Paradigm Biopharmaceuticals

Adapted therapies to meet unmet demand

Paradigm Biopharmaceuticals is a late-stage Australian drug developer focused on developing injectable pentosan polysulfate sodium (PPS). The company's most advanced clinical programme is investigating injectable PPS (iPPS, Zilosul) as a potentially disease modifying treatment for knee osteoarthritis (kOA), a globally prevalent condition with unmet medical needs. We believe Paradigm's comprehensive Phase III programme is designed to maximise the potential of iPPS in kOA. The company is also investigating the use of iPPS in mucopolysaccharidosis (MPS) types I and VI, rare genetic diseases. At end-September 2022, the company had A$92.4m in cash, supported by an August 2022 capital raise of A$66.0m, which management expects will provide a runway into Q124. Additional cash will be needed to fund the final part of the Phase III programme.

Development supported by ample clinical data

Paradigm's development programme in kOA is supported by data from several Phase II studies, the most recent of which demonstrated a clinically relevant change in synovial joint biomarkers associated with pain, inflammation and cartilage degradation, and patient reported pain and function scores. We see this as encouraging support for iPPS's utility; however, long-term efficacy and safety data from Phase III will be crucial in fully establishing the drug's impact.

Disease modification would maximise impact

In our view, the key to maximising Zilosul's commercial success will be the demonstration of a disease-modifying profile in kOA, which we believe is the primary design of the clinical programme. If no disease modification is observed, iPPS could still form an important part of OA treatment regimens as a symptomatic treatment for pain and stiffness. Altogether, management estimates the opportunity for iPPS in knee and hip OA could be over US$10bn pa.

R&D expenses to increase; funded into 2024

R&D expenditure constitutes over 80% of Paradigm's total operating expenses, resulting in an operating cash burn of A$32.2m in FY22. Management expects higher cash burn in future as the company progress its Phase III programme. Considering the current run-rate and recent equity financing, management estimates a cash runway into Q124; however, the company is actively pursuing an out-licensing partnership, payments from 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	0.0	(58.5)	(0.20)	0.0	N/A	N/A
06/24e	64.5*	(12.7)	0.04	0.0	N/A	N/A

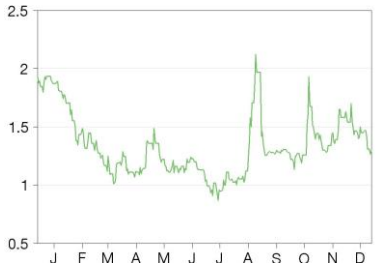
Source: Refinitiv. Note: *Revenue may reflect market expectations on potential licensing revenue.

Pharma and biotech

14 December 2022

Price	A$1.47
Market cap	A$410m

Share price graph



Share details

Code	PAR
Listing	Australian Stock Exchange
Shares in issue	285m
Net cash at end-September 2022	A$92.4m

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 Phase III programme.

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Company description: Repurposing to maximise utility

Paradigm Biopharmaceuticals is an Australia-based, late-stage pharmaceutical company focused on the development of known therapeutics to address unmet medical needs in conditions where sustained inflammation is present. The current strategy is centred on the clinical development of an injectable formulation of PPS (iPPS, Zilosul) for the treatment of kOA and MPS, with the former representing the company's most advanced clinical campaign. Management has capitalised on interaction with the regulators to design a comprehensive late-stage development programme for iPPS in kOA. According to the company's communicated timelines, Paradigm intends to run a separate pivotal and confirmatory Phase III trial over CY23–25 and the pivotal trial will be accompanied by extension studies to assess the durability iPPS treatment. Additional retreatment and mechanistic investigations will be conducted to support a potential new drug application (NDA), which management expects to file in late-CY25. This busy clinical schedule has been designed to investigate both the acute and chronic safety and efficacy of iPPS in addition to its potential as a disease-modifying osteoarthritis drug (DMOAD).

In our view, demonstrating iPPS has a disease-modifying profile, which current clinical biomarker data and animal studies suggest it could, is key to maximising the commercial impact of the drug, which the company expects could be over US$10bn per year. Management's current strategy is to find a global licensing partner to commercialise iPPS in kOA, and if the Phase III programme proves positive (especially if iPPS is demonstrated as a DMOAD), we anticipate the drug could garner significant industry attention. Paradigm is also conducting two Phase II trials, investigating iPPS as a treatment for pain and joint stiffness in MPS types I and VI, rare genetic diseases with serious impacts on patients' life expectancy and quality.

