PARADIGM BIOPHARMA

PAINWeek 2023 Abstract

Clinical Development of Pentosan Polysulfate Sodium for Treatment of Pain and Inflammation

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PURPOSE

Current pharmacologic pain therapies, such as acetaminophen/paracetamol, topical and oral NSAIDs, corticosteroid injections, and opioids, provide short-term and/or minimal improvements in pain symptoms. In addition, the safety profile of some pharmacologic therapies further limits their extended use, leading to recommendations against their use by relevant guidelines.

Pentosan polysulfate sodium (PPS), is a non-opioid, semi-synthetic xylose-based polysaccharide that is highly sulphated during the manufacturing process. The multiple actions of PPS involve anti-inflammatory effects via inhibition of NF-κB, analgesia by normalizing the pain mediator, NGF, and chondroprotection by inhibiting ADAMTS-5 degradation of aggrecan in cartilage. Via these modes of actions, PPS has potential as a treatment of musculoskeletal pain mediated by a variety of causes associated with joint degeneration by ageing or post-traumatic injury, genetic predisposition, and viral induced arthralgia. The multiple mechanisms of action of PPS may provide durability in symptomatic relief not achieved by current pharmacologic pain therapies.

The proof-of concept model in a collagen-induced arthritis model supports the actions of PPS in vivo and the translational model in naturally occurring osteoarthritis (OA) in canines support clinical outcomes of pain reduction and joint function improvement.

Evidence of reduced joint pain and inflammation with subcutaneous PPS treatment has been provided in Paradigm clinical trials in OA, mucopolysaccharidoses (MPS), and alpha virus arthropathy. Results of these clinical trials have further shown therapeutic efficacy in the long-term remission of pain.

Four Paradigm clinical studies in OA (PARA_OA_008, PARA_005), alpha virus (PARA_004), and MPS I (PARA_MPSI_001) have been completed to date. Two additional clinical studies in OA (PARA_OA_002) and MPS (PARA_MPSVI_001) are ongoing.

Clinical safety data have been collected from a minimum of 995 participants enrolled in Paradigm- clinical programs, an Expanded Access Program (EAP), and a Therapeutic Goods Administration (TGA) Special Access Scheme (SAS). These data support an acceptable safety profile for ongoing development of PPS for pain-related indications.

The effects of PPS on clinical and biomarker measurements of pain and inflammation are reported for 4 completed investigations in three indications conducted at Paradigm.

METHODS

PARA_005 was a phase 2b, randomized, double-blind study of 2 mg/kg PPS vs placebo administered twice weekly for 6 weeks. There were 126 participants enrolled in the study, 64 and 62 were randomized to receive PPS and placebo, respectively. Clinical assessments of pain were assessed by Knee Injury and Osteoarthritis Outcome (KOOS) Pain score.

PARA_OA_008 is a phase 2, randomized, double-blind, study to investigate changes in biomarkers in subjects with knee osteoarthritis pain treated with PPS compared with placebo-treated subjects. There were 20, 19 and 22 subjects randomized to iPPS once-weekly, twice-weekly, and placebo, respectively and 17, 15 and 21 subjects completed study treatment, respectively. Clinical assessments of pain have been performed through Day 168 using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC®) NRS 3.1 Index scores.

PARA_MPSI_001 was a phase 1/2 study that evaluated the effects of PPS in subjects ≥5 years of age, diagnosed with MPS I, who previously received ERT and/or HSCT. Four subjects were enrolled in MPS 1 001, and received PPS weekly for 12 weeks, then every other week for 34 weeks. Subjects may have entered a 6-month extension. Clinical assessments of pain were measured by PROMIS T scores conducted up to 73 weeks. Biomarkers were measured at 13, 24, 49, 60 and 73 weeks. Three subjects continued through 73 weeks of assessments.

PARA_004 was a randomized, double-blind, phase 2a study that evaluated the safety and efficacy of PPS in subjects with alpha virus-induced arthralgia. Twenty subjects were randomized 2:1 to PPS or placebo twice weekly for 6 weeks. Efficacy assessments included joint function (hand grip strength and RAPID3) and quality of life (SF-36) at Days 15, 29, 39 and 81. Inflammatory and cartilage degradation biomarkers were explored.

