

Serene

Canadian Association of Nuclear
Medicine

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Serene, LLC

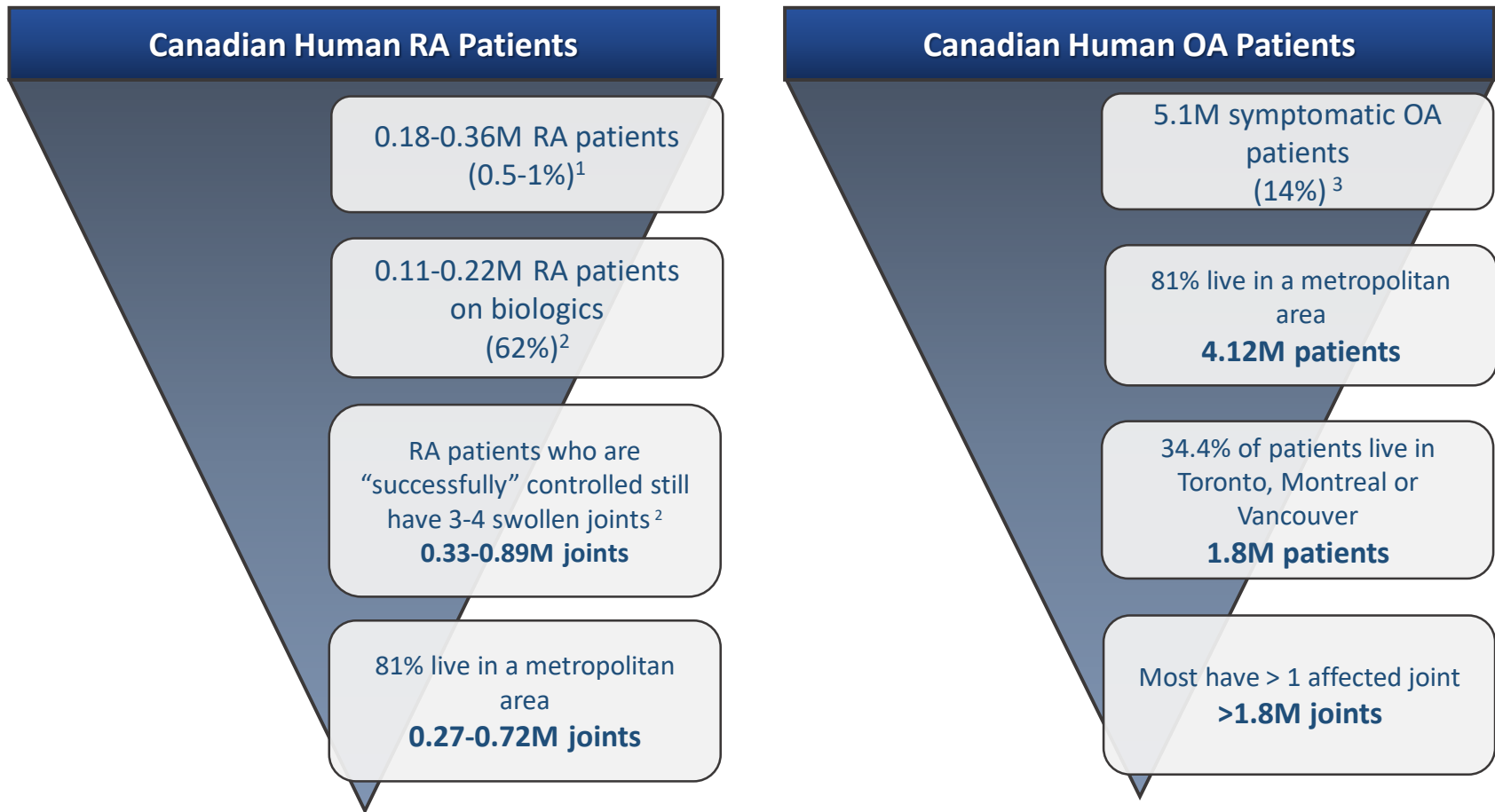
Experience Using Homogeneous Sn-117m Colloid for Radiosynoviorthesis (RSO)

Disclosure:

Cynthia Doerr MD is employed by Serene, LLC

Canadian Phase 1/2 RSO Trial

Synovitis-Related Conditions in Canada



¹ CDC; ² Zhang et al, Arthritis Care Res, 2011 december;63(12):1672-9; ³ Cisternas et al, Arthritis Care Res, 2016 May; 68(5)

