PARADIGM BIOPHARMACEUTICALS LTD

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PARADIGM'S ORPHAN PHASE 2/3 CLINICAL PROGRAM PROGRESSES

HIGHLIGHTS

- Paradigm conducted a satellite meeting on 3-4th February at the "*World Symposium 2019, 15th Annual Research Meeting on Lysosomal Disease Research*" in Orlando, USA to discuss plans for its upcoming randomised double-blind placebo-controlled multicentred multinational Phase 2/3 Mucopolysaccharidosis (MPS) clinical trial.
- The clinical trial discussion panel included world renowned key opinion leaders (KOLs) in Lysosomal storage Disease and MPS from USA, UK, Germany and Japan, members of Paradigm's clinical team and the manufacturer of PPS - bene PharmaChem.
- The outcome of the panel discussion addressed the unmet medical need in MPS types with musculoskeletal pain and dysfunction and lead to preliminary discussions around the proposed clinical trial study design and site locations for the multi-centre study across the USA, Australia and Europe.
- Paradigm plans to submit an Investigational New Drug (IND) application to the US FDA for the pivotal Phase 2/3 MPS trial in Q2 CY2019.
- Paradigm's recently acquired Phase 2a MPS clinical data was further validated by paper presented by Dr Furujo at the WORLD symposium that demonstrated injectable pentosan polysulfate sodium (iPPS) has a positive impact on pain and physical function in patients with MPS types I, II and VI (see clinical data below).
- Australian clinicians will submit applications to the Therapeutic Goods Administration (TGA) Special Access Scheme (SAS) for the treatment of MPS and other lysosomal storage diseased patients as additional real-world evidence in parallel to the clinical trial.
- An orphan indication with market exclusivity and high profit margins.

Paradigm Biopharmaceuticals Ltd (ASX: PAR) is pleased to announce it has begun discussions with International Key Opinion Leaders (KOL's) for the MPS clinical trial design and site selection. After hosting a satellite symposium with KOL's and clinicians in the field of MPS and lysosomal storage diseases the company can report on a number of developments and findings from the event.

MPS is a progressive rare disease that has a severe unmet need. 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. The evidence presented from clinicians regarding the need for a product to assist with pain associated with musculoskeletal problems associated with MPS was very relevant to Paradigm's proposed forthcoming MPS clinical trial.

The pioneering pre-clinical work on the effects of PPS in animal models of MPS presented by Professors Schuchman and Calogera (Mt Sinai) defined the rationale for PPS in human clinical trials. Their data demonstrated that PPS was able to reduce the levels of Glycosaminoglycans (GAGs),

