D.J. Carmichael Pty Limited
ABN 26 003 058 857
Australian Financial Services Licence No: 232571
Level 14, Parmelia House
191 St Georges Terrace, Perth, Western Australia 6000
PO Box Z5186, Perth, Western Australia 6831
T: +61 (0)8 9263 5200 F: +61 (0)8 9263 5280
info@djcarmichael.com.au
www.djcarmichael.com.au

Date: **15 December 2016**

Recommendation: Speculative Buy

Valuation: $1.18 to $1.50 per share

Company Information

ASX Code	PAR
Last Price ($)	$0.40
12 month share low	$0.26
12 month share high	$0.62
Shares on Issue (m)	101.5
Market Capitalisation ($m)	40.1
Daily Volume	53,161

Factset, DJC Research

Business Description

Paradigm Biopharmaceuticals Ltd. is a biopharmaceutical company, which focuses on repurposing the drug, pentosan polysulphate sodium for the treatment of bone marrow edema. It also develops pentosan polysulphate sodium to treat respiratory diseases including allergic asthma, allergic rhinitis and chronic obstructive pulmonary disease. The company was founded on May 2, 2014 and is headquartered in Melbourne, Australia.

Factset, DJC Research

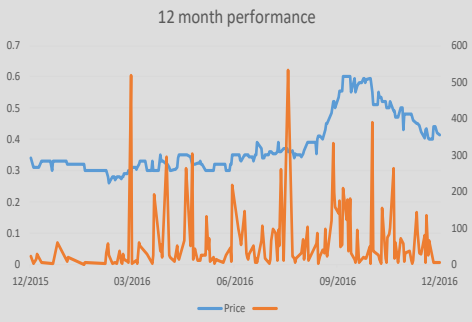
Directors & Management

Mr Graeme Kaufman	N.E. Chairman
Mr Paul Rennie	Managing Director
Mr Christopher Fullerton	N.E. Director
Mr John Gaffney	N.E. Director
Dr Ravi Krishnan	Chief Scientific Officer
Mr Kevin Hollingsworth	CFO/Co-Sec

Major Shareholders

Paul Rennie	21.8%
Other Board and Management	7.1%
MJGD Nominees	6.9%
Irwim Biotech	6.3%

Performance



Source: Factset

CONTACT:
Paul Adams
+618 9263 5234
padams@djcarmichael.com.au

Paradigm Biopharmaceuticals Ltd (PAR)

Paradigm is an ASX listed biopharmaceutical company focused on repurposing the historic drug pentosan polysulphate sodium (PPS). PPS has non-steroidal anti-inflammatory properties and has potential for its novel use in the treatment of many inflammatory diseases such as (1) Allergic Rhinitis (AR) (also known as hay fever), (2) Alpha Virus infection such as Ross River Virus and (3) Orthopaedic indications such as Bone Marrow Edema (BME). We initiate with a Speculative Buy.

Summary Key Points

- **Paradigm Biopharmaceutical Ltd (PAR) Strategy.** Paradigm's strategy is to repurpose pentosan polysulphate sodium (PPS) in three distinct clinical indications. Repurposing means finding new clinical indications for previously approved drugs. Repurposing drugs increases the rate of clinical trial success, reduced cost of development and shorter time to revenue.

- **Potentially Disruptive Therapeutic Product:** PAR's product Rhinosul® has potential to disrupt the global intranasal spray hay fever market. Rhinosul has the potential to be the first non-steroidal nasal spray effectively treating both the early and late phases of hay fever. PAR's IP may be attractive to competitors due to patent expiry of dominant competitor products and the threat of generic manufacturers to incumbents.

- **Paradigms Prudent Use of Shareholder Funds.** In comparison to the average drug repurposing company, PAR's productivity is exceptional; its trial sizes are small, they cost 85% less and take 50-60% less time to complete.

- **Large Addressable Global Target Markets.** The addressable markets for all potential products are global with varying degrees of maturity and size. The AR market is by far the most mature and identifiably largest with approximately US$12 billion in sales per annum.

- **Drug Repurposing Industry.** PAR is operating very efficiently as a repurposing Biopharmaceutical company using PPS as its candidate drug. The drug repurposing industry contributes 25% (up to US$500bn) to the gross revenues generated in the pharmaceutical industry. PAR has positioned its strategy in the sector to maximise value-creating opportunities.

- **Multi-faceted IP Approach**. PAR has developed a multifaceted and diversified IP concurrently with a focused manufacturing strategy creating a long-term, defendable position with respect to its product development and IP portfolio.

- **Innovative Business Model.** PAR has built an innovative business model around its core competence and knowledge of PPS to its novel application in specifically targeted medical conditions.

- **Corporate Activity Focused on Respiratory Sector.** Globally over the last three years there have been a series of targeted acquisitions (some undisclosed), in the respiratory, orthopaedics and virology sectors with a minimum value of US$11.63 bn.

- **Fully Funded.** PAR operations and clinical trial development for all three potential products is fully funded through to early CY 2018.

Catalysts Summary

PAR will have a number of catalytic events through CY 2017 with significant news flow from a number of trials. See the Catalysts section for a full list but the major events are summarised below:

- **Hay fever.** Q4 2016/Q1 2017: Phase II(a) allergen challenge trial commences in Sweden; Q3 2017 Read out of that clinical trial. Q1 2017 Peer reviewed publication of hay fever preclinical trial. Q2 -Q4 2017 Potential expressions of commerce interest from large pharma companies

- **Alphavirus.** Q4 2016/Q2 2017, Phase II trials ethics approval and trial initiation for Ross River virus and Chikungunya virus.

- **Bone Marrow Edema.** Q3 2017 Close-out Phase 2 open label clinical trial investigating the use of PPS to treat bone marrow lesions arising from acute injuries associated with sporting activities such as ruptured anterior cruciate ligament (ACL).

- **Corporate Activity.** Q1-Q3 2017, Potential licensing agreements/ takeover interest in PAR's hay fever and/or bone marrow edema developing products.

Valuation and Recommendation Summary

We value PAR at between $120m and $152m, or $1.18 and $1.50 per share, is based firstly on a peer-group comparison analysis of ASX-listed biopharma companies with compounds currently going through either Phase I or Phase II trials. The mid-point between the two estimation methods is $1.34 per share.

Secondly, we have used a weighted NPV methodology based on cumulative revenues from Rhinocort (marketed by AstraZeneca) using conservative assumptions. We view Rhinocort to be a good comparative drug with similar efficacy based on comparative analysis of Rhinosul and Rhinocort in an industry standard pre-clinical model of Allergic Rhinitis.

We note there is usually a significant share price catalyst for companies moving from a successful Phase I trial to a successful Phase II trial.

As a result of the analysis, we initiate on PAR with a Speculative Buy recommendation noting that commencement of the important Phase II trial is imminent.

We stress that PAR is significantly under-valued compared to peers who have compounds undergoing Phase II trials. We believe a successful outcome will be a major catalytic event for PAR and is likely to initiate interest from big pharma who are looking to replace revenues from drugs going off-patent.

Investors should seek to acquire stock before this event. In addition, it has been shown that once a Phase II trial starts, it often acts as a minor catalytic event making the market aware that the Phase II process has already begun.

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Executive Summary

Investment Rationale

Paradigm Biopharmaceutical Ltd (PAR) Strategy

- Paradigm's strategy is to repurpose pentosan polysulphate sodium (PPS) in three differentiated medical conditions (1) respiratory disease, Allergic Rhinitis (AR); (2) Alphavirus, Ross River Virus (RRV) and Chikungunya Virus (CHIKV). (3); orthopaedics, Bone Marrow Edema (BME);

Large Addressable Target Market

- The addressable markets for all potential products are global with varying degrees of maturity and size. The AR market is by far the most mature and identifiably largest with approximately US$12 billion in sales per annum. PAR's potential product, Rhinosul®, may disrupt the global market for intranasal sprays for the treatment of allergic rhinitis by being the first in class, non-steroidal nasal spray effectively treating both early and late phases of hay fever, if its efficacy is demonstrated in Phase II & III and if the FDA consider its method of action (MOA) differentiated enough to support approvals.

- PAR's contemporary comparator drug, Dymista, has cumulative projected revenues 2015/26 of US$2.4b and in 2015 annual revenues of US$119m.

- PAR's two other markets, in Alphavirus and BME, are emerging and less clearly defined in terms of existing pharmaceutical manufacturers product sales. With respect to PAR's potential product sales in the Alphavirus and BME products, market size has been extrapolated based on research data and reported incidence of disease states. According to our estimates, this translates into multi-million dollar markets.

Drug Repurposing Industry

- PAR is operating a repurposing R&D company using PPS as the repurposed drug candidate. The repurposing industry contributes 25% (up to US$500b) to the gross revenues generated in the pharmaceutical industry.

- Repurposed drugs have greater rates of success, costs significantly less to develop and take significantly less time to product registration compared to de novo drug development. In terms of sales potential, repurposed drugs have the same market potential as de novo drugs.

- Importantly the repurposed drug candidates are afforded the same IP protections compared to traditional de novo drugs.

- PAR has positioned itself in the lowest 20% of the cost curve for its drug development compared to the industry norm in the drug repurposing industry and secured long term IP protection for its products targeted at large addressable markets.

- This efficiency positioning may potentially drive higher internal rates of return and produce greater net present values from its products.

Multi-faceted IP Approach

- PAR has developed a multifaceted IP strategy in conjunction with a focused manufacturing strategy to create a long-term defendable position in the repurposed industry. PAR's potential product pipeline addresses three differentiated markets through two different approval pathways. The Alphavirus product will seek a fast-track approval or use the orphan drug pathway application process.

- On the other hand PAR's AR and BME products will seek to access the market through the traditional FDA (505)(b)(2). .

Innovative Business Model

- PAR has built an innovative business model around its knowledge of PPS and its application in specifically targeted disease states.

- Independent outsourced research facilities have been engaged to undertake early phase research. Licencing and royalty agreements are established with key educational institutions and furthermore, PAR has executed a unique supply agreement with the well-established manufacturer of PPS (bene pharmaChem) who are the only supplier of the FDA approved PPS.

- Finally, PAR has demonstrated excellent control and management of its product development processes.

Corporate Pharmaceutical Activity Focused on Respiratory Sector.

- Globally over last three years there has been a series of targeted acquisitions in the respiratory, orthopaedics and virology sectors with a minimum value of US$11.63 bn.

- Since 2015 big pharmaceutical companies have targeted a small number of early phase Australian biotech companies who have managed to secure licensing agreements worth US$600m.

- These transactions suggest there is a willingness by large pharmaceutical companies to grow market share by acquisition and secure new product development in the early phase to bolster existing pipeline activities.

Fully Funded.

- Operations and clinical trial development for all three potential products is fully funded through to 1H 2018. Prior to the recent oversubscribed placement and share purchase plan on 18 Oct 2016 of AU$6.2m, PAR's Phase II Trial design and management for its AR and BME clinical development activity was fully funded from IPO funds with cash on hand to fund activities through to September 2017.

- Currently PAR has approximately AU$8.5 m cash on hand with another AU$1.25 in R&D grants due.

Valuation and recommendation

We value PAR at A$120M using a comparative company analysis method. In the investment rationale, we have not factored into the financial modelling the potential value of PAR's other products for Alphavirus infection and BME. Our financial modelling is based on the hay fever product. We apply repurposing industry standards and assume a 1:4 ratio of success from PAR product pipeline.

The list of ASX listed comparable companies with an assets(s) in Phase 1 – Phase 2 stage is provided below. For our analysis, we selected companies with a lead asset(s) that we believe have a high probability to move to the next stage of clinical development. Table 1 also demonstrates that moving from Phase 1 to Phase 2 development represents a significant upside catalyst. PAR I significantly under-valued compared to the peer group with a market capitalisation of just $40m

Valuation Comparable Companies

Company	Lead Asset	Indication	Stage	Trial Status	Patients in Study	EV $USM
Innate Immunotherapeutics	MIS416	Secondary Progressive Multiple Sclerosis	Phase 2	Completed Recruitment	93	170
Bionomics	BNC210	Anxiety an Depression	Phase 2	Data Out	24	130
Viralytics	CAVATA	Oncology	Multiple Phase 2s	Recruiting	100+	252
Pharmaxis	PXS4728A	NASH	Phase 1	Data Out/Partnered	24	44
Opthea	OPT-302	Wet AMD	Phase 1/2A	Recruiting	51	94
Actinogen Medical	Xanamem	Alzheimer's Disease	Multiple Phase 1s	Data Out	88	30
Average						120

Table 1: Valuation Comparables Source: Medtrack 2016

Our second valuation approach is based on a probability weighted NPV of cumulative revenues from Rhinocort (marketed by AstraZeneca). As described below we view Rhinocort as a good comparative drug with similar efficacy based on comparative analysis of Rhinosul and Rhinocort in pre-clinical model of Allergic Rhinitis.

Once again, we have chosen not to include the potential value of PAR's Alphavirus and BME products and focus on the most critical key asset in PAR's portfolio – the hay fever product. Similarly, we apply repurposing industry standards and assume a 1:4 ratio of success from PAR product pipeline.

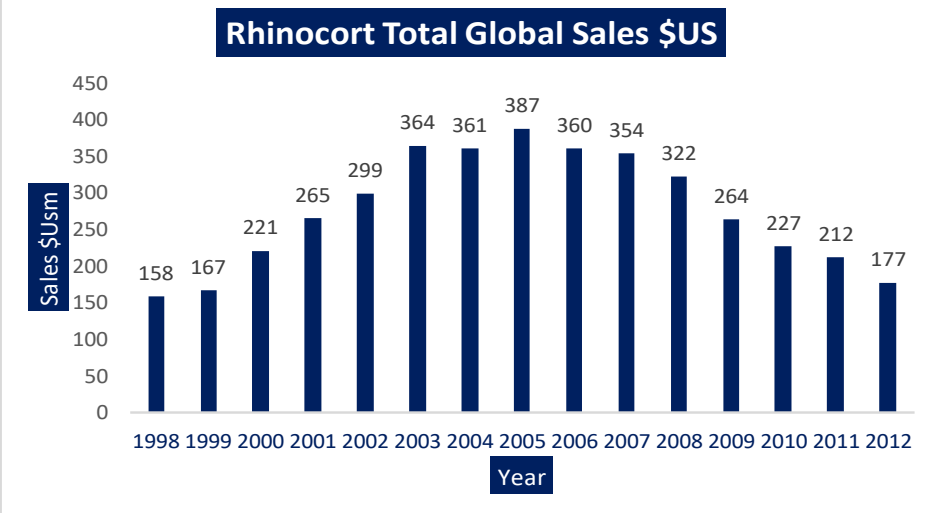


Figure 1: Rhinocort Total Global Sales $US Source: Visiongain & Medtrac

For the NPV calculation we used Rhinocort's annual sales 1998 – 2012 (marketed by AstraZeneca during this period). We assumed 5 years of additional development with approval in Year 6. We assumed 20% probability of approval and a 15% discount rate. Based on that analysis we value PAR at A$152M.

Thus, our valuation range is between A$120M and A$152M which corresponds to share price of A$1.18 and A$1.50 respectively, or a mid-point of $1.34 per share.

Recommendation

We initiate on PAR with a Speculative buy recommendation. We stress that PAR is significantly under-valued compared to peers who have compounds undergoing Phase II trials. We believe a successful outcome will be a major catalytic event for PAR and is likely to initiate interest from big pharma who are looking to replace revenues from drugs going off-patent.

Investors should seek to acquire stock before this event. In addition, it has been shown that once a Phase II trial starts, it often acts as a minor catalytic event making the market aware that the Phase II process has already begun.

Precedent Transactions in Pharma

There have been five transactions by large pharmaceutical companies in the respiratory, orthopaedic and virology sectors since May 2013.

Two transactions completed in 2014 with a combined value of US$3.85b and two completed in 2016 with a combined value of US$7.78b.

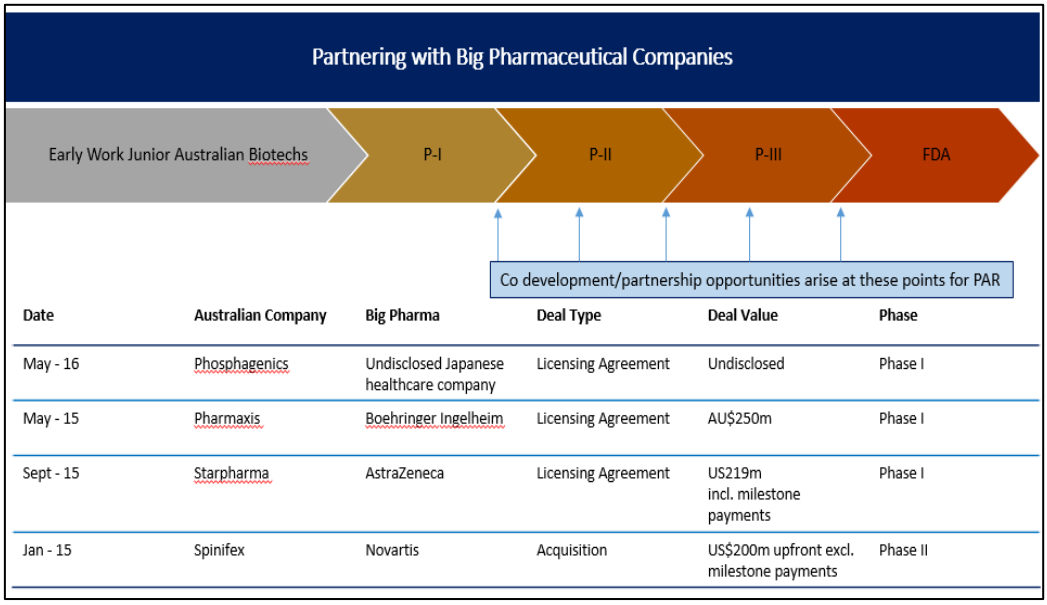
The purchase of MEDA by Mylan is of most interest as MEDA's financial performance of 16% EBIT margin of US$379m and 32% EBITDA margins on sales of US$2.3b is dilutive to its historic and current 19% EBIT margins but accretive to its 29% EBITDA margins. Additional sales from MEDA will add 24% to Mylan's gross sales.

Transaction Analysis of Pharmaceuticals Companies within Respiratory, Orthopaedics and Virology Sector						
Comp Date	Target	Acquirer	Deal Value	EV/ Sales (LTM)	EV/ EBITDA (LTM)	Details
Aug -16	MEDA	Mylan	US$7.2b	4.3	12.9	• MEDA's total revenues 2015 US$2.3b. Key **respiratory** drug Dymista revenues US$119m. • 55% premium to 30 day VWAP
May-16	Takeda	AstraZeneca	US$ 575	2.9	N/A	• Takeda's core r**espiratory** business and assets acquired with annual global sales US$198m. Includes right to COPD and Asthma product
Nov 14	Almirall	AstraZeneca	US$2.1b	N/A	N/A	• Almirall's **respiratory** business(focused on asthma and COPD) and assets acquired.
Sept -14	Alios Biopharma	J & J	US$1.75	N/A	N/A	• Acquires Alios' portfolio of potential therapeutics for viral infections such as rhinovirus and emerging **viral** diseases.
May-13	Knee Creations	Zimmer Holding	Undisclosed	N/A	N/A	• Acquisition of Knee Creations subchondroplasty procedure tech for **BME (orthopaedics)**

Table 2: Recent Transactions. Source: Factset

ASX Company Partnering Agreements

In the last two years, there have been three early phase licensing agreements with ASX listed biotech companies. A fourth deal in 2015 was an early phase acquisition. The key driver behind these acquisitions for large pharmaceuticals is the need to replenish pipeline development activities and capture potential market threats.



Date	Australian Company	Big Pharma	Deal Type	Deal Value	Phase
May - 16	Phosphagenics	Undisclosed Japanese healthcare company	Licensing Agreement	Undisclosed	Phase I
May - 15	Pharmaxis	Boehringer Ingelheim	Licensing Agreement	AU$250m	Phase I
Sept - 15	Starpharma	AstraZeneca	Licensing Agreement	US219m incl. milestone payments	Phase I
Jan - 15	Spinifex	Novartis	Acquisition	US$200m upfront excl. milestone payments	Phase II

Table 3: Pharma Partnering Source: PAR

Given the potential for Rhinosul to be disruptive to currently marketed drugs in the AR sector, it would not be unusual to see larger biopharma take an interest in partnering with PAR or making an acquisition to replenish patent expiring drugs and/or to maintain market share in the sector.

Catalysts

PAR has several near-term price catalysts across its portfolio of potential products:

Hay Fever

- **Q4 2016-Q2 2017**, Phase II(a) allergen challenge trial commences at Lund University in Sweden.
- **Q4 2016-Q2 2017**, Publication by internationally recognised respiratory researcher, Professor Jonas Erjefält, from Department of Experimental Medical Sciences, Clinical Immunology, Allergy and Pulmonology, of the ***comparator research*** paper; "Th2, Neutralisation and *In Vivo* Anti-inflammatory Action of Pentosan Polysulphate Sodium (PPS) in an Allergic Rhinitis Model".
- **Q4 2016-Q2 2017**, Potentially interest from a few key respiratory pharmaceutical companies following the publication of the Professor Erjefält research and or before Phase II trials commence.
- **Q3 2017,** Completion and publication of Phase II(a) allergy challenge trials.
- Other uses of PPS in respiratory diseases. PAR's respiratory patent includes the use of PPS to treat allergic asthma and chronic obstructive pulmonary disease (COPD).

