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Injectable PPS Demonstrates Multiple Signals of a DMOAD in PARA_OA_008 Phase 2 Clinical Study

KEY HIGHLIGHTS

- Day 168 data from Paradigm's phase 2 PARA_OA_008 clinical trial demonstrates multiple signals that injectable pentosan polysulfate sodium (**iPPS)** may slow disease progression in knee osteoarthritis (**OA**).
- Structural changes in several disease features as measured by magnetic resonance imaging (**MRI**) were consistent with potential DMOAD activity. Most notably, iPPS demonstrated:
  - 21% improvement in mean cartilage loss score compared to 4% worsening in the placebo group,
  - Statistically significant reductions in bone marrow edema lesions compared to placebo, and
  - Reduction of marginal osteophytes compared to increases in the placebo group.
- The disease modifying OA drug (**DMOAD**) potential for iPPS in knee OA treatment is also supported by changes and trends in four key biomarkers (ARGS, COMP, C2C, and CTX-II) evaluated in this phase 2 study.
- Persistent positive clinical responses in WOMAC pain, function, stiffness and overall WOMAC scores have been observed in the twice-weekly iPPS compared to placebo to Day 168.
  - In addition to durable pain responses, the average number of days participants used rescue medication was four times higher in the placebo group (23 days) compared to the twice-weekly iPPS group (5 days) to Day 168.
- The results of these new MRI, molecular biomarker and clinical outcomes will be presented to the Regulatory Authorities (FDA and EMA). Paradigm will seek their input as to what additional data, from a larger controlled study (PARA_OA_003), may be required to obtain a DMOAD label.
- Paradigm will be hosting an investor webinar today, 4 April 2023 at 9:30am (AEST), to present and discuss the novel Day 168 data from the PARA_OA_008 clinical trial.

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, is pleased to announce top-line data from the Day 168 (6-month) time point in the PARA_OA_008 study exploring the disease modifying potential of iPPS. Data received at Day 168 analysed by independent clinical research organisations and key opinion leaders in osteo and rheumatoid arthritis, demonstrates iPPS is not only having a durable response on Western Ontario and McMaster Universities Osteoarthritis Index (**WOMAC**) pain, function and stiffness scores, but also showing multiple signals of slowing or halting the OA disease progression through structural biomarkers identified by

MRI and improvements of key molecular biomarkers associated with cartilage degradation.

Data from PARA_OA_008 confirms a continuation of positive clinical outcomes from Day 56 through to Day 168 in WOMAC pain, function, and stiffness. Despite the study not initially being powered to demonstrate significance, several time points reached statistical significance for the twice-weekly iPPS-treated group compared to placebo. Trends or statistically significant differences in several serum, urine, and synovial fluid biomarkers of osteoarthritis progression were observed through Day 168 in iPPS-treated groups, reinforcing the disease-modifying potential of iPPS. New data includes the semi-quantitative analysis of structural markers of OA progression with the comparison of MRI at Day 168 compared to baseline scores established from the screening MRI images. Positive signals for iPPS-treated subjects compared to placebo were observed (including for cartilage loss and bone marrow edema lesions) indicating a potential slowing of the disease process.

All trends, results and signals in all tests and biomarkers indicated that iPPS is beneficial for treating both the symptoms and diseases progression of knee OA.

Paradigm Chief Medical Officer, Dr Donna Skerrett commented: "We *are seeing clinical and biomarker responses in both iPPS treatment groups over the 168-day study period. Although many of the clinical responses are stronger in the twice-weekly group, biomarker and MRI responses are present in both iPPS groups. Given the small sample sizes in this study, variability is expected however the signals we have identified are consistent and concordant and support DMOAD mechanisms. Moving forward we will work to establish the clinical and regulatory characterisation of these findings for defining the DMOAD pathway for iPPS in order to confirm these findings in our larger clinical trial program."*

Paradigm Managing Director and Chairman, Paul Rennie also commented: "*A non-opioid drug for treating the symptoms of osteoarthritis (pain and joint stiffness) with durability of effect out to 168 days (6 months) plus signals of disease modifying potential, is well poised to address a major unmet medical need. These data are expected to assist our partnering discussions*."

