Lodge Partners Research
ABN: 25 053 432 769
AFSL: 246271

BUY	12 Month Target	$0.65
	Price	$0.31
	Implied Return	110%

Paradigm BioPharmaceuticals Ltd

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30 November, 2015

Repurposing with purpose

Company Details

ASX Code:	PAR
Price:	31 cents
Shares on Issue:	87.6m
Market Capitalisation:	$27.2m
12-Month Price Range:	25 – 40 cents
Monthly Volume (shares, Oct 15)	224k

Comparable Companies

Company	Enterprise Value[1,2]
Starpharma Ltd (ASX: SPL)	$226.8
Viralytics Ltd (ASX: VLA)	$102.9
Verona Pharma Plc (LON: VRP)	$52.5
Suda Ltd (ASX: SUD)	$28.8
Paradigm (ASX: PAR)	**$20.8**
Invion Ltd (ASX: IVX)	$6.3

[1] Enterprise value = Market capitalisation minus cash
[2] As of 30 November 2015
[3] 1 AUD = 0.4783GBP

Directors & Chief Executive

Mr Graeme Kaufman	Non-Executive Chairman
Mr Paul Rennie	Managing Director
Mr Christopher Fullerton	Non-Executive Director
Mr John Gaffney	Non-Executive Director

Major Shareholders

Paul Rennie	24.2%
MJGD Nominees	8.1%
Irwin Biotech Nominees	7.8%

Share Price Chart

Source: FactSet

Paradigm BioPharmaceuticals Limited is a recently ASX-listed (ASX: PAR) Australian drug repurposing company. Repurposing is a proven drug development strategy built around finding new uses for old drugs. It is a quick, low cost, low risk strategy, because it allows the company to leverage the abundance of previous scientific and human data on the drug at every step of the commercialisation pathway. Importantly, executed properly, it can yield the extraordinary returns seen with successful traditionally developed drugs.

Programs & progress: Paradigm's primary repurposing candidate is pentosan polysulfate sodium (PPS). PPS has previously been approved for certain indication(s) in the US and some European countries, but the relevant patents have expired.

Paradigm owns fresh method patents over the use of PPS to treat:

- Bone marrow edema (BME, bone bruising)
- Allergic rhinitis (AR, hay fever)

Its patents also cover allergic asthma and chronic obstructive pulmonary disease, but these indications won't be a near term priority.

Since its IPO, Paradigm has progressed the BME and AR projects significantly, having obtained ethics approval for its first clinical trial in BME and having finalised a nasal spray formulation of its PPS for AR.

Intellectual property (IP): IP is key to successful drug repurposing. Method, formulation and delivery patents will play a role in protecting Paradigm from competition. Exclusive rights to the only US-approved version of PPS for human use (bene pharmaChem) are very important. Compositional/activity differences with other PPS sources and bene's manufacturing trade secrets obviating substitution risk. Paradigm has/will have further protections, as well.

Clinical activities: Paradigm's immediate plans include these clinical trials:

- ZILOSUL® (PPS for BME): Open label, single arm, multicentre, n=40, phase II trial; start:Q1 CY16; complete: late Q4 CY16
- RHINOSUL® (PPS for AR): (i) Standard phase I safety study (n=20); start: 2H CY16; complete: late CY16/early CY17. (ii) Phase II trial similar to that for ZILOSUL®; estimated start: 2H CY17

The phase II trials are open label primarily because it gives the company an inexpensive look at likely product safety/efficacy before committing to more expensive standard regulatory agency suitable (multicentre, double blind, etc) trials. The open label nature of the trials mean a steady flow of results for investors to assess and, if warranted, it gives the company the ability to start the more expensive trials before the open label studies complete.

Market characteristics: The markets for both BME and AR are substantial, with BME being an essentially substantially unmet medical need.

BME has only recently been recognised as a clinical entity, through the wider use of newer imaging technologies. But when you consider that *hospital charges alone* were USD14b in 2004 for treating osteoarthritis (OA) and that 75% of OA cases are associated with and may stem from BME, doctors will be eager to use and payers pay for an efficacious BME drug.

A range of drugs exist to treat AR, but no single drug treats both its early and late phases. PPS exhibits properties indicating it may be able to, with animal studies demonstrating activity equivalent to a standard late phase drug. AR afflicts 10% to 30% of the world's population. Should PPS be able to replace two drugs with one, intuitively, blockbuster revenues would follow.

Methodology & Valuation: We have compared Paradigm to a basket of five listed companies. Based on a proportional approach to the comparables' enterprise values (EV), we believe a fair EV for Paradigm to be **$45.3m**. When Paradigm's cash and the time value of an investment (12%) are considered, we believe Paradigm should have a market capitalisation of **$57.0m** in one year's time.

Recommendation: We believe Paradigm represents a potential low risk/high return drug development investment and initiate coverage with a **BUY** recommendation and a 12-month price target of **65 cents** per share.

Introduction & Background

DE novo drug development (developing drugs from first principles) is a difficult game. While estimates vary, only 5% -10% of new chemical entities (NCEs) that enter phase I clinical trials will ever make it to market. This is not to mention the numerous other candidates that fail in preclinical trials. The drugs that do make it through to market often deliver investors incredible returns, but this is the exception, rather than the rule.

Paradigm is finding new uses for old drugs; a process termed drug repurposing

Paradigm BioPharmaceuticals Ltd is focused on a proven drug development strategy that is becoming more and more common among pharmaceutical companies, regardless of their size. This strategy is drug repositioning or drug repurposing.

Drug repurposing is the process of taking a drug that has or is being developed for one clinical indication and developing it for another, generally unrelated, indication.

Drug repurposing is a proven, low risk, potentially high return strategy

The reason for engaging in such a strategy is that it often cuts the cost, reduces the development time and increases the probability of success, when compared to traditional drug development, *while providing for returns equivalent to drugs developed using the de novo method.*

Paradigm's core business is devoted to the repurposing of a drug termed pentosan polysulfate sodium (PPS) for a number of indications unrelated to its already approved uses. These are:

Two initial target indications

First target indications:

- Bone marrow edema (BME, bone bruising)
- Allergic rhinitis (AR, hay fever)

Further indications to follow

Secondary indications:

- Asthma
- Chronic obstructive pulmonary disease (COPD) (conditions of the lungs which cause air flow through them to be reduced)

PPS is currently approved in the United States for interstitial cystitis (painful bladder syndrome) and sold under the brand name Elmiron® by Janssen Pharmaceuticals. It is also an approved anti-thrombotic (blood clot dissolving) agent in certain, predominantly European, countries.

