A New Radioisotope-based Treatment for Veterinary and Human Arthritis

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Sn-117m Emissions

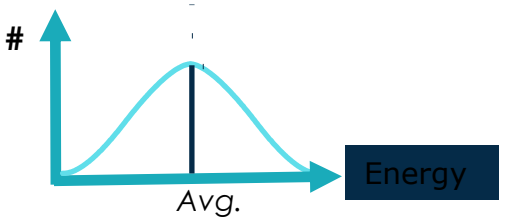
Major Emissions	Energy (KeV)	Intensity (%)
Auger-L	3	91
Auger-K	21	10.8
CE-K1	126.8	66.3
CE-K2	129.4	11.9
CE-L1	151.6	27.3
CE-L2	154.1	1.5
CE-M1	155.1	5.6
Gamma	158.6	86.4

No High Energy Emissions

- **Mono-energetic conversion electrons** of ~140 KeV discrete energy for therapy have an average **range of ~300 µm in tissue**
  - Lower external radiation
  - Easier handling
- **Half-life of 14 days** is consistent with treatment requirements
  - Logistic flexibility
- **Gamma emission (159 KeV) similar to Tc-99m** (140 KeV) allowing for existing standard gamma camera imaging & techniques

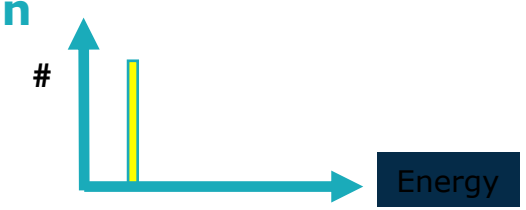
Characteristics of Sn-117m C.E.

Beta Particles

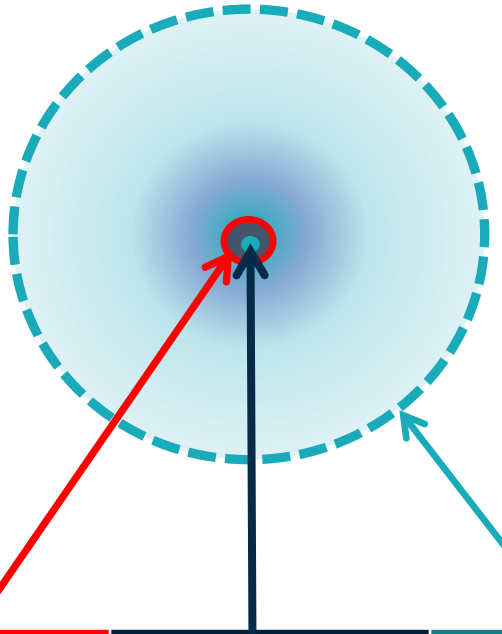


Produces a *range* of tissue penetration

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

Osteoarthritis - Synovitis

- OA is not simply a disease of cartilage, but a **'total joint disease'.**
- Substantial **synovial inflammation** can occur in early-stage degenerative joint disease (DJD), late-stage DJD or both.
- **Synovitis triggers several symptoms and clinical signs of OA**.
- OA synovitis can be assessed by MRI, ultrasonography and arthroscopy; however, the gold standard for detecting OA synovitis is histological analysis of biopsy samples.
- Synovial inflammation can predict **cartilage breakdown** in OA.
- DJD synovitis perpetuates the process of cartilage degradation.
- The DJD synovium releases soluble mediators that hold promise as biomarkers or therapeutic targets.

Radiosynoviorthesis "Restoration of the Synovium"

- Sn-117m colloid is utilized in the procedure called **Radio-Synovi-Orthesis (RSO)**
- RSO is a well-established human procedure that has been successfully and **safely used for over 60 years around the world***

Human patients who have had RSO:

More than **670,000**

Human joints injected using RSO:

Over **830,000**

40,000 to 50,000

procedures in Germany annually

*Dr William Uwe Kampen, Nuclear Medicine Spitalerhjof, Hamburg, Germany, European Association of Nuclear Medicine, 2015

EXUBRION THERAPEUTICS

What is Synovetin OA™?

