PARADIGM BIOPHARMA

CLINICAL TRIAL SYMPOSIUM | MARCH 16, 2023

DR. DONNA SKERRETT | CHIEF MEDICAL OFFICER

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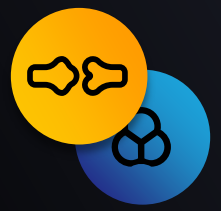
About Paradigm

Paradigm Biopharmaceuticals Ltd is an Australian public company founded in 2014 that listed on the Australian Stock Exchange (PAR.ASX) in 2015.

SAS – Special Access Scheme
EAP – Expanded Access Program
ADL – Activities of Daily Living
PGIC – Patient Global Impression of Change

Proven Molecule



Lead Programs

Established Safety & Efficacy

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.

Osteoarthritis (OA) ZILOSUL®

- Zilosul® is a **phase 3 asset** being studied to treat pain & function, inflammation, and cartilage degeneration in OA.
- OA program granted FDA Fast Track.
- Globally harmonized protocol to secure simultaneous approval in all key jurisdictions.

Mucopolysaccharidosis (MPS I & VI)

- Phase 2 asset in ultra rare disease.
- PPS has demonstrated potential to treat residual musculoskeletal symptoms in MPS as adjunct to standard of care therapy.

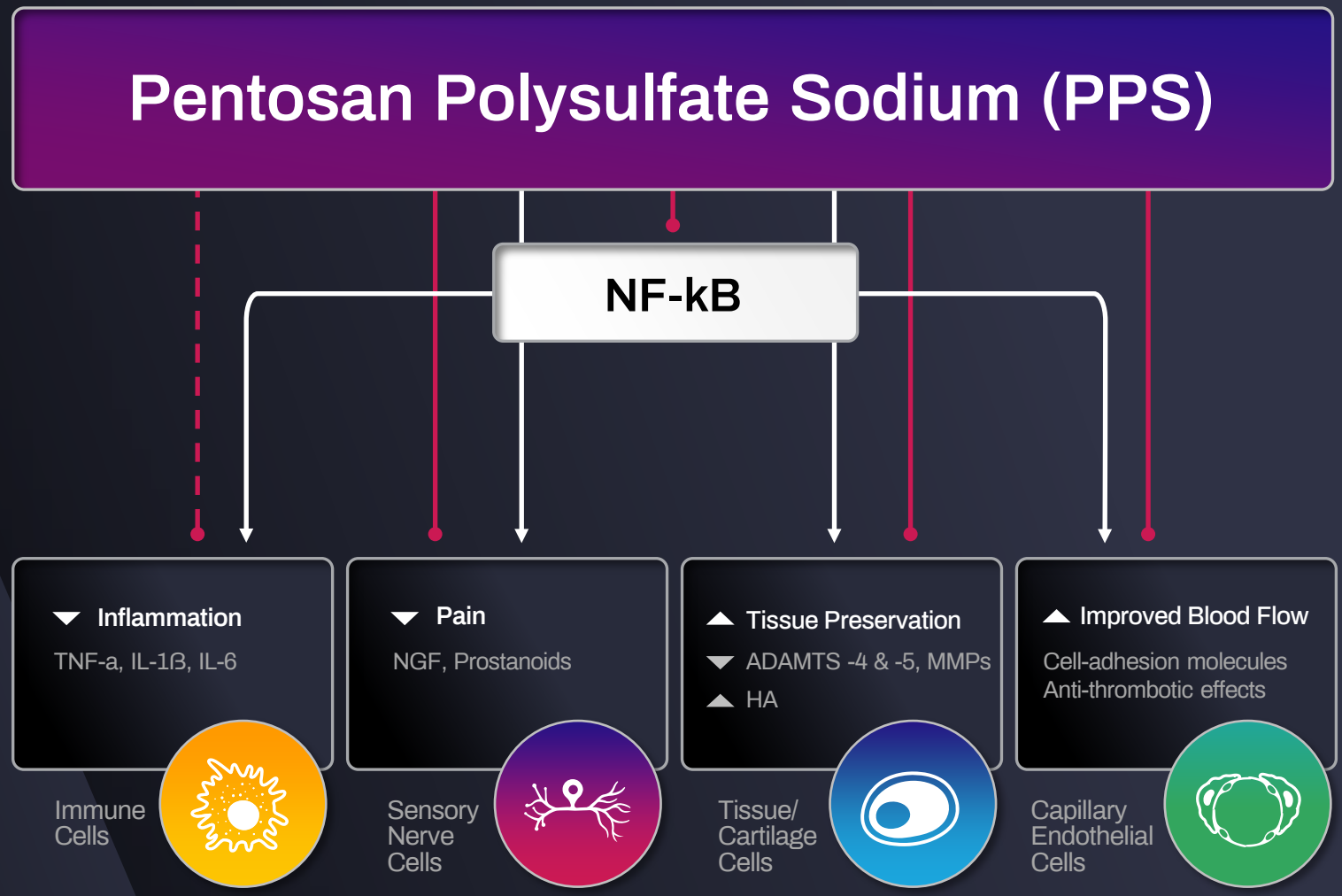
- Phase 2 OA trial provided encouraging evidence of **meaningful treatment effects** compared to placebo overall for pain, ADL, and PGIC.
- Real world evidence with 700+ OA patients treated via SAS in Australia and EAP in the US.

Mechanism of action

Pentosan polysulfate sodium (PPS), a semi-synthetic macromolecular carbohydrate that resembles glycosaminoglycans, has several proposed mechanisms of action (Figure 1.)

- Inhibition of transcription factor NF-κB-mediated activation of the inflammatory cytokines, IL-1β and TNF-α (Sunaga et al, 2012; Bwalya et al, 2017)
- Reduce expression of NGF, a pain mediator, in osteocytes in subchondral bone (Stapledon et al, 2019)
- Inhibition of cartilage-degrading enzymes known to play a key role in progression of OA (Troeberg and Nagase, 2012; Troeberg et al, 2012)
- Mild antithrombotic activity, which acts to improve blood flow in subchondral bone (Kutlar et al, 2012), which is thought to help reduce the size of bone marrow lesions

Figure 1. Proposed pentosan polysulfate sodium mechanism of action



ADAMTS = a disintegrin and metalloproteinase with thrombospondin motif; ARGS = aggrecan amino acids alanine, arginine, glycine, and serine; β NGF = beta nerve growth factor; C2C = c-terminal telopeptide;COMP = cartilage oligomeric matrix protein; CTX–II = Type II collagen; IL= Interleukin; TNF-α = tumour necrosis factor alpha; TIMP-1 = tissue inhibitor matrix metalloproteinase 1.

