iPPS: Shifting the OA treatment paradigm

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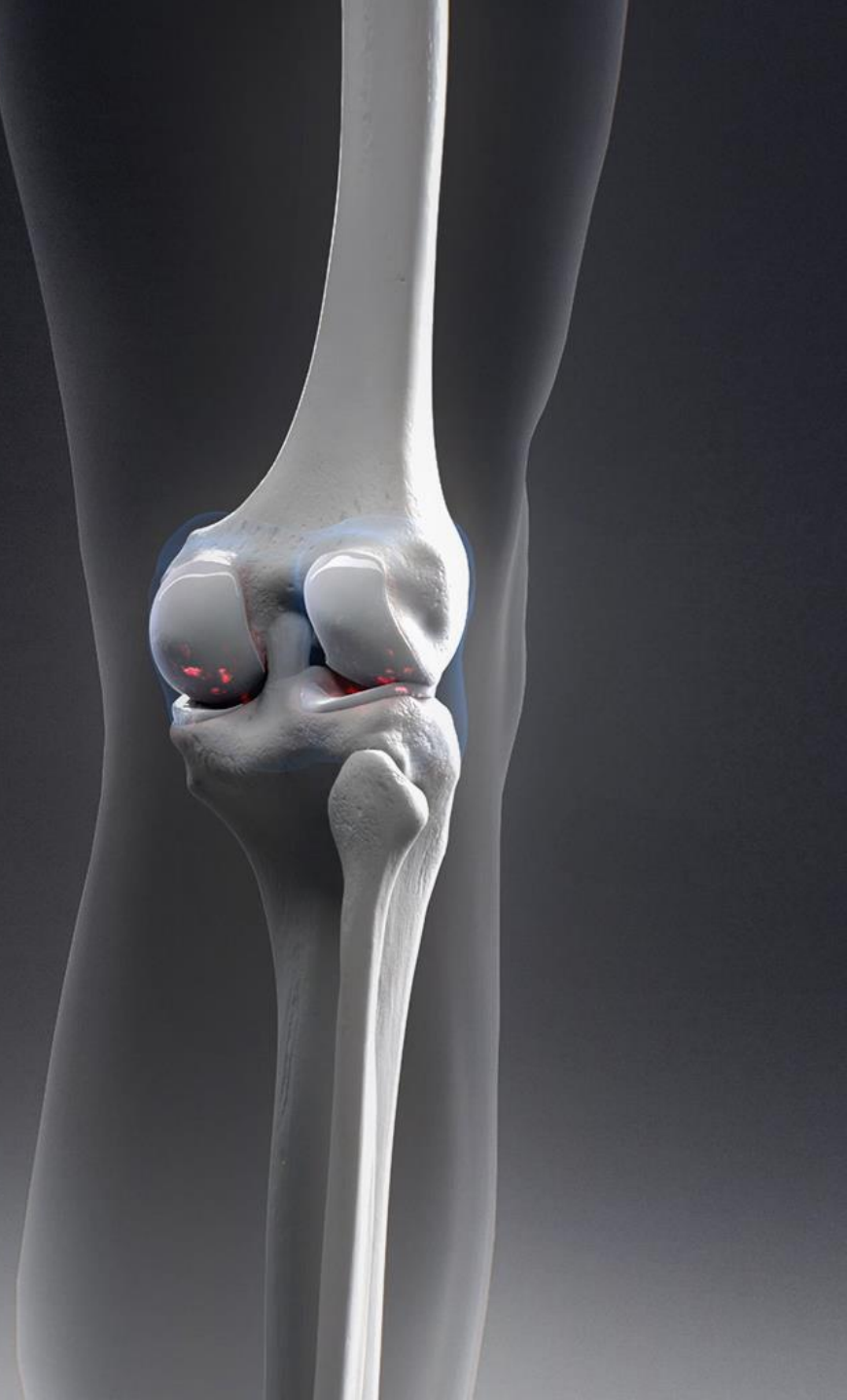
Financial disclosures: Employed by Paradigm Biopharmaceuticals Ltd.; stocks in Paradigm Biopharmaceuticals Ltd. and ChitogenX; consulting with Rush University Medical Center.



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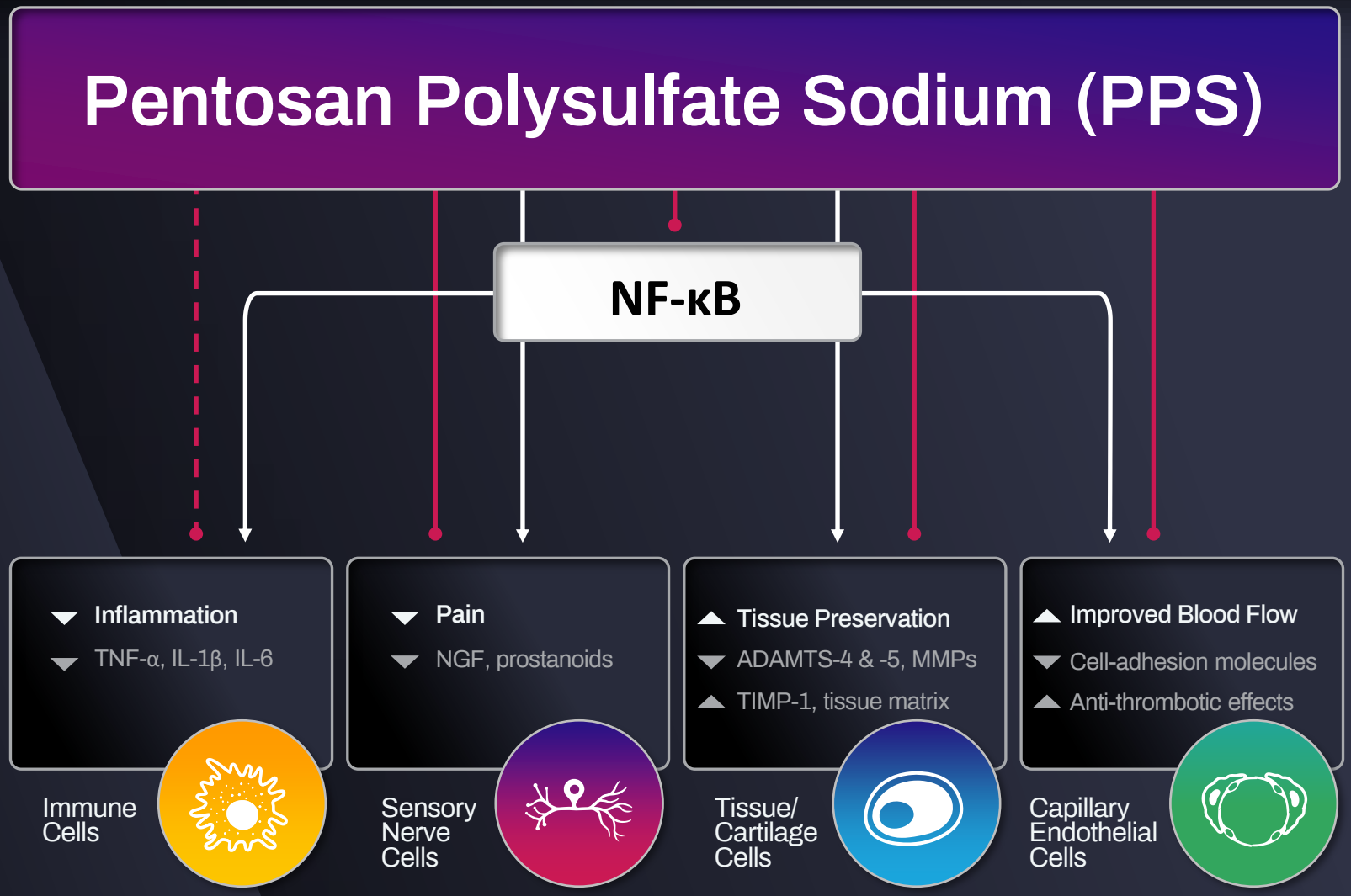
PPS

- Semi-synthetic xylose-based polysaccharide (hemicellulose) that is derived from beechwood and is highly sulfated during its manufacturing process.
- **Non-opioid** with a 60-year track record treating pain, inflammation, and thrombosis in humans.
- 100 mg/mL solution for injection in a 2-mL vial.



