PARADIGM BIOPHARMACEUTICALS LIMITED

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PARADIGM (ASX: PAR) DISCOVERS ZILOSUL® (iPPS) PROTECTS CARTILAGE IN KNEE OSTEOARTHRITIS

KEY HIGHLIGHTS

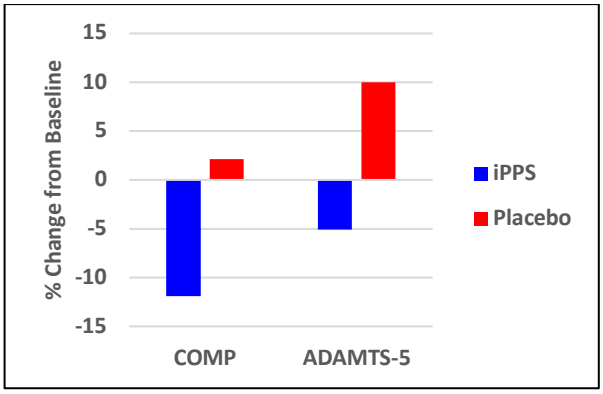
- **Breakthrough - new data from Paradigm's Phase 2b Clinical Trial demonstrating injectable Pentosan Polysulfate Sulfate (iPPS) reduces cartilage degradation.**
- **Paradigm reports its exploratory endpoints which have discovered that treatment with Zilosul® (iPPS) demonstrated significant reduction in the levels of two key biomarkers (COMP and ADAMTS-5) which are associated with cartilage degradation in knee osteoarthritis. These biomarkers are elevated in the serum of people with advancing osteoarthritis.**
- **Cartilage degradation measured by the detection of Cartilage Oligomeric Matrix Protein (COMP) in serum showed a mean percentage reduction of 11.9% from baseline at Day 1 to Day 53 in the iPPS treatment group in contrast to a mean percentage increase of 2.1% in placebo.**
- **ADAMTS-5, the enzyme which degrades the major cartilage component aggrecan showed a mean percentage reduction of 5.1% from baseline at Day 1 to Day 53 in the iPPS treatment group in contrast to a mean percentage increase of 10% in placebo.**
- **Among subjects with symptomatic knee OA, a single measurement of increased COMP predicted subsequent cartilage loss on MRI[1].**
- **These data supports iPPS as a cartilage-protective agent which potentially blocks the progression of knee osteoarthritis**

Paradigm Biopharmaceuticals Ltd (ASX: PAR) Paradigm is pleased to report an exciting new discovery within its prespecified exploratory endpoints (serum biomarkers of cartilage destruction) from its Phase 2b Osteoarthritis (OA) clinical trial.

The most significant of which was the discovery that the two Biomarkers; Cartilage Oligomeric Matrix Protein (COMP) and ADAMTS-5 both associated biomarkers of patients with progressive OA, resulted in a meaningful reduction when treated with Zilosul (iPPS) when compared to the placebo arm of the trial. This is a groundbreaking discovery as the data is suggesting that Paradigm's Zilosul® protects the cartilage from progressive degradation as well as reducing pain and improving the joint function in osteoarthritic patients.

[1] Hunter D et al; Arthritis Research & Therapy 2007, 9:R108 (doi:10.1186/ar2314)

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 – exploratory endpoints).



Among subjects with symptomatic knee OA, a single measurement of increased COMP predicted subsequent cartilage loss on MRI[2].

In Paradigm's Phase 2b osteoarthritis clinical trial, the biomarker COMP demonstrated a mean percentage reduction of 11.9% from baseline at Day 1 to Day 53 in the serum of iPPS treated subjects. In contrast the levels of COMP showed a mean percentage increase of 2.1% in the placebo group (Figure 1). In parallel with COMP, ADAMTS-5, the key enzyme involved in the degradation of aggrecan in cartilage showed a mean percentage reduction of 5.1% in the serum of iPPS treated subjects in contrast, to the mean percentage increase of 10% in the serum of the placebo group (Figure 1).