History and Development of Homogeneous Sn-117m colloid

- History, development, and characteristics of Sn-117m
- Sn-117m production, and homogeneous Sn-117m colloid (HTC) manufacturing
- Synovitis and RSO
- Sn-117m pre-clinical data
- Sn-117m Canadian human clinical trials

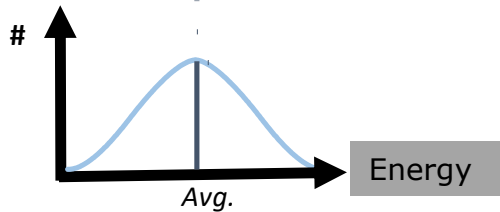
History, Development and Characteristics of Sn-117m

Prior Technical and Clinical Development

- Brookhaven National Laboratory 1980s
- Initiatives for Proliferation Prevention (IPP) under the US dept of Energy → low specific activity advancements developed by Serene
- High specific activity in cyclotrons developed by Serene
- 10 years of work in colloid completed in preclinical animals
- Decades of Sn-117m labeled compound characterization
- Preclinical work in numerous models (pig, rodent etc.)
 - Tox Study: LD₅₀ for Sn-117m DOTA annexin V is 50X therapeutic dose
 - Locally delivered on electroplated devices in vascular lumen in animals
- Human clinical trials
 - 120 human subjects safely and effectively treated with Sn-117m DTPA in oncology
 - 15 human subjects safely treated with Sn-117m DOTA annexin V in cardiovascular
 - Systemically delivered with distribution and toxicology in humans
- No local or systemic adverse events in animals or humans

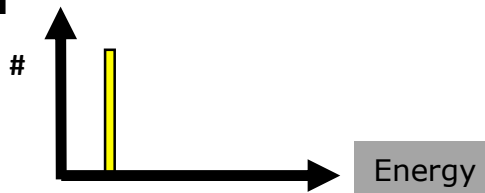
Characteristics of Sn-117m

Beta Particles

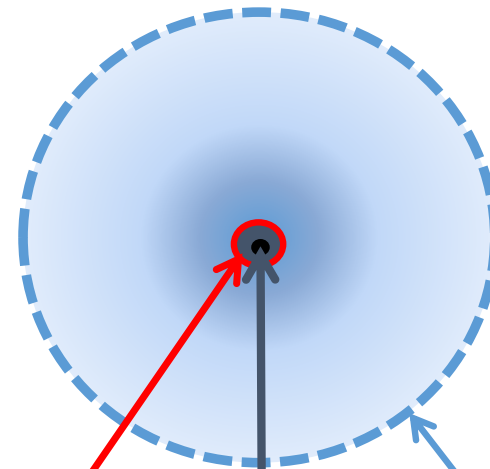


Produces a *range* of tissue penetration

Conversion Electron (CE)



Penetrates up to a *set distance* (discrete energy)



**Sn-117m
(CE)**

**Alpha
Particles**

**Beta
Particles**

Range in tissue (µm)

