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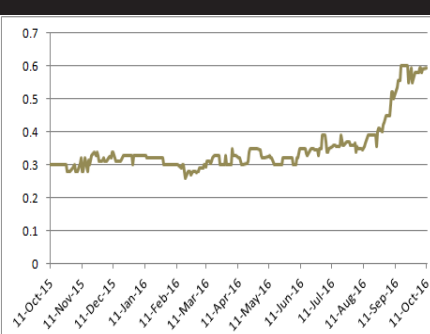
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PARADIGM BIOPHARMACEUTICALS LTD
(PAR.ASX)**RESEARCH NOTE****11 October 2016****RECOMMENDATION****Buy****PRICE****\$0.595****TARGET PRICE****\$1.02****RISK****High (Speculative)****BRIEF COMPANY DESCRIPTION**

Paradigm Biopharmaceuticals listed on the ASX in August 2015, is focused on repurposing Pentosan Polysulphate Sodium (PPS) for new orthopedic and respiratory applications. Pentosan Polysulfate Sodium was developed in Germany in 1949 and has established anti-inflammatory and anti-thrombotic properties. It has been in use for over 60 years and as such its safety profile has been firmly established. The Company addresses conditions that start with and are sustained by inflammation. Lead clinical indications involve treating injury that results in bone marrow edema (BME), the allergic inflammatory response in allergic rhinitis (AR), which is commonly known as 'Hay fever' and alpha-viruses for which there are currently no cures (Ross River and CHIKV). The combined markets for these indications are well in excess of US\$14.5B.

COMPANY DATA (11/10/2016)

ASX Code	PAR.ASX
Market Capitalisation (fully diluted)	~\$52.1m
Enterprise Value	~\$49.1m
Shares on Issue	~87.5m
12 Month High/Low	\$0.62/0.26
Ave Monthly Turnover	~0.883m
Cash – July 2016	~A\$3m

12 MONTH SHARE PRICE

Paradigm Biopharmaceuticals Hayfever - Blockbuster Potential

The Australian Biotechnology company, Paradigm Biopharmaceuticals Ltd ('Paradigm' or 'PAR') are repurposing the existing drug Pentosan Polysulfate Sodium (PPS) for treating Hay fever (Allergic Rhinitis), Bone Bruising (Bone Marrow Edema) and have recently added alphavirus (Ross River and chikungunya virus – viral arthritis) as their third PPS program.

The last two months has seen leading Immunologist Professor Jonas Erjefalt (Lund University, Sweden) present positive preclinical efficacy data on Rhinosul® (PPS) for allergic rhinitis (hay fever) treatment at the Australian Society of Clinical Immunology and Allergy, Paradigm successfully complete its Phase I clinical trial for Hay fever and the execution of a strategic partnership with Griffith University to develop a PPS treatment for alphavirus – which would be a world first.

By repurposing an existing drug with a well known and established safety profile Paradigm is significantly reducing the risk and cost of bringing the drug to market for other uses. Trial costs are greatly reduced and trial result timelines (price catalysts) are significantly brought forward all without diminishing the end potential payoff. Coupled with the multi-billion dollar target market potential (combined US\$14.5B) we believe there is a very real potential for a circa billion-dollar partnering transaction to be executed between Paradigm and a global pharmaceutical company upon conclusion of the upcoming Phase II Hay fever and/or BME trials – with the pivotal Phase II Hay fever trial expected to complete Q2CY2017.

We maintain coverage of Paradigm with a BUY recommendation and we increase our valuation of PAR to \$1.02 per share which is derived from using a combination of probability weighted DCF methodology (\$1.14) and peer group valuation (\$0.90 implied PAR share price). Our target price of \$1.02 per share sits in the midpoint of our valuation range.

Repurposing an existing drug – Pentosan Polysulfate Sodium (PPS) greatly improves chances of clinical success
Repurposed drugs have a 2.5 times better chance of being successfully commercialised compared to "de novo" (new drugs).¹ With over 60 years of global sales, PPS has a host of human data and an excellent safety profile. This well known safety profile should lead to a significantly lower cost of development, reduced clinical trial timelines and a reduced risk of clinical failure. It is this primary factor, which distinguishes Paradigm from the majority of biotechnology companies on the ASX.

Targeting very large addressable markets in excess of US\$14.5B+

PPS is set to be a new, multi-acting treatment for bone marrow edema (estimated >US\$2.5B market)², a condition currently with no effective treatment and allergic rhinitis – Hay fever (>US\$11B market³), a widespread condition currently treated by largely ineffective antihistamines and perceived harmful corticosteroids. We conservatively estimate the global CHIKV/RRV addressable market to be circa US\$1B. There is also great potential for other disease states involving inflammation such as Chronic Obstructive Pulmonary Disease (COPD) and Asthma to be treated with PPS thus opening up new markets and increasing the potential value of the compound.

Highly experienced board and management team that have delivered large licensing transactions

Paradigm's board and senior management have held positions with top ASX listed companies, CSL (CSL.ASX) and Mesoblast (MSB.ASX) and were part of the team that executed the US\$1.7B Cephalon partnership.

Compelling Pre-clinical and clinical data indicates PPS could be very effective treatment in humans with Hay fever, BME and viral arthritis/alphavirus

Professor Jonas Erjefalt proved the anti-inflammatory effects of PPS were the same if not better than comparator drug – budesonide. Combined with independent and peer reviewed data from Chiang et al (paper attached) PPS was shown to be a potent mast cell stabilizer (anti-histamine) PPS could be first in class i.e. one drug treating both the early and late stage of the immune response. Furthermore PPS was shown to be as good as/better than the leading intranasal corticosteroid, AstraZeneca's Rhinocort® / Budesonide). Professor Erjefalt's data has been submitted to the renowned scientific journal 'Allergy'.

Multiple share price catalysts expected over the coming 12 months

Over the next 12 months Paradigm will have numerous major clinical milestones, namely: initiation of the Hay fever Phase II trial, Phase II completion and results, BME Phase II ongoing and interim results, Peer Review Publication for Hay fever, initiation of RRV/viral arthritis Phase II. This newsflow will be complemented by the Company's reporting on operations, IP and other programs.

The addition of alphavirus as Paradigm's third PPS program further diversifies the company

Paradigm's strategic partnership with Griffith University was formed following peer reviewed published preclinical data demonstrating efficacy of PPS in the mouse models of Ross River virus (RRV) and Chikungunya virus CHIKV infection. Five patients with RRV-arthritis (joint pain) have already been treated with PPS under the TGA Special Access Scheme demonstrating tolerance and potential clinical effects and we believe that mid-tier to small pharmaceutical companies would be interested in partnering with Paradigm on developing a treatment for RRV/CHIKV in the medium term.

Recent Transactions highlight big pharma interest in respiratory and BME spaces

Generic drug maker Mylan NV (MYLO) acquired Meda AB (MEDAA.ST) in a US\$7.2 billion cash-and-stock deal that was a 92% premium to last close. One of Meda's main drugs was Dymista® which is RHINOSUL®'s closest comparative product.

1. Khanaoua A, Chuki P & De Sousa A (2014) Ind J Appl Res 4: 462-466. Drug Repositioning: Old Drugs for New Indications

2. Paradigm Company Presentation 16/03/2016

3. V Visiongain: Allergic Rhinitis Drugs Market Forecast 2015-2025: Future Prospects for Companies in Antihistamines, Corticosteroids, Immunotherapy & Vaccines & Paradigm Company Presentation

(All dollars referred to in this report are in Australian dollars unless otherwise stated)

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10 Reasons to Invest in Paradigm Biopharma

Repurposing an existing drug with excellent safety profile greatly improves chances of clinical success. With over 60 years of global sales, PPS has a host of human data available and an excellent safety profile. This will greatly reduce the risk of clinical failure.

Compelling pre-clinical data from peer reviewed publications support Paradigm's programs. Paradigm's three lead indications – BME, Hay fever and alphavirus/viral arthritis have had pre-clinical data published in or submitted to scientific journals showing that PPS could be an effective treatment in humans for these disease states. This pre-clinical data is independent and peer reviewed and would not be published if it didn't show strong signs of efficacy or present an argument warranting further clinical analysis.

Paradigm is targeting Bone Marrow Edema and alphavirus, conditions with no effective treatment. PPS has the opportunity to be 'first in class' for treating both BME and alphavirus, a US\$2.5B and >\$US1B markets respectively and potentially much larger when you take into account other forms of bone bruising and other mosquito borne viruses. There are very strong links between BME being left untreated and early onset of osteoarthritis indicating that PPS may one day be a treatment for the prevention of OA resulting from traumatic injury.

An experienced board and management team that are industry leaders, having held senior management positions with top ASX listed companies, CSL (CSL.ASX) and Mesoblast (MSB.ASX). The Paradigm board/management has the ability to bring biopharmaceutical products from clinical development to commercialisation and the proven track record of transacting with big pharma.

Targeting very large addressable markets in excess of US\$14.5bn+ will attract big pharma interest should PPS be a new, multi-acting treatment for bone marrow edema, a condition currently with no effective treatment, allergic rhinitis (hay fever), a widespread condition currently treated by largely ineffective antihistamines and perceived harmful corticosteroids and alpha-viruses for which there are currently no cures (Ross River and CHIKV).

Short and inexpensive trials mean Paradigm's is able to achieve clinical milestones much quicker than traditional biotechnology companies. Shorter/Cheaper trials result in less dilution, which means far greater shareholder returns in the event of successful licensing. With several major clinical trial and product development catalysts expected over the next 1-12 months investor interest in the company will be maintained.

Potential to disrupt the dissatisfied Hay fever market. Over half of patients are dissatisfied with available hay fever medications, with 60% indicating they would be very interest in new treatments. With the potential be an effective treatment in a growing US\$11 billion market, RHINOSUL® may become a very interesting proposition for big pharma.

Multi-faceted IP strategy which covers manufacturing, formulation and delivery patents protects Paradigm from competition. Exclusive rights to the only FDA-approved version of PPS (bene pharmaChem) for human use ensure protection of Paradigm's position.

Management/Board own ~33% of the company and are very much aligned with shareholders. Having Management/Board own such a meaningful position as this means they will always act in the best interest of shareholders, this has been shown by their prudent cash management and efficient use of shareholders funds.

Arguably one of the best risk-reward plays in the ASX listed biotechnology sector. Paradigm's strategy of repurposing and small market capitalisation compared to the potential payout of a successful licensing deal makes the Company a unique and desirable risk/reward investment opportunity.

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Company Overview

Paradigm Biopharmaceuticals listed on the ASX in August 2015 and is focussed on repurposing pentosan polysulphate sodium (PPS) for new orthopaedic and respiratory applications. PPS was developed in Germany in 1949 and has established anti-inflammatory and anti-thrombotic properties. It has been in use for over 60 years and as such its safety profile has been firmly established. The Company addresses conditions that start with and are sustained by inflammation. Lead clinical indications involve treating injury that results in bone marrow edema (BME), the allergic inflammatory response in allergic rhinitis (AR), which is commonly known as 'Hay Fever' and alpha-viruses for which there are currently no cures (Ross River and CHIKV).

Given the pitfalls, time and costs involved in new drug (De Novo) development repurposing existing registered drugs has become more popular over recent times. From 2007-09, 30-40% of drugs or biologics that were approved or launched for the first time in the US were either drugs repurposed for new indications, reformulations or new combinations of existing drugs.

Paradigm's core business revolves around the repurposing of PPS for a number of indications unrelated to its already approved uses. These are:

First target indications:

- **Bone marrow edema** (ZILOSUL® - PPS for bone bruising) – currently in clinical trial
- **Allergic rhinitis** (RHINOSUL® – PPS for hay fever) – about to enter clinical trial
- **Viral Arthritis – Alphavirus** – PPS to treat both acute and chronic symptoms associated with mosquito transmitted alphavirus infections such as Ross River virus (RRV) and Chikungunya virus CHIKV infection.

Secondary indications:

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

Primary PPS Indications

- Bone Marrow Edema
- Zilosul®
- Hay Fever - Rhinosul®
- Viral Arthritis

About Pentosan Polysulphate Sodium (PPS)

The oral formulation of PPS, manufactured by Bene PharmaChem ("Bene"), was approved by the US FDA in 1996 for the treatment of interstitial cystitis, commonly known as painful bladder syndrome, where it is 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. The patents covering the oral formulation expired in 2010. Although due to the extremely complex manufacturing process, no generic competition has been formulated, suggesting other companies are unable to manufacture or source PPS to the approved standard. 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 sulphatation of the actual PPS sample. Since this is tied to the manufacturing method, the method used to create the PPS with consistent, well characterised content and biological activity, already deemed acceptable by the US FDA, is a key component of the company's IP of its product.

The Company also has a proprietary platform technology based on exosomes. Exosomes are unique small bodies secreted by human cells and are thought to be responsible for part /all the regenerative characteristics of stem cells. The Company plans to continue further development of exosomes in line with its other programs as potential mono therapies or in combination with PPS, however due to the early stage of this program we will expand on this platform technology in the future once it has progressed further.

Regional Approval for PPS

The injectable form of PPS has been sold in Germany since 1949, approved for the prevention of thromboembolism and the treatment of acute blood vessel occlusions. It is the injectable formulation (intramuscular) that Paradigm will employ for the treatment of Bone Marrow Edema.

The injectable formulation of PPS is not presently approved for human use (approved for veterinary use to treat osteoarthritis) in Australia. The safety profile of the injectable form is proven, being approved for use in numerous countries, including four of the prevalent pharmaceutical markets, being Germany, Spain, Italy and France. Since approval, there have been in excess of 100 million injectable doses administered.

The Oral formulation of PPS is approved by the TGA in Australia and FDA in the United States and is sold under the name Elmiron, by Janssen Pharmaceuticals, for the treatment of interstitial cystitis (painful bladder syndrome).

Paradigm is the first Company to formulate PPS into a nasal spray form and will require a short phase I safety and tolerability clinical trial. The nasal spray form has been formulated to standard, enabling PPS to be finely dispersed in a stable manner. Importantly, the nasal spray form can be manufactured to either be preservative free or contain preservatives to suit individual markets.