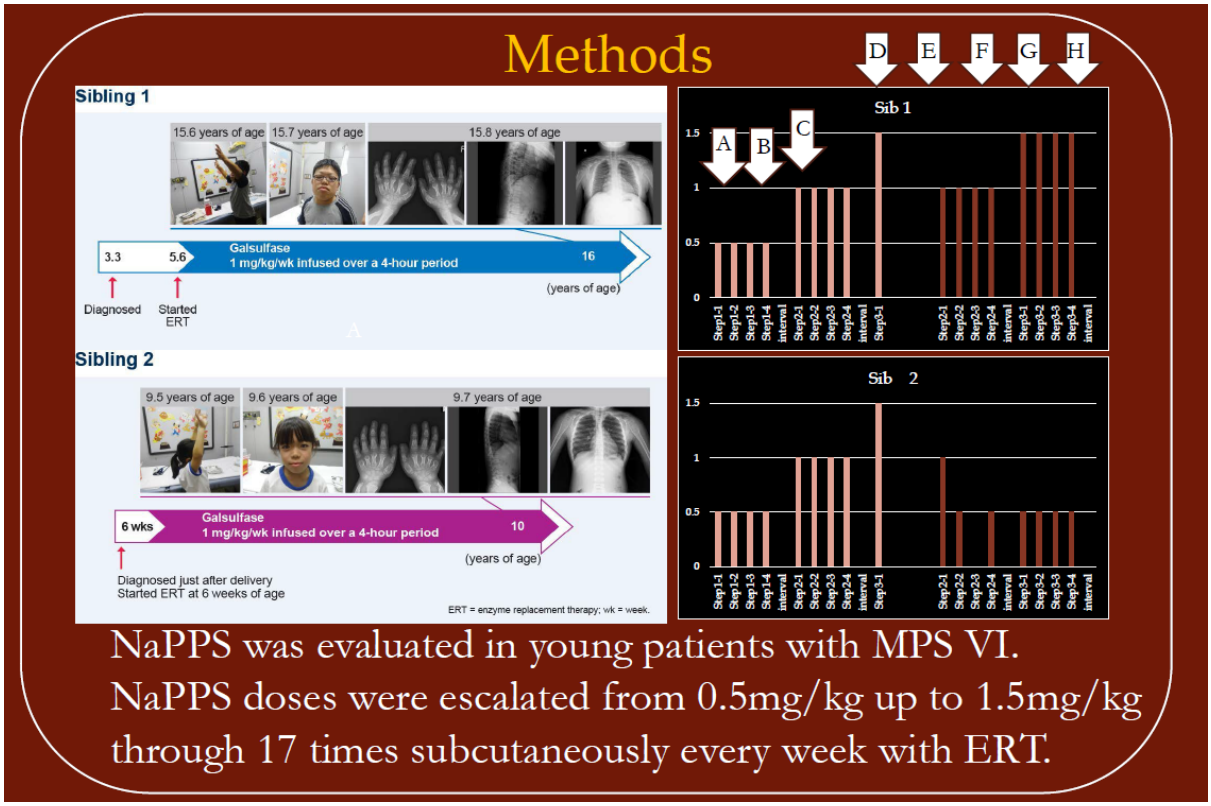
which accumulate as a result of enzyme deficiency in cells and tissues leading to joint pain and dysfunction. In addition, the anti-inflammatory actions PPS inhibited inflammatory responses due to TLR-4 signalling by the accumulated GAGs.

While Enzyme Replacement Therapy (ERT) and Bone Marrow Transplantation (BMT) are current standard of care, patients still suffer from joint pain and dysfunction, which remains a significant unmet medical need.

MPS RESULTS – DR FURUJO

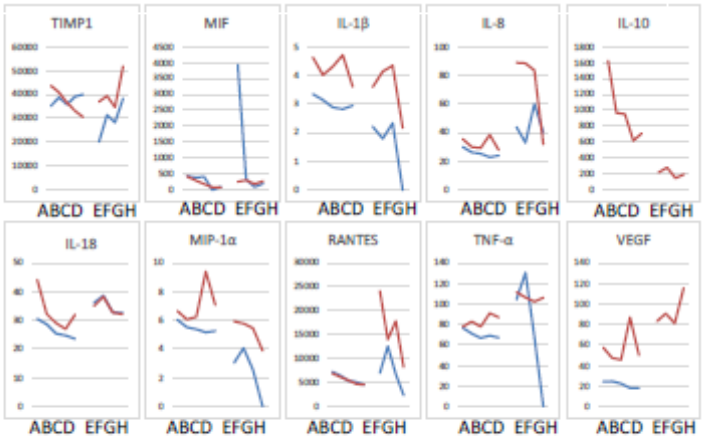
The findings presented by Dr Furujo at the WORLD Symposium further demonstrate that iPPS could have a positive impact on pain and physical function in patients suffering from MPS while maintaining an excellent safety profile with no serious adverse events reported.

The below are sections from Dr Furujo's poster and these show an escalating dosage of iPPS used in conjunction with current standard of care (ERT) in siblings suffering with MPS VI.