Alphavirus

- **Q1-Q2 2017** Phase II trials ethics approval and trial initiation for Ross River Virus/Chikungunya virus.
- Potential for PPS to treat other autoimmune inflammatory joint disease states such as Rheumatoid Arthritis.

BME

- **Q4 2016-Q1 2017**, Open label trial may potentially confirm PPS efficacy and optimised dosage in the treatment regime management of BME. This will potentially bring forward the fully funded Phase II(b) closed label trial.

Corporate Opportunities

- **Q1-Q3 2017,** Potential licensing agreements/ takeover interest in PAR may be sparked by the publication of the Th2, Neutralisation and *In Vivo* Anti-inflammatory Action of Pentosan Polysulphate Sodium (PPS) in an Allergic Rhinitis Model, paper.
- **Q1-Q3 2017,** Potential licensing agreements/ takeover interest in PAR may be sparked by the Phase II(b) closed label trials for PPS in the treatment of BME.
- Development and maturation of existing manufacturing agreements.

Market Expansion

- Following on from Phase II trial in BME PAR may identify expanded market opportunities beyond the acute orthopaedic management options.
- Similarly depending on the success of its AR product further application expansion in the respiratory medicine sector for allergic asthma and chronic obstructive pulmonary disease may be identified.

Company Overview

History

PAR was founded May 2 2014 and listed on the Australian Stock Exchange in August 2015. Its focus lies in repurposing pentosan polysulphate sodium (PPS) for new orthopaedic, respiratory and mosquito borne viral diseases.

Capital Structure

Paradigm Biophamceuticals Ltd - Capital structure

Securities	No.(m)	MCAP $ (m)
Quoted FPO Shares	57.84	24.3
Unquoted FPO shares	43.66	18.3
	101.50	42.6
Unlisted options - $0.37	3.02	
Unlisted options - $0.50	1.71	
Total Securities	106.24	

Table 4: PAR Capital Structure Source: Factset

Price performance

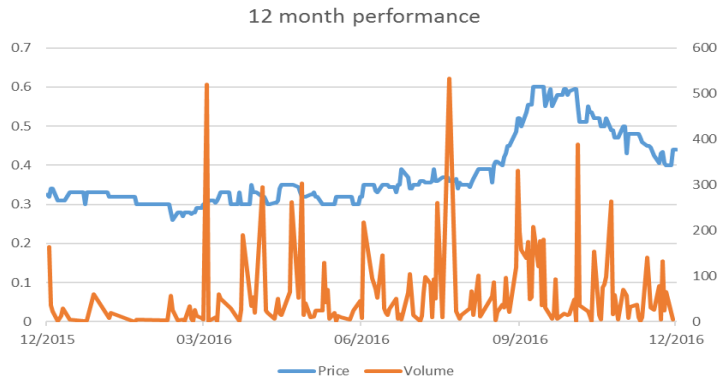


Figure 2 : 12 Month Price and Volume Chart. Source: Factset.

Major Shareholders

No.	Holder	No. Shares	%
1	Paul Rennie	22.1	21.8
2	MJGD Nominees	6.9	6.9
3	Other Board and management	7.1	7.1
4	Irwin Biotech	6.3	6.3

Paradigm's Strategy

PAR has a simple, focused, low cost, low risk strategy to its business model, targeting medical conditions of allergic rhinitis, alphavirus and bone marrow edema. It works closely with proprietary manufacturers of PPS and leverages historic knowledge and expertise from previous regulatory filings to assist it in the development of its proposed drugs.

This process leverages off decades of toxicology studies and human safety data, formulation know how and bodies of independent peer-reviewed published information regarding PPS's mode of action.

This strategy minimises the risk profile as an early phase drug development company, which in turn, reduces the drug development cycle time and cost for their clinical trials.

Understanding PAR's Position & AR Market is Key to Rhinosul's Full Market Potential

The investment rationale of PAR is predicated on understanding the massive upside of PPS in Allergic Rhinitis. Recognising that PAR is uniquely positioned to take a significant share in AR market is important. It's potential ability to capture market share is dependent on success of its Phase II trials. These trials will demonstrate if Rhinosul ® has superior efficacy to intranasal steroids. PPS already has the established safety profile and Rhinosul ® could be first in class, dual (early & late phase AR) acting nasal spray.

Should it show efficacy signals better or comparable to Dymista and based on historic peak annual sales of Rhinocort (AstraZeneca's product), we estimate that Rhinosul® could reach a blockbuster drug status with sales in excess of US$1.0bn. Full analysis of the AR market is outlined in the Product and Market Analysis Appendix below.

Dymista is highlighted in the appendix section below as this drugs' mechanism of action is similar to PAR's Rhinosul® in terms of its dual action on acute and chronic phases of AR.

Most importantly, PAR's product treats both the early phase and late phase with a **non-corticosteroid anti-inflammatory** which may prove to have significant clinical benefits over Dymista and attract greater consumer demand, particularly for paediatric applications.

Paradigm's Business Model Summary

Key Activities

PAR is a drug repurposing company focused on project managing the development of its pipeline of potential repurposed PPS products. It uses a supply and royalty payment agreement to gain access to PPS for repurposing across specific disease states in specific key jurisdictions.

PAR strategy for creating its product pipeline is predicated on a 'risk controlled model', by which it researches globally for specific inflammatory disease state conditions that it may

target. Based on PAR's scientific knowledge of tissue inflammation response it then seeks to research how the target diseases could respond to PPS. This model reduces risk, time and cost for developing potential candidate drugs.

Using this business model, it has commenced development of two promising orphan disease state therapeutics and one potential disruptive therapeutic alternative targeted at a very large global market.

PAR's pipeline development and management is driven by its current supply agreement with bene pharmaChem which gives its access to 10 years' supply of PPS with a 10-year option to renew on the condition PAR achieves regulatory approval for one of its products. Hence, its key activities and skill set are focused on early phase research and development management and sales.

A review on PAR timeline and product development management is outlined below in Section- "Development Management and Pipeline Development".

Key Relationships

PAR has developed key strategic relationships with specific suppliers for not only PPS but its independent intellectual property and independent advisory opinion pieces. These relationships have been targeted in support of their strategic intent; the development of a commercial relationship with a large pharmaceutical company prior to, during or after the completion of Phase II trials for either of its products.

Bene pharmaChem

PAR has entered a 10-year supply agreement for PPS (with an option to extend for a further 10 years) provided that within the first 10 years PAR obtains regulatory approval for a product incorporating PPS supplied by the German manufacturer bene pharmaChem.

Under the supply agreement bene pharmaChem's PPS is manufactured in a cGMP (current Good Manufacturing Practice, regulations) production facility which is owned by bene pharmaChem and audited by the US FDA.

Currently bene pharmaChem makes the only FDA approved form of PPS for human use. Even though PPS is off patent Bene's manufacturing methods are a trade secret. Carbohydrate based compounds such as PPS are notoriously difficult to manufacturer which will help Bene retain its position as the global leader in PPS production. Bene also have the capacity to expand the production of PPS to meet PAR's future demands for the drug. .

PPS was first discovered and manufactured by bene pharmaChem in 1947 and has a well established safety profile in humans.

Pharmaceutical Development Partners

PAR has made a conscious decision to only use world-leading intranasal device manufacturers, toxicology laboratories, preclinical and clinical trial centres who have a demonstrated track record of working with Big Pharma respiratory companies.

Lund University, is Sweden's strongest comprehensive research university and in recent years has been awarded more research funding than any other Swedish full-scale

university. Internationally recognised respiratory researcher, Professor Jonas Erjefält, from Department of Experimental Medical Sciences, Clinical Immunology, Allergy and Pulmonology, supervised the recent ***independent***, gold standard ***comparator-drug preclinical research*** study which is entitled, "Th2, Neutralisation and *In Vivo* Anti-inflammatory Action of Pentosan Polysulphate Sodium (PPS) in an Allergic Rhinitis Model". The *In Vivo* model used was a validated Guinea-Pig model of allergic rhinitis and has been used at Lund University by Big Pharma companies such as AstraZeneca in the clinical development of the corticosteroid budesonide the active ingredient in their flagship product Rhinocort®.

Charles River Laboratories, provides essential products and services to help pharmaceutical and biotechnology companies, government agencies and leading academic institutions around the globe with toxicological studies for clinical development. PAR successfully completed a bridging intranasal toxicology study at Charles River Laboratories (USA) in Q2 2016.

MoNoChem has global sales of US$712m and PAR's used MoNoChem's Austrian offices to partner with in the development of its intranasal spray formulation.

APTAR (Germany) is the major global supplier of intranasal delivery medical devices for the pharmaceutical industry. The APTAR device has European Medical Agency (EMA) approval. The state-of-the-art APTAR actuator can deliver intranasal delivery of either preservative-free solution of PPS or PPS nasal formulations which containing preservatives. The EU market has a strong preference for preservative-free intranasal formulations whereas the US market is dominated by formulations which contain preservatives. The APTAR actuator provides one device which can deliver intranasal solutions which either are preservative-free or contain a preservative. his is a unique advantage of PAR Rhinosul® PPS solution in combination with the APTAR actuator/medical device.

Bene pharmaChem, is an intergenerational private company manufacturing and supplying high quality pharmaceutical products. Its first medicinal product, pentosan polysulphate sodium (PPS), was first authorised and marketed in Germany in 1947. In the USA, Bene supply PPS to Johnson & Johnson for the oral PPS product to treat the painful bladder condition of for interstitial cystitis. Bene are the only FDA approved and audited supplier of PPS in the USA for human therapeutic use. .

Glycomics Department, Griffith University, Queensland. The Glycomics Institute is the only one of its kind in Australia and one of a handful in the world. Established in 2000 the Institute is based on the study of carbohydrates or sugars.

Dr Lara J Herrero, Research Leader, Institute of Glycomics, supervised a fully independent research paper, 'Pentosan Polysulfate: a Novel Glycosaminoglycan-Like Molecule for Effective Treatment of Alphavirus-Induced Cartilage Destruction and Inflammatory Disease' that established in a In Vivo', using a mouse model. This established that PPS reduced the clinical disease severity of alphaviruses such as RRV and CHIKV in wild type (C57BL/6) mice.

PAR has the exclusive world-wide rights to commercialise the patent as well as the right to acquire (assign) from Griffith University the patent after PAR commences a Phase II clinical trial.

PPS – PAR's Key Resource

PPS is the key resource in PAR's business strategy. Although PPS is manufactured in other countries throughout the world, the molecular fingerprint of bene's product is difficult to replicate. Hence bene pharmaChem's product is the only FDA approved PPS.

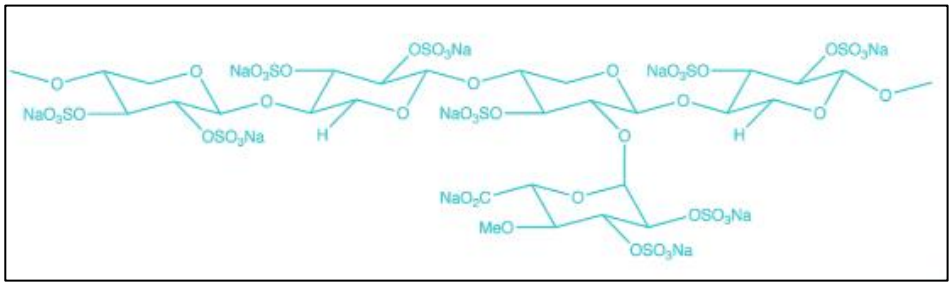


Figure 3: Pentosan Polysulphate Sodium Molecule. Source: PAR

PPS is a semi synthetic polysulphate xylan molecule (a form of carbohydrate/glucose) derived from beech wood grown by bene pharmaChem in its vertically integrated facilities in Germany.

Simply put a xylan is carbohydrate-based molecule from beech wood contains up to 35% xylans. Added to this xylan in a complex and highly regulated chemical process, under extreme heat, are a series of sodium and sulphate ions forming pentosane polysulphate sodium (PPS). This process is a trade secret and difficult to replicate.

This well controlled process produces a consistent high-grade medicinal product that is currently used to treat inflammatory conditions such interstitial cystitis (painful bladder) in the US and in EU it is used as an anti-thrombotic (anti blood clot) agent.

PPS has a substantial, well-documented safety record and has been used in humans for almost 70 years. It was first approved by the FDA in 1996. The patents on the US based product expired in 2010 and since its approval in EU there have been more than 100 million injectable doses administered.

Generic competition has been unable to replicate the sulphated polysaccharides to the same high standard as bene and according to management no known generic has received FDA approval.

PARs' supply and royalty agreement hand them a sustainable competitive advantage over any competitor seeking to replicate any product PAR should successfully develop.

Revenue Streams

Currently, PAR has three potential revenue streams that may be derived from their product pipeline. It is acknowledged that PAR does not intend to undertake the sales and distribution of any of its products and will seek sale/upfront payment/milestone payments and/or royalty/license agreements with one or several potential pharmaceutical companies.

If positive signals are observed in the Phase II(a) Alpha Virus (AV) trials early sales of this product may occur which will assist PAR's fast track FDA approvals.

These commercial events may occur before, during or after Phase II trials in any of its products. However given the significance of the market size and the corporate activity in the respiratory business, and on the balance of probabilities, PAR may attract interest from a pharmaceutical group with an interest in the respiratory sector.

The timing of the most recent transactions has occurred at various clinical development stages of the potential products from Phase I/II(a) to commercialisation/Phase III. The higher values were offered to those companies further progressed in their clinical development.

Development Management and Drug Pipeline

PAR has announced that is has three candidate drugs in its pipeline, Rinosul®, Zilosul® and its Alpha Virus therapeutics. Currently PAR is fully funded to complete Phase II Trials for its pipeline of candidate drugs.

PAR's has demonstrated a strong focus on cash management and spends almost 80% of its total operating expenditure of R&D indicating a sound alignment of managements interest to that of shareholder returns. The R&D expenditure is eligible for R&D tax refund.

The company has demonstrated strong operational and drug development management since listing and has met all short-term operation milestones and has met multiple clinical trial developments within the timelines outlined in the tables below. Slight delays were noted in PAR's BME trials due to patients seeking to opt out of the trial as surgeons recommended surgical treatment ahead of trial completion. This issue has now been remedied.

PAR's concurrent drug pipeline and management process creates several catalysts over the next 12 months.

1. Allergic Rhinitis

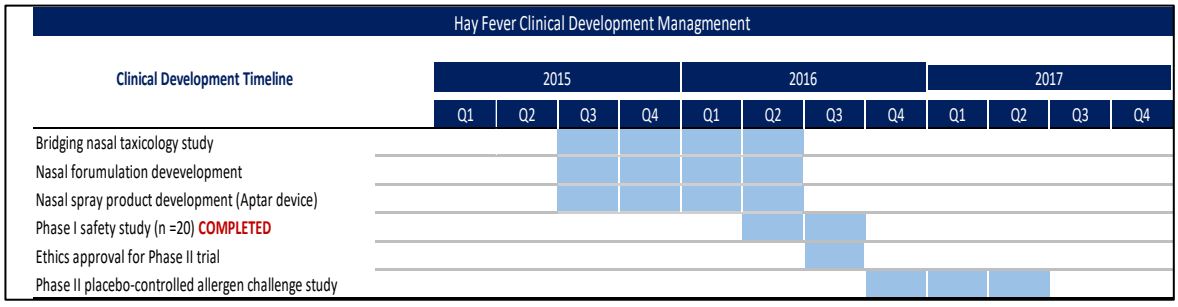


Table 5: Hay Fever Clinical Trial Source: PAR

PAR demonstrates by its clinical development management activities with its AR product efficient process controls as outlined

APTAR Pharmaceutical developed PAR's nasal spray product and solution to world industry standards. PAR's actuator has specifically designed particle size and plume design to maximise effective of dosage. In addition, the actuator and solution has been designed with the option to include preservatives (required for the US market) or to exclude them (preferred by the European market).

The bridging nasal toxicology study was conducted by world leading, US based, Charles River Laboratories in January 2016 and, the nasal formulation and actuator were developed by Aptar Pharmaceuticals in Austria, Q3 2015-Q2 2016.

Further, Phase I Pre-Clinical trial using AstraZeneca's Guinea Pig Model, was independently conducted by Lund University with the research supervision and write up by world leading respiratory researcher, Professor Jonas Erjefalt. Peer review of research is currently underway. AstraZeneca's guinea pig model was used by PAR as it is recognised by the respiratory pharmaceutical industry to reflect results that are highly translatable to human testing. AstraZeneca used it to test Rhinocort® (budesonide) with 2015 annual revenues US$250m.

The Phase II(a) Challenge Study is to be conducted in Sweden at Lund University (ex-AstraZeneca respiratory facility) and PAR aim to have the results published by end of Q2 2017.

2. Alphavirus

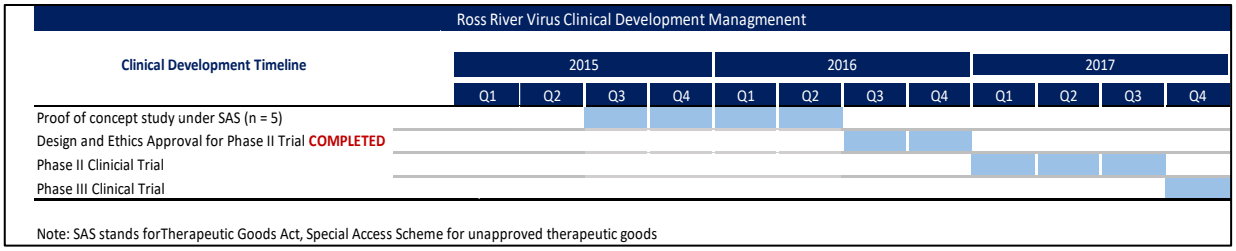


Table 6: Alphavirus Clinical Timeline. Source: PAR

With its Alpha Virus clinical development management PAR has been able to leverage existing research activities from the Institute of Glycomics, Griffith University, Queensland creating commercial efficiencies in its pipeline management (see Key Relationships). Total expenditure for Phase II Trial is approximately AU$2.0m.

Phase II research findings will leverage off Phase I research and proof of concept work directed by Dr Lara Herrero, Institute of Glycomics, Griffith University, Queensland. Five patients with RRV arthralgia have already been treated under TGA's special access scheme demonstrating tolerability and potential clinical effects.

Phase II (a) Trial design and ethics approval has been received in Q4 2016 with Phase II clinical trial work to commence in Q1 2017 to develop PPS for the treatment of RRV and CHIKV induced arthritis and arthralgia.

Depending on the early clinical signals identified throughout Phase II (a) PAR will consider applying for a fast track FDA approval. Fast track approval is available for compounds that modify disease states to affect a positive outcome in patient health that reduce healthcare costs.

The impact of a successful fast track application to PAR will be to reduce the costs of Phase III trials as clinical data will be collected and monitored contemporaneously throughout the Phase II process and within a clinical setting with patients.

3. Bone Marrow Edema

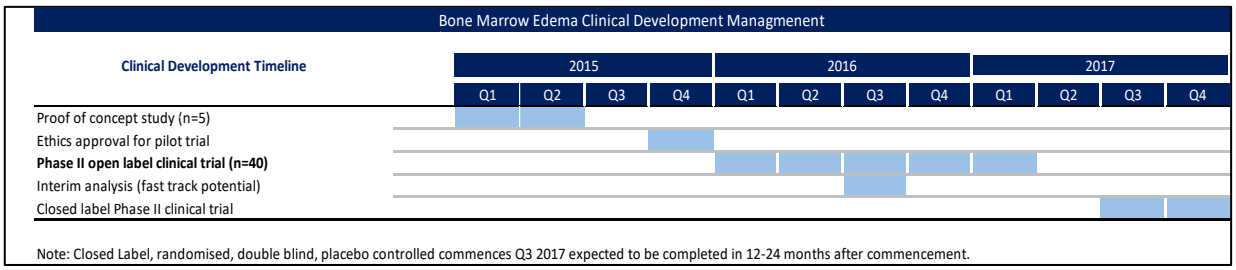


Table 7: Bone Marrow Edema Clincal Timeline Source: PAR

PAR is currently conducting an open label clinical trial in Australia investigating the safety, tolerability and efficacy of Zilosul®. The institutions who are conducting this research have not been given PAR permission to disclose their involvement, but total expenditure for completion of Phase II Trial is AU$2.1m

The open label trial design requires 40 patients and means that the PPS dosage levels can be changed and optimised in response to real time data transparency.

PAR has secured approval for patients to participate in this clinical trial under TGA's Special Access Scheme. Pending interim results analysis, a fast track approval application may be made in Australia for the use of PPS for the treatment of BME.

Investment Rationale - Detail

Pharmaceutical Industry

The pharmaceutical industry globally is made up of thousands of entities with activities across discovery, manufacturing and sales of drugs. The global market for pharmaceuticals was typically valued at around US$ one (1) trillion in 2014[1].

Research based pharmaceutical companies invest in R&D to develop drugs for medical treatments. Each drug must be evaluated in clinical trials for their safety and efficacy before the US Food and Drug Administration (FDA) will allow them to be manufactured and sold. The cost is enormous (average US$1.8bn) and it takes up to 15 years. Not all trials are successful but if they are, significant profits can be made from "blockbuster" drug products sales which is defined by sales that exceed US$1.0bn in annual revenues.

