# PARADIGM BIOPHARMACEUTICALS LIMITED

ASX RELEASE

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## PARADIGM RECEIVES CRITICAL APPROVALS AND FEEDBACK FROM AGENCIES TO PROGRESS MPS CLINICAL AND COMMERCIAL DEVELOPMENT

### KEY HIGHLIGHTS

- **MPS-VI receives Orphan Status from the European Medical Agency.**
- **Paradigm now has approved Orphan Designations for MPS-I and MPS-VI in the US and the EU.**
- **Paradigm receives positive feedback from its Parallel Scientific Advice meeting with the FDA and the EMA. Both Agencies agreed on the ultra-rare nature of MPS VI and provided clarification on both the clinical trial design and regulatory path forward.**
- **MPS-I Phase 2 clinical trial approved by the Human Research Ethics Committee.**
- **Paradigm's proposed clinical trial for MPS-I to be conducted at Adelaide's Women's & Children's hospital with Dr David Ketteridge as the Principal Investigator.**
- **Paradigm's investigation of PPS for MPS seeks to establish whether PPS may be an effective adjunct/combination therapy with current Enzyme Replacement Therapy treatments.**

**Paradigm Biopharmaceuticals Ltd (ASX: PAR)** is pleased to announce a number of critical developments required to progress investigation into the use of its core drug Pentosan Polysulfate Sodium (PPS) in the treatment of the rare disease mucopolysaccharidosis (MPS).

The Company has gained ethics approval for its proposed pilot study for the ultra-rare Orphan disease Mucopolysaccharidosis Type 1 (MPS-1). The ethics approval is validation from the medical / scientific community that PPS may provide benefit to patients who continue to experience this unmet need.

The Company has also received approval from the European Medical Agency (EMA) for its Orphan designation application for MPS-VI. Such approvals from the EMA can take up to 90 days; Paradigm received a decision on Day 60 of the process.

The Company can also report positive feedback from a Parallel Scientific Advice (PSA) meeting with the Federal Drug Administration (FDA) and EMA. Paradigm received clarification on the design of the clinical program and feedback on the regulatory pathway for its submission for a Phase 2/3 Clinical trial in MPS-VI.

## What is Parallel Scientific Advice (PSA) with EMA and US FDA?

The EMA and the FDA have initiated a pilot programme to provide parallel scientific advice (PSA). Paradigm was accepted into this pilot program for discussion on our MPS VI development program.

Paradigm's PSA meeting took place in June 2020, with the Company now receiving feedback from both agencies on its clinical program and clarification on the regulatory pathway for MPS-VI. This is valuable feedback for the Paradigm regulatory team as they continue to prepare the joint submission for the Company's proposed Phase 2/3 clinical trial.

**The goal of the PSA program** is to provide a mechanism for EMA assessors and FDA reviewers to concurrently exchange with sponsors their views on scientific issues during the development phase of new medicinal products. Such interactions are expected to increase dialogue between the two agencies and sponsors from the beginning of the lifecycle of a new product, provide a deeper understanding of the bases of regulatory decisions, optimize product development, and avoid unnecessary testing replication or unnecessary diverse testing methodologies.[1]

## Mucopolysaccharidosis type 1 and 6 – Orphan Status

The US Food and Drug Administration (FDA) created the Orphan Drug Act to encourage and provide special incentives to drug companies that undertake the development of orphan drugs that target diseases affecting fewer than 200,000 people in the United States.

Paradigm has now received, from the FDA and the EMA, confirmation that both MPS-I and MPS-VI are orphan diseases. The benefits that the orphan designation approval provides to Paradigm include:

- Tax credits for qualified clinical testing;
- Waiver of New Drug Application (NDA)/Biological Licensing Application (BLA) user fees;
- Eligibility for a 7-year marketing exclusivity upon marketing approval. If granted, the drug will have a status which gives companies exclusive marketing and development rights along with other benefits to recover the costs of researching and developing the orphan drug.

