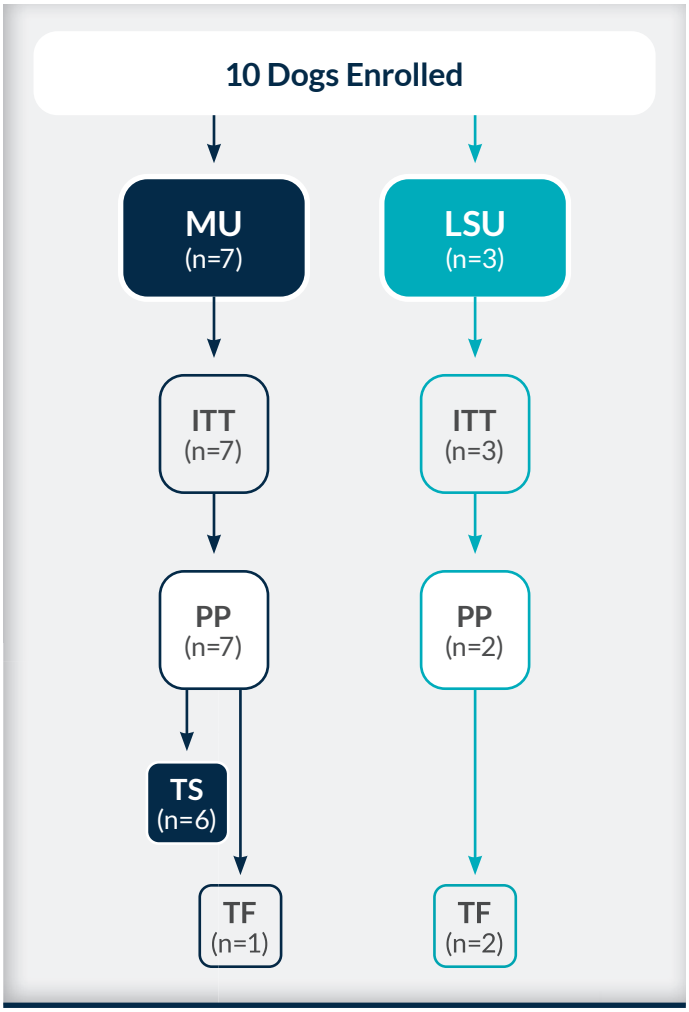


Figure 4. The Synovetin OA® treatment response rate is shown for the reinjection trial that evaluated dogs with Grade 1 and 2 elbow osteoarthritis previously treated at two study sites, the University of Missouri (MU) and Louisiana State University (LSU). Following reinjection of Synovetin OA® one year after the initial dose, the per-protocol (PP) population (n=9) had a 66.7% (6/9) overall treatment success (TS) rate. Treatment failure (TF) occurred in one dog at the MU site and two dogs at the LSU site. The intent-to-treat population had a 60% (6/10) overall treatment success rate.

Discussion and Conclusions

Radiosynoviorthesis using Synovetin OA® has at least two key distinctions from traditional DJD therapies such as NSAIDs, oral corticosteroids, and piprants. Although these classes of drugs provide analgesia of short duration, they are non-targeted agents in that they are distributed and metabolized systemically with the potential for unwanted side effects. Moreover, systemic anti-inflammatory agents are widely available from OTC sources and, as owner-administered treatments, have a strong potential for irregular compliance. Consistent absence of local or systemic side effects in tin-117m–treated dogs in all three trials was a strong affirmation of the safety of intra-articular injection with Synovetin OA®. These observations were at the medium (optimum) dosage as well as the high dosage, which contained a 43% greater tin-117m concentration compared to the medium dosage.

Because tin-117m is phagocytized and held in situ within the synovium and has a radiologic range confined to the synovial intima thickness, its local sequestration without systemic activity is assured. This dosing precision makes Synovetin OA® a truly targeted treatment distinct from systemic OA therapies. By altering cellular composition within tissue critical to the origin of the OA pathway and the durability of a favorable treatment response, radiosynoviorthesis with Synovetin OA® potentially affects the progression of OA disease. For example, clinician assessments of lameness in dogs with Grade 1 and 2 OA (Table 2) showed little if any increase in lameness scores versus BL at 9 and 12 months in dogs given the medium and high tin-117m dosages. This suggests that characteristic disease progression in these dogs was either minimal or absent altogether.