The global price performance of the pharmaceutical sector (big pharma and generics) has underperformed compared to PAR and the ASX All Ord in the previous 12 months as outlined in the comparative index chart below.

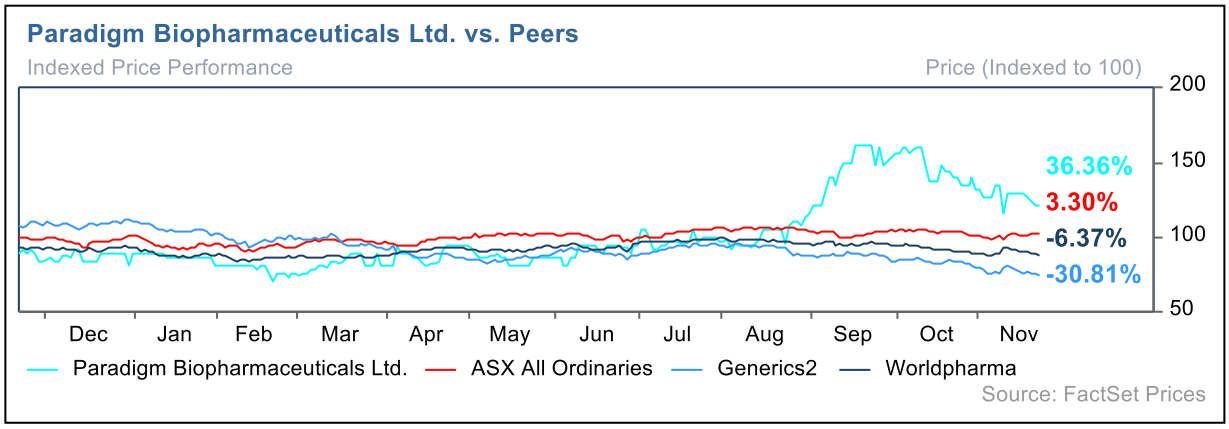


Figure 4: Indexed Comparison. Source: Factset

PAR's price outperformance was compared against three indices, the ASX All Ords, the top 10 Generic and major De Novo Pharmaceuticals companies. Bases on this index chart in last 12 months the generics market has significantly underperformed the majors with -30.81% compared to -6.37%. Current growth rates in the generic and major comparative groups (see Appendix 1) are -14.7% and 6% respectively[2].

Manufacturing of drugs is strictly regulated and held to high standards such as the FDA Good Manufacturing Practice (cGMP) requirements. Drug products have a long value chain with end users, such as hospitals, pharmacies being reached through well-established wholesalers and distributors. Revenues from drug sales depend on national healthcare providers and insurance companies agreeing to purchase the product for a set price (reimbursement).

PAR is a small cap ASX listed R&D drug repurposing (See Drug Repurposing Section below) company specialising in the R&D of three key products targeting allergic rhinitis, alphaviruses and, bone marrow edema.

[1] Visiongain PHA0142 Allergic Rhinitis

[2] Factset 2016

When PAR is charted against a custom indexed peer group (See Appendix) it demonstrates a 12-month outperformance to its peers.

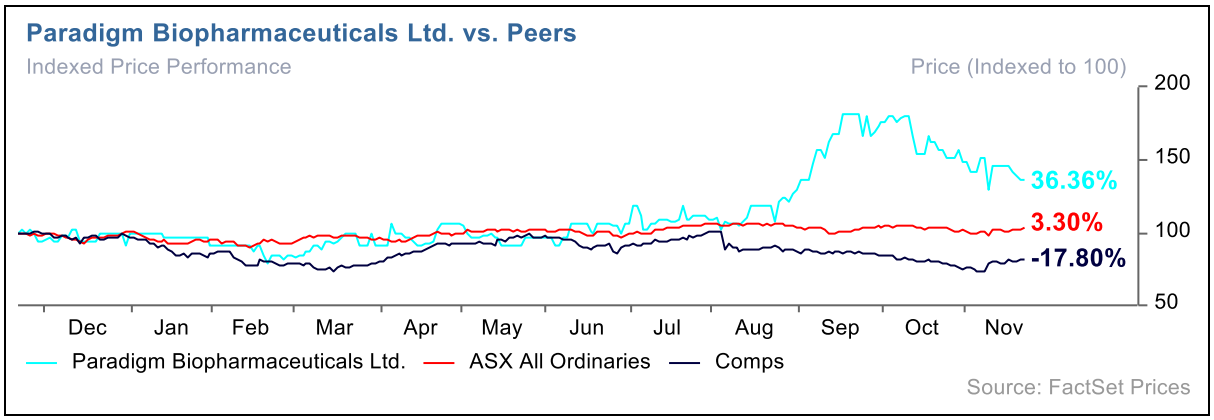


Figure 5: PAR Comps Index Comparison. Source: Factset

The Drug Repurposing Industry

Summary

PAR has positioned itself in the lowest quintile of the cost curve compared to the average drug repurposing company.

The key drivers behind the sustainability in the DRPx industry are derived from the current business models of large pharmaceuticals companies that are faced with escalating costs, poor productivity and protracted timelines to bring a therapeutic drug to market.

The drug repurposing sector does impact the prescription drug industry for all stakeholders. Currently the pharmaceutical industry accrues 25% (US$250b-$500b)[3] of its annual revenues from repurposed drug products.

The key value drivers favouring the repurposing industry and PAR are:

1. Higher success rate of 25% in bringing repurposed drugs to market.
2. Safety of repurposed drugs is already established truncating the clinical management process by eliminated the need for expensive and time consuming Phase I Trials.
3. Cost saving in the regions of 70% are experience for drug repurposing companies.
4. Time savings, repurposing companies on average demonstrate a 3-5-year time saving.
5. IP protection if managed well by a repurposing company can provide candidate repurposed drugs the same protections as de novo drugs.
6. Market opportunities can be the same for repurposed drugs affording them the ability to reach blockbuster status.

Drug Repurposing - Industry Review

The consensus is that the Drug Repurposing and Repositioning (DRPx) industry and its impact on the pharmaceutical industry is sustainable[4]. The generic drug sector and a well-informed consumer population drive the need for development of safe and efficacious therapeutic drugs. Figure 6 below outlines the features of PAR's DRPx business strategy that PAR it is managing with respect to the development of its pipeline of potential products.

Drug Repurposing Model

The repurposing sector like all pharmaceutical R&D companies requires management to oversee the concurrent development of the various value adding elements as represented in Figure 6 below.

It is DJC's view that PAR has aligned its repositioning strategy and critical elements of its business model to complement the expectations large pharmaceutical companies seek with outsourced DRPx opportunities like PAR.

[3] Persidis, A, Biovista website. http/biovista.com/stakeholders/generics-companies/. Cited Drug Discovery World, Spring 2015.
[4] Dr Stephen Naylor, David M. Kauppi and Judge M Schonfeld, Drug Discovery World Spring (2015), Therapeutic Drug Repurposing, Repositioning and Rescue, Part II.

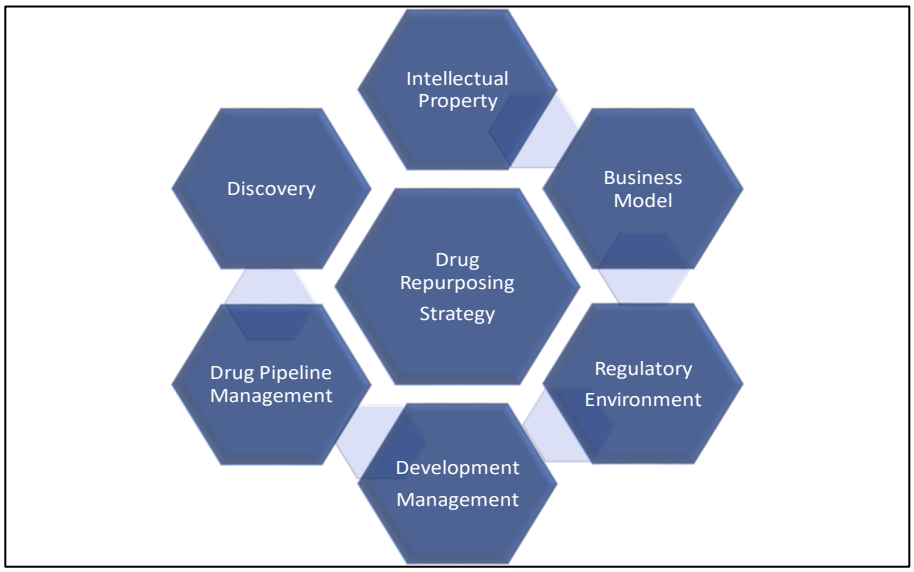


Figure 6: PAR Repurposing Model Features. Source: DJ Carmichael

Drug Repurposing Industry

The DRPx does impact the prescription drug industry for all stakeholders. Currently the pharmaceutical industry accrues 25% (US$250b-$500b)[5] of its annual revenues from DRPx products. Several mini-blockbuster and blockbuster drugs are outlined in Table 9.

Table 8 below outlines the key issues besetting the pharmaceutical industry and are important elements to consider when evaluating PAR's position in this sector.

Challenging Features of the Incumbent Pharmaceutical Industry		
Variable	**Features**	**Quantitative Analysis**
Cost	Prohibitive Risk to bring a new drug to market	US$1.77 billion (average)
Time	Time to launch a new discovery	12-15 years
Risk- stratospheric	8% chance of success in clinical trials • Phase I, 45% failure rate ***- lack of safety*** • Phase II, 65% failure rate– ***lack of efficacy*** • Phase III to market, 50% chance of success • **ONLY** max 10% chance of new drug making it to market ***from Phase II trials***	90-92% failure rate
Safety Efficacy	Elevated concerns due to business model which creates conflicts of interest.	Serious ethical concerns arise
Competition	Generic Competition captures huge number of US prescriptions	70% of all prescription in US
Patents	Cost of patent cliff 2001-2016 in lost sales	US$ 245.5 billion
Regulation	Due to costs more stringent oversight is required	Drug discovery development phase
Consumer Sentiment	Seeking safety and Efficacy	Consumer concern is HIGH

Table 8: De Novo Industry Features. Source: Drug Discovery World 2015.

[5] Persidis, A, Biovista website. http/biovista.com/stakeholders/generics-companies/. Cited Drug Discovery World, Spring 2015.

Drug Repurposing Industry Dynamics

Most large pharmaceutical industry players approach DRPx in either a formal or ad hoc manner. Some large Pharmaceuticals such as Novartis and TEVA dedicate internal resources to DRPx where Pfizer closed its DPRx discovery unit to join National Centre for Advanced Translational Sciences (NCATS).

NCATS is a therapeutics discovery program launched in 2012 and funded by US National Institute of Health, (NIH). Fifty-eight compounds have been made available to NCATS for DRPx evaluation by AstraZeneca, Bristol Myers Squibb, Lilly, GlaxoSmithKline, Sanofi-Aventis, Jansen, AbbieVie and Pfizer.

In the US Roche formalised its DRPx strategy by announcing a collaboration with the Broad Institute in 2012, agreeing to provide 300 of its failed compounds to be screened for new potential uses.

In the UK, the Medical Research Council (MRC) partnered with AstraZeneca and expanded into Cancer Research through a relationship that allows unprecedented access to AstraZeneca's compound library.

The primary driver behind the for-profit corporations and other large pharmaceutical companies DRPx strategies is the **need to generate revenues**. Not for profit organisations such as 'Cures Within Reach' and 'Centre for World Health and Medicine' on the other hand will pursue different goals and focus specifically on rare and neglected diseases of limited commercial value.

Approximately 80 DRPx drugs have hit the market since 1987. Several of these have been discovered serendipitously with significant success; outlined below in Table 9 are the top performing repurposed or repositioned drugs since 1997.

	Original Drug	Original Indication	Repurposed Brand Name	New Indication	Year	Pharma Company	Annual Peak Sales US$
1	Thalidomide	Structural Analogue	Revlmid	Multiple Myeloma	2006	Celgene	$4.28b
2	Fumaderm	Psoriasis	Tecfidera	Multiple Sclerosis	2013	Biogen IDEC	$2.91b
3	Sildenafil	Angina	Viagra	Erectile Dysfunction	1998	Celgene	$2.05b
4	Gemcitabine	Anti-viral	Gemzar	Various Cancers (various)	2014	Lilly	$1.72b
5	Rituximab	Various Cancers	Rixutan	Rheumatiod Arthritis	2004	Biogen/IDEC Roche	$1.28b
6	Raloxifene	Osteoporosis	Evista	Invasive Breast Cancer	2007	Lilly	$1.098
7	Finesteride	Hypertension	Proscar	BHP	1992	Merck	$741.4m
8	Sildenafil	Angina/ED	Revatio	PA Hypertension	2005	Pizer	$525.0m
9	Thalidomide	Hypertension	Propecia	Male Pattern Baldness	1997	Merck	$429.1m

Table 9: Mini-blockbuster and blockbuster Repurposed and Repositioned Drugs Source: Dr S Nalyor 2015.

The nature of the repurposing industry has several key advantages that DRPx companies leverage and reduce the risk, cost, time then improve productivity in the drug development phase compared to large pharma counterparts.

The drug repurposing process is significantly truncated during the discovery phase as outlined in Table 10 below.

Since the lead drug in a DRPx strategy has likely been subjected to the toxicology and safety regimes for the original indication, the Pre-Clinical phase only requires a demonstration of efficacy for the new indication in either a cell or animal model. Thus, unless the lead candidate drug is using a new mechanism of delivery such as Rhinosul®,

the trials commence at Phase II(a). This is permitted under Section 508(b) (2) or the US Department of Health and Human Services, FDA application process.

In summary, the market potential of a DRPx is the same as a de novo and they can achieve blockbuster market potential (over US$1 billion in peak annual sales) in the same way.

The same well known market forces exist for repurposed drugs as they do for conventional de novo drugs: drug differentiations; consumer need; patient acceptance; market strategy and, intellectual property protection and position. As discussed above the AR market is very big with only one company, GSK, achieving blockbuster status in 2015 but with several others achieving this status historically.

PAR's repurposing strategy is very low cost, time efficient, has the tail winds of consumer sentiment behind it and strong IP protection, which means **if** PAR's Phase III AR Trials achieve success and it receives FDA approval, the Rhinosul® product may be perfectly positioned to reap the financial benefits availed by current market forces.

Compelling Features of PAR Compared to Average Performance of the DRPx Industry

Variable	Features	Quantitative Analysis	PAR
Cost Savings	85% cost reduction to relaunch	US$ 300m (average)	US$ 40m (85% less cost compared to average DRPx Co's)
Time Savings	Significant efficiency improvement	Overall saving 3-5 year in time as drug development timeline truncated	3.5- 5 years in total (50-60% less time compared to average DRPx Co's)
Risk- significantly reduced as is time to market	25% chance of success in clinical trials	75% failure rate.	Unknown
	• Phase I, usually not required ***safety already proven*** • Phase II to market, 25% chance of market success ***improved efficacy*** • Phase III to market, 65% chance of market success • **ONLY** max 10% chance of new drug making it to market ***from Phase II trials***	Phase I required if new pathways of administration used.	Rhinosul ®Phase I Trial complete at AU$1.0m cost. Phase II Trials in AR and AV commence in Q4 2017, cost US$2.0m. Phase III AR Trials cost US$20m.
Safety & Efficacy	The probability of success increases as the safety of the drug has already been demonstrated in humans		PAR's supply of PPS has almost 70 years of safety data associate with its use globally.
Competition	Strong patent protection available.	New application may require new delivery pathways	
Patents	Cost of patent cliff 2001-2016 in lost sales	Big pharma stand to lose US$ 245.5 b in revenues in the coming years to generics.	PAR has strong IP and manufacturing protection.
Regulation Pathways faster	FDA (505)(b)(2)	DRPx can rely on data not developed by DRPx company.	PAR has access to bene's MDF in support of it applications.
Regulation- Orphan Drug status	FDA fast track approval.	Neglected disease states may get faster approval	PAR is targeting AV and BME orphan disease states.
Consumer Sentiment	Seeking safety and Efficacy – DRPx achieve this early	Consumer sentiment is met with safer new product	PAR AR meets consumer demands with Rhinosul® and AV.

Table 10: Drug Repurposing Industry Features Compared to De Novo and PAR Source: Dr S Naylor & PAR.

Pharmaceutical Productivity and R&D support innovation with DRPx Opportunities.

One of the critical issues facing the pharmaceutical industry is productivity according to Paul SM et al [6]. Without an increase in R&D productivity the pharmaceutical industry cannot sustain enough innovation to replace lost revenues due to patent expirations.

We considered this critical element in relation to PAR's strategic alignment as repurposing companies must align their R&D, in the early phases of the drug development, to the quality and standards of large pharmaceutical companies. This is to attract strong and early interest for potential licencing agreements or to receive potential takeover interest.

PAR achieves a high degree of productivity as its trials are inexpensive and trial sizes are small and short. Further, they leverage researchers with specific international industry reputations to conduct independent research in industry recognised respiratory and glycomics universities.

PAR achieves this high degree of productivity through a masterful approach in applying gold standard independent research and development for two of its key products. Further they can leverage bene pharmaceuticals Drug Master File (DMF) to potentially assist in its FDA approval process.

PAR has managed its pipeline of potential new drugs strategically well, developing three differentiated products all aimed at global markets, (see Section "Development Management' above).

1. An allergic rhinitis respiratory product differentiated by its safety, efficacy and pricing strategy aimed at a global market.
2. A virology product aimed at a global orphan disease state.
3. An orthopaedic product aimed at a global orphan disease state.

The series of tables below provide an evaluation of the productivity and efficiency created by PAR's business model.

The Comparative Productivity In Drug Development Models.

De Novo Drug Development and Delivery Productivity Model

	Discovery	Pre Clinical	Clinical			Review to Launch	
	Target to Lead Optimisation	ADMET	P-I	P-II	P-III	FDA	
Probability (%) of Success	75-86%	69%	54%	34%	70%	91%	
Work in Progress to Launch	14-24	12. 4	8.6	4.6	1.6	1.1	**24:1**
Capital Cost –Launch Cost (US$M)	674	150	273	319	314	48	**$1.78B**
Cycle Time (Years)	4-5	1	1.5	2.5	2.5	1.5	**14 Years**

Probability (%)	Probability of technical success
Work in Progress	Projects necessary for a drug product
Cost of Capital- Launch Cost	Capitalised cost in $USD @ 11% WACC
Cycle Time	Time taken for each phase in years

Table 11: Paul's De Novo Productivity Model Source: Drug Discovery 2015/16

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

The Paul model was developed using R&D performance productivity data from 13 pharmaceutical companies and this model can be used on a per project or portfolio basis. Essentially this suggests that starting from a baseline value for the estimated cost of a single new molecular entity (NME) they could evaluate which operating parameters need to be changed to enhance productivity[7].

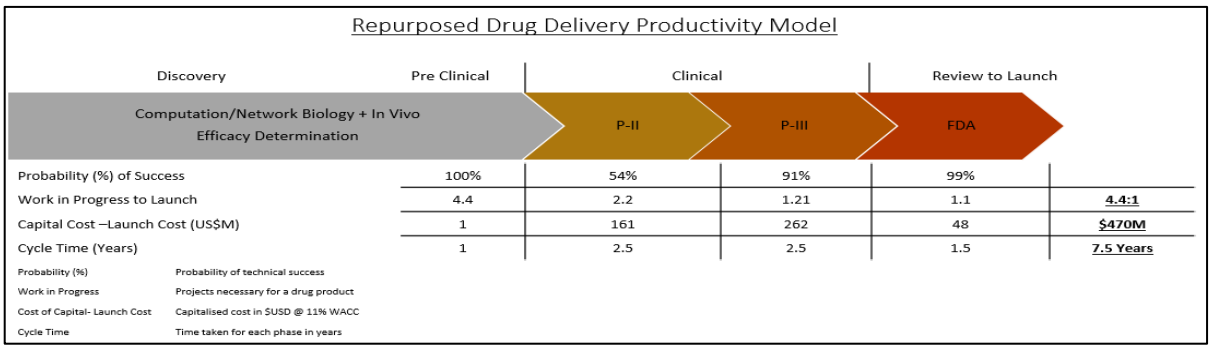


Table 12: Kauppi- Naylor Drug Repurposing Company Productivity Model Source: Drug Discovery 2015/16

The Kauppi Naylor model built on the Paul model but adjusted it for the significant differences the DRPx industry, namely, time and costs. The Kauppi Naylor model has been used to evaluate and compare PAR productivity model against the norm in Table 13 below.

Applying the DRPx modified productivity model to PAR's strategy demonstrates the efficiency of its business model compared to the average productivity of DRPx strategies outlined in Table 13. The most significant elements to consider from this model are the timing and costs of development in Phase II, bringing cash flows forward.

The other critical factor highlighted in this model is the time lines and the apparent efficiency in which PAR can achieve with its clinical trial management. The highlighted "blue' oval indicates the current position of PAR's product development. This apparent efficiency increases NPV's and reduces payback periods.