- A **veterinary medical device**
- **Sn-117m** in colloidal suspension
- Therapeutic conversion electrons emit **discrete energy only in the joint space** (0.3mm penetration)
- Proven to provide up to 1 year of pain relief
- No systemic side effects
- Half-life of 14 days achieves **long term effect**
- **Decays to harmless microparticles of tin**, naturally removed from body via lymphatic system

Synovetin OA™ is intended to reduce synovitis and associated pain and inflammation of joints afflicted with osteoarthritis.

The initial focus is on canine elbow dysplasia.

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Background and Aim of Trials

RSO Commonly used isotopes in humans are **Y-90/P-32** (large joints), **Re-186** (medium joints) and **Er-169** (small joints). All are β emitters with penetration often beyond the tissue of interest

Use of multiple isotopes causes **logistics problems** for users

Sn-117m has superior qualities that allows for:

- "One size fits all" treatment of all joints
- Only treats inflamed synovial tissue and macrophages
- Handling logistics greatly simplified

The **trial aims** were to validate the **safety and efficacy of therapeutic RSO injections** in canines for the treatment of osteoarthritis leading to a subsequent human trial

Summary of Canine Trials

Normal hounds (n=5)

- Demonstrated safety at 6 weeks (euthanasia)

Grade 1-2 elbow OA (n= 34 dogs and 34 elbows per protocol (PP))

- Safe (n = 44 dogs intended to treat population (ITT)
- Effective based on canine brief pain inventory (cBPI), lameness examination and force plate

Grade 3 elbow OA (n= 14 dogs and 25 elbows PP)

- Safe (n = 15 dogs and 27 elbows ITT)
- Effective based on cBPI and clinicians' lameness exam

Reinjection of Grade 1-3 elbow OA (n=9 dogs and 18 elbows PP)

- Safe (n = 10 dogs and 20 elbows ITT)
- Effective based on cBPI, clinicians' assessment and force plate

General Design and Definitions

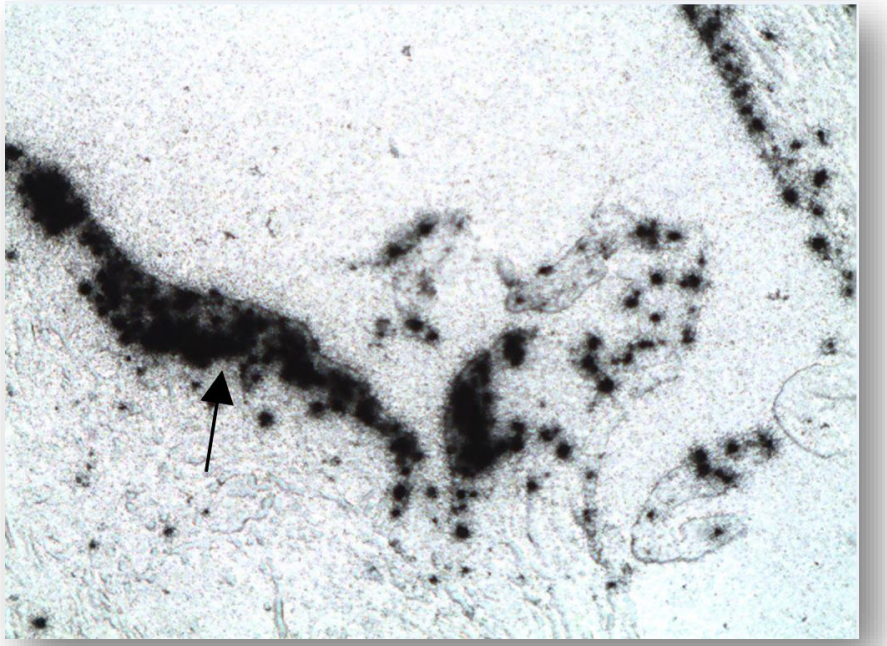
Dogs with elbow OA received baseline measurements, and received an **intraarticular RSO injection of Sn-117m colloidal suspension** (1.7 mCi/63 MBq per elbow normalized to the BSA of a 50 lb/22 kg dog) in one or both elbows and were **followed for up to 12 months for safety, and effectiveness** as defined by:

