# Results of an Open-label, Single-Center, Clinical Study Evaluating the Safety and Tolerability of Pentosan Polysulfate Sodium in Subjects With Mucopolysaccharidosis I

P016

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## Background

### Mucopolysaccharidosis I

Mucopolysaccharidosis (MPS) I is the most common of the MPS diseases. MPS I is caused by a deficiency of the lysosomal enzyme α-L-iduronidase, which catalyzes the breakdown of the glycosaminoglycans (GAGs), dermatan sulfate (DS) and heparan sulfate (HS). The deficiency of α-L-iduronidase results in chronic and progressive accumulation of these GAGs in the lysosomes, manifesting in multiorgan dysfunction[1]. Patients with MPS I may present with coarse facial features, short stature, skeletal abnormalities, delayed growth and/or corneal clouding.
In MPS I, higher tumor necrosis factor alpha (TNF-α) levels are associated with increased pain and decreased physical function. Current disease modifying treatment approaches for MPS I include enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT). The GAG-reduction[2, 3], anti-inflammatory[4, 5], analgesic[6], and tissue remodeling properties[7, 8] of pentosan polysulfate sodium (PPS) may provide beneficial therapeutic effects in patients with MPS I.

### Etiology of MPS I

Mucopolysaccharidosis I is caused by a mutation in the α-L-iduronidase gene, resulting in a deficiency of α-L-iduronidase[9]. The α-L-iduronidase enzyme catalyzes the breakdown of the GAGs, DS and HS. The enzyme deficiency leads to progressive accumulation of DS, the primary GAG responsible for symptoms in MPS I. The widespread pathology of MPS I in various body systems is due to both the direct effects of DS and HS accumulation on cellular enlargement and dysfunction and to the indirect effects on cellular signaling[10, 11].

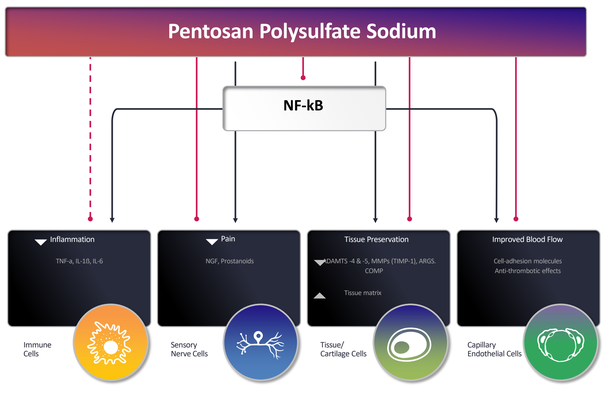
The accumulation of GAGs in the growth plate of long bones interfere with control of chondrocyte development[12]. In addition, GAG accumulation activates the Toll-like receptor-4 (TLR-4), which leads to the release of inflammatory cytokines and the proliferation of immature chrondrocytes, causing abnormal matrix formation[2]. The GAG accumulation also interferes with major cartilage and bone development signaling pathways, leading to short stature and skeletal deformities such as hip dysplasia, gibbus deformity, and kyphosis[12].

### PPS in MPS I

Pentosan polysulfate sodium is a plant-derived polysaccharide with xylose subunits which is chemically sulfated resulting in a semi-synthetic non-biologic. Preclinical and clinical evidence suggests that PPS may treat the pain and arthropathy in osteoarthritis, filling a significant unmet medical need for a safe and effective therapy.

The safety and efficacy of PPS on pain and physical function in patients with MPS I have been evaluated as an adjunctive therapy to ERT and/or HSCT.

### Figure 1. PPS Mode of Action in Patients with MPS I




### PPS Mechanisms of Action in MPS I

The key mechanisms of action of PPS that may be relevant to MPS are mediated through inhibition of NF-kB (Figure 1) resulting in:

- Reduced systemic and accumulated GAGs in multiple tissues[2, 3].
- Directly binding to the transcription factor, NF-kB, in the cytoplasm inhibiting its activation and therefore translocation into the nucleus. The inhibition of nuclear translocation of NF-kB results in the reduction of gene expression of pro-inflammatory mediators including inflammatory cytokines, IL-1β and TNF-α[4, 5].
- Reduced expression of the pain mediator nerve growth factor in osteocytes from degenerating joints[6].
- Inhibit the cartilage degrading enzymes that are related to joint dysfunction observed in MPS[7, 8].

### Study Objectives

Primary: Assessment of the safety and tolerability of PPS in subjects with MPS I.
Secondary and exploratory: Assessment of efficacy of PPS in subjects with MPS I:

- Patient reported outcomes (PROs) measuring pain, function, fatigue, quality of life.
- Physical assessments of mobility and dexterity.

