PITT STREET RESEARCH

Paradigm Biopharmaceuticals

A legitimate osteoarthritis solution

Share Price: A$0.23

ASX: PAR

Sector: Biotechnology

6 September 2024

Paradigm Biopharmaceuticals is an ASX-listed drug development company. Paradigm's flagship asset is Zilosul, an injectable form of pentosan polysulfate sodium (PPS). Zilosul is a non-opioid, anti-inflammatory drug that Paradigm is seeking to use to treat multiple indications, most particularly osteoarthritis. Zilosul is in Phase 3 for osteoarthritis having passed multiple Phase 2 trials. The drug has been Fast Tracked by the FDA and has the opportunity for expedited approval in Australia through TGA Provisional Approval.

Zilosul is a proven upgrade over existing treatments

At first glance, given the abundance of drugs available to people suffering from osteoarthritis, investors may be forgiven for believing the company is going after an established, saturated market and therefore cannot disrupt it. However, this is not the case. The vast majority of treatment options available for osteoarthritis require frequent administration and/or suffer reduced effectiveness over time. Many of them can be opioid-based and cause side-effects not just harmful to individual patients but to society as a whole. Paradigm has an enormous market facing it, and even if the company takes a small share, it could be highly lucrative.

Pivotal clinical results aren't far away

Paradigm is expecting interim results from the next stage of its Phase 3 OA program, the PARA_OA_012 Phase 3 trial in CY25/26. Thereafter, the company has potential to apply for accelerated regulatory approval and could commercialise Zilosul within less than 3 years from today. Even prior to regulatory approval, we see upside in the company that could result from potential licensing deals for Zilosul as well as clinical progress against other indications the company is targeting, particularly Mucopolysaccharidosis (MPS).

Valuation range of A$0.76-1.06 per share

We value Paradigm Biopharmaceuticals at A$0.76 per share in our base case scenario and A$1.06 per share in our optimistic (or bull) case scenario. We believe Paradigm can re-rate if the current clinical trial is a success and the company can subsequently commercialise the drug. Other catalysts include potential licensing deals which could be sealed even prior to the release of clinical trial results. Please see p.24 for the key risks associated with our investment thesis.

Market cap. (A$ m)	69.0
# shares outstanding (m)	299.8
# shares fully diluted (m)	361.7
Market cap ful. dil. (A$ m)	83.2
Free float	100%
52-week high/low (A$)	0.745/0.22
Avg. 12M daily volume ('1000)	716.1
Website	paradigmbiopharma.com

Source: Company, Pitt Street Research

Share price (A$) and avg. daily volume (k, r.h.s.)

Source: Refinitiv Eikon, Pitt Street Research

Valuation metrics	
DCF fair valuation range (A$)	0.76-1.06
WACC	14.9%
Assumed terminal growth rate	2%

Source: Pitt Street Research

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Introduction to Paradigm Biopharmaceuticals (ASX:PAR)

Paradigm Biopharmaceuticals is developing Zilosul, a repurposed injectable form of pentosan polysulfate sodium (PPS).

Paradigm Biopharmaceuticals is developing Zilosul, a repurposed injectable form of pentosan polysulfate sodium (PPS), to address unmet medical needs.

The indication Zilosul is most advanced against is osteoarthritis, a condition that has an addressable population of over 72m in identified key markets[1]. Accordingly, osteoarthritis will be the key focus of this report, although Paradigm's endeavours against other indications (particularly MPS) are addressed in its own sections.

Ten key reasons for investors to look at Paradigm Biopharmaceuticals

1) **Paradigm has a drug with blockbuster potential.** In the osteoarthritis market, Paradigm serves an important market that is lucrative enough as it is currently, but is only expected to grow further in the years to come. There are varying estimates of how large the market is, although the CDC estimates that over 30 million people suffer from osteoarthritis in the US alone, representing about 60% of people who suffer from arthritis generally. Applying a similar logic to Australia, where 3.7 million suffer from arthritis generally, this would indicate there are over 2 million sufferers in Australia. There are several other lucrative markets including in China where there are at least 100 million people with osteoarthritis.
2) **iPPS has a proven track record of treating pain, spanning several decades**. The drug has a 60-year track record of treating pain, inflammation and thrombosis. There is also extensive clinical evidence gathered by Paradigm first hand (i.e. in several hundred patients) that iPPS can work against osteoarthritis. By that term we do not just mean the pain is relieved, but the underlying condition is treated first hand. In one Phase 2 clinical trial (PARA_008), subjects treated with 2 SC injections of iPPS a week for 6 weeks, at 6 months post treatment demonstrated positive structural improvements in the knee, including reduced synovitis, reduced bone marrow edema lesions, reduced osteophyte formation and increased cartilage thickness.
3) **Zilosul fills an urgent need for osteoarthritis treatments.** Any 'treatments' that exist are only about addressing the pain or other symptoms rather causing a cure or remission. These treatments tend to need frequent administration or lose effectiveness over time. This is particularly true with opioid medications, an increasingly popular resort turned to by patients. Zilosul does not just make the brain forget temporarily that the body has osteoarthritis, which is essentially all opioid medications do in regard to osteoarthritis. Zilosul goes further and downgrades or inhibits cartilage degrading enzymes.
4) **The company is at a late stage with Zilosul, amidst a pivotal clinical trial that could enable its regulatory approval.** Paradigm is in the middle of a pivotal Phase 3 trial that could deliver results toward the end of CY25. The company plans to submit to the FDA 6 months afterwards, and this could see Zilosul given regulatory approval by the FDA in CY27. Zilosul could even be approved in Australia earlier than that where it will also undergo a fast-tracked progress. The company is currently finalising a TGA provisional approval determination for submission, based off already

[1] This includes the US, EU5, Canada and Australia altogether and was estimated by the Institute for Health and Metrics Evaluation at the University of Washington.

completed clinical trials and feedback could be received in a matter of weeks from now (during August 2024).

5) **There's potential for a quicker market penetration** with the prospect of provisional approval in Australia and accelerated approval in the USA. This is not just because Paradigm is eligible to do so and pursuing these pathways that would enable a faster path to the market, but also because the company is operationally ready. It has commercial scale manufacturing capabilities, and worked closely with the original manufacturers of Zilosul - building upon the substantial knowledge and expertise available from earlier regulatory filings.
6) **Once Zilosul is approved, there'll be a significant degree of protection.** Paradigm has an exclusive 25-year supply agreement with bene parmaChem, the only manufacturer of PPS worldwide (which is FDA approved in humans), as well as multiple method of use patents that are continually being refined, as well as a molecular platform technology and complicated trade-secret manufacturing process that would be very difficult to replicate.
7) **Other indications represent further opportunity for the creation of shareholder value** including MPS, Alphavirus induced arthralgia, acute respiratory distress syndrome and Heart failure. Of these indications, Paradigm is most advanced with respect to MPS where it has completed multiple Phase II studies with iPPS. Paradigm is seeking a commercial partner for its MPS program. Alphavirus induced arthritis is another opportunity.
8) **Paradigm has a quality leadership team** led by Paul Rennie who founded the company, has headed the company since listing and advanced it to the present stage of a pivotal clinical trial. His supporting cast on the board has a diverse set of skills and experience in the biotech sector and in business generally. We have every confidence that the company's leadership can guide it over the coming months and years towards the eventual goal of regulatory approval for iPPS/Zilosul.
9) **Paradigm is in a secure funding position.** The most recent capital raising, completed in November 2023, is projected to be sufficient through to the end of CY24 with options to be exercised by the end of November providing further runway to the middle of CY25, even without additional licensing revenue. The company closed the March quarter of CY23 with A$26.2m in funding.
10) **We believe Paradigm is undervalued** at its current market value. We have valued Paradigm at $227.9m in our base case and $318.2m in our bull case. These figures equate to A$0.76 per share in our base case and A$1.06 per share in our bull case, based on 299.8m shares outstanding. Our report will outline why we believe the company can re-rate, the potential catalysts that could lead to this and when they might happen.