The injectable form of PPS has been sold in Germany since 1949.

Since approval, there have been in excess of 100 million injectable doses of PPS administered.

Paradigm is the first Company to formulate PPS into a spray form.

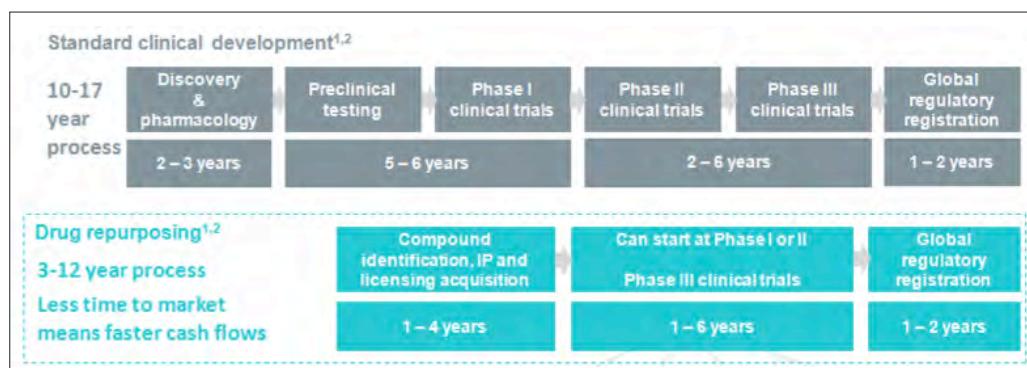
Why Repurpose Compounds?

The quote of Dr Stephen Naylor & Judge M. Schonfeld rings true for the global pharmaceutical industry: "The pharmaceutical industry is still beleaguered by escalating costs, stagnant productivity and protracted timelines as it struggles to bring therapeutic drugs to market. This situation has been compounded by a ravenous generic drug sector, and patients that have morphed into a discerning consumer population."⁴

Value and challenges of Drug Repurposing/Repositioning/Rescue ("DRPx")

There are a number of substantial benefits of utilising a DRPx strategy in comparison to conventional de novo drug development programs, which result in a greater chance of clinical success, in a reduced timeframe for a fraction of the traditional capital outlay. The most prevalent benefits include:

- I. **Cost Savings** – It is suggested by Dr Aris Persidis, President and co-founder of Biovista Inc, that the cost "to relaunch a repositioned drug averages US\$8.4 million."⁵ This figure is at the low end of the spectrum, relatable to line extension DRPx cases, thus may be multiplied to a high case of US \$100-300 million if the DRPx drug has to undergo complex Phase II and Phase III clinical trials. This figure represents a fraction of the average de novo drug development cost of US\$1.778 billion.⁶
- II. **Time Savings** – Repurposing a compound dramatically reduces the clinical approval process due to the established clinical data that accompanies it. The average cycle time of a DRPx drug is approximately 3-12 years, considerably less than de novo drug development at 10-17 years.⁷



- III. **Risk/Productivity** – The attrition rate of conventional de novo drug drugs is a staggering ~95%. The leading factor of the high attrition rate is due to a compound's lack of safety (~45% failure in Phase I) and efficacy (65% failure rates in Phase II).⁸ As a result of the high attrition, there is an increased pressure on the drug pipeline, which negatively affects the productivity/focus of pharmaceutical companies.
- IV. **Higher Success Rates** – As DRPx drugs have been either been approved or shown to be safe in late stage trials, they can enter the clinical cycle at the efficacy stage, therefore the failure rate is significantly decreased, promoting the chances of a successful launch. Approximately 25% of DRPx drugs successfully make it from Phase II to launch, in comparison to only 10% for conventional de novo drugs.
- V. **Market Potential** – The market potential for a DRPx drug is subject to the same market forces as a conventional de novo drug, such as, market need, patient acceptance, market strategy and intellectual property position.⁹ Therefore a DRPx drug has the same potential to reach 'blockbuster drug status' as a de novo drug. A recent example of a DRPx blockbuster drug is dimethyl fumarate (brand name Tecfidera) from Biogen IDEC. It was approved for a new indication to treat multiple sclerosis (MS) in 2013 and achieved revenue sales of >\$2.5 billion worldwide in 2014. This represented ~30% of total revenues for Biogen IDEC last year
- VI. **Intellectual Property** – Utilising a DRPx strategy can help elongate a drugs patent life, thus prolonging product life-cycle and reducing the 'patent cliff' effect.

The pharmaceutical industry is still beleaguered by escalating costs, stagnant productivity and protracted timelines as it struggles to bring therapeutic drugs to market.

Repurposing reduces the cost of development by approximately ~90%.

The average cycle time of a DRPx drug is approximately 3-12 years, considerably less than de novo drug development at 10-17 years.

Figure 1.
Standard Drug Development vs Drug Repurposing

Source: PAR Company Presentation

Approximately 25% of DRPx drugs successfully make it from Phase II to launch, in comparison to only 10% for conventional de novo drugs.

Repurposed drugs have the same potential to reach 'blockbuster drug status' as a de novo drug.

4. Therapeutic Drug Repurposing: repositioning and rescue. Winter 14 by Dr Stephen Naylor & Judge M. Schonfeld.

5. Persidis, A. The Benefits of Drug Repositioning. Drug Discov. World Spring Edition: 9-12 (2011).

6. <http://www.ddw-online.com/drug-discovery/p274232-therapeutic-drug-repurposing-repositioning-and-rescue-winter-14.html>

7. Source: PAR Company Presentation

8. Paul, SM et al. How to Improve R&D Productivity: the Pharmaceutical Industry's Grand Challenge. Nature Reviews: Drug Discovery, 9, 203-214 (2010).

9. Persidis, A. The Benefits of Drug Repositioning. Drug Discov. World Spring Edition: 9-12 (2011).

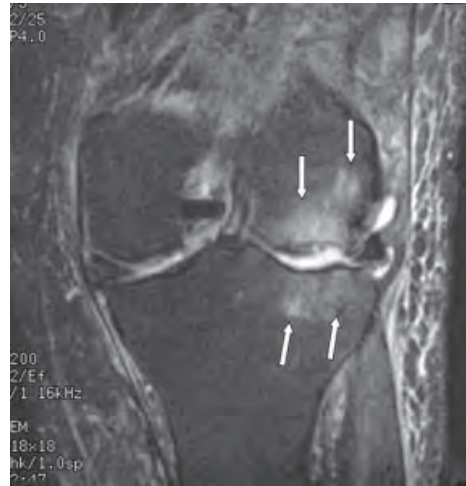
Bone Marrow Edema

– What is BME (bone bruising)?

Bone Marrow Edema (“BME”) commonly known as ‘bone bruising’ is the accumulation of interstitial fluid or inflammation within bone marrow structure (figure 2). With the development of magnetic resonance imaging (MRI), BME lesions are now easily identified and diagnosed. BME lesions are typically associated with or a consequence of a direct impact to the bone, bone fractures, ligament injury, bone tumours, invasive surgery, osteoarthritis or synovitis.

Among medical professionals it is accepted there are two distinct forms of BME:

1. Traumatic BME, such as a rupture of the anterior cruciate ligament of the knee (focus of Paradigm Phase II trial), which may resolve over a period of weeks to months.¹⁰
2. Atraumatic BME, which occurs without trauma and may be associated with the rapid progression of osteoarthritis.¹¹



There are two forms of BME:

1. Traumatic BME
2. Atraumatic BME

Figure 2.
MRI of Bone Marrow Edema
– indicated by the arrows

Source: Company Reports and BYS

Why focus on BME? - No regulatory approved pharmaceutical therapeutic options

The presence of bone marrow edema results in severe and chronic pain in the affected area. Apart from prolonged rest and immobilisation of the affected joints/anatomical region there is currently no effective, regulatory approved, therapeutic treatment available for sufferers.

The traditional treatment via rest and immobilisation may result in resolution of symptoms of pain & joint dysfunction and the normalisation in MRI within 6-18 months, although during this period the patient's quality of life is usually considerably diminished.¹²

Other treatments may include analgesics and anti-inflammatories, physiotherapy and surgical treatment (core decompression). Analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) are usually prescribed to provide some relief for BME, although it is widely accepted that NSAIDs and corticosteroids have a detrimental side-effects on the metabolism of bone and cartilage. More importantly, all current treatment options are considered as symptomatic therapy since they have little or no effect on the underlying pathophysiology responsible for BME. No treatments are currently available that influence the underlying pathology.¹³

There is currently no effective, regulatory approved, therapeutic treatment available for BME sufferers.

Acute impact injuries, Bone Marrow Lesions and BME

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:

- 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-α), 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).

There is a substantial body of research demonstrating that BME lesions are associated with acute joint injury, cartilage loss and progressive joint degeneration.

¹⁰. Meaney, Falko-Alexander Stichnoth, Clinical MR Imaging: A Practical Approach

¹¹. Rimm, J., et al., MRI of transient osteoporosis of the hip. Arch Orthop Trauma Surg, 1991. 110(2): p. 98-102.

¹². Krause, R., et al., [The transitory bone marrow edema syndrome of the hip]. Z Orthop Ihre Grenzgeb, 2002. 140(3): p. 286-96.

¹³. Ibid.

Bone Marrow Edema – What is BME (bone bruising)? Continued

- 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).

BME and Osteoarthritis

There is a growing link between BME and joint cartilage degeneration that leads to osteoarthritis (OA) and this is further evidenced by the above studies. It is believed that there are chronic health impacts associated with untreated BME, with patients having 10x greater likelihood of developing OA. It has been said by some industry participants that nearly 100% of people who have had an ACL injury will develop osteoarthritis at some point in their lives.

Assuming the direct link between BME and OA becomes proven, we see ZILOSUL[®] - PPS in BME – becoming a broader treatment for those suffering OA.

The Addressable Market for BME

The worldwide hip & knee surgical implant market is US\$16.7bn, will be US\$33bn by 2022.¹⁴ There is a current focus is on acute knee injuries but we see potential to use PPS to treat other major joints (ankle, shoulder, elbow, hip, etc.) and chronic injuries (BME case study).

Addressable market based on acute traumatic injuries:

ACL injuries associated with BME per annum in USA ¹⁵	160,000
Meniscal injuries associated with BME per annum in USA ¹⁶	800,000
Ankle injuries associated with BME per annum in USA	480,000
TOTAL - Knee & ankle Injuries Associated with BME in USA (Excludes shoulder, elbow and hip injuries as well as chronic injuries).	1,440,000

Source: Company Reports

Utilising the data above, the potential addressable market in the United States alone, based on a treatment cost of US\$1,750 is \$2.52 billion. It is important to note that this figure does not include shoulder, elbow, hip injuries and BME associated with invasive surgery.

The baseline BME market in the United States alone is US\$2.52 billion.

¹⁴. Winter Green Research (2016), Hip and Knee Orthopaedic Surgical Implants Market Shares, Strategies, and Forecasts, Worldwide, 2016 to 2022

¹⁵. Based on 200k ACL injuries per annum, with 80% being associated with BME – Niall D, et al. (2004) and Friedberg R, et al. (2016)

¹⁶. Based on 1m meniscal injuries per annum, with 80% assumed as being associated with BME – Jones C, et al. (2012)

Rationale to use ZILOSUL[®] (PPS) to treat Bone Marrow Lesions/Edema

The emergence of a BME is understood to be the initial signal demonstrating the pathophysiology of cartilage breakdown. The Synovial fluid of patients with an acute injury and consequent BME, presents substantial increases in inflammatory cytokines (principally TNF α and IL-1), cartilage degrading enzymes (MMP's and ADAMTS-5) and signs of hypercoagulability.

To effectively address this pathophysiology a compound must have multiple pharmaceutical actions, namely, anti-inflammatory (importantly Anti TNF α and anti IL-1), block the matrix metalloproteinases (MMP's and ADAMTS) and improve microcirculation.

It has been published in a variety of peer-reviewed scientific studies that PPS has demonstrated the aforementioned pharmaceutical actions, supporting the rationale for its use to treat BME.

PPS has demonstrated:

- The inhibition of cartilage degrading enzymes that are released post-acute injury.¹⁸
- Anti-inflammatory effects, whilst blocking the effects of the pro-inflammatory cytokine TNF and pro-inflammatory interleukin IL-1.¹⁹
- Antithrombic and antilipadaemic effects, which enhance microvascular circulation in the subchondral bone. Improving the microvascular circulation is believed to be a critical factor in resolving BME.²⁰
- To be safe and well tolerated in patients.²¹

Put simply, PPS is likely to reduce swelling (i.e. anti-inflammatory) improve blood flow which greatly assists the healing process.

Biomarkers (CTX I & CTX II)

Synovial fluid post an acute joint injury presents a rapid increase in levels of key inflammatory cytokines and cartilage breakdown biomarkers CTX I and CTX II, which are measurable in urine and serum. Increased levels of CTX I and CTX II indicates cartilage breakdown and subsequently the onset of osteoarthritis.

Results from a placebo controlled pre-clinical study, demonstrated that PPS administered post-acute injury maintained the pre-injury levels of the key inflammatory cytokines and cartilage breakdown biomarkers CTX I and CTX II.²² In comparison, the post-acute knee injury group administered with the placebo showed substantial increases in serum levels of cytokines (TNF α and IL-1 β) and the cartilage breakdown biomarkers of CTX I and CTX II. These increased levels occurred immediately and were maintained for up to 48 weeks, therefore it was concluded that PPS is protective to cartilage post acute injury.

The multiple pharmacological properties of PPS supports Paradigm's reasoning for further investigation into its application for the treatment of Bone Marrow Edema.

The emergence of a BME is understood to be the initial signal demonstrating the pathophysiology of cartilage breakdown.

Increased levels of CTX I and CTX II results in cartilage breakdown and subsequently the onset of osteoarthritis.

