Wednesday, 23 January, 2019

RESEACH REPORT

LODGE PARTNERS

Paradigm Biopharmaceuticals

Mucoplysaccharidosis and What's to Come Going Forward

BUY

12 Month Target	$2.17
Price	$1.055
Implied Return	106%

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Company data

ASX code	PAR
ASX price	$1.055
Shares on issue	140m
Market capitalisation	$148m
Cash on hand	~$10.4[1]
12-month price range	$0.25 – $2.15
ASX turnover (shares Dec 2018)	19.2m

[1] Cash = Latest 4C balance + Raisings + Tax + 4C Expected outflows

Comparable Enterprise Values[1, 2]

Company	Enterprise Value[1]
Flexion Therapeutics (NASDAQ: FLXN)	$467m
Starpharma (ASX: SPL)	$385m
Paradigm Biopharma. (ASX: PAR)	**$265m[2]**
BioXcel Therapeutics (NASDAQ: BTAI)	$80m
Actinogen Medical (ACW)	$43m
Suda Limited (ASX: SUD)	$9m

[1] As of 24 January 2019; [3] 1 AUD = 0.0.717 USD;

[2] Enterprise value = Market capitalisation minus cash;

[3] Comparable estimated present value of Paradigm Biopharmaceuticals

Key Personnel

Graeme Kaufman	Non-Executive Chair.
Paul Rennie	Managing Director
Christopher Fullerton	Non-Executive Dir.
John Gaffney	Non-Executive Dir.

Major Shareholders

Paul Rennie	16.7%

Events: At the end of last year, Paradigm Biopharmaceuticals (ASX: PAR) released truly solid results from its phase II trial of pentosan polysulfate sodium (PPS) in treating bone marrow edema (BME) associated knee osteoarthritis (KOA). While we have already commented on those results, they have provided the impetus for us to take a closer look at a new indication added to their pipeline, mucopolysaccharidosis (MPS), and what we can expect from Paradigm, in general, going forward.

Mucopolysaccharidosis: MPS is a disease with seven different types, depending on the gene affected, and multiple subtypes. They each cause the breakdown of a particular type of molecular waste to cease prematurely at a given, but different point, leading to the uncontrolled accumulation of the last waste product in the lysosomes of cells. Lysosomes function as the waste bins and recycling centres of cells. Eventually, in MPS, the cell dies, and these products are released into the blood stream and cerebrospinal fluid of the patient where they again accumulate, overtime causing severe health problems and shortened lives.

MPS and its subtypes represent excellent indications for a small company to develop treatments for a variety of reasons, including orphan drug status, fast track designation, the potential for breakthrough therapy designation and small enough patient numbers, such that phase II trials are often good enough for registration and the company developing the drug can market it themselves, capturing 100% of the value chain. The severity and rarity of MPS also means that companies can largely charge what they like for the drug. The five drugs currently sold into the MPS market generated USD1.4b in combined sales revenues in 2017.

Importantly, animal and human data collected using injected PPS (iPPS) to treat different forms of MPS indicates PPS may be able to treat all seven types of the disease and improve the prognosis of patients for which a treatment already exists.

MPS has the potential to be just as big for Paradigm as BME/KOA.

What's to Come: Known activities/milestones for Paradigm going forward largely relate to moving iPPS through the single pivotal trial expected to suffice for approval of iPPS for BME/KOA by the US Food and Drug Administration (FDA). Prior activities will/likely include submitting an Investigational New Drug Application, a Fast Track Designation application, commencing an Expanded Access Program and a pre-phase III meeting with the FDA. We expect the phase III trial to comprise approximately 300 patients, cost $40m and take a year to complete. A positive result will bring a pre-New Drug Application (NDA) meeting with the FDA and its eventual submission. We believe iPPS will be given a standard review time (10 months).

The company is also expected to apply for provisional approval to sell iPPS in Australia, which could bring revenues in early-mid 2020.

A licencing deal, which we view as reasonably likely, with a larger partner could change all of this, leaving Paradigm to focus on MPS.

Valuation: We have valued Paradigm based on comparison to five similar companies. These companies and where we have placed Paradigm are shown in the left-hand panel on this page. Accordingly, we believe Paradigm is deserving of an enterprise value of $265m at present.

Recommendation: With excellent results from the BME/KOA trial and a highly desirable, scientifically well supported, new indication in MPS, we believe Paradigm is a **BUY** and have set a **price target of $2.17**. Confirmation of the quality of the BME/KOA results via publication and/or a licencing deal, plus further clarity on the MPS program will drive this target price.

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Introduction

Paradigm Biopharmaceuticals is an ASX listed drug development company focused on the repurposing of pentosan polysulfate sodium (PPS) for a wide variety of diseases.

The drug is currently approved for human use to treat interstitial cystitis (painful bladder syndrome), sold under the tradename Elmiron® by Janssen Pharmaceuticals. Janssen is ultimately owned by Johnson and Johnson. In the EU, PPS is also used as an anticoagulant. PPS is thought to possess, both, anti-inflammatory and anticoagulant properties.

PPS has also been used in veterinary practice for many decades to treat inflammatory issues in the joints of animals, principally horses.

Through an exclusive supply agreement with bene pharmaChem GmbH & Co. KG ("bene"), the only maker of PPS with a biologics master file (BMF) registered with the United States (US) Food and Drug Administration (FDA), and a series of specific use patents it has acquired, Paradigm has effectively walled off PPS from other companies. Paradigm is consistently looking for new disease states in which to test PPS and for which it can gain suitable intellectual property.

