Paradigm Biopharmaceuticals

Bolstering the iPPS data package for OA

Paradigm is focused on the development of injectable pentosan polysulfate (iPPS) for the treatment of osteoarthritis (OA). While the company has several active human clinical trials, it is also assessing iPPS in a canine model due to the similarities in disease biology. Furthermore, since dogs have a shorter lifespan than humans, the full progression of the condition can be assessed over a condensed period. Management believes that this could be advantageous in evaluating the disease-modifying OA drug (DMOAD) status of iPPS, a key goal for Paradigm. The latest data show that iPPS demonstrates durable effects on pain, function and cartilage volume in the canine OA model at the three-year human equivalent time point (canine 26 weeks). These positive results add to a growing data package to support iPPS as a potential DMOAD. Paradigm intends to present this to the FDA and EMA in H2 CY23, and the outcome of these discussions could represent a significant catalyst for the company, in our view.

Not barking up the wrong tree

Paradigm has several active clinical programmes in OA (more information on these is detailed in a prior update), and has also designed a canine study to gain additional proof-of-concept and translational data. Since the lifespan of a dog is shorter than a human, all stages of disease development are represented over a shorter timeframe, and management hopes this will help it to better understand the long-term effects of iPPS. Its double-blinded study involves 20 companion dogs with naturally occurring OA randomised to either subcutaneous iPPS or saline as a placebo, in a 2:1 ratio. Pain, function and cartilage volume were measured at 8 and 26 weeks, assumed to be equivalent to a three-year human timepoint.

Pushing toward a DMOAD label for iPPS

A key goal for Paradigm is to achieve a DMOAD label for iPPS. The company is putting together a comprehensive data package to support this. In H2 of CY23, Paradigm intends to present this data package to key regulatory agencies in the US and the EU (FDA and EMA, respectively). As a reminder, in April 2023, Paradigm announced day 168 data from the ongoing PARA_OA_008 study (n=61). The results showed a continuation of favourable effects on clinical outcomes and on objective measures of disease progression in the patients receiving iPPS versus placebo. Collectively, we believe that this encouraging data is supportive of iPPS as a potential DMOAD, and view the outcome from discussions with regulatory authorities as a potentially significant catalyst 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

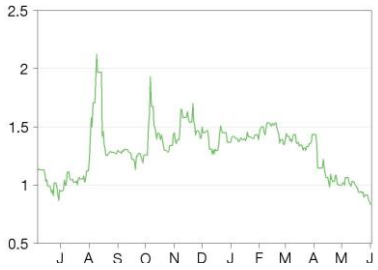
Source: Refinitiv. Note: *Revenue may reflect market expectations on potential licensing revenue.

Pharma and biotech

5 June 2023

Price	A$0.88
Market cap	A$248m

Share price graph



Share details

Code	PAR
Listing	Australian Stock Exchange
Shares in issue	282.1m
Net cash at end-March 2023	A$73.2m

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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Canine model to support iPPS in osteoarthritis

The canine study involves 14 iPPS-treated dogs and six placebo-treated dogs, comprised of various breeds and sexes. The dogs, all diagnosed with OA of the knee/stifle (hind limb) or elbow (front limb), were randomised to receive subcutaneous iPPS at 3mg/kg (a human equivalent dose of 1.7mg/kg) weekly for six weeks. Clinical measures were taken at baseline, eight weeks and 26 weeks. Paradigm has now announced that iPPS demonstrated durable effects in all tested disease measurements.

Given the small sample size, this study utilised effect size calculations to assess the differences between iPPS and the placebo. The effect size is based on the magnitude of difference in measurements between the two groups, is independent of sample size and is categorised as either small (0.20–0.49), medium (0.50–0.79) or large (>0.80). The Hedges' g calculation was imputed in all measurements, determining the iPPS effect size versus placebo, considering sample bias, the difference in means, and standard deviations between the iPPS-treated dogs and the placebo-treated dogs.