Blue-sky exosome project

In addition to its PPS programs, Paradigm also has a discovery stage project looking at the use of exosomes to treat orthopaedic indications, in the first instance. Exosomes are small packages (vesicles) containing various potentially therapeutic molecules. While the technology is quite exciting and gaining significant industry attention, it is at a very early stage and, as such, we will expound on it in a future report, once the project is more visibly defined.

In Brief: The Paradigm Business Case

Paradigm has developed a core competency in PPS

Paradigm has and is developing a core competency in the existing drug, PPS, and using that competency to repurpose the drug for new clinical indications. The indications that have been chosen are those where PPS is highly likely to have a clinically and commercially meaningful effect based on PPS' mechanism(s) of action (MOA) and Paradigm's ability to effectively protect the indication with meaningful and effective intellectual property (IP).

Investment returns can be as for an NCE

The development of PPS for these indications is made easier relative to standard NCEs, because Paradigm can draw upon the extensive research already undertaken with the drug by commercial and academic groups. This is expected to reduce the cost, decrease the time and increase the probability of success of Paradigm's projects. Importantly, should Paradigm successfully gain regulatory approval for one or more of the indications it is targeting, pricing will very likely be as for an NCE.

Overall, Paradigm is, therefore, a drug development story with low hurdles (cost, time, etc) in the development phase, but with standard pay-offs in the marketing phase relative to NCEs.

Valuation

BUY recommendation; Price target: 65 cents

Based on a comparable valuation methodology, we have arrived at a fully diluted 12-month price target for Paradigm of **65 cents per share**. Accordingly, we ascribe the company a **BUY recommendation**.

Valuation methodology based on comparables

To avoid all of the assumptions and the additive inherent uncertainty required to perform a probability weighted discounted cash flow valuation, we have instead chosen to value Paradigm on the basis of comparables, restricting ourselves to a group of five companies we see as most similar to Paradigm. In the first instance, we restricted ourselves to companies repurposing drugs, but, then extended the screen to include companies that are, in effect, making something old new. The comparables method readily allows us to incorporate the market's view of the investment space in our valuation. See page 16 for a detailed explanation of the valuation methodology.

Drug Repurposing

Because of the high risk and cost associated with traditional drug development, many companies have turned to a new drug development model; a model known as drug repurposing. This model is a relatively new concept in Australia, although it is well-known abroad.

The process of drug repurposing, as implied, involves finding a new use(s) for an old drug. This strategy obviates many of the pitfalls of traditional drug development. Some of those pitfalls being:

Numerous pitfalls of traditional drug development

- The extensive discovery efforts required
- The difficulty in successfully finding a suitable lead candidate
- The risk the compound won't demonstrate suitable drug like properties in preclinical studies
- Manufacturing the drug on industrial-scale can consume significant resources (time and money)
- The risk, cost and length of time of the clinical and regulatory processes required to achieve drug approval.

These pitfalls, to a certain extent, and a lack of productivity, in general, have meant that the number of NCEs in late stage development for a cohort of 40 large and mid-sized pharmaceutical companies fell between 2002 and 2010, as illustrated in table 1. Over the last few years, this lack of productivity has led to a large scale shake-up in the way larger pharmaceutical companies develop drugs.

A feature of this shake-up was the outsourcing of a large amount of research and development (R&D) to small, nimble companies with tightly defined core competencies. In some cases, large internal R&D teams were retained, but restructured to resemble a number of small drug development companies under the umbrella of a large company.

Paradigm is part of the new breed of drug development companies

Paradigm is very much within this new breed of drug development company, specifically applying its talents to drug repurposing.

Table 1. NCEs in late stage development by a cohort of 40 large and mid-sized pharmaceutical companies.

Number of Projects	2002	2010
Phase 2	79	71
Phase 3	59	47

Source: Drug Repositioning – Bringing new life to shelved assets and existing drugs. Barratt, M & Frail D, 2012, J Wiley & Sons.

The risk, cost and length of time of the clinical and regulatory processes required to achieve drug approval is significantly reduced with drug repurposing. Some reasons for this are as follows:

Many advantages to a drug repurposing strategy

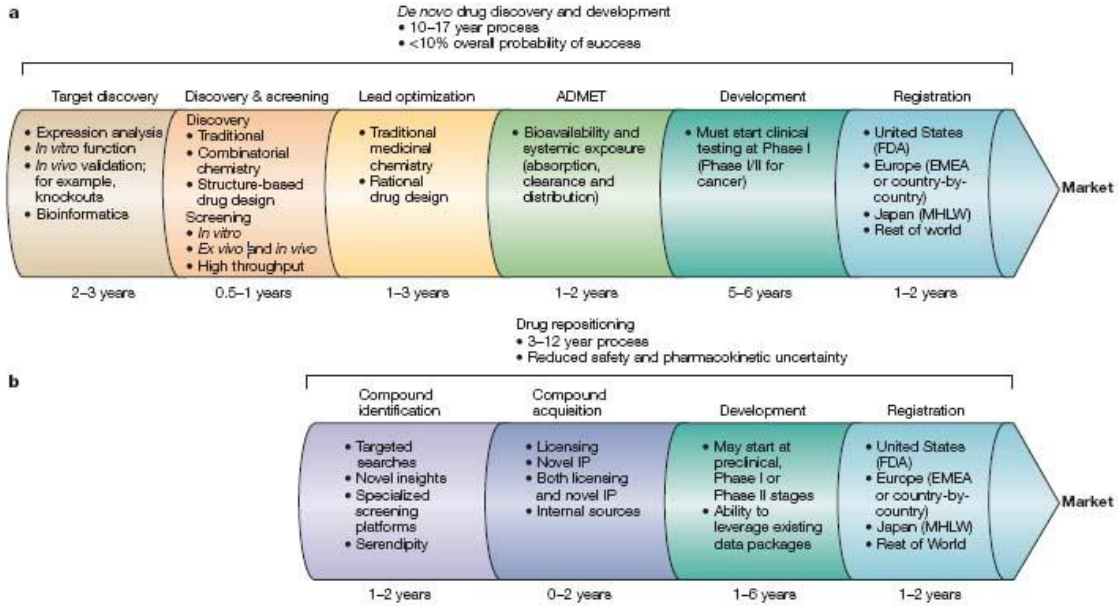
- The safety of the drug has already been demonstrated in humans
- The drug has already been shown to have biological activity, albeit in another indication
- Pharmaceutical companies can generally commence their clinical development at phase II clinical trials rather than the pre-clinical stage, as in *de novo* R&D
- Extensive work has already gone into understanding the drug (i.e. MOA(s) is understood and large-scale manufacturing processes are validated)

Match an old compounds known attributes with a disease based on its biology

Because of the R&D that has already gone into the drug and that its properties are, generally, well understood, the drug can be easily matched with a disease with biology the drug is likely to suit. Importantly, much of the work/data that has gone into the drug's original development doesn't need to be redone and can be used both to speed development of repurposing of the drug and in supporting regulatory approval applications.

