Injectable Pentosan Polysulfate Sodium For Knee Osteoarthritis: A Potential Disease-Modifying Osteoarthritis Drug

Mukesh Ahuja MBBS, MS
Global Head of Osteoarthritis
Paradigm Biopharmaceuticals Ltd

Disclaimer

This document, together with any information communicated by Paradigm Biopharmaceuticals Ltd ASX:PAR (known as “Paradigm”, “Paradigm Biopharma” or “the Company”), in any presentation or discussion relating to this document (collectively, “Information”) is confidential, and has been prepared by the Company on the condition that it is for the exclusive information and use of the recipient. The Information is proprietary to Paradigm and may not be disclosed to any third party or used for any other purpose without the prior written consent of the Company.

The Information is based upon management forecasts and reflects prevailing conditions, which are accordingly subject to change. In preparing the Information, the Company has relied upon and assumed, without independent verification, the accuracy and completeness of all information available from public sources, or which was otherwise reviewed by it. In addition, the analyses are not and do not purport to be appraisals of the assets, stock or business of the Company. Even when the Information contains a kind of appraisal, it should be considered preliminary, suitable only for the purpose described herein and should not be disclosed or otherwise used without the prior written consent of Paradigm. The Information is provided on the understanding that unanticipated events and circumstances may occur which may have significant valuation and other effects.

This Company presentation 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. The rate and timing of enrolment of our clinical trials and the timing of top-line results of our clinical trials should be regarded as forward-looking statements and the actual dates could differ materially from the expectations and projections set forth in Company presentations or statements especially during a pandemic.

Osteoarthritis: a significant unmet need

Osteoarthritis (OA) is an inflammatory disease of the joint causing chronic pain, disability, and reduction in quality of life.

Despite numerous therapies available, the currently approved drug treatments for OA are palliative and are not disease-modifying.

People affected by OA in 2020[1]

72m+

People affected by OA by 2030[1]

120m+

Countries: US, EU5, Canada and Australia.

In the US alone, OA is predicted to increase by 86% to 67 million by 2030.[2]

Knee and Hip (Global)

69% of all OA

OA patients dissatisfied with current treatments[3]

81%

1. Long, H. et al. (2022), Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the Global Burden of Disease Study 2019. Arthritis Rheumatol.
2. OARSI. Osteoarthritis: A Serious Disease, Submitted to the U.S. Food and Drug Administration December 1, 2016
3. National Institute of Health; Emerging drugs for osteoarthritis; Hunter DJ and Matthews G 16(3): 479–491; 2011 September.

Paradigm Biopharmaceuticals has initiated a clinical development plan (CDP) to repurpose Pentosan Polysulfate Sodium in an injectable form (iPPS, Zilosul™) for the treatment of pain and dysfunction caused by OA. The CDP includes evaluation of disease-modifying potential of drug in OA.