1. Improvement in **canine brief pain inventory** (cBPI)
   - Reduction (improvement) of ≥1 of pain severity score (PSS) *AND* ≥2 of pain interference score (PIS); published definition of success
   - Reduction (improvement) of ≥1 of pain severity score (PSS) *OR* ≥2 of pain interference score (PIS), indicative of improvement

2. **Force plate**—improvement from baseline of ≥5% in any timepoint in the peak vertical force (PF) or the mean vertical impulse (IMP) at 3, 6, 9 and 12 months

Safety: Clinicians and Pet Parents

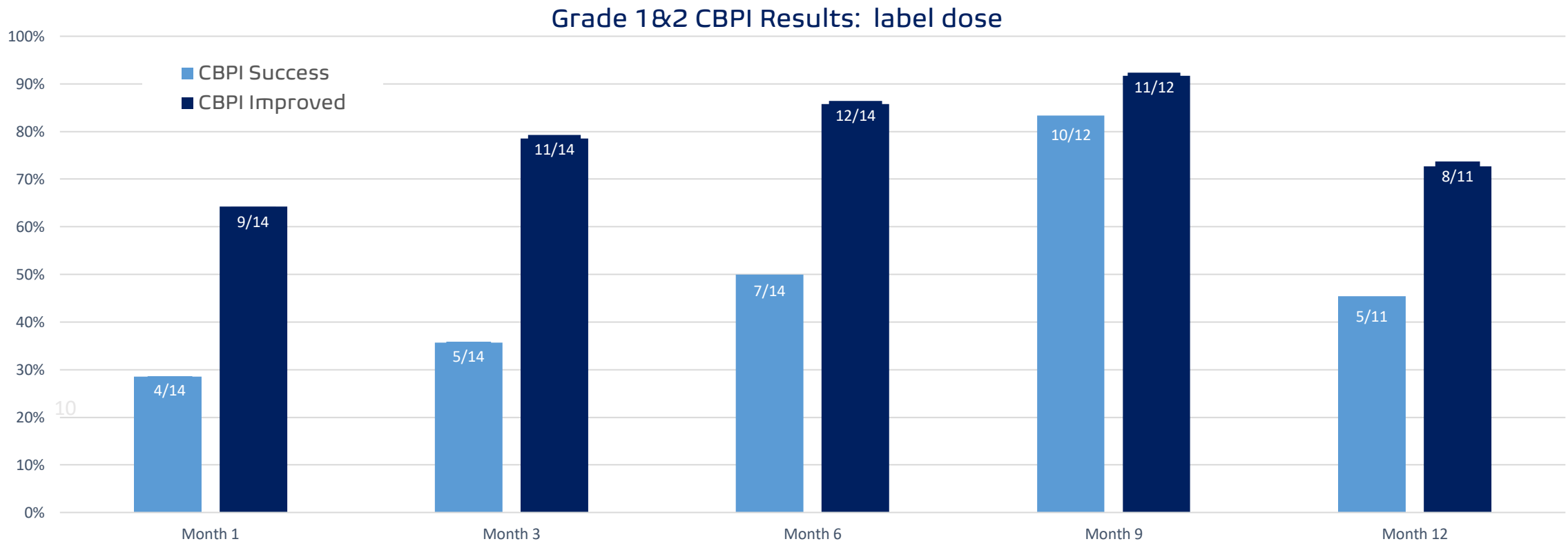
- **Perfect colloid size** means colloid remains in the joint
- Therapeutic conversion electrons do not escape from the treated joint
- **No systemic activity**; no residue in body fluids, hair-coat or skin
- Gamma levels are well-below limits established by NRC
- Treated dogs can recover in general clinic recovery ward
- Dogs can be **released to owner the same day** as treatment