ADAMTS = a disintegrin and metalloproteinase with thrombospondin motif; ARGS = aggrecan amino acids alanine, arginine, glycine, and serine; COMP = cartilage oligomeric matrix protein; MMP = matrix metalloproteinase; NF-κB = nuclear factor kappa B; NGF = nerve growth factor; IL= interleukin; TIMP = tissue inhibitor of metalloproteinase; TNF-α = tumour necrosis factor alpha. Bwalya et al 2017; Sunaga et al 2012; Troeberg et al 2012; Stapledon et al 2019; Ghosh et al 1999; Wu et al 2017; Miyata et al 2010; Kumagai et al 2010; Budsberg et al 2007; Kutlar et al 2012.

Current hypothesis for PPS mechanism of action

Osteoarthritis: In vivo investigations

- **Preclinical** - rodent model demonstrates biological activity of PPS in collagen-induced arthritis (CIA) model (Wijekoon 2019).
- **Translational** - canine model of naturally occurring OA demonstrates improved pain and function (Read 1996) and durable remission of OA symptoms with disease modifying effects (Paradigm data).
- In two **clinical studies**, PPS has been shown to reduce pain and improve joint function in patients with knee OA (Ghosh 2005, Kumagai 2010).

Paradigm Biopharmaceuticals is developing an injectable PPS (iPPS) for the treatment of OA pain and as a potential disease modifying treatment for OA.

Wijekoon et al (2019); Res Vet Sci; 122:179-185; Read et al (1996) J Small Anim Pract; 37(3):108-14; Ghosh et al (2005) Curr Ther Res Clin Exp; 66(6):552-71) ; Kumagai et al (2010) BMC Clin Pharmacol; 28;10:7; Paradigm data

Translation – Read et al, 1996

Systemic use of pentosan polysulfate in the treatment of osteoarthritis

METHODS

- Subcutaneous PPS in naturally occurring OA in dogs
- Dose-response analysis in a double-blind study using 1-5 mg/kg PPS SC, 4 injections at 1-week intervals.

RESULTS

- PPS 3 mg/kg effectively reduced lameness and joint pain upon manipulation.
- PPS improved body condition, and willingness to exercise.
- Orthopedic score was reduced by >50% 3-8 weeks post-PPS administration (*p<0.05 vs baseline; Figure 3).
- Pain scores were significantly reduced from 3-weeks post PPS-administration (*p<0.05 vs baseline; Figure 4).