Pentosan Polysulfate Sodium

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

Proof of Concept – Wijekoon et al, 2019

Anti-arthritic effects of pentosan polysulfate in rats with collagen induced arthritis

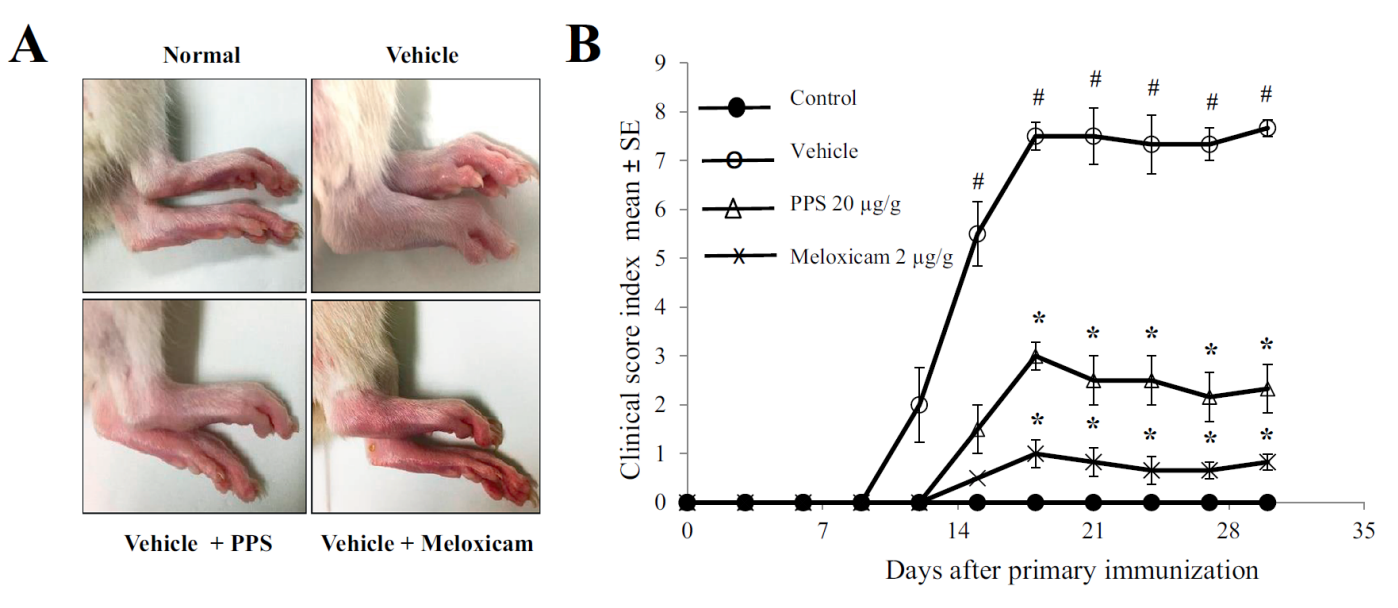
METHODS

- Rheumatoid arthritis (RA) induced in female rats by intradermal administration of Type II collagen (CII) in incomplete Freund's adjuvant.
- Drug administration and model induction at Day 0.
- Two drug approaches were studied:
  - iPPS administration 20 mg/kg SC (human equivalent dose [HED] 3.22 mg/kg).
  - Non-steroidal anti-inflammatory drug (NSAID) meloxicam 2mg/kg.
- RA symptoms were monitored visually (A) and using Clinical Score Index (B).

RESULTS

- PPS and meloxicam significantly ($p<0.05$) delayed the onset of arthritis and reduced ankle swelling, deformity and ankylosis (Figure 2A).
- Both drugs significantly ($p<0.05$) reduced the magnitude of arthritic effects measured by a clinical score index (Figure 2B).

Figure 2. Visual Effects (A) and Clinical Score Index (B) in Rats Treated with PPS



Proof of Concept – Wijekoon et al, 2019

Anti-arthritic effects of pentosan polysulfate in rats with collagen induced arthritis

RESULTS

- PPS and meloxicam prevented cartilage degradation, bone erosions, and reduced inflammatory markers in synovial membranes (Table 1).
- Proof of in vivo mechanism of action of PPS was shown by reduction of markers of joint inflammation such as cathepsin k (CTK), tartrate-resistant acid phosphatase (TRAP) and cytokines, IL-1β, TNF-α in synovial membrane of rats.

Table 1. Histological Score in Rats Treated with PPS and Meloxicam

Histological score of rats.

Histological parameter	Vehicle (n = 6)	PPS (n = 6)	Meloxicam (n = 6)
Synovial mononuclear infiltrate (0–3)	2.8 ± 0.20	0.5 ± 0.22**	0.16 ± 0.30**
Synovial hyperplasia (0–3)	2.8 ± 0.20	0.83 ± 0.30**	0**
Pannus extension (0–3)	2.8 ± 0.20	0.16 ± 0.16**	0**
Synovial fibrosis (0–3)	2.4 ± 0.24	0.83 ± 0.30**	0.16 ± 0.16**
Cartilage erosions (0–3)	2.4 ± 0.40	0.1 ± 0.16**	0.6 ± 0.33**
Cartilage degradation (0–3) (Based on safranin-O staining of proteoglycans)	2 ± 0.31	0.8 ± 0.30*	1.16 ± 0.30
Bone erosions (0–3)	2.8 ± 0.20	0.16 ± 0.16**	0.16 ± 0.16**

CONCLUSIONS

- In this translational study, PPS showed potential disease-modifying effects on collagen-induced arthritis in Sprague-Dawley Rats.
- PPS was shown to be well tolerated and effective in this rat model of arthritis.
- Optimization of PPS dose is required.

