ASX RELEASE

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A PARADIGM SHIFT IN TREATING OSTEOARTHRITIS PAIN

Key Highlights:

- Peer-reviewed publication (*BMC Musculoskeletal Disorders*) of a patient case study confirms the significant potential of Pentosan Polysulfate Sodium (PPS) to treat subchondral Bone Marrow Edema Lesions (BMELs) in people with osteoarthritis (OA).
- Case study showed treatment with PPS resolved the BMELs and significantly reduced OA pain, knee swelling and improved joint function. Patient and surgeon no longer consider a total knee replacement is warranted.
- Over the past year, an additional 30 people with BMELs and OA have been treated with PPS with similar clinical outcomes.
- Both results provide the rationale for Paradigm's Phase 2b clinical trial to investigate PPS in subjects with BMELs and OA, which is scheduled to commence later this year.
- OA is a condition with a significant unmet medical need: market size is US$5bn p.a., while the total economic burden in the US alone, is estimated to be US$128bn[1].

Paradigm Biopharmaceuticals Ltd (ASX:PAR) is pleased to announce the peer-reviewed publication of a patient case study which confirms the significant potential of Pentosan Polysulfate Sodium (PPS) to treat Bone Marrow Edema Lesions (BMELs) in people with osteoarthritis (OA).

The publication is a case-study of one subject, although over the past 12 months, an additional 30 patients with BMELs and OA have also been treated with PPS. Paradigm is pleased to

[1] National Institute of Health; Emerging drugs for osteoarthritis; Hunter DJ and Matthews G 16(3): 479–491; 2011 September.

announce that all patients experienced similar clinical outcomes of reduced BMEL volume (on MRI), significant reduction in pain and knee effusions (excessive fluid around the knee). Together, these results provide the rationale for Paradigm's randomised, double-blind, placebo-controlled Phase 2b clinical trial to investigate PPS in subjects with BMELs and OA, which is scheduled to commence later this year. A positive result from the trial would be a major valuation inflection point for Paradigm.

There is increasing evidence that BMELs play an important role in the development of knee OA. In established OA, BMELs are associated with knee pain, progression (on x-ray or MRI) of knee OA and cartilage loss. Enlargement of BMELs is strongly associated with increased cartilage loss and reduction of the extent of BMELs is associated with a decrease in cartilage loss.

The case study of a 70-year-old female patient with BMELs and advanced OA treated with PPS was published in *BMC Musculoskeletal Disorders* entitled: "*Improved clinical outcome measures of knee pain and function with concurrent resolution of subchondral Bone Marrow Edema Lesion and joint effusion in an osteoarthritic patient following Pentosan Polysulphate Sodium treatment: A case report*".

The study showed that treatment with PPS:

- eliminated the patient's subchondral (the layer of bone just below the cartilage in a joint) BMELs;
- eliminated the patient's pain level (from a score of **8 out of 10** on a Numerical Rating Scale [NRS] to **0 out of 10**);
- significantly reduced knee swelling; and
- significantly improved joint movement (**43% improvement** from a Lysholm Knee Score).

Before the PPS treatment, the patient was being treated with a Non-Steroidal Anti-Inflammatory Drug (NSAID) and on a public hospital waiting list for a total knee replacement. Post PPS treatment, the patient discontinued the use of the NSAIDs and the surgical procedure was no longer required.

The Publication has been accepted. A copy of the Publication will be available on the Paradigm Biopharma website within the next week.

The case study confirms that there is significant potential for PPS to treat BMELs in people with painful OA - a condition with significant unmet medical need. Current OA treatments do not have adequate pain-relieving effects, provide no protection for the degenerating joint structures and they are also associated with significant adverse side effects, such as opioids, which are highly addictive.

Addressable market

OA is a condition with a significant unmet medical need, with a market size of US$5 billion per

annum,[2] for which is a large proportion is attributed to low-cost, generic treatments. This figure could potentially be multiples higher if new, effective, patented treatments are commercialised.

It is the most common form of joint disease worldwide, affecting as much as 13% of the world's population.

In the US alone, the financial burden of OA has been estimated to be US$81 billion in medical costs and US$128 billion in total costs, given approximately 21 million people have OA associated limitations, while there are 36 million outpatient visits and 750,000 hospitalisations per year[3].

In Australia, arthritis affects around three million people or around 15% of the population. OA is the leading cause of pain and disability among the elderly in Australia and the third-leading cause of life-years lost due to disability. Moreover, currently about 19,000 hip replacements and 25,000 knee replacements are performed for osteoarthritis in Australia each year[4], representing a direct healthcare cost in excess of A$475 million and $500 million, respectively.[5] The prevalence of OA is also set to rise globally with ageing populations accompanied by the rising epidemic of obesity. OA most commonly affects large weight-bearing joints, affecting the knees in up to 37% of adults over 60.

Pain is the major symptom for people with OA, with 17% of US adults aged 45 and older reporting pain as the predominant clinical problem. OA pain is most commonly treated with analgesics, NSAIDs and corticosteroids. In addition to safely treating OA pain, physicians would like treatments to also slow, stop or even reverse the degeneration of joint structures.

