ASX RELEASE 31st July 2025

Investor Webinar Presentation: Phase 3 Update and Probability of Success

Paradigm Biopharmaceuticals Ltd (ASX: PAR) ("Paradigm" or "the Company"), a late-stage drug development company focused on delivering new therapies to address unmet medical needs, advises that the investor webinar, held today, provided an update on the Company's global Phase 3 clinical trial (PARA_OA_012) of injectable pentosan polysulfate sodium (iPPS) for knee osteoarthritis.

The presentation used during the webinar is now available and attached to this announcement.

A recording of the session will be made available shortly on the Paradigm website: https://paradigmbiopharma.com/performance-progress/#announcements

About Paradigm Biopharmaceuticals

Paradigm Biopharmaceuticals Ltd. (ASX: PAR) is a late-stage drug development company driven by a purpose to improve patients' health and quality of life by discovering, developing, and delivering pharmaceutical therapies. Paradigm's current focus is developing iPPS for the treatment of diseases where inflammation plays a major pathogenic role, indicating a need for the anti-inflammatory and tissue regenerative properties of PPS, such as in osteoarthritis (phase 3).

Forward Looking Statements

This Company announcement contains forward-looking statements, including statements regarding anticipated commencement dates or completions dates of preclinical or clinical trials, regulatory developments, and regulatory approval. These forward-looking statements are not guarantees or predictions of future performance, and involve known and unknown risks, uncertainties, and other factors, many of which are beyond our control, and which may cause actual results to differ materially from those expressed in the statements contained in this presentation. Readers are cautioned not to put undue reliance on forward-looking statements.

Authorised for release by the Paradigm Board of Directors.

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Paradigm Biopharma

PARADIGM BIOPHARMA

PHASE 3 CLINICAL TRIAL
WEBINAR JULY 2025

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Executive Summary

Background

Paradigm Biopharmaceuticals (ASX: PAR) is a **late-stage drug development company** focused on delivering new treatments for diseases with high unmet medical need. Our lead program, **injectable pentosan polysulfate sodium (iPPS)**, is being developed for **osteoarthritis (OA)**, a debilitating condition affecting millions worldwide.

Mission

To develop and commercialise **first-in-class therapies** for musculoskeletal diseases, targeting **inflammation, pain relief, and disease modification**.

Market potential

- Late-stage clinical development with Phase 3 trial commenced in the US and AUS.
- Robust clinical and real-world data supporting iPPS.
- Addressing one of the largest unmet needs in musculoskeletal medicine.

2025

Recent News-Flow

- Phase 3 OA program commencement – Site Activation, First Participant Consent Australia
- First Participant Consented in US
- New IP Acquisition – Building out Paradigm OA portfolio.
- Funding Secured to provide runway through many significant milestones.

Advancing iPPS Toward a Differentiated OA Therapy

Robust data and regulatory momentum underpin a well-defined path through Phase 3

01

SAFETY & EFFICACY PROFILE

- Strong efficacy and safety shown across a broad dataset
- Durable benefits sustained to 12 months in Phase 2 studies
- Imaging and biomarker data suggest effects beyond symptom relief

02

PHASE 2 AND REAL-WORLD EVIDENCE

- Multiple Phase 2 studies underpin Phase 3 program, showing consistent efficacy across patient types and timepoints
- Real-world insights from Australia's SAS program show long-term benefits with repeat courses

