Paradigm Biopharmaceuticals

Durable responses observed for kOA

Paradigm has announced positive day-365 data from its Phase II trial (PARA_OA_008) assessing injectable pentosan polysulfate (iPPS) as a potentially disease-modifying treatment for knee osteoarthritis (kOA). The latest data show durable responses based on measures of pain and function, while confirming the company will be pursuing an iPPS (2mg/kg) twice-weekly regimen for six weeks across all of its clinical programmes for kOA. Based on this update, Paradigm now plans to proceed with a Provisional Approval application to the Therapeutic Goods Administration (TGA, the Australian regulatory authority). The day-365 data are encouraging for iPPS as a potential treatment for kOA, in our view, adding to the company's data package to support discussions with regulatory authorities and potential partners. We note that Paradigm is awaiting full analysis of MRI data from this trial, and plans to share it in the near term.

PARA_OA_008 results build on prior readouts

Paradigm has shared data from the day 365 timepoint of its Phase II trial. The treatment group that received iPPS (2mg/kg) twice weekly for six weeks (n=19) showed significant reductions in pain and durable improvements in functionality based on WOMAC, alongside other measures of personal effectiveness of the treatment, and reduced need for rescue medications. These data build on previous readouts at day 56, where the primary endpoint was achieved (change in one or more synovial fluid biomarkers associated with OA disease progression). Further, previously reported results at day 168 included MRI measures to assess disease progression, and an analysis of biomarkers that collectively may support iPPS as a disease-modifying OA drug (DMOAD). This could maximise the opportunity in this indication; discussions with the FDA and EMA on a potential DMOAD pathway are planned for Q1 CY24. Management intends to share updated MRI data in Q4 CY23, which may add to this growing data package. With a durable response to 12 months demonstrated, Paradigm is submitting a Provisional Approval application to the TGA, the outcome of which could represent a major catalyst for the company, in our view.

kOA represents a serious unmet medical need

kOA is a prevalent condition lacking effective treatments. It was estimated that in 2019, there were c 528 million people living with OA, with the knee being the most frequently affected joint. We also note that >75% of OA patients report a need for additional treatment options. With the OA market projected to be worth c $15.3bn by 2030, we believe this is a sizeable opportunity for Paradigm.

Consensus estimates

Year end	Revenue (A$m)	PBT (A$m)	EPS (A$)	DPS (A$)	P/E (x)	Yield (%)
06/22	0.08	(39.2)	(0.17)	0.0	N/A	N/A
06/23	0.05	(51.9)	(0.21)	0.0	N/A	N/A
06/24e	32.3*	(32.4)	(0.07)	0.0	N/A	N/A
06/25e	35.7*	12.9	0.04	0.0	17.7	N/A

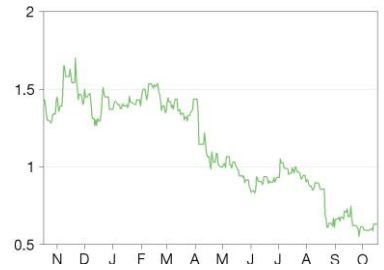
Source: Refinitiv. Note: *Revenue may reflect market expectations on potential licensing revenue.

Pharma and biotech

17 October 2023

Price	A$0.63
Market cap	A$178m

Share price graph



Share details

Code	PAR
Listing	Australian Stock Exchange
Shares in issue	282.1m
Net cash at end-June 2023	A$56.4m

Business description

Paradigm Biopharmaceuticals is an Australian biotechnology company focused on the development of injectable pentosan polysulfate (iPPS). The company's most advanced clinical programme is investigating the drug's use as a potentially disease-modifying treatment for knee-osteoarthritis, a degenerative disease with significant unmet medical needs. iPPS is in pivotal Phase III trials.

Bull

- Knee osteoarthritis (kOA) is a prevalent indication with large commercial potential.
- Comprehensive late-stage development programme to maximise opportunity in kOA.
- iPPS has a known safety profile, which somewhat de-risks development.

Bear

- Failure to meet clinical endpoints would significantly affect the value of iPPS.
- Historically the development of disease modifying drugs in OA has been unsuccessful.
- Funding is needed to complete the Phase III programme.

