Effects of pentosan polysulfate sodium on clinical outcomes and disease modifying biomarkers in moderate to severe knee osteoarthritis

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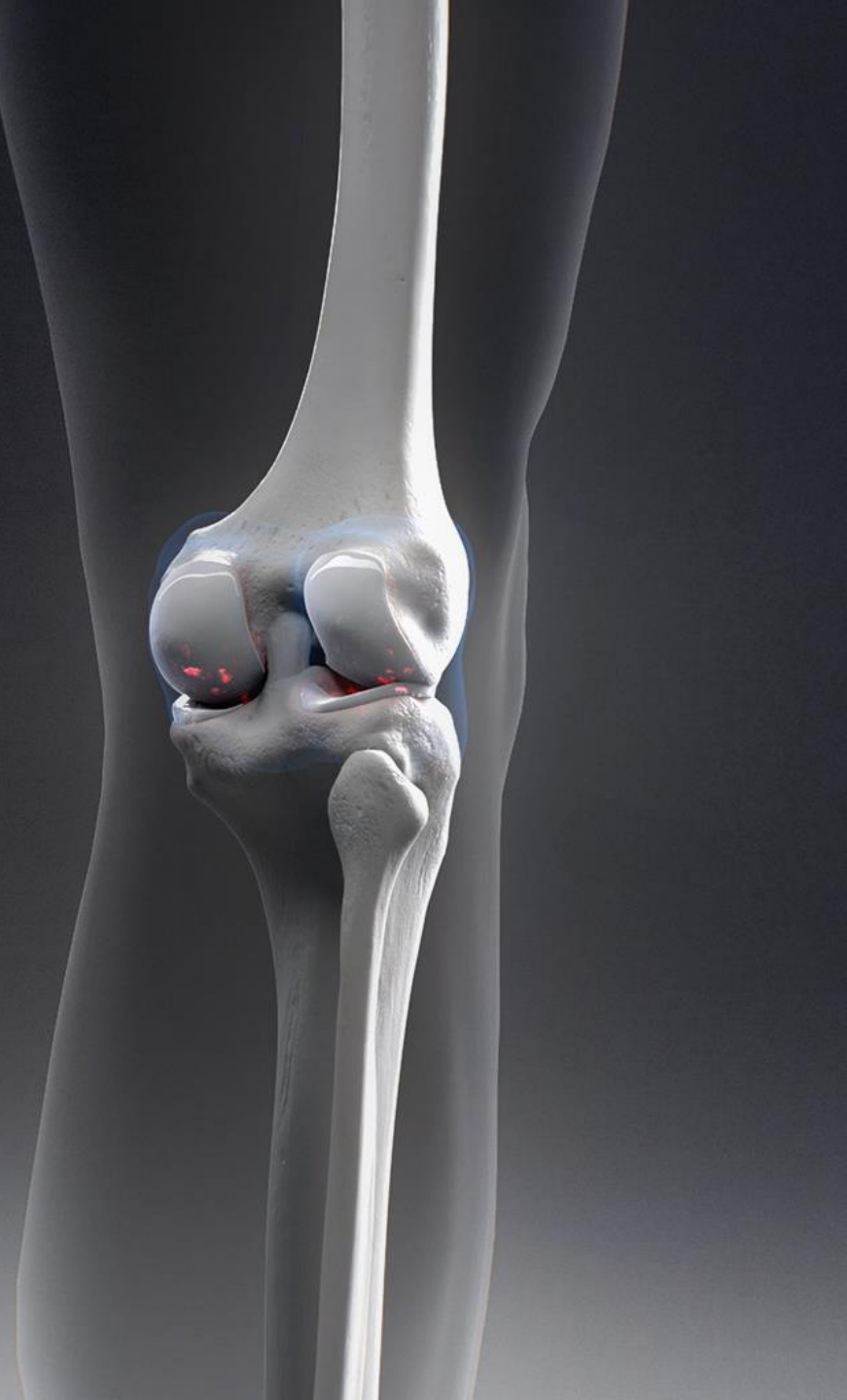


PPS

Pentosan polysulfate sodium is a semi-synthetic xylose-based polysaccharide (hemicellulose) that is derived from beechwood and is highly sulfated during its manufacturing process.