Table 2 outlines the benefits of drug repurposing relative to *de novo* drug discovery.

Table 2. The benefits of drug repurposing compared to de novo drug development



Source: Drug Repositioning – Bringing new life to shelved assets and existing drugs. Barratt, M & Frail D, 2012, J Wiley & Sons.

IP is the big issue with drug repurposing

The main issue with drug repurposing is intellectual property (IP) protection. Because the drug is already in the public domain, it cannot be patented as an NCE. NCE patents are considered the strongest form of IP in drug development.

Very solid IP protection, however, can still be obtained, using a project specific strategy, which combines some or all of the following:

Multiple other forms of IP protection

- Non-NCE patents
  - Method patents (i.e. the drug's use for a new indication)
  - Formulation patents (e.g. the development of an injectable formulation)
- The use of regulatory exclusivities, other than the standard five-year exclusivity the US Food and Drug Administration (FDA) grants to NCE's (e.g. using the FDA's 505(b)(2) regulatory pathway, explained later)
- Trademarks

- Trade secrets/technical expertise.

Well-constructed strategies can yield protection equivalent to that of an NCE patent

Appropriately constructed, such a strategy can yield marketing protection rivalling that obtained through traditional NCE drug development (Smith, RB: Repositioned drug: integrating intellectual property and regulatory strategies; Drug Discovery Today: Therapeutic Strategies; 2011).

There are numerous examples of highly successful repositioned drugs. One of the most notorious drugs in history, thalidomide, is now a lifesaving drug. Thalidomide was used to alleviate morning sickness, among other things, and is thought to have been responsible for one to two hundred thousand severe birth defects in the 1950's and 1960's. Today, thalidomide has found a new home in treating the blood cancer multiple myeloma. In 2006, the FDA approved thalidomide under the brand name THALOMID® (Celgene Corporation) for the treatment of that disease, with the drug becoming quite commercially successful post-approval. THALOMID® generated USD245m in 2013 in sales, down from sales well in excess of USD300m, based on increased competition.

THALOMID® is an excellent example of a repurposed drug that has delivered big returns AND lead to the development of better drugs

Another drug from Celgene, REVLIMID® (lelanidomide) and one of the drugs responsible for THALOMID®'s declining sales, is a derivative of thalidomide. It grossed revenues USD4.3b in 2013. While not specifically a repurposed drug, it does demonstrate how a repurposed drug can lead to the development of better drugs, with even greater revenue potential. Here, the logic was develop the re-purposed drug, increase your understanding of it in the process and then use that understanding to refine the repurposed drug into an optimised NCE. While early days, one can see the scope for applying the same logic to a second generation PPS, given the heterogeneous nature of the compound and the potential to tweak its chemical structure/signature.

This possibility gives Paradigm the longer term development vision associated with the most successful of pharmaceutical companies.

Pentosan Polysulfate Sodium

Plant cell walls contain sugar polymers called cellulose (which are based on glucose) and xylans (based on xylose). Hardwoods (e.g. European beech) contain 10-35% xylans. Xylans form the backbone of PPS. To produce PPS, xylans are extracted from European beech and treated in an industrial process to add sulphate groups and sodium ions.

The method of manufacture of PPS is very important

It is believed that the biological activity of a sample of PPS is tied to and varies according to the set of polysaccharides (xylose chains) and the degree of sulphation of the actual PPS sample. Since this is tied to the manufacturing method, the method used to create the PPS is likely to be extremely important. As will be seen, Paradigm's ability to source PPS with consistent, well characterised content and biological activity, already deemed as acceptable by the US FDA, is *a key component of the company's IP of its product.*

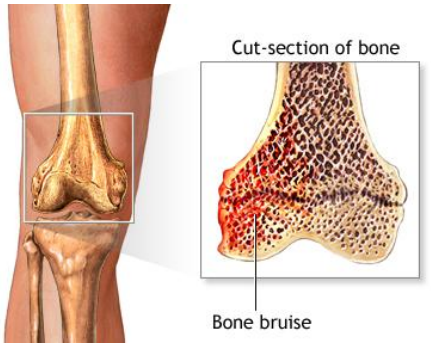
bene's manufacturing method appears to be a very well kept trade secret

The oral formulation of PPS sold in the US is manufactured by bene PharmaChem and is the only PPS product approved by the US FDA. It is used for a disease called interstitial cystitis (also known as painful bladder syndrome). The drug was approved by the FDA in 1996 and the patents covering it expired in 2010. *Interestingly, no generic competition is yet to appear, suggesting other companies are unable to manufacture or source PPS of the appropriate quality.*

Bone Marrow Edema

BME can be viewed as damage to the structure and composition of the marrow underlying the bone (termed subchondral bone) associated with joints, in particular the joints of the knee and ankle. Basically, a BME is a bruise occurring within a bone (see figure 1).

Figure 1. Illustration of a bone bruise.



(source: MDhealth.com)

BME has only been recently identified as a distinct clinical entity

Increased use of magnetic resonance imaging to assess acutely injured knees has led to greater awareness that BME or bone bruising represents a distinct clinical entity. It is visualised as an area of increased signal intensity within a region of bone marrow. The occurrence and progression of BMEs have been shown to be associated with development of knee pain. Importantly, BMEs are also associated with structural changes in bone and cartilage and predict eventual knee replacement surgery.

There is a substantial body of research demonstrating that BME lesions are associated with acute joint injury, cartilage loss and progressive joint degeneration, as evidenced by the following studies:

Numerous journal articles link BME to joint degeneration

- Acute-impact joint injuries initiate a sequence of biologic events that cause the progressive joint degeneration that leads to a condition known as Post Traumatic Osteoarthritis (PTOA) (J Orthop Res 2011, 29:802–809).
- Joint injuries cause striking alterations in synovial fluid levels of compounds that may contribute to joint degeneration, including pro-inflammatory cytokines and mediators such as tumor necrosis factor alpha (TNF-a), interleukin (IL)-1, nitric oxide, and matrix metalloproteinases (MMPs) (Biorheology 2006, 43:517–521).
- Follow up of people who suffered knee ligamentous and meniscal injuries demonstrated that they had a 10-fold increased risk of OA as compared with those who did not have a joint injury (Sports Med 1999, 27:143–156) and (Arthritis Rheum 1998, 41:687–693).
- Many patients with a torn ACL develop osteoarthritis of the knee irrespective of current treatment (BMJ 2013:346:f232 doi: 10.1136/bmj.f232).
- Many acute joint injuries are characterized by Bone Marrow Lesions (BML's) as detected by Magnetic Resonance Imaging (MRI).
- The occurrence and progression of BMLs have been shown to be associated with progression to osteoarthritis and joint pain (Osteoarthritis and Cartilage 2012, 20:1514-1518).
- Importantly, BMLs are also associated with structural changes in bone and cartilage and are a potent risk factor to joint pain and osteoarthritis (Rheumatology 2010, 49:2413-9).
- Patients who present with BML were nearly 9 times as likely to progress towards total knee replacement (Skeletal Radiol 2008, 37:609–617).

