ASX RELEASE 10 October 2023

Osteoarthritis pain breakthrough

Paradigm reports successful Day 365 clinical trial outcome. iPPS demonstrates significant osteoarthritis pain reduction at 12 months

Webinar

Paradigm Senior Management will be hosting a webinar at 11:00 AM (AEDT) to discuss the exciting Day 365 data from this phase 2 clinical trial and the next steps for the Paradigm OA program.

When: Oct 10, 2023 11:00 AM Canberra, Melbourne, Sydney (AEDT) time

Topic: Paradigm Biopharma's PARA_OA_008 Day 365 Clinical Results Webinar

Register for this webinar via:

https://us02web.zoom.us/webinar/register/WN_L_koPcfdRo21b1rhHZXVYA

After registering, you will receive a confirmation email containing information about joining the webinar.

KEY HIGHLIGHTS

- Study data for the PARA_OA_008 demonstrates duration of effect with 12 months of pain reduction and functional improvements in a phase 2 clinical trial of knee osteoarthritis (OA). This phase 2 clinical trial was performed concurrently with the Company's ongoing phase 3 study.
- No OA drug has previously shown durable and meaningful improvements in pain and function at 12 months after a single course of treatment (1,2).
- Paradigm previously reported attaining the primary endpoint at Day 56, significant improvement in pain and function at Day 56, and structural improvements in bone marrow lesions, cartilage, and osteophytes (bone spurs) by MRI at Day 168.
- In the PARA_OA_008 clinical trial, participants receiving 2 mg/kg iPPS twice weekly for 6 weeks, reported clinically meaningful outcomes at 12 months (Day 365) compared to placebo as follows:
    - Significant pain reduction (p=0.054).
    - Significant functional improvement (p=0.048).
    - Durable improvements in stiffness.
    - Significant improvement in overall WOMAC scores (p=0.054).
- Patient Global Impression of Change (PGIC) results demonstrated highly statistically significant improvements for iPPS, at a dose of 2 mg/kg twice weekly versus placebo (p=0.005) at 12 months.

- Cumulative rescue pain medication use was over five times higher in the placebo group at Day 365.
- These results establish that a short course of iPPS dosed at 2 mg/kg twice weekly for 6 weeks has durable clinical effects on OA symptoms, induces positive structural changes in the affected knee joint, and provides mechanistic indicators of osteoarthritis disease modifying effects.
- Based on this data Paradigm intends to proceed with a Provisional Approval application to the TGA.
- Paradigm has multiple data sets to demonstrate the 2 mg/kg twice weekly dose is highly effective. Two phase 2 clinical trials (PARA_005 and PARA_OA_008) and over 600 TGA SAS cases have been dosed at 2 mg/kg twice weekly for between 4 to 6 weeks. PARA_OA_008 also confirmed that the once weekly regimen of iPPS did not demonstrate meaningful improvement over the placebo control. As a result, Paradigm believes the optimal dose regimen for further development is likely to be 2 mg/kg twice weekly, as such the Company intends to focus its clinical development on the 2mg/kg twice weekly dose. (See Twice Weekly Dosing vs Once Weekly Dosing below).

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 the remarkable and successful study data from the phase 2 PARA_OA_008 clinical trial demonstrating a single 6-week treatment course of injectable pentosan polysulfate sodium (iPPS) has durable pain reduction and functional improvement effects through the 12-month study duration.

As previously reported (ASX releases 4 October 2022 and 4 April 2023), the results of the phase 2 PARA_OA_008 randomised controlled clinical trial (n=61) investigating iPPS in knee OA, with a dose of 2 mg/kg of iPPS twice weekly, were as follows:

- Primary endpoint achieved – change in one or more synovial fluid biomarkers associated with osteoarthritis disease progression at Day 56.
- Significant and clinically meaningful improvements in knee pain, function, stiffness, and overall scores in participants receiving twice weekly iPPS compared to placebo at Day 56 as measured by the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) scores.
- Positive structural changes in the knee as measured by semi-quantitative MRI analysis. At Day 168, iPPS treatment demonstrated reduced cartilage loss indicating cartilage preservation, reduced bone marrow lesions, and reduced osteophyte formation (bone spurs) in the iPPS treatment groups compared to placebo.
- And new data of significant improvements in patient reported outcomes of WOMAC pain and function, and patient global impression of change (PGIC) scores for participants receiving twice weekly iPPS compared to placebo at Day 365.

Twice Weekly v Once Weekly iPPS Dosing

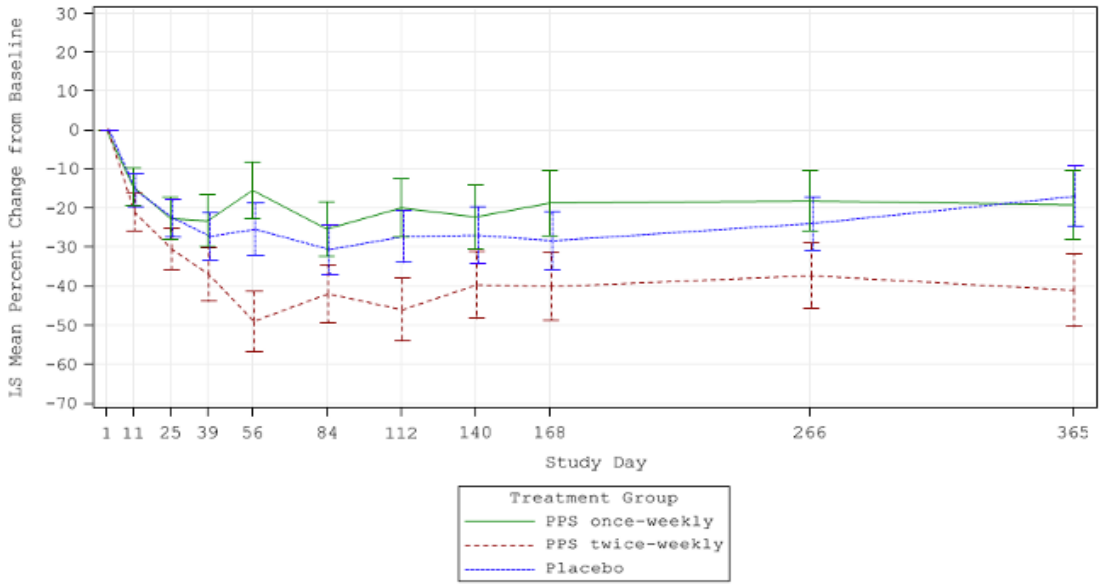


Figure 1. A single 6-week course of twice weekly iPPS demonstrates durable **overall WOMAC** scores incorporating pain, function and stiffness clinical outcomes out to 12 months (Day 365 timepoint) in PARA_OA_008 clinical trial participants with knee osteoarthritis.

As demonstrated in the WOMAC Overall scores (Figure 1 above), the Day 56, Day 168, and Day 365 results of the phase 2 PARA_OA_008 clinical trial demonstrated that the treatment regimen of 2 mg/kg **iPPS** once weekly was not efficacious over placebo.

Since this dose is included in the phase 3 PARA_OA_002 study (**phase 3 trial**) protocol, but the twice weekly dose of 2 mg/kg is not, Paradigm requested the Data Monitoring Committee (**DMC**) to the phase 3 trial to undertake an interim analysis of the performance of all treatment arms in stage 1 of the phase 3 trial. It appears all doses (less than 2 mg/kg twice weekly) included in the dose determination part of phase 3 trial are not efficacious. The interim analysis was performed when 300 patients reached 56 days of follow up. The timing of this interim analysis was chosen to inform the program in advance of the formal dose selection procedure scheduled for CY Q1 2024.

The findings of this interim analysis have shown that the PARA_OA_002 stage 1 doses do not demonstrate the performance of 2 mg/kg twice weekly as demonstrated in the PARA_OA_008, PARA_005 (previous phase 2b) studies and the TGA Special Access Scheme (SAS). On that basis, the Company has determined that the 2 mg/kg twice weekly regimen must be included in our development program for OA and is now working on the best pathway forward for introducing this dose regimen into the registration programs as well as opportunities for expedited or provisional registration in Australia based on the PARA_OA_008 data. The OA development program is expected to now focus on achieving the results of 2 mg/kg twice weekly regimen going forward in the phase 3 OA program.

Next Steps

- Now that duration of effect of iPPS has been demonstrated out to 12-months, the Company intends to proceed with a Provisional Approval application to the TGA.

- Paradigm is awaiting the full quantitative analysis of the 6-month MRI data from this PARA_OA_008 study and expects to report these findings shortly.
- The overall results produced in the PARA_OA_008 phase 2 clinical trial are currently being compiled into a manuscript for peer review and publication.

