STUDY PROTOCOL FOR NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY (PASS)

Title:	**Morquio A Registry Study (MARS)**
Protocol version identifier	Version 6
Date of last version of protocol	European Union version: 15 June 2018 United States version: 26 July 2018
Date of updated version of protocol	23 February 2021
EU PASS register number	EUPAS6835
Active substance	Recombinant human N-acetylgalactosamine-6-sulfatase
Medicinal product	Vimizim® (elosulfase alfa)
Product reference	EMEA/H/C/0002779
Procedure number	EMEA/H/C/0002779/0000
Marketing authorisation holder	BioMarin International Limited Shanbally, Ringaskiddy County Cork P43 R298 Ireland
Joint PASS	No
Research question and objectives	The objectives of this PASS are: 1. To characterize and describe the Mucopolysaccharidosis IV type A (MPS IVA) population as a whole, including the heterogeneity, progression, and natural history of MPS IVA. 2. To evaluate the long-term effectiveness and safety of Vimizim, including, but not limited to, the occurrence of serious hypersensitivity reactions, anaphylaxis, and changes in antibody status. 3. To help the medical community with the development of recommendations for monitoring MPS IVA patients and reports on patient outcomes to optimize patient care. 4. To collect data on other treatments and evaluate the prevalences of their use and their effectiveness. 5. To characterize the effects and safety of Vimizim treatment up to 5 years from enrolment in the Registry for patients under 5 years of age. 6. To monitor pregnancy exposure, including maternal, neonatal, and infant outcomes. 7. To monitor patients who have completed the MOR-005 and MOR-007 clinical trials. These patients will be encouraged to enroll in the applicable Registry Substudy and will be monitored using the MOR-005 and MOR-007 assessment schedules respectively.

Country(-ies) of study	Australia; Austria; Belgium; Canada; Czech Republic; Denmark; France; Germany; Italy; Malaysia; Netherlands; Poland; Portugal; Puerto Rico; Taiwan; United Kingdom; Ireland; United States of America
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1 LIST OF ABBREVIATIONS

3MSCT	3-Minute Stair-Climb Test
6MWT	6-Minute Walk Test
ADL	activities of daily living
AR	adverse reaction
AE	adverse event
AP	anteroposterior
BiPAP	bi-level positive airway pressure
BMT	bone marrow transplant
BPV	BioMarin Pharmacovigilance
CFR	Code of Federal Regulations
CPAP	continuous positive airway pressure
eCRF	Electronic Case Report Form
CRA	Clinical Research Associate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DXA	dual-emission x-ray absorptiometry
ECG	electrocardiogram
EDC	electronic data capture
ERT	enzyme replacement therapy
FDA	Food and Drug Administration
GAG	glycosaminoglycan
GALNS	N-acetylgalactosamine-6-sulfatase
GCP	Good Clinical Practice
HSCT	hematopoietic stem cell transplant
IBD	International Birth Date
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IRB	Institutional Review Board
IV	Intravenous
MARS	Morquio A Registry Study
MedDRA	Medical Dictionary for Regulatory Activities
MPS IVA	Mucopolysaccharidosis IV type A
MRI	magnetic resonance imaging
NAb	neutralising antibody
NAb	neutralising antibodies

OAE	otoacoustic emissions
OTC	over-the-counter
O_2	oxygen
PASS	post-authorisation safety study
PedsQL™	Measurement Model for the Pediatric Quality of Life Inventory
PIAF	patient information and authorisation form
REB	Research Ethics Board
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	standard of care
SDV	source document verification
SRM	study reference manual
TAb	total anti-drug antibody
uKS	urinary keratan sulfate
US	United States
VRA	visual reinforcement audiometry

2 RESPONSIBLE PARTIES

The Registry will be administered by and monitored by employees or representatives of BioMarin Pharmaceutical Inc. (BioMarin). Clinical Research Associates (CRAs) or trained designees will monitor each site on a periodic basis and perform verification of source documentation for each patient as well as other required review processes. BioMarin's Pharmacovigilance Department (or designee) will be responsible for the timely reporting of suspected, adverse reactions (ARs) to appropriate regulatory authorities as required. Institutions participating in the Registry may also be responsible for the reporting of these events per country specific regulatory requirements.

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3 ABSTRACT

A multicentre, multinational, observational Morquio A Registry Study (MARS) will be established to characterise and describe the Mucopolysaccharidosis IV type A (MPS IVA) population as a whole, including the heterogeneity, progression, and natural history of MPS IVA and to track the safety and clinical outcomes of patients with MPS IVA patients treated with Vimizim®. The Registry will enroll and collect data on patients over a period of at least 8 years from the time of the first marketing approval globally, and data on individual patients will continue to be collected for at least 2 years from the time the last patient was enrolled or until the Registry is completed. Patients are not required to receive Vimizim to be eligible to participate in this Registry; however, they must have a confirmed diagnosis of MPS IVA. Patients currently participating in a BMN 110 (elosulfase alfa) clinical trial will not meet inclusion criteria, but will be able to enroll after completion of or withdrawal from the clinical trial. Investigators will determine the actual frequency of necessary assessments according to a patient's individualized need for medical care and routine follow-up. Data may be collected for all or some of the assessments as outlined in Table 8.1.1.1 dependent upon the patient's current standard of care (SOC).

In addition, this Registry will collect additional data on patients who have completed the MOR-005 and MOR-007 clinical trials. The MOR-005 and MOR-007 clinical trial patients will be enrolled into the appropriate Registry Substudy for a minimum of 5 years from the time of the patient's enrolment in the MOR-005 clinical study or MOR-007 clinical study. After the 5-year period, these patients should remain in MARS until the Registry is complete.

Registry data collected using a validated web-based application will be analysed as per the Registry's Statistical Analysis Plan (SAP) and reported periodically. The MARS will provide the necessary data to further characterise the spectrum of clinical signs and symptoms of the disease, and to further characterise the safety profile of Vimizim in a broader population.

3.1 Title

Morquio A Registry Study (MARS) Version 6: 23 February 2021

3.2 Rationale and Background

The purpose of the MARS will be to characterise and describe the MPS IVA population as a whole, including the heterogeneity, progression and natural history of MPS IVA, and to track the safety and clinical outcomes of patients with MPS IVA treated with Vimizim.

3.3 Research Question and Objectives

The objectives of this Registry are (1) to characterize and describe the MPS IVA population as a whole, including the heterogeneity, progression, and natural history of MPS IVA, (2) to evaluate the long-term effectiveness and safety of Vimizim, including, but not limited to, the occurrence of serious hypersensitivity reactions, anaphylaxis, and changes in antibody status, (3) to help the medical community with the development of recommendations for monitoring MPS IVA patients and reports on patient outcomes to optimize patient care, (4) to collect data on other treatments and evaluate the prevalences of their use and their effectiveness, (5) to characterize the effects and safety of Vimizim treatment up to 5 years from enrolment in the Registry for patients under 5 years of age, (6) to monitor pregnancy exposure, including maternal, neonatal, and infant outcomes, and (7) to monitor patients who have completed the MOR-005 and MOR-007 clinical trials. These patients will be encouraged to enroll in the applicable Registry Substudy and will be monitored using the MOR-005 and MOR-007 Substudy assessment schedules, respectively.