The subjective CBPI assessments by pet owners were statistically correlated with objective clinician assessments of lameness and force plate gait results. This indicated that owner assessments can be useful, valid components of the patient's presentation and medical history record in cases of clinical OA. Mean CBPI scores were significantly improved in Synovetin OA®–treated dogs at all post-treatment intervals. For example, at 9 and 12 months, dogs with Grade 1 and 2 OA given the medium or high tin-117m dose had mean PSS and PSI scores that were ≥2.33 points lower versus BL and mean QOL scores that were ≥0.92 points higher versus BL (Table 1). Similarly, mean clinician assessment scores of lameness at a walk or trot in Grade 1 and 2 OA cases were improved from BL for all dosage levels at all post-treatment intervals except at 1 and 3 months for the high dose (Table 2). Force plate gait analysis provided objective corroboration of significant post-treatment improvement in lameness at 1, 3, 6, and 9 months in dogs with Grade 1 and 2 OA (see Figure 2 for treatment response from representative Trial 1 dogs). At the medium and high dosages, dogs with Grade 1 to 2 OA had a >83% TS rate based on force plate gait results (Table 3). The overall TS rate of 88.2% (Figure 1) in the PP population was a strong indication that a single dose of tin-117m consistently provides pain relief and functional improvement in dogs with mild to moderate OA.

Dogs with more severe, Grade 3 OA showed a similar improvement in clinician assessments of lameness following treatment with Synovetin OA® at the label dosage (Table 4). Dogs showed improvements in clinician assessments at all post-treatment time points up to 9 months (Table 4). The overall TS rate of 71.4% in the PP population (Figure 3) was comparable to that for Trial 1 dogs (88.2%).

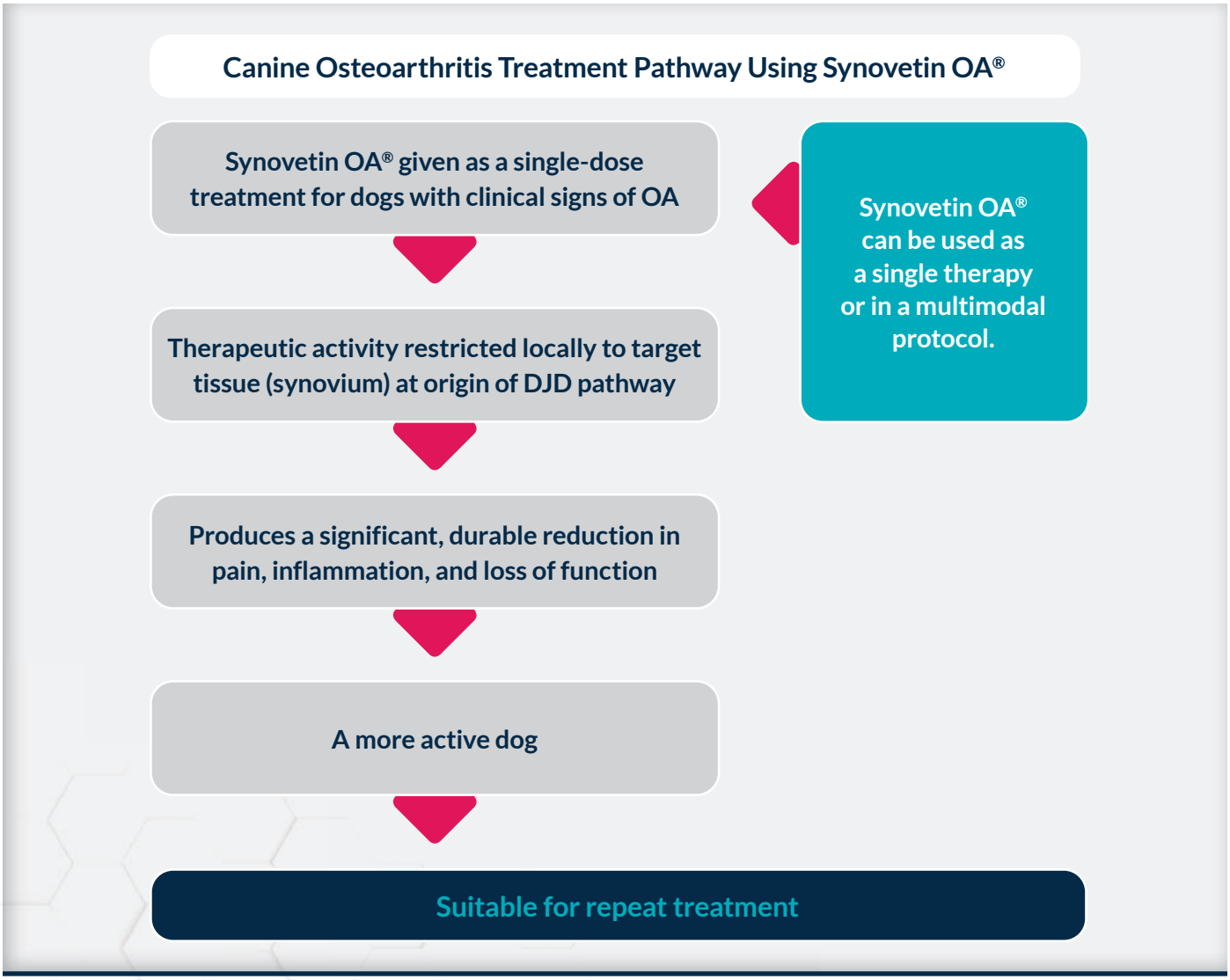
Table 4. Clinician assessment of lameness in dogs with Grade 3 elbow osteoarthritis treated with Synovetin OA®