Despite the abundance of evidence, there are no validated pharmaceutical therapies for the treatment of BME. The pharmacological properties of PPS strongly suit the biological issues created by a BME, including the associated pain.

The pain, discomfort and temporary disability caused by BME means that, in its own right, it is a significant medical issue and that the use of appropriately safe clinical interventions to treat it is justified.

BME may give rise to OA, such that treating BME will prevent OA

The studies above also reveal, BMEs are also closely associated with the subsequent development of osteoarthritis (OA). OA is a painful disease characterised by the progressive degeneration of a joint, often eventually to the point where the joint, such as a knee, needs to

be replaced. Obviously, joint replacement is a very costly and invasive procedure that payers and patients want to avoid.

The Market - Bone Marrow Edema

BME is a new area of research

Because of the variable number of joints that BME can affect, its various degrees of severity, the advent of better imaging techniques and the general lack of survey data, it is difficult to determine the incidence/prevalence of BME with any degree of certainty.

Knee replacement surgeries provide an insight into the market

Some idea of the problem posed by BME can be derived by looking at the association of BME with OA and the number of total knee arthroplasties (TKA, total knee replacement surgeries) conducted each year, given the association between BME and OA.

It is estimated that one in two Americans will have painful knee OA in their lifetime (Arthritis Rheum. 2008 Sep 15;59 (9):1207-13). The socioeconomic impact of this is considerable. In 2004, USD14b in hospital charges alone were attributed to the disease in the US (http://www.hcup-us.ahrq.gov/nisoverview.jsp).

BMEs in other joints only add to the size of the potential market

In 2008, there were more than 600,000 TKA's conducted in the US (Arthritis Rheum. 2008 Sep 15;59(9):1207-13), with each TKA costing approximately USD50k. When these numbers are multiplied, approximately USD30b are spent each year on TKAs in the US.

When one factors in that approximately 75% of knee OA cases are associated with BME (Ann Intern Med. 2001 Apr 3;134(7):541-9), USD22.5b in healthcare costs could ultimately lead back to BME through TKAs alone. These figures would be even higher if the markets for OA associated with other joints and/or for painful BME not associated with OA are included.

Insurance companies will be willing to pay handsomely for a product that can even marginally reduce these costs. Prevention of major surgery is a strong focus of health insurance companies, who are constantly seeking to reduce costs.

Why Pentosan & Bone Marrow Edema?

There are three mainstay treatments for BME. They are:

Current treatments for BME inadequate

- Rest and physiotherapy
- Drugs called bisphosphonates and vasodilators
- Surgery called core decompression

All have significant drawbacks. Rest obviously takes time, between 6 and 24 months as an industry rule, while bisphosphonates appear to have limited efficacy (Arch Orthop Trauma Surg. 2012 Dec;132(12):1781-8).

Drugs have been studied in BME, but failed to take hold as treatments

Iloprost (a vasodilator) is a vasoactive drug that has been used to treat bone marrow edema and it has shown some moderately promising results (J Bone Joint Surg Br. 2001 Aug;83(6):855-8). It continues to be studied in the treatment of BME, but in the fourteen years since the above study was done, it has failed to catch-on as a routine treatment. Iloprost was originally developed by Schering AG for the treatment of pulmonary arterial hypertension (high blood pressure in the lungs). Ibandronate (a bisphosphonate) is another drug that has been used in experimental clinical trials to treat BME. Ibandronate, developed by Roche, has also had limited success as a treatment for BME. A major drawback of both drugs is their need to be delivered intravenously thereby making their wide-spread use for the treatment of BME unlikely, given the unpleasantness of the process.

ZILOSUL® has a delivery advantage over other drugs that have been studied

Paradigm's product for PPS, trademarked ZILOSUL®, will be delivered by simple intramuscular (IM) injection.

The examples of Iloprost and Ibandronate do, however, demonstrate that the major pharmaceutical companies do see significant value in a treatment for BME.

Core decompression is a surgical procedure that involves drilling a hole into the head of the bone to release the pressure that has built up in it due to the BME. Post decompression, it is

hoped that the natural healing process will take over and resolve the BME. This surgery is, however, only reserved for the most severe cases.

The use of PPS has been linked to markers of resolving BMEs

In 2010, a paper was published in BMC Clinical Pharmacology by Kumagai et al that indicated PPS provided improvements in clinical assessments and cartilage metabolism in cases of OA. Importantly, the clinical assessments related to pain (e.g. pain while walking) showed significant improvement, which is important, because the pain associated with OA is thought, in fact, to be caused by a concomitant BME. Although this study was single-armed and the results need to be treated with caution for that reason, when taken in combination with another paper, the evidence supporting a beneficial effect of using PPS to treat BME becomes much stronger.

Evidence that BMEs lead to OA

That paper (Semin Arthritis Rheum. 1999 Feb;28(4):211-67) showed that PPS improved markers from the subchondral bone associated with BME, such as increased blood flow. A reasonable hypothesis becomes that the improvements seen in the Kumagai study were due to PPS's effect on reducing/eliminating BME, rather than a direct effect on OA.

Without getting too technical, PPS appears to have several properties, which make it a good fit for the treatment of BME. Those properties are:

PPS is thought to have multiple mechanisms of action

- Anti-inflammatory
- Fibrinolytic
- Mild anticoagulant

The effects of the properties on BME are likely to include reducing swelling (i.e. anti-inflammatory), effects on tissue remodelling (i.e. multiple properties of PPS) and, importantly, improving blood flow (also, due to multiple properties of PPS).

From a scientific point of view, there is clearly enough evidence to support the repurposing of PPS for BME.

Potential direct effect of PPS on OA

Of course, PPS may also have a direct beneficial effect on OA, as suggested by some research, and, if approved for BME, PPS could find substantial use in patients with OA, as well as those with BME.

Market Exclusivity Protection

From a patent protection position, Paradigm has filed a patent that covers the treatment of BME with PPS. The title of the patent is as follows:

"A method for the treatment of bone marrow edema in a mammal comprising administering an effective amount of polysulfated polysaccharide (PPS) including salts thereof, to a mammal in need to such treatment"

Critically, this patent has been granted in the US, Australia and New Zealand, with more jurisdictions expected to follow.