Complex Molecule

Multivariate MoA

Existing registrations

Pentosan polysulfate sodium for subcutaneous use (PPS, iPPS)

- PPS is a **non-opioid** with a 60-year track record treating pain, inflammation, and thrombosis in humans.
- PPS in a 100 mg/mL solution for injection in a 2-mL vial.

Proposed mechanisms of action

Anti-inflammatory

- Blocks NF-kB-mediated activation of inflammatory cytokines, IL-1β. IL-6, and TNF-α.

Analgesic

- Normalizes expression of pain mediator NGF in osteocytes, chondrocytes, and synovial cells.

Anti-catabolic

- Inhibition of cartilage-degrading enzymes known to play a key role in OA progression.

Anti-thrombotic

- Has anti-thrombotic, fibrinolytic, and antilipidemic effects, which may assist with improved microvascular circulation in the subchondral bone.

Registered products

- PPS (100 mg oral capsules) registered in Australia, EU, and USA for the treatment of interstitial cystitis.
- PPS (100 mg injection) registered in Italy for thromboprophylaxis.

iPPS in Knee OA

PARA_OA_008

An exploratory phase 2, randomised, double-blind, placebo-controlled study to evaluate the treatment effect of pentosan polysulfate sodium compared with placebo on synovial fluid biomarkers in participants with knee osteoarthritis pain.

Treatment arms

- iPPS twice weekly: 2.0 mg/kg IBW PPS twice weekly for 6 weeks.
- iPPS once weekly: 2.0 mg/kg IBW PPS once weekly + placebo (0.9% saline) once weekly for 6 weeks.
- Placebo: placebo (0.9% saline) twice weekly for 6 weeks.
    - Total of 61 participants (1:1:1).

Primary objective

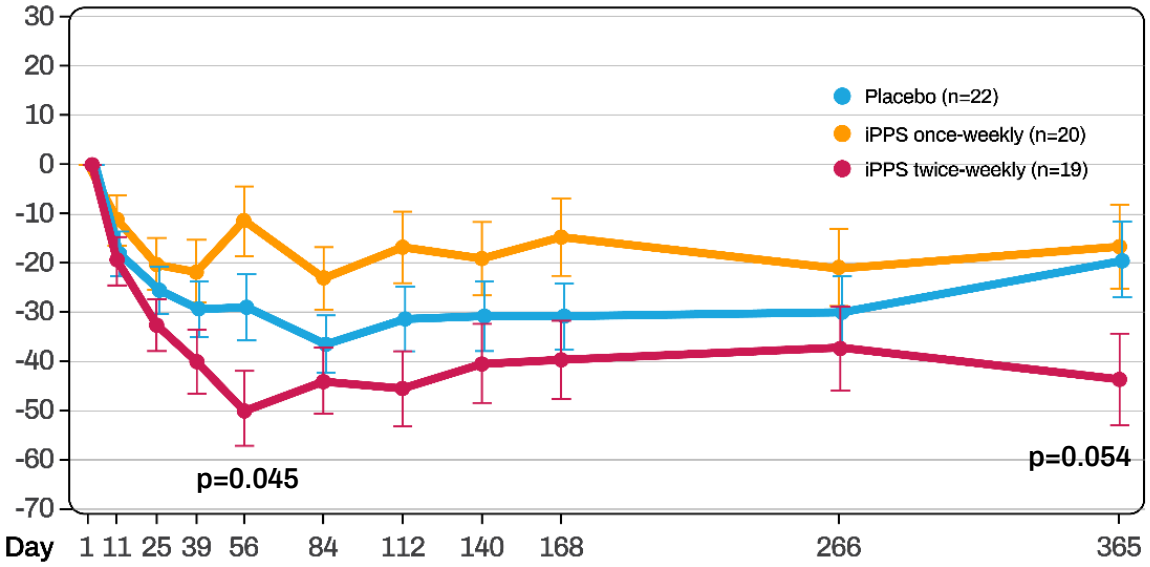
Effect of iPPS on synovial fluid biomarkers associated with inflammation and OA disease progression (Day 56).

Secondary objectives

- Effect of iPPS treatment on synovial fluid, serum and urine biomarkers associated with inflammation and OA disease progression (Day 56 and Day 168).
- Effect of iPPS on WOMAC pain, function, stiffness, and overall (Day 56, Day 168 and Day 365).
- Effect of iPPS on structural imaging biomarkers (Day 168).

Clinical Results

Pain Reduction | WOMAC least squares adjusted mean change from baseline. FAS.