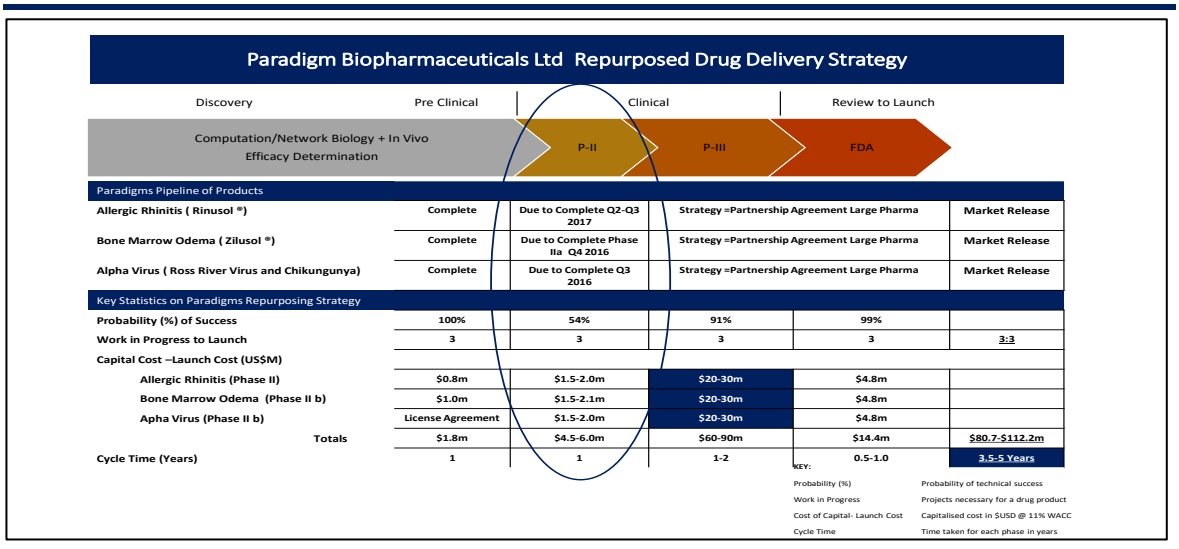


Table 13: PAR's Modified Kauppi-Naylor Model Source: PAR, Drug Discovery 2015/16

[7] M Kauppi and Dr S Naylor Drug Discovery World Winter 2015/16

DRPx Breakeven analysis & Potential Revenue

The sensitivity analysis

Table 14 below, developed by M Kauppi and Dr S Kaplan for the DRPx industry, allows participants to comparatively analyse the De Novo and DRPx business models and consider the viability of new drug development and disease targets. It demonstrates the revenue needed from an approved drug to recoup R&D costs and break even. *Further a comparative analysis of previous successful repurposed drug has been included based upon peak annual revenues alone*. Using this Table and considering the variables it is estimated PAR may breakeven well below total revenues of US$85m in two of three of its potential products, Rinosul ®AR and AV therapeutics.

The breakeven point for a De Novo drug development is total revenues of US$375 assuming gross profit margin of 70%. As highlighted in the red boxes below, a target disease state for De Novo manufacturers must produce significantly higher revenues for relatively lower NPV's which will influence their drug development focus.

The breakeven point for an average DRPx approved drug is total revenues of US$85m with gross profit margins of 70% and based on the following assumptions:

- 4.5 years and US$219 m in discovery expense is ***eliminated*** as outline in Table 13.
- 2.5 years and US$190 m in Phase I clinical trials ***eliminated.***

The following criteria was applied to the model below.

- Using the Costs and Time lines outlined in Pauls Model
- Table 11 and Kauppi and Kaplans model, Table 13 above to compare.
- Cost of Capital 10%.
- DRPx process using candidate drugs approved for use in humans.
- Data mining of clinical trial data for high probability safe drugs for new indications.
- Regulatory exclusivity for repurposed drugs of 13 years.

PAR DRPx Potential Breakeven Position

PAR's product development costs are in the lower quintile of the average drug repurposing strategy cost curve, improving its breakeven analysis significantly. The other key elements that improve the potential financial performance of PAR are listed below:

1. Lower cost Phase II and Phase III Trials for AR and Alpha Virus with Phase II Open Label Trials for BME almost complete. Fast tracking approval process may be applied for pending interim results and critical signals identified from the Phase II (a) studies in AR and BME.

2. Shorter trial periods for AR and Alpha Virus with potential fast tracking options for AR due to potential Orphan drug status and PPS's disease modifying efficacy with AR and BME that will further reduce the cost and trial size of Phase II (b) to less than US$10m.

3. Regulatory exclusivity across all potential products for up to 20 years.

4. PAR has stated that it has gross profit margins larger than 70%.

Successful Repurposed Drugs Peak Annual Sales Compared [8]	Potential Drug Product Breakeven Total Revenue US$	De Novo Development		DRPx Development		PAR Products Targeted Annual Revenue Position		
						AR	AV	BME
Dymista ($119m)	100m	NPV $US m	**(340)**	NPV $US m	44	Potential	Potential	Potential
	100m	IRR (%)	**(2)**	IRR (%)	12			
	200m	NPV $US m	**(215)**	NPV $US m	308	Potential		
	200m	IRR (%)	**4**	IRR (%)	22			
	300m	NPV $US m	**(91)**	NPV $US m	573	Potential		
	300m	IRR (%)	8	IRR (%)	28			
Revatio ($525m), Propecia ($429m)	500m	NPV $US m	158	NPV $US m	1,102	Potential		
	500m	IRR (%)	13	IRR (%)	37			
Proscar ($741)	750m	NPV $US m	470	NPV $US m	1,763	Potential		
	750m	IRR (%)	17	IRR (%)	44			
Evista ($1.1b), Rixutan ($1.3b)	1.0b	NPV $US m	781	NPV $US m	2,425			
	1.0b	IRR (%)	20	IRR (%)	50			
Viagra ($2.0b), Gemzar ($1.7b)	2.0b	NPV $US m	2,027	NPV $US m	5,071			
	2.0b	IRR (%)	27	IRR (%)	61			

Table 14: De Novo v Repurposing Industry Sensitivity Analysis. Source: Kauppi and Kaplan 2015/16

[8] Note: Peak annual sales have been used to align successful DRPx drugs with NPV and IRR **not** total revenues to break even.

Paradigms IP Portfolio & Intellectual Capital Review

A key risk for a DRPx company, like PAR, is the intellectual property protection and control. As PPS is off patent. composition of matter patents like that afforded a new chemical entity (NCE) are not available to PAR. PAR's IP includes of method of use (MOU) patents, exclusive supply of PPS from bene pharmaChem, , licensing agreements with research institutes, regulatory exclusivity benefits and trademarks.

PAR IP is a robust multifaceted and defendable strategy which has been achieved with very efficiently with relatively low expenditure to date. DJC believe that PAR has achieved market protection for its products through a sophisticated construction of its IP portfolio and commercial relationships.

To review PAR's IP strategy, we must briefly dissect the IP options available then match these backs to the three key products that leverage of the existing active pharmacological ingredient (API) as outlined in Table 15.

The clear majority of patent issues are in the form of a utility patent. A utility patent is issued for a "new" invention and exist for 20 years. There are four principle categories of utility patents:

1. Composition of matter (COM); New formulation for AR
2. Method of use (MOU); Can be just as effective as a COM in the right circumstances.
   a. new specific diseases - Allergic Rhinitis, BME, Alpha Virus
   b. new treatment and dosage regime for BME and Alpha Virus
3. Machine;
4. Manufacture.

In the DRPx industry COM and MOU patents are primarily granted.

PAR uses a combination of regulatory, trademark and MOU patent protection structures and regulatory protection to capture greatest value in its DRPx strategy. Each product has been given 20 years' patent protection in specific jurisdictions as of the priority date outlined below.

PAR leverages other market exclusivities such as orphan disease state qualifications, (giving it additional 7 years' regulatory exclusivity for Alpha Virus), paediatric extension rights (an additional 6 months' protection for Rhinosul®) and then all three products are all given additional regulatory protection under the Waxman Hatch Act providing an additional 7 years' patent extension.

This patent and regulatory framework is in addition to secure commercial relationships with its key supplier to capture long term protection in the market for its future potential products.

PAR have indicated that they will apply for an orphan disease state for its Alpha Virus. In terms of the Alpha Virus product a fast tract through Phase II through to Phase III may occur as PPS has demonstrated safety and has shown early signs of modifying disease states in Phase I trial results. Disease modification evidence is required for fast track FDA approval which means patient may access PPS for treatments prior to completion of Phase III and the clinical evidence collected from these patients can be used to form part of a Phase III trial. This being the case significant time and cost savings will be gained by PAR in its Alpha Virus product development process.

Similarly, PAR will monitor critical key clinical signals in its BME Phase II(a) studies which may assist it with its fast track approach in its Phase II(b).

Its potential AR product leverages a unique MOU, with a multi mechanisms of action, with PPS demonstrating high affinity binding to IL-4, IL-5 and IL-13 compared to other test molecules, plus it inhibits the growth of TH2 cytokine dependent responder cell-lines and reduces nasal tissue infiltration or eosinophils and CD3+T cells in the last phase response of AR.

The Alpha Virus MOU patent is potentially also differentiated with studies identifying that treatment of Alphavirus with PPS impacts the predominant natural killer cells, leukocytes infiltration characterised by inflammatory monocytes. These cells that were substantially reduced in the infected mice.

There is potential to leverage a particular BME MOU patent as well with product trial results suggesting that it might be classified as a disease modifying agent in osteoarthritis because of its ability to preserve the integrity of the articular cartilage and bone, whilst improving the quality of the joint synovial fluid. PPS in BME trials was shown to support chondrocyte and fibroblast anabolic activities while attenuating catabolic events associated with destruction of the cartilage extracellular matrix

Further they have developed a unique delivery system via an actuator/nasal spray with a novel formulation. Similarly, with BME and Alphavirus new drug regimens and dosages coupled with the MDF expedite its clinical trial programs for all products within regulation 505 (2) (b) of the FDA approval process.

The potential product Rhinosul® may disrupt the global intranasal spray allergic rhinitis market by being a first in class, safe, non-steroidal spray effectively treating the early and late phases of hay fever. As its MOA and safety demonstrate significant differentiation than its competitors FDA application success is most probable if efficacy can be demonstrated in Phase II and III.

Because of the DRPx process (as outlined in Table 13) later stage filing occurs and hence increases the period of patent protection. As generics cannot compete alongside PAR due to manufacturing and licensing agreements around PPS from bene pharmaChem the threat of substitution by off-label generic competitors is significantly diminished.

IP Protection and Evaluation					
	IP Protection Mechanism	**Respiratory Diseases, Allergic Rhinitis, Astham & COPD**	**Bone Marrow Odema**	**Alpha Virus (Ross River Virus and Chikungunya)**	**Comments**
Evaluation					
1	**Patents Jurisdiction**	EU, China, Australia, New Zealand	US, Japan, Australia, China, New Zealand	Patent Applications afoot for RRV and ChikV, Aust, US.	US is largest immediate market of AR and Alpha Virus. Department of Health and Human Services focused on ChikV threat.
2	**Patent Priority/Filing Date**	30 May 2008	02 February 2012 -Aust	Pending	
3	**Patent Period New indication/Formulation exclusivity**	20 years	20 years	In the Process of establishing approval. Potentially 20 Years	New MOU applications are being applied for.
4	**COM**	No	No	No	Insignificantly weakens PAR patent protection.
5	**MOU**	Yes	Yes	Yes	AR uses a new delivery of PPS for a new disease state. BME and AV use new dosage and regime for new disease states
6	**FDA 505 (b)(2) approval pathway**	Yes	Yes- Potential fast track approval from Phase II b if demonstrable efficacy and disease modification results are shown.	Yes- Potential fast track approval from Phase II b if demonstrable efficacy and disease modification results are shown.	Fast Tracks the approval process and reduces costs and may potentially lead to the development of early revenue streams from AV and BME disease treatment in AUS and US markets.
7	**Orphan Drug Status exclusivity**	No	Yes, potentially adds another 7 years protection.	Yes, potentially adds another 7 years protection.	Orphan disease status is defined as conditions that affect less than 200,000 or can be applied where no other form of treatment is available/effective.
8	**Regulatory Extensions- Waxman Hatch Patent Extension Principle Apply**	Yes – 5 Year patent extension from date of FDA approval	Yes – 5 Year patent extension from date of FDA approval	Yes – 5 Year patent extension from date of FDA approval	There is a high degree of uncertainty around potential extensions.
9	**Regulatory Extensions- Paediatric Exclusivity**	Potentially Yes- 6 months' extension.	NO	Potentially Yes- 6 months' extension.	There is a high degree of uncertainty around potential extensions
10	**Trademarks**	Yes	Yes	In the Process of establishing	
11	**Exclusive Rights**	N/A	N/A	Yes - with Griffith University.	PAR has the exclusive world-wide rights to commercialise the patent.
12	**Manufacturing agreement with bene PharmaChem**	10 years with a 10 Year Option	10 years with a 10 Year Option	10 years with a 10 Year Option	Supply outside nominated territories currently remain in negotiation. Option is conditional.
13	**Access to Drug Master File (DMF).**	Expedites clinical trials. PAR can file new drug application (NDA) with regulatory authorities.	Expedites clinical trials. PAR can file new drug application (NDA) with regulatory authorities.	Expedites clinical trials. PAR can file new drug application (NDA) with regulatory authorities.	Supply agreement grant PAR "Right of reference to drug master file (DMF).
Summary					
Patent & Manufacturing IP Protection Periods		**19-20 years' product protection in specific jurisdictions.**	**Up to 28 years' product protection in specific jurisdictions.**	**Up to 29 years' product protection in specific jurisdictions.**	**Long dated duration of protection is dependent on manufacturing agreement option being granted by bene and exclusivity to PPS supply.**

Table 15: PAR's IP Strategy Review. ` Source: PAR and Drug Discovery 2015/2016.

Management & Board

PAR's board and management are renowned leaders in the biopharmaceutical industry, having held senior management positions with top ASX-listed companies CSL (CSL.ASX) and Mesoblast (MSB.ASX). They have extensive experience bringing biopharmaceutical products to commercialisation. PAR's small and highly specialised team focused on product development utilising outsourcing effectively.

Graeme Kaufman - Non-Executive Chairman, BSc, MBA

Graeme has broad experience in development and commercialisation of pharmaceutical drugs and has worked with PAR in his current role for the last 2.5 years. Concurrently he holds the position of Chairman of Bionomics Ltd and IDT Australia Ltd and Non-Executive Director of Cellmid Ltd. His most recent previous employment was with Mesoblast as Executive Vice President, Corporate Finance. CFO at CSL and executive VP of Mesoblast.

Paul Rennie - Managing Director, BSc, MBM, Grad Dip Commercial Law, MSTC.

Paul has extensive experience in drug development and commercialisation in the biopharmaceutical industry and has worked in his role as MD of PAR for the last 2.5 years. His most recent prior position was held as COO & Executive VP, New Product Development of Mesoblast. Before this he worked in a national sales role for Boehringer Mannheim, as a marketing manager with Merck and as national sales manager/ Director of business development at FH Faulding Ltd. He also worked in a commercialisation role at the University of Melbourne, Dental School.

John Gaffney, LL.M. – Non-Executive Director

John has over 30 years of experience as a lawyer and worked as a senior lawyer with a major national law firm and as a Barrister at the Victorian Bar. He has experience in financial services compliance and corporate governance. John's most recent role was a Non-Executive of a US biotechnology company,

Christopher Fullerton BEc. - Non-Executive Director

Chris is a Chartered Accountant with extensive experience in investment banking. His most recent experience in the field of biotechnology and healthcare technology was gained in his roles as Non-Executive Chairmanships of Bionomics Ltd, Cordlife Ltd and Health Communications Networks Ltd in addition he held a Non- Executive Directorship of Global Health Ltd.

Dr Ravi Krishnan - Chief Scientific Officer

Ravi has extensive experience in experimental pathology, gene an stem cell therapy and investigating novel compounds with immune modulatory effects, antiogenic and anti-inflammatory properties. Ravi has experience in the biotech and large pharmaceutical companies with his most recent experience gained working in Mesoblast.

Kevin Hollingsworth (Contracted) - Chief Financial Officer and Company Secretary

Previously CFO and Co-Sec of two ASX listed biotech companies ie Mesoblast Ltd and Patrys Ltd.

Risk Factors

Funding Risk:
The funding level currently held is based on limits required to execute on the company's projected expenditure for the next 1-2 years and is an estimate. The ability to fund product trials will depend on R&D rebates and the successful outcome of each step in the trial process, which may impact the value of PAR and its ability to raise additional funds if required.

Delays in trial design, trial execution and/or poor trial results may delay or prevent the likelihood of future commercial partnerships, impacting future cash flow events, such as milestone payments and/or royalty payments should they be available.

Key Commercial Relationship Risk: A key supply risk.
PAR has a 10-year supply agreement with a 10-year option to extend within the first 10 years provided that PAR has obtained regulatory approval for sale of a product incorporating PPS within specific ASIA PAC Territories. There is a risk that PAR will not obtain regulatory approval inside these territories.

Where PAR pursues regulatory approval outside agreed exclusive territories and with respect to supply of PPS for products outside these territories there is a risk that bene pharmaChem may not agree to supply PAR with PPS. Further, it is unknown whether bene pharmaChem has the capacity to respond to an increase in demand from PAR to supply PPS should they access larger markets than originally agreed.

Whilst bene pharmaChem has almost 70 years of experience manufacturing cGMP commercial quantities of PPS, should bene have difficulties producing PPS or should the supply agreement with PAR be terminated for any reason, clinical development and commercialisation of PAR's potential products will be affected and adversely impact potential cash flows and value.

Key Commercial Relationship Risk: A Key Partnership Risk.
PAR is a DRPx (drug repurposing) company specialised in the R&D of PPS and will seek to partner with a large pharmaceutical company before, during or after Phase II Trials of AR, BME or Alphavirus. There is no assurance that PAR will attract these partnerships within Q2 2017-Q4 2017, nor is there any certainty surrounding the terms of such a potential transaction which, if not secured, will have a material negatively impact on future cash flows and valuation.

Intellectual Property:
There is no guarantee that PAR's IP comprises all the rights that the company may require to freely commercialise its product candidates. Patents can at any time be challenged by a competitor and in turn PAR may lose any exclusive patent rights which may impact it developing its commercial products. Current Patent applications that have been lodged are subject to examiner approval and review and there is no assurance that these applications will result in granted patents.

Speculative Nature of Investment:
PAR is a very speculative investment and as such an investor considering a position in this company should be aware that shares in this company carry no guarantee with respect to return on investment, payment of dividends, returns on capital or market value of the shares.

Industry Competition:
Industry competition in the allergic rhinitis industry and specifically the intranasal corticosteroid and intranasal anti-histamine segment is very high. Responses from competitors cannot be predicted and whilst PAR may develop a clinical beneficial product for the market competitor's responses to new entrants can be deleterious to new products entries and therefore PAR cannot be certain as to the revenues or the margins it will attain with its AR product or any other product it develops.

Health insurers and reimbursement risk:
In the early stages of sales for all PAR's product it is likely to require reimbursements from third party insurers or government agency payer approvals. Full or partial support and/or full or partial reimbursement approval for PAR products may not be received from these payer groups, which may impact PAR's ability to generate cash flows from its products.

Early Stage Development:
All PAR's products are early stage and there is no guarantee that the proposed clinical work will be successful.

Clinical Trial Risk:
PAR is at the early stage of product development having completed Phase I trials in all three target diseases. Human trials are very expensive and difficult to design and implement due to regulatory and legal requirements. Correct Phase II clinical design is critical for the success of the trial. There is a risk that the design is poor and that the FDA or other regulatory authority may not approve PAR's proposed new drug application in the first instance and require it to undertake further refinements or trials. This could cause delays and add costs to the development program that in turn will delay cash flows and add costs. There is no guarantee that these trials will be successful and the products will make it to market. PAR does not have access exclusivity to bene pharmaChem drug master file (DMF).

Key Personnel:
PAR is reliant on specific key personnel and contractors for the development and execution of current business plan and for the protection of its intellectual property. The loss of any one of these key personnel may pose a risk to PAR's ability to execute on its strategy which may impact the value of the company.

Market Conditions:
PAR is targeting three different disease states in three independent markets.

The conditions in the allergic rhinitis market is extremely competitive and whilst their potential product may have clinical benefit differentiated from that of existing market participants, PAR cannot guarantee nor predict any competitive market responses which may impact their ability to sell products into the market. Innovation within other segments such as immunotherapies and by other competitors in the intranasal AR sector is unknown and there are no guarantees that alternative discoveries will not be made that could impact on PAR future sales.

In terms of PAR's Alpha Virus and BME potential products, whilst there is currently no known treatment for these disease states, there is no guarantee that an alternative treatment will not be developed in the future to treat these conditions.

Product & Market Analysis Appendices

1. Allergic Rhinitis (AR)
2. Alpha Virus (AV)
3. Bone Marrow Edema (BME)

PAR's Targeted Clinical Indications

1. Allergic Rhinitis

Allergic Rhinitis (AR) is common. It currently affects 10%-30% of the world population with the World Allergy Organisation estimating in 2015 that over 400 million people suffer from AR globally[9]. It's an industry estimated at US$11.9 billion in 2016.

The anticipated rate of growth in the condition is enormous. The prevalence of AR is expected to increase from 20-28% of the population in 2009 to 61-70% by 2060. This increasing prevalence is a pattern that has been documented worldwide and is driven by geographically specific conditions.

Despite significant price competition from generic drugs in recent years, the overall AR market continues to grow in terms of dollar value. Developing healthcare standards contribute to this growth as access to treatment becomes easier and cheaper.