We have previously looked closely at three of Paradigm's programs; allergic rhinitis, bone marrow edema (BME) associated knee osteoarthritis (KOA) and alphaviruses (e.g. Ross River Virus (RRV)). The following explains where these programs currently stand:

1) Allergic rhinitis – Paradigm's program for this indication failed its initial phase II trial. The company appears to be continuing a root cause analysis of the failure in the hope of finding a way forward for the program, but that failure was some time ago now

2) BME associated KOA: **Paradigm's randomised, controlled, phase II trial of subcutaneously injected PPS (iPPS) in BME/KOA returned very promising data in December 2018**. We eagerly await publication of the complete data set to understand the role iPPS plays in treating KOA and its chances of gaining marketing approval. Paradigm looks to be quickly moving to start **the single-phase III trial** they believe will be needed to submit the regulatory application to the US FDA to gain clearance to market iPPS' for BME/KOA. **However, the data looks to be of a quality that will lend itself to a licencing deal**.

3) Alphaviruses: The market is currently waiting on the results from a randomised, controlled trial of iPPS in the treatment of the chronic phase of RRV induced arthralgia. These results are due this month.

Paradigm also holds IP covering PPS for asthma, chronic obstructive pulmonary disease and heart disease, but these indications are still early in the planning stage. In addition, Paradigm holds IP related to a peptide trialled for rheumatoid arthritis and IP related to exosomes. Since there appears to be little actively happening with these PPS programs and non-PPS programs, they will, at most, be touched upon in this report.

Paradigm did, however, in-license some very interesting IP for a disease called mucopolysaccharidosis (MPS). MPS are a group of rare heritable diseases that have significant health and life limiting effects on sufferers. Given their severe nature, a general lack of treatments and orphan standing, it is conceivable that Paradigm could be able to grab the benefits of Orphan Status, fast track status and, even, the coveted break-through therapy designation, with decent results.

In this report, the first thing we will do is take a closer look at MPS and the evidence supporting the use of PPS to treat these diseases. We will then look at the activities/milestones that Paradigm has coming up and what they could mean for the company. Finally, we will provide a valuation for Paradigm using a series of comparable companies.

Mucopolysaccharidosis

MPS are a subset of diseases known as lysomal storage diseases.

Lysosomes are "organelles" found inside cells which, crudely put, act as the cell's rubbish bin and recycler of unwanted cellular and extracellular molecules. Unwanted molecules are shipped into the lysosome where they are degraded by enzymes to the point at which they can be excreted or used by the cell in its normal biological processes.

A person has mucopolysaccharidosis when they lack one of the enzymes that would normally breakdown mucopolysaccharides (now, formerly referred to as glycosaminoglycans (GAGS)). The result is that the lysosomes keep accumulating the substrate that the missing enzyme would normally breakdown. The net result is cellular damage and, ultimately, progressive damage to significant parts of the patient's body.

There are seven clinical classifications of MPS depending on the substrate that accumulates, which, in turn, is dependent on the enzyme that is missing (in some case, defective). Sufferers appear normal at birth, but the effects of the disease soon become

apparent through declines in physical and/or mental function. Depending on the severity of the specific form of the disease the patient has, they may die in early childhood or live several decades. Figure 1 is an image of sufferers of MPS VI.

Readers can find a review of MPS here.

Figure 1. Three patients with MPS VI with typical features such as short stature, skeletal and joint abnormalities, coarse facial features, and tracheostomy. Age are 16, 30, and 12 years old, left to right.

Source: http://pediatrics.aappublications.org

The progressive damage in MPS patients is thought to be due, at least, in part, to the damage caused by the build-up of GAGS within cells and a heightened state of inflammation throughout the body due to the high levels of GAGS in the blood and cerebrospinal fluid. The specific GAG and its levels determine the patients' symptoms.

Treatment

Two treatments are available to some patients with MPS. Neither represents a cure, but they do slow the disease, often considerably.

With enzyme replacement therapy (ERT), patients are treated with a form of the enzyme they are deficient in. ERT is available for MPS I, II, IVA, VI and VII and is seen as effective at slowing those forms of the disease. There are shortcomings, though. For example, Aldurazyme™ (laronidase, SanofiGenzyme) for MPS I does not pass the blood-brain barrier, such that progressive neurocognitive damage continues to occur at rate like normal disease progression.

In extreme cases of MPS, a hematopoietic stem cell transplantation may be undertaken. The theory appears to be that the "new" normal immune cells can bare the load for patients' enzyme deficient cells. It has also been shown to slow the neurocognitive effects of the disease. Unfortunately, HSCT has only been shown to be beneficial in MPS I, VI and VII. HSCT is also, itself, a risky procedure and those risks must be balanced against the severity of the MPS of the specific patient.

Why PPS for MPS?

The rationale for trying PPS in MPS patients came about because it was found that GAG accumulation in lysosomes in MPS results in the activation of toll-like receptor 4, ultimately leading to an inflammatory response. This led to the hypothesis that GAG-induced inflammation is important in causing the skeletal and other pathology observed in MPS. Where PPS comes in is that it is a known anti-inflammatory agent.

