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Paradigm Acquires Proteobioactives Pty Ltd to Expand Osteoarthritis Portfolio with Oral Combination Therapy

Key Highlights

- Paradigm acquires Proteobioactives Pty Ltd (**Proteobioactives**), securing global patent rights for an oral PPS and COX-2 inhibitor combination therapy.
- The oral combination will target early-stage, minor to mild osteoarthritis (**OA**) in both human and veterinary markets, expanding Paradigm's portfolio of chronic (non-opioid) pain treatments.
- Preliminary Pilot data shows meaningful pain reduction in patients with hand and knee OA.
- Strategic alignment with Paradigm's core iPPS program, offering a complementary asset for broader market coverage across OA severity spectrum.
- Despite the acquisition of Proteobioactives, Paradigm's primary focus remains on completing its phase 3 program for Zilosul® in subjects with moderate to severe OA.

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 acquisition of Proteobioactives, a company founded by Professor Peter Ghosh and based on his pioneering research into pentosan polysulfate sodium (**PPS**).

Through this acquisition, Paradigm obtains exclusive global rights to develop and commercialise a patented oral combination of PPS and a COX-2 inhibitor (**Coxib**) for the treatment of pain and inflammation. The acquisition of this oral combination broadens Paradigm's OA pipeline beyond its current injectable PPS (**iPPS**) phase 3 program for moderate to severe disease, allowing potential expansion into earlier-stage disease segments where large unmet needs remain.

A significant advantage to the combination product allows for lower doses of Cox-2 inhibitors, which is important for both the veterinary and human markets. Strategically, adding a new composition of matter patent to our current portfolio enables Paradigm to expand our product portfolio in the OA-related pain market, such as hand OA, mild knee OA, as well as OA in dogs and horses.

Paradigm will acquire all relevant intellectual property through the acquisition of Proteobioactives, including the granted global patent (WO2019157560) (**Patent**), formulation know-how, and exclusive rights to the Pentacoxib™ product. The intellectual property in the pharmaceutical and veterinary combination compositions is covered by granted patents in the United States, United Kingdom, Australia, and by pending applications in Europe, Canada and New Zealand.

Paul Rennie, Managing Director of Paradigm Biopharmaceuticals, said: "Our immediate focus remains on the successful execution of our ongoing Phase 3 clinical trial

for injectable PPS in knee osteoarthritis. The acquisition of this oral combination IP allows us to broaden our long-term strategy. We anticipate initial development activities will concentrate on the veterinary field, where there is a clear and timely opportunity. Importantly, through this veterinary development program, we expect to generate valuable preclinical and field data that will ultimately support our transition to human clinical development. This staged approach enables us to responsibly expand our OA portfolio while maintaining strict capital discipline and focus on our core late-stage phase 3 asset."

Acquisition Details

Paradigm has entered into a binding agreement to acquire 100% of the issued share capital of Proteobioactives (**Acquisition**).

Consideration for the Acquisition comprises:

(a) AUD $500,000 in cash on completion; and
(b) the following milestone payments (**Milestone Payments**), payable in cash on satisfaction of the relevant milestone:
    (i) AUD $1,000,000 on successful completion of a human phase 2 clinical trial for the product as evidenced by public release by Paradigm of a clinical study report confirming that the trial meets its primary endpoints;
    (ii) AUD $5,000,000 on successful completion of a human phase 3 clinical trial for the product as evidenced by public release by Paradigm of a clinical study report confirming that the trial meets its primary endpoints;
    (iii) AUD $5,000,000 on registration of the product with the U.S. Food and Drug Administration (**FDA**), evidenced by receipt of formal FDA approval confirming that the product has been successfully registered with the FDA; and
    (iv) AUD $5,000,000 on the first commercial sale of the FDA registered product, as evidenced by the submission of a sales invoice, proof of delivery, or other relevant documentation.

The agreement is otherwise on terms and conditions considered customary for a transaction of this nature.

There are no assumed liabilities or ongoing obligations associated with the Acquisition, other than the Milestone Payments should the relevant milestones be satisfied. Since Paradigm intends to pursue the veterinary application first, the FDA base milestone payments above are not expected to become payable in the near or medium term.

