PARADIGM BIOPHARMA

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

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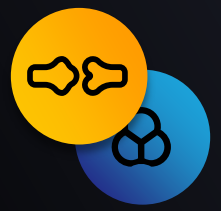
About Paradigm

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

<u>Pentosan polysulfate sodium for subcutaneous use (PPS, iPPS)</u>

- PPS is a **non-opioid** with a 60-year track record treating pain, inflammation, and thrombosis in humans.

<u>Osteoarthritis (OA) ZILOSUL®</u>

- 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 harmonised protocol to secure simultaneous approval in all key jurisdictions.
- 6-week treatment course.

<u>Mucopolysaccharidosis (MPS I & VI)</u>

- 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.

Executive Summary

PARA_OA_008

Key Highlights – from PARA_OA_008 to Day 168

- At Day 56 Primary Endpoint achieved, change in 1 synovial fluid biomarker compared to placebo.
  - PAR reported 7 favourable changes in synovial fluid biomarkers compared to placebo.
- Statistically significant improvements at day 56 in pain (p=0.05), function (p=0.017), and overall WOMAC scores for twice-weekly iPPS compared to the placebo arm.
- Multiple signals at Day 168 of DMOAD efficacy with iPPS following 6-week treatment course.
- 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 at Day 168.
- 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 through to Day 168.

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 signals of iPPS as a potential DMOAD

PARA_005 – Australia (completed)

- 126 participants randomized to iPPS or placebo.
- 2mg/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)

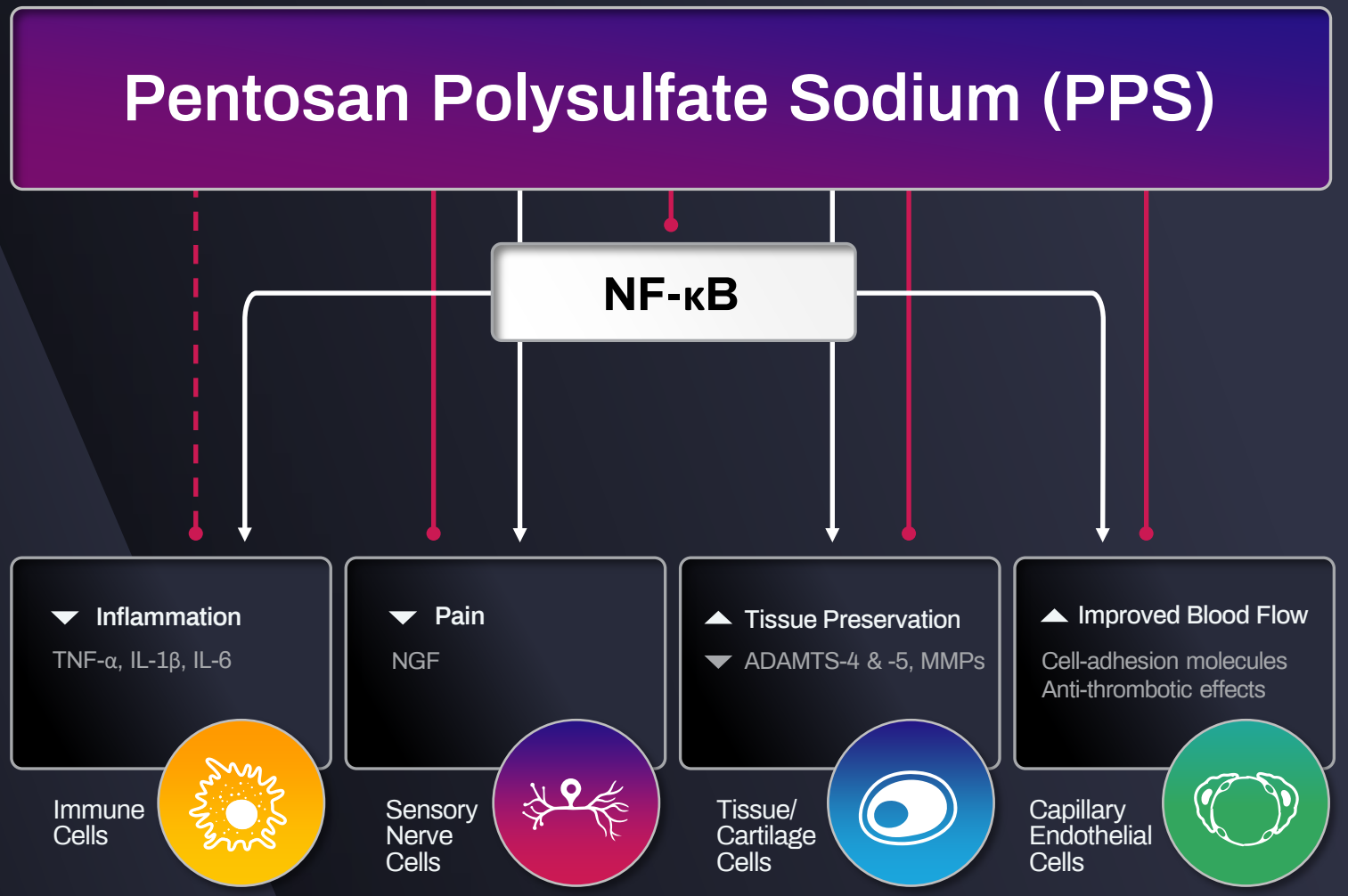
PARA_008 – Australia (ongoing)