Financials: Recent equity raise provides funding to Q124

As a late-stage clinical development company, Paradigm is yet to generate a recurring revenue stream. However, current cash inflows comprise other income through the Australian Special Access Scheme and R&D tax incentives. Given the high development cost involved in its Phase II and III clinical programmes, R&D expenditure constitutes over 80% of the company's total operating expenses, resulting in an operating cash burn of A$32.2m in FY22 and a net loss for FY22 of A$39.2m, 14.4% higher than FY21. For funding requirements, Paradigm has historically raised funds through issuing share capital, indicating investors' confidence in its development programme. The company's cash balance at the end-September 2022 stood at A$92.4m (A$39.7m at end FY22), supported by a capital raise of A$66.0m in August 2022. As the company progresses the clinical development of Zilosul, management expects higher cash outflows in the coming years, but anticipates a cash runway into CY24.

Sensitivities: Known profile de-risks development slightly

Paradigm is subject to all the regular sensitivities associated with drug research and development. The company's prospects may be affected by development delays or failures, regulatory risks, competitor successes, partnering setbacks and financing risks. We believe the known safety profile of iPPS lowers the company's development risk somewhat, however failure to demonstrate an effective profile in kOA represents a significant near-/medium-term risk for the company and may affect future partnership opportunities. Management's estimated cash runway will fund the company into 2024 and it will need to raise additional funds to complete the planned iPPS Phase III trial programme. Capital could be raised through an equity offering, which could result in significant dilution of existing shareholders.

Maximising the potential of iPPS

PPS is a sulphated semi-synthetic form of the naturally occurring xylan pentosan, a polysaccharide mainly comprised of xylose. PPS itself has a long medical history and is currently approved globally as an oral treatment for interstitial cystitis/painful bladder syndrome, as it forms a protective barrier over the bladder lining. Paradigm believes its injectable PPS formulation has significant potential as a possible DMOAD in the treatment of human kOA. The company hypothesises that iPPS acts on the nuclear factor-κB (NF-κB) pathway in the knee joint to reduce signs and symptoms of kOA such as inflammation, pain and cartilage degradation and increases blood flow, an assertion supported by in vitro animal and human biomarker data. iPPS is available to patients through a Special Access Scheme in Australia, meaning acute and chronic anecdotal data is available during development. Paradigm does not sell iPPS for veterinary use, but the drug is approved for the treatment of osteoarthritis in dogs and horses (Australia) and is used off label in cats, meaning a wealth of animal data is available to the company. We believe this is broadly supportive of the investigation of iPPS in treating human kOA, however the comparison between animal and human data must be undertaken with care.

kOA programme presents multiple catalysts over CY23–25

To increase the likelihood of iPPS approval in OA, Paradigm has constructed a comprehensive late-stage clinical programme, which is supported by previous human clinical and real-world (from the Special Access Scheme programme) evidence and is intended to identify the acute and chronic clinical impact of the drug (Exhibit 1). As a result, we expect many share price catalysts over CY23–25. Paradigm is currently running a randomized, triple-blinded (investigator, patient, outcomes assessor) pivotal Phase III trial (PARA_OA_002), and a corresponding duration of treatment effect extension study (PARA_OA_006), which began in October 2022. Furthermore, the company intends to initiate a separate Phase III confirmatory trial (PARA_OA_003), which will also be followed by its own extension study (PARA_OA_007), in CY23. A separate retreatment trial (PARA_OA_009) is also planned, to assess the feasibility of multiple treatment regimens of iPPS. A Phase II biomarker study (PARA_OA_008), which met its primary endpoints in October 2022, is currently in the follow-up stage. In addition, the company is conducting supportive canine model studies and also plans a separate human study to investigate the possibility of effectiveness in hip OA (PARA_OA_010). In total, management expects this clinical programme could support an NDA filling with the US Food and Drug Administration (FDA) at end-CY25.

Exhibit 1: kOA development programme

Study	Objective	Key Milestone
002	NDA pivotal	DSMB Review Q4 2022, dose selection 1H CY2023
003	NDA confirmatory	First subject randomised 1H CY2023
006 / 007	Establish durability of effect	First subject enters 006 observational study 2H CY2022
008	DMOAD	Primary endpoint readout Q3 CY2022, 6-month MRI data Q1 CY2023
Canine study	DMOAD (equivalent to 3-year follow-up)	Data available Day 56 Q3 CY2022, 20-week follow-up 1H CY 2023
009	Retreatment	Timelines will be confirmed following dose selection
010	Establish safety and efficacy in hip OA	

Source: Paradigm Biopharma investor update August 2022

KOA has substantial unmet medical need

Osteoarthritis is a degenerative joint disease in which cartilage within a joint begins to break down causing considerable quality-of-life affecting symptoms such as pain, stiffness and decreased range of motion. The disease is common in individuals aged over 45 years of age; however, it can occur in younger populations. Osteoarthritis is highly prevalent and as of 2022, the US Centers for Disease Control and Prevention (CDC) estimates that over 32.5 million individuals in the United States are living with some form of the disease, a number that is expected to increase driven by an ageing population and rising obesity levels. As the knee is a highly weight-bearing and mechanically active joint, kOA is estimated to account for more than 80% of OA diagnoses.

