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Paradigm Achieves Primary Endpoint in Phase 2 Multi-centre MPS VI Randomised Controlled Clinical Trial

KEY HIGHLIGHTS

- **Primary Endpoint of Safety achieved:** once weekly iPPS treatment for 24 weeks well-tolerated in MPS VI participants 5 years old and over.
- **Improvement in Pain Assessments**: MPS VI participants reported improvements in PROMIS and VAS pain assessments from baseline following 24 weeks of iPPS treatment.
- **Functional Improvement**: Participants receiving iPPS treatment demonstrated functional improvement in the 9-hole peg test assessment.
- **Improved Disability Index Score**: Clinically meaningful improvements in childhood health assessment questionnaire (**CHAQ**) disability index scores following iPPS treatment.
- Paradigm's MPS program has received Orphan Drug Designation status in the US and EU for MPS-I and MPS-VI.

Paradigm Biopharmaceuticals Ltd (ASX: PAR) ("Paradigm" or "the Company"), a late-stage drug development company focused on delivering new therapies to address unmet medical needs, is pleased to announce the multi-centre double-blind randomised phase 2 clinical trial PARA_MPSVI_001, has successfully met the primary endpoint. The phase 2 trial was designed to evaluate the use of Paradigm's injectable pentosan polysulfate sodium (**iPPS**) compared to placebo in 13 participants (iPPS n=8, placebo n=5) with the rare inherited disorder mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome) (**MPS VI**).

Current treatments for MPS VI include disease-modifying enzyme replacement therapy (**ERT**) and supportive medical and surgical interventions. All participants in the phase 2 study were on ERT for over 1 year and at stable dose for 3 months prior to baseline. Despite available therapies there remains an unmet need for MPS VI patients treated with enzyme replacement therapy who continue to experience musculoskeletal pain and symptoms that reduce their quality of life [1,2,3]. iPPS presents the first drug therapy targeted specifically at complications associated with MPS including pain and arthropathy in the MPS VI patient population.

Paradigm's Managing Director, Mr Paul Rennie, said "*Paradigm is pleased with the initial analysis of this first phase 2 clinical trial evaluating iPPS compared to placebo in MPS VI sufferers. To achieve the primary endpoint of the study of iPPS dosed weekly for 24-weeks is safe and well tolerated in MPS VI patients 5 years old and over and to demonstrated improvements in pain and function measures is a positive outcome for the*

Company. Current MPS therapies such as ERT are essential for MPS patients, however, they don't provide relief from the daily pain and discomfort caused by their disorders. Alongside our robust osteoarthritis clinical program, Paradigm believes the data produced in both the MPS I and in this phase 2 study with MPS VI participants will form important data packages for discussions with our key opinion leaders and ongoing commercial activities, to progress the planning and design for the registration of injectable PPS as an adjunctive therapeutic option for patients with MPS I and MPS VI".

Study Design

The primary objective of this phase 2 study was to evaluate the safety and tolerability of iPPS in participants with MPS VI at 6, 12, and 24 weeks. Participants were randomised to receive blinded subcutaneous iPPS or placebo (2:1 ratio) injections, weekly for 24 weeks, with follow up 1 week after the last injection. Participants were dosed according to age (Figure 1).

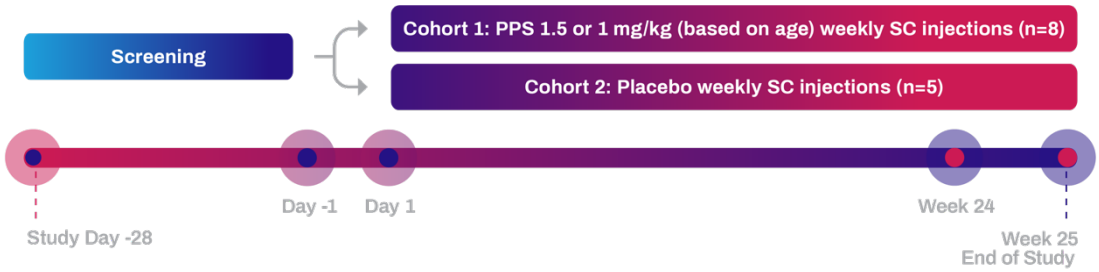

Figure 1: PARA_MPSVI_001 phase 2 study design.

