BELL POTTER

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Speculative

See key risks on Page 5 and Biotechnology Risk Warning on Page 8. Speculative securities may not be suitable for Retail Clients.

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Paradigm Biopharmaceuticals (PAR)

CY21 Overview

Recommendation
Buy (unchanged)
Price
$2.32
Valuation
$3.15 (previously $3.36)
Risk
Speculative

GICS Sector

Pharmaceuticals & Biotechnology

Expected Return	
Capital growth	**35.8%**
Dividend yield	**0.0%**
Total expected return	**35.8%**

Company Data & Ratios	
Enterprise value	**$439m**
Market cap	**$524m**
Issued capital	**225.9m**
Free float	**91%**
Avg. daily val. (52wk)	**$4.2m**
12 month price range	**$1.08 - $3.88**

Price Performance

	(1m)	(3m)	(12m)
Price (A$)	2.64	3.04	2.91
Absolute (%)	-10.98	-22.70	-19.24
Rel market (%)	-10.17	-24.27	-24.71

Absolute Price

SOURCE: IRESS

Clinical Program About To Recommence

PAR is now entering a period of high news flow commencing with the submission within the next few weeks of the Investigate New Drug application (IND) for the US clinical program. The IND becomes active 30 days after submission subject to any questions from the FDA. The company has received extensive guidance from the Agency in the preparation of the dossier, hence we do expect any delay.

Shortly thereafter PAR will commence recruitment of two clinical programs – one in Australia (PAR008) and the second being the phase 3 approval study in the US (PAR002). The latter commences with a short dose escalation study prior to commencement of the large randomised component in early CY2022. The US study will recruit patients across 57 sites in the US and 8 in Australia. At that time the confirmatory study will also commence in Europe.

PAR008 is a randomised controlled study being run in Australia and will provide further data in relation to biomarker analysis necessary to substantiate theories on mechanism of action. The earlier phase 2b provided ground breaking analysis of the association between the reduction in certain biomarkers and degradation of bone cartilage and bone edemas. The data from PAR008 should be available in 2HCY21. Once the recruitment of this trial and PAR006 are completed, we expect the company to commence a paid special access program for patients in Australia. This patient pay program is expected to commence in CY22.

Investment View: Retain Buy Valuation $3.15

There are no changes to earnings in FY21/22. Forecast milestone income and royalties slated for FY23 have now been pushed to FY24. PAR had $85m in cash at 31 December 2020. Cash burn in the December quarter was $13.0m. We estimate PAR has sufficient cash for at least 18 months covering a substantial portion of the clinical trial program outlined here. Valuation is reduced by 6% to $3.15.

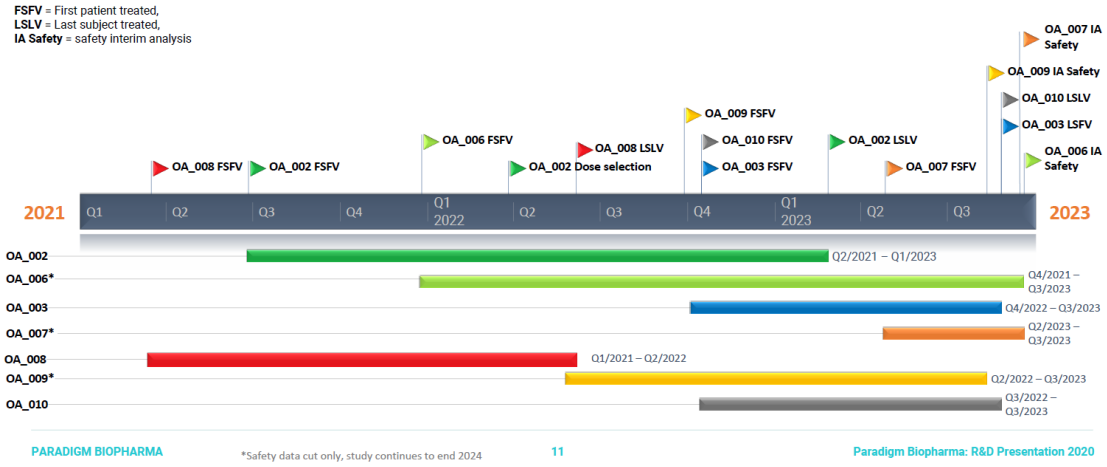
Earnings Forecast

June Year End	FY20	FY21e	FY22e	FY23e
Revenues	4.7	3.0	3.0	5.2
EBITDA $m	-12.3	-41.4	-42.6	-21.4
NPAT (underlying) $m	-12.3	-40.9	-42.1	-20.9
NPAT (reported) $m	-12.3	-40.9	-42.1	-20.9
EPS underlying (cps)	-6.1	-17.8	-18.4	-9.1
EPS growth %	na	na	na	-50%
PER (x)	nm	nm	nm	nm
FCF yield (%)	nm	nm	nm	nm
EV/EBITDA (x)	nm	nm	nm	nm
Dividend (cps)	-	-	-	-
Franking	0%	0%	0%	0%
Yield %	0.0%	0.0%	0.0%	0.0%
ROE %	-11.4%	-60.7%	-164.4%	-421.5%

