ASX RELEASE

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**Canine PPS Study Demonstrating Sustained Pain, Function and Structural Benefits Published in *PLOS One***

Key Highlights

- **Peer-reviewed translational publication:** Paradigm-supported study evaluating pentosan polysulfate sodium (PPS) in naturally occurring canine osteoarthritis has been published in *PLOS ONE,* a leading international peer-reviewed scientific journal.
- **Durable clinical and functional benefits:** PPS-treated dogs demonstrated sustained reductions in chronic pain and normalization of gait symmetry through 26 weeks (six months), compared with placebo.
- **Structural and biomarker evidence supporting disease modification:** MRI and serum biomarker findings were consistent with slowed cartilage degradation and altered bone and cartilage turnover following PPS treatment.
- **Peer-reviewed translational validation:** Study in naturally occurring canine osteoarthritis, closely mirroring human disease, demonstrates durable PPS effects over six months, providing a compressed analogue of longer-term human outcomes.
- **Pharmaceutical industry highly regards the canine OA model as a translational model:** The pharmaceutical industry considers the canine model for translational osteoarthritis (OA) research, as it closely mimics the naturally occurring, age-related, and progressive nature of human joint disease.

**Paradigm Biopharmaceuticals Ltd. {ASX: PAR) {"Paradigm" or "the Company")** a late-stage drug development company focused on delivering new therapies to address unmet medical needs, is pleased to announce the publication of a peer-reviewed manuscript titled *"Effects of pentosan polysulfate sodium on joint structure and function out to six months in naturally-occurring canine osteoarthritis"* in *PLOS One*, a globally recognised peer-reviewed open-access scientific journal.

The online version of the publication can be viewed here: *PLOS One*

The study was conducted in collaboration with the University of Melbourne, Clinical Sciences and evaluated the durability and potential disease-modifying effects of a six-week course of subcutaneous PPS in companion dogs with naturally occurring osteoarthritis of the stifle and/or elbow joints.

## Study Design Overview

- Randomised, placebo-controlled, exploratory translational study,
- Companion dogs with naturally occurring, radiographically confirmed osteoarthritis,
- PPS administered once weekly for six weeks (3 mg/kg),
- Follow-up assessments conducted out to 26 weeks (six months),
- Endpoints included pain (Helsinki Chronic Pain Index), objective gait analysis, MRI-based cartilage volume, and serum biomarkers of bone and cartilage turnover.

Study inclusion criteria required radiographic evidence of osteoarthritis, together with clinical pain and functional impairment. Baseline gait analysis, pain scores, and MRI findings were consistent with established joint disease at study entry, rather than early or induced osteoarthritis.

## Key Published Findings

### Sustained reductions in pain

- PPS-treated dogs entered the study with significantly higher baseline pain than placebo.
- After adjustment for baseline differences, PPS-treated dogs demonstrated sustained reductions in Helsinki Chronic Pain Index (HCPI) scores out to week 26, whereas placebo-treated dogs showed worsening pain scores over the same period.

### Improved function and gait normalisation

- Objective gait analysis demonstrated progressive normalisation of gait symmetry in PPS-treated dogs at weeks 8 and 26.
- Improvements in weight-bearing and symmetry indices were consistent with reduced lameness and improved joint function, supported by medium to large effect sizes.

### Structural joint effects on MRI

- Quantitative MRI analysis demonstrated stabilisation and modest increases in total cartilage volume in PPS-treated dogs at weeks 8 and 26 relative to baseline.
- In contrast, placebo-treated dogs demonstrated continued cartilage volume loss.
- These findings support a potential structural disease-modifying effect of PPS.