Sn-117m retained in synovium

EXUBRION THERAPEUTICS

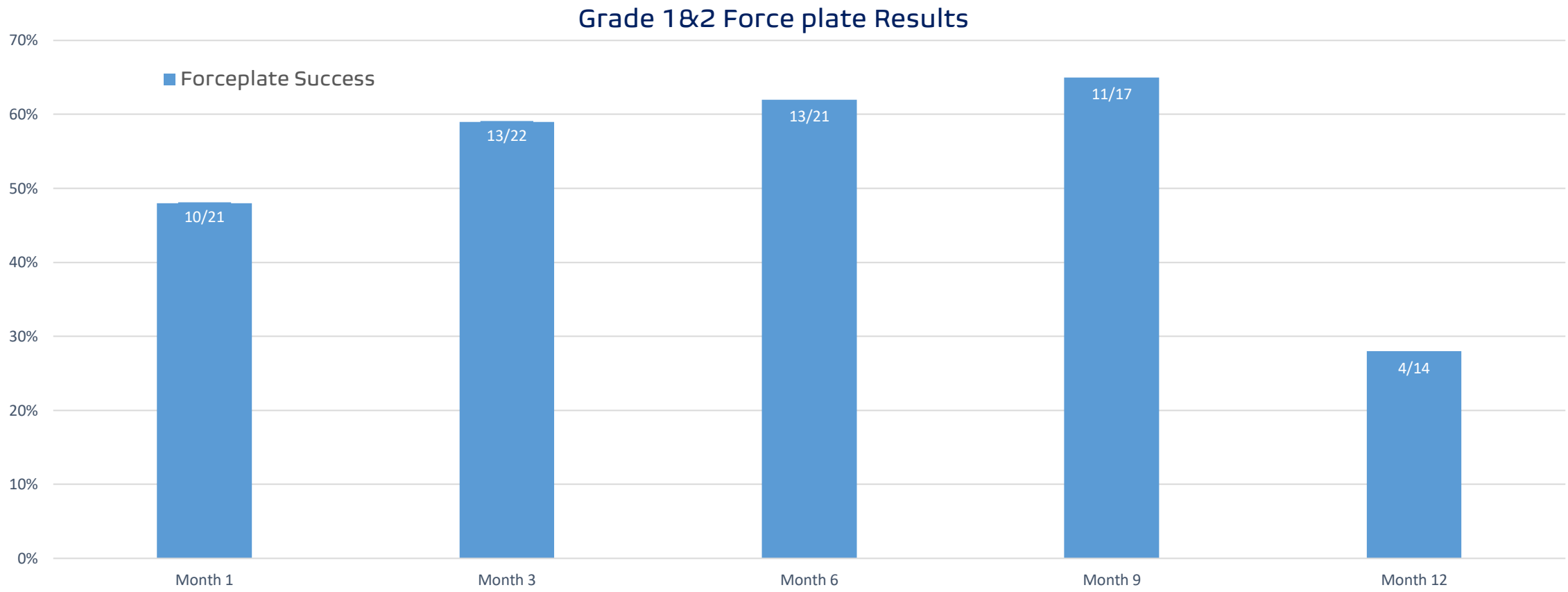
Label Dose Effectiveness: Grade 1 and 2 Elbow OA Study CBPI



- CBPI Success (successful reduction of pain AND successful increase in level of activity as compared to baseline)
- CBPI Improved (successful reduction of pain OR successful increase in level of activity with no worsening from baseline)

EXUBRION THERAPEUTICS

Effectiveness: Grade 1 and 2 Elbow OA Study (Force Plate)



- Success is ≥ 5% increase in peak vertical force and/or ≥ 5% increase in mean vertical impulse.
- Both variables were normalized to body weight.