With no disease-modifying osteoarthritis drugs (DMOADs) currently approved for the treatment of kOA, the market is dominated by symptomatic treatments for the pain and inflammation associated with the disease. Non-steroidal anti-inflammatory drugs (NSAIDs), analgesics (including opioids such as tramadol) and glucocorticoid injections are commonly prescribed for the treatment of kOA. However, each of these classes of drugs have problems associated with chronic usage (Exhibit 2) and only provide symptomatic treatment, meaning the underlying degenerative mechanisms are left untreated. Hence, there is a considerable unmet medical need for disease-modifying agents in OA.

Exhibit 2: Standards-of-care in kOA

Class	Examples	Limitations
NSAIDs	Ibuprofen, naproxen, imrecoxib, diclofenac, celecoxib	Side effects associated with chronic use include peptic ulcers, renal failure, risk of stroke and heart disease
Analgesics	Paracetamol, tramadol, prescription opioids	Opioid analgesics are addictive; patients may experience tolerance, dependence, and risk of overdose
Glucocorticoids	Cortisone, prednisone, triamcinolone	Side effects associated with chronic use can include weight gain, water retention, trouble sleeping and stomach irritation

Source: Edison Investment Research

Phase III development underway

Paradigm's clinical programme in kOA is in its later stages, following the first patient dosing in a pivotal, global, Phase III trial (PARA_OA_002, NCT04809376) in January 2022. The PARA_OA_002 trial is a two-stage, adaptive, randomised, double-blind, placebo-controlled study that will investigate the effect of PPS in participants with kOA pain. The trial is currently enrolling patients with moderate to severe kOA who have failed NSAID therapy in the United States (58 sites), Australia (8 sites) and UK (1 site). Following regulatory and ethical approval in July 2022 in Canada, management expects new European and Canadian sites to be activated from Q422. In stage 1 of the trial design (a Phase IIb dose selection portion) randomised kOA patients (expected n=468) will be receive once or twice weekly iPPS treatment for 39 days, and will be assessed over six weeks versus a placebo (sodium chloride solution) to confirm the lowest effective dose of subcutaneous iPPS. Stage 2 will then assess the efficacy of the selected stage 1 dose versus a placebo (expected n=470) after a 39-day treatment period and will be followed by an 18-week follow-up period (to day 168).

The primary endpoint for PARA_OA_002 is the change from baseline at day 56 in WOMAC score (Western Ontario and McMaster University Arthritis Index), a widely employed, self-administered questionnaire used to asses pain, stiffness and physical function. Based on the Osteoarthritis Research Society International Responder Index response rate criteria (OMERACT-OARSI, a more comprehensive set of patient reported OA measurements, which include WOMAC scores), we believe a reduction in WOMAC pain and/or function score of ≥50% would be significant here. Importantly, the company believes the primary endpoint measurement at day 56, following a 39-day treatment period, should increase the chance of observing a peak treatment effect. Secondary endpoints include longer-term and more detailed WOMAC assessments, and measures based on the more comprehensive OMERACT-OARSI response rate criteria, Patient Global Impression of Change (PGIC) assessment and overall quality of life improvement.

The company expects this combination of endpoints will provide broad data to support Zilosul's use in the treatment of kOA. The first data safety monitoring board review for PARA_OA_002 is expected to be reported in the fourth quarter of CY22, with stage 1 dose selection to follow in the first half of CY23. The company currently expects to report top-line data from PARA_OA_002 at end-CY24.

Chronic data important to support approval

To gather long-term treatment data, which given the chronic nature of OA we expect will be important to support the potential registration of iPPS, Paradigm is conducting PARA_OA_006 (NCT04814719), an extension of PARA_OA_002, for which the first patient was enrolled in October 2022. Patients who complete day 168 of the parent study (PARA_OA_002) will be eligible for enrolment into PARA_OA_006 (a 28-week follow-up study), to establish the duration of response out to 52 weeks from final treatment. A confirmatory Phase III trial (PARA_OA_003) will also be conducted, with a second follow-up study (PARA_OA_007) to assess durability. The company has yet to confirm details of the confirmatory study design, however we anticipate they will be similar to PARA_OA_002.

Paradigm also intends to initiate a separate retreatment study (PARA_OA_009), where iPPS treatment naïve participants will receive additional iPPS treatment rounds (twice weekly injections) for at clinically indicated intervals.