3.4 Study Design

This is a voluntary multicentre, multinational, observational Registry in patients diagnosed with MPS IVA. Investigators will determine the actual frequency of necessary assessments according to a patient's individualized need for medical care and routine follow-up. Data may be collected for all or some of the assessments as outlined in Table 8.1.1.1 dependent upon the patient's current SOC. The Registry will enroll and collect data on patients according to current SOC over a period of at least 8 years from the time of the first marketing approval globally, and data on individual patients will continue to be collected for at least 2 years from the time that the last patient was enrolled or until the Registry is completed. These assessments are designed to further characterise the spectrum of clinical signs and symptoms of the disease, and to further characterise the safety profile of Vimizim in a broader population. Patients are not required to receive Vimizim to be eligible to participate in this Registry.

In addition, this Registry will collect additional data on patients who have completed the MOR-005 and MOR-007 clinical trials. The MOR-005 and MOR-007 clinical trial patients will be enrolled into the appropriate Registry Substudy for a minimum of 5 years from the time of the patient's enrolment in the MOR-005 clinical study or MOR-007 clinical study. After the 5-year period, these patients should remain in the MARS until the completion of the Registry. Patients initially enrolling into 1 of the Substudies will give their consent to participate in both the applicable Substudy and to continue participation in the MARS Registry, following the completion of the respective Substudy, by signing an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research

Ethics Board (REB)-approved informed consent form (ICF)/patient information and authorisation form (PIAF) and assent, if applicable, for both the relevant Substudy and the MARS Registry.

3.5 Population

All patients with a confirmed diagnosis of MPS IVA disease may be eligible to participate in this Registry. Patients are not required to receive Vimizim to be eligible to participate in this Registry.

3.6 Variables

The medical histories and clinical and safety assessments are designed to help further characterise the spectrum of clinical signs and symptoms of the MPS IVA disease, and to further characterise the safety profile of Vimizim in a broader population. Patients are not required to receive Vimizim to be eligible to participate in this Registry. The assessments are listed in the Data Elements of Interest in Section 8.1.1 and Table 8.1.1.1.

3.7 Data Sources

Investigators treating MPS IVA patients are encouraged to participate in the Registry by enrolling patients and entering all data from these assessments outlined in the Data Elements of Interest (Table 8.1.1.1) into the Registry database. Data may be collected for all or some of the assessments as outlined in Section 8.1.1 and Table 8.1.1.1, dependent upon the individual's current SOC, and whether or not the patient is receiving treatment for MPS IVA such as Vimizim, hematopoietic stem cell transplant (HSCT), or bone marrow transplant (BMT).

3.8 Study Size and Statistical Methods

All MPS IVA patients will be invited to enroll in the Registry, assuming all regulatory requirements are met for sites that have agreed to participate, in countries where marketing authorisation has been granted.

Registry data will be analysed as per the Registry's SAP and reported periodically. Data from patients enrolled in the Registry Substudies will also be analysed as per the MOR-005 and MOR-007 sub-study SAP, as applicable.

All data collected from the Registry patients will be captured in the Registry database. Patient baseline information, including medical history, growth history, prior medications and demographics, will be summarised using descriptive statistics. Safety data, including vital signs, findings from physical examinations, concomitant medications, and other safety assessments, will be summarised descriptively. Incidence rate calculations will be completed. Where applicable, descriptive statistics will include the number of patients, mean, median, standard deviation (SD), minimum, maximum, nominal p-values,

95% confidence interval and/or inter-quartile range for continuous variables, as well as count and percent for categorical variables. For purposes of analyses, the terms Baseline and Index are defined in Section 11.1.

3.9 Milestones

Progress updates will be reported annually, based on the International Birth Date (IBD) of 14 February 2014, with the final Clinical Study Report due March 2025 (See Section 5).

4 AMENDMENTS AND UPDATES

4.1 Amendment 1 (EU)

Date: 15 June 2018

As a result of interaction with and correspondence from the United States (US) Food and Drug Administration (FDA), dated 19 August 2014, the post-authorisation safety study (PASS) protocol was updated to reflect the following changes:

- Specify that patients in the MOR-005 and MOR-007 clinical trials will be enrolled in the appropriate Registry Substudy for a minimum of 5 years from the time of the patient's enrolment in Study MOR-005 or MOR-007. This change impacts the following sections of the PASS protocol: Section 9.1 Study Design
- Section 13 MOR-005 and MOR-007 Substudies

- Add the statement that any decision to terminate the Registry early will only be made with concurrence of Regulatory Agencies. This change impacts the following section of the PASS protocol:
  - Section 11 Study Time Period
- Include references to a Study Reference Manual (SRM) in all assessment descriptions. This change impacts the following sections of the PASS protocol:
  - Table 9.1.1.1 Data Elements of Interest
  - Section 12 Variables
- Add centralized reading of radiologic studies. This change impacts the following sections of the PASS protocol:
  - Section 12.19 Imaging
  - Section 13 MOR-005 and MOR-007 Substudies
- Add Pregnancy Substudy assessments. This change impacts the following sections of the PASS protocol:
  - Table 9.2 Pregnancy Substudy Data Elements of Interest
  - Section 14 Pregnancy Substudy
- Add dual-emission x-ray absorptiometry (DXA) scans for patients in the MOR-007 Registry Substudy. This change impacts the following sections of the PASS protocol:
  - Table 9.1.1.1 Data Elements of Interest
  - Section 12.19 Imaging
  - Section 13 MOR-005 and MOR-007 Substudies

- Change terminology from “infusion reaction” or infusion associated reactions” to “hypersensitivity reaction.” This change impacts the following sections of the PASS protocol:
    - Section 9.1.1 (Table 9.1.1.1)
    - Section 12.22.3 Immunogenicity Testing
    - Section 24.3 Adverse Event (AE) Reporting Instructions
- Include a separate schedule of immunogenicity assessments for the Pregnancy Substudy. This change impacts the following sections of the PASS protocol:
    - Table 9.2 Pregnancy Substudy Data Elements of Interest
    - Section 14 Pregnancy Substudy
- Add patient recruitment strategy information. This change impacts the following sections of the PASS protocol:
    - Section 20.1 Study Monitoring and Auditing

Additional changes to the PASS protocol are as follows:

- Remove the Evaluable Analysis Population; analyses of the natural history of MPS IVA are to be performed, instead, in the Efficacy Population. This change impacts the following sections of the PASS protocol:
    - Section 19.1.5 Analysis Populations
    - Natural History of MPS IVA Population

Additional editorial changes were made for clarity and consistency.

In order to align with Global Pharmacovigilance Practice, version 5 of the protocol was created to include Unusual Failure in Efficacy as a reportable AE in Section 23.1 Safety Parameters and Definitions. Additionally, the Author name and phone number was updated.