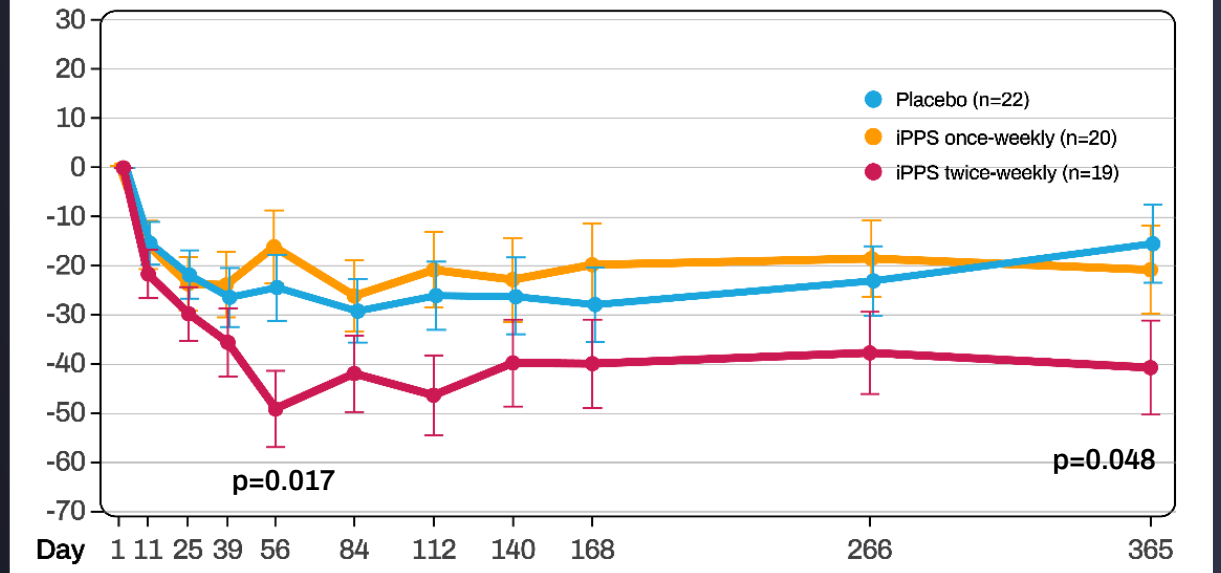


LS Mean Change +/- Standard Error; FAS: Full Analysis Set; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; P values for twice-weekly PPS vs placebo

≥30% improvement in pain

- Day 168: 60% twice-weekly iPPS vs 41% placebo
- Day 365: 54% twice-weekly iPPS vs 33% placebo

Improved Function | WOMAC least squares adjusted mean change from baseline. FAS.



LS Mean Change +/- Standard Error; FAS: Full Analysis Set; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; P values for twice-weekly PPS vs placebo