300

40-90

50-5000

**Shielding needed during
administration**

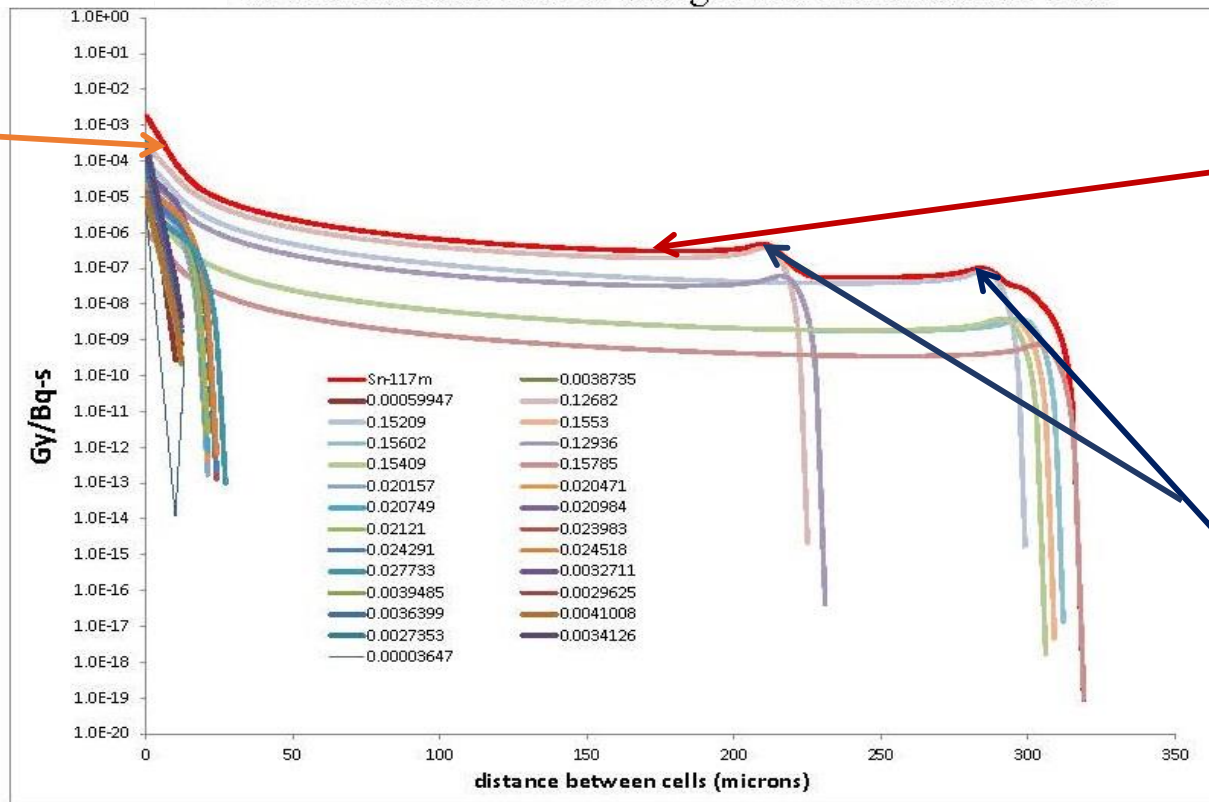
No

No

Yes

Well-defined Range of Sn-117m in Tissue

Sn-117m absorbed dose to a target cell from a source cell.



Short-range dose boost from Auger electrons

Relatively uniform total dose over 300 μm tissue depth

Bragg peaks (end points) for higher energy C.E.

Radiosynoviorthesis (RSO) Isotopes

Isotope	$t_{1/2}$ (d)	Imaging Particle	Energy (keV)	Therapy Particle	Maximum Energy (keV)	Range (mean) Tissue (mm)	Range (max) Tissue (mm)	Typical Dose (MBq)	Joint Size
Sn-117m	14	γ	158.6	C.E.	151	0.27	0.29	18.5-111+	S/M/L(?)
Er-169	9.3	None	-	β^-	350	0.14	1.1	18.5-37	S
Re-186	3.7	γ	137	β^-	1070	1.1	4.4	74-111	M
Y-90	2.7	None	-	β^-	2280	4.1	11	148-222	L

Characteristics of Sn-117m

Solve the issues related to current commercial RSO isotopes

- **Mono-energetic conversion electrons** of ~ 140 KeV discrete energy for therapy have an average range of ~ 300 μm
- **On-demand production**—no need to “batch” patients
- **Easier handling and shipping**—easy to shield, and track
- **Readily imaged**—gamma ray (159 KeV) similar to Tc-99m (140 KeV) proves you are in the joint space
- **Homogeneous colloid**—large enough to stay in joint, small enough for macrophage engulfment
- **Retained at injection site**—remains in joint
- **No need for splinting**—product does not leak from joint
- **One product for all size joints**

Sn-117m Production and Homogeneous Sn-117m Colloid Manufacturing

Sn-117m Production

Reactors

Sn-116(n, γ)Sn-117m (BNL/MURR)

- Requires 2-3 week irradiation
- Low specific activity (~ 1 Ci/37 MBq per g)
- Electromagnetic/laser separators to increase specific activity to 100-1,000 Ci/g (3,700-37,000MBq)

Sn-117(n, n' γ)Sn-117m (BR2)

- Higher specific activities (~ 2 -20 Ci/74-740MBq per g)
- Higher yields but post electromagnetic enhancement is not possible