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12-month data demonstrate durable responses

The PARA_OA_008 study is a Phase II clinical trial based at two sites in Australia. The purpose of the study is to assess pentosan polysulfate sodium (delivered as a subcutaneous injection) in patients with kOA, compared to placebo. The primary objective is based on synovial fluid biomarkers associated with pain and OA disease progression. Patients (n=61) were randomised to receive one of three treatment groups (1:1:1 ratio):

- iPPS twice-weekly: iPPS (2mg/kg) calculated for ideal body weight (IBW) twice weekly for six weeks (n=19)
- iPPS once-weekly: iPPS (2mg/kg) calculated for IBW once weekly + one placebo injection once weekly for six weeks (n=20)
- Placebo: placebo injection twice weekly for six weeks (n=22)

In October 2022, day-56 data were reported, and in April 2023, day-168 data were reported. Now, in October 2023, Paradigm has shared highly encouraging day-365 data.

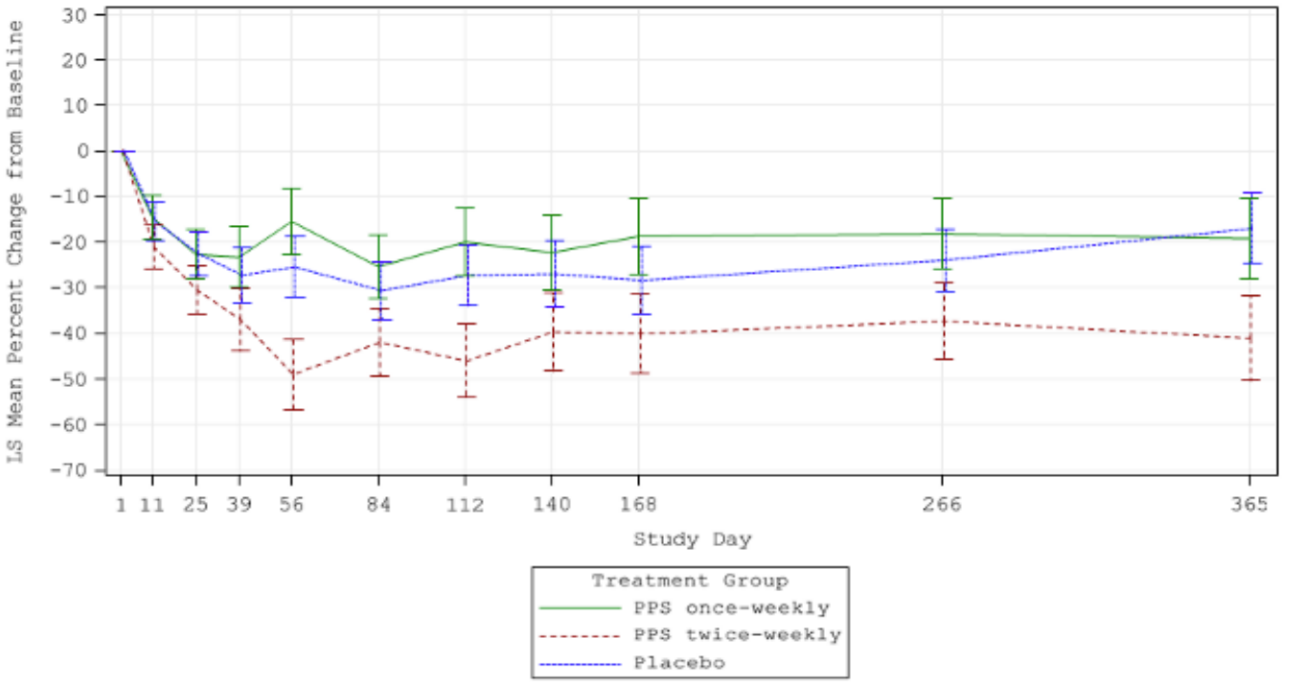
A key takeaway from this latest update is that the iPPS twice-weekly dosing regimen (2mg/kg for six weeks) demonstrated durable clinical effects. However, the day-365 data have also shown that the iPPS once-weekly dosing regimen was not efficacious over placebo, based on measures using the Western Ontario and McMaster University Arthritis Index (WOMAC) overall scores (Exhibit 1). Importantly, we highlight that the PARA_OA_008 Phase II trial is taking place at the same time as the pivotal PARA_OA_002 Phase III trial, which has the following treatment groups):

