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MPS Clinical Program Update and Paradigm to Present at the International Conference on Lysosomal Diseases

KEY HIGHLIGHTS

- Paradigm has been invited to present results from the mucopolysaccharidosis (**MPS**) program, with an oral presentation at the XVII International Conference on Lysosomal Diseases (**ICLD 2023**), to be held in Sydney, Australia, February 20-21, 2023.
- Dr Drago Bratkovic, Head of the Metabolic Clinic at the Adelaide Women's and Children's Hospital, will present the research entitled: *Pentosan Polysulfate Sodium: A Potential Treatment to Improve Bone and Joint Manifestations of Mucopolysaccharidosis I*.
- Three of the four subjects included in Paradigm's open-label Phase 2 trial of pentosan polysulfate sodium (**PPS**) in MPS-I have completed the 48-week study, with a 6-month treatment extension available.
- Preliminary data from the MPS-I study were previously presented at 14th International Congress of Inborn Errors of Metabolism in Sydney in 2022 and indicated favourable clinical responses and overall tolerance to PPS.
- In Paradigm's **MPS-VI** phase 2 trial based in Brazil, 50% of planned number of subjects have been recruited to the 24-week study comparing PPS to placebo in a blinded, randomised and controlled trial.
- The Safety Monitoring Physician for the MPS-VI study confirmed successful evaluation of subjects aged 16 and above and the study is now scheduled to assess PPS in two younger cohorts (9 to 16 years, then following another safety review, 5 to 9 years).
- During the Bio International Partnering conference in June 2022, Paradigm saw significant interest in its rare disease clinical development program. Paradigm is currently exploring strategic partnerships to progress current and future clinical studies to further evaluate PPS as a treatment to address the critical unmet need in MPS patients.

Paradigm Biopharmaceuticals Ltd (ASX: PAR) ("Paradigm" or "the Company"), a late-stage drug development company, is pleased to announce that it is scheduled to present data from the open-label phase 2 study of pentosan polysulfate sodium (PPS) for mucopolysaccharidosis type I (**MPS-I**), and an update on the ongoing multi-centre double-blind randomised phase 2 study comparing PPS to placebo in mucopolysaccharidosis type VI (**MPS-VI**) patients as an oral presentation at the 2023 ICLD meeting.

The mucopolysaccharidoses and related disorders belong to a group of more than 40 inherited lysosomal storage diseases. Lysosomes are the recycling centres of all cells that break down excess or worn-out cell parts with their digestive enzymes.

Mucopolysaccharidoses disorders are due to errors with one of the enzymes that break down and recycle glycosaminoglycans (**GAGs**), previously known as mucopolysaccharides. As these waste products cannot be eliminated, they accumulate within the lysosomes of virtually every type of cell in the body, causing cells, tissues, and organs to function abnormally, leading to progressive damage. The heart, bones, joints, respiratory system, and central nervous system, including cognitive function, may eventually be affected. In most cases, symptoms are not apparent at birth, but emerge gradually as a result of defective lysosomal storage and resulting cell damage over time [1,2]. Eleven different types of mucopolysaccharidosis have been described, where each is the result of a deficiency in one of the enzymes in the glycosaminoglycan degradation pathway.

Mucopolysaccharidosis type I

Mucopolysaccharidosis type I is a relentlessly progressive and potentially fatal rare genetic disorder with a spectrum of disease. It is caused by reduction or absence in the amount of enzyme responsible for the catabolism (break down) of glycosaminoglycans, resulting in the progressive GAG accumulation in tissues. The disorder causes problems with neurological, skeletal, and cardiovascular development.

There is no cure and children born with the most severe form of MPS-I do not typically survive beyond 10 years of age, without treatment. Current standard treatments include bone marrow transplant and enzyme replacement therapy to address the underlying cause of the disease.

MPS-I open-label trial

Paradigm is partnering with the Adelaide Women and Children's Hospital, South Australia for a study evaluating PPS as an adjunctive therapy to enzyme replacement therapy and/or haematopoietic stem cell transplantation in an open-label, single-centre, phase 2 trial. The primary aim of the study is to evaluate safety and tolerability of PPS over an initial 48-week period, with a 6-month treatment extension available, in patients treated with the current standard of care. Secondary and exploratory objectives include examining the effects of PPS on pain, function, and quality of life, pharmacokinetics, biomarkers, and inflammatory processes.

Four patients with this rare disease have been enrolled, and three have completed the 48-week treatment regimen with no serious adverse events reported to date. Interim results presented at the 14th International Congress of Inborn Errors of Metabolism in Sydney (2022) indicated an overall trend toward providing meaningful improvements in pain, function, activities of daily living, and overall improvement in quality of life [3]. PPS was well tolerated at weekly doses of 0.75 and 1.5 mg/kg for 47 weeks.

The data from the clinical trial participants treated to date is due to be presented at ICLD 2023 to be held in Sydney, Australia, February 20-21, 2023, by Dr Drago Bratkovic, Head of the Metabolic Clinic at the Adelaide Women and Children's hospital. The presentation of the research is titled: *Pentosan Polysulfate Sodium: A Potential Treatment to Improve Bone and Joint Manifestations of Mucopolysaccharidosis I*. The presentation will report on the safety and effect of pentosan polysulfate sodium in MPS-1 subjects along with clinical data including the clinical endpoints of pain, joint function, activities of daily living and biomarkers of disease.