4.2 Amendment 1 (US)

Date: 26 July 2018

The protocol was amended to include Unusual Failure in Efficacy as a reportable safety event. The purpose of this change was to align with global Good Pharmacovigilance Practices. Additionally, the name and contact information for the BioMarin Medical Monitor was updated.

4.3 Amendment 2 (Current amendment, Global)

Date: 23 February 2021

A summary of changes covered by Amendment 2 is provided below.

1. Establishment of a global protocol.
   Rationale: Prior to this amendment, there was a separate protocol for the US (version 3) and PASS protocol for the EU (version 5). BioMarin's objective was to create a global protocol based off the EU PASS protocol. Hence, content from the US protocol not included in the EU protocol has been included herein, and this global protocol is now identified as version 6.
2. Change in address of marketing authorisation holder, author, and medical monitor.
   Rationale: Administrative changes.
3. Language amended throughout to state that assessments be carried out according to current standard of care.
   Rationale: Clarification that assessments are performed or data collected per current standard of care.
4. Footnotes in Data Elements of Interest (Table 8.1.1.1) and frequency of assessments, text in immunogenicity testing (Section 11.23.3), general analysis considerations (Section 18.1.4), and treatment groups (Section 18.1.5.3) were edited.
   Rationale: For clarity and to reflect updates made to the SAP.
5. Removal of immunogenicity and breast milk sample events from Pregnancy Substudy (Section 8.2) and Data Elements of Interest (Table 8-2), including corresponding footnotes.
   Rationale: Removed as requested by PRAC as these events are considered to be interventional.
6. Amendment of language in Section 11 and Section 12 concerning participation in the MARS registry.
   Rationale: Clarification that assessments are per current standard of care, and that the sponsor wishes to follow-up on patients by encouraging them to remain in the Registry.
7. Baseline, Index, Registry Entry, Treatment Discontinuation, and Follow-up definitions were added throughout the protocol, the Full Analysis Set was defined in Section 11, and objectives were redefined in Section 18.1.7 for consistency with the SAP.
   Rationale: Text modified based on a revision to the planned analysis.

Specific changes included in this amendment are outlined in Section 30.

5 MILESTONES

Milestone	Planned or Actual Time
Start of data collection	Q3-2014 (actual)
Progress reports	To be provided annually by the end of Q2, dependant on the International Birth Date (IBD)
End of data collection	September 2024
Registration in the EU PASS register	Q2-2014/prior to data collection
Final report of study results	Study ends in September 2024, Final report available in March 2025

6 RATIONALE AND BACKGROUND

Mucopolysaccharidosis IV type A (Morquio A syndrome, MPS IVA) is a rare inherited disorder caused by mutations of the gene that codes for the lysosomal enzyme, N-acetylgalactosamine-6-sulfatase (GALNS), which degrades glycosaminoglycans (GAGs) including keratan sulfate (KS) and chondroitin-6-sulfate. With insufficient GALNS, GAGs progressively accumulate in multiple organs and tissues. The pervasive and progressive accumulation of GAGs leads to significant morbidities and multisystemic clinical impairments resulting in diminished functional capacity, decreased endurance, impaired quality of life, and early mortality. The most common features of patients with MPS IVA are progressive skeletal dysplasia, frequent surgical procedures mostly related to musculoskeletal or respiratory dysfunction, and a significant limitation in mobility, endurance, and respiratory function (Montano, 2007), (Harmatz P, 2013). Many patients end up using scooters, wheelchairs or other devices by their teen years. All patients have a profound skeletal dysplasia, which commonly results in severe short stature and malformations of the knees, chest, and spine. The skeletal dysplasia, short stature, and joint abnormalities all restrict patient mobility. Patients may experience both restrictive lung disease due to thoracic deformity and obstructive disease due to laryngeal narrowing and tracheal and bronchial abnormalities. These mechanical impediments often result in dyspnoea and recurrent respiratory infections, and potentially progress to respiratory failure. Additional symptoms may include hearing loss, cataracts, corneal clouding, and heart valvular disease, among others. Intelligence is normal (Neufeld, 1995), (Kakkis, 1996), (Northover, 1996).

Survival in untreated patients with rapidly progressing phenotypes is limited to the second or third decade of life. Rarely, patients with slowly progressing forms of the disorder have been reported to survive beyond 60 years. Mortality is commonly due to cardiorespiratory or neurologic complications (i.e., spinal cord compression). Obstructive and restrictive lung disease predisposes patients to developing fatal pneumonia and respiratory failure (Neufeld, 1995), (Kakkis, 1996), (Hendriksz, 2010), (Hendriksz, 2012). Regardless of the rate of disease progression, all patients already have or will develop serious and debilitating morbidities.

Completed and ongoing MPS IVA clinical studies conducted by BioMarin are summarised in Table 6.1.1 .

6.1 Clinical Studies

Table 6.1.1: Clinical Studies

Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Study Population	Duration of Treatment	Date of Trial Initiation	Date of Last Patient Visit
MOR-001 (MorCAP)	• To quantify endurance and respiratory function in subjects with Mucopolysaccharidosis IV type A (MPS IVA) and to better characterise the spectrum of symptoms and biochemical abnormalities in MPS IVA over time.	Natural History Study	Not applicable	353	MPS IVA patients	Duration of participation: up to 10 years	Oct 2008	Jul 2014 (actual)

Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Study Population	Duration of Treatment	Date of Trial Initiation	Date of Last Patient Visit
MOR-002	• To evaluate the safety of weekly infusions of BMN 110 administered in escalating doses to subjects with MPS IVA.	Phase 1/2, Multicentre, Open-Label, Dose-Escalation Study	BMN 110; Dose-Escalation Period: • Weeks 1-12: 0.1 mg/kg/week • Weeks 13-24: 1.0 mg/kg/week • Weeks 25-36: 2.0 mg/kg/week Optional continuation period: 1.0 mg/kg/week for an additional 36-48 weeks. Weekly 4- to 5-hour intravenous (IV) infusions	20 (actual)	MPS IVA patients aged 5-18 years	Dose-escalation period: 36 weeks Optional continuation period: 36-48 weeks Total duration: 72-84 weeks	Apr 2009	Feb 2011 (actual)
MOR-100	• To evaluate the long-term safety and efficacy of weekly infusions of 2.0 mg/kg of BMN 110 administered in subjects with MPS IVA who participated in MOR-002	Multicentre, Open-Label, Extension Study	BMN 110: 2.0 mg/kg/week 4-hour IV infusions	17 (actual)	MPS IVA patients who completed MOR-002	Up to 240 weeks	Nov 2010	Jul 2014 (actual)

Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Study Population	Duration of Treatment	Date of Trial Initiation	Date of Last Patient Visit
MOR-004	• To evaluate the ability of 2.0 mg/kg/week BMN 110 and 2.0 mg/kg/qow BMN 110 compared with placebo to enhance endurance in subjects with MPS IVA, as measured by an increase in the number of meters walked in the 6-Minute Walk Test (6MWT) from Baseline to Week 24.	Phase 3, Multinational, Multicentre, Double-blind, Placebo-controlled Study	BMN 110: 2.0 mg/kg/week and 2.0 mg/kg/every other week Placebo 4-hour IV infusions	177 randomized; 176 dosed (actual)	MPS IVA patients age 5 years and older who are able to walk ≥ 30 and ≤ 325 meters in the 6MWT	24 weeks	Jan 2011	Aug 2012 (actual)
MOR-005	• To evaluate the long-term safety and efficacy of BMN 110 administration at 2.0 mg/kg/every week (qw) and 2.0 mg/kg/qow in subjects with MPS IVA.	Phase 3 Extension, Multinational, Multicentre, Double-Blind followed by Open-Label Study	BMN 110: Double Blind: 2.0 mg/kg/week and 2.0 mg/kg/every other week Open-Label: 2.0 mg/kg/week as determined after analysis of the final primary efficacy and safety results in MOR-004 4-hour IV infusions	173 (actual)	MPS IVA patients who completed MOR-004	Up to Week 240	Jul 2011	Q2 2015

Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Study Population	Duration of Treatment	Date of Trial Initiation	Date of Last Patient Visit
MOR-006	• To evaluate the efficacy and safety of weekly IV infusions of 2.0 mg/kg BMN 110 in an MPS IVA patient population with limited ambulation (efficacy as defined by the domains of upper extremity function and dexterity, mobility, pain and self-care functional abilities).	Phase 2, Multinational, Open-Label Study	BMN 110: 2.0 mg/kg/week 4-hour IV infusions	15 (actual)	MPS IVA patients aged 5 years and older who have severely limited ambulation, defined as an inability to walk ≥ 30 meters in the 6MWT	48 weeks	Aug 2012	Q4 2014

Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Study Population	Duration of Treatment	Date of Trial Initiation	Date of Last Patient Visit
MOR-007	Primary treatment phase: • To evaluate safety and tolerability of infusions of BMN 110 at a dose of 2.0 mg/kg/week over a 52-week period in MPS IVA subjects less than 5 years of age Extension phase: • To evaluate the long-term safety of BMN 110 at a dose of 2.0 mg/kg/week in subjects with MPS IVA less than 5 years of age at enrolment	Phase 2, Multinational, Open-Label Study	BMN 110: 2.0 mg/kg/week 4-hour IV infusions	15 with 8 subjects <5 (but ≥3 years of age) (actual)	MPS IVA patients less than 5 years of age	Primary treatment phase: 52 weeks Total study duration including extension treatment phase: Up to 209 weeks	Oct 2011	Q2 2015

Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Study Population	Duration of Treatment	Date of Trial Initiation	Date of Last Patient Visit
MOR-008	Primary treatment phase: • To evaluate the safety of 2.0 and 4.0 mg/kg/week BMN 110 administered for 27 weeks Extension phase: • To evaluate the long-term safety of 2.0 and 4.0 mg/kg/week BMN 110 in subjects with MPS IVA	Phase 2, Randomized, Double-Blind, Multicentre study	BMN 110 2.0 mg/kg/week and 4.0 mg/kg/week 4-hour IV infusions	25 (actual)	MPS IVA patients age 7 years and older who are able to walk at least 200 meters in the 6MWT	Primary treatment phase: 27 weeks Extension phase: up to 130 weeks Total study duration: Up to 157 weeks	Apr 2012	Q4 2014
110-502	•Initial Phase: To evaluate the safety and tolerability of BMN 110 administration in Australian patients with MPS IVA. •Extension Phase: To provide patients enrolled in the Initial Phase access to BMN 110 until commercial product becomes available in Australia and continue to assess long-term safety.	Phase 3B, Multicentre, open-label	BMN 110 2.0 mg/kg/week	13 (actual)	MPS IVA patients at least 12 months of age	57 weeks Initial Phase: 48 Weeks of treatment. Extension Phase: Treatment continuation until BMN 110 is commercially available in Australia	July 2013	Q1 2016

Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Study Population	Duration of Treatment	Date of Trial Initiation	Date of Last Patient Visit
110-503	•To provide patients who have been diagnosed with MPS IVA access to BMN 110 in the United States (US) until commercial product becomes available. •To collect additional information on the safety and tolerability of BMN 110 administration in patients with MPS IVA.	Expanded Access Program (EAP)	BMN 110 2.0 mg/kg/week	57 (actual)	MPS IVA patients (no age limit)	Patients enrolled into the BMN 110 US EAP were eligible to participate in the program until BMN 110 became commercially available.	June 2013	Mar 2014 (actual)

6.2 Study Rationale

The MARS is an observational Registry for patients with MPS IVA. The data collected by this Registry will provide information to better characterise the natural history and progression of MPS IVA in both treated and untreated patients. Data from periodic patient assessments, which are part of current SOC, may be collected to provide long term effectiveness and safety data.

6.3 Summary of Overall Risks and Benefits

There are no additional medical risks for patients participating in the Registry because the Registry collects information from assessments that the patient's doctor may perform during MPS IVA management and/or treatment.

There is no direct medical benefit to patients for being in the Registry. Participation in the Registry may help doctors and researchers learn more about MPS IVA and its treatment and progression. Patients may choose not to participate in this Registry. The decision whether or not to join the Registry will not affect the patient's medical care.

7 RESEARCH QUESTION AND OBJECTIVES

The objectives of the MARS are:

1. To characterize and describe the MPS IVA population as a whole, including the heterogeneity, progression, and natural history of MPS IVA.

2. To evaluate the long-term effectiveness and safety of Vimizim, including, but not limited to, the occurrence of serious hypersensitivity reactions, anaphylaxis, and changes in antibody status.

3. To help the medical community with the development of recommendations for monitoring MPS IVA patients and reports on patient outcomes to optimize patient care.

4. To collect data on other treatments and evaluate the prevalences of their use and their effectiveness.

5. To characterize the effects and safety of Vimizim treatment up to 5 years from enrolment in the Registry for patients under 5 years of age.

6. To monitor pregnancy exposure, including maternal, neonatal, and infant outcomes.

7. To monitor patients who have completed the MOR-005 and MOR-007 clinical trials. These patients will be encouraged to enroll in the applicable Registry Substudy and will be monitored using the MOR-005 and MOR-007 assessment schedules respectively.

8 RESEARCH METHODS

8.1 Study Design

The MARS is a multicentre, multinational, observational Registry for patients with MPS IVA disease, intended to characterise and describe the MPS IVA population as a whole, including the heterogeneity, progression, and natural history of MPS IVA, and to track the safety and clinical outcomes of patients with MPS IVA treated with Vimizim. The data collected by the Registry are intended to enable better characterization of the natural history of MPS IVA and to track patients' clinical responses to various therapies. All patients with a confirmed diagnosis of MPS IVA disease may be eligible to participate in this Registry. Patients are not required to receive Vimizim to be eligible to participate in this Registry.