Accelerators

Sb(p,x)Sn-117m (Nordion)

- Free of Sn-113 at < 55 MeV
- High power 30-42 MeV cyclotrons can use standard targets

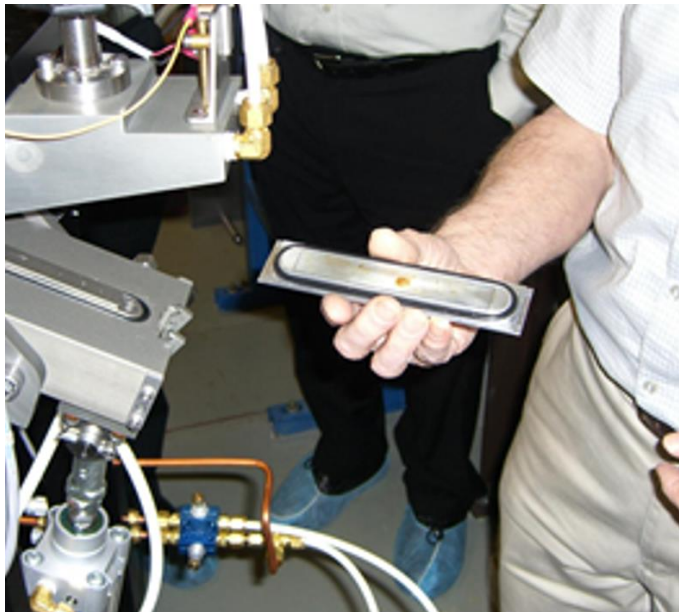
Cd-116(α ,3n)Sn-117m (Univ of Washington)

- Target electroplated at ITG in Texas \rightarrow shipped (FedEx) to UW
- Irradiated (typically 20 hours) with 60-80 μ A @ 47.3 MeV \rightarrow Produces ~ 10 mCi/370 MBq per hr
- Shipped (FedEx) to ITG in Texas for processing

Sn-117m Processing at ITG in Texas

Reactor

- Quartz ampule opened; irradiated metal extracted
- Metal Sn dissolved in acid/solvent
- Filtered
- Dispensed and shipped as dry product to Theragenics Corp



Accelerator

- Target layer removed in etch cell with acid
- Separation of Sn-117m from Cd-116 by either:
 - Anion exchange column
 - Liquid-liquid separation (organic/aqueous)
- Reconstituted in HCl
- Dispensed and shipped as tetrachloride solution to Theragenics Corp

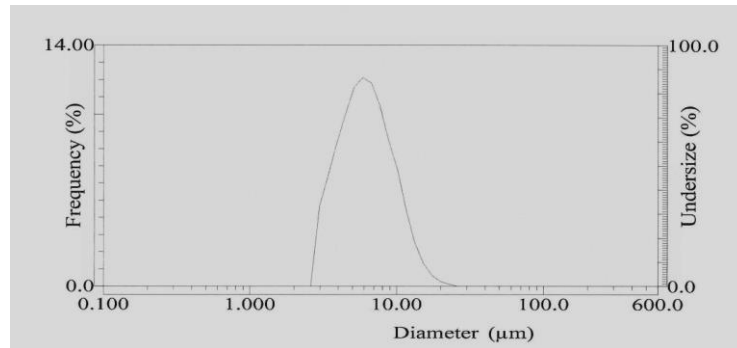
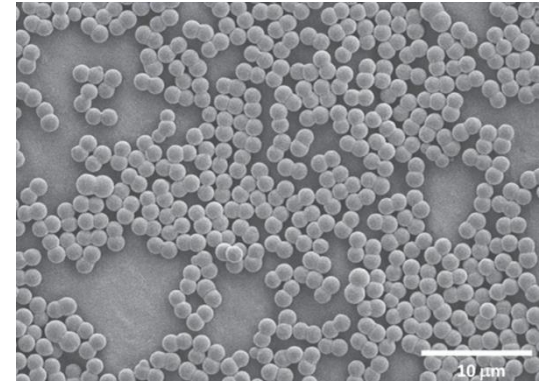
Homogeneous Sn-117m Colloid Manufacturing

- cGMP production at Theragenics Corp, Georgia USA
- Radiochemical starts in acidic (pH <1) form
- Homogeneous precipitation with controlled particle size using temperature, concentration etc
- Bulk or unit doses (aseptic filling)
- Terminally sterilized
- Shipped (FedEx)