Further patents surrounding the formulation of the drug are also likely, once an exact formulation(s) has been chosen. For example, there is no approved form of injectable PPS, which is suitable for human use.

Paradigm has and is building IP protection around its proposed uses for PPS that is equivalent to an NCE patent

Patent protection is, thus, likely to extend out beyond 2030.

As stated earlier, while a number of companies make PPS, the activity and chemical signatures appear to vary widely. Paradigm has exclusively licensed the Australian, New Zealand and ASEAN (Association of South-East Asian Nations) rights for the supply of PPS for BME from a company that has been making the drug for decades (bene-pharmaChem) and for which a monograph for the production of its version of PPS is already on file with the FDA. Given the complex nature of PPS, this provides very strong trade secret type protection.

At a minimum, the FDA grants a product an automatic three to five year period of exclusivity as long as the drug approval is for a new indication, even if the drug is not a NCE, and there is no other marketed product protected by IP that would prohibit the product's marketing.

In terms of market exclusivity, Paradigm appears to have constructed suitable protection for its repurposed PPS using patents and manufacturing barriers, ultimately giving it coverage similar to an NCE patent.

BME - Toward Marketing Approval

Accelerated regulatory pathways are available to ZILUSOL®

It looks like Paradigm will be able to follow the FDA's 505(b)(2) regulatory pathway to gain marketing approval for PPS to treat BME. The EU has an analogous pathway, termed a "hybrid application", which the company may be able to follow in that jurisdiction.

The 505(b)(2) pathway is available to products which represent a significant change to an already approved product/NCE (e.g. an injectable version of an approved oral drug). The exclusivity period, however, must have expired for the NCE. Paradigm's PPS for BME appears to fit within this definition, based on the reference product, Elmiron®, and the fact that Elmiron®'s exclusivity period has expired.

Other than the three to five year exclusivity period mentioned above (the degree of change to the reference product determines the precise exclusivity period), the 505(b)(2) pathway provides a further major distinct advantage.

Paradigm will be able to use data from others in its regulatory applications

That advantage is that the applicant may rely, at least, in part, on the FDA's findings of safety and/or efficacy for the previously approved reference drug. This has the potential to significantly reduce the number and size of the experiments that the applicant (Paradigm) needs to perform. Obviously, this saves both time and money. For example, while a standard 505(b)(1) New Drug Application (NDA) generally requires two phase III trials (an initial pivotal trial and a confirmatory one), products being assessed under the 505(b)(2) pathway may only need one phase III trial. This difference alone could save the applicant several years and tens of millions of dollars during the product development phase of commercialisation and represents one of the real advantages of some drug repurposing projects.

While Paradigm has not yet made public its PPS development plans for BME, based on discussions with the company prior to its Initial Public Offering, there is some colour around their plans available.

Ethics approval obtained for a single arm phase II study in patients who have suffered an ACL injury

Firstly, we believe the company will commence an open label, single arm, phase II study in patients in 2016, with company announcing receipt of ethics approval to commence such a study recently. We also believe, due to the prevalence of BME in the population, that this study will centre largely on professional and semi-professional athletes who have had an anterior cruciate ligament (ACL) injury with an associated BME. The trial will study 40 patients with an interim analysis after 20 patients have finished treatment. The open label pilot study should be concluded by December 2016 (subject to patient recruitment).

Primary study objectives are likely to be to evaluate the safety and tolerability of IM ZILOSUL® in subjects with BMEs following an ACL injury.

Secondary study objectives will evaluate the:

- Effect of IM ZILOSUL® on BMEs following an ACL injury as assessed by magnetic resonance imaging
- Effect of IM ZILOSUL® on functional capacity following an ACL injury

The phase II study will yield a substantial amount of data

The study is also likely to evaluate exploratory endpoints, such as the:

- Effect of IM ZILOSUL® on pain following an ACL injury
- Effect of IM ZILOSUL® on biomarkers of inflammation, and bone and tissue remodelling.
- Relationship between changes in BMEs with changes in the functional capacity of the knee and changes in the intensity of pain

The open label nature of the study allows the company to track the trial results in real time

While the study will not provide definitive data on ZILOSUL®'s ability to resolve BME due to its design limitations, it should provide sufficient data to determine whether it is worth proceeding to a larger, standard, multicentre, double blind, randomised, placebo controlled trial. Since the study is open label, Paradigm does not need to wait until the trial completes to review the data and decide whether to proceed with the larger trial, because the company will

see the data in real-time. Paradigm can initiate the larger trial as soon as it has convincing enough data from the open label study to determine whether it is worth proceeding to the larger study. If treatment with PPS is drastically reducing the time it takes for the target BMEs to resolve, it will be evident quite quickly. In which case, Paradigm may commence the larger study quite soon.

Open label studies serve a risk mitigation purpose, but provide other advantages, as well

Incorporating open-label studies, as Paradigm has done, adds a significant degree of risk management to the company's programs, with the resulting data likely to be helpful to the company not only in determining whether to commence blinded studies, but in other areas, as well, like partnering.

A blinded study in 200 patients could be commenced at anytime

We believe a larger study could involve approximately 200 patients and, like the open label study, take approximately 18 months to complete. Because BMEs are common, patient recruitment is unlikely to be the rate limiting step in terms of completing the trial and, hence, the trial can be completed in a similar amount of time, as that required for the open label study.

Prior to commencing the larger study, it is a certainty that Paradigm will seek feedback on their plans from the FDA and make any suggested adjustments to their development plans.

PPS for Allergic Rhinitis, Asthma & Lung Conditions

IP in-licensed for other PPS indications

In August of last year (2014), Paradigm agreed to acquire IP, including patents, developed by US-based Glycan Biosciences relating to the use of PPS to treat allergic rhinitis (AR, hay fever), allergic asthma (AA) and chronic obstructive pulmonary disease (COPD, a group of long term diseases which restrict the flow of air through the lungs). Based on the limited amount of publically available information, the deal looked pretty typical for assets of this nature, with Paradigm paying a modest upfront fee, initially, plus milestones and royalties on net sales.