18. Troeberg L, Mulloy B, Ghosh P, Lee MH, Murphy G, Nagase H. Pentosan Polysulfate increases affinity between ADAMTS-5 and TIMP-3 through formation of an electrostatically driven trimolecular complex: Biochem. J. 2012; 443, 307-315

19. Smith JG, Hannon RL, Brunnberg L, Gebiski V, Cullis-Hill D. A multicentre clinical study of the efficacy of sodium pentosan polysulfate and carprofen (Pfizer) in canine osteoarthritis (osteoarthritis), VETERINÄR-MÖTET 2002.

20. Ghosh P and Cheras P Vascular mechanisms in osteoarthritis: Best Practice & Research Clinical Rheumatology 2001; 15: 693-701.

21. Kumagai K, Shirabe S, Miyata N, et al. Sodium Pentosan Polysulfate Resulted in Cartilage Improvement in Knee Osteoarthritis - An Open Clinical Trial. BMC Clin Pharmacol. 2010; 10: 1-24.

22. Ibid.

Further clinical studies of PPS

It has been established that PPS has the ability to suppress osteoarthritis (OA) progression in dogs and substantially reduce pain and cartilage metabolism in humans with OA.²³

Recent studies assessed the efficacy, safety and patient satisfaction in patients with a BME and associated mild radiographic knee OA. Twenty patients were administered 2mg/kg of PPS subcutaneously for a six week period. All patients demonstrated a significant improvement in clinical assessments, which included, knee flexion, pain while walking, pain after climbing up and down stairs, and more importantly these clinical improvements continued for approximately one year post-treatment.²⁴

Additionally, a randomised, double-blind, placebo controlled pilot study, administering 3mg/kg of PPS intramuscularly (IM) for a four week period, showed a significantly improved duration of joint stiffness and pain at rest in comparison to controls, for a duration of 20 weeks post-cessation of treatment. There was also significantly improved pain when walking and overall function for eight weeks post-cessation of treatment was observed in these patients with OA of the knee.²⁵

Given its properties and the stage of clinical development of PPS for the treatment of joint pathologies, it was determined an ideal candidate for further investigation into its application for the treatment of BME and hence Paradigm moved in to clinical trials with it.

It has been established that PPS has the ability to suppress osteoarthritis (OA) progression in dogs and substantially reduce pain and cartilage metabolism in humans with OA.

PPS significantly improved duration of joint stiffness and pain.

23. Ghosh, P 2012 Treatment of bone marrow edema (oedema) with polysulfated polysaccharides. WIPO Patent Application WO/2012/103588.

24. Kumagai, K., et al., Sodium pentosan polysulfate resulted in cartilage improvement in knee osteoarthritis--an open clinical trial. BMC Clin Pharmacol, 2010. 10: p. 7.

25. Ghosh, P 2012 Treatment of bone marrow edema (oedema) with polysulfated polysaccharides. WIPO Patent Application WO/2012/103588.

ZILOSUL®/PPS - Multi-acting treatment that addresses the underlying pathology of BME

ZILOSUL®, a registered trademark of Paradigm is the injectable form of PPS produced by bene pharmaChem GmbH and is the formulation that is being utilised in the ongoing BME clinical trials. It is the only known compound that addresses multiple pathways to treat BME.

In a proof of concept trial recently conducted by Paradigm, it was highlighted by the complete resolution of BME and associated pain in 5 patients that ZILOSUL® may be a complete solution to BME. ZILOSUL® has demonstrated it has the necessary characteristics (Figure 3) to treat BME, which are not present in the limited competing treatments. Competing treatments have failed to capture market share due to limited efficacy and safety profiles, enabling ZILOSUL® to quickly establish itself as market leader if clinically successful.

ZILOSUL®, a registered trademark of Paradigm is the injectable form of PPS.

ZILOSUL® Proof of concept trial demonstrated a complete resolution of BME and associated pain in 5 patients.

	 ZILOSUL®	 Iloprost®	 Ibandronate®
Anti-inflammatory	✓	✓	
Fibrinolytic agent (anti-clotting)	✓	✓	
Prevents cell death and necrosis	✓		
Increase in cartilage synthesis	✓		
High safety profile	✓		✓
Hospitalisation not required	✓		
Not administered intravenously	✓		

Figure 3.
Comparative Advantages
of ZILOSUL®

Source: PAR Company Presentation

Blood Coagulation

There has been extensive investigation into the effect of PPS on the coagulation of blood in adult humans as it has been prescribed clinically as an antithrombotic agent for a number of decades throughout Europe.

Studies in human subjects, utilising intravenously, intramuscularly and subcutaneous forms of administration at doses up to 4 mg/kg/day revealed that PPS has little or no effect on primary haemostasis or bleeding time, or platelet numbers in peripheral blood. This is important as it shows that PPS is only a very mild anticoagulant and thus should not have any adverse side effects regarding bleeding.

PPS in Dogs and Horses

As a result of the established anti-inflammatory properties of PPS, it has become the leading treatment for arthritis/osteoarthritis related musculoskeletal disorders in dogs and horses. Sold under the name Cartrophen Vet by Biopharm Australia, it acts as a disease modifying osteoarthritis drug and importantly, it helps maintain joint health, including preserving joint cartilage that is damaged by the arthritic process.

Similar to the Paradigm BME trial, the treatment requires an initial course of one injection a week for four weeks and has proven to be an effective treatment in over 80% of cases²⁶ by way of disease modification.

Doses up to 4 mg/kg/day revealed that PPS has little or no effect on primary haemostasis or bleeding time.

PPS is the leading treatment for osteoarthritis in dogs and horses.

²⁶. (Francis and Read, 1993; Cullis-Hill and Ghosh, 1994; Bouck et al, 1995; Read et al, 1996; Smith et al 2001)

BME: Clinical development program

In February 2016, Paradigm commenced an open-label Phase II(a) clinical trial in 40 patients to determine the safety and tolerability of ZILOSUL[®] in patients with a BME lesion. Patients exhibiting a BME lesion identified by MRI in association with bone pain and reduced joint function following an Anterior Cruciate Ligament (ACL) injury are administered ZILOSUL[®] twice weekly for a period of three weeks. As it is an open-label trial, there are no placebo controls and no blinding, which promotes trial flexibility and enables interim result analysis.

The clinical study is currently being undertaken across two Medical Centres in Australia, Southern Orthopaedics in Adelaide, South Australia and Box Hill in Melbourne, Victoria. Paradigm has indicated that it expects the duration of the study to be 12 months, subject to patient recruitment.

Clinical Trial Objectives:

Primary Objectives – Evaluate the:

- safety and tolerability of IM ZILOSUL[®] in subjects with bone marrow lesions following an ACL injury.

Secondary Objectives – Evaluate the:

- effect of IM ZILOSUL[®] on bone marrow lesions following an ACL injury as assessed by magnetic resonance imaging (MRI)
- effect of IM ZILOSUL[®] on functional knee joint capacity following an ACL injury.

Exploratory Study Objectives – Evaluate the:

- effect of IM ZILOSUL[®] on pain following an ACL injury and to evaluate the effect of IM ZILOSUL[®] on biomarkers of inflammation, bone and tissue remodelling
- relationships between changes in bone marrow lesions with changes in functional knee joint capacity and changes in pain intensity.

Key inclusion criteria:

Subjects who have experienced an acute anterior cruciate ligament (ACL) injury a minimum of 2 weeks and maximum of 8 weeks prior to Day 0, and have been managed conservatively with physical therapy and medications.

OR

Subjects who have experienced an acute ACL injury and have been treated with surgical intervention a minimum of 2 weeks and maximum of 8 weeks prior to Day 0.

The Company is of the opinion that the commencement of Phase II(b) may be brought forward pending the strength of the results of interim analysis. We share this view because if the results are compelling enough then why waste time proving what is already known.

Paradigm may be able to rely on the FDA's findings of safety and/or efficacy for the previously approved reference drug. This has the potential to significantly reduce the size and number of additional clinical trials required. 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. By only having to conduct one Phase III trial Paradigm could save tens of millions of dollars and several years in the development and commercialisation of both ZILOSUL[®] and RHINOSUL[®].

Paradigm commenced their BME open-label Phase II(a) clinical in February 2016.

Primary Objective is to evaluate the safety and tolerability of ZILOSUL[®].

The Company is of the opinion that the commencement of Phase II(b) may be brought forward pending the strength of the results of interim analysis.

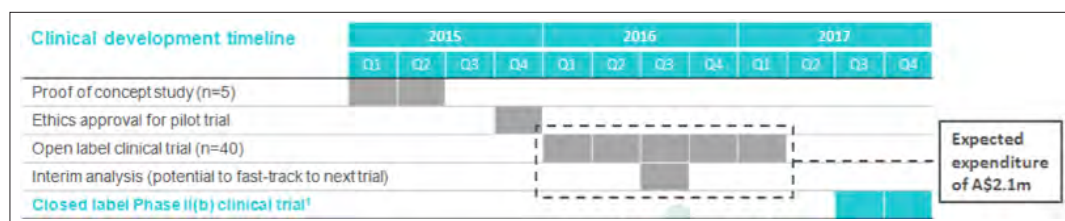


Figure 4. The Clinical Development Timeline for ZILOSUL[®] - PPS in BME

Source: PAR Company Presentation

Elite Athlete Case Study

The potential for ZILOSUL[®] to be a successful treatment for BME has been strengthened by the promising results from an 'elite athlete case study' conducted under the Therapeutic Goods Administration's (TGA's) Special Access Scheme (SAS).

The patient is an elite athlete within the Australian Football League (AFL) with an un-resolving bone marrow lesion as a result of an ACL injury, which has considerably restricted his training and ability to play over the past 2-3 years. The patient was able to gain access to the treatment under the SAS because treatments such as, prolonged rest, anti-inflammatories, corticosteroids, fluid draining and surgical intervention had failed to resolve the BME, leaving no other option.

Commencing in November 2015, the athlete had a total of six intramuscular injections of ZILOSUL[®] over six weeks. ZILOSUL[®] was well tolerated with no signs of adverse effects/events. The prescribing doctor has advised Paradigm that the initial clinical response to the ZILOSUL[®], has been very positive/encouraging, particularly given the refractory nature of symptoms in this patient.

Results – Elite Athlete Case Study

Pre-Treatment Wellbeing

- ✗ Un-resolving bone marrow lesion (2-3 year issue)
- ✗ No success with multiple therapeutic and surgical interventions
- ✗ Fluid had to be drained from the knee at least once a week

Post-Treatment

- ✓ Patient completed whole pre-season training at full capacity, first time in 2 years
- ✓ Patient has not had to drain fluid from knee since the treatment in November 2015
- ✓ Encouraging result that significantly improved patient's well-being

The potential for ZILOSUL[®] to be a successful treatment for BME has been strengthened by the promising results from an 'elite athlete case study'.

Patient completed whole pre-season training at full capacity, first time in 2 years.

	Pre treatment	Post treatment	Change
Pain	8.5 (very bad)	3.2 (mild)	↓ 62%
Joint function	69 (fair)	95 (excellent)	↑ 37%

Allergic Rhinitis (Hay Fever) – what is Hay Fever?

Paradigm is developing RHINOSUL®, the first intra-nasally applied PPS product to be used in humans for the treatment of allergic rhinitis/hay fever, a common disease that affects between 10-30% of the world's population depending on region. Due to hay fever's prevalence, it attracts a growing market in excess of US \$11 billion.

Hay fever is the result of an excessive immune system reaction to widespread allergens in the air, such as pollen, dust and pet hair. The current treatments for sufferers are somewhat lacking, as the two prevalent treatments for hay fever, antihistamines and intranasal corticosteroids do not provide a complete resolution to the issue and have perceived negative side effects.

Two Phases of Hay Fever

Upon exposure to a particular allergen, an early, acute phase response is elicited within 30 minutes. Subsequently a chronic phase response occurs after 6-8 hours, which continues throughout the allergen exposure (Figure 5).

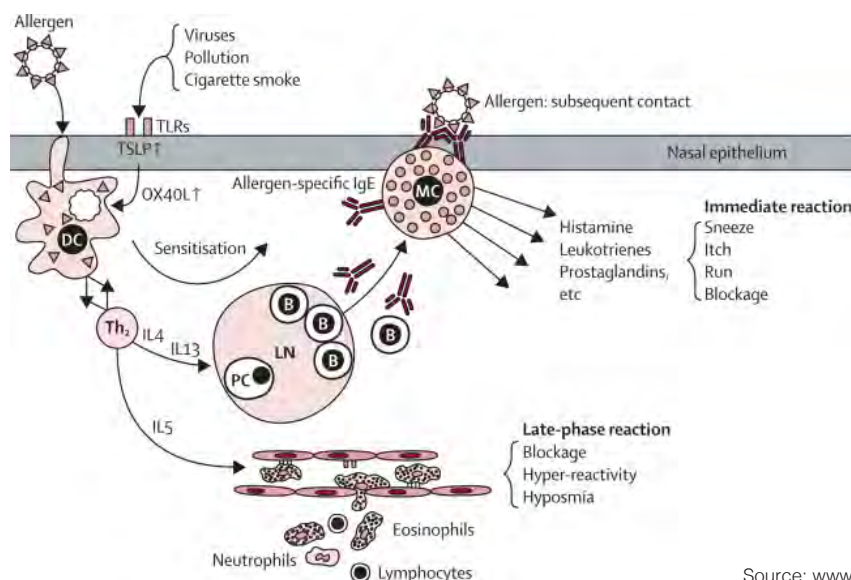
Acute Phase Response

- The acute phase of hay fever is identified by nasal itching, sneezing and rhinorrhea, resulting in the activation of mast cells, by cross-linking of IgE-allergen complexes on the cell surface.²⁷ Once activated, mast cells release histamine, which, in conjunction with additional mediators including prostaglandins, leukotrienes and cytokines, mediates the acute inflammatory effects and local symptoms.²⁸ The prevalence of histamine in the acute phase is highlighted the initial effectiveness of anti-histamines.