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).

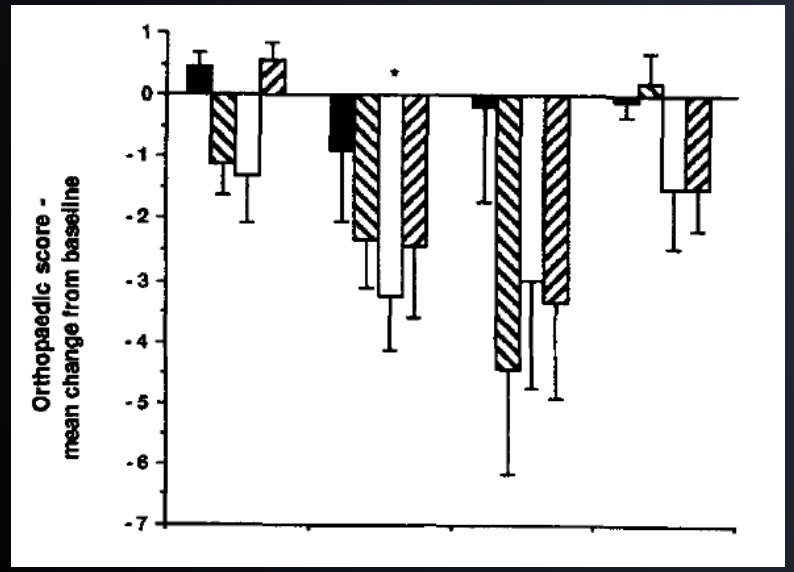


Figure 3. Orthopedic Scores

Legend
- Week 2
- Week 3
- Week 4
- Week 8

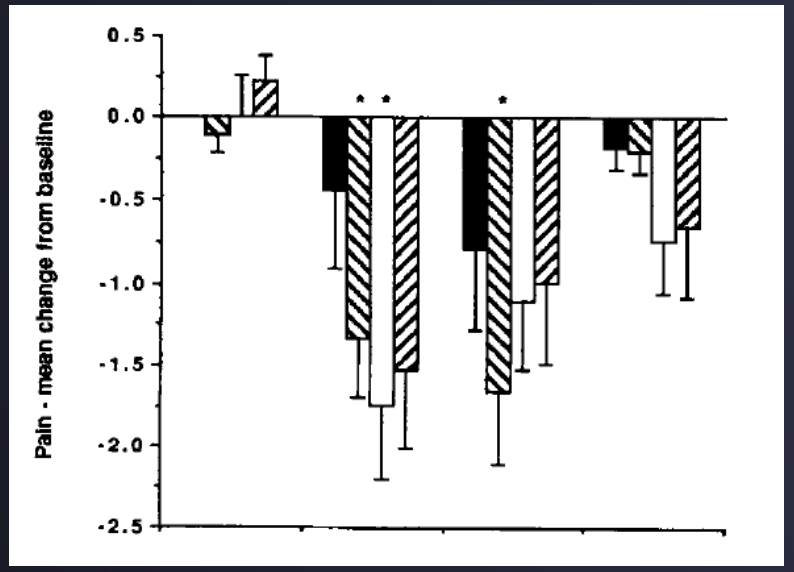


Figure 4. Pain Scores

Legend
- Week 2
- Week 3
- Week 4
- Week 8

Pilot Trial – Ghosh et al, 2005

Effects of pentosan polysulfate on osteoarthritis of the knee

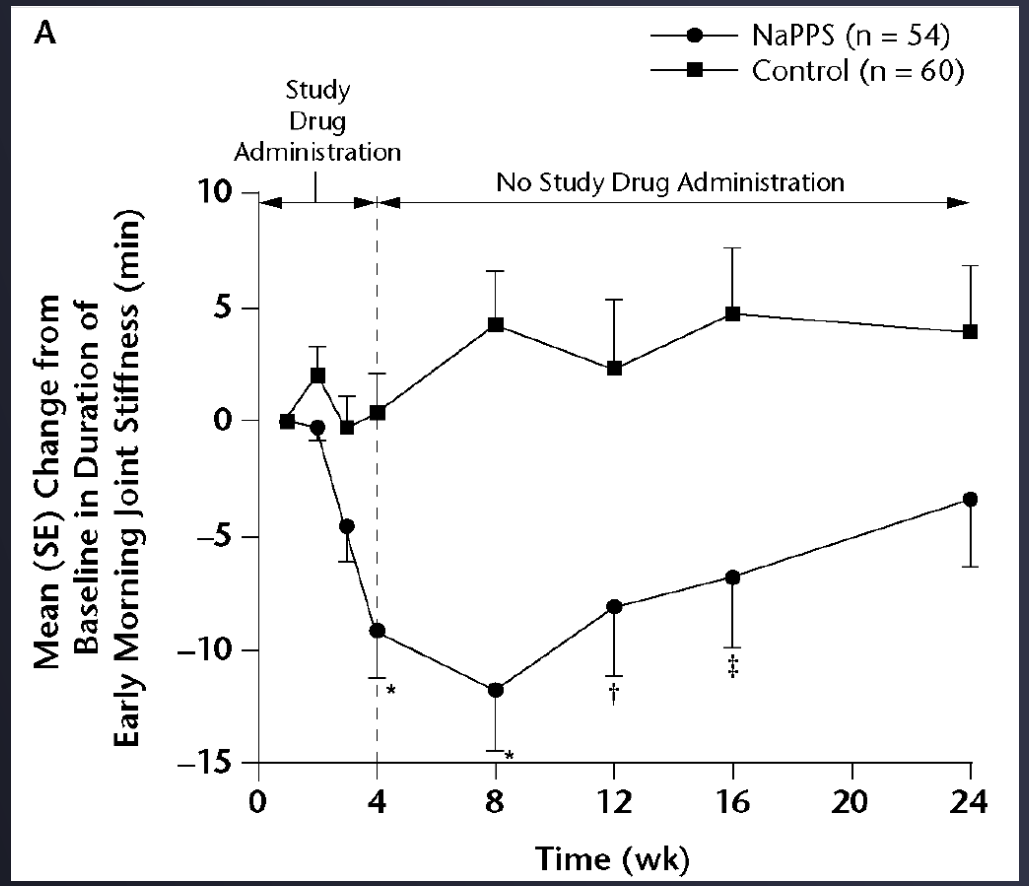
METHODS

- 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 stiffness with long duration (Figure 5).
- Reduced pain with long duration (Figure 6).
- Global assessment improved for 20 weeks after 4 weeks dosing- durable improvement (Figure 7)