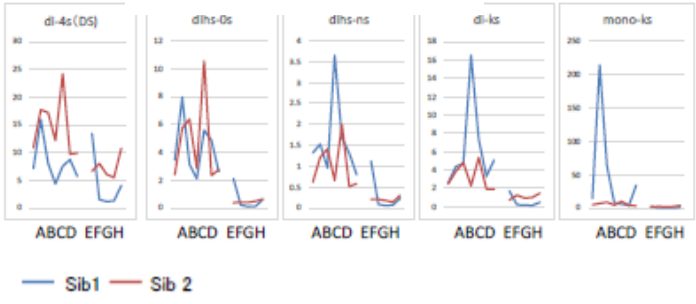


The results below show that there was a reduction in the inflammatory markers (Graph 1) and urinary GAG levels (Graph 2) with no serious adverse events.

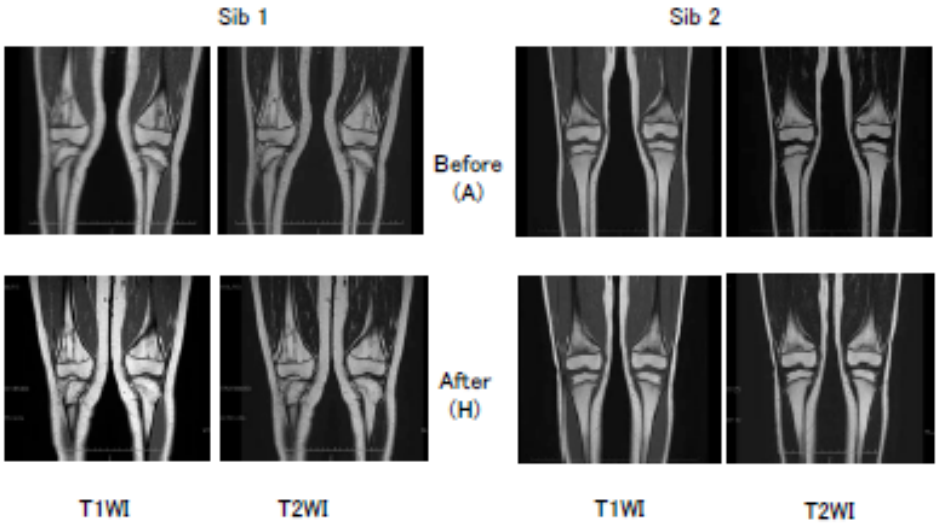
1. Inflammatory Markers



2. Urinary GAG Levels

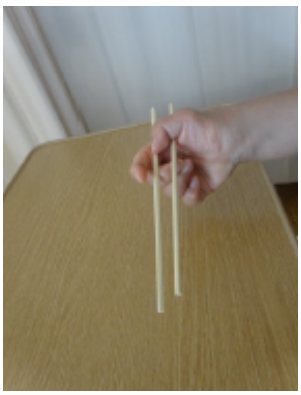


3. Knee MRI



Conclusion - The preliminary findings of this open label study were encouraging, demonstrating a reduction in the inflammatory markers and urinary GAG levels with visible signs of improved joint function and pain reduction.

As demonstrated below, ongoing assessment of the physical improvement in a 50yo female with MPS 1. The subject is now able to use chop-sticks and kneel, physical tasks which had previously been very painful or not possible.



MPS RESULTS – PARADIGM/HENNERMANN et al.

Included in Paradigm's MPS in-licensing agreement (November 2018) was valuable Phase 2a MPS clinical trial data (conducted by Hennermann et al[1]). **The results from this clinical trial were consistent with Dr Furujo's findings above.**

Study Design

The goals of the study were to investigate, primarily the safety and secondary the clinical effects concerning mobility and pain, of PPS treatment in MPS I patients.