SOURCE: BELL POTTER SECURITIES ESTIMATES

Beginning with end in mind

Figure 1 - Clinical Program Overview



			N		
002	United States/Australia	Phase 2b/3	938	Randomised Controlled	Knee osteo arthritis
006	United States/Australia	Phase 2b/3	750	Randomised Controlled	Knee osteo arthritis
003	Europe/United States	Phase 3	700	Randomised Controlled	Knee osteo arthritis
007	Europe/United States	Phase 3	560	Randomised Controlled	Knee osteo arthritis
008	Australia	Phase 3	60	Randomised Controlled	Synovial fluid
009	TBA	Phase 3	270	Randomised Controlled	Retreatment
Previous	Australia	Phase 2	243	Single Arm	

002 and 006 are not mutually exclusive. Patients from 002 will continue treatment in the US extension study (i.e. 006)
003 and 007 are not mutually exclusive. Patients from 003 will continue treatment in the European extension study (i.e. 007)

SOURCE: COMPANY DATA

PAR remains on track to commence its phase 3 clinical study in the US later this year. The program has taken longer to commence recruitment than was envisaged 12 months ago, however, that is not to say there has been no progress.

The phase 3 program to examine the efficacy of PPS(Zilosul) in knee OA is now likely to begin recruitment in June 2021 (Previously 1Q CY21). Recruitment will take place across 65 centres in the US and Australia with the vast majority (i.e. 57 sites) in the US. We believe it is crucial for the majority of the trial participants to be US residents treated by US physicians. When the data from the trial is published in a few years time, the regulator, payers and physicians will pay careful attention to the patient demographics, specifically age, BMI and ethnic background to ensure these match a likely patient population in the United States.

The ethics approval documents for each site are due to be submitted at the same time as the investigative new drug application (IND) submission. The IND is due to be lodged later this month and is active 30 days later (subject to any questions from the FDA). Ethics approval must be obtained from each individual participating site. Ethics is in all cases the subject of an extensive review process and Ethics Committee review.

The phase 2b component of 002 is a dose escalation study, followed by recruitment of patients into the randomised study on the final dose from approximately 1Q22. The dose escalation study was required by the FDA.

All patients in the confirmatory studies (003 & 007) are to be treated at the same final dose.

The company is now in the final stages of this arduous process in preparing to commence these ground breaking studies. The design and planning for these trials has been meticulous and represents a case book study of how to plan a clinical program across multiple jurisdictions and involving multiple regulatory authorities. The phase 3 programs have the same admission criteria and identical treatment protocols which facilitates ease of comparison.

Both the EMA and the FDA have agreed to the clinical endpoints in these trials and the basis for the statistical analysis that follows. These commonalties seem incidental now, however, they may potentially maximise and simplify the label claims for the product in years to come. Most importantly, there will be ample to data to determine the effect size from the treatment (i.e. by how much does the drug improve patient impression of change).

PAR 008

The purpose of this trial is to provide further evidence of the mechanism of action for PPS in the reduction of pain. The data from this study will be included in future submissions to the TGA for product approval.

In the short term the company will imminently commence recruitment of this 60 participant study in Australia. Participants will be randomised 1:1 to receive PPS or placebo (saline).

- Primary endpoint will assess a change from baseline to day 56 in synovial fluid biomarkers.

Secondary endpoints to include:

- Correlation between synovial fluid biomarker changes and clinical outcomes;
- Changes from baseline at 6 months in one or more synovial fluid biomarker;
- Changes from baseline at designated time points of WOMAC pain; and
- Function, Stiffness and Quality of life (Patient Global Impression of Change).

Exploratory endpoints will assess radiographic changes in the bone and joint of participants from baseline to day 168.

Primary Endpoint data readout expected in Q321.

The identification of biomarkers was first discussed by the company in 2019 shortly after the initial results from the phase 2b study. The data from PAR006 will confirm these earlier findings.

For the regulators, the data will further enhance the theories in relation to PPS's mechanism of action.