Paradigm assessed a number of key secondary and exploratory endpoints to identify meaningful endpoints to best measure patient outcomes following iPPS treatment, including the effect of iPPS on:

- Pain and function (mobility and fine motor skills);
- Urinary GAG levels;
- Pharmacokinetics; and
- Quality of Life, activities of daily living, participant/parent global impression of response to therapy.

Top-Line Results

Primary Endpoint – Safety

This is the first placebo-controlled phase 2 study evaluating the safety and tolerability of iPPS in participants with the rare lysosomal disorder MPS VI. Phase 2 enrollment was completed for PARA_MPSVI_001 with 13 (6 male, 7 female) participants enrolled. There were 8 participants 5 to <16 years of age and 5 participants ≥16 years of age (Figure 2). iPPS was well-tolerated and all adverse events were mild to moderate. The majority of adverse events were associated with injection site reactions. No adverse events led to discontinuation of the study treatment, nor were there any serious adverse events or adverse events of special interest (thrombocytopenia, changes in retinal examination, relevant changes in cortisol levels). Analysis of this phase 2 study demonstrates that iPPS is a safe adjunctive therapy to ERT for the continual joint pain, stiffness and functional disability associated with MPS VI.

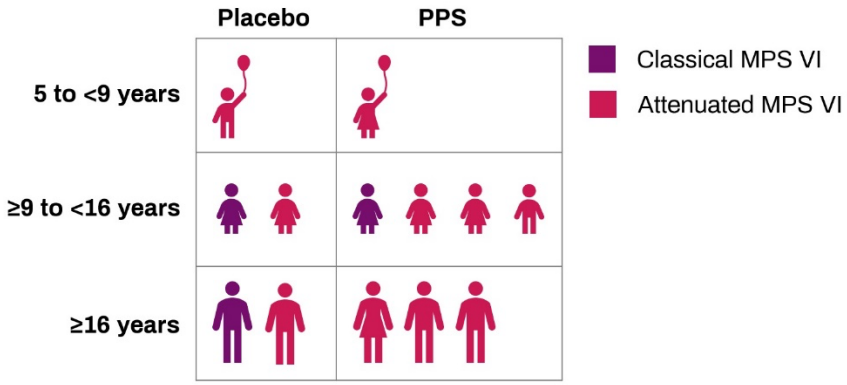

Figure 2: Participant age group, sex, and disease severity.

Secondary Endpoints

Multiple clinical endpoints were explored to identify relevant responses for future clinical trial development.

Pain Assessment

The PROMIS (Patient-Reported Outcomes Measurement Information System) pain assessment is a valuable tool in evaluating and understanding pain experienced by individuals with MPS VI. The PROMIS pain assessment specifically caters to the unique pain experiences of MPS VI patients by utilising patient-reported outcomes. This comprehensive tool encompasses a range of measures such as intensity, interference, and behaviour, allowing a holistic understanding of the impact of pain on patients' lives.

An improvement in PROMIS pain interference is indicated by a lower score. An improvement in PROMIS pain interference was greater in the iPPS-treated group compared to placebo at 25 weeks.

The Visual Analog Scale (**VAS**) was also utilised during the phase 2 clinical trial to assess changes in pain from baseline following iPPS treatment compared to placebo. The VAS is a subjective measure that allows individuals to express their pain levels by indicating a point on a continuum, typically a 10-centimeter line ranging from "no pain" to "worst pain imaginable." For MPS VI patients who may have difficulty communicating their pain experiences verbally, the VAS provides a visual representation that aids healthcare professionals in understanding and quantifying their pain.

Results from the phase 2 trial indicate overall average VAS pain calculated over 7 days at baseline and after 25 weeks showed improvement in both iPPS and placebo groups.

Functional Assessment

The NIH Toolbox 9-hole peg test (**9-HPT**) assessment plays a crucial role in evaluating motor function and dexterity in individuals with MPS VI, as it aids in monitoring disease progression and assessing the effectiveness of therapies.

The 9-HPT involves manipulating pegs within a pegboard as quickly and accurately as possible, providing a quantitative measure of upper extremity function and fine motor control. Results are reported for both the dominant hand and the non-dominant hand.

Additionally, the NIH Toolbox 9-HPT offers the advantage of being a standardised and easily administered test, allowing for consistent and comparable assessments across different clinical settings. This contributes to the establishment of a baseline for motor function and facilitates longitudinal monitoring of individuals with MPS VI.