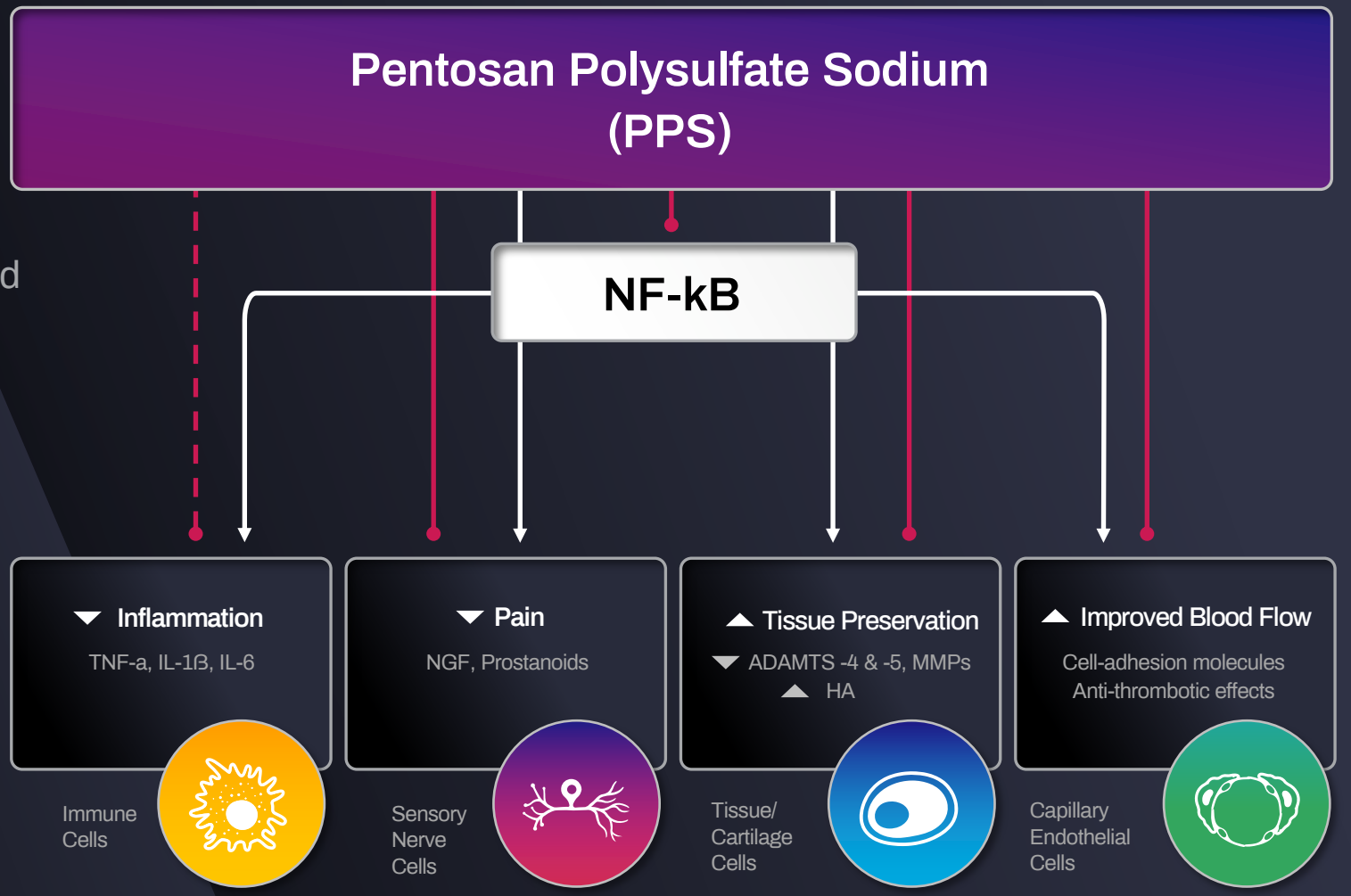
Recent Highlights

- First US and Australian subjects dosed in the phase 3 study in knee OA.
- UK Regulatory and Ethics approval received for the phase 3 study in knee OA.
- Fast Track designation from the US FDA for Investigation of PPS for the treatment of OA.

Mechanism of action

Multiple mechanisms of action are proposed

- Inhibition of transcription factor NF-κB-mediated activation of the inflammatory cytokines, IL-1β and TNF-α (Sunaga et al, 2012)
- Inhibition of expression of NGF, a pain mediator, in osteocytes in subchondral bone (Stapledon et al, 2019)
- Inhibition of cartilage-degrading enzymes known to play a key role in progression of OA (Troeberg et al, 2012)
- Mild antithrombotic activity, which acts to improve blood flow in subchondral bone (Kutlar et al, 2012), which is thought to help reduce the size of bone marrow lesions



MOA Video: Click HERE to view, or via https://www.youtube.com/watch?v=rjZ-L_cHbm0

Clinical Experience

- Clinical safety data have been collected from a total of 674 participants enrolled in Paradigm-sponsored clinical studies (n = 112), an Expanded Access Program (EAP; n = 10 participants), and a Therapeutic Goods Administration Special Access Scheme (n = 553 participants). These data support an acceptable safety profile for Paradigm's PPS product for the OA indication development
- A pilot phase 1, open-label study of 2 mg/kg PPS administered IM on Day 0, 4, 7, 11, 14 and 18 for knee pain from anterior cruciate ligament (ACL) injury (PARA_001); n= 11 participants.
- Phase 2b, randomised, double-blind, placebo-controlled clinical study of 2 mg/kg PPS administered SC twice weekly for 6 weeks vs placebo for knee OA pain (PARA_005), n=126 participants
- Expanded Access compassionate use program (EAP) for patients with knee OA with bone marrow lesions. participants received 2 mg/kg PPS to a maximum of 200 mg administered SC twice for six weeks. Real-world setting program (PARA_EAP_ OA_001); n = 10 participants.

