A Phase 2, Randomized, Double-blind, Placebo-controlled, Multicentre Study to Evaluate the Efficacy and Safety of Pentosan Polysulfate Sodium in Treating Subjects with Mucopolysaccharidosis VI: Study Update

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Background

MPS VI

MPS VI is a rare autosomal recessive inherited lysosomal storage disorder in which the lysosomal enzyme N acetylgalactosamine-4-sulfatase (arylsulfatase B, ASB) is deficient. The ASB deficiency results in accumulation of glycosaminoglycans (GAGs) in the lysosomes. Manifestations of GAG accumulation in patients with MPS VI include inflammation, musculoskeletal pain and limited physical function[1].

The global incidence of MPS VI ranges from 0.36 to 1.30 per 100,000 live births[2] with Brazil having one of the highest incidence rates worldwide (1.02 per 100,000 live births)[3]. An estimated 1,472 patients were diagnosed with MPS (any type) in Brazil between 1982 and 2016, of which 326 (22.1%) are MPS VI patients[4].

Etiology of MPS VI

Mucopolysaccharidosis VI is caused by a mutation in the ASB gene, resulting in a deficiency of ASB[5]. The ASB enzyme catalyzes the breakdown of the GAGs dermatan sulfate (DS) and chondroitin-4-sulfate. The ASB deficiency leads to progressive accumulation of DS, the primary GAG responsible for symptoms in MPS VI (Figure 1). The accumulation of GAGs in the growth plate of long bones interfere with control of chondrocyte development[6]. The accumulation of GAGs 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[7]. 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[6].

Figure 1. Arylsulfatase B Activity in Unaffected and MPS VI Patients

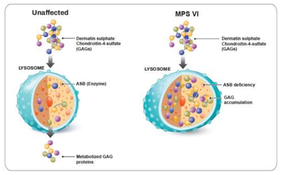
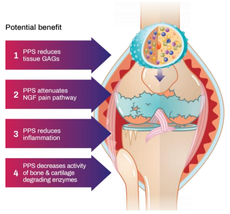


Figure 2. Potential Benefit of PPS in MPS VI Patients



Current Treatment Options / Unmet Need

Current treatments for MPS VI include disease modifying enzyme replacement therapy (ERT) and supportive medical and surgical interventions. Treatment with ERT reduces the accumulation of GAGs, improves pulmonary function and improves function (including 6-minute walk test [6MWT], 12-minute walk test [12MWT], and 3-minute stair climb test [3MSCT][8]). Supportive (eg, physical therapy, splints, analgesics) and surgical therapies provide some relief and temporary benefit however, these therapies can be invasive and have potential dependency issues (eg, opioids). Despite available therapies patients with MPS VI continue to experience musculoskeletal pain and reduced physical function, limiting quality of life[1,9,10]. Pentosan polysulfate sodium (PPS) is a potential treatment to improve pain and function in these patients. The GAG-reduction[7, 11], anti-inflammatory[12, 13], analgesic[14], and tissue remodeling properties[15,16] of PPS may provide beneficial therapeutic effects in patients with MPS VI.

PPS in MPS VI

Pentosan polysulfate sodium (PPS), is a semisynthetic polysaccharide that resembles glycosaminoglycans. Preclinical and clinical evidence suggests that PPS may treat the pain and arthropathy in MPS patients, filling a significant unmet medical need for a safe and effective therapy in MPS VI[7,11]. Human studies have investigated doses ranging from 0.5mg/kg-2mg/kg subcutaneous (SC) PPS in MPS I[17, 18], MPS II[19] and MPS VI[20]. In these studies, PPS was well-tolerated and demonstrated reduction in urinary GAG levels, reductions in pain, inflammatory biomarkers and cytokine levels, and improved joint mobility.

PPS Mechanisms of Action in MPS VI

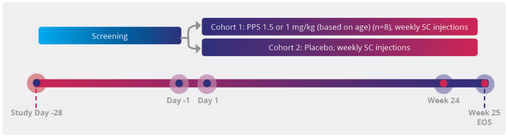
As shown in Figure 2, the key mechanisms of action of PPS that are relevant to the treatment of MPS are its ability to:

- Reduce systemic and accumulated GAG in multiple tissues[7,11].
- Directly bind 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[12,13].
- Reduce the expression of the pain mediator nerve growth factor in osteocytes from degenerating joints[14].
- Inhibit the cartilage degrading enzymes that are related to joint dysfunction observed in MPS [15, 16].

Study Description

Design

Subjects are randomized to receive blinded subcutaneous investigational product injection (PPS) or placebo (2:1 ratio), weekly for 24 weeks, with follow up 1 week after the last injection. Subjects are stratified by ages 5 to <16 and ≥16 years.



Objectives

The primary objective of the study is to assess the safety and tolerability of PPS in subjects with MPS VI. The secondary objectives are to evaluate the effects of PPS on pain and function in subjects with MPS VI.

Primary Objective Assessments

- Adverse events (AEs).
- Lab assessments including platelet factor 4 (PF4).
- Electrocardiogram.
- Retinal examinations.
- Physical examinations.

Secondary Objective Assessments

Function Assessments
- 2-minute walk test (2MWT).
- 6-minute walk test (6MWT).
- Range of motion (ROM).
- 9-Hole Peg Test (9HPT).

Patient Reported Assessments
- Faces pain scale – revised (FPS-R) visual analog scale (VAS).
- Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference Short Form.
- Pediatric quality of life (PedsQL)/36-Item short form survey (SF-36).
- Childhood health assessment questionnaire(CHAQ)/health assessment questionnaire (HAQ).
- Patient global impression of change (PGIC).

Key Eligibility Criteria

- Subjects ≥ 5 years of age.
- Confirmed diagnosis MPS type VI.
- On ERT for ≥1 year, at stable dose for 3 months prior to baseline.
- FPS-R pain score of a minimum of 3 and a maximum of 9.
- 6MWT ≤70% predicted of normative mean value for age.
- No previous treatment with HSCT.

Study Subjects

Demographics

- 9 subjects (4 male, 5 female) have been randomized into the study.
- 6 subjects are 5 to <16 years of age.
- 3 subjects are ≥16 years of age.

Baseline Characteristics

Clinical Assessments
- All subjects reported joint stiffness and short stature.
- 8 subjects had joint contracture.
- 8 subjects had corneal clouding.
- 7 subjects had genu valgum.

Measurements
- Baseline FPS-R scores were 3 - 9.
- 5 and 3 subjects completed the pediatric and adult PROMIS.
- 7 subjects completed the HAQ or CHAQ.
- 6 subjects completed the PedsQL.
- Baseline 2MWT were 60 - 140m.
- Baseline 6MWT were 167 - 420m.

Study Status

Study Status - Treatment

- 6 subjects have completed treatment through Week 24.

Study Status - Assessments

Function Assessments
- 5 subjects have completed 2MWT through Week 25.
- 5 subjects have completed 6MWT through Week 25.
- 5 subjects have completed ROM through Week 25.
- 5 subjects have completed 9HPT through Week 25.

Patient Reported Assessments
- 5 subjects have completed FPS-R through Week 25.
- 2 subjects have completed the pediatric PROMIS and 3 subjects have completed the adult PROMIS through Week 25.
- 3 subjects have completed CHAQ/HAQ through Week 25.
- 2 subjects have completed PedsQL through Week 25.
- 5 subjects have completed PGIC through Week 25

Study Status - Safety

- There have been no serious treatment-emergent AEs to date.
- All treatment-emergent AEs have been mild or moderate in severity.
- The majority of treatment-related AEs are associated with injection site reactions.
- Subject safety data is continually monitored.

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