MPS, in various forms, has been studied in rats, mice and dogs, with a small study undertaken in humans. These studies are easily found by searching for "pentosan" and "mucopolysaccharidosis" at www.pubmed.com. The search returns five (5) results as of 20 January 2019.

In general, the animal studies have shown reduced GAG concentrations in tissues and other body fluids and improvement in cartilaginous (cartilage) and osseous (bone) deformations. The data from these studies was, generally, in line with a positive effect of MPS. They also showed that injected MPS appeared to work better than oral MPS.

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The human study (here) only included 4 MPS I type patients (three MPS I-Scheie; one MPS I-Hurler/Scheie), making solid conclusions hard to reach. All patients in the study had been on Aldurazyme™ for between 3 and 13 and a half years, such that any improvements in status should be due to iPPS. Two patients were given iPPS at a dose of 1mg/kg weekly for 12 weeks and, then, biweekly for 12 weeks, while the other two received 2mg/kg in the same manner. Urinary GAG concentrations decreased from 4.13 +/- 1.17 at baseline to 2.69 mg/mmol creatine after 24 weeks of treatment with the lower dose, while the higher dose saw urinary GAG decrease from 6.17 +/- 0.62 to 2.65 +/- 0.09 mg/mmol creatine. Improvement in range of motion was seen in 3 out of 4 patients. Pain intensity score was reduced in the lower dose group from 4.5 +/- 1.77 at baseline to 1.8 +/-0.47 after 24 weeks. Pain intensities for the higher dose group were already low at baseline, making the measurements meaningless in this group. As with the many other studies using PPS, safety wasn't an issue.

The authors concluded "PPS treatment in a small number of adult MPS I patients was well tolerated and resulted in a significant reduction of urinary GAG excretion and in an improvement of joint mobility and pain." In the paper, they acknowledge the need for the treatment to be studied in a randomised, placebo controlled, double-blind clinical trial.

Given the strength of the trial results, it is obvious that Paradigm should continue to study iPPS in larger trials and types of MPS.

The authors do speculate further on the MOA of PPS in MPS, indicating PPS could:

- Inhibit GAG synthesis
- Enhance GAG degradation
- Directly affect lysosomal storage function

Obviously, this moves us away from the idea that it may be PPS' general anti-inflammatory activity that results in the improvements.

The fact that MPS was able to decrease urine concentrations of urinary GAGs could be very important, because it raises the possibility that iPPS on top of ERT in treating MPS I sufferers may provide additional benefits to patients. It also raises the possibility that iPPS could be a pan treatment all forms of the disease.

MPS Prevalence, Drug Prices and PPS' Way Forward

According to www.rarediseases.org about 1 in 25,000 babies are born with some form of MPS. The rarest form appears to be MPS I-Scheie with an incidence of 1 in 500,000, while the most common, MPS I-Hurler and MPS II (Hunter) have incidences around 1 in 100,000, although MPS II may be slightly rarer.

We haven't been able to find any prevalences for MPS. This is the number of patients with MPS or a given form of MPS alive at any one time. At a birth incidence of 1 in 25,000, that accounts for 13,000 babies with any form of MPS being born in the United States per year. In terms of MPS I-Hurler, it equates to 3,250, and to MPS I-Scheie, it equates to about 650. Life expectancy for MPS I-Hurler is late teens to early twenties according to the US National Institutes of Health. If one assumes the average life expectancy to be twenty, then there are about 65,000 patients with MPS I - Hurler alive at any one time in the US. This is well below the limit of 200,000 individuals set by the FDA for Orphan Status, with the same being true for European Orphan Status. Estimated average prevalences are hard to calculate for each subtype of MPS, because they all have their own average life expectancy. It becomes even more difficult, because incidences can vary considerably by population, partly because of the diseases' genetic origins.

Despite the small populations each ERT drug serves, they remain enticing markets. Table 1. details the markets for the five MPS ERTs:

As can be seen, most of the drugs are now 10 year's old, but still bring in hundreds of millions in USD revenues. The apparent exception is Aldurazyme®, but this drug was co-developed by SanofiGenzyme and it is that company which receives most of the revenues from it. The other point that stands out is the relatively small numbers of patients required for the drug to gain FDA approval. They range from 45 to 176, although a couple of the drugs were the subject of some post-marketing approval requirements. These small numbers represent, both, the dire need for drugs to treat these diseases and the fact that there just aren't that many patients which can be recruited into clinical trials.

Patient numbers like those above are well within the capability of a company like Paradigm, both, from a clinical trial and marketing point of view.

While each of these drugs is specialised to a subtype of MPS, PPS may not be, based on the animal and human studies that have been done with it. In fact, it is possible that iPPS could be a pan-treatment for all forms of PPS, as stated above.

The primary endpoint for the approval for these drugs tended to be the six-minute walk test, although Aldurazyme® also showed a significant improvement in forced expiry volume (the amount of air that can be exhaled per unit time). Paradigm could target this same

sort of endpoint, but it would be relying on beating the ERT in the control arm. A safer route may be to look for another clinically meaningful endpoint that skirts direct comparisons with ERT or to go after MPS subtypes for which there is no approved ERT initially.