Figure 5. Change from Baseline in Early Morning Joint Stiffness

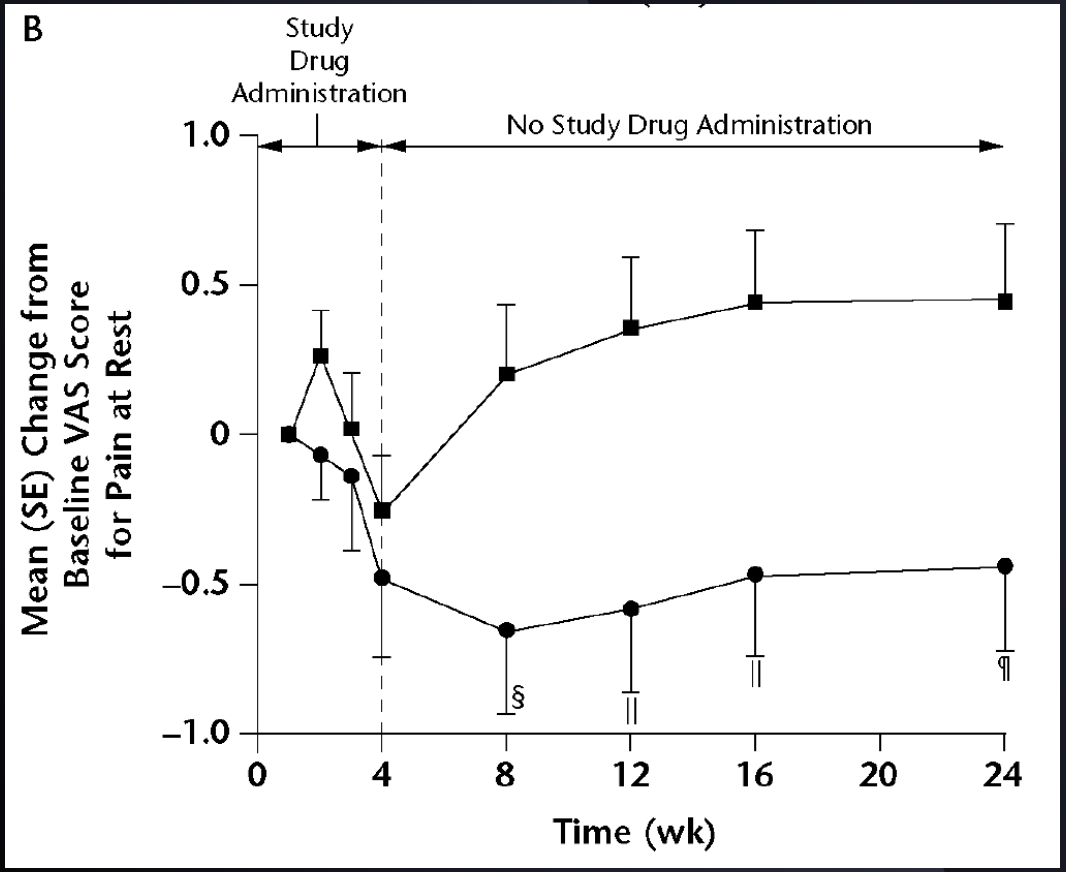


Min = minutes; NaPPS = pentosan polysulfate sodium; SE = standard error; wk = weeks. P versus control group: *< 0.001; †=0.015; ‡=0.008.

Pilot Trial – Ghosh et al, 2005 contd.

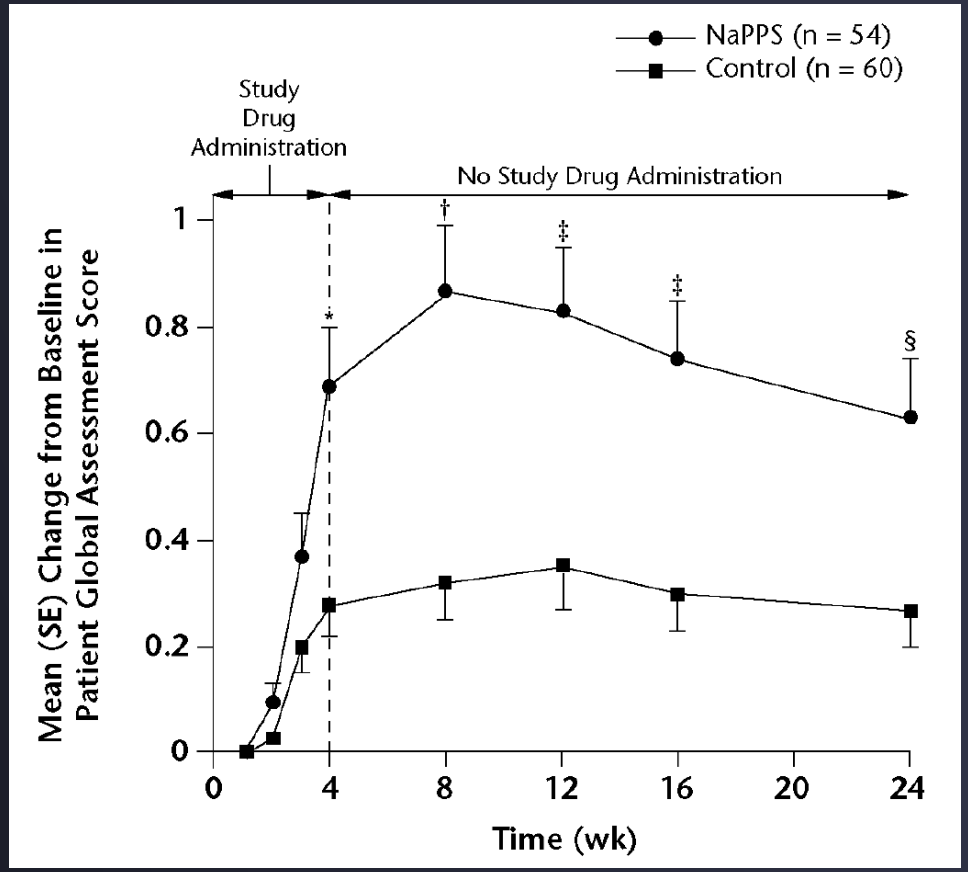
Effects of pentosan polysulfate on osteoarthritis of the knee

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.