The endpoints in PARA_OA_006 are based largely on the assessment of OMERACT-OARSI response rate criteria, a set of pain and function measures used to assess patient responses in OA clinical trials. In contrast to WOMAC scores (which assess pain based on a specific activity) the OMERACT-OARSI response rate criteria have been developed using a data-driven approach and expert opinions to assess a more comprehensive evaluation of OA pain, regardless of function. Hence, we believe the incorporation of the OMERACT-OARSI criteria should provide more detailed

and relevant data to support iPPS's potential approval in kOA. OMERACT-OARSI response rates will be measured as secondary endpoints in PARA_OA_002. The primary endpoints in the PARA_OA_006 extension trial will measure the duration from initial patient response in PARA_OA_002 (based on the OMERACT-OARSI response rate criteria) over 52 weeks from the last treatment with iPPS in PARA_OA_002, which will demonstrate the duration of effect of iPPS. Secondary endpoints will provide OMERACT_OARSI response rate data, WOMAC pain and function scores, PGIC scores and Quality of Life assessment data. In addition, the company will continue to monitor joint structure by MRI and X-ray, important data for establishing disease modification. The company enrolled the first patient into PARA_OA_006 in October 2022.

Demonstrating disease-modification to the regulators

To prove an objective, disease-modifying profile to the regulators (which we expect would maximise the potential commercial impact of iPPS), we expect Paradigm will need to demonstrate not only a durable pain response (primary endpoints of PARA_OA_002/003 and accompanying extension studies) but clinically relevant narrowing of the knee joint space and reduction in bone marrow legion (BML) volume. To address this, the company has included a range of other X-ray and MRI-based outcome measures in its current Phase III clinical trials to measure joint space width, BML area, bone shape, cartilage volume and joint synovitis/effusion volume. In our view, this again demonstrates the comprehensiveness of Paradigm's OA programme and will provide the data points that may be helpful in demonstrating a disease modifying profile to the European Medicines Agency (EMA) and FDA, should iPPS reach registration.

Biomarker data supports use in kOA

The company's Phase III development programme in kOA is supported by recent biomarker data from its PARA_OA_008 Australian Phase IIb trial, which met its primary biomarker-based endpoints in October 2022. The main target of PARA_OA_008 was to assess the impact of iPPS treatment on synovial fluid biomarkers related to pain, inflammation and disease progression in kOA patients. Patients (n=61) 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 relevance of the assessed biomarkers in kOA is presented in Exhibit 3.

Exhibit 3: Synovial fluid biomarkers assessed in PARA_OA_008

Biomarker	Function	Relevance in kOA
Nerve growth factor (NGF)	Neuropeptide involved in the proliferation and survival of neurons	Mechanical stimuli in OA causes NGF release, resulting in pain. NGF pathway blockade has become an attractive target for the treatment of osteoarthritis-related pain
Tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6)	Cytokines involved in inflammation	TNFα expression is associated with progression of osteoarthritis although the mechanism of this is unknown. IL-6 is present in elevated levels in synovial fluid of OA patients, which may contribute to joint inflammation.
Cartilage oligomeric matrix protein (COMP) and a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5)	Enzymes that degrade extracellular matrix proteins, a crucial part of cartilage structure	Increased COMP and ADAMTS5 activity causes cartilage degradation in the joint. Overactivation of ADAMTS5 and COMP is correlated with disease progression in OA
Tissue inhibitor of metalloproteinases-1 (TIMP-1)	Inhibits the function of endogenous matrix metalloproteinases such as COMP and ADAMTS5. Can promote cell proliferation.	Increased TIMP-1 activity reduces COMP and ADAMTS5 mediated degradation of cartilage in the joint. May also promote tissue remodelling.

Source: Edison Investment Research, Ther Clin Risk Manag. 2017; 13: 951–956, Curr Opin Rheumatol. 2017, 29(1): 110–118, Exp Ther Med 2018, 16: 4737-4744, J Funct Morphol Kinesiol. 2017; 2(3): 27, Front. Mol. Biosci. 2021, 8:703110, Cartilage. 2021;13:1421S-1430.