With the proceeds from its IPO, Paradigm expects to take PPS into a phase I trial in AR and to the point of being phase I ready for asthma. Since listing the company has reported a large amount of work has been undertaken on the AR project, suggesting it is moving up the company's list of priorities. Outcomes achieved on the AR project so far are the:

A large amount has been achieved with the AR program since IPO

- Registration of RHINOSUL® trademark for the proprietary nasal spray PPS formulation
- Appointment of key staff to manage the operations of the preclinical and clinical development of the RHINOSUL® nasal spray
- Commencement of a preclinical nasal toxicology study to Good Laboratory Practice (cGLP) standards
- Appointment of key respiratory physicians and regulatory consultants to develop the clinical trial protocol
- Appointment of a Principal Investigator for the AR clinical trial
- Appointment of experienced regulatory and clinical trial personnel to advise on the product development pathway
- Finalisation of a proprietary nasal formulation with a leading European contract manufacturer
- Finalisation of a manufacturing agreement for the production of the nasal spray formulation for the phase 1 clinical trial, scheduled to commence in Australia 2H CY16
- Securing of a long-term supply of FDA approved nasal spray devices from a German manufacturer

We believe little near-term work will be done, at this stage, on the AA and COPD indications, although both of the indications will certainly be the subject of further work once the BME and AR programs have been well and truly bedded down. As such, we will examine AA and COPD in depth in a later report.

AR is a very common disease

Allergic Rhinitis

AR or, as it is more commonly referred to, hay fever, is a very common disease, affecting 10% to 30% of the world's population and 7.8% of adults in the US (or, approximately, 25 million Americans) according to figures quoted by the American Academy of Allergy, Asthma and Immunology. AR is the result of the immune system over-reacting to allergens, such as pollen, dust and/or pet hair, in the air.

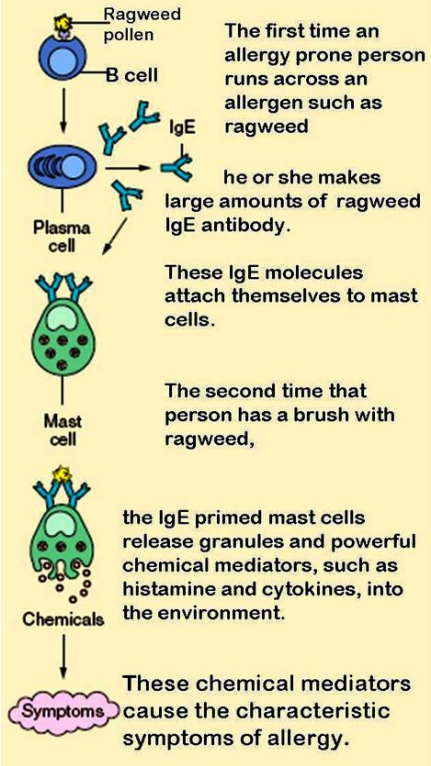
AR has two phases

There are two phases in AR experienced by patients.

Early phase

- Early phase response: This phase is characterised by sneezing, nasal itching and rhinorrhoea (a runny nose) commencing within approximately 30 minutes after contact with the allergen. The early response is the result of IgE antibodies binding to the specific allergen. This triggers the mast cells (a specific immune cell to which the IgE antibodies are attached) to release histamine and other chemicals which cause the symptoms of the early phase of AR (see figure 2). Histamine is the key substance released by mast cells, as evidenced by the efficaciousness of anti-histamines for this phase of the disease.

Figure 2. Graphical representation of the early phase response in allergic rhinitis.



(Source: University of Melbourne website)

Late phase

- Late phase response: The late phase response is signalled by the arrival of inflammatory (immune) cells into the tissue lining the nasal passage and dilation of the blood vessels in the area, leading to what is commonly referred to as a stuffy nose. A range of chemicals, such as interleukins are involved in this phase, as well. This phase commences approximately 6 hours post allergen challenge.

Treatment - Allergic Rhinitis

There are essentially two treatments used for AR, depending on the severity and duration of the symptoms the patient experiences.

Mild AR is treated with common anti-histamines

Mild, intermittent AR is generally treated using anti-histamines (e.g. oral: chlorphenyramine; loratadine, Claritin®; cetirizine, Zyrtec®; intranasal: levocabastine), while severe, persistent AR is generally treated using intranasal corticosteroids (budesonide, Rhinocort; beclomethasone, Beconase®).

Other drugs (e.g. pseudoephedrine, a decongestant) may also be used, but generally are not as effective as those listed above.

Intranasal corticosteroids work in late phase

Antihistamines are, generally, very good drugs, but they don't deal with the characteristic congestion of late phase AR. Intranasal corticosteroids also work well, but they do have drawbacks/side effects. The common issues raised are:

But intranasal corticosteroids have drawbacks

- The requirement for pre-treatment for 10 to 14 days and consistent use thereafter to be effective
- Thinning of the lining of the nasal passages and, in particular, damage/ulceration to the nasal septum
- Postulated, but controversial, systemic effects, including growth retardation, reduced bone density, skin thinning and cataracts. Additionally, the potential suppression of the hypothalamic-pituitary-adrenal axis (part of the neuroendocrine system, which produces hormones regulating certain bodily functions; Respir Med. 2006 Aug;100(8):1307-17.).

The bottom line is that while adequate treatments for AR exist, there are significant opportunities for improved products, particularly for severe, persistent AR.

PPS for Allergic Rhinitis

The scientific rational for developing PPS for the treatment of allergic rhinitis is outlined in a patent owned by Paradigm, titled "Sulphated xylans for treatment of prophylaxis of respiratory diseases" (WO 2088/144836) A1.

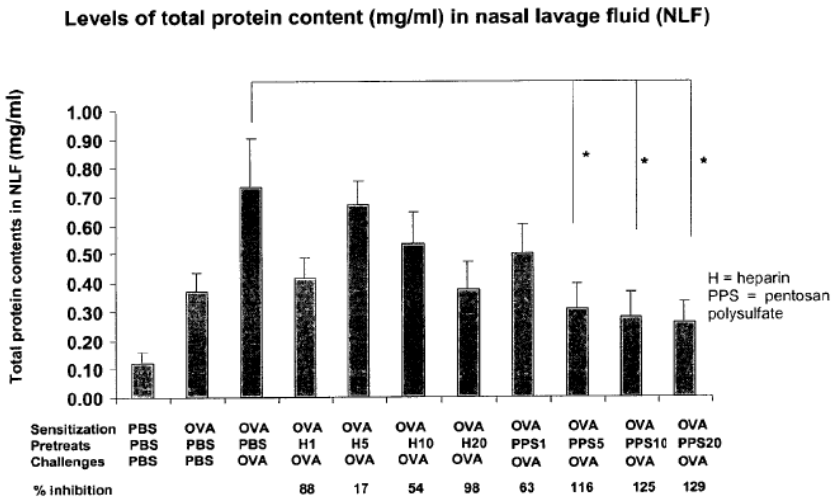
Data supporting the use of PPS in AR is contained in the patent acquired by Paradigm

Figures 3 & Figure 4 provide results from preclinical studies using a common animal model of allergic rhinitis. This model involves sensitising guinea pigs to the protein ovalbumin and then challenging the animals with ovalbumin after various pre-treatments (PBS (phosphate-buffered saline), control; heparin; PPS). As can be seen, pre-treatment with PPS preparations significantly reduced the total amount of protein and number of leukocytes (white blood cells) in the nasal lavage fluid of the animals when they were challenged with ovalbumin, except in one case (PPS1) and only where total protein content was concerned. The significant reduction in protein and leukocytes confirms the anti-inflammatory effect of PPS in the AR animal model.

