Paradigm Biopharmaceuticals

Pharma and biotech

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Active year ahead with significant catalysts

Paradigm has presented its half yearly results and accounts, reflecting an active period. This included an encouraging safety review for injectable pentosan polysulfate sodium (iPPS, Zilosul) in the pivotal Phase III trial (PARA_OA_002) for patients with knee osteoarthritis (kOA) pain. The Phase II (PARA_OA_008) biomarker trial reached its primary endpoint, positioning iPPS as a potentially disease-modifying drug. In our opinion, the initiation of the confirmatory Phase III trial (PARA_OA_003) and six-month follow-up results from the PARA_OA_008 trial represent major catalysts expected in CY23. At end-December 2022, the company had A$83.9m cash, supported by an August 2022 capital raise of A$66.0m.

Active clinical pipeline backed by encouraging data

Paradigm's development pipeline for iPPS as a treatment for kOA is supported by several Phase II studies. The company is now assessing the long-term efficacy and safety of iPPS in Phase III. The most advanced programme (PARA_OA_002) is a two-stage, pivotal Phase III trial to assess the effect of iPPS in patients with kOA pain. Patient enrolment began in H222 and the first formal safety data review (December 2022) reported an encouraging tolerability profile with no adverse events; we believe this is supportive of all ongoing clinical activity involving iPPS. Management expects recruitment for stage 1 to be completed in H1 CY23.

Potential for disease modification to maximise impact

In our view, maximum impact for iPPS may be achieved by demonstrating a disease-modifying profile in kOA. The Phase II trial (PARA_OA_008) is an ongoing biomarker study to investigate iPPS as a potential disease-modifying osteoarthritis drug (DMOAD). Positive top-line data was announced for this study in October 2022, and an update is expected in Q1 CY23 on the six-month follow-up results, involving biomarker data and MRI data, representing a significant near-term catalyst for the company's share price, in our view.

A$66m funding to support clinical development

During H123, R&D expenses accounted for over 80% of the company's operating expenses, indicating continued focus on preclinical and clinical activities. We believe Paradigm's net cash position of A$83.9m, supported by the A$66m raised in August 2022, provides an adequate cash runway in the near term, but the company is actively pursuing an out-licensing partnership, which could extend this runway.

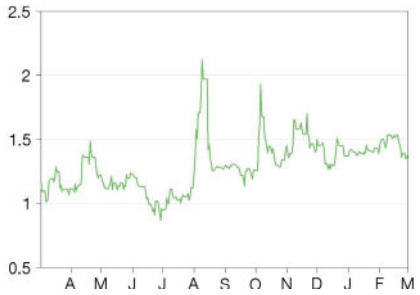
Consensus estimates

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	0.00	(58.5)	(0.20)	0.0	N/A	N/A
06/24e	64.5*	(12.7)	0.04	0.0	N/A	N/A

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

Price	A$1.35
Market cap	A$395m

Share price graph



Share details

Code	PAR
Listing	ASX
Shares in issue	282.2m
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 Phase III programme.

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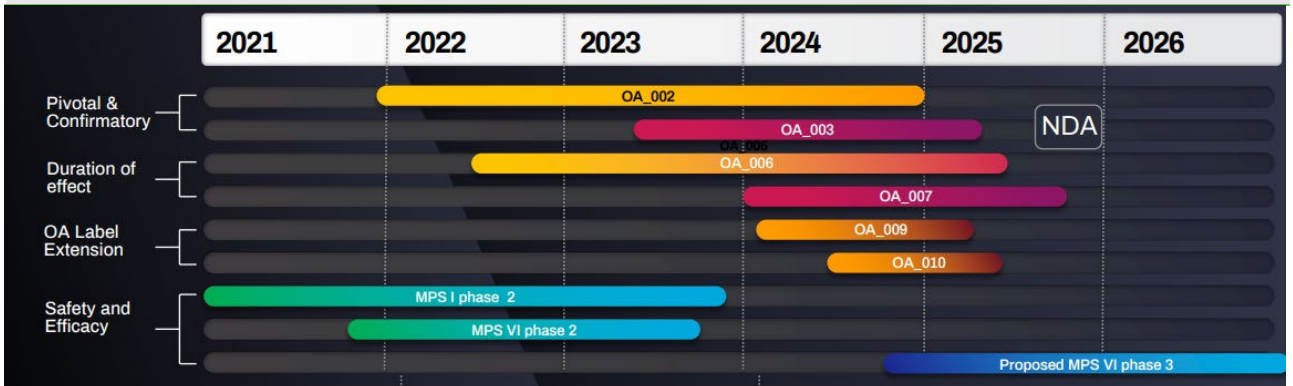
Pipeline striving towards Phase III

Paradigm has an active late-stage clinical pipeline to support the approval of iPPS as a treatment for OA, and CY23–25 is expected to be a busy period with multiple catalysts (Exhibit 1). The company's comprehensive development programme seeks to characterise both the acute and chronic impact of iPPS in OA patients using previous human clinical data (from prior trials) as well as real-world data from the Therapeutic Goods Administration's (TGA, the Australian regulatory authority for therapeutic goods under the Australian Government Department of Health) Special Access Scheme (SAS), an initiative providing iPPS for OA patients in Australia beyond those enrolled in clinical trials. Current ongoing clinical studies include the pivotal Phase III trial (PARA_OA_002) and a corresponding duration of effect trial (PARA_OA_006), which began in October 2022. Paradigm is also preparing for a separate confirmatory Phase III trial (PARA_OA_003), which will be followed by a corresponding duration of effect trial (PARA_OA_007); initiation is expected in CY23. Further to this, the company intends to initiate a retreatment trial (PARA_OA_009) in CY24, which will assess the feasibility of multiple treatment regimens for iPPS. In our view, updates from the variety of ongoing clinical trials represent multiple upcoming catalysts across CY23–25 and, with retreatment and mechanistic investigations planned, management expects to file an NDA with the FDA by end-CY25, provided that positive clinical readouts continue to be observed.

