

PARADIGM

B I O P H A R M A

PHASE 2 PARA_OA_008 CLINICAL TRIAL DAY 168
TOP-LINE RESULTS PRESENTATION



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Executive Summary

PARA_OA_008

Key Highlights – Day 168 Results



- Multiple signals at Day 168 of DMOAD efficacy with iPPS.
- MRI at Day 168 demonstrated changes in several structural disease features, consistent with DMOAD efficacy.
 - Most notably improvements in cartilage loss, bone marrow lesions and marginal osteophytes.
- Four key biomarkers ARGS, C2C, COMP, and CTX II demonstrated favourable changes in iPPS-treated subjects compared to placebo.
- Durable positive clinical responses in WOMAC pain, function, stiffness, and overall WOMAC score.
 - Rescue medication use over 4 times more frequent in the placebo group compared to twice-weekly iPPS.
- New MRI, molecular biomarker, and clinical outcomes will be presented to the Regulatory Authorities (FDA & EMA).



Exploratory Rationale

DMOAD Program

Why Paradigm is exploring iPPS DMOAD potential in parallel to pain and function



- **High unmet need for new OA therapies to slow OA progression in tandem with symptomatic improvement (pain reduction and functional improvement).**
- **Currently there are no approved DMOAD therapies for OA.**
- 81% of OA patients are dissatisfied with current OA therapies (Matthews GI et al, Expert Opin Emerg Drugs. 2011;16)
- Independent global market research conducted in 2021 stated that a DMOAD label for iPPS would:
 - Significantly increase price per treatment course.
 - Physicians would be more likely to use iPPS as a first-line therapy.



Potential DMOAD

Programs investigating iPPS as a potential DMOAD

PARA_005 – Australia (completed)



- 126 participants randomised to iPPS or placebo.
- 2 mg/kg PPS twice weekly for 6 weeks vs placebo.
- **Day 53 Molecular Biomarker Results:**
 - Reduction in serum levels of COMP ($p=0.0024$) and ADAMTS-5.
 - Reduction in urinary levels of CTX II ($p=0.0116$)
- **MRI Outcomes:**
 - Bone Marrow Edema Lesion (BML) Grade by MRI demonstrated clinically meaningful reduction in the iPPS group compared to placebo ($p=0.03$)

PARA_008 – Australia (ongoing)



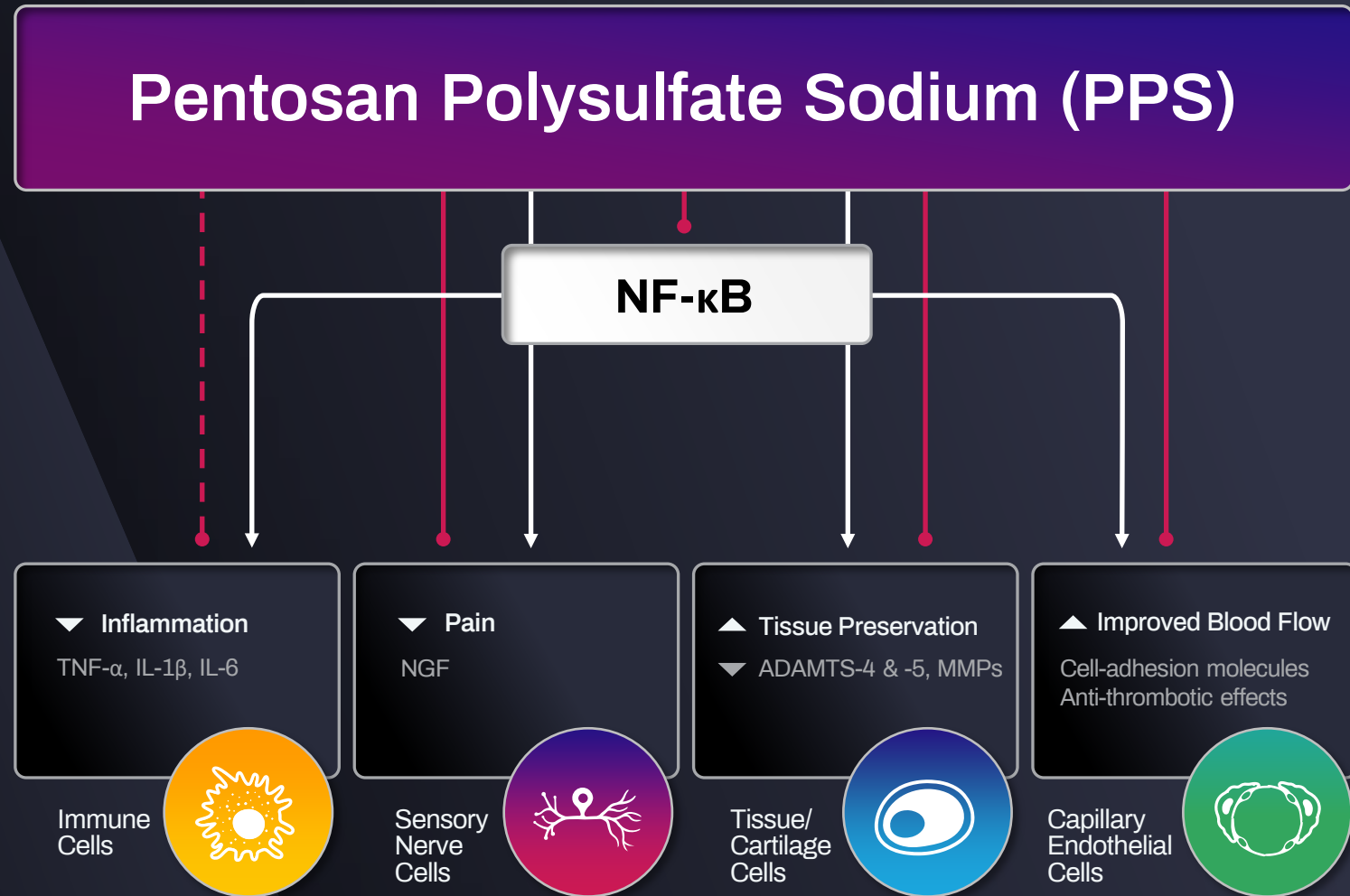
- 61 participants randomised to iPPS or placebo.
- 2 mg/kg ideal body weight (IBW) twice weekly, 2 mg/kg IBW once weekly plus placebo once weekly or placebo twice weekly for 6 weeks
- **Day 56 Synovial Fluid Biomarker Results:**
 - Reduction in inflammatory cytokines (TNF- α and IL-6),
 - Reduction in pain mediator NGF,
 - Reduction in by-products of cartilage degradation COMP and ARGS
 - Increase in inhibitor of cartilage degrading enzymes TIMP-1



Mechanism of action

- Multiple modes of action
- Previous phase 2B, SAS, and EAP experience
- New phase 2 data

OA ● ● ● ●
MPS ● ●
ARDS ●
HF ● ● ●
Viral ● ●
Arthralgia



Current hypothesis for PPS mechanism of action



PARA_OA_008

OA



DMOAD Program

PARA_OA_008

Exploring the potential of iPPS as a disease modifying OA drug (DMOAD)



- Biomarker study assessing change from baseline in multiple objective measures associated with disease progression of OA.
 - 61 participants received iPPS 2 mg/kg once or twice weekly, or placebo.
 - Follow-up period out to 12 months.
- Outstanding top-line results reported at Day 56.
 - iPPS improved multiple biomarkers measured in the synovial fluid.
 - iPPS treatment showed statistically significant improvements at Day 56 in pain, function, stiffness, and overall WOMAC scores for twice-weekly iPPS compared to the placebo arm.
 - Significant changes in pain and function were not apparent in the once-weekly iPPS group compared to placebo



Imaging Biomarkers

DMOAD Investigation

Structural imaging biomarkers being evaluated for PPS as a potential disease modifying treatment for OA

Biomarker	Evaluated	Biomarker Pathology
Subchondral BML area and volume	MRI	Pain and cartilage degeneration
Joint synovitis / effusion volume	MRI	Inflammation and pain
Cartilage thickness	MRI	Cartilage degeneration
Bone shape / osteophytes	MRI	Adverse bone remodelling
Joint space width	MRI & X-Ray	Adverse bone remodelling



MRI Outcomes

PARA_OA_008

Day 168 Top-Line Results – Structural changes in the bone and knee joint via MRI

- Baseline levels of OA disease were established by MRI prior to treatment.
- Follow-up MRIs were obtained at Day 168 to identify any differences in disease progression between the iPPS groups versus placebo.
- Despite the relatively small number of subjects in each arm and the short follow-up interval compared to the generally slow structural progression in OA, changes consistent with DMOAD efficacy were observed in a number of disease features.
- Structural changes were most noticeably observed in:
 - Cartilage loss
 - Bone marrow lesions
 - Osteophyte formation



MRI Outcomes

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Day 168 Top-Line Results – Structural changes in the bone and knee joint via MRI



Cartilage Loss

- Considered the most important feature of OA disease.
- Predictive of knee replacement surgery in OA sufferers.
- Once-weekly iPPS showed an average 21% improvement in mean cartilage loss score in the medial femur, whereas the placebo arm showed a 4% worsening of cartilage loss ($p=0.065$).
- Twice-weekly iPPS group, showed stabilisation of cartilage preservation compared to the placebo group.

Bone Marrow Lesions

- Predictive of knee replacement.
- Bone marrow lesions in the lateral femur decreased by an average 38% in the once-weekly iPPS arm, whereas in the placebo arm it increased by 47% ($p=0.056$).
- Bone marrow lesions in the entire lateral tibiofemoral compartment decreased by an average 17% in the once-weekly iPPS arm, whereas they increased by 56% in the placebo arm ($p=0.028$).
- Twice-weekly iPPS group showed improvement compared to placebo.



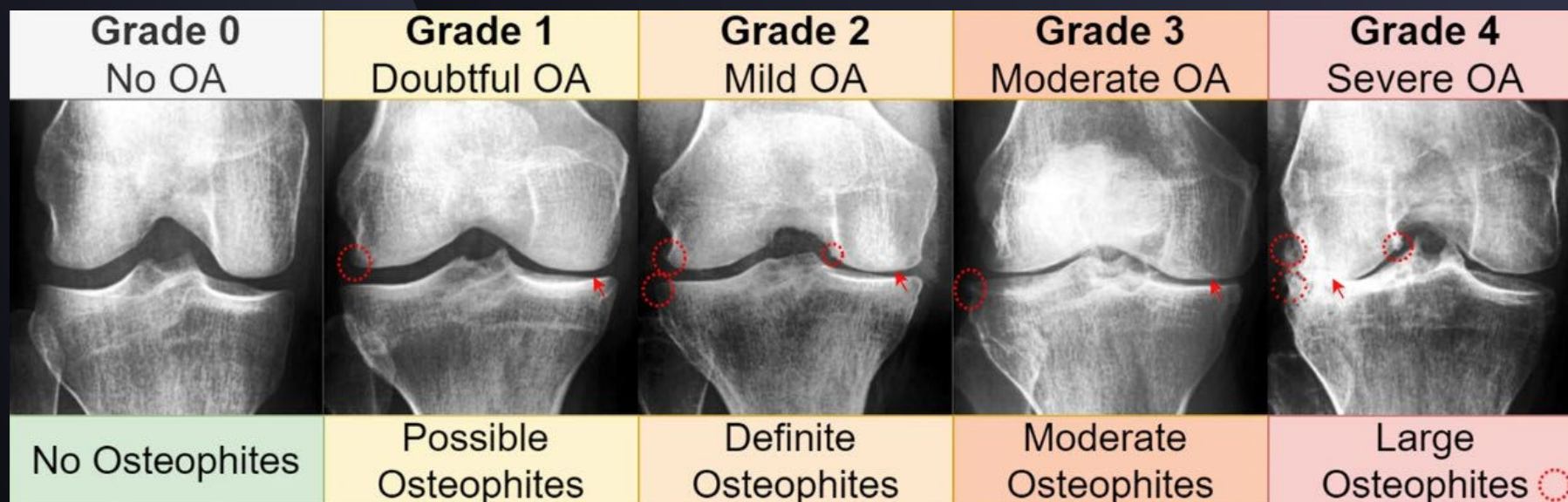
MRI Outcomes

PARA_OA_008

Day 168 Top-Line Results – Structural changes in the bone and knee joint via MRI

Marginal Osteophytes

- "Bone spurs" that form between the cartilage and bone are an early finding in OA.
- Osteophytes increase in number and size as the disease progresses.
- Osteophytes decreased slightly or remained stable in all three compartments of the knee among patients treated with iPPS, compared to an increase in the placebo arm.



Representative image
of osteophytes from
Prezja F et al. Sci
Reports 2022;12.



Clinical Outcomes

PARA_OA_008

Day 168 Top-Line Results – Changes in WOMAC Pain, Function, Stiffness and PGIC

- Twice-weekly iPPS demonstrated durable responses in WOMAC scores for pain, function, stiffness and overall WOMAC scores compared to placebo.
- Twice-weekly iPPS compared to placebo showed:
 - Durable WOMAC pain reduction
 - WOMAC function: 50% improvement for 53.3% of twice-weekly iPPS compared to 22.1% of placebo ($p=0.067$).
 - PGIC favourable at Day 168 ($p=0.061$)
 - Day 112 iPPS showed WOMAC stiffness ($p=0.029$), function ($p=0.059$), and overall ($p=0.067$)
- Placebo group used rescue medications four times as often as the twice-weekly iPPS group, on 23 days versus 5 days.



Molecular Biomarkers

DMOAD Investigation

Molecular biomarkers being evaluated for PPS as a potential disease modifying treatment for OA

Biomarker	Biological Fluids
Pro-inflammatory Cytokines	
IL-1 β	Synovial Fluid
IL-6	Synovial Fluid
TNF- α	Synovial Fluid
Pain Mediator	
NGF	Synovial Fluid, Serum
Joint Degradation Biomarkers	
ARGS	Synovial Fluid, Serum
TIMP-1	Synovial Fluid, Serum
CTX-I	Synovial Fluid, Serum, Urine
CTX-II	Synovial Fluid, Urine, Plasma
C2C	Synovial Fluid, Serum
COMP	Synovial Fluid, Serum
ADAMTS-4	Serum
ADAMTS-5	Synovial Fluid, Serum
MMP-3	Serum



Molecular Biomarkers

PARA_OA_008

Day 168 Top-Line Results – Changes in Synovial Fluid, Serum, and Urinary Biomarkers



- iPPS disease modifying potential in knee OA treatment as demonstrated by alterations in four of the biomarkers.
- Synovial fluid and serum samples of ARGs and COMP showed favourable changes in the iPPS group compared to placebo.
- Data analysed from serum C2C and urinary CTX II also demonstrated persistent beneficial effects of iPPS compared to placebo.
- These four biomarkers have been extensively researched. The literature highlights their relationship to cartilage breakdown in OA subjects.



Molecular Biomarkers

PARA_OA_008

Day 168 Top-Line Results – Changes in Synovial Fluid, Serum, and Urinary Biomarkers

- Molecular biomarkers of cartilage degradation in iPPS-treated subjects were favourable compared to placebo control.