## MPS-I Pilot Study

Paradigm's proposed open-label, single centre pilot study to evaluate the safety and tolerability of PPS in subjects with MPS-I has been approved by the Human Research Ethics Committee, a precursor to commencing this pilot study. The study will be conducted at the Adelaide Women's and Children's Hospital (WCH) with Dr David Ketteridge, the Principal Investigator (PI) and Dr Drago Bratkovic (Head of the Metabolic Clinic) leading the clinical trial. The Data from this trial will be used to support future regulatory filings and applications.

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[1] https://www.fda.gov/media/105211/download "GENERAL PRINCIPLES EMA-FDA PARALLEL SCIENTIFIC ADVICE (HUMAN MEDICINAL PRODUCTS).

**Paul Rennie, Paradigm Interim Chairman and CEO, commented:**

*"Paradigm recently reported very positive pain reduction and functional improvement data in 10 ex-NFL players with osteoarthritis treated under the US FDA Expanded Access Program (EAP). The mean reduction in WOMAC pain from baseline was 65% and this compares very favourably with the common oral treatments for patients with Osteoarthritis of roughly 30% reduction in WOMAC pain from baseline (NSAID's and opioids). We had a number of important take-aways from the EAP notably (i) Paradigm was able to execute on this program, in the USA, during the height of the COVID-19 pandemic (on time and on budget), (ii) the EAP used the same batch of Zilosul (iPPS) that will be used in Paradigm's Phase 3 clinical trial as well as using the same pain scoring system (WOMAC), and (iii) all subjects who commenced the program completed it with no drop outs and no serious adverse events reported. So good safety and outstanding efficacy are very pleasing outcomes as Paradigm prepares for its Phase 3 clinical trial.*

*I am pleased to report that the second clinical program in our pipeline has also made considerable progress. MPS has gained orphan disease status from both the US FDA and EMA. Additionally, positive feedback on Paradigm's clinical trial protocol and regulatory pathway was received from both the US FDA reviewers and EMA assessors at the Parallel Scientific Advice meeting. Paradigm is pleased to receive very clear directions on the regulatory pathway for the MPS program.*

*It is also important validation from the Investigators and Ethics Committee at the internationally recognised MPS centre, the Women's and Children's Hospital in Adelaide, with the Ethics Committee approval to commence a Phase 2 clinical trial in MPS-1. Current treatment options for MPS-1 (such as bone marrow transplant or Enzyme Replacement Therapy (ERT)) have limited effects on some organs, especially the skeletal system, with MPS-1 patients experiencing joint pain and dysfunction. The goals of this study are to investigate the safety and clinical effects, concerning mobility and pain, of PPS treatment in MPS I patients. Helping to relieve joint pain and stiffness is Paradigm's mission and we are making rapid progress to achieving our goals".*

**PARADIGM'S CHIEF MEDICAL OFFICER'S BACKGROUND NOTE**

Dr Donna Skerrett, Paradigm's Chief Medical Officer, has prepared the following notes, providing background information in support of this announcement.

Mucopolysaccharidosis type I **(MPS-I)** is a rare inborn metabolic disorder caused by a genetic defect in the catabolism of two glycosaminoglycans (GAGs): heparan sulfate and dermatan sulfate. Disorders in the catabolism of these GAGs interfere with cellular function, resulting in abnormal bone development, growth retardation, cardiac and respiratory problems, and sometimes cognitive impairment[2]. The current treatments Enzyme Replacement Therapy (ERT) and/or Hematopoietic Stem Cell Therapy are available and indicated for people diagnosed with MPS-I to treat the underlying disease by reducing the accumulation of glycosaminoglycans (GAGs).

[2] Aldenhoven, Sakkers, Boelens, de Koning, & Wulffraat, 2009; Beck et al., 2014; Bittar, 2018; Schroeder et al., 2013.

The Adelaide WCH and the South Australian Health and Medical Research Institute (SAMHRI) have been pioneers in the research of Lysosomal Storage Disorders (LSD's). Led by Emeritus Professor John Hopwood AM FAA, who established the Lysosomal Diseases Research Unit (LDRU) - a large multidisciplinary group researching lysosomal storage disorders nationally and internationally.