Paradigm and Zilosul

In this section we recap:

- The history of Zilosul,
- How Paradigm reached the point it has now including its data from clinical trials conducted and concluded up until now,
- The current clinical trials that are proceeding at the present time (PARA_OA_002 & PARA_OA_003), and
- What will happen if and when Zilosul passes the trials.

In the next section of the report, we will delve into the market opportunity Paradigm has against osteoarthritis and how Zilosul is superior to existing 'treatment' options. But first, we briefly address how Paradigm has been advantaged compared to its peers (from operational and investor perspectives) by repurposing a drug rather than using an entirely new formulation of its own.

The strategy of repurposing a drug

Repurposed drugs tend to have well-established safety data and sometimes efficacy data in other conditions.

One of Paradigm's selling points from an investor perspective has always been its push to obtain approval for a repurposed drug, rather than one of its own. This was pursued by Paradigm for the several advantages it would derive including the higher likelihood of success, quicker path to market and potentially lower costs. Repurposed drugs tend to have well-established safety data and sometimes efficacy data in other conditions – although in other cases, repurposing occurs because the drug is not as effective as hoped against the initial condition (with one famous example being the erectile dysfunction drug Viagra which was initially developed for hypertension and angina[2]).

Nonetheless, the path of repurposing a drug is not always smooth sailing. Companies need to identify the right therapeutic area or condition for the drug and decide where abouts to start the process (in other words, what phase of the clinical trial process). And there is the risk that regulators may not find old data satisfactory. These were not challenges that Paradigm faced given the drug's long use history and existing data.

How repurposing a drug works in the USA

For the purposes of regulatory approval in the USA, there is a specific pathway - 505(b)(2), named after the specific section of the Food, Drug and Cosmetic Act. While the FDA still requires the same information required for any drug with a regulatory case before it, the 505(b)(2) pathway allows for some information to come from studies not conducted by or for the applicant. The conventional application - 505(b)(1) – requires data to be obtained from studies conducted by the applicant or sponsor. Inevitably, in allowing the hard work done by others to count in the same way as if the company had done so itself, the duration to market is faster assuming the data is positive and there are no other issues in the clinical trial.

How repurposing a drug works in Australia

There is a similar process in Australia that Paradigm is undertaking, called the provisional approval pathway. It provides a time-limited registration on the

[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9945820

Australian Register of Therapeutic Goods (ARTG), a registration that automatically lapses at the end of that time which is limited to six years. The pathway is open to new prescription medicines or for already registered prescription medicines that a company is seeking to use for a new indication.

A party submitting under this pathway will need to submit more comprehensive data at a later date to obtain full registration. Accordingly, when the company pursues the provisional approval pathway, it will need to submit evidence of a plan to submit this necessary data down the track. For Paradigm, this data would inevitably be from the PARA_OA_002 and PARA_OA_003 clinical trials which would most likely be complete well before any 'deadline'. This pathway was introduced as part of the Turnbull government's response to the Review of Medicines and Medical Devices Regulation (MMDR review) and the TGA estimated that such medicines could reach the market up to two years sooner than the current framework[3].

Zilosul/PPS

The term Zilosul alludes to Paradigm's specific proprietary formulation of PPS.

PPS is a heterogeneous semi-synthetic drug manufactured from European beech-wood hemicelluloses (in other words, from the bark of beech trees) by sulphate esterification. The term Zilosul alludes to Paradigm's specific proprietary formulation of PPS. Paradigm has commonly alluded to PPS as iPPS because its particular form of PPS is injectable, although the term iPPS will not be used any further to avoid confusion and also because PPS has the same Method of Action regardless of how it is administered.

PPS' primary use (at least in Europe) has been to treat and prevent blood clots. PPS had been FDA approved for interstitial cystitis (a bladder inflammation condition) as well as in Australia under the brand name Elmiron, by the Johnson & Johnson subsidiary Janssen Pharmaceuticals. It is important to note this was only when administered orally as opposed to being administered by way of injection. Additionally, PPS has been used in veterinary practices to treat inflammatory issues in the joints of animals, for over 20 years.

Nonetheless, an advantage Paradigm has was that it worked closely with the proprietary manufacturer of PPS (Germany's Bene Parmachem), building upon the substantial knowledge and expertise available from earlier regulatory filings, including accumulated safety data, manufacturing 'know how', and extensive published information about PPS's mechanisms of action. In fact, Paradigm has an exclusive supply deal signed in 2020 as a 25-year deal. Although all patents covering the oral formulation expired some years ago, no generic competition has been formulated since then, likely because of the complexity involved in manufacturing it.

PPS works against osteoarthritis by blocking or inhibiting cartilage degrading enzymes.

How does PPS work against osteoarthritis? Simply put, PPS blocks or inhibits cartilage-degrading enzymes. These include ADAMTS-4, ADAMTS-5a MMP-13 and MMP-3b. In so doing, PPS prevents further cartilage damage, reduces signs and symptoms of osteoarthritis and increases blood flow. PPS shares structural similarities with glycosaminoglycans (GAGs) and heparin, which are carbohydrates with an immunomodulatory role in the body, via interactions with proteins involved with inflammation. Additionally, PPS is a broad acting anti-inflammatory known to reduce the inflammatory cytokines of TNF alpha, IL-1 and IL-6.

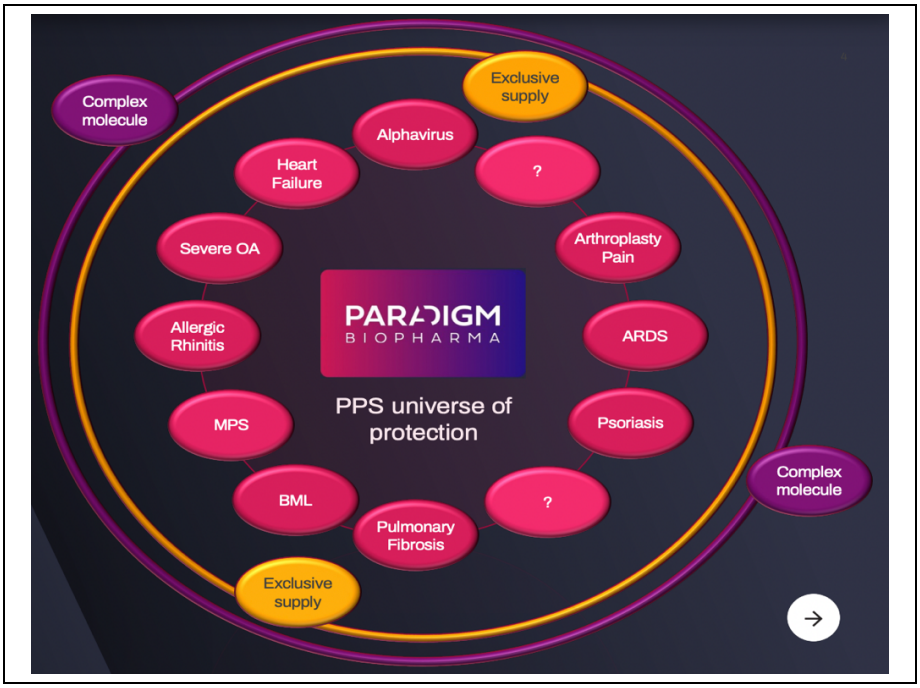
[3] https://www.tga.gov.au/provisional-approval-pathway-prescription-medicines

Paradigm's protections for PPS include an exclusive 25-year supply agreement with Bene ParmaChem and multiple method of use patents.

