A double-blind placebo-controlled phase 2 study to evaluate the safety and tolerability of pentosan polysulfate sodium in subjects with mucopolysaccharidosis type VI (MPS VI)

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Background

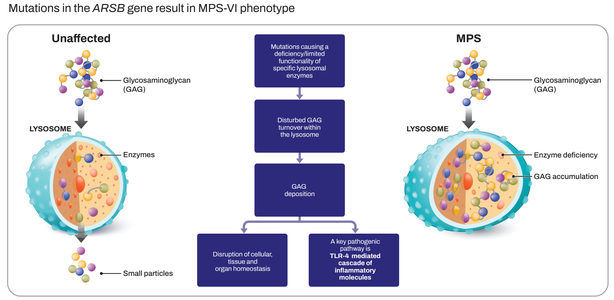
MPS VI

MPS VI is a rare autosomal recessive inherited lysosomal storage disorder caused by a deficiency of the lysosomal enzyme N acetylgalactosamine-4-sulfatase (arylsulfatase B, ASB), leading to accumulation of glycosaminoglycans (GAGs) in the lysosomes and physical manifestations including inflammation, musculoskeletal pain and progressive arthropathy. MPS VI is predominantly characterised by somatic features (organomegaly, cardio-pulmonary abnormalities, middle ear disease, deafness, visual impairment, upper airways obstruction), and severe bone dysplasia.

Brazil has one of the highest number of cases of MPS VI worldwide, second only to Saudi Arabia.[1] It is currently estimated that of a total of 1,472 patients were diagnosed with MPS (any type) in Brazil between 1982 and 2016, of which 326 (22.1%) are MPS VI patients, the second commonest type of MPS in Brazil.[2]

Etiology of MPS-VI

Mutations in the *ARSB* gene result in MPS-VI phenotype



TLR-4=Toll-like Receptor-4

Current Treatment Options / Unmet Need

Current treatments for MPS VI are disease modifying (enzyme replacement therapy, or ERT) or supportive (medical and surgical interventions). While replacing the missing or deficient enzyme by ERT helps prevent accumulation of macromolecules in the lysosomal compartments of cells in various organs and tissues, it does not improve existing skeletal manifestations. Despite available therapies people with MPS VI continue to experience significant musculoskeletal pain, inflammation and arthropathy, limiting their quality of life.[3-13,17]

Current therapies	Limitations of current therapies
Enzyme Replacement Therapy	
• Improved distance walked in 6MWT and 12MWT • Improvement in 3MSCT- both the number of stairs climbed and rate of climb • Reduced urinary GAG • Improved pulmonary function • Preserves cardiac dimensions, though no impact on valve disease • Improved growth, most benefit in pre-pubescent patients	• Residual bone abnormalities • Ongoing pain • Ongoing inflammation • Ongoing fatigue • Impact on activities of daily living
Supportive therapies	
• Surgery • Physical therapy • Hydrotherapy • Splints • Analgesics – opioid and non-opioid	• Invasive • Limited published evidence of effect • Potential for adverse effects with long term use

3MSCT=3 minute stair climb test[12]

PPS in MPS VI

Pentosan polysulfate sodium (PPS), a semisynthetic polysaccharide that resembles glycosaminoglycans, has been shown to improve pain and function in patients with MPS I, MPS II and MPS VI.

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.[22, 23] Human studies have investigated doses ranging from 0.5mg/kg-2mg/kg subcutaneous (SC) PPS in MPS I[18-19], MPS VI[20], and MPS II[21], and indicated that PPS is well-tolerated, with indication of efficacy supporting those seen in preclinical studies, including reduction in urinary GAG levels, reduction in pain, inflammatory biomarker and cytokine levels, and improvement in joint mobility.

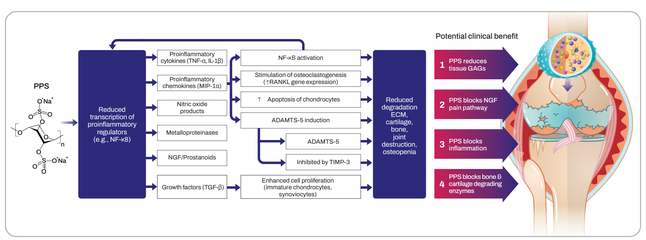
PPS is being developed as an adjunctive therapy and presents the first drug therapy with the potential to specifically target pain, musculoskeletal and functional symptoms in patients with MPS VI.

PPS Mechanisms of Action in MPS-VI

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[22-23]
- Reduce inflammatory effects via the inhibition of NF-kB resulting in the reduction in pro-inflammatory mediators[24]
- Reduce the expression of the pain mediator nerve growth factor in osteocytes from degenerating joints[26]
- Inhibit the cartilage degrading enzymes that are related to joint dysfunction observed in MPS[27, 28]

The progressive accumulation of GAGs leads to cellular injury in multiple organs and tissues, both directly through excess GAG storage and indirectly through to chronic inflammation through the activation of the toll-like receptor 4 (TLR 4) pathway, oxidative stress, and impaired vesicle trafficking.