SUMMARY DATA FROM EARLIER CLINICAL TRIALS

In Paradigm's Phase 2b osteoarthritis clinical trial, the biomarker COMP demonstrated a mean percentage reduction of 11.9% from baseline at Day 1 to Day 53 in the serum of iPPS treated subjects[1].

In contrast the levels of COMP showed a mean percentage increase of 2.1% in the placebo group.

ADAMTS-5, the key enzyme involved in the degradation of aggrecan in cartilage showed a mean percentage reduction of 5.1% in the serum of iPPS treated subjects in contrast to the mean percentage increase of 10% in the serum of the placebo group.

The reduction of COMP and ADAMTS-5 by iPPS are supportive of radiological data from the phase 2b study which demonstrated that the iPPS group had clinically meaningful regression of Bone Marrow lesions (BML) in the medial compartment (50.0% vs. 27.3%, p=0.03) compared to placebo.

[1] COMP – Cartliage Oligomeric Matrix Protein,

The company has also published the results of extensive research conducted by U. Adelaide regarding the impact of PPS on Nerve Growth Factor (NGF) production. Simply put, when PPS is added to TNF-α stimulated bone cells it showed a statistically significant reduction in the secretion of NGF, being the potential source of pain within patients with OA. The reduction observed in these biomarkers correlates with the observed reductions in the bone lesion (bone bruising or deformation) as observed in the radiology images from patients on the trial.

We concluded that the reduction of these biomarkers responsible for cartilage degradation and the improvement in structural changes in the subchondral bone are complementary with the clinical outcome of pain reduction.

Figure 2 - Changes to earnings

	2021			2022			2023		
	New	Old	% change	New	Old	% change	New	Old	% change
Revenues	3.0	3.0	0%	3.0	3.0	0%	5.2	47.7	-89%
EBITDA	-41.4	-41.4	0%	-42.6	-42.6	0%	-21.4	35.3	na
NPAT	-40.9	-40.9	0%	-42.1	-42.6	1%	-20.9	35.8	na
EPS	-17.8	-18.2	2%	-18.4	-18.8	2%	-9.1	15.9	na

SOURCE: BELL POTTER SECURITIES ESTIMATES

No changes to FY21/FY22. EPS is lowered in these years due to minor share dilution from the exercise of options.

For FY23 we had previously assumed revenues from a partnering deal. While this is still possible, the delay in the commencement of the final dosing trial to 2022 means there won't be data from the phase 3 until at least mid 2023. The Board is most unlikely to engage a partner before the clinical data from the phase 3 trial is available, hence we have pushed back the timing of milestone income.

Based on our projections the company has cash until mid/late CY22, but may consider further funding arrangements at some point. This may include non-dilutive funding from the sale of rights to certain countries (Japan, China) or a further capital raise from shareholders.

The data from ongoing patients in the Australian Special Access Scheme continues to be very consistent and supportive of ongoing investment in the clinical program. Most recently 13 patient's data was added showing a mean pain reduction of 49.6%. The mean pain reduction across all 89 patients in the SAS program is now very close to 50% relative to minimum 30% reduction required for a clinically significant result in a clinical trial.

The delay in the recruitment of the phase 3 trials reduced the valuation to $3.15 from $3.36. We maintain our Buy (Speculative) rating.

Paradigm Biopharmaceuticals

Paradigm Biopharmaceuticals is an Australia biotechnology company focused on repurposing Pentosan Polysulfate Sodium (PPS) for the treatment of Osteoarthritis (OA) in the knee. If approved the drug will have the brand name Zilosul.

The global market for a safe, effective treatment that provides superior patient outcomes compared to the standard of care is a multiple blockbuster. The recently completed phase II study produced some highly encouraging results that are worthy of further clinical trials.

In the US along the incidence of moderate to severe osteoarthritis is estimated at 30m persons. The pricing of the drug will ultimately be determined by the economic benefit associated with its use as well as the cost of other therapies. The conservative estimate is US$2,500 per year which places the addressable market in the tens of billions of US$.

PROGRESS IN THE CLINIC

December 2018 - PAR announced headline results from its phase 2b randomised, double blind, placebo controlled multicentre trial, investigating subjects with Osteoarthritis and concurrent Bone Marrow Edema (BME) lesions (n=112). The trial met the clinical endpoint of change in Knee Injury and Osteoarthritis Outcome Score (KOOS) pain achieving both clinically meaningful and statistically significant results between placebo and PPS.

The headline results were followed up with strong signals of efficacy in the secondary endpoints (including KOOS function). This phase II trial was conducted at 6 sites in Australia.