What protection does Paradigm have for PPS? Beyond the exclusive 25-year supply agreement with bene parmaChem, the company also has:

- Multiple method of use patents that are continually being refined and expanded,
- A molecular platform technology and complicated trade-secret manufacturing process that would be very difficult to replicate; and
- Growing evidence that PPS can work against other conditions, meaning the company won't necessarily fall over if the current clinical trial fails and/or the company is unable to penetrate the market even if given FDA approval (Figure 1).

Figure 1: Paradigm's defensive 'moat' with PPS



Source: Company

How Paradigm reached the current point

Paradigm listed in mid-2015, raising $8m in an IPO that valued the company at ~$30.6m. In listing, it sought to fund a Phase II trial of PPS, specifically against Bone Marrow Edema (BME), a condition where fluid builds up in the bone marrow following acute knee injuries, and against respiratory disease Allergic Rhinitis (AR). Both BME and AR are conditions involving inflammatory pathways and where current therapeutics were sub-optimal. A Phase 2 study for BME began in March 2016 and it closed out in October 2017. The subjects of the trial were experiencing BME as a consequence of ACL injuries. It also briefly pursued PPS against hay fever, although this failed due to the delivery system and therefore won't be mentioned further.

Paradigm commenced another Phase 2 for Bone Marrow Edema, but in people with Osteoarthritis, which read out in the last quarter of CY18. This trial was a success, with the primary endpoint (namely a reduction in pain from the baseline) successfully met.

Paradigm also conducted other programs including:

- A treatment program under the TGA's Special Access Scheme (SAS) with knee osteoarthritis. The program found a 50% reduction in pain, compared to just a 15% average pain reduction score using opioid treatments.
- Ten former NFL footballers were treated under US Expanded Access Program where patients experienced an average 65% reduction in pain. These results led to the company entering a formal research partnership with NFL Alumni Health in July 2022 to inform NFL Alumni members about osteoarthritis and potential clinical trial participation.
- Paradigm also successfully completed a Phase 2 clinical trial in people with an alpha-virus infection (Ross River virus) which when untreated leads to debilitating pain and cartilage loss.

The company then moved towards another Phase 2 trial in osteoarthritis, although it took some time to commence this given COVID-19 delays.

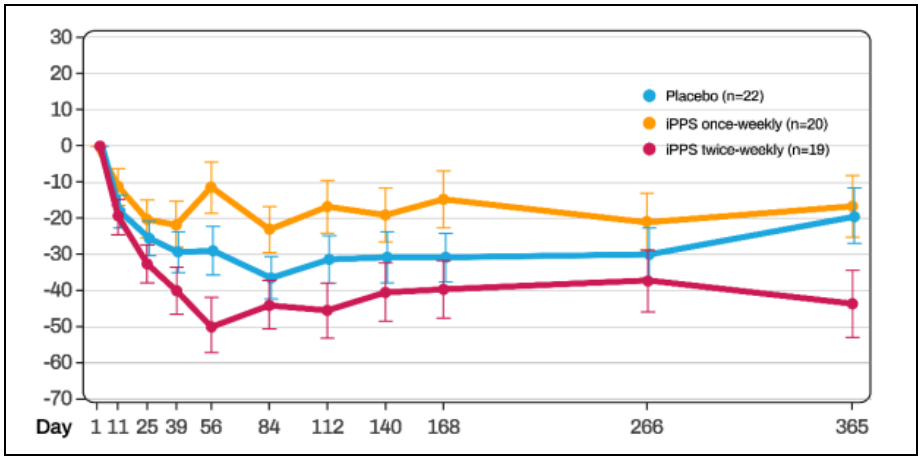
PARA_OA_008 (Phase II)

Paradigm's protections for PPS include an exclusive 25-year supply agreement with Bene Parmachem and multiple method of use patents.

PARA_OA_008 kicked off in mid-2021. Its objective was to evaluate biomarkers in the blood and synovial fluid as indicators of the Mechanism of Action (MOA) of PPS in knee OA. In October 2022, Paradigm released the results and PPS passed the trial with flying colours. The primary endpoint – a change in one or more synovial fluid biomarkers associated with osteoarthritis disease progression – was achieved at Day 56 and at Day 168. The other endpoint was also achieved, which was structural changes in the knee as determined by MRI.

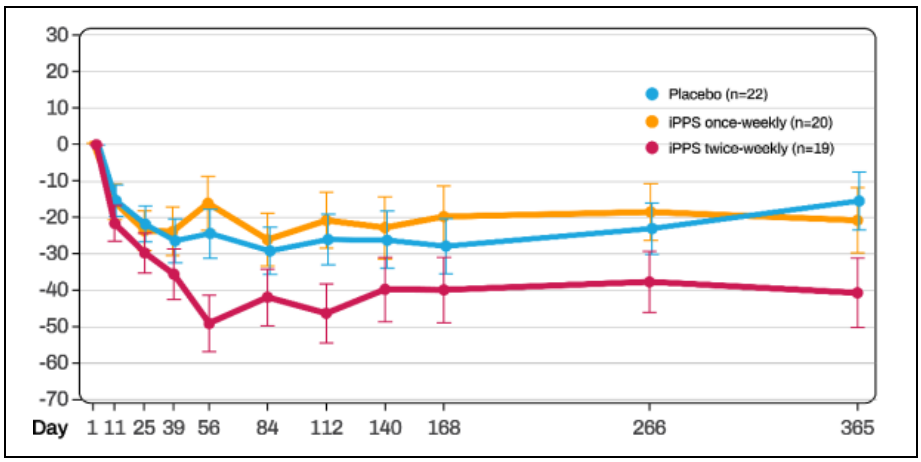
Beyond those two objective data measures, subjective data measures were achieved as well. Figures 2 and 3 depict the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scores from the trial, which showed similar improvement compared to the placebo, including an ongoing impact over several months, especially when dosage was twice weekly. Specifically, 73% saw a 30% or greater improvement in pain, whilst 60% saw 50% or greater. There were no serious adverse events, or adverse events of special interest.

Figure 2: Pain perception in the PARA_OA_008 trial (y axis is WOMAC scores)



Source: Company

Figure 3: Function perception in the PARA_OA_008 trial (y axis is WOMAC scores)



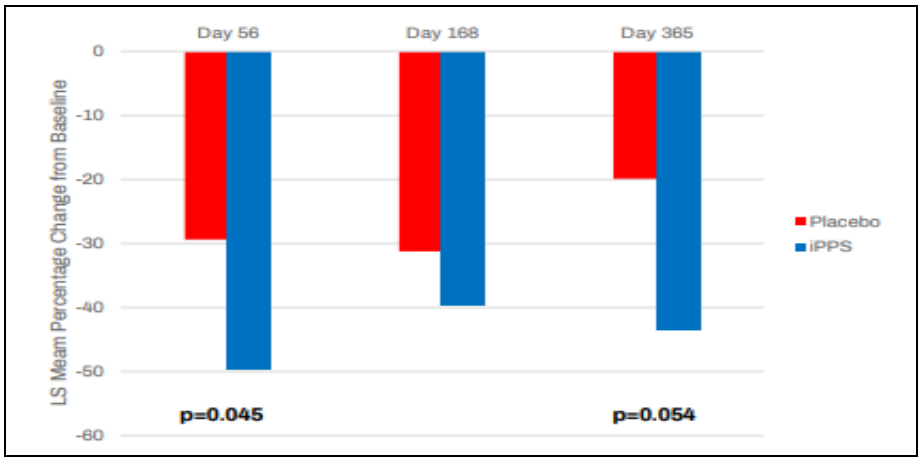
Source: Company

Although there were only 20 patients in each of the three arms of the study, the result was statistically significant - i.e. the p value at Day 56 for WOMAC pain was 0.45. If replicated on an enrolment of several hundred, the result would almost certainly have been statistically significant. Concurrently, Paradigm conducted a trial in dogs with naturally occurring osteoarthritis and this study also showed positive times, with 7/9 dogs treated having a clinically meaningful improvement in affected limbs.