It will be interesting to see what Paradigm decides to do. A good clinical strategy here could equate to a very valuable drug post-trials. It will also be important that Paradigm finds a way to effectively ensure that its iPPS clinical application for BME/KOA does not cannibalize its application to MPS, since the cost/benefit equation will be substantially different. **For the minute, though, having two excellent opportunities (KOA &and MPS) puts Paradigm in an enviable position to be in.**

We regard MPS to be as exciting as Paradigm's BME/KOA opportunity at present, mainly because, as an orphan disease with few treatment options available, it fits the type of indication many industry watchers believe small pharmaceutical companies should be going after, because they can market the drug themselves and catch the entire value chain. We do need to caution, though, that we have not looked at the MPS competitive space in terms of other drugs in development. The reason is straightforward. With so many types and subtypes of MPS, such an analysis is likely to take a lengthy period and as such, we will wait until Paradigm has disclosed its first target indication in MPS for iPPS before undertaking this task. Given the apparent broad applicability of iPPS to MPS, there are likely to be several paths open to Paradigm. In that respect, we have few worries that that the indication is a dead end for the company.

One point that needs re-iterating, is that due to the nature of MPS, it is likely that Paradigm will find an indication where a phase II trial will suffice as a pivotal trial and that there is likely to be no need for a phase III trial. The FDA may make post-marketing requests upon the company, but, importantly, these will be while the company is earning income from the drug.

Table 1. Drugs to treat various forms of MPS and their details by originator company.

Drug	Year Approved	Company at Approval	Condition	2017 Revenues (USD million)	Patients in NDA
Aldurazyme™	2003	BioMarin Pharmaceuticals	MPS I	$90.0[2]	45
Elaprase®	2006	Shire Pharmaceuticals	MPS II	$615.7	96[1]
Naglazyme®	2005	BioMarin Pharmaceuticals	MPS VI	$332.2	56[1]
VIMIZIM®	2014	BioMarin Pharmaceuticals	MS IVA	$413.3	176
Mepsevii™	2017	Ultragenyx Pharmaceuticals	MPS VII	$5.4[3]	23

[1] The FDA attached further post-marketing requirements

[2] The bulk of Aldurazyme® revenues are reported by its co-developer SanofiGenzyme, which were €207m (USD235.4m) in 2017

[3] Q1 to Q3 FY18. Product only approved in November 2017

Source: Lodge estimates and company reports

As a pan treatment for all or even a few forms of MPS, iPPS has billion-dollar potential in this area alone.

Upcoming Milestones

Paradigm has not yet made many of its plan's public. In that way, this section requires a bit of guess work and investors should not rely on it as a hard and fast timeline. The timeline does not include the allergic rhinitis, asthma, COPD and heart failure PPS indications, nor the anti-IL-1 inhibitor peptide project, largely because, as stated before, they are early stage, or they haven't been extensively discussed by Paradigm for a reasonable amount of time or both. The following should be read in conjunction with figure 3 on page 10.

A) The RR phase II to results are do any day now, according to multiple statements from the company, although we have noticed they are slated for Q1CY19 in the latest presentation. This is odd given the last patient was recruited into the study some time ago. Due to the limited geographic nature of RR, we expect this trial may result in an application to the Australian Therapeutic Goods Administration (TGA) for an approval for that indication, if successful, but little else. The pre-clinical study on which this phase II trial was justified, saw both the virus and the iPPS injected into the joints of mice at the same time. Clearly, this is unlikely to occur in the clinical setting, where patients seem just as likely to present to the doctor in late acute phase of the infection, or early chronic phase. Thus, there is a disconnect between the animal trial and the human trial. There is, of course, no BME, that we know of, associated with RRV infection, as well. If/ridding reducing the amount of BME associated with KOA

is iPPS' primary mode of action, it could spell trouble for his trial. The market for RRV is also small and the payment landscape for drugs in Australia is drastically different to that of the United States. Consequently, we believe the trial has a relatively low probability of being positive, say 20%-25%, and the revenues that could flow from the drug are modest. A clearly positive result in our eyes, is likely to move the stock 10% in a northerly direction.

We believe it is unlikely that Paradigm will proceed with chikungunya virus (CHIKV), unless the RR results are clearly positive. CHIKV is also an alphavirus and, in terms of a significant market (US or EU) much more important than RR. We have chosen to leave CHIKV off our timeline, given its likely fate should be determined soon. A positive result from the RR trial would bode well for a CHKV trial and its result.

B) Paradigm has flagged the first quarter of this calendar year (1QCY19) for release of the full set of results from the phase II BME associated KOA study, most likely in conjunction with a publication or presentation at a conference. The primary results release and a follow-up release, two days later, focused primarily on the results from a per-protocol assessment of a subset of patients with a numerical pain score rating (NRS) of 4-6 and were further analysed by patients who achieved a reduction of 50% based on the knee osteoarthritis outcome score (KOOS; pain subsection). No mention of the key secondary endpoint, function, was made. Once a pivotal trial is complete, the FDA will want to see results on an intention to treat basis, relative to the placebo and may inquire to the reasoning behind restricting the trial to patients with an NRS of 4-6. The release of the full results will provide us with a lot of the information we need to assess iPPS' regulatory chances post a phase III trial. **The data that was released, though, was impressive, with patients overall appearing to show a significant solid response to drug over placebo. The dissemination of clearly robust overall could well cause the stock to move up 10% to 20%.**

C) Submission and approval of an Investigational New Drug Application (IND) for iPPS to the FDA is a requirement for Paradigm before the drug can be trialled or used in an expanded access setting. Approvals of INDs are tacit, rather than explicit. If the Paradigm does not hear back from the FDA within 30 days of its IND submission, Paradigm is free to commence its phase III trial in BME/KOA.