03

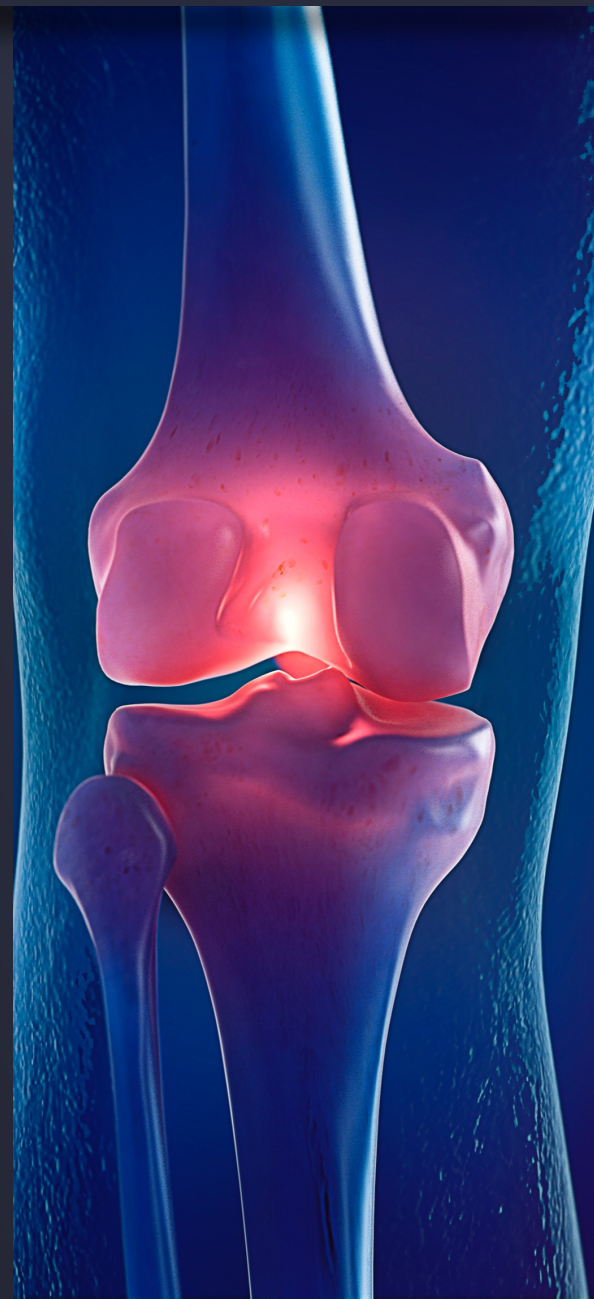
MECHANISM OF ACTION

- Demonstrated across preclinical models and human studies
- Anti-inflammatory, cartilage-protective, and matrix-restoring properties
- Biomarker data from Phase 2 suggests activity beyond symptom relief

04

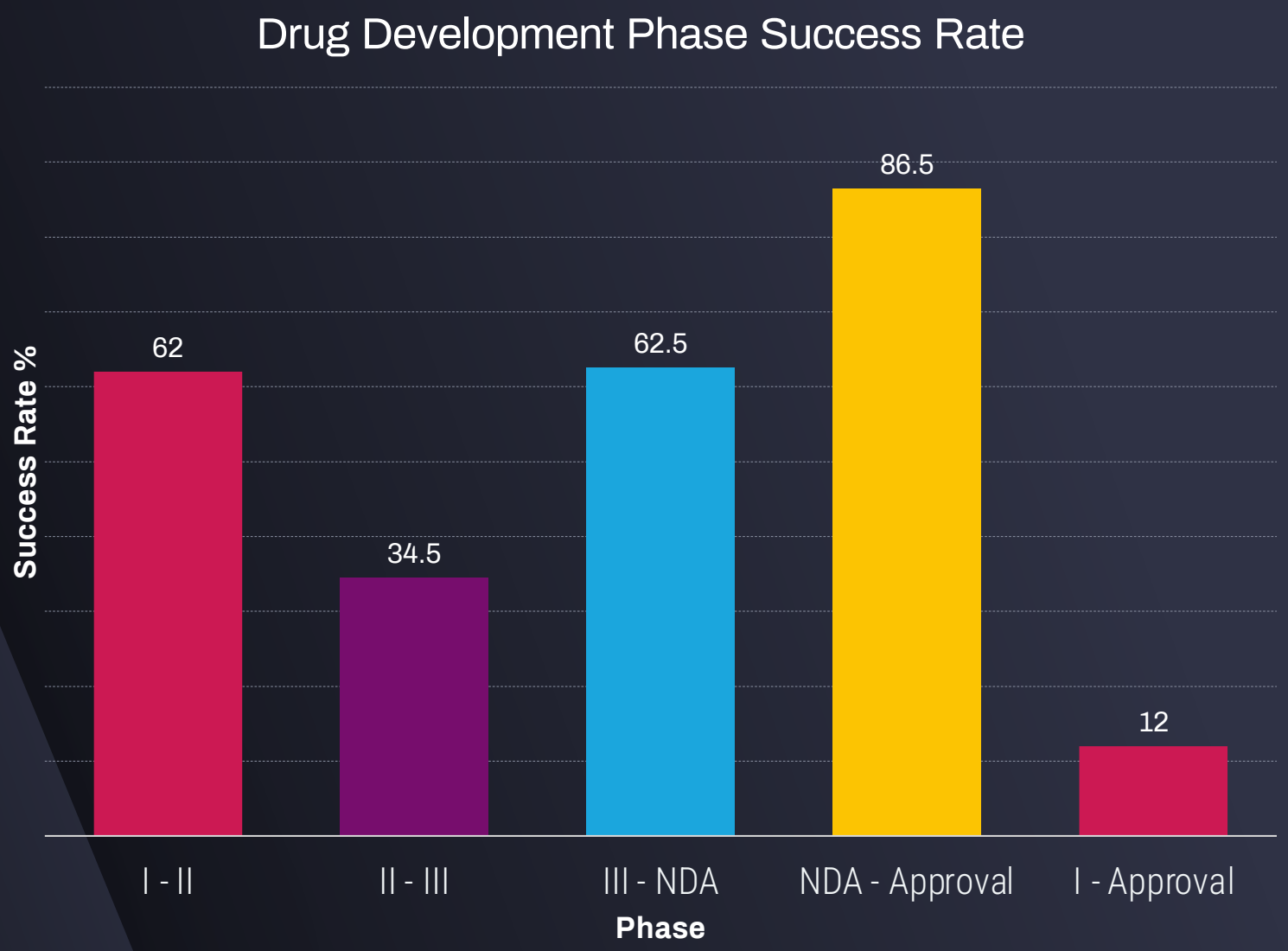
OPTIMISED PHASE 3 PROGRAM

- Fast Track designation granted by FDA
- Protocol refined following extensive FDA engagement (Type C and D meetings)
- Endpoints, statistical powering, and assessment windows aligned with regulatory expectations



Drug Development Phase Success Rates

- Only about 12% of drugs entering Phase I ultimately receive regulatory approval, highlighting the high attrition rate in drug development.
- The biggest drop-off occurs in Phase II, where just over one-third of candidates advance, often due to efficacy or safety issues.
- Success rates rebound in later stages, with over 60% of drugs in Phase III progressing to regulatory submission.
- Once a drug is submitted for approval, the likelihood of approval is high (around 86%).

