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iPPS demonstrates durable effects on pain, function and cartilage volume in canine osteoarthritis model at 3-year human equivalent time point.

KEY HIGHLIGHTS

- Injectable pentosan polysulfate sodium (**iPPS**) provided durable improvements in pain, joint function, and cartilage volume compared to placebo at both 8 and 26 weeks from baseline.
- The 26-week timepoint in the canine model is equivalent to approximately 3 years in humans, highlighting the durability of positive iPPS treatment effects on osteoarthritis pain, joint structure and function.
- iPPS was shown to stabilise disease progression at week 8 and week 26 in osteoarthritic dogs.
- iPPS favourably regulates serum levels of molecular biomarkers CTX-1, HA, and TIMP-1 at week 8 and week 26 in osteoarthritic dogs. The observed biomarker data changes support the proposed PPS mechanisms of action.
- The canine study provides consistent supporting evidence which mirror the improvements in clinical outcomes previously reported from the phase 2 PARA_OA_008 Day 168 results. It supports the clinical development of Paradigm's phase 3 trials PARA_OA_002/003 (treatment of pain and improvement in function) and observational follow-up studies PARA_OA_006/007 (duration of treatment effect).

Paradigm Biopharmaceuticals Ltd (ASX:PAR) (Paradigm or the Company) is pleased to present positive data from the double-blinded study of 20 companion dogs with naturally occurring osteoarthritis (**OA**), randomised to either subcutaneous iPPS (1.7 mg/kg human equivalent dose) or placebo in a 2:1 ratio, respectively. Data analysed from the canine study at 26 weeks demonstrates positive trends with meaningful effect size on subjective measurements of pain, objective functional clinical outcomes, and objective measurements of cartilage volume and biomarkers, following iPPS administration.

The canine model of naturally occurring OA was designed to gather further preclinical proof-of-concept and translational data to determine the long-term effects of iPPS out to an equivalent of 3 years in humans. These durable effects of iPPS out to at least 26 weeks in dogs support the findings from the recently reported phase 2 PARA_OA_008 Day 168 clinical data (1).

The positive data produced from this canine model will be packaged with the MRI, molecular biomarker, and clinical results from the phase 2 PARA_OA_008 and will be presented to the US and EU regulatory authorities (FDA and EMA). We aim to determine the necessary requirements to achieve a disease modifying OA drug (**DMOAD**) label for iPPS through the Company's current phase 3 program. The canine model data will also be prepared for a peer-reviewed publication and conference presentation.

Paradigm CEO, Paul Rennie commented: "iPPS has again shown consistent clinical and functional improvements, this time in a double-blinded, placebo-controlled study of osteoarthritis in dogs. Pleasingly, this canine study provides consistent and supporting evidence which mirror the improvements in clinical outcomes previously reported from

the phase 2 PARA_OA_008 study at Day 168. In addition, and similarly to the PARA_OA_008 study, the canine study was performed concurrently with the PARA_OA_002 phase 3 study and therefore, did not interfere with nor impede the progress of our pivotal Phase 3 clinical trial. The market for OA is seeking safe and effective treatments for patients which provide clinically significant improvements in pain and function, and for those effects to be durable. Additionally, the canine data demonstrated that iPPS reduced cartilage degradation at the 3-year human equivalent time-point (canine 26 weeks) and improved the disease biomarker profile by reducing CTX-1 and hyaluronic acid and increasing TIMP-1 compared to placebo. Paradigm will use these canine data in our ongoing discussions with the Regulators".

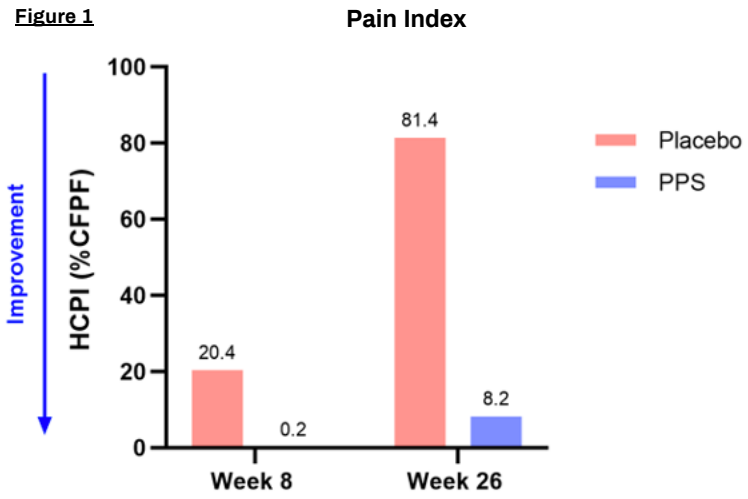
Top-Line Results on the Effects of iPPS at 26 Weeks in the Canine Model of Naturally Occurring OA

