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Second site initiated in Paradigm's PARA_OA_008 Synovial Fluid Biomarker Study in participants with knee Osteoarthritis (OA).

KEY HIGHLIGHTS

- Ethics committee approval received for the amendment to the Phase 2 study to evaluate the treatment effect of pentosan polysulfate sodium (PPS) (Zilosul®) compared with placebo on synovial fluid biomarkers in participants with knee OA pain.
- The study is investigating changes in synovial fluid biomarkers associated with pain, inflammation and disease progression of OA.
- To date 30 subjects have been randomised to either PPS twice weekly or placebo and have completed the treatment phase. Paradigm has added a once weekly dosing regimen to the trial design with the remaining 30 subjects to be enrolled using a randomisation scheme which will provide a balanced number of patients to each treatment group according to 1:1:1 ratio by the end of the trial (i.e., 20 randomised to PPS twice-weekly, 20 randomised to PPS once-weekly, 20 randomised to placebo).
- A second trial site in NSW has been initiated to assist with patient recruitment (which has been slowed due to Victorian lockdowns), to broaden the geographic footprint and converting the study to a multicentre study.
- An additional follow-up period to 12-months has also been accepted by the ethics committee to assist Paradigm gather additional data on the medium-long term combined structure-modifying and symptom-modifying effects of PPS on Knee OA (KOA).
- The additional follow-up period to 12 months and the disease modifying synovial fluid biomarkers are important to the Company to support maximum reimbursement price for Zilosul® once registered.
- Ethics approval for translational study in canine OA model for evaluating disease modification by PPS has been obtained.

Paradigm Biopharmaceuticals Ltd (ASX: PAR) (Paradigm or the Company) clinical stage biopharmaceutical company focussed on repurposing existing molecules for new indications with unmet clinical needs, wishes to provide an update on its phase 2 clinical trial to evaluate the treatment effects of pentosan polysulphate sodium (**PPS**) against placebo on synovial fluid biomarkers in participants with knee osteoarthritis pain. Paradigm submitted a number of changes to the Human Research Ethics Committee (**HREC**) for the PARA_OA_008 clinical trial protocol. The amendments include the initiation of an additional site in NSW, a once weekly dosing regimen and extension of the follow-up from 6 to 12 months.

The randomised, double-blind, placebo-controlled phase 2 study will enrol a total of 60 (n=60) patients and hopes to provide evidence that certain biomarkers are more prevalent in the synovial fluid of symptomatic OA patients with radiographic evidence of joint

damage. The clinical trial is also designed to determine changes in biomarker concentrations in the synovial fluid with PPS treatment, and to assess possible disease modifying effects of PPS in patients with knee OA pain.

The biomarker analysis in synovial fluid samples aims to provide scientific evidence to test the hypothesis that PPS acts locally in the knee joint of OA subjects. If positive, the biomarker data will support the multiple proposed pathways of action of PPS in OA. In contrast to date, many single pathway agents have failed to demonstrate meaningful clinical outcomes of improved pain and/or function. The biomarkers analysed will include inflammatory cytokines (TNF-α, IL-1β and IL-6); pain mediator NGF and cartilage degrading enzymes ADAMTS-4 and -5 in association with structural analysis of change involving X-ray and MRI.

To date, 30 subjects have been randomised in the PARA_OA_008 clinical trial between PPS twice weekly dosing or placebo. All subjects have completed the treatment course and reached day 56, the primary endpoint for the study.

Amendment to Trial Design

The purpose of Paradigm's Phase 2 study is to measure the changes in synovial fluid biomarkers associated with inflammation and OA disease progression following treatment with subcutaneous injections of PPS compared with subcutaneous injections of placebo in participants with knee OA. Sixty (n=60) participants with Kellgren-Lawrence grade 2, 3 or 4 and OA pain will be enrolled and randomised to receive either PPS or placebo. The following amendments have been approved by HREC.

Additional Trial Site

Following 30 subjects completing randomisation at the Victorian site in Box Hill, recruitment for PARA_OA_008 was paused to update the clinical trial protocol to include an additional site to broaden the geographic footprint creating a multicentre study. An additional trial site has been initiated in Newcastle, NSW to assist with the remaining 30 subjects to be recruited into the Phase 2 study. Recruitment will now re-commence at both sites.

Once Weekly Dosing

Once weekly dosing regimen is part of the dose-ranging stage of the large Phase 2/3 study. Paradigm has added a once weekly dosing regimen to the trial design with the remaining 30 subjects to be enrolled using a randomisation scheme which will provide a balanced number of patients to each treatment group according to 1:1:1 ratio by the end of the trial (i.e., 20 randomised to PPS twice-weekly, 20 randomised to PPS once-weekly, 20 randomised to placebo). Addition of once weekly arm to this study provides an opportunity to evaluate the effects of once-weekly dosing regimen on biomarkers compared to twice weekly regimen and placebo.

Extension of Follow-up

The original protocol for PARA_OA_008 detailed that Paradigm would assess a number of key secondary and exploratory endpoints in the Phase 2 study to 6-months or Day 168.

Given that patients with knee osteoarthritis (KOA) live with their condition for an average of 30-years and to enable improved clinical acumen in managing the disease, KOA management algorithms are shifting from a short- to long-term viewpoint, with a focus on the long-term safety and efficacy of the treatment options.