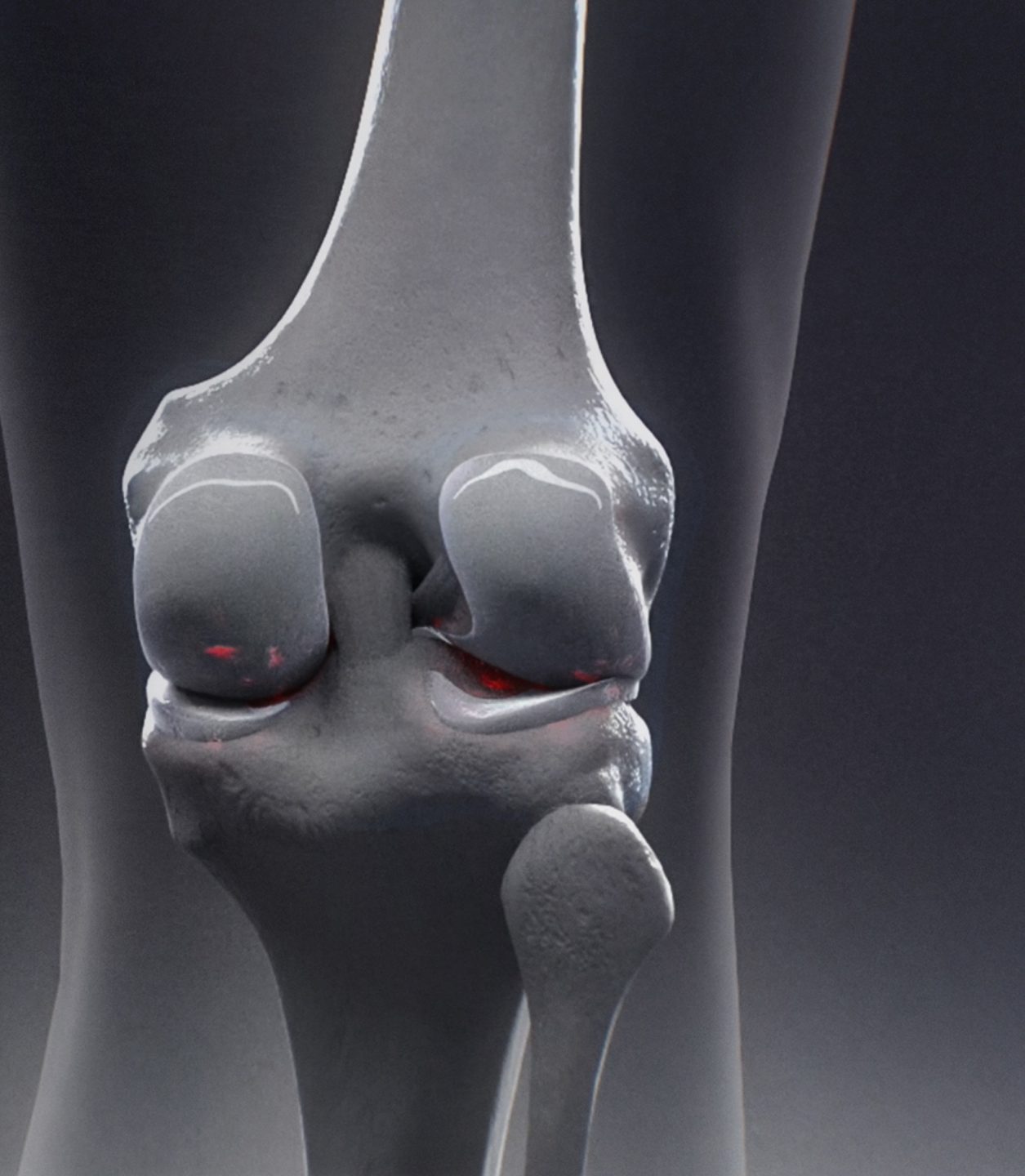


Source: "Benchmarking R&D success rates of leading pharmaceutical companies" (*Drug Discovery Today*, 2025)

