PARADIGM BIOPHARMACEUTICALS LIMITED (PAR)

ASX RELEASE 7 August 2019

PARADIGM FILES FIRST IND WITH US FDA

KEY HIGHLIGHTS

- **Paradigm has filed its first IND submission to the US FDA for an Expanded Access Program under which ten people from the USA may be treated with Zilosul® (iPPS).**
- **The ten Americans are anticipated to include some retired NFL players who have early-onset Osteoarthritis and have also failed standard of care.**
- **In males under the age of 60, osteoarthritis is over 3 times more prevalent in retired NFL players than in the general U.S. population. This excess of early-onset arthritis may be due to the high incidence of injury in football[1].**
- **Paradigm's Clinical and Regulatory Teams continue to work on submissions to the US FDA for the Phase 2/3 Clinical Trial in the very rare lysosomal storage disease (MPS), the Phase 3 Clinical Trial in Osteoarthritis and the Australian Therapeutic Goods Administration for the Provisional Approval of Zilosul® (iPPS) to treat Osteoarthritis.**
- **Commercial discussions are ongoing regarding potential partnership deals or commercial transactions.**

Moving towards commercialisation

Paradigm Biopharmaceuticals Ltd (ASX: PAR) continues its drive towards commercialisation of Zilosul® (iPPS) as a potential first line therapeutic treatment of osteoarthritis and other diseases affecting the musculoskeletal system.

Paradigm will be filing a number of submissions to Global Regulatory Authorities and therefore provides this update on the planned filings being submitted in the next two quarters of CY 2019.

Summary of Expected future market updates prior to end of CY 2019:

- **File Expanded Access Program (EAP) for 10 patients with US FDA Q3 CY 2019;**
- **File initial submission with the TGA for Provisional Approval Application of Zilosul® (iPPS) for treatment of osteoarthritis, Q3 CY 2019;**
- **Pre-IND meeting with US FDA Orphan Indication (MPS) Phase 2/3 clinical Trial Q4 CY 2019;**
- **Pre-IND Meeting with US FDA Osteoarthritis Phase 3 Clinical Trial Q4 CY 2019;**
- **Commercial Discussions – ongoing;**

[1] Golightly YM et al Early-onset arthritis in retired National Football League players, J Phys Act Health. 2009 Sep;6(5):638-43.

- **Discussions with US DoD for Ross River/CHIK-V treatment – ongoing.**

Paradigm Expanded Access Program

Paradigm has filed a submission to the US FDA for Expanded Access Program IND (Investigational New Drug) under which ten people from the USA may be treated with Zilosul® iPPS and it is anticipated to include some retired NFL players who have early-onset Osteoarthritis who have also failed standard of care.

What is The FDA Expanded Access Program?

"Expanded access", also called "compassionate use," provides a pathway for patients to gain access to investigational drugs, biologics, and medical devices used to diagnose, monitor, or treat patients with serious diseases or conditions for which there are no comparable or satisfactory therapy options available outside of clinical trials"[2].

FDA recognizes that osteoarthritis (OA) can be a serious disease with an unmet medical need for therapies that modify the underlying pathophysiology of the disease and potentially change its natural course to prevent long-term disability.

Through this Expanded Access Program (EAP), Paradigm (the Sponsor) seeks to provide Zilosul® (iPPS) to a limited number of patients who have failed other conservative therapies (standard of care), and for whom access is requested by the treating physician. The Sponsor plans to further its understanding of the potential utility of Zilosul® (PPS) for the treatment of BML-associated pain and joint stiffness in a small group of knee OA patients while it prepares applications for a larger Phase 3 clinical trial.

The unmet clinical need

Osteoarthritis (OA) is a disabling disease leading to chronic pain, disability and a decreased quality of life. It is the most common joint disorder in the developed world, with the lifetime risk of developing symptomatic knee osteoarthritis before age 85 years estimated in one US study at 44.7% ([95% CI] 40.0–49.3%)[3].

Injury, particularly to the joints, has been identified as a potential risk factor for OA. Annually, sports contribute to 7 million injuries in Americans, and reports have suggested that the development of OA may be more prevalent and occur prematurely in individuals who regularly participate in sports. In addition, a strong association between post-traumatic injury history incurred during sporting activity and OA has been reported by Golightly et al (2009)[4]. It is estimated, 31 million people in the USA suffer from OA[5]. The therapeutic market for the treatment of OA is a multibillion-dollar opportunity.

Although loss of joint cartilage is a hallmark of OA, it is increasingly recognized that bone marrow edema lesions (BMLs) in the subchondral bone are involved with the pathogenesis of cartilage degeneration in OA. BMLs (as detected on MRI) result from increased blood and interstitial fluid collection in areas of trabecular microfractures and collapse within the bone marrow[6]. The prevalence

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[2] https://www.fda.gov/news-events/public-health-focus/expanded-access

[3] Murphy L, Schwartz TA, Helmick CG, Renner JB, Tudor G, Koch G, Dragomir A, Kalsbeek WD, Luta G, Jordan JM. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum. 2008; 59:1207-13. doi: 10.1002/art.24021

[4] Golightly, Yvonne & W Marshall, Stephen & Callahan, Leigh & Guskiewicz, Kevin. (2009). Early-Onset Arthritis in Retired National Football League Players. Journal of physical activity & health. 6. 638-43. 10.1123/jpah.6.5.638.