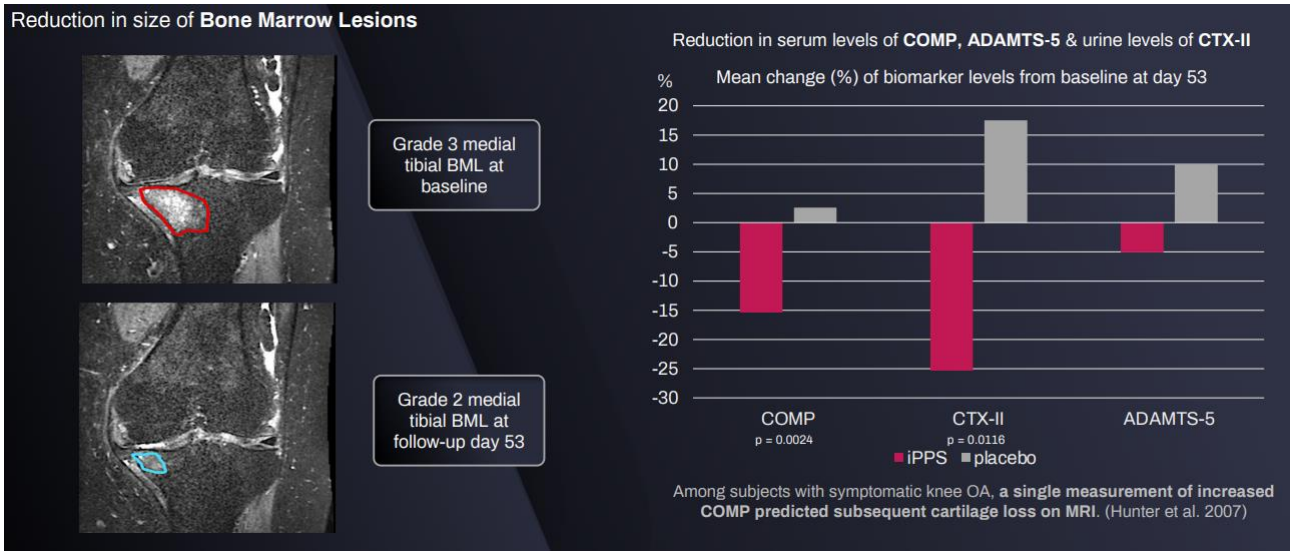
Top-line results from PARA_OA_008 demonstrated that treatment with iPPS reduced nerve growth factor (NGF), tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6) levels and reduced cartilage oligomeric matrix protein (COMP) and a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5) activity related by-products in the synovial fluid of kOA patients, with an accompanying increase in tissue inhibitor of metalloproteinases-1 (TIMP-1) activity. In addition, patient reported WOMAC scores in pain, function and stiffness showed statistically significant improvement for patients treated with twice weekly iPPS compared to the

placebo group. 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. Importantly, while full details on the top-line biomarker data are still to be reported, management has stated that the trial was not powered to show statistical significance; the fact that it has done so for patient WOMAC scores is encouraging support for iPPS's potentially disease modifying action in the treatment of kOA, in our view.

Patients enrolled in PARA_OA_008 are now in a 12-month follow-up phase and Paradigm expects to report six-month clinical outcome biomarker and MRI data from this in Q1 CY23. In our view, this six-month data will be key in establishing the durability of Zilosul's effect on joint structure, WOMAC pain and function scores and disease biomarkers and, if positive, could provide the company with additional data to approach the regulators with as evidence of iPPS's potential as a DMOAD.

PARA_OA_008 was conducted off the back of previously gathered Phase IIb data (PARA_OA_005), which showed that treatment with iPPS twice weekly caused significantly lowered serum levels of COMP, ADAMTS5 and CTX-II (a by-product of cartilage degradation), along with a reduction in the size of bone marrow legions at the knee joint (Exhibit 4). The drug's mechanism of action is further supported by canine model data in natural occurring OA, in which iPPS also reduced OA-associated biomarkers in the synovial fluid.

Exhibit 4: Previous Phase IIb biomarker data



Source: Paradigm Biopharma investor update October 2022

We see this data, in combination with that from PARA_OA_008 as supportive that iPPS could potentially have a disease modifying profile, due to the lowering of key biomarker levels that are associated with progressive kOA. In our opinion this is encouraging, particularly when viewed in combination with patient reported WOMAC scores. However, we note that Phase III long-term efficacy and safety data will be critical in defining the drug's full clinical utility.

Development in kOA supported by real-world data

Paradigm's clinical development endeavours in kOA are supported by real-world data gathered through the Australian Special Access Scheme (SAS) and FDA Expanded Access Program (EAP). kOA patients receiving iPPS as part of the SAS have consistently reported meaningful reductions in knee pain with twice weekly administration. In 2019, assessment of 205 SAS patients revealed an average reduction in pain scores (measured on a numerical pain rating scale) of 51.3% and an average improvement in knee function of 58.4% compared to pre-treatment status. In addition, a 2021 assessment of a further 89 SAS patients demonstrated a mean reduction in WOMAC pain scores of 49.6%. In the FDA EAP, an average 65% reduction in WOMAC pain scores was observed in a small set (n=10) of OA patients administered iPPS twice weekly for six weeks. While we see

the real-world data gathered by Paradigm as encouraging support for the company's development programme in kOA, we note that care must be taken when generalising the uncontrolled, unblinded, real-world observations to a clinical meaningful effect. Results from the Phase III programme will be crucial in corroborating this real-world data.