PARADIGM

Osteoarthritis

Pivotal PH3 Trial



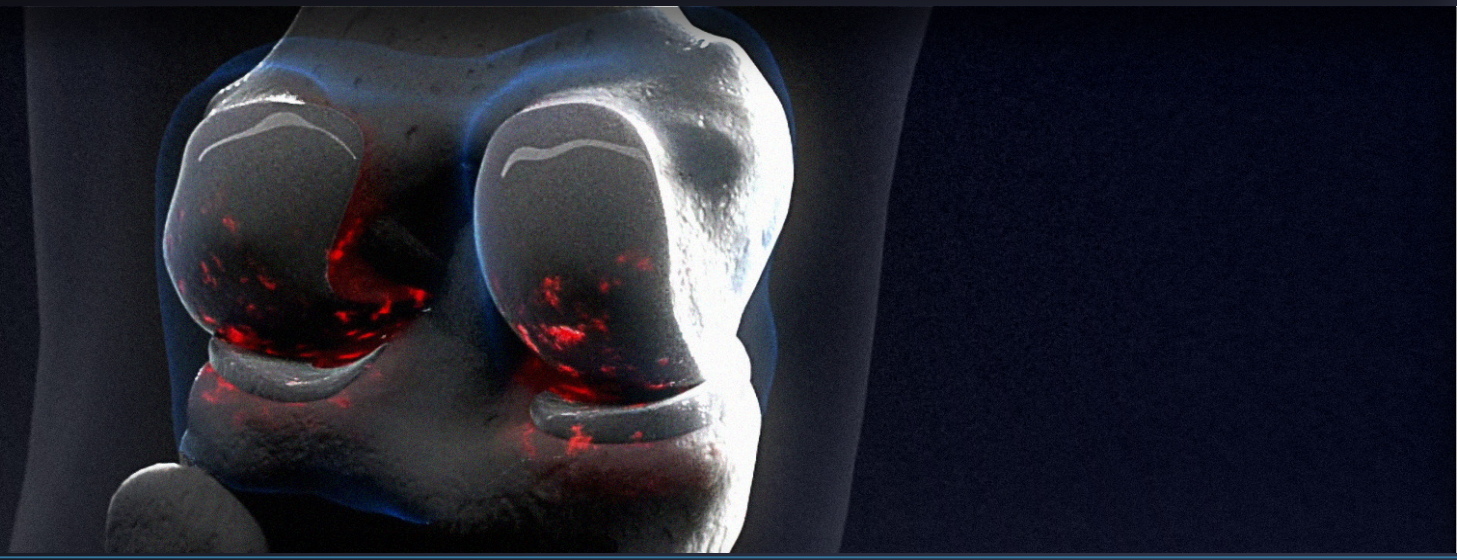
Study Overview

A Phase 3, Double-blind, Placebo-controlled, Multicenter Study to Evaluate Treatment Effect of Pentosan Polysulfate Sodium Compared with Placebo in Participants with Knee Osteoarthritis Pain.

Trial Type:	Phase 3
Study Drug:	Pentosan Polysulfate Sodium (PPS) - Injectable
Patient Population:	Adults with moderate to severe knee osteoarthritis with pain
Study Centres:	Total: 65 sites ➢ Australia: 15 sites ➢ United States: 50 sites
Number of Participants:	Enrollment goal: 466 participants ➢ Randomised 1:1 PPS to Placebo

Phase 3 Objectives

Key objectives for the Phase 3 PARA_OA_012 study



Primary Objectives

- To evaluate the treatment effect of PPS on knee pain in participants with knee OA pain. (Weekly Average ADP Day 112)

Key Secondary Objectives

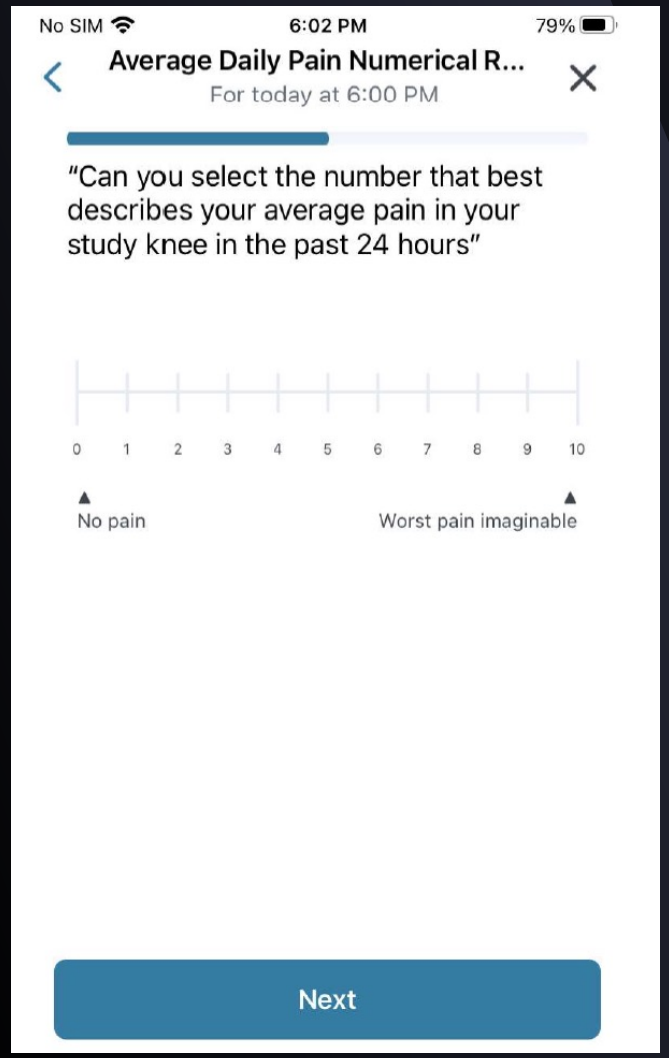
- To evaluate the treatment effect of PPS on knee pain function in participants with knee OA pain. (WOMAC Day 112)
- To evaluate the effect of PPS treatment on PGIC in participants with knee OA pain. (PGIC Day 112)
- To evaluate the efficacy of PPS treatment on knee pain, function, stiffness, and overall, in participants with knee OA pain