Parameter	Test interval (month[s])	Mean change in lameness score from BL (± SEM)*
Lameness at walk	3	-0.86
	6	-0.50
	9	-0.40
	12	0.60
Lameness at trot	3	-0.85
	6	-0.18
	9	-0.20
	12	0.27

*A negative change is an improvement in the lameness score.
BL = baseline; SEM = standard error of the mean.

Dogs in Trial 3 had already shown overall improvement in pain and lameness following their initial tin-117m treatment a year earlier as part of the Trial 1 population. In these dogs with a previous favorable treatment response, retreatment with Synovetin OA® resulted in a high TS rate (66.7%, Figure 4). This indicates that retreatment is useful either as maintenance therapy or with the possibility of further symptomatic improvement from BL. Importantly, at the conclusion of Trial 3, two years after the initial dose, none of the participants experienced clinically significant adverse safety effects as determined by CBC, clinical chemistry, urinalysis, and joint fluid analysis following two tin-117m treatments.

Collectively, the three trials are the first large-scale demonstration of the therapeutic effectiveness of Synovetin OA® in treating canine OA in a clinical setting. The fact that trial results were consistently favorable over an extended period (up to 12 months) in separate canine populations evaluated by different institutional investigators was a strong affirmation of the safety and effectiveness of tin-117m given at an intermediate (label) dose of 1.75 mCi for a 50 lb dog. When used as a targeted treatment (Figure 5), either as a single treatment or in a multimodal protocol, Synovetin OA® can be expected to provide reduction in pain and lameness and improved QOL. This was observed in a large cohort of dogs diagnosed with elbow OA and would, presumptively, be expected in other joints as well.



DJD = degenerative joint disease OA = osteoarthritis

Figure 5. The diagram shows the osteoarthritis treatment pathway used in the Synovetin OA® clinical trials. Synovetin OA® can be used as a single therapy or in a multimodal protocol.

Because Synovetin OA® has an extended duration of favorable treatment effects in dogs suffering from chronic OA and demonstrates an exceptional safety profile as confirmed in the three trials, it represents a **unique and valuable addition to the veterinarian's OA treatment options.**

APPENDIX

Canine Brief Pain Inventory assessment items and assignment to pain severity and pain interference factors[14]

CBPI factor	Item	Factor–item correlation*
Pain severity	**Item 1:** Pain at its worst in last 7 days	0.86
	Item 2: Pain at its least in last 7 days	0.85
	Item 3: Pain at its average in last 7 days	0.90
	Item 4: Pain right now	0.86
Pain interference	**Item 5:** General activity in last 7 days	0.68
	Item 6: Enjoyment of life in last 7 days	0.65
	Item 7: Ability to rise to standing in last 7 days	0.63
	Item 8: Ability to walk in last 7 days	0.72
	Item 9: Ability to run in last 7 days	0.89
	Item 10: Ability to climb stairs in last 7 days	0.85
Quality of life	**Item 11:** Overall QOL in last 7 days	NA

*Correlation between factors and constituent items (correlations >0.4 indicate that an item is highly correlated with its factor).
NA = not applicable.