Considerable opportunity for disease-modifying agents

In 2021, the osteoarthritis drug market (of which kOA is a significant subset) was estimated to be worth US$1.82bn (EvaluatePharma), with the majority of sales being attributed to symptomatic treatments. Given the high prevalence and degenerative nature of kOA and the limitations associated with current symptomatic treatments, we believe there is an opportunity for DMOADs to significantly expand the kOA drug market size and garner considerable market share. Company research indicates iPPS could be priced at US$2,000–3,000 pa and receive reimbursement for the treatment of kOA pain and function in the United States. However, this price could rise to c US$6,000 if the drug can demonstrate of disease-modifying mechanism of action, management asserts. Hence, Paradigm believes the opportunity for iPPS in knee and hip OA could potentially be over US$10bn pa (based on 10% penetration of dissatisfied patients with knee and hip OA from a 72 million addressable market, at price of US$2,500 per year).

We view the potential for iPPS in kOA (and potentially other OA indications) as significant, especially if the drug can demonstrate a disease-modifying profile in Phase III. With relatively effective symptomatic treatments already established (NSAIDs, analgesics and steroids), much of the pipeline for the treatment of kOA is concerned with the development of the next generation of these drug classes. However, an increasing number of potential DMOADs are in late-stage development, presenting an increasingly competitive potential landscape for Paradigm and iPPS. Exhibit 5 presents a selection of possible DMOADs that we see as meaningful potential competitors for iPPS, if approved.

Exhibit 5: kOA DMOAD development pipeline

Drug	Company	Phase	Mechanism of action	Notes
Sprifermin	High Line Bio/Merck	Phase II	Recombinant human fibroblast growth factor-18 (FGF-18)	Results from 2020 Phase II FORWARD trial (NCT01919164) demonstrated a statistically significant increase in knee cartilage thickness in KOA patients (n=549) treated with sprifermin after 5-years (6-monthly treatments) and c 50% decrease in WOMAC pain scores in all treatment groups versus placebo. A further meta study of eight trials supports sprifermin's use in kOA. Merck out licensed sprifermin to TrialSpark in January 2022, forming High Line Bio. Estimated world-wide launch date end-2024 (EvaluatePharma).
Lorecivivint	Biosplice Therapeutics	Phase III	Dual CLK/DYRK-inhibitor	Post-hoc analysis of Phase IIb trial (NCT03122860) data showed significant improvement in pain in kOA patients treated with lorecivivint versus placebo (n=700) at 12 weeks. However, while efficacy signals were observed, Phase III development has so far missed clinical endpoints. Biosplice initiated a third Phase III trial in November 2022.
Invossa	Kolon TissueGene	Phase III	Allogenic TGF-β1 chondrocyte cell therapy	Phase IIb (NCT01221441) treatment groups showed improvement in multiple knee pain scores compared to placebo group, which was maintained up to one year. Currently recruiting for two pivotal Phase III trials (NCT03291470, NCT03203330).
LNA043	Novartis	Phase II	Modified, recombinant human angiopoietin-like 3 (ANGPTL3) protein	Randomised, placebo-controlled, double blinded Phase II trial (NCT03275064) showed treatment with LNA043 (4, weekly injections) caused regeneration of damaged knee cartilage. Two further Phase II trials are currently recruiting investigating LNA043's efficacy, safety and tolerability in kOA patients as a monotherapy (NCT04864392) and in combination with canakinumab (anti-IL-1β antibody, NCT04814368)

Source: Edison Investment Research, clinicaltrials.gov, company websites

From this landscape, we highlight sprifermin (High Line Bio/Merck) a recombinant human fibroblast growth factor 18 analogue that has demonstrated a potentially disease-modifying profile in human kOA. Data from the Phase II FORWARD trial showed that patients treated with sprifermin benefited from a statistically significant increase in knee cartilage thickness (+0.05mm) at three years versus a placebo, which was accompanied by a c 50% reduction in patient WOMAC scores. In addition, a further meta study of eight clinical trials demonstrated that patients receiving sprifermin injections gained more, and lost less, cartilage thickness in the knee versus placebo. As such, we believe sprifermin represent a significant potential DMOAD competitor in kOA, if it can objectively

demonstrate a disease-modifying profile and is approved in this indication. We note that many cell therapies are under investigation for the treatment of OA (see Invossa, Exhibit 5) and while these may offer a potentially curative approach, restrictive pricing and complex manufacturing are likely to limit their impact on the OA landscape, in our view. Hence, we do not view development of cell therapies in OA as a substantial commercial threat to iPPS.

Strategy for success in osteoarthritis

In April 2022, the company received Fast Track Designation (FTD) from the FDA for its Phase III OA programme. Paradigm has constructed a comprehensive development programme for iPPS in kOA, which management believes will clarify the drug's potential as a DMOAD and utility as a chronic kOA treatment. In addition, we believe the data generated by human and animal biomarker studies (PARA_OA_008 and canine models) may provide further support for iPPS's potential disease modifying mechanism of action to support the drug's registration. The well-studied use of iPPS as a veterinary treatment for OA provides support for the drug's utility, in our view; however, the usual caveats associated with generalising animal data to humans apply.