## Methods

### Study Design

This was an open-label, single-center, phase 1/2 study, evaluating the effects of PPS in subjects ≥5 years of age with a diagnosis of MPS I, experiencing pain and/or arthropathy, and previously received ERT and/or HSCT.

Subjects were sequentially allocated to Cohort 1 or Cohort 2 and administered PPS subcutaneous (SC) injections once weekly to Week 12 then fortnightly to Week 48. Eligible subjects may have continued PPS administration every 2 weeks in the study extension for an additional 6 months.

### Key Eligibility Criteria

- ≥5 years of age.
- Diagnosis of MPS I.
- Experiencing pain and/or arthropathy.
- Previously received ERT and/or HSCT.

### Treatment and Follow-up

Subjects received 0.75mg/kg or 1.5mg/kg PPS weekly for Weeks 1 through 12, and every other week from Weeks 14 through 48. Assessments were conducted at Weeks 2, 6, 13, 25, 37, and 49. At the end of the 48 weeks, subjects may have entered a 6-month treatment extension.

### Assessments

#### Physical Assessments

- 2-minute walk test (2MWT).
- 6-minute walk test (6MWT).
- 9-hole peg test (9HPT).
- Gait, stair, gowers, chair (GSGC).
- Grip strength.
- Joint passive range of motion (ROM).

#### Patient-Reported Outcomes

- Pediatric, proxy, or adult Patient-Reported Outcomes Measurement Information System (PROMIS) - pain intensity, pain interference, pain behavior, fatigue, upper extremity and mobility/physical function with mobility aid short forms.
- Patient global impression of change (PGIC).
- Subjects under 18 years had parent 'proxy' questionnaires completed as well as self-assessment.

#### Safety Assessments

- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).
- Clinically significant changes from baseline in clinical laboratory data.

## Results

### Study Subjects

#### Population

- Three white, female, patients with MPS I-Hurler ages 14, 15, and 19 years, and one, white male patient aged 15 years are enrolled.

#### Baseline Characteristics

- All subjects were diagnosed at ≤2 years of age.
- All patients received HSCT ≤6 months after diagnosis.
- All patients had musculoskeletal symptoms, pain, and reduced function at study entry.
- Two subjects received the 0.75mg/kg dose and 2 subjects received the 1.5mg/kg dose of PPS.

### Study Results

#### Subject Disposition

- All 4 subjects completed treatment at Week 48 and physical assessments at Week 49.
- All 4 subjects completed the PGIC assessment at Week 49.
- Three subjects continued dosing and physical/PGIC assessments (through Week 73) in the 6-month study extension.

#### Physical Assessments

- The results of the 2MWT tended to show improved function from baseline to Week 49 in 3 subjects (8.2 - 105.1%) and the same 3 subjects showed no change or improvement (up to 51.6%) in the 6MWT from baseline to Week 49 (Figure 2).
- The results of the 2MWT tended to show improved function from baseline to Week 73 in 3 subjects (11.6% - 71.0%: Figure 2). The fourth subject did not continue in the extension study. There was a trend toward improvement in 2 subjects (9.0% and 58.1%) in the 6MWT at Week 73. The third subject was not able to walk at baseline (0 meters) in the 6MWT, therefore the % change was not able to be calculated. The absolute change at Week 73 was 368 meters (Figure 2).
- The results of the 9HPT showed improved dominant hand function (decreased time) from baseline to Week 49 in 3 subjects (8.0 - 28.6%) and improved non-dominant hand function in 3 subjects (8.0 - 28.6%; Figure 3). The results of the 9HPT showed improved dominant and non-dominant hand function from baseline to the study extension visit at Week 73 in 3 subjects (8.0%, 28.6% and 13.3%, Figure 3).
- The results of the grip strength showed improved dominant hand function from baseline to Week 49 in 3 subjects (19.4 - 80.8%) and improved non-dominant hand function in 2 subjects (38.2 - 65.9%; Figure 4).
- The results of GSGC showed improved function (decreased score) from baseline to Week 49 in all 4 subjects (8.0 - 28.6%).
- In general, subjects exhibited either improvement or no significant change in ROM on most parameters (shoulder abduction, shoulder flexion, knee extension, knee flexion).