Acknowledgements

The authors thank the principal investigators who conducted the trials: Jimmy C. Lattimer, DVM, MS, DACVR, University of Missouri College of Veterinary Medicine; Lorrie Gaschen, DVM, PhD, Dr. habil., Dr. med. vet., DECVDI, and Karanvir S. Aulakh, BVSc & AH, MS, DACVS-SA, CCRP, both of Louisiana State University School of Veterinary Medicine; and Michelle Fabiani, DVM, DACVR, Brian Beale, DVM, DACVS, and Caleb Hudson, DVM, DACVS, all of Gulf Coast Veterinary Specialists. The authors acknowledge the contribution of Mark Dana of Scientific Communications Services, LLC, in the writing and editing of this report.

References

1. Stevenson NR, St. George G, Simon J, et al. Methods of producing high specific activity Sn-117m with commercial cyclotrons. *J Radioanal Nucl Chem.* 2015;305:99-108.
2. Doerr C, Stevenson N, Gonzales G, et al. Homogeneous Sn-117m colloid radiosynovectomy results in rat models of joint disease. *J Nucl Med.* 2015;suppl 3:1243.
3. Lattimer JC, Selting KA, Lunceford JM, et al. Intraarticular injection of a TIN-117m radiosynoviorthesis agent in normal canine elbows causes no adverse effects. *Vet Radiol Ultrasound.* 2019;1-8.
4. Stevenson NR, Lattimer J, Selting K, et al. Abstract S6-03: Homogenous SN-117m colloid – a novel radiosynovectomy agent. *World J Nucl Med.* 2015;14(Suppl 1):S15-S68.
5. Benito MJ, Veale DJ, FitzGerald O, et al. Synovial tissue inflammation in early and late osteoarthritis. *Ann Rheum Dis.* 2005;64:1263-1267.
6. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. *Nat Rev Rheumatol.* 2010;6:625-635.
7. Wenham CY, Conaghan PG. The role of synovitis in osteoarthritis. *Ther Adv Musculoskelet Dis.* 2010;2:349-359.
8. Bondeson J, Wainwright SD, Lauder S, et al. The role of synovial macrophages and macrophage-produced cytokines in driving aggrecanases, matrix metalloproteinases, and other destructive and inflammatory responses in osteoarthritis. *Arthritis Res Ther.* 2006;8:R187.
9. de Lange-Brokaar BJ, Ioan-Facsinay A, van Osch GJ, et al. Synovial inflammation, immune cells and their cytokines in osteoarthritis: a review. *Osteoarthritis Cartilage.* 2012;12:1484-1499.
10. Scanzello CR, Umoh E, Pessler F, et al. Local cytokine profiles in knee osteoarthritis: elevated synovial fluid interleukin-15 differentiates early from end-stage disease. *Osteoarthritis Cartilage.* 2009;17:1040-1048.
11. Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. *Ther Adv Musculoskelet Dis.* 2013;5:77-94.
12. Roemer FW, Guermazi A, Felson DT, et al. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. *Ann Rheum Dis.* 2011;70:1804-1809.
13. Brown DC, Boston RC, Coyne JC, et al. Ability of the Canine Brief Pain Inventory to detect response to treatment in dogs with osteoarthritis. *J Am Vet Med Assoc.* 2008;233:1278-1283.
14. Brown DC, Boston R, Coyne JC, et al. A novel approach to the use of animals in studies of pain: validation of the Canine Brief Pain Inventory in canine bone cancer. *Pain Med.* 2009;10:133-142.
15. Brown DC, Boston RC, Farrar JT. Comparison of force plate gait analysis and owner assessment of pain using the Canine Brief Pain Inventory in dogs with osteoarthritis. *J Vet Intern Med.* 2013;27:22-30.

EXUBRION THERAPEUTICS

 Printed in USA. July 2020 EXN-SYN-024