PARADIGM BIOPHARMA

18TH BIOSHARES BIOTECH SUMMIT | JULY 2024

FREMANTLE | WA

MR. PAUL RENNIE | MANAGING DIRECTOR

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Executive Summary

Paradigm Biopharmaceuticals Ltd. (PAR.ASX)

Established Molecule

Pentosan polysulfate sodium for subcutaneous use (PPS, iPPS,Zilosul®)

- **Non-opioid** with a 60-year track record treating pain, inflammation, and thrombosis in humans.
- Extensive clinical data and Real-world evidence of iPPS effect in OA

Lead Program

Osteoarthritis (OA) ZILOSUL®, high unmet need with blockbuster potential

- FDA Fast Tracked phase 3 OA program.
- Opportunity for expedited approval in Australia
- Primary endpoint achieved across two phase 2 studies – confirmed same primary endpoint as phase 3.
- 12-month durability from one 6-week course of treatment.
- Treatment effect beyond just the relief of OA symptoms

TAM

Blockbuster Market potential

- Clinical program supports broad label, maximises reimbursed price and market penetration from launch.
- 5% penetration of 72m+ addressable market from launch >$5B revenue opportunity.

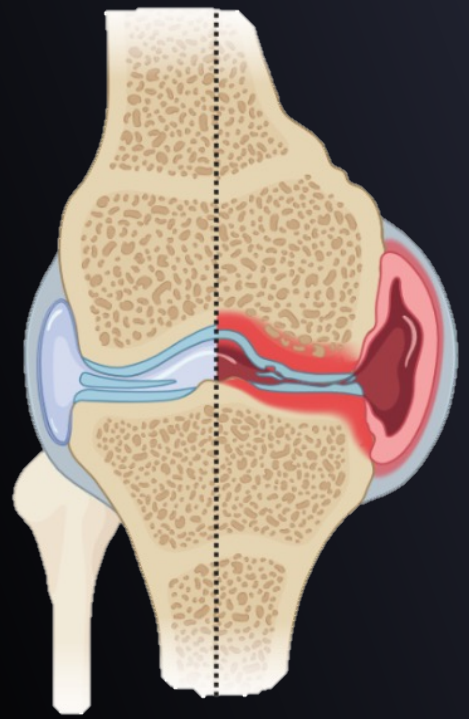
Extensive Market Protection

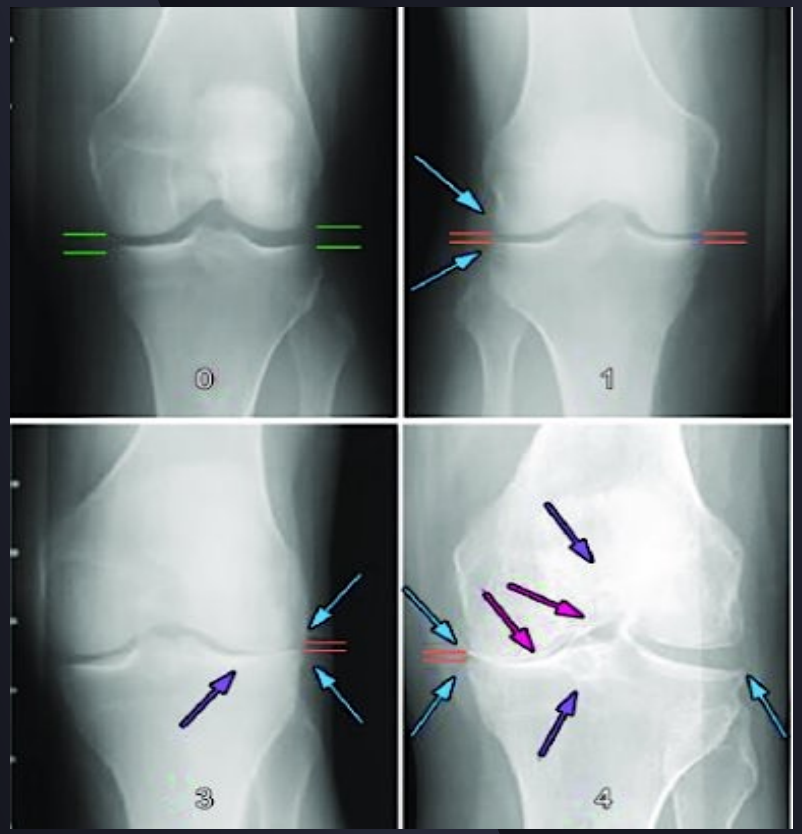
Exclusivity & market protection

- **25-year post-marketing exclusivity** with bene pharmaChem FDA-approved API manufacturer of PPS for human use.
- Commercial scale manufacturing capabilities completed.
- Additional global protection via several method of use patents.

Knee

Osteoarthritis





Knee Osteoarthritis (OA)

- Most common musculoskeletal problem.
- Global prevalence:
  - 16% in people aged 15+ years
  - 23% in people aged 40+ years
- There are 654 million worldwide with knee OA. 14 million people in the USA have symptomatic knee OA.
- In OA, the cartilage within the joint begins to break down causing slowly worsening changes in the underlying bone.
- Obesity and repeated trauma are two key risk factors.

Schematic from BioRender.com

Blockbuster market opportunity

Zilosul® is a **non-opioid subcutaneous injectable aimed to treat pain and function in osteoarthritis.**

People affected by OA in 2020[3]

72m+

People affected by OA by 2030[3]

120m+

Markets: US, UK, France, Germany, Italy, Spain, Canada and Australia.

Knee and Hip (Global)

69% of all OA

OA patients dissatisfied with current treatments[1]

81%

Target uptake: 10% dissatisfied market[1]

Zilosul indicative price: US$2500 per year[2]

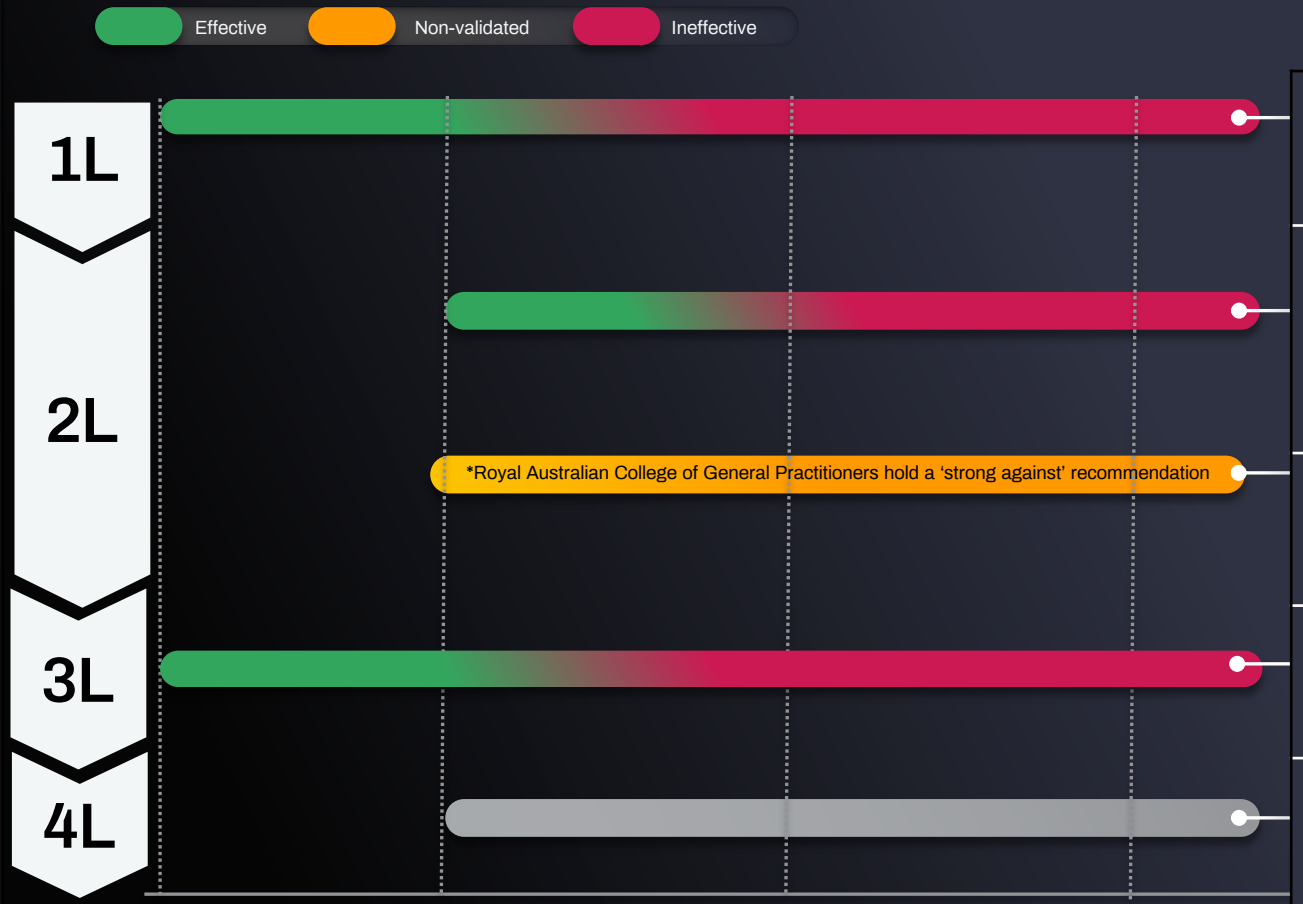
Compared with 2020, cases of OA are projected to increase 74·9% for knee and 78·6% for hip by 2050.[5]

1. National Institute of Health; Emerging drugs for osteoarthritis; Hunter DJ and Matthews G 16(3): 479–491; 2011 September.
2. Global Pricing Research conducted by Paradigm.US, UK Germany, France
3. OARSI. Osteoarthritis: A Serious Disease, Submitted to the U.S. Food and Drug Administration December 1, 2016
4. Calculation based on 10% penetration dissatisfied patients with Knee and Hip OA in the 72m addressable market, at price of US$2500.
5. **Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021**

"Most patients with OA of the hip and/or knee either initiate on or switch to opioids for long-term management of OA-related pain despite known risks. This highlights the need for new treatments that delay or prevent use of opioids[1]".