To assess differences between iPPS and placebo, effect size calculations were performed as this exploratory pilot study had low numbers between the groups. The effect size is the magnitude of difference between groups and provides a meaningful relationship between variables or the differences between groups. Effect sizes are independent of the sample size and are categorised as small (0.20–0.49), medium (0.50–0.79) or large (>0.80). The Hedges' *g* calculation (https://www.statology.org/hedges-g/) was imputed in all the assessments reported in this study. The Hedges' *g* effect size determines the iPPS effect size compared to placebo and considers sample bias, difference in the means, and standard deviations between treatment groups.

iPPS reduces pain at week 8 and week 26 in osteoarthritic dogs with meaningful effect size (Figure 1).

iPPS demonstrated pain reductions compared to placebo at week 8 and week 26 in osteoarthritic dogs with meaningful effect sizes based on the mean scores of the Helsinki Chronic Pain Index (**HCPI**). The HCPI is an owner-based subjective questionnaire developed to assess chronic pain in the dog (2). The data demonstrate a large meaningful effect size of 1.79 in pain reduction at week 26 compared to the percentage change from the previous follow-up (%**CFPF**) at week 8. This suggests that iPPS treatment results in a durable reduction in pain compared to placebo for up to 26 weeks.

Figure 1



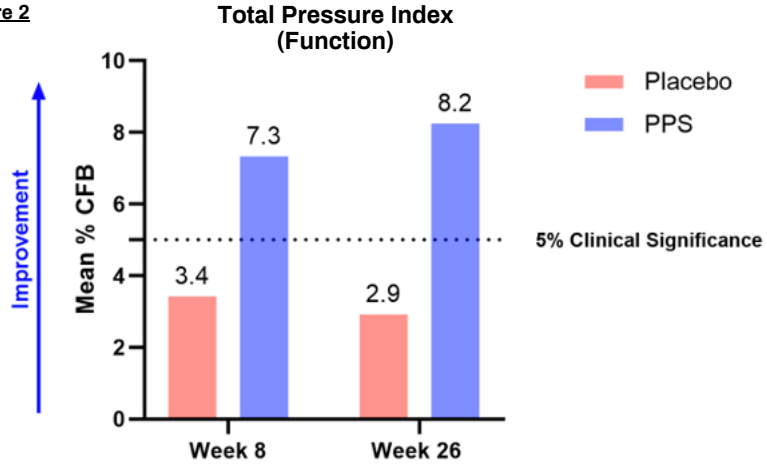
Effect size of PPS: % Change from Previous Follow Up for HCPI	
At 8 Weeks	At 26 Weeks
Small (0.39)	Large (1.79)

*Effect Size Ranges: Small (0.2 – 0.49); Medium (0.5 – 0.79); Large (>0.8)

iPPS improves joint function at week 8 and week 26 in osteoarthritic dogs with meaningful effect size (Figure 2).

iPPS improves joint function at week 8 and week 26 in osteoarthritic dogs with a meaningful effect size on gait assessment by Total Pressure Index (**TPI%**). The dogs enrolled in the study were assessed with GAITRite®, a system successfully used in different clinical lameness studies in dogs. The effect size in improvement of function due to iPPS was a medium effect of 0.5 at both week 8 and week 26 based on the mean percentage change from baseline (%**CFB**) in TPI%. Furthermore, the responses to iPPS compared to placebo were considered to be clinically meaningful improvements in function, passing a benchmark of 5% change from baseline (3).

Figure 2



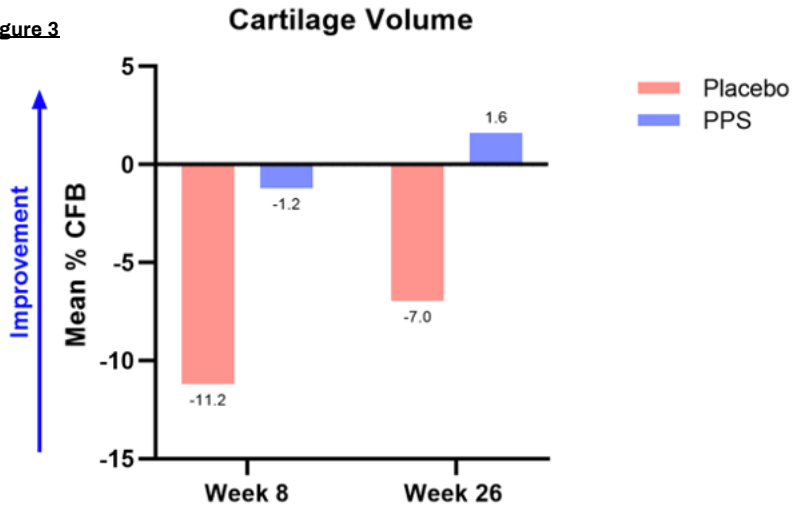
Effect size of PPS: % Change from Baseline for TPI%	
At 8 Weeks	**At 26 Weeks**
Medium (0.55)	Medium (0.50)