Clinical data has shown that pain relief was sustained over time (i.e. 12 months instead of 6 months).

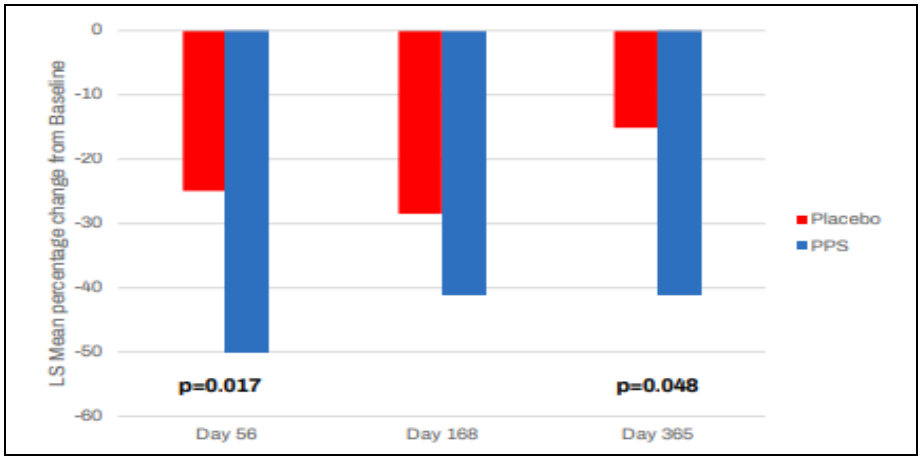
In April 2023, Paradigm released 168-day data, while 365-day data came in October 2023 (Figures 4 and 5). Data at day 365 showed pain relief was sustained over time (i.e. 12 months instead of 6 months), a duration not seen in any other drugs. Looking across the entire cohort, patients on placebo reported that they had far less pain relief (33% of placebo patients reported pain). 55% of patients receiving Zilosul reported pain relief, comparing to 33% of patients with the placebo drug *receiving* pain relief.

Figure 4: Change in WOMAC pain at days 56, 168 and 365 from baseline



Source: Company

Figure 5: Change in WOMAC function at days 56, 168 and 365 from baseline



Source: Company

Moreover, Zilosul also resulted in an improvement in the cartilage – we're not talking a mere prevention of further damage, but an improvement in cartilage thickness and volume. Specifically:

- Cartilage thickness increased by 0.17mm whilst the placebo showed an 0.09mm decrease.
- Overall cartilage volume increased by 1.9% whilst the placebo group saw a volume decrease of 1.58%.
- A resolution or decrease in bone marrow lesions volume by 17% for Zilosul, whilst placebo subjects suffered a 2% increase, and
- Reduced area and intensity by 1% of synovitis in the Zilosul group compared with a 4% increase in placebo.

Zilosul is not just pain relief, it regenerates joint tissues in a way that existing treatments do not.

Evidently Zilosul is not just another form short-term pain relief, or even longer-term pain relief (although of course it does relieve pain). **It regenerates joint tissues in a way that existing treatments do not.**

PARA_OA_002 (Phase III)

The company is undertaking a Phase 3 trial – PARA_OA_002

Paradigm is now undertaking a Phase 3 trial - PARA_OA_002. The company was given regulatory approvals to conduct the study in the USA, Australia, the UK and Canada in the first half of 2022.

PARA_OA_002 was planned with two stages, first a dose selection for the next step of PARA_OA_002. In the second stage, dosage will be administered, as determined in the first stage.

The **First Stage of PARA_OA_002** is now complete. It involved a 6-week treatment with 4 different dosages as follows:

- 1.5mg/kg SC twice weekly for 6 weeks
- 2mg/kg SC one weekly + placebo for 6 weeks
- Weight-dependant fixed Dose SC once weekly[4] + Placebo for 6 weeks
- Placebo SC twice weekly for 6 weeks

Each of these 'arms' of the study had roughly the same number of patients under each – 117. Regulatory authorities requested that the minimal effective

[4] 100mg PPS if <65kg, 150mg if between 65kg and 90kg and 180mg if above 90kg

dose be identified. The company opted for the second of those four options: 2mg/kg twice weekly, a step that required a change to the study's protocol. This was not just because lower dose regimens did not demonstrate a material efficacy vs placebo, but the higher one did – according to 12-month data from PAR_OA_008 – although that had been initially excluded in order to determine the lowest efficacious dose.

Judging by the share price performance of the company, some investors were concerned about the drug's efficacy and that the clinical and regulatory processes may take further time because the protocol would need to be amended. However, the company will not need to perform additional toxicity or efficacy study because there is existing data on this dosage. And most importantly, the objective of determining the lowest efficacious dose was reached.

The **Second Stage of PARA_OA_002** will see administration of that dosage with 235 patients receiving the chosen regimen and 235 receiving placebo. The primary endpoint in the trial is the change from baseline at Day 56 in the standardised WOMAC pain questionnaire. Secondary outcomes will include change from baseline at multiple time points out to day 168 in WOMAC, as well as Patient Global Impression of Change (PGIC) and Quality of Life (QoL) assessments. It is likely that the number of patients enrolled will be around 600.

Paradigm has finalised and submitted the study protocol to the FDA, justifying the dosage. Subject to FDA clearance, Paradigm intends to commence subject enrolment in the second half of this calendar year. Clinical trial sites in Australia and the USA are planned to commence preparation activities during the June quarter of CY24 to ensure the program can proceed as quickly and efficiently as possible.

The next steps

Results from the trial are expected in the first half of CY25.

Subject to the next phase of the Phase 3 proceeding, the new study PARA_OA_012 expects first results toward the end of CY25 (subject to recruitment rate), given it will be initially testing at the 56-day mark. The company plans to submit to the FDA following the conclusion of the pivotal and confirmatory trial completion in CY26. Thereafter, the FDA could take up to 9 months to give an answer. In our valuation model, we have assumed that Paradigm obtains approval within those time frames and is able to enter the market in FY27 (the year starting 1 July 2026-30 June 2027). Even while the current trial is ongoing, Paradigm has been working with the FDA to ensure that the program can continue, including justification for the current dosing regimen compared to others that have been used. Feedback from the FDA is expected during the September quarter of CY24 on the company's dosage plans.

In our view, it is plausible that regulatory approval in Australia could be achieved ahead of the US. PAR has made a TGA provisional approval determination application, including outcomes from the PARA_OA_008 trial and a manuscript providing a comparison of PPS clinical data with other available treatments for osteoarthritis. PAR is expecting results in a matter of weeks (during August CY24). Should the determination application be positive, PAR will prepare a full dossier submission for TGA provisional approval marketing authorisation, on the basis of existing clinical data (i.e. just Phase 2 data and not Phase 3). The deadline to make the full submission to the TGA is 6 months from provisional approval, and the TGA has a maximum timeline of 220 business days to make a response.

Osteoarthritis

People suffering from osteoarthritis have their cartilage breaking down which can cause pain, swelling and problems moving the joint.

Osteoarthritis is a degenerative joint disease, impacting the tissue known as cartilage in the joints. Cartilage acts as a kind of shield between the bones and provides a smooth surface for joint motion. People suffering from osteoarthritis have their cartilage breaking down which can cause pain, swelling and problems moving the joint. Bits of the cartilage or even the bone may chip off and float around, causing even further damage. In the worst instances, joint replacement may be required. To make a long story short, people suffering from osteoarthritis experience joint pain and struggle to exercise or do everyday ordinary activities.

