



ASX RELEASE

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Ethics Approval Received for Phase 2b clinical trial for Osteoarthritis

Key Highlights:

- Ethics approval received for Phase 2b clinical trial to investigate Pentosan Polysulfate Sodium (PPS) in subjects with knee osteoarthritis (OA) and bone marrow edema lesions (BMELs).
- 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\$128bn¹.
- It is hoped that injectable PPS could be a safe and effective treatment for OA: current treatments do not have adequate pain-relieving effects, provide no protection for the degenerating joint structures and are also associated with significant adverse side effects.
- Trial will recruit 100 patients across four trial sites in Queensland, South Australia, Victoria, and Western Australia.
- Trial subjects will be evaluated for safety, tolerability, pain levels and effects on disease symptoms, with results anticipated in early 2019.

Paradigm Biopharmaceuticals Ltd (ASX:PAR) is pleased to announce it has received ethics approval for its Phase 2b clinical trial to investigate Pentosan Polysulfate Sodium (PPS) in subjects with knee osteoarthritis (OA) and bone marrow edema lesions (BMELs).

The randomised, double-blind, placebo-controlled Phase 2b clinical trial will treat a total of 100 patients with results expected in Q1 CY2019. A positive result from the trial would be a major valuation inflection point for Paradigm.

The ethics approval allows Paradigm to commence the trial at its four clinical trial sites: the Griffith University Clinical Trials Unit in Queensland, Sportsmed SA Hospital in Stepney, South Australia,

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

Emeritus Research in Malvern East, Victoria and Linear Clinical Research in Nedlands, Western Australia.

First participant dosing is expected in the coming weeks. Participants with OA of the knee and subchondral bone marrow lesions will be evaluated for safety, tolerability, pain levels and effects on disease symptoms of PPS subcutaneous injections. The trial will be run by Principal Investigator, Associate Professor Andrew Ostor, Paradigm's clinical research partner.

Market opportunity

The OA market represents a significant opportunity for Paradigm. It is a condition with a large and, as yet, unmet medical need as most current treatments prescribed for the condition do not have adequate pain-relieving effects, provide no protection for the degenerating joint structures and are also associated with significant adverse side effects.

It is estimated that the size of the market is US\$5 billion per annum² and this figure could potentially be multiples higher if new, effective, patented treatments such as PPS are commercialised.

OA also remains the most common form of joint disease globally. In the US alone, it affects more than 27 million adults³, while in Australia, arthritis affects around three million people. In both countries, the condition is a leading cause of pain and disability among the elderly and a cause of life-years lost due to disability.

Moreover, the condition is expected to increase with an ageing population and increasing obesity rates. By 2030, approximately 20 percent of Americans (about 70 million people) will have passed their 65th birthday and will be at increased risk for the disease. Today, 39 million people (13 percent of the US population) are 65 and older, and more than half have developed OA.⁴

The financial burden of the condition is also significant. In Australia, about 19,000 hip replacements and 25,000 knee replacements are performed for OA patients each year⁵, representing a direct healthcare cost in excess of A\$475 million and A\$500 million, respectively.⁶

In the US, the financial burden has been estimated to be US\$81 billion in medical costs and US\$128 billion in total costs, given approximately 27 million people have OA associated limitations, while there are 36 million outpatient visits and 750,000 hospitalisations per year.⁷

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, Non-Steroidal Anti-Inflammatory Drugs (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

Most of the current drugs prescribed to treat OA do not have adequate pain-relieving effects, provide no protection for the degenerating joint structures and are also associated with significant adverse

² National Institute of Health; Emerging drugs for osteoarthritis; Hunter DJ and Matthews G 16(3): 479–491; 2011 September.

³ <http://ard.bmj.com/content/annrheumdis/early/2017/07/12/annrheumdis-2017-211396.full.pdf>

⁴ <http://most.ucsf.edu/studyoverview.asp>

⁵ <https://www.mja.com.au/journal/2004/180/5/epidemiology-osteoarthritis-australia>

⁶ <http://www.hica.com.au/health-insurance-news/the-growing-cost-of-hip-and-knee-replacements>

⁷ National Institute of Health; Emerging drugs for osteoarthritis; Hunter DJ and Matthews G 16(3): 479–491; 2011 September.

side effects with long-term use.

Of particular concern, OA patients globally are increasingly prescribed with opioids, which can cause significant risk to patients including addiction, abuse, overdose and potentially life-threatening adverse effects.⁸ Reliance on prescription opioids for management of chronic pain, including OA, is now recognised as a serious public health issue by physicians, the health-care system and Governments around the world.⁹ Additionally, the FDA has warned that taking NSAIDs such as ibuprofen increase the risk of having a heart attack or stroke¹⁰, compounding the significant need for safe and effective alternatives.

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

- Has been shown to reduce pain in patients with OA;
- Has good long-term safety and tolerability data and a long history of human use for other indications;
- Is not associated with the significant gastro-intestinal side effects commonly caused by long-term use of oral anti-inflammatories.
- Is not addictive; and
- Has positive regenerative properties which may help to stop or slow the degenerative process of OA.

The link between BMELs and OA

Bone marrow edema lesions (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.

Paradigm hopes that by targeting the resolution of BMELs, 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.

Positive clinical outcomes from PPS treatment

The ethics approval follows Paradigm confirming case reports of strong clinical outcomes for PPS, which confirm the significant potential for the drug to treat BMELs in people with OA.

A case study of a 70-year-old female patient with BMELs and advanced OA treated with PPS was recently published in the peer-reviewed publication, *BMC Musculoskeletal Disorders*. <https://bmcmusculoskeletdisord.biomedcentral.com/articles/10.1186/s12891-017-1754-3>

The study showed that treatment with PPS:

- Eliminated the patient's subchondral (the layer of bone just below the cartilage in a joint) BMELs;

⁸ Roche. Naproxen label information. *US Department of Health and Human Services, FDA approved Drug products*. [Online] 2007. [Cited: August 15, 2017.] <https://www.accessdata.fda.gov>.

⁹ <https://www.drugabuse.gov/drugs-abuse/opioids/opioid-crisis>

¹⁰ <https://www.health.harvard.edu/blog/fda-strengthens-warning-that-nsaids-increase-heart-attack-and-stroke-risk-201507138138>

- 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 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.

In addition, over the past 12 months, an additional 30 patients with BMELs and OA have also been treated with PPS by physicians applying for access to the drug under the TGA Special Access Scheme. Paradigm is pleased to 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).

Mr Paul Rennie, Paradigm's Chief Executive Officer said: *"This is an important clinical trial as injectable PPS could be a promising, safe and effective treatment for BMELs in people with knee OA – a condition with significant unmet medical need. Most current 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 recruitment for the trial over the coming weeks."

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