Market Demand

Limited treatment options as degenerative OA disease progresses



Analgesics, NSAIDS,Cox-2	• Daily use • GI, CV risk with prolonged use.
*Hyaluronic Acid Injectable*Platelet-rich Plasma, *Stem Cells	• Limited pain relief • Royal Australian College of General Practitioners hold a 'strong against' recommendation.
Steroid injectable	• Limited pain relief • Evidence of further cartilage degradation
Opioids	• Severe side-effects • Addictive
Surgery - Total Knee Arthroscopy	• High cost • Patients opting for alternative treatments

CV = Cardiovascular; GI = Gastrointestinal

1. Source: https://www.tandfonline.com/doi/full/10.1080/03007995.2023.2234727?scroll=top&needAccess=true&role=tab

Zilosul's (iPPS) proposed profile was regarded positively compared to current therapies

Assuming sustained efficacy and robust safety data, physicians and payers believe Zilosul will provide high value to the treatment of kOA by covering some important unmet needs

ZILOSUL®

- New MoA
- Favourable safety profile with no renal, GI, CV side effects or cartilage degradation ★
- No drug abuse potential ★
- Meaningful and durable pain reduction, functional improvement and potential DM effect ★
- Subcutaneous RoA vs. IA injections ★
- Convenient dosing regimen (6 week treatment) vs. daily intake

Zilosul is expected to cover the main residual unmet needs highlighted by physicians and payers as it will provide an alternative treatment to kOA patients that is well-tolerated and potentially preserving structural changes in kOA

CV = Cardiovascular; DM = Disease Modification; GI = Gastrointestinal; IA = Intra-articular; kOA = Knee Osteoarthritis; MoA = Mechanism of Action; RoA = Route of administration

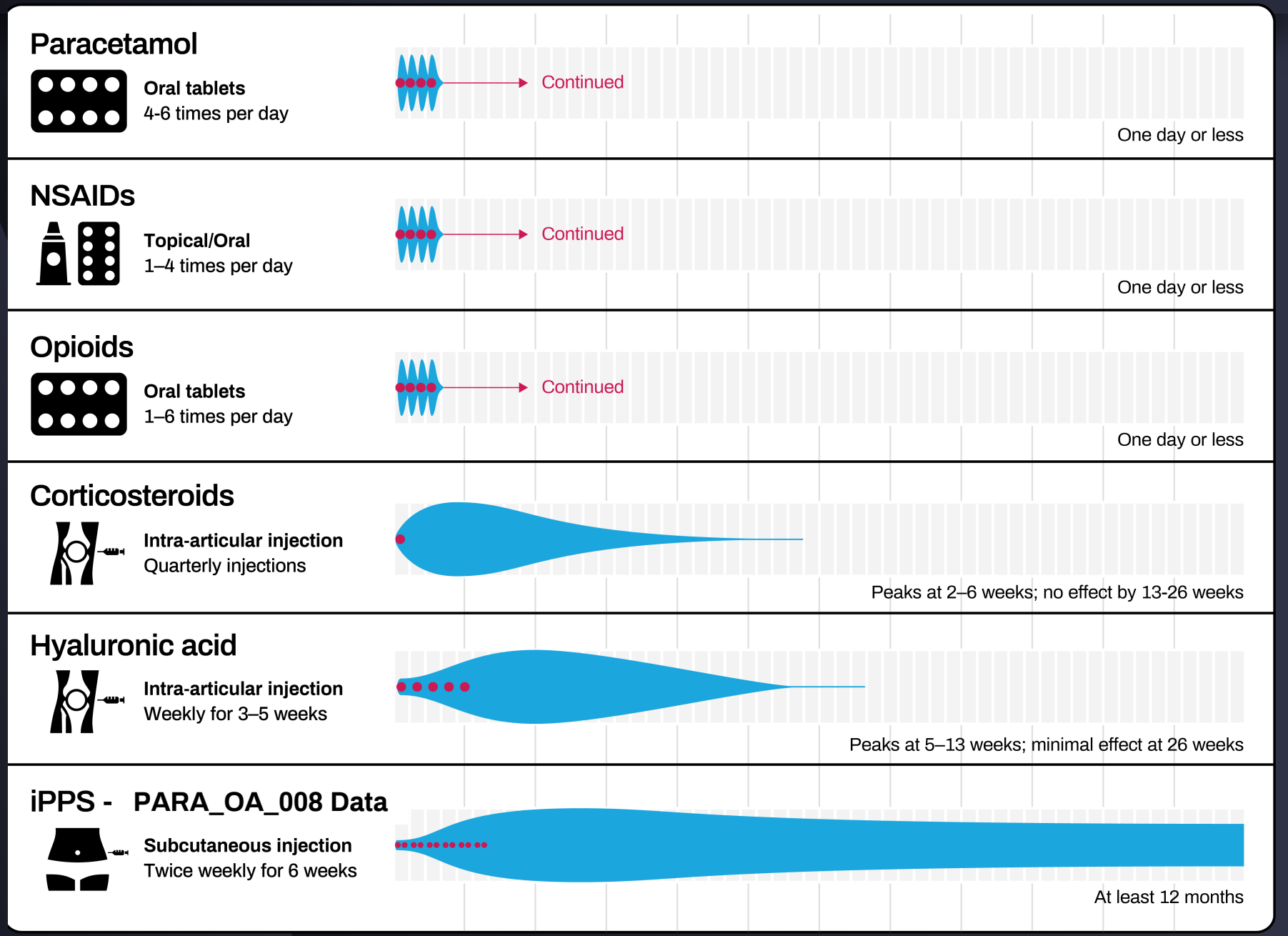
★ *Zilosul addresses the key residual unmet needs identified by payers and KOLs*

Current Therapies

Effect Duration

- 1 week
- Treatment
- Approximate timing & duration of peak effect

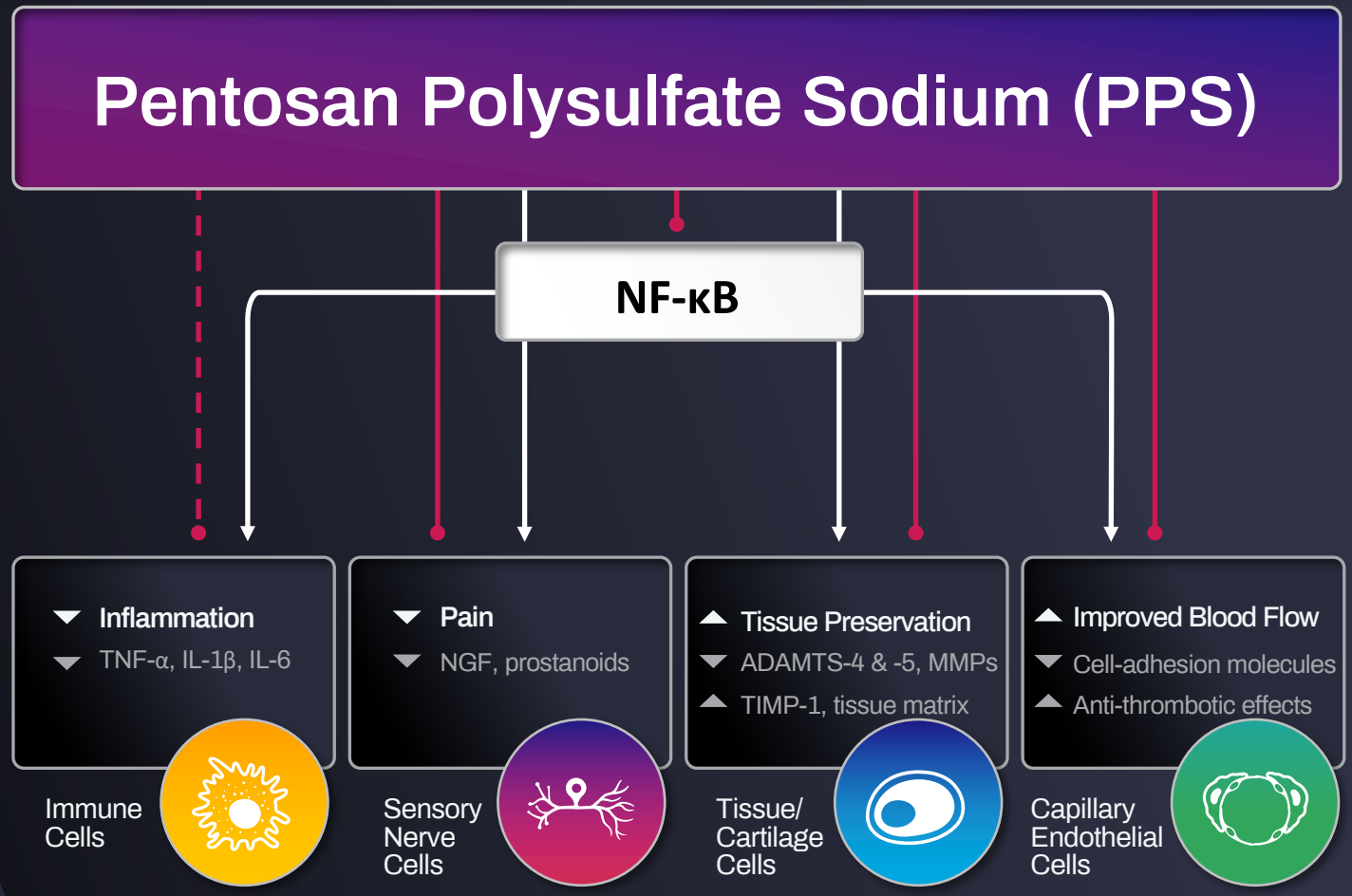
Current OA medication effect duration. Representative infographic reflecting current literature on the timing of the peak and estimated duration of treatment effect of currently available OA medications* and iPPS data from the PARA_OA_008 clinical trial. *References in Day 365 ASX release.