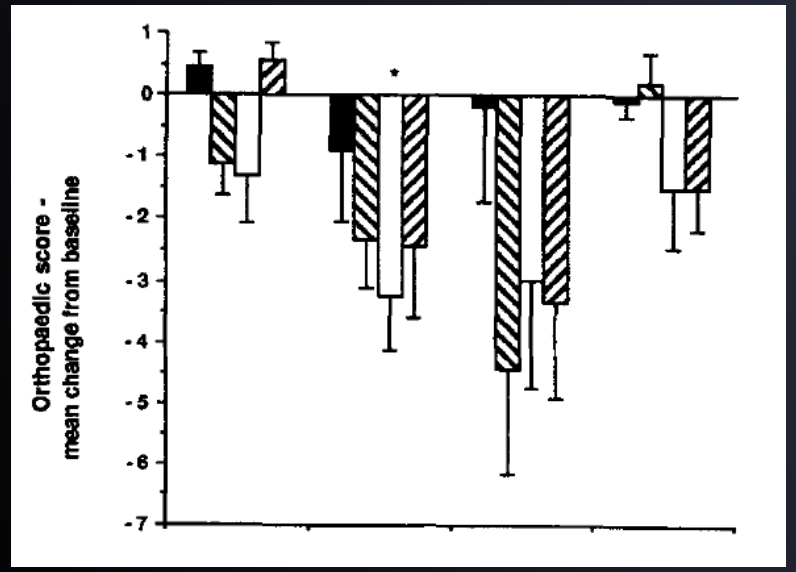


Figure 3. Orthopedic Scores

Legend
Week 2
Week 3
Week 4
Week 8

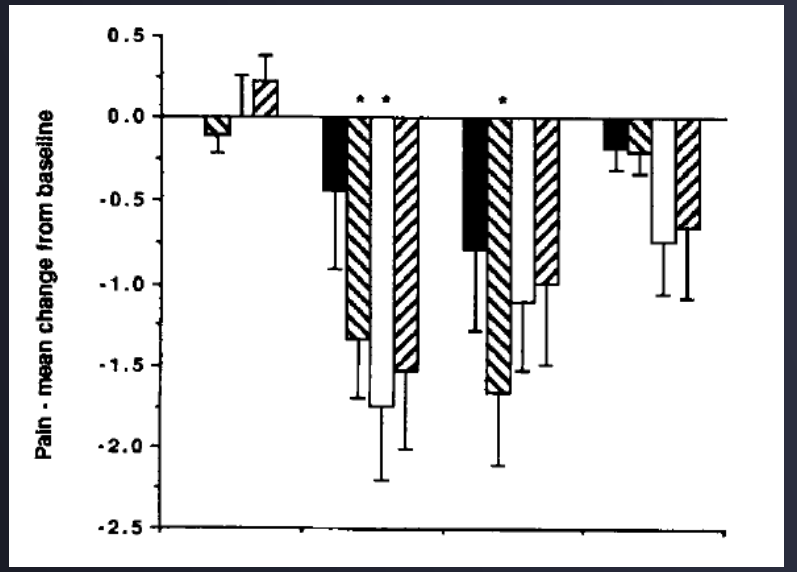


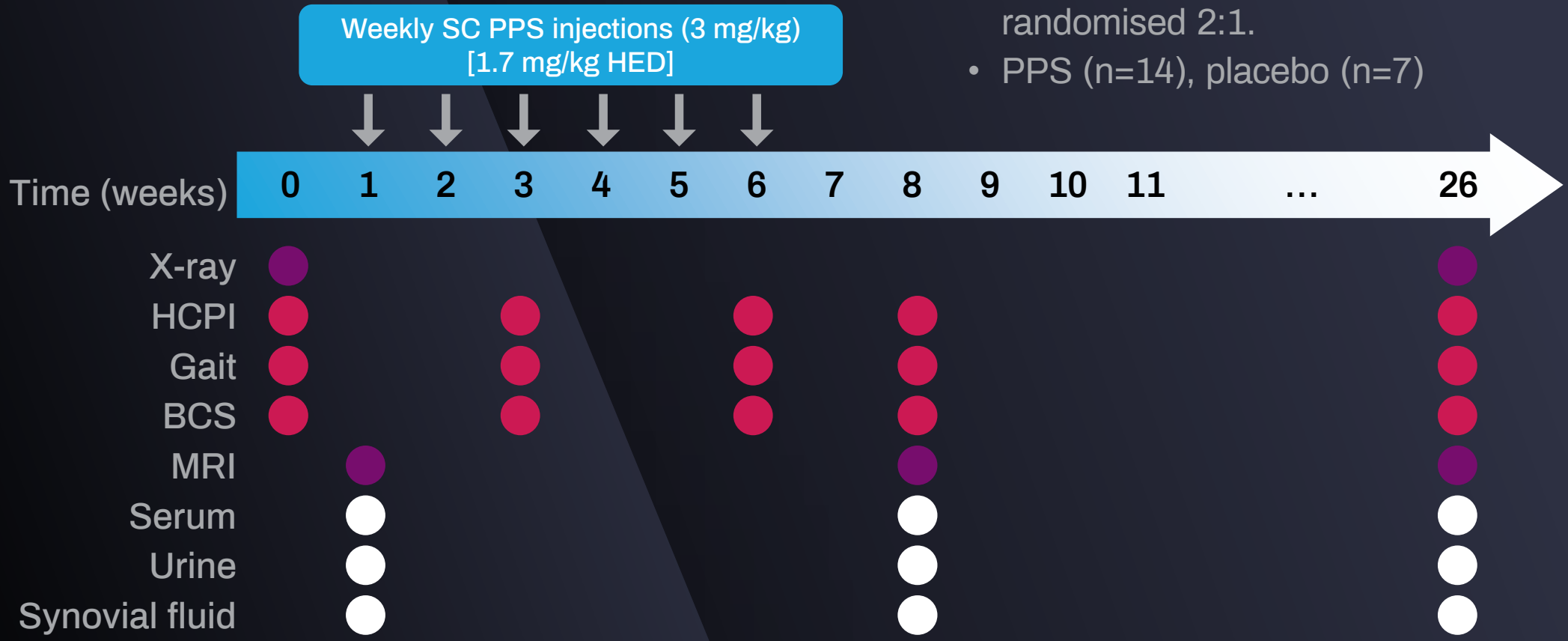
Figure 4. Pain Scores

Legend
Week 2
Week 3
Week 4
Week 8

Canine model of natural osteoarthritis

Study design

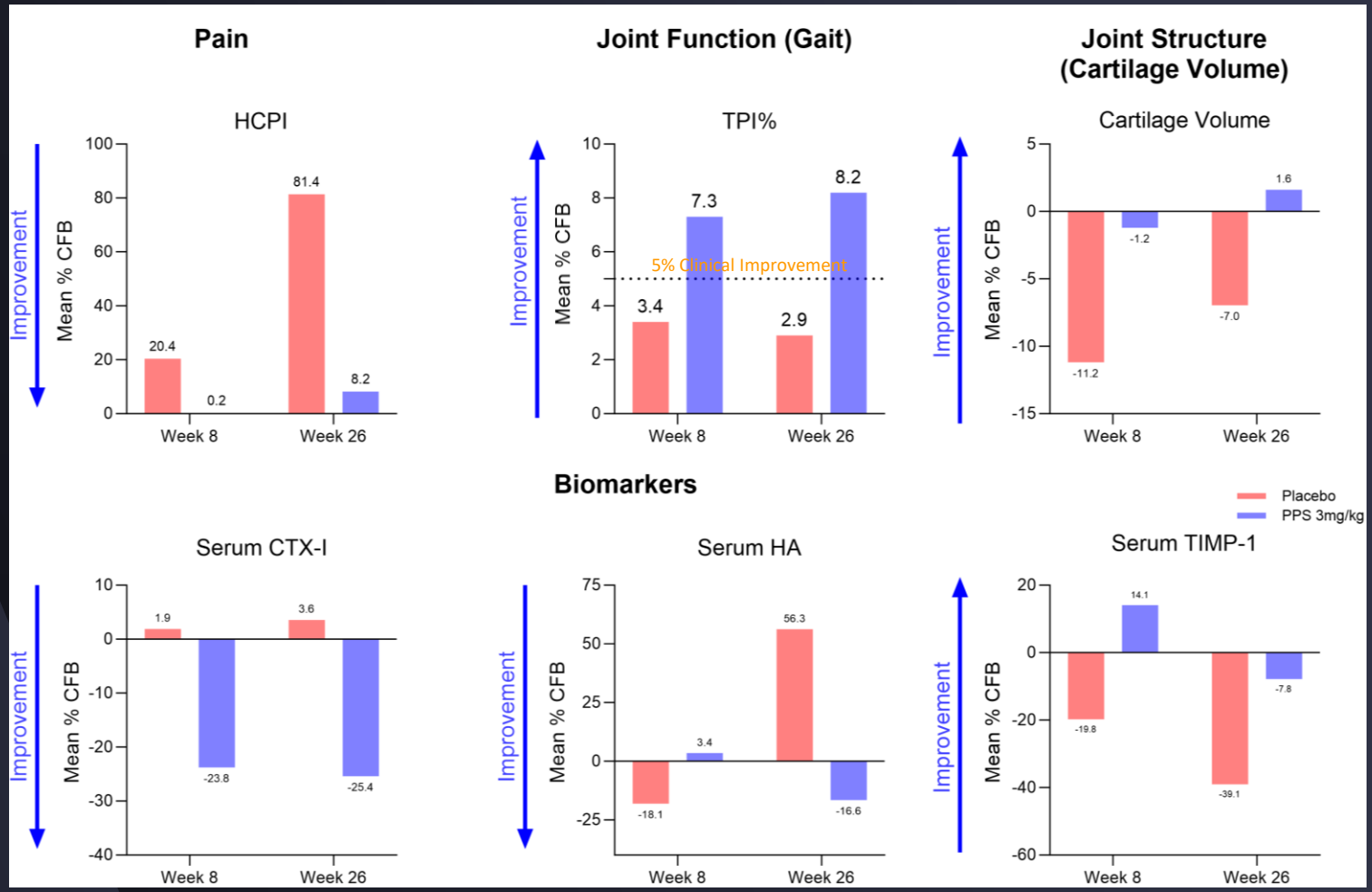
- Double blinded, placebo-controlled, randomised 2:1.
- PPS (n=14), placebo (n=7)



HED = Human Equivalent Dose; HCPI = Helsinki Chronic Pain Index; BCS = Body Condition Score; MRI = Magnetic Resonance Imaging;

Disease modifying actions of PPS: canine model of natural osteoarthritis

- Durable improvements in pain, joint function, cartilage volume & biomarkers at weeks 8 and 26 with subcutaneous PPS vs placebo
- PPS improves serum levels of CTX-I, HA, & TIMP-1 biomarkers at both time points, supporting the proposed mechanisms of action
- In canines, 26-week timepoint is approximately equivalent to 3 years in humans
  - Highlighting durability of PPS treatment effects