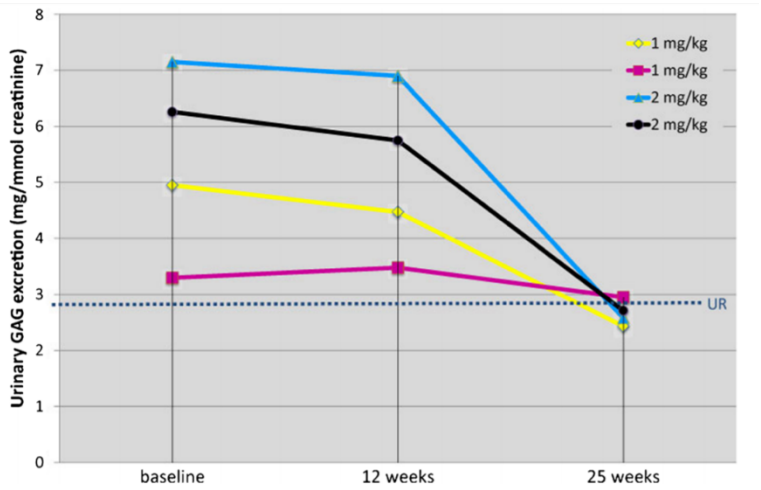
Four MPS I patients were included in the study. PPS was applied subcutaneously in two patients with 1 mg/kg and in two patients with 2 mg/kg, weekly for 12 weeks and then biweekly for 12 weeks.

[1] https://www.ncbi.nlm.nih.gov/pubmed/27590017

Results

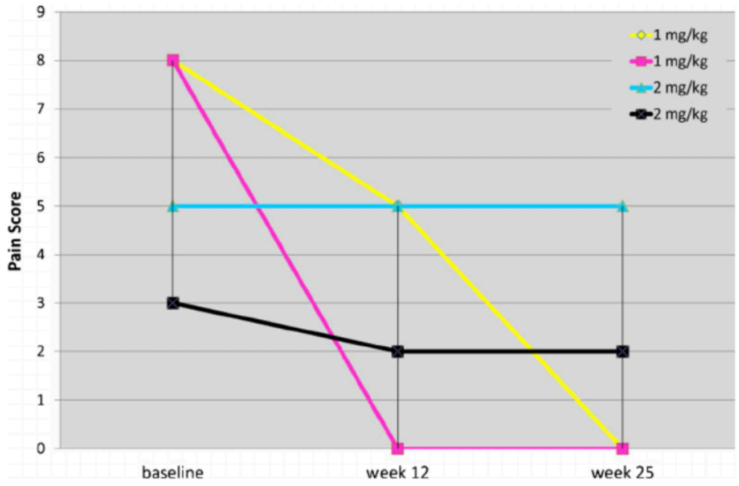
Safety – The 24-week treatment with PPS was well tolerated by all patients

Urinary GAG concentrations – Reduced from 4.13 ± 1.17 at baseline to 2.69 ± 0.36 mg/mmol creatinine after 24-week treatment with 1 mg/kg PPS, and from 6.71 ± 0.62 to 2.65 ± 0.09 mg/mmol creatine with 2 mg/kg PPS.



Range of Motion – An improvement in range of motion was noted in three out of four patients.

Pain – The pain intensity score was reduced from 4.5 ± 1.77 at baseline to 1.8 ± 0.47 after 24-week treatment with 1mg/kg PPS; patients with 2 mg/kg PPS already had minimal pain at the start of the study.



Conclusion of the trial

PPS treatment was well tolerated (safe) and resulted in a significant reduction of urinary GAG excretion and in an improvement of joint and mobility and pain.

Paradigm views the safety and efficacy shown in these two MPS clinical trials as particularly important because it shows i) the very strong safety profile of repeat long-term iPPS administration in a sick patient population and ii) the large reduction in pain and improvement in motion, thus indicating iPPS is having a real benefit for the patients receiving the treatment.

Of additional commercial importance, is that iPPS could be a very good adjunct/combination therapy for existing ERT treatments, enhancing the attractiveness of this program to large pharma companies currently serving the MPS market with ERT treatments.