AR revenues are derived from the various regional markets as outlined in Table 16 below.

Global Allergic Rhinitis Market by Regions

Region	Revenue (US$m)	Market Share (%)
US	3895	34%
EU	1916	17%
China	1605	14%
Japan	741	6%
Russia	299	3%
India	270	2%
Brazil	219	2%
Rest of World	2634	23%
Total	**11579**	**100%**

Table 16: Global Market by Region Source: Visiongain 2016

Prevalence of the Disease

Allergic rhinitis is a chronic respiratory disease characterized by inflammation of the nasal cavity and affects people of all ages. The main symptoms of allergic rhinitis are sneezing, nasal itching, a blocked or runny nose and sore throat (NHS, 2012; WHO, 2013). Research suggests that a combination of genetic factors such as family history and environmental factors, such as exposure to allergens, including smoke, dust, pollen, insects, moulds, or animal dander, may increase the risk for developing allergic rhinitis (NHS, 2012; WHO, 2013).

[9] Visiongain Allergic Rhinitis Drugs Market Forecast 2016-202

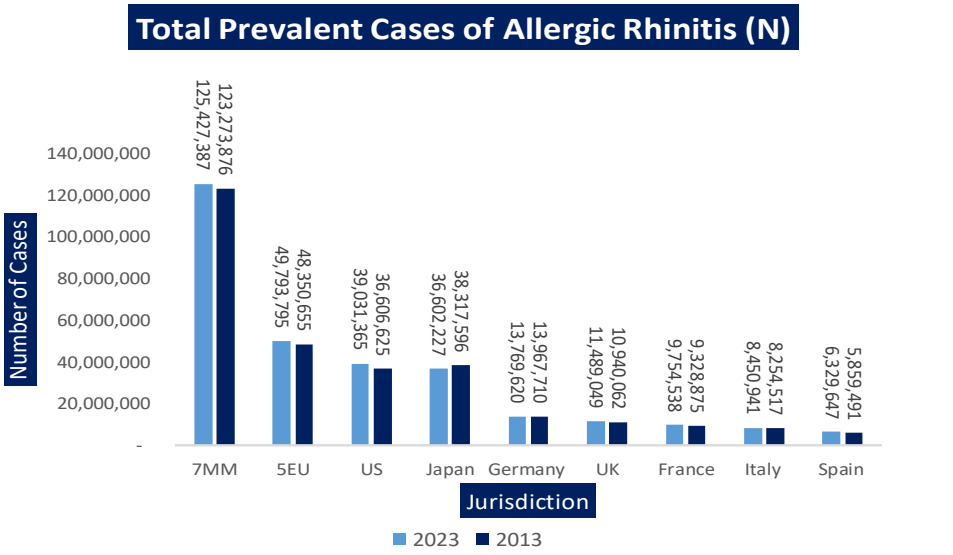


Table 17: Global AR Prevalence. **Source: Medtrack 2016**

The estimated total prevalent cases of allergic rhinitis in the 7MM countries (US, France, Germany, Italy, Spain, UK, and Japan) will increase from 123.3M total prevalent cases in 2013 to 125.4M cases in 2023, equivalent to an annual growth rate (AGR) of 0.17%. In 2023, the US will have the highest number of the total prevalent cases of allergic rhinitis with 39,031,365 cases, followed by Japan with 36,602,227.

Although the number of cases are higher in the US, in percentage terms, Japan leads the way with 35.1% in men and 39.3% in women compared to 13.7% in men and 14.3% in women in the US (Bauchau and Durham, 2004; Konno et al., 2012; Nathan et al., 1997; Ozdoganoglu and Songu, 2012).

Classification of AR

A widely used international classification for allergic rhinitis is commonly used by physicians and is described as seasonal, perennial or occupational.

- **Seasonal**: Occurs particularly during pollen seasons
- **Perennial**: Occurs throughout the year

The new classification is based on the frequency and duration of symptoms (intermittent or persistent), and the severity of symptoms and effect on quality of life (mild or moderate-severe). Classification of allergic rhinitis, per frequency and duration of symptoms, and their impact on quality of life is provided below:

- **Intermittent:** Occur 4 days or less per week or for less than 4 weeks
- **Persistent:** Occur more than 4 days per week and for more than 4 weeks
- **Mild:** All the following: normal sleep; normal daily activities, sport, leisure; normal work and school; symptoms not troublesome.
- **Moderate-severe:** Effects and restricts normal daily activities

Causes

An over sensitive immune response causes allergies. The immune system normally protects the body against harmful substances such as bacteria and viruses. Allergy symptoms occur when the immune system reacts to substances (allergens) that are generally harmless and in most do not cause an immune response.

The pollens that cause hay fever vary from person to person and from region to region. Large, visible pollens are rarely responsible for hay fever. Tiny, hard to see pollens are more often the cause. Examples of plants commonly responsible for hay fever include:

- Trees (deciduous and evergreen)
- Grasses
- Ragweed

The amount of pollen in the air can play a role in whether hay fever symptoms develop. Hot, dry, windy days are more likely to have increased amounts of pollen in the air than cool, damp, rainy days when most pollen is washed to the ground. Some disorders may be associated with allergies. These include eczema and asthma. Allergies are common. Genes and the environment may make people more prone to allergies.

Allergic Rhinitis – Early and Late Stage Response - Important Biomarkers

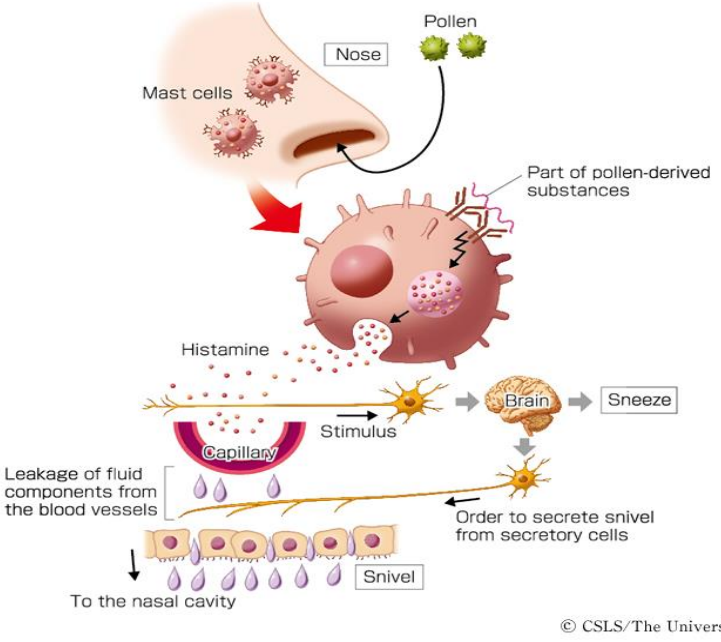


Figure 7 : Allergic Rhinitis Symptom Development. Source: http://csls-text2.c.u-tokyo.ac.jp

Early Stage

In seasons when pollen is scattered, airborne pollen meets the nasal mucosa prompting the immune system to produce antibodies corresponding to the pollen antigens. These antibodies bind the surfaces of mast cells in the mucosa and tissues, which store various chemical compounds in their granules. Of these chemical compounds, histamine is an epitome of allergic substances, involved not only in nasal symptoms but also in skin itchiness (See Figure 7 above).

Mast cells also secrete different inflammatory mediators, such as prostaglandin D2 and the sulfidopeptidyl leukotrienes C4, D4 and E4. The latter, as bradykinin, cause blood vessels to broaden and leak and thus lead to the clinically important mucosal edema and the watery rhinorrhea. Furthermore, numerous cytokines are produced, such as tumour necrosis factor (TNF).

Late Stage

During late stage, specific molecules, called chemoattractants (such as IL-5) promote the infiltration of the mucosa with eosinophils, neutrophils, basophils, T lymphocytes, and macrophages. These cells become activated and release inflammatory mediators (which reactivate many of the proinflammatory reactions of the early-phase response).

T helper (Th) 2 lymphocytes release IL-3, IL-4, IL-5 and other cytokines that promote IgE production, eosinophil chemoattraction, and eosinophil survival, as well as mast cell recruitment. Currently all the biomarkers mentioned above are considered as potential therapeutic targets.

When patients are repeatedly challenged with an allergen, the amount of allergen necessary to lead to an allergic response decreases, which is known as the priming effect. This effect is hypothesized to be due to inflammatory cell actions during late-phase response.

The Phases of Allergic Rhinitis and the Response			
Early Phase Response from Mediators		Late Phase Allergic Response form Mediators	
Key Mediators	**Effect in Upper Airway**	**Key Mediators**	**Effect in Upper Airway**
Histamine	Congestion	IL-4,IL-5,IL-13	Congestion
Proteases	Rhinorrhea (runny nose)	Eotaxin	Nasal Hyperactivity
Leukotrienes	Itching	RANTES	**Effect in Lower Airway**
Prostoglandins	Sneezing	Luekotrienes	Prolonged bronchial constriction
TSPL	**Effect in Lower Airway**	TNF	Increased airway hyperactivity
Bradykinin	Acute Bronchoconstriction	GM-CSF	Airway modelling
PAF		MBP,ECP	
		Neuropeptides	
		Adhesion Molecules	
		TGF	

Table 18:Phases of AR Disease. Source: Diamant et.al., Pulmonary Pharmacology & Therapeutics

Treatment of Allergic Rhinitis

The goal of treatment of AR is to reduce the allergy symptoms. Avoidance of the allergen, or minimization of contact with it, is the best treatment. But some relief may be found with the following classes of medications[10].

Antihistamines and Decongestants:

Oral decongestants alone may be helpful, including pseudoephedrine. Antihistamines are available as tablets, capsules and liquids and may or may not be combined with decongestants. Common antihistamines include brompheniramine or chlorpheniramine, and clemastine. Non-sedating (less likely to cause drowsiness) long-acting antihistamines include loratidine and fexofenadine.

Nasal sprays:

For rhinorrhea, a nasal spray of cromolyn sodium (Nasalcrom) or a steroid nasal spray, such as flunisolide (Nasalide), beclomethasone dipropionate (Beconase, Vancenase), triamcinolone acetonide (Nasacort), and fluticasone (Flonase), may work so well that additional antihistamines or decongestants are unnecessary. It is important to remember that improvement may not occur for one to two weeks after starting therapy with steroid nasal sprays. Short courses of oral corticosteroids may usually be indicated when severe nasal symptoms prevent the adequate delivery of topical agents.

Immunotherapy (Allergy shots):

Immunotherapy involves giving gradually increasing doses of the substance (or allergen) to which the person is allergic. This works by making the immune system less sensitive to that substance, probably by causing production of a particular "blocking" antibody, which reduces the symptoms of allergy when the substance is encountered in the future. Skin or sometimes blood tests are performed to confirm the specific allergens to which the person has antibodies. Immunotherapy is usually indicated for patients who are:

- Unresponsive to medical therapy
- Have side effects from medications
- Have recurrent sinusitis or otitis (an ear infection)
- Are unwilling or unable to use medication

Allergic Rhinitis – Market Dynamic

During the past decade, the market for branded products for allergic rhinitis has come under intense pressure, owing to a combination of over-the-counter (OTC) switches, patent expirations, poorer insurance tiering in the United States and exclusivity challenges.

Never the less, **the AR market continues to represent significant interest to large pharma companies especially as companies diversify their business models into generics and OTC businesses**. For example, for both major drug classes for allergic rhinitis — antihistamines and intranasal steroids, new products have been launched, major deals have been made and OTC sales have been strong. In addition, the intranasal steroids class has shown considerable resilience to generic competition and health insurance pressure.

[10] Medtrack 2016

Good Reimbursement Continues

Unlike the antihistamine class, intranasal steroids products remain well covered by most US health insurance plans, generally with second-tier status. In addition, insurance companies have not required prior treatment with generic fluticasone as a basis to reimburse branded products[11].

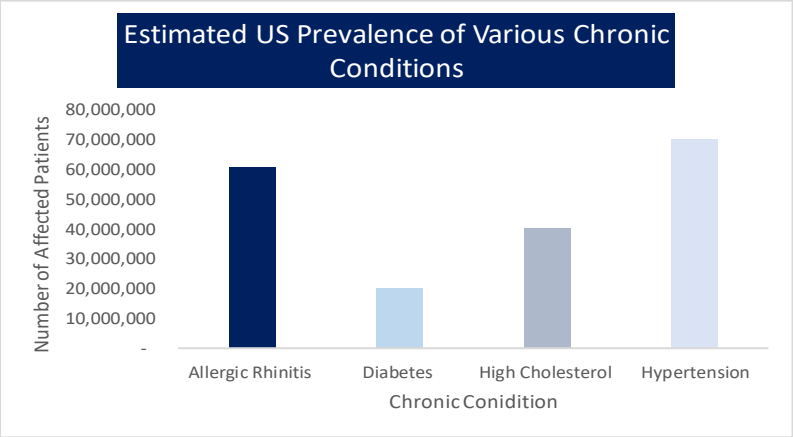


Table 19: AR's Prevalence Compared. Source: Nature Reviews Drug Discovery 2009

Despite the entrance of generics and other challenging events, the allergic rhinitis market has seen substantial activity in recent years, indicating that the field should still be monitored by major companies. The market potential is considerable, given that allergic rhinitis affects a large number of people in both developed and emerging markets, comparable to other major chronic conditions, such as diabetes, high cholesterol and hypertension (Table 19).

There are 8–20 million drug-treated patients in the United States alone, and worldwide sales of allergic products have reached almost $12bn per year.

PAR Clinical Development Program for AR

Developing PPS for Allergic Rhinitis - Why Pentosan Polysulfate?

Pentosan polysulfate (PPS) is a semi-synthetic, sulphated polysaccharide (Figure 3), similar to heparin and resembles the glycosaminoglycans produced by cells in the body. Anticoagulant and fibrinolytic properties are characteristic of pentosan polysulfate, although its anticoagulant activity is 15 times less than that of heparin.

The exact mechanism of action of pentosan polysulfate is not yet known, although there are several possible ways in which it may provide relief of symptoms and pain of AR. It has been suggested that pentosane polysulfate may have cytoprotective effects resulting in a reduction in the inflammation of the airways lining (i.e. mucosa).

[11] Nature Reviews Drug Discovery 2009, Clark and Million

Pentosan polysulphate also appears to inhibit (in a dose-dependent manner) the stimulation of connective tissue mast cells and mucosal mast cells. Pre-clinical studies showed that mast cell inhibition by pentosan polysulphate results in a significant reduction in histamine secretion (compared with untreated mast cells), which may be an additional mechanism of action of the drug and play a part in the alleviation of AR symptoms.

PPS is likely to have a good safety profile since it has been used in the clinic to treat other disease conditions (e.g. interstitial cystitis). Since original approval, there have been more than 100 million injectable doses of PPS administered. 28 Day study of intranasal toxicology in rats have observed no adverse effects at high doses with safety margin of about 20x of estimated dose.

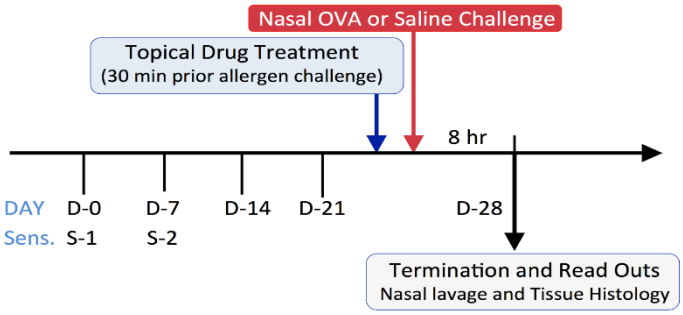


Figure 8: Preclinical Model Study Design. Source: Erjefalt et.el., Scientific Poster, 2016

In Vivo Effects of Topical PPS on Nasal Allergic Inflammation

The anti-inflammatory *in vivo* actions of PPS were explored in a validated drug screening Guinea pig model of allergic rhinitis (Figure 8). Chicken ovalbumin (OVA) is a T Cell-dependent antigen commonly used as a model protein for studying antigen-specific immune responses in rodents.

The OVA model has been the most widely used pre-clinical allergic asthma model and replicates many of the hallmarks of allergic asthma in humans. These include elevated IgE and TH2 related cytokines, mucus hypersecretion, airway inflammation, goblet cell hyperplasia, epithelial hypertrophy, and airway hyperreactivity to stimuli.

In the pre-clinical study of PPS, OVA-sensitized animals were subjected to nasal allergen challenge and key *in vivo* readouts were measured corresponding to the late phase allergic reaction.

The experimental measures included:

(a) Influx of immune cells into the Nasal Cavity with lesser cells the better, see Figure 7.
(b) Plasma extravasation (i.e. leakage of plasma from vessels into surrounding tissues) with less is better
(c) Tissue accumulation of immune cells (T-lymphocytes and eosinophils) with less is better
(d) Allergen-induced hyper secretion of mucus that often causes most notable symptoms in AR such as airway closure, with less is better

For the efficacy tests the animals were pre-treated with either vehicle (i.e. saline solution) or drug (PPS, Bene Pharma or clinical formulation of Budesonide, Rhinocort Aqua,

AstraZeneca) at Day 28 which is three weeks after the last sensitization with OVA, 30 min prior to intranasal instillation of OVA.

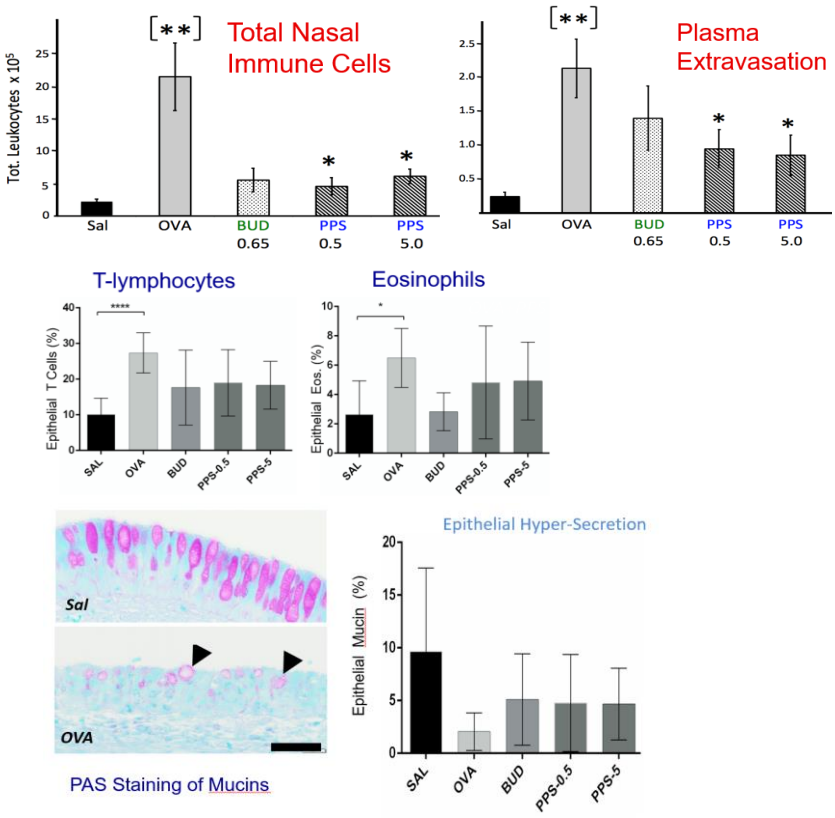


Figure 9: Capacity of Rhinosul & Rhinocort to Reduce Major Effects of AR. Source: Erjefalt et.el., Scientific Poster, 2016.

This model has been used in a Big Pharma setting and has confirmed translatability to many features of clinical AR

Results (Figure 9) showed that PPS significantly reduces allergen-induced plasma extravasation and influx of leukocytes into the nasal cavity.

Both PPS and nasal steroid (Budesonide) treatment also resulted in reduction of numbers of eosinophils and T-lymphocytes as well as epithelial mucus hypersecretion.

This data from pre-clinical animal model warranted further investigation of PPS in human studies and suggest a therapeutic profile of Rhinosul similar or better to Rhinocort.

Phase I Clinical Study of PPS Nasal Spray Formulation in Healthy Volunteers

The first Phase I clinical study of PPS as a nasal spray formulation in healthy volunteers (n=18) was conducted at Linear Clinical Research in Australia.

Stage 1		Stage 2		Finish
Day 1 Single Admin	Days 2-4 Clinical Obs	Days 5-11 7 days Daily Admin	Days 12-14 Clinial Obs	Day 15 Finish study.
N=9, 40 mg		N=9, 40 mg		
N=9, 80 mg		N=9, 80 mg		

Figure 10: PPS in AR, Phase I Study Design, Linear Research Perth. Source. PAR

Phase I data demonstrated that multiple dose administration of PPS has no safety issues or any adverse effects and is well-tolerated in humans. Results suggest that further clinical studies capturing efficacy are highly warranted.

Phase II (a) clinical study in AR – Data in Q3 2017

The Company recently announced that it has received approval from the Independent Ethics Committee in Lund, Sweden and regulatory approval from the Swedish Medical Product Authority (the Swedish MPA) to proceed with a Phase II(a) clinical trial in Lund, Sweden.

The trial will commence in December 2016. The treatment of trial participants will take between 2-3 months, with readout of results anticipated in Q3 CY2017.