Mechanism of action

PPS, a semi-synthetic glycosaminoglycan mimetic, has several proposed mechanisms of action.

- Inhibits activation of inflammatory cytokines via NF-κB.
- Reduces expression of NGF, a pain mediator, in osteocytes in subchondral bone.
- Inhibits cartilage-degrading enzymes known to play a key role in OA progression.
- Mild antithrombotic activity, improves blood flow in subchondral bone, which is thought to help reduce the size of bone marrow lesions (BML), a key cause of pain and inflammation in OA.
- **Non-opioid** with a 60-year track record treating pain, inflammation, and thrombosis in humans.



Video link explanation of MOA: https://www.youtube.com/watch?v=rjZ-L_cHbm0

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.

Non-clinical Development supporting iPPS

Completed Non-clinical studies 2018-2024	
3x	Safety Pharmacology Studies
7x	PK Studies
6x	Repeat Dose Tox Studies
1x	Local injection site tolerance study
5x	DART Studies
3x	Genotoxicologial studies
1x	Naturally Occurring Canine OA Safety and Efficacy
3x	Mechanism of Action Studies
3x	Adrenal Gland Function Studies

Numerous nonclinical toxicology studies on PPS with various routes and regimens have been conducted by Paradigm. The list of studies summarise the current nonclinical development program to support an NDA filing.

Clinical Development supporting iPPS for knee OA

Paradigm Initiated and Completed Clinical Programs	Clinical Safety & Efficacy
PARA_005 (N=126) A Phase 2b, randomized double-blind placebo controlled multicenter study to evaluate the effects of PPS in treating participants with knee OA and subchondral BML.	✓
PARA_OA_008 (N=61) An exploratory Phase 2, randomized, double-blind, placebo-controlled study to evaluate the treatment effect of PPS compared with placebo on synovial fluid biomarkers in participants with knee OA pain.	✓
PARA_OA_002 (N=602) A Phase 2b adaptive dose-finding, randomized, double-blind, placebo-controlled, multicenter study to identify the lowest effective dose for the treatment of knee OA pain.	✓
PARA_OA_006 (N=132) An observational follow-up study to PARA_OA_002 to evaluate duration of treatment effect of PPS in participants with knee OA pain.	✓
PARA_001 (N=11) A Phase 1 open label, non-randomized study to assess the safety and tolerability of the intramuscular formulation of PPS in participants with BML following an acute anterior cruciate ligament (ACL) injury.	✓
PARA_OA_004 (N=24) A Phase 2, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of PPs 2 mg/kg twice weekly for 6-weeks in participants with Ross River Virus-induced arthralgia.(Krishnan et al., 2021 [8])	✓
PARA_PK_001 (N=23) A Phase 1 open-label study to determine the safety, tolerability, and PK of multiple SC doses of PPS in healthy adult participants.	✓
Compassionate Use Programs TGA Special Access Scheme: 600+ subjects treated with iPPS. US FDA Expanded Access Program: 10 subjects treated.	

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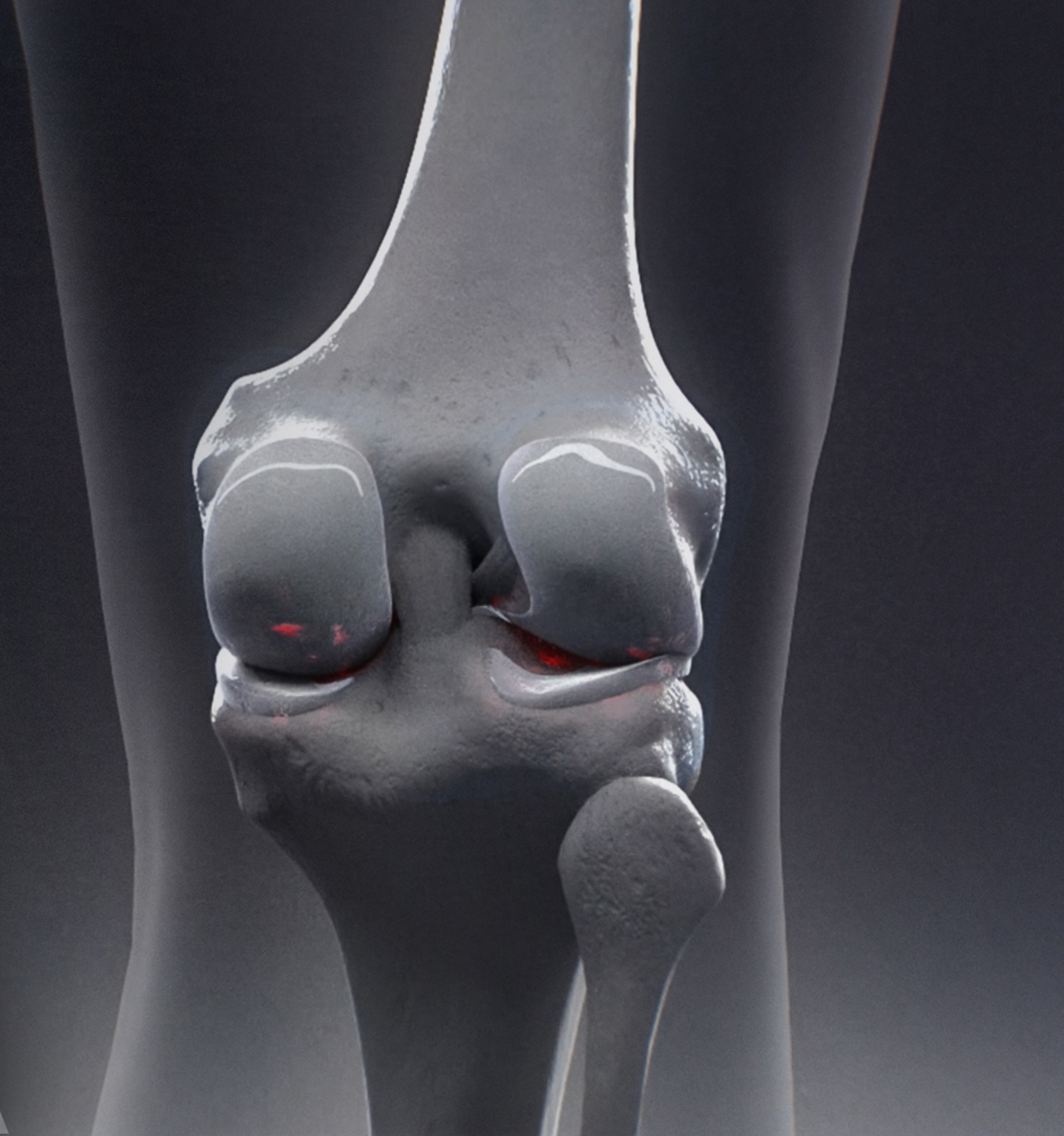
Osteoarthritis

OA

PHASE TWO



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;

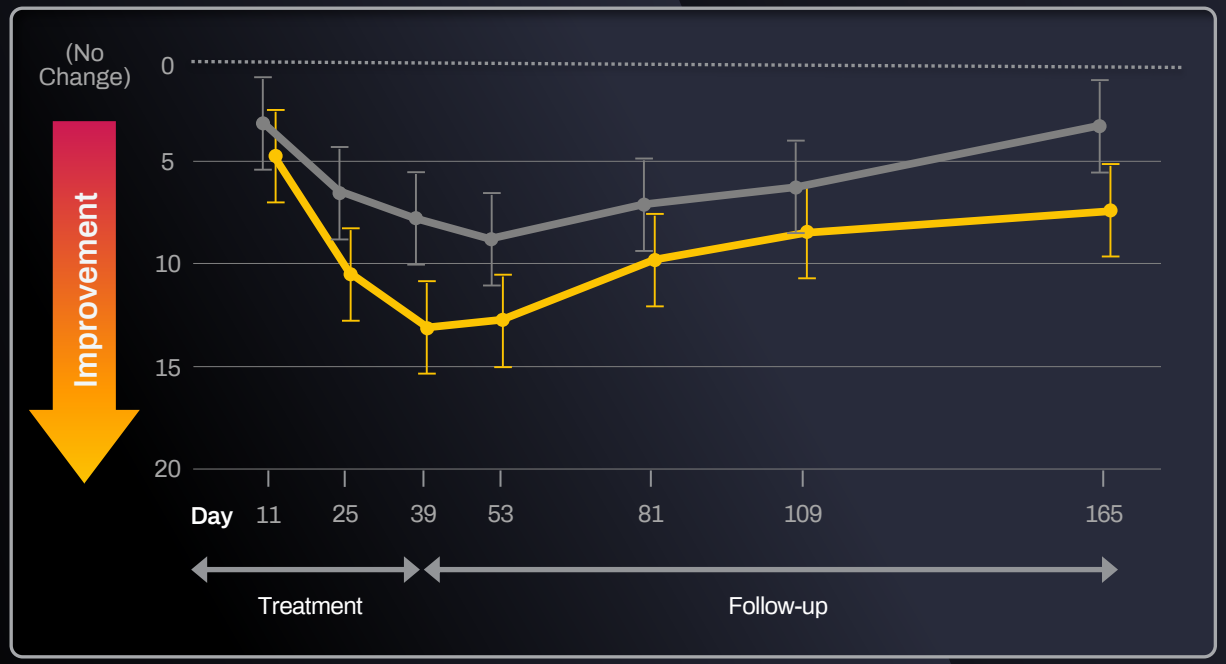
- Change in Knee Injury and Osteoarthritis Outcome Score (KOOS) pain and activities of daily living from baseline to day 165.
- Patient Global Impression of Change (PGIC).
- Change in bone marrow lesions (BML) on MRI from baseline to day 53.
- Change in serum biomarker from baseline to Dy 53