Limitations of current treatments

In terms of unmet medical need, most drugs prescribed to treat OA pain have limited pain-relieving efficacy and they cannot stop joint structure degeneration. In fact, most existing therapies have adverse effects on the joint structure. Several NSAIDs and steroid-based anti-inflammatories, when used regularly to treat OA pain, also have adverse side effects.

Opioids to treat OA pain are well-known to be highly addictive and are causing serious issues for physicians, the health-care system and Governments around the world.

There is the potential for PPS to be a safe and effective treatment for osteoarthritis as it:

- Significantly reduces pain with long durability of pain remission;
- Has good long-term safety and tolerability data;
- Does not have toxicity or adverse side-effects and is not linked to co-morbidities;
- Is not addictive; and

[2] National Institute of Health; Emerging drugs for osteoarthritis; Hunter DJ and Matthews G 16(3): 479–491; 2011 September.
[3] National Institute of Health; Emerging drugs for osteoarthritis; Hunter DJ and Matthews G 16(3): 479–491; 2011 September.
[4] https://www.mja.com.au/journal/2004/180/5/epidemiology-osteoarthritis-australia
[5] http://www.hica.com.au/health-insurance-news/the-growing-cost-of-hip-and-knee-replacements

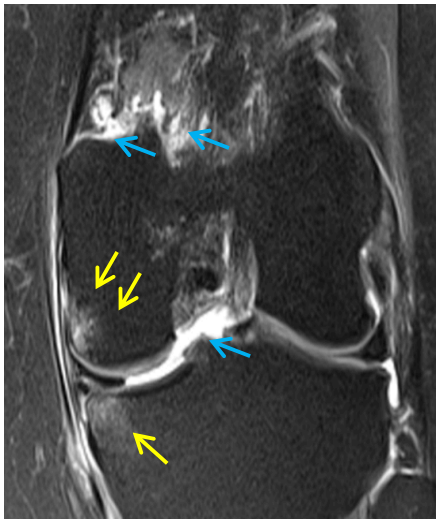
- Has positive regenerative properties to stop or slow the degenerative process of OA.

Mr Paul Rennie, Paradigm's Chief Executive Officer said: "Targeting the entire degenerative joint, including the cartilage breakdown and the bone marrow edema lesions in the underlying bone of the joint, represents a Paradigm shift in treating painful OA. This case study underlines that PPS could be a promising, safe and effective treatment for BMELs in people with OA – a condition with significant unmet medical need."

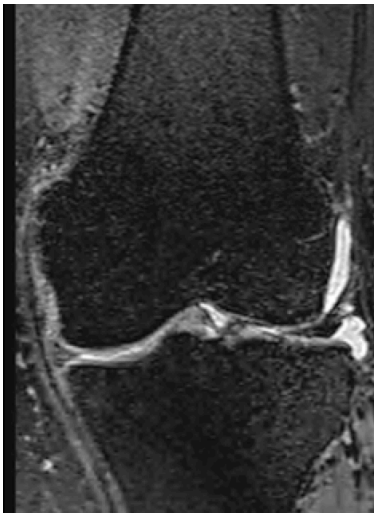
Mr Rennie added: "Most current OA treatments do not effectively address the disease and can have destructive effects on joint structure or adverse side effects. We hope PPS can provide the two major goals of physicians and their OA patients alike - i.e. significantly reduce OA pain and stop or slow the structural destruction of the joint. Additionally, we hope PPS may offer an alternative to the use of opioids for treating OA pain. We look forward to commencing our Phase 2b trial of PPS for this condition and will update investors on our progress with this important clinical trial."

Clinical Overview

The case study was a 70-year-old female on a waiting list for total knee replacement with knee osteoarthritis presenting with a high level of knee pain, scoring eight on the Numerical Rating Scale (NRS), and functional limitation, demonstrating a poor Lysholm Knee Score of 37. MRI scans of the knee revealed subchondral bone marrow edema lesions in the medial femoral condyle and medial tibial plateau. The patient was administered a course of PPS intramuscularly twice weekly, for three weeks. MRI scans taken two weeks post-treatment showed complete resolution of the bone marrow edema at the medial femoral condyle and medial tibial plateau with concomitant recovery from pain (NRS pain score of 0), and a 43% improvement of the Lysholm Knee Score. In addition, marked reduction in joint effusion was also demonstrated in the MRI scan post-PPS therapy.



Before PPS, MRI showing BME Lesions (yellow arrows) effusions in joint space (blue arrows)
High NRS Pain Score =8
Lysholm Score: 37 (Poor knee function)



Post-PPS treatment MRI Showing complete resolution of BME lesions and effusions
Pain NRS =0 (pain resolved)
Lysholm Score:65 (Fair knee function)

BMELs and OA

BMELs are linked to pain and the progression of OA, while the prevalence and severity of the lesions are associated with less cartilage volume and greater cartilage loss over two years. Moreover, the severity of BMELs is positively associated with risk of knee joint replacement.

By targeting the resolution of BMELs, it is hoped that this could provide the two major goals of treating physicians and their OA patients alike - i.e. significantly reduce pain and stop or slow the structural destruction of the joint.

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