Pain assessment

Pain was measured using the Helsinki Chronic Pain Index (HCPI), an owner-based questionnaire. It was found that iPPS demonstrated meaningful pain reductions versus placebo at weeks eight and 26. For the iPPS-treated group, a large effect size (1.79) in pain reduction at week 26 was reported compared to the small percentage change from the previous follow up at week eight (0.39). The results indicate that iPPS treatment gives a durable reduction in pain versus placebo for up to 26 weeks.

Functional gait analysis

A gait assessment was conducted on the dogs enrolled in the study, with total pressure index percentage (TPI%) as the measurement. This involved the use of GAITRite, a system to measure clinical lameness in dogs. The effect size in improvement of function with the iPPS-treated group was a medium effect at both week eight (0.55) and week 26 (0.5), based on the mean percentage change from baseline (%CFB) in TPI%. However, it was noted that the responses in the iPPS-treated group versus placebo were considered by the company to be clinically meaningful functional improvements, given that they passed a benchmark 5% change from baseline.

Cartilage volume analysis

An analysis of the mean %CFB in cartilage volume showed that iPPS gave a large effect size (1.06) at week eight, and a medium effect size (0.73) at week 26 versus placebo. This indicates a reduction in cartilage loss in the stifle joint (knee equivalent) of the affected limb versus placebo. These results suggest a stabilisation of disease progression in the stifle joints of dogs with OA at both timepoints.

Serum biomarker analysis

It was found that iPPS favourably regulates the levels of a panel of biomarkers in the blood (serum) of dogs with OA. This was determined by effect size on:

- CTX-1, a degradation fragment of type 1 collagen – large (1.15) at eight weeks; large (1.60) at 26 weeks.
- HA or hyaluronic acid, a marker of cartilage degradation – medium (0.58) at eight weeks; large (1.19) at 26 weeks.

- TIMP-1, an endogenous inhibitor of the cartilage degradation enzyme ADAMTS-5 – large (0.96) at eight weeks; large (0.27) at 26 weeks.

The desired treatment effect sizes at for these biomarkers at 26 weeks are indicative of the durability of iPPS in inhibiting cartilage degradation, and potentially promoting structural stabilisation of cartilage.

Translation potential from OA in canines to humans

It is believed that the canine model provides relevant translational data that accurately reflects OA in humans, due to the similarity of both phenotypic characteristics and the heterogeneity of the condition. In humans, OA primarily affects the knee, hip and shoulder joints; pathological changes have been found to be comparable to those seen in canine stifle (knee), hip, and shoulder joints. However, due to the relatively shorter dog lifespan, all stages of disease development, from birth through to adulthood and ageing, present themselves over a condensed period, serving as a potential advantage in Paradigm's approach to conducting canine studies to assess iPPS as a potential DMOAD.

Management has communicated that the encouraging data from the canine model will be packaged with the MRI, biomarker and clinical results from the Phase II PARA_OA_008 trial (discussed in a prior update). This will then be presented to US and EU regulatory authorities (the FDA and European Medicines Agency, respectively), aiming to support Paradigm's goal of determining the requirements to achieve a DMOAD label for iPPS. As a reminder, Paradigm is also involved in additional Phase II trials to complement the clinical development of iPPS: PARA_OA_002 (treatment of pain and improvement in function) and PARA_OA_006 (duration of treatment effect). The encouraging data from the canine study are consistent with the clinical improvements observed from the PARA_OA_008 day 168 results. We continue to believe that the outcome from discussions with regulatory authorities regarding a potential DMOAD label for iPPS, along with advancements in the Phase III development pathway, may represent a significant catalyst for the company.

Financials

As discussed in our prior note, in Q323, net cash outflow from operating activities amounted to A$10.3m (A$28.1m for the first nine months of FY23). R&D costs stood at A$9.0m, mainly attributed to recruitment and analytical activities associated with the PARA_OA_008 study, site operations for Phase II clinical trials in mucopolysaccharidosis, and ongoing NDA-enabling non-clinical studies. The expenditure was similar to the previous quarter (A$13.2m), but we anticipate an increase in burn rate across the coming months due to the company's active clinical pipeline. At end-March 2023, Paradigm reported a cash position of A$73.2m, and at the current quarterly burn rate, management has guided that this will fund operations into CY24.

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