PATHWAY TO APPROVAL

The company is pursuing a 505(b)2 registration pathway in the US. We expect the company to apply for the IND relating to the pivotal study in late calendar 2020. PAR aims to begin a phase III trial in the US in CY2021.

ADJACENT INDICATIONS

Paradigm recently executed an Exclusive In-License Agreement for the use of iPPS in the treatment of mucopolysaccharidoses (MPS), a group of inherited lysosomal storage disorders. A key unmet medical need in this class of inherited disease is the lack of treatment of joint pain and dysfunction akin to osteoarthritis, hence the applicability of iPPS in treating these rare joint diseases. MPS is classified as an Orphan Indication/Designation in the US/EU and provides Paradigm the opportunity to serve a US$1.4bn p.a. market that is in desperate need of new cost-effective treatments.

Key Risk Areas

Regulatory Pathway

PAR is seeking registration for iPPS under the 505(b)2 regulatory pathway. The pathway is designed specifically for repurposed drugs including changes in dose form, strength, route of administration, formulation, dosing regimen or indication.

This proposed repurposing of PPS has some rare characteristics.

While the drug has been approved for years as an oral format and there is ample safety data, the proposed format, the dose and the indication (being OA) are all new.

There is also the issue of the opioid crisis. PPS is a non steroid, non opioid, non addictive substance that has been shown to have a significant impact of pain levels associated with OA. It may help to reduce the accidental deaths from opioid overdose.

PAR intends to conduct two phase 3 studies, one pivotal study of 750 subjects and a confirmatory phase 3 study of ~400 subjects.

PAR will present a comprehensive set of safety data from the recent Phase II trial together with data from subjects treated in the compassionate use program and two phase 3 trials, thus representing a safety set of nearly 1,400 subjects. The evidence of treatment will be established from two adequate and well controlled studies and further supported by the phases 2 data set.

Intellectual Property

The company has several patents over the formulation and dosing on iPPS for the treatment of OA. The validity of these patents is highly likely to be challenged at some point, especially if the drug is a commercial success.

The company has an exclusive supply contract with Bene Pharmaceuticals (Bene). We understand the exclusivity applies to human use only (excludes veterinary use). Bene holds the only drug Masterfile with the FDA to manufacture PPS. This supply contract represents a crucial piece of the company's value as it effectively prevents or delays the creation of generics.

We are not aware of the contractual conditions that may lead to a termination of this contract (if any).

We understand there are some other manufacturers of PPS, however, these products are not registered for human use and may not be referenced in any application for registration for human use. We understand the primary use of these products is veterinary.

Clinical Risk

The efficacy of iPPS has not been validated in a large, multicentre, randomised, controlled clinical trial. There is no guarantee that the results from earlier studies will be repeated in a larger phase III study.

Commercial Validation

Our valuation makes assumptions regarding selling price and volume in relation to future revenues from the sale of iPPS. In order for physicians to prescribe the drug and for payers to offer reimbursement, the clinical trials will need to demonstrate clinically significant improvement over the standard of care i.e. meaningful improvement in patient quality of life for pain reduction, side effect management and mobility amongst others. Early indicators based on the data from the phase II study are encouraging.

Paradigm Biopharmaceuticals

as at 11 March 2021

Recommendation	Buy, Speculative
Price	$2.32
Valuation	$3.15

Table 1 - Financial summary

Profit & Loss (A$m)	FY19	FY20	FY21e	FY22e	FY23e
Year Ending June					
Gross royalties	-	-	-	-	-
Gross milestones	-	-	-	-	-
Gross revenues	-	-	-	-	0.4
Risk adjusted revenues	-	-	-	-	0.2
COGS (Bene Royalty expense)	-	-	-	- -	0
Gross profit	-	-	-	-	0
GP margin	na	na	na	na	na
R&D incentive/Upfront receipts	3.2	4.7	3.0	3.0	5.0
Total revenues	**3.2**	**4.7**	**3.0**	**3.0**	**5.2**
Other expenses	**-11.9**	**-17.0**	**-44.4**	**-45.6**	**-26.6**
EBITDA	**-8.7**	**-12.3**	**-41.4**	**-42.6**	**-21.4**
Depreciation	-	-	-	-	-
Amortisation	- 6.9	-	-	-	-
EBIT	-15.6	-12.3	-41.4	-42.6	-21.4
Sundry income	-	-	0.5	0.5	0.5
Pre tax profit	-15.6	-12.3	-40.9	-42.1	-20.9
Tax expense	-	-	-	-	-
NPAT- normalised	-15.6	-12.3	-40.9	-42.1	-20.9
Net abnormal items	-	-	-	-	-
Reported NPAT	-15.6	-12.3	-40.9	-42.1	-20.9