Study design

PARA_OA_005

Evaluating the effects of iPPS in subjects with knee OA and subchondral bone marrow lesions

- A phase 2b randomized, double-blind, placebo-controlled study.
  - 112 participants received placebo or iPPS 2 mg/kg twice weekly for 6 weeks.
  - Follow-up period out to 24 weeks.

Study population	
Participants (N)	112
OA history (years; mean)	10.0
K-L Grade 3 or 4 (%)	81
Baseline KOOS score (mean) – all subjects	45
iPPS	44
Placebo	47
Baseline NRS score 4–6 (n)	79
Baseline NRS score 7–8 (n)	33

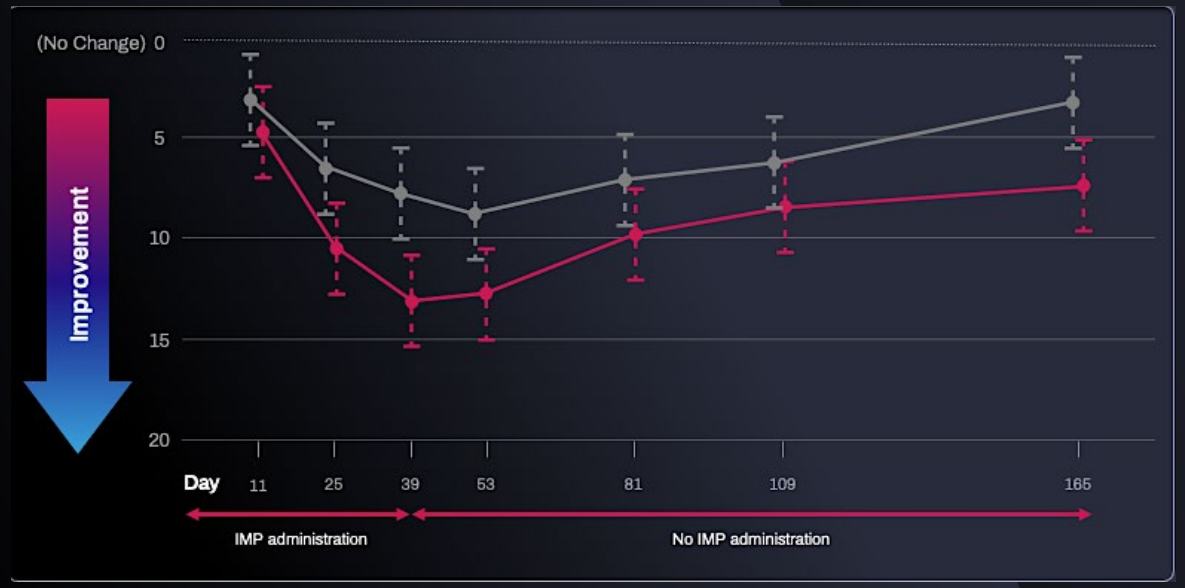
IPPS = injectable pentosan polysulfate sodium; K-L = Kellgren-Lawrence; KOOS = Knee Injury and Osteoarthritis Outcome; NRS = Numeric Rating Scale; OA = osteoarthritis

PARA_OA_005
Phase 2 Clinical Study

TREATMENTS:
- 2 mg/kg SC twice weekly for 6 weeks.
- Placebo SC twice weekly for 6 weeks.
- Randomized 1:1.

ASSESSMENTS:
- Knee Injury and Osteoarthritis Outcome (KOOS) Pain and Function
- Patient Global Impression of Change (PGIC) - Mean PGIC significantly higher in the PPS group at Day 53.

1 Pain Reduction (KOOS)
Adjusted Mean Change From Baseline (N=112)

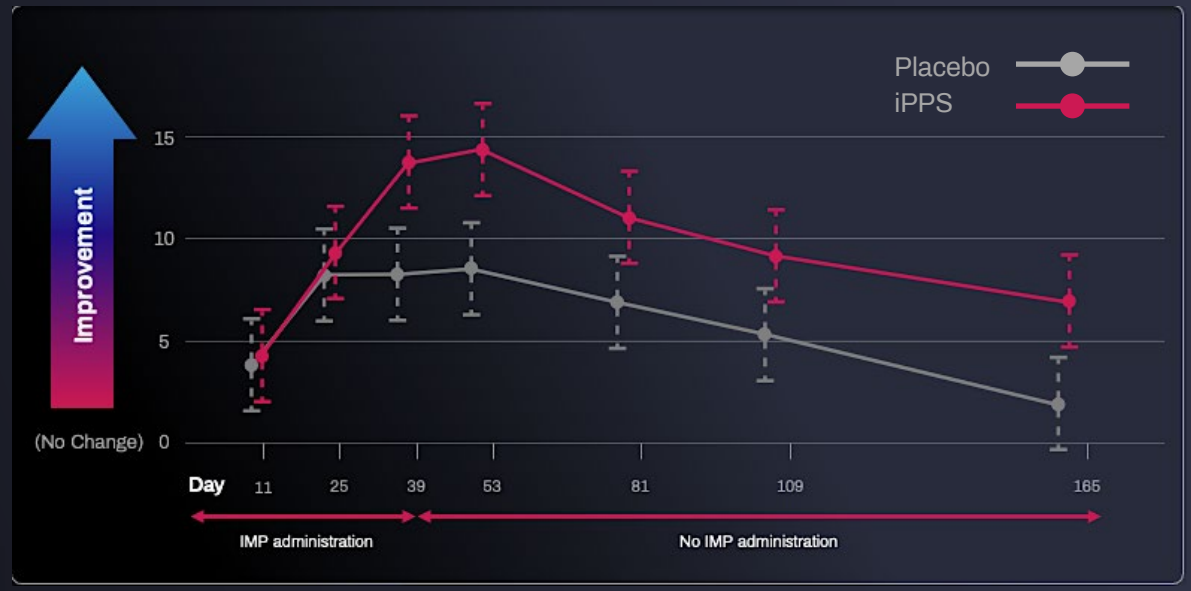


LS mean change +/- standard error

IMP = investigational medical product; KOOS = Knee Injury and Osteoarthritis Outcome