- 61 participants 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
- **Day 56 Synovial Fluid Biomarker Results achieved primary endpoint:**
  - 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, 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

PARA_OA_008

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 increased by 56% in the placebo arm (p=0.028).
- Twice-weekly iPPS group, showed improvement compared to placebo.

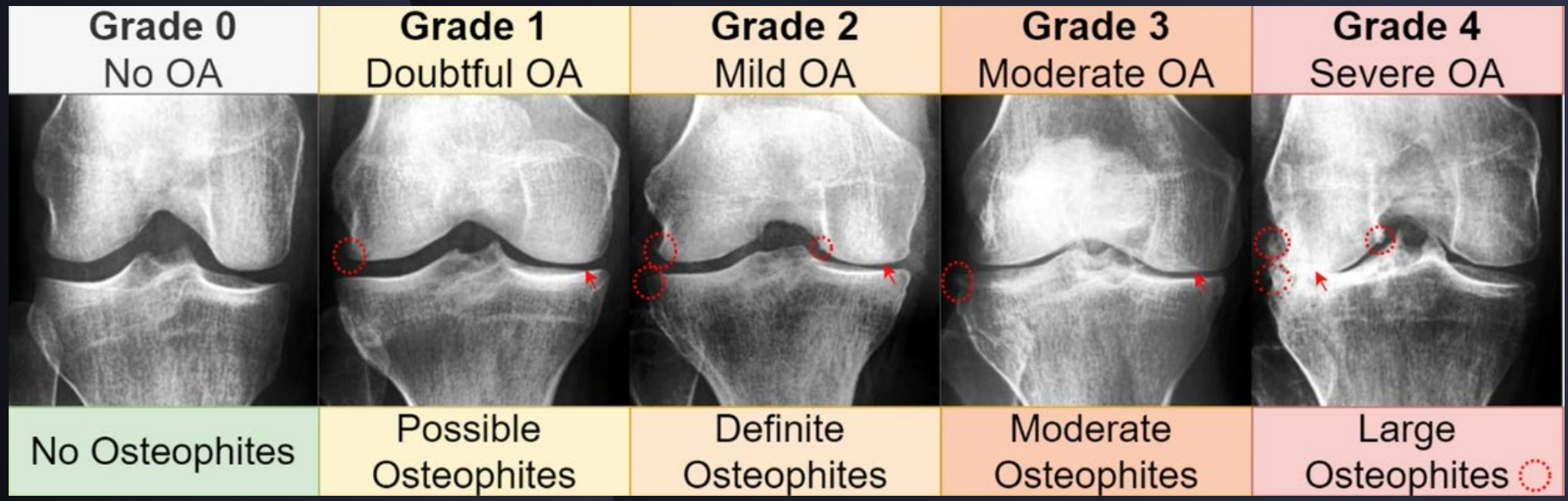
MRI Outcomes

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 and 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-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

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.
- The four biomarkers of focus have been extensively researched in literature for their role of 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 Program

