Synovetin OA™

Results of Clinical Trials Using a Homogeneous Tin Colloid for Treatment of Elbow Osteoarthritis

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Chief Veterinary Officer
Convetra, Inc.
Disclosures:
Dr. J. Donecker is an employee of Convetra, Inc.
Dr. S. Fox is a consultant for Convetra, Inc.

Acknowledgements:
This presentation is a compilation of clinical research conducted at the University of Missouri College of Veterinary Medicine, Louisiana State University School of Veterinary Medicine, Gulf Coast Veterinary Specialists (Houston, TX) and by consultants at the University of Texas MD Anderson Cancer Center (Houston, TX) and Isotherapeutics Inc. (Angleton, TX)
Clinical signs: synovial hyperplasia, joint swelling, pain, “morning stiffness”

Present from earliest stages of DJD

Precedes development of OA

Early intervention can prevent, delay, or limit arthritic changes (DJD modifier)

Arthrosopic view of a canine diarthroidial joint with early-onset DJD reveals robust synovitis and synovial hyperplasia, the initial event in the histopathology of DJD. (Photo, S. M. Fox, Chronic Pain in Small Animal Medicine, used with permission.)

The Role of Synovitis in DJD Progression – Inflammatory Cascade, Angiogenesis

- Right: Early synovitis initiates intra-articular inflammatory cascade
- Macrophages, other pro-inflammatory cells are activated
- Synovial angiogenesis → edema, inflammatory cell infiltration

Canine Pain Management

~$3B Market\(^5\) (Med + Surg)

Few effective, minimally-invasive options
Compliance, safety concerns with daily pain meds
Lengthy, inconvenient rehabilitation
Patients often refractory to traditional pain meds

2M Cases\(^5\)

1.1M Don’t Go\(^5\)

Referral practice

300K Opt Out\(^5\)

Painful dogs, dissatisfied owners = lost revenue

5. Harmony Marketing Data – on file
Synovetin OA™: A Device Containing HTC

- 6+ month duration of action
- Device designation
- Intra-articular (IA) mode of administration
- Low energy conversion electron radiation

Scintigraphy of an HTC injected canine elbow shows >99% retention in synovial tissue (Image courtesy of Jimmy Lattimer, DVM.)
Synovetin OA™: A Homogenous Colloid Suspension of Tin-177m

**Mode of action (MOA):**

- Emits discrete low-energy conversion electron emission (0.3 mm radiation range),

- Colloid containing micro particles retained in joint space for at least 42 days (3 half-lives)

- Particles absorbed by synoviocytes and macrophages reducing pain and swelling

Scintigraphy of an HTC injected canine elbow shows >99% retention in synovial tissue (Image courtesy of Jimmy Lattimer, DVM.)
OA Disease Modifying Effects of Synovetin OA™

• Pro-inflammatory macrophages recruited during synovial hyperplasia engulf colloid embedded tin-117m particles

• Phagocytized tin-117m is transported to synovium and held in situ

• Conversion electron emissions destroy macrophages responsible for inflammation (apoptosis)

• Synovium more closely resembles the pre-inflammatory state post treatment
Preclinical Studies Trialing Synovetin OA™

**Tin-117m clinical trials**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Study Number</th>
<th>Experiment Date</th>
<th>Number Evaluated</th>
<th>Site / PI</th>
<th>Notes</th>
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<td>databook # 0202-03</td>
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<td>Effects of tin-117m-annexin and Sm153 colloid on developing type II collagen arthritis in rats</td>
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<td>Meniscal tear model of osteoarthritis in rat (ROA)</td>
<td>ITG # 2014-02</td>
<td>October 28, 2014 - January 6, 2015</td>
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<td>Meniscus tear model of OA in rats 2</td>
<td>ITG # 2015-01</td>
<td>January 29, 2015 - April 16, 2015</td>
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<td>Tin-117m radiosynoviorthesis missed injection and topical exposure study</td>
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<td>Mis-administration of IV dose</td>
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<td>Non-GLP IV exposure</td>
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<td>Long term toxicity</td>
<td>ITG # 2017-04</td>
<td>October 5, 2017 - February 28, 2018</td>
<td>89</td>
<td>IsoTherapeutics Group, LLC Jaime Simon, PhD</td>
<td>GLP LTT</td>
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</table>

- These studies validated homogeneous tin colloid (HTC) to be a therapeutic device for radiosynoviorthesis (RSO).
- Bolder BioPATH, Inc. validated HTC to be an OA disease modifying device with beneficial cartilage effects seen in rats at 1, 4 and 6 weeks.
Synovetin OA™ Five Normal Dog Safety Study

- No dog exhibited any lameness after injection during 6 week study
- Gamma camera confirmed retention in joint at 24 hours
- Urine and feces collection indicated > 99% average joint retention
- Imaging studies were normal and static between studies
- Post mortem studies
  - Organ and elbow activity indicated > 99% retention in elbow
  - No histologic abnormalities were found in organs or joints
  - Micro autoradiography confirmed synovial localization
Normal Dog Safety Study: Results

Top Histopathology Slide (Dog 1):
- Inflammatory cells (arrow) below synovial surface
- Normal articular cartilage (arrowhead) of humerus (H), 16x

Bottom Autoradiograph (Dog 1):
- HTC particles phagocytized by sub-synovial macrophages (arrow)
- Normal articular cartilage of humerus (arrowhead), 400x

Interpretation:
- No histopathology in non-target tissue (top)
- Intra-articular injection of HTC results in uptake of tin-117m by inflammatory cells at target site (bottom)
## Synovetin OA™ Canine Clinical Studies