In addition, this Registry will collect additional data on patients who have completed the MOR-005 and MOR-007 clinical trials through 2 Substudies of this Registry. Patients enrolled in the MARS who previously participated in the MOR-005 and MOR-007 clinical studies will be enrolled into the appropriate Substudy (MOR-005 or MOR-007) for a minimum of 5 years from the time of the patient's enrolment in the MOR-005 clinical study or MOR-007 clinical study. After this 5-year period, these patients should remain in the MARS until the Registry is complete. Patients initially enrolling into 1 of the Substudies will give their consent to participate in both the applicable Substudy and to continue participation in the MARS Registry, following the completion of the respective Substudy, by signing an IRB/IEC/REB-approved ICF/PIAF and assent, if applicable, for both the relevant Substudy and the MARS Registry. Patients who become pregnant and are taking Vimizim may also participate in a pregnancy sub-study (see Section 13).

Investigators are encouraged to record data in line with the Data Elements of Interest, which includes assessments that are currently used to monitor MPS IVA-related clinical manifestations and to stage disease progression across the life-long course of the disease. Data may be collected for all or some of the assessments as outlined in Section 11 and Table 8.1.1.1, dependent upon the individual's current SOC, and whether or not the patient has received treatment for MPS IVA such as Vimizim, HSCT, or BMT.

No specific criteria have been established for the conclusion or early termination of the Registry; however, the approval of new treatments that alter the course of the disease may impact the direction of the program. Investigators will determine the actual frequency of necessary assessments according to a patient's individualized need for medical care and routine follow-up. Data may be collected for all or some of the assessments as outlined in Table 8.1.1.1 dependent upon the patient's current SOC. The Registry will enroll and collect data on patients according to current SOC over a period of at least 8 years from the time of the first marketing approval globally, and data on individual patients will

continue to be collected for at least 2 years from the time that the last patient was enrolled or until the Registry is completed. All of the Registry-specific clinical data collected will be entered into the Registry database.

8.1.1 Data Elements of Interest

Table 8.1.1.1: Data Elements of Interest

Registry Data Elements of Interest[a]	Registry Entry[b]	Every 6 Months	Annually
Confirmation of Mucopolysaccharidosis IV type A (MPS IVA) disease	X		
Informed consent form (ICF)/patient information and authorisation form (PIAF)	X		
Demographics	X		
Medical history[c]	X	X	
Mechanical Ventilation (continuous positive airway pressure [CPAP]/bi-level positive airway pressure [BiPAP]/other)[d]	X	X	
Vital signs	X	X	
Physical examination	X	X	
Tanner Staging[e]	X	X	
Anthropometric measurements[f]	X	X	
Dental examination	X		X
Enzyme replacement therapy (ERT) (Vimizim IV Infusions, if prescribed)	**ERT may be recorded at entry, at any time during Registry participation for newly prescribed use, and for subsequent regimen changes**		
Audiometry[g]	X		X
Ophthalmologic assessments	X	X	
Respiratory function tests	X	X	
Sleep study[h]	X		X
Liver and spleen assessment	X	X	
Electrocardiogram (ECG)	X	X	
Echocardiogram[i]	X		X
6-Minute Walk Test (6MWT)[j]	X	X	
3-Minute Stair-Climb Test (3MSCT)	X	X	

Registry Data Elements of Interest[a]	Registry Entry[b]	Every 6 Months	Annually
Imaging studies:			
Chest x-ray (anteroposterior [AP], lateral)	X		X
Hands/wrists x-ray (AP)	X		X
Hips/pelvis and knees x-ray (AP)	X		X
Lower extremities x-ray (standing AP)	X		X
Plain x-ray of spine (AP view of thoracic and lumbosacral regions and AP lateral flexion-extension view of cervical regions)	X		X
Magnetic resonance imaging (MRI), computed tomography (CT) cervical spine	X		X
MRI, CT hips	X		X
MRI, CT knees	X		X
Upper limb assessment[k]	X	X	
EQ-5D-5L test	X		X
Visual analog scale test (pain measurement scale)	X	X	
Urinary keratan sulfate (KS) and creatinine (to normalize KS)	X	X	
Urinary protein	X	X	
Immunogenicity tests (for immune response to Vimizim)[l]	X	X	
Immunogenicity tests (Drug-specific immunoglobulin E (IgE), Total IgE, Serum tryptase, Complement consumption [C4])[m]	After a severe hypersensitivity adverse event (AE)		
Occurrence of menarche or pregnancy in patient	X	X	
Occurrence of hematopoietic stem cell transplant (HSCT)/bone marrow transplant (BMT)	X	X	
Concomitant medications[n]	X	X	X
AEs[o]	X	X	X
MOR-005 Substudy Additional Assessments[p]	**Registry Substudy Entry**		
MPS Health Assessment Questionnaire	X	X	
MOR-007 Substudy Additional Assessments[p]	**Registry Substudy Entry**		

Registry Data Elements of Interest[a]	Registry Entry[b]	Every 6 Months	Annually
PedsQL™	X	X	
Dual-emission x-ray absorptiometry (DXA) scans[q]			X

[a] Data on all recommended assessments should be collected until conclusion of the Registry at intervals specified in the Data Elements of Interest if consistent with local current SOC. Data for assessments performed at additional time points and as medically indicated at the discretion of the Investigator should also be collected. Additional details are provided in the SRM.

[b] The data to be collected at entry include current as well as historic data, as available. Index is defined as the date of first exposure to Vimizim (may precede or follow Registry entry). Historic data prior to index collected with the data point closest to index in the 12 months prior to index or 1 month after index (except for measurement of urinary keratan sulfate [uKS]) is considered the baseline measurement.

[c] Medical history may be collected at Registry entry and every 6 months thereafter. Detailed medical history may be collected as described in Section 11.4, and will include additional information such as surgical procedures of knee, hip, ankle, and neck and other surgical history, hospitalisations; any complications or sequelae related to surgeries and hospitalisations; history of respiratory infections.

[d] Mechanical ventilation information may be collected on assisted breathing history for CPAP/BiPAP/other.

[e] The developmental history of young patients under the age of 18 may include specific information relating to puberty using the Tanner Series/Scales.

[f] Anthropometric measurements will include height, sitting height, length, head circumference, and weight.

[g] Conventional ear checks for patients ≥ 3 years old should include otoacoustic emissions (OAE). Visual reinforcement audiometry (VRA) should be assessed on patients between the ages of 8 months to 3 years of age.

[h] It is recommended that Sleep study assessment be performed at diagnosis, annually, or as clinically indicated.

[i] Echocardiograms should be performed at diagnosis and repeated after 1 year. If no apparent cardiac involvement is observed, these assessments can be repeated every 3 years. In addition, it is recommended that these assessments be collected prior to major operative intervention.

[j] In additional to the 6MWT findings, information pertaining to the use of wheelchairs and walking aids may be collected.

[k] Upper limb assessment should be performed to test pinch and grip strength (with standardized wrist position), and a 9-hole peg test should also be performed.