Paradigm's Managing Director, Mr Paul Rennie commented *"To achieve clinically meaningful and significant results with iPPS at a dose of 2 mg/kg twice weekly compared to placebo at 12 months in only a small number of subjects per treatment arm shows clear strength in this treatment regimen over placebo. The 12-month durability of effect on OA pain and function following one 6-week course of treatment is truly an outstandingly positive trial outcome and separates iPPS from all currently available therapies for knee OA."*

"We have consistently received positive patient and prescribing doctor testimonials relating to iPPS use through the TGA Special Access Scheme. They indicate that a large proportion of patients receiving a dose of 2 mg/kg twice weekly are experiencing at least 12 months of reduced pain and improved function following the treatment course. The confirmation of our real-world evidence with this clinical data in a double-blinded placebo-controlled trial is a remarkable outcome for Paradigm, it provides clarity for the appropriate dosing regimen for iPPS in treating knee osteoarthritis and also support for the Company's global partnering prospects moving forward."

Summary of Day 365 Top-Line Results

Durable and significant responses in WOMAC scores for pain, function, stiffness and overall are observed for iPPS twice weekly compared to placebo control through to Day 365. The once weekly iPPS dose did not result in meaningful or sustainable improvement in clinical outcomes over placebo.

Durable WOMAC Pain Reduction

From a single 6-week iPPS treatment course, participants receiving twice weekly iPPS experienced persistent improvements in knee OA pain compared to before treatment, out to the 12-month study endpoint.

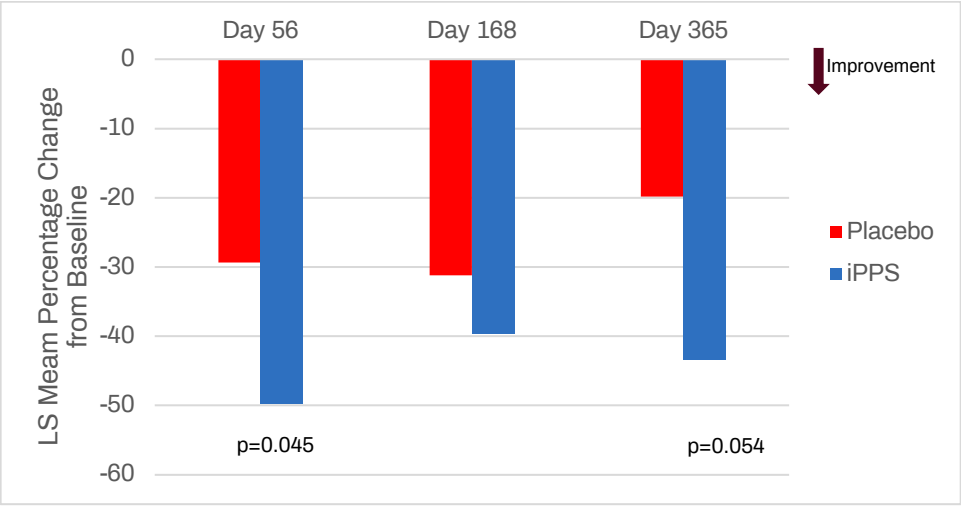


Figure 2: Adjusted LS mean % change in WOMAC pain from baseline at Day 56, 168 and 365 of participants treated with twice weekly iPPS versus placebo.

WOMAC pain improvement in the twice weekly iPPS group was significant (p=0.054) at Day 365 compared to placebo. The improved pain response for the twice weekly group (Figure 2) peaked at Day 56 (p=0.045) and the response was sustained through to 12 months compared to the placebo group which regressed towards baseline.

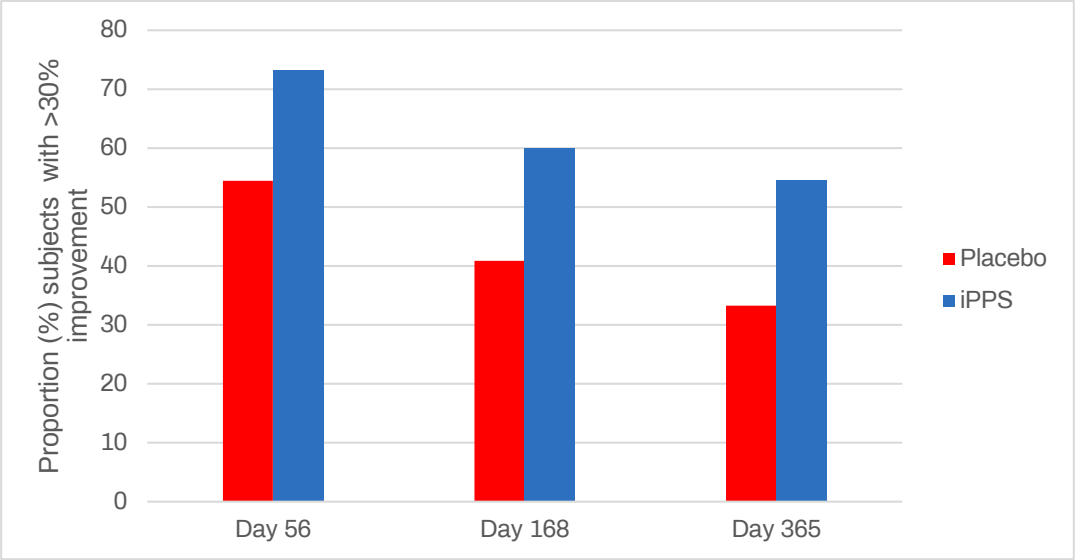


Figure 3: Proportion of participants treated with twice weekly iPPS reporting 30% or greater improvement in pain versus placebo.

Furthermore, 55% of participants in the twice weekly iPPS treatment group reported WOMAC scores demonstrating clinically meaningful improvements in chronic pain (>30% reduction in pain) at Day 365. There were consistently more participants who had received iPPS experiencing at least 30% improvement in pain compared to participants in the placebo group at Days 56, 168, and 365 (Figure 3).

Durable Functional Improvement

Significant functional improvements were reported by the twice weekly iPPS group at Day 365 compared to placebo (p=0.048). Twice-weekly iPPS demonstrated significant functional improvement at Day 56 (p=0.017) and the twice weekly iPPS arm continued to outperform the placebo group through to Day 365 (Figure 4).

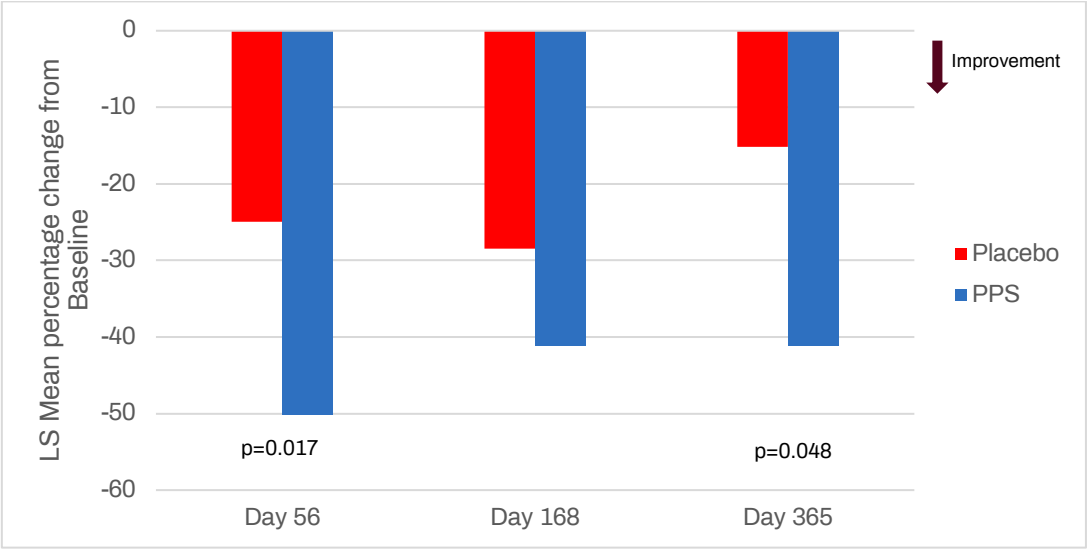


Figure 4: Adjusted LS mean % change in WOMAC function from baseline at each visit in participants treated with twice weekly iPPS versus placebo.

A 50% improvement in function was reported for 53% of participants receiving twice weekly iPPS at Day 168 and 55% of participants at Day 365, compared to 22% and 28% in the placebo-treated group, respectively.

Patient Global Impression of Change

Patient Global impression of Change (PGIC) is a self-reported measure that reflects the patient's belief about the overall efficacy of the treatment. Participants rate their change from a score of 1 (no change or condition worsened) through to 7 (considerable improvement that has made all the difference). PGIC scores are used to capture the patient's perspective, which is valuable in evaluating the effectiveness of a treatment beyond the more objective clinical measures. Paradigm's phase 3 PARA_OA_002 clinical trial includes an improved PGIC as an endpoint.