UPCOMING PHASE 2/3 CLINICAL TRIAL

Paradigm is confident that a single successful Phase 2/3 clinical trial will enable iPPS to be registered as a treatment for certain MPS indications. MPS is classified as an Orphan Indication/Designation in the US and EU and this should help accelerate the regulatory approval process and ultimately the time it takes for the treatment to enter the market as well as providing for a minimum 7 years (10 for EU) market exclusivity.

The panel concurred that the trial design will likely involve patients receiving ERT or BMT as standard of care and that PPS treatment be used as an adjunct therapy (i.e. therapy that is given in addition to the primary or initial therapy to maximize its effectiveness). Paradigm's clinical and regulatory team in conjunction with the KOLs will be preparing a detailed study protocol and regulatory documents for the Phase 2/3, which will be a multi-national, multi-centre trial likely incorporating centres in Australia, USA, UK and Germany.

It is anticipated these documents will be submitted to the regulatory agencies in Q2 CY2019.

COMMERCIAL OPPORTUNITY

Given the critical unmet need for new treatments, Paradigm believes iPPS could have strong commercial success in treating MPS as demonstrated from the clinical trials mentioned above. While MPS is a rare disease, the demand for such a product would likely be very strong given the evidence and advice presented in the research papers and from KOLs and clinicians at the *World Symposium 2019*. A successful clinical trial and drug registration would likely result in rapid take up of the product once commercially available and attract a premium pricing as is normally the case with orphan indications.

Big Pharma have a growing interest in orphan indications given the exclusivity from regulators and strong demand due to the critical unmet needs and attractive margins. Paradigm will continue to actively engage with potential big pharma partners on this blockbuster indication.

WHAT IS MPS?

The mucopolysaccharidoses (MPS) are a family of disorders caused by inherited defects in the catabolism of sulfated components of connective tissue known as glycosaminoglycans (GAGs). The crude cumulative rate for all types of MPS is around 3.5 in 100 000 live births[2] 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)

ABOUT PARADIGM PHARMACEUTICALS LTD

[2] https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/mucopolysaccharidosis

Paradigm Biopharmaceuticals Limited (ASX: PAR) is an ASX-listed biotechnology company focused on repurposing Pentosan Polysulfate Sodium (PPS), an FDA approved drug that has a long track record of safely treating inflammation over 60 years.

On 18 December 2018 the Company announced the successful results from their phase 2b randomised, double blind, placebo controlled multicentre trial, investigating subjects with osteoarthritis and concurrent bone marrow edema lesions (n=112). There is a global trend for safe and effective non- opioid and non-steroid pain relief for chronic disease such as osteoarthritis which presents a huge market opportunity for Paradigm's PPS treatment.

The Company is aiming to achieve Fast-Track designation and begin a phase 3 trial in the US in CY2019, both these initiatives are expected to attract significant big pharma interest.

Paradigm recently executed an Exclusive In-License Agreement for the use of iPPS in the treatment of mucopolysaccharidoses (MPS), a group of inherited lysosomal storage disorders. A key unmet medical need in this class of inherited disease is the lack of treatment of joint pain and dysfunction akin to osteoarthritis, hence the applicability of iPPS in treating these rare joint diseases. MPS is classified as an Orphan Indication/Designation in the US/EU and provides Paradigm the opportunity to serve a US$1.4bn p.a. market that is in desperate need of new cost-effective treatments.

In parallel to its clinical programs, Paradigm is pursuing a Provisional Approval for iPPS for OA pain via the Australian Therapeutic Good Administration (TGA), in addition to treating retired elite sportspeople and past NFL players via a US Expanded Access (Compassionate Use) program.

In July 2017 the Company commenced a phase 2a clinical trial to treat people recently infected with the Ross River virus. The results of this trial are also expected to be released in Q2CY2019.

The Company continues to execute on its drug repurposing strategy. The key benefits of this strategy are lower costs, accelerated development timelines and higher success rates than the standard clinical development timeline.

To learn more please visit: www.paradigmbiopharma.com

For more information, please contact

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