Participants receiving iPPS in the phase 2 clinical trial demonstrated greater improvement than placebo in the 9-hole peg test from baseline to week 25 on at least one hand.

Global impression of change & childhood health disability assessment

Patient global impression of change (PGIC) was self-reported or reported by parent proxy on a scale from 1–5, where 1 is much better and 5 is much worse. The average response at the end of the study period was 2 for the PPS group, and 1 for the placebo group. There were no observable differences between iPPS and placebo for the PGIC measure.

The childhood health assessment questionnaire (**CHAQ**) disability index score, where 0 = no disability and 3 = very severe disability, demonstrated a response to treatment. When compared to baseline, the change in disability score for the PPS group was -0.350 versus placebo -0.125, where a minimally clinically important difference for improvement is -0.188.

Urinary Glycosaminoglycan (GAG) Measurements

Excess GAG levels in the urine reflect a build-up of GAGs in the tissues, a pathogenic hallmark of MPS disease. Enzyme replacement therapy has shown promise in reducing urinary GAG excretion and ameliorating some clinical manifestations of MPS VI. Prior studies have shown that iPPS may reduce urinary GAGs in MPS I patients by an unknown mechanism. Hennermann et al. (2016) found that iPPS significantly reduced urinary GAG excretion at doses of 1 and 2 mg/kg in four participants with MPS I (1).

In this phase 2 study, urinary GAGs were established at baseline and measured again at week 25 using the DMB spectrophotometric method (DMB/creatinine ratio). The DMB method is commonly used for urinary GAG analysis due to its technical simplicity, low cost, and precise quantitative results (2). Although GAG levels changed slightly from baseline in both placebo and iPPS groups at 25 weeks, the values generally fell within the normal range for healthy controls as established in the literature (3), indicating that neither the iPPS treatment arm nor placebo contributed any additional effect to GAG levels over ERT.

Next Steps

Paradigm has now completed clinical studies for MPS I and VI with strong data sets and meaningful endpoints identified to progress the clinical development of iPPS as an adjunctive therapy with a commercial partner.

The data produced in this study is being presented today as a moderated poster presentation at the 20th Annual WORLDSymposim, the largest international scientific meeting dedicated to advancing lysosomal disease research. The poster will be available on the Paradigm website at the conclusion of the conference.

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

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, 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 (4,5). 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.

Brazil has one of the highest rates of MPS-VI globally (6) and researchers there are evaluating the use of Paradigm's PPS to treat MPS-VI patients in a phase 2 study. The study is a randomised, double-blind, placebo-controlled study to evaluate the safety and tolerability of PPS in patients with MPS-VI. According to the study protocol, 13 patients were randomised 2:1 to receive iPPS or placebo. Participants dosed weekly for 24 weeks with the primary endpoint being safety. The secondary endpoints are pharmacokinetics, glycosaminoglycans changes and improvements in pain and function following iPPS treatment compared to placebo.

The Principal Investigator for the Phase 2 study is Dr. Roberto Giugliani, MD, PhD, MSc. Dr. Giugliani is a Professor at the Department of Genetics of the Federal University of Rio Grande do Sul and Chief of the Medical Genetics Service of Hospital de Clinicas de Porto Alegre, Brazil. Dr. Giugliani was past President of the Brazilian Society of Clinical Genetics, President of the Latin American Society of Inborn Errors of Metabolism and Neonatal Screening and President of the Latin American Network of Human Genetics.

About iPPS

IPPS is a non-opioid subcutaneous injectable with the potential to treat residual musculoskeletal symptoms in MPS as an adjunct therapy to current standards of care. Previous studies have shown iPPS improves pain and function in patients with MPS I, MPS II, and MPS VI (1,7,8).

About Paradigm Biopharmaceuticals

Paradigm Biopharmaceuticals Ltd. (ASX:PAR) is a late-stage drug development company driven by a purpose to improve patients' health and quality of life by discovering, developing, and delivering pharmaceutical therapies. Paradigm's current focus is developing injectable (subcutaneous) pentosan polysulfate sodium (**iPPS**) for the treatment of diseases where inflammation plays a major pathogenic role, indicating a need for the anti-inflammatory and tissue regenerative properties of iPPS, such as in osteoarthritis (phase 3) and mucopolysaccharidosis (phase 2).

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.

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Authorised for release by the Paradigm Board of Directors.

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