ASX RELEASE

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First Participant Successfully Dosed in Phase 2b Clinical Trial for Osteoarthritis

Key Highlights:

- The first participant in the Phase 2b clinical trial was dosed at Emeritus Research in Malvern East, Victoria.
- This is a randomised, double-blind, placebo-controlled Phase 2b clinical trial investigating the drug pentosan polysulfate sodium vs placebo in people with knee Osteoarthritis and concurrent Bone Marrow Lesions. One hundred participants will be recruited across five trial sites in Queensland, South Australia, Victoria, and Western Australia with results anticipated in Q1 CY2019.
- OA is a condition with a significant unmet medical need: therapeutic market size is US$5bn p.a., while the total economic burden in the US alone, is estimated to be US$128bn[1].
- Injectable PPS has the potential to be a 'break-through' in the treatment of OA. Current therapies do not have adequate pain-relieving effects, provide no protection for the degenerating joint structures and are also associated with significant adverse side effects.
- Recent licensing deal highlights significant potential commercial opportunity for PPS: French pharmaceutical group, Servier, licensed a Phase 1 OA drug candidate for US$346 million for rights to the European region.

Paradigm Biopharmaceuticals Ltd (ASX:PAR) is pleased to announce the first participant was successfully dosed at the clinical trial site - Emeritus Research in Malvern East, Victoria. The participant is the first dosed under the Phase 2b clinical trial of the drug, Pentosan Polysulfate Sodium (PPS), to treat knee osteoarthritis (OA) with concurrent bone marrow lesions (BMLs).

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

In addition, the Paradigm sponsored clinical trial has received strong interest from prospective participants and the Company expects to give an update on the enrolment progress over the coming weeks.

This strong interest follows physician reports of very favourable response in twenty-four patients with OA and BMLs who were treated with Pentosan Polysulfate Sodium (PPS), under the Therapeutic Goods Administration's (TGA) Special Access Scheme (SAS). In the twenty-four patients with a median age of 57.5 years (range 31 to 84 years), joint pain was reduced in 83% and knee function was improved in 80% of all cases treated.
http://www.asx.com.au/asxpdf/20171010/pdf/43n308fhttgqgl.pdf

The announcement of the twenty-four patients treated by their Doctor followed Paradigm's announcement earlier in September of the peer-reviewed published case study of a 70-year-old female treated with PPS by her Doctor. The published case study can be viewed here:
https://bmcmusculoskeletdisord.biomedcentral.com/articles/10.1186/s12891-017-1754-3

Paradigm's randomised, double-blind, placebo-controlled Phase 2b clinical trial will dose a total of one hundred participants across five trial sites in Queensland, South Australia, Victoria, and Western Australia. Participants with OA of the knee and concurrent subchondral bone marrow lesions will be screened for their eligibility into the clinical trial. In these clinical trial participants, injectable (subcutaneous) PPS will be evaluated for safety, tolerability, pain levels and effects on disease symptoms. The trial is being run by Principal Investigator, Associate Professor Andrew Ostor, Paradigm's clinical research partner.

Please see the complete clinical trial details on the ANZCTR website:
https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373400&isReview=true

Results from the trial are expected in Q1 CY2019. A positive result from the trial would be a major valuation inflection point for Paradigm.

In parallel to the one hundred participant randomised, double-blind, placebo-controlled Phase 2b trial, Paradigm will continue to support those Doctors wishing to treat their eligible patients with injectable PPS under the SAS. The OA patients treated under the SAS will provide important supporting Real-World Evidence (RWE) data. These RWE data will be disclosed to the market on a regular basis.

The need for new OA treatments

In addition, OA 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 annum[2] and this figure could potentially be multiples higher if new, effective, patented treatments such a PPS are commercialised.

OA also remains the most common form of joint disease globally. In the US alone, it affects more than 27 million adults[3], 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.

[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

Of particular concern, OA patients globally are increasing prescribed with opioids, which can cause significant risk to patients including addiction, abuse, overdose and potentially life-threatening adverse effects.[4] 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.[5] Additionally, the FDA has warned that taking NSAIDs such as ibuprofen increase the risk of having a heart attack or stroke[6], 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.

Licensing deal highlights significant potential commercial opportunity for PPS

In July this year, French pharmaceutical group, Servier licensed an OA drug, in early clinical development, from Belgian-based clinical-stage biotechnology company, Galapagos for US$346 million for the European region (no US or RoW rights).

The drug, GLPG1972, is a potential cartilage protective oral therapy for OA and is a highly selective inhibitor of ADAMTS-5. The licensing deal was secured after the release of only Phase 1 clinical trial data for the drug.

Unlike GLPG1972, PPS has been shown to inhibit both ADAMTS-5 as well as ADAMTS-4. In addition to PPS' cartilage protective properties it also has anti-inflammatory effects and improves micro-circulation in the subchondral bone.

Mr Paul Rennie, Paradigm's Chief Executive Officer said: *"We are very pleased to confirm the first participant has been treated in this important clinical trial. Injectable PPS could be a promising, safe and effective treatment for OA with concurrent BMLs – a condition with significant unmet medical need. Moreover, the Servier deal for GLPG1972, a Phase 1 drug that only inhibits ADAMTS-5, illustrates the potentially significant commercial value of PPS as PPS inhibits both cartilage destroying enzymes ADAMTS-4 and ADAMTS-5."*

The commencement of participant dosing follows ethics approval being received which confirms that the trial is ethically acceptable and in accordance with relevant standards and guidelines for research involving humans as set out by the Australian National Health and Medical Research Council.

The link between BMEs and OA

[4] 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.
[5] https://www.drugabuse.gov/drugs-abuse/opioids/opioid-crisis
[6] https://www.health.harvard.edu/blog/fda-strengthens-warning-that-nsaids-increase-heart-attack-and-stroke-risk-201507138138

Bone marrow edema lesions (BMLs) 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 BMLs is positively associated with risk of knee joint replacement.

Paradigm hopes that by targeting the resolution of BMLs, 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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