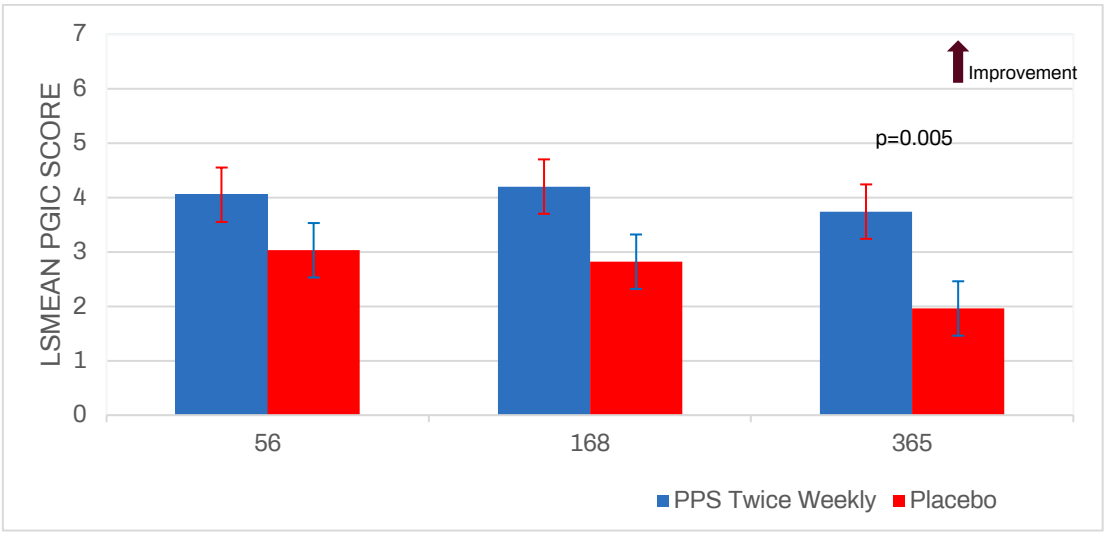


Figure 5: Average patient-reported PGIC scores in participants treated with twice weekly iPPS versus placebo.

Average PGIC scores trended towards significance up to Day 365 and then demonstrated highly statistically significant scores for the twice weekly iPPS group compared to placebo. The average Day 365 score was 3.74 for twice weekly iPPS versus 1.96 in the placebo group (p=0.005) indicating that participants receiving iPPS felt an overall improvement or stabilisation in their OA disease progression (Figure 5).

Rescue Medication Use

Rescue medication use provides an objective and quantifiable measure of a patient's pain relief needs. It is an important measure to determine how much additional pain relief participants require beyond the trial treatment. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA), often consider rescue medication use when evaluating the efficacy of a new pain treatment.

The PARA_OA_008 clinical trial allowed participants who had unacceptable pain due to knee OA or other conditions to use paracetamol as rescue medication during the study. The placebo group's cumulative use of paracetamol remained at over 5 times higher at Day 365 (28,947 mg) compared to the twice weekly iPPS group (5,147 mg).

Summary of currently available medications for OA (see Appendix)

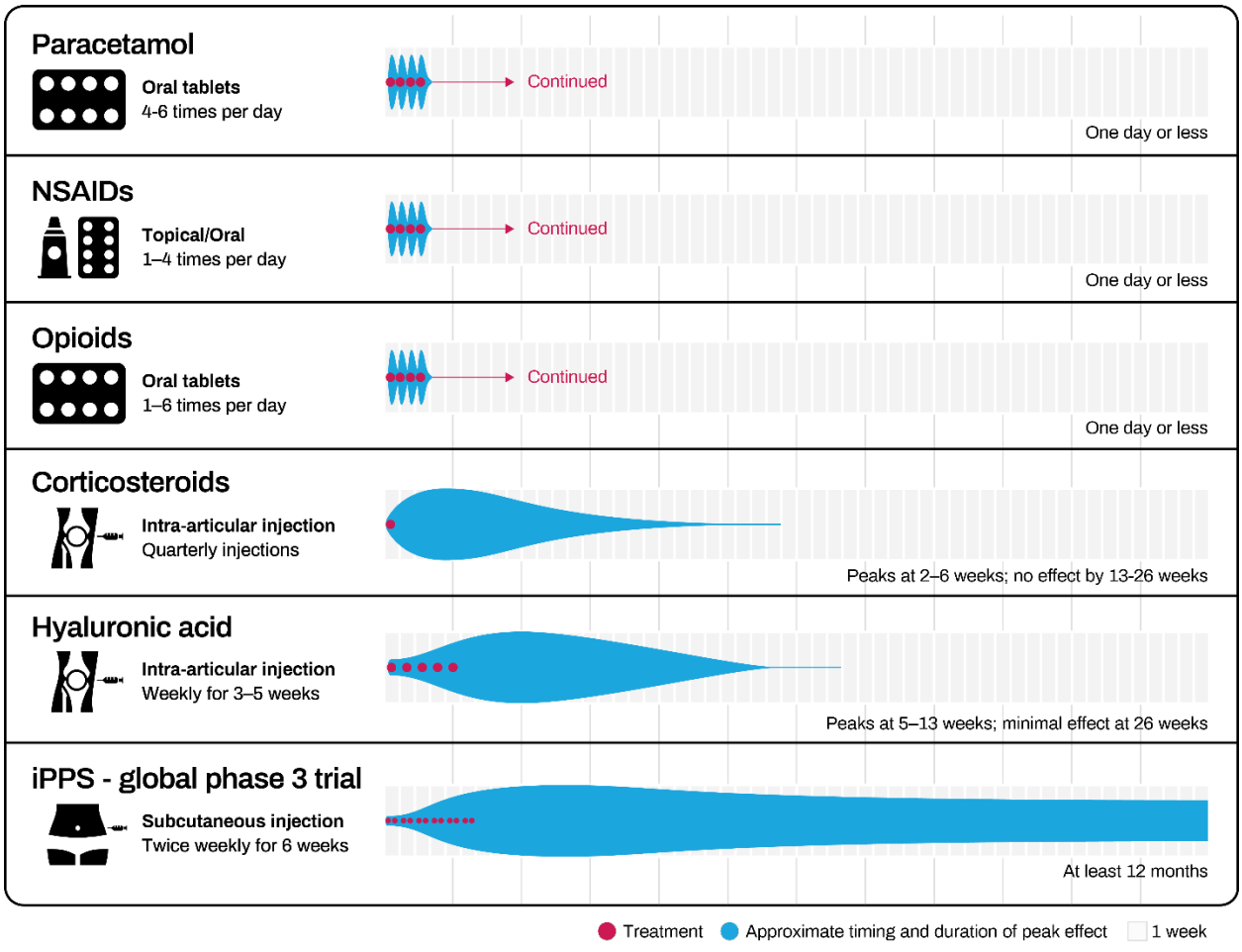


Figure 6: Current OA medication effect duration. Representative infographic reflecting current literature on the timing of the peak and estimated duration of treatment effect of currently available OA medications (2–16) and iPPS data from the PARA_OA_008 clinical trial.

Dr Philip Bloom, Medical Director at Sportsmed Biologic in Melbourne, principal investigator of the PARA_OA_008 trial, and who has significant experience prescribing iPPS via the TGA Special Access Scheme, commented *"The mainstays in managing osteoarthritis pain are simple analgesics like paracetamol or aspirin, along with more anti-inflammatory types of analgesics like ibuprofen or diclofenac (Voltaren), along with changes to diet and movement. We see osteoarthritis patients in the clinic when the simple analgesics have failed, the anti-inflammatories are failing, they're not progressing with physiotherapy and their lifestyles are starting to be affected, so they come looking to us for help. We can then try prescription-only pain medications, platelet rich plasma derivatives, joint lubricants [hyaluronic acid], or corticosteroid injections. There are pros and cons with each of them, but generally we find they're only effective for a short period of time."*

"After prescribing PPS to more than 300 patients via the TGA's Special Access Scheme I've seen a myriad of people seeing positive changes to their lifestyles and able to get back to things they previously may have been unable to do due to the pain and dysfunction caused by their disease. It also seems that most people receive meaningful pain relief out to about 18 months to two years, which is much longer than any currently available treatment. It would make sense to me to see PPS used as an earlier stage intervention to help maintain and preserve joint health and normal life activities, rather than only when the disease has significantly progressed."

-Ends-

About Paradigm Biopharmaceuticals Ltd.

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 iPPS, 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.

APPENDIX

Summary of currently available medications for OA

Numerous pharmacological agents have been investigated for their potential in managing OA-related pain. Medical societies in the field of bone and joint disease regularly issue updated evidence-based treatment guidelines (1,17–19). The major categories of approved therapies for OA pain relief include:

1. **Paracetamol:** Paracetamol (acetaminophen) ranges from not recommended, to conditionally or positively recommended for patients with mild OA pain. It has a lower risk of adverse effects compared to NSAIDs and opioids. It is thought to exert its analgesic effects through central nervous system modulation.