- iPPS (1.5mg/kg) calculated for IBW twice weekly for six weeks
- iPPS (2mg/kg) calculated for IBW once weekly + placebo once weekly for six weeks
- fixed doses:
  - iPPS (100mg) for ≤65kg IBW once weekly + placebo once weekly for six weeks
  - iPPS (150mg) for >65kg to ≤90kg IBW once weekly + placebo once weekly for six weeks
  - iPPS (180mg) for >90kg IBW once weekly + placebo once weekly for six weeks

Since the PARA_OA_002 study lacks an iPPS (2mg/kg) IBW twice-weekly treatment group, Paradigm requested that the data monitoring committee (DMC) for this Phase III trial conduct an interim analysis of the performance of all treatment groups in stage 1 (dose escalation stage, which is ongoing currently). This is due to the data from the PARA_OA_008 study indicating that doses at 2mg/kg once weekly, and below, may not be efficacious.

The interim analysis was performed on 300 participants who had reached the day-56 timepoint, and the findings have shown that the PARA_OA_002 stage 1 doses (as described above) do not demonstrate the same performance of the iPPS (2mg/kg) IBW twice-weekly dosing regimen as observed in the PARA_OA_008 study (or the PARA_005 study, a previous Phase IIb trial). Consequently, Paradigm is now focused on proceeding with all clinical development at the iPPS (2mg/kg) IBW twice-weekly dosing regimen, and is in the process of planning the best path forward to introduce this dose treatment group into all of its registrational programmes, and opportunities for expedited or provisional registration in Australia. While we do not yet know the precise impact that this will have on the company's ongoing Phase III trials, we note that the information (ie selection of the most appropriate dosing regimen) has come ahead of the formal dose selection procedure for the PARA_OA_002 study, which was previously scheduled for Q1 CY24, meaning the company can be proactive with making the appropriate arrangements. We await an update from management as to how Paradigm will proceed.

Exhibit 1: Effect of iPPS twice-weekly and once-weekly compared to placebo (based on WOMAC overall scores)



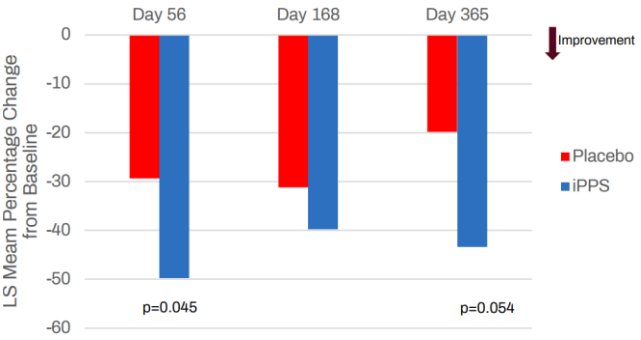
Source: Paradigm Biopharma ASX announcement

WOMAC scores: Reduced pain and improved functionality

The day-365 data for the PARA_OA_008 study have shown durable and significant responses in WOMAC scores, a scale used to quantify knee pain severity from daily activities, covering: pain, function, stiffness and an overall assessment. While the iPPS once-weekly treatment group did not see meaningful clinical outcomes compared to placebo, the iPPS twice-weekly treatment group showed WOMAC pain improvement (p=0.054) at day 365 compared to placebo. The pain response for this group peaked at day 56 (p=0.045), with the response sustained through to day 365 (Exhibit 2). The results also showed that 55% of participants in the twice-weekly group reported WOMAC scores showing meaningful improvements in chronic pain (defined as a >30% reduction in pain) at day 365.

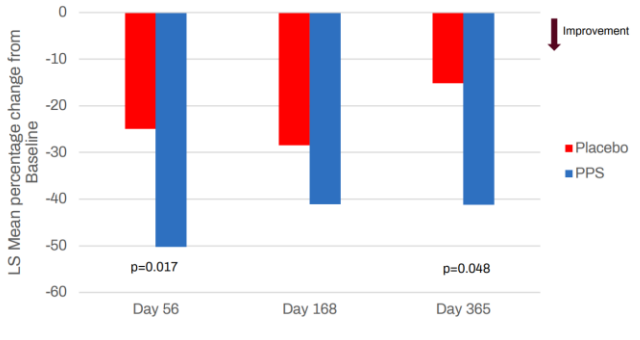
Further, significant functional improvements were recorded in the twice-weekly group at day 365 compared to placebo (p=0.048). Again, functional improvement peaked at day 56 (p=0.017), and this was sustained through to day 365 (Exhibit 3).