PARA_OA_005

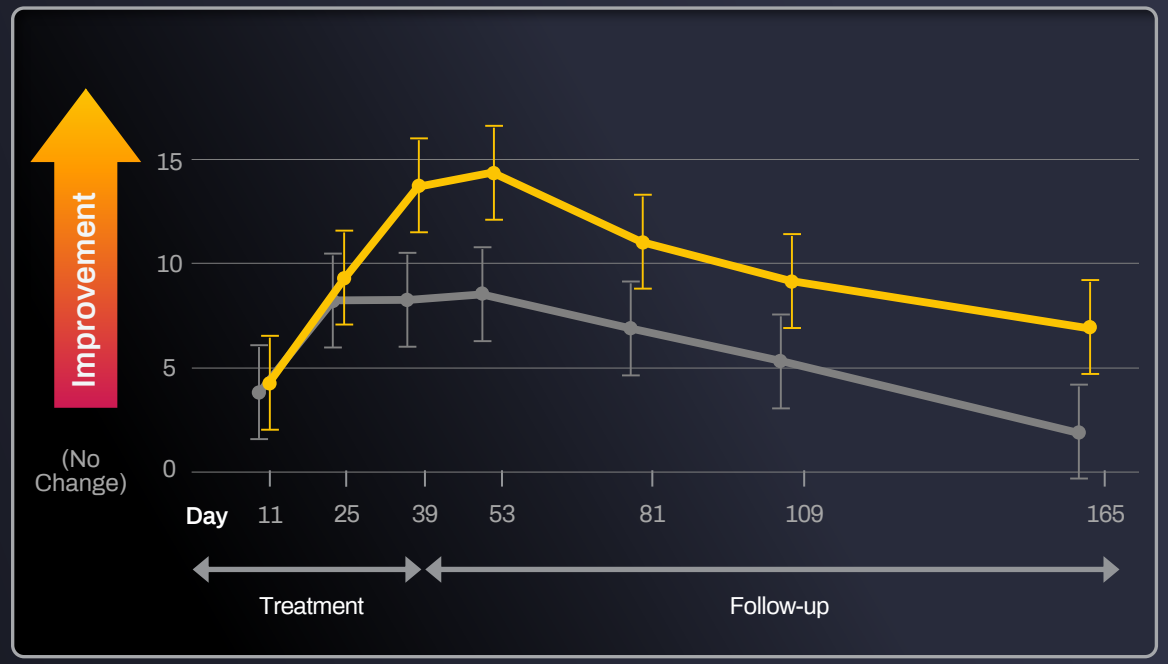
Phase 2, N=126
2 mg/kg SC twice weekly v placebo

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).

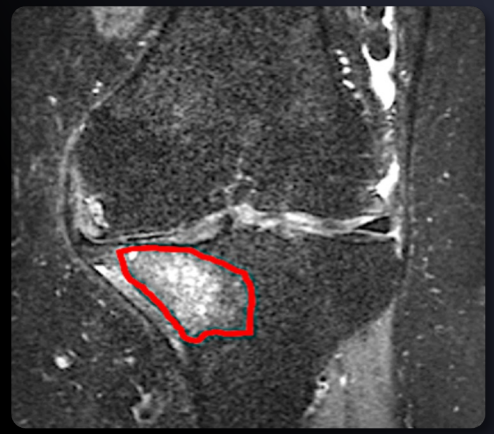
PARA_OA_005

Exploratory Endpoints

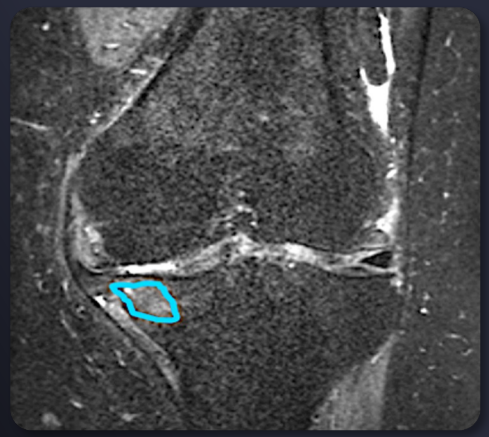
- 2 mg/kg SC twice-weekly v placebo
- PPS showed significantly reduced serum levels of cartilage degradation biomarkers
- Significant reduction in BML size as compared with placebo controls, in the medial tibia, medial femur (p=0.02), medial compartment (p=0.03), and total knee.

Reduction in size of bone marrow lesions

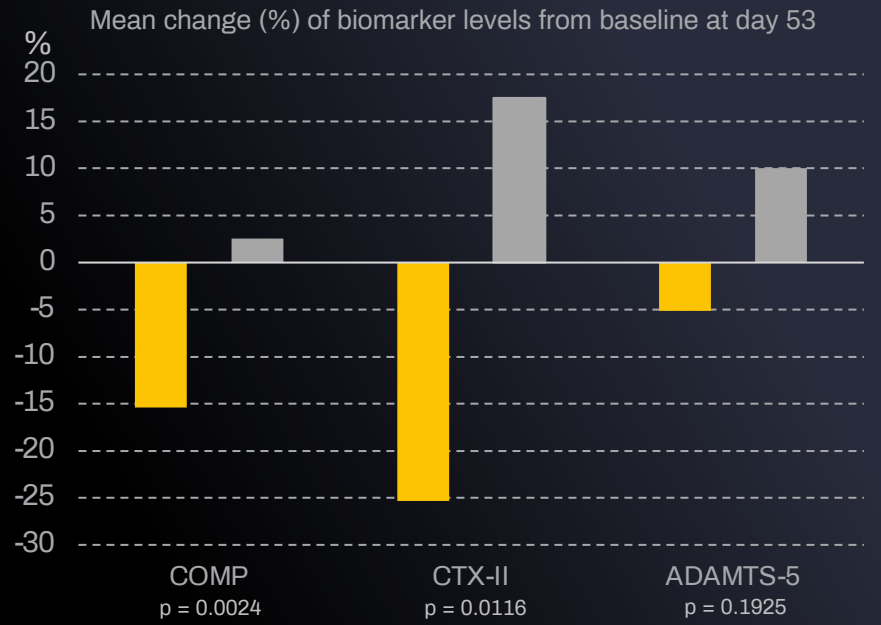
Grade 3
medial tibial BML
at baseline



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

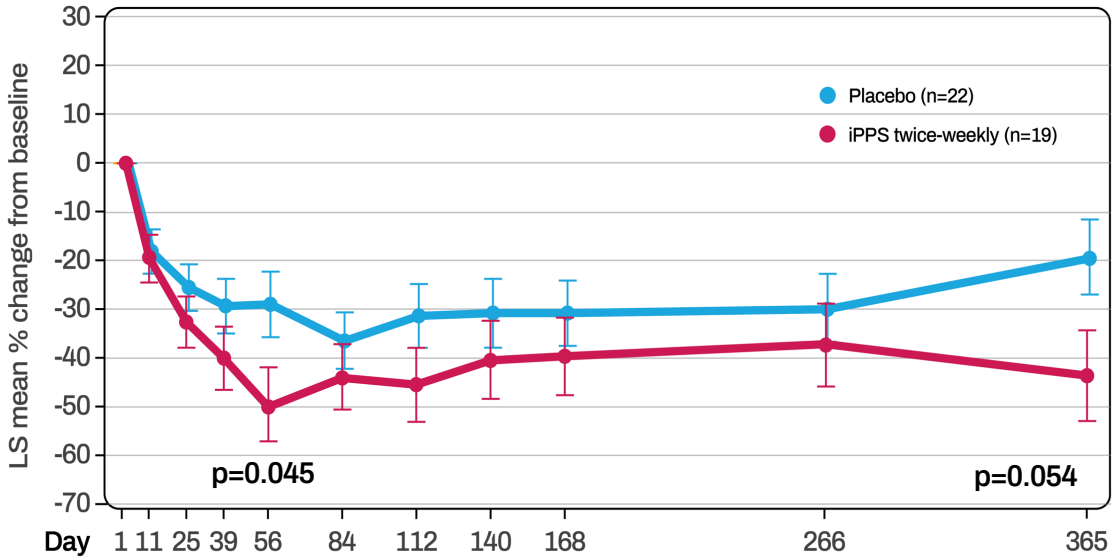
- Primary endpoint – change in 1+ synovial fluid biomarkers at Day 56
- Synovial fluid, serum and urine biomarkers associated with inflammation & OA disease progression (Day 56 & Day 168)
- Improvement in WOMAC pain, function, and stiffness (Day 56, Day 168 & Day 365)
- Structural imaging (MRI) endpoints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

DMOAD - Disease modifying osteoarthritis drug

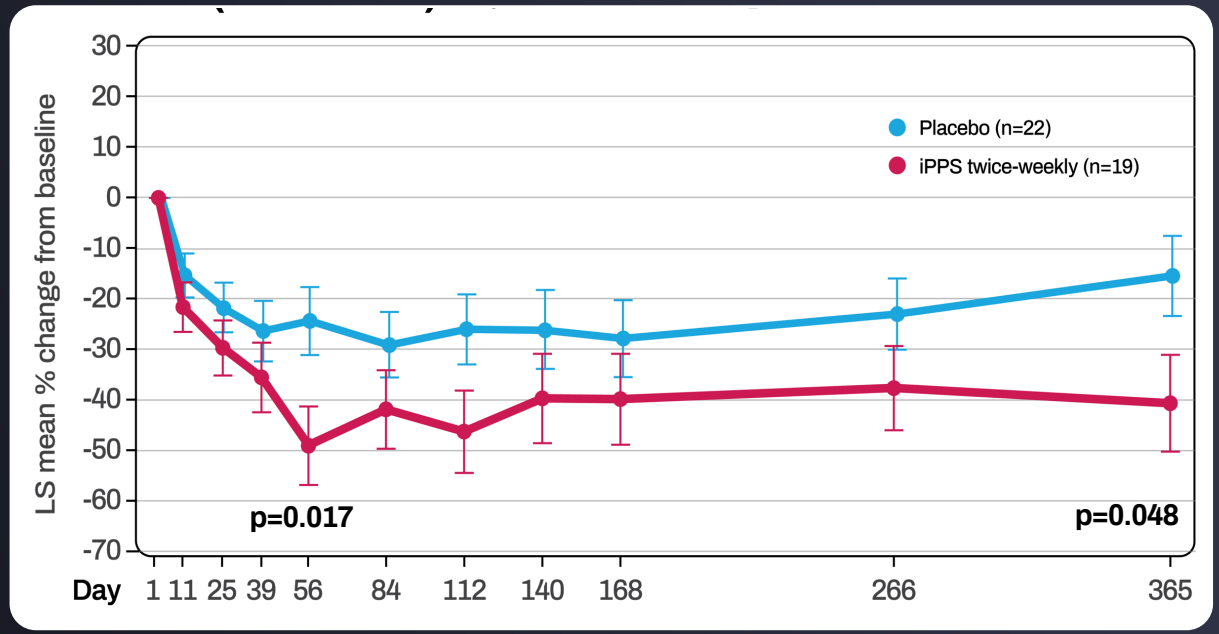
Phase 2: PARA_OA_008 | 2 mg/kg IBW SC twice weekly v placebo for 6 weeks, followed up for 12 months (n=61)

A single 6-week course of twice-weekly iPPS demonstrates durable clinical outcomes out to 12 months

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



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



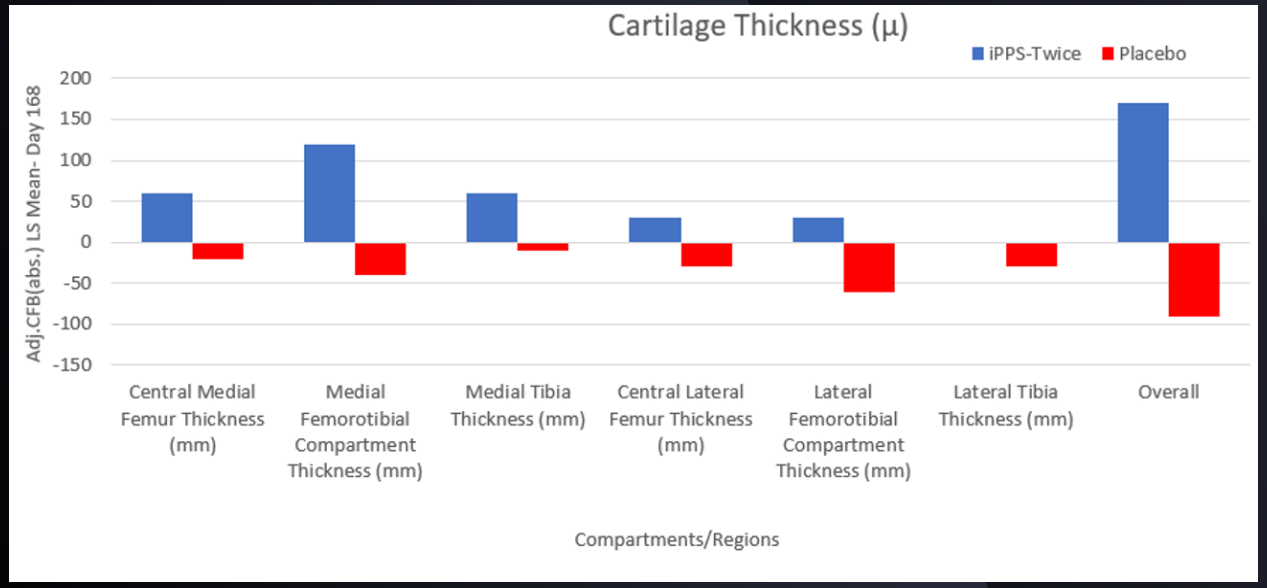
Rescue medication use

- 5x higher cumulative doses of rescue medication
- 4x more days rescue medication

used in the placebo cohort compared to iPPS twice weekly cohort at Day 365

LS Mean Change +/- Standard Error
FAS: Full Analysis Set
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

PARA_OA_008 | Top-Line Day 168 Quantitative MRI Results

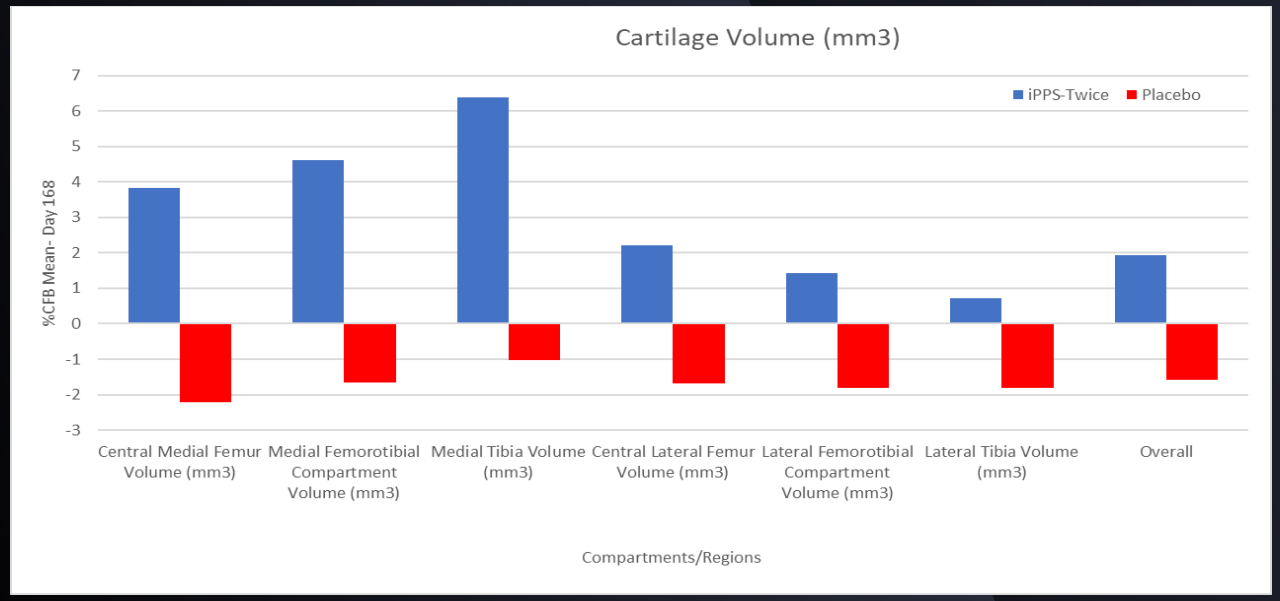


Cartilage Thickness (µm) Adj. CFB (abs.) LSM results by key regions of the medial and lateral compartments in knee

Changes in Cartilage Thickness from baseline

- Twice weekly iPPS arm, demonstrated a consistent pattern of improvement in cartilage thickness across all key regions of medial and lateral compartments at 6 months
- Placebo showed a loss in cartilage thickness in all key regions at 6 months.
- iPPS increased the cartilage thickness in the central medial femur by 60µm (0.06mm) compared to a reduction of -20µm (-0.02mm) in the placebo group at 6 months.
- Placebo group demonstrated cartilage loss rate consistent with the natural progression of knee OA (-40µm or 0.04mm per year).

PARA_OA_008 | Top-Line Day 168 Quantitative MRI Results



Average percentage (%) change from baseline (CFB) in cartilage volume (mm) by key regions of the medial and lateral compartments in knee.

Changes in Cartilage Volume from baseline

- iPPS showed an average increase in cartilage volume of 4.6%, in the medial femorotibial compartment compared to baseline, whereas the placebo arm showed a loss of cartilage volume of -1.7%.
- iPPS is reversing the breakdown of cartilage at 6 months, compared to placebo which is showing further cartilage volume loss from baseline consistent with the natural progression of the disease (4% reduction in cartilage volume per year).

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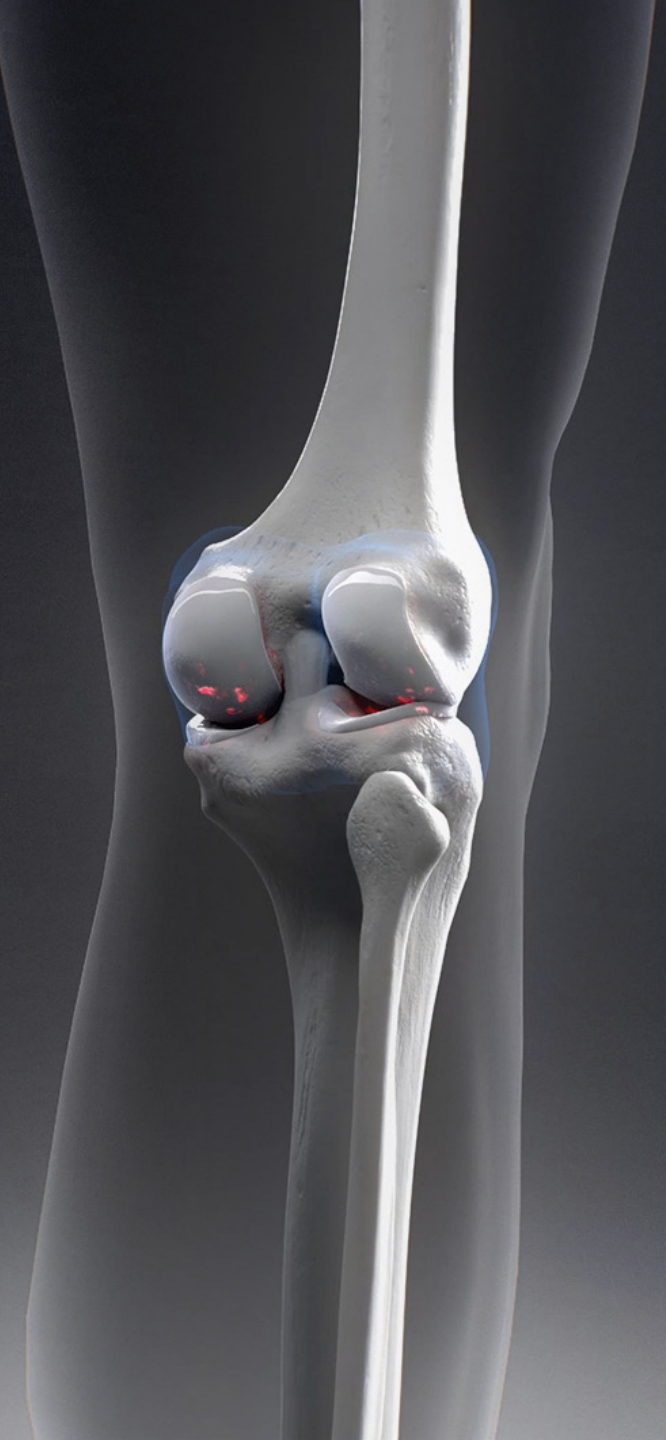
Osteoarthritis

OA

PHASE THREE



PARA_OA_002

Phase 2b Study

Evaluate Dose and Treatment Effect of iPPS in Participants with Knee Osteoarthritis Pain: 2-stage, Adaptive, Randomised, Double-blind, Placebo-controlled, Multicentre Study

Stage 1 Dose Finding Treatment arms

- iPPS twice weekly: 1.5 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.
- iPPS Fixed Dose: 100 mg PPS if <65 kg IBW, 150 mg PPS if ≥65 to ≤90kg IBW, or 180 mg PPS if >90 kg IBW once weekly + placebo once weekly
- Placebo: placebo (0.9% saline) twice weekly for 6 weeks.
  - Total of 602 patients (1:1:1:1)

Stage 1 Purpose

- Identify lowest effective dose

Outcome

- No doses performed to the same effectiveness level as PPS 2mg/kg twice weekly for 6 weeks. Study concluded and further development to be conducted at PPS 2mg/kg twice weekly dose.
- No new safety issues identified. No pigmentary maculopathy or Primary Adrenal Insufficiency identified.

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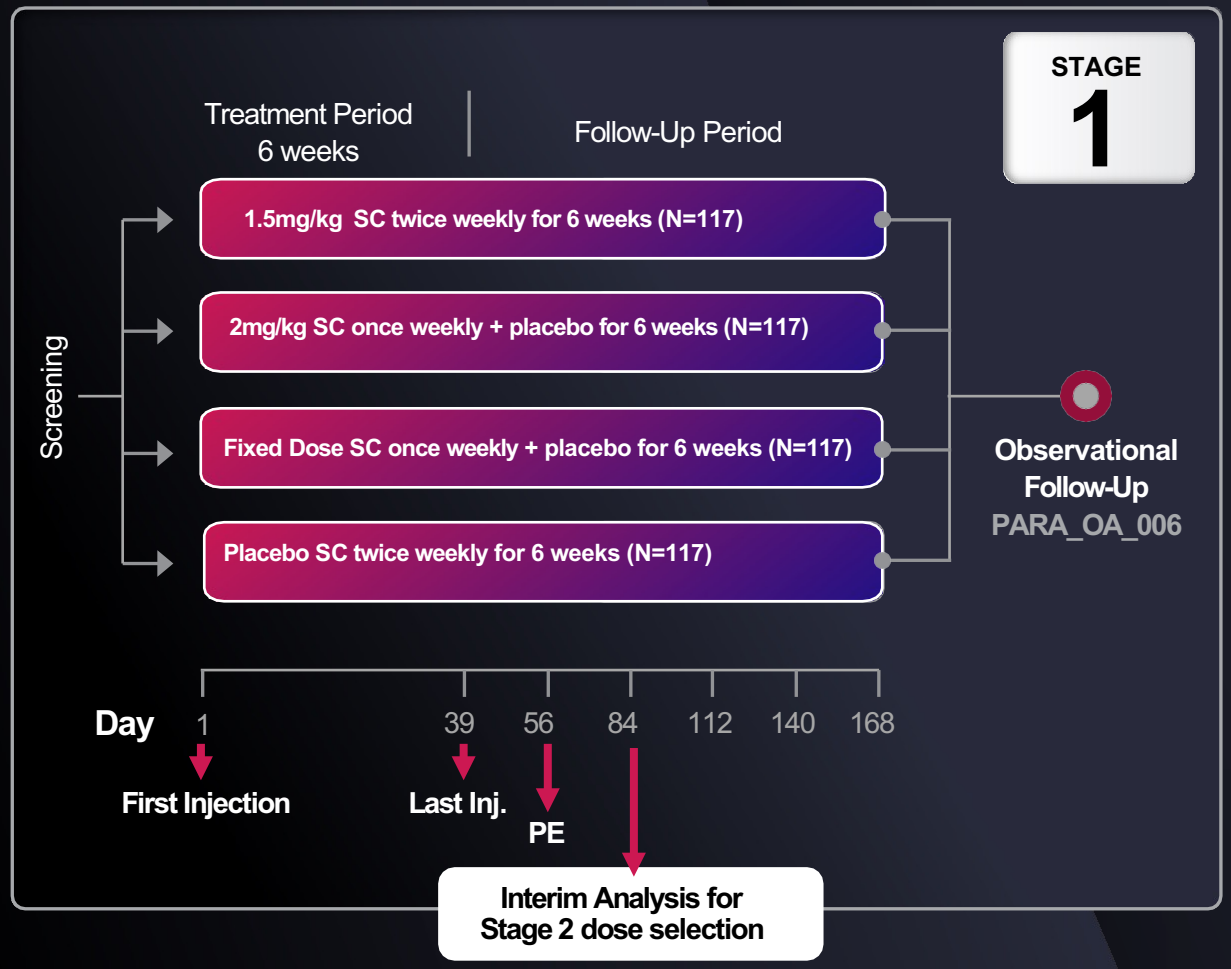
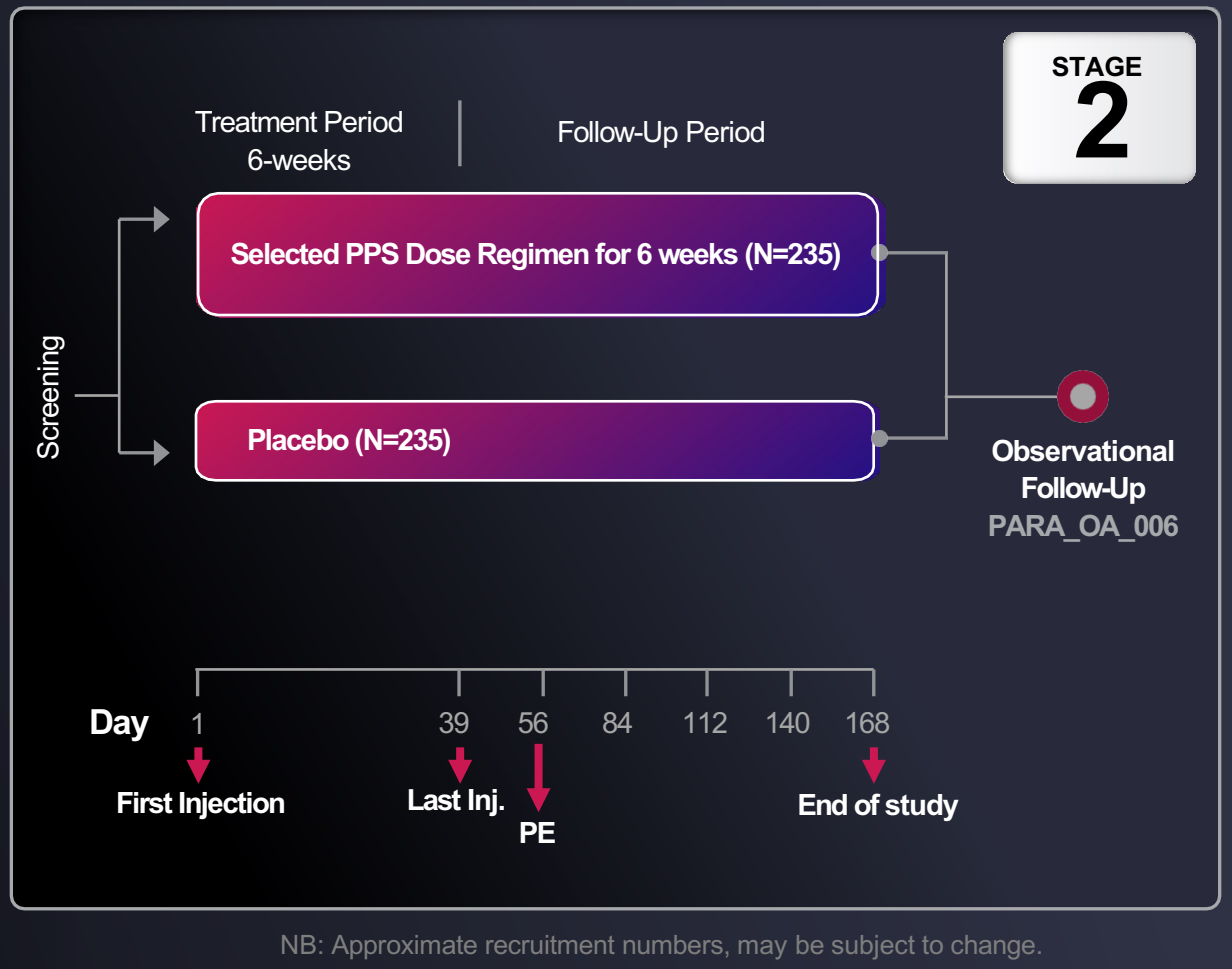
PARA_OA_002

Phase 2b Trial Design (Dose Ranging)

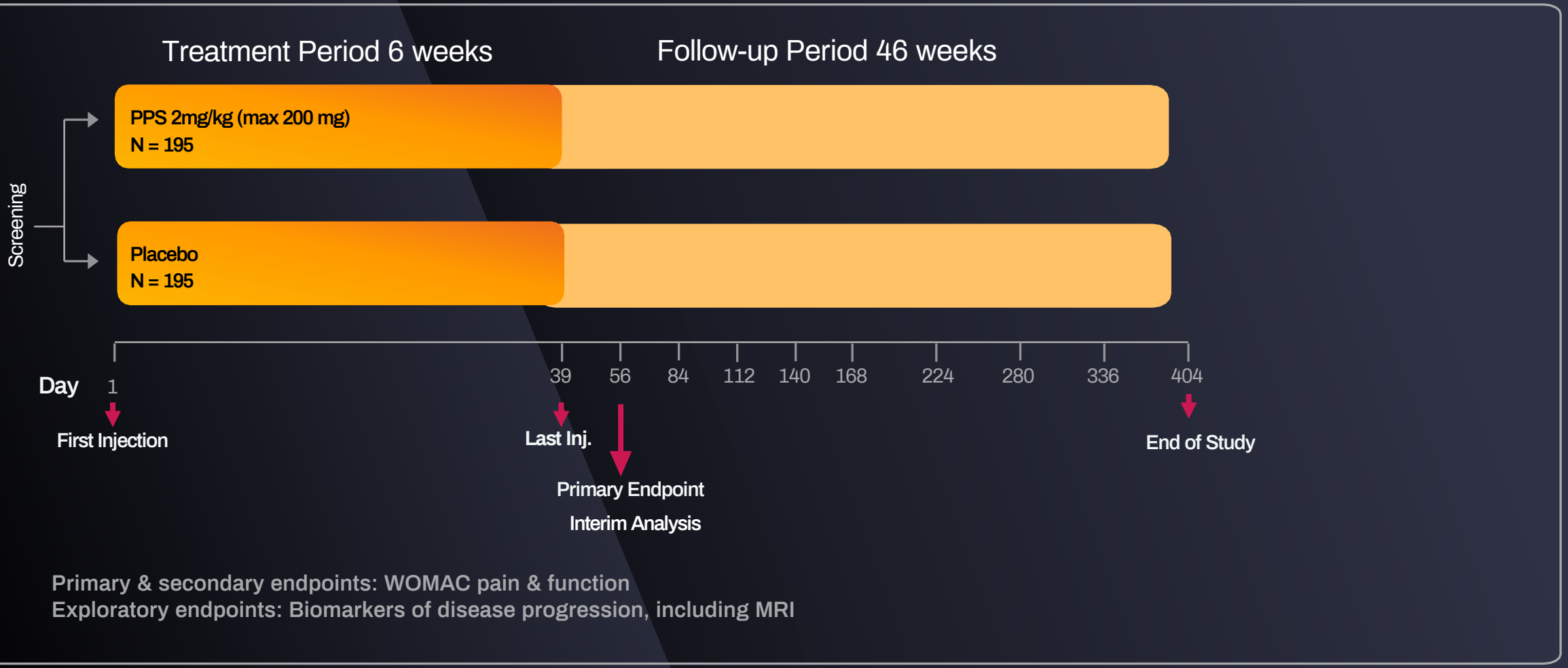




NB: Approximate recruitment numbers, may be subject to change.

PARA_OA_012

Phase 3 trial design



Primary & secondary endpoints: WOMAC pain & function
Exploratory endpoints: Biomarkers of disease progression, including MRI

Near-term News flow

Upcoming Catalysts

Event	Target Date
Phase 3 OA program – FDA protocol submission next stage of Phase 3 program.	Submitted
TGA Provisional Approval OA - submission for next stage determination application.	Submitted
Potential Regional licensing agreement(s) in OA and MPS	Ongoing
Phase 3 OA program – Enrollment commencement, subject to regulatory agreement.	H2 CY2024
TGA Provisional Approval OA - Dossier Submission, pending determination application approval.	H2 CY2024
PARA_OA_008 – Manuscripts completed and being prepared for peer review and publication.	CY2024
iPPS Comparison Manuscript– Manuscript comparing Paradigm's phase 2 clinical data to other available therapies for OA. Manuscript being prepared for peer-review and publication.	CY2024

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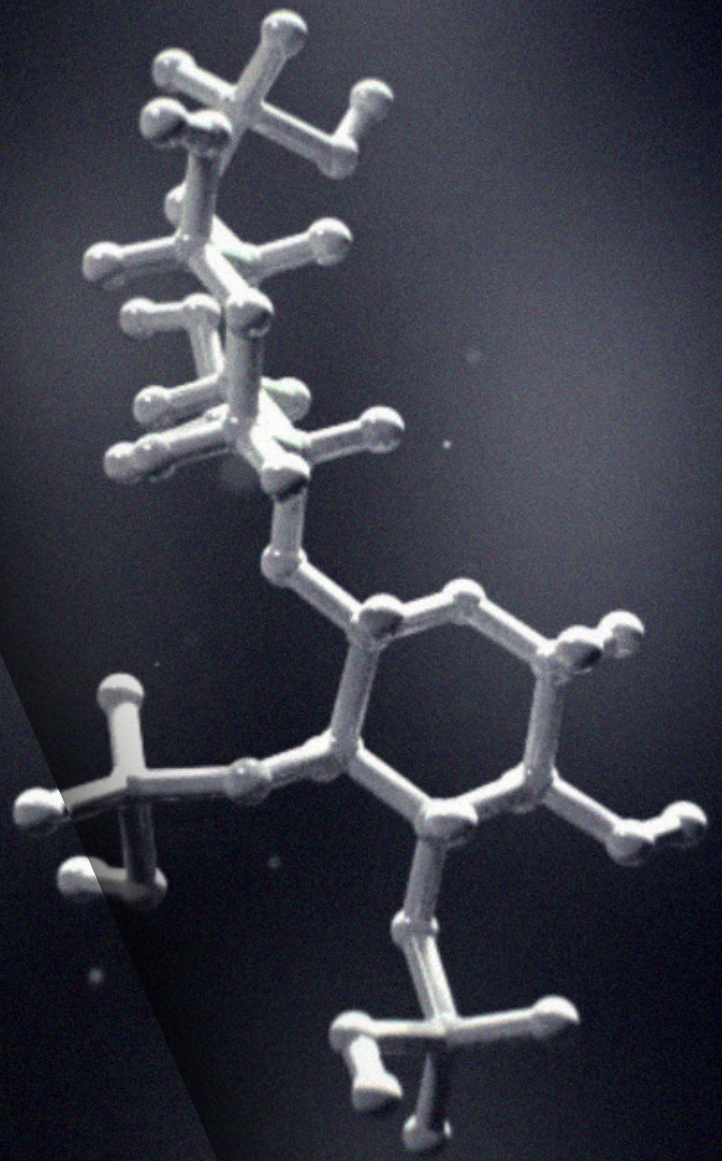
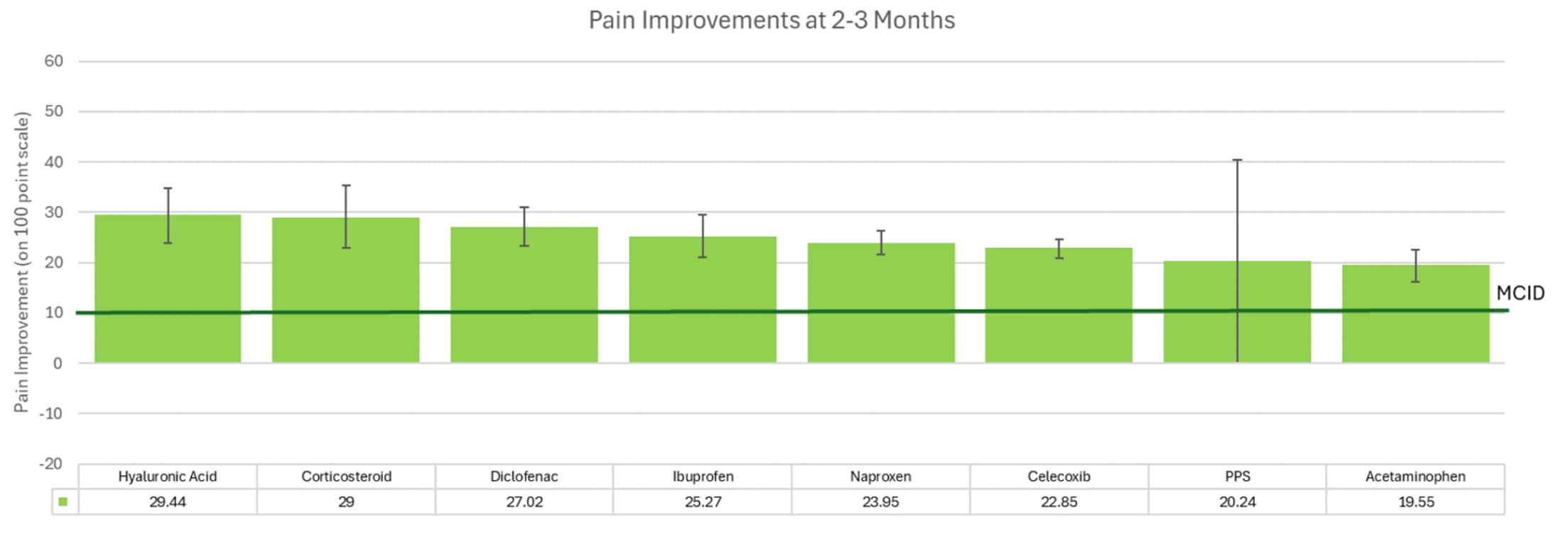
APPENDIX