2. **Nonsteroidal anti-inflammatory drugs (NSAIDs):** Topical or oral NSAIDs are commonly prescribed to manage OA pain and inflammation, particularly as a first-line treatment. They act by inhibiting cyclooxygenase enzymes, thereby reducing prostaglandin synthesis. While NSAIDs provide rapid pain relief, their long-term use may be associated with gastrointestinal and cardiovascular risks.

3. **Opioids:** Opioid analgesics are reserved for severe OA cases when other options are inadequate. They bind to opioid receptors in the central nervous system, effectively modulating pain perception. However, the potential for tolerance, dependence, and side effects limits their long-term use.

4. **Intra-articular corticosteroids:** Injections of corticosteroids directly into the affected joint offer localised anti-inflammatory effects and pain relief. Meta-analyses and randomised controlled clinical trials investigating intra-articular corticosteroid efficacy in knee osteoarthritis are conflicting, with treatment outcomes varying from no efficacy, to low efficacy with a short duration of improvement in pain and/or joint function, to several weeks of pain relief (20). Their use is limited by the potential for cartilage degradation with repeated injections.

5. **Viscosupplementation:** Intra-articular hyaluronic acid injections provide joint lubrication and potentially reduce pain, although their long-term benefits are not demonstrated (21). The American Academy of Orthopaedic Surgeons and the American College of Rheumatology/Arthritis Foundation do not support the routine use of intra-articular hyaluronic acid injections in knee OA (1,18).

What does this new clinical data mean?

- iPPS has the potential to change the OA treatment landscape as no approved OA drug has shown durable and meaningful improvements in pain and function at 12 months after a single course of treatment.
- iPPS could become an early intervention or first-line therapy in the OA treatment algorithm, with the potential to reduce reliance on other agents such as opioids, NSAIDs, and corticosteroids.

- This 12-month duration data provides substantial support to progress regulatory discussions with the TGA to obtain a provisional approval application for iPPS.
- Data demonstrating the ability of iPPS to reduce the use of other pain medications or OA therapies are expected to facilitate negotiations with pricing and reimbursement authorities globally.
- There are an estimated 500 million OA sufferers worldwide, with reports that up to 81% of OA sufferers are dissatisfied with current treatment options (22,23). iPPS, a non-opioid, subcutaneous injectable with 12-month durability has the potential for rapid uptake from launch as a treatment for knee OA.
- This new data demonstrating 12-month durability of iPPS forms an invaluable milestone to progress discussions with both regional and global pharmaceutical partnering companies.

PARA_OA_008 Clinical Trial Design

PARA_OA_008 is a phase 2 exploratory study conducted at two sites in Australia. It investigates changes in synovial fluid biomarkers with pentosan polysulfate sodium (iPPS) treatment compared with placebo in participants with knee osteoarthritis pain.

Sixty-one (61) eligible participants were enrolled and randomly assigned to a study intervention. Participants were administered twice weekly subcutaneous (SC) injections of iPPS calculated for ideal body weight (IBW):

- iPPS twice weekly: 2.0 mg/kg IBW PPS twice weekly for 6 weeks, (N = 19).
- iPPS once weekly: 2.0 mg/kg IBW PPS once weekly + placebo once weekly for 6 weeks, (N = 20).
- Placebo: placebo twice weekly for 6 weeks, (N = 22).

The primary objective of the study is to evaluate the effect of iPPS on synovial fluid biomarkers associated with pain and OA disease progression in participants with knee OA pain. The effect of iPPS on serum and urine biomarkers and their correlation with synovial fluid biomarkers were also evaluated. The correlation of changes in biomarkers with clinical outcomes could further elucidate the proposed mechanisms of action of PPS and may also provide insight into the potential protective/disease modifying effect of iPPS.

The Primary Endpoint was change from baseline at Day 56 in one or more synovial fluid biomarkers of inflammation, pain, and joint degradation, including but not limited to cartilage oligomeric matrix protein (COMP), c-terminal telopeptide II (CTX-II), nerve growth factor (NGF), interleukin-1β (IL-1β), tumor necrosis factor alpha (TNFα), IL-6, a disintegrin and metalloproteinase with thrombospondin motif 5 (ADAMTS-5), aggrecan ARGS fragment, tissue inhibitor matrix metalloproteinase 1 (TIMP-1), CTX-I, and type II collagen (C2C).

Secondary Objectives included determining the correlation between synovial fluid biomarkers and clinical outcomes, determining the correlation between biomarkers in synovial fluid and biomarkers in serum and urine, and evaluating the effect of iPPS on serum and urine biomarkers associated with inflammation and OA disease progression in participants with knee OA pain.

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 were 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).

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 (22):

- 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.

References

1. American Academy of Orthopaedic Surgeons (AAOS). Management of Osteoarthritis of the Knee (Non-Arthroplasty) Evidence-Based Clinical Practice Guideline. [Internet]. American Academy of Orthopaedic Surgeons; 2021. Available from: https://www.aaos.org/oak3cpg
2. Gregori D, Giacovelli G, Minto C, Barbetta B, Gualtieri F, Azzolina D, et al. Association of Pharmacological Treatments With Long-term Pain Control in Patients With Knee Osteoarthritis: A Systematic Review and Meta-analysis. JAMA. 2018 Dec 25;320(24):2564–79.
3. Leopoldino AO, Machado GC, Ferreira PH, Pinheiro MB, Day R, McLachlan AJ, et al. Paracetamol versus placebo for knee and hip osteoarthritis. Cochrane Database Syst Rev. 2019 Feb 25;2(2):CD013273.
4. Concoff A, Rosen J, Fu F, Bhandari M, Boyer K, Karlsson J, et al. A Comparison of Treatment Effects for Nonsurgical Therapies and the Minimum Clinically Important Difference in Knee Osteoarthritis: A Systematic Review. JBJS Rev. 2019 Aug;7(8):e5.
5. Zeng C, Doherty M, Persson MSM, Yang Z, Sarmanova A, Zhang Y, et al. Comparative efficacy and safety of acetaminophen, topical and oral non-steroidal anti-inflammatory drugs for knee osteoarthritis: evidence from a network meta-analysis of randomized controlled trials and real-world data. Osteoarthritis Cartilage. 2021 Sep;29(9):1242–51.
6. da Costa BR, Pereira TV, Saadat P, Rudnicki M, Iskander SM, Bodmer NS, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. BMJ. 2021 Oct 12;375:n2321.
7. Bannuru RR, Dasi UR, McAlindon TE. Reassessing the role of acetaminophen in osteoarthritis: systematic review and meta-analysis. In: Osteoarthritis and Cartilage [Internet]. 2010 [cited 2023 Oct 4]. p. S250. Available from: https://www.infona.pl//resource/bwmeta1.element.elsevier-19fb7607-d1c4-3992-b0c5-a8ba568746dd
8. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative Effectiveness of Pharmacologic Interventions for Knee Osteoarthritis: A Systematic Review and Network Meta-analysis. Ann Intern Med. 2015 Jan 6;162(1):46–54.

9. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet Lond Engl. 2017 Jul 8;390(10090):e21–33.
10. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis – meta-analysis. Osteoarthritis Cartilage. 2011 Jun;19(6):611–9.
11. Trigkilidas D, Anand A. The effectiveness of hyaluronic acid intra-articular injections in managing osteoarthritic knee pain. Ann R Coll Surg Engl. 2013 Nov;95(8):545–51.
12. Juni P, Hari R, Rutjes AW, Fischer R, Silletta MG, Reichenbach S, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Musculoskeletal Group, editor. Cochrane Database Syst Rev. 2015 Oct 22;10(CD005328):1–78.
13. Campbell KA, Erickson BJ, Saltzman BM, Mascarenhas R, Bach BR, Cole BJ, et al. Is Local Viscosupplementation Injection Clinically Superior to Other Therapies in the Treatment of Osteoarthritis of the Knee: A Systematic Review of Overlapping Meta-analyses. Arthrosc J Arthrosc Relat Surg Off Publ Arthrosc Assoc N Am Int Arthrosc Assoc. 2015 Oct;31(10):2036-2045.e14.
14. Osani MC, Vaysbrot EE, Zhou M, McAlindon TE, Bannuru RR. Duration of Symptom Relief and Early Trajectory of Adverse Events for Oral NSAIDs in Knee Osteoarthritis: A Systematic Review and Meta- analysis. Arthritis Care Res. 2019 Mar 25;acr.23884.
15. Zeng C, Wei J, Persson MSM, Sarmanova A, Doherty M, Xie D, et al. Relative efficacy and safety of topical non-steroidal anti-inflammatory drugs for osteoarthritis: a systematic review and network meta-analysis of randomised controlled trials and observational studies. Br J Sports Med. 2018 May;52(10):642–50.
16. da Costa BR, Nüesch E, Kasteler R, Husni E, Welch V, Rutjes AW, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Musculoskeletal Group, editor. Cochrane Database Syst Rev [Internet]. 2014 Sep 17 [cited 2019 Sep 25];(9). Available from: http://doi.wiley.com/10.1002/14651858.CD003115.pub4
17. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019 Jul;27(11):1578–89.
18. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol. 2020 Feb;72(2):220–33.
19. Bruyere O, Honvo G, Veronese N, Arden NK, Branco J, Curtis EM, et al. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Semin Arthritis Rheum. 2019;49(3):337–50.
20. Heidari P, Heidari B, Babaei M. Efficacy and predictive factors of response to intra-articular corticosteroids in knee osteoarthritis. Rheumatology. 2020 Dec 23;58(6):424–35.
21. Trojian TH, Concoff AL, Joy SM, Hatzenbuehler JR, Saulsberry WJ, Coleman CI. AMSSM scientific statement concerning viscosupplementation injections for knee osteoarthritis: importance for individual patient outcomes. Br J Sports Med. 2016 Jan;50(2):84–92.
22. Matthews GI, Hunter DJ. Emerging drugs for osteoarthritis. Expert Opin Emerg Drugs. 2011 Sep;16(3):479–91.
23. Long H, Liu Q, Yin H, Wang K, Diao N, Zhang Y, et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the Global Burden of Disease Study 2019. Arthritis Rheumatol [Internet]. 2022 [cited 2022 Mar 4];74(7). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/art.42089