Background to the Pentacoxib™ Patent and Oral PPS

OA is the most prevalent form of joint disease resulting in direct healthcare costs and clinical symptoms of pain and joint stiffness. OA leads to structural deterioration of the joint structures. Drugs aiming to reduce pain and/or inflammation most often do not address the structural deterioration. Some pharmaceutical agents, currently in clinical trials, have shown some improvement in slowing the rate of structural destruction and these are known as disease-modifying osteoarthritis drugs or DMOADs. Promising DMOADs under investigation have demonstrated some structural improvements on MRI, X-ray and biomarkers of disease, but many have not yet demonstrated a reduction in the primary symptoms of pain and joint dysfunction. PPS has been cited as a potential DMOAD.[1]

PPS, in promising preclinical and clinical data (currently unpublished Paradigm data), is administered by subcutaneous injection and showed both improvement in OA symptoms and structural improvements (as measured by X-Ray, MRI and synovial fluid biomarkers

of disease). These promising results, with injectable (subcutaneous) PPS need to be confirmed in a phase 3 double-blind, placebo-controlled clinical trial. Paradigm has commenced the phase 3 clinical trial and recently advised the first participant consented into the trial. It is expected the phase 3 clinical trial will have up to 15 sites in Australia and 50 sites in the United States of America.

PPS is registered for human use (Elmiron®) for a bladder condition, interstitial cystitis and in this condition, PPS is administered orally. Apart from interstitial cystitis, the use of oral PPS is limited, because of its poor bioavailability. In the US Prescribing Information for Elmiron® (Janssen Pharmaceuticals, Revised June 2020), approximately 6% of the administered oral dose was reported to reach systemic circulation following single-dose pharmacokinetic studies. Oral PPS has therefore not previously been considered to treat diseases like OA due to its poor bioavailability.[2]

Peter Ghosh (PhD, DSc), a renowned scientist and researcher of PPS for over 40 years, patented a finding that oral PPS when combined with an oral anti-inflammatory (COX-2 inhibitors such as Celebrex® or Mobic®) increased PPS' bioavailability and potentially makes the combination a therapeutic option for both veterinary and human use. A small proof-of-concept clinical study demonstrated in both hand OA and knee OA that the combination product (Pentacoxib™) improved clinical outcomes compared to the Coxib alone.

Strategically, adding a new composition of matter patent to our current portfolio opens new sectors of the OA market, such as hand OA or the veterinary sector. Acquiring the Proteobioactives patents adds significant value to Paradigm and affords to it an expanded landscape over the chronic pain field. The Pentacoxib™ product could be an alternative to existing nonsteroidal anti-inflammatory drugs (**NSAIDs**) which are not known to improve structures of the arthritic joint.

The global market for COX-2 inhibitors is estimated to be around USD 8.19 billion in 2024 and projected to reach USD 11.33 billion by 2030, representing a compound annual growth rate of 5.4%.[3] This growth is primarily driven by the increasing prevalence of musculoskeletal disorders and other pain conditions, despite known safety concerns associated with some COX-2 inhibitors. This invention could be viewed as an improved COX-2 inhibitor due to the potential DMOAD activity of PPS and a lower dose of COX-2 inhibitor and potentially improved tolerance.

Rationale for Combining PPS and a COX-2 Inhibitor

"Cyclooxygenase COX-1, COX-2 and 5-lipoxygenase (5-LOX) are enzymes which produce effectors of pain and inflammation in OA and many other diseases. All three enzymes play a key role in metabolism of arachidonic acid, which contributes to the deterioration of cartilage. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the COX enzymes but show no anti-5-LOX activity to prevent the formation of leukotrienes. Current therapeutics under development, the so-called "dual inhibitors" of COX and 5-LOX may (i) provide a broader anti-inflammatory compound compared to NSAIDs that only target the COX pathway and (ii) show improved side-effect profiles and may represent a new option for the management of OA."[4]

It is thought that PPS and a COX-2 inhibitor act in a synergistic manner. Research suggests that PPS may inhibit lipoxygenase (5-LOX) activity, thus reducing the production of leukotrienes, known pro-inflammatory factors. The COX-2 inhibitors also reduce pain and inflammation via the cyclooxygenase (COX) pathway by reducing the production of prostaglandins. "It is believed there are no reports that selective COX-2 inhibitors, such as Celebrex® (celecoxib), can also inhibit the production of leukotrienes."[5] On the contrary, they may exacerbate the levels of these inflammatory mediators. In view of this

deficiency, investigators have sought to develop drugs for inflammatory diseases capable of inhibiting both 5-LOX and cyclooxygenase pathways ("dual inhibitors") of arachidonic acid metabolism. [6]

Therefore, this invention is a potential dual inhibitor of the three key enzymes which produce pain and inflammation in OA.