Key to regulatory and commercial success in kOA, in our view, will be the demonstration of durable and statistically significant reductions in patient reported WOMAC scores (a ≥ 50% decrease if reported would likely be significant, in our view) and improvements in patient quality of life measures in global Phase III trials (PARA_OA_002 and PARA_OA_006). We note that in the current clinical programme, iPPS is administered by the relevant clinician. However, a focus on self-administration will be important post-commercialisation to expand the market impact.

If the company can demonstrate a disease modifying mechanism of action, we believe iPPS could be an attractive target for a commercialisation deal. Paradigm does not intend to commercialise iPPS in kOA itself and management is already actively pursuing a global development/commercialisation deal for the drug. Management has engaged two business development consultants to secure a global partnership and is open to partnering at any stage. However, we believe potential partners would likely require positive data from randomised Phase III trials (PARA_OA_002) before seriously engaging in partnership discussions. Licensing activity in OA has been limited over the last decade, likely due overcrowding of the development pipeline with symptomatic treatments and the difficulties associated with developing disease-modifying drugs. However, given the market potential for DMOADs in OA, we believe that iPPS could gain significant attention from large, global commercialisation partners, if data from Phase III are positive.

A new indication for iPPS: MPS-I and MPS-VI

In addition to the company's kOA development programme, Paradigm is also investigating the use of iPPS as an adjunctive therapy for the treatment of MPS types I and VI (MPS-I and MPS-VI), rare genetic lysosomal storage diseases (the prevalence of all MPS types in the United States is estimated at 2.67 per one million people). MPS has seven distinct types, which are characterised by genetic deficiencies in different enzymes involved in the breakdown of glycosaminoglycans, important molecules involved in the formation of bone, cartilage and connective tissues. Depending on the type, MPS symptoms can vary from mild to severe. However, similar groups of clinical features are present across types, with abnormalities normally beginning to develop in infancy or later childhood. Common complications associated with MPS types include:

- central nervous system disease,
- cardiovascular disease,
- pulmonary disease,
- ophthalmological disease,
- hearing impairment, and
- musculoskeletal disease.

Of the common symptoms mentioned above, musculoskeletal disease is observed in all but one MPS types (the exception being MPS-IS), with joint stiffness being a common complication. Currently, treatment options for MPS revolve around separate surgical interventions (eg valve replacement surgery for cardiovascular disease), enzyme replacement therapy and bone marrow transplants. Despite these treatment options, patients with MPS-I and MPS-VI still experience bone and joint problems, chronic pain and physical disability, and while the types (and severity) of MPS come with varying prognoses, most patients have a shortened life expectancy, with some dying in infancy. Management believes MPS-1 and MPS-6 are indications where the company may be able to leverage the apparent anti-arthritic effects seen in the kOA programme to reduce pain, increase function and improve quality of life in these patients.

iPPS in Phase II trials for MPS-I and MPS-VI

To investigate iPPS's utility in the treatment of MPS-I and MPS-VI, Paradigm entered into an exclusive license agreement with bene pharmaChem (the only FDA approved manufacturer of PPS) to investigate the use of iPPS in the treatment of MPS (in addition to other lysosomal storage diseases). The company has received orphan drug designation for iPPS in MSP-I and -VI in the United States and EU, allowing an expedited regulatory process and up to seven years market exclusivity provided it is approved in the United States.

Paradigm initiated an open-label, single-centre, Australian Phase II pilot study in 2020, investigating the safety and efficacy of once-weekly or twice-weekly administration of iPPS in patients over the age of five years who have previously received enzyme replacement or bone marrow transplant. Interim results, reported in November 2021, demonstrated an overall trend in three patients (target enrolment n=10) towards improvement in pain, function and quality of life at week 25, supported by a range of positive patient reported outcomes. The trial is currently ongoing and clinical data will be presented at the International Conference on Lysosomal Disorders in February 2023. iPPS is also being investigated in MPS-VI in a double-blinded, randomised, placebo-controlled Brazilian Phase II trial, which is similar to the trial in MPS-I and is assessing the safety and efficacy of weekly iPPS for 24 weeks (target enrolment n=12). Interestingly, Brazil has one of the highest prevalence rates of MPS-VI worldwide, which has led to relatively quick patient enrolment in this trial. As of August 2022, 50% of patients had been enrolled and the remaining patients potentially identified.