PARA_OA_002 is an on-going, 2-stage, adaptive, randomized, study to evaluate dose and treatment effect of PPS in participants with knee OA. PARA_MPSVI 001 is an on-going phase 2, randomized, study to evaluate the safety and tolerability of PPS in subjects with MPS VI.

RESULTS

In PARA_005, pain reduction by KOOS Pain score was observed through Day 165. At Day 39, 62.5% and 42.4% of PPS and placebo treated participants with a 25% reduction in KOOS Pain scores (P=0.0308). There were 41.1.% and 22.0% of PPS and placebo treated participants with a 50% reduction in KOOS Pain scores (P=0.0278).

In PARA_OA_008, there were lower mean percentage changes from baseline at Day 56 in the pain biomarker, nerve growth factor (NGF) in PPS-treated participants versus placebo-treated participants. The mean difference in the PPS- and placebo-treated participants for NGF were -55.01, -9.21, and -26.47 for PPS once-weekly, PPS twice-weekly, and PPS pooled, respectively.

There were differences in mean percentage change from baseline at Day 56 in inflammatory biomarkers of IL-6 and TNF-α, in the PPS treated participants versus placebo treated participants. The mean difference in the PPS- and placebo-treated participants for IL-6 were -81.66, 25.48, and -17.32 for PPS once-weekly, PPS twice-weekly, PPS pooled, respectively. The mean differences in the PPS- and placebo-treated participants for TNF-α were -180.45, -60.75, and -100.97 for PPS once-weekly, PPS twice-weekly, and PPS pooled, respectively.

At Day 56, the mean percentage change from baseline WOMAC pain scores were -50% and -30% in the PPS twice weekly and placebo treated participants (P=0.050). There were 73.3% and 54.5% of PPS twice-weekly and placebo-treated participants achieving ≥30% improvement in pain and 60.0% and 36.4% of PPS twice-weekly and placebo-treated participants achieving ≥50% improvement in pain.

In PARA_MPSI_001, there was an improvement in PROMIS T scores for Pediatric Pain Behavior (7.2–25.1%), Pain Interference (5.5–11.7%), and Fatigue (0–34.5%) at 49 weeks in the 3 pediatric subjects and for Adult Pain Interference (40.7%), and Fatigue (41.4%) in the one adult subject. There was a decrease in PROMIS T scores for Pediatric Pain Interference (10.9–

13.6%), Pain Behavior (11.6–21.0%), and Fatigue (25.9–29.2%) in 2 pediatric subjects and Adult Pain Interference (40.7%), and Fatigue (41.4%) in one adult at Week 73.

In PARA_004, hand grip strength and SF-36 scores improved with PPS at all time points. Hand grip strength improved 6.99 kg (P=0.0189) higher than placebo at Day 15. PPS showed significant improvements versus placebo in mean relative change from baseline for RAPID3 Pain (P=0.0197) and Total (P=0.0101) scores. Joint symptoms showed near remission in 61.5% and 14.3% of PPS and placebo subjects, respectively. PPS treatment improved pain and inflammation biomarkers versus placebo treatment.

CONCLUSIONS

Clinical and biomarker data from the PARA_005, PARA_OA_008, PARA-004, and PARA_MPSI_001 clinical studies have shown positive outcomes related to pain and inflammation. These positive results across disease states of OA, MPS I and alpha virus indicate possible wide-ranging applications of PPS in the treatment of pain and inflammation.

Paradigm continues to evaluate the effects of PPS on clinical and biomarker measurements of pain and function in the long term follow up PARA_OA_002 and in the ongoing PARA_MPSVI_001 clinical study. To date 325 blinded participants have been enrolled in PARA_OA_002. Based on 3:1 randomization scheme, approximately 243 participants have received PPS and 82 participants have received placebo. There have been 13 blinded participants enrolled in PARA_MPSVI_001 clinical study. Based on a 2:1 randomization scheme, approximately 9 participants have received PPS and 4 participants have received placebo. Final data analysis is to occur in late 2023. Participants completing the PARA_OA_002 clinical study are being enrolled into a long-term evaluation of safety and efficacy in the PARA_OA_006 study. A phase 3 study in patients with MPS VI is planned upon completion of the phase 2 program.