Serene

Canadian Association of Nuclear Medicine
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Director of Clinical Programs
Serene, LLC
Experience Using Homogeneous Sn-117m Colloid for Radiosynoviiorthesis (RSO)

Disclosure:
Cynthia Doerr MD is employed by Serene, LLC
Canadian Phase 1/2 RSO Trial
Canadian Human RA Patients
- 0.18-0.36M RA patients (0.5-1%)¹
- 0.11-0.22M RA patients on biologics (62%)²
- RA patients who are “successfully” controlled still have 3-4 swollen joints²
  - 0.33-0.89M joints
- 81% live in a metropolitan area
  - 0.27-0.72M joints

Canadian Human OA Patients
- 5.1M symptomatic OA patients (14%)³
- 81% live in a metropolitan area
  - 4.12M patients
- 34.4% of patients live in Toronto, Montreal or Vancouver
  - 1.8M patients
- Most have > 1 affected joint
  - >1.8M joints

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: LD$_{50}$ 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
- No local or systemic adverse events in animals or humans
Characteristics of Sn-117m

**Beta Particles**
- Energy: Produces a range of tissue penetration

**Conversion Electron (CE)**
- Energy: Penetrates up to a set distance (discrete energy)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sn-117m (CE)</th>
<th>Alpha Particles</th>
<th>Beta Particles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range in tissue (µm)</td>
<td>300</td>
<td>40-90</td>
<td>50-5000</td>
</tr>
<tr>
<td>Shielding needed during</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>administration</td>
<td></td>
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</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Isotope</th>
<th>$t_{1/2}$ (d)</th>
<th>Imaging Particle</th>
<th>Energy (keV)</th>
<th>Therapy Particle</th>
<th>Maximum Energy (keV)</th>
<th>Range (mean) Tissue (mm)</th>
<th>Range (max) Tissue (mm)</th>
<th>Typical Dose (MBq)</th>
<th>Joint Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sn-117m</td>
<td>14</td>
<td>$\gamma$</td>
<td>158.6</td>
<td>C.E.</td>
<td>151</td>
<td>0.27</td>
<td>0.29</td>
<td>18.5-111+</td>
<td>S/M/L(?)</td>
</tr>
<tr>
<td>Er-169</td>
<td>9.3</td>
<td>None</td>
<td>-</td>
<td>$\beta^-$</td>
<td>350</td>
<td>0.14</td>
<td>1.1</td>
<td>18.5-37</td>
<td>S</td>
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<tr>
<td>Re-186</td>
<td>3.7</td>
<td>$\gamma$</td>
<td>137</td>
<td>$\beta^-$</td>
<td>1070</td>
<td>1.1</td>
<td>4.4</td>
<td>74-111</td>
<td>M</td>
</tr>
<tr>
<td>Y-90</td>
<td>2.7</td>
<td>None</td>
<td>-</td>
<td>$\beta^-$</td>
<td>2280</td>
<td>4.1</td>
<td>11</td>
<td>148-222</td>
<td>L</td>
</tr>
</tbody>
</table>
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 (3,700-37,000 MBq)

Sn-117(n,n’y)Sn-117m (BR2)
• Higher specific activities (~2-20 Ci/74-740 MBq 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)
• Irradiated (typically 20 hours) with 60-80 μA @ 47.3 MeV
  Produces ~ 10 mCi/370 MBq per hr

Targets shipped by 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 RSV 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 (Er-169 feedstock depleted)
  - Expensive
  - Different isotopes for each joint size
    - 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
  o Dose escalation, toxicology, histopathology, metabolic, organ distribution, excretion, autoradiography, dosimetry, radiation field
• GLP OA
  o Same data collection as non-GLP study
• Non-GLP intentional mis-administration
  o 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 plus CT, force-plate, etc

- **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**
HTC Distribution Data on Study Dog

### D15-57

<table>
<thead>
<tr>
<th>Date</th>
<th>Background</th>
<th>Blood</th>
<th>Urine</th>
<th>Feces</th>
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<tbody>
<tr>
<td>3-Apr</td>
<td>1353</td>
<td>1294</td>
<td>1867</td>
<td>1259</td>
</tr>
<tr>
<td>6-Apr</td>
<td>1260</td>
<td>1236</td>
<td>1849</td>
<td>1205</td>
</tr>
<tr>
<td>7-Apr</td>
<td>1238</td>
<td>1240</td>
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<td>1162</td>
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<tr>
<td>8-Apr</td>
<td>1274</td>
<td>1274</td>
<td>1446</td>
<td>1252</td>
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</table>

### Distance

<table>
<thead>
<tr>
<th>Distance</th>
<th>8-Apr-15</th>
</tr>
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<tbody>
<tr>
<td>1 Meter</td>
<td>155 µR/hr</td>
</tr>
<tr>
<td>Surface (2 in/5cm)</td>
<td>15.3 mR/hr</td>
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</table>
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

<table>
<thead>
<tr>
<th>Joint size</th>
<th>Joint</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
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<tbody>
<tr>
<td>Medium</td>
<td>Elbow</td>
<td>11</td>
<td>30</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Wrist</td>
<td>11</td>
<td>30</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Ankle</td>
<td>11</td>
<td>30</td>
<td>74</td>
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<tr>
<td>Large</td>
<td>Knee</td>
<td>37</td>
<td>89</td>
<td>222</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Procedure/parameter</th>
<th>Screening</th>
<th>Study Week</th>
<th>EOS</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>$^{117m}$Sn scan (y camera)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ultrasound, MRI</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>X</td>
<td></td>
<td></td>
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</tbody>
</table>

Serene
Thank You

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www.serene-llc.com
Backup Slides
Sn-117m is a Unique Isotope

All known isotopes (natural and artificial):

>3339

Potential for therapy: (half-life> 30 mins; I>10%; E>10 keV)
391 e- emitters; 75 α emitters

Conversion and Auger electron sources: 68

>5 day half-life: 20

5-30 day half-life;
>50 keV; >10%
electron intensity: 5

Possibility of commercial production and chemistry: 2
Imaging capability: 1 (Sn-117m)

Includes Xe-129m and Xe-131m: inert gases; impossibly difficult conjugation chemistry

Includes Ir-193m: But no detectable/imageable photons; shorter range electrons

Includes Hf-179m2: Difficult to manufacture commercially; shorter range electrons; high energy photons hinder handling

Sn-117m is unique!