Cashflow (A$m)	FY19	FY20	FY21e	FY22e	FY23e
Gross cashflow	-6.5	-11.2	-40.8	-42.6	-21.3
Net interest	0.1	1.1	0.5	0.5	0.5
Tax paid	0.0	0.0	0.0	0.0	0.0
Operating cash flow	-6.4	-10.1	-40.3	-42.1	-20.8
Maintenance capex	0.0	-0.1	0.0	0.0	0.0
Capitalised clinical trial spend	0.0	0.0	0.0	0.0	0.0
Free cash flow	-6.4	-10.2	-40.3	-42.1	-20.8
Business acquistions	0.0	0.0	0.0	0.0	0.0
Proceeds from issuance	82.8	34.2	0.7	0.0	0.0
Movement in investments	0.0	0.0	0.0	0.0	0.0
Dividends paid	0.0	0.0	0.0	0.0	0.0
Change in cash held	76.4	24.0	(39.6)	(42.1)	(20.8)
Cash at beginning of period	2.5	72.4	104.0	64.4	22.3
Cash at year end	72.4	104.0	64.4	22.3	1.5

Balance Sheet (A$m)	FY19	FY20	FY21e	FY22e	FY23e
Cash	72.4	104.0	64.4	22.3	1.5
Receivables	3.5	3.5	3.0	3.0	3.0
Other current assets	6.6	0.9	0.9	0.9	0.9
Intangibles	-	0.1	0.1	0.1	-
Intangibles	3.0	3.0	3.0	3.0	3.0
Other	-	1.0	1.0	1.0	1.0
Total assets	85.5	112.4	72.4	30.3	9.4
Trade payables	2.3	2.8	2.8	2.8	2.8
Other liabilities	-	0.9	0.9	1.0	1.0
Other provisions	0.4	0.5	0.4	0.6	0.6
Total Liabilities	2.7	4.2	4.2	4.3	4.4
Net Assets	82.8	108.2	68.2	25.9	5.0
Share capital	109.5	145.9	146.6	146.6	146.6
Retained earnings	(30.7)	(41.3)	(82.2)	(124.3)	(145.2)
Reserves	4.1	3.7	3.8	3.7	3.7
Shareholders Equity	82.8	108.2	68.2	25.9	5.1

Last sale 11/03/2021	2.32
Recommendation	Buy (Spec)
Issued Capital	225.9
Market Cap	524.0

Valuation Ratios (A$m)	FY19	FY20	FY21e	FY22e	FY23e
Reported EPS (cps)	-10.5	-6.1	-17.8	-18.4	-9.1
Normalised EPS (cps)	-10.5	-6.1	-17.8	-18.4	-9.1
EPS growth (%)	na	na	na	na	-50%
PE(x)	**nm**	**nm**	**nm**	**nm**	**nm**
EV/EBITDA (x)	nm	nm	nm	nm	nm
EV/EBIT (x)	nm	nm	nm	nm	nm
NTA (cps)	41.5	46.8	28.5	10.0	0.9
P/NTA (x)	0.1	0.0	0.1	0.2	2.5
Book Value (cps)	43.1	48.2	29.8	11.3	2.2
Price/Book (x)	0.1	0.0	0.1	0.2	1.0
DPS (cps)	-	-	-	-	-
Payout ratio %	0%	0%	0%	0%	0%
Dividend Yield %	0.0%	0.0%	0.0%	0.0%	0.0%
Franking %	0%	0%	0%	0%	0%
FCF yield %	-143%	-196%	-758%	-792%	-391%
Net debt/Equity	0%	0%	0%	0%	0%
Net debt/Assets	0%	0%	0%	0%	0%
Gearing	net cash	net cash	net cash	net cash	net cash
Net debt/EBITDA (x)	n/a	n/a	n/a	n/a	n/a
Interest cover (x)	n/a	n/a	n/a	n/a	n/a

SOURCE: BELL POTTER SECURITIES ESTIMATES

Recommendation structure

Buy: Expect >15% total return on a 12 month view. For stocks regarded as 'Speculative' a return of >30% is expected.

Hold: Expect total return between -5% and 15% on a 12 month view

Sell: Expect <-5% total return on a 12 month view

Speculative Investments are either start-up enterprises with nil or only prospective operations or recently commenced operations with only forecast cash flows, or companies that have commenced operations or have been in operation for some time but have only forecast cash flows and/or a stressed balance sheet.

Such investments may carry an exceptionally high level of capital risk and volatility of returns.

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