Paradigm Biopharmaceuticals

Potential for disease-modifying kOA treatment

Paradigm has announced day 168 (six-month) data from the PARA_OA_008 trial, which is evaluating injectable pentosan polysulfate sodium (iPPS) as a potentially disease-modifying treatment for knee osteoarthritis (kOA). Highlights from the interim data include: structural changes in several disease features as measured by magnetic resonance imaging (MRI), potential support for disease-modifying OA drug (DMOAD) activity from trends in biomarker data, and persistent positive responses in WOMAC scores. During the second half of CY23, Paradigm intends to discuss with the FDA and EMA a potential regulatory pathway for DMOAD indication labelling; we believe that the outcome, along with clarification on the Phase III development pathway, could represent a significant catalyst for the company.

kOA is a serious unmet medical need

kOA is a highly prevalent disease that lacks disease-modifying treatments and therefore provides a significant opportunity for Paradigm. The company has several active clinical programmes in this indication; more information on these is detailed in our previous update.

Encouraging data throughout PARA_OA_008 trial

The PARA_OA_008 study previously showed encouraging data at day 56 (reported in October 2022). Key highlights from this stage included biomarker analyses in the knee joint space (synovial fluid) consistent with DMOAD efficacy and improvements in Western Ontario and McMaster University Arthritis Index (WOMAC) scores for pain and function versus the placebo group. Paradigm has now provided an update at day 168, showing a continuation of the favourable effects on clinical outcomes and on the objective measure of disease progression at day 56. We believe these results are encouraging for a potential DMOAD indication label for iPPS.

DMOAD label potential to increase impact of iPPS

During H2 of CY23, Paradigm intends to initiate discussions with key regulatory agencies (the FDA and EMA) to agree on potential DMOAD indication label pathways for iPPS. The outcome of these discussions could represent a significant catalyst for the company, in our view. A DMOAD indication label would increase both the clinical and commercial impact of iPPS upon regulatory approval; iPPS could become a first-line therapy and strengthen the revenue opportunity for Paradigm.

Consensus estimates

Year end	Revenue (A$m)	PBT (A$m)	EPS (A$)	DPS (A$)	P/E (x)	Yield (%)
06/21	8.94	(34.3)	(0.17)	0.0	N/A	N/A
06/22	0.08	(39.3)	(0.17)	0.0	N/A	N/A
06/23e	0.005	(58.5)	(0.20)	0.0	N/A	N/A
06/24e	64.5*	(12.7)	0.04	0.0	33.6	N/A

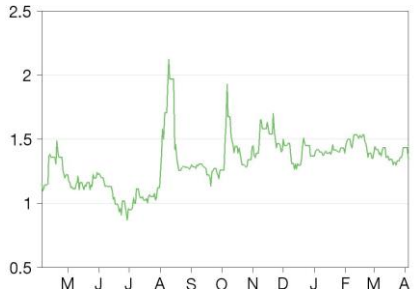
Source: Refinitiv. Note: *Revenue may reflect market expectations on potential licensing revenue.

Pharma and biotech

5 April 2023

Price	A$1.35
Market cap	A$381m

Share price graph



Share details

Code	PAR
Listing	Australian Stock Exchange
Shares in issue	282.1m
Net cash at end-December 2022	A$83.9m

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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Supportive data in all tested disease measurements

The Phase II trial (PARA_OA_008) is assessing iPPS as a potential DMOAD, and in this study patients (n=61) were randomised into three treatment groups according to a 1:1:1 ratio:

- a subcutaneous injection of 2mg/kg iPPS twice weekly (n=19),
- iPPS plus one placebo injection once weekly (n=20), and
- placebo injection twice weekly (n=22).

Now in the 12-month follow-up stage, Paradigm has announced an update on multiple objective measures associated with disease progression from the day 168 (six-month) data.

MRI measurements to assess OA progression

Prior to the commencement of this study, patients underwent MRI scans to determine their baseline levels of OA. Patients then received follow-up MRIs at day 168 to establish differences in disease progression between the iPPS-treated arms versus placebo. While we acknowledge that this study has a relatively small patient population, the MRI measurements did show some improvements in those receiving iPPS, consistent with a demonstration of DMOAD efficacy. A 21% improvement in mean cartilage loss score in the medial femur was observed in the once-weekly iPPS group versus a 4% worsening with placebo. The twice-weekly iPPS group also showed trends of improvement, although not of statistical significance.

In addition, bone marrow lesions in the lateral femur showed an average reduction of 38% in the once-weekly iPPS arm versus an average increase of 47% in the placebo group. Furthermore, statistically significant reductions in bone marrow edema lesions in the lateral tibiofemoral compartment were observed in the once-weekly iPPS group (average reduction of 17%) versus the placebo group (average increase of 56%).

Analysis of OA biomarkers

A broad panel of key biomarkers were also assessed in the blood (serum), urine and knee joint space (synovial fluid):

- ARGS (an articular cartilage breakdown product – serum & synovial fluid),
- COMP (a marker of cartilage turnover – serum & synovial fluid),
- C2C (a marker of cartilage breakdown – serum), and
- CTX II (a marker of cartilage breakdown – urine).

Generally, it was found that the trends of these biomarkers of cartilage degradation in iPPS-treated patients were favourable, with reductions in all cases. Further, these reductions were deemed statistically significant for the measurements of serum C2C levels and synovial fluid ARGS levels in the day 168 data versus the placebo group.

WOMAC scores

Patients provided baseline scores using the WOMAC index, and after initiation of treatment, these were assessed at pre-determined timepoints. Following statistically significant improvements at day 56, persistent responses have been observed since then in pain, function and stiffness scores. Notably, at day 168, a 50% improvement in function was reported in 53.3% of twice-weekly iPPS patients versus 22.1% of placebo patients. Furthermore, the average number of days that patients used rescue medication (such as paracetamol or NSAIDs to manage pain symptoms) was around four times lower in the twice-weekly iPPS group (five days) versus placebo (23 days).

An active year ahead for Paradigm

We believe that these data are positive for iPPS as a potentially disease-modifying treatment for kOA and recognise that a DMOAD indication label could help maximise the impact of the therapy. Management has communicated that it is currently evaluating the data to prepare for discussions with the FDA and EMA in H2 CY23. The outcome of these discussions, along with clarification on the Phase III development pathway, could represent a significant catalyst for the company, in our view. PARA_OA_008 is an ongoing trial, and we anticipate that the 12-month clinical outcome data will be shared in H2 CY23.

Regarding other ongoing clinical activities, the PARA_OA_002 Phase III trial is a two-stage pivotal study to assess the effect of iPPS in patients with kOA pain, and is the company's most advanced-stage clinical programme. Patient enrolment began in H222 and management has said that it expects to share an update from this trial in Q2 CY23, representing the next material near-term catalyst. Paradigm is also currently in active discussions with multiple potential partners for its Phase II asset in mucopolysaccharidosis (MPS), an orphan indication, and top-line data from the ongoing clinical trials in MPS, as discussed in our initiation note, are expected in Q4 CY23.

Financials

As discussed in our prior note, in H123, net cash outflow from operations was A$17.8m, 6.1% higher (y-o-y) than A$16.7m in H122. The cash balance at the end of H123 was A$83.9m, supported by a total A$66m capital raise in August 2022. If it is assumed that the cash burn rate remains similar to recent run rates (A$17.8m in H123), the company's funds on hand would be anticipated to provide an operating cash runway at least into CY24.

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