Secondary Objectives

- WOMAC Pain and function assessments at multiple timepoints to Day 404
- IPPS effects on Rescue Medication use
- Structural changes via X-Ray and MRI from baseline day 168, 404

PARA_OA_012

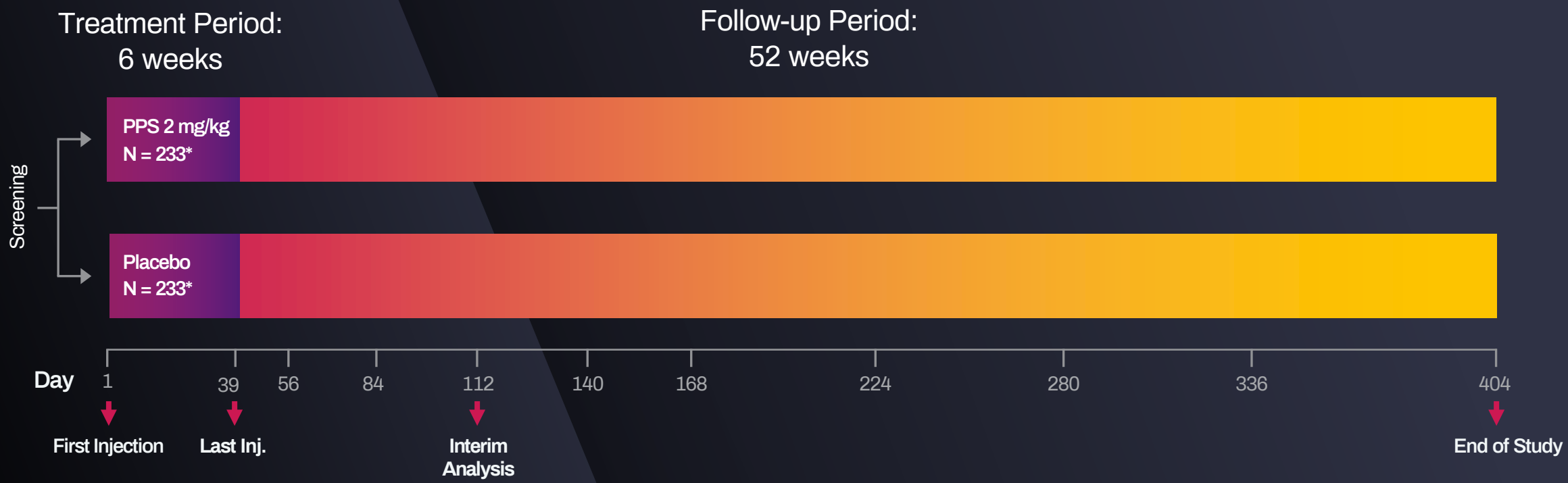
Optimised Endpoint Design and Pain Scoring



- Following FDA discussions, the primary efficacy endpoint is now assessed 8 weeks post-final injection, aligning with recent OA and chronic pain studies and reflecting the durable therapeutic effect of iPPS.
- Independently scored and self reported by patient.
- Pain is assessed via daily scores recorded through a smart device and averaged weekly to minimise day-to-day variability and ensure a more robust signal of clinical benefit.
- A 14-day pre-dosing familiarisation period allows participants to practise consistent reporting and ensures compliance from the outset.
- Automated daily alerts at a standardised time of day promote high-quality data capture and time-aligned pain scoring.

PARA_OA_012

Phase 3 trial design



Primary endpoint: Change from baseline in weekly ADP NRS pain score at Day 112.