D) Paradigm has stated that it will be applying for fast track designation to the US FDA. Fast track designation brings with it a range of benefits, including more frequent meetings with the FDA, eligibility for accelerated review and the potential for priority review, among other things. Fast track designation does not require that the drug fill an unmet medical need, but that it represents a substantial improvement on existing treatments. As an extended release version of an old corticosteroid, Zilretta® (triamcinolone acetonide, Flexion Therapeutics) gained fast track designation from the FDA. **In this light, we see little reason why iPPS would not also be granted such designation**. The granting of fast track designation tends not to have a great impact on a company's share price these days, so we would expect it to cause only a minor tick-up in Paradigm's case. It does open the door for things like rolling submissions and priority reviews, which do result in significant share price increases, though.

E) Paradigm will engage in a pre-phase III meeting with the FDA. They are used by companies to get feedback on their pivotal clinical trial plans and other aspects of the drug development process, like manufacturing of the drug. As a repurposed drug, like Flexion's triamcinolone acetonide, we would expect the FDA's advice to Paradigm to be similar in terms of trial requirements. Firstly, a single trial should suffice. That trial is likely to be a multi-centre, international, randomised, double blind, placebo-controlled study in approximately 300 patients with pain as a primary endpoint and function as a significant secondary endpoint. Paradigm may choose to include an active control arm, such as standard triamcinolone acetonide like Flexion did, in addition to the placebo arm. A third arm would be likely to push the trial numbers out to about 500. The advantage of including an active control arm is that it would more forcefully push iPPS up in the BME/KOA treatment hierarchy (i.e. iPPS is better than X). The down side is cost and that it may do the opposite in terms of treatment hierarchy, although the company is not obliged to provide the active comparator data. Flexion's trial took one year to complete and, adequately funded, Paradigm should be able to do theirs in the same amount of time. In Flexion's trial patients, spent 24 weeks in it and, again, we would expect Paradigm's to be the same, although a shorter or longer on-trial period may be possible. Paradigm's phase II BME/KOA trial had patients on trial for about 12 weeks. Should Paradigm choose to run the phase III trial on its own, as we expect, the cost is likely to come in it at around the AUD40m mark. Pre-phase III meetings are largely process and unlikely to have a significant impact on Paradigm's share price, unless something unusual comes out of it.

It is likely that Paradigm will run more than one trial in BME/KOA, at least, in a post marketing setting, as Flexion is doing. Paradigm has claimed and there is some data to support that iPPS may have disease modifying activity (i.e. it slows, stabilizes or improves knee biology). This was not apparent in their phase II results, where the effect of iPPS wore off reasonably quickly after the last injection. Showing a disease modifying effect for iPPS may take quite a long trial (years) and it makes sense to tackle this aspect of the drug's commercialisation later if iPPS is approved. **If a disease modifying effect can be shown, though, it will be a big deal.**

F) Submission of an iPPS IND for MPS has been slated by the company for some time during CY19. It involves major decisions, such as which form of MPS to go after first and what the best primary endpoint is likely to be. Given the trial in MPS that

comes following the IND application may well be a single pivotal trial enabling registration, getting the application and trial right is of the utmost importance.

G) Commencement of Elite Athlete Expanded Use Program (equivalent to Australian compassionate use) in the US. The Australian compassionate use program clearly drove Paradigm's share price in the lead up to its phase II results. The question here is will further expanded use continue to drive the share price? At some point, further pre-approval use will begin, if it hasn't already begun, to have diminishing returns. It also needs to be remembered that without a positive phase III trial, compassionate use or real-world data becomes irrelevant. Use by ex-US National Football League players may draw some US interest into Paradigm. Alternatively, in the light of the compassionate use data already released by Paradigm, after further research, US investors may see these results as already priced into the stock. We believe that the US expanded use program may drive some US retail interest into Paradigm, but it will do little in terms of institutional interest, who are more likely to see the results as priced into the stock. Over the period of the expanded program, the share price might move up a bit, say 30%, but the multiples in rises the compassionate use program appeared to bring prior to the phase II trial results are probably gone. There is also the small possibility of a significant adverse event or two linked to iPPS during expanded access use, which may give the FDA pause about the drug's safety. We do view this as unlikely, though.

H) The starting of the phase III study of iPPS in BME/KOA is another milestone that is more process than value adding, but it could cause a blip up in the company's share price. **Completion of the trial and the results from the phase III trial will, of course, be extremely important.** Strong intention to treat results from the phase III trial would obviously have a positive effect on the company's share price and would only be boosted by a strong showing for the secondary endpoint of function. Without an understanding of the actual trial design, nor the precise set of phase II data that underpins it, it is hard to ascribe a probability of success to the trial and, consequently, an impact on share price. We are going to start with a probability of success of 50%, with an expected doubling of the share price. While 50% might seem low, as we have said, there are still things we don't know about the phase II results, nor the phase III trial design. Phase III results tend not to be as good as phase II results, which is why 30%-40% of phase III trials fail, despite positive phase II results. The major reason for these failures is that a phase III study is generally a much larger undertaking involving more patients, more doctors and more study sites, all in more countries. This makes the trial harder to run and good results less likely due the variability the extra burden a phase III brings. That is, however, what the FDA wants to know. If we let this drug on the market to be used in a widespread manner, is it drug still safe and does it still work?