EXUBRION THERAPEUTICS

Effectiveness: Grade 3 Elbow OA

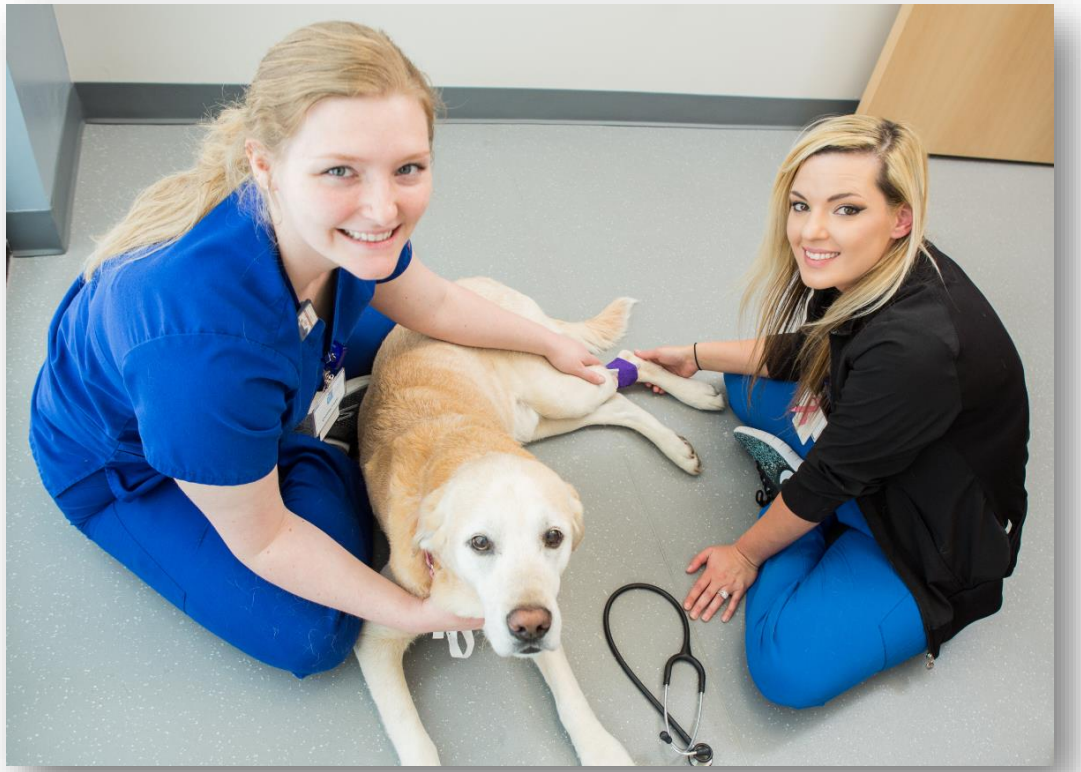
- 14 dogs and 25 elbows (PP)
- Objectives: safety and effectiveness
- Duration: 12 months
- 2 study sites (GCVS, LSU)
- Measurements: Composite of client CBPI survey and Clinician's assessment
- **Overall treatment success was 71%** (10/14)
- Clinician assessments showed mean **reductions in lameness** scores at each post-treatment interval except at 12 months when compared to baseline assessments
- McNemar's test of agreement showed that CBPI and clinicians' assessment were in agreement