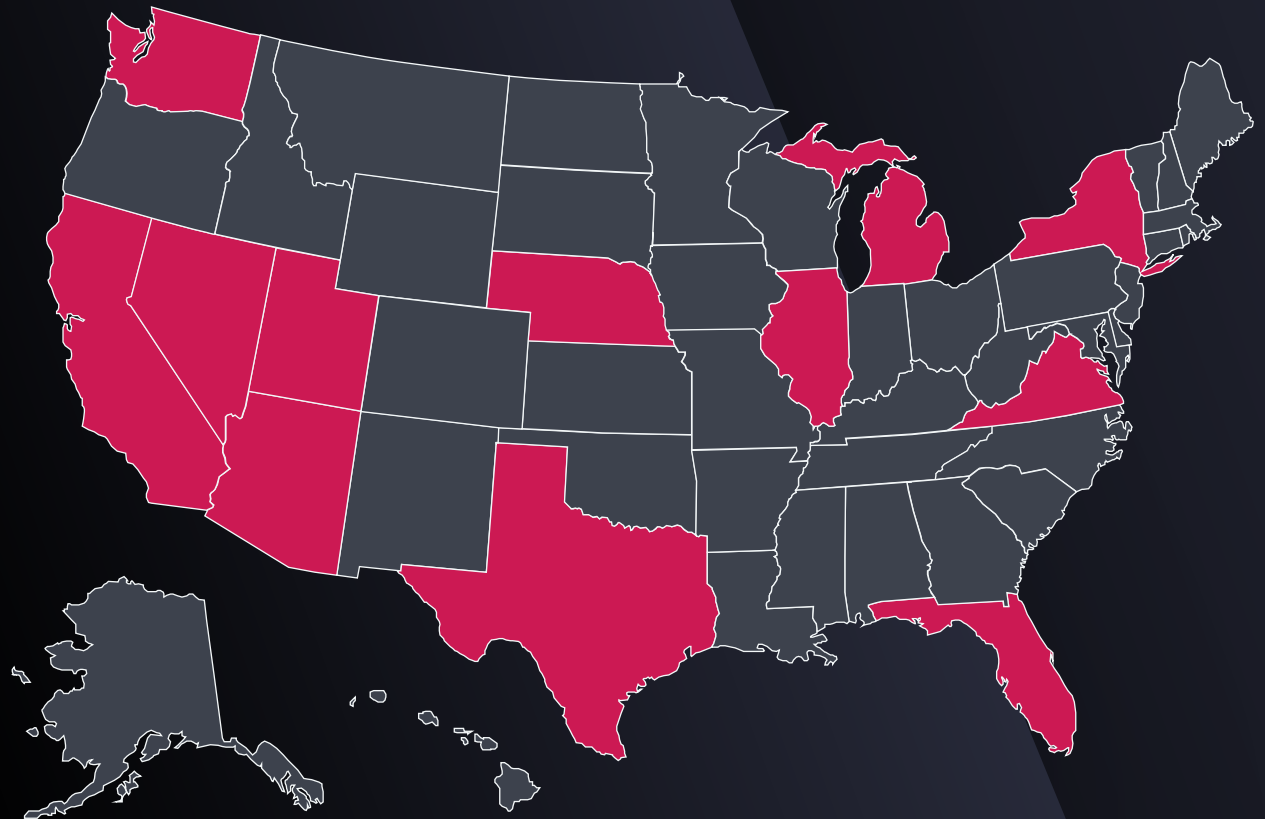
Secondary endpoints: Function, PGIC, rescue medication, biomarkers of disease progression, including MRI & X-Ray.