PARA_005 phase 2B Clinical Study

Randomised, double-blind, 2mg/kg twice weekly or placebo, n = 112

Clinical Outcomes

- Knee injury and Osteoarthritis Outcome Score (KOOS)
  - Pain
  - Function (ADL)
- Patient Global Impression of Change (PGIC)
- Bone marrow lesions by MRI

Serum biomarkers

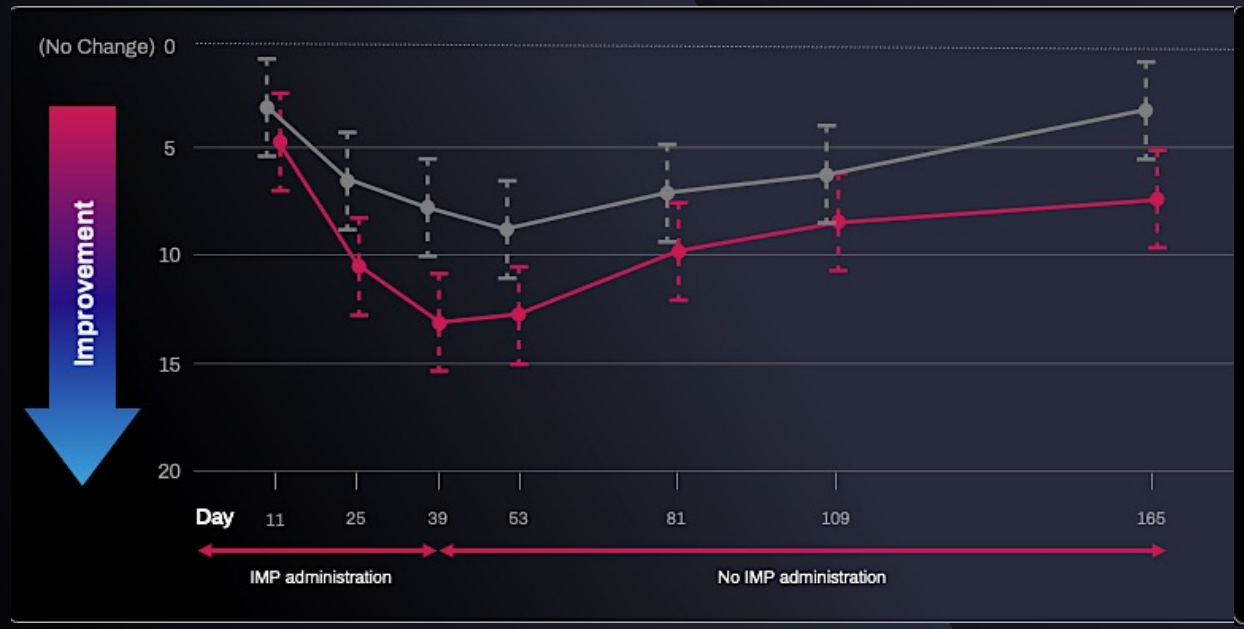
- Cartilage degradation (CTX-II, COMP, ADAMTS-5)