Placebo
iPPS

2 KOOS Function (ADL)
Adjusted Mean Change From Baseline (Overall FAS Population)



LS mean change +/- standard error

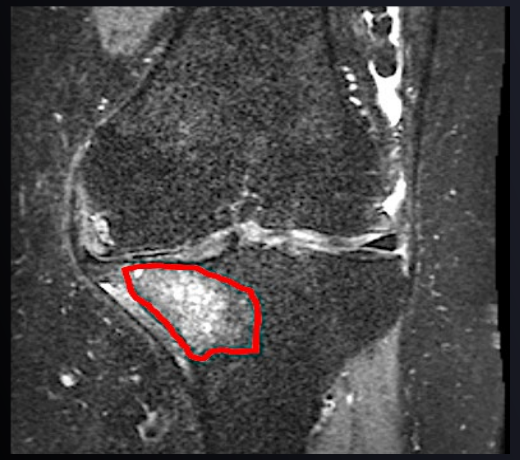
FAS = Full analysis set

ADL = Activities of Daily Living; FAS = Full Analysis Set; IMP = investigational medical product; KOOS = Knee Injury and Osteoarthritis Outcome

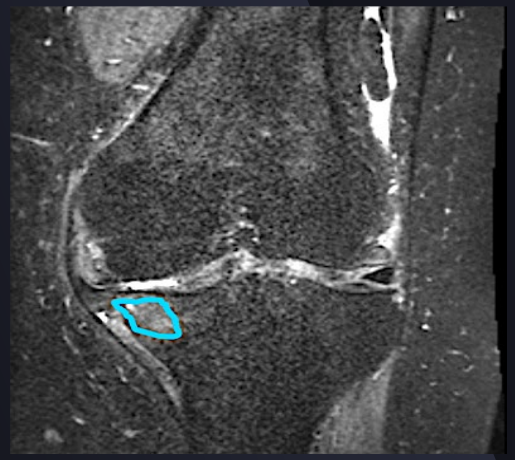
PARA_OA_005
Phase 2 Clinical Study

- iPPS showed significant reduction in **bone marrow lesion** size as compared with placebo controls.

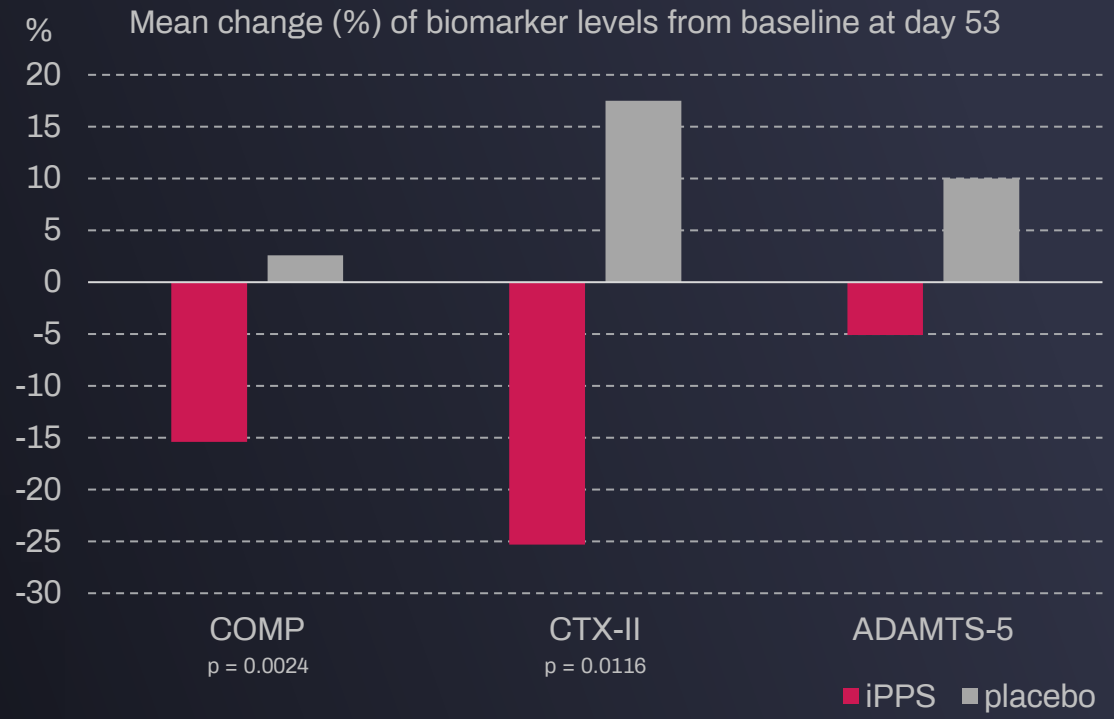
Grade 3 medial tibial BML at baseline



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).



Potential Disease Modifying Osteoarthritis Drug

Current programs investigating Zilosul® as a potential DMOAD

PARA_OA_008 – AUSTRALIA

- Exploratory phase 2 study to assess iPPS effects on synovial fluid biomarkers and other objective measures associated with disease progression of OA.
- 60 participants received placebo or 2 mg/kg iPPS once- or twice-weekly for 6-weeks.
- Follow-up to 12 months.
- Interim analysis performed at 56 days.