Exhibit 2: Data demonstrating durable pain reduction (based on WOMAC pain score measures)



Source: Paradigm Biopharma ASX announcement

Exhibit 3: Data demonstrating durable functional improvement (based on WOMAC function score measures)

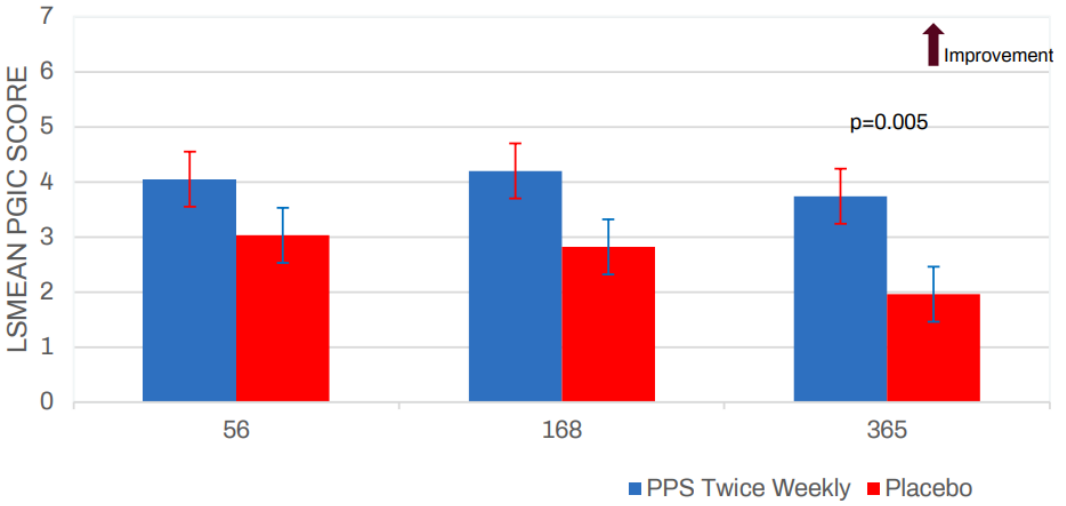


Source: Paradigm Biopharma ASX announcement

PGIC scores demonstrate positive patient perception of iPPS

The Patient Global Impression of Change (PGIC) uses a participant-rated assessment to reflect a patient's personal perception of the overall efficacy of a treatment. The scale ranges from 1–7 (a higher score indicates greater improvement). The 365-day data for PARA_OA_008 demonstrated statistically significant scores for the twice-weekly group compared to placebo (average score of 3.74 versus 1.96, p=0.005) (Exhibit 4). These data are encouraging, as they suggest that the patients receiving iPPS experienced a general improvement or stabilisation in the progression of their OA.

Exhibit 4: Average PGIC scores showing improved perceptions of iPPS across 365 days