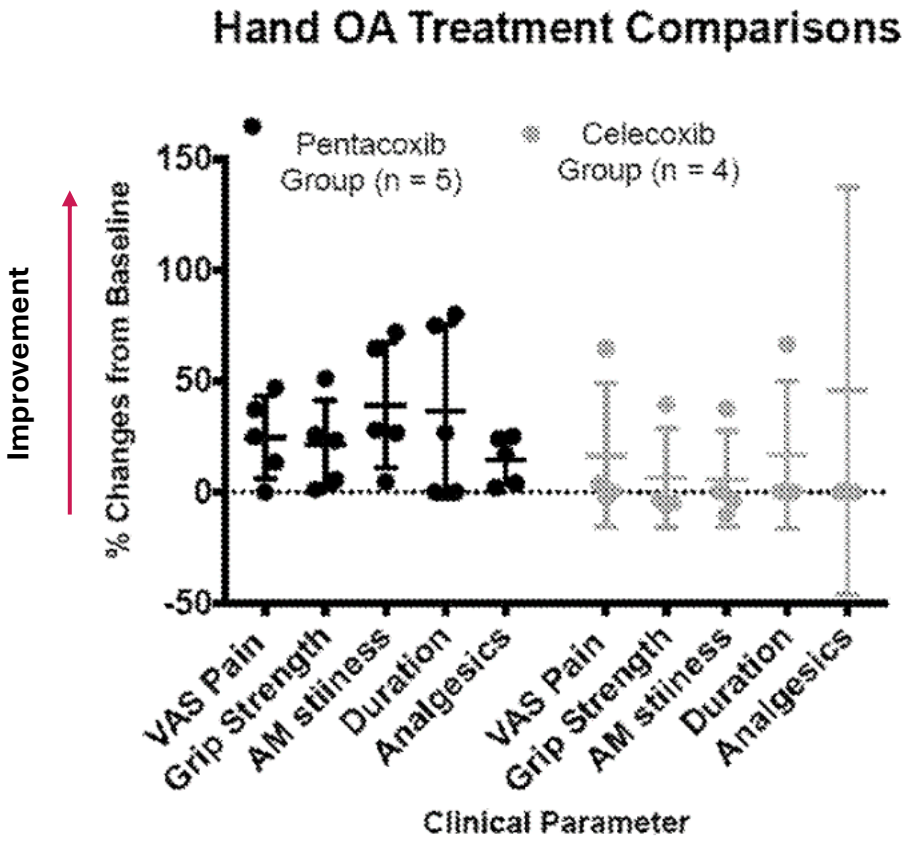
The proof-of-concept clinical trial results shown below in hand and knee OA was a double-blind, drug comparator study where the combination product, 2 x 250mg Pentacoxib™ capsules (125mg PPS / 125mg celecoxib), taken three times a week, was compared to 2 x 250mg Celebrex® capsules three times a week. Importantly, the Pentacoxib™ product contained half the dose of the COX-2 inhibitor alone. A significant advantage to the combination product is that it allows for lower doses of COX-2 inhibitors, which is important from a safety perspective for both the veterinary and human markets.

Paradigm will undertake non-clinical studies that will support both human and veterinary use and registration. These studies are likely to be outsourced, and the expenditure limited.