*Effect Size Ranges: Small (0.2 – 0.49); Medium (0.5 – 0.79); Large (>0.8)

iPPS inhibits OA disease progression by stabilising cartilage volume changes at week 8 and week 26 in the stifle joints of osteoarthritic dogs (Figure 3).

iPPS stabilises OA disease progression as seen by effect size on cartilage volume changes from baseline at week 8 and week 26 in the affected stifle joint (knee equivalent) of osteoarthritic dogs. Analysis of the mean %CFB in cartilage volume at week 8 and week 26 indicated that iPPS demonstrated a large effect size (1.06) at week 8 and a medium effect size (0.73) at week 26 relative to placebo in reducing cartilage loss in the stifle joint of the affected limb. Results at both time points suggest stabilisation of OA disease progression in the stifle joints of osteoarthritic dogs.

Figure 3



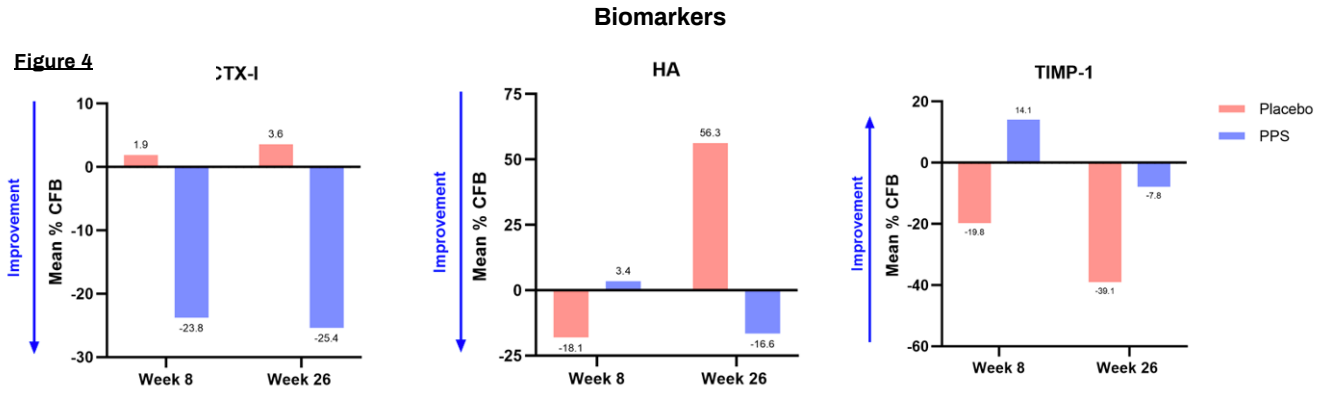
Effect size of PPS: % Change from Baseline for Cartilage Volume	
At 8 Weeks	**At 26 Weeks**
Large (1.06)	Medium (0.73)

***Effect Size Ranges: Small (0.2 – 0.49); Medium (0.5 – 0.79); Large (>0.8)**

***iPPS favourably regulates serum levels of the biomarkers CTX-1, HA and TIMP-1 with meaningful effect size at week 8 and week 26 in osteoarthritic dogs (Figure 4*).**

iPPS favourably regulates serum levels of molecular biomarkers determined by effect size on CTX-1 (4) a degradation fragment of type 1 collagen, hyaluronic acid (5) (**HA**) a marker of cartilage degradation, and TIMP-1 (6,7) an endogenous inhibitor of the cartilage degradation enzyme ADAMTS-5, at week 8 and week 26 in osteoarthritic dogs. The observed biomarker changes support PPS mechanisms of action targeting structural biomarkers of cartilage degradation as detailed in prior clinical results. The large favourable treatment effect sizes at week 26 observed for these biomarkers support the durability of iPPS effects inhibiting cartilage degradation and promoting structural stabilisation of the cartilage.