The Urgent Need for a Disease Modifying OA Drug (DMOAD)

Osteoarthritis is the most prevalent form of arthritis, with the risk of developing OA rising with age. This degenerative disorder can significantly reduce quality of life as it primarily affects the hands, lower back, neck, and weight-bearing joints such as knees, hips, and feet. A recent 2022 analysis of results from the 2019 Global Burden of Disease Study found that approximately 397.6 million cases of hip and knee OA existed worldwide, and that global trends showed a 114.5% increase in years lived with disability due to OA from 1990 to 2019 (1). Further underlining the economic burden, a comprehensive 2013 study estimated that total US arthritis-attributable medical expenditures reached almost $US140 billion, which when combined with wage losses, totalled losses of over $US303 billion (2).

A disease modifying OA drug (DMOAD) is defined as a drug that will "alter the natural history of disease progression by arresting joint structural change and ameliorate symptoms, either by reducing pain or improving physical function" (3). However, there are no established DMOADs, as current treatments such as paracetamol, opioids, and nonsteroidal anti-inflammatory drugs (**NSAIDs**), as well as intra-articular medications, such as corticosteroids and hyaluronic acid, are solely focused on symptom management

(3). Due to patient dissatisfaction with current OA treatments (4), there is a high unmet medical need for new therapies that can effectively reduce pain, improve joint function, and impede OA progression in tandem with symptomatic improvement.
Market research conducted through a global market intelligence and research organisation (ASX release 8 November 2021) found that payers in the United States would likely accept a price of US$2,000 to US$3,000 per year for iPPS as a therapy to reduce pain and improve function in knee OA. If approved by the FDA with a disease modifying label, the price per year of therapy in the US could increase to US$6,000 and potentially higher. The first registration of a drug proven to prevent progression of the disease of OA, rather than merely alleviate symptoms, is likely to encourage a review of the treatment recommendations and prescribing behaviour. Such an agent would likely be recommended as a first-line treatment.

PARA_OA_008 Day 168 Top-Line Results

The Australian clinical trial operating at two sites in Victoria and NSW aims to gather data on the medium-term structure-modifying and symptom-modifying effects of iPPS on knee OA. Participants have been randomised into three treatment groups according to a 1:1:1 ratio (19 randomised to iPPS twice weekly, 20 randomised to iPPS once weekly plus a placebo injection once weekly, 22 randomised to placebo twice weekly). Of the 61 patients, 48 (78%) had Kellgren Lawrence (KL) grades 3-4 (where 4 is the most severe), and the average median baseline self-reported WOMAC scores were 6.6 for pain and 6.9 for function. This phase 2 clinical study was designed to identify trends in clinical outcomes, and to explore the potential of iPPS as a DMOAD through changes in chemical and structural biomarkers. It is therefore exploratory in nature and is not powered for significance.

MRI Outcomes (semi-quantitative analysis)

During the screening process for this phase 2 study, potential participants underwent examination by MRI to determine their baseline level of OA disease. Participants then received follow-up MRIs at Day 168 which aimed to identify any differences in disease progression between the iPPS groups versus placebo. Semi-quantitative MRI analysis was performed, which involves systematically interpreting MRI images using a rating scale or scoring system. This approach is often used in research studies to objectively evaluate changes in disease severity or treatment response over time. The rating system typically assigns scores to specific imaging features, such as the presence of lesions, the size and location of lesions, and the degree of contrast enhancement. The scores are then used to calculate a total score or index, which provides a quantitative measure of disease activity or severity. Whole-ORgan MRI Scoring (WORMS) was used to assess changes in joint structures considered to be important to the functional integrity of the knee and associated with OA.

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. These changes were most notably related to cartilage loss, bone marrow lesions, and osteophyte formation, as early as 6 months after initiating treatment with iPPS. Collectively, the majority of the statistically significant changes observed were consistent with a positive disease modifying effect of treatment with iPPS on OA.

Cartilage loss is generally considered to be the most important disease feature of OA. Numerous studies have shown cartilage loss to be predictive of knee replacement surgery

for OA (8,9). In this study, subjects receiving once-weekly iPPS demonstrated an average 21% improvement in mean cartilage loss score in the medial femur, whereas the placebo arm showed a slight (4%) worsening of cartilage loss (p=0.065). The twice-weekly iPPS group, showed trends of improvement (though not statistical) or stabilisation of cartilage preservation compared to the placebo group.

A build-up of fluid in the bone marrow (subchondral bone marrow edema lesions) is a common finding in OA and is believed to be related to microtrauma resulting from overloading. Like cartilage loss, bone marrow edema lesions have been shown to be predictive of knee replacement (10–12). In this study, 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 edema lesions in the entire lateral tibiofemoral compartment decreased by an average 17% in the once-weekly iPPS arm, but increased by 56% in the placebo arm (p=0.028).