Paradigm's Global Head of Safety and Head of the MPS program, Dr. Michael Imperiale, said "Current MPS therapies are essential for MPS patients, however, they don't provide relief from the daily pain and discomfort caused by their disorders. We are very excited by the global recognition of Paradigm's clinical development in this rare disease and the opportunity to present the exciting work we are undertaking at the International Conference on Lysosomal Diseases early next year".

Mucopolysaccharidosis type VI

Mucopolysaccharidosis type VI, also known as Maroteaux-Lamy syndrome, is a rare autosomal recessive lysosomal storage disorder that affects between 0.36 and 1.30 of every 100,000 live births[(4)]. It results in the development of multisystem clinical manifestations. Mucopolysaccharidosis type VI ranges from very slowly to rapidly progressing disease, depending on the specific disease-causing mutation.

Current treatments for MPS VI patients include enzyme replacement therapy, however MPS-VI patients undergoing this therapy continue to report ongoing stiffness, pain, and inflammation. The current standards of care are not adequate in treating the pain associated with joint inflammation and musculoskeletal issues.

MPS-VI multi-centre double-blinded phase 2 trial

Brazil has one of the highest rates of MPS-VI and researchers there are evaluating the use of Paradigm's PPS to treat patients with MPS-VI in a Phase 2 study. The study is a randomized, double blind, placebo-controlled study to evaluate the safety and tolerability of PPS in patients with MPS-VI. According to the study protocol, approximately 12 patients will be randomised 2:1 to receive PPS or placebo. Participants are dosed weekly for 24-weeks with the primary endpoint being safety. The secondary endpoints are improvements in pain and function. The study is the largest of its kind in the world and has attracted the interest of medical researchers and MPS patient advocacy groups globally.

To date, three adult subjects have been enrolled in the study and fifty-two weeks of cumulative data across the subjects have been assessed. Under the clinical protocol, a mandated safety review has been completed with no serious adverse events reported. This is a key milestone for the phase 2 study, which now allows the inclusion of subjects aged between ages of 9 to 16 years to assess the safety and tolerability of PPS among paediatric populations. An additional safety review will be completed once 3 patients in this age group have been enrolled and reach the specified timepoint.

A positive additional safety review will support the inclusion of subjects in the 5- to 9-year-old age group. These additional age groups are highly relevant to future potential therapeutic registration as the disease is detected and can manifest early in children and adolescents. Additionally, a 5-year extension program is being offered to subjects who, after completion of the trial, are deemed by their physician to benefit from ongoing treatment per local regulatory requirements.

Paradigm's CEO, Marco Polizzi, said "Alongside our robust osteoarthritis clinical program, Paradigm is proud to work with specialists in the field of lysosomal storage diseases to potentially enable MPS sufferers to function more easily in their day-to-day activities. We are continuing discussions to progress the development of PPS for patients with MPS and believe that this data will contribute to planning and design for the

registration of injectable PPS as an adjunctive therapeutic option for patients with MPS-I and MPS-VI."

Dr Donna Skerrett (Chief Medical Officer) and Dr Michael Imperiale (Global Head of Safety and Head of MPS) attended the BIO International partnering conference that was held in June in San Diego. Dr Skerrett delivered a presentation on Paradigm's clinical development program and with Dr Imperiale undertook many 1 on 1 meetings with potential partner companies. During the conference Paradigm saw significant interest in its rare disease clinical development program. Paradigm is currently exploring strategic partnerships to progress current and future clinical studies to further evaluate PPS as a treatment to address the critical unmet need of ongoing musculoskeletal symptoms in this rare patient population.

About Paradigm Biopharmaceuticals

Paradigm Biopharmaceuticals LTD (ASX: PAR) is a late-stage drug development company whose mission is to develop and commercialise Pentosan Polysulfate Sodium for the treatment of pain associated with musculoskeletal disorders driven by injury, inflammation, aging, degenerative disease, infection, or genetic predisposition. Paradigm is also exploring proof-of-concept studies for the use of PPS in respiratory and heart failure indications.

Forward Looking Statements

This Company announcement contains forward-looking statements, including statements regarding anticipated commencement dates or completions dates of preclinical or clinical trials, regulatory developments and regulatory approval. These forward-looking statements are not guarantees or predictions of future performance, and involve known and unknown risks, uncertainties and other factors, many of which are beyond our control, and which may cause actual results to differ materially from those expressed in the statements contained in this presentation. Readers are cautioned not to put undue reliance on forward-looking statements.

References:

1. Kobayashi H. Recent trends in mucopolysaccharidosis research. J Hum Genet. 2019 Feb;64(2):127–37.

2. Peters H, Ellaway C, Nicholls K, Reardon K, Szer J. Treatable lysosomal storage diseases in the advent of disease-specific therapy. Intern Med J. 2020 Nov;50 Suppl 4:5–27.

3. ASX Release 23rd November 2021: Positive interim data from phase 2 rare disease trial presented at international medical congress.

4. Muenzer J. Overview of the mucopolysaccharidoses. Rheumatology. 2011 Dec 1;50(suppl 5):v4–12.

Authorised for release by the Paradigm Board of Directors.

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