[l] Refer to Section 11.23.3 for details.

[m] For patients who experience a severe hypersensitivity reaction temporally associated with a Vimizim infusion. Refer to Section 11.23.3 for details.

[n] Medications (i.e., prescription, over the counter, and herbal) and nutritional supplements taken at Registry entry should be recorded. At each subsequent visit, changes since the previous visit should be recorded.

[o] All serious adverse events (SAEs) occurring in patients administered Vimizim, regardless of causal attribution, should be entered into the Registry database and reported to the BioMarin Pharmacovigilance (BPV) Department. In addition, all AEs, regardless of causality, occurring within 24 hours of Vimizim infusion; all non-serious adverse reactions (ARs) to Vimizim; all occurrences of spinal cord compression in patients participating in the Registry or the Registry Substudies (which are to be reported as SAEs), whether Vimizim was administered or not; and any pregnancy that occurs in a patient administered Vimizim, should be reported both in the Registry database as well as to the BPV Department as outlined in Section 22. General definitions of AEs, SAEs, and severity are provided in Section 22.1 and may be used as reference by the participating Registry sites.

[p] Patients initially enrolling into the Substudies will give their consent to participate in both the applicable Substudy and to continue participation in the MARS Registry, following the termination of the respective Substudy, by signing an ICF/PIAF and assent, if applicable, for both the Substudy and the MARS Registry.

[q] If DXA scans are performed as part of SOC, scan results will be collected.

8.2 Pregnancy Substudy Data Elements of Interest

Table 8.2.1: Pregnancy Substudy Data Elements of Interest

Pregnancy Substudy Data Elements of Interest[a]	Pregnancy Substudy Entry	Pregnancy Month 6	At Birth	Post-Partum			
				Weeks 2-4	2 months	3 months	12 months
ICF/ PIAF	X						
Pregnancy-specific history[b]	X	X		X	X		
Current pregnancy information[c]	X		X				
Neonatal information[d]			X				
Infant information[e]			X			X	X

a. Data on all recommended assessments should be collected until conclusion of the Registry at intervals specified in the Data Elements of Interest if consistent with local current SOC. Data for assessments performed at additional time points and as medically indicated at the discretion of the Investigator should also be collected. Additional details are provided in the SRM.

b. Pregnancy-specific history information will, if possible, include (with sources [e.g., obstetrician, mother] of information provided): known maternal risk factors for adverse pregnancy outcomes including environmental or occupational exposures, and obstetrical history (number of pregnancies and outcome of each [live birth, spontaneous abortion, elective termination, ectopic pregnancy, molar pregnancy], previous maternal pregnancy complications, previous foetal/neonatal abnormalities and type).

c. Current pregnancy information will, if possible, include (with sources [e.g., obstetrician, mother] of information provided): date of last menstrual period; number of foetuses; MPA IVA-specific disease course(s) during pregnancy and any complications; complications during pregnancy (including any adverse drug reactions) and dates; exposures to medications (prescription drugs, over-the-counter [OTC] products, and dietary supplements), including name, dosage, route, date of first use, duration of use, and indication for each; recreational drug use (e.g., tobacco, alcohol, illicit) and amount; and labour and delivery complications.

d. Neonatal information will, if possible, include (with sources [e.g., paediatrician, mother] of information provided): gestational age at birth or termination of pregnancy; gestational outcome (live born, foetal death/stillborn, elective/spontaneous abortion); sex; condition at birth using Apgar scores at 1 and 5 minutes (minimum) plus additional data when available including additional Apgar scores, abnormalities in umbilical cord vessels, blood gases, need for resuscitation, admission to intensive care nursery; weight, length, and head circumference at birth, indicating whether small, appropriate, or large for gestational age; results of neonatal physical examination, including anomalies diagnosed at birth, termination, or in the neonatal period; neonatal illnesses, hospitalisations, and drug therapies.

e. Infant information will, if possible, include (with sources [e.g., paediatrician, mother] of information provided): anomalies diagnosed since initial report; infant weight gain and growth, including percentiles; infant illnesses, hospitalisations, drug therapies, and developmental delays.

8.3 Setting

8.3.1 Study Population

All patients with a confirmed diagnosis of MPS IVA disease may be eligible to participate in this Registry. Patients are not required to receive Vimizim to be eligible to participate in this Registry.

During administration of informed consent, expectations regarding participation in the Registry should be made clear to patients. Patients who are not willing and/or are not able to comply with all aspects of the Registry should not be encouraged to participate.

8.3.2 Inclusion Criteria

Individuals eligible to participate in this Registry must meet all of the following criteria:

- Diagnosed with MPS IVA as confirmed by either GALNS enzymatic test or by a diagnostic molecular test.
- Willing and able to provide written, signed informed consent or, in the case of patients age <18 years, provide written assent (if required) and written informed consent by a legally authorised representative after the nature of the Registry has been explained and prior to any Registry-related procedures.
- Willing to undergo entry assessments to establish baseline data or permit Investigator to enter assessment data recorded prior to Registry entry if available in the patient's medical records. Entry assessments may include: demographics, medical history, urinary keratan sulfate [uKS] level, urinary protein level, immunogenicity testing, vital signs, physical examination, and height and weight.

Patients eligible to participate in the Registry Substudy for MOR-005 must meet all of the following criteria:

- Must have completed the MOR-005 clinical trial.
- Willing and able to provide written, signed informed consent, or, in the case of patients age <18 years, provide written assent (if required) and written informed consent by a legally authorised representative after the nature of the Registry Substudy has been explained and prior to any Registry-related Substudy procedures.
- Willing to permit the Investigator to enter assessment data recorded after completing the MOR-005 clinical trial but prior to Registry Substudy entry if available in the patient's medical records.

Patients eligible to participate in this Registry Substudy for MOR-007 must meet all of the following criteria:

- Must have completed the MOR-007 clinical trial.
- Willing and able to provide written, signed informed consent, or in the case of patients age <18 years, provide written assent (if required) and written informed consent by a legally authorised representative after the nature of the Registry Substudy has been explained and prior to any Registry-related Substudy procedures.
- Willing to permit the Investigator to enter assessment data recorded after completing the MOR-007 clinical trial but prior to Registry Substudy entry if available in the patient's medical records.

8.3.3 Exclusion Criteria

Patients who meet the following exclusion criterion will not be eligible to participate in the Registry or Registry Substudies:

- Currently participating in a BMN 110 (elosulfase alfa) clinical trial.

9 GENETIC TESTING DATA

Morquio A syndrome is a rare, inherited condition with significant heterogeneity in presentation. Morquio A syndrome is caused by mutations in the *GALNS* gene. The precise number of people with Morquio A syndrome is not known, but estimates of global prevalence range from 3,000-3,500. In MPS IVA patients currently identified, to date, more than 220 different variants for the *GALNS* gene have been identified. However, not in all cases has there been an identifiable correlation between genotype and phenotype. In order to more comprehensively understand the relationship (if any), between genotype and disease severity, the Registry will collect genotyping data on the enrolled patients, if available. Permission for collection of this information will be outlined in the Registry informed consent and patients have the right to choose whether or not this data may be included in the Registry database.