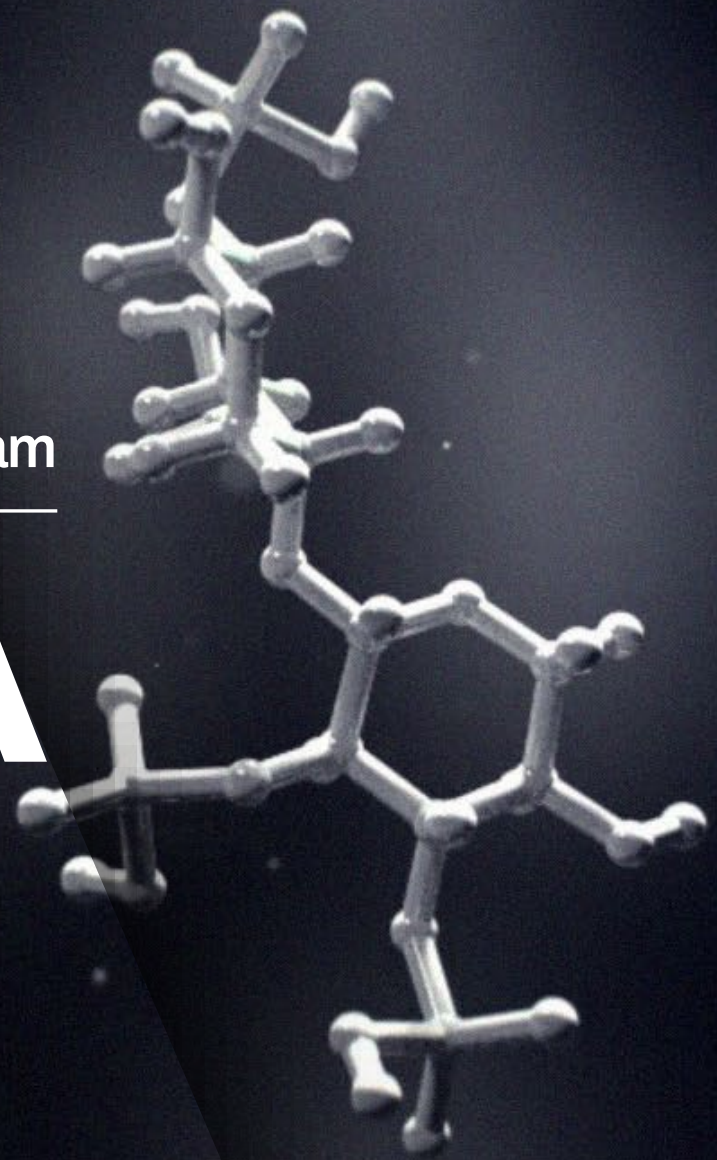
Expected regulatory discussions following data release

- New MRI, molecular biomarker, and clinical outcomes will be presented to the Regulatory Authorities (FDA and EMA).
- Paradigm intends to initiate discussions with FDA during the second half of 2023 to understand what additional data, from a larger controlled study (PARA_OA_003), may be required to obtain a DMOAD label.
- This is not expected to effect any of Paradigm's current clinical timelines for OA.
- Fast Track designation facilitates easier access to FDA and opportunity for more frequent dialogue on the development program for iPPS in OA.
- Feedback from 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.

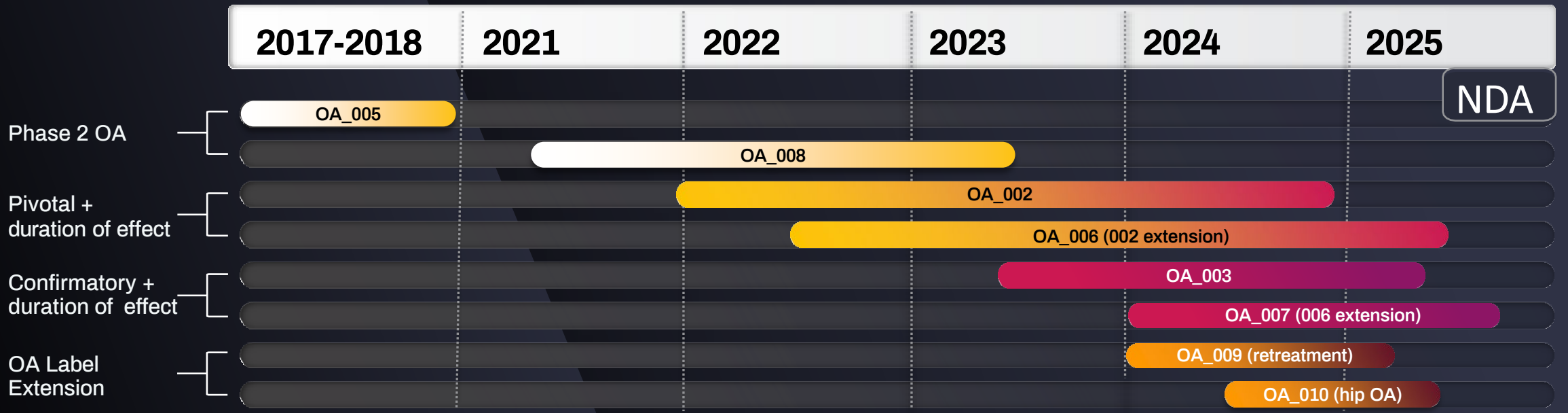
PARADIGM

Phase 3 Program

OA



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.

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 2HCY2023.
- MPS I & VI phase 2 clinical trials – top-line data Q4CY2023
- Paradigm is currently in active discussion with multiple potential partners for its phase 2 asset in mucopolysaccharidosis (MPS).

For more information please visit:
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