The trial will be conducted under the leadership of Professor Lennart Greiff at Skane University Hospital who has previously conducted similar clinical trials using the established Phase 2 clinical model for allergic rhinitis by Big Pharma, including Astra Zeneca.

Expected Study Design

The study will involve patients with allergic rhinitis examined outside the pollen season and subjected to repeated allergen challenges once daily for 7 days.

It will be a double blind, placebo controlled, cross over design, conducted in 40 participants (cross over design means that each patient will receive both PPS and placebo at one stage or another).

Figure 11: How does the Study Work? Source: Greiff et.al., Inflamm. Res. (2015)

To establish individually tolerable, repeatable, yet symptom-producing allergen challenge-doses, a titration procedure will be performed. Increasing doses of grass pollen allergen will be administrated at 10-min intervals using a spray-device.

This scheme will be followed until the subject responded with at least 5 sneezes or recorded a symptom score of 2 or more on a scale from 0 to 3 for either nasal secretion or nasal blockage. The dose that produced this effect will be chosen for the allergen challenge series and will be given in the morning once daily for 7 days, starting 24 h after the final dose of the study drug.

Nasal symptoms will be scored 10 min after each allergen challenge as well as every morning and evening during the allergen challenge series.

Patients with seasonal allergic rhinitis are chosen (over those with perennial rhinitis) because they present low baseline values of symptoms and biological parameters out of season, which is an experimental advantage.

Clinical Evaluation – What Efficacy Signal is the Study Looking For?

In typical studies of seasonal allergic rhinitis, efficacy is determined by analyzing the change from baseline in a patient-reported measure of symptom severity: the 12-h reflective total nasal symptom score (TNSS) consisting of nasal congestion, rhinorrhea, sneezing and nasal itching.

The TNSS is the preferred efficacy variable recognized by the US FDA as evidence of efficacy for allergic rhinitis drugs. To report this efficacy outcome, the patients record their nasal symptom scores in diaries twice daily, in the morning and again in the evening each day for the duration of the study. The symptoms are scored on a 4-point scale, with 0 being symptom free; 1: mild symptoms; 2: moderate symptoms and 3: severe symptoms.

The number of sneezes could be also counted and transformed into a sneezing score by the investigators: 0 sneezes = 0, 1–4 sneezes = 1, 5–9 sneezes = 2, and 10 or more sneezes = 3.

What to Expect from Study Results?

We will be focusing on the analysis of biomarkers chosen to reflect PPS-mechanism of action (MOA), during the treatment period and on symptoms as well as on safety profile of the drug.

While the study does not have enough subjects to reflect statistical significance in TNSS, we believe it has enough subjects to demonstrate clinical efficacy trend, i.e. a dose dependent reduction in symptomatic score comparing to baseline or placebo.

While it is hard to assume what will constitute a good efficacy trend, we believe a reduction by 1.5-2.0 (on a scale from 0-9) or 2.0-3.0 (on a scale from 0-12) will suggest that PPS could be efficacious in treating AR.

Indicatively, one of the registration studies of Rhinocort (AstraZeneca) in AR with 318 patients enrollment have demonstrated a difference between 1.5 – 2.0 on a scale of 0 – 9 in nasal symptom scores comparing to baseline (see Figure 12 below). Recall, that Rhinocort (budesonide) showed similar results with PPS in pre-clinical guinea pig model. Rhinocort had combined sales of US$4.1B between 1998 and 2012.

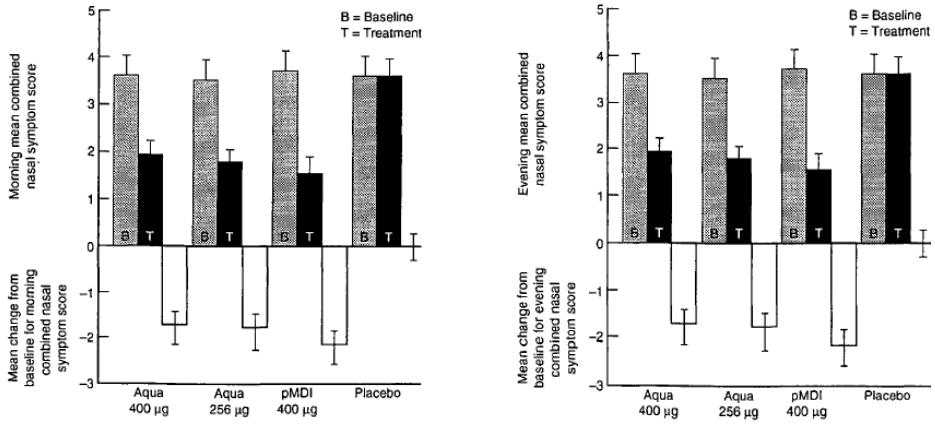


Figure 12: Effect of Treatment with Rhinocort on Combined Symptoms. Source: Day et.al., Am J Rhinol. 1997.

AR - The Market Opportunity

PAR's research in the application of PPS for treatment of AR suggests from the Preclinical Phase I Trial that its product Rhinosul® is positioned well to capture market share in dual acting/combined therapeutics segment of the intranasal spray AR market.

What is unknown is how well PAR's potential first in class, dual acting antihistamine and non-steroidal anti-inflammatory treatment will perform. However, the detailed analysis of the market outlined below, suggests it may perform better than MEDA's Dymista product given Rhinosul's ® safety and potential efficacy outcome which will be better understood after its Phase II trials complete Q2, 2017.

In the following analysis sections estimate revenue figures are based on manufacturers selling price, not retail value to consumers. It is estimated that the manufacturers selling price is **50%-70%** below retail price for each product.

Treatment of AR is broken into four main categories of therapeutics as outlined in Table 20. This table establishes the main manufacturing focus of those AR focused pharmaceutical companies.

	Drug	Delivery & Access	Comments	Target Symptom
1	Antihistamines	Oral & Nasal Rx and OTC	First Line Treatment- Favoured for Flexibility and convenience	Nasal irritation, sneezing, congestion, eczma
2	Corticosteroids	Oral & Nasal Rx and OTC	First line treatment for moderate to severe AR	Provide better overall relief of symptoms as above
3	Immunotherapy	Vaccines Oral, Injection	Developing treatment for allergies, **may** lead to long term prevention-closest thing to a cure.	Allergic response to house dust, cats, grass pollen and mould.
4	Other drugs	Oral & Nasal	Combination of antihistamines and decongestant and/or intranasal corticosteroid with antihistamine	Nasal irritation, sneezing, congestion, eczma

Table 20: Allergic Rhinitis Drug Delivery Source: Visiongain

PAR Rhinosul ® product is intending to compete against established products delivered orally and nasally that provide relief from AR via antihistamine and corticosteroid pathways. Table 21 outlines PAR potential strategy

Therapeutic Feature	PAR Rhinosul®	J&J Zyrtec®	Astra's Rhinocort®	Mylan/Meda Dymista®	Merk Nasonex®	GSK Flixonase
Delivery	Intranasal	Oral	Intranasal	Intranasal	Intranasal	Intranasal
Treats early phase AR symptoms (antihistamine)	✓	✓	×[12]	✓	×	×
Treats late phase AR symptoms	✓	×	✓	✓	✓	✓
Side effects	×	✓	✓	✓	✓	✓
Corticosteroid (anti-inflammatory)	×	×	✓	✓	✓	✓
Non-Corticosteroid (anti inflammatory)	✓	×	×	×	×	×
Simple to manufacture	✓	×	×	×	×	×
Established market size $US m	0	615	250	119	858	1228
Patent Protected	✓	×	× [13]	✓	×	✓
Over the counter (OTC) or Prescription (Rx)	Likely Rx for 2 years post approvals	OTC	OTC/Rx-US	OTC	OTC	OTC

Table 21: Select AR Drug Comparison

Source: Visiongain and PAR

The leading antihistamine drugs for AR are outline below in Table 22. Six (6) pharmaceutical companies dominated the antihistamine sector in 2015.

Leading Antihistamine Drugs for AR in 2015		
	Drug	Manufacturer
1	Allegra	Sanofi
2	Allelock	Kyowa Hakko Kirin
3	Astelin	Meda
4	Benadryl	Johnson & Johnson
5	Chlor Trimeton	Merck and Co
6	Clarinex	Merck and Co
7	Claritin	Merck and Co
8	Patanase	Novartis
9	Xyzal	Sanofi
10	**Zyrtec**	**Johnson & Johnson**

Table 22: Leading Antihistamines.

Source: Visiongain 2016

[12] Note that long term use of Rhinocort will be effective for the acute phase of AR.
[13] Rhinocort Aqua is off patent only, Rhinocort is off patent 2017.

It's important to note, Johnson & Johnson manufacture and distribute ELMIRON®, exclusively in the US for treatment of interstitial cystitis. This product uses PPS supplied by bene pharmaChem. Further, Zyrtec another Johnson & Johnson owned drug is, by sales revenue the 4th largest OTC pharmaceutical product sold globally in 2015[14].

The leading Corticosteroids are outlined below in Table 23. Five (5) pharmaceutical companies dominate the AR corticosteroid market in 2015.

Leading Corticosteroid Drugs for AR in 2015		
	Drug	**Manufacturer**
1	Beconase	GSK
2	Nasacort	Sanofi
3	Rhinocort	AstraZeneca
4	Flonase	GSK
5	Nasonex	Merck and Co
6	Omnaris	Takeda
7	Vermamyst	GSK

Table 23: Leading AR Corticosteroids. Source: Visiongain 2016

Common Combination Drug Products are listed below in Table 24

Common Combination Drug Products for AR in 2015		
	Drug	**Manufacturer**
1	Claritin -D 24 Hour	Merck and Co
2	Allegra D	Sanofi
3	**Dymista**	**Meda**

Table 24: Combination Drugs and Manufacturers. Source: Visiongain 2016

Dymista is highlighted as this drug action is similar to PAR's Rhinosul® in terms of its dual action for the acute and chronic phase of AR but PAR's product treats the chronic phase with a non- corticosteroid which may prove to have significant clinical benefits over Dymista and attract greater consumer demand, particularly for paediatric applications, (see intranasal antihistamine section below).

The other drugs on the market include the following combination products outlined Table 25.

Other Common Combination Drugs & Products for AR in 2015		
	Drug	**Manufacturer**
1	Singulair	Merck and Co
2	Nasalcrom	Prestige Brands
3	**Zyrtec-D**	**Johnson & Johnson**
4	Saline Nasal Sprays	Generics

Table 25: Other Common Drugs and Manufacturers. Source: Visiongain 2016

[14] Visiongain, World OTC Pharmaceutical Market Forecast 2016-2026.

The global AR drugs can be grouped into five key categories defined by delivery method as outlined below in the list and in Table 27, global revenues and market share are outlined.

1. Oral antihistamines
2. Intranasal antihistamines
3. Intranasal corticosteroids
4. Immunotherapies and vaccines
5. Others

As outlined below oral antihistamines represent US$4.8 billion in sales revenue, with the intranasal sprays (corticosteroids, US$4.3 billion and anti-histamines, US$502) representing a total of US$4.8 billion in market share. Whilst immunotherapies represent the third largest segment of the market and are projected to grow rapidly over the next 10 years to US$2.4 billion in sales, they currently only represent a relatively low proportion of US$1.2billion in sales revenues[15].

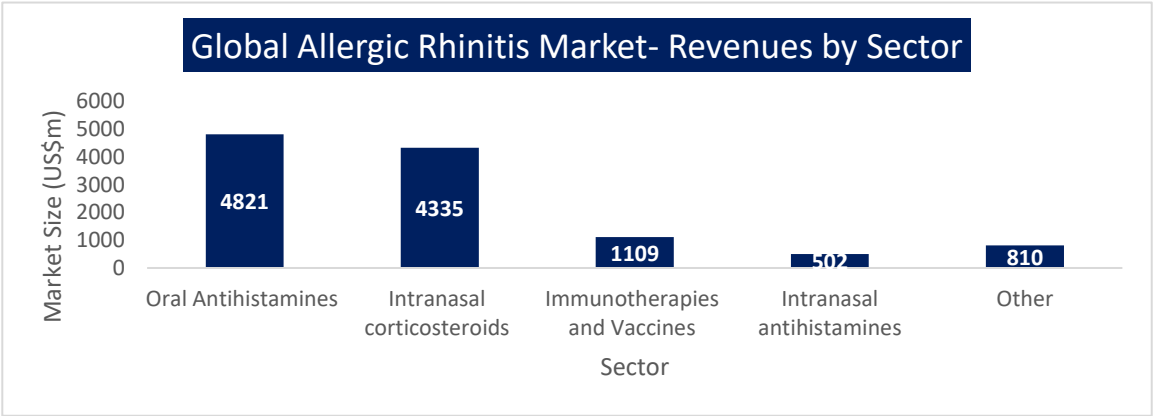


Table 26: Global AR Market By Delivery Type. Source: Visiongain 2016.

Global Allergic Rhinitis Market - Revenues & Market Share Percentage 2015		
Sector	**Revenue (US$m)**	**Market Share**
Oral Antihistamines	4,821	42%
Intranasal corticosteroids	4,335	37%
Intranasal antihistamines	502	4%
Immunotherapies and Vaccines	1,109	10%
Other	810	7%
Totals	11,577	100%

Table 27: AR Drug Revenues and Market Share. Source: Visiongain 2016.

Growth in the global market is forecast by Visiongain to grow by CAGR 3.1% between 2015-2020 and reach US$13,515m in 2020. Between 2020-2026 the market is expected to grow faster again, at 3.4% CAGR with an estimated market size of $16,500m being reached in 2026[16].

[15] Visiongain 2016 pp119
[16] Visiongain 2016 pp60

The largest segment in the global AR market is the oral antihistamines segment, accounting for almost 42%. This market segment faces tough competition and is in general decline due to generics competition and patent expiry. Demand in this sector is high and remains so as oral formulations are commonly used and accepted by the patients for immediate relief of AR.

Intranasal corticosteroids and antihistamines make up approximately 41% of the market, with the corticosteroids expected to remain the standard of care for allergic rhinitis through to 2026. The expiry of the patent for Nasonex and competition from generics will impact this market.

Combination drugs (combining antihistamine and corticosteroids) like Dymista fall within the "other" segment. PAR's Rhinosul® will compete in this market along with other novel pipeline drugs in early stages of development.

If Phase II trials are successful PAR's Rhinosul ® product may pose a significant threat to incumbents in both the intra nasal corticosteroid & antihistamine markets which represent US$4,937m or 41% of the global AR market.

Whilst the oral antihistamine market is the largest market segment in the treatment of AR a deeper analysis of this segment will not be undertaken as PAR's product is aiming to compete in the intranasal spray market. The market share of this oral therapeutics segment is expected to remain strong through to 2026.

An important fact to consider in relation to this segment is Zyrtec/Zyrtec-D a Johnson & Johnson owned product has sales that represent 12.8% of the market with revenues of US$615m generated from this oral formulation. [17] **Sales of Zyrtec has been sold OTC since 2002. Johnson & Johnson are key customers to bene pharmaChem**[18]. Zyrtec lost patent protection in 2007 and sales are expected to fall to US$444 by 2026, creating a significant fall in revenues for J&J's AR business unit.

The intranasal corticosteroid market.

The intranasal corticosteroid market is similarly competitive and very well established, outlined below in Table 28 is the leading drugs that compete in this segment.

Rhinocort has been highlighted in this report as PAR has referred to AstraZeneca's product in its investor presentations as the comparator drug used in Phase I Pre-clinical trials at Lund University, Sweden.

As mentioned the Phase I Pre-clinical trials demonstrated PAR's PPS formulation in Rhinosul ® performing as well if not better than Rhinocort ® at treating the acute and chronic phase AR response in the highly translational guinea pig model.

This segment of the market is expected to grow from US$4,345m in 2015 to $7,605 in 2026 with the growth driven by Over the counter (OTC) switches (from prescription to OTC) and the introduction of innovative products into the market.

Drugs such as Rhinocort, Avamys, Beconase and Nasonex are facing challenges with respect to future sustainable revenues as competition from generics is and/or will be strong since patent protection has or is going to be extinguished for these dominant products in the near term.

[17] Visiongain 2016 pp66
[18] Paradigm Biopharmceuticals Ltd, Investment Presentation August 2016.

AstraZeneca's Rhinocort was still prescription only in the US in 2015 but is OTC in EU markets and other markets such as China. In 2016 Rhinocort's OTC product was introduced in the US but will be off patent by 2017 and future sales revenues will fall from US$250m to $133m in 2026[19]. **Rhinocorts cumulative project revenues from 2015-2026 is US$1.975b.**

Leading Intranasal Corticosteroids Drug Market by Revenue (US$) and Market Share (%) 2015		
Drug	**Revenue (US$m)**	**Market Share (%)**
Flixonase/Flonase/Flonase OTC	1,228	28%
Nasonex	858	20%
Avamys/Veramyst	350	8%
Rhinocort	**250**	**6%**
Nasocort/Nasocort/OTC	135	3%
Omnaris	66	2%
Beconase/Beconase AQ	62	1%
Qnasl	60	1%
Zetonna	51	1%
Other	1,275	29%
Total	**4,335**	**100%**

Table 28: Global Intranasal Corticosteroid Market. Source: Visiongain 2016.

The intranasal corticosteroid drugs market is facing significant competition from generics and new entrants and will continue to do so through to 2026.

The intranasal anti-histamine.

Combination treatments such as Dymista (Azelastine-***antihistamine***, & Fluticason-***steroid***) and generic azelastine are the two leading intranasal antihistamines in market 2015. They are both non-sedating products; other leading brands include Meda Pharma's Astelin and Astepro. The market leader's respective sales values are outlined in Table 29 below.

These treatments are a relatively new alternative for patients with AR but they may provide benefits as they are effective in mild, moderate and severe AR cases, they are fast acting and, convenient.

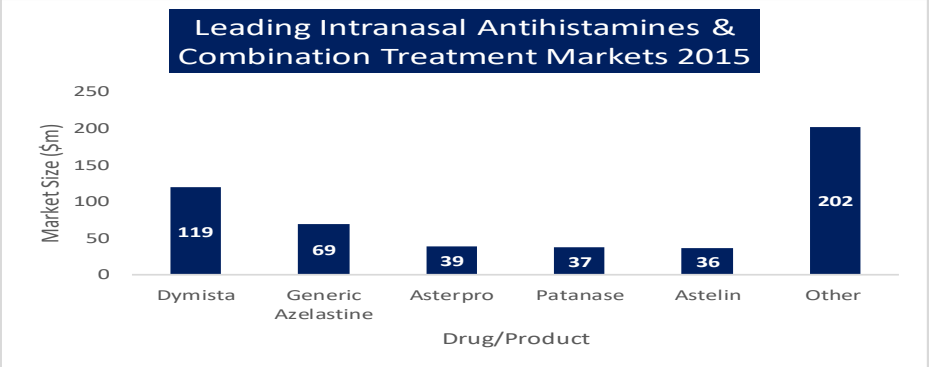


Table 29: Leading Intranasal Antihistamine Market 2015. Source: Visiongain 2015

The intranasal antihistamine/combination market share outlined below in Table 30 suggests the market dynamics are not as competitive as the well-established intranasal corticosteroid market. Dymista a relatively new entrant has grown to hold 24% of the

[19] Visiongain 2016.

market share in just over 2 years, indicating a strong consumer/physician demand in the market for this style of a dual acting product. Dymista's cumulative projected revenues from 2015-2026 is US$2.468 bn.

PAR intends to compete directly with MEDA's Dymista but will differentiate itself by being the first in class, safe, non-steroidal dual acting, odourless and tasteless AR intranasal spray.

Currently 66% of AR patients are prescribed a combination of oral antihistamines with intranasal corticosteroids, regardless of the frequency or severity of symptoms, this is the dominant approach to treatment.

A small percentage of people with AR use a combination of intranasal antihistamine and steroid spray, however this treatment strategy creates two critical problems:

1. Adherence to treatment is reduced due to the displeasure of using spray pumps;
2. Patients increase the frequency of use with sprays which increase the risk of potential side effects from multiple corticosteroid dosages.

Leading Instranasal Antihistamine Drug Market, Revenues ($m) and Market Share (%) 2015		
Drug	**Revenue ($m)**	**Market Share (%)**
Dymista	119	24%
Generic Azelastine	69	14%
Asterpro	39	8%
Patanase	37	7%
Astelin	36	7%
Other	202	40%
Total	**502**	**100%**

Table 30: AR Intranasal Antihistamine Revenues and Market Share. Source: Visiongain 2016

Given the **lack of clear clinical advantage** it is considered that the anti-histamine intranasal spray market will maintain its niche market position [20]. **However, this position may be disrupted if PAR's product can offer significant clinical benefits which it claims it may do**.

The estimates by Visiongain suggest the market of US$502m will grow to US$821 by 2026. With most of this growth occurring between 2015-2020. Dymista's CAGR in revenue is 17.9% from 2015-2020 which rapidly declines from forecast peak annual sales of US$283m (representing 36.8% of the market) in 2021 to US$135m (representing 16.4% of the market) in 2026[21].

If PAR is to disrupt the intranasal spray market based on performance alone, it must demonstrate an efficacy better than that of Dymista and additional clinical benefit to existing antihistamine and intranasal corticosteroid combinations. The key efficacy and safety performance measures

[20] Visiongain 2016.
[21] Visiongain 2016.