Pilot Trial – Ghosh et al, 2005

Effects of pentosan polysulfate on osteoarthritis of the knee

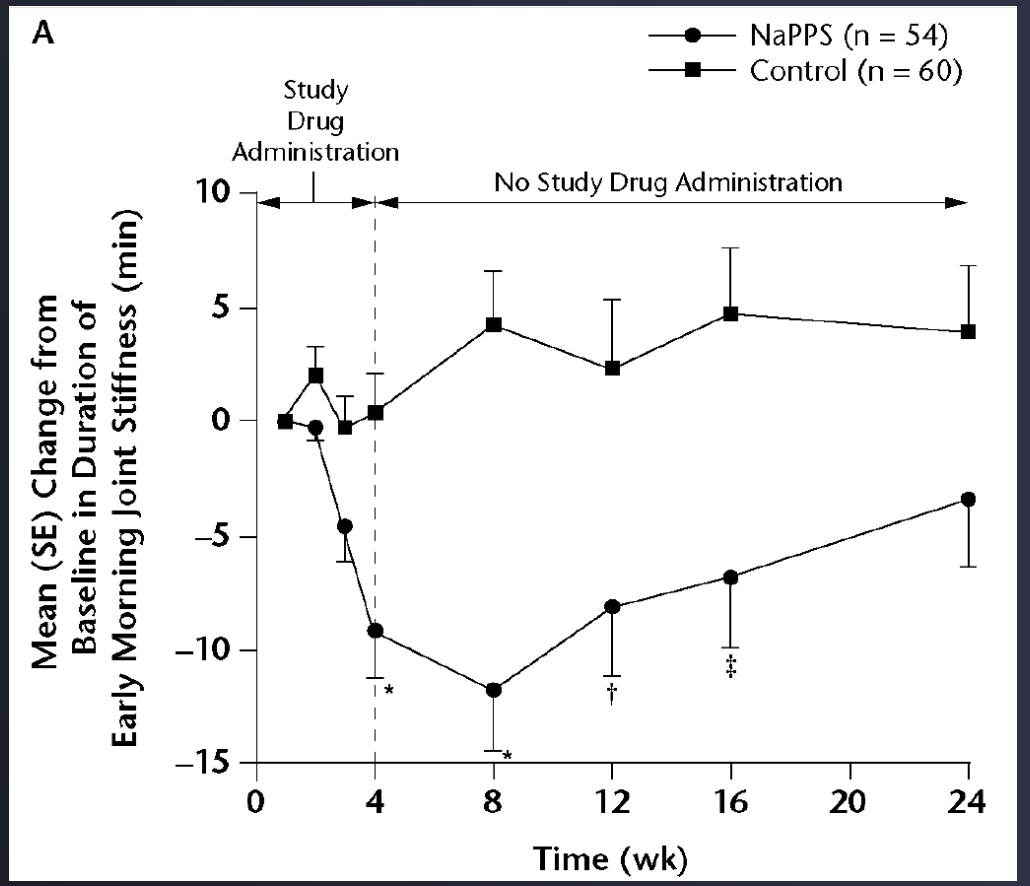
METHODS

- A randomized, double-blind, placebo-controlled study.
- Patient inclusion criteria:
  - ≥ 18years
  - OA of 1 or both knees
  - Score ≥ 4 on a 10-point Visual Analog Score (VAS) scale.
- Clinical trial design - PPS 3 mg/kg intramuscular once weekly for 4 weeks - clinical score was assessed at enrolment and weekly during the 4 weeks of treatment and at weeks 8, 12, 16, and 24.

RESULTS

- Reduced duration of morning stiffness (Figure 5).
- Reduced pain (Figure 6 – next slide).
- Global assessment improved for 20 weeks after 4 weeks dosing- durable improvement (Figure 7 – next slide)

Figure 5. Change from Baseline in Early Morning Joint Stiffness

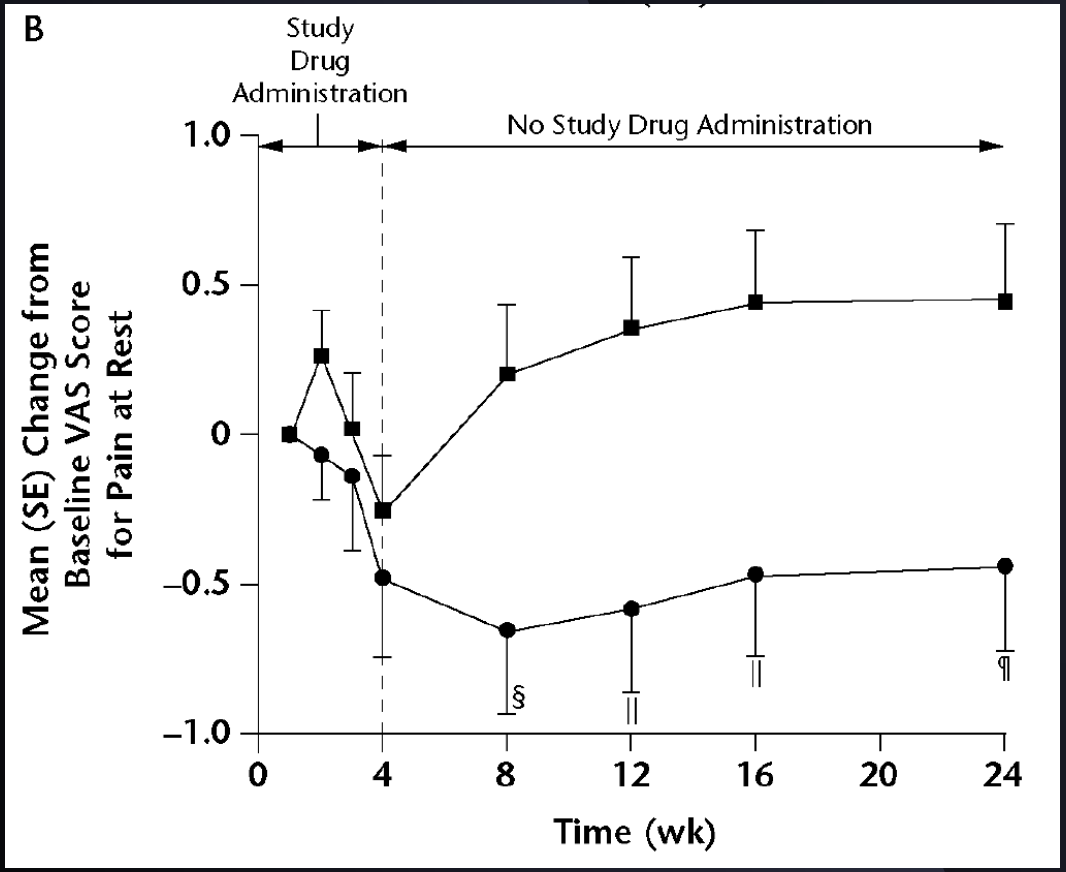


Min = minutes; NaPPS = pentosan polysulfate sodium; SE = standard error; wk = weeks. P versus control group: *< 0.001; †=0.015; ‡=0.008.

Pilot Trial – Ghosh et al, 2005 contd.

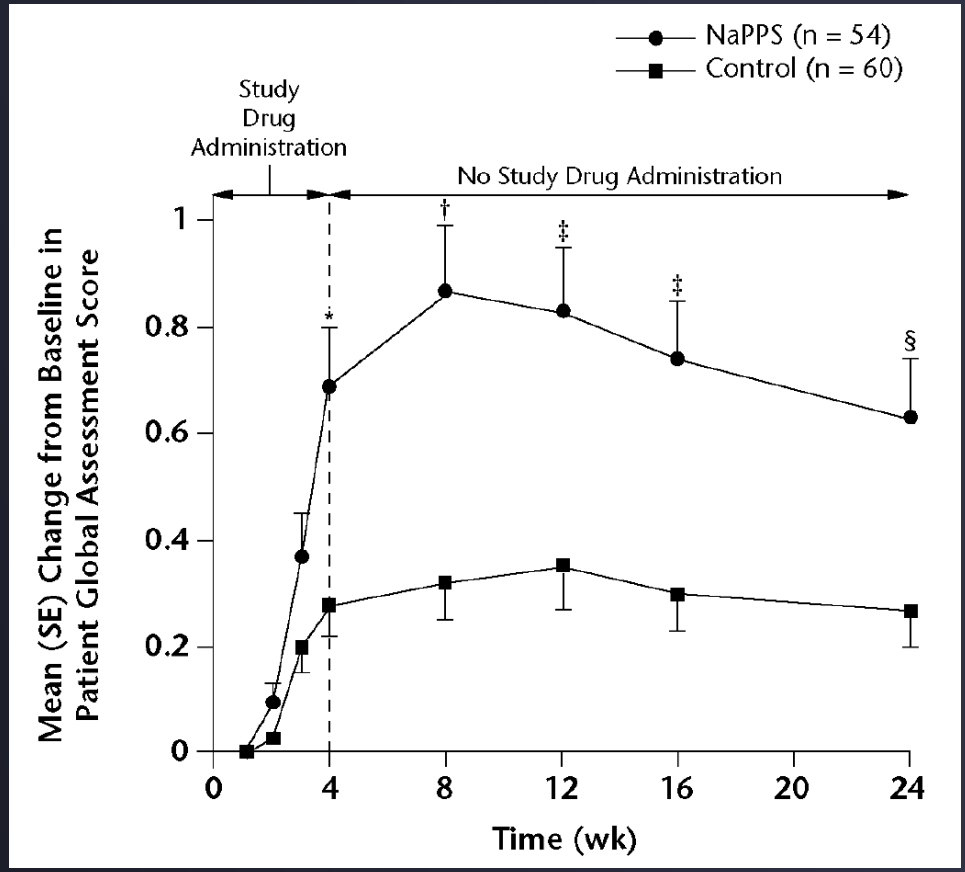
Effects of pentosan polysulfate on osteoarthritis of the knee

Figure 6. Change from Baseline in Visual Analog Scale for Pain



NaPPS = pentosan polysulfate sodium; SE = standard error; VAS = visual analog scale; wk = weeks. P versus control group: §=0.016; II=0.014; ¶=0.017.