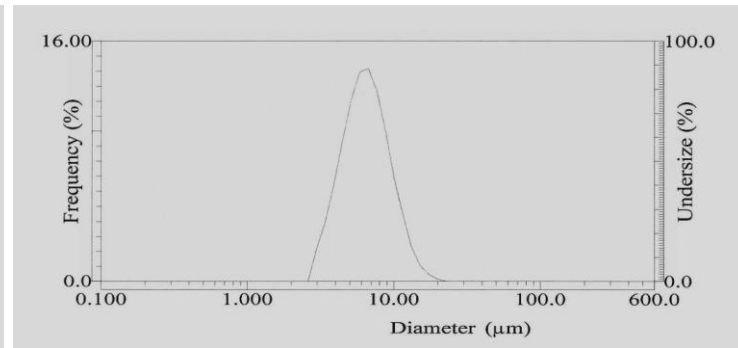
Colloid Characteristics

- A colloid is a substance in which microscopically dispersed insoluble particles are suspended throughout another substance
- HTC-- tight range of particle sizes
- HTC is stable at room temperature and *in vivo*



Stability studies – colloid size particle distribution at manufacture

Mean =6.28 μm SD=2.76 μm



Stability studies – colloid size particle distribution at 5 weeks in room temperature

Mean =6.43 μm SD=2.47 μm

Synovitis and RSO

Radiosynoviorthesis (RSO)

- A.k.a. Radiosynovectomy/RSV
- Treatment for synovitis (RA, OA, psoriatic arthritis etc.)
- Used worldwide for over 60 years
- Radioisotope injected directly into the synovial cavity
 - Intracavitary radiotherapy to reduce pain, effusion, and inflammation (synovitis)
- German data demonstrates RSO is 86% effective in RA and 79% effective in OA who have failed all other therapies
- All currently commercialized isotopes have significant issues that are resolved with HTC:
 - Leakage from joint (systemic and excretion issues)
 - Short half-life creates shipping logistical issues
 - Production issues
 - Expensive
- Global commercial isotopes:
 - Y-90 for large joints (knee)
 - Re-186 for mid-size joints (elbow, wrist, ankle)
 - Er-169 for small joints (fingers etc.)

Sn-117m Pre-Clinical Data

Pre-Clinical RSO Rat Studies Summary

- Normal rats POC to demonstrate colloid joint retention at 5 $t_{1/2}$ (10 wks)
- Non-GLP OA
 - Dose escalation, toxicology, histopathology, metabolic, organ distribution, excretion, autoradiography, dosimetry, radiation field
- GLP OA
 - Same data collection as non-GLP study
- Non-GLP intentional mis-administration
 - Full dose deposited orally, cutaneously, injected subcutaneously and IV
- GLP long term toxicology

Results:

- HTC is safe (even in intentionally mis-administered high dose)
- HTC is retained in knee > 99% (no systemic effects for 5 half-lives)
- All doses efficacious
- No evidence of fibrosis on histopathology
- No evidence of long term toxicity