**Biomarker evidence of altered disease biology**

- PPS treatment resulted in reductions in serum CTX-I, a marker of bone resorption, at weeks 8 and 26, with a statistically significant treatment effect at week 26 (p=0.007).
- Hyaluronic acid (HA), a biomarker associated with synovial inflammation and osteoarthritis progression, showed favourable reductions at week 26 in PPS-treated dogs compared with placebo.[1] Elevated circulating and synovial HA levels in osteoarthritis are generally considered markers of synovitis and inflammatory joint turnover, and independent longitudinal studies have demonstrated that higher serum HA concentrations are associated with increased risk of radiographic progression and joint space narrowing.[1] Accordingly, the reduction in HA observed following PPS treatment is consistent with decreased synovial inflammation and reduced disease activity, rather than reduced joint lubrication.
- TIMP-1, an endogenous inhibitor of cartilage-degrading enzymes, increased following PPS treatment, supporting chondroprotective activity.
- Collectively, biomarker changes were consistent with slowed cartilage degradation and altered bone and cartilage turnover.

PPS was well tolerated throughout the study, with no treatment-related adverse events and no clinically meaningful abnormalities in hematology or biochemistry.

## Translational Relevance

Unlike surgically induced or laboratory-based osteoarthritis models, this study evaluated PPS in naturally occurring, spontaneously developing osteoarthritis, closely reflecting the biological, mechanical, and inflammatory drivers of human disease.

Dogs entered the study with radiographically confirmed and clinically established osteoarthritis, enabling assessment of treatment effects in a true disease setting.

Due to osteoarthritis progressing more rapidly in dogs than in humans, the 26-week follow-up period is considered broadly analogous to multiple years of disease progression in people. This study therefore provides a compressed, real-world translational view of longer-term biological, structural, and functional outcomes.

Independent longitudinal human studies have demonstrated that biomarker and MRI changes predict multi-year disease progression[1]. The sustained effects observed in this study therefore provide important insight into potential long-term outcomes of iPPS in human osteoarthritis.

## Relevance to Paradigm's Human Development Program

The findings from this naturally occurring canine model align closely with outcomes observed in Paradigm's Phase 2 human studies, including PARA_005 and PARA_OA_008, which demonstrated favourable biomarker, imaging, and clinical responses following iPPS treatment.

Together, the canine and human datasets provide complementary evidence across species that PPS influences key biological pathways associated with cartilage degradation, inflammation, pain signalling, and joint remodelling.

Importantly, the durability of effects observed in the canine model over 26 weeks provides a translational look-through to longer-term outcomes that are difficult to assess within the duration of early-phase human trials.

This integrated data package strengthens the scientific and regulatory foundation supporting Paradigm's ongoing Phase 3 iPPS program.

**Dr Catherine Stapledon, lead author and Paradigm's Translation Research Manager, said: "** *This study is particularly important because it evaluates PPS in dogs with naturally occurring osteoarthritis, rather than in induced laboratory models. This provides a clinically relevant translational bridge to human disease. The six-month follow-up in this setting offers insight into longer-term biological and structural effects that would typically require several years to assess in people. The consistency between these findings and Paradigm's human Phase 2 data strengthens confidence in the durability and disease-modifying potential of iPPS*."

## What does this mean for Paradigm

The published findings further strengthen Paradigm's osteoarthritis development strategy by:

- Demonstrating the translational canine study shows reductions in pain, improvements in joint function, and potential disease-modifying activity of iPPS, supported by MRI and biomarker findings consistent with PARA_005 and PARA_OA_008.
- Demonstrates durable biological, structural, and functional effects of PPS in a naturally occurring disease model.
- Provides a compressed translational view of longer-term treatment outcomes relevant to human osteoarthritis.
- Reinforces alignment between canine and human biomarker and imaging datasets.
- Strengthens the overall scientific and regulatory data package supporting Paradigm's Phase 3 iPPS program.

## 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 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).

## 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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Authorised for release by the Paradigm Board of Directors.

Reference

[1] Sasaki E, et al. *Serum hyaluronic acid concentration predicts the progression of joint space narrowing in normal knees and established knee osteoarthritis.* Arthritis Research & Therapy. 2015;17:283.

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