The reduction of COMP and ADAMTS-5 by iPPS are supportive of Paradigm's previous objective data which demonstrated that the iPPS group had clinically meaningful regression of Bone Marrow lesions (BML) in the medial compartment (50.0% vs. 27.3%, p=0.03) compared to placebo.

Therefore, the reduction of biomarkers responsible for cartilage degradation and the improvement in structural changes in the subchondral bone are complementary with the clinical outcome of pain reduction as determined by the KOOS pain score.

Summary of Findings: Put simply, COMP & ADAMTS-5 are reliable indicators of progressively worsening OA, meaning, those patients with elevated levels of these biomarkers in their blood have experienced an increased level of cartilage degeneration. As the cartilage around the joint breaks down, these biomarkers found in the joint cartilage are released into the blood. Cartilage degeneration is the hallmark outcome of patients with progressive OA.

The discovery by Paradigm, that patients treated with Zilosul® (iPPS) saw a meaningful reduction in these biomarkers when compared to the placebo arm. This discovery appears to indicate that treatment with Zilosul® protects, slows or stops the cartilage around the joint from degrading – slowing the progression of the disease.

[2] Hunter D et al; Arthritis Research & Therapy 2007, 9:R108 (doi:10.1186/ar2314)

This is a major new discovery made by the team at Paradigm which adds to the clinical evidence that Zilosul® could materially impact the progression of a disease that previously was thought to have no effective disease modifying treatment options.

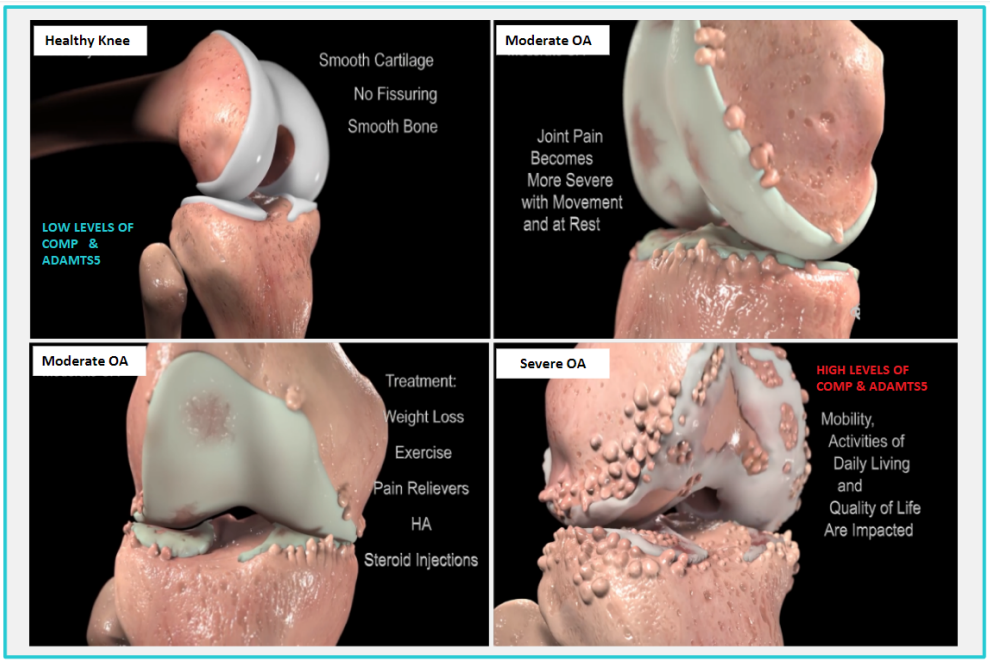


Figure 2: Showing cartilage breakdown associated with OA & levels of COMP & ADAMTS-5

Mr. Paul Rennie, Paradigm's Chief Executive Officer said:
"We are very pleased to demonstrate that iPPS was able to reduce levels of the biochemical markers COMP and ADAMTS-5 which predict disease progression in OA. Of important relevance for Paradigm's clinical development is that the biomarker results further validate the objective measures of the therapeutic effects of iPPS in association with the objective MRI reduction of subchondral BML and the clinically meaningful reduction of pain".

