spryng™
with OsteoCushion™ Technology

Efficacy report:

Evaluating the benefit and tolerability of an intra-articular injection of a collagen-elastin biomaterial into the stifle joint of dogs with suspected cruciate ligament rupture.

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Poster presentation at the
2023 ACVS Surgery Summit
Louisville KY, October 12-14, 2023

ACVS
AMERICAN COLLEGE of VETERINARY SURGEONS

STUDY OBJECTIVE:

Determine if MHB* injection of the biomaterial will help alleviate acute pain
cranial cruciate disease, despite the kinematic disadvantages of lacking a

METHODS

Methods and Experimental Design:

Inclusionary criteria:
- > 6mo with unilateral partial or complete CCD, determined by physical and orthopedic examination, Stifle radiographs to confirm CCD.

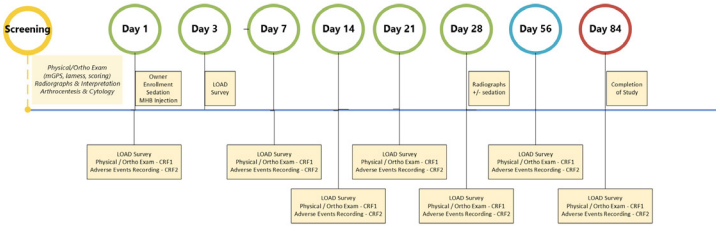
Null hypothesis
- The true response rate is 10% will be tested against a one-sided alternative that the true response rate is 25% of the study population.

Simon's Two Stage Study Design (Simon, 1989).
- Initial cohort: 22 patients with unilateral CCD.
- Second cohort: additional 18 patients enlisted (total of 40) if proven effective.

Primary endpoint
- Response rate from day 1 to day 28 as measured by the modified Glasgow Composite Pain Score (mGCPS), in which a reduction in the mGCPS by 25% or greater would be considered a beneficial response

Secondary endpoints
- Change in mGCPS from Day 1 to all subsequent study days
- Change in visual lameness score (VLS) and the Liverpool Osteoarthritis in Dogs (LOAD) survey score from Day 1 to all other subsequent study days

Methods and Study Design:



Lameness Grade	Definition
0	Normal
1	Mild subtle lameness with partial weight bearing
2	Obvious lameness with partial weight bearing
3	Obvious lameness with intermittent weight bearing
4	Full non-weight bearing

Score Variable	Grade Range
Posture	0 – 3
Lameness at walk	0 – 4
Lameness at trot	0 – 4
Willingness to raise contralateral limb	0 – 4
Cranial drawer	0 – 3
Tibial thrust	0 – 3
Pain on extension	0 – 3
Pain on full flexion	0 – 3
Meniscal click	0 – 1

CONCLUSIONS AND FUTURE STUDIES

- **Final combined cohort's response rate: 22/40 (55%, 95% CI: 40% - 69%)**
- **Null hypothesis: Rejected, Alternate hypothesis: Accepted**
- **The MHB injection appears to be a reasonable, non-invasive alternative for patients with CCD when patient and/or owner factors preclude surgical intervention**
  - The study noted a reduction in all of the measured parameters (mGCPS, VLS, and LOAD scores) for responders resulting in clinical improvement across all time points.
  - The MHB injection appears to be a reasonable, non-invasive alternative for patients with CCD, where owners are not pursuing surgical intervention.
- **This preliminary data supports additional, larger prospective trials and studies to evaluate Spryng injections for medically managing patients with CCD**

n and loss of function associated with partial or complete unilateral surgically-altering procedure to the stifle.