Marginal osteophytes—also known as bone spurs—form between the cartilage and bone and are an early finding in OA. They are associated with bone remodelling, as osteophytes typically increase in number and size as the disease progresses. In this study, osteophytes decreased slightly or remained stable in all three compartments of the knee among patients treated with iPPS, compared to an increase (numerically, though not statistically significantly) in the placebo arm.

Paradigm intends to complete additional quantitative analysis on the full MRI dataset to further characterise the structural changes identified to date.

Clinical Outcomes

Participants in the study were asked to provide baseline pain scores using the self-assessed WOMAC osteoarthritis index. After patients had initiated treatment, their pain scores are measured at predetermined timepoints from Day 11 out to Day 365 (12 months), with Day 56 the first predetermined timepoint for WOMAC assessment after the completion of treatment (Day 39). Paradigm's primary endpoints in the current PARA_OA_002 phase 3 trial are improvements in pain and function from baseline at Day 56 using the WOMAC osteoarthritis index.

Paradigm previously reported that participants receiving twice-weekly iPPS demonstrated a statistically significant improvement at Day 56 in pain, function, stiffness, and overall WOMAC scores compared to the placebo arm. The proportions achieving ≥30% and ≥50% improvement in pain were 73% and 60%, respectively.

Persistent responses out to Day 168 in WOMAC index scores for pain, function, stiffness, and overall are observed for twice-weekly iPPS compared to placebo control. Positive trends or statistical significance are demonstrated at days 112 for stiffness (p=0.029), function (p=0.059), and overall (p=0.067). At Day 168, a 50% improvement in function was reported in 53.3% of twice-weekly iPPS compared to 22.1% of placebo (p=0.067).

WOMAC pain demonstrated a durable response and separation from the placebo group at Day 168. At Day 168, statistically significant changes in pain and function were not demonstrated in the once-weekly iPPS group compared to placebo, however this group demonstrated variability in responses with improvement noted in some subjects. The patient global impression of change (PGIC) remained favourable showing a positive trend for iPPS compared to placebo at Day 168 (p=0.061).

The twice-weekly iPPS treatment group used rescue medication the least during the first six months of the study (Day 168). Rescue medications could include paracetamol or NSAIDs used by participants to manage pain symptoms. The placebo group reported using rescue medication on an average of 23 days compared to an average of only 5 days in the twice-weekly iPPS group.

Biomarkers

A broad panel of potential biomarkers in the blood (serum), urine, and the knee joint space (synovial fluid) were assessed. Specifically, markers of OA progression such as serum and synovial fluid ARGs (an articular cartilage breakdown product), serum and synovial fluid COMP (a marker of cartilage turnover), serum C2C and urinary CTX II (markers of cartilage breakdown) were informative. DMOAD potential for iPPS in knee OA treatment has been identified by the patterns of change of four biomarkers evaluated in this study. Namely, serum and synovial fluid ARGs, serum and synovial fluid COMP, serum C2C and urinary CTX II show persistent beneficial effects of PPS compared to placebo. These biomarkers of cartilage matrix degradation (5–7) and risk of osteoarthritis progression (COMP, C2C and urinary CTXII) indicate cartilage sparing changes in iPPS subjects when measured by serum, urine, or synovial fluid at Days 56 and 168. Molecular biomarkers of cartilage degradation in iPPS-treated subjects were favourable compared to placebo control (Table 1).

Table 1: Molecular biomarkers of cartilage degradation

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.

Safety

Safety data through to Day 168 has been assessed with no new safety signals identified in the study. A summary of the safety profile during the PARA_OA_008 phase 2 study determined iPPS was well tolerated. The majority of the treatment-emergent adverse events (TEAEs) reported were injection site reactions, which were mild in severity and mostly self-limiting, which is consistent with the known safety profile of PPS.

Next Steps

During the second half of CY2023, Paradigm intends to initiate discussion with key regulatory agencies (FDA and EMA) in order to reach agreement on disease modification label pathways for iPPS. The Fast Track designation granted by the FDA for Paradigm's OA program allows for easier access to the FDA and opportunities for more frequent dialogue on the development program for iPPS in OA. Through meetings with the FDA and EMA, Paradigm aims to agree with the agencies on the required regulatory pathway for DMOAD indication labelling. By obtaining feedback from key regulators, Paradigm hopes to continue to harmonise global regulatory requirements for further indication labelling. Additional Disease modifying outcomes will be assessed for confirmation in the phase 3 clinical program.