To learn more please visit: https://paradigmbiopharma.com

Approved for release by the Paradigm Board of Directors.

FOR FURTHER INFORMATION PLEASE CONTACT:
Simon White
Director of Investor Relations
Tel: +61 404 216 467
Paradigm Biopharmaceuticals Ltd
ABN: 94 169 346 963
Level 15, 500 Collins St, Melbourne, VIC, 3000, AUSTRALIA
Email: investorrelations@paradigmbiopharma.com

PARADIGM BIOPHARMA

PHASE 2 PARA_OA_008 CLINICAL TRIAL DAY 365 TOP-LINE RESULTS PRESENTATION

Disclaimer

This document, together with any information communicated by Paradigm Biopharmaceuticals Ltd ASX:PAR (known as “Paradigm”, “Paradigm Biopharma” or “the Company”), in any presentation or discussion relating to this document (collectively, “Information”) is confidential, and has been prepared by the Company on the condition that it is for the exclusive information and use of the recipient. The Information is proprietary to Paradigm and may not be disclosed to any third party or used for any other purpose without the prior written consent of the Company.

The Information is based upon management forecasts and reflects prevailing conditions, which are accordingly subject to change. In preparing the Information, the Company has relied upon and assumed, without independent verification, the accuracy and completeness of all information available from public sources, or which was otherwise reviewed by it. In addition, the analyses are not and do not purport to be appraisals of the assets, stock or business of the Company. Even when the Information contains a kind of appraisal, it should be considered preliminary, suitable only for the purpose described herein and should not be disclosed or otherwise used without the prior written consent of Paradigm. The Information is provided on the understanding that unanticipated events and circumstances may occur which may have significant valuation and other effects.

This Company presentation 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. The rate and timing of enrolment of our clinical trials and the timing of top-line results of our clinical trials should be regarded as forward-looking statements and the actual dates could differ materially from the expectations and projections set forth in Company presentations or statements especially during a pandemic.

Executive Summary

PARA_OA_008

Key Highlights – Day 365

- First controlled study with iPPS following subjects out to 12-months following 6-week iPPS treatment course.
- 6-week iPPS treatment course demonstrated significant improvements in pain, function and overall WOMAC measures compared to placebo at Day 365.
- No OA drug has shown significant pain reduction and functional improvements at 12 months after a single course of treatment.
- iPPS could become an early therapy in the OA treatment algorithm, with the potential to reduce reliance on other OA therapies as demonstrated through reduction in rescue medication use.
- Based on this data Paradigm intends to proceed with a Provisional Approval application to the TGA.
- This phase 2 study was performed concurrently with the Company's ongoing phase 3 study.

Top-Line Results

PARA_OA_008

Recap

PARA_OA_008

Exploring the durable effects of iPPS on pain, function and OA disease progression.

Biomarker study assessing change from baseline in multiple objective measures associated with disease progression of OA.

- 61 participants received iPPS once or twice weekly, or placebo.
- Follow-up period out to 12 months.

Previously reported outstanding top-line results:

- **Primary Endpoint Achieved** - change in one or more synovial fluid biomarkers associated with osteoarthritis disease progression at Day 56.
- Significant improvements at Day 56 in pain, function, stiffness, and overall WOMAC scores for twice-weekly iPPS compared to the placebo arm.
- Positive structural changes in the knee as measured by semi-quantitative MRI analysis. At Day 168 iPPS treatment demonstrated:
  - Reduced cartilage loss indicating cartilage preservation,
  - Reduced bone marrow lesions,
  - Reduced osteophyte formation (bone spurs).

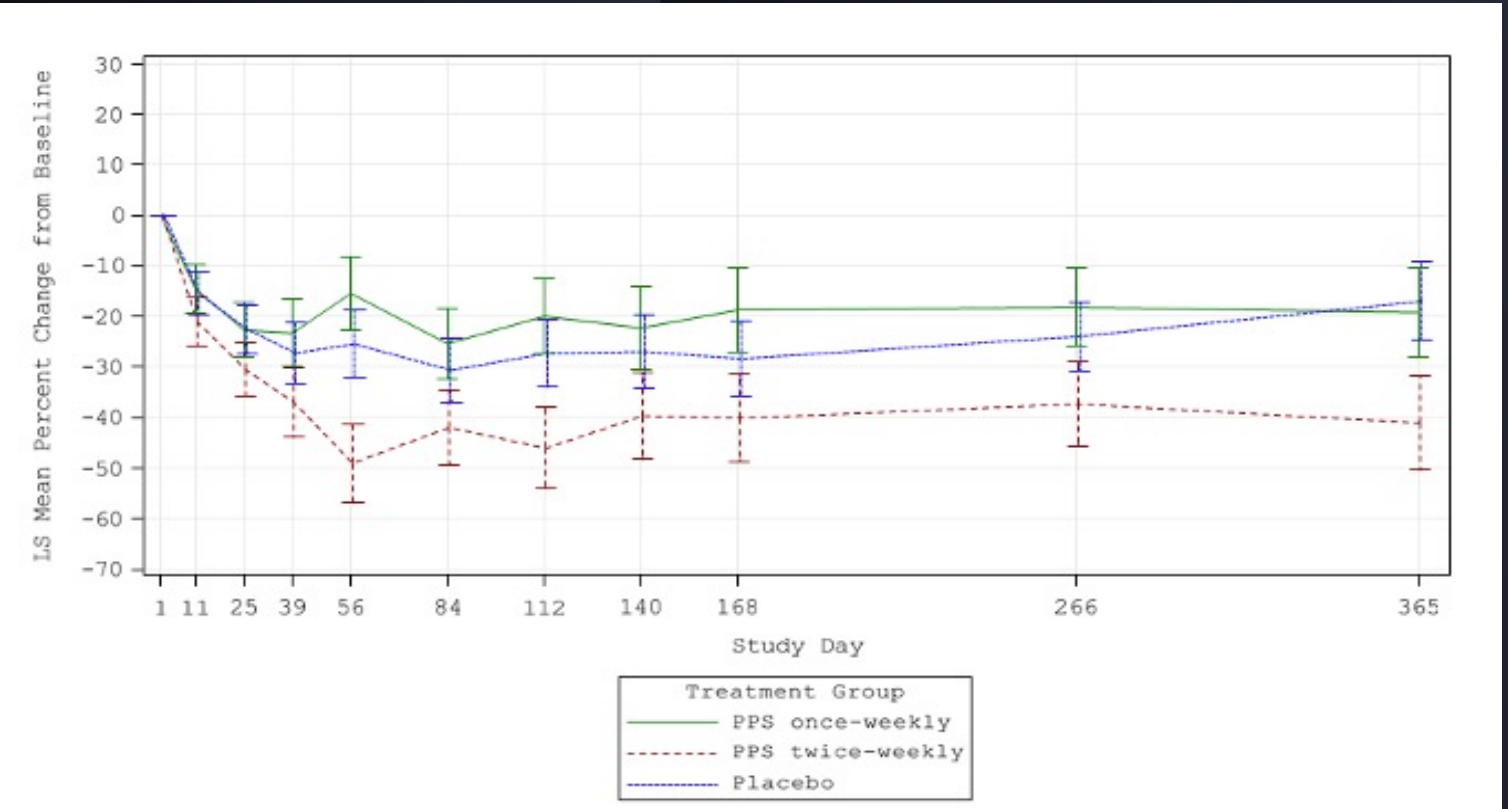
Top-Line Results

PARA_OA_008

Top-Line Results – Day 365 Results

- 6-week 2 mg/kg twice-weekly iPPS treatment course compared to placebo at Day 365 demonstrated:
  - Significant reduction from baseline in WOMAC pain (p=0.054)
  - Significant improvement from baseline in WOMAC function (p=0.048)
  - Durable improvements in WOMAC stiffness
  - Significant improvement in overall WOMAC scores (p=0.054)
- PGIC at day 365 following iPPS was statistically significant (p=0.005) compared to placebo.
- Rescue medication use five times lower in twice-weekly iPPS group compared to placebo