In addition to the ongoing clinical activities supporting the development of iPPS as a treatment for OA, Paradigm is also conducting two Phase II trials to investigate iPPS as a treatment for pain and joint stiffness in mucopolysaccharidosis (MPS) types I and VI (rare genetic diseases). Patient enrolment, including three cohorts of ages (5–9, 9–16, and >16 years), is nearing completion for these studies and primary endpoint readouts are expected in the second half of CY23.

Exhibit 1: Paradigm's clinical development pipeline



Source: Paradigm presentation to JP Morgan Healthcare Conference (January 2023)

Formal safety review encouraging for ongoing Phase III trial

As a reminder, the ongoing pivotal Phase III trial (PARA_OA_002, NCT04809376) is a multicentre (US/Australia/UK/EU/Canada), two-stage, adaptive, randomised, double-blind, placebo-controlled study to investigate the effect of iPPS in patients with kOA pain. In stage 1, using the Phase IIb

dose selection, randomised kOA patients (expected n=468) will either receive placebo twice weekly, or one of three iPPS dose regimens:

- 1.5 mg/kg calculated for ideal body weight (IBW) iPPS twice weekly; or
- 2mg/kg IBW iPPS once weekly + placebo once weekly; or
- fixed doses:
  - 100mg iPPS for ≤65 kg IBW once weekly + placebo once weekly; or
  - 150mg iPPS for >65 to ≤90 kg IBW once weekly + placebo once weekly; or
  - 180mg iPPS for >90 kg IBW once weekly + placebo once weekly.

These will be issued for six weeks to confirm the lowest effective dose of subcutaneous iPPS. Stage 2 of this Phase III trial will assess the efficacy of the selected stage 1 dose versus a placebo (expected n=470) across six weeks. The primary endpoint for the trial is the change from baseline at day 56 according to the WOMAC score (Western Ontario and McMaster University Arthritis Index), a widely employed, self-administered questionnaire used to asses pain, stiffness and physical function.

Enrolment for PARA_OA_002 commenced in H2 of CY22 and the results from the first formal safety review were announced in December 2022. This review from the Data Monitoring Committee (DMC) concluded that the clinical trial should proceed without modification. It was reported that iPPS was well tolerated across all of Paradigm's clinical programmes. This review included real-world data arising from the SAS involving >600 patients. We believe that this update effectively validates the trial, and is supportive of ongoing clinical activity involving iPPS.

Assessing iPPS as a disease-modifying treatment

The clinical development of iPPS is supportive of a symptomatic treatment for pain and stiffness in patients with OA. However, in our view, the key to maximising the commercial success of the drug is in demonstrating a disease-modifying profile in kOA, and we believe that this is the primary design of Paradigm's clinical programme. The Osteoarthritis Research Society International estimates that more than 240 million people are affected by OA globally, with knee and hip OA comprising approximately 69% of this population. We believe this represents a significant market opportunity for the company, and altogether management expects the potential for iPPS in knee and hip OA to be greater than US$10bn pa.

The potential for iPPS to be a DMOAD is supported by clinical biomarker data and animal studies. (see our initiation note for further details). A Phase II biomarker study (PARA_OA_008) conducted by the company reached its primary endpoints in October 2022. The objective of the trial (n=61) was to assess the impact of iPPS treatment on synovial fluid biomarkers related to pain, inflammation and disease progression in patients with kOA. Patients were randomised to a once-weekly iPPS, twice-weekly iPPS, or placebo arm for six weeks of treatment and primary biomarker endpoints were assessed at day 56 along with WOMAC scores. The mean change from baseline WOMAC score in twice-weekly treated patients was recorded as 50% for pain and 50% for function, versus 30% and 25% for the placebo group, respectively. No serious adverse events were recorded, providing further encouragement of iPPS as a potential DMOAD, in our view. The PARA_OA_008 trial is now in the 12-month follow-up stage; management expects to report an update on the six-month biomarker data, and MRI data, in Q1 of CY23.

Financials

As a late-stage clinical development company, Paradigm does not generate a recurring revenue stream. However, it recorded revenue of A$4.7k in H123 through the TGA-approved SAS, along with an R&D tax incentive of A$0.8m. Total pre-tax (and net) loss was A$31.9m, up from A$26.9m in H122, driven by higher R&D expenses related to ongoing preclinical and clinical activities, in particular for preclinical activity related to chronic dosing toxicity studies and higher clinical costs related to patient enrolment in the MPS VI Phase II study. Paradigm's R&D costs are notably

higher, comprising 83.9% of the total operating expenses, followed by general and administrative expenses (13.8%), which also increased due to a rise in employee headcount. In H123, net cash outflow from operations was A$17.8m, 6.1% higher (y-o-y) than A$16.7m in H122. As Paradigm progresses the clinical development of Zilosul, followed by the commercialisation process if the above is successful, it is possible that its losses will be extended in the near future, absent any milestone income or a partnering deal.

The cash balance at the end of H123 was A$83.9m, supported by a total A$66m capital raise in August 2022. The fund-raise was a two-step process: A$45.7m by institutional placement and the rest (A$20.3m) through a pro rata, non-renounceable entitlement offer in the ratio of 1:15 at A$1.30 per share. Post completion of the share placement, we believe this provides an operating cash runway into CY24, based on 2022 run rates (A$17.8m in H123).

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