RESULTS

TABLE 1: mGCPS Day 1 to subsequent study days

Clinical Variable	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Day 56	Day 84	P-value
n	43	41	41	41	41	40	35	24	
Average mGCPS (Range)	4 (1 – 10)	N/A	3 (1 – 10)	3 (0 – 8)	3 (0 – 8)	3 (1 – 10)	3 (0 – 7)	2 (0 – 7)	**0.0063**
Average VLS (Range)	16 (5 – 32)	N/A	14 (2 – 23)	14 (2 – 27)	12 (2 – 30)	13 (3 – 27)	12 (0– 27)	10 (0 – 26)	**<0.0001**
Average LOAD (Range)	19 (0 – 32)	20 (0 – 36)	17 (1 - 31)	17 (0 – 32)	15 (0 – 27)	13 (0 – 25)	14 (0 – 37)	12 (0 – 37)	**<0.0001**

P-values calculated using general linear mixed models

On average there was significant improvement in all of the clinical variables throughout the study period (Table 1). The table notes the range for the gradual improvement of mGCPS, VLS and LOAD scores were statistically significant throughout the study.

TABLE 2: Multiple comparisons of mGCPS

Comparison Days	Mean Difference	95% CI of Difference	Adjusted p-value
Day 1 vs. Day 7	-0.65	-1.29 to -0.01	**0.0430**
Day 1 vs. Day 14	-0.74	-1.56 to +0.08	0.0896
Day 1 vs. Day 21	-0.61	-1.36 to +0.13	0.1384
Day 1 vs. Day 28	-1.11	-1.97 to -0.26	**0.0060**
Day 1 vs. Day 56	-0.72	-1.71 to +0.27	0.2294
Day 1 vs. Day 84	-1.57	-2.52 to -0.61	**0.0006**

P-values calculated using Dunnett's multiple comparison test

TABLE 3: Multiple comparisons of VLS

Comparison Days	Mean Difference	95% CI of Difference	Adjusted p-value
Day 1 vs. Day 7	-2.54	-5.26 to +0.44	**0.0030**
Day 1 vs. Day 14	-2.47	-5.87 to +1.53	**0.0361**
Day 1 vs. Day 21	-3.69	-5.95 to -0.44	**0.0002**
Day 1 vs. Day 28	-3.59	-6.89 to +0.34	**0.0018**
Day 1 vs. Day 56	-4.51	-11.12 to -1.16	**0.0004**
Day 1 vs. Day 84	-6.57	-13.95 to -2.63	**<0.0001**

P-values calculated using Dunnett's multiple comparison test

TABLE 4: Multiple comparisons of LOAD

Comparison Days	Mean Difference	95% CI of Difference	Adjusted p-value
Day 1 vs. Day 3	+0.1310	-2.335 to +2.60	>0.9999
Day 1 vs. Day 7	-2.883	-5.535 to -0.23	**0.0279**
Day 1 vs. Day 14	-2.784	-5.346 to -0.22	**0.0281**
Day 1 vs. Day 21	-4.869	-7.473 to -2.27	**<0.0001**
Day 1 vs. Day 28	-6.006	-9.059 to -2.95	**<0.0001**
Day 1 vs. Day 56	-5.750	-9.515 to -1.99	**0.0012**
Day 1 vs. Day 84	-6.929	-11.28 to -2.58	**0.0007**

P-values calculated using Dunnett's multiple comparison test

ACKNOWLEDGEMENTS

Ethos – Wisconsin Veterinary Referral Center
Samuel Stewart DVM, DACVECC – Ethos Veterinary Healthy Science Consultancy
Garrett Tougas – Ethos Veterinary Healthy Science Consultancy
PetVivo, Inc.
Bridger Veterinary Specialists

*Novel intra-articular injection: Mastergel Hydophilic Biomaterial (MHB) is Spryng with OsteoCushion Technology, manufactured by PetVivo, Inc. MHB product is formulated with a collagen, elastin bio-matrix on a heparin scaffold and is classified as a medical device, NOT a therapeutic.

spryng™
with OsteoCushion™ Technology

Instructions for use

Veterinary medical device for use in dogs.

Veterinary Use Only
Federal law restricts this device to use by or on the order of a licensed veterinarian.

1. Product Description
Spryng is an intra-articular injection that is designed to prevent the occurrence and re-occurrence of joint pain from loss of cartilage or tissue-bone mechanical malfunction by augmenting and reinforcing cartilage to assist in the normalization of joint function. The Spryng gel-particles act as a micro-cushion mass of material that integrate into the synovial fluid and surrounding space to provide a soft, lubricous, elastic cushion. The synovial fluid is absorbed by and passes through the gel-particles, which are insoluble and will slowly absorb into the surrounding tissues within the joint.