Furthermore, recently completed market access research with key physicians and funding bodies (payers) in the US and Europe found that longer follow-up is preferred to support safety and efficacy claims for products that manage the symptoms and potentially attenuate disease progression in OA.

With the extension of follow-up out to 12-months in PARA_OA_008, the Company aims to gather pilot data for the medium-long term combined structure-modifying and symptom-modifying effects of PPS on KOA.

Why Paradigm has made these changes to the PARA_008 protocol

Paradigm has undertaken market access research with KOLs, patients and payers in the US and Europe to better understand the reimbursement potential for the indication of pain and function in the US. The recently received research report, indicated that demonstration of a durable effect on pain and function (up to 12 months) and long-term data to support claims of disease modification support maximal reimbursement potential in government funded markets. To inform our future clinical studies exploring the disease modifying effects of PPS in the treatment of OA, Paradigm is extending the duration of follow-up in PARA_OA_008 to 12 months.

PARA_OA_008 Updated Timelines

The Phase 2 study was paused to amend the protocol for the addition of a second trial site and the weekly dosing regimen. As a result, the timeline for primary analysis readout is adjusted to Q3 2022.

Translational Studies with the Canine OA Model for Evaluating Disease Modification by PPS

To support in vivo mechanism of action of PPS for disease modification and provide complimentary data to parallel the PARA_OA_008 human clinical trial, Paradigm is also conducting a trial in dogs with naturally occurring osteoarthritis in U-Vet Werribee Animal Hospital. Paradigm has received ethics approval to commence the proposed investigation.

Since the pathophysiology of OA is similar in humans and dogs it is expected that the canine model of OA would provide relevant translational data that parallel the human clinical scenario[1]. Moreover, human and canine OA occurs in a progressive manner and is influenced by similar risk factors. The joints primarily affected by OA in humans such as the knee, hip and shoulder closely resemble the pathological changes observed in canine stifle (knee), hip and shoulder joints[1]. Although the lifespan of the dog is shorter relative to that of humans, all stages of development from birth to adulthood and aging are represented over a shorter time frame including disease onset and manifestation[1]. This aspect of the canine model is potentially advantageous in the rapid evaluation of disease modifying OA drugs (DMOAD) that require longer assessment periods in humans for OA joint structural changes.

In the proposed investigation, dogs with osteoarthritis of the stifle joint are treated with PPS at a dosing of 3mg/kg (1.7mg/kg human equivalent) subcutaneous weekly for 6-weeks. Clinical outcomes of pain and function will be assessed together with structural changes from baseline as determined by the global OA score measured by X-ray and bone marrow lesions and cartilage volume by MRI. In addition, molecular biomarkers associated with inflammation, cartilage degradation and pain will be assessed in the synovial fluid and serum to ascertain correlations with clinical outcome measures of pain

and function and structural changes. The longer follow up period of 20 weeks (equates on average to a period of 3 years in human lifespan) from the cessation of treatment in the study will assess the durability of response and structural changes following therapy. The collective analyses of pain, function, joint structure, and biomarker levels following PPS therapy will provide informative data to assess the potential of PPS as a DMOAD.

Current OA therapies such as paracetamol, opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) are focused on symptom management and there are no established disease modifying therapies in OA. Due to patient dissatisfaction[2] with current treatment for OA there is a high unmet medical need for new therapies that are effective in reducing pain, improving joint function and impeding the progression of OA in association with symptomatic improvement.

Dr Donna Skerrett, Paradigm's Chief Medical Officer said:

"Paradigm is embarking on a number of approaches to further value PPS in the knee OA indication by exploring synovial biomarkers and evaluating duration of effect in clinical studies. Simultaneously, we are enhancing our understanding of mechanism of action and disease modifying potential by evaluating PPS in a canine OA study. The combined information of these two studies will allow us to assess the potential disease modification capability of our OA program while we initiate the phase 2/3 pivotal study activity to assess PPS safety and efficacy for the pain and function indication. We are excited about moving forward with these additional studies as well as initiating our phase 2/3 global clinical program for knee OA global registration."

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 Para_OA_008

Osteoarthritis (OA) is a heterogenous and chronic disease of the whole joint which is progressive with persisting symptoms of pain and joint function experienced by patients. The disease pathogenesis in OA is mediated by inflammation, cartilage degradation, and adverse remodelling of the subchondral bone. Pre-clinical and clinical evidence to demonstrate that PPS is active through multiple modes of action including decreasing inflammation by down-regulating inflammatory cytokines, reducing pain by reducing the production of NGF, protecting cartilage by downregulating degrading enzymes and repairing bone through improved blood flow. Until now these have all been evaluated by

measuring serum biomarkers which do not define the local biomarker changes within the OA joint. Therefore, the PARA_OA_008 study will evaluate molecular biomarkers in the synovial fluid to demonstrate the potential disease modifying effect of PPS on the diseased joint.

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.

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. Meeson RL, Todhunter RJ, Blunn G, Nuki G, Pitsillides AA. Spontaneous dog osteoarthritis - a One Medicine vision. Nat Rev Rheumatol. 2019 May;15(5):273-287
2. National Institute of Health; Emerging drugs for osteoarthritis; Hunter DJ and Matthews G 16(3): 479–491; 2011 September

Authorised for release by the Paradigm Board of Directors.

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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