



Paradigm Reports Successful Phase 2a BML/ACL Clinical Trial Results

Highlights

- Paradigm announces the successful completion of its Phase 2a clinical trial in bone marrow lesions (BML) (bone bruising) as a result of an anterior cruciate ligament (ACL) injury.
- The primary endpoint of safety & tolerability was met.
- Paradigm was also successful in meeting its secondary endpoint, demonstrating a statistically significant reduction in bone marrow lesion (BML) volume as measured by MRI.
- Trial success confirms the Company's hypothesis that Pentosan Polysulfate Sodium (PPS) could be a new treatment for acute joint injuries.
- There is mounting evidence that suggests that ACL injuries result in cartilage degeneration and the progression of early onset osteoarthritis (OA).
- The data gathered from the Phase 2a trial supports Paradigm's recently initiated, double blinded, placebo controlled, 100 patient, Phase 2b clinical trial investigating PPS in subjects with knee OA and BMLs.

Melbourne 14 November 2017 Paradigm Biopharmaceuticals Ltd (ASX: PAR) today announced that its phase 2a clinical trial in bone marrow lesions (BML) (bone bruising) met its primary endpoint of safety & tolerability. Additionally, the secondary endpoint was met and showed a statistically significant reduction in bone marrow lesion volume.

The company received the top line results following analysis of safety data on 11 people who participated in the phase 2a open label trial to evaluate pentosan polysulfate (PPS) for the treatment of bone marrow lesions associated with acute anterior cruciate ligament (ACL) injuries. 9 of the 11 participants completed the course of treatment, while two participants withdrew for family and other reasons unrelated to PPS.

PPS was administered as a course of 6 intramuscular injections, given twice weekly over 3 weeks. All participants tolerated the injections and no serious adverse events were reported. There were no clinically significant changes in clinical laboratory parameters (haematology and biochemistry) or physical examination findings during treatment or the 8-week follow-up period, demonstrating safety and tolerability of PPS.

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In addition to the safety and tolerability (primary endpoint) the clinical trial investigated the effect of PPS on the bone marrow lesion volume as measured by MRI (the secondary endpoint). Baseline MRI's were taken prior to the first injection of the drug (pre-treatment MRI). Following a 3-week course of PPS injections, a post-treatment MRI was performed at the final follow up visit in week 8. The independent MRI reviewer was blinded to the pre-and-post PPS treatment MRI's. The results showed a statistically significant reduction in BML volume following PPS treatment. In addition, the blinded MRI results showed a statistically significant reduction in knee effusion-synovitis volume.

The changes in BML and effusion-synovitis from baseline to End of Study were examined in 9 subjects who had completed the course of PPS treatment. Overall 6/9 (66.6%) participants showed reduction in BML; 8/9 (88.8%) had reduction in effusion-synovitis volume. There was a significant reduction in BML volume in lateral tibia [$p=0.046$], and a marginally significant reduction for total tibia [$p=0.06$]. Similarly, there was a significant reduction in BML maximal area in lateral tibia [$p=0.03$] and total tibia [$p=0.02$]. There was a significant reduction in effusion-synovitis volume in suprapatellar pouch [$p=0.02$] and total knee [$p=0.01$]. There was also a significant reduction in effusion-synovitis maximal area in suprapatellar pouch [$p=0.03$] and total knee [$p=0.04$].

In contrast, clinical studies reporting the natural history of BMLs and joint fluid in people with ruptured ACLs show slow reduction in BML volume and joint fluid volume over a 12-24-month period post-acute injury^{1&2}. The pathology occurring in the bone and overlying cartilage during this time is known to cause progressive joint damage, pre-disposing patients to long term changes and development of Osteoarthritis.

These results indicate that PPS has potential to significantly improve recovery from acute ACL injury, with significant improvement in both bone marrow lesion volumes and effusion volumes, function improvement and improved long term outcomes for patients.

Sports physician and clinical trial Investigator in the clinical trial, Dr Ruben Branson, said "Early results suggest that the therapeutic intervention in acute traumatic joint injuries such as ACL ruptures may reduce BML volume and synovitis – effusion volume within the acute phase of the injury. The hope is that this may then reduce the risk of post-traumatic osteoarthritis (PTOA) but further larger scale trials are needed."