Figure 4



Effect size of PPS : % Change from Baseline for Biomarkers		
Biomarker	*At 8 weeks*	*At 26 weeks*
CTX-1	Large (1.15)	Large (1.60)
HA	Medium (0.58)	Large (1.19)
TIMP-1	Large (0.96)	Large (1.27)

**Effect Size Ranges* *Small (0.2 – 0.49); Medium (0.5 – 0.79); Large (>0.8)*

Paradigm Chief Scientific Officer, Dr Ravi Krishnan, commented on the study: *"Naturally occurring osteoarthritis in this translational model in dogs mirror the characteristics of osteoarthritis progression in humans. We are pleased that we have good preclinical translational supportive evidence for iPPS as a potential treatment to modify the progression of OA and provide long term durability of effect corresponding to 3 years in humans. Furthermore, these data provide confidence in our ongoing phase 3 clinical program evaluating pain, function, and durability of response in humans."*

Study Design

This study consisted of 14 iPPS treated dogs and 6 placebo treated dogs of varying breeds that presented at the U-Vet Werribee Animal Hospital, Victoria, Australia, for lameness assessment. A broad range of breeds comprising 12 males and 8 females were recruited and randomised in the study. Dogs of both genders with either radiologically and/or clinically defined OA of the knee/stifle (hind limb) or elbow (front limb) were randomised to receive subcutaneous iPPS at a dose of 3 mg/kg (human equivalent dose of 1.7 mg/kg) weekly for 6 weeks.

Clinical outcome measures of pain, function, joint structure imaging by MRI and biomarkers were determined at baseline, 8 weeks and at the final follow-up at 26 weeks from the initiation of treatment.

Pain Assessment: Helsinki Chronic Pain Index is an owner-based subjective questionnaire developed to assess chronic pain in the dog.

Functional Gait Analysis: Dogs enrolled in the study were assessed on a GAITRite® Portable Walkway System (http://www.gaitrite.com) for gait analysis. GAITRite is a portable walkway validated for use in dogs.

Cartilage Volume Analysis: Total cartilage volume was assessed by measurements of Magnetic Resonance Imaging (**MRI**) image sequencing of regions of the patella, tibial plateau, and femoral condyle that were acquired at baseline, week 8 and week 26.

Serum Biomarker Analysis: Serum levels of the molecular biomarkers CTX-1 (degradation fragment of type 1 collagen); Hyaluronic Acid (**HA**) (marker of cartilage degradation in serum); and TIMP-1 (endogenous inhibitor of cartilage degradation enzyme ADAMTS-5) were determined at baseline, week 8 and week 26 in osteoarthritic dogs. The studies of other biomarkers such as the inflammatory biomarkers (IL-1 beta, TNF-alpha, IL-6 and NGF) were unsuccessful since the assays were not verified to detect canine antigens. Furthermore, since synovial joint aspirates from these dogs were not subject to lavages (ethics requirement) the volumes were limited and did not allow the processing for further biomarker analysis.

Naturally Occurring Canine OA and Translational Relevance of the Canine OA Model

The phenotypic characteristics and heterogeneity of OA are similar in both humans and dogs. Therefore, it is expected that the canine model of OA would provide relevant translational data that parallel the human clinical scenario (1).

Both human and canine OA are progressive degenerative disorders and are influenced by similar risk factors. OA in humans primarily affects the knee, hip, and shoulder joints, and pathological changes closely resemble those observed in the canine stifle (knee), hip, and shoulder joints (1). Because the dog's lifespan is shorter relative to that of humans, all stages of development from birth to adulthood and ageing are represented over a shorter time frame, including disease onset and manifestation. This aspect of the

canine model is potentially advantageous in rapidly evaluating DMOAD status of iPPS that otherwise would require a longer assessment period in humans to analyse OA joint structural changes.

About Paradigm Biopharmaceuticals

Paradigm Biopharmaceuticals Ltd. (ASX:PAR) is a late-stage drug development company driven by a purpose to improve patients' health and quality of life by discovering, developing, and delivering pharmaceutical therapies. Paradigm's current focus is developing injectable (subcutaneous) pentosan polysulfate sodium (**iPPS**) for the treatment of diseases where inflammation plays a major pathogenic role, indicating a need for the anti-inflammatory and tissue regenerative properties of PPS, such as in osteoarthritis (phase 3) and mucopolysaccharidosis (phase 2).

Forward Looking Statements

This Company announcement contains forward-looking statements, including statements regarding anticipated commencement dates or completions dates of preclinical or clinical trials, regulatory developments and regulatory approval. These forward-looking statements are not guarantees or predictions of future performance, and involve known and unknown risks, uncertainties and other factors, many of which are beyond our control, and which may cause actual results to differ materially from those expressed in the statements contained in this presentation. Readers are cautioned not to put undue reliance on forward-looking statements.

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