Figure 7. Change from Baseline in Patient Global Assessment



NaPPS = pentosan polysulfate sodium; SE = standard error; wk = weeks. P versus control group: *= 0.002; †< 0.001; ‡=0.001; §=0.006.

PARA_PK_001 Pharmacokinetic Study

Phase 1 open-label safety, tolerability, and PK of multiple subcutaneous PPS doses

PROTOCOL

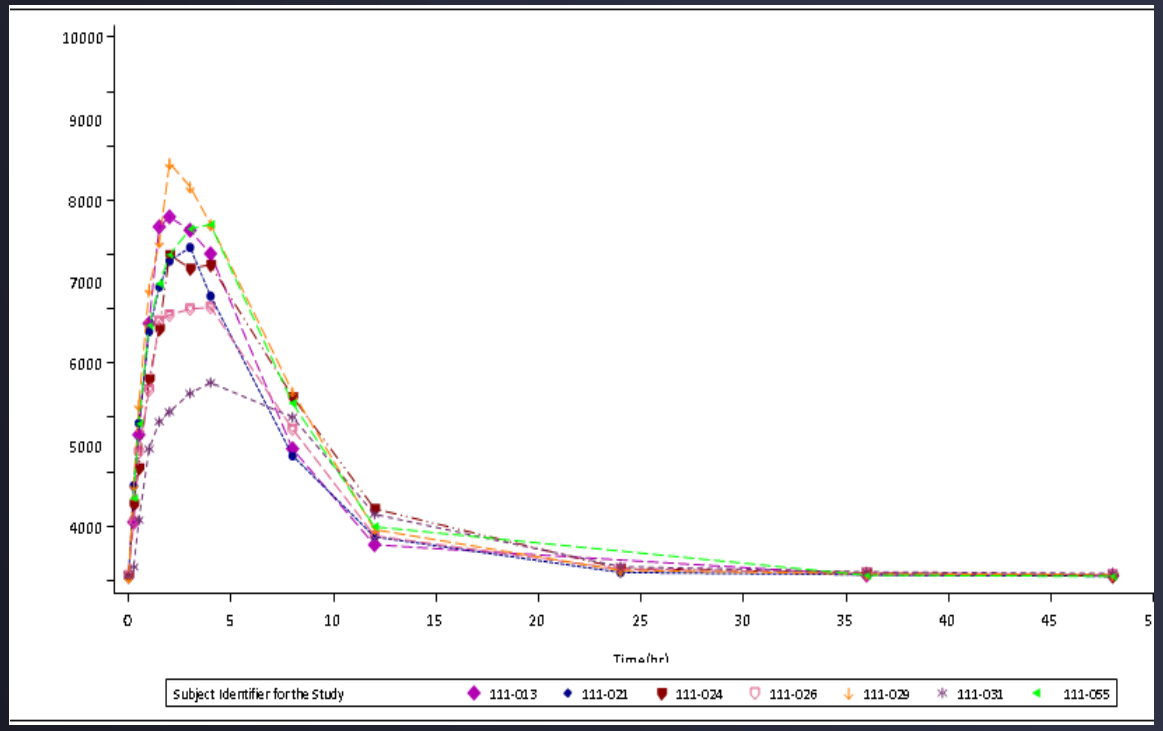
- 23 participants (~50% ≥60 years of age), 2 mg/kg SC PPS for 6 weeks
  - Cohort 1 PPS once weekly for 6 weeks (N=11)
  - Cohort 2 PPS twice weekly for 6 weeks (N=12)
- Treatment up to 42 days; follow-up up to 7 days.

CONCLUSIONS

- Plasma levels show no change from Day 1.
- Exposure parameters (AUC) and C_{max} showed no discernible PK difference between cohorts.
- There was no evidence of accumulation of PPS in plasma in each group.
- PPS was generally safe and well tolerated at 2 mg/kg either once weekly or twice weekly for a total of 6 weeks.

RESULTS

Individual Plasma PPS Concentrations (Linear) (PK Population)
– Cohort 2 (twice-weekly), Day 38



PARA_OA_005

Phase 2 Study

Exploring the effects of iPPS on knee OA with BML

Treatment arms

- Treatment period: 6 weeks
- iPPS twice weekly; placebo twice weekly

Endpoints

Effect of iPPS vs placebo on;

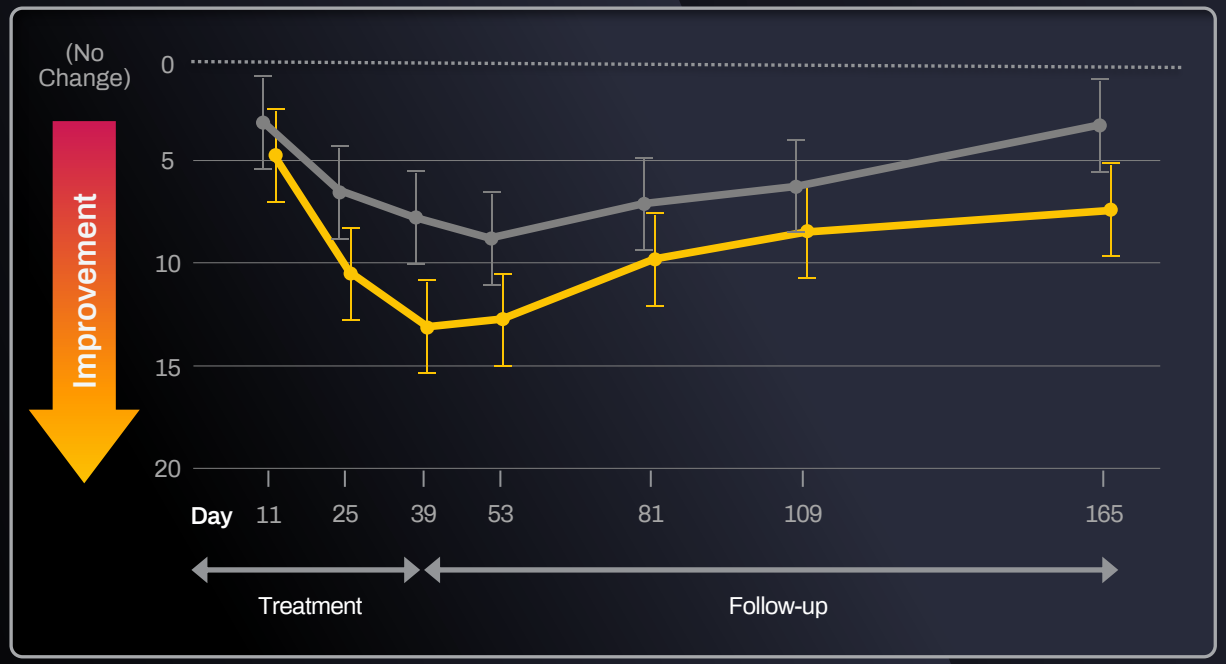
- Change in Knee Injury and Osteoarthritis Outcome Score (KOOS) pain and activities of daily living from baseline to day 165.
- Patient Global Impression of Change (PGIC).
- Change in bone marrow lesions (BML) on MRI from baseline to day 53.
- Change in serum biomarker from baseline to Dy 53