Under Professor Hopwood's stewardship, the LDRU has become world-renowned for its research capabilities in this area and the translation of research findings into state-of-the-art diagnostic services and therapeutics. The LDRU has remained at the international forefront of research into the diagnosis, treatment and biology of lysosomal diseases.

The LDRU has generated several world firsts, particularly the isolation of the genes involved in some of these disorders and the development of first-ever FDA- approved treatments for two disorders, which in 2005 and 2006 were marketed world-wide. These outcomes have led to improved quality of life for patients and multi-million dollar royalty returns to South Australia. This represents one of the largest public sector commercialisation outcomes in South Australia and possibly Australia.

**Adelaide Women's and Children's Hospital – Metabolic Clinic**

The Metabolic Clinic at the Women's and Children's hospital in Adelaide, aims to make children and adults with metabolic problems as healthy as they can be, treating each person as an individual, but part of a family and society. The clinic works in partnership with families to provide the best possible care.

The Clinic provides a multidisciplinary service caring for children and adults who are born with problems caused by missing enzymes affecting their metabolism, and also with children and adults whose doctors suspect they might have a problem. The Clinic looks after most of the children in South Australia who have problems picked up by the Newborn Screening Test.

The Clinic is headed up by Dr Drago Bratkovic and has a number of skilled specialists including metabolic doctors, dietitians, psychologists, social workers and nurses who have been trained to look after people with metabolic disorders. Dr David Ketteridge is a Staff Specialist Paediatrician and Metabolic Physician at the Women's and Children's Hospital and works part time in the Metabolic Clinic. Dr Ketteridge will be the Principal Investigator for Paradigm's Pilot Study.

## Eligibility for PSA

- Important medicinal products, such as medicinal products for oncology, anti-infectives, rare diseases, the paediatric population, and cardiovascular disease.
- For indications lacking development guidelines, or if guidelines do exist, those for which EMA's and FDA's guidelines differ significantly.
- Products with significant clinical safety, animal toxicology, or unique manufacturing concerns.

## Background on MPS

The mucopolysaccharidoses (MPS) are a family of Orphan Diseases. The cumulative rate for all types of MPS is around 3.5 in 100,000 live births and generally the patients present in one of three ways:

1. As a dysmorphic syndrome (MPS IH, MPS II, MPS VI) often with early onset middle ear disease, deafness, or upper airways obstruction.

2. With learning difficulties, behavioural disturbance and dementia and mild somatic abnormalities (MPS III).
3. As a severe bone dysplasia (MPS IV).

**MPS VI** is recognized as an orphan designation, and classified as a rare autosomal recessive, inherited lysosomal storage disorder caused by a deficiency of N- acetylgalactosamine 4–sulfatase, leading to accumulation of glycosaminoglycans (GAGs) in the lysosomes and physical manifestations.

Current treatment for MPS patients includes Enzyme Replacement Therapy (ERT) which acts to reduce non-neurological symptoms and pain. MPS patients undergoing approved ERT however, continue to report ongoing stiffness, pain, inflammation, and heart and airway soft tissue manifestations. **The current standards of care are not adequate in treating pain** associated with joint inflammation and musculoskeletal issues and these drugs currently equate to a market size of around **US$1.4b per annum, with** BioMarin's ERT treatments costing US$300k – US$600k p.a.

In November 2018, Paradigm in-licensed the MPS indication from the Icahn School of Medicine at Mount Sinai, New York.

## About Injectable PPS (iPPS).

Injectable PPS (iPPS) is not currently registered in Australia, but it is was previously registered in four of the seven major global pharmaceutical markets. In those European markets, iPPS is registered as an antithrombotic agent. In Australia, iPPS for human use is not currently available for sale.

Authorised for release by Paul Rennie, CEO and Interim Chairman.

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To learn more please visit: www.paradigmbiopharma.com

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