

The MPS VII Disease Monitoring Program (DMP) is a Novel, Longitudinal, Cohort Program With Rigor Beyond a Traditional Registry

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INTRODUCTION

- Mucopolysaccharidosis VII (MPS VII), or Sly syndrome, is a very rare, chronically debilitating, and life-threatening lysosomal storage disorder
  - It is estimated that there are 200 patients living with MPS VII worldwide
- MPS VII is caused by a deficiency of beta-glucuranidase (GUSB) enzyme activity, leading to accumulation of dermatan, chondroitin, and heparan sulfate glycosaminoglycans in a wide range of tissues
- Symptoms of MPS VII can present in the prenatal or postnatal period
- Patients with MPS VII may present with hydrops fetalis at birth
- Most common characteristics of MPS VII:
  - Abnormal coarsened facies
  - Cardiac/pulmonary disease
  - Enlarged liver/spleen
  - Severe joint and bone abnormalities
  - Short stature
  - Cognitive impairment
  - Cornelia de Lange
- The rate of progression is variable, and likely multifactorial
- Many patients with MPS VII die from the disease before the second or third decade of life due to complicating medical problems
- Enzyme replacement therapy with vestronidase alfa (recombinant human GUS) is the only approved treatment for MPS VII
  - Vestronidase alfa was approved by the US Food and Drug Administration in November 2017 and by the European Medicines Agency in August 2018
- In a phase 3 trial with a novel Blind Start study design, 10/12 patients with MPS VII showed meaningful improvement in at least 1 domain of a Multi-Domain Responder Index (MDRI) after 24-weeks of treatment with vestronidase alfa
- Efficacy and safety of vestronidase alfa have been consistent across the MPS VII clinical development programs (phase 1/2, NCT01850218; phase 2, NCT02418545; phase 3, NCT02432144; phase 3, NCT02235056)
- Given the rarity of the disease and the newly available treatment, there is a critical need to:
  - Increase disease awareness and advocate the importance of early diagnosis
  - Understand clinical heterogeneity
  - Characterize clinical presentation and progression of disease, both in untreated and treated patients
- The MPS VII Disease Monitoring Program (DMP) is an innovative, global, multicenter, longitudinal program that will:
  - Collect long-term data from untreated and treated patients
  - Follow Good Clinical Practice (GCP) standards
  - Provide comprehensive, systematic, clinically relevant, standardized, GCP-quality datasets

OBJECTIVES

- Characterize MPS VII disease presentation and progression over 10 years in patients treated and not treated with vestronidase alfa
- Assess long-term effectiveness of vestronidase alfa in patients with MPS VII
- Assess long-term safety of vestronidase alfa in patients with MPS VII, including hypersensitivity reactions and immunogenicity
- Prospectively investigate the longitudinal change in biomarker(s), clinical assessments, patient/caregiver-reported outcome measures, and other possible predictors of MPS VII disease progression and mortality

REFERENCES


CONTACT INFORMATION

MPS VII Disease Monitoring Program information: medinfo@ultradynex.com

DISCLOSURES AND ACKNOWLEDGMENTS

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DMP STUDY DESIGN

Study Population

- The MPS VII DMP will collect longitudinal data in patients with a confirmed diagnosis of MPS VII
- Informed consent and/or assent from the patient or caregiver is required to participate
- Target enrollment is 35 patients, across 15 sites in the US, EU, and LATAM (Figure 1)

Site Selection, Training, and Compensation

- All program sites will be academic centers with experience in managing and assessing patients with MPS VII
- Each site will be trained on assessment measures to facilitate standardization and decrease variability
- Sites will be appropriately compensated for their efforts
- Patients may be receiving vestronidase alfa where access is available; vestronidase alfa will not be provided as part of the study

Data Handling, Record Keeping, and Retention

- Data will be sourced for completeness and accuracy based on standard GCP monitoring methods
  - Validated Electronic Data Capture (EDC) system will be used
  - Monitoring and auditing procedures will be implemented to ensure compliance with ICH GCP standards
  - All records will be retained for at least 25 years after the end of the program or in accordance with national law