In addition to the animal studies, the patent contains *in vitro* data showing that PPS inhibits a number of cytokines (IL-4, IL-5, eotaxin, etc.) involved in the AR response. PPS also inhibits the activity of human leukocyte elastase, an enzyme involved in the later stages of AR.

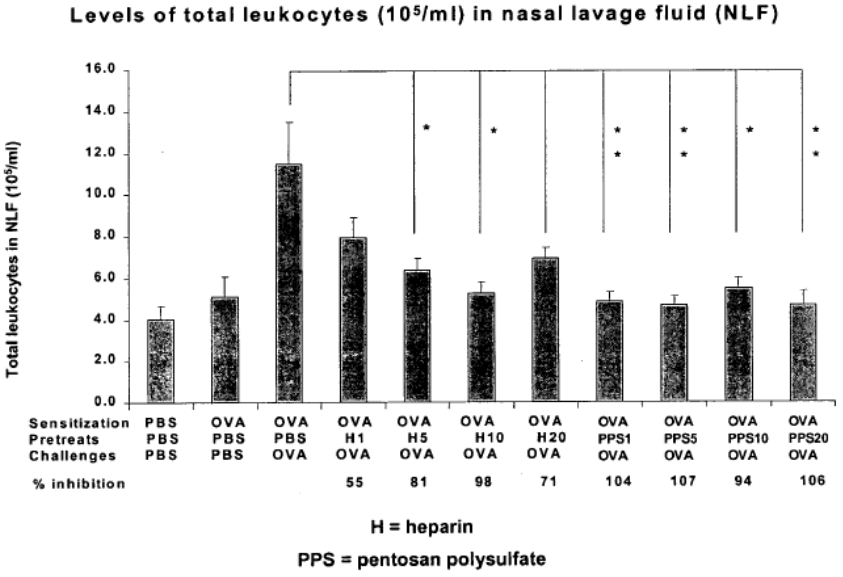
Heparin was included in a number of the studies, because it is a compound related chemically to PPS and it has been studied in patients. In particular, in a study of ten patients treated with intranasal heparin, symptom scores were significantly reduced after 10 minutes, as were nasal fluid eosinophil (a particular white blood cell associated with AR) counts (J Allergy Clin Immunol. 2001 Nov;108(5):703-8).

Figure 3. Effect of PPS and other pre-treatments on nasal lavage fluid protein content.



(source: patent WO 2088/144836)

Figure 4 Effect of PPS and other pre-treatments on nasal lavage fluid leukocyte levels.



(source: patent WO 2088/144836)

The development of heparin for AR (and asthma) has been limited, however, because of the safety risk heparin's anticoagulant activity represents. Regardless, the results in the patent application indicate PPS is more active in AR than heparin and, moreover, PPS is only a mild anticoagulant.

The data in the patent combined with other studies indicate PPS could be the first effective drug for both the early and late phases of AR

The preclinical data confirms that PPS is both a mast cell stabilizer (reduces mast cell degranulation and therefore acts as an anti-histamine) and an anti-inflammatory (like a corticosteroid). *Therefore and very importantly, PPS is potentially the first dual-acting (effective in both the early and late AR responses) product that could enter the very large market for AR.*

The results, above, when combined with further published research, supports the development of PPS for AR.

PPS for Allergic Rhinitis – the clinical development plan

We understand the company's clinical development plans for its AR product are as follows:

- Animal intranasal toxicology study complete in Q1 CY16
- Clinical trial product (PPS in FDA approved nasal spray device) manufactured in Q1 CY16
- Ethics approval for a pilot open label clinical study targeted for Q3 CY16
- Commence pilot open label clinical study Q4 CY16/Q1 CY17

The PPS Repurposing Business Case

Following are the main attributes surrounding Paradigm's business case:

A very strong business case

- A very large core potential market for treatment of BME and AR
- Potential significant use in many joints
- A strong likelihood of PPS demonstrating benefit in an area of strong clinical need (BME), based on good clinical data and a sound biological hypothesis
- A good likelihood that PPS will prove to be the first dual acting treatment for AR
- A large body of evidence indicating that the product is safe (used for decades in humans and animals)
- Abbreviated approval pathways (i.e. quicker to market) available
- Multiple forms of IP protection in place and available
    - Method patent being prosecuted
    - Reformulation patents likely (no approved forms of injectable/nasal PPS in humans)
    - Regulatory exclusivity
    - Trademarks
    - Exclusive access to the only FDA-approved form of PPS (the active pharmaceutical ingredient), with strong evidence it is very difficult to suitably reproduce
- Demonstrated big pharmaceutical company interest in treatments for BME and AR
- Further potential indications in AA and COPD, and the possibility of creating refined second generation versions of PPS

To summarise, Paradigm appears to have all of the components required to form a very strong business case for repurposing PPS for BME and AR, with significant upside if successful.

Paradigm's Key Personnel

Mr Graeme Kaufman BSc, MBA
Chairman & Non-Executive Director
Mr Kaufman has had a very long distinguished career in Australian biotechnology, having held senior executive positions spanning each of the key functional areas in large and small life science companies. At CSL (ASX: CSL), he held various positions culminating in his appointment as General Manager, Finance (Global). After CSL, he served as Executive Director of Circadian Technologies (ASX: CIR) and Non-Executive Director of Amrad Corporation (now owned by CSL). He then served as Executive Vice President Corporate Finance with Mesoblast Limited (ASX: MSB). Now operating as a professional director, Mr Kaufman is Chairman and Non-Executive Director of Bionomics Limited (ASX: BNO) and Non-Executive Chairman of IDT Australia Limited (ASX: IDT). Over the last few years, he is one of the best, if not the best, performing life science directors in Australia.

Mr Paul Rennie, BSc, MBM, MSTC
Chief Executive Officer
Mr Rennie recently held several positions at Mesoblast Limited (ASX: MSB). He joined Mesoblast in Dec 2004 as its inaugural COO followed by several other positions including those of Special Projects Consultant, Vice President of Special Projects, and Executive Vice

President of New Product Development and Preclinical Operations. Mr Rennie has over 25 years' experience in marketing and business development within the Australian biomedical and pharmaceutical industry. Prior to Mesoblast, Mr Rennie served as Director of Business Development for Soltec, a wholly owned subsidiary of F H Faulding & Co., and, prior to that, he was Business Development Manager for the Biosciences Division of Bonlac where he orchestrated the commercialization of Recaldent™. From 1990 to 1994 he held various positions with the global pharmaceutical company Merck Ltd.