*May be subject to change

PARA_OA_012 Phase 3 Site Locations by State

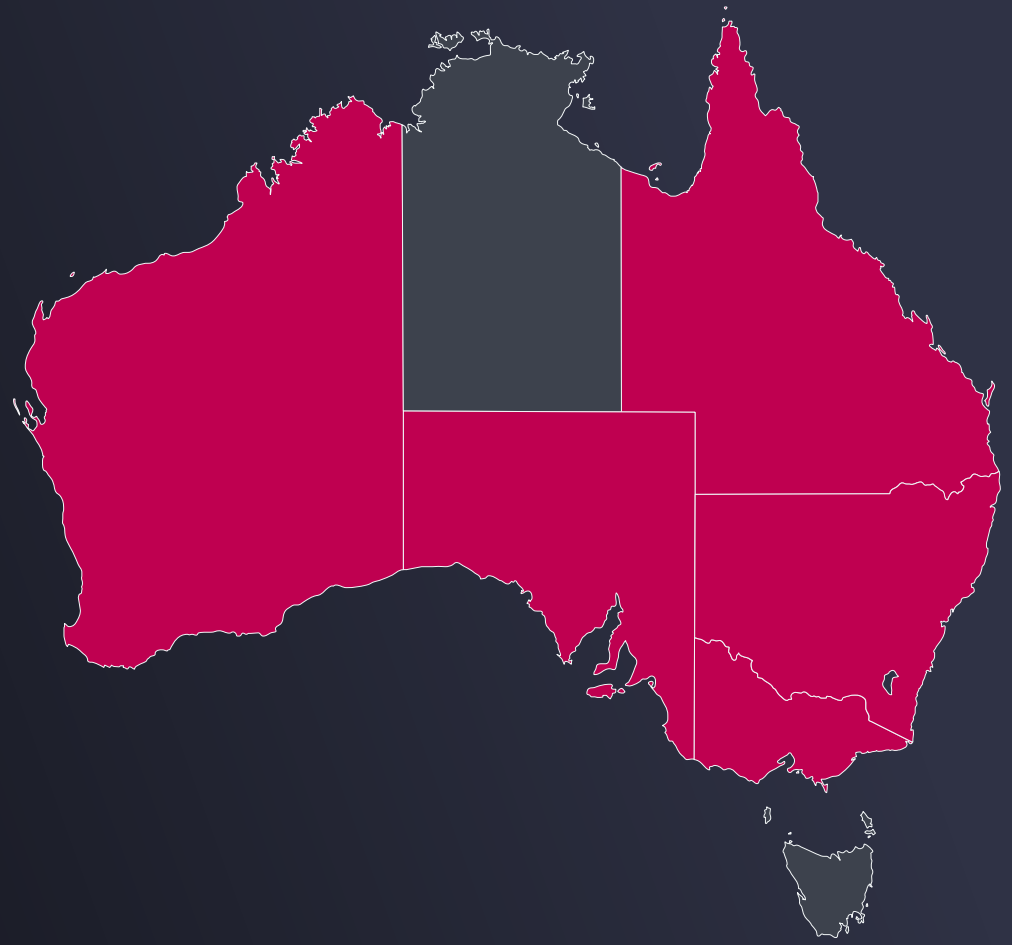
United States

50 sites



Australia

15 sites



PARA_OA_012 Considerations in Evaluating Probability of Success

NRS 0-10 endpoint, average daily pain

- What is a meaningful difference – statistical or clinical (anchor to PRO)
- FDA recommended endpoint to ”reduce recall bias and capture day to day variability”

Magnitude of Effect

- How does the change from baseline in pain score relate to benchmarks of clinical meaning or MCII, MCID, PRO anchors such as PGIC

Effect size-distribution based method of meaningful difference

- Assessment of mean difference between groups corrected for standard deviation
- What is relationship of ES to study power, sample size, and probability of success

FDA: Analgesic Indications: Developing Drug and Biological Products — Guidance for Industry, February 2022.

PRO: Patient Reported Outcomes
MCII: Minimal Clinically Important Improvement
MCID: Minimal Clinically Important Difference

PARA_OA_005

Magnitude: NRS 0-10, absolute and %Change from Baseline

	iPPS Day 53	iPPS Day 81
NRS Med % CBL	-33.33	-16.67
4-6	-36.67	-8.33
7-8	-14.29	-28.57
Absolute pain NRS	-1.81 (2.31)	-1.22 (2.32)
4-6	-1.61 (2.17)	-1.15 (2.19)
7-8	-2.28 (2.63)	-1.81 (2.04)
KOOS ADL Med %CBL	35.91	26.67
4-6	37.85	26.67
7-8	29.39	26.11
PGIC mean	4.42, 87% ≥5	

NRS-valid and reliable measure of pain intensity

- NRS assessed for prior 48 hours
- Clinical MCID is one unit difference or 15% NRS (6)
- 2-point reduction or 30% NRS anchors with clinically important PGIC change
- PGIC MCID is one unit difference at 3 month (6)
- Clinically important PGIC is much improved and very much improved (5)

PARA_OA_008

Magnitude: WOMAC, %Change from Baseline[1]

	iPPS Day 56	iPPS Day 112
Pain	-49.33*	-45.05
Function	-49.38*	-46.58*
Stiffness	-45.51	-47.45
Overall	-48.97	-46.02

[1]MMRM-mixed model repeated measures

- Sustained improvements in both pain and function scores were observed in the iPPS twice-weekly treatment group
- These improvements* exceeded the Minimum Clinically Important Improvement (MCII) thresholds[(2,3)]:
  - Pain: 17%
  - Function: 12%
- Pain reductions in the iPPS group approached the "substantial improvement" benchmark of 50% recommended by IMMPACT[(1)]:
  - 49% reduction at Day 56
  - 45% reduction at Day 112
- Patient Global Impression of Change (PGIC) 7-point scale:
  - **Day 365:** 3.55 (2.11) vs 2.06 (1.70), *p = 0.005*
  - **Day 112:** 4.07 (2.16) vs 3.10 (2.26)
  - **Day 56:** 3.93 (2.09) vs 3.15 (2.30)

PARA_OA_012

Endpoint: Observed effect size for Pain Scores (Scale 0-10)

Time	Para_005	Para_OA_008	Pooled-weighted
Day 39	0.33	0.38	0.34
Day 56 (53 for 005)	0.25	0.66	0.34
Day 112 (109 for 005)	0.20	0.46	0.30
Day 168 (165 for 005)	0.28	0.26	0.28

Study Population Considerations
- SC 2mg/kg twice weekly x 6

Patient Populations
- 005 BML 95%, KL 3-4~ 80%
- 008 BML 70%, KL 3-4 79%

Subgroup Observations
- NRS 4-6 (70%) and KL4 (28%) improved pain responses in 005.

Effects sizes form the basis for sample size calculations

PARA_OA_012 – Probability of Success

Clinically Important response on NRS Scale

- **Sample Size**: ~466 participants with moderate to severe knee OA (KL Grade 2–4), randomised 1:1
- **Primary Endpoint**: Change from baseline in weekly average pain (NRS 0–10) at Day 112
- **Standard Deviation (SD)**: Estimated between 2.0 and 2.5 for NRS change

Effect Size (ES) and Detectable Differences

- **For ES = 0.3**:
  - Difference between means = 0.6 (SD 2.0)
  - Difference between means = 0.75 (SD 2.5)
- **For ES = 0.2**:
  - Difference between means = 0.4 (SD 2.0)
  - Difference between means = 0.5 (SD 2.5)

Clinical and Statistical Relevance

- **MCID** (Minimal Clinically Important Difference): ~1 point or 15% on NRS
- **Power Assumptions**:
  - N=233 per group detects ES = 0.2 for SD 2–2.5
  - Minimum observed effect size for significance at final analysis: **0.18** (N=466, p<0.024, 1-sided)