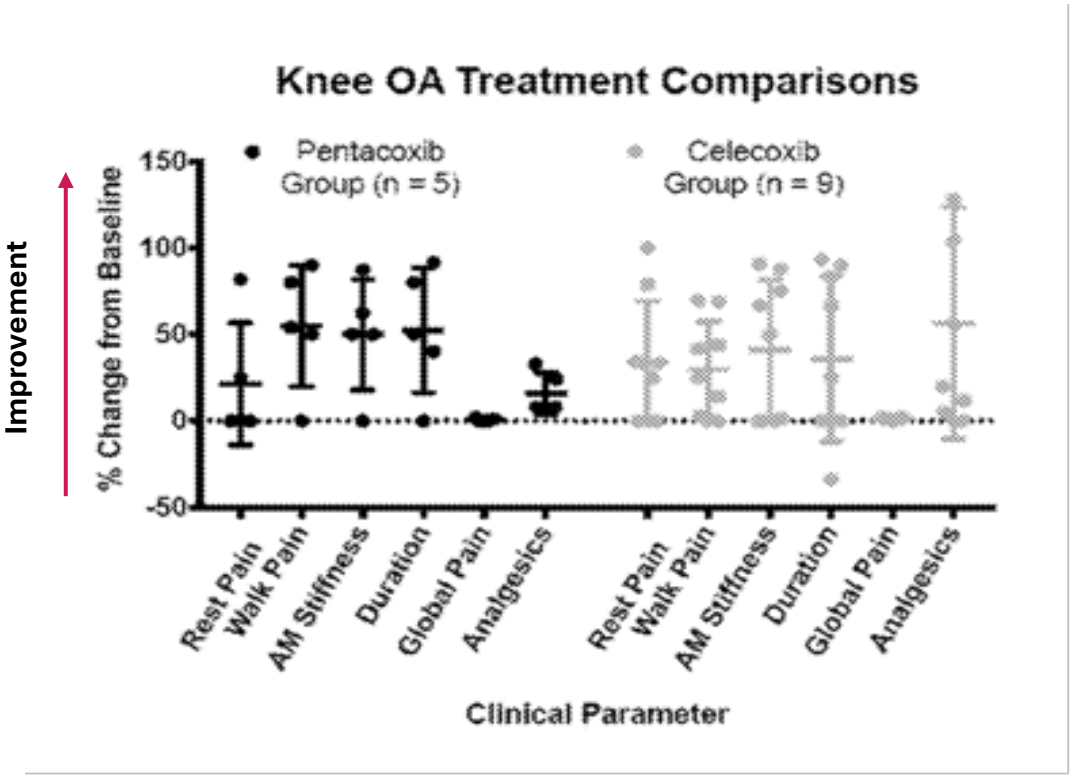
Data Supporting the Oral Combination

The Patent includes pilot clinical data in patients with hand OA, where 2 x 250mg Pentacoxib™ capsules (125mg PPS / 125mg celecoxib) were administered three times weekly over six weeks. The combination showed:

- Meaningful improvements in visual analogue scale (**VAS**) pain, grip strength, morning stiffness, and reduced need for analgesics
- Greater overall symptom improvement versus celecoxib alone, as shown in the accompanying figure below.



In addition, a Pilot clinical knee OA study was undertaken, and the clinical data (shown below) also forms part of the Patent. In a comparator trial for patients with symptomatic knee OA, were randomised to receive either the PPS + celecoxib combination or celecoxib alone for 6 weeks. The combination group received 2 x 250 mg Pentabrex™ capsules (125 mg PPS / 125 mg celecoxib) taken three times weekly, while the celecoxib-only group received 250 mg celecoxib three times weekly.



Assessments included VAS pain, walking distance, duration of morning stiffness, and analgesic use. Both groups showed improvement over baseline; however, the combination group demonstrated greater reductions in pain and analgesic usage, and improvements in joint function. While statistical significance

This trial supports the rationale for further development of the oral Pentacoxib™ combination in knee OA and confirms alignment with the hand OA data already referenced in the same Patent. Importantly, the studies suggest that co-administration with a COX-2 inhibitor may enhance the oral bioavailability of PPS, overcoming the historic absorption limitations and enabling effective oral dosing without penetration enhancers or injections.

Animal Health

The veterinary market for osteoarthritis is expanding rapidly, particularly among companion animals. In the U.S., approximately 40% of the 90 million dogs are estimated to show signs of OA[7], yet fewer than half are formally diagnosed. Contributing factors include obesity, aging, and breed-related risk.

The current treatment landscape includes NSAIDs and more recently, Librela™, a monthly injectable monoclonal antibody targeting nerve growth factor (NGF). While Librela™ has gained strong early uptake, veterinarians have raised several concerns:

- Cost and accessibility of monthly injections,
- Questions around long-term inhibition of NGF and implications for nerve function,

- Need for improved compliance and chronic treatment practicality.

Paradigm believes this new potential oral liquid formulation combining PPS and a COX-2 inhibitor may offer veterinarians and pet owners a more convenient, cost-effective alternative. The formulation is designed for administration with food, potentially improving compliance, and reducing overdose risks associated with solid-dose NSAIDs.

Importantly, both PPS and Coxibs are well-documented and widely used in veterinary medicine. Veterinarians are familiar with their respective safety profiles, supporting near-term development and adoption potential.

Paradigm plans to progress formulation work and early-stage development of this veterinary asset in parallel with its p3 clinical program for injectable PPS.

Human Health

OA is the most prevalent joint disease globally, affecting over 500 million people. While Paradigm's injectable PPS program is targeting moderate to severe knee OA, a significant proportion of patients, up to 60%,[8] experience mild or early-stage symptoms, where treatment options remain limited.

Current therapies are typically limited to oral NSAIDs, which carry risks of gastrointestinal and cardiovascular side effects, especially in long-term use.

The oral PPS + Coxib combination offers a differentiated therapeutic option for early-stage OA. By combining two well-tolerated and established anti-inflammatory agents, the formulation may address pain and stiffness in patients not yet requiring injection-based therapies. This expansion into mild OA enables Paradigm to serve a broader spectrum of patients and align with existing prescribing practices.

This development will follow the completion of Paradigm's current phase 3 clinical trial and regulatory filings for injectable PPS.

References

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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) and mucopolysaccharidosis (phase 2).

Forward Looking Statements

This Company announcement contains or may contain 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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Approved for release by the Paradigm Board of Directors.

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