

Orthopaedic Product



Zilosul[®]: a disease modifying agent for acute and chronic joint pain associated with bone marrow edema lesions

Partnership Opportunity:

Currently no approved treatments for joint pain associated with bone marrow edema lesion (BML) – an emerging market. Compelling clinical data in osteoarthritic patients with bone marrow edema lesions of the knee propel Paradigm towards Phase 2b clinical trial, anticipated to commence in Q2 2017. Phase 2 Clinical Trial in Acute ACL-Knee Injury-current.

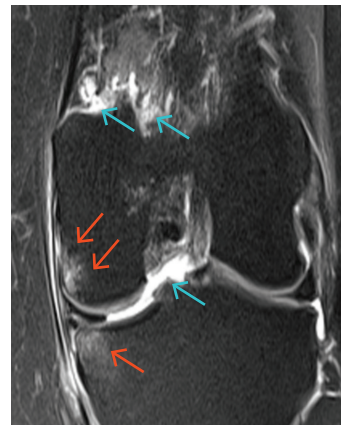
Bone Marrow Edema Lesions (BML) are changes that occur in the subchondral bone and are detected by Magnetic Resonance Imaging (MRI) signifying the severity of symptoms including pain and cartilage degeneration in osteoarthritic patients. BMLs are assessed using fat-suppressed proton density or T2-weighted MRI sequences. In addition to the chronic inflammatory setting in osteoarthritis, BML occur in acute injury e.g. in Anterior Cruciate Ligament (ACL) injury and strongly correlate with knee pain and joint dysfunction. At present, there are no registered products for the treatment of subchondral BML. Patients who do not respond to current anti-inflammatory therapies are left with limited treatment options, and may resort to operative management with Total Knee Arthroplasty (TKA). Paradigm's, Zilosul[®] (IM or SC administered) provides an effective treatment for an unmet medical need to treat a large population of patients with acute traumatic joint injuries or osteoarthritis presenting with BML.

- 1.4 million knee and ankle injuries associated with BML.
- Over 100 million osteoarthritis sufferers in the US of which 48 million have knee osteoarthritis.
- It is estimated that 70% of patients with knee OA have BML, and BMLs in OA are associated with poorer patient outcomes including a 9-fold higher incidence of TKA.
- Market projected to increase from USD3.2 billion in 2014 to USD10.5 billion in 2024.
- High Safety profile.
- Compelling scientific data on the anti-inflammatory and chondro-protective properties of PPS.
- Clinical evidence for therapeutic effects.

Data supporting Zilosul[®] (Pentosan Polysulphate Sodium) as a treatment for bone marrow edema lesions of the joint:

- PPS inhibits the cartilage degrading enzymes which are upregulated post-acute injury (Budesberg et al).
- PPS inhibits the nuclear translocation of NF-kappaB and the regulation of transcription of the pro-inflammatory cytokines TNF-alpha and interleukin IL-1 beta (Sunaga et al, 2012).
- PPS has anti-thrombic and anti-lipadaemic effects facilitates microvascular circulation (Ghosh et al 2001) in the subchondral bone and assists in resolving BML.
- Safety profile of PPS has been further validated in two clinical trials in osteoarthritis patients (Kumagai et al 2010; Ghosh et al 2005).

Effects of Zilosul[®] treatment in a 70-year-old patient with BML and joint effusion: After a course of IM injection Zilosul[®] patient showed pain resolution, improvement in knee function and resolution of BML.



Before PPS MRI showing BME Lesions (orange arrows) effusions in joint space (blue arrows) High NRS Pain Score =8 Lysholm Score:37 (Poor knee function)



Post-PPS treatment MRI Showing complete resolution of BME lesions and effusions Pain NRS =0 (pain resolved) Lysholm Score:65 (Fair knee function)