Chronic Phase Response

- The chronic phase response of hay fever is characterised by the permeation of inflammatory cells into the nasal mucosa, and capsular changes that result in nasal congestion. Eosinophilic infiltration usually predominates, and a range of leucocytes (TH-2 lymphocytes, neutrophils), cytokines (IL-4, IL-5, IL-13), chemokines (eotaxin, RANTES) and adhesion molecules (VCAM-1, ICAM, E-selectin) are involved.²⁹ Anti-histamines are not effective during the late stage response, leaving corticosteroids as the next available treatment option.

Figure 5: Allergic Rhinitis (Hay fever) Cycle – showing the dual state of the reaction³⁰



Source: www.nature.com

The understanding in the market about the two phases of hay fever leads to miss treatment and subsequent consumer dissatisfaction. Paradigm's compound RHINOSUL® has been shown, in preclinical models, to have both anti-histamine and anti-inflammatory effects, making it a potential first in class non-steroid based treatment for hay fever.

27. Min 2010
28. Ibid
29. (Howarth 2000)
30. Alexander N Greiner, et al, Lancet 2011; 378: 2112-22

Allergic Rhinitis (Hay Fever) – what is Hay Fever? Continued

Increased Prevalence of Hay fever

The global incidence of allergic rhinitis has been on the rise for the past century. According to the American College of Allergy, Asthma and Immunology (ACAAI), allergic rhinitis has increased 100 percent in each of the last three decades.³¹

Experts continue to debate on the reasoning for this trend, whether it is due to mounting air pollution, indoor environmental factors, improved hygiene practices, genetics, geographic location or all of the above, but there is little doubt that the disorder has been increasing at an alarming rate.

“There is clear evidence that much of that increase has occurred in developing countries,” said Matthew Ryan, MD, assistant professor of otolaryngology at the University of Texas Southwestern Medical Center in Dallas. Although it is difficult to get a handle on the epidemiology of allergic rhinitis, studies have shown that the occurrence of allergic rhinitis is increasing in areas that used to have a low prevalence, such as developing countries, Dr. Ryan said.³² The leading theoretical reasoning for the dramatic increase in hay fever is related to the fact that developing countries are adopting more western lifestyles. People are moving from rural, agricultural settings, which traditionally have had lower rates of allergies, to more urban settings, which have higher levels of air pollution.³³

Addressable market for Hay Fever

There are in excess of 600 million people worldwide³⁴ that suffer from hay fever. The market for therapeutic hay fever treatments is over US\$11 billion.³⁵ As noted above the prevalence of hay fever is increasing, leading to these market size figures to be understated.

Notwithstanding the direct therapeutic expense of hay fever there is a growing, substantial economic burden, such as missed days at work/school. A Swedish study (2016) indicated the size of the AR market may be significantly underestimated in current literature. The total cost of hay fever in Sweden (population 9.5 million) is estimated to be US\$1.4 billion annually.³⁶

An additional report by the Australian Institute of Health and Welfare on the cost of care for allergic rhinitis alone in 2011 estimating that 3.1 million (or 15% of the population) were affected (mainly those aged 25-44 years) with medication costs doubling from an estimated \$107.8 million/year in 2001 to \$226.8 million in 2010.

Current Hay Fever Treatment Options

Treatment of hay fever is typically treated with ‘over the counter’ oral and nasal formulations at a pharmacy level. The leading treatments are:

Antihistamines

- Administered orally or intra-nasally
- Typically a first line approach for mild forms of hay fever
- Block the histamine response in the early acute phase of hay fever
- Ineffective treatment for the chronic phase of hay fever, which result in chronic symptoms
- Additional downsides include drowsiness or cardiac arrhythmias in some patients

Intranasal Corticosteroid (“INCS”)

- Leading treatment for more severe and chronic hay fever symptoms
- Anti-inflammatory targeting both acute and chronic phase inflammatory responses
- Prolonged, long-term use causes concern for sufferers because of side effects, such as, the thinning of the nasal lining, potential systemic effects including growth retardation in children and hormonal complications.³⁷

Combination – Dual Acting Treatment (Antihistamine + INCS)

- Meda (MEDA.STO, US\$7.2bn takeover) have commercialised ‘Dymista®’ a new class of dual acting treatment.
- Has a number of undesirable side effects

Allergic rhinitis has increased 100 percent in each of the last three decades.

There are in excess of 600 million people worldwide that suffer from hay fever.

The market for therapeutic hay fever treatments is over US\$11 billion and growing.

Treatment of hay fever is typically treated with ‘over the counter’ oral and nasal formulations at a pharmacy level.

31. <http://www.enttoday.org/article/upward-trend-whats-to-account-for-the-increased-prevalence-of-allergic-rhinitis/>

32. (Allergy, 2008;63 Suppl 86:8-160)

33. <http://www.enttoday.org/article/upward-trend-whats-to-account-for-the-increased-prevalence-of-allergic-rhinitis/>

34. PAR Company Presentation

35. PAR Company Presentation

36. PAR Company Presentation

37. (Licari et al 2014)

Allergic Rhinitis (Hay Fever) – what is Hay Fever? Continued

Immune Response

- Newer therapies are aimed at modulating specific aspects of the allergic immune response, however so far none have been as effective as the INCS at relieving symptoms.

	paradigm RHINOSUL®	Anti-histamines	Corticosteroids	MEDA Dymista®
Treats acute phase symptoms (histamine mediation)	✓	✓	✓	✓
Treats chronic phase symptoms (tissue inflammation)	✓		✓	✓
No undesirable side effects	✓			
Anti-inflammatory	✓		✓	✓
Simple to manufacture	✓			

Figure 6.
Current Hay Fever Treatments

Source: PAR Company Presentation

Consumer Dissatisfaction

A survey conducted in 2005 by the Asthma and Allergy Foundation of America, identified that more than half of patients were dissatisfied with the available medications, with 60% indicating they would be very interest in new treatments. Based on the high level of dissatisfaction for current treatment options, through RHINOSUL®, Paradigm is aiming to disrupt the forever growing US\$11 billion hay fever market.

More than 50% of hay fever sufferers are dissatisfied with the available medications.

Rationale for the use of RHINOSUL® (PPS) to treat Hay Fever

Utilising a range of pre-clinical data it is anticipated that in comparison to other hay fever treatments, Rhinosul® may have the following advantages:

- Inhibiting histamine release from mast cells within the nasal passage. It has been identified that RHINOSUL® restricts histamine released from the mast cells in a greater degree than clinically available mast cell stabilizer, disodium cromoglycate (Cromolyn, IVAX Pharmaceuticals).³⁸
- Demonstrating significant efficacy in reducing infiltrating leukocytes in the nasal passage post an allergen challenge. The reduction of eosinophils is essential in both the acute and chronic phases of hay fever.³⁹
- Blocking key pro-inflammatory cytokines (IL-4, IL-5 and IL-13) that target cell populations (TH2 cells, B cells, mast cells, eosinophils) involved in hay fever.⁴⁰
- Imposing an aggressive action against eotaxin-1 (CCL11) and eotaxin-2 (CCL24) involved in the penetration of eosinophils into the nasal passage.⁴¹
- Demonstrating in pre-clinical studies to have a notable action against chemokines IL-8, MIP-1 alpha, MCP-1, consequently restricting the infiltration of leukocytes (eosinophils; neutrophils) to sites of allergen induced inflammation in the nasal passage.⁴²

Preclinical Data Underpins Efficacy of Paradigm's Rhinosul®

In September the presentation of key preclinical data (pending peer review publication) provided a valuable independent validation of Paradigm's hay fever program. The trials conducted by Professor Jonas Erjefalt's Lund University team in an industry standard, validated animal model demonstrated that PPS is as effective as the industry leading treatment, an intra-nasal corticosteroid, Budesonide. If the results can be replicated in human models, RHINOSUL has the potential to attract a significant licensing transaction and become a blockbuster treatment for hay fever.

Key preclinical data provides valuable independent validation

38. Cromolyn, IVAX Pharmaceuticals

39. MacDowell and Peters 2007

40. Howarth 2000

41. Ibid.

42. Ibid.

Rationale for the use of RHINOSUL® (PPS) to treat Hay Fever - Continued

Compelling Pre-clinical Data Overview

Pentosan Polysulfate Sodium (PPS) is a semi-synthetic heparin like macromolecular carbohydrate. TH2 cytokines are key effectors in the allergy response. Molecular studies investigating ligand-binding interactions have demonstrated that PPS is a potent and specific antagonist to the TH2 cytokines IL-4, IL-5 and IL-13 compared to heparin. The TH2 cytokine antagonistic activity of PPS was functionally effective since PPS was shown to inhibit IL-4, IL-5 and IL-13 dependent growth of cell lines.

Preclinical translational studies using the guinea pig model of ovalbumin-induced allergic rhinitis demonstrated that intra-nasal administration of PPS prophylactically to nasal allergen challenge of sensitized animals significantly reduced the late phase plasma extravasation and luminal influx of eosinophils, neutrophils, and total lavage leukocytes. PPS also reduced nasal tissue levels of CD3+ T cells and eosinophils in allergic animals. These effects were comparable to the intra-nasal corticosteroid, budesonide in the guinea pig model (Mori et al Internal Medicine Journal (2016) 46 (Suppl. 4): 5–29). In addition other findings by other researchers have demonstrated that PPS is a potent mast cell stabilizer by inhibiting histamine release compared to cromolyn (Chang et al J Urol. 2000 Dec;164(6):2119-25) and therefore potentially reduces the early phase allergic response.

Paradigm's Chief Scientific Officer Dr Ravi Krishnan stated "Independent and peer-reviewed experimental data has also demonstrated that PPS is an effective mast cell stabiliser (reduces histamine release)." He also stated "Anti-histamines are important in the early phase of the allergic response and combined with the anti-inflammatory activity would suggest that Rhinosul® has the hallmark of a first-in-class drug for the treatment of hay fever symptoms".

Therefore PPS fulfills the role as a potential candidate molecule for the treatment of allergic rhinitis targeting the early and late phase allergic response, making it the first of its kind.

Professor Erjefalt said, "Our research showed that the drug, PPS, blocked the TH2 cytokines, such as IL-4, IL-5 and IL-13 which are known to be responsible for the late stage of the disease causing nasal congestion. Our data showed that the anti-inflammatory properties of PPS were as effective as well-known intra-nasal corticosteroid-based treatments". Corticosteroids are known to have undesirable side effects so treatment with this drug represents a potential breakthrough for those people wanting a steroid-free treatment for hay fever.

PPS was shown to inhibit IL-4, IL-5 and IL-13 dependent growth of cell lines

PPS is a potent mast cell stabilizer by inhibiting histamine release

PPS fulfills the role as a potential candidate molecule for the treatment of allergic rhinitis targeting the early and late phase allergic response.

AR - Clinical Development Program

Successful Phase I Clinical Trial paves the way for commencement of pivotal Phase II Clinical Trial
Paradigm successfully completed its phase I, randomised, double blind, placebo-controlled clinical trial with initial results released in August 2016. The trial was designed to evaluate the safety and tolerability of single and multiple doses of RHINOSUL® (intranasal pentosan polysulfate sodium) in healthy individuals. The trial included 18 randomised individuals, with 9 individuals per dose level cohort and 2 dose level cohorts.

Paradigm successfully completed its phase I clinical trial.

Following the successful toxicology study Paradigm undertook a Phase 1 safety study. The study was conducted to Good Clinical Practice (GCP) standards in a dedicated Phase 1 Clinical Trial Unit. The study is the first ever to evaluate the new nasal route of administration for PPS, in a randomised double-blind, placebo-controlled design. Participants were monitored intensively with full blood analysis, daily clinical observations and a general and nasal examination. With the trial successfully completed, the Company has been able to collate valuable and comprehensive safety data for single and 7-day dosing periods.

Phase II(a) placebo controlled allergen challenge study will commence in December 2016.

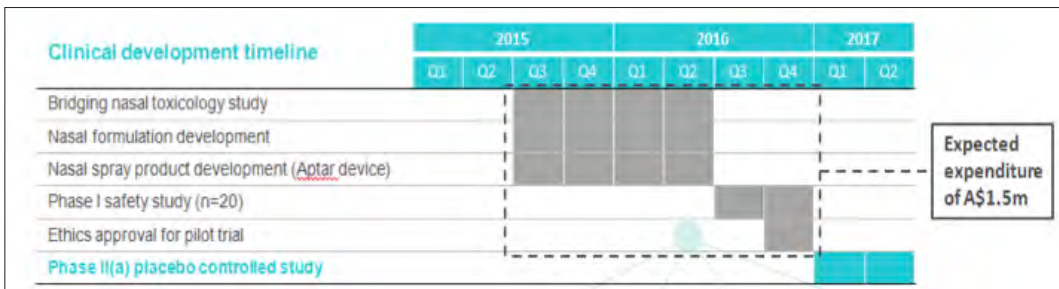
With the database now locked and analysis underway, the final report from the Phase 1 study is due in October 2016. In the interim, the Company announced that, "in the absence of any significant safety concerns in any treated participant, the appointed Phase 1 Data and Safety Monitoring Committee has endorsed the Company's proposed dosing regime for a second clinical trial".

Phase II(a) Clinical Trial

The phase II(a) clinical trial is a challenge study, which will be randomised, double blinded, cross over with placebo control. Paradigm is utilising the leading facility in Sweden and clinical trial model, which was implemented by AstraZeneca to screen for its hay fever compounds (Budesonide), including the top selling Rhinocort®.

Following AstraZeneca's trial design is a significant advantage for Paradigm, as the trial process and therefore data collected will be in a format that is accepted by big pharma and the regulatory bodies. Positive results are expected to attract significant partnering interest.

Figure 7: Hay fever Clinical Trial Timeline*



* Phase II(a) placebo controlled study has been brought forward and will now commence in December 2016

Viral Arthritis - Alpha Viruses

What is Viral Arthritis?

Viral arthritis is defined by inflammation of the joints resulting from a viral infection, in particular arthritogenic alphaviruses.