PAR need to improve on are

- Dymista's Phase 3 clinical trials showed 49.1% of patients achieved 50% improvement in AR symptoms as measured by the Total Nasal Symptom Score, (see below).
- Industry risk measures associated with taking long term repeated dosages of corticosteroids in adults and children.

What is Dymista?

Dymista is is a novel intranasal product comprising a unique formulation and delivery system of azelastine hydrochloride and fluticasone propionate in a stable, structured suspension. It is the only currently available agent in the class of intranasal therapies for allergic rhinitis to provide H1-receptor antagonism and anti-inflammatory effects, thereby providing inhibitory effects on both the early- and late-phase allergic reaction in a single product.

The complementary pharmacology of Dymista may contribute to the efficacy that was seen when compared with the recognized effective active controls in the clinical studies. In the USA, Dymista is indicated for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief. In the EU, Dymista is indicated for seasonal allergic rhinitis and perennial allergic rhinitis.

Dymista Clinical Results Good Reference Point for PPS

In clinical studies of Dymista efficacy was determined by analyzing the change from baseline in a patient-reported measure of symptom severity: the 12-h reflective total nasal symptom score (TNSS) consisting of nasal congestion, rhinorrhea, sneezing and nasal itching.

One of the notable findings in these studies was that Dymista, as a single product, improved nasal symptoms of SAR to a substantially greater degree than two active comparators (fluticasone and astelin) alone. Onset of action with MP29-02 was as early as 30 min.

Following positive results of a small pilot study, four key Dymista efficacy and safety studies were conducted in which more than 4000 patients 12 years of age and older with moderate-to-severe SAR were enrolled for a 2-week study period. See summary of efficacy results below in Figure 13.

Study/treatment	Patients analyzed (n)	Mean baseline TNSS (SD)‡	Change from baseline (SD)	Treatment difference	p-value§
Study MP 4001					
MP29-02	153	18.6 (3.1)	−5.3 (5.1)		
Fluticasone	151	18.1 (3.5)	−3.8 (4.8)	MP29-02-FP	0.003
Astelin	152	17.9 (3.7)	−3.3 (4.2)	MP29-02-AZE	<0.001
Placebo	150	18.5 (3.5)	−2.2 (4.2)	MP29-02-PLA	<0.001
Study MP 4002					
MP29-02	207	18.3 (3.0)	−5.6 (5.2)		
Fluticasone	207	18.2 (3.2)	−4.7 (4.7)	MP29-02-FP	0.034
Azelastine	208	18.3 (3.5)	−4.2 (4.6)	MP29-02-AZE	0.001
Placebo	209	18.6 (3.2)	−2.9 (3.9)	MP29-02-PLA	<0.001
Study MP 4004					
MP29-02	193	18.3 (3.3)	−5.5 (5.2)		
Fluticasone	188	18.6 (2.9)	−4.6 (5.1)	MP29-02-FP	0.038
Azelastine	193	18.5 (3.1)	−4.5 (4.6)	MP29-02-AZE	0.032
Placebo	199	18.2 (3.1)	−3.0 (3.9)	MP29-02-PLA	<0.001
Study MP 4006					
MP29-02	448	19.3 (2.4)	−5.5 (5.2)		
Fluticasone	450	19.4 (2.4)	−4.9 (4.7)	MP29-02-FP	0.029
Azelastine	443	19.5 (2.5)	−4.8 (4.8)	MP29-02-AZE	0.016
Placebo	448	19.4 (2.4)	−3.4 (4.3)	MP29-02-PLA	<0.001

Figure 13: Dymistas Clinincal Study Results. Source: Berger et.al., Expert Rev. Clin. Immunol. (2013**).**

While it is hard to assume what will constitute a good efficacy trend in current Phase II study of Rhinosol®, we believe a reduction by 1.5-2.0 (on a scale from 0-9) or 2.0-3.0 (on a scale from 0-12) will suggest that PPS could be efficacious in treating AR.

Current and Future AR Intranasal Spray Market Dynamics.

Analysis of the major manufacturers and distributors of intranasal corticosteroids and anti-histamines indicates GSK controls 39% of the intranasal corticosteroid market, whilst Meda Pharmaceuticals controls 39% of the intranasal anti-histamine market.

The revenues generated by GSK from these therapeutics represent 3.36% of its total annual revenues in 2015 and the revenues generated by Meda represent 7.10% of its total annual revenues. The projected global growth in revenues in the AR market from oral AR therapeutics is set to reach US$8.4 billion in 2026 from US$4.8 billion in 2015/16.

Data from Table 31 below indicate a significant decline in market share in terms of corticosteroid product sales for Merck & Co, GSK, and AstraZenica over the next 10 years. This may prompt demand from these groups to seek replacement products, such as PAR's Rhinosul® for their AR business units or develop new ones.

No one company is dependent on AR nasal therapeutics for its overall revenues, moreover the top four products sold by 3 different pharma companies represent 60% of the current market share.

This dominant position suggests the threat of a new entrant to groups like GSK, Merck & Co and to a lesser degree, AstraZeneca, is low within the next 5-10 years. Moreover, should a threat of a new entrant occur in this market, groups like GSK and Merck & Co could respond with price reductions to retain market share, however this is unlikely given

the generic manufacturers near term threat. Alternatively, these groups may be interested in acquiring PAR's AR product IP to protect their intranasal corticosteroid market share against potential threats.

Intranasal Corticosteroid, Anti-inflamatory and Combined Therapy Market Analysis								
Company	Annual Revnues 2015 (US$m)	Drug	Revenue (US$m) 2015/16	Market Share (%) 2015/16	Revenue (US$m) 2026	Market Share (%) 2026	% of Owners Co Revenue 2015	Overall % of Revenue of Owner Co 2015
		Corticosteroid						
GSK (37% of Market Share)	36,550	Flixonase/Flonase/Flonase OTC	1228	28%	2340	31%	3.36%	4.49%
Merck & Co	38,773	Nasonex	858	20%	189	2%	2.21%	2.21%
GSK (37% of Market Share)	36,550	Avamys/Veramyst	350	8%	75	1%	0.96%	
Astrazeneca	24,708	**Rhinocort**	**250**	6%	133	2%	1.01%	1.01%
Sanofi	38,304	Nasocort/Nasocort/OTC	135	3%	196	3%	0.35%	0.35%
Takeda/Dainippon Sumitomo	16,183	Omnaris	66	2%	84	1%	0.41%	0.72%
GSK (37% of Market Share)	36,550	Beconase/Beconase AQ	62	1%	40	1%	0.17%	
TEVA Branded Pharma	19,624	Qnasl	60	1%	88	1%	0.31%	0.31%
Takeda/Sunovian Pharmaceuticals	16,183	Zetonna	51	1%	21	0%	0.32%	
		Other	1275	29%	4440	58%		
		Total	4335	100%	7606	100%		
		Antihistimine/Combination						
Meda Pharma (39% Market Share)	1,677	**Dymista**	**119**	24%	135	16%	7.10%	11.57%
Apotex/Sun Pharma (combined revs)	29,287	Generic Azelastine	69	14%	108	13%	0.24%	
Meda Pharma (39% Market Share)	1,677	Asterpro	39	8%	67	8%	2.33%	
Novartis/ Icon Laboratories	12,520	Patanase	37	7%	21	3%	0.30%	0.30%
Meda Pharma (39% Market Share)	1,677	Astelin	36	7%	52	6%	2.15%	
		Other	202	40%	438	53%		
		Total	502	100%	821	100%		

Table 31: Intranasal AR Market Analysis and Pharma Revenues. Source: Factset and Visiongain 2016

Patent Expiries and Pharmaceutical Company Revenues

Several key product patents have expired since 2007 and/or will expire over the next 5-10 years, opening the market to aggressive generic manufacturing and sales competition. The generics market will continue to cannibalise the established pharmaceutical industry revenues in the AR market.

Importantly this market dynamic change creates an opportunity for PAR to enter the market with its first in class, dual acting intranasal spray. Table 32

Table 32 lists those pharmaceutical companies who may be looking to substitute their existing products with potential new alternatives.

The loss of patent protection is anticipated to impact several pharmaceutical company's revenues in AR product sales at various rates of decline over the next 10 years

We believe those companies with well-established relationships in the global AR sales and distribution networks that face the fastest rate of decline may be the most interested in acquiring/licensing PAR's IP for its potential Rhinosul® product. Alternatively, companies such Johnson & Johnson may seek to restore its AR revenues which have declined from US$2.3b in 2005 to $615m in 2015 with a potentially new complimentary product such as Rhinosul®.

Company	Product	Patent Expiry Year	Revenues from product sales US$(m) 2015	Decline Rate forecast to 2026
Merck & Co	Nasonex	2014	$858	Rapid
GSK	Xyzal	2014	$260	Rapid
AstraZeneca	Rhinocort Aqua	2017	$250 (estimate includes Rhinocort sales)	Rapid
GSK	Veramyst	2021/23	$350	Slight
Sanofi	Nasocort AQ	2018	$135	No decline
Meda	Dymista	2023/26	$119	No decline
Johnson & Johnson	Zyrtec	2007	$615	Slight

Table 32: Patent Expiry and Projected Revenue Decline Rates. Source: Visiongain 2016

Products, Big Pharma and Method of Actions Comparison

Product name	Company	Active Ingredient	MOA
Xolair	Novartis, Roche	omalizumab	Immunoglobulin E (IgE) Receptor Antagonist
Singulair	Kyorin , Merck	montelukast sodium	Leukotriene D4 (LTD4) Receptor Antagonist
Nasonex	Merck & Co	mometasone furoate	Glucocorticoid Receptor (GR) Agonist
Claritin	Bayer	loratadine	Histamine H1 Receptor Antagonist
Veramyst	GSK	fluticasone furoate	Glucocorticoid Receptor (GR) Agonist
Allegra	Sanofi	fexofenadine hydrochloride	Histamine H1 Receptor Antagonist
Clarinex	Merck & Co Inc	desloratadine	Histamine H1 Receptor Antagonist
Talion	Dong-A Socio Mitsubishi Tanabe	bepotastine besilate	Histamine H1 Receptor Antagonist
Zyrtec	UCB SA	cetirizine hydrochloride	Histamine H1 Receptor Antagonist
Dymista	Meda AB	azelastine hydrochloride, fluticasone propionate	Glucocorticoid Receptor (GR) Agonist, Histamine H1 Receptor Antagonist
Onon	Ono Pharmaceutical Co Ltd	pranlukast hydrate	Leukotriene C4 (LTC4) Receptor Antagonist, Leukotriene D4 (LTD4) Receptor Antagonist
Nasacort	Sanofi	triamcinolone acetonide	Glucocorticoid Receptor (GR) Agonist
Xyzal	GSK	levocetirizine dihydrochloride	Histamine H1 Receptor Antagonist
Oralair	Laboratoire Stallergenes	grass allergens	Not provided
Alesion	Santen Pharmaceutical Co Ltd	epinastine hydrochloride	Histamine H1 Receptor Antagonist
Astelin	Meda AB	azelastine hydrochloride	Histamine H1 Receptor Antagonist
Rizaben	Kissei PharmaCo Ltd	tranilast	Inhibitor
Erizas	Nippon Shinyaku	dexamethasone cipecilate	Glucocorticoid Receptor (GR) Agonist
Allegra FX	Hisamitsu Pharma	fexofenadine hydrochloride	Histamine H1 Receptor Antagonist
Baynas	Nippon Shinyaku	ramatroban	Chemoattractant Receptor-Homologous Molecule Expressed on TH2 Cells (CRTH2) Antagonist
Rupafin	Recordati SpA	rupatadine fumarate	Histamine H1 Receptor Antagonist, Platelet-Activating Factor (PAF) Receptor Antagonist
Alamast	Alfresa Pharma	pemirolast potassium	Histamine Release Inhibitor
Livostin	Nippon Shinyaku , Santen Pharma	levocabastine hydrochloride	Histamine H1 Receptor Antagonist

Table 33: Select AR Drug MOU Comparison Source: Medtrack 2016.

PAR's Targeted Disease States

2. Alphaviruses (Ross River virus and Chikungungya)

Chikungunya (CHIKV) is a viral disease transmitted by the bite of infected mosquitoes. The mosquito is the world's deadliest animal.

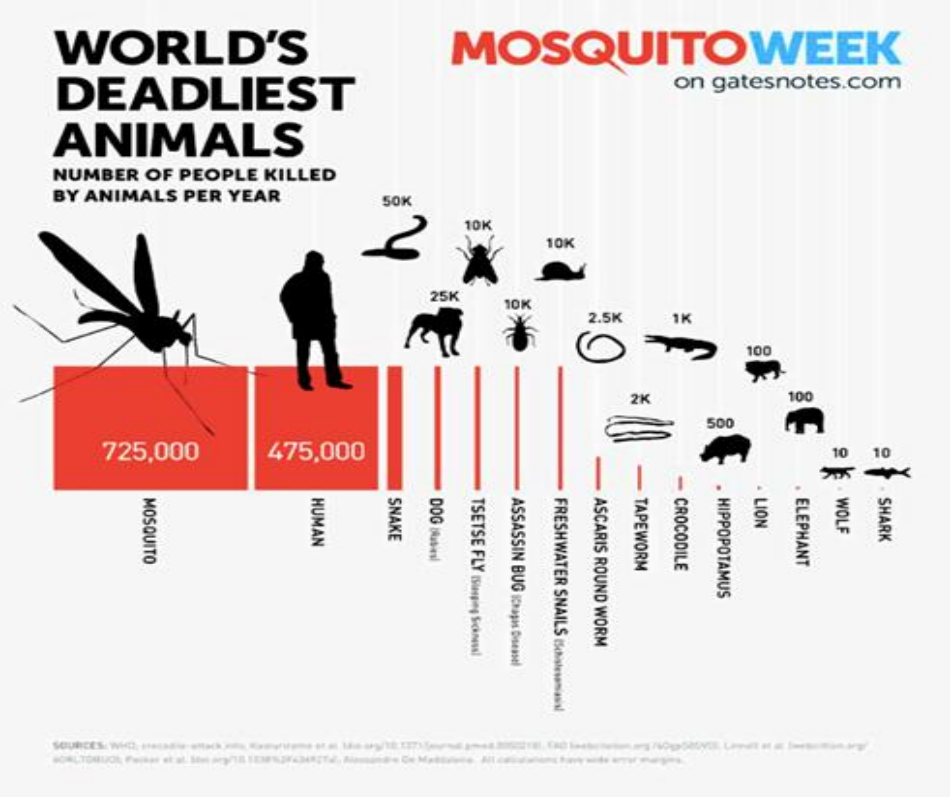


Figure 14: World's Deadliest Animals. Source: Griffith University 2016.

It can cause high fever, join and muscle pain, and headache. Chikungunya does not often result in death, but the joint pain may last for months or years and may become a cause of chronic pain and disability.

There is no specific treatment for chikungunya infection, nor any vaccine to prevent it.

Pending the development of a new vaccine, the only effective means of prevention is to protect individuals against mosquito bites. Ross River Virus (RRV) is a small encapsulated virus endemic to Australia, Papua New Guinea and other islands in the South Pacific.

Similar to CHIKV, RRV can cause symptoms of polyarthritis or joint pain with other signs which include rashes, headaches, fever, lethargy and muscle pain. Lymph nodes can become enlarged, and occasionally neuralgic pain of 'pins and needles' in the hands and feet, can be experienced.

There is no specific treatment for RRV infection, nor any vaccine to prevent it.

PAR Material and Progress

The Alpha Viruses are a group of arthropod-borne viruses within the Togavididae family and include RRV, CHIKV and BFV (Barmah Forest virus). They are all a major cause of debilitating arthritic disease worldwide.

Three distinct mouse models were used to assess the alphavirus pathogenesis by the institute of Glycomics. These models identify a critical role for macrophages in the pathogenesis of disease

1. RRV- C57BL/6 mice adolescent
2. CHIKV – C57BL/6 mice adult
3. BFV C57BL/6 mice adolescent.

Research method used by the institute is outlined in Figure 15 below.

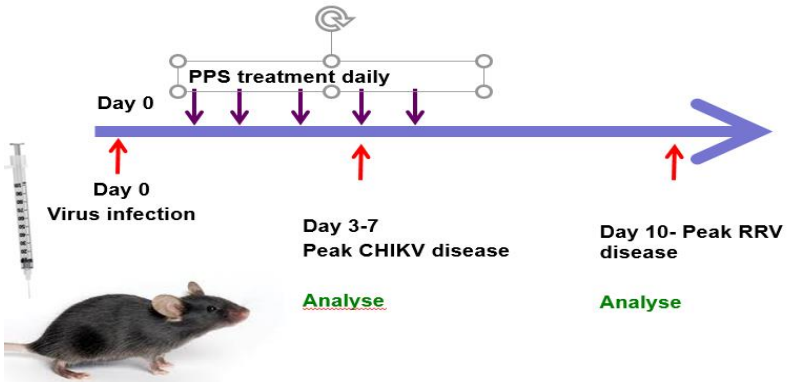
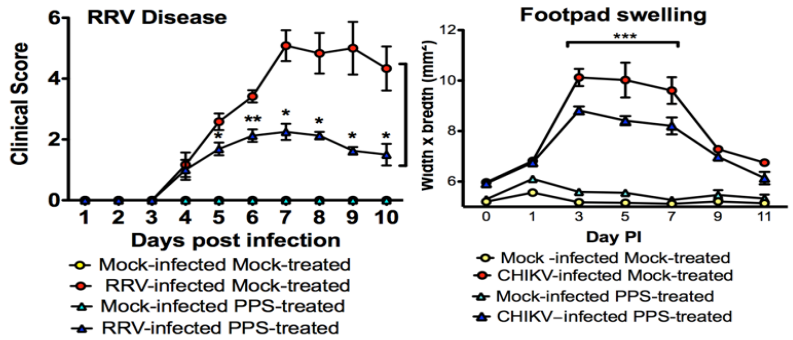


Figure 15: AV Research Method Used Source: Institute of Glycomics Griffith Uni 2016

The research findings indicated that PPS reduced the severity of Alpha Virus-induced disease, Figure 15 and the reduced Alpha Viral disease in mice is not due to a decreased viral burden Figure 17.



•C57BL/6 WT mice mice were s.c. infected with 10^4 pfu of RRV or CHIKV or mock-infected with PBS alone and then treated i.p. with either PPS at 3mg/kg or with vehicle daily

Figure 16: PPS Reduces AV Induced Disease. Source: Griffith University 2016

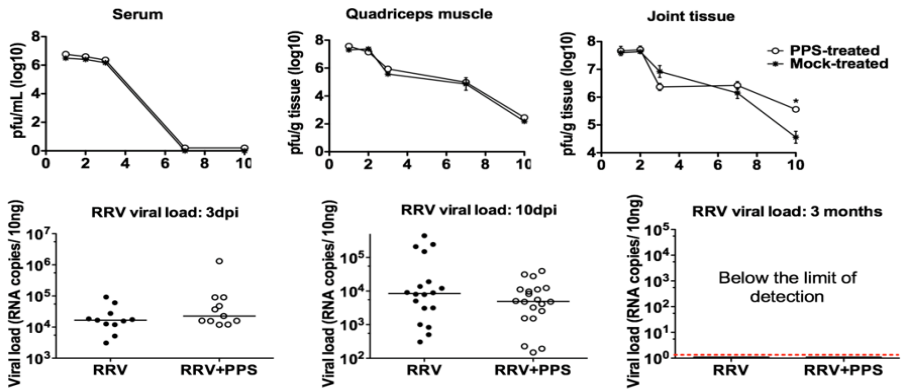


Figure 17: Reduced AV Disease: Source: Griffith University 2016.

The treatment with PPS was found to alter the classic type I and type II cytokine response induced by the alphavirus infection outlined in Figure 18.

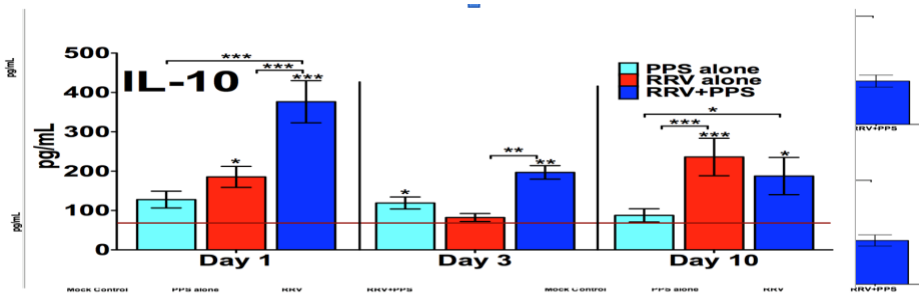


Figure 18: PPS Reduces Classic Cytokine Response. Source: Griffith University 2016.

In turn it was discovered in these trials that PPS protected the joints from Alpha Virus infections as outlined in the trial results in Figure 19.

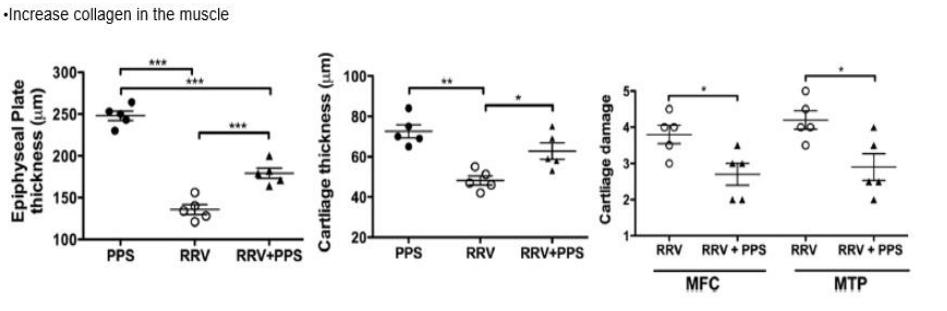


Figure 19: PPS Found to Protect Joints Source: Griffith University 2016.