76% of all osteoarthritis occurs in the knees and/or hips. Furthermore, it is not just middle aged and elderly people that suffer from it. Younger adults, and even children, can be susceptible especially in long-term situations where they are vulnerable to injuring or overusing their joints such as in professional sports, the military or other physically demanding jobs.

Osteoarthritis is the most prevalent type of joint disease in general, impacting up to 16% of people in the developed world.

Osteoarthritis is merely one type of arthritis despite the two terms (i.e. arthritis and osteoarthritis) often being used interchangeably. That mistake is, however, understandable since osteoarthritis is easily the most common form of arthritis. In fact, osteoarthritis is the most prevalent type of joint disease in general, impacting up to 16% of people in the developed world with over 72 million people in the US, EU5[5], Canada and Australia[6]. It is anticipated that the amount of people affected by osteoarthritis in these markets will grow to 250m over the course of the 2020s, up from 150m at the start of the decade. Our valuation of the company assumes continued growth although to maintain our independence, we have used different estimations. We have also only accounted for Australia and the USA because these will be the first two markets where PPS will be commercialised if the drug can pass the current clinical trial and obtain the green light from those regulators.

But aren't there existing osteoarthritis treatments already?

Although there are existing treatments (Figure 6 and Figure 7), there is high dissatisfaction with current treatments from patients because:

1) **Many require frequent administration and/or suffer reduced effectiveness over time**. For instance, typical oral tablets like paracetamol only last for a day or less. Intra-articular injections last 2-6 weeks, but have no effect by 13-26 weeks. A subcutaneous injection can last at least 12 months, but it requires a twice weekly injection for 6 weeks, but is no guarantee. PAR's solution offers at least 12 months of relief with just a 6-week course of twice weekly injections.
2) **A significant proportion of treatments are opioid or steroid based** which is not ideal. Opioids can become addictive and cause serious social problems, the worst of which is death by overdose – a significant proportion of opioid-related deaths are amongst those who had prescriptions for them for osteoarthritis[7]. Opioids are seen as a 'quick fix' because they can cause short-term relief and are not a surgical solution. Arguably this is why up to 40% of people with knee osteoarthritis in the US take opioid-based medicines[8]. The USA is by

[5] France, Germany, Italy, Spain and the United Kingdom (even post-Brexit).
[6] In Australia, 3 million people are estimated to suffer from osteoarthritis.
[7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2789126/
[8] https://pubmed.ncbi.nlm.nih.gov/33629485/

no means the only country where opioids are consumed, but the country is by far and away the largest opioid consumer.

Research has shown that the total life-time opioid-related costs generated by the specific population was US$14bn, of which barely over half are direct medical costs[9]. It is important to note that this is just one estimate, and may well be just the tip of the iceberg. And yet, no research has demonstrated long-term improvement in osteoarthritis pain or joint function due to opioids[10].

3) **All of these just relieve symptoms as opposed to treating the underlying pathology of the disease**. In other words, they may reduce pain in ways such as making the brain forget there is pain, but administration does not cause a remission or cure of the disease. They do not improve cartilage thickness nor increase cartilage volume.

Figure 6: Osteoarthritis solutions today

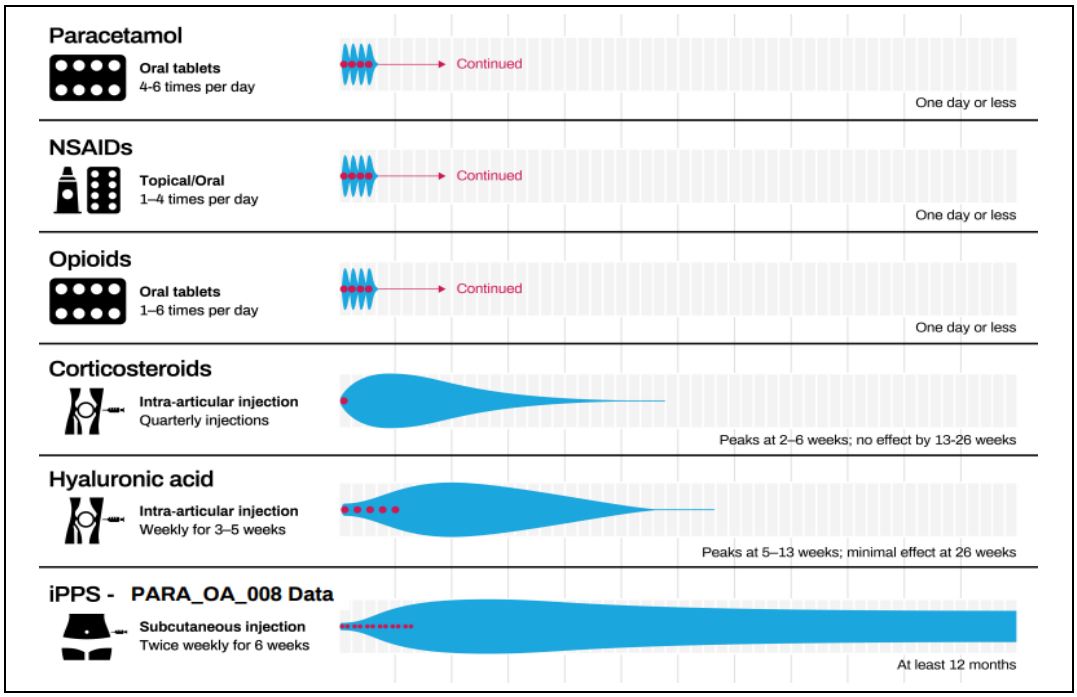
Type	Description
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	• These are considered the most effective oral medicines for osteoarthritis[11]. • These can be in oral or topical format. Oral NSAIDs include aspirin, ibuprofen (Advil and Motrin), naproxen (Aleve), and celecoxib (Celebrex). Topical NSAIDs include diclofenac gel (Voltaren). • These drugs help reduce pain and inflammation, yet they need to be taken frequently to have any impact and do not address the underlying cause. Some of these can be bought at pharmacies without a prescription in lower doses, but doses sufficient to relieve pain may need to be prescribed by a doctor. • These can cause side effects, particularly stomach problems like gastritis. Higher doses can increase the risk of cardiovascular problems such as heart effects when used for an extended period of time[12].
Acetaminophen	• A non-opioid analgesic and antipyretic agent. The most common brand is Tylenol. • Acetaminophen is often recommended as a first-line treatment for mild to moderate osteoarthritis pain. It can reduce pain, but has been shown in recent studies less effective at reducing inflammation. • Thr drug can cause harm to the liver. As a consequence, the Arthritis Foundation and American College of Rheumatology recommended in 2020 it should only be used by people who cannot use NSAIDs.
Corticosteroids/ Steroids	• Injectable steroids like triamcinolone and methylprednisolone can be injected directly into the joint to provide relief from severe inflammatory pain. • These can cause pain relief, but the impact is reduced over time.

