

Ethics Approval Received for Paradigm's PARA_OA_008 Synovial Fluid Biomarker Study in Participants with Knee OA.

BACKGROUND

Osteoarthritis (OA) is a heterogeneous and chronic disease of the whole joint which is progressive with persisting symptoms of pain and deteriorating joint function experienced by patients. The disease pathogenesis in OA is mediated by inflammation, cartilage degradation, adverse remodelling of the subchondral bone. Pre-clinical and clinical evidence 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 modalities have all been evaluated by measuring serum biomarkers which may not reflect local biomarker changes within the OA joint. Therefore, the PARA_OA_008 study will evaluate molecular biomarkers in the synovial fluid to demonstrate the mechanism of action and disease modifying potential of iPPS on the diseased joint.

KEY HIGHLIGHTS

- Ethics committee approval received for Phase 2 exploratory study to evaluate the Treatment Effect of Pentosan Polysulfate Sodium (PPS) (Zilosul®) compared with Placebo on Synovial Fluid Biomarkers in participants with Knee Osteoarthritis (OA) Pain.
- The study will investigate changes in synovial fluid biomarkers associated with pain, inflammation and disease progression of OA.
- Trial will recruit sixty (n=60) participants from one site in Victoria.
- Primary endpoints will assess a change from baseline to day 56 in synovial fluid biomarkers.
- Secondary endpoints to include:
 - Correlation between synovial fluid biomarker changes and clinical outcomes,
 - Changes from baseline at 6 months in one or more synovial fluid biomarker,
 - Changes from baseline at designated timepoints of WOMAC® Pain, Function, Stiffness and Quality of life (PGIC), and
- Exploratory endpoints will assess radiographic changes in the bone and joint of participants from baseline to day 168.
- Patient recruitment and screening to begin imminently, with first patient dosing expected in Q2, CY2021.
- Primary Endpoint data readout expected in Q3.

- Paradigm believes biomarker data collected from this study will strengthen the application package to be submitted to the TGA for provisional approval.
 - Paradigm remains on track to submit its Investigational New Drug (IND) application to the FDA during the quarter.
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Paradigm Biopharmaceuticals Ltd (ASX: PAR) is pleased to announce it has received ethics approval for its phase 2 clinical trial to evaluate the treatment effects of Pentosan Polysulfate Sodium (PPS) against placebo on synovial fluid biomarkers in participants with Knee Osteoarthritis Pain.

The randomised, double-blind, placebo-controlled phase 2 study will investigate PPS or placebo treatment in a total of 60 (n=60) patients. Primary endpoint data expected to read out in Q3, CY2021. With this study, Paradigm hopes to provide further evidence that certain biomarkers are more prevalent in the synovial fluid of symptomatic OA patients with radiographic evidence of joint damage¹, determine if biomarker concentrations change in the synovial fluid with PPS treatment, and to assess possible disease modifying effects of PPS on patients with Knee OA pain.

The biomarker analysis in synovial fluid samples will provide key scientific evidence as to whether PPS is acting locally in the knee joint of OA subjects and may further support the multiple actions of PPS in OA. The biomarkers analysed will include inflammatory cytokines (TNF- α , IL-1 β and IL-6); pain mediator NGF and cartilage degrading enzymes ADAMTS4 and 5 in association with other molecular biomarkers potentially associated with disease modification. The data will be part of the submission package to the TGA for provisional approval.

Primary Endpoint

The Primary Endpoint for PARA_OA_008 will be change from baseline at day 56 (two weeks post final injection) in one or more synovial fluid biomarkers. The biomarkers that will include but not limited to:

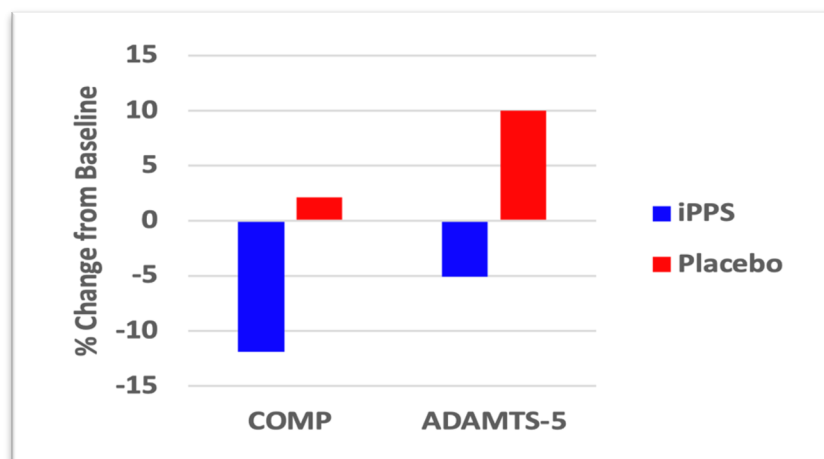
- Cartilage Oligomeric Matrix Protein (COMP);
- C-Terminal Telopeptide (CTX) -II;
- Nerve Growth Factor (NGF);
- Interleukin (IL) -1 β ;
- Tumour Necrosis Factor Alpha (TNF α);
- IL-6;
- A disintegrin and metalloproteinase with thrombospondin motif 5 (ADAMTS-5);
- Aggrecan ARGS fragment;
- Tissue inhibitor matrix metalloproteinase 1 (TIMP-1);
- CTX-I; and
- Type II collagen fragment (C2C).

The biomarkers evaluated in this study are among the biomarkers most often associated with OA symptoms (pain and inflammation), and disease progression (cartilage

degradation). Literature suggests that PPS may be a potential treatment for OA because PPS has been shown to exert anti-inflammatory activity by blocking the effects of proinflammatory cytokines, such as $\text{TNF}\alpha$ and $\text{IL-1}\beta$, associated with OA (Sunaga et al, 2012²); inhibit the expression of NGF, a pain mediator, in osteocytes in subchondral bone of OA (Stapledon et al, 2019³); and inhibit cartilage degrading enzymes known to play a key role in OA disease progression (Troeberg et al, 2012⁴). In small clinical studies, PPS has been shown to reduce pain and improve joint function in patients with knee OA (Ghosh et al, 2005⁵, Kumagai et al, 2010⁶).

Paradigm has previously reported exploratory endpoint data from its Phase 2B OA Clinical Trial (August 2019) where it demonstrated a reduction of two key biomarkers (COMP and ADAMTS-5) in the serum which are associated with cartilage degradation, in patients treated with Zilosul® compared to increase levels placebo.

Figure 1: Mean percentage changes of the biomarkers comp and ADAMTS-5 in the serum of subjects treated with IPPS or placebo (Paradigm's Phase 2b OA clinical trial (n=112)).



(Refer ASX announcement 29th August 2019)

Among subjects with symptomatic knee OA, a single measurement of increased COMP predicted subsequent cartilage loss on MRI. (Hunter et al, 2007^[7])

Secondary and Exploratory Endpoints

Paradigm will assess a number of key secondary and exploratory endpoints in the Phase 2 study.

Correlation between synovial fluid biomarker changes and clinical outcomes

The change from baseline of synovial fluid biomarkers will be assessed to investigate whether the down regulation of certain biomarkers post PPS treatments is related to patient reported outcomes compared to placebo.

Changes is baseline to 6 months in one or more Synovial fluid biomarkers

Changes of one or more synovial fluid biomarkers from baseline out to Day 168 will be measured to provide Paradigm important data on the durability of effect of PPS against placebo. Paradigm has previously reported data from the Phase 2B clinical trial of a reduction from baseline of COMP and ADAMTS-5 levels in the serum to day 53 following PPS treatment.

Changes from baseline at designated timepoints of WOMAC® Pain, Function, Stiffness and Quality of life (PGIC)

Participants in the study will be asked to provide baseline pain scores using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)®. Once patients have initiated treatment, they will have pain scores measured at predetermined timepoints out to day 168. Paradigm's primary endpoints in the forthcoming Phase 3 trial design will be an improvement in pain and function from baseline at day 56 using the WOMAC® osteoarthritis index. This study will provide further clinical data on the effects Zilosul® versus placebo prior to the Phase 3 study.