Feedback from the EMA may be further useful for assessing the next steps towards TGA provisional approval as Australia follows the EMA's guidelines on "*Clinical investigation of medicinal products used in the treatment of osteoarthritis*" which details expectations for structure modification studies.

The complete 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.

Investor Webinar

Paradigm Biopharmaceuticals will hold an investor webinar today, 4 April 2023 at 9:30am (AEST), to present and discuss the novel Day 168 data from the PARA_OA_008 clinical trial. The webinar will feature Managing Director, Mr Paul Rennie; Chief Medical Officer, Dr Donna Skerrett; and Global Head of OA, Dr Mukesh Ahuja.

Please register for the webinar via the following link:
https://us02web.zoom.us/webinar/register/WN_HL24yen3SKuWLoZxuTJG1A

After registering, you will receive a confirmation email. A copy of the presentation is available via the ASX or on the Paradigm website. Following the webinar, a recording will become available on the Paradigm website.

PARA_OA_008 Clinical Trial Design

The PARA_OA_008 phase 2 clinical trial is designed to evaluate the treatment effects of iPPS on synovial fluid biomarkers associated with OA-related pain, inflammation, and disease progression in humans. The study also evaluates the effect of iPPS on these biomarkers in serum and urine and investigates any correlation with synovial fluid biomarkers. In a prior phase 2b clinical trial, Paradigm observed serum and urine changes in COMP, ADAMTS-5, and CTX-II biomarkers, providing promising signals of iPPS mechanisms of action on joint preservation.

In the PARA_OA_008 clinical trial, subjects (n=61) were randomised and received either a subcutaneous injection of 2 mg/kg iPPS twice weekly, iPPS once weekly plus one placebo injection, or two placebo injections for 6 weeks. Patients had moderate to severe arthritis with Kellgren Lawrence (KL) grade 2-4 (where 4 is the maximum indicating severe OA), and baseline WOMAC pain scores of 4.6 to 10. This phase 2 clinical trial is an exploratory study and was not intended to be powered to obtain statistical significance. The aim is to provide novel scientific evidence to test the hypothesis that iPPS acts locally in the knee joint of OA subjects as well as provide data on whether biomarker changes correlate with clinical outcome (WOMAC pain and function assessments). Further

evaluation on serum, synovial fluid and urine biomarker correlations, and further longer-term clinical outcomes are in progress.

Biomarkers that alter in relation to clinical outcomes could help further clarify the multiple proposed mechanisms of action for iPPS in OA. This contrasts with currently available pharmacological agents which have thus far failed to deliver durable satisfactory patient outcomes of improved pain and/or function and disease modification.

About WOMAC Scores

The Western Ontario and McMaster Universities Osteoarthritis Index (**WOMAC**) is a widely used, proprietary set of standardised questionnaires used by health professionals to evaluate the condition of patients with OA of the knee and hip, and includes pain, stiffness, and physical functioning of the joints. The WOMAC has also been used to assess back pain, rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia. It consists of 24 items divided into 3 sub-scales (13):

- Pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing upright;
- Stiffness (2 items): after first waking and later in the day;
- Physical function (17 items): using stairs, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy domestic duties, light domestic duties.

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 injectable (subcutaneous) pentosan polysulfate sodium (**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) and mucopolysaccharidosis (phase 2).

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.

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To learn more please visit: www.paradigmbiopharma.com

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PARADIGM BIOPHARMA

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 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)