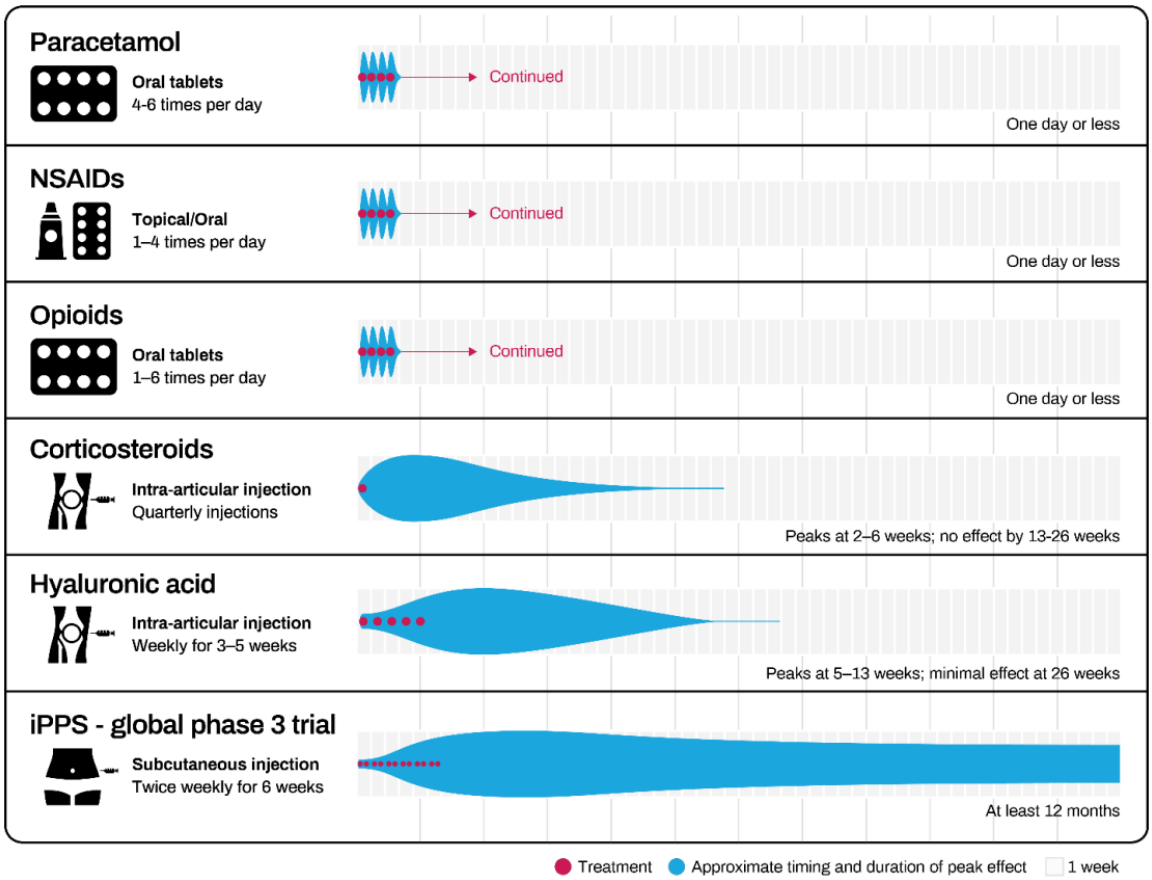


Source: Paradigm Biopharma ASX announcement

Rescue medication use may help on the regulatory front

The PARA_OA_008 study was designed to allow patients who had unacceptable levels of pain (whether due to kOA or other conditions) to use paracetamol as a rescue medication throughout the duration of the trial. The use of rescue medication provides a real-world measure of a patient's pain relief needs. This provides an objective measure for regulatory authorities to consider when assessing potential new pain treatments. Notably, the results from this trial showed a c 5.6x greater use of paracetamol in the placebo group (28,947mg versus 5,147mg with the iPPS twice-weekly treatment group at day 365). These results could help support applications for regulatory approval, in our view, and we highlight that, to our knowledge, no other OA drugs have demonstrated such durable responses after one year after a single course (six weeks) of treatment (Exhibit 5).

Exhibit 5: Durations of effect for OA pain medications (based on data compiled by management)



Source: Paradigm Biopharma ASX announcement

iPPS for mucopolysaccharidosis types I and VI

Beyond OA, we highlight that Paradigm is also investigating iPPS for mucopolysaccharidosis (MPS) types I and VI, adding some diversity to its active clinical pipeline. In June 2023, the company announced that its Phase II trial for MPS I met its primary endpoint, showing desirable tolerability with no serious adverse events out to 73 weeks of treatment. Additionally, in April 2023, Paradigm announced that it had completed patient enrolment for its Phase II trial from MPS VI. In the latest update, management confirmed that topline results for the MPS VI Phase II study will be shared in Q4 CY23, consistent with prior guided timelines. Paradigm is currently in active discussions with potential regional partners for its MPS programmes.

Financials

Since our previous note, Paradigm has published its FY23 annual report, for the year ended 30 June 2023. In FY23, net cash outflow from operating activities was A$45.2m (versus A$32.2m in FY22). R&D costs were A$52.7m (versus A$39.0m in FY22), mainly attributed to increased expenditure relating to clinical development programmes for iPPS for the treatment of kOA. The FY23 expenditures were partially offset by a tax incentive rebate of A$7.0m. Paradigm ended the period with cash and cash equivalents of A$56.3m. If the burn rate remains at the FY23 level of A$45m, the company should be funded through key near-term inflection points, into Q125 (Q3 CY24).

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