Arthritogenic Alphaviruses

Alphaviruses are a genus of enveloped, positive sense, single-stranded RNA viruses belonging to the Togaviridae family. Typically transmitted via mosquitoes, the arthritogenic alphaviruses comprise of chikungunya virus (CHIKV), Ross River virus (RRV), Barmah Forest virus (BFV), o'nyong-nyong virus, the Sindbis group of viruses and Mayaro virus. Alphavirus infection is associated with rheumatic disease, principally polyarthralgia and/or polyarthritis⁴³ (aches in the joints, joint pains), which are often prolonged, leaving patients bed-ridden and incapacitated.

Acute phase

The primary symptoms of arthritogenic alphaviruses summarised below (Figure 8), occur across both the acute phase and chronic phase of the disease. Post infection of CHIKV, the virus is present in the blood for 5-7 days and is characterised by an immediate onset of fever, reaching 40 C in some cases, resulting in chills and rigors. Polyarthralgia and/or polyarthritis usually initiates in conjunction with the onset of fever, with peripheral joints (hands, wrists & ankles) and large joints (shoulders, knees and back) typically affected.⁴⁴ Joint effusions (increased amount of fluid within the synovial compartment of a joint) are experienced in the majority of cases, resulting in pain and reduced mobility. Skin manifestation, the final symptom of the acute phase can appear 2-4 days post the onset of fever. Haematological findings include leukopaenia with lymphocyte predominance, occasionally thrombocytopenia, and elevated erythrocyte sedimentation rate and C reactive protein levels.

The acute phase for other alphaviral arthritides such as Ross River virus is similar to that of CHIKV. Polyarthralgia and/or polyarthritis is severe with the presence of joint effusions. Raised erythrocyte sedimentation rates also occur but begin to normalise within a few weeks.⁴⁵

Chronic Phase

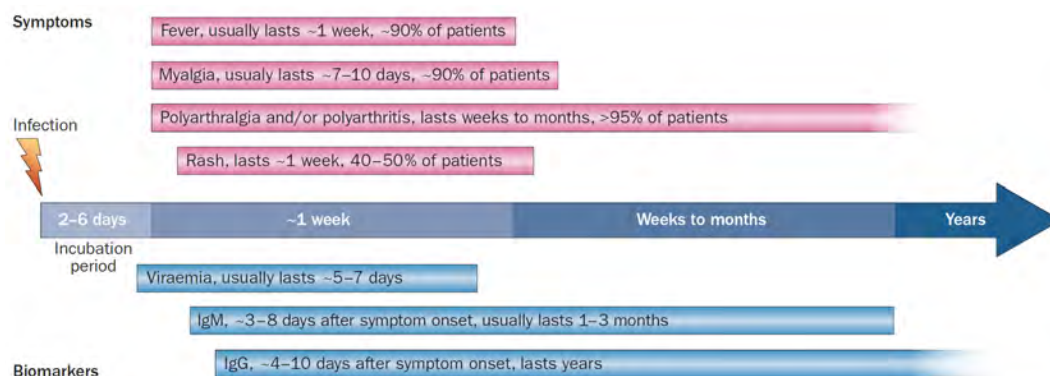
The central feature of the majority of alphaviral arthritides, especially CHIKV and RRV is a prolonged and debilitating polyarthralgia and/or polyarthritis, which is accompanied by fatigue (Figure 8). Patients usually recover over several weeks, but in some cases the disease can last for a 6-12 months, leaving the sufferer completely debilitated, whilst placing serious pressures on healthcare systems worldwide.⁴⁶

Viral arthritis is defined by inflammation of the joints resulting from a viral infection, in particular arthritogenic alphaviruses.

Symptoms occur across both acute and chronic phases of the disease.

Polyarthralgia and/or polyarthritis is severe with the presence of joint effusions

Figure 8 - Alphavirus Symptoms



Source: Subrbier, A .et al. (2012)

43. Suhrbier, A. et al. Nat. Rev. Rheumatol. 8, 420-429 (2012); published online 8 May 2012; doi:10.1038/nrrheum.2012.64

44. Ibid

45. Ibid

46. Ibid

Alpha Virus - Epidemics

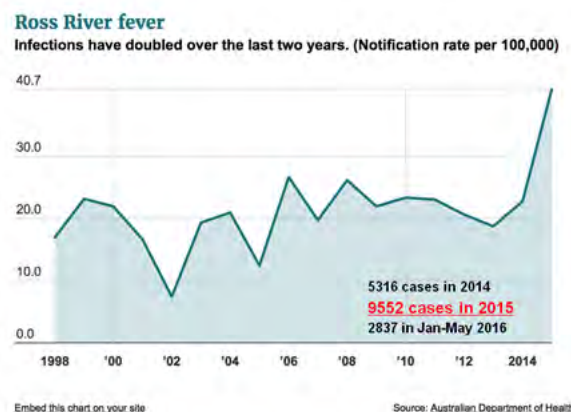
Mosquito-transmitted arthritogenic alphaviruses such as CHIKV and RRV cause significant epidemics of debilitating musculoskeletal disease across the world. Global distribution has been progressively expanding, increasing the occurrence and severity of epidemics. This can be attributed to increased international travel, economic development and changes in mosquito vectors, all of which will continue to compound, highlighting the serious need for an effective treatment.

CHIKV

CHIKV has continued to expand its global presence by breaching the Americas in 2014. As of August 2016, the Pan American Health Organisation (PAHO) reported in excess of 1.7 million cases in the region from 2014. The rapid spread of CHIKV can be partly attributed to an adaptive mutation, an alanine-to-valine substitution at position 226 in the E1 glycoprotein gene (E1:A226V) on an ESCA-CHIKV strain circulating on Reunion Island after September 2005.⁴⁷ This mutation enabled CHIKV to forego cholesterol dependence for growth, thus enhancing its infectivity, replication and transmission by mosquito (typically *Ae. Albopictus*). The *Ae. Albopictus* strain is very effective at transmitting the virus, thriving in temperate climates, enabling it to cause severe urban breakouts.⁴⁸

RRV

Ross River virus is prevalent in Australia, Papua New Guinea and other islands in the South Pacific. Similar to other arthritogenic alphaviruses it is maintained in the wild by continuous cycles of transmission between mosquitoes and vertebrate hosts. In 2015, Queensland experienced the worst outbreak in almost 20 years (Figure 9) as authorities were virtually powerless to stop the spread of the disease, resulting in 9552 cases for the year.⁴⁹



Mosquito-transmitted arthritogenic alphaviruses such as CHIKV and RRV cause significant epidemics of debilitating musculoskeletal disease.

1.7 million cases of CHIKV reported in the Americas since 2014.

Figure 9.
RRV - Australian Infections

Source: Australian Department of health

Rational for PPS to Treat Viral Arthritis

Paradigm formed a collaborative partnership with the Institute for Glycomics at Griffith University subsequent to compelling preclinical results, which demonstrated efficacy of PPS in the mouse models of CHIKV and RRV infection.

As previously discussed, it has been established that PPS significantly increases the production of anti-inflammatory cytokine (IL-10) and reduces the production of pro-inflammatory cytokines (TNF and IL-1). PPS also has the ability to inhibit enzymes that degrade the joint cartilage and proteoglycans.

As a result of these established anti-inflammatory properties, PPS was identified as a suitable treatment for the polyarthralgia and/or polyarthritis responses of alphaviruses, with initial focus on RRV and CHIKV.

Preclinical Study

In mice, infection resulted in a significant acute inflammatory response and cartilage destruction. The severity of disease was alleviated by PPS therapy as assessed by histological analysis, gene expression and soluble biomarkers. Severe RRV-induced joint pathology, including thinning of articular cartilage and loss of proteoglycans in the cartilage matrix, was diminished with PPS treatment.

PPS was identified as a suitable treatment for the polyarthralgia and/or polyarthritis responses of alphaviruses

47. Simon, Fabrice et al. "Chikungunya Virus Infection." *Current Infectious Disease Reports* 13.3 (2011): 218-228. PMC. Web. 10 Oct. 2016.

48. Ibid

49. Australian Department of Health

Rational for PPS to Treat Viral Arthritis

- Preclinical Results⁵⁰

Ross River virus infection stimulates the production of proteases ADAMTS-4, MMP-3, and MMP-9 and causes damage to the articular cartilage in joints

- At the peak of the disease, the occurrence of notable joint inflammation in conjunction with pannus-like formation and thinning of articular cartilage were observed (Figure 10 & 11). Safranin O staining also revealed considerable disruption of the proteoglycans in the cartilage matrix.
- Figure 11 highlights the stimulated production of proteases ADAMTS-4, MMP-3, and MMP-9 at early time points (i) and at peak disease (ii).

Figure 10 - Safranin O staining of Knee Joint

Source - J Herrero et al (2015)

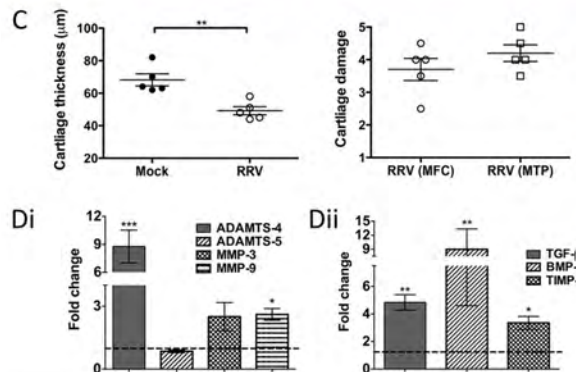
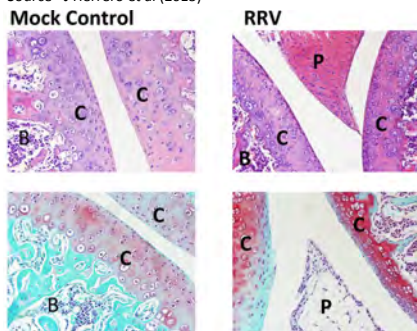


Figure 11 - Cartilage & Proteases Production

Source - J Herrero et al (2015)

PPS reduces the severity of RRV-induced disease and inflammation

- Mice treated with PPS resulted in a ~65% decrease (P 0.05) in clinical disease score in RRV-infected mice (Figure 12) and a corresponding protection from disease-associated weight loss (Figure 12).

Reduced disease in treated mice is not due to decreased viral burden

- The viral titers (presence and amount of antibodies in blood) in the sera of PPS-treated and mock-treated mice were comparable on all days tested, which is indicative of equivalent systemic replication.
- The study confirms that PPS treatment does not affect viral clearance.
- PPS does not compromise the bodies ability to clear the virus, unlike other compounds such as Methotrexate

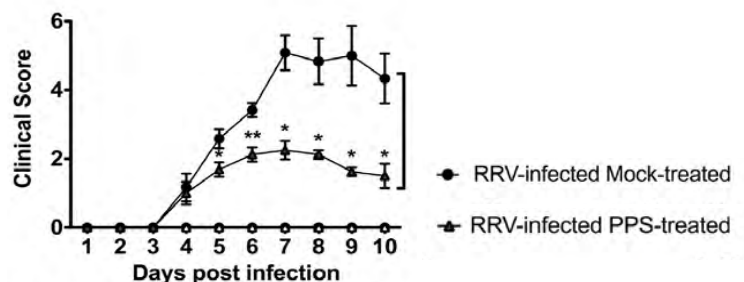


Figure 12 - PPS reduces the severity of acute RRV-induced inflammatory disease.

Source - J Herrero et al (2015)

Treatment with PPS increases the level of anti-inflammatory IL-10 and decreases pro-inflammatory factors associated with RRV disease.

- RRV infection resulted in an increase of (P < 0.05) of pro-inflammatory factors (both cytokines and chemoattractants) at peak disease (Figure 13).
- Treatment with PPS also had an effect on the levels of the macrophage M2 anti-inflammatory cytokine interleukin 10 (IL-10). The IL-10 kinetics corresponded to the kinetics of disease, with serum levels increasing over time in RRV-infected mock-treated mice (Figure 13).
- PPS treatment significantly reduced the serum levels of IL-1 α , IL-2, IL-6, CCL-2, and macrophage inflammatory protein 1 α (MIP-1 α) at peak disease (P < 0.05) (Figure 13).

50 - Herrero LJ, Foo S-S, Sheng K-C, Chen W, Forwood MR, Bucala R, Mahalingam S. 2015. Pentosan polysulfate: a novel glycosaminoglycan-like molecule for effective treatment of alphavirus-induced cartilage destruction and inflammatory disease. J Virol 89:8063–8076. doi:10.1128/JVI.00224-15.