CANINE OA STUDY

- Aims to confirm the in vivo iPPS mechanism of action and to define potential disease modification outcomes.
- Dogs with OA of the stifle joint are treated with 3 mg/kg (1.7 mg/kg HED) iPPS weekly for 6 weeks.
- Pain and function will be assessed together with structural changes from baseline as determined by the Global OA Score measured by X-ray and bone marrow lesions (BMLs), and cartilage volume by MRI.
- Serum samples taken to measure biomarker levels associated with inflammation, cartilage degradation, and pain.
- 20-week follow-up period (equates on average to a period of 3 years in human lifespan)

Clinical Outcomes

PARA_OA_008

DAY 56 TOP-LINE RESULTS – CLINICAL OUTCOMES

Changes in Western Ontario and McMaster Universities Osteoarthritis (WOMAC) NRS 3.1 pain and function from baseline

Study population	
Participants (N)	61
OA history (years; mean)	6.8
K-L Grade 3 or 4 (%)	80
Baseline WOMAC NRS 3.1 (mean)	6.7

K-L = Kellgren-Lawrence; NRS = Numeric Rating Scale; OA = osteoarthritis; WOMAC = Western Ontario and McMaster Universities Osteoarthritis (index).

- Participants in the study were asked to provide baseline pain scores using the WOMAC Osteoarthritis Index.
- 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.

Synovial Fluid Biomarkers

PARA_OA_008

DAY 56 TOP-LINE RESULTS – BIOMARKERS

The synovial biomarker changes in iPPS-treated subjects at Day 56 were favorable 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.

Phase 3 Program

OA

Phase 3 Program

PARA_OA_002

PIVOTAL PHASE 3 TRIAL

A 2-stage, adaptive, randomized, double-blind, placebo-controlled, multicentre study to evaluate dose and treatment effect of iPPS compared with placebo in participants with knee osteoarthritis pain

STUDY POPULATION

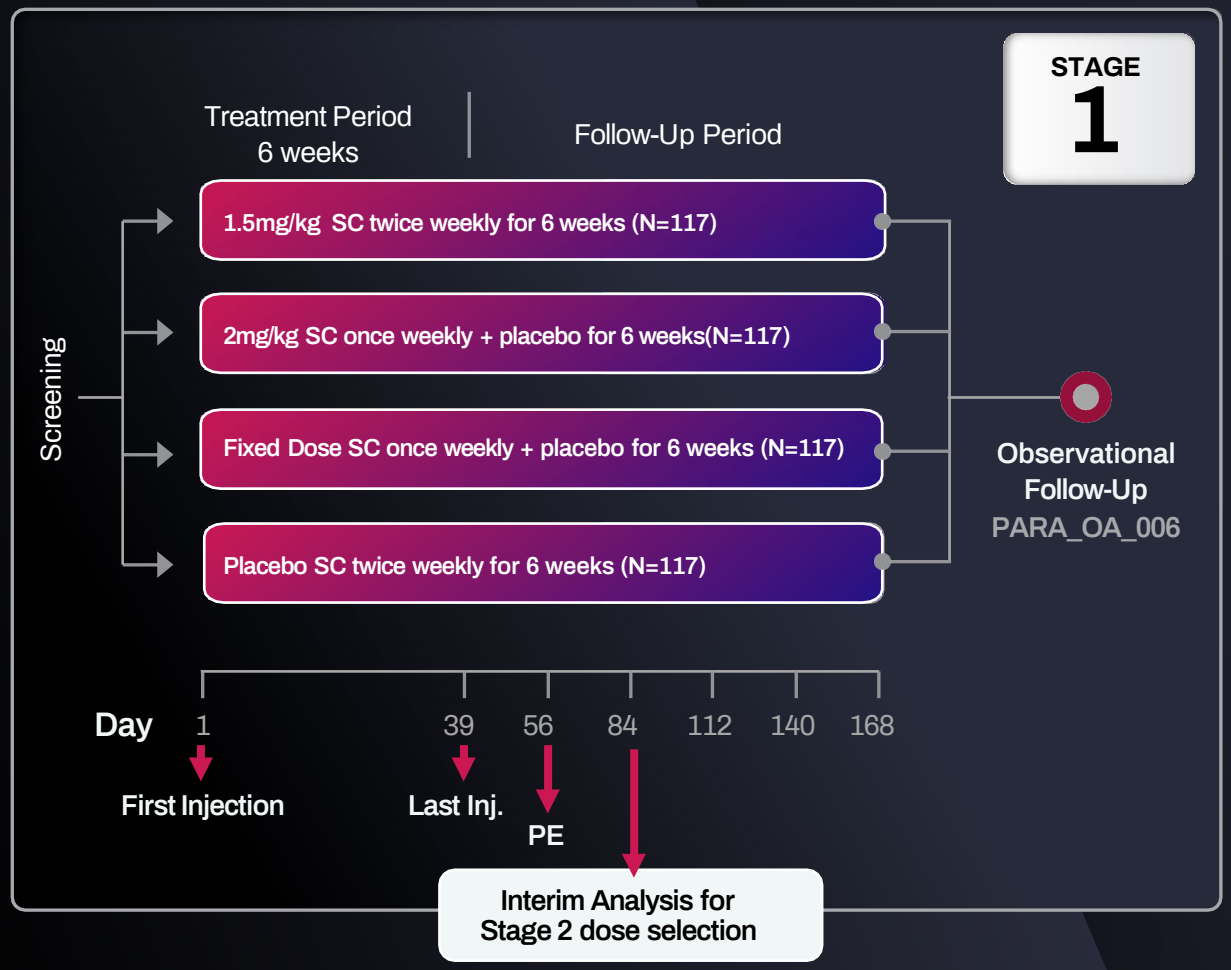
- Baseline K-L Grade 2 - 4 index knee.
- Baseline WOMAC NRS 3.1 pain score 4 - 10 and function score 4 – 10.
- Conservative treatment ≥ 6 months.
- Insufficient relief or intolerance to paracetamol and/or NSAID.