Very high quality directors and management

Kevin Hollingsworth FCPA, FCMA
Chief Financial Officer
Mr Hollingsworth, in addition to his duties at Paradigm, serves as Principal of Hollingsworth Financial Services. Prior to that he served as Chief Financial Officer and Company Secretary of Mesoblast Limited (ASX: MSB), before which he held the same positions at Patrys Limited (ASX: PAB). At Alpha Technologies Corporation Limited (ASX: ASU), Mr Hollingsworth served as a Non-Executive Director. He has also served as Chairman of the National and Victorian Industry and Commerce Accountants Committees. Mr Hollingsworth is also a Fellow of CPA Australia and Chartered Management Accountants.

Dr Ravi Krishnan PhD
Chief Scientific Officer
Dr Ravi Krishnan is a basic scientist with a long-standing interest and experience in experimental pathology, transplantation immunology, gene and stem cell therapy. He has also had significant experience in investigating novel compounds with immune modulatory effects, anti-inflammatory and anti-angiogenic properties.

Dr Keith Williams AM, FTSE
Business Development Manager
Dr Keith Williams is a scientist who has been involved in the Biotechnology field for 35 years. He was founder and CEO of Proteome Systems Ltd, which listed on the ASX in 2004, and has helped grow several other biotech enterprises. Before establishing Proteome Systems, Dr Williams built the Biotechnology program at Macquarie University in Sydney and established the world's first Major National Proteomics facility. His team coined the word "proteome". He has extensive experience in building partnerships with major international companies in the biotechnology space, with particular focus on the US and Japan.

Dr Claire Kaufman BVSc
Operations Manager (Respiratory)
Dr Claire Kaufman, is an experienced Veterinary Surgeon. After 8 years of clinical veterinary and organisational experience in private practice and large animal welfare organisations, Claire pursued work in pre-clinical Immunology research and was responsible for the co-ordination of preclinical therapeutic trials. She is also has experience in reviewing research proposals as a Category A Animal Ethics Committee member. As a practicing veterinarian, Dr Kaufman has extensive prior experience with the use of Pentosan Polysulphate Sodium.

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. Given a slight lack of availability of similar local companies, we have included one overseas company, Verona Pharma Plc (LON: VRP), in our group of comparables. 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 65 cents per share**.

Table 2. Comparable companies used to determine a fair enterprise value for Paradigm Limited.

Company	Exchange	Ticker	Mkt Cap[1,2]	Cash[1]	EV[1,3]
Starpharma Holdings Limited	ASX	SPL	256.1	29.5	226.8
Viralytics Ltd	ASX	VLA	122.4	19.5	102.9
Verona Pharma Plc[4]	LON	VRP	65.3	12.7	52.5
Suda Ltd	ASX	SUD	33.1	4.2	28.8
Invion Ltd	ASX	IVX	8.2	1.9	6.3

[1]Million AUD; [2]As of 30 November 2015; [3]EV = Enterprise Value = Market Capitalisation minus Cash; [4]1 AUD = 0.4781 GBP

Company	Overview
Starpharma Holdings Ltd	Commercialising an old technology of synthetic branching polymers (dendrimers). Lead product VivaGel® is in phase III trials for the prevention of bacterial vaginosis (BV), approved to provide symptomatic relief of BV in Europe and is used as a coating on Ansell condoms. Starpharma's dendrimers-based DEP™ drug delivery platform has been licenced to AstraZeneca for multiple programs (first product returns USD126m in milestones plus royalties; subsequent programs deliver USD93m in milestones plus royalties). Starpharma has multiple oncology focussed DEP™ programs, the most advanced of which is in phase I trials. Finally, Starpharma has a dendrimer-based technology, termed, Priostar®, designed to enhance the performance/activity of agrochemicals. It has several internal programs based on the technology (e.g. glyphosate), as well as several programs partnered with agrochemical companies.
Viralytics Ltd	Principally focussed on developing CAVATAK™ (naturally occurring cocksackievirus 21) as an anticancer immunotherapy. CAVATAK™ has completed a phase II study in melanoma. It is in a further four phase 1b studies: One a collaboration with Merck & Co. in lung and bladder cancers in combination with Keytruda (pembrolizumab, Merck & Co.); two in melanoma, one combined with Yervoy™ (ipilimumab, Bristol-Myers Squibb) and one combined with Keytruda; and one in superficial bladder cancer.
Verona Pharma Plc	Is almost exclusively focused on commercialising RPL554. It is an old compound co-invented by a former Director of Research at Glaxo. The company believes it has a dual mechanism of action relevant to respiratory diseases, acting as an anti-inflammatory agent and a bronchodilator. Previous attempts aimed at the targets of RPL554 have failed for safety reasons. It is in a phase II trial for chronic obstructive pulmonary disease, a phase II trial in asthma and a phase I trial in cystic fibrosis is planned.
Suda Ltd	Suda is reformulating a number of standard of care tablet 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.
Invion Ltd	Invion's lead product is oral INV102 (nadolol). Nadolol is a generic drug used in the treatment of hypertension and chest pain and Invion is repurposing the drug for smoking cessation, where it has completed a phase II trial, and asthma, where enrolment for an n=66 phase II trial has been completed. Invion envisages developing inhaled versions of INV102 for asthma, COPD and cystic fibrosis. INV104 is a program aimed at reformulating the oral drug zafirlukast into an inhaled form and is next expected to enter preclinical toxicology studies. INV103 (ala-Cpn10) is in a phase II studies for lupus and is a legacy asset from when Invion was known as CBio.

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

Comparables	Weighting (%)
Starpharma Holdings Ltd	3
Viralytics Ltd	3
Verona Pharma Plc	50
Suda Limited	28
Invion Limited	16

Price Target Calculation	
Present Estimated PAR EV	**$45.3m**
Discount Rate	12.0%
12-Month Estimated PAR EV	$50.7m
12-Month Estimated PAR Mkt Cap	$57.0m
12-Month Price Target	**$0.65**

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Expected total Return is measured as (capital gain (or loss) + dividend)/purchase price

We have divided our recommendations into three main categories:

Buy: Expected Total Return in excess of 15% over a 1 year period.

Hold: Expected Total Return between 0% and 15% over a 1 year period.

Sell: Expected Total Return less than 0% over a 1 year period.

Analyst Verification

I verify that I Marc Sinatra, have prepared this research report accurately and that any financial forecasts and recommendations that are expressed are solely my own personal opinions. In addition, I certify that no part of my compensation is or will be directly or indirectly tied to the specific recommendation or financial forecasts expressed in this report.

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