

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

Deborah Marsden, MD*; Robert Hostutler, MS; Tricia Cimms, MPH

Ultragenyx Pharmaceutical Inc., Novato, California

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-glucuronidase (GUS) 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
 - Corneal clouding
- 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 compounding medical problems¹
- 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 2018²
- 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 alfa³
 - Efficacy and safety of vestronidase alfa have been consistent across the MPS VII clinical development programs (phase 1/2, NCT01856218; phase 2, NCT02418455; phase 3, NCT02432144; phase 3, NCT02230566)
- 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

- Montano AM, et al. *J Med Genet*. 2016;53(6):403-418.
- MEPSEVII (vestronidase alfa-vjvk) [package insert]. Novato, CA: Ultragenyx Pharmaceutical Inc.; 2017.
- Harmatz P, et al. *Mol Genet Metab*. 2018. doi: 10.1016/j.ymgme.2018.02.006

CONTACT INFORMATION

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

DISCLOSURES AND ACKNOWLEDGMENTS

- DM, RH, and TC are employees of and shareholders in Ultragenyx Pharmaceutical Inc.
- This study was sponsored by Ultragenyx Pharmaceutical Inc.
- Third-party writing assistance was provided by Rezan Sahinkaya, PhD, of TSG Carbon, and funded by Ultragenyx Pharmaceutical Inc.
- Allison Saviano, of Saphirus Communications, provided graphic and layout support.

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 source verified 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 and cardiac 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

Inclusion Criteria

- Diagnosis of MPS VII based on laboratory diagnosis, including either enzymatic or mutation analyses
- Willing and able to provide written informed consent or, in the case of patients <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
- Willing to comply with DMP visit schedule

Exclusion Criteria

- Concurrent enrollment in an Ultragenyx-sponsored clinical trial
- Participation in any other pharmaceutical company-sponsored interventional clinical trial, unless permission is provided by Ultragenyx

Figure 1. Geographic Distribution of Disease Monitoring Program Sites

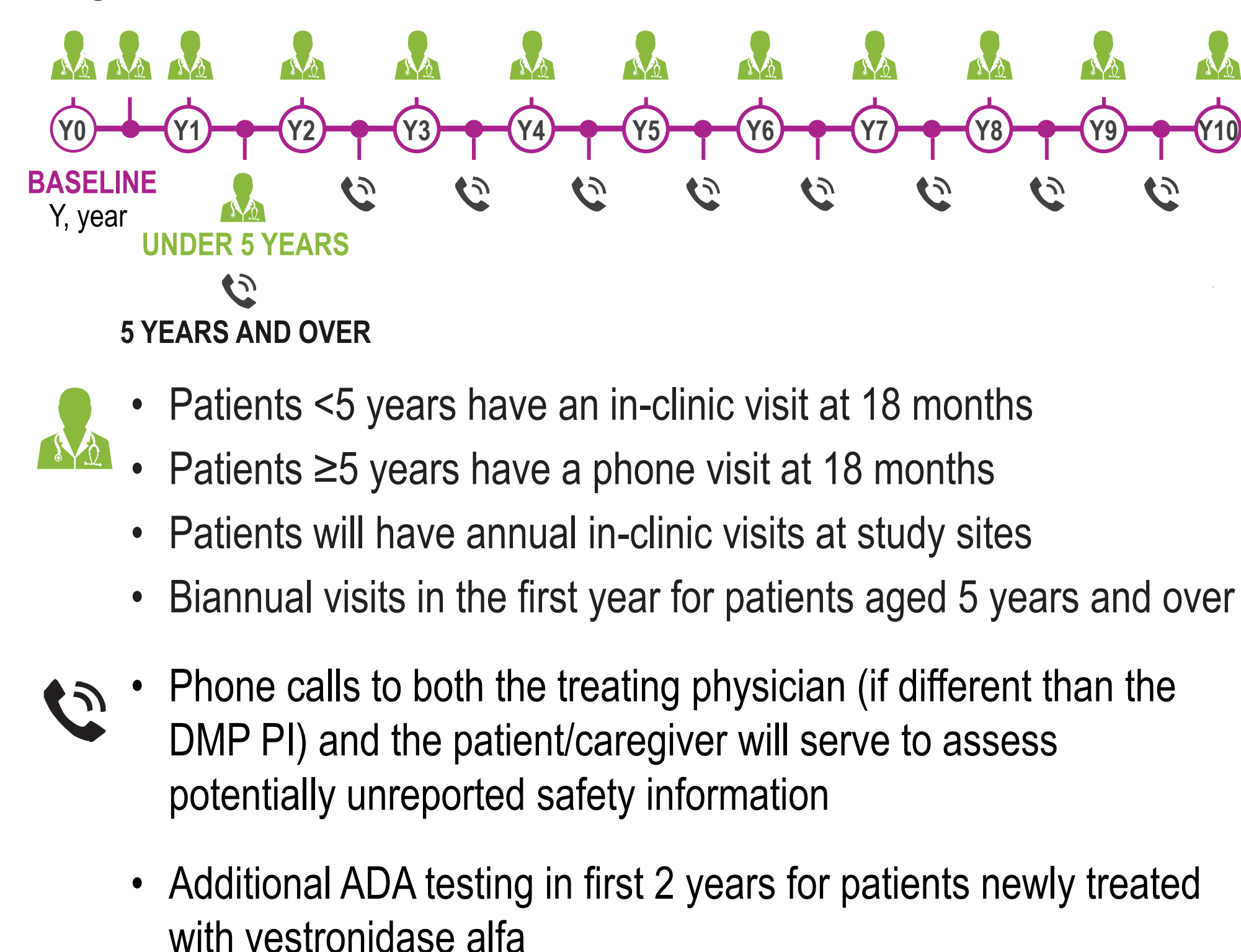


- Currently, sites in the US and Brazil are active and open for enrollment

Table 2. Key Assessments

Assessment Type	Measures
General	<ul style="list-style-type: none"> Demographics Family, medical, and diagnostic history Physical examination Clinical laboratory tests (uGAG, anti-drug antibody)
Adaptive Behavior and Cognitive Assessment	<ul style="list-style-type: none"> Vineland Adaptive Behavior Scales Age-appropriate cognitive assessment
Motor Function	<ul style="list-style-type: none"> Gross Motor Milestone Checklist (<5 years of age)
Mobility and Endurance	<ul style="list-style-type: none"> Six-minute walk test (6MWT; ≥5 years of age)
Patient/Caregiver Reported Outcomes	<ul style="list-style-type: none"> 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)
Caregiver Reported Outcomes	<ul style="list-style-type: none"> Work Productivity and Activity Impairment (WPAI) Questionnaire
Pulmonary Function	<ul style="list-style-type: none"> Spirometry (≥5 years of age) Cough peak flow (CPF)
Cardiac Function	<ul style="list-style-type: none"> Electrocardiogram (EKG) 2D-echocardiogram
Visual Acuity	<ul style="list-style-type: none"> Snellen Eye Chart (≥5 years of age)
Hearing Impairment	<ul style="list-style-type: none"> Audiometry

Figure 2. Assessment Schedule



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