ASX RELEASE

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Manuscript on Phase 2 iPPS Biomarker Study, PARA_OA_008, Accepted for Publication in Leading Peer-Reviewed Journal

Key Highlights

- **Independent scientific validation:** Paradigm's Phase 2 iPPS biomarker study has been published online in *Arthritis Research & Therapy*, a leading international rheumatology journal (impact factor ~4.6).
- **Evidence of biological activity in the osteoarthritic joint:** The study demonstrated favourable changes in synovial fluid biomarkers associated with cartilage degradation, inflammation, and pain in patients with moderate to severe knee osteoarthritis treated with iPPS.
- **Strengthens scientific foundation for Phase 3 program:** Peer-reviewed biomarker findings provide mechanistic support for Paradigm's ongoing pivotal PARA_OA_012 Phase 3 clinical trial of iPPS in knee osteoarthritis.

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 that its manuscript titled: *"Effects of Pentosan Polysulfate Sodium on Synovial Fluid Biomarkers in Moderate to Severe Knee Osteoarthritis: an Exploratory, Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial"* has been published online in *Arthritis Research & Therapy*, a respected international peer-reviewed journal specialising in inflammatory and degenerative joint diseases.

The online version of the publication can be viewed here: Arthritis Research & Therapy

Acceptance and publication into *Arthritis Research & Therapy* is independent validation of the scientific rigor, study design, biomarker methodology, and statistical analysis underpinning the PARA_OA_008 Phase 2 trial. Manuscripts accepted by the journal undergo a stringent peer-review process focused on clinical relevance and translational significance in rheumatology.

The publication highlights the success of the study methodology in that it included:

- A successful design and robust execution of an exploratory Phase 2 randomised, placebo-controlled trial in patients with moderate to severe knee osteoarthritis;
- repeated ultrasound-guided synovial fluid sampling;
- coordinated multi-site clinical operations and specialised laboratory analyses; and
- in-depth evaluation of synovial fluid, serum, and urinary biomarkers relevant to osteoarthritis disease biology.

The publication reports findings from Paradigm's PARA_OA_008 Phase 2 trial, an exploratory randomised, placebo-controlled study designed to evaluate the biological effects of injectable pentosan polysulfate sodium (iPPS) in patients with moderate to severe knee osteoarthritis

Key Scientific Observations

Treatment with injectable pentosan polysulfate sodium (iPPS) was associated with biologically meaningful changes across multiple biomarker categories relevant to osteoarthritis:

Cartilage degradation biomarkers

- Synovial fluid ARGS (aggrecanase-derived aggrecan neoepitope), a direct marker of cartilage matrix breakdown, was significantly reduced in iPPS-treated patients versus placebo at Day 56 (p=0.028) and remained significantly reduced at Day 168 (p=0.024).

- Serum C2C (Type II Collagen Cleavage Neoepitope), a marker of type II collagen degradation, showed a statistically significant reduction at Day 168 versus placebo (p=0.024).

Bone and cartilage turnover

Serum CTX-I (C-terminal Telopeptide of Type I Collagen), which is released into the bloodstream when bone is being broken down and remodelled, demonstrated a statistically significant increase at Day 56 (p=0.022) and Day 168 (p=0.025), consistent with altered bone and cartilage remodelling dynamics.

Inflammatory mediators within the joint

Favourable changes were observed in key synovial fluid inflammatory mediators, including TNF-α (tumour necrosis factor alpha) and IL-6 (interleukin-6). In addition, increases in TIMP-1 (tissue inhibitor of metalloproteinases-1), an endogenous inhibitor of cartilage-degrading enzymes, were observed, consistent with a shift toward reduced tissue breakdown.

Pain-associated biomarkers

Reductions were observed in NGF (nerve growth factor), a biomarker involved in pain sensitisation and nociceptive signalling within the osteoarthritic joint.

Importantly, several of these effects were observed directly in synovial fluid, reflecting biological activity at the site of disease. Some biomarker changes persisted months after completion of dosing, suggesting durable biological effects beyond the active treatment period.

iPPS was generally well tolerated, with no serious treatment-related adverse events reported.