I) Paradigm intends to apply to Australia's Therapeutic Goods Administration (TGA) for provisional use of iPPS under the proposed trade tradename "Zilosul". The provisional approval pathway has been designed to allow therapeutics meeting certain criteria to become available in Australia up to two years before they might have before, according to the government. Since the process is new and relatively little known, figure 2. provides an outline of it. If the sponsor (Paradigm) does as the TGA suggests, the process should take a minimum of 220 days (31 weeks or 8 months), although the process is likely to take 5.5 months longer before the first round of assessment occurs (about 13.5 months in total). PPF refers to the pre-submission phase questionnaire.

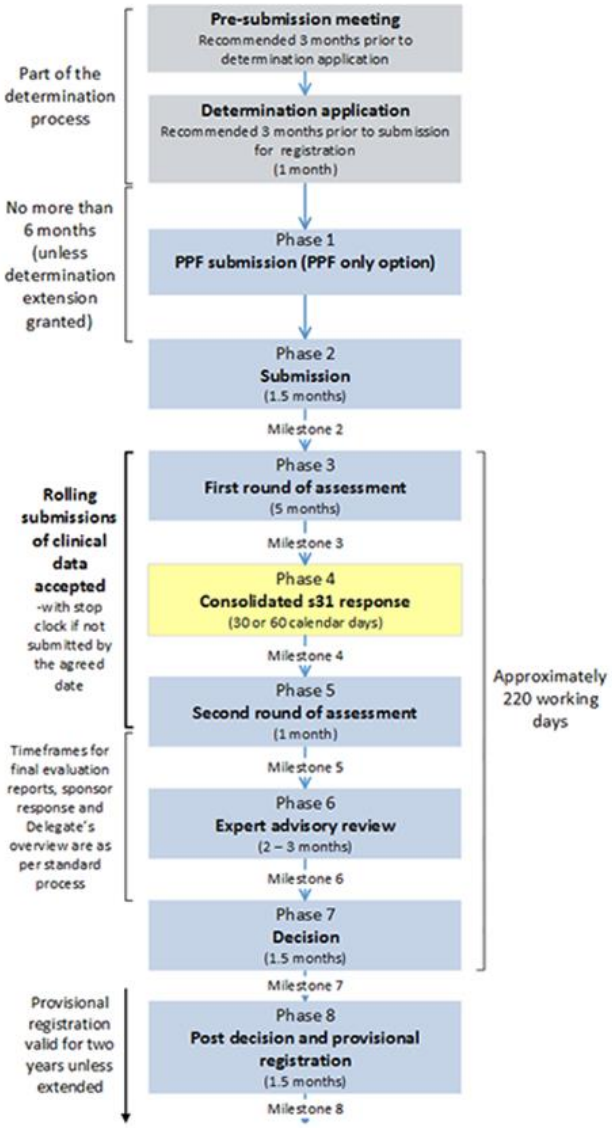
iPPS appears suitable for provisional approval. Approval and listing on the Australian Therapeutics Goods Register (ARTG, A register which lists all drugs approved in Australia) is initially for two years and can be extended two times for a maximum of six years, before a full application must be received by the TGA. If a full application is not received within six years, the drug is removed from the ARTG. There are also a range of post market requirements a provisionally approved drug must meet.

Simply because a therapeutic is listed in the ARTG does not mean it is automatically listed in the Medicare Benefits Schedule Book, which provides for government subsidisation of the drug. Listing in the book is a separate discussion and one that would be unlikely, if not impossible, for a provisionally approved product to gain. Thus, revenues would be confined to those whom could afford and would be willing to part with what we believe is likely to be AUD1,000 to AUD1,500 per six-week course, plus doctor expenses. This will limit uptake of the drug in a country where citizens are not accustomed to paying full price for its medications.

Nonetheless, Australian provisional approval of iPPS for BME/KOA would be a positive signal for Paradigm, even if just for the fact the drug got through the review process. The stock could be expected to jump 15% to 20% on positive news.

J) It is traditional for companies submitting a New Drug Application (NDA) to hold a pre-NDA meeting with the FDA. The aim of the meeting is to ensure that the FDA believes you have all the information required to submit an NDA and to find out how the FDA would like to see you set the data out. Again, this tends to be very much process, but downside shocks can occur if the FDA provides advice that indicates you need to collect more data.

Figure 2. Australian TGA Provisional Approval Pathway.



Source: Australian Government, Therapeutics Goods Administration

K) We expect iPPS to be handed a standard 10-month review time, plus clock stops if the FDA asks and Paradigm needs to answer questions. The review of Zilretta took approximately 10 months. Depending on classifications (e.g. priority review) and FDA questions, 505(b) review times over the course of 2017 had a median time of 10.0 months, with 6/63 (6.3%) having a review time of less than 6.0 months, while 14/63 (22.2%) had review time of greater than 13 months (reference here). Any impact of the approval decision on the stock price will be governed by many factors, including the quality of the phase III results, the emergence of any competition and the contents of the review by the FDA. On approval we would expect the share price to go up in a meaningful way (e.g. minimum 25%), but how meaningfully depends on a lot of factors that will become clear between now and the completion of any FDA review.

L) Paradigm or its designated distributor may commence sales of iPPS in Australia as soon as it receives provisional approval from the TGA.