Spryng is composed of a protein-carbohydrate matrix made from purified, natural materials. Each Spryng micro-cushion is a purified composition of two proteins (collagen, elastin) and a carbohydrate (heparin glycan) that self-assemble to form a sterile, insoluble, and pliable matrix using a proprietary, patented process. This process naturally forms a strong, sterile hydrated biomaterial that mimics natural cartilage.

1.1 How Supplied
Spryng material is sterile and supplied in aseptically filled, luer lock syringes. Syringes contain 2 cc of Spryng. Each package contains one (1) syringe of Spryng (needle not included).

Figure 1.

1.2 Storage
Spryng particles are recommended to be kept at approximately 40°–90°F. Use of Spryng particles is recommended within 26 months of the manufacture date on the package.

2. Intended Use and Indications for Use
Spryng particles for intra-articular injection are intended for cartilage reinforcement and/or augmentation. It is indicated to aid in the management of joint pain from loss of cartilage or tissue-bone mechanical malfunction caused by joint dysfunction not associated with infection (e.g., lameness, osteoarthritis, degenerative joint disease). Spryng matrices restore proper joint mechanics by adding natural, viscosolid matrices to the joint's synovial fluid.

For use in dogs to maintain and/or improve articulation.

3. Contraindications
Spryng is contraindicated in the following conditions:

- If there is an infection.
- If significant inflammation is present in the joint (i.e. swollen, tenderness, erythema).

Note: Spryng particles can be injected if there is no or mild inflammation in the joint or if the inflammation has been effectively treated with an anti-inflammatory agent. If inflammation exists, prior effective treatment with anti-inflammatory agents is recommended.

4. Warnings
Spryng particles must not be injected into blood vessels. Injection of Spryng particles into blood vessels can interfere with local circulation, resulting in vessel laceration, occlusion, infarction, embolic phenomena, and/or abscess at injection site.

Not for use in humans. Keep this device out of the reach of children.

5. Precautions
Using drugs that reduce coagulation (e.g., NSAIDs) may cause increased bruising or bleeding at the injection site. Injection should be performed only by a licensed veterinarian skilled in the delivery of intra-articular (IA) injections.

6. Directions for Use
Spryng material is sterilized and aseptically filled in syringes containing 2 cc of material. It is intended for single-use, intra-articular injection (Figure 1). Use clinical judgement pertaining to volume needed. The amount of Spryng particles injected should represent an appropriate volume as determined by the veterinarian.

Preparation for use

- The injection site should be thoroughly disinfected.
- Follow aseptic techniques.
- Animal restraint and sedation is recommended.
- The injection technique, location, amount of synovial fluid removal, depth of injection, needle type, and the administered quantity of Spryng, may vary based on veterinarian clinical judgment and the joint selected.
- Spryng particles should be administered using a sterile needle (e.g., 18-23G). The needle should be inserted based on the veterinarian's assessment of the needle tip location.
- Settling of Spryng particles in the buffer solution during storage is normal; injection in the settled state will not impact its efficacy. Shaking to disperse particles may be performed.
- Inject Spryng particles by applying even pressure on the plunger rod.
- Route of administration is via intra-articular injection. Multiple joints may be injected as a part of the same treatment.
- Spryng is recommended for repeat administration depending on the veterinarian's assessment, animal activity levels, and age of the animal. In case studies, Spryng particles provided beneficial effect for greater than one year.
- There is no maximum annual administration frequency.
- Each syringe is for a single use only. Do not use if the package is open or the syringe is damaged.

Disposal
The syringe and any unused material must be discarded after a single treatment visit. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices.

7. Potential Adverse Reactions
Mild, short-term injection-site swelling has been observed. Adverse events should be reported to PetVivo at 844-PET-VIVO (738-8486) or info1@petvivo.com

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SACVS-01-0923