Rational for PPS to Treat Viral Arthritis

- Preclinical Results - Continued

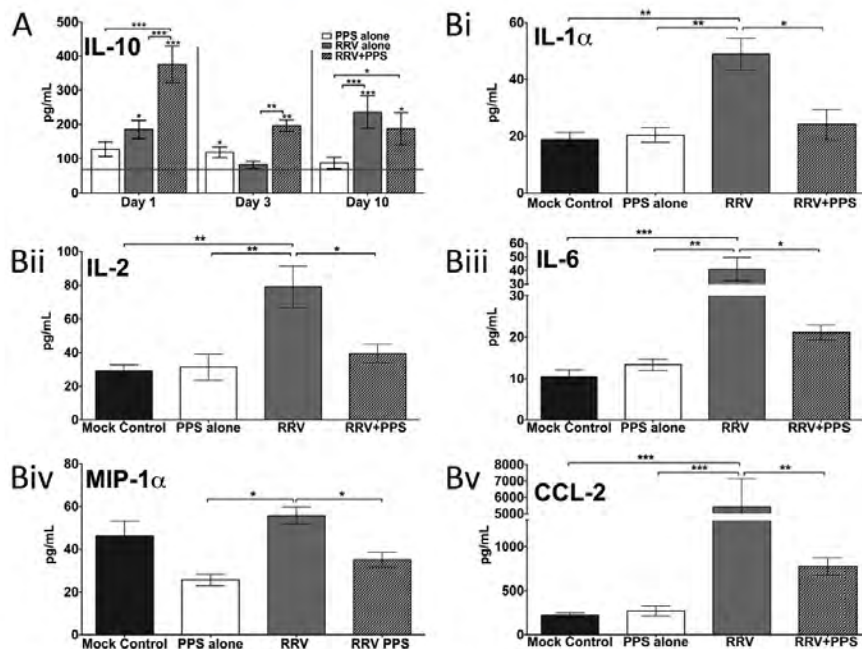


Figure 13 - Twenty-day-old C57BL/6 mice were infected s.c. with 104 PFU RRV or mock infected with diluent alone and then either treated daily i.p. with PPS at 3 mg/kg in 100 ml PBS or mock treated with PBS alone (Mock control, mock infected mock treated; PPS alone, mock infected PPS treated; RRV, RRV infected mock treated; RRV PPS, RRV infected PPS treated). At days 1, 3, and 10 p.i., serum was collected and analyzed for levels of soluble factors using Bio-Plex pro mouse cytokine 23-plex microarray kits (Bio-Rad). PPS treatment (A) altered the kinetics of macrophage M2 cytokine IL-10 and (B) reduced the levels of proinflammatory factors at day 10 p.i. The horizontal line represents the level for the mock control. Each bar represents the mean result standard error for 5 to 6 mice. (A) *, P 0.05; **, P 0.01; ***, P 0.001; two way ANOVA with Bonferroni posttest. Asterisks directly on top of bars show comparison to mock control levels. (B) *, P 0.05; **, P 0.01; ***, P 0.001; one-way ANOVA with Tukey's posttest.

Source - J Herrero et al (2015)

PPS treatment protects the joints from cartilage damage associated with RRV infection

- Masson's trichrome staining of the tibialis anterior highlights that PPS treatment protected the morphology of striations within the skeletal muscle, with sections of collagen formation characteristic of muscle repair and fibrosis.
- PPS treatment significantly reduced the levels of ADAMTS-5 and TIMP-3 at peak disease ($P < 0.01$) but not at the early stages of infection. RRV infection also resulted in increased levels of the cartilage components aggrecan, collagen I, and collagen II, which were largely reduced with PPS treatment. The genes associated with signaling pathways for cartilage development (TGF- β 1 and BMP-1) and the metalloproteinases were unaffected by PPS.

PPS treatment is a safe long-term treatment strategy for chronic RRV disease

- No adverse clinical signs over the 3-month duration of the trial.
- PPS-treated mice showed less joint damage and had significantly decreased expression of aggrecan, back to baseline levels ($P < 0.001$). The levels of ADAMTS-4 expression were also reduced ($P < 0.01$).

Other key highlights from the alphavirus program:

- Preclinical data suggests PPS has the potential to treat both acute and chronic symptoms associated with mosquito transmitted alphavirus infections.
- Five patients with RRV-arthritis (joint pain) have already been treated with PPS under the TGA Special Access Scheme demonstrating tolerance, potential clinical effects and improved quality of life.
- Paradigm has exclusive world-wide rights to commercialise the patent along with Paradigm's sole right to acquire (assign) from Griffith University the patent after Paradigm commences a Phase 2 clinical trial.
- There are no specific therapeutics or vaccines to treat RRV and CHIKV infections, so there is a pathway for accelerated approval for the treatment in some countries (equivalent of orphan status).
- This strategic partnership with the Institute for Glycomics at Griffith University highlights that the known anti-inflammatory properties of PPS can potentially treat a wide variety of indications. We believe there is potential for other types of arthritis to be treated by PPS in the future.

Paradigm is understandably very encouraged and will look to enter Human Phase II Clinical Trials as soon as practical. In the week after the announcement of the strategic partnership with Griffith University Paradigm received no less than 180 inbound requests to participate in a clinical trial or receive PPS treatment under the SAS thus indicating the desperate public need for an effective treatment.

PPS treatment is a safe long-term treatment strategy for chronic RRV disease

Five patients with RRV-arthritis (joint pain) have already been treated with PPS

Rational for PPS to Treat Viral Arthritis

- Preclinical Results - CHIKV

PPS is a potential treatment for CHIKV-induced inflammation, reducing disease by altering the cytokine response.

- PPS decreased the degree of joint swelling of CHIKV-infected mice, resulting in a reduction in inflammatory cells infiltrating into the joint (Figure 14).
- PPS did not affect the kinetics of the virus infection and did not increase the viral persistence in the joint tissues (Figure 14).
- The reduced disease also correlated with an early surge in anti-inflammatory IL-10 and reductions in the levels of soluble factors CCL-2, IL-6, IL-9, and granulocyte colony-stimulating factor (G-CSF) at peak disease (day 3 p.i.) (Figure 14B)

PPS decreased the degree of joint swelling of CHIKV-infected mice

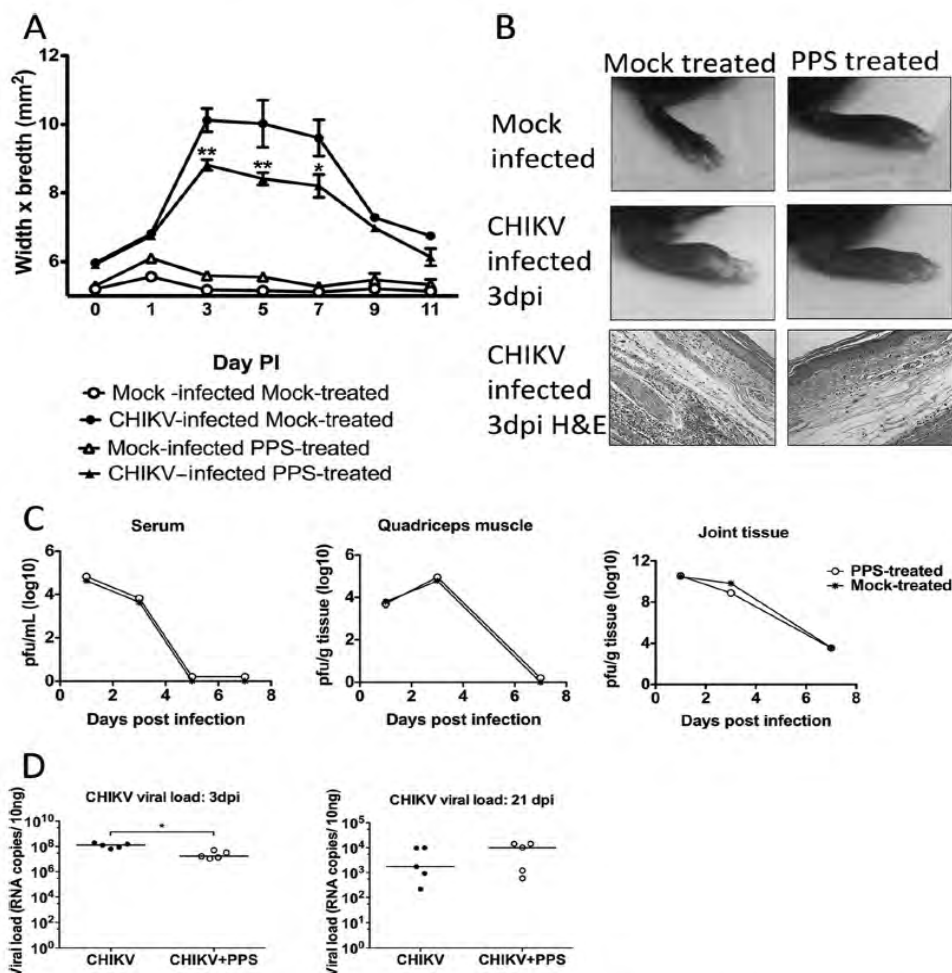


Figure 14 - Pentosan Polysulfate Sodium reduces the severity of acute CHIKV inflammation without affecting the kinetics of viral infection. Twenty-five-day-old C57BL/6 mice were infected s.c. with CHIKV or mock infected with diluent alone and then either treated daily i.p. with PPS at 3 mg/kg in 100 PBS or mock treated PBS alone. (A) CHIKV-induced footpad swelling was assessed daily by measuring the height and width of the perimetatarsal area of the hind foot. PPS treatment resulted in a significant reduction in swelling. (B) Histological analysis after H&E staining showed that PPS treatment decreased the levels of inflammatory infiltrates in CHIKV-infected mouse joints at peak swelling 3 days p.i. (C, D) Both infectious virus and viral RNA levels were measured, and the results indicate that PPS treatment did not affect viral clearance. At days 1, 3, and 7 p.i., serum and quadriceps and ankle tissues were harvested and homogenized, and the viral loads determined. (C) For infectious virus, viral load was determined by plaque assay on Vero cells. (D) For viral RNA in joint tissues, viral load was determined by qPCR with CHIKVE2-specific primers. Each symbol represents the result for a single mouse, and the horizontal lines represent the median values. **, P 0.01; two-way ANOVA with Bonferroni posttest or foot swelling and plaque assays and Mann-Whitney for PCR. Source - J Herrero et al (2015)

"These collective results, whereby PPS was found to reduce the disease severity of two critical alphaviral diseases, suggest that PPS may be a promising broad-range treatment for alphavirus disease manifestations in general."⁵¹

Paradigm's CEO, Mr Paul Rennie said "given (i) the safety of PPS in humans is established, (ii) the route of administration and dosage has been confirmed in humans, (iii) the preclinical study has been peer-reviewed and published demonstrating both safety and efficacy and (iv) the scarcity of any registered pharmaceutical agents to treat this disease, Paradigm is hopeful to receive accelerated approval for the treatment in some countries". This clinical program may be a partnering opportunity for big pharma companies developing products for musculoskeletal indications and/or as an addition to the product portfolio of those big pharma companies developing therapies and vaccines for other infectious diseases.

51. Herrero LJ, Foo S-S, Sheng K-C, Chen W, Forwood MR, Bucala R, Mahalingam S. 2015. Pentosan polysulfate: a novel glycosaminoglycan-like molecule for effective treatment of alphavirus-induced cartilage destruction and inflammatory disease. J Virol 89:8063–8076. doi:10.1128/JVI.00224-15.

Manufacturing

The Company has entered into a long term supply agreement (20 years) with the German pharmaceutical company, bene pharmaChem, for the supply of FDA-approved cGMP-grade PPS. This is anticipated to overcome potential manufacturing and scale-up issues for Paradigm and is aimed at ensuring the clinical trials are conducted using PPS with the same pharmaceutical activities as would be available in commercial quantities.

Paradigm are the first to formulate PPS into a nasal spray. Paradigm has established this manufacturing capability through a partnership with MoNo chem-pharm GmbH. This partnership enables global distribution scalability at a low and sustainable cost base. It is important to note that the formulation can be manufactured with or without preservatives, which enables Paradigm to satisfy regional preference. The spray device technology has been sourced from Aptar Group Inc, the worldwide leader in nasal spray pumps for Allergic Rhinitis, Nasal Decongestant and Nasal Saline.

Investment View

The key factor in making Paradigm a desirable biotech investment revolves around the repurposing of an existing, safe drug that is known to work in similar indications. Thus we believe Paradigm is well positioned to provide a new treatment for both Hay fever, BME alphavirus/viral arthritis and potentially a number of inflammatory/coagulant related diseases through their novel but logical approach of using PPS's known anti-inflammatory properties. The established medical evidence and extensive publications confirm PPS's use in other areas of inflammation and importantly confirm and reconfirm its safety profile – something that the FDA considers to be more and more important.

When looking at BME there are now well established links that bone bruising leads to the early onset on OA and while it may be years before ZILOSUL® could be called a treatment for OA caused by BME we believe its acceptance as treatment for BME (and other associated bone bruising i.e. surgical implants etc) will lead to market launch and subsequent reputation as the standard of care. It is well established that PPS reduces the biomarkers for cartilage breakdown CTX-1 and CTX-2 and that the cytokines and proteins for inflammation (TNF-Alpha and IL-1b) which are released from the stress of a bone bruise. These cytokines and proteins degrade and destroy cartilage – the hallmarks of Osteoarthritis. By PPS targeting these inflammation channels and blocking the production of these harmful proteins, logic would dictate that PPS will have a positive effect on recovery and therefore the long term health of one's cartilage. The plethora of animal data and anecdotal evidence showing dogs/horses recovering from debilitating OA adds further weight to our view on this matter.

We believe that should Paradigm be successful in proving ZILOSUL® is an effective treatment for bone bruising in humans as a result of sports injuries, it will be viewed as an additional valuable treatment solution for other surgeries in humans where the bone is bruised – i.e. pins and plates being hammered/screwed into bones as a result of break and fractures. We are of the view that complexity of the disease state for both BME and Hay fever is somewhat lesser than that of oncology but in no way does this mean the target market and ultimately the end prize is any less. But it does possibly indicate that it may be easier for Paradigm to bring (via a partner) a drug successfully to market.

Furthermore, should RHINOSUL® be successful in its pivotal Phase II trials for hay fever (Phase I successfully completed) and the data shows that RHINOSUL® is as good or better than Rhinocort® at treating Hay fever than the unmet clinical need, sheer market size and potential economic opportunity represents a significant opportunity to big Pharma. This opportunity is further enhanced by repurposing likely requiring only one Phase III trial to enable FDA approval for either treatment. Despite the potential reward for junior drug discoverers and large Pharma, development in this area has been somewhat lacking, another reason which indicates that a superior safe treatment will become class leading and likely hold a market leading position for some time. We believe Paradigm ticks all the necessary boxes to be positioned to enter partnering discussions on both indications of hay fever and BME, assuming Phase II clinical success:

- Excellent safety profile and very well known drug tolerability,
- Hypothesis backed by very good pre-clinical and clinical data,
- Long history of being a safe effective treatment for OA in animals,
- Small but very effective treatment in SAS & a scoping study in humans with BME,
- Known and well understood mechanism of action,

Novel but logical approach of using PPS's known anti-inflammatory properties.

PPS reduces the biomarkers for cartilage breakdown CTX-1 and CTX-2 and that the cytokines and proteins for inflammation (TNF-Alpha and IL-1b) which are released from the stress of a bone bruise.