PARA_OA_005

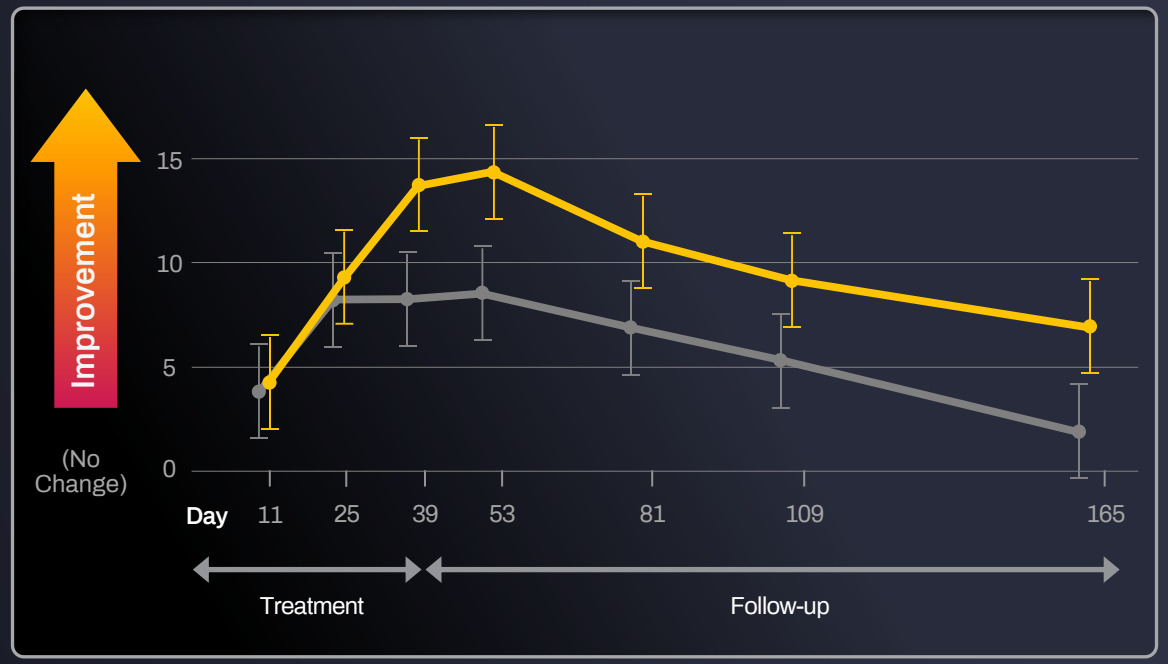
Phase 2, N=126
2 mg/kg SC twice weekly v placebo

iPPS Placebo

Pain Reduction (KOOS) Adjusted mean change from baseline N=126



Function ADL (KOOS) Adjusted mean change from baseline N=126



KOOS: Knee Injury and Osteoarthritis Outcome Score
ADL: Activities of Daily Living

Patient Global Impression of Change (PGIC)

Mean PGIC significantly higher in the PPS group than placebo group at Day 53 (4.42 versus 3.42, respectively; mean difference between PPS and placebo 1.0 [95% CI 0.24, 1.8]; p=0.0106).

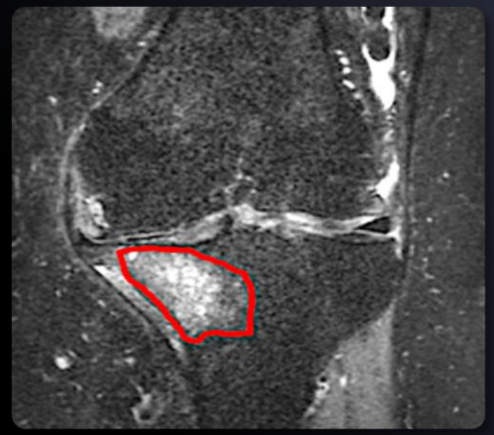
PARA_OA_005

Exploratory Endpoints

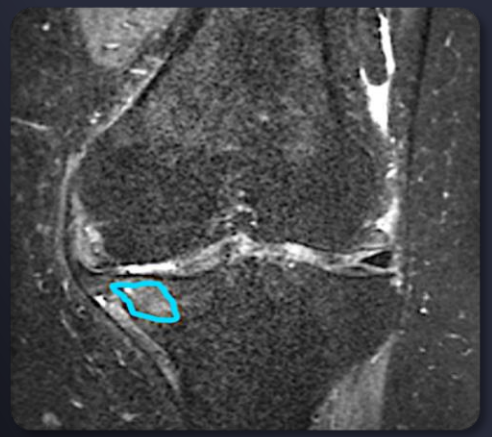
- 2 mg/kg SC twice-weekly v placebo
- PPS showed significantly reduced serum levels of cartilage degradation biomarkers
- Significant reduction in BML size as compared with placebo controls, in the medial tibia, medial femur (p=0.02), medial compartment (p=0.03), and total knee.

Reduction in size of bone marrow lesions

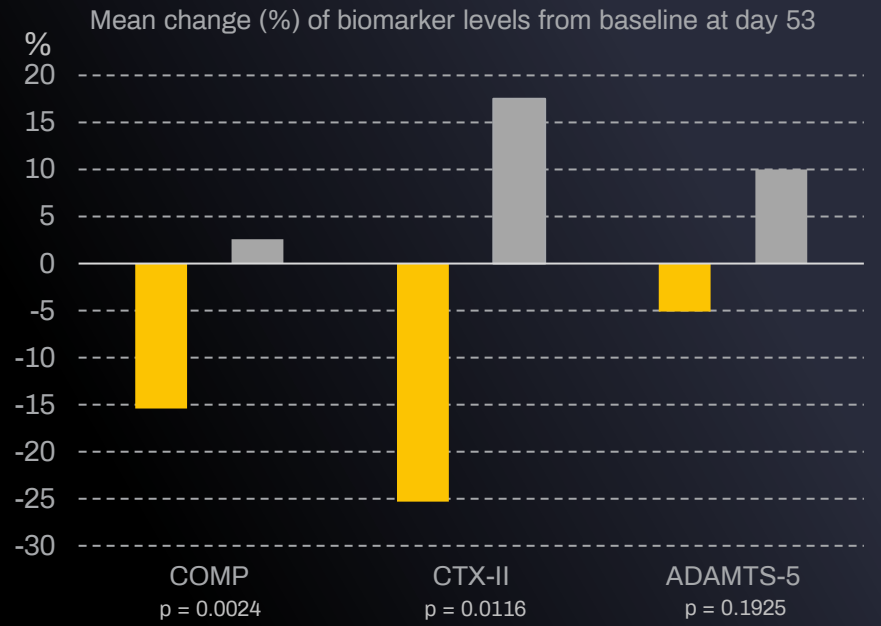
Grade 3
medial tibial BML
at baseline



Grade 2
medial tibial BML
at follow-up day 53



Reduction in serum levels of COMP & CTX-II biomarkers



Among subjects with symptomatic knee OA, **a single measurement of increased COMP predicted subsequent cartilage loss on MRI**[1]

1. Hunter DJ et al. Arthritis Res Ther. 2007;9(5):R108

PARA_OA_008

Phase 2: Disease Modification Study

Exploring the effects of iPPS as a DMOAD

Treatment arms

- Treatment period: 6 weeks
- iPPS twice weekly; iPPS once weekly + placebo once weekly, Placebo twice weekly (N=61)

Endpoints

- Primary endpoint – change in 1+ synovial fluid biomarkers at Day 56
- Synovial fluid, serum and urine biomarkers associated with inflammation & OA disease progression (Day 56 & Day 168)
- Improvement in WOMAC pain, function, and stiffness (Day 56, Day 168 & Day 365)
- Structural imaging (MRI) endpoints (Day 168)
- Patient Global Impression of Change (PGIC)

DMOAD - Disease modifying osteoarthritis drug

Clinical trial outcomes of PPS in osteoarthritis

PARA_OA_008 – DMOAD effects

- iPPS once-weekly (n=20), twice-weekly (n=19), & placebo (n=22).
- Results to be discussed during the podium presentation include;
  - Synovial fluid and serum biomarkers at Day 168
  - Pain, function, and PGIC at Days 56, 168, and 365
  - WORMS MRI analysis at Day 168
  - Quantitative MRI analysis at Day 168

The analysis of DMOAD effects will be presented tomorrow:

Concurrent Session 09: News in Therapies
Saturday, April 20, 2024
2:00 PM to 3:30 PM

3:10 PM: Effects of PPS on clinical outcomes and disease modifying biomarkers in moderate to severe knee osteoarthritis - Mukesh Ahuja, MBBS, MS

Safety Profile

Pentosan polysulfate sodium

Over 1200 people have been treated with iPPS through Paradigm clinical and early access programs.