[5] Arthritis By The Numbers, US Arthritis Foundation. https://www.arthritis.org/Documents/Sections/About-Arthritis/arthritis-facts-stats-figures.pdf

[6] Starr, A.M., Wessely, M.A., Albastaki, U., Pierre-Jerome, C., and Kettner, N.W. (2008). Bone marrow edema. Pathophysiology, differential diagnosis, and imaging. Acta radiologica (Stockholm, Sweden: 1987) *49*, 771-786.

and severity of BMLs are associated with symptoms of pain[7], greater cartilage loss and risk of joint replacement[8]. In regard to progressive osteoarthritis, data have suggested that BMLs are more likely to persist and enlarge in size with an associated increase in cartilage loss[9]. Further, BMLs, synovitis and effusion have been associated with long-term risk of total knee arthroplasty (TKA) and increasing degree of changes were associated with faster progression to TKA[10].

Paradigm's Bone Marrow Edema Lesion (BML) clinical data.

Paradigm's successful Phase 2b clinical trial reported (objective data) the secondary end-point of Bone Marrow Edema Lesion (BML) **Grade** by MRI demonstrated that number of subjects receiving iPPS treatment had a clinically meaningful reduction in the Grade of their BML compared to placebo. The iPPS group's reduction was also statistically significant over placebo at 50% vs 27.3% (P=0.03) by Chi-squared analysis.

Given the unmet clinical need in OA and Paradigm's positive BML Phase 2b clinical data, US Physicians are requesting access to iPPS where standard of care has failed.

Early Onset of Osteoarthritis in Retired NFL Footballers.
In males under the age of 60, arthritis is over 3 times more prevalent in retired NFL players than in the general U.S. population. This excess of early-onset arthritis may be due to the high incidence of injury in football[11].

What is an FDA IND?
An Investigational New Drug Application (**IND**) is a request for authorization from the US Food and Drug Administration (**US FDA**) to administer an investigational drug or biological product to humans.

If the IND is cleared by the US FDA, within 30 days, treatment of the retired NFL players could occur in September 2019.

Q2 CY 2019 Milestones already achieved:

- **Pain reduction Mechanism of Action (MoA) of iPPS in osteoarthritis complete and manuscript has been sent for peer review and publication.**
- **Reported on 205 patients treated by their Doctor under the TGA SAS with an average pain reduction of > 50% from baseline.**
- **Reported on the successful Phase 2a Ross River Clinical Trial.**
- **Employed 5 new Clinical and Regulatory Staff;**
- **Completed cGMP Manufacturing of Phase 3 product.**
- **Face-to-Face Meetings with Key Pharmaceutical Companies in Europe and Japan.**
- **Completed the successful capital raise which strengthened the shareholder register;**

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[7] Felson, D.T., Chaisson, C.E., Hill, C.L., Totterman, S.M., Gale, M.E., Skinner, K.M., Kazis, L., and Gale, D.R. (2001). The association of bone marrow lesions with pain in knee osteoarthritis. Ann Intern Med *134*, 541-549.

[8] Tanamas, S.K., Wluka, A.E., Pelletier, J.-P., Pelletier, J.M., Abram, F., Berry, P.A., Wang, Y., Jones, G., and Cicuttini, F.M. (2010). Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement. A longitudinal study. Rheumatology (Oxford, England) *49*, 2413-2419.

[9] Hunter, D.J., Zhang, Y., Niu, J., Goggins, J., Amin, S., LaValley, M.P., Guermazi, A., Genant, H., Gale, D., and Felson, D.T. (2006). Increase in bone marrow lesions associated with cartilage loss. A longitudinal magnetic resonance imaging study of knee osteoarthritis. Arthritis Rheum. *54*, 1529-1535.

[10] Risk factors for joint replacement in knee osteoarthritis; a 15-year follow-up study https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5715644/

[11] Golightly YM et al Early-onset arthritis in retired National Football League players, J Phys Act Health. 2009 Sep;6(5):638-43.

- **Established a scientific advisory committee for Orphan indication for the rare disease Mucopolysaccharidosis (MPS).**

About injectable iPPS (Zilosul®)

Injectable PPS is not currently registered in Australia, but it is registered in four of the seven major global pharmaceutical markets. In those European markets, injectable PPS is registered as an antithrombotic agent. In Australia, injectable PPS for human use is not currently available for sale. Injectable PPS for human use is only available by inclusion into a Paradigm Sponsored clinical trial or via a treating physician applying for its use in patients via the TGA's SAS - Category B.

To learn more please visit: www.paradigmbiopharma.com

Zilosul® is a registered Trademark of Paradigm Biopharmaceuticals Ltd.

Zilosul® is the registered Trademark of the final product i.e. injectable Pentosan Polysulfate Sodium (iPPS).

For more information, please contact

CORPORATE ENQUIRES

Paul Rennie
Director & CEO
Paradigm Biopharmaceuticals Ltd
E: info@paradigmbiopharma.com