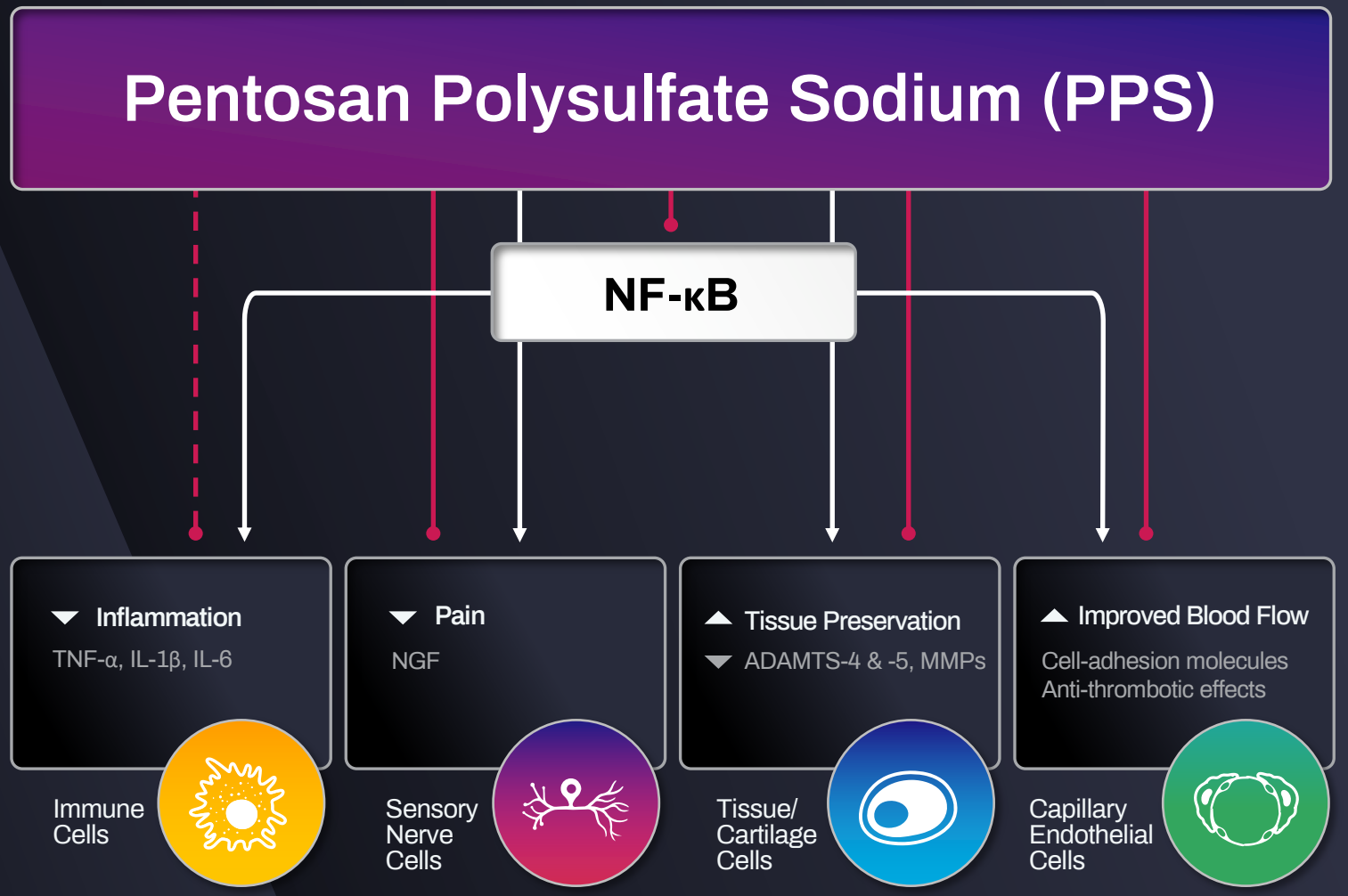
PARA_008 – Australia (ongoing)

- 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:**
  - 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