ZILOSUL® could be an additional valuable treatment solution for other surgeries in humans where the bone is bruised – i.e. pins and plates being hammered/screwed into bones as a result of break and fractures.

Repurposing often requires only one Phase III trial to enable FDA approval for either treatment.

Investment View Continued

Experienced management is crucial

- Multi-faceted IP protection comprised of Disease specific patents and manufacturing IP surrounding the production of PPS,
- Trials have been designed following the same protocols as Astra Zeneca established for Rhinocort® and will adhere to the strict expectations surrounding analysis of clinical data required by big pharma,
- Potential for PPS to treat other joints (hips, ankles, shoulders and elbows) and further potential indications in other respiratory diseases which will increase the overall attractiveness of PPS,
- Due to existing long term contracts struck with Bene Pharma, PPS is not an expensive drug to make or deliver intranasally thus increasing its marketability,
- RHINOSUL® could be an Over the Counter (OTC) treatment, meaning it would not be required to be prescribed thus dramatically opening up potential markets, and
- Corporate transactions in this space demonstrate the interest by big pharma and large sums they are willing to pay to acquire such companies.

When talking biotechs, equally important as the actual compound under investigation is the board and management who will be driving the company forward and ultimately negotiating any licensing transactions. Not many junior ASX listed biotech companies can boast a Board/Executive that has top tier experience at CSL and Mesoblast. Paul Rennie was the inaugural COO at Mesoblast and was solely responsible for the in-licensing of the dental pulp stem cells from the US National Institute of Health. The dental pulp stem cells were key to the CNS component of the Cephalon licensing transaction with Mesoblast in 2010 worth up to US\$1.7B and accompanied by a US\$220m equity investment in MSB. Paul's other previous experience includes senior positions at Boehringer Mannheim (now Roche Diagnostics), Merck KGGA and Soltec (FH Faulding Ltd). Chairman Graeme Kaufman is renowned in the Australian biotechnology industry where he has held various top level executive roles at Mesoblast until 2013 (and was likewise heavily involved in the Cephalon transaction). He was instrumental in the privatisation and ASX listing of CSL, including the negotiation of key contracts with stakeholders prior to listing and served as its Chief Financial Officer. Ravi Krishnan, also ex-Mesoblast, is the Chief Scientific Officer at Paradigm and was instrumental in the formative stages which led to Paradigm acquiring the rights to PPS for the given indications.

Strong Newsflow will stoke and maintain investor interest

From an investor viewpoint the key attractiveness for investing in Paradigm now as opposed to six months time is a strong amount of newsflow from this point until mid CY2017. This newsflow can be summarised as the following major events:

- BME Phase II Open Label results on a selected basis
- Full release of results from the Phase I Hay fever Trial (preliminary results already released)
- Publication of the Peer Review Journal comparing PPS (RHINOSUL) vs Budesonide (Rhinocort)
- News of the commencement of the pivotal Phase II Challenge Study for Hay fever
- News around the alphavirus program - Phase II design, start, completion and results
- Results from the Phase II Challenge Study in Hay fever
- Potential Partnering discussions on the Hay fever (assuming positive results) and alphavirus programs

This newsflow will stoke investor interest, both domestically and internationally and will display to the market (and potential partners) the company's ability to achieve important milestones. The Phase I hay fever trial has been successfully completed showing that PPS is safely tolerated via the new nasal route of administration. Full Phase I results are expected in October. The hay fever Phase I results also provide the necessary data to support the pivotal Phase II Challenge study in patients with hay fever, planned to commence late 2016. During this period the Company is expecting the release of a Peer Review Publication which compares PPS to Budesonide through various pre-clinical/animal models using the same protocols and trial design that Astra Zeneca used for Budesonide. Assuming the outcomes detailed in the Peer Review Publication show PPS is as good as/better than Budesonide than this will highlight to various big Pharma that Paradigm are on to something very exciting. BME SAS case studies reports are anticipated in the short term in addition to the results from the Open Label Phase II BME trial which should have interim patient data read outs over the coming months. The company notes that many professional sportspeople have been treated under both the SAS and Open label trial.

Few junior ASX listed biotech companies can boast a Board/Executive that has top tier experience at CSL and Mesoblast.

Strong amount of newsflow from this point until mid CY2017.

Phase II Challenge study in patients with Hay fever, planned to commence late 2016.

Peer Review Publication which compares PPS to Budesonide due to be released 2HCY2016

Growing investor interest in PAR stock from completion of the Phase I trial

Investment View Continued

Investment View Summary

The importance of a successful peer review publication should never be underestimated due to its power in confirming that other respected scientists support the said hypothesis and findings and this has enormous weight in the industry.

The Phase II Trial results due Q2 CY2017 and the BME interim results will ultimately determine the near term value for PAR stock as they will dictate the ability of the two programs to be partnered and for how much, however we anticipate there will be growing investor interest in PAR stock from commencement of the Phase II trials. We note that investor interest in biotechs always starts to increase with upcoming clinical trial outcomes and given the process is effectively 'sped up' with Paradigm we don't expect it to be any different, suffice to say more pronounced. Given the enormous positive feedback the company has received from Ross River virus (RRV) sufferers following the announcement of its strategic partnership with Griffith University and intention to enter Phase II trials to show PPS is an effective treatment for viral arthritis we believe this program has real medium term partnering ability as well. Whilst the market for RRV in Australia is not large by global standards (est ~A\$112.5m p.a.), the initial in-human SAS case studies point to signs of efficacy and we believe this program would be attractive to a mid to small size pharmaceutical company and therefore we attribute licensing value to it.

We are interested in Paradigm's novel approach to treating inflammation and have often asked how something as simple and logical has been overlooked by the industry? But it is often the case in drug development and medicine that serendipity results from simple logical thinking and we certainly see compelling logic to Paradigm's different approach.

For the reasons outlined above we think ZILOSUL®, RHINOSUL® and PPS for alphavirus will provide investors with the opportunity for a significant licensing event upon the release of successful Phase II trial results from either clinical trial. We feel the best way to play this type of investment is investing early, whilst the company represents good value compared to other drug discovery companies. Management/board have extensive experience in designing and managing clinical trials and drug discovery and importantly have designed the trials in the fashion that is expected (demanded) by big Pharma, thus significantly reducing the risk that a prospective partner will ask for additional clinical data. The company has funds to be able to complete the trials and the management/board have the proven ability to execute a licensing transaction given their roles at MSB and CSL. So the only variable is the actual trial results and given the plethora of animal data but even more importantly the first people treated under the special access program we feel this risk is somewhat reduced, at least for the BME trial, which in itself would be a company maker. But, this clinical risk is the case with every biotech investment and hence why investors can achieve extraordinary returns (i.e. many multiples on their initial investment).

Given the inherent difficulty in arriving at a current value for Paradigm we have used the probability weighted DCF methodology of what ZILOSUL®, RHINOSUL® and PPS for alphavirus (and hence Paradigm) would potentially be worth under licensing transaction. This gives us a DCF valuation of \$1.14 per share. We have then combined this with an implied price of \$0.90 per PAR share derived from an average enterprise valuation of listed peers. We therefore arrive at a present day combined average valuation of \$1.02 per share assuming successful Phase II trial results and a partnering (or takeover) transaction of US\$750m for hay fever, US\$500m for BME and \$40m for RRV alone (not including CHIKV). We do believe that CHIKV would be wrapped up with RRV in any potential licensing transaction that would likely be worth circa \$200-300m total deal value + double digit royalties but for the purposes of this report we have not included CHIKV. In future reports, as the CHIKV program becomes clearer we will include our estimates on its valuation in the financial model. We note that Meda was acquired for US\$7.2bn and manufacture the only commercialised new class of dual acting treatment – Dymista® and Rhinocort®, the current 'gold standard' for hay fever, is a multi-billion dollar OTC Hay fever treatment and this just further reinforces the fact that Paradigm is hunting in elephant country and in the event their trial results point to a new treatment, it will likely result in a circa billion dollar licensing transaction with potential \$50-100m (or greater) upfront payment.

Significant licensing opportunity upon the release of successful Phase II trial results from either clinical trial.

We therefore arrive at a combined average present day valuation of \$1.02 assuming successful Phase II trial results and a partnering (or takeover) transaction of US\$750m for Hay fever, US\$500m for BME and US\$40m for RRV alone.

IP Portfolio & Market Exclusivity

Paradigm has multi-faceted IP protection that increases barriers to entry for potential competitors in a number of ways:

- Disease specific patents for BME treatment with PPS have been secured in the US, Japan, Australia, and New Zealand with other geographic regions to follow.
- The company is likely to attain reformulation patents for alternative PPS delivery methods in humans (once a form of injectable PPS is approved for human use).
- Established and standard regulatory exclusivity and trademarks around products. Furthermore, Bene pharmaChem's manufacturing process add further layers of protection
- The only FDA-approved form of PPS from Bene PharmaChem.
- Paradigm's IP. Although other 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.
- 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, and there is no other marketed product protected by IP that would prohibit the product's marketing.

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

Recent Transactions

Recent transactions highlight big pharma interest in respiratory and BME spaces

- Mylan's recent takeover offer of Meda was at a 92% premium to last close, with Dymista® being RHINOSUL®'s closest comparative product
- AstraZeneca's transactions highlight the potential value attributed to respiratory business units

Paradigm has multi-faceted IP protection that increases barriers to entry for potential competitors in a number of ways.

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

Recent transactions highlight big pharma interest in respiratory and BME spaces.

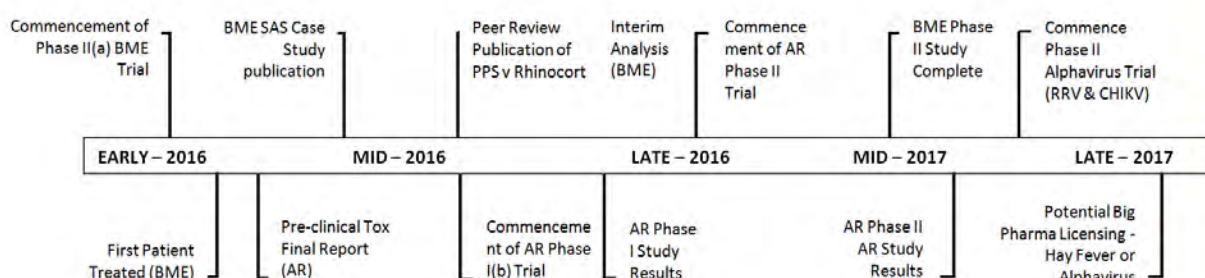
Figure 15: Recent Transactions in the respiratory and BME spaces

Date ↓	Target	Acquirer	Deal value (US\$m)	Relevance
Feb-16			7,200	<ul style="list-style-type: none"> Meda's third biggest product is Dymista®, which is a dual acting AR product
Dec-15		AstraZeneca	575	<ul style="list-style-type: none"> Acquired Takeda's respiratory business only Acquisition includes expanded rights to roflumilast, used to treat COPD
Jul-14		AstraZeneca	2,100	<ul style="list-style-type: none"> Acquired Almirall's respiratory products only Products focused on asthma and COPD
May-13		ZIMMER BIOMET	Undisclosed	<ul style="list-style-type: none"> Zimmer Biomet acquired Knee Creations for its Subchondroplasty procedure, designed to treat BME

Source: Bloomberg, company filings

Source: PAR Company Presentation

Timeline



Valuation Methodology & Assumptions

Given the inherent difficulty in valuing junior biotech companies we have had to make a series of assumptions and use the probability weighted valuation methodology which we feel is most appropriate for a company like Paradigm.

- We have assumed a Weighted Average Cost of Capital (WACC) of 16% in line with industry standard for early stage drug discovery companies.
- Market size and sales are predicted in US\$ but revenues to PAR are converted to AU\$ using a AUD:USD exchange rate of 0.75
- Two years post marketing approval, we have assumed RHINOSUL® will be Over the Counter (OTC) and thus equally available as market leading Hay fever treatments Rhinocort and Dymista – both multi-billion dollar treatments.
- We have used the global market size of all Hay fever treatments and assumed RHINOSUL® will account for 20% (due to its superior action) of the market in its 10th year – date of patent expiry thus making peak sales of \$2.2B before dropping off by 95% as generics come in.
- ZILOSUL total market penetration - assume 40% of the current US\$2.5B Market in 2029 - 10 years from launch as it will be first in class and will make \$940m pa at peak sales.
- We have assumed a CAGR of ~3% in line with growth estimates for similar markets.
- Based on the launches for other blockbuster drugs we assume to following growth rates.

Year Sales	1	2	3	4	5	6	7	8	9	10
Percentage of RHINOSUL® Peak Sales	20.0%	35%	44%	53%	62%	71%	80%	88%	94%	100%

Source: BYS Estimates

- RHINOSUL® will be considered a superior product to Rhinocort and therefore will be able to be priced at a slight premium.
- We apply a probability weighting of 25% on net gross sales for ZILOSUL® and 12.5% probability to RHINOSUL® in line with the industry standard commercialisation success rate for repurposed drugs.
- We estimate that R&D and Overheads to be minimal and a company tax rate of 30%.
- We assume Paradigm will have pivotal Phase II results in Q1 2017 Calendar year. Based on the successful result Management would seek to partner RHINOSUL®. Paradigm and their partner would then commence a Phase III Trial which we estimate would take 1 year to complete i.e. CY2018. We envisage registration will occur FY2018/19 thus we estimate sales will commence in FY2018/19.
- We assume a License Agreement with a large Pharmaceutical company will be US\$750m for Hay fever and US \$500m for BME total deal size + 12.5% royalties on sales (low double digit royalties in line with industry standards). For our model will have applied the 25% and 12.5% probability respectively to all milestones.
- We assume manufacturing costs to Bene are 2% of the gross sale price.
- We assume royalties to Bene are 2% on gross sales and view this as being conservative.
- In the event of partnering we assume this cumulative 4% to Bene will continue to be paid and will need to come out of what Paradigm receive from the transaction.
- We assume upfront payments will be 10% of total deal size and milestones will be:
Phase III Completion 20% of total deal size
FDA Approval and Registration 25% of total deal size
First US\$1B cumulative sales 45% of total deal size
- PPS for RRV we have assumed that 7,500 cases will be treated p.a. This number is greater when there are outbreaks and lower in other years but there is an unquantifiable backlog – perhaps of 30,000+ people who have been infected and still have debilitating symptoms and will want to a PPS treatment, hence we assume a steady state of 7,500 treatments p.a. This number most likely would be larger in the years directly after approval and then increase/decrease depending on outbreaks.
- We assume a treatment will cost \$15,000 per person and the Australian Govt through the PBS will contribute \$12,500 of this treatment thus arriving at a total estimated market of A\$112.5m. We believe the PBS cover the treatment due to extended time off for infected people 6-9 months and ongoing disease related health issues especially arthritis.
- Being the only effective treatment for RRV we assume total market penetration will be 90% and for simplicity we therefore assume steady state of A\$101.25m p.a. as being a realistic addressable market for Australia.
- We consider RRV POS to be between phase I and phase II - POS of 22.75% being midpoint - as there have already been 5 successfully treated patients under SAS and Paradigm will go straight into Phase II Clinical Trials for which there is very strong patient demand, therefore recruitment will not be an issue.