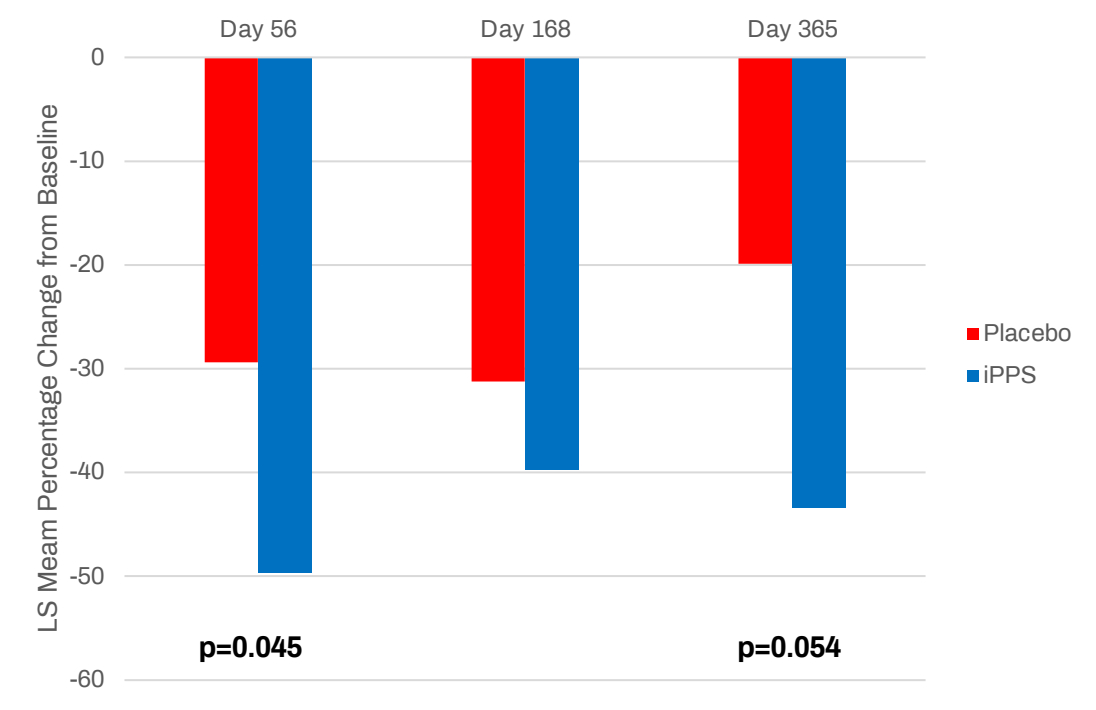
PARA_OA_008 | Once-weekly versus Twice-weekly dosing



A single 6-week course of twice-weekly iPPS demonstrates durable overall WOMAC scores incorporating pain, function and stiffness clinical outcomes out to 12 months (Day 365 timepoint) in PARA_OA_008 clinical trial participants with knee osteoarthritis.

- Clear out performance of 2 mg/kg twice-weekly over once-weekly and placebo.
- Phase 3 PARA_OA_002 program stage 1 has once-weekly arms being investigated.
- PAR requested DMC to undertake interim analysis of dosing arms in phase 3 stage 1 based on once-weekly performance in PARA_OA_008.
- Stage 1 dosing performance does not reflect the efficacy of PAR's previous phase 2 studies (008 & 005) and SAS data.
- OA development program will now focus on achieving the results of the 2 mg/kg twice-weekly regimen in the phase 3 OA registrational program.

PARA_OA_008 | Top-Line Clinical Endpoints at Day 365

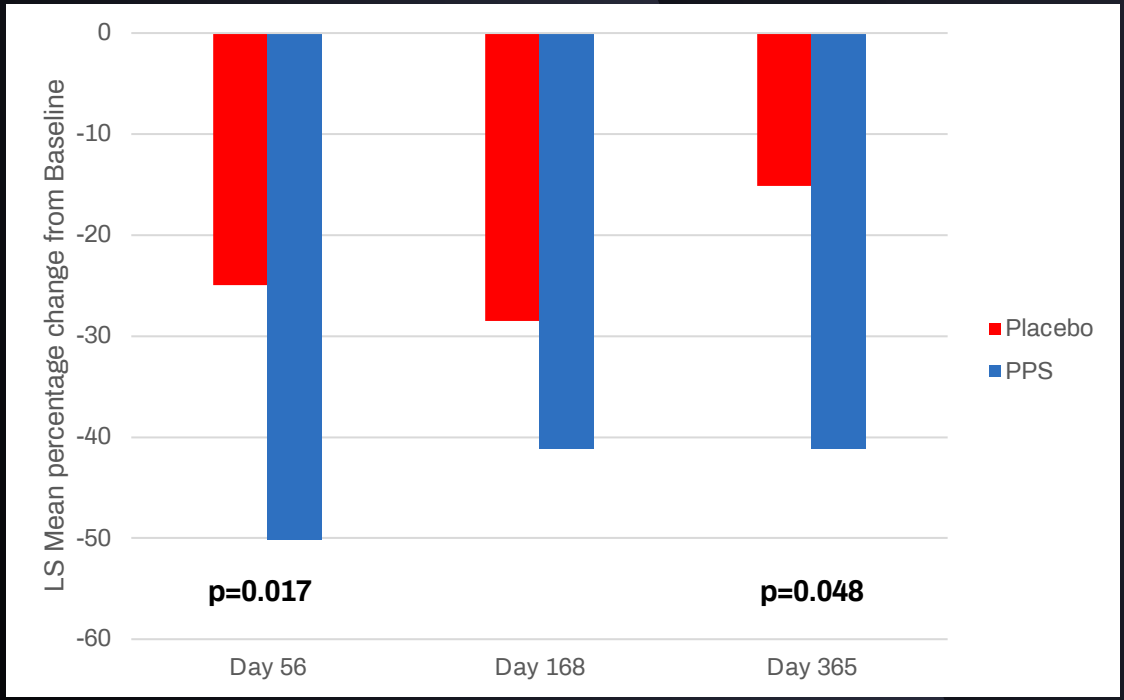


Adjusted LS mean % change in WOMAC pain from baseline at Day 56, 168, and 365 in participants treated with twice-weekly iPPS versus placebo .

Changes in WOMAC pain from baseline

- Twice-weekly iPPS treatment showed significant improvement at Day 56 (p=0.045) and Day 365 (p=0.054) in WOMAC pain compared to the placebo arm.
- iPPS treatment demonstrated clinically meaningful response to pain.
- The proportions achieving ≥30% improvement in pain in the twice-weekly group were 54.5% compared to 33.3% in the placebo group

PARA_OA_008 | Top-Line Clinical Endpoints at Day 365



Adjusted LS mean % change in WOMAC function from baseline at each visit in participants treated with twice-weekly iPPS versus placebo.