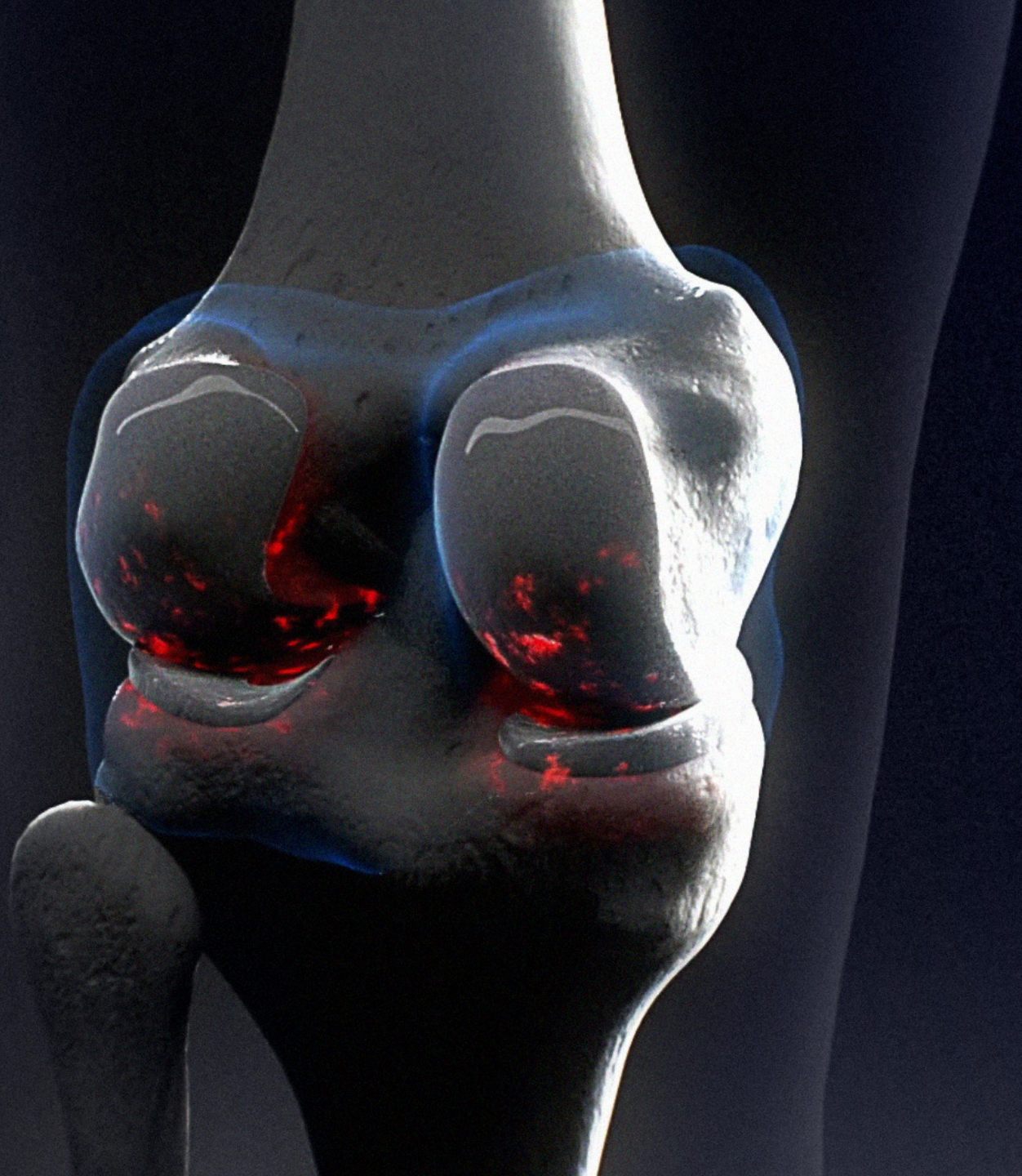
OA
MPS
ARDS
HF
Viral Arthralgia



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

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 trends of improvement (though not statistical) or 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).

