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PARADIGM's INVESTIGATIONAL NEW DRUG (IND) APPLICATION CLEARED BY THE US FDA.

PHASE 3 STUDY IN KNEE OA CAN COMMENCE IN USA.

KEY HIGHLIGHTS

- Paradigm's IND application to commence its phase 3 pivotal clinical trial investigating Pentosan Polysulphate Sodium (PPS) for the treatment of pain associated with knee osteoarthritis (the Trial) has been cleared by the US FDA.
- The US central ethics committee has already approved the Trial.
- Australian ethics approval for the Trial was previously announced on 24 September 2021.
- Approximately 65 sites have been identified throughout the US and Australia. Contracting with many of those sites has been completed. The first 4 sites in Australia have initiated screening participants. Screening at the US sites is expected to begin prior to the end of CY2021.
- The Company is now in a position to accelerate recruitment by adding approximately 10 sites in the United Kingdom (UK) and Europe, with site initiation and subject screening expected to commence in 1H CY 2022.

Paradigm Biopharmaceuticals Ltd (ASX: PAR) ("Paradigm" or "the Company"), a clinical stage biopharmaceutical company focussed on repurposing existing molecules for new indications with unmet clinical needs, is pleased to report that the US Food and Drug Administration (**FDA**) has cleared its IND application to proceed with a phase 3 trial, evaluating injectable pentosan polysulfate sodium (**PPS/Zilosul®)** for the treatment of pain associated with knee osteoarthritis.

The FDA gave notice to Paradigm that the IND Is now "open" allowing the Company to commence the Trial. The FDA advised that the Company's responses sufficiently addressed the questions raised by the FDA in regard to the IND application submitted on 26th March, 2021[1].

Clearance to commence the Trial is supported by 26 non-clinical studies that Paradigm conducted, including studies that inform of the tolerance profile of PPS, its pharmacokinetics profile and information needed to formulate an initial dose-finding stage which is designed to identify the minimal effective dose.

Central ethics committee (US) approval has been received with the Company now focussed on site initiation in the US. Patients are expected to begin screening in both the US and Australia during Q4 2021. Ethics approval had already been achieved in Australia and the first 4 of 8 sites have been initiated, with the remaining sites expected to be initiated prior to the end of CY2021.

In addition to commencing in the US and Australia, Paradigm is also entitled to commence clinical trials in EU member countries. As a result, Paradigm has a clear harmonised path to global approval of Zilosul®.

Ten sites in Europe and the United Kingdom have been identified and are expected to be initiated and subject screening commencing 1H CY 2022. Paradigm will provide a further update once first patient milestones are achieved and include a detailed overview of the clinical trial design and proposed timelines for completion of the Trial.

About the Trial (PARA_OA_002)

The purpose of the Trial is to measure the change in pain and function after subcutaneous injections of PPS compared with subcutaneous injections of placebo in participants with knee osteoarthritis pain.

This is a 2-stage, adaptive, randomised, double-blind, placebo-controlled, multicentre (US/AUS/UK/EU) study that will evaluate the dose and treatment effect of PPS in participants with pain associated with knee osteoarthritis.

The primary endpoint in the Trial will be change from baseline at Day 56 in WOMAC® pain with secondary outcomes to include change from baseline at multiple time points out to day 168 in WOMAC® Pain and Function, Patient Global Impression of Change (PGIC) and Quality of Life (QoL).

Observational Follow-up

The PARA_OA_006 observational study is designed as a follow-up to the Trial, which will evaluate the duration of treatment effect and safety up to 60 weeks following first injection with PPS in the Trial. All participants who complete the Trial will be invited to participate in the follow-up study. Paradigms previous phase 2b study completed in Australia followed patients out to day 165, so this follow-up study will provide important additional data on the duration of effect of PPS on patients over 12 months post treatment. The data collected in this follow-up is expected to be highly valuable for the Zilosul® label and reimbursement discussions once registration can be achieved.