Very common adverse events (AEs):

- Injection site reactions (bruising, erythema, pain, pruritus, swelling).

Common AEs:

- Headache (mild and self-limiting), transient thrombocytopenia.

Uncommon AEs:

- Heparin-induced thrombocytopenia (HIT) has been observed in ~1% of patients.

Other relevant information:

- Pigmentary maculopathy (PM) has been observed following long-term cumulative dosing of oral PPS (Elmiron®).
- With iPPS, no cases have been observed in either the clinical or nonclinical programs.

Comparison with existing therapies

Versus PARA_OA_008

JAMA | Original Investigation

Association of Pharmacological Treatments With Long-term Pain Control in Patients With Knee Osteoarthritis

A Systematic Review and Meta-analysis

Dario Gregori, PhD; Giampaolo Giacovelli, PhD; Clara Minto, MA; Beatrice Barbetta, MS; Francesca Gualtieri, MA; Danila Azzolina, MS; Paola Vaghi, MS; Lucio C. Rovati, MD

ELSEVIER
Osteoarthritis and Cartilage
Volume 23, Issue 12, December 2015, Pages 2086-2093

Review

Recommendations for an update of the 2010 European regulatory guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis and reflections about related clinically relevant outcomes: expert consensus statement

J.-Y. Reginster †, S. Reiter-Niesert ‡, O. Bruyère †, F. Berenbaum §, M.-L. Brandi ¶, J. Branco #, J.-P. Devogelaer ‡‡, G. Herrero-Beaumont §§, J. Kanis ‖‖, S. Maggi ¶¶, E. Maheu ##, P. Richette †††, R. Rizzoli §§§, C. Cooper ‖‖‖ ¶¶¶

Reviews | 6 January 2015

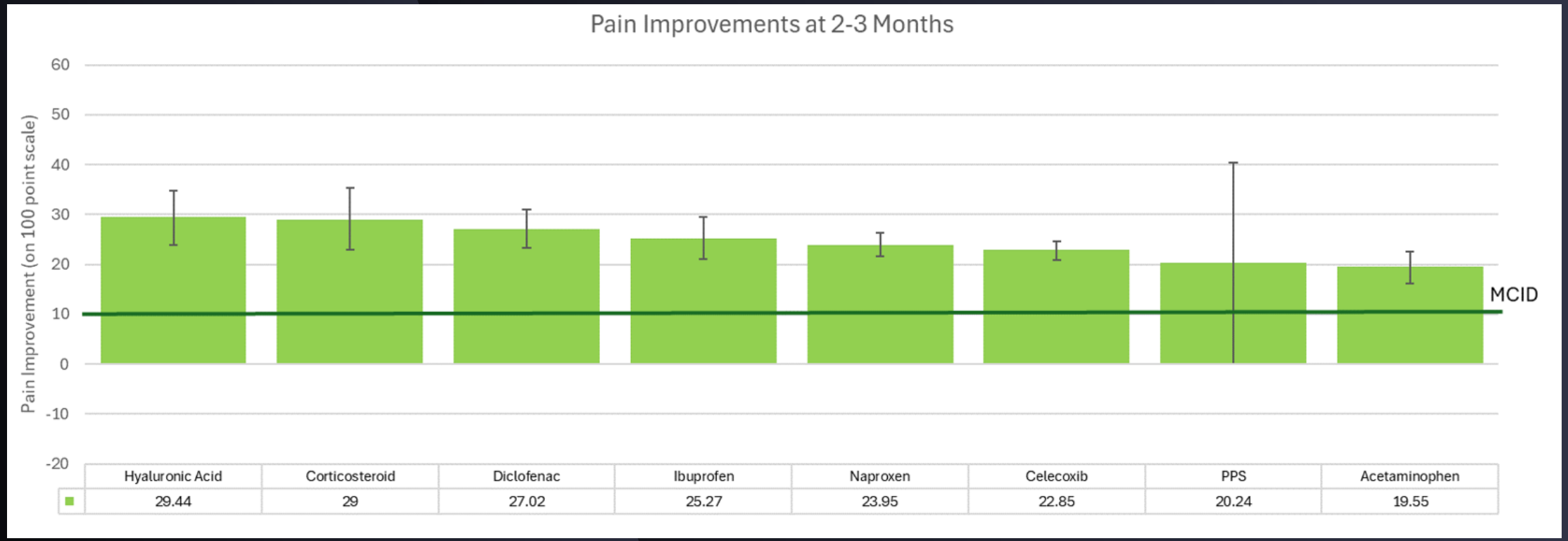
Comparative Effectiveness of Pharmacologic Interventions for Knee Osteoarthritis: A Systematic Review and Network Meta-analysis

Authors: Raveendhara R. Bannuru, MD, Christopher H. Schmid, PhD, David M. Kent, MD, Elizaveta E. Vaysbrot, MD, John B. Wong, MD, and Timothy E. McAlindon, MD | AUTHOR, ARTICLE, & DISCLOSURE INFORMATION

Publication: Annals of Internal Medicine • Volume 162, Number 1 • https://doi.org/10.7326/M14-1231

Comparison with available OA medications

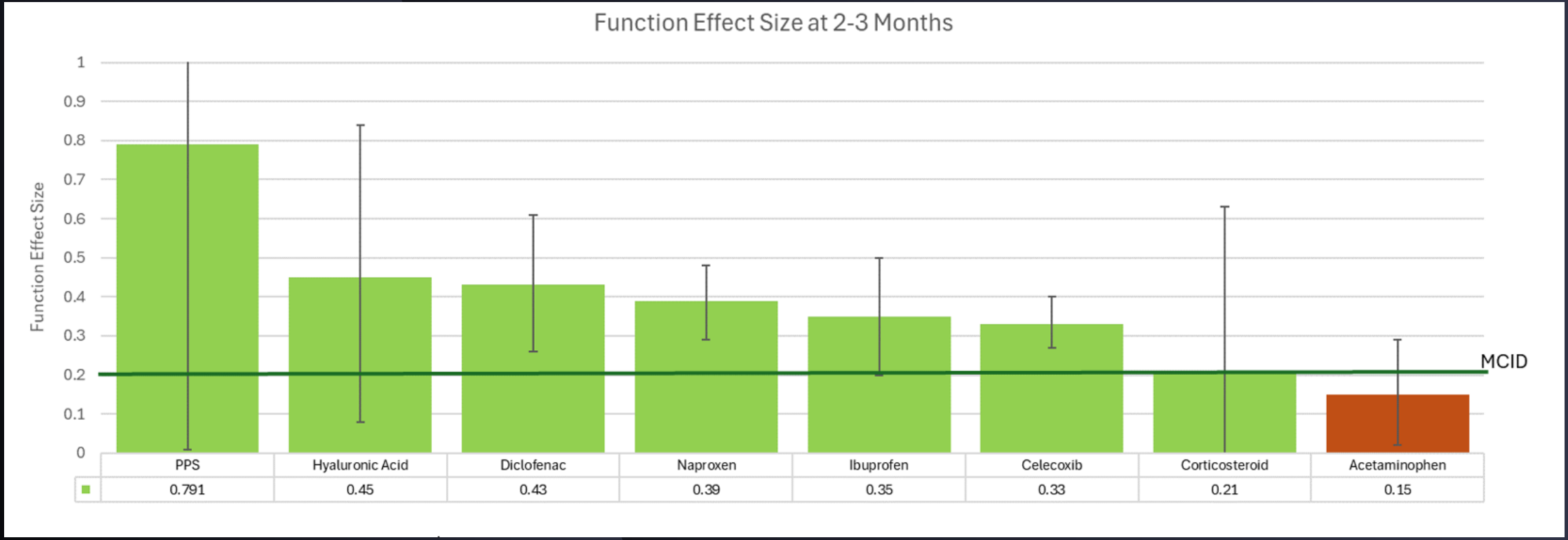
Pain improvement at 2–3 months



Treatment estimates taken from Bannuru 2015[1]. PPS estimate from PARA_OA_008 trial. MCID value marked at 10 points on 100-point pain scale[2]. [1]Bannuru RR et al. Ann Intern Med. 2015 Jan 6;162(1):46-54.