Inclusion/Exclusion Criteria

- The MPS VII DMP is designed to be inclusive, without restrictions on patient treatment status (Table 1)

Patient Assessments

- Families will receive travel assistance (with certain restrictions) to facilitate patient retention
- Age-appropriate assessments (Table 2) will be collected at specified intervals (Figure 2) depending on the patient’s age at the time of the visit
- Key assessments will include:
  - Functional assessments of cognition, mobility, skeletal disease, and pulmonary function
  - Clinical assessment of urinary glycosaminoglycans (uGAGs)
  - Patient/caregiver-reported outcomes
  - Quality-of-life assessments
  - Effectiveness and long-term safety data will be collected for patients receiving vestronidase alfa therapy
  - Immunogenicity profile of vestronidase alfa at each scheduled visit

Table 1. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Diagnosis of MPS VII based on laboratory diagnosis, including either enzymatic or mutation analyses</td>
<td>Concurrent enrollment in an Ultragenyx-sponsored clinical trial</td>
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<td>Willing and able to provide written informed consent and, in the case of patients &lt;18 years of age (or 16 years, depending on the region) or patients ≥18 years of age who have cognitive deficiencies, provide written assent (if required) and written informed consent by a legally authorized representative after the nature of the DMP has been explained, and prior to any research-related procedures</td>
<td>Participation in any other pharmaceutical company-sponsored interventional clinical trial, unless permission is provided by Ultragenyx</td>
</tr>
<tr>
<td>Eligibility of MPS VII patients for enrollment in the DMP will be based on the following factors:</td>
<td></td>
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Table 2. Key Assessments

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<tr>
<th>Assessment Type</th>
<th>Measures</th>
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<tr>
<td>General</td>
<td>Demographics, Family, medical, and diagnostic history, Physical examination, Clinical laboratory tests (uGAG, anti-drug antibody)</td>
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<td>Adaptive Behavior and Cognitive Assessment</td>
<td>Vineland Adaptive Behavior Scales, Age-appropriate cognitive assessment</td>
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<td>Motor Function</td>
<td>Gross Motor Milestone Checklist (&lt;5 years of age)</td>
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<tr>
<td>Mobility and Endurance</td>
<td>Six-minute walk test (6MWT: ≥5 years of age)</td>
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<td>Patient/Caregiver Reported Outcomes</td>
<td>Pediatric Quality of Life Inventory™ (PedsQL) Multidimensional Fatigue Scale, EuroQol Five Dimensions Questionnaire Five Levels (EQ-5D-5L), MPS Health Assessment Questionnaire (≥5 years of age)</td>
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<td>Caregiver Reported Outcomes</td>
<td>Work Productivity and Activity Impairment (WPVI) Questionnaire</td>
</tr>
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<td>Pulmonary Function</td>
<td>Spirometry (≥5 years of age), Cough peak flow (CPF)</td>
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<td>Cardiac Function</td>
<td>Electrocardiogram (EKG)</td>
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<tr>
<td>Visual Acuity</td>
<td>Snellen Eye Chart (≥5 years of age)</td>
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<tr>
<td>Hearing Impairment</td>
<td>Audiometry</td>
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SUMMARY

- The MPS VII DMP will provide a prospective, comprehensive, and standardized dataset over 10 years
  - Site selection requirements, standardized assessments, site monitoring, source document verification, and patient retention measures will contribute to the robustness of the dataset
  - The MPS VII DMP will provide a greater understanding of MPS VII disease progression and response to enzyme replacement therapy
- This novel and unique approach may overcome issues encountered by previous patient registries and may provide more useful outcomes for rare diseases

Figure 1. Geographic Distribution of Disease Monitoring Program Sites

Figure 2. Assessment Schedule

- Currently, sites in the US and Brazil are active and open for enrollment

Table 2. Key Assessments