Jonah
Treated at GCVS

EXUBRION THERAPEUTICS

Effectiveness: **Re-injection** of Grade 1 and 2 Elbow OA

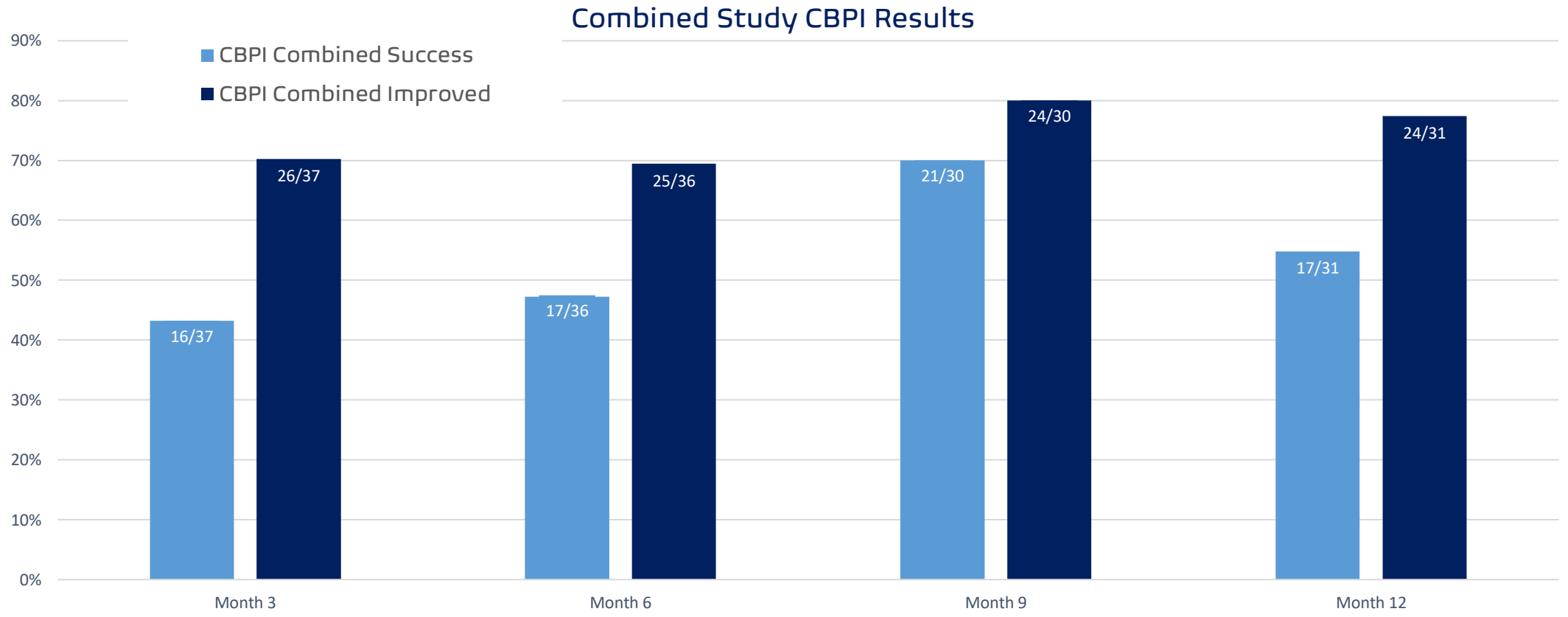
- 9 dogs and 18 elbows (PP)
- Objectives: safety and effectiveness following reinjection
- Duration: 12 months
- Measurements: composite of client CBPI survey, clinician's assessment and force plate
- Overall **treatment success was 66.7%** (6/9)
- McNemar's test of agreement showed that CBPI and clinicians' assessment were in agreement



GCVS Technicians with sedated patient for Synovetin OA™ treatment

EXUBRION THERAPEUTICS

Overall Treatment Success (label dose)



