



ASX RELEASE

Paradigm Enters Heart Failure Market

Key Highlights:

- Paradigm has expanded its drug development pipeline by in-licensing Pentosan Polysulfate Sodium (PPS) for the treatment of heart failure from the University of Oslo, Norway
- PPS has demonstrated beneficial effects in an established preclinical heart failure model, specifically:
 - improved systolic function of the heart (pressure in the arteries)
 - the potential to stop or reverse disease progression in heart failure, addressing an important unmet medical need
- Exciting medical potential in a disease area where mortality from first diagnosis is high, reaching 50% at five years from diagnosis¹
- The global market for heart failure drugs is estimated to be US\$18 billion per annum² with all currently available treatments unable to stop or reverse disease progression
- Paradigm to utilise PPS's well-established safety data to fast-track development under the FDA 505(b)(2) pathway (drug repurposing)

Melbourne 20 June 2017 Paradigm Biopharmaceuticals Ltd (Paradigm, ASX: PAR) announces the in-licensing of a heart failure patent from the University of Oslo, Norway as it enters the US\$18 billion global heart failure market.

Paradigm has signed a worldwide exclusive in-license agreement for the patent entitled "*Inhibitors of ADAMTS4 or ADAMTS5 for use in preventing or treating cardiac remodelling and chronic heart failure*" from the University of Oslo.

The agreement comes ahead of Paradigm presenting and holding discussions with potential commercial partners at the 2017 BIO International Convention this week. The convention will be held from 19-22 June in San Diego, California and attracts more than 16,000 leading innovators and companies from the biotech industry.

Heart failure is a disease whereby the heart experiences high blood pressure as a result of a blockage of vessels or a heart attack, that results in damage to the heart muscle. When damaged,

¹ New England Journal of Medicine, Levi D et al. 2002

² Calculated from information relating to the sales of compounds/treatments in the heart failure market from 2014-2016 – Statins US\$13.1bn (Research and Markets - Global Statin Market 2015-2016), Clopidogrel bisulphate US\$1.8bn, Beta-blockers US\$1.55bn, ACE inhibitors US\$0.47bn, Aspirin US\$0.54bn, Vitamin K antagonist US\$0.5bn (www.pharmacompass.com), <http://www4.dr-rath-foundation.org/Newsletter/articles/bad-news-for-the-pharma-cartel-statin-profits-collapsing-cholesterol-bubble-has-burst.html>, www.gbiresearch.com

the heart has great difficulty pumping blood to organs such as the lungs, liver and kidneys. To allow blood circulation to these organs, the heart compensates by changing its shape and the chambers of the heart. These changes make the heart work harder, causing heart muscle to degenerate further, eventually leading to death. Mortality is high for patients with heart failure, reaching 50% at five years from diagnosis¹.

The new patent is founded upon compelling preclinical data (peer-reviewed and published) using Pentosan Polysulfate Sodium (PPS) as the inhibitor of ADAMTS4 versicanase, a key enzyme involved in the degenerative process in heart failure. This data demonstrates that PPS reduced the amount of ADAMTS4 versicanase activity in a recognised heart failure model.

Studies also showed that PPS treatment improves systolic function of the heart (the amount of pressure in the arteries during contraction of the heart muscle) in the heart failure model and that it has the potential to stop or reverse disease progression in heart failure, addressing an important unmet medical need for patients.

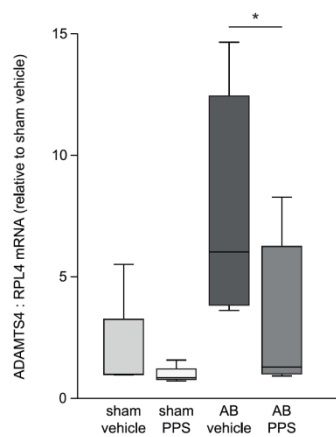


Figure A

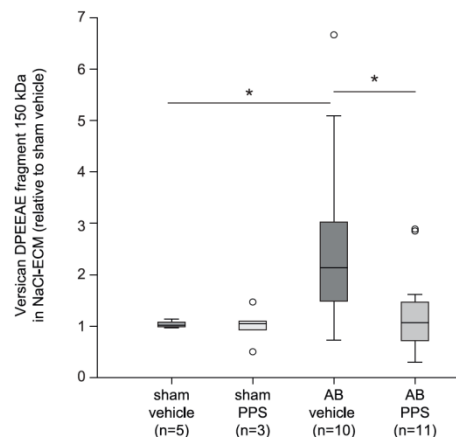


Figure B

Figures A and B: Preclinical data showing efficacy of PPS in Aortic Banding rat model of heart failure - PPS downregulates ADAMTS4 activity at the mRNA level (Figure A) in the Aortic banding rat model which translated to reduction of ADAMTS4 enzymatic activity shown by reduction in versican cleavage fragments (Figure B). Versican cleavage fragments also contribute to cardiac edema (Vistnes et al 2014).

Mr Paul Rennie, Paradigm's Chief Executive Officer said: "This collaboration with the University of Oslo provides Paradigm with an exciting novel approach to treat heart failure with PPS and provides an extended portfolio of clinical indications targeted by our drug repurposing business model."