#### Patient-Reported Outcomes

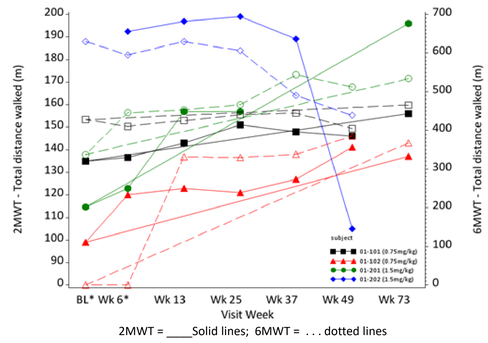
- The 3 subjects that completed the 6-month extension study (Week 73) and proxies reported "worthwhile difference" (n=1), or "made all the difference" (n=2) improvement in pain assessed by PGIC (Figure 5).
- In general, subjects exhibited either improvement or no significant change in PROMIS on most parameters.

### Study Results

#### Safety Assessments

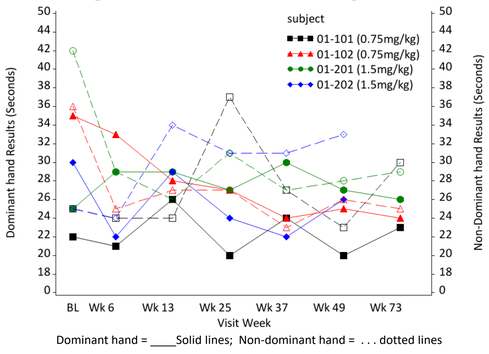
- PPS was well tolerated at doses of 0.75 and 1.5 mg/kg to 48 weeks of dosing in 4 subjects and 72 weeks of dosing in 3 subjects.
- Of the 29 TEAEs, 2 were related to PPS. One related TEAE was moderate in severity (pre-syncope) and 1 was mild in severity (injection site bruising), experienced in the same subject. All TEAEs were reported as mild or moderate in severity. There were no SAEs.
- PPS was interrupted in 1 subject due to coronavirus infection and in a second subject due to 3 TEAEs (liver function test increased, "COVID-19 symptoms", and blood creatinine phosphokinase increased). All events were unrelated to PPS treatment.
- There were no TEAEs resulting in treatment or study discontinuation through 72 weeks of dosing.

### Figure 2. Results of 2- and 6-Minute Walk Tests



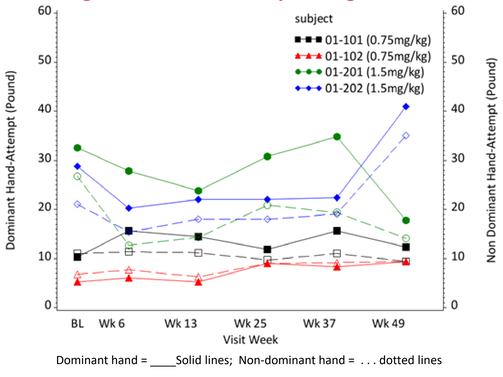

2MWT = ____Solid lines; 6MWT = . . . dotted lines

### Figure 3. Results of 9 Hole Peg Test



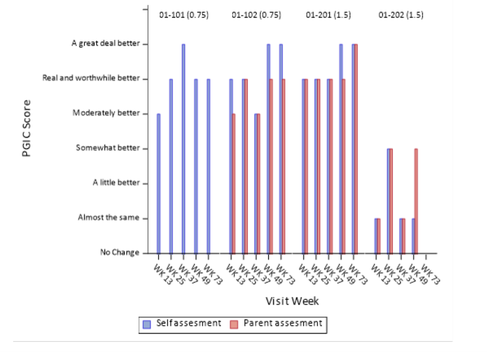

Dominant hand = ____Solid lines; Non-dominant hand = . . . dotted lines

### Figure 4. Results of Grip Strength Test




Dominant hand = ____Solid lines; Non-dominant hand = . . . dotted lines

### Figure 5. Results of Patient Global Impression of Change




## Conclusions

In general, patients with MPS I continue to report pain and arthropathy after HSCT and/or ERT. Due to the very limited sample sizes, comparisons between subjects receiving 0.75mg/kg or 1.5mg/kg PPS were not performed, however the therapeutic properties of PPS across both doses show promise of improving pain and function issues related to MPS I.

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## Acknowledgements

The authors acknowledge Maria Fuller, PhD, FFSc (Genetics and Molecular Pathology, SA Pathology, Adelaide). The authors acknowledge Michael Sheehan and Aditya Shrivastava for their critical reviews of this presentation.

This study is funded by Paradigm Biopharmaceuticals Ltd. CG, RK, DN, and MI are employees of Paradigm Biopharmaceuticals Ltd.