M) As with Australian approval, Paradigm or, almost certainly its licencee, can commence the sale of iPPS in the US as soon as the FDA has approved the drug. The BME/KOA market is a big one with lots of touch points. It would be nearly impossible for

Paradigm to look to market iPPS for KOA on its own. Paradigm could licence the drug at any stage prior to that and, hence, we have not included licencing in figure 3 at a discreet point or even over a time period.

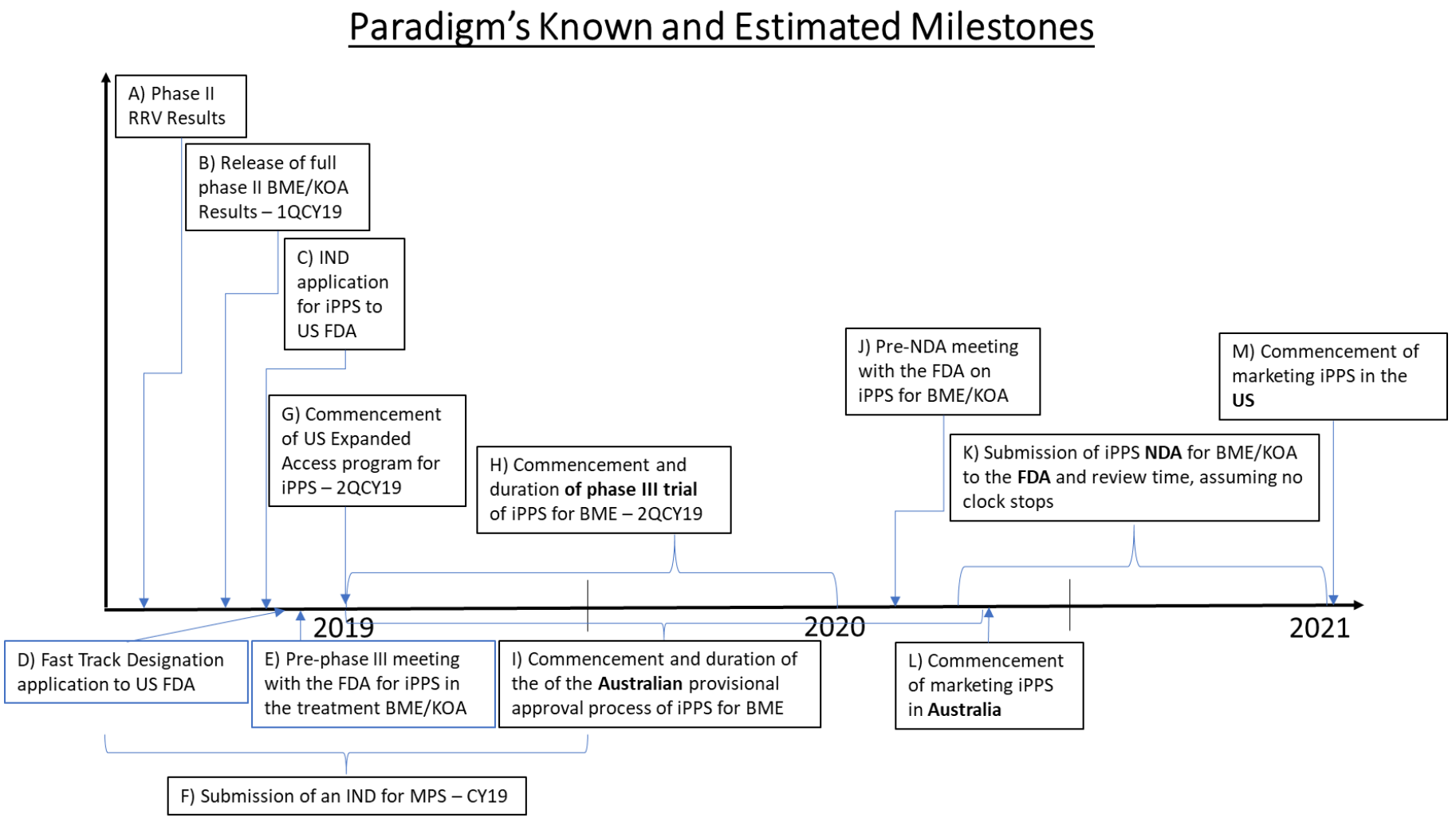
Valuation

Using a table of companies, we believe to be comparable to Paradigm, we have used their enterprise values (EV; market capitalisation minus cash), pipelines and management teams to determine in a subjective manner where we believe Paradigm fits amongst them. To provide some form of quantification to the process, we have allocated a percentage for each comparable (to a total of 100%) which contributes to Paradigm's value and target price. This process is more clearly laid out on pages 9-10 under the heading Valuation and Methodology. Using the methodology, we have arrived at a 12-month target price of $2.17 per share for Paradigm. It does need to be remembered, though, that stocks such as Paradigm are highly volatile and can be very much driven by market sentiment. The simple fact that Paradigm has settled at price well below the one it was at just prior to the announcement of the positive BME/KOA results highlights the unexpected reactions certain events can trigger.

Conclusion

Paradigm has done well to get where it is today. Further detail on the phase II BME/KOA results could push the stock higher as investors become more comfortable with the data, although we already regard it highly. Except for the phase II RRV results, which are due any day now, the company faces a period with a lot to do, but most of it is process work; Collating data, filling out forms and meeting with various groups required to get a drug developed. The one unknown is whether Paradigm will receive an offer that causes it to licence iPPS for KOA/BME. Even a regional deal would be significant positive signal for the stock by proving definite interest from others. A full licensing deal leaves the company in a position to focus almost solely on MPS. We maintain a **BUY** on the stock and set a 12-month price target of $2.17.

