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Phase 2 MPS VI Clinical Trial Completes Enrolment

KEY HIGHLIGHTS

- Paradigm's MPS VI phase 2 trial based in Brazil has now completed enrolment of participants. This placebo-controlled, double-blind, and randomised 24-week study compares iPPS to placebo in participants with the ultra-rare disease MPS VI.
- The primary objective of the study is to evaluate the safety and tolerability of iPPS in subjects with MPS VI at 6, 12, and 24 weeks.
- Secondary endpoints include iPPS effects on pain, function and glycosaminoglycan (**GAG**) levels at 6, 12, and 24 weeks.
- The safety monitoring physician has completed multiple protocol-mandated safety reviews allowing inclusion of subjects aged 5 and over into the study.
- Paradigm's MPS program has received Orphan Drug Designation status in the US and EU for both MPS I and MPS VI.

Paradigm Biopharmaceuticals Ltd (ASX:PAR) ("Paradigm" or "the Company"), a late-stage drug development company, is pleased to announce that the multi-centre double-blind randomised phase 2 clinical trial comparing injectable pentosan polysulfate sodium (**iPPS**) to placebo in mucopolysaccharidosis type VI (**MPS VI**) patients has completed enrolment, with the 13th and final participant, completing the screening process.

Once the data from the study is complete, Paradigm plans to meet with key regulatory bodies in jurisdictions where the MPS disease is most prevalent to determine if its phase 2 clinical data is sufficient for registration due to the high unmet medical need in this ultra-rare disease, or whether a phase 3 clinical trial is required. Paradigm's commercial strategy is to partner this indication. A commercial transaction is expected to generate non-dilutive funding for the MPS phase 3 clinical trial, should one be required.

For completeness, the MPS VI phase 2 clinical trial is a separate program from Paradigm's phase 3 clinical program relating to improvements in pain and function in people afflicted with knee osteoarthritis.

During the phase 2 MPS VI study, protocol-mandated safety reviews were conducted by the safety monitoring physician. Two separate reviews of subjects aged 16+ and 9–16 years of age have been completed with no serious adverse events reported in both cohorts, allowing for inclusion of subjects 5+ years of age into the study. Early therapeutic intervention to improve symptoms is critical in this population of MPS VI sufferers, who continue to experience joint pain and stiffness that limits their mobility and function despite enzyme replacement therapy

(**ERT**). 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.

Paradigm's Global Head of Safety and Head of the MPS program, Dr. Michael Imperiale, said "*Enrolling thirteen participants in a blinded controlled study in this rare disease is a fantastic milestone for Paradigm. Paradigm and the key opinion leaders associated with this study are encouraged about the potential of iPPS addressing this critical unmet medical need in the MPS community. We look forward to the completion of the study and providing further updates as the study reaches completion*".

Trial Design

Brazil has one of the highest rates of MPS VI. The phase 2, randomised, double-blind, placebo-controlled study is evaluating the safety and tolerability of iPPS in treating subjects with MPS VI who exhibit pain and functional deficiency due to musculoskeletal symptoms associated with the underlying disease. All MPS VI subjects either have received or will receive current standard of care, ERT, throughout the study. Subjects either have or will receive iPPS at a dose of either 1.5 mg/kg (≥9 years of age) or 1.0 mg/kg (<9 years of age) or placebo by subcutaneous injection once weekly for 24 weeks. The phase 2 clinical trial was initially targeting up to 12 MPS VI patients to participate in the study, however as screening was being finalised for the last participant in the study, an additional patient completed the screening process and as a result Paradigm has allowed a 13th patient into the study.

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 Clínicas 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.

Study Endpoints

The primary objective of the phase 2 study is to evaluate the safety and tolerability of iPPS in subjects with MPS VI at 6, 12, and 24 weeks.

Following completion for all study participants of the 24-week treatment period, Paradigm will assess a number of key secondary and exploratory endpoints, including effect of iPPS on:

- Pain and function (mobility);
- Urinary GAG levels;
- Walking-related pain;
- Quality of Life, activities of daily living, subject/parent global impression of response to therapy; and
- Pulmonary function.

Mucopolysaccharidosis type VI

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 cell type within 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 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[3]. It results in the development of multisystem clinical manifestations. Mucopolysaccharidosis type VI disorders range from very slowly to rapidly progressing, depending on the specific disease-causing mutation.

Current treatments for MPS VI patients include ERT, 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.

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.

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. 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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