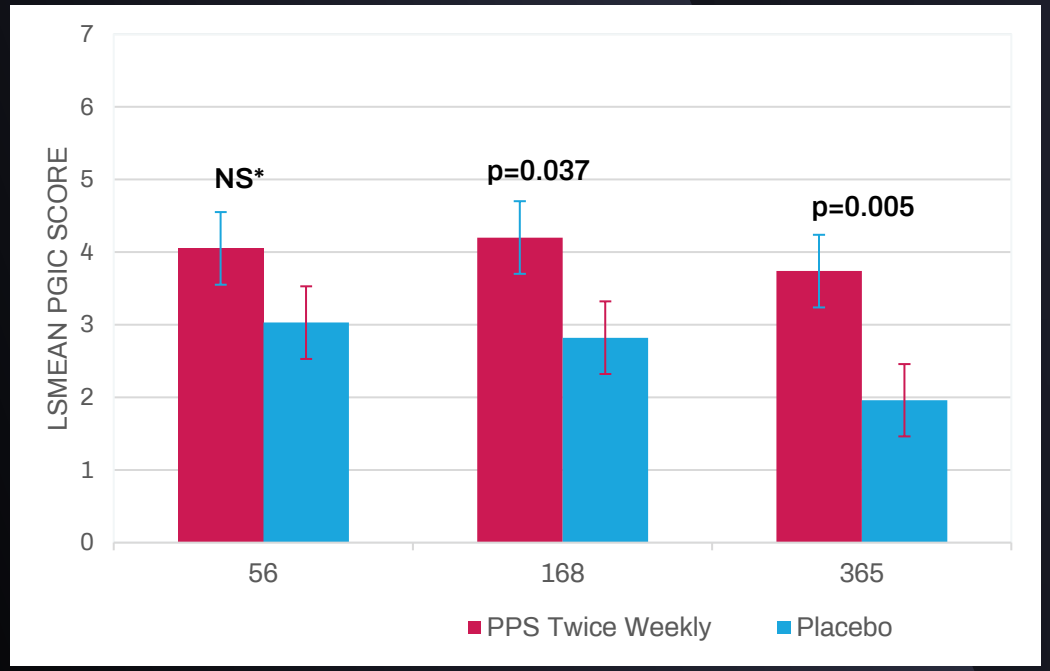
≥50% improvement in function

- Day 168: 53% twice-weekly iPPS vs 22% placebo (p=0.067)
- Day 365: 55% twice-weekly iPPS vs 28% placebo

Clinical Results

Patient Global Impression of Change (PGIC)

- Twice-weekly iPPS had a mean Day 168 PGIC score of 4.20 vs 2.82 for placebo (p=0.037).
- Twice-weekly iPPS had a mean Day 365 PGIC score of 3.74 vs 1.96 for placebo (p=0.005).



Average patient-reported PGIC scores in participants treated with twice-weekly iPPS versus placebo.

Rescue medication use

- 5–6x higher cumulative doses of rescue medication in placebo:
  - Day 168: mean cumulative use was 25,018 mg in placebo vs 4,144 mg in twice-weekly iPPS
  - Day 365: mean cumulative use was 28,947 mg in placebo vs 5,144 mg in twice-weekly iPPS
- 4–5x more days of rescue medication in placebo:
  - Day 168: mean 22.8 days use for placebo vs 4.4 days for twice-weekly iPPS
  - Day 365: mean 19.5 days use for placebo vs 4.6 days for twice-weekly iPPS

*NB: Error in abstract, D56 PGIC was not significantly different, whereas D168 and D365 were.

Molecular Biomarkers

Origin	Biomarker	Biomarker Function	Unit	Day 56	D168
Synovial fluid	IL-6	Pro-inflammatory cytokine	pg/mL	-4.22 (-154.62, 146.18)	697.47* (-325.77, 1611.60)
	TNF-α	Pro-inflammatory cytokine	pg/mL	-110.15 (-270.57, 50.27)	-16.70 (-60.56, 27.15)
	βNGF	Pain mediator	pg/mL	-36.05 (-97.86, 25.77)	-7.49 (-43.55, 28.57)
	COMP	By-product of cartilage degradation	µg/mL	-23.60 (-62.60, 15.40)	-24.40 (-68.99, 20.20)
	ARGS	By-product of cartilage degradation	ng/mL	-56.60 (-106.59, -6.62) p=0.028	-74.01 (-137.57, -10.45) p=0.024
	TIMP-1	Endogenous inhibitor of cartilage degradation	µg/mL	10.55 (-35.35, 56.45)	-3.16, (-48.87, 42.55)
Serum	ARGS	By-product of cartilage degradation	ng/mL	-4.63 (-13.24, 3.97)	-7.79 (-16.22, 0.63)
	COMP	By-product of cartilage degradation	µg/mL	-10.64 (-17.48, 2.88)	-10.85 (-26.03, 4.33)
	C2C	By-product of cartilage degradation	ng/mL	-7.30 (-17.48, 2.88)	-29.25 (-54.45, -4.04) p=0.024
Urine	CTX-II	By-product of cartilage degradation	ng/mmol	-53.27 (-157.40, 50.86)	-8.03 (-38.00, 21.94)

Least squares mean % difference in change from baseline of pooled iPPS groups vs placebo (confidence intervals). *Due to one outlier iPPS subject with >8000% CFB result which skewed the LS Mean value at Day 168. ARGS = Aggrecan amino acids alanine, arginine, glycine, and serine; C2C = type 2 collagen; COMP = cartilage oligomeric matrix protein; CTX-II = c-terminal telopeptide II; IL-6 = Interleukin-6; NGF = nerve growth factor; TIMP-1 = tissue inhibitor matrix metalloproteinase 1; TNF-α = tumour necrosis factor alpha.