Long-Term Clinical Outcomes

Clinical outcomes including pain, physical function, stiffness, and patient global impression of change assessments were followed for up to 12 months (Day 365). While the study was exploratory and not powered to demonstrate long-term statistical separation versus placebo, patients treated with iPPS generally maintained improvements from baseline over the 12-month follow-up period.

Early improvements in pain and function observed in the twice-weekly iPPS dosing group were consistent with the biological activity demonstrated through synovial fluid and systemic biomarker changes. The durability of clinical outcomes over extended follow-up provides supportive clinical context for the mechanistic findings reported in the study.

Relevance to Paradigm's Phase 3 Program

While PARA_OA_008 was not designed to support drug registration, the biomarker findings provide important mechanistic support for Paradigm's ongoing pivotal Phase 3 clinical trial (PARA_OA_012) in knee osteoarthritis.

The data strengthen the biological rationale for iPPS by demonstrating effects on pathways associated with inflammation, cartilage metabolism, and pain processes, which are increasingly recognised by clinicians, and researchers as central to osteoarthritis disease progression.

The publication further enhances Paradigm's scientific credibility and supports ongoing engagement with regulatory authorities, investigators, and potential strategic partners.

First Author and Chief Medical Officer of Paradigm Biopharmaceuticals, Dr Donna Skerrett commented: "Acceptance and publication of this manuscript by *Arthritis Research & Therapy* is an important validation of the quality and depth of the PARA_OA_008 study. Conducting a trial of this complexity, involving repeated synovial fluid sampling and detailed biomarker analysis, required a significant collaborative effort by investigators, laboratories, and Paradigm's clinical team".

The peer-reviewed findings provide valuable insight into the biological activity of iPPS within the osteoarthritic joint and further strengthen the scientific foundation underpinning our ongoing Phase 3 program."

Publication Timing & Next Steps

In addition to the published biomarker manuscript, Paradigm notes that the MRI outcomes from the PARA_OA_008 study demonstrated clinically meaningful findings. A separate manuscript focusing on these imaging-based results is in preparation and once complete, will be submitted to a relevant scientific journal for peer review.

Paradigm will provide further updates to the market as this work progresses.

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.

Authorised for release by the Paradigm Board of Directors.

Investor Q&A

What does acceptance for publication mean?

It means independent experts have reviewed the study and agreed it meets the scientific and clinical standards required for publication in a leading medical journal.

Why is this journal important?

Arthritis Research & Therapy is a respected international journal focused on arthritis and inflammatory joint disease. Its impact factor reflects strong citation rates and influence within the field.

What are biomarkers and why do they matter?

Biomarkers are objective, measurable indicators of what is happening inside the joint at a biological level, beyond what a patient feels or reports as pain. They generally fall into two broad categories:

Molecular biomarkers are measured in biological samples such as joint (synovial) fluid, blood, or urine. These biomarkers can indicate:

- Inflammation within the joint,
- Cartilage breakdown or repair**,** and
- Biological processes linked to pain signalling.

Because synovial fluid sits directly inside the joint, changes measured there can provide particularly strong evidence of local activity at the site of osteoarthritis disease.

Imaging biomarkers are assessed using technologies such as MRI or X-ray. These can show:

- Structural changes in cartilage and bone,
- Joint space narrowing,
- Bone marrow lesions, and
- Other physical features associated with osteoarthritis progression.

Together, molecular and imaging biomarkers help researchers and clinicians understand how a treatment is affecting the underlying disease process**,** not just whether pain scores improve. This is increasingly important in osteoarthritis, where symptoms alone do not always reflect what is happening inside the joint.

Why is synovial fluid important?

Synovial fluid sits inside the knee joint. Changes here suggest the treatment (iPPS) is acting directly at the site of osteoarthritis disease, even when it is injected subcutaneously.

What did the study show in simple terms?

Patients treated with iPPS showed reductions in markers linked to joint damage, inflammation, and pain compared with placebo.

Does this prove iPPS slows osteoarthritis progression?

No. This was not a registration study. However, the biomarker results support the biological rationale for iPPS and help explain how it may affect underlying disease pathways.

How does this relate to Phase 3?

The Phase 2 biomarker data complement Paradigm's ongoing Phase 3 trial by providing peer-reviewed evidence of biological activity relevant to osteoarthritis.

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