[9] Ibid
[10] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3520677/
[11] Arthritis Foundation – Comparing Pain Meds for Osteoarthritis
[12] https://www.ncbi.nlm.nih.gov/books/NBK544987/

Opioids/Narcotics	• They trigger the release of endorphins which are naturally occurring pain relievers in our body. • Even when they work in reducing osteoarthritis, their effect is short-lived and iPPS has been proven to be stronger. During the 2018 SAS trial in Australia, Paradigm found that iPPS resulted in an average 52.9% reduction in pain scores while opiods only resulted in a 15% reduction. • They can cause several problematic side effects including constipation, nausea, lower concentration and drowsiness. It is easy to become addicted to them because of the short-term relief they can bring about.
Hyaluronic Acid Injections	• Sometimes referred to as viscosupplementation, products like Hyalgan, Synvisc, and Euflexxa are injected into the knee to provide lubrication and potentially reduce pain. • Some studies have shown pain relief can last for some months, but data is limited.
Duloxetine	• Originally an antidepressant, duloxetine (Cymbalata) is FDA-approved to treat chronic musculoskeletal pain, including where caused by osteoarthritis.

Source: Pitt Street Research, Arthritis Foundation

Figure 7: Current effect duration of competing therapies



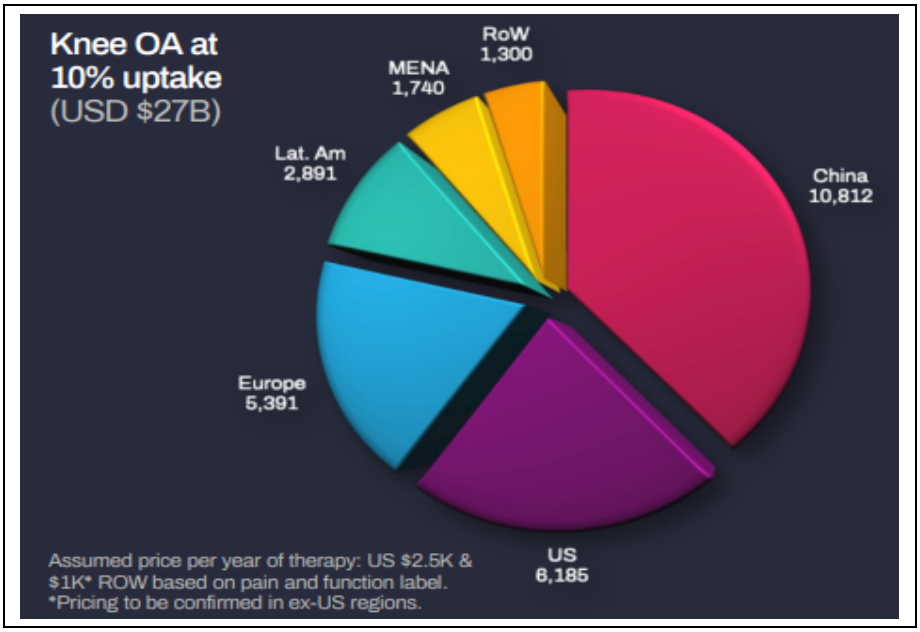
Source: Company

Paradigm's market opportunity for osteoarthritis

The USA and Australia are all but certain to be the first two markets for Zilosul.

Paradigm's two key markets are the USA and Australia. These jurisdictions are by no means the only opportunities but are all but certain to be the first two given these are where the company has applied for regulatory approval. There are varying estimates for how to value the total market and Paradigm has derived its own (Figure 8). It has estimated its opportunity as US$27bn, of which US$6.2bn is in the US and US$10.8bn is in China.

Figure 8: Pain perception in the PARA_OA_008 trial (y axis is WOMAC scores)



Source: Company

Instead, we will outline the number of patients, and the potential revenue opportunity for Paradigm utilising its public plans for commercialisation – specifically, its planned pricing and intended market capture.

For the **USA**, the CDC has estimated that 32.5 million people suffer from osteoarthritis[13]. This is approximately 60% of the total people who suffer from arthritis generally, which is 53.2 million people or 21.2% of all adults[14]. 10% of osteoarthritis sufferers – the market openly dissatisfied with current treatments according to the company – would be 3.25m. Our model does not assume the company will capture this entire revenue opportunity, given we assume a licensing with royalties business model and a gradual ramp up over the first five years, but our ultimate valuation will show there is a vast market opportunity to capture, even if Paradigm only gets a small share.

For **Australia**, Paradigm has not specifically singled out the opportunity, but we have used our own estimations. We have used the estimate the Australian Bureau of Statistics' that 3.7 million Australians suffer from arthritis[15]. There was no separate data for osteoarthritis, but we calculated the Australian market as being ~60% of the former figure which is 2.1 million. Assuming 2% growth in the market per annum and 2% cost inflation, 10% of the market

[13] https://www.cdc.gov/arthritis/types/osteoarthritis.htm
[14] https://www.cdc.gov/arthritis/types/osteoarthritis.htm
[15] https://www.abs.gov.au/statistics/health/health-conditions-and-risks/arthritis/latest-release

would equate to a revenue opportunity US$2.4bn, which is evidently higher than what the company assumed.

China may be another opportunity for Zilosul in the future.

China may be another opportunity down the track. For conservatism's sake, we have only included Australia and the USA in our final valuation, but we think the Chinese market is worthy of a mention because it is over US$10bn, easily the largest market, not just because of its large population, but because of the ageing population. In 2019, there were 10,681,311 cases of osteoarthritis according to the Global Burden of Disease Study conducted by the Institute of Health Metrics and Evaluation (IHME), an increase of 133% compared with 1990[16].

Access to the Chinese market has historically been difficult, although a 2018 regulatory change opened the door for companies like Paradigm. Prior to then, new drugs required domestic clinical trials, but foreign trials are now permissible provided a subset of the participants are ethnic Chinese, suggesting drug is safe and effective for use in China proper. These regulations also provide for imported medicines to be registered and reimbursed in China. Data suggesting ethnic inconsistencies in effectiveness and safety are now considered 'partially acceptable' under the Guidelines, requiring applicants to work with local authorities on targeted clinical trials.

What might be next for Paradigm in relation to osteoarthritis?

Plans for commercialisation

There are faster pathways to regulatory approval for drugs that are approved for other conditions and are being repurposed against others.

As noted earlier, the company has a specific pathway – 505(b)(2) - available to it because it is repurposing a drug. While the FDA still requires the same information for any drug with a regulatory case before it, the 505(b)(2) pathway allows for some information to come from studies not conducted by or for the applicant. Paradigm therefore has a quicker path to market than it otherwise would and could attract a premium in certain scenarios outlined below. The company could opt to commercialise the drug in its own right or seek a licensing model.

A Licensing deal?

In this scenario, another company would sell Zilosul and pay Paradigm royalties for the privilege as well as potential milestone payments as the company progresses to and commences sales. Based on recent precedent with companies such as Dimerix (ASX:DXB), a deal could be agreed upon even prior to successful trial results and run into the hundreds of millions of dollars– subject to the trial's ultimate success. We have assumed this is the path that Paradigm takes in our model. We assume a deal with a modest upfront payment, with milestone payments as it passes the current clinical trial, is approved and commences sales. Further details are outlined in our valuation section.

Some recent deals in the knee osteoarthritis space include:

- Merck selling the rights of its drug M6495 to Novartis for €50m upfront, with a further €400m based on development and commercial milestones as well as royalties on future net sales of the drug. This deal was completed in October 2020, but is noteworthy because it occurred after

[16] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10876716/

two phase 1 studies. A deal at a later clinical stage, and in 2024, could potentially be more valuable.

- Biosplice Therapeutics signed multiple licensing deals for its late-stage knee osteoarthritis treatment including US$140m for the rights in China to Haisco Pharmaceuticals and US$70m to Samil Pharmaceuticals for the rights to commercialise the treatment in Sout Korea.
- Juniper Biologics paid US$600m to Kolon Life Science obtain the licensing rights to develop and commercialise TG-C LD (TissueGene-C), a cell therapy-based treatment for knee osteoarthritis. Phase II trials were completed with flying colours, although Phase III had not even begun. The deal covered the Asia Pacific, the Middle East and Africa.
- Grunenthal licensed its osteoarthritis stem cell medicine Resiniferatoxin (RTX) to Shionogi. The deal was for a total consideration of up to US$525m despite only including one country - Japan. Crucially, however, this drug was in Phase III at the time.