"Paradigm is expecting the release of more biomarker data in the coming months as the results are provided to the company by the reference laboratory. The most pleasing outcome of the Phase 2b clinical trial was the positive correlation between the clinical outcomes and the objectively measured structural outcomes. The clinical outcomes saw the reduction in pain and improvement in joint function AND additionally the objective disease modifying outcomes of reduced BML and reduction of cartilage degrading biomarkers".

The Importance of Biomarkers: A biomarker is a naturally occurring molecule, gene, or characteristic by which a particular pathological or physiological process, disease, etc. can be identified. In the case of progressive osteoarthritis, several molecules are released from the bone and cartilage. These compounds are known to be associated with the breakdown of cartilage. For example, the protein COMP levels are elevated in the serum of patients with OA, making COMP a reliable biomarker of patients who have OA[3].

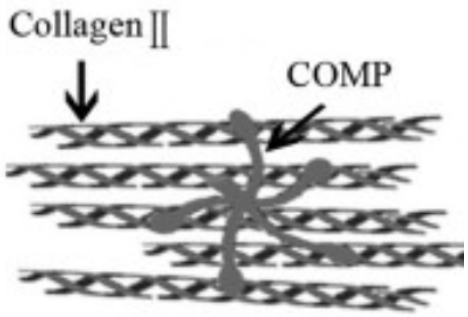
What is the importance of COMP and ADAMTS-5 in OA?

COMP
COMP could be considered as the glue that holds cartilage together. The cartilage matrix in diseased joints produces fragments of extracellular matrix molecules, and degradation products of cartilage which are released into the synovial fluid and subsequently into the blood serum. One such biomarker

[3] Verma P and Dalal K; Int. J Orthop Res 31:999–1006, 2013.

which is the most investigated to predict knee OA progression is COMP. COMP is a pentameric non-collagenous glycoprotein belonging to the heterogeneous family of thrombospondin which can bind type to collagen type I, II, and IX. COMP pentamer bound up to five collagen molecules thereby retaining them in close proximity. By this process, COMP facilitates the collagen–collagen interactions (Figure 3).

Figure 3: COMP facilitates collagen to collagen interaction in cartilage



Several studies reached the consensus that COMP levels in synovial fluid and serum are indicators of cartilage damage. It was also reported that COMP level is elevated in the knee joint synovial fluids of patients with OA. **Among subjects with symptomatic knee OA, a single measurement of increased COMP predicted subsequent cartilage loss on MRI[4].** The other biochemical markers of cartilage synthesis and degradation do not facilitate prediction of cartilage loss.

ADAMTS-5

A disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5) is the main enzyme that degrades aggrecan, a major component of cartilage found in animal and human OA articular cartilage. Consequentially, it is the degradation of collagen and aggrecan from cartilage, without the compensatory synthesis of new macromolecules to replace those lost through degradation, which significantly compromises the biomechanical strength of articular cartilage leading to its degradation.

Increased aggrecanase activity is a well-known trigger factor for osteoarthritis, initiating loss of cartilage aggrecan that precedes more severe cartilage degradation. Recently, ADAMTS-5 was validated as a drug target for OA and experimental ADAMTS-5 inhibitors were shown to reduce synovial joint damage in OA animal models[5].

About injectable PPS (iPPS)

Injectable PPS (iPPS) is not currently registered in Australia, but it is was previously registered in four of the seven major global pharmaceutical markets. In those European markets, iPPS is registered as an antithrombotic agent. In Australia, iPPS for human use is not currently available for sale.

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

To learn more please visit: www.paradigmbiopharma.com

[4] Hunter D et al; Arthritis Research & Therapy 2007, 9:R108 (doi:10.1186/ar2314)

[5] Apte S; Biochem J. 2016 January 01; 473(1): e1–e4. doi:10.1042/BJ20151072.

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