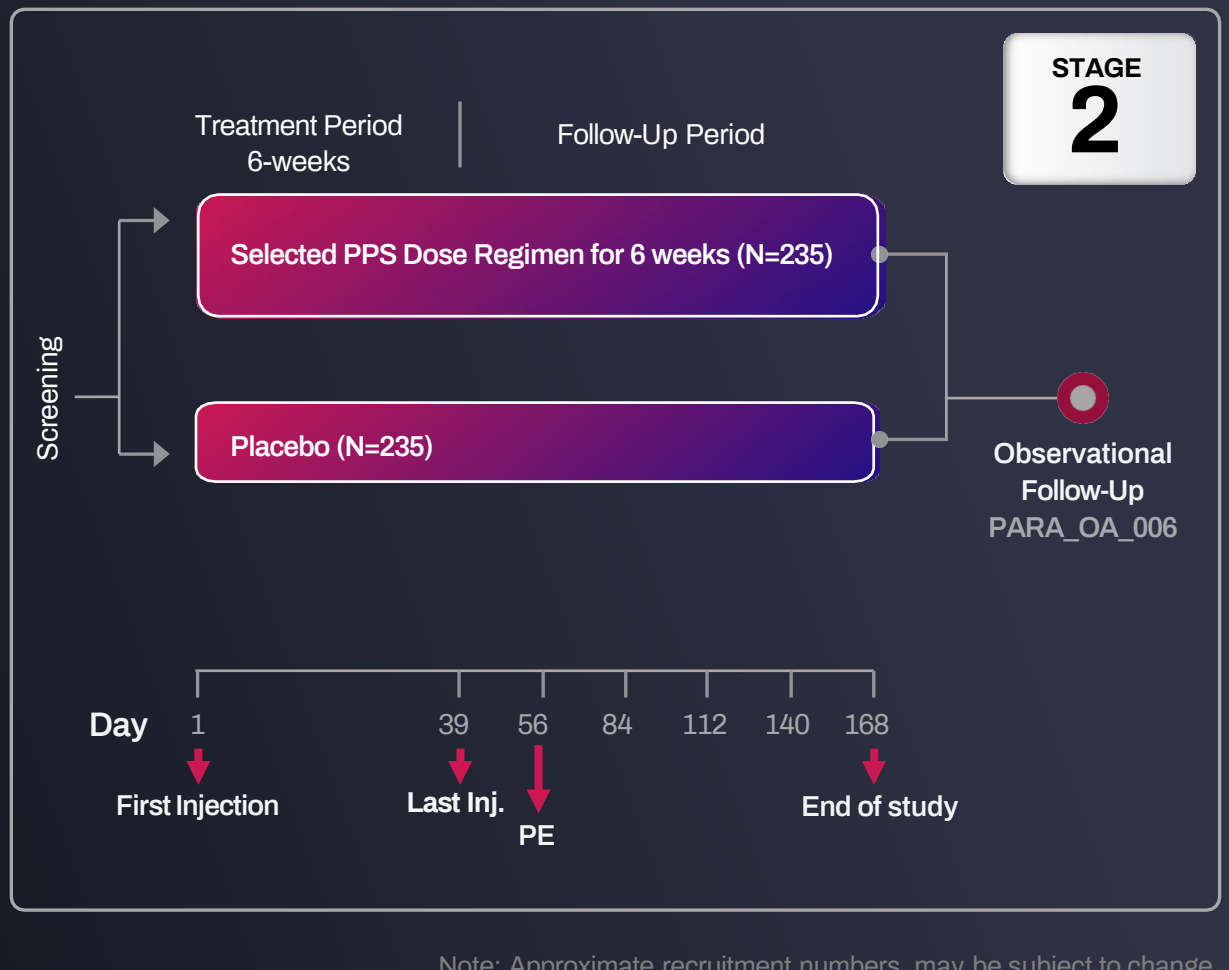
STUDY ENDPOINT

- Change from baseline at Day 56 in knee pain as assessed by the average pain subscale score of the WOMAC NRS 3.1 Index.

PARA_OA_002

Phase 3 - Adaptive trial design to identify minimal effective dose, evaluate 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

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

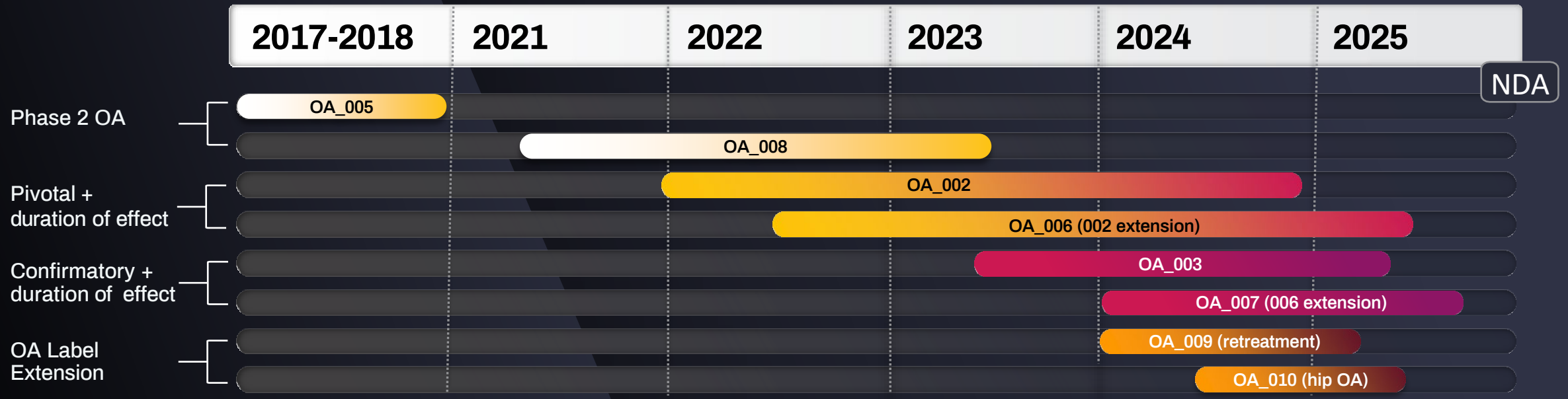
Other adverse events:

- 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.

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.

OA Clinical Development

Challenges

- Managing the placebo effect
- Relationship of clinical and structural effects.
- Concordance of biomarkers with outcomes-clinical and structural.
- Pleiotropic mechanisms of action advantages and considerations.

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