10 STUDY TIME PERIOD

Investigators will determine the actual frequency of necessary assessments according to a patient's individualized need for medical care and routine follow-up. Data may be collected for all or some of the assessments as outlined in Table 8.1.1.1 dependent upon the patient's current SOC. The Registry will enroll and collect data on patients over a period of at least 8 years from the time of the first marketing approval globally and data on individual patients will continue to be collected for at least 2 years from the time that the last patient was enrolled or until the Registry is completed. Any decision to terminate the Registry early will only be made with concurrence of Regulatory Agencies.

10.1 Withdrawal of Patient from the Registry

Patients (or their legally authorised representatives) may withdraw their consent to participate in the Registry at any time without prejudice. The Investigator must withdraw from the Registry any patient who requests to be withdrawn. A patient's participation in the Registry may be discontinued at any time at the discretion of the Investigator and in accordance with his/her clinical judgment.

BioMarin also reserves the right to discontinue the Registry at any time for either clinical or administrative reasons (with concurrence of Regulatory Agencies) and to discontinue participation by an individual Investigator or site for poor enrolment or noncompliance.

Reasons for which the Investigator or BioMarin may withdraw a patient from the Registry include, but are not limited to, the following:

- Patient was erroneously admitted into the Registry or does not meet entry criteria
- Patient was lost to follow-up

Specific reason for withdrawal of consent from the Registry will be captured in the Registry database. The Investigator or designee must explain to each patient, before enrolment into the Registry, that, for evaluation of Registry results, the patient's protected health information obtained during the Registry may be shared with the Registry sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act in the US, from each patient or, if appropriate, the patient's legally authorised representative. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request and to ensure that no further data will be collected from the patient and the patient will be removed from the Registry.

11 VARIABLES

Recommended assessments and suggested collection time points are provided in Section 8.1.1, Table 8.1.1.1. A description of each assessment is detailed in the following subsections.

It is anticipated that very young patients or patients with advanced impairment may not be able to complete all assessments requiring physical effort (i.e., 6MWT, 3MSCT, and respiratory function tests) or have the ability to follow complex instructions. All assessments will be performed per the professional judgment of the patient's Investigator or the healthcare team.

11.1 Timepoints

Among enzyme replacement therapy (ERT)-treated patients:

- Registry Entry is defined as at the date of patient signed consent to participate in MARS
- Index is defined as the date of first exposure to Vimizim (may precede or follow Registry Entry)
- Baseline is defined as within 12 months prior to index or within 1 month after index. Historic data prior to index collected with the data point closest to index in the 12 months prior to index or 1 month after index (except for measurement of urinary keratan sulfate [uKS]) is considered the baseline measurement
- Follow-up is defined as the time period after index plus 1 month (Index Date + 30 days +1) to last data point.

Among ERT-naive patients:

- Registry Entry is defined as at the date of patient signed consent to participate in MARS
- Follow-up is defined as the time period from Registry Entry (exclusive) to last data point

11.2 Registry Assessments.

To be included in the Registry, the patient or patient's authorised representative must provide a signed ICF/PIAF. The patient must also have a confirmed diagnosis of MPS IVA.

11.3 Demographics

Demographic information including gender, date of birth (when permitted), and race/ethnicity (when permitted) is collected at Registry entry.

11.4 Medical History

The detailed medical history may include specific information, regardless of relationship to MPS IVA, relating to any prior or existing medical conditions; surgical procedures for knee, hip, ankle, and neck; other surgical history; hospitalisations; any complications or sequelae related to surgeries and hospitalisations; history of respiratory infections; and assisted breathing history, if any. Information on prior (including ERT) and concomitant medications will also be collected.

Assisted breathing history includes duration and number of times continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP), or any other ventilator was used since last visit. Refer to Mechanical Ventilation Section 11.5 for further information on collection of Mechanical Ventilation data.

Medical history may be performed at timepoints indicated in the Data Elements of Interest (Table 8.1.1.1).

11.5 Mechanical Ventilation

For patients requiring mechanical ventilators to assist breathing for any length of time during the Registry, the following information may be collected at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1) and provided for Registry database entry: start and change in ventilator use, frequency of use of ventilator assistance, time spent on ventilator per use, and type of ventilator machine (CPAP, BiPAP or other). Additional details are provided in the SRM.

11.6 Vital Signs

Vital signs, including systolic and diastolic blood pressures (millimeters of mercury), heart rate (beats/minute), respiratory rate (breaths/minute), oxygen (O_2) saturation, and temperature (degrees Celsius) will be performed as per SOC and data collected at timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.7 Physical Examination

Physical examinations may include assessments of general appearance; head, ears, eyes (including evaluation of corneal clouding), nose, and throat; and the cardiovascular; dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems.

Physical examinations will be performed as per SOC and data collected at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.8 Tanner Staging

In patients under 18, specific information relating to puberty (assessment using the Tanner Series/Scales, if available) may be collected, and Tanner Series/Scales may be obtained from the patients' primary care providers to document Tanner staging.

Tanner staging will be performed as per SOC and data collected at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.9 Anthropometric Measurements

Height, sitting height, length, head circumference, and weight will be performed as per SOC and data collected at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1).

For patients unable to stand for height measurements, measurements may be taken in the supine position (length). Additional details are provided in the SRM.

11.10 Dental Examination

Patients may undergo a full dental examination as per SOC and data collected as outlined in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.11 Enzyme Replacement Therapy

Patients do not have to be receiving Vimizim to participate in the Registry; however, for patients receiving Vimizim, ERT information, including the duration of the therapy, should be recorded in the Registry database at Registry Entry, at any time during Registry participation for newly prescribed use, and for subsequent dose changes as outlined in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.12 Audiometry

Age-appropriate audiometry assessments may be performed as per SOC and data collected at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Audiometry data may be used to test the patient's ability to hear various sound frequencies. In addition, the patient's hearing status, including deafness, may be assessed.

Conventional ear checks for patients ≥ 3 years old should include otoacoustic emissions (OAE). Visual reinforcement audiometry (VRA) may be assessed on patients between the ages of 8 months to 3 years of age.

Additional details are provided in the SRM.

11.13 Ophthalmologic Assessments

Ophthalmologic assessments include measurement of visual acuity using a standard eye chart (e.g., Snellen eye chart), and examination of the cornea and the retina and optic nerve. Examination of cornea for evidence of corneal clouding should be performed with a direct ophthalmoscope and graded per treatment centre's guidelines or published methods, (Couprie, 2010), (Fahnehjelm, 2010). Information regarding cornea transplants should also be obtained.

Ophthalmologic assessments may be performed as per SOC and data collected at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.14 Respiratory Function Tests

Results from respiratory function tests should be collected.