These studies identified that treatment of Alphavirus with PPS reduces the clinical disease severity of RRV and CHIKV in C57BL/6 mice. The predominant natural killer cells, leukocytes infiltration characterised by inflammatory monocytes were substantially reduced in the infected mice treated with PPS.

This multiplex analysis shows PPS treatment results in a reduction of proinflammatory cytokines which is known to be instrumental in driving the severity of disease. Finally, the results of this early study show the dysregulation of the production of cartilage matrix is reversed with PPS.

The Market Opportunity

Alphaviruses such as Ross River virus (RRV) and chikungunya virus (CHIKV) cause large-scale multijurisdictional epidemics of severe musculoskeletal disease.[22]

These diseases have been progressively expanding across the globe and CHIKV is currently posing a progressive threat into the United States from the South and Central Americas regions as outlined in Figure 20 below.

The target market for these disease states are the US Department of Health, Australian Department of Health and relevant Health Authorities in specific jurisdictions within the Americas.

CHIKV was first detected in Tanzania in 1952. CHIKC is currently circulating in several of the Caribbean Islands and as of October 2014, the Pan American Health Organisation (PAHO) reported an estimated 946 341 cases worldwide with the first reports of the transmission into the United States being documents in July 2014 with 693,489 cumulative suspected cases reported in the Americas, see Table 34.

The diseases geographical spread encompasses Africa, Indian Ocean and Pacific Islands regions, Australia, Asia (India, Indonesia, Maldives, Myanmar, Sri Lanka and Thailand), Brazil, Canada, Dominican Republic, French Guiana, Guadeloupe, Martinique.

Country Territory	Cases of CHIKV Formed in Country		Incidence Rate/100,000 pop
	Suspected	Confirmed	
North America	0	11,577	2.4
Central American Isthmus	249,950	12,314	561.7
Latin Caribbean	8,960	2,317	30.2
Andean Area	402,164	8,772	295.1
Southern Cone (South America)	26,231	1,696	10.2
Non-Latin Caribbean	6,184	804	95.1
Total	693,489	37,480	73.8

Table 34: Cumulative Number or Reported CHIKV in Americas 2015. Source: World Health Organisation & PAHO.

[22] L Herrero, Journal of Virology, August 2015, Volume 89, No 15.

According to PAR, since 2014 there have been 1.4 million reported cases of CHIKV in the US alone.

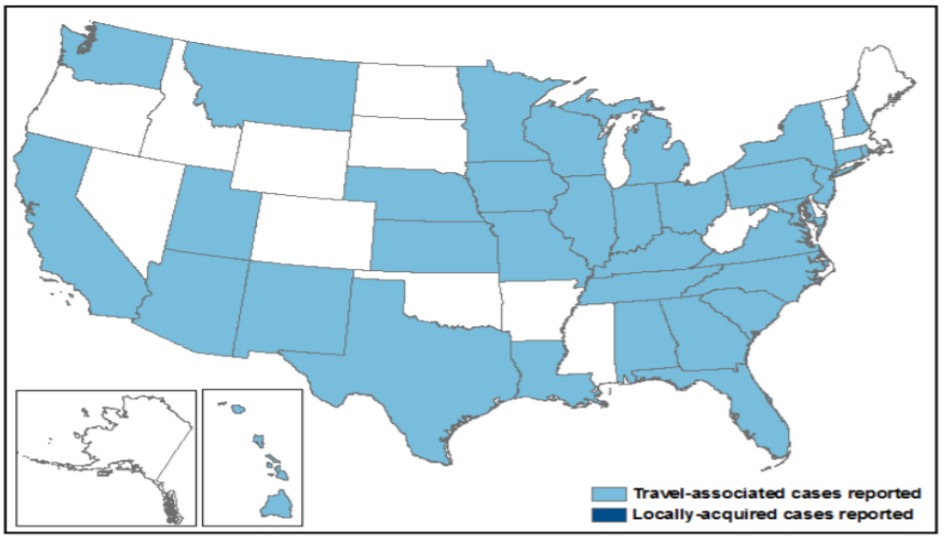


Figure 20: US States Reporting CHIKV Incidence 2016. Source: US DOH & HS, Centre of Disease Control and Prevention

The challenges governments face with CHIKV are bundled into two major categories:

1. Acute Impact
   i. The effect on health service networks at the time of outbreak due to high service demand
   ii. Then services must be able to hand cases on chronic sequelae left by the disease.[23]
2. Immediate Economic impact
   a. In consideration of acutely incapacitated patients
      i. Lost time at work and school.
   b. Potential impact on economic activities such as tourism
   c. Long term economic impact due to disabilities and chronic sequelae left by the disease.

Statistics on the regional reported cases for RRV is more difficult to identify, however in Australia the Department of Health, Annual Report on the Notifiable Disease Status in 2014 reported a 5-year mean number of cases of RRV of 4,801 patients since 2009.

RRV was first identified in Queensland in 1959 and it has been established that the healthcare costs for RRV disease are high per patient and, taken with productivity loss, were estimated to be between AU$1,018-$1,180 per person.[24]

The challenges facing governments and the potential economic impacts in Australia and surrounding regions related to RRV are the same as CHIKV outbreaks internationally. Throughout the parts of the world impacted by these alphaviruses, Federal, State and Local governments are spending significant resources on vector control, education campaigns and research. In Queensland alone in 2004 it has been estimated that the Government spent AU$10 million protecting the public from Ross River Virus infection. [25]

[23] PAHO & WHO Report on CHIKV virus transmission and its impact in the region of the Americas.
[24] Yu et al, July 2014, Epidemiologic Patterns of Ross River Virus Disease in Queensland, The American Journal of Tropical Medicine and Hygiene.
[25] Garnuat Climate Change Review, June 2008.

Figure 21: Territories with Cases of CHIKC Formed in Country. Source: WHO and PAHO.

PAR's Targeted Disease States

3. Bone Marrow Edema

What is Bone Marrow Edema?

In simple terms, Bone Marrow Edema (BME or sometimes referred to as Bone Marrow Lesions, BML) is a condition where fluid is found within the bone.

After the ever-increasing use of magnetic resonance imaging in clinical practice, bone marrow lesions (BML) due to excessive water signals in the marrow space have emerged as a central component of many different diseases affecting the musculoskeletal system. BMLs have been associated with a wide variety of inflammatory and non-inflammatory rheumatologic conditions (see Table 1 below).

(1) Trauma
Fracture (acute, osteoporotic and stress)
Local transient osteoporosis
Altered stress/biomechanics (plantar fasciitis, tendinitis/entesitis)
Bone bruise
Osteochondral injuries (osteochondritis dissecans)

(2) Degenerative lesions
Osteoarthritis (hip, knee, other)
MODIC lesions (spine)

(3) Inflammatory lesions
Inflammatory arthropathies and enthesitis (rheumatoid arthritis (RA), Ankylosing spondylitis, psoriasis)
Systemic chronic inflammation with fibrosis

(4) Ischaemic lesions
Avascular necrosis (AVN)
Complex regional pain syndrome (Sudeks atrophy of bone)
Sickle cell anaemia (SCA)

(5) Infectious lesions
Osteomyelitis
Diabetic foot, Charcot foot
Sepsis (bone incfarcts)

(6) Metabolic/endocrine lesions
Hydroxyapatite deposition disease (HADD)
Gout

(7) Iatrogenic lesions
Surgery
Radiotherapy
Immunosuppressants (glucocorticoids, cyclopsorin)
Cytostatics

(8) Neoplastic (and neoplastic-like) lesions

Table 35:BME Etiology. Source: Fink Eriksen et.al., Rheumatol Int (2012)

As mentioned, initial description of BME is water signals on MRI. However, the lesion is not a typical edema by histological criteria. Rather fibrosis, lymphocytic infiltrates and increased vascularization characterize it. It is probably the latter which is responsible for the water signal seen on MR.

The histological and biochemical marker profiles reported in numerous studies indicate that BMLs constitute a local area of high bone turnover and increased expression of cytokines and angiogenic factors. The common notion is that BMLs represent repair phenomena, elicited by trauma or inflammation in the area.

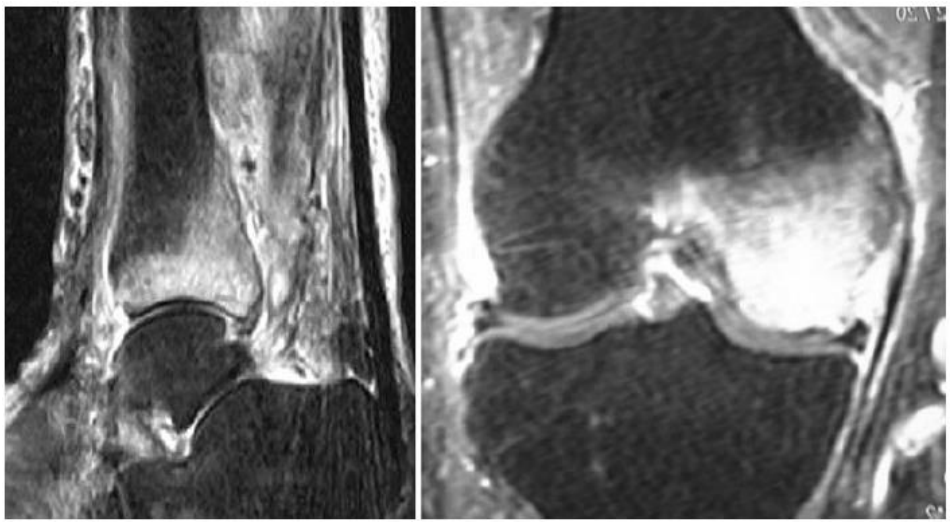


Figure 22: Example of BML.Examples of BML. BML in lower tibia in 64-year-old female with pain in her ankle and leg over a period of 6 months (*left panel*); b Lateral knee tendinitis and BML of lateral condyle in 35-year-old male training for marathon (*right panel*)

Source: Fink Eriksen et.al., Rheumatol Int (2012) 32:575–584.

Potential Role of PPS in Bone Disease and Application to Bone Edema

The results from numerous in vitro and animal studies of the PPS have led to the suggestion that it might be classified as a disease modifying agent in osteoarthritis because of its ability to preserve the integrity of the articular cartilage and bone while improving the quality of the joint synovial fluid.

PPS was shown to support chondrocyte and fibroblast anabolic activities while attenuating catabolic events associated with destruction of the cartilage extracellular matrix [26].

A pilot study of PPS in osteoarthritis suggested that under controlled, double-blind conditions, 4 consecutive weekly IM injections of PPS 3 mg/kg improved joint stiffness, pain at rest, and patient assessment of the effectiveness of treatment for up to 20 weeks after treatment cessation, and pain on walking for 4, 12, and 20 weeks after treatment cessation.

These findings suggest that the drug could improve functional disability in OA, but most importantly reads well for Paradigm's currently ongoing Phase 2 study of PPS in bone marrow edema.

PPS, however, was never considered as a treatment for OA, as results of the pilot study also suggested that 8 to 12 weeks after the end of drug treatment represents the time frame for the pathology associated with symptoms to become re-established. We believe this should not affect the ongoing Phase 2 study in BME, due to a different nature of the disease.

[26] Fink Eriksen et.al., Rheumatol Int (2012)

The Market Opportunity

The BME market is not clearly defined and is based upon extrapolated and potentially correlated data. As the market is still developing there has be no detailed reporting by clinicians on the treatment and management of BME.

PAR is researching the impact PPS has upon BME signs and symptoms using quantifiable magnetic resonance imaging assessment and a reliable subject patient measurement framework called Lysholm Knee Score, with eight functional activity responses before and after treatment for BME.

It is not researching the impact the effect PPS has upon the incidence of osteoarthritis although the corollary to treating patients for BME may be to reduce the incidence or severity of post traumatic osteoarthritis risk. This corollary will require further discrete research.

According to PAR there are potentially 1.4 million ankle and knee injuries that may be associated with clinically significant bone bruising per year. Studies in 2001 highlight BME as a potential underlying risk factor in osteoarthritis, with and an estimated 75% of knee osteoarthritis in the US may be associated with BME[27].

It is known that BME arises from a wide variety of traumatic (mechanical) and non-traumatic causes. Hence there may be two way to assess the market size for BME which may be extrapolated from the incidence of acute traumatic injuries and perhaps from the prevalence of people with osteoarthritis (OA) who have a history of joint trauma.

1. **Traumatic Injury Rates in the US.**
    - In the US, anterior cruciate injuries occur at a rate of 40/100,000 in the population, which equates to approximately **100,000** reconstruction per year in the US, some of whom may suffer from BME.
    - Similarly, in the US, cartilage tears occur at a rate of 90/100,000 in the population, which equates to **300,000** cartilage tears per year, some of whom may suffer from BME.
2. **Incidence of Osteoarthritis in the US.**
    - As of 2010 there were over 600,000 knee replacements performed annually in the US, with approximately 4.7 million individuals in the US living with either hip or knee replacements.[28]

Facts to Consider when Assessing BME Market Opportunity

Bone marrow lesions (BMLs) have been shown to be associated with pain and progression of knee osteoarthritis (OA) in those with disease. Thus, a therapeutic approach towards BML could be preventative for more serious osteopathologies.

Persistence of BME/BML depends on the etiology of the condition. After trauma, the bone marrow edema will subside on its own. Just like most any other bruise you have had. In osteonecrosis, the bone marrow edema will also subside. In many cases of osteonecrosis the bone will grow new blood vessels and regrow itself. Osteoarthritis on the other hand is a progressive condition. It only gets worse over time. That means that the edema is unlikely to improve either. In cases of severe pain that is thought to be due to bone marrow edema, certain treatments might be indicated.

[27] Annals of Internal Medicine, April 2001.
[28] Journal of Bone Joint Surgery, Sept 2015.

BML Has A Very High Prevalence in Population

A recent Australian population study showed The prevalence of BML in the knee joint was 17 % (grade 1: 10.7 %, grade 2: 4.3 %, grade 3: 1.8 %). They were associated with increasing age, previous knee injury, increased knee symptoms and structural abnormalities such as meniscal lesions and cartilage defects. Furthermore, moderate physical activity and higher HDL cholesterol were associated with decreased BML while vigorous activity was weakly associated with increased BML, suggesting that BMLs in younger adults are modifiable. [29]

Why Upcoming Phase II Data Is Important?

While there are some pre-clinical and clinical data suggesting therapeutic benefits of PPS in BML, it does not provide enough information to estimate clinical utility of PPS in this indication and perform cost benefit economic analysis in order to properly define the pricing point and targeted patient population of PPS in BML.

Assuming a % of all bone marrow lesions as a target population would be incorrect as in most of the cases edema will subsid on its own. However in some progressive conditions, like osteoarthritis, the situation only gets worse overtime and edema is unlikely to resolve on its own. PPS could be beneficial for these patients.

Studies in 2001 highlight BME as a potential underlying risk factor in osteoarthritis, with and an estimated 75% of knee osteoarthritis in the US may be associated with BME[30].

We believe the upcoming Phase 2 data would be a great tool understand the potential market size and pricing of PPS in BML.

Upcoming Phase II Data

Paradigm is currently running a 40-patient open-label pilot clinical trial to determine the safety and tolerability of Paradigm's proprietary formulation of Pentosan Polysulphate Sodium (PPS), ZILOSUL® in patients with a BME lesion. ZILOSUL® will be administered intramuscular twice weekly for a period of three weeks at a dose of 2mg/kg in patients exhibiting a BME lesion identified by MRI in association with bone pain and reduced joint function following an Anterior Cruciate Ligament (ACL) injury.

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.

The trial will be looking whether Zilosul can reduce pain and resolve the bone marrow lesion and hopefully protect the cartilage in the long-term. The trial will be looking for the following efficacy endpoints (see Table below):

[29] Antony et al. Arthritis Research & Therapy (2016) 18:31
[30] Annals of Internal Medicine, April 2001.

Efficacy endpoint 1
Change in bone marrow lesions assessed by MRI
Timepoint
8 weeks post first injection
Efficacy endpoint 2
functional knee joint capacity assessed by Lysholm Knee score and Tegner Activity score
Timepoint [2]
Day: 0, 4, 7, 11, 14, 18, 28, 42, 56
Day 0=first dose of study drug
Efficacy endpoint 3
Biomarkers- serum biomarkers of bone and collagen activity and inflammation
Timepoint [3]
Day: 0, 7, 14, 28, 42, 56
Day 0=first dose of study drug
Efficacy endpoint 4
Pain assessed by Numeric Rating Scale NRS-11
Timepoint [4]
Day: 0, 4, 7, 11, 14, 18, 28, 42, 56
Day 0=first dose of study drug

Table 36: Treatment of BME Trail. Source: PAR

We believe that any significant change in bone marrow lesions on MRI will attract interest from potential partners with the view of conducting larger efficacy studies.

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Private Client Dealing		Email	Telephone
Chad South	Head of Retail Advisory	csouth@djcarmichael.com.au	+61 8 9263 5225
Tim Bennett	Private Client Adviser	tbennett@djcarmichael.com.au	+61 8 9263 5351
Matthew Blake	Executive Director - Private Client Adviser	mblake@djcarmichael.com.au	+61 8 9263 5248
Eve Broadley	Private Client Adviser	ebroadley@djcarmichael.com.au	+61 8 9263 5324
Gregory Chionh	Private Client Adviser	gchionh@djcarmichael.com.au	+61 8 9263 5302
Gerry Connolly	Private Client Adviser	gconnolly@djcarmichael.com.au	+61 8 9263 5265
Paul Covich	Private Client Adviser	pcovich@djcarmichael.com.au	+61 8 9263 5257
Andrew Cox	Private Client Adviser (Equities & Derivatives)	acox@djcarmichael.com.au	+61 8 9263 5237
Toby Jefferis	Private Client Adviser	tjefferis@djcarmichael.com.au	+61 8 9263 5217
Chris Jones	Private Client Adviser	cjones@djcarmichael.com.au	+61 8 9263 5232
Michael Marano	Private Client Adviser	mmarano@djcarmichael.com.au	+61 8 9263 5238
Derek Steinepreis	Private Client Adviser	dsteinepreis@djcarmichael.com.au	+61 8 9263 5292
James Titcombe	Private Client Adviser	jtitcombe@djcarmichael.com.au	+61 8 9263 5254
Jason Murray	Dealers Assistant	jmurray@djcarmichael.com.au	+61 8 9263 5260
Ben Osborne	Dealers Assistant	bosborne@djcarmichael.com.au	+61 8 9263 5251
Zac Paul	Dealers Assistant	zpaul@djcarmichael.com.au	+61 8 9263 5272

Wealth Management		Email	Telephone
Brad Clarke	Wealth Manager	bclarke@djcarmichael.com.au	+61 8 9263 5224
Paul Elkington	Wealth Manager	pelkington@djcarmichael.com.au	+61 8 9263 5285
Domenic Macri	Wealth Manager	dmacri@djcarmichael.com.au	+61 8 9263 5263
Nick Casale	Portfolio Administration Manager	ncasale@djcarmichael.com.au	+61 8 9263 5215

Research		Email	Telephone
Paul Adams	Director - Head of Research and Natural Resources	padams@djcarmichael.com.au	+61 8 9263 5234
Michael Eidne	Director - Research	meidne@djcarmichael.com.au	+61 8 9263 5213
Michael Ron	Research Analyst	mron@djcarmichael.com.au	+61 8 9263 5264

Corporate Finance		Email	Telephone
Davide Bosio	Managing Director & Head of Corporate Finance	dbosio@djcarmichael.com.au	+61 8 9263 5210
Scott Robertson	Director – Corporate Finance Executive	srobertson@djcarmichael.com.au	+61 8 9263 5218
Adam Russo	Associate Director - Corporate Finance Executive	arusso@djcarmichael.com.au	+61 8 9263 5290
Hugo McChesney	Institutional Client Manager	hmcchesney@djcarmichael.com.au	+61 8 9263 5214
Carly Circosta	Manager - Corporate Finance Executive	ccircosta@djcarmichael.com.au	+61 8 9263 5268

Administration		Email	Telephone
Cadell Buss	Chief Executive Officer	cbuss@djcarmichael.com.au	+61 8 9263 5204
Belinda Roychowdhury	Administration Manager	broychowdhury@djcarmichael.com.au	+61 8 9263 5216
Gabrielle Bouffler	Head of Compliance and Risk	gbouffler@djcarmichael.com.au	+61 8 9263 5221
Janelle Whyte	Chief Financial Officer	jwhyte@djcarmichael.com.au	+61 8 9263 5241
Fiona Garvie	Assistant Accountant	fgarvie@djcarmichael.com.au	+61 8 9263 5220
Kerry Morrice	Administration Assistant	KMorrice@djcarmichael.com.au	+61 8 9263 5279
Brenda Woodenberg	Reception	bwoodenberg@djcarmichael.com.au	+61 8 9263 5200

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RCAN1367

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