Opportunity in MPS

According to Paradigm, the global market value for MPS-I and -VI treatments in 2021 was US$434m (expected by the company to grow to c US$828m by 2027) and US$432m (which it expects to grow to c US$708m by 2027), respectively. We note, however, that these figures include very costly enzyme replacement and stem-cell therapies. In our view it is unlikely that iPPS would be able to substitute treatments of this type, suggesting the addressable market for Paradigm in these indications is smaller than the (estimated) global market size implies. We therefore see the market opportunity in MPS-I and MPS-VI as modest relative to kOA. However, depending on the results seen in kOA, iPPS may be able offer important quality of life improvements for patients, if approved, which may result in incremental revenues for Paradigm. Nevertheless, the MPS programme will provide the company with further, important data concerning iPPS's utility in treating bone and joint related pain and inflammation.

Paradigm protected by IP estate

Despite PPS being a generic medicine, there is only one FDA-approved manufacturer of the drug: the German pharmaceutical company bene pharmaChem (bene). Paradigm has negotiated an exclusive global supply and manufacture agreement for multiple indications with bene that will last for 25 years post approval of iPPS. Bene maintains that the manufacture and composition of PPS is a tightly held trade secret that the company has possessed for over 60 years. We therefore believe the threat of generic competition is somewhat mitigated as a potential generic manufacturer would

be required by the FDA to produce identical formulation data to the bene product, which given the secretive manufacture process for, and complex structure and formulation of PPS, would require significant time and resources, in our view. If a competitor cannot demonstrate an identical molecular fingerprint to the bene PPS, a full clinical development programme would be required.

Additionally, Paradigm possesses patents for the use of iPPS in OA and MPS (among other indications) with a minimum life of existing patents to 2030 and new patents to 2043. We note that method of use patents, while providing some security, are not as protective as composition of matter patents. Management continues to pursue new patent protection for iPPS in new potential indications and formulations. The company's primary and foundational patents concern the use of PPS to treat bone marrow oedema (BME) in the United States and several other jurisdictions, a commonly associated pathology in painful knee OA. Further, these patents are designed to protect Paradigm from the generic use of PPS to treat knee OA in the absence of BME.

The IP suite and commitments Paradigm has built around iPPS are a useful asset in our view, making the potential for direct competition with another form of PPS unlikely. We believe the considerable length of the manufacture and supply agreement with bene (25 years post approval) will help protect the commercial opportunity for Paradigm, should iPPS be approved in kOA.

Sensitivities

As a pureplay biotech, Paradigm is subject to all the regular sensitivities associated with drug research and development. The company's prospects may be affected by development delays or failures, regulatory risks, competitor successes, partnering setbacks and financing risks. As Paradigm is focused on the repurposing of iPPS, a well-studied drug with a known safety profile in oral use, we believe this lowers the company's development risk somewhat. While iPPS is approved for use in animals for the treatment of kOA, industry efforts so far have failed to produce effective DMOADs for use in humans. Failure to demonstrate an effective profile in kOA for iPPS in Phase III trials represents a significant near-/medium-term risk, in our view, and may affect the company's prospects of finding a commercialisation partner.

Paradigm does not generate any revenues from its drug discovery and development operations and as the company advances through several large Phase III clinical trials, expenses are expected to increase significantly. Consequently, the company will require additional capital to fund its development objectives. Management's estimated cash runway will fund the company into 2024, and it will need to raise additional funds to complete the planned iPPS Phase III trial programme. Capital could be raised through an equity offering, which could result in significant dilution of existing shareholders.

Financials

As a late-stage clinical development company, Paradigm is yet to generate a recurring revenue stream. However, current cash inflow comprises revenue generated through the TGA approved Special Access Scheme (A$0.08m in FY22) and R&D tax incentives (A$8.7m in FY22). Given the high development cost involved in its key clinical programmes (PARA_OA_002 and PARA_OA_008), R&D expenditure constitutes over 80% of the total operating expenses, resulting in a high operating cash burn of A$32.2m and A$34.9m in FY22 and FY21, respectively. R&D expenditure was up 16.4% (y-o-y) in FY22 to A$39.0m, primarily due to initiation of the Phase III trial (PARA_OA_002) across 58 sites, following US FDA approval of its IND application, along with increased expenses relating to PARA_OA_008 and canine model studies. Accordingly, the company reported a Q123 cash burn of A$10.0m (unaudited, Appendix 4C), a 58% increase from the same period 12 months prior (Q122 cash burn: A$6.3m).

Paradigm has historically raised funds by issuing share capital, which is dilutive in nature, but a true testament of investor confidence in the company's development programmes. The cash balance at end-September 2022 stood at A$92.4m (A$39.7m at end FY22), supported by a capital raise of A$66m in August 2022 through existing as well as new institutional investors (both in domestic and international markets). The net loss for FY22 stood at A$39.2m, 14.4% y-o-y higher than FY21. As the company progresses through the clinical development of Zilosul, followed by the commercialization process if the above is successful, management expects a higher net loss in the near future. Considering the current run-rate and recent equity financing, management estimates that the company has a cash runway until CY24.

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