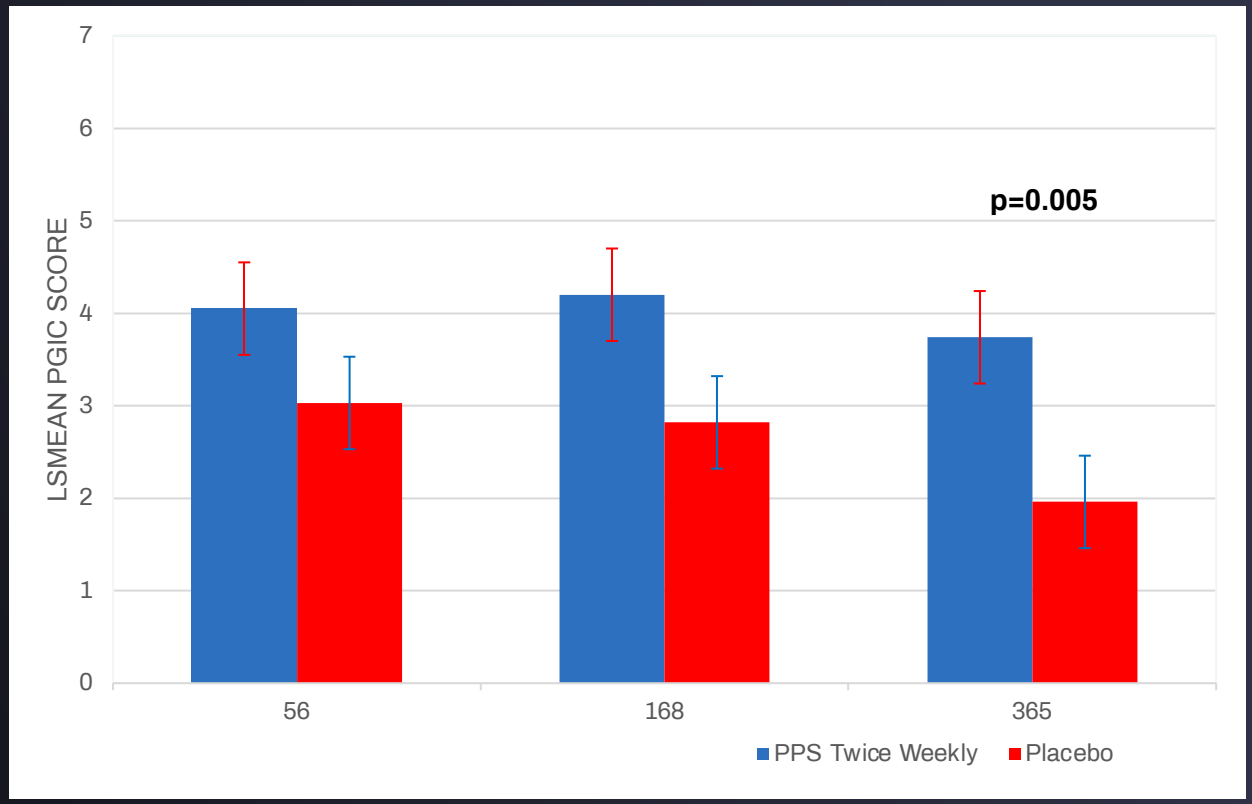
Changes in WOMAC function from baseline

- Significant improvements in function at Day 56 (p=0.017) and Day 365 (p=0.048) in iPPS twice-weekly compared to placebo.
- iPPS treatment demonstrated clinically meaningful response to WOMAC function.
- 55% of participants receiving iPPS twice-weekly reported >50% improvement in pain compared to 28% in the placebo arm.

PARA_OA_008 | Top-Line Clinical Endpoints at Day 365

Patient Global Impression of Change (PGIC)

- Self-reported measure that reflects the patient's belief about the overall efficacy of the treatment.
- Valuable in evaluating the effectiveness of a treatment beyond the more objective clinical measures.
- The average Day 365 PGIC score was highly statistically significant (p=0.005) for twice-weekly iPPS (3.74) versus the placebo arm (1.96).
- Participants receiving iPPS felt an overall improvement or stabilisation in their OA disease progression.



Average patient-reported PGIC scores in participants treated with twice-weekly iPPS versus placebo.

Rescue Medication

PARA_OA_008

Day 365 – Use of protocol-approved rescue medication

- Objective and quantifiable measure of a patient's pain relief needs.
- Important measure to determine how much additional pain relief participants require beyond the trial treatment.
- Placebo arm's cumulative use of paracetamol remained over five times higher at Day 365 (28,947 mg) compared to the twice-weekly iPPS group (5,147 mg).
- Regulatory agencies, such as the U.S. Food and Drug Administration (FDA), often consider rescue medication use when evaluating the efficacy of a new pain treatment.

Therapy Options

OA

Blockbuster market opportunity

Zilosul® aims to meet a significant unmet need in osteoarthritis.

FDA Fast Track Designation

Market size potential US$10B+ p.a.[4]

People affected by OA in 2020[3]

72m+

People affected by OA by 2030[3]

120m+

Markets: US, EU5, Canada and Australia.

In the US alone, OA is predicted to increase by 86% to 67 million by 2030.[3]

Knee and Hip (Global)

69% **of all OA**

OA patients dissatisfied with current treatments[1]

81%

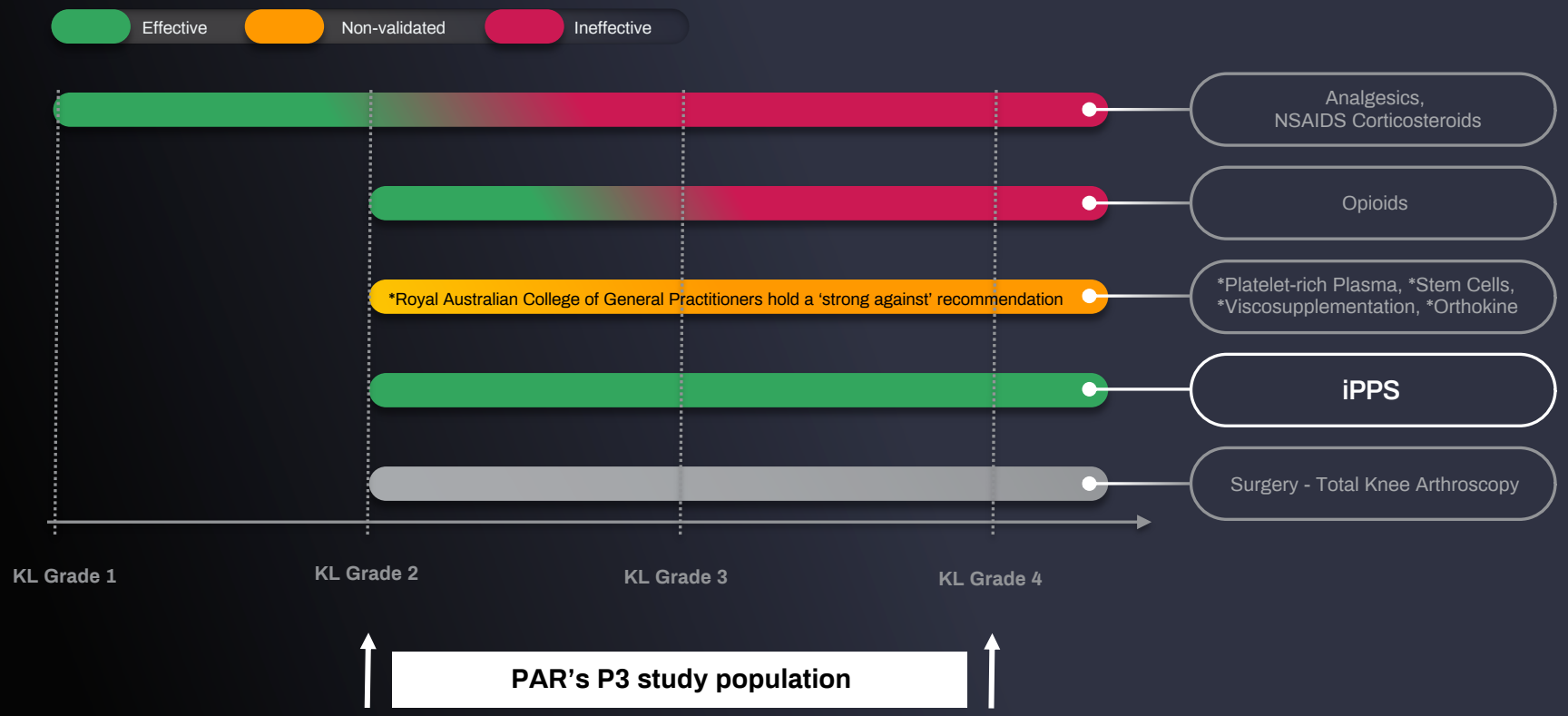
Target uptake: 10% dissatisfied market[1]

Zilosul® indicative price: US$2500 per year[2]

1. National Institute of Health; Emerging drugs for osteoarthritis; Hunter DJ and Matthews G 16(3): 479–491; 2011 September.
2. Global Pricing Research conducted by Paradigm. EU5: Germany, UK, Spain, France, Italy
3. OARSI. Osteoarthritis: A Serious Disease, Submitted to the U.S. Food and Drug Administration December 1, 2016
4. Calculation based on 10% penetration dissatisfied patients with knee and hip OA in the 72m addressable market, at price of US$2500.

Market Demand

There are no effective treatments for moderate to severe OA



"Most patients with OA of the hip and/or knee either initiate on or switch to opioids for long-term management of OA-related pain despite known risks. This highlights the need for new treatments that delay or prevent use of opioids[1]".