Figure 3. Paradigm's Upcoming Known and Estimated Milestones. (Source: Lodge Research and Company Announcements)



Paradigm Biopharmaceuticals

Mucoplysaccharidosis and What's to Come Going Forward

Valuation and Methodology

We have valued Paradigm and set our 12-month price target based on the enterprise values (EV) of comparable companies. Table 1 provides an overview of those comparables used in deriving a value for Paradigm. The commonality between the companies is that they are either repurposing an old drug or, more broadly, developing a new product from old technology. It was difficult to find a good spread of companies, with many repurposing with market capitalisations below USD15M. EV has been calculated simply as market capitalisation minus cash, since few of these companies of this nature carry debt and those that do generally only have a small amount. Table 2 outlines the weightings given to each of the comparables and shows how we have derived our 12-month price target from our comparable-derived fair EV of Paradigm. The derived fair EV was multiplied by one (1) plus a discount rate of twelve percent (12%) to determine a 12-month EV target. Paradigm's current cash balance was then added to the EV target and the resultant number (essentially a 12-month market capitalisation target) divided by the number of Paradigm shares on issue to give a **12-month price target of $2.17 cents per share**.

Table 2. Comparable companies used to determine a fair enterprise value for Paradigm Limited (million AUD).

Company	Exchange	Ticker	Mkt Cap[1,2]	Cash[1]	EV[1,3]
Flexion Therapeutics	NASDAX	FLXN	769.8	302.9	466.90
Starpharma Holdings Limited	ASX	SPL	434.8	49.6	385.17
BioXcel Therapeutics	NASDAQ	BTAI	127.9	47.64	80.23
Actinogen Medical	ASX	ACW	60.6	18.8	41.8
Suda Limited	ASX	SUD	12.9	6.3	9.21

[1]Million AUD; [2]As of 21 January 2019; [3]EV = Enterprise Value = Market Capitalisation minus Cash; [4]1 AUD = 0.717 USD
Source: Lodge Research and company announcements.

Company	Overview
Flexion Therapeutics	Flexion has developed and gained FDA approval for a product called Zilretta® (triamcinolone acetonide). It is a sow release drug, injected intra-articularly (i.e. in the knee joint). It was developed from the generic corticosteroid triamcinolone acetonide. It provides relief from KOA for 12 weeks. was approved in October 2017 specifically for KOA. For the first nine months of Flexion's 2018 FY, Zilretta sales amounted to USD12.0m, growing at a rate of approximately 70%
Starpharma Holdings Ltd	Commercialising an old technology of synthetic branching polymers (dendrimers) to deliver old or new drugs. The company was just asked by the FDA for further clinical data before it would accept the company's NDA for VivaGel for the treatment and prevention of bacterial vaginosis. EU approval has already been obtained. VivaGel is also now market as a condom coating in Japan, where the condoms are being sold by the Japanese company Okamoto Industries. Starpharma did not see the launch of the product as a material event and it seems likely that revenue from it won't be high. The company also has DEP® docetaxel in a phase II trial, while DEP® cabazitaxel and DEP® irinotecan are in phase I/II trials. All three programs are partnered with Astra Zeneca.
BioXcel Therapeutics	BioXcel re-invents existing drugs through proprietary technologies, to generate candidates it believes will have a higher chance of making it to the market and, once there, providing a significant therapeutic benefit. BioXcel has BXCL501 in phase ½ trial for acute agitation and Schizophrenia/bipolar disorders. BXCL701 in phase1/2 trial for neuroendocrine prostate cancer and pancreatic cancer.
Actinogen Medical	Actinogen is developing Xananem™ as a treatment for AD. Cortisol itself is essentially a naturally corticosteroids and, in cases of cortisol deficiency, corticosteroids. Actinogen suggests that persistently high cortisol leads to cognitive decline and that these persistently high levels result in AD. Xananem blocks the enzyme in the body responsible for producing inactive cortisone into cortisol. Xananem is currently in a phase II trial for AD with an estimated primary completion date fo April 2019.
Suda Ltd	Suda is reformulating several drugs where the standard is in care tablet form and reformulating into oral sprays using its in-licensed OroMist® technology. Suda licensed ZolpiMist® (OroMist® delivered zolpidem) for insomnia post-FDA approval and have, at least, five more generic drugs at various stages of being combined with the OroMist® technology. Most recently, Suda signed a licensing agreement for its spray form of sumatriptan (for migraines) to Strides Pharma Sciences for $560k upfront and $830k milestone. Suda will also receive a royalty on sales and a handling fee.

Source: Lodge Research, company announcements and websites.

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Table 3. Comparable weightings ad Paradigm Biopharmaceuticals Limited price target calculation.

Comparables	Weighting (%)
Flexion Therapeutics	35
Starpharma Holdings Ltd	20
BioXcel Limited	25
Actinogen Limited	10
Suda Limited	10

Price Target Calculation	
Present Estimated PAR EV	**$265.6m**
Discount Rate	12.0%
12-Month Estimated PAR EV	$297.5
12-Month Estimated PAR Mkt Cap	$303.8
12-Month Price Target	**$2.17**

(Source: Lodge Research and Company Announcements)

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