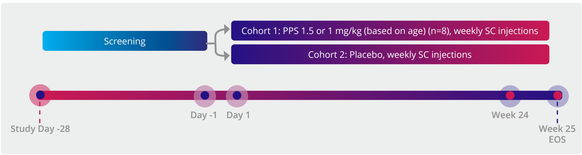


PPS=Pentosan Polysulfate Sodium, TNF-α=Tumour Necrosis Factor-α, IL-1β=Interleukin-1β, MIP-1α=Macrophage Inflammatory Protein-1α, NGF=Nerve Growth Factor, ADAMTS-5= A Disintegrin and Metalloproteinase with Thrombospondin Motifs-5, TGF-β=Transforming Growth Factor-β, NF-KB=Nuclear Factor kappa-B, RANKL=Receptor Activator of Nuclear Factor kappa-B Ligand, TIMP-3=Tissue Inhibitor of Metalloproteinases-3, ECM=Extracellular Matrix, GAGs=Glycosaminoglycans

Study description

Design

Patients 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.



Objectives

Endpoints and assessments were informed by a MPS VI patient focus group[25] and discussions with US and EU regulators.

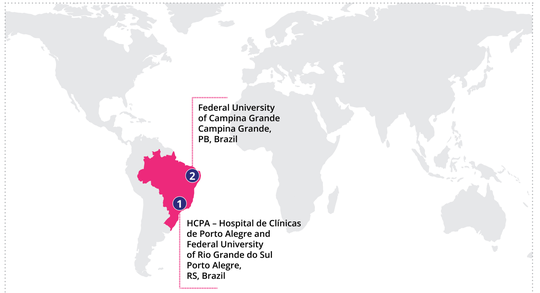
Primary objective	Assessments include
To assess the safety and tolerability of PPS in subjects with MPS VI	• Lab assessments including platelet factor 4 (PF4) • Electrocardiogram • Retinal examinations • Physical examinations
Secondary and exploratory objectives	**Assessments include**
To evaluate the effect of PPS on • Pain • Pharmacokinetics of repeat doses of PPS • Urinary GAGs • Upper body function and dexterity • Range of motion • Pain and function (mobility) • Walking related pain • Global impression of change (PGIC), QOL and ADL • Pulmonary function	• 2/6MWT • Range of motion (ROM) • 9-Hole Peg Test • Pharmacokinetic assessments at repeat doses • FVC/FEV1 Patient reported assessments • FPS-R, VAS • PROMIS Pain Interference Short Form • PedsQL/SF-36 • CHAQ/HAQ • PGIC

2/6MWT=2 and 6 minute walk test; FVC=forced vital capacity; FEV1= forced expiratory volume in one second; FPS-R=Faces pain scale – revised; VAS=Visual analogue scale; PROMIS= Patient-Reported Outcomes Measurement Information System; PedsQL=Pediatric quality of life; SF-36=36-Item short form survey; CHAQ=Childhood health assessment questionnaire; HAQ=Health assessment questionnaire; PGIC=Patient global impression of change; QOL=Quality of life; ADL=Activities of daily living

Key Eligibility Criteria

Inclusion criteria	Exclusion 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 • Pain score of a minimum of 3 and a maximum of 9 • Able to walk 30 meters • 6MWT ≤70% predicted of normative mean value for age • Impairment of ROM in at least one shoulder • Subject or parent/legally acceptable representative sufficiently able to understand the purposes and risks of the study and able to provide written informed consent • If applicable, subjects must be willing to comply with contraceptive requirements • Subjects should not be pregnant or breastfeeding • Subjects able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures	• History of increased bleeding tendency • History of heparin induced thrombocytopenia • History of significant hypersensitivity to PPS or drugs of a similar chemical or pharmacological class • Current treatment with anticoagulants or antiplatelet drugs, excluding aspirin ≤100 mg/day • Absence of limitation in upper extremity fine motor skills and shoulder joint ROM limitations • Subject taking opioids • Currently active or recent history of gastric or duodenal ulcer, or suspicion of gastrointestinal (GI) tract bleeding, or any clinically significant active or chronic condition (except if related to MPS VI) • Coagulation parameters or platelets outside laboratory reference range, liver function tests significantly abnormal • History of HSCT • Major surgery within 12 weeks • Current or recent immunosuppressive or immunomodulatory systemic therapy • Participation in another clinical trial or administration of any experimental product

Participating sites



Enrollment commencement:	August 2021
Enrollment status:	Enrolling
Current enrollment:	2
Participating sites:	1. HCPA – Hospital de Clínicas de Porto Alegre and UFRGS – Federal University of Rio Grande do Sul, Porto Alegre - RS, Brazil 2. Federal University of Campina Grande, Campina Grande, PB, Brazil
Registry ID:	RBR-2tz9dky (CAEE)

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Information

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Disclosures

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