KL = Kellgren & Lawrence Classification of OA

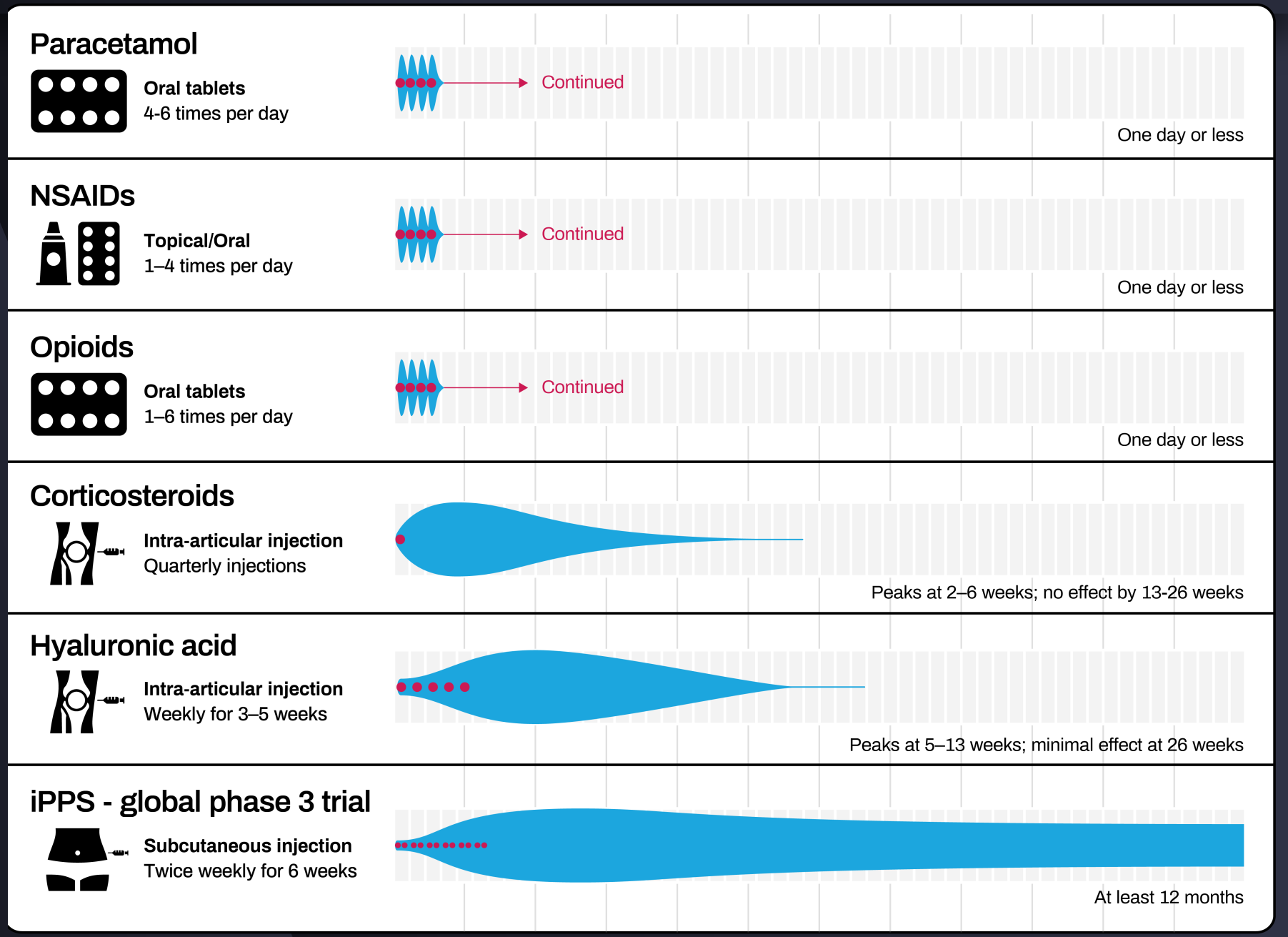
1. Source: https://www.tandfonline.com/doi/full/10.1080/03007995.2023.2234727?scroll=top&needAccess=true&role=tab

Current Therapies

Effect Duration

- 1 week
- Treatment
- Approximate timing & duration of peak effect

Current OA medication effect duration. Representative infographic reflecting current literature on the timing of the peak and estimated duration of treatment effect of currently available OA medications* and iPPS data from the PARA_OA_008 clinical trial. *References in Day 365 ASX release.



Next Steps

OA Program

Expected next steps following data release

- Provisional Approval application to the TGA following PARA_OA_008 iPPS 12-month duration of effect data. Timing to be confirmed to the market when available.
- Full quantitative analysis of PARA_OA_008 6-month MRI data will be reported shortly.
- PARA_OA_008 phase 2 clinical trial data are currently being compiled into a manuscript for peer review and publication.

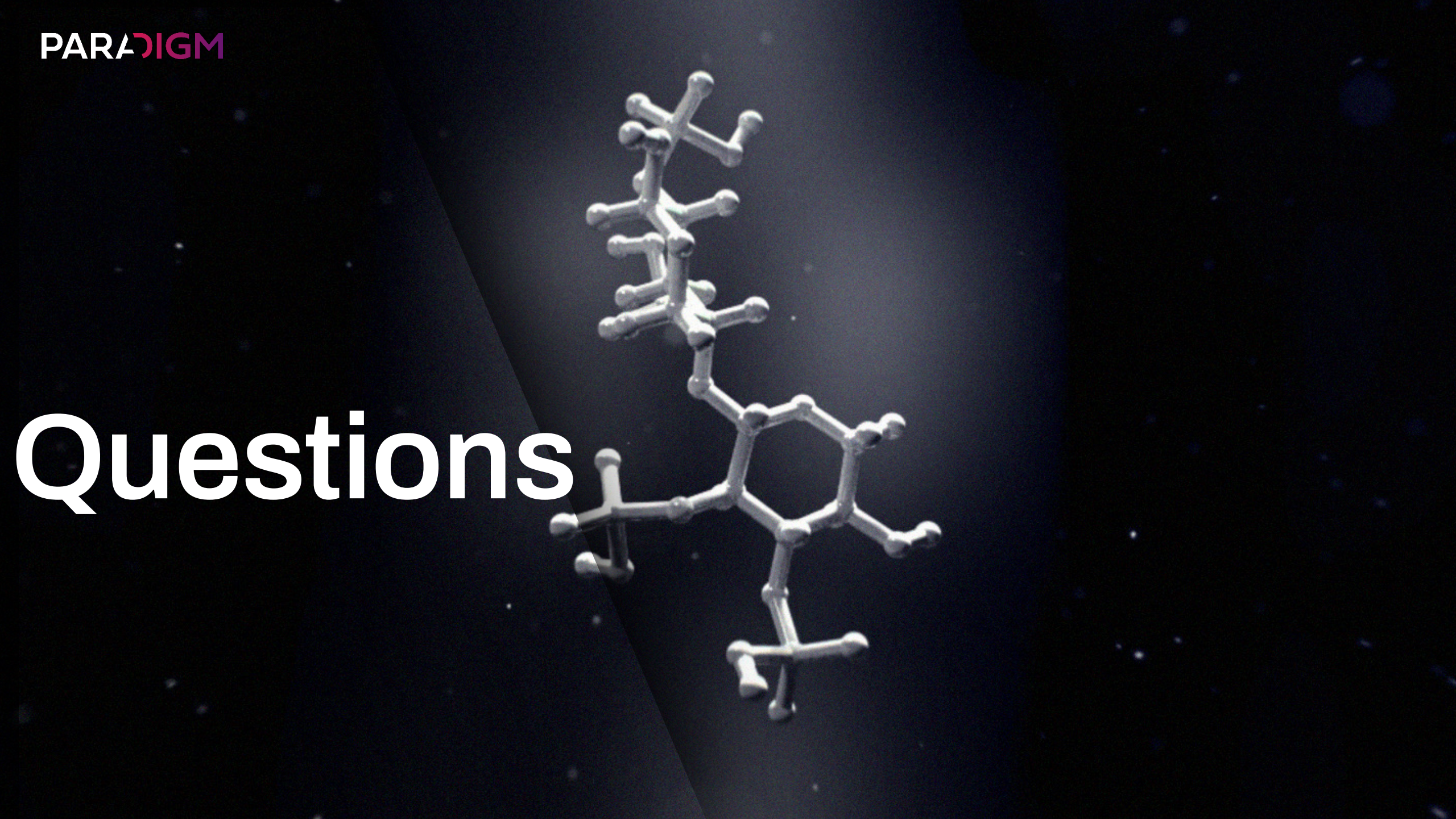
Near-term News flow

Upcoming Catalysts

Near-term news flow

- ✓ PARA_OA_002 clinical trial – recruitment completed stage 1 of phase 3 clinical trial.
- ✓ PARA_OA_008 clinical trial – 12-month clinical outcome data.
- PARA_OA_008 clinical trial – 6-month quantitative MRI data.
- DMOAD pathway – discussion with regulatory agencies (FDA, EMA) Q1 CY2024.
- MPS VI phase 2 clinical trials – top-line data Q4 CY2023.
- PARA_OA_002 Dose Selection – Q1 CY2024.
- The MPS I and PARA_OA_008 – clinical data sets are currently being prepared for peer review. Publication likely in CY2024.
- Paradigm is currently in active discussion with potential regional partners for its phase 2 asset in mucopolysaccharidosis (MPS) and phase 3 asset in OA.

PARADIGM



Questions

Contacts

For more information please visit:
paradigmbiopharma.com

CORPORATE ENQUIRIES:

Paul Rennie
Managing Director
Email: prennie@paradigmbiopharma.com

INVESTOR RELATIONS ENQUIRIES:

Simon White
Director IR
Email: swhite@paradigmbiopharma.com

MEDIA ENQUIRIES:

Rachel Peat
PR and Communication
Email: rpeat@paradigmbiopharma.com