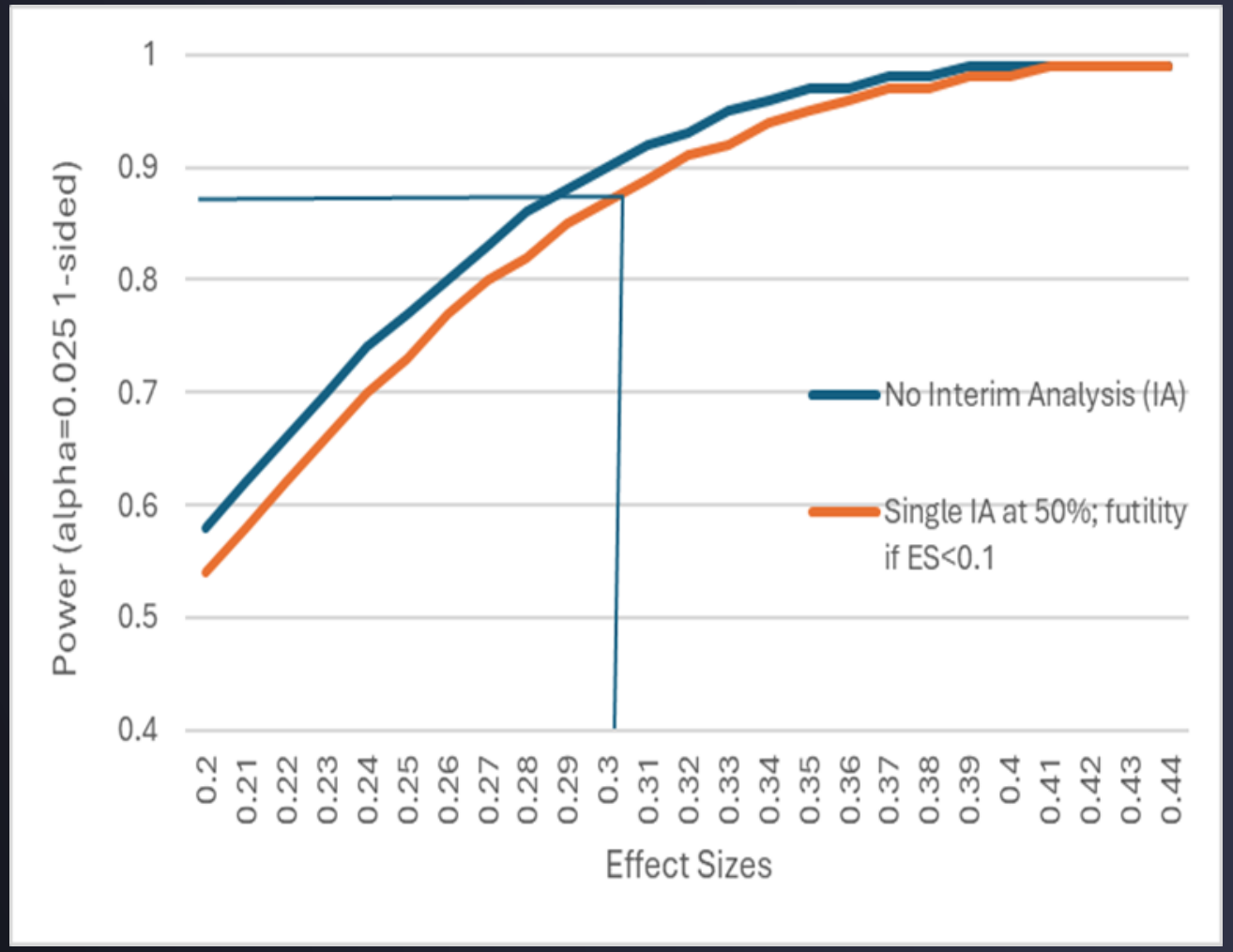
PARA_OA_012

Interim & Final Analysis

Interim analysis (IA) is planned after pain intensity data are available from 50% of total planned sample size 466 (randomised 1:1). Outcomes of IA could be:

- Early conclusion of futility if an observed effect size of 0.1 (between-group difference in means divided by SD).
- Early conclusion of efficacy if an observed effect size of 0.39 (p-value < 0.002, O'Brien-Fleming type 1 error spending function to control the overall type 1 error at 0.025 1-sided.

If neither a futility or efficacy conclusion can be reached at the IA, the trial will continue to the final analysis with planned N=466 and require p<0.024, 1-sided for success.



News flow & catalysts

Upcoming Clinical Catalysts

Event	Target Date
PARA_OA_012 – First participant dosed US and Aus	Q3 CY2025
PARA_OA_012 – 50% Recruitment of participants	2H CY2025*
PARA_OA_012 – 100% Recruitment	1H 2026*
PARA_OA_012 Interim Analysis – 50% participants reach Day 112	Mid-CY2026*

*The above is a statement of current intentions as at the date of this presentation. Investors should note that the above upcoming events are subject to funding or new circumstances.

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