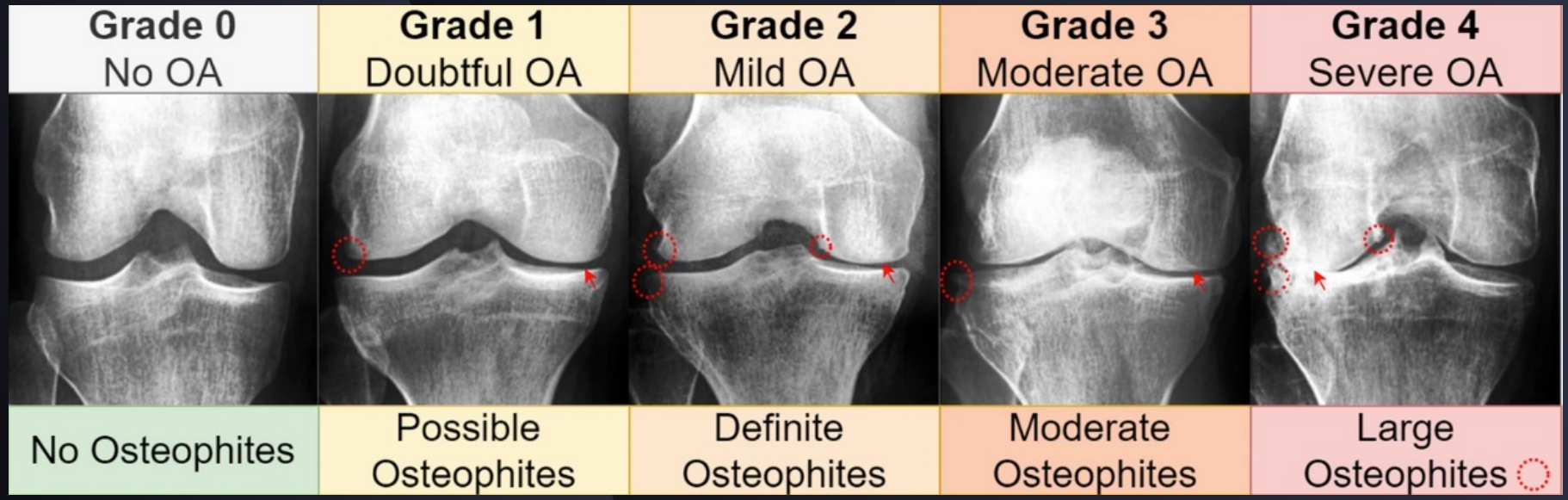
MRI Outcomes

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 in PARA_OA_008 decreased slightly or remained stable in all three compartments of the knee among patients treated with iPPS, compared to an increase (numerically, though not statistically significantly) 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.

PARADIGM

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 Bio markers

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 are extensively researched in literature in their role of cartilage breakdown in OA subjects.

Molecular Biomarkers

PARA_OA_008

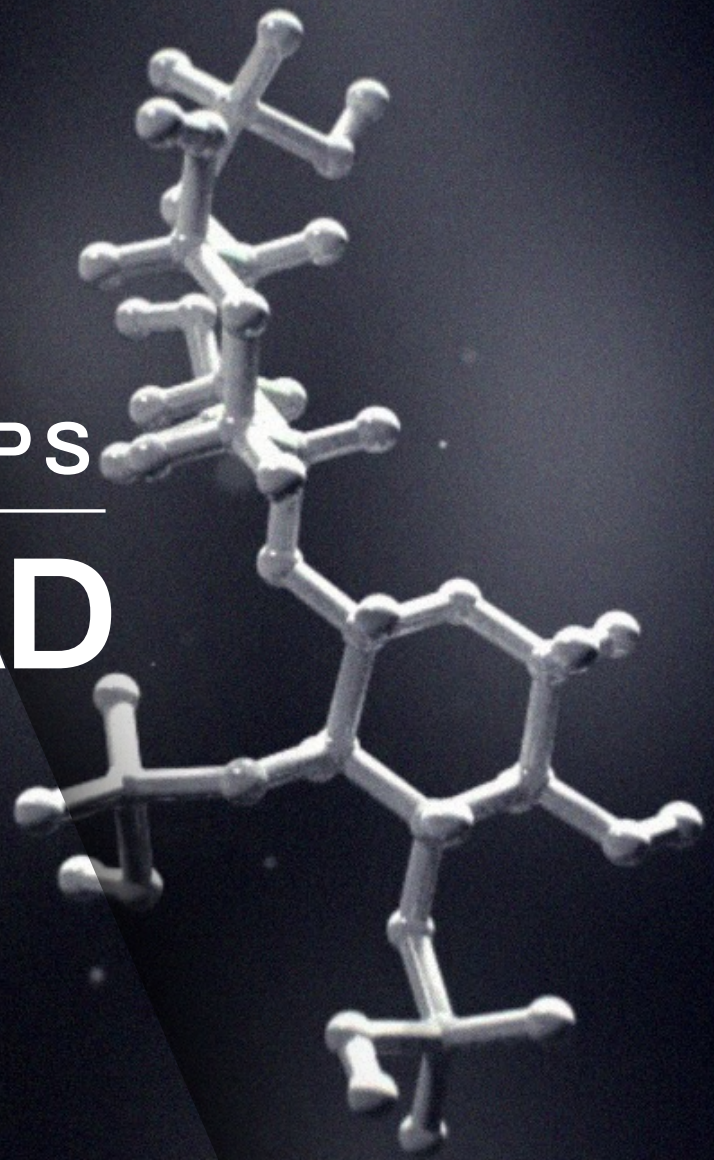
Day 168 Top-Line Results – Changes in Synovial Fluid, Serum, and Urinary Biomarkers

- 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.

PARADIGM



NEXT STEPS

DMOAD

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.
- Fast Track designation facilitates easier access to 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 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.

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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