Comparison with available OA medications

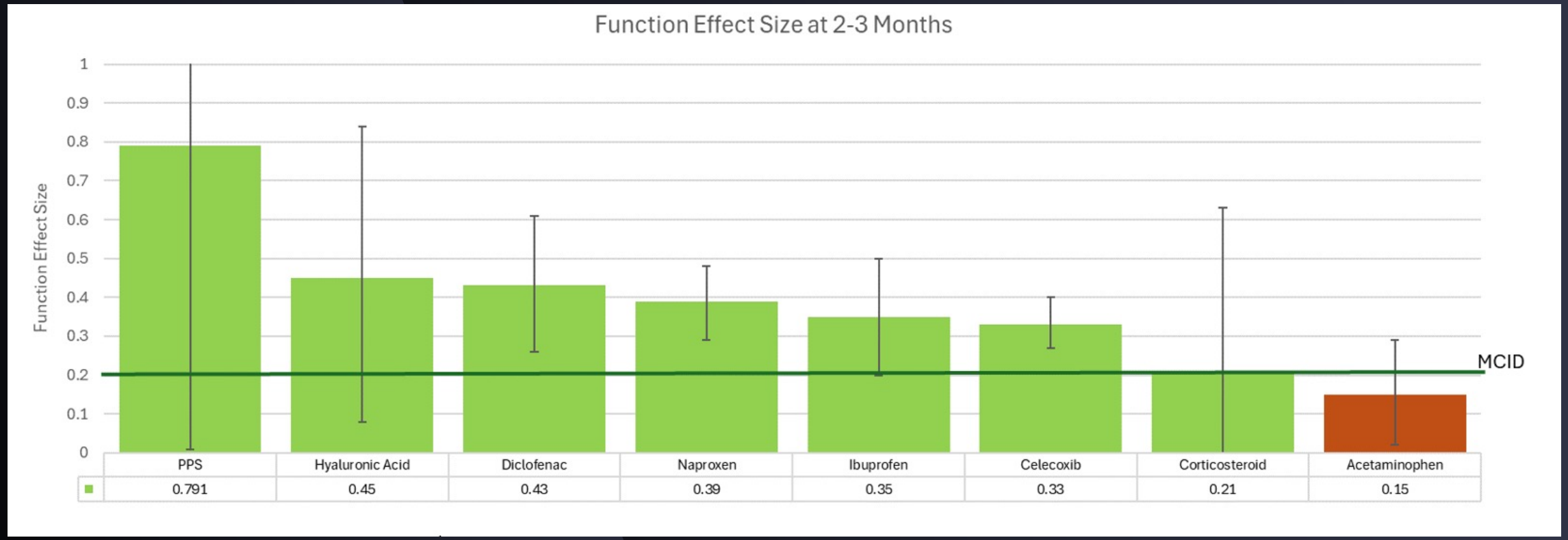
Pain improvement at 2–3 months



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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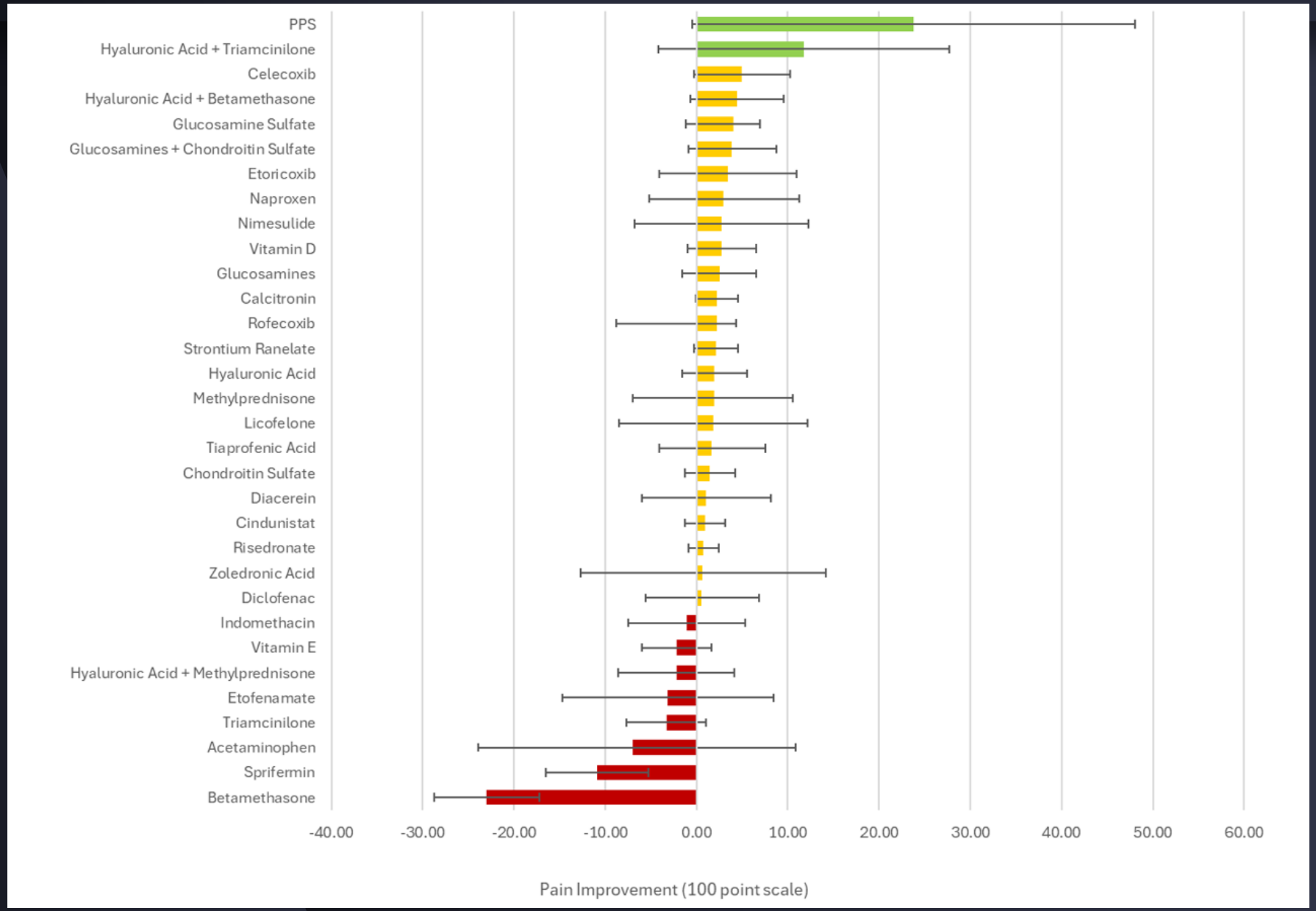
Comparison with available OA medications

Pain improvement at 1 year



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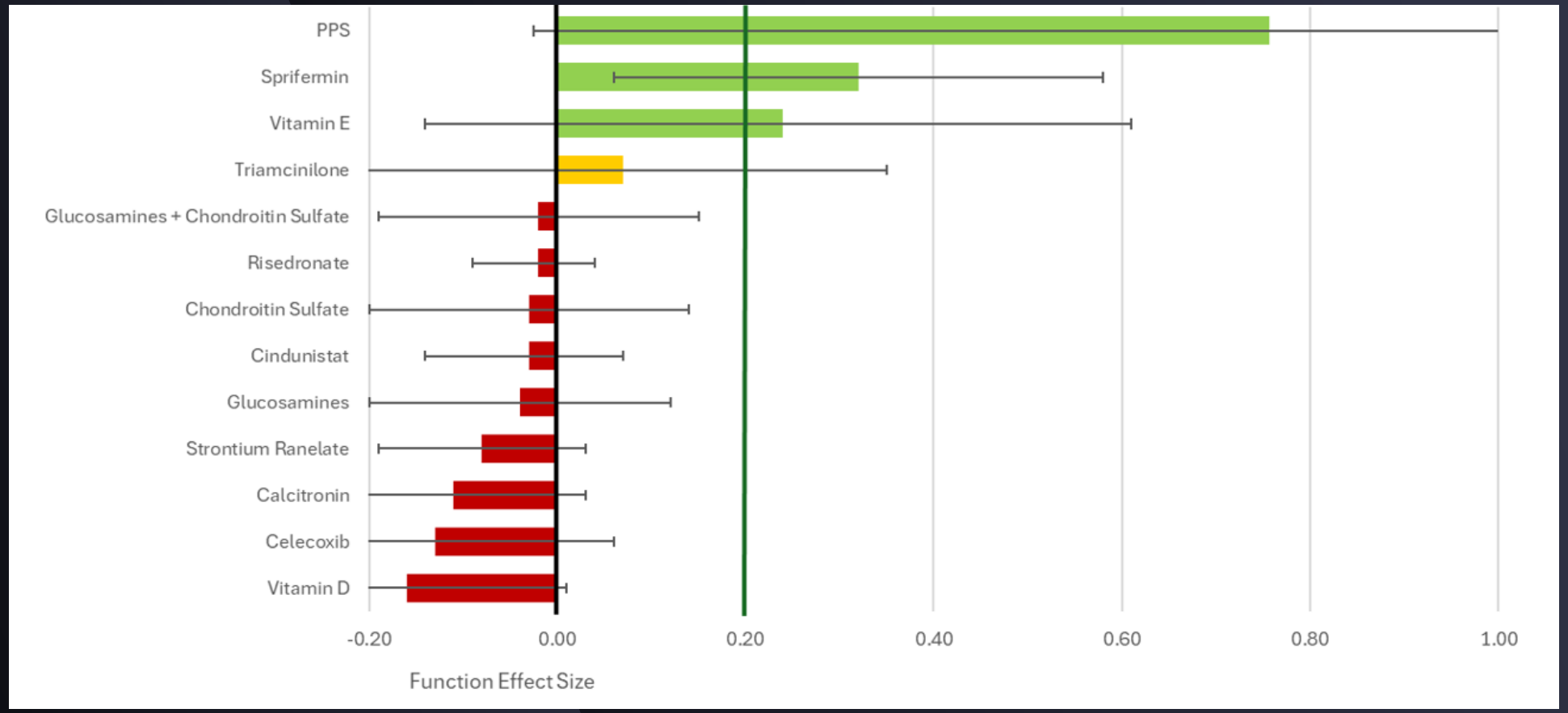
Comparison with available OA medications

Functional effect size at 1 year



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.