All these depict that a licensing deal could be nine figures, particularly given the late stage of development and the strong data behind it. This could be the case even for a licensing deal covering one or two jurisdictions.

Our Valuation of Paradigm Biopharmaceuticals

We value Paradigm at $227.9m in our base case and $318.2m in our bull case. These equate to A$0.76 per share in our base case and A$1.06 per share in our bull case.

We value Paradigm at $227.9m in our base case and $318.2m in our bull case. These equate to A$0.76 per share in our base case and A$1.06 per share in our bull case, based on 299.8m shares outstanding. The key assumptions driving our DCF valuation are outlined below and summarised in Figure 10:

- **Licensing particulars.** We assume the company opts for the licensing route and takes a 12% royalty on all sales. We assume a total of A$110.7m of milestone payments, with $10.7m upfront upon execution on the deal during the second half of CY24. We assume $20m upon success of the trial, $20m on regulator submission, $30m on regulatory approval in the USA, $5m on regulatory approval in Australia, $10m upon commencement of sales and $5m on the first anniversary of sales.
- **Timeline.** We assume approval in FY26 with sales in Australia and the USA in FY27. We have only modelled Australia and the USA.
- **Market size.** We model the osteoarthritis market by the number of patients. We model the US market at 32.5 million patients, as estimated by the CDC which is roughly 60% of the total people who suffer from arthritis generally[17]. For Australia, we took the Australian Bureau of Statistics' estimation that 3.7 million Australians suffer from osteoarthritis[18], then calculated the Australian market as being ~60% of that which is 2.1 million. Throughout the life of our model, both figures increase at 2% per annum.
- **Market penetration.** Having calculated the total market, then model Paradigm's starting point of 10% of the total market and measure market penetration as a percentage of that 10%. We assume low penetration to start with, gradually growing to reach 10% in the US by CY33 and 30% in Australia by CY33. These equate to 396,173 patients in the USA and 77,126 patients in Australia which are 1% and 3% of the total addressable markets by that year respectively – which are 39.6m patients in the USA and 2.6m in Australia.
- **Pricing.** We have used Paradigm's assumptions of US$2,500 per treatment in the US and US$1,000 in the Rest of the World (including Australia). We assume A$1 is US$0.67 which translates to A$1.50 per US$1.00. From this starting point, we assume 2% growth per annum.
- **Costs.** The biggest expense is R&D revenue and we model A$70m in FY24 and $35m in FY25. Once Zilosul is commercialised, we integrate R&D into cost of sales which we assume to be 45% of revenues. We assumed general & administrative and other commercial expenses increase by 3% per annum. This means the company will reach bottom line profitability in FY26 of $13.3m, then just under $7m for FY27 and FY28 as milestone payments moderate and sales slowly increase. In those years, the net margin is 20%, thereafter growing to reach 35% by FY33.
- **Tax.** We assume a 30% corporate tax rate.
- **Discount rate.** We arrive at a WACC of 14.9%, reflecting a 4.4% risk free rate of return (the 10 year government bond rate), a 7% equity premium and a 1.5x beta.
- **Terminal growth.** We have opted to use terminal growth because we think Paradigm can stand above its peers even once market exclusivity ends 7 years post commercialisation.

[17] https://www.cdc.gov/arthritis/types/osteoarthritis.htm
[18] https://www.abs.gov.au/statistics/health/health-conditions-and-risks/arthritis/latest-release

Figure 9: Our key DCF assumptions

Assumptions	Base	Bull
Launch (USA)	CY27	CY27
Launch (Australia)	CY27	CY27
Estimated market size (patient numbers - US)	3,517,905	3,517,905
Estimated market size (patient numbers - AU)	228,285	228,285
Potential market penetration	3%	3%
Realised price ($US) for USA	2,500	2,500
Realised price ($US) for ROW	1,000	1,000
Peak sales (A$m)	1,914	2,292
Peak royalty revenue (US$m)	230	275
Discount rate	14.90%	14.90%
Royalty rate	12%	12%
Tax rate	30%	30%
AUD/USD	0.67	0.67
Net margin (by CY33)	35%	38%

Estimates: Pitt Street Research

Figure 10 shows our valuation summary for Paradigm, while Figure 11 depicts the sensitivity of our valuation to various WACCs and the upside potential of the stock. The midpoint of our valuation range is A$0.91 per share.

Figure 10: DCF calculation

Valuation (A$m)	Base Case	Bull case
Present Value of FCF	38.5	69.1
Present Value of Terminal Value	197.3	256.9
Enterprise Value (A$ m)	**235.8**	**326.1**
Net (debt) cash	7.9	7.9
Equity value (A$ m)	**227.9**	**318.2**
Share outstanding (Diluted)	299.8	299.8
Implied price (A$ cents)	**0.76**	**1.06**
Current price (A$ cents)	0.23	0.23
Upside (%)	230.4%	360.9%

Estimates: Pitt Street Research

Figure 11: Sensitivity analysis of DCF calculation (base case)

		WACC						
		11.9%	12.9%	13.9%	14.9%	15.9%	16.9%	17.9%
Terminal Rate	0.5%	1.05	0.91	0.78	0.68	0.60	0.52	0.46
	1.0%	1.10	0.94	0.81	0.71	0.62	0.54	0.47
	1.5%	1.15	0.98	0.85	0.73	0.64	0.56	0.49
	2.0%	1.21	1.03	0.88	**0.76**	0.66	0.57	0.50
	2.5%	1.27	1.07	0.92	0.79	0.68	0.59	0.52
	3.0%	1.34	1.13	0.96	0.82	0.71	0.62	0.54
	3.5%	1.41	1.18	1.00	0.86	0.74	0.64	0.55

Estimates: Pitt Street Research

We foresee the stock being re-rated to our valuation range if the following factors eventuate:

- Successful results from the PAR_OA_002 and PAR_OA_003 clinical trials.
- Regulatory approval, in both Australia and the USA,
- Commercial partnerships, either before or after regulatory approval, including potential licensing deals or even potential M&A, and
- Progress against other indications, particularly MPS.

Risks facing Paradigm Biopharmaceuticals

We see the following major risks for Paradigm as a company and as a listed stock:

- **Timing risk.** There is the risk that the company's products may take longer than expected to move through the clinic, leading to investor inertia and potentially the need to raise more capital.
- **Regulatory risk**. There is the risk that regulators may decline to approve PAR products. Even if PAR considers the data submitted to be adequate, the regulator may beg to differ, and even if the data is supportive, regulators still may decline for other reasons, such as the potential for negative interactions with other drugs. Even prior to the final submission, a key risk is that the FDA will not find the minimum dosing regimen found to be effective (namely 2mg/kg) acceptable to use.
- **Uptake risk**. There is the risk that the company products may not be taken up by its target markets. This may be due to poor sales and marketing efforts or disillusion from target markets that the solution is any different to existing solutions out on the market.
- **Funding risk**. There is the risk the company may not be able to secure finding to bring the drug through the clinic and regulators to market. Even if secured, future capital raisings may prove dilutive to existing shareholders. Moreover, a key assumption of ours is that a licensing transaction is conducted – although it is not impossible the company could opt to commercialise the drug in its own right, this would require a lot more capital.
- **Key personnel risk**. There is the risk that the company may lose key personnel and be unable to replace them and/or their contribution to the business.

Risks related to pre-revenue Life Science companies in general.

The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.

Since most biotechnology and medical device companies listed on stocks exchanges in Australia and around the world fit this description, the 'term' speculative can reasonably be applied to the entire sector.

