Therapeutic Effects of Pentosan Polysulfate Sodium on Clinical and Disease Modifying Outcomes in Moderate to Severe Knee Osteoarthritis

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INTRODUCTION: Osteoarthritis (OA) is an inflammatory joint disease, causing chronic pain, disability, and reduced quality of life. Affected joints most commonly include the knee, hip, and hands. This study evaluated clinical and disease modifying molecular and structural changes in participants with knee OA pain treated with injectable pentosan polysulfate sodium (iPPS) or placebo.

METHODS: In this phase 2, double-blind study, participants were randomized to iPPS 2.0 mg/kg ideal body weight (IBW) twice weekly, 2.0 mg/kg IBW PPS once weekly + placebo once weekly, or placebo twice weekly for 6 weeks, followed by a 46-week follow-up. Participants were evaluated at baseline, Days 56, 168, and 365 for clinical outcomes using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Synovial fluid (SF), serum and urine samples were obtained at baseline, Days 56 and 168 for biomarker assays. Magnetic resonance imaging (MRI) was performed at baseline and Day 168 to assess joint structure changes. Safety was evaluated by assessing adverse events (AEs). All comparisons were exploratory at 5% significance. The percentage change from baseline to Days 56, 168, and 365 were compared between treatment groups using a mixed model for repeated measures (MMRM) analysis. Biomarkers were quantitated using verified ELISA kits. Whole-Organ MRI Scoring (WORMS) and quantitative (qMRI) analyses were performed to assess changes in the joint structures which included regional changes in articular cartilage thickness and volume, subchondral bone marrow lesions (BML) and synovitis based on gadolinium contrast enhancement. This study was approved by the Bellberry Ethics Committee and all participants consented to the research study.

RESULTS: A total of 61 participants were randomized to twice-weekly iPPS, once-weekly iPPS, or placebo groups, where 17, 15, and 21 participants completed the study to Day 168, respectively. Through to Day 365, 15, 11, and 18 participants were assessed at this follow-up timepoint, respectively. The median age was 60 years; 57% were male; median BMI was 28.8 and KL grade 3-4 was 78% overall. Baseline clinical values were similar among groups. Significant improvements in WOMAC pain (p=0.045), function (p=0.017), and overall (p=0.022) scores were observed in participants treated with iPPS twice weekly vs placebo at Day 56 and all improvements continued through to Day 365. A ≥30% improvement in pain was reported for 60% of the twice-weekly iPPS group at Day 168 and 54% at Day 365, compared to 41% and 33% in the placebo group, respectively. A ≥50% improvement in function was reported for 53% of the twice-weekly iPPS group at Day 168 and 55% at Day 365, compared to 22% (p=0.067) and 28% in the placebo group, respectively. The once-weekly iPPS group showed improvements from baseline and numeric differences from placebo, but the latter did not reach statistical significance. Patient Global Impression of Change (PGIC) was significantly improved for the twice-weekly iPPS group at Day 56 (p=0.037) and Day 168 (p=0.005) vs placebo. WORMS showed signals of improvement or stabilization of BML, cartilage, and osteophytes in the iPPS vs placebo groups. The qMRI analysis of participants receiving twice-weekly iPPS showed an increase in cartilage volume and mean cartilage thickness of 4.6% and 4.2%, respectively, in the medial tibiofemoral (TF) compartment at Day 168 compared to baseline, whereas the placebo arm and once-weekly iPPS arm each showed a slight loss of cartilage volume (-1.7% and -1.1%, respectively) and cartilage thickness (-1.7% and -1.9%, respectively). In the lateral TF compartment, cartilage volume and thickness increased slightly in the twice-weekly iPPS arm (1.4% and 1.2%, respectively), remained stable in the once-weekly iPPS arm (0.1% and 0.0%, respectively), while again decreasing in the placebo arm (-1.8% and -1.9%, respectively). An 18% reduction of overall bone marrow lesions (BML) was observed in the twice-weekly iPPS group, whereas placebo participants saw a 2% overall increase in BML. Participants receiving twice-weekly iPPS also demonstrated a 1% reduction in overall synovitis compared to a 4% increase in overall synovitis in the placebo group. Favorable changes (adjusted change from baseline LSM difference) were observed at Day 56 in six SF biomarkers (IL-6, TNF-α, βNGF, COMP, ARGS [p=0.028], and TIMP-1) in iPPS-treated participants vs placebo. At Day 168, SF biomarkers ARGS and COMP, serum biomarker ARGS (p=0.024), COMP and C2C (p=0.024), and urine biomarker CTX II demonstrated favorable changes in iPPS-treated participants vs placebo. (Table 1) Related AEs occurred in 55%, 74%, and 36% of participants in the iPPS once weekly, iPPS twice weekly, and placebo-treated participants, respectively. There were no related serious AEs or AEs of special interest, and one unrelated SAE. Most AEs were mild to moderate in severity, the most common related AEs were headache and injection site reactions.

DISCUSSION: Despite the relatively small number of participants, these findings show promising effects of iPPS for durable pain relief and improved function out to at least 12 months in participants with severe to moderate knee OA. Furthermore, changes in molecular biomarkers and via MRI assessment show potential disease-modifying osteoarthritis drug (DMOAD) effects of iPPS in patients with knee OA. Larger studies are needed to confirm the observed clinical and DMOAD effects of iPPS.

SIGNIFICANCE/CLINICAL RELEVANCE: iPPS is a well-tolerated non-opioid, semi-synthetic highly sulphated polysaccharide. 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. The multiple mechanisms of action of PPS may provide durability in symptomatic relief not achieved by current pharmacologic pain therapies and have the potential to provide DMOAD activity.

IMAGES AND TABLES: Table 1: Summary of Biomarkers with Favorable Changes from Baseline in iPPS-Treated Participants.

Biomarker	Sample Type	Day 56	Day 168
IL-6 pg/mL	Synovial Fluid	-4.22	642.92
TNF-α pg/mL	Synovial Fluid	-110.15	-16.70
βNGF pg/mL	Synovial Fluid	-36.05	-7.49
TIMP-1 µg/mL	Synovial Fluid	10.55	-3.16
COMP µg/mL	Synovial Fluid	-23.60	-24.40
	Serum	-10.64	-10.85
ARGS ng/mL	Synovial Fluid	-56.60 (p=0.028)	-74.01 (p = 0.024)
	Serum	-4.63	-7.79
C2C ng/mL	Serum	-7.3	-29.25 (p=0.024)
CTX-II ng/mmol	Urine	-52.56	-9.3