Structural Biomarkers

MRI Analysis

- Structural biomarkers:
  - Articular cartilage loss.
  - Subchondral bone marrow lesions (BML).
  - Synovitis (gadolinium enhanced).
  - Osteophytes.

- Assessment methods:
  - Whole-Organ MRI Scoring (WORMS).
  - Quantitative measurements (qMRI).

Structural Biomarkers

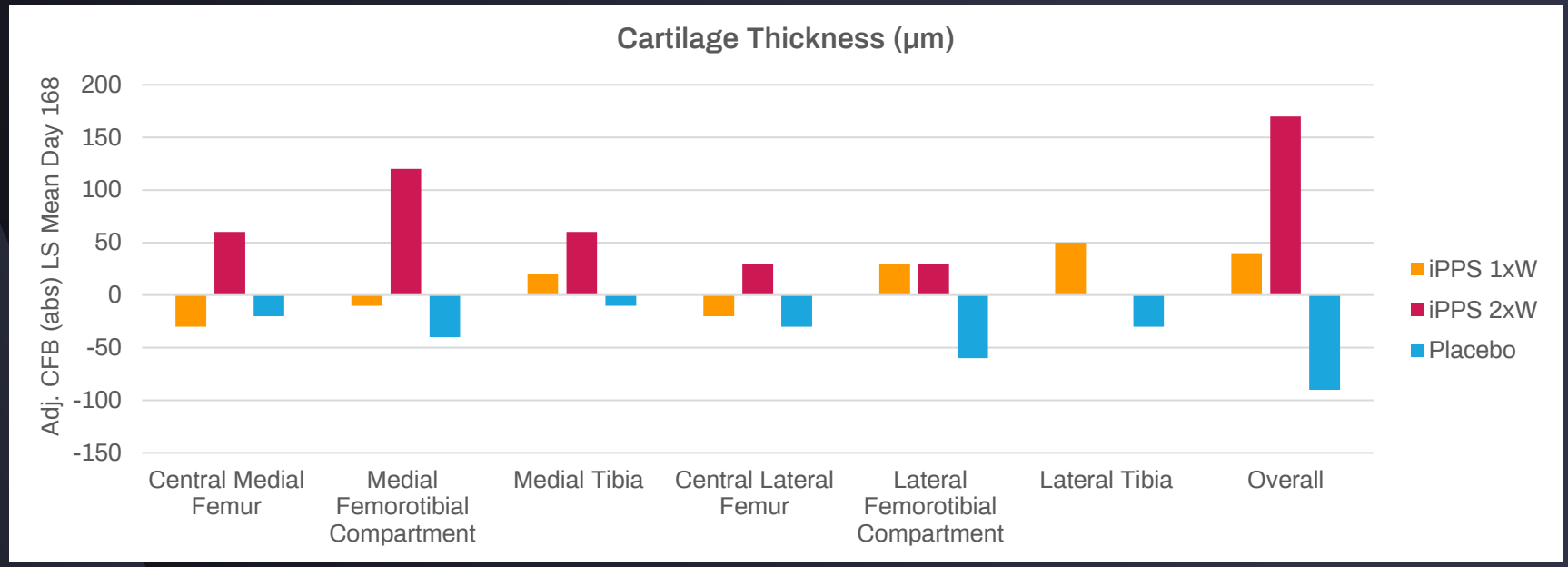
MRI Analysis

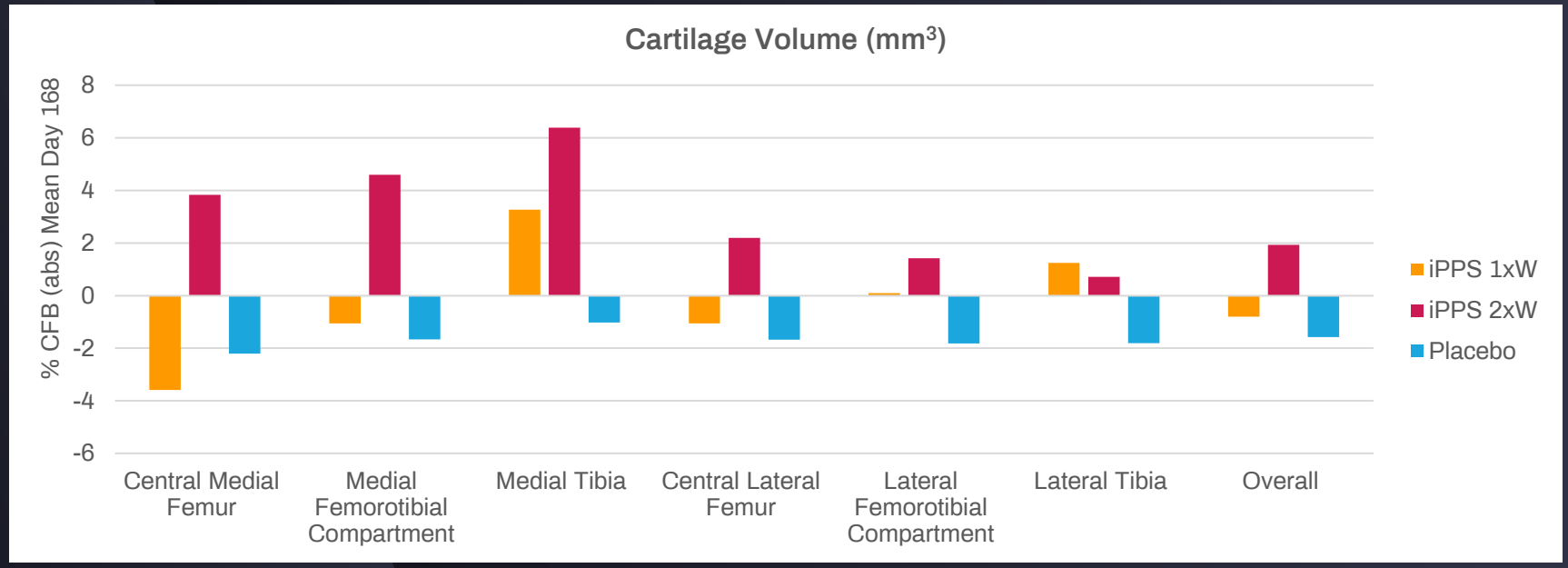
Whole-Organ MRI Scoring (WORMS)

- WORMS showed signals of improvement in the iPPS vs placebo groups:
  - Stabilization of BML.
  - Stabilization of cartilage (but not increase in thickness and volume).
  - Stabilization of osteophytes.