The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

Caveat emptor. Investors are advised to be cognisant of the abovementioned specific and general risks before buying any the stock of any biotechnology and medical device stock mentioned in this report, including Paradigm.

Appendix I – Paradigm's leadership

The company's current board and leadership composition is as below (Figure 12).

Figure 12: PTX's Board members and senior management

Name and Designation	Profile
Paul Rennie Founder and Chairman	• Mr Rennie is recognised as a leading authority in drug development and has been involved in a number of pre-clinical and clinical trial programs over his accomplished career. • He was the inaugural COO of Mesoblast and most recently as Executive VP, New Product Development at Mesoblast. Mr. Rennie has extensive experience in commercialising Intellectual Property
Donna Skerrett Executive Director	• Ms Skerrett has more than 30 years' experience in transfusion medicine, cellular therapy, and regenerative medicine. • She was the CMO of Mesoblast, a stem cell development company (2011-2019), Dir. Transfusion Medicine & Cellular Therapy at Weill Cornell Medical Center, NY (2004-2011), and Ass. Dir. Transfusion Medicine at Columbia University's NY-Presbyterian Hospital. • She has chaired the NY State Governor's Council on Blood and Transfusion Service and served on the Board of Directors of the Fox Chase Cancer Center. • She currently serves in an advisory role on the Board of Visitors for the Lewis Katz School of Medicine of Temple University.
Amos Meltzer Non-Executive Director	• Mr Meltzer is a scientist and an intellectual property lawyer with over 25 years of experience in international trade and in commercialising technologies, principally in the life sciences sector. • He has presided over life science research and product development projects, clinical trials, as well as the commercialisation of life sciences assets through both licensing and the direct sales and marketing of pharmaceutical products. • Previously he served as in-house consel and IP director at NASDAQ-listed companies Cgen and Gilat, as a non-executive director of biotechnology company Evogene and as a VP of Business Development and then CEO of Immuron (ASX:IMC), an ASX-listed biotechnology company. • Mr Meltzer currently serves as Chief Operating Officer of neuro-medical device company Synchron, chairman of the board of surgeons' education services company Vasculab & as a legal adviser to a number of public and private life sciences companies.
Matthew Fry Non-Executive Director	• Mr Fry joined the Paradigm board in March 2024. He brings over 25 years experience in business creation, strategy and expansion in healthcare and medical diagnostics globally. • He is currently the CEO, Managing Director and Founder of AM Diagnostics, a manufacturer and distributor of world class medical diagnostic products. Through this role, he bring significant experience with the US market having driven his company's expansion into the US. Mr Fry's company also boasts of attaining the first regulatory approval in Australia for a COVID-19 diagnostic test.

Appendix II - Comparable companies

Phase 3 companies on the ASX

Opthea (ASX: OPT) – Opthea has a drug called OPT-302 that is in a Phase 3 trial for wet-AMD, an eye condition where fluid leaks in back of the eye and blindness occurs as a result. The company announced successful Phase 2 results for this condition in mid-2019 and started the current Phase 3 trial in 2021.

Dimerix (ASX: DXB) – Dimerix has a drug tackling a kidney disease known as focal segmental glomerulosclerosis (FSGS). It is in the middle of a Phase 3 trial and recorded positive interim results in March 2024. The next set of results is due in mid-CY25.

Telix Pharmaceuticals (ASX: TLX) – Although this company has got a drug on the market, it has a significant pipeline, led by an early-stage Phase 3 trial for kidney cancer imaging agent TLX-250-CDx. The first patient in the trial was dosed in early December.

Appendix III - Glossary

Alphavirus – In general terms, arthropod-transmitted RNA-viruses, in other words insects.

Arthritis – a term used to refer to joint pain and joint diseases caused degradation. Osteoarthritis is one kind of arthritis.

Articular – Relating to a particular joint or joints generally.

Biomarkers – In diagnostics generally, these are characteristics or measures that detect or confirm the presence of a disease or condition of interest.

Bone lesion – Any process that replaces normal healthy bone with abnormal bone or tissue.

Endpoint – In the context of a clinical trial, a targeted outcome that is statistically analysed to help determine the efficacy and safety of the therapy being studies.

Heterogeneous – Where a disease has several etiologies (root causes). This is in contrast to homogenous conditions, which have the same root cause for all patients in a given group.

Intra-articular injection - Into the arteries.

Mechanism of Action (MOA) - a term used to describe how a drug or other substance produces an effect in the body, such as by affecting a specific target in a cell or cell function (such as growth).

Opioid – A term used to describe compounds resembling opium that are medications prescribed by doctors to treat persistent or severe pain. They are sometimes called narcotics.

Osteoarthritis – A disease where sufferers have their cartilage breaking down which can cause pain, swelling and problems moving the joint.

Quality of Life (QoL) – A concept which aims to capture the well-being, whether of a population or individual, regarding both positive and negative elements.

Patient Global Impression of Change (PGIC) - A single, self-administered question asking respondents to rate how their condition has changed since a certain point in time.

Placebo – A drug used in a clinical trial just to contrast with the drug that is the subject of the study, to see how it compares.

Repurposed/Repurposing - Drug repurposing is the technique of using an existing drug or drug candidate for a new treatment or medical condition for which it was not indicated before**.**

Subcutaneous - Beneath, or under, all the layers of the skin.

Sulphate esterification – The formation of an ester through the process of combining an organic acid with an alcohol. An ester is essentially the compound resulting from the alcohol with the acid.

Synthetic – Made from chemicals or artificial substances rather than from natural ones.

Tissue – A Group of cells that have similar structure and that function together as a unit.

Topical (administration) – Administered through the skin, typically by cream.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) – A widely used instrument in patients with knee of hip osteoarthritis. It measures pain, stiffness and function of patients.

Appendix IV – Capital Structure

Class	in millions	% of diluted
Ordinary Shares	299.79	82.9%
Options	61.90	17.1%
Fully diluted shares	**361.69**	

Source: Company

Appendix V – Analysts' Qualifications

Stuart Roberts, lead analyst on this report, has been an equities analyst since 2002.

- Stuart obtained a Master of Applied Finance and Investment from the Securities Institute of Australia in 2002. Previously, from the Securities Institute of Australia, he obtained a Certificate of Financial Markets (1994) and a Graduate Diploma in Finance and Investment (1999).
- Stuart joined Southern Cross Equities as an equities analyst in April 2001. From February 2002 to July 2013, his research speciality at Southern Cross Equities and its acquirer, Bell Potter Securities, was Healthcare and Biotechnology. During this time, he covered a variety of established healthcare companies, such as CSL, Cochlear and Resmed, as well as numerous emerging companies. Stuart was a Healthcare and Biotechnology analyst at Baillieu Holst from October 2013 to January 2015.
- After 15 months over 2015–2016 doing Investor Relations for two ASX-listed cancer drug developers, Stuart founded NDF Research in May 2016 to provide issuer-sponsored equity research on ASX-listed Life Sciences companies.
- In July 2016, with Marc Kennis, Stuart co-founded Pitt Street Research Pty Ltd, which provides issuer-sponsored research on ASX-listed companies across the entire market, including Life Sciences companies.
- Since 2018, Stuart has led Pitt Street Research's Resources Sector franchise, spearheading research on both mining and energy companies.

Nick Sundich is an equities research analyst at Pitt Street Research.

- Nick obtained a Bachelor of Commerce/Bachelor of Arts from the University of Sydney in 2018. He has also completed the CFA Investment Foundations program.
- He joined Pitt Street Research in January 2022. Previously he worked for over three years as a financial journalist at Stockhead.
- While at university, he worked for a handful of corporate advisory firms

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