A number of peer-reviewed publications highlight the association between the acute injury and osteoarthritis within a 10-15-year time-frame. "As many as 80% of knees post-ACL injury will progress to radiographic and symptomatic osteoarthritis after 5 to 15 years - despite corrective ACL surgery".³

"A very high prevalence of radiographic knee osteoarthritis, pain, and functional limitations was observed in young women who sustained an ACL tear during soccer play 12 years earlier. By 1 year, more than 30% have radiographic evidence of knee osteoarthritis and by 10 years, more than 60% have clinical osteoarthritis (pain and loss of function), irrespective of ACL surgical repair".⁴

Dr Ravi Krishnan, Paradigm's Chief Scientific Officer said "Paradigm's Phase 2a open labelled clinical trial was a proof-of-concept study to determine the safety, tolerability and effect of PPS on

¹ Frobell RB, et al. The acutely ACL injured knee assessed by MRI: changes in joint fluid, bone marrow lesions, and cartilage during the first year. *Osteoarthritis Cartilage* 2009;17(2):161-7.

² Frobell RB. Change in Cartilage Thickness, Posttraumatic Bone Marrow Lesions, and Joint Fluid Volumes After Acute ACL Disruption: A Two-Year Prospective MRI Study of Sixty-One Subjects. *J Bone Joint Surg Am* 2011;93(12):1096-103.

³ Simon D, et al. The Relationship between Anterior Cruciate Ligament Injury and Osteoarthritis of the Knee. *Advances in Orthopedics*: (2015), 1-12.

⁴ Lohmander S et al "The long-term consequence of anterior cruciate ligament and meniscus injuries". *American Journal of Sports Medicine*; 2007, 35:1756-69.

participants with recently ruptured ACL's. To our current knowledge this is the first time a therapeutic agent has been reported to show statistically significant reduction in both BML volume and effusion-synovitis volume within 2 months post-surgical reconstruction. This clinical trial data provides support for further investigation of early pharmaceutical intervention of injectable PPS in the treatment of acute joint injuries to delay or halt the progression to post traumatic osteoarthritis. The full study will be written-up and the manuscript submitted for peer-review publication in the coming 12 months".

Paradigm's patent to treat BMLs with PPS is already granted in the USA, Japan and Australia. The European BML patent is still undergoing prosecution.

The market size of post-traumatic osteoarthritis (PTOA) is very large market with unmet medical needs. Currently there are no pharmaceutical agents approved for the treatment or prevention of PTOA following acute traumatic injury. "Post-traumatic OA of the knee, hip and ankle accounts for approximately 5.6 million cases of OA in the United States."⁵. This number of cases is confirmed by another study. "A study of patients presenting with disabling hip, knee, and ankle OA showed that 1.6% of patients with hip OA, 9.8% of patients with knee OA, and 79.5% of patients with ankle OA had a verified history of one or more joint injuries. Extrapolation from this patient population indicates that the number of patients in the United States with disabling PTOA of the hip, knee, or ankle approaches 6 million and accounts for approximately 12% of annual societal expenditures for OA, or about 3 billion dollars. Adding to this burden is the fact that, unlike most other forms of OA, PTOA often affects younger adults for whom joint replacement or joint fusion are not desirable treatments"⁶.

Paradigm CEO Mr. Paul Rennie said "the statistically significant reduction of both bone marrow lesion volume and effusion-synovitis volume is very encouraging data. Paradigm is delighted that the open labeled clinical trial (with blinded analysis of MRI's before and after PPS treatment) successfully achieved its primary and secondary endpoints. We are also delighted to show for the first time both BML volume and effusion-synovitis volume was significantly reduced within a 2-month period post-acute injury. We are hopeful the drug PPS could become standard of care, post-surgical reconstruction, with the potential to reduce the risk of a person developing PTOA".

In addition to the ACL clinical trial, Paradigm is also conducting two phase 2 clinical trials in degenerative osteoarthritis and viral induced arthritis. The degenerative osteoarthritis is a phase 2b randomised, double-blind, placebo-controlled clinical trial (n=100). The viral induced arthritis is a phase 2a randomised, double-blind, placebo-controlled clinical trial (n=24). Paradigm will update the market on the recruitment status of these two trials in the coming weeks.

FOR FURTHER INFORMATION PLEASE CONTACT:

Paul Rennie
Director & CEO
Paradigm Biopharmaceuticals Ltd
Level 2, 517 Flinders Lane, Melb, VIC, 3000, AUSTRALIA
ABN: 94 169 346 963
Web: <http://paradigmbiopharma.com/>
Email: prennie@paradigmbiopharma.com
Mobile International: +61 437 778 300
Mobile (Australia): 0437 778 300

⁵ Thomas A, et al (2017) Epidemiology of Post Traumatic Osteoarthritis. Journal of Athletic Training 52(6): 491-496

⁶ Buckwalter A et al. Post-Traumatic Osteoarthritis: Improved Understanding and Opportunities for Early Intervention; Journal of Orthopedic Research (2011).

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