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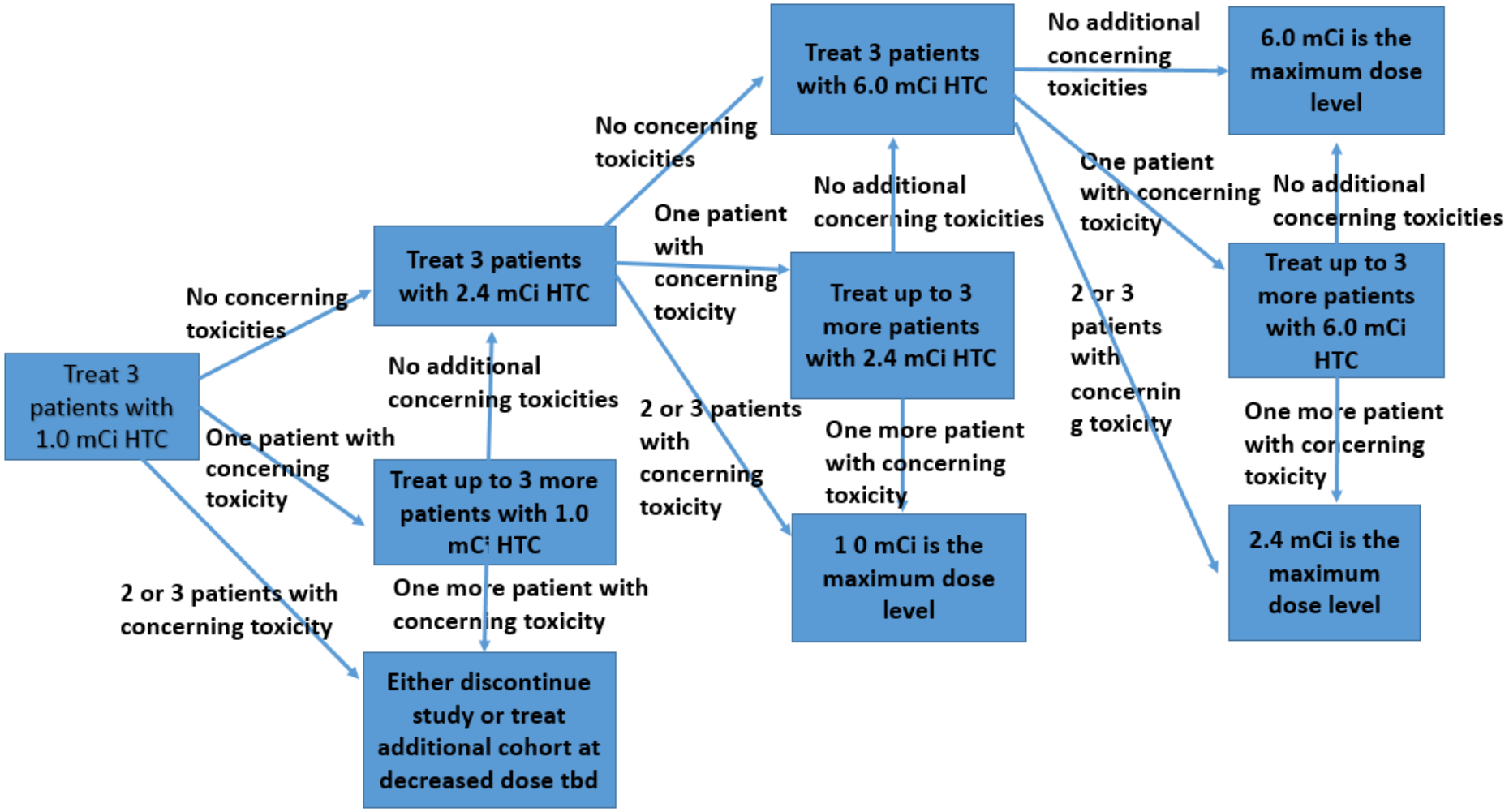
EXUBRION THERAPEUTICS

Canadian RSO Trial in Knee Arthritis Study Design (n=36)



Canadian RSO Trial in Knee Arthritis Imaging Schedule

Dose	mCi	MBq
Low	1.0	37.0
Medium	2.4	88.8
High	6.0	222.0

Procedure/ parameter	Screening	Study Week								EOS
		1	2	3	5	9	14	27	40	53
^{117m}Sn scan (γ camera)		X	X		X					
Plain X-rays of both knees	X									
Ultrasound	X				X		X	X		X
Treatment (RSO)		X								

Conclusions

The **therapeutic success and safety of homogeneous Sn-117m colloid** for OA in dogs has provided support for commercial sales of RSO **therapy in dogs** in the United States.

These canine data also provide support for similar use in **humans**. **Health Canada has approved a Phase 1B clinical trial** that will commence in Canada in the near future.