"We believe that the unique properties of PPS - its anti-inflammatory action and its ability to slow or stop the tissue degenerative process in heart failure - provides a novel therapeutic approach not reported in other heart failure pharmaceutical drugs. This is enormously exciting as it means the product can potentially meet market needs that are not effectively managed by current cardiac drugs."

Paradigm will develop PPS for the treatment of heart failure in partnership with the University of Oslo, with preparation for the clinical development set to commence in the coming months. It is anticipated that the development program will advance straight to Phase 2 clinical trials, after the

completion of the Company's Phase 2 Bone Marrow Edema, hay fever, osteoarthritis and Ross River Clinical Trials .

Given the recent completion of the Phase 2 hay fever trial (results upcoming), the Company will focus on completing the Phase 2 Bone Marrow Edema clinical trial and commencing the Ross River clinical trial. Post the completion of these trials Paradigm will commence the Phase 2 pilot heart failure clinical Trial (n=24) before commencing the Phase 2b heart failure in 2018. Management believes its cash position, including the anticipated R&D rebate in Q3CY2017, is more than sufficient to progress all the company's current programs, and commence planning for the upcoming osteoarthritis and Phase 2 pilot heart failure clinical trials.

Dr Maria Vistnes of the University of Oslo said: "Our studies were the first to report the increased production of the enzyme, ADAMTS4 versicanase in heart failure. This is a key enzyme involved in the degenerative process in heart failure. Most importantly, the data demonstrated that PPS treatment improved contractility of the heart in the pressure-overloaded heart failure model and was correlated with a reduction of ADAMTS4 versicanase activity." He added that: "the preclinical findings firstly shed light on a novel mechanism for heart failure development, and the role of PPS as a potential new heart failure therapy."

Heart failure is divided into two categories: heart failure with reduced ejection fraction (HFrEF), accounting for 50% to 70% of cases and heart failure with preserved ejection fraction (HFpEF).

Professor Tim Martens who is a leading cardiothoracic surgeon at the Loma Linda Medical Centre at Los Angeles and Paradigm's cardiology consultant in the clinical development program was very encouraged with Dr Vistnes' data and remarked that: "Currently, there are no registered heart failure pharmaceutical agents that directly target the destructive enzymes that change the shape and size of the damaged heart (extracellular matrix remodelling) in the transition to heart failure and it will be very interesting to see if PPS demonstrates protective and beneficial effects in patients with heart failure with HFpEF as well as those with HFrEF. There is still an unmet need to effectively treat heart failure patients with HFpEF."

Paradigm is further encouraged of the potential of this new heart failure indication as there has been increasing research connecting the use of oral non-steroidal anti-inflammatory drugs (NSAIDs, e.g. ibuprofen) to increased risk of heart failure³. The peer-reviewed study recently published in the British Medical Journal (<http://www.bmj.com/content/357/bmj.j1909>) concluded that: "All NSAIDs, including naproxen, were found to be associated with an increased risk of acute myocardial infarction." Management believe that PPS's well-documented safety profile and known anti-inflammatory properties will make it an excellent new treatment in the heart failure, thus offering a solution to the potential issue of using NSAIDs under certain circumstances.

ADDRESSABLE MARKET: The global heart failure market is estimated to currently be US\$18 billion⁴ per annum and is made up of the six main treatments that address conditions associated with heart failure: Statins US\$13.1billion, Clopidogrel bisulphate US\$1.8 billion, Beta-blockers US\$1.55 billion, Ace inhibitors US\$0.47 billion, Aspirin US\$0.54 billion, Vitamin K antagonist US\$0.5 billion.

³ Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data - <http://www.bmj.com/content/357/bmj.j1909>

⁴ Calculated from information relating to the sales of compounds/treatments in the heart failure market from 2014-2016 – (Research and Markets - Global Statin Market 2015-2016), www.pharmacompass.com, <http://www4.dr-rath-foundation.org/Newsletter/articles/bad-news-for-the-pharma-cartel-statin-profits-collapsing-cholesterol-bubble-has-burst.html>

The total cardiovascular disease market, which includes hypertension, dyslipidemia, and thrombotic events, is set to grow from \$129.2 billion in 2015 to \$146.4 billion by 2022, at a very modest compound annual growth rate of 1.8%, according to business intelligence provider GBI Research⁵.

There are numerous blockbuster drugs aimed at the heart failure market that have come off patent with the most well-known being Lipitor (Warner-Lambert then Pfizer) which was first approved in 1997. Whilst under patent protection it was the highest-selling drug of all time, with worldwide sales peaking in 2006 at more than US\$13 billion a year⁶. AstraZeneca's Crestor (rosuvastatin), generated peak sales of around \$7 billion in 2011, however revenues are expected to drop sharply following the expiration of its patent on July 8, 2016.⁷

Current standard of care and therapeutics used for heart failure patients include ACE inhibitors, calcium antagonists, angiotensin receptor blockers, beta blockers and diuretics.

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⁵ <http://www.gbiresearch.com/media-center/press-releases/cardiovascular-disease-market-set-to-grow-very-slowly-to-1464-billion-by-2022-says-gbi-research>

⁶ <http://www.drugsdb.com/blog/the-5-most-profitable-medications-ever-produced.html>

⁷ <http://www.gbiresearch.com/media-center/press-releases/cardiovascular-disease-market-set-to-grow-very-slowly-to-1464-billion-by-2022-says-gbi-research>