The respiratory function assessments may include forced vital capacity, forced expiratory volume in 1 second, forced expiratory time, maximum voluntary ventilation, forced inspiratory vital capacity, total lung capacity and forced inspiratory rate in accordance with American Thoracic Society standards (American Thoracic Society, 1995). If available, respiratory function data for patients with tracheostomies will also be collected. For patients who have a tracheostomy, respiratory function should be evaluated (using a spirometer, if possible) by occluding the tracheostomy and documenting airflow above the tracheostomy, but only if the patient can tolerate the procedure and the Investigator judges that the procedure can be done safely.

Respiratory function tests may be performed as per SOC and data collected at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.15 Sleep Study

Sleep studies should be conducted by standard procedure, including an overnight stay, to determine an apnoea/hypopnea index and level of hypoxia. Support such as CPAP or BiPAP should not be utilized during this assessment, unless clinically indicated. Time spent under O_2 saturation level of 90% may be recorded along with number of O_2 saturation decreases below 90% in a 24-hour period.

Sleep studies may be performed as per SOC and data collected at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.16 Liver and Spleen Assessment

Liver and spleen volume/size may be assessed by palpation, magnetic resonance imaging (MRI), computed tomography (CT) scan, or ultrasonography.

Liver and Spleen Assessments performed per the current SOC should be collected in the Registry. Additional details are provided in the SRM.

11.17 Electrocardiogram and Echocardiogram

Standard 12-lead electrocardiograms (ECGs) including heart rate, rhythm, intervals, axis, conduction defects performed per the current SOC should be collected in the Registry.

Cardiac anatomy and function should be evaluated by a standard 2-dimensional Doppler echocardiogram, and the data recorded should include valve characterization, ventricular wall thickness, and septal wall motion. Data from an echocardiogram performed within 1 year prior to enrolment may be used. If no apparent cardiac involvement is observed after the 1-year assessment, it is recommended that these assessments can then be repeated every 3 years. In addition, it is recommended that these assessments be collected prior to major operative intervention.

Additional details are provided in the SRM**.**

11.18 6-Minute Walk Test

A 6MWT should be performed per the treatment centre's endurance testing protocol. In addition, information pertaining to the use of wheelchairs and walking aids may be collected. Patients are instructed to walk as far as possible in 6 minutes. Data from this test will provide information about the patient's endurance (McGavin, 1976); (Butland, 1982), (Nixon, 1996).

The 6MWT may be completed at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.19 3-Minute Stair Climb Test

A 3MSCT should be performed per the treatment centre's protocol as a measure of endurance (Pollock, 1993); (Bolton, 1994.) unless clinically contraindicated. Patients are instructed to walk upstairs as far as possible in 3 minutes.

The 3MSCT may be completed at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.20 Imaging

The views typically included for imaging assessment are x-ray of spine (anteroposterior [AP] view of thoracic and lumbosacral regions, and AP lateral, flexion-extension view of cervical regions), x-ray of the chest (AP and lateral view), x-ray of the hips/pelvis and

knees (AP view), lower extremities x-ray (standing AP), and x-ray of hands/wrists (AP view).

Imaging performed per the current SOC should be collected in the Registry. Additional details are provided in the SRM.

11.20.1 MRI and CT of Spine, Hips, and Knee

MRI and CT data of spine, hips, and knees may be collected if these are performed per the current SOC. MRI and CT data for cervical spinal stenosis or cervical cord compression should be recorded in the Registry database.

Imaging studies will also be read centrally for patients in the MOR-005/007 Substudies.

Additional details are provided in the SRM.

11.20.2 Dual-Emission X-ray Absorptiometry

Data from DXA bone mineral density will be collected from patients in the MOR-007 Registry Substudy if these are performed per the current SOC. Additional details are provided in the SRM.

Imaging studies will also be read centrally for patients in the MOR-007 Substudy.

11.21 Upper Limb Assessment

Upper limb assessment should be performed to test pinch and grip strength (with standardized wrist position), and a 9-hole peg test should be performed.

The Upper Limb Assessment Imaging performed per the current SOC should be collected in the Registry (Table 8.1.1.1). Additional details are provided in the SRM.

11.22 Quality of Life Assessments

11.22.1 EQ5D5L Test

The EQ-5D-5L (EuroQol Group, Rotterdam, Netherlands) test is used to evaluate patient perception of impairment and improvement. The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and is applicable to a wide range of health conditions and treatments, and it provides a simple descriptive profile and a single index value for health status. The test will be completed by parent or guardian for patients who are under 14 years of age with patient input.

The EQ-5D-5L test may be completed at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.22.2 Visual Analog Scale

The Visual Analog Scale measures pain perception. The test will be completed by parent or guardian for patients who are under 14 years of age with patients input.

The Visual Analog Scale may be completed at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.22.2.1 MPS Health Assessment Questionnaire

MARS Registry patients enrolled in the MOR-005 Registry Substudy will be asked to complete the MPS Health Assessment Questionnaire.

The MPS Health Assessment Questionnaire was developed to assess the self-care and mobility skills of patients with Mucopolysaccharidosis type I. The questionnaire includes self-care (eating/drinking, dressing, bathing, grooming, tooth brushing, and toileting) and mobility domains (dexterity, mobility, walking, stair climbing, and gross motor skills). Caregiver assistance items are also included to assess the extent to which assistance is required for the performance of activities related to the self-care and mobility domains.

The MPS Health Assessment Questionnaire will be completed by a parent or guardian for patients who are under 14 years of age with patient input. Refer to Section 12 for further details of the MOR-005 Registry Substudy.

The MPS Health Assessment Questionnaire will be completed at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.22.3 PedsQL™ Measurement Model for Pediatric Quality of Life Inventory

MARS Registry patients enrolled in the MOR-007 Registry Substudy will be asked to complete the Measurement Model for the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales, which are designed to measure Quality of Life in children and adolescents. The assessments are brief, practical and developmentally appropriate. The instrument is responsive to clinical change over time (Msall, 2005). There are 2 parent reports, which cover the ages from 2-4 years and 5-7 years and include questions regarding physical, emotional, and social functioning, with school functioning where applicable. Patients who become older than age 7 years during the Registry Substudy will no longer be assessed using this tool. Refer to Section 12 for further details of the MOR-007 Registry Substudy.

The PedsQL Generic Core Scales Questionnaire may be completed at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.23 Clinical Laboratory Tests

11.23.1 Urinary Keratan Sulfate and Creatinine Levels

Urine KS and urine creatinine (for normalization of KS levels) are assessed to determine the level of KS through quantitative analysis. Urine samples collected to monitor uKS

may be assayed at the participating Registry site as per the institutions' laboratory guidelines and procedures and/or at BioMarin's designated laboratory. Typically, a sample of approximately 30 mL of midstream urine is collected (should be first morning void) from each patient, frozen for storage (-70 °C) and shipped to the laboratory.

Urine KS and urine creatinine testing may be completed as per SOC and data collected at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.23.2 Urinary Protein

Urinary protein levels, to track proteinuria, should be collected for all MPS IVