PARADIGM BIOPHARMA

OARSI WORLD CONGRESS ON OSTEOARTHRITIS
SPONSOR THEATRE SYMPOSIUM | MARCH 18, 2023
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PPS

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

Pentosan polysulfate sodium for subcutaneous use (PPS, iPPS)

- Pentosan polysulfate sodium 100 mg/mL solution for injection

ZILOSUL®

- Zilosul® is the registered trademark of iPPS being studied to treat pain & function, inflammation, and cartilage degeneration in OA.

Mechanism of action

- Inhibits NF-κB-mediated activation of proinflammatory cytokines
- Inhibits the expression of the pain mediator, nerve growth factor, in osteocytes, chondrocytes, and synovial cells
- Inhibits cartilage degrading enzymes (ADAMTS4 and ADAMTS5) known to play a key role in the progression of OA and/or MPS
- Has antithrombotic, fibrinolytic, and antilipidemic effects, which may assist with improved microvascular circulation in the subchondral bone

Marketing experience

- Elmiron® (100 mg oral capsules) registered in Australia, EU, and USA for the treatment of interstitial cystitis
- Fibrase® (100 mg PPS injection) registered in Italy for thromboprophylactic action

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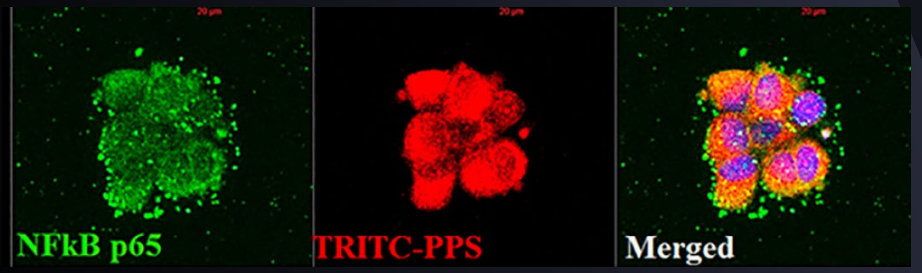
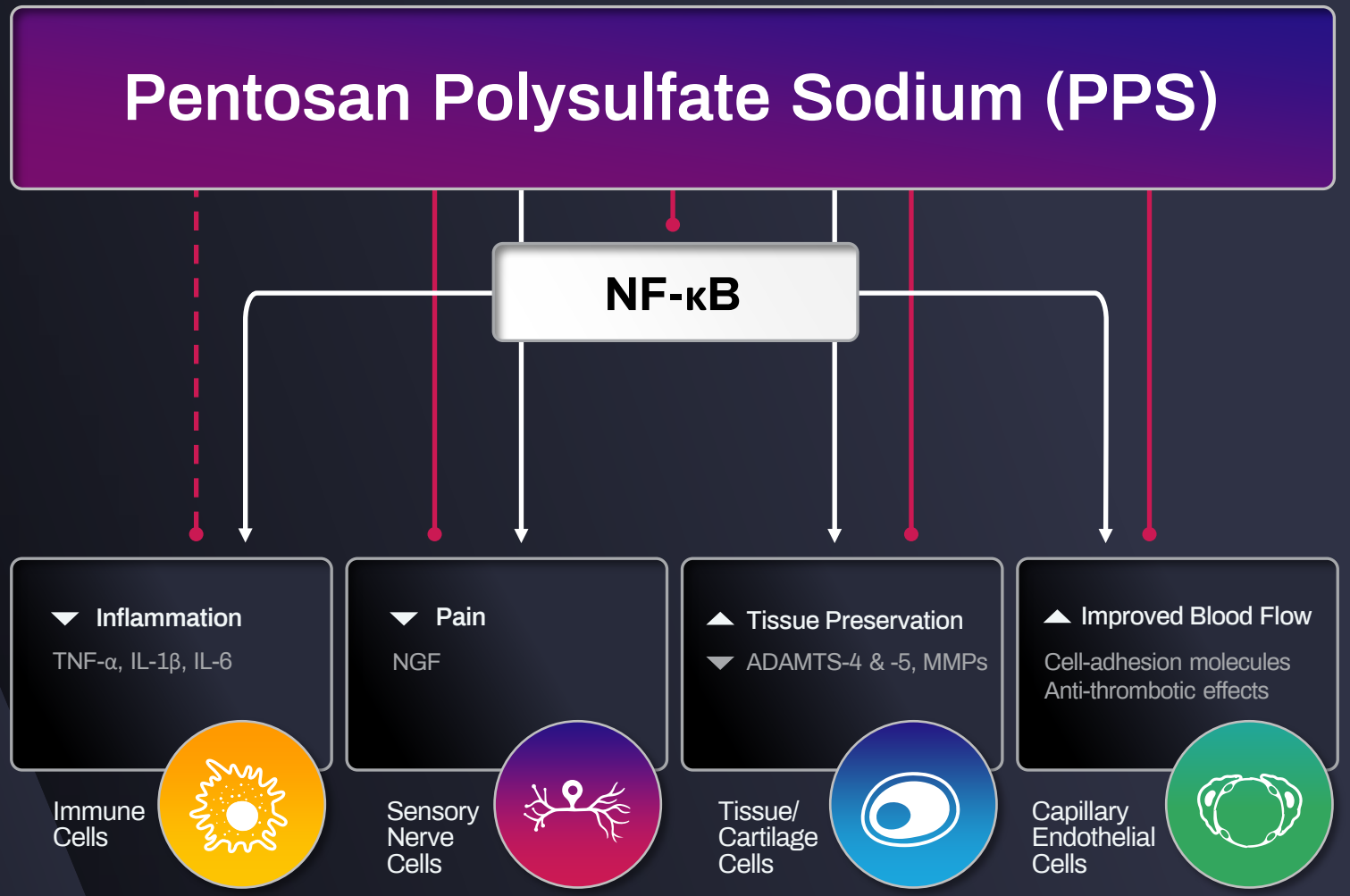
Mechanism of Action

- Upon entry into cells PPS interacts with the transcription factor NF-κB
- PPS co-localizes with NF-κB
- Multiple modes of action



Bwalya et al 2017 PLoS ONE 12(5): e0177144.



References: Sunaga 2012, Troeberg 2012, Bwalya 2017, Stapledon 2019, Ghosh 1999, Wu 2017, Miyata 2010, Kumagai 2010, Budsberg 2007, Kutlar 2012.

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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-1β	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

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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

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Pentosan Polysulfate Sodium

Translational Models

Osteoarthritis (OA)

- Proof of concept - rodent model demonstrates biological activity of PPS in collagen-induced arthritis (CIA) model (Wijekoon et al, 2019).
- Translational - canine model of naturally occurring OA demonstrates improved pain and function (Read et al, 1996).
- In two clinical studies, PPS has been shown to reduce pain and improve joint function in patients with knee OA (Ghosh et al, 2005; Kumagai et al, 2010).

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

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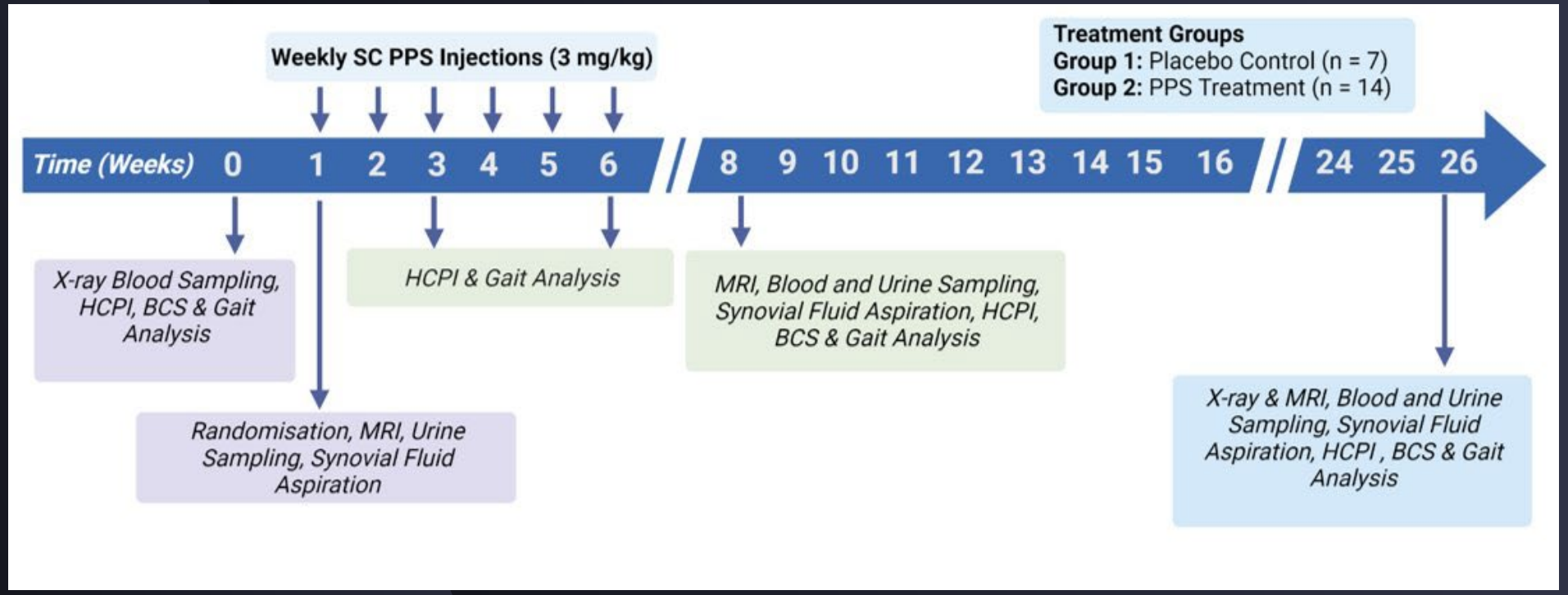
Pilot Natural Canine OA Model

DMOAD Investigation

STUDY DESIGN



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Pilot Natural Canine OA Model

DMOAD Investigation

DMOAD activity of PPS in Pilot Canine Model of Natural OA – Interim Data

Assessment of functional changes by gait analysis

- iPPS treatment in osteoarthritic dogs demonstrated a functional improvement in Body Weight Distribution% (BWD%) as measured by the Total Pressure Index% (TPI%).
- Seven of nine dogs treated with iPPS had a clinically meaningful improvement in the affected limb as measured by TPI% at week 8 compared to baseline
- A mean percentage change (improvement) from baseline in TPI% of 10.08% was observed for the affected hind limb (n=5) and 5.6% for the affected front limb (n=4). A mean increase of 5% in TPI% is considered to be a clinically meaningful improvement.

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Pilot Natural Canine OA Model

DMOAD Investigation

DMOAD activity of PPS in Pilot Canine Model of Natural OA – Interim Data

Biomarker changes following PPS treatment at 8 weeks

- PPS treatment in osteoarthritic dogs demonstrated reduction in cartilage degradation biomarkers locally within the joint (synovial fluid) and systemically (serum).
- Data presented are change in biomarker level from baseline at week 8.
- Responders are defined as dogs that demonstrated a reduction in the level of a specific biomarker at week 8 when compared to the biomarker level at baseline.

Synovial fluid Biomarker	Responders	% Responders
ARG	(3/4)	75%
HA	(4/4)	100%
Serum Biomarker	**Responders**	**% Responders**
ARG	(3/6)	50%
HA	(5/9)	56%
C3M	(7/9)	78%
CTX-I	(6/9)	67%
CTX-II	(4/9)	44%

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Pilot Natural Canine OA Model

DMOAD Investigation

DMOAD Activity of iPPS in Pilot Canine Model of Natural OA

Study Follow-Up Report

- Recruitment for the pilot canine OA study of 20 animals has now been completed
- The longer follow-up period at week 26 (equivalent to 3 years in human terms) will allow for collective analyses of pain, function, joint structure, and biomarker levels following iPPS therapy, and will provide informative data to assess the potential of iPPS as a DMOAD.
- The complete study report examining both week 8 and week 26 responses in the final cohort of dogs will be reported in 1H CY2023.
- This pilot study will be extended to an additional number of 40 dogs to support clinical submissions to regulatory bodies for potential DMOAD claims for PPS.

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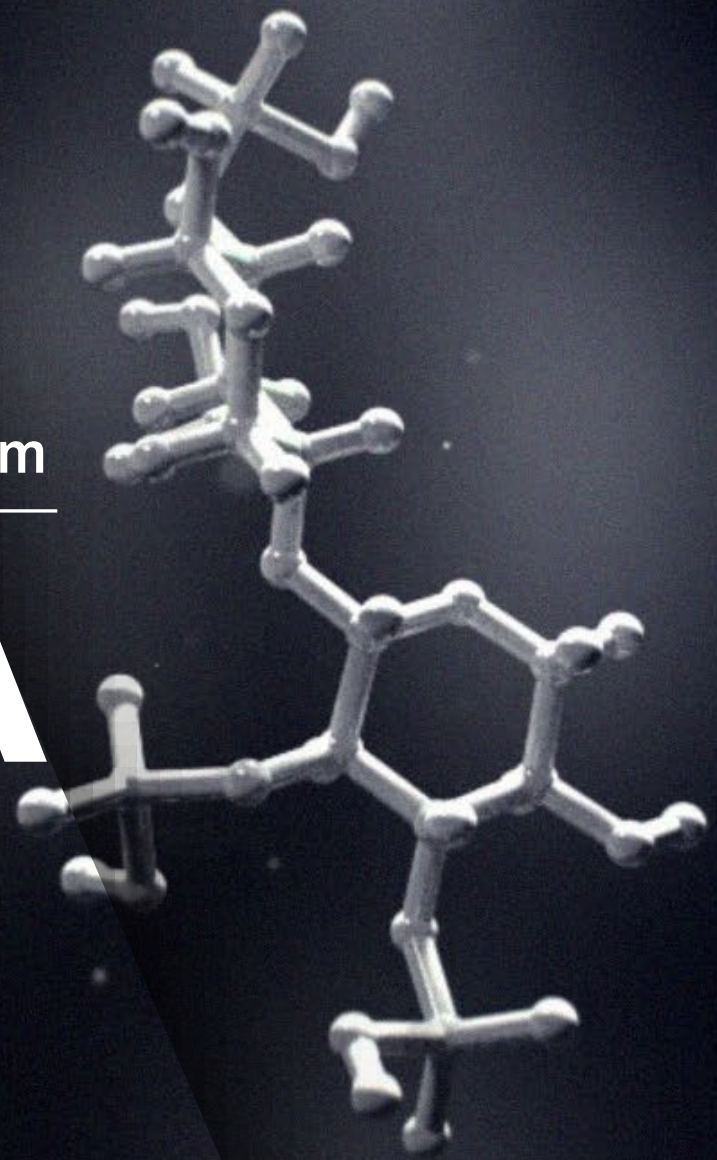
Clinical Program

OA



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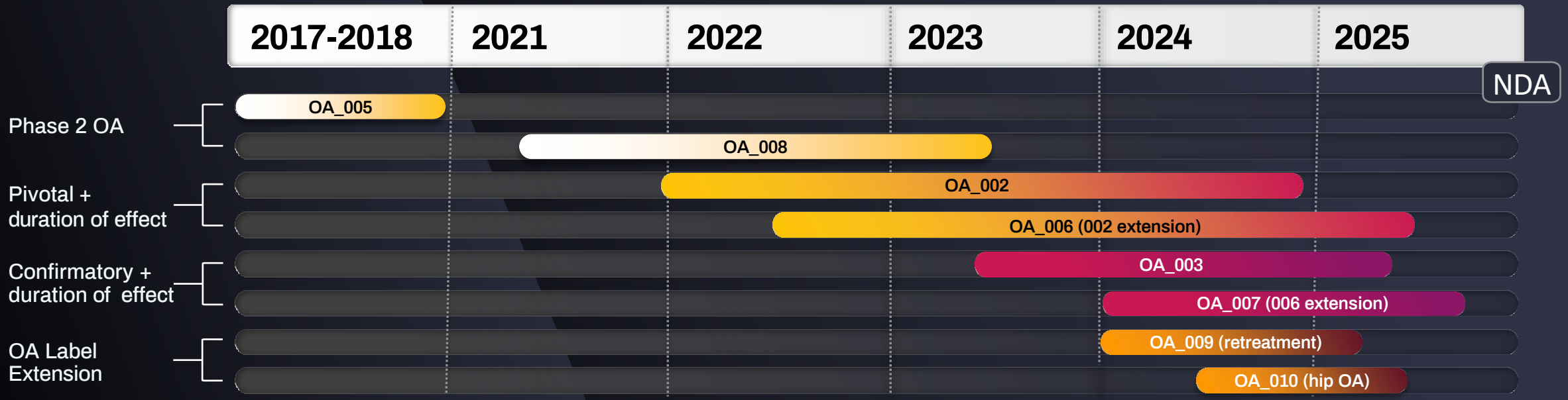
OA Clinical Development



Study	Objective	Status
005	To evaluate the effects of PPS on knee OA pain, function, and disease modification biomarkers at Day 53	Complete
008	To evaluate the effects of PPS on knee OA pain, function, and disease modification biomarkers up to Day 365	Ongoing
002 / 003	To provide evidence of effect for treatment of pain and improvement of function knee OA at Day 183	002 Enrolling
006 / 007	To evaluate the duration of treatment effect and safety up to 52 weeks from the last treatment in the parent study (002 / 003)	006 Enrolling
009	To establish efficacy and safety data to support repeat dosing in the label.	Planned
010	To establish efficacy and safety data to support adding Hip OA to the label.	Planned

6 weeks treatment duration in all OA studies

Timelines based on enrolment projections and may be subject to change.

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Potential Disease Modifying Osteoarthritis Drug

Current programs investigating Zilosul® as a potential DMOAD

PARA_005 – Australia (completed)

- Phase 2 efficacy and safety study
- 126 participants randomized to iPPS or placebo.
- 2mg/kg PPS twice weekly for 6 weeks vs placebo
- Serum: ADAMTS-4, ADAMTS-5, MMP-3, CTX-I, COMP
- Plasma: CTX-II
- Urine: CTX-I, CTX-II
- MRI: Subchondral BML area and volume, synovitis, joint effusion

PARA_008 – Australia (ongoing)

- Phase 2 exploratory study assessing change from baseline in multiple biomarkers associated with disease progression of OA.
- 60 participants randomized to iPPS or placebo.
- 2mg/kg ideal body weight (IBW) twice weekly, 2mg/kg IBW once weekly plus placebo once weekly or placebo twice weekly for 6 weeks
- Synovial fluid: IL-1β, TNFα, IL-6, NGF, COMP, CTX-I, CTX-II, C2C, ADAMTS-5, aggrecan ARGS fragment, TIMP-1
- Serum: COMP, ADAMTS-5, aggrecan ARGS fragment, TIMP-1, CTX-I, C2C
- Urine: CTX-II
- MRI: Subchondral BML area & volume, synovitis, joint effusion, cartilage thickness, bone shape, joint space width

PARA_002 – Global (enrolling)

- Pivotal phase 3 study
- 900+ participants randomized to iPPS or placebo.
- 1.5 mg/kg IBW PPS twice weekly; 2.0 mg/kg IBW PPS once weekly + placebo once weekly; 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 twice weekly for 6 weeks
- MRI: Subchondral BML area and volume, synovitis, joint effusion, cartilage thickness, bone shape, joint space width

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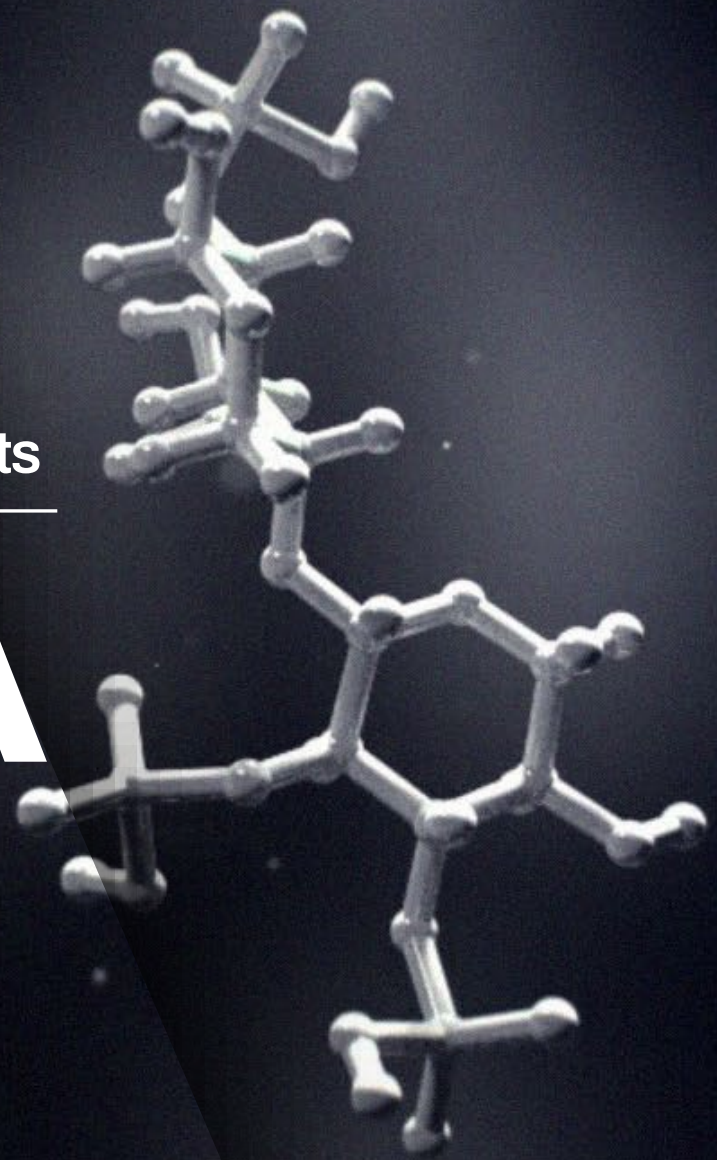
Phase 2 Results

OA



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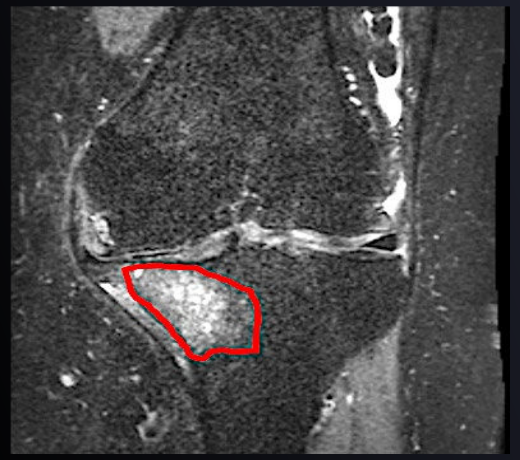
PARA_OA_005

Exploratory Endpoints

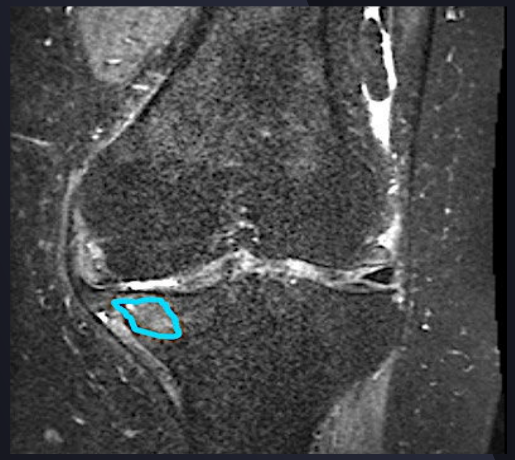
Study population: Mean age 57.5 (range: 40-75 years), 65% males, BMI up to 35, OA history mean 9.9 years, 82% with K-L Grade 3 or 4, mean baseline KOOS pain 44.

- MRI analysis showed that iPPS group had statistically significant **BML regression** in the Medial femur (p=0.02) and Medial compartment (p = 0.03)

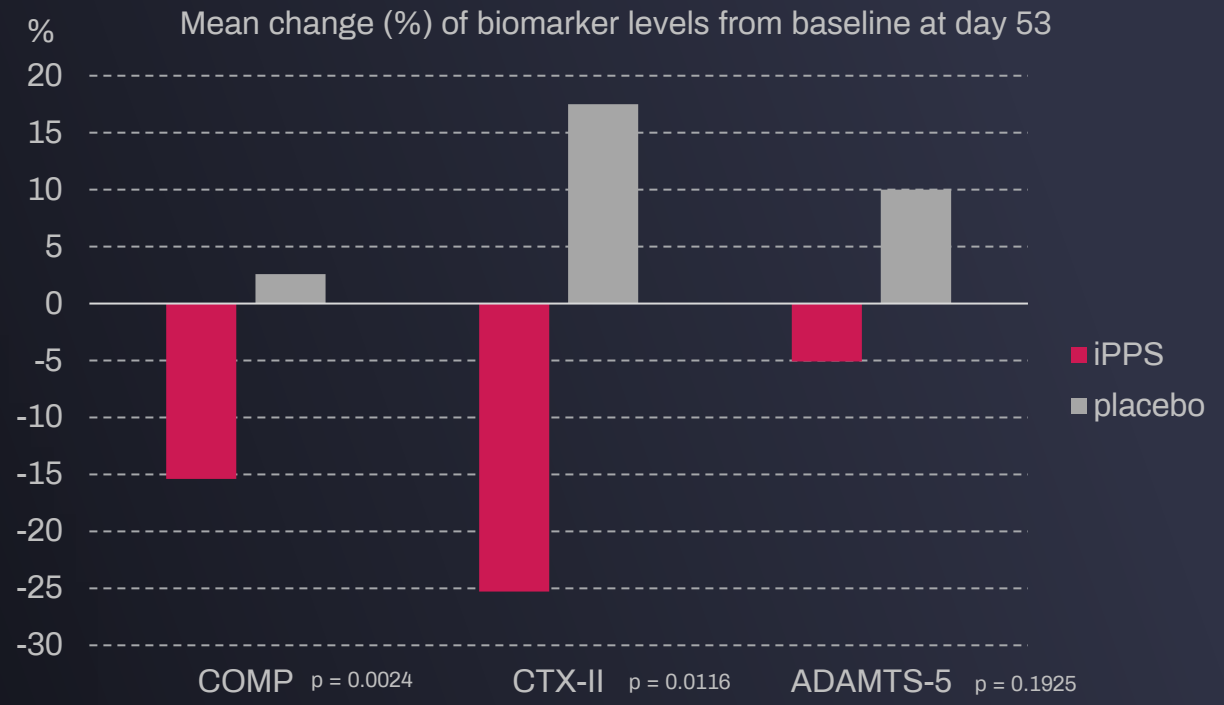
Grade 3 medial tibial BML at baseline



Grade 2 medial tibial BML at follow-up day 53



- iPPS showed significantly reduced serum levels of cartilage degradation biomarkers **COMP**, **ADAMTS-5** & urine levels of **CTX-II**.
- A single measurement of **increased COMP predicted subsequent cartilage loss on MRI** in symptomatic knee OA subjects (Hunter et al. 2007).



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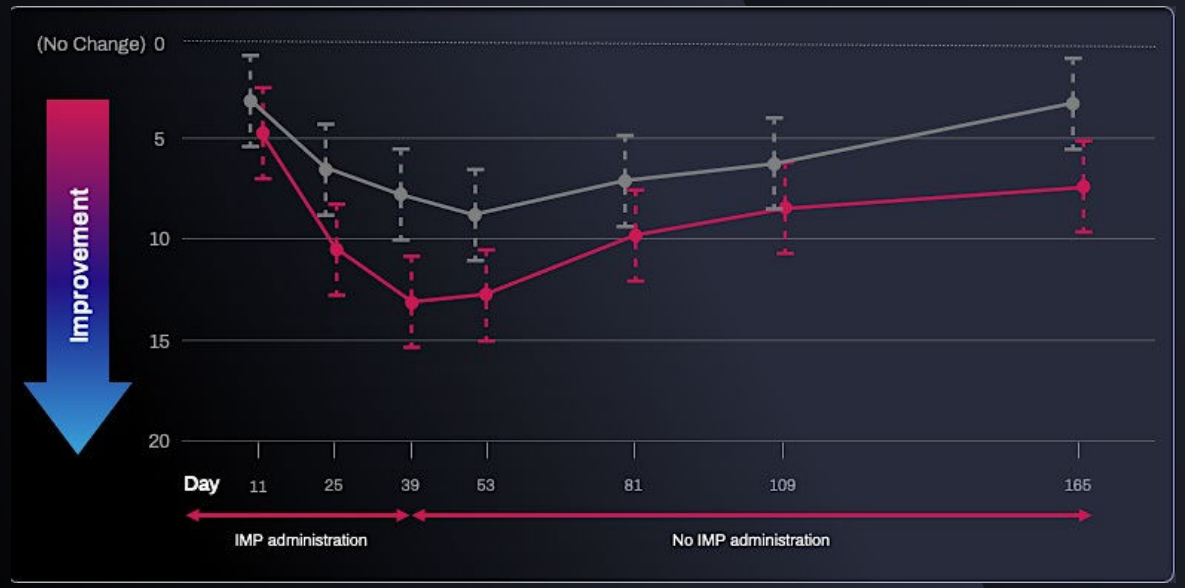
PARA_OA_005

Clinical Endpoints

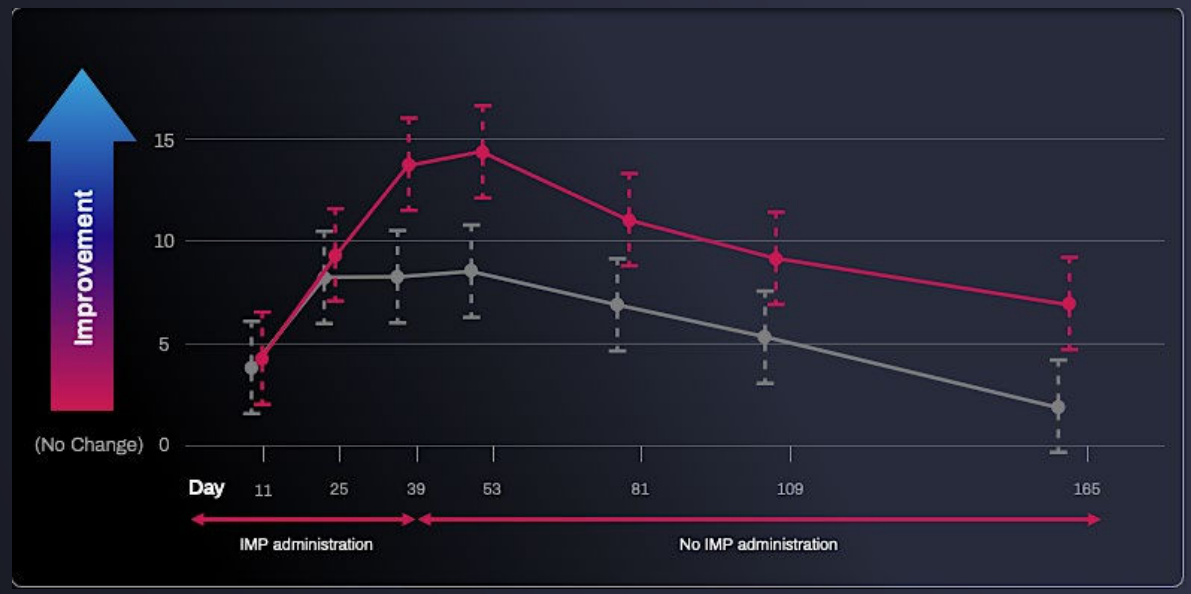
1 Pain Reduction (KOOS)

Adjusted mean change from baseline to days 11, 25, 39, 53, 81, 109, and 165.



2 KOOS Function (ADL)

Adjusted mean change from baseline to days 11, 25, 39, 53, 81, 109, and 165

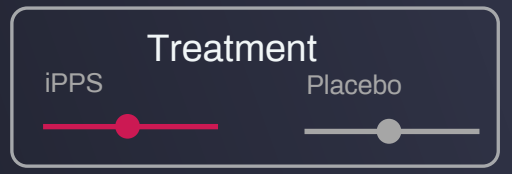


LS mean change +/- standard error

FAS = Full analysis set

Patient Global Impression of Change (PGIC)

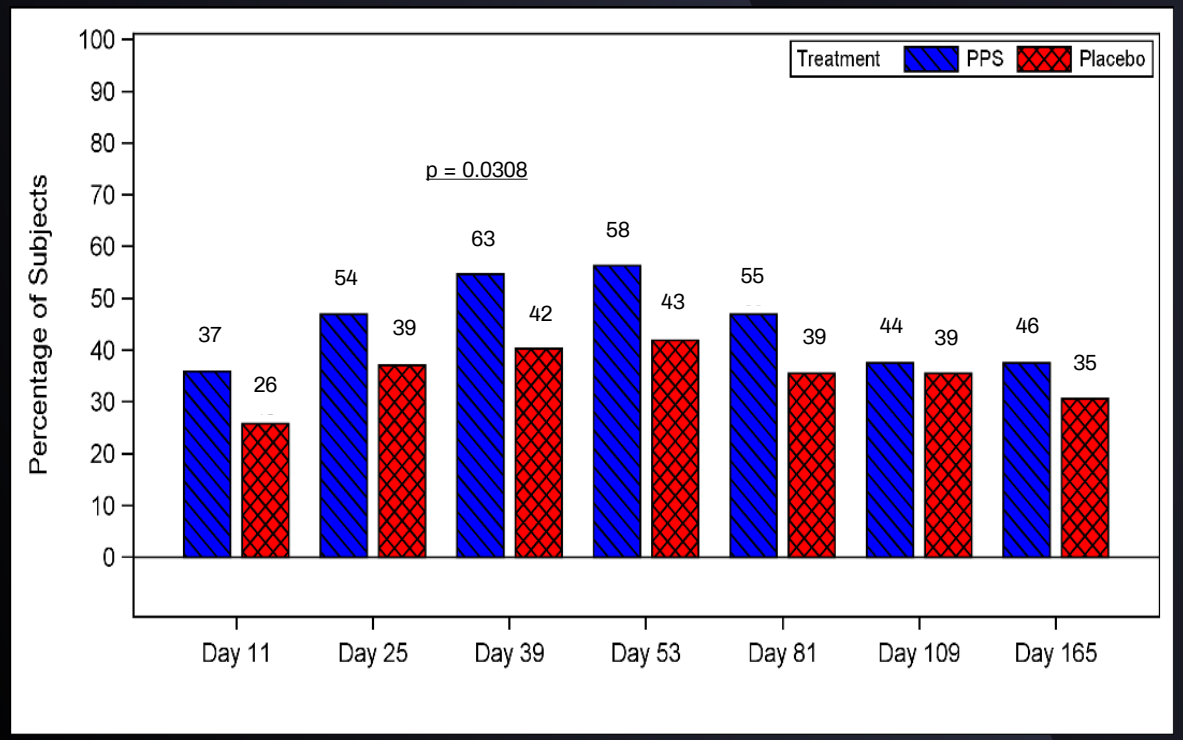
- Mean PGIC significantly higher in the iPPS group than placebo group at day 53 (4.42 versus 3.42, respectively; mean difference between iPPS and placebo 1.0 [95% CI 0.24, 1.8]; p=0.0106).



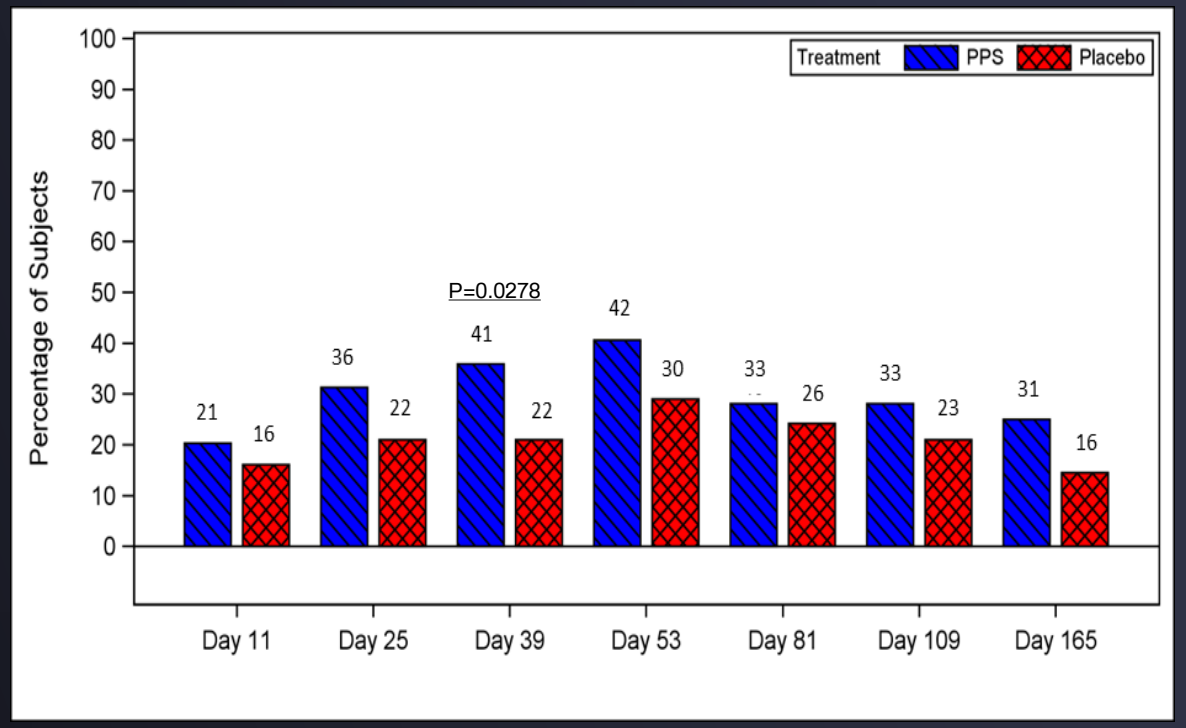
PARA_OA_005

Clinical Endpoints

3 KOOS Pain: Proportion of participants with 25% Pain Reduction



4 KOOS Pain: Proportion of participants with 50% Pain Reduction



FAS = Full analysis set

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Biomarker Study

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. 61 participants (1:1:1).

Treatment arms

- PPS twice weekly: 2.0 mg/kg IBW PPS twice weekly for 6 weeks
- PPS 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

Primary objective

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

Key objectives

- Correlation between synovial fluid biomarkers and clinical outcomes (Day 56 and Day 168)
- Effect of PPS treatment on synovial fluid, serum and urine biomarkers associated with inflammation and OA disease progression in participants with knee OA pain (Day 56 and Day 168)
- Effect of PPS on improvement in WOMAC pain, function, and stiffness in participants with knee OA pain (Day 56, Day 168 and Day 365)
- Structural imaging objectives and endpoints (Day 168)

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Synovial Fluid Biomarkers

PARA_OA_008

DAY 56 TOP-LINE RESULTS

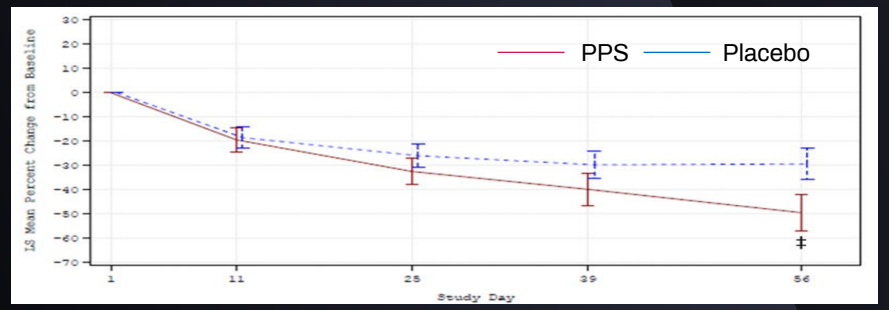
The synovial biomarker changes in iPPS-treated subjects at day 56 were favourable overall compared to placebo control.

Synovial Biomarker	iPPS compared to placebo	Biomarker Function
NGF	Reduced	Pain mediator
IL-6	Reduced	Pro-inflammatory cytokine
TNF-α	Reduced	Pro-inflammatory cytokine
COMP	Reduced	By-product of cartilage degradation
ARGS	Reduced	By-product of cartilage degradation
TIMP-1	Increased	Endogenous inhibitor of cartilage degradation

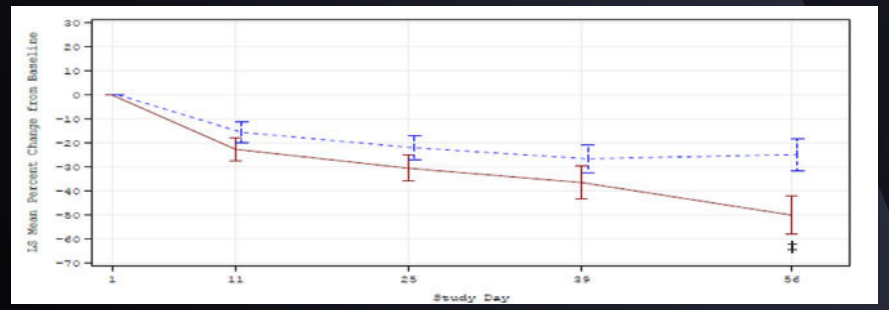
ARGS = Aggrecan amino acids alanine, arginine, glycine, and serine; COMP = cartilage oligomeric matrix protein; IL-6 = Interleukin-6; NGF = nerve growth factor; TIMP-1 = tissue inhibitor matrix metalloproteinase 1; TNF-α = tumor necrosis factor alpha.

PARA_OA_008: Clinical Endpoints

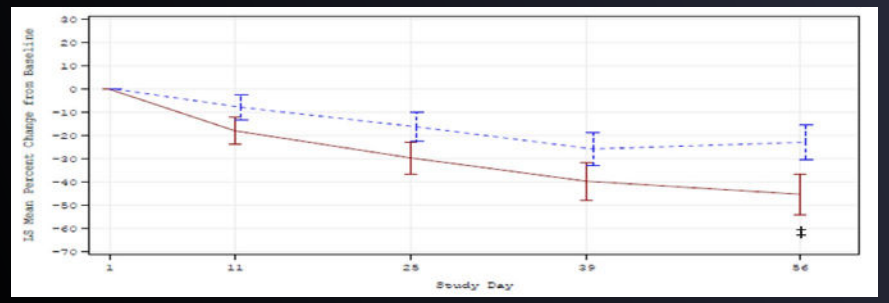
Percentage Change from Baseline in WOMAC NRS 3.1 Index Pain, Function and Stiffness Subscale



‡ p = 0.050



‡ p = 0.017



‡ p = 0.058

DAY 56 TOP-LINE RESULTS – CHANGES IN WOMAC PAIN, FUNCTION AND STIFFNESS FROM BASELINE

- Participants in the study were asked to provide baseline pain scores using the WOMAC NRS 3.1 Index.
- Study population: OA history mean 6.8 years, 80% with K-L Grade 3 or 4, mean baseline WOMAC pain 6.7.
- 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.
- The proportions achieving ≥30% and ≥50% improvement in pain were 73% and 60%, respectively.
- The responses in pain for iPPS-treated subjects are consistent with the clinical effects observed in this and prior studies of iPPS in osteoarthritis.

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Pentosan Polysulfate Sodium

Safety Profile

Over 800 people have been treated with iPPS in the clinical and early access programs.

Very common or common adverse events (AEs) observed in Paradigm clinical studies:

- Injection site reactions (bruising, erythema, pain, pruritus, swelling) and headaches, which were mild and self-limiting

Other adverse events:

- Thrombocytopenia, including heparin-induced thrombocytopenia. Has been observed in <2% of patients in Paradigm clinical studies and managed access programs.

Other relevant information:

- Pigmentary maculopathy has been observed following long-term cumulative dosing of oral PPS.
- It has not been observed with iPPS in the Paradigm clinical and nonclinical programs. It is being monitored in the phase 3 iPPS program.

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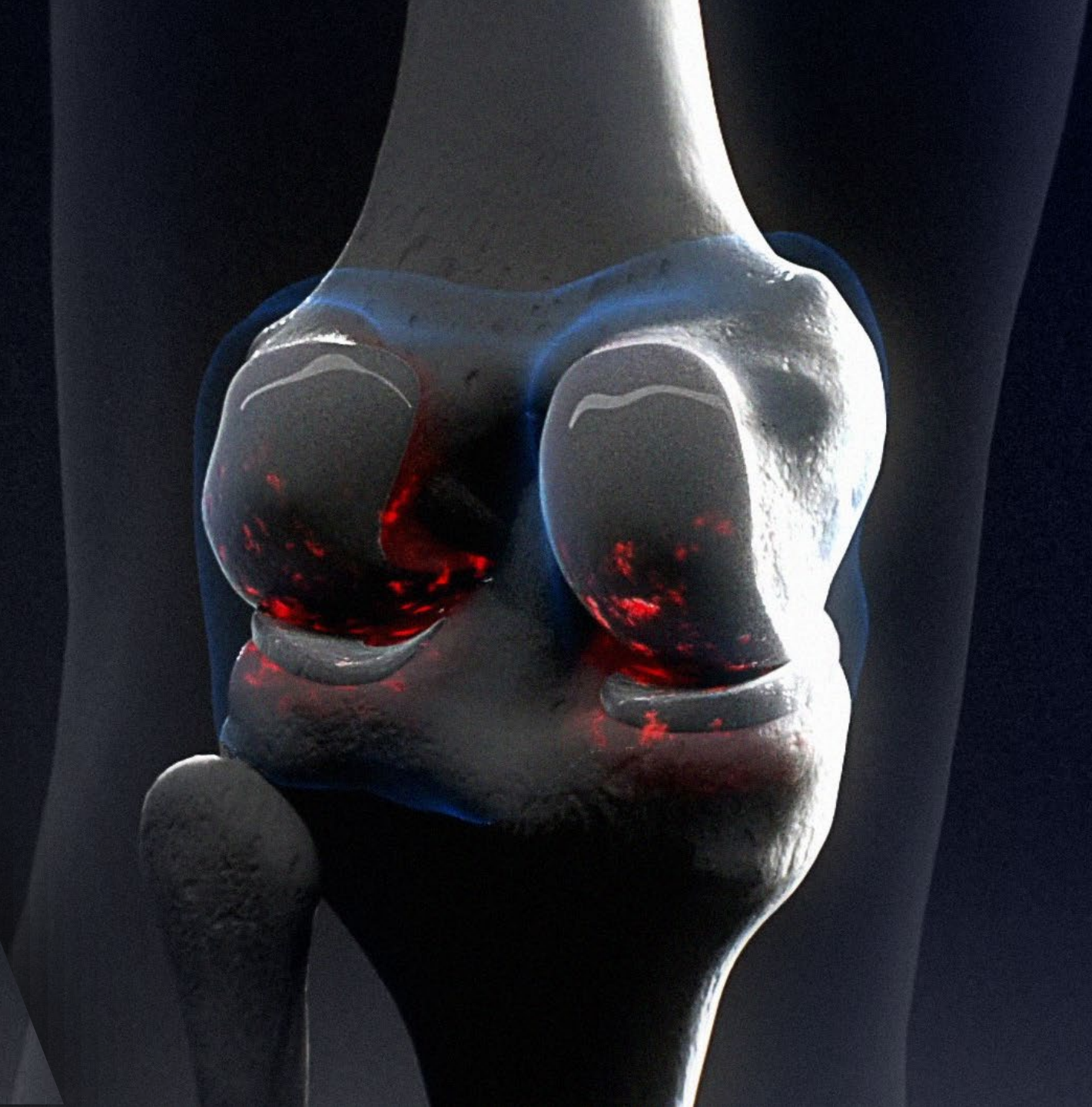
Phase 3 Program