Comparison with available OA medications

Functional improvement at 2–3 months (effect size)



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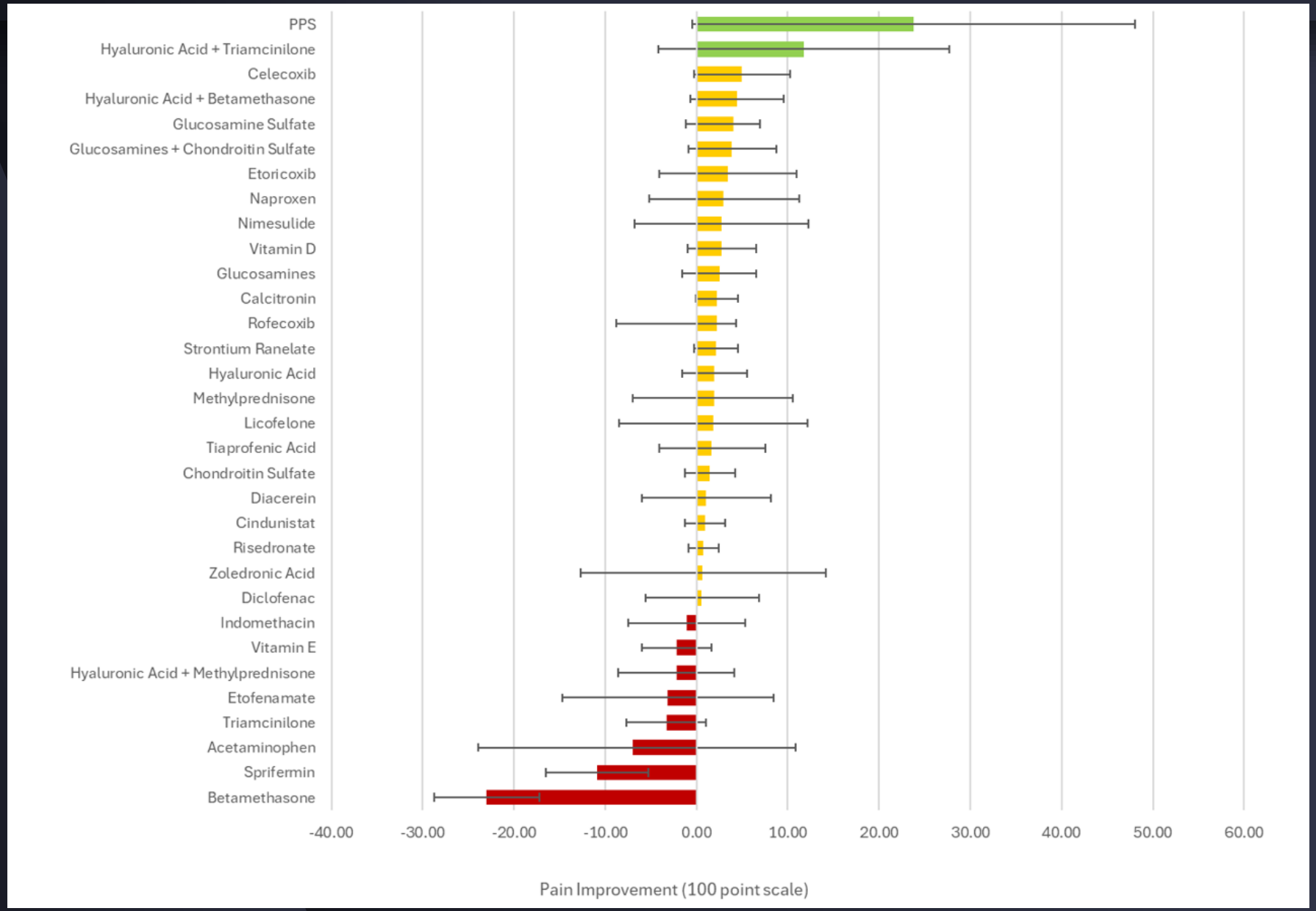
Comparison with available OA medications

Pain improvement at 1 year



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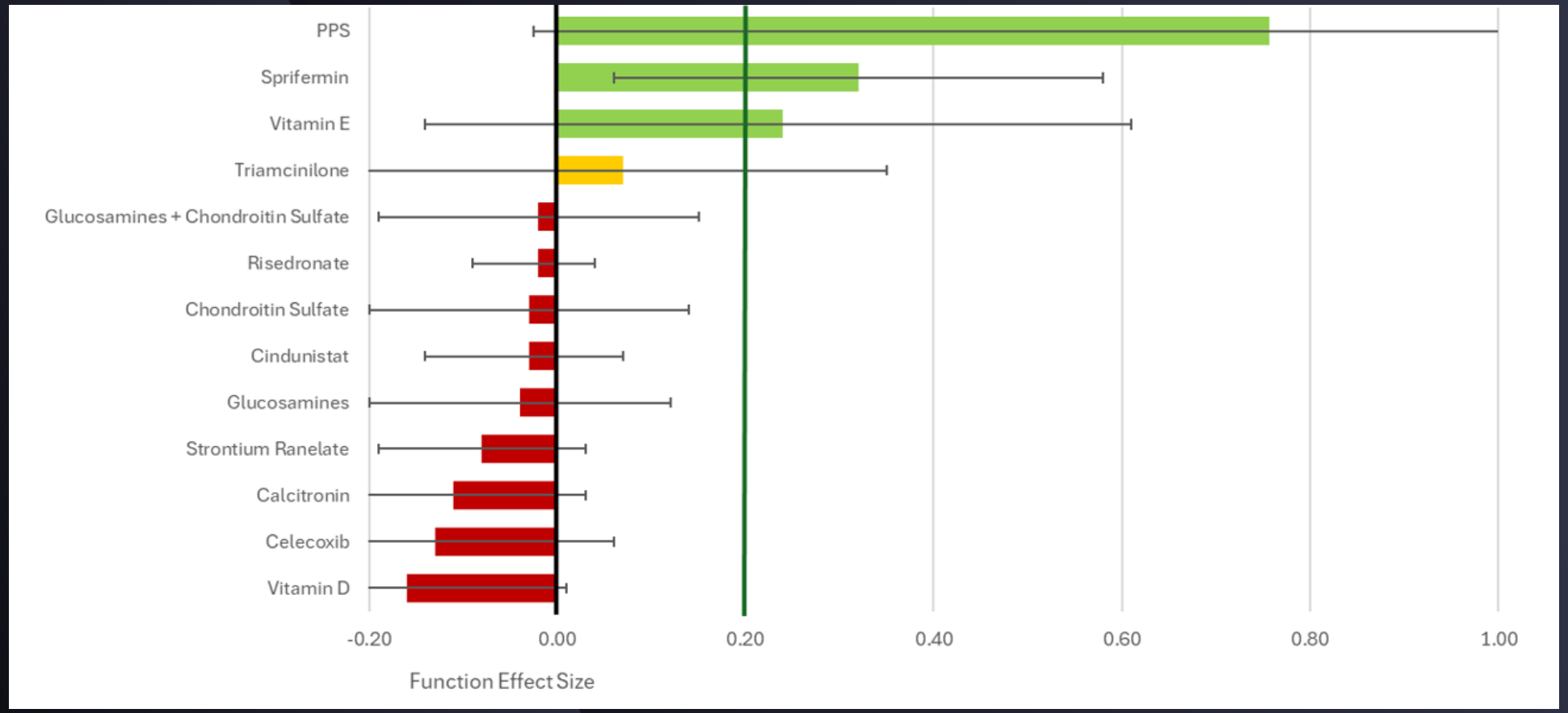
Comparison with available OA medications

Functional effect size at 1 year



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