Mr Paul Rennie, Paradigm CEO and Interim Chair said: "*The opening of the Trial in the USA – the largest global pharmaceutical market, is a major milestone for the Company. This milestone represents a substantial de-risking of the Company's lead clinical program and is a testament to the Company's expertise, commitment and determination. As the Company progresses with the Trial, we expect there will be increasing interest from the pharmaceutical industry in the commercial value of this potential blockbuster therapeutic".*

Market Potential in Osteoarthritis

Osteoarthritis (OA) is the most prevalent form of joint disease, affecting up to 16% of the population in the developed world, with more than 72 million people in the US, EU5, Canada and Australia suffering from osteoarthritis.[2]

OA has a significant impact on day-to-day functioning and, although the levels of pain and disability may fluctuate, it has no known cure or spontaneous remission and is associated with irreversible structural damage and progression over time. Presently there are no drugs approved that can prevent, stop, or even restrain progression of OA. Moreover, the available medications that claim to mitigate the pain of OA have numerous

risk/benefit considerations and market research indicates that only 19% of knee OA patients are satisfied with currently available treatments. [3,4]

The prevalence of OA is increasing in line with the aging population and increasing rates of obesity. By 2030 the number of people suffering from OA in the US alone is predicted to increase by 86% to 67 million.[3] If we assume a similar increase across the other markets defined above, even allowing for lower rates of obesity in non-US markets, it is plausible that more than 120 million people will be suffering from osteoarthritis by 2030.

About injectable PPS

Pentosan polysulfate sodium (PPS) is a medication that has been used in humans for over 60 years. Injectable PPS has previously been approved in European markets, where it is registered as an antithrombotic agent. In Australia, injectable PPS for human use is not currently available for sale. Injectable PPS is available via a Paradigm sponsored clinical trial or under the TGA Special Access Scheme to physicians for individual patients who satisfy strict criteria and is subject to approval from the TGA. Elmiron (the oral formulation utilised for interstitial cystitis) is the only PPS product approved in the US. A subcutaneous injectable formulation of PPS is currently being evaluated by Paradigm for the treatment of osteoarthritis and other inflammatory diseases in the US and other major global markets.

About Paradigm Biopharmaceuticals

Paradigm Biopharmaceuticals LTD (ASX: PAR) is a late-stage drug development company with the mission to develop and commercialise pentosan polysulfate sodium for the treatment of pain associated with musculoskeletal disorders driven by injury, inflammation, ageing, degenerative disease, infection or genetic predisposition. Paradigm is also investigating proof-of-concept for the use of PPS in respiratory and heart failure indications.

Forward Looking Statements

This Company announcement contains forward-looking statements, including statements regarding anticipated commencement dates or completions dates of preclinical or clinical trials, regulatory developments and regulatory approval. These forward-looking statements are not guarantees or predictions of future performance, and involve known and unknown risks, uncertainties and other factors, many of which are beyond our control, and which may cause actual results to differ materially from those expressed in the statements contained in this presentation. Readers are cautioned not to put undue reliance on forward-looking statements.

References:

1. ASX Announcement 27th May 2021, Paradigm delivers IND to US FDA for Pivotal OA Program. https://asx.api.markitdigital.com/asx-research/1.0/file/2924-02357703-3A564234?access_token=83ff96335c2d45a094df02a206a39ff4.
2. Global Health Data Exchange, Institute for Health and Metrics Evaluation, University of Washington. Accessed June 2021 http://ghdx.healthdata.org/gbd-results-tool
3. OARSI. Osteoarthritis: A Serious Disease, Submitted to the U.S. Food and Drug Administration December 1, 2016
4. Matthews GL, Hunter DJ. Emerging drugs for osteoarthritis. Expert Opin Emerg Drugs. 2011;16(3):479-491. doi:10.1517/14728214.2011.576670

Authorised for release by the Paradigm Board of Directors.

Zilosul® is a registered Trademark of Paradigm Biopharmaceuticals Ltd (ASX: PAR).

To learn more please visit: www.paradigmbiopharma.com

FOR FURTHER INFORMATION PLEASE CONTACT:
Simon White
Director of Investor Relations
Tel: +61 404 216 467
Paradigm Biopharmaceuticals Ltd
ABN: 94 169 346 963
Level 15, 500 Collins St, Melbourne, VIC, 3000, AUSTRALIA
Email: investorrelations@paradigmbiopharma.com