Dog RSO Studies

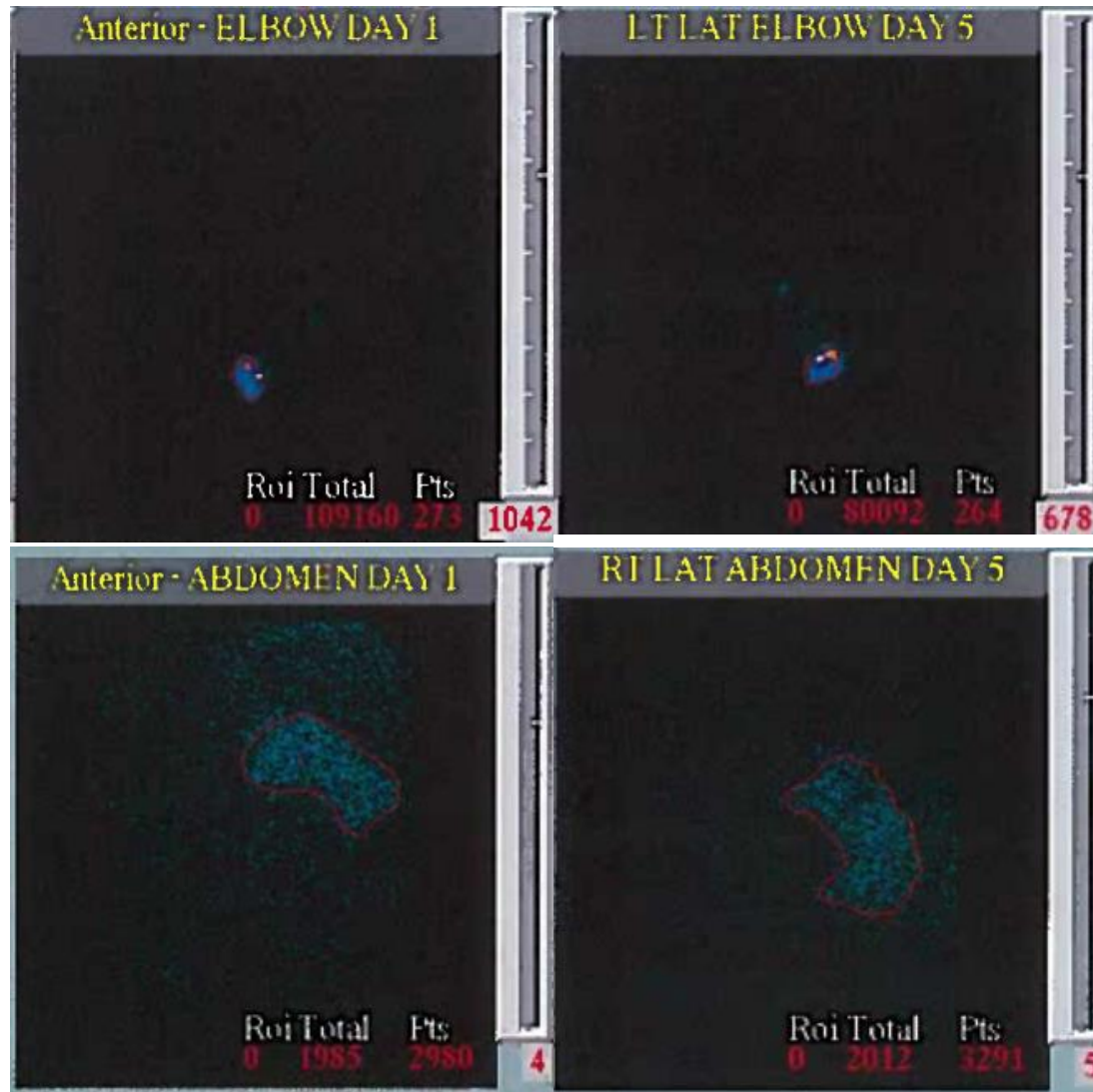
- Normal dogs—(n=5)
 - Data collected included: blood chemistry, PET/MRI, scintigraphy, histopathology, autoradiography, radiation excretion and radiation field
- Client-owned grade 1-2 elbow OA—(n=42 dogs, 43 elbows)
 - Testing: similar to above
- Client-owned grade 3 elbow OA—(n=15 dogs, 27 elbows)
 - Testing: similar to above
- Client-owned with grade 1-3 elbow OA re-injection—(n=10 dogs, 20 elbows)
 - Testing: similar to above

Conclusions From Dog Trials

- HTC is **safe** (even in unintentionally mis-administered high dose) with no incidence of radio-necrosis in all dogs
- HTC is **efficacious**
 - **PET SUV**
 - Medium dose showed significant improvement (less uptake) vs. low dose at 3 and 6 months
 - High dose showed significant improvement (less uptake) vs. medium dose at 3 and 6 months
 - **CBPI**
 - “Quality of Life” scoring for medium dose had the best success rate at 9 and 12 months vs. low and high dose
- HTC is **retained in elbow > 99%**
- **No evidence of fibrosis** on histopathology of normal elbow at 6 weeks (3 half-lives) with high dose
- HTC is **completely phagocytosed by 2 weeks** (1 half-life) and distributed throughout synovium with no distribution to adjacent tissue
- **Radiation field is below NRC release criteria** immediately after administration
- Product preparing for **US veterinary launch 2H18** using the medium dose