OA



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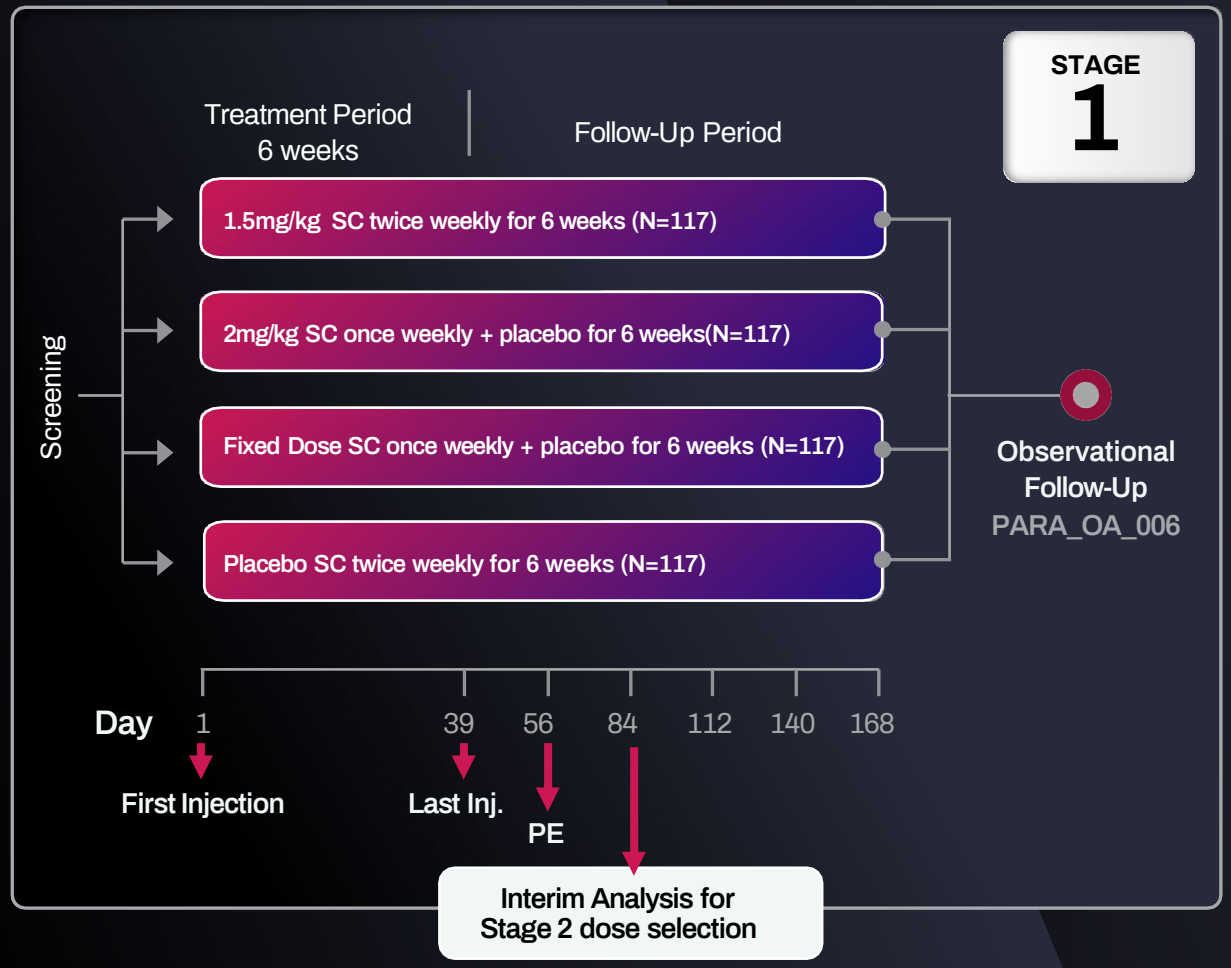
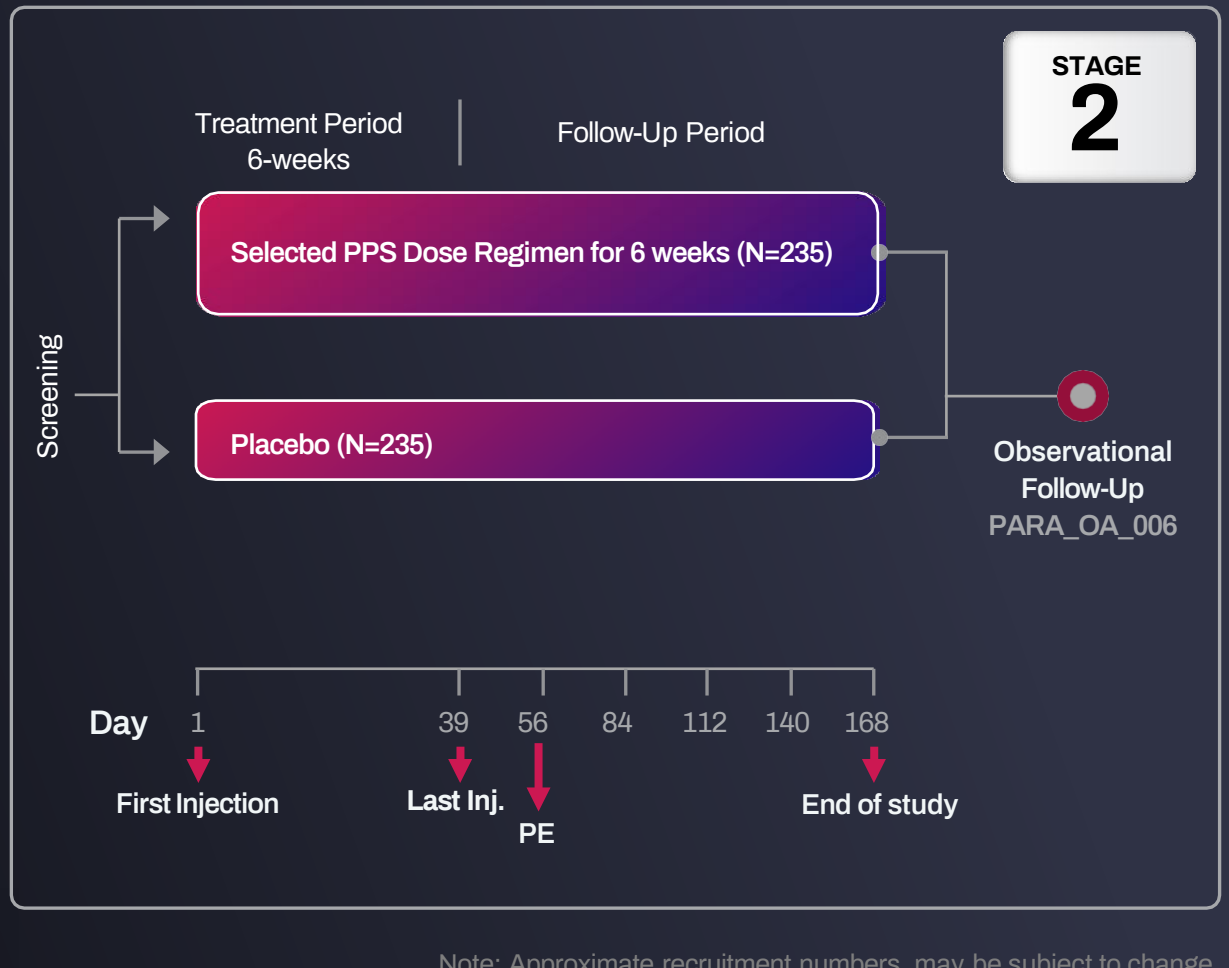
PARA_OA_002

Phase 3 Trial Design – Primary Endpoint: WOMAC Pain and Function





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

Osteoarthritis - Global Phase 3 Enrolment

- Harmonized clinical protocol to achieve simultaneous registration in key jurisdictions
- 120+ sites planned across the US, EU, UK, Canada and Australia

PARA_OA_002 Global Progress

USA
- Fast Track Designation
- 76 active sites
- 14 sites selected
- US enrolling

Australia
- 4 active sites
- 12 sites selected
- AU enrolling

UK and Europe
- 1 active site
- 12 sites selected
- UK enrolling

Canada
- 5 active sites
- 6 sites selected
- CA enrolling