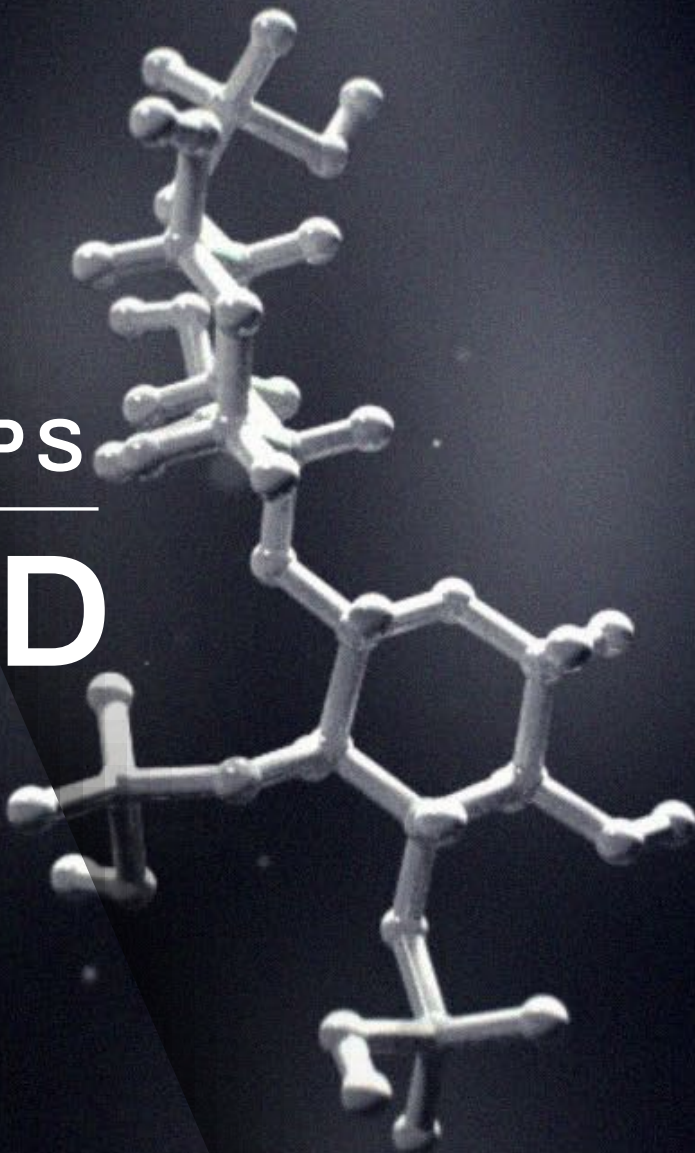
Molecular Biomarker	Day 168 iPPS v placebo
C2C (Se)	Reduced (p=0.024)
CTX II (U)	Reduced
COMP (SF)	Reduced
COMP (Se)	Reduced
ARGS (SF)	Reduced (p=0.024)
ARGS (Se)	Reduced

ARGS = Aggrecan amino acids alanine, arginine, glycine, and serine; C2C = collagen type-II C-terminal cleavage neoepitope; COMP = cartilage oligomeric matrix protein; CTX II = C-terminal crosslinked telopeptide type II collagen; Se = serum; SF = synovial fluid; U = urine.



NEXT STEPS

DMOAD



Expected regulatory discussions following data release



- New MRI, molecular biomarker, and clinical outcomes will be presented to the Regulatory Authorities (FDA and EMA).
- Paradigm intends to initiate discussions with the FDA during the second half of 2023.
- Fast Track designation facilitates easier access to the FDA and opportunity for more frequent dialogue on the development program for iPPS in OA.
- Paradigm aims to agree with the FDA and EMA on the required regulatory pathway for a DMOAD indication.
- Feedback from the EMA will be particularly useful to assess next steps with TGA provisional approval.
- Data set from the Day 56 and Day 168 timepoints in the PARA_OA_008 phase 2 clinical study will be prepared for peer review and publication.

Next Steps

DMOAD Program



Near-term News flow

Upcoming Catalysts

Near-term news flow



- MPS VI phase 2 clinical trial – 100% recruitment Q2 CY2023.
- Canine OA Model – 26-week (3-year human equivalent) data Q2 CY2023.
- PARA_OA_002 clinical trial – update Q2 CY2023.
- PARA_OA_008 clinical trial – 12-month clinical outcome data 2H CY2023.
- MPS I & VI phase 2 clinical trials – top-line data Q4 CY2023
- Paradigm is currently in active discussion with multiple potential partners for its phase 2 asset in mucopolysaccharidosis (MPS).





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