HTC Distribution Data on Study Dog

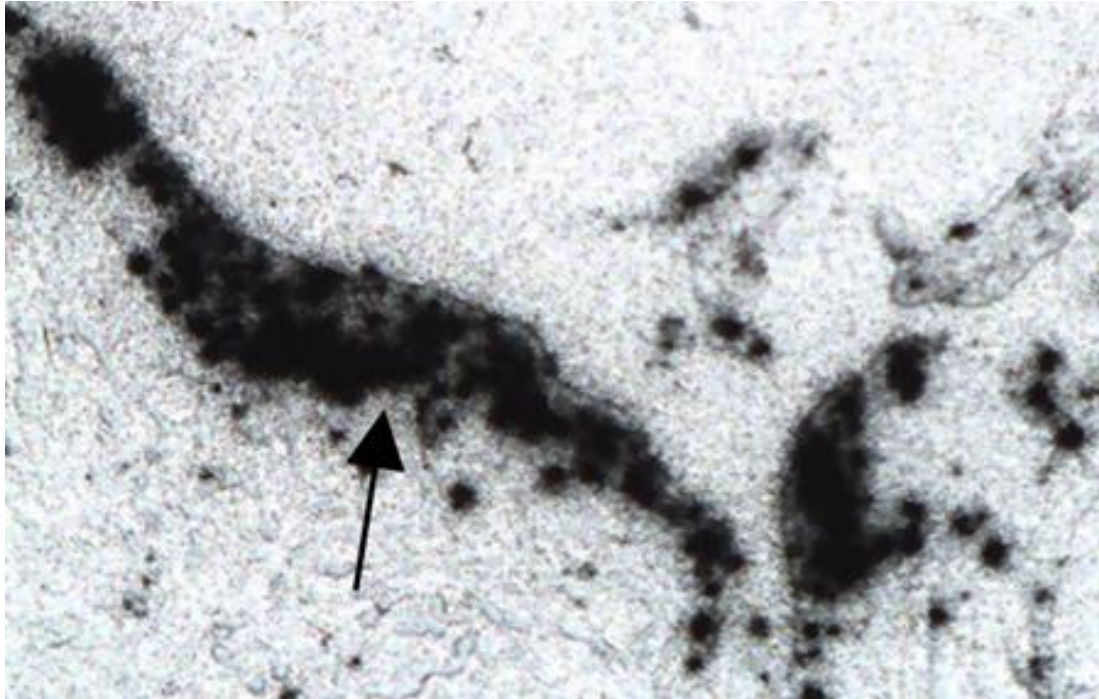


D15-57	3-Apr	6-Apr	7-Apr	8-Apr
Background	1353	1260	1238	1274
Blood	1294	1236	1240	1274
Background	1353	1260	1238	1274
Urine	1867		1849	1446
Background	1353	1260	1238	1274
Feces	1259	1205	1162	1252

Distance	8-Apr-15
1 Meter	155 μ R/hr
Surface (2 in/5cm)	15.3 mR/hr

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Autoradiography Shows Migration Into Synovium



Autoradiography of normal canine elbow at ~ 3 half-lives shows macrophage distribution of the Sn-117m colloid throughout the synovium (arrow).

Larger Joint Examples



Positive response through 3 months
(died of volvulus)

148 pound/67kg Great Dane
3.7 mCi/137 MBq



Larger Joint Examples



Positive response through 12 months

126 pound/57kg Newfoundland 2.04
mCi/75.5 MBq



Sn-117m Canadian Human Clinical Trials

Canadian RSO Trial in OA and RA (Draft)

Initiate 4Q of 2018

- Phase I/II of HTC using RSO in OA/RA in large/medium joints, (n=36)
- 6-8 sites in Canada
- Objectives:
 - Primary—safety, side effects
 - Secondary—efficacy via VAS pain score, selection of doses
- Population:
 - RA or seronegative spondyloarthritis with one medium or large joint poorly controlled
 - OA of medium or large joint poorly controlled with standard therapy

		Dose, MBq		
Joint size	Joint	Low	Medium	High
Medium	Elbow	11	30	74
	Wrist	11	30	74
	Ankle	11	30	74
Large	Knee	37	89	222

Procedure/ parameter	Screening	Study Week								EOS
		1	2	3	5	9	14	27	40	
^{117m} Sn scan (γ camera)		X	X		X	X				X
Ultrasound, MRI	X					X		X		
Treatment		X								

Thank You

Backup Slides

Sn-117m is a Unique Isotope