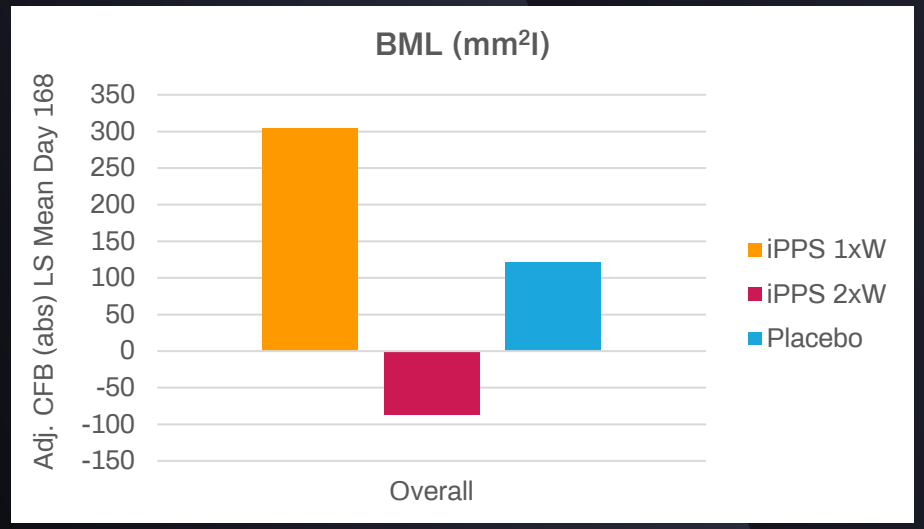
Structural Biomarkers

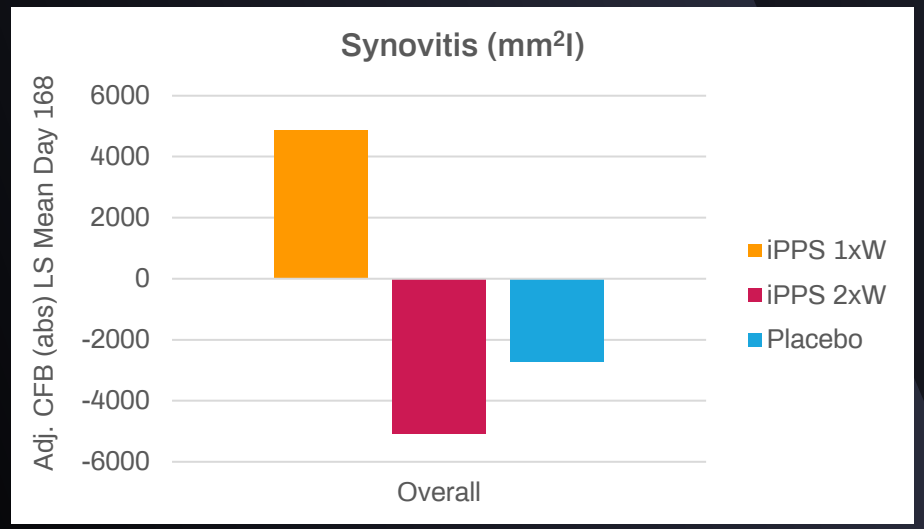
Quantitative Analysis





Structural Biomarkers | Quantitative Analysis



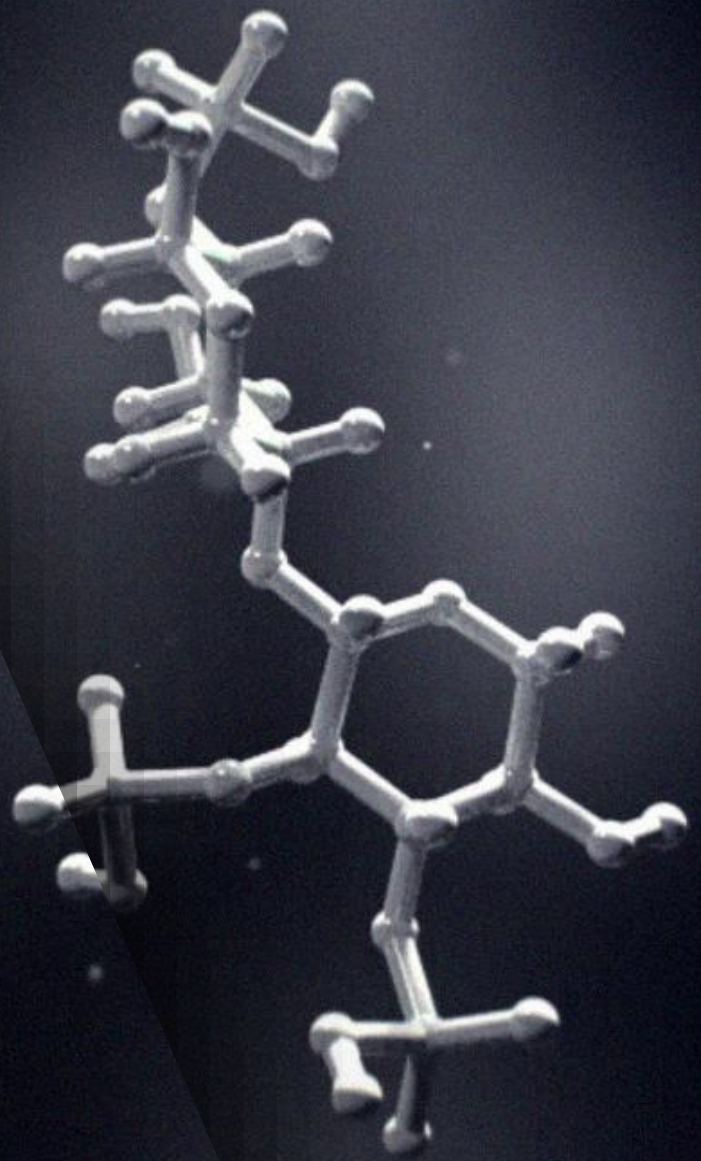


All compartments/ regions at D168	iPPS twice-weekly (n=15)	Placebo (n=22)
Cartilage thickness overall (mm)	0.17 p=0.05	-0.09
Cartilage volume overall (mm^3)	191.51 p=0.07	-86.81
Bone marrow lesion overall (mm^2I)	-86.26	120.65
Synovitis overall (mm^2I)	-5086.13	-2707.38

Overall adjusted change from baseline (absolute) least squares mean (LSM) for cartilage thickness and volume, bone marrow lesions, and synovitis.

Thank you

QUESTIONS?



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