ASX RELEASE

10 October 2017

PARADIGM REPORTS PAIN REDUCTION IN 83% OF OSTEOARTHRITIS PATIENTS

Key Highlights:

- Paradigm reports pain and knee function scores for 24 patients with Osteoarthritis (OA) and Bone Marrow Edema Lesions (BMELs) who have been treated with Pentosan Polysulfate Sodium (PPS) under the TGA Special Access System.
- In the 24 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.
- Results provide important Real-World Evidence data; US FDA allows the use of this data to be used in combination with Randomised Controlled Clinical Trials to support product registration for repurposed pharmaceuticals under the 505(b)(2) regulatory pathway.
- Paradigm plans to generate an additional 75 case studies by Q4 CY2018 in addition to the results of its Phase 2b randomised, double-blind, placebo-controlled clinical trial which commenced in September 2017.
- 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].

Paradigm Biopharmaceuticals Ltd (ASX:PAR) is pleased to announce the results of 24 patient case studies with Osteoarthritis (OA) and Bone Marrow Edema Lesions (BMELs) that were treated with Pentosan Polysulfate Sodium (PPS) under the Therapeutic Goods Administration's (TGA) Special Access System.

These results follow the release of the published case study of PPS in an additional patient with OA and BMELs in September 2017. The published case study can be viewed here: https://bmcmusculoskeletdisord.biomedcentral.com/articles/10.1186/s12891-017-1754-3

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

In these 24 additional patients, joint pain was reduced in 83% and knee function was improved in 80% of all cases treated.

Details of case study patients and outcomes

The 24 patients [15 males and 9 females, median age of 57.5 years (range 31 to 84 years)] had been clinically diagnosed with OA and subchondral BMELs through an MRI. At the onset of PPS treatment:

- All patients were symptomatic with OA pain for at least 6 months and had failed current standard of care which involved treatment with analgesics, NSAIDs (non-steroidal anti-inflammatory drugs) or corticosteroids.
- 70% of the patients had moderate to severe BMELs with a size ranging from five millimetres to more than 20 millimetres in diameter.
- 30% had lesions less than five millimetres in diameter.

Patients were administered two injections of PPS per week for three weeks (a total of six injections) and followed up at six weeks following the initiation of treatment. During the course of PPS treatment, patients did not receive NSAIDs or corticosteroid treatment.

At six weeks after the initiation of PPS treatment:

- 20 out of 24 patients (83.3%) showed a reduction in pain;
- Of the 15 out of those 20 patients that showed a reduction in pain, 75% showed a reduction of 50% or more;
- In addition, 19 out of 24 patients (79.1%) showed an improvement in knee function; and
- 9 out of those 19 patients (47.3%) showed an improvement in knee function scores of 50% or more.

Importance of case study data

These case studies are important to Paradigm as they provide Real World Evidence (RWE) data – i.e. the data from sources other than traditional clinical trials. The United States Food and Drug Administration (US FDA) allows RWE data to be used in combination with Randomised Controlled Clinical Trials (RCCT) to support product registration for repurposed drugs such as PPS under the FDA 505(b)(2) regulatory pathway. (For further details on RWE data, please see section towards the end of this announcement).

In addition to the 24 case studies, Paradigm plans to generate an additional 75 case studies by Q4 CY2018. These additional 75 case studies will be administered with increased doses compared to the first 24 cases. This means by Q4 CY2018, Paradigm will have RWE data on 100 case studies in addition to the results of its Phase 2b randomised, double-blind, placebo-controlled clinical trial, which commenced in September 2017 and will enroll a total of 100 patients.

Details about Paradigm's Phase 2b clinical trial can be found on the Australian and New Zealand Clinical Trial Registry website:
https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373400&isReview=true

Proposed RWE cases planned:

- 24 cases dosed with 2.0mg/Kg PPS twice a week for three weeks (complete);

- 25 cases dosed with 2.0mg/Kg PPS twice a week for four weeks;
- 50 cases dosed with 2.0mg/Kg PPS twice a week for six weeks.

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 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.

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 year[5], 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, 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 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

[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.

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 stroke[10], 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.

About RWE data

With the signing of the 21st Century Cures Act in December 2016, the US Congress tasked the FDA with developing a framework to evaluate how the use of data from sources other than traditional clinical trials may be used to support drug approvals. This brings a further advantage to sponsors utilising the 505(b)(2) pathway, in addition to the already recognised benefit of streamlined development programs.

The act amended the US Federal Food, Drug, and Cosmetic Act by inserting, among other things, a provision to assess the potential for use of Real-World Evidence (RWE) in drug approval programs.

The act defines RWE as 'data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.' The sources of data include 'ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities.'

Typically, RWE is not be available for use with a new drug, but can be applicable to products suitable for approval via the 505(b)(2) pathway (Repurposed Drugs).

[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

FOR FURTHER INFORMATION PLEASE CONTACT:

Paul Rennie
Director & CEO
Paradigm Biopharmaceuticals Ltd
Level 2, 517 Flinders Lane, Melb, VIC, 3000, AUSTRALIA
ABN: 94 169 346 963
Web: http://paradigmbiopharma.com/
Email: prennie@paradigmbiopharma.com
Mobile International: +61 437 778 300
Mobile (Australia): 0437 778 300