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Study Number</th>
<th>Date Completed</th>
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<td>Safety and efficacy of tin-117m colloid for treatment of canine osteoarthritis</td>
<td>None assigned by University of Missouri</td>
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<td>Gulf Coast Veterinary Specialists (Michelle Fabiani DVM) Louisiana State University School of Veterinary Medicine (Karanvir Aulakh DVM) University of Missouri College of Veterinary Medicine (Jimmy Lattimer DVM)</td>
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<td>The use of tin-117m colloid (Synovetin OA™) for treatment of naturally occurring grade 3 osteoarthritis of the elbow in client owned dogs</td>
<td>C-22017</td>
<td>July 2018</td>
<td>15 (27 elbows)</td>
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<td>Re-injection of tin-117m colloid (Synovetin OA) in naturally occurring grade 1 or 2 osteoarthritis of the elbow in client owned dogs</td>
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<td>June 2018</td>
<td>10 (20 elbows)</td>
<td>Louisiana State University School of Veterinary Medicine (Karanvir Aulakh DVM) University of Missouri College of Veterinary Medicine (Jimmy Lattimer DVM)</td>
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- Studies C-22017 and C-80817 are GMP, GLP, GCP and GDP studies validating commercially produced Synovetin OA™ and the commercial manufacturing process utilizing the Belgium reactor (BR2) and Theragenics, Inc. a human medical radioisotope manufacturer based in Buford, GA (NE of Atlanta)
Client Owned Dog Naturally Occurring Grade 1 & 2, 3 Elbow OA and Reinjection Studies

- **3 Clinical Sites**
  - University of Missouri CVM - Principal Investigator: Dr. Lattimer
  - Louisiana State University SVM - Drs. Aulakh and Gaschen
  - Gulf Coast Veterinary Specialists - Drs. Fabiani, Hudson and Beale

- **Facility Requirements**
  - Radioactive material license to include tin-117m (State or NRC)
  - Dose calibrator
  - Ludlum dosimeter
  - MRI

- **Inclusion Criteria**
  - Radiographic grade 1-3 elbow OA with documentable lameness
  - dogs > 8 kg and 1 yo
  - No co-morbid condition that may preclude survival for 1 year
# Client Owned Dog 12 Month Study Sampling

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<th>Client-owned dogs schedule</th>
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Synovitis Pre and 9 mos. Post Treatment with Synovetin OA™

(Fused PET/MRI images courtesy of Jimmy Lattimer DVM, MS, DACVR)
Determination of Treatment Success
Treatment Success (TS) was defined as an improvement (>5%) and/or a significant (P<0.05) increase in mean PF and/or IMP at Months 1, 3, 6, 9, and/or 12, compared to baseline (0 Month) for that individual dog evaluated on the force plate.

Example Figure: Treatment success (TS) shown here and defined as a 5% increase or significant (P<0.05) increase in the mean PF (5 trials) for each month. The dashed line denotes baseline values and solid line denotes a 5% increase from baseline.
**Determination of Treatment Success**

Treatment Success (TS) was defined as an improvement (>5%) and/or a significant (P<0.05) increase in mean PF and/or IMP at Months 1, 3, 6, 9, and/or 12, compared to baseline (0 Month) for that individual dog evaluated on the force plate.

**Example Figure:** Treatment success (TS) shown here and defined as a 5% increase or significant (P<0.05) increase in the mean PF (5 trials) for each month. The dashed line denotes baseline values and solid line denotes a 5% increase from baseline.
Client Owned Dog Elbow OA Trials Status

- Data validation and source documentation followed by statistical analysis underway for all 3 studies

- Currently 69 dogs and 93 elbows treated with no clinically significant adverse reactions
  - 1 missed IA injection with no complications other than ineffective

- Final Force Plate conclusions – significant treatment effect in > 80% of dogs treated

- INTERIM PET analysis – reduction in synovitis seen in > 70%

- INTERIM Canine Brief Pain Inventory scores analysis – reduction of pain, increased level of activity and/or Quality of Life scores were improved at 6 months and beyond for 80% or more for the 3 study populations
Synovetin OA™: A Safe and Effective Radiosynoviorthesis (RSO) Radionuclide

Synovetin OA™ treatment can be used as part of a multi-modal approach

Device with disease modifying mode of action

Autoradiography, distal humerus & synovium, 16x.
(Image courtesy of Allison Bendele DVM, PhD, DACVP)
Release of Dogs Following Synovetin OA™ Intra-Articular Injections\textsuperscript{6}

**M. D. Anderson Cancer Center Dosimetry Modeling:**
- Measured external radiation exposure following unilateral or bilateral canine elbow joint intra-articular (IA) joint administration
- Measurements of gamma radiation obtained from 12 dogs treated for grade 3 elbow OA using label dose

**Conclusions:**
- Dogs may safely be released immediately after treatment
- People should avoid more than momentary touching of the treated joint (e.g., they should not sleep with the dog) for at least a month after the treatment.

\textsuperscript{6} Wendt RE et al, “Release of Dogs Following Sn-117m Colloid Intra-articular Injections”, June 26, 2018 presentation SNMMI, Philadelphia, PA
How many of you are already associated with a practice which has a radioactive materials license or would like to obtain one?

J Donecker contact information:

jdonecker@convetra.com
1(336) 552 - 6027
Comparing Synovetin OA™ with Iodine-131

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Tin-117m</th>
<th>Iodine-131</th>
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</thead>
<tbody>
<tr>
<td>Indication</td>
<td>OA</td>
<td>Feline hyperthyroidism</td>
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<td>Administration</td>
<td>Local device</td>
<td>Systemic drug</td>
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<td>Radionuclide distribution</td>
<td>Intra-articular</td>
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<td>Isolation</td>
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