Patient Global impression of Change (PGIC) is a self-reported measure that reflects the patient's belief about the overall efficacy of the treatment. Patient's rate their change from No Change (or condition worsened) through to considerable improvement that has made all the difference. Paradigm's Phase 3 trial will include an improved PGIC at day 56 as an endpoint.

Radiographic changes in the bone and joint

The exploratory endpoint will investigate the structural changes from baseline of the participants joint using MRI to day 168. Changes in Bone Marrow Lesion (BML) area and volume will be assessed as well as structural changes to the joint. Paradigm has previously reported data on reduction of BML's from baseline to day 53 following PPS treatment in its Phase 2B clinical trial. This data will provide Paradigm with important information on the disease modifying potential of PPS over 6 months.

Trial Design

The purpose of Paradigm's Phase 2 study is to measure the change in synovial fluid biomarkers associated with inflammation and osteoarthritis disease progression following treatment with subcutaneous injections of pentosan polysulfate sodium compared with subcutaneous injections of placebo in participants with knee OA. Sixty (n=60) participants with Kellgren-Lawrence grade 2, 3 or 4 and have OA pain will be enrolled and randomised 1:1 to receive either PPS (n=30) or placebo (n=30).

Participants will receive twice weekly subcutaneous injections for six weeks.

ANZCTR number 12621000136808p.

Mr. Paul Rennie, Paradigm's Chief Executive Officer said:

"Investigating the disease modifying effects of Zilosul® in subjects with osteoarthritis is important for our regulatory filing in Australia (TGA provisional approval) and our clinical and regulatory filings in the USA and Europe. The two unmet medical needs for osteoarthritis are (i) safe and effective pain relief and (ii) therapies that can slow or halt the disease progression. Biomarkers are an excellent way to assess the stage of the disease and the disease progression. We look forward to announcing the top-line results of this clinical trial in Q3 CY 2021."

About injectable PPS

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 currently only available by inclusion into a Paradigm Sponsored clinical trial.

About WOMAC® Scores

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)® is a widely used, proprietary set of standardized questionnaires used by health professionals to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints. It consists of 24 items divided into 3 subscales^[8]:

- **Pain** (5 items): during walking, using stairs, in bed, sitting or lying, and standing upright.
- **Stiffness** (2 items): after first waking and later in the day.
- **Physical Function** (17 items): using stairs, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy domestic duties, light domestic duties.

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, aging, 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 Haraden CA, Huebner JL, Hsueh M-F, et al. Synovial fluid biomarkers associated with osteoarthritis severity reflect macrophage and neutrophil related inflammation. *Arthritis Res Ther* [Internet]. 2019
- ² Sunaga T, Oh N, Hosoya K, et al. Inhibitory Effects of Pentosan Polysulfate Sodium on MAP-Kinase Pathway and NF- κ B Nuclear Translocation in Canine Chondrocytes In Vitro. *J Vet Med Sci*. 2012.
- ³ Stapledon CJM, Tsangari H, Solomon LB, et al. Human osteocyte expression of Nerve Growth Factor: The effect of Pentosan Polysulphate Sodium (PPS) and implications for pain associated with knee osteoarthritis. Heymann D, editor. *PLOS ONE* [Internet]. 2019.
- ⁴ Troeberg L, Mulloy B, Ghosh P, et al. Pentosan polysulfate increases affinity between ADAMTS-5 and TIMP-3 through formation of an electrostatically driven trimolecular complex. *Biochem J* [Internet]. 2012.
- ⁵ Ghosh P, Edelman J, March L, et al. Effects of pentosan polysulfate in osteoarthritis of the knee: A randomized, double-blind, placebo-controlled pilot study. *Curr Ther Res* [Internet]. 2005.
- ⁶ Kumagai K, Shirabe S, Miyata N, et al. Sodium pentosan polysulfate resulted in cartilage improvement in knee osteoarthritis - An open clinical trial. *BMC Clin Pharmacol* [Internet]. 2010.
- ⁷ Hunter D et al; *Arthritis Research & Therapy* [Internet]. 2007,
- ⁸ https://www.physio-pedia.com/WOMAC_Osteoarthritis_Index

Authorised for release by Paul Rennie, CEO & Interim Chairman.

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

To learn more please visit: www.paradigmbiopharma.com

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