Valuation Methodology & Assumptions - Continued

- We assume the RRV program will get partnered for US\$30m (A\$40m) based on estimates and have used the milestone split detailed in this section and applied the 22.75% probability to payments. Royalty payable to PAR will be 20% reflecting the stronger position PAR is in with this program and also the very short time to market being 2 years (fast track status/orphan drug). See PAION / Cosmo Pharmaceuticals license agreement where total structured deal was EUR 52.5 with EUR 10m upfront for a program in Phase III <http://www.businesswire.com/news/home/20160624005684/en/PAION-Grants-Cosmo-Pharmaceuticals-remimazolam-License-U.S>.
- Nominal royalties are payable to Griffith University on total sales and revenues received by PAR.
- A licensing transaction involving CHIKV would be multiples larger than the RRV only transaction and would be most likely be partnered with RRV to a mid-tier pharmaceutical company.
- **CHIKV is much harder to value and for the purposes of this report we have not included it in our valuation model.** We do however attempt to estimate the potential global market p.a. and base this on 1.7m cases being reported since 2014 (likely to be more cases that were not reported) and we assume that someone infected in the USA will pay a similar amount to Australians (and we assume will have re-imbursement from insurance), however Aid Agencies will have access to discounted treatments at cost of A\$50 per treatment thus an average cost of treatment being \$752.50 per person. Using a 1m cases p.a. we arrive at a total market size A\$1.05B.
- As a market measure that gives us comfort in our probability weighted valuation of PAR we note that:
On the low end:
Bionomics was able to licence their pre-clinical CNS Ion Channel Modulator compound BNC375 to Merck in 2014 for \$526m total deal size AstraZeneca acquired Takeda respiratory business for US\$575 in December 2015
On the high end:
Mylan acquired Meda for US\$7.2B of which the Dymista Hay fever drug was a significant revenue generator AstraZeneca acquired Almirall's respiratory business only for US\$2.1B in May 2013
- Our DCF Valuation arrives at a \$1.14 per share valuation on a fully diluted basis or ~\$105m market capitalisation which we feel is not too onerous assuming positive results from the upcoming trials and in fact this could be well conservative.
- We cross check our DCF valuation by comparing this to peer companies as per the table below which gives us an average enterprise value of A\$112m, however we remove MVP.ASX due to it being a more mature company with revenues and arrive at a peer average enterprise valuation of \$82.9m or an implied peer valuation of \$0.90 per share for PAR.
- **We use a 50:50 combination approach of peer group valuation and DCF to arrive at a weighted valuation and target price of \$1.02 per share.**

Peer Comparison Chart

Company Name	ASX Code	Share Price	Market Cap (fully Diluted)	Enterprise Value (EV)	Indication	Stage	Market Size
Paradigm BioPharma	PAR.ASX	\$0.595	A\$55m	A\$53m	Hay Fever and BME	Phase I(b) & II(a)	US\$15bn+
Medical Developments International	MVP.ASX	\$5.42	A\$319m	A\$314m	Respiratory Disease	Commercialisation	US\$1.5bn+
Starpharma	SPL.ASX	\$0.625	A\$234.4m	A\$188.5m	Oncology	Phase III & Commercialisation	US\$3bn+
Verona Pharma	VRP.LN	£0.034	A\$140m	A\$68m	Respiratory Disease	Phase I/ii(a)	US\$12bn+
AXSOME Therapeutics	ASXM.NASDAQ	US\$8.22	A\$207m	A\$159m	BME/CNS Disorders	Phase III	US\$2.5bn+
Suda Limited	SUD.ASX	\$0.02	A\$26.7m	A\$25.9m	Oro-mucosal	Phase II/III	US\$11bn+
Invin	IVX.ASX	\$0.004	A\$5.1m	\$A4.3m	COPD & Inflammation	Phase II	US\$10bn+
Average Mkt Cap			A\$111.3m				
Average Mkt Cap ex MVP			A\$82.9m				

Top 10 Shareholders

No	Investor	No. of Shares	%
1	PAUL JOHN RENNIE	10,313,468	11.75%
2	KZEE PTY LTD <KZEE SUPERANNUATION FUND A/C>	10,301,075	11.76%
3	MJGD NOMINEES PTY LTD <BSMI A/C>	6,915,809	7.88%
4	IRWIN BIOTECH NOMINEES PTY LTD <BIOA A/C>	6,310,313	7.19%
5	PETER MILONAS	4,873,810	5.55%
6	BILL PASPALIARIS	4,873,810	5.55%
7	NANCY EDITH WILSON-GHOSH <GHOSH FAMILY A/C>	3,910,935	4.45%
8	V REDFORD PTY LTD <REDFORD SUPER FUND A/C>	2,505,419	2.86%
9	JGM INVESTMENT GROUP PTY LTD <MUCHNICKI FAMILY A/C>	2,285,715	2.61%
10	GRAEME ROY KAUFMAN	1,900,000	2.17%

Financial Summary

Paradigm Biopharma Ltd (PAR.ASX)

Date: 11-Oct-16
 Share Price (\$A): \$ 0.595
 Year End: 30-Jun

Probability Weighting (applied to sales and milestones) BME 25%
 Hay fever 12.5%
 Alphavirus 22.75%

Shares on Issue 87,580,220 Un-Diluted Mkt Cap \$52.1 million
 Share + Options 92,318,317 Fully Diluted Mkt Cap \$54.9 million
 Share Price \$0.595 Cash (Jun Qtr) \$3.0 million
 Rating: Buy
 Price Target \$1.02 per Share
 Valuation: High Case/Base Case \$1.14/0.90 DCF WACC 16.0%
 Valuation Method Probability Weighted DCF with implied PAR peer share price
 Upside/(Downside) to Base Case: 71%
 Risk High (Speculative)

PROFIT & LOSS (A\$m) - year ended 30th June	FY15/16A	FY16/17E	FY17/18E	FY18/19E	FY19/20E
Revenue	0.00	0.00	22.785	79.55	48.20
Other Income	1.39	2.50	3.70	5.50	5.50
Total Revenue	1.39	2.50	26.49	85.05	53.70
Total Operating Expenses	4.40	7.00	9.00	11.50	12.00
EBITDA	-3.01	-4.50	17.49	73.55	41.70
Depreciation & Amortisation	0.00	0.00	0.00	0.00	0.00
Share based payments	0.00	0.40	0.41	0.42	0.42
EBIT	-3.01	-4.90	17.08	73.13	41.28
Interest Revenue	0.09	0.10	0.35	1.30	1.30
Net Interest Expense	0.00	0.00	0.00	0.00	0.00
Net Profit Before Tax	-2.92	-4.80	17.43	74.43	42.58
Income Tax Expense	0.00		2.61	22.33	12.77
Net Profit After Tax	-2.92	-4.80	14.81	52.10	29.81

BALANCE SHEET (A\$m)	FY15/16A	FY16/17E	FY17/18E	FY18/19E	FY19/20E
Current Assets					
Cash	3.00	6.78	21.59	73.69	103.50
Receivables	1.34	0.50	0.56	0.83	0.83
Inventories	-	-	-	-	-
Other	0.02	0.03	0.05	0.10	0.10
Total Current Assets	4.36	7.31	22.20	74.62	104.42
Non Current Assets					
Property, Plant and Equipment	0.01	0.06	0.15	0.50	0.50
Intangibles	7.99	10.00	12.50	14.00	16.50
Other					
Total Non Current Assets	8.00	10.06	12.65	14.50	17.00
Total Assets	12.36	17.37	34.85	89.12	121.42
Current Liabilities					
Trade and other Payables	1.03	1.57	1.85	2.30	2.60
Employee Benefits	0.09	0.00	0.00	0.00	0.00
Total Current Liabilities	1.11	1.57	1.85	2.30	2.60
Non-Current Liabilities					
Borrowings					
Total Non Current Liabilities	0.00	0.00	0.00	0.00	0.00
Total Liabilities	1.11	1.57	1.85	2.30	2.60
NET ASSETS	11.25	15.80	33.00	86.82	118.82
Contributed Capital	15.00	21.50	26.50	26.50	26.50
Other component of equity	0.00				
Accumulated Losses	4.64	4.80	0.00	0.00	0.00
Total Equity	19.64	26.30	26.50	26.50	26.50

EARNINGS	FY15/16A	FY16/17E	FY17/18E	FY18/19E	FY19/20E
EPS - Basic	-0.033	-0.055	0.169	0.595	0.340
EPS - Diluted	-0.032	-0.052	0.160	0.564	0.323
EPS Growth (%)	n/a	64.38%	408.57%	251.77%	-42.79%
DPS	0	0	0	0	0
Franking (%)	0%	0%	0%	0%	0%
Payout Ratio (%)	0%	0%	0%	0%	0%

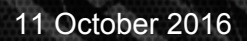
VALUATION	FY15/16A	FY16/17E	FY17/18E	FY18/19E	FY19/20E
P/E (x)	-17.85	-10.86	3.52	1.00	1.75
EV/EBIT (x)	-15.49	-9.52	2.73	0.64	1.13
EV/EBITDA (x)	-15.97	-9.71	2.68	0.63	1.10
Dividend Yield (%)	0%	0%	0%	0%	0%
Price/Book (x)	11.95	7.13	2.35	0.70	0.50
Price/NTA (x)	11.92	7.07	2.33	0.69	0.50
Price/Cash/Flow per Share (x)	n/a	260.55	3.52	1.00	1.75

GROWTH	FY15/16A	FY16/17E	FY17/18E	FY18/19E	FY19/20E
Total Rev. Growth (% pcp)	n/a	80%	959%	221%	-37%
Op. Exp. Growth (% pcp)	n/a	59%	29%	28%	4%
EBITDA Growth (% pcp)	n/a	50%	489%	321%	-43%
EBIT Growth (% pcp)	n/a	63%	448%	328%	-44%
NPBT Growth (% pcp)	n/a	64%	463%	327%	-43%
NPAT Growth (% pcp)	n/a	63%	409%	252%	-43%

MARGINS & RETURNS	FY15/16A	FY16/17E	FY17/18E	FY18/19E	FY19/20E
EBITDA Margin (%)	n/a	n/a	66%	86%	78%
EBIT Margin (%)	n/a	n/a	64%	86%	77%
NPBT Margin (%)	n/a	n/a	66%	88%	79%
ROIC (%)**NO DEBT***	n/a	n/a	56%	197%	112%
ROE (%)	n/a	n/a	56%	197%	112%
ROA (%)	n/a	n/a	43%	58%	25%
Effective Tax Rate (%)					

GEARING	FY15/16A	FY16/17E	FY17/18E	FY18/19E	FY19/20E
Net Debt (A\$m)		0			
Net Debt/Equity (%)					

CASH FLOW (A\$m)	FY15/16A	FY16/17E	FY17/18E	FY18/19E	FY19/20E
Cash at Start	3.0	6.58	6.78	21.59	73.69
Cash Flow from Ops	-2.92	-4.80	14.81	52.10	29.81
Cash Flow From Financing/Options	6.5	5.00			
Net Cash Flow	3.58	0.20	14.81	52.10	29.81
Cash At End	6.58	6.78	21.59	73.69	103.50



Key Risks

Dependence on a partnership to drive value: Paradigm must engage strategic partnering deals for its lead drug formulations RHINOSUL[®] and ZILOSUL[®] in order to execute its business model and receive notable cash flows. Failure to enter a favourable partnership will have detrimental consequences.

Clinical Trial Risk: Despite there being ample evidence that PPS could be an effective treatment for the indications that Paradigm is investigating there is no guarantee that trials will be successful and that the Company's drugs will make it to market.

Poor Design of Clinical Studies: It is imperative that the correct personnel are in place to optimally design the Phase II clinical trial. As many biotech companies have experienced, an incorrectly designed study will inevitably lead to detrimental results, which will adversely affect our valuation and forecasts.

Paradigm derives its value from PPS™, which is currently undergoing a Phase II(a) study for the treatment of Bone Marrow Edema and is set to initiate a Phase I study for the treatment of Allergic Rhinitis. Unsuccessful results and a subsequent failure to attract a partnering deal will significantly adversely impact the valuation and forecasts we have formulated for Paradigm.

Timing Risks: The Company will be looking to partner at the completion of their phase II trials. Delay in timelines may inhibit optimal potential partnerships. Furthermore, once partnered, timeline delays will affect milestone payments as well as long-term revenues.

Funding Risks: A delay in achieving a partnership and subsequent upfront/milestone payments may have an impact on Paradigm's funding capabilities.

Competition Risks: The emergence of new competitors in the market or advancements in the treatment of either BME or AR may render ZILOSUL[®] or RHINOSUL[®] redundant. This may affect the commercial value of the compound.

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