Phase 2 – Para_005 2mg/kg SC twice weekly v placebo

PPS Placebo

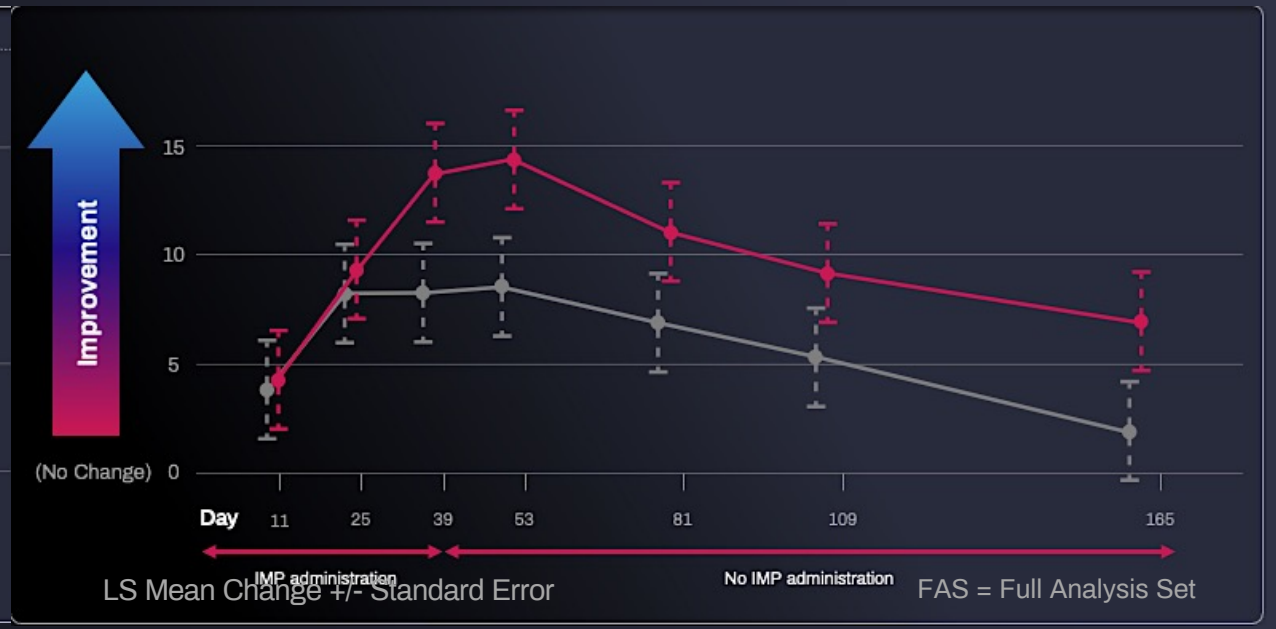
1 KOOS Pain

Adjusted Mean Change From Baseline. (N=112) (1:1 randomised)



2 KOOS Function (ADL)

Adjusted Mean Change From Baseline (Overall FAS Population)



LS Mean Change +/- Standard Error

FAS = Full Analysis Set

3 Patient Global Impression of Change (PGIC)

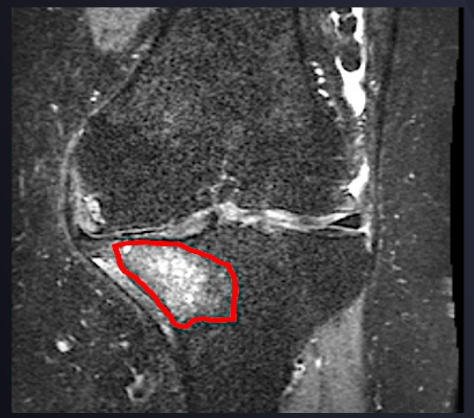
Para_OA_005

- Mean PGIC significantly higher in the PPS group than placebo group at Day 53 (4.42 versus 3.42, respectively; mean difference between PPS and placebo 1.0 [95% CI 0.24, 1.8]; p=0.0106).

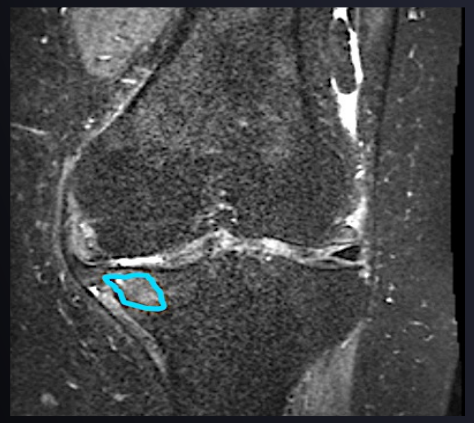
Phase 2 – PARA_005 2mg/kg SC twice weekly v placebo

PPS showed significantly reduced serum levels of cartilage degradation biomarkers and significant reduction in BML size as compared with placebo controls.

Reduction in size of **Bone Marrow Lesions**

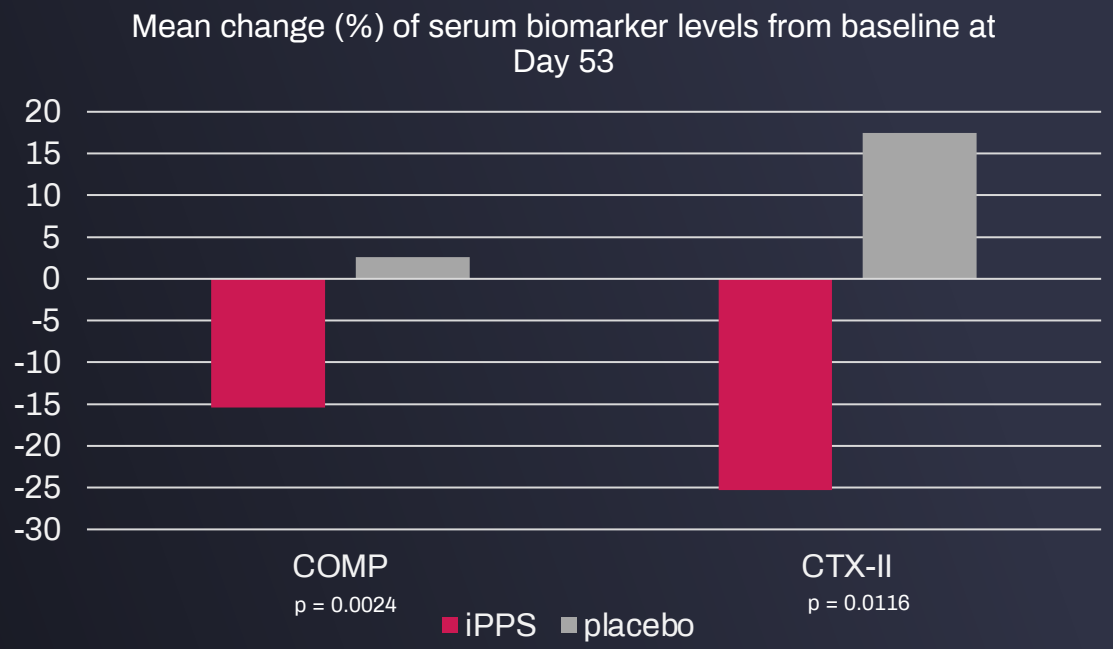


Grade 3 medial tibial BML at baseline



Grade 2 medial tibial BML at follow-up Day 53

Reduction in serum levels of **COMP & CTX-II**



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

DMOAD

Current programs to inform of Zilosul® potential as a DMOAD

PARA_008 - Australia

- Biomarker study assessing change from baseline in multiple objective measures associated with disease progression of OA.
- 60 participants randomized to PPS or placebo.
- Synovial fluid: COMP, CTX-II, NGF, IL-1β, TNFα, IL-6, ADAMTS-5, aggrecan ARGS fragment, TIMP-1, CTX-I, C2C
- Serum: COMP, ADAMTS-5, aggrecan ARGS fragment, TIMP-1, CTX-I, C2C
- Urine: CTX-II
- MRI: Subchondral BML area and volume, joint synovitis/effusion volume, cartilage volume, bone shape, joint space width

PARA_002 - Global

- Pivotal Phase 3 OA knee
- 900+ participants randomized to PPS or placebo.
- MRI: Subchondral BML area and volume, joint synovitis/effusion volume, cartilage volume, bone shape, joint space width

Canine OA Study

- 21 Dogs with OA of the stifle joint are treated with PPS at a dosing of 3mg/kg (1.7mg/kg human equivalent) weekly for 6-weeks.
- 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.
- Serum samples will also be taken to measure biomarker levels associated with inflammation, cartilage degradation and pain.
- 20 weeks follow-up period (equates on average to a period of 3 years in human lifespan)

For more information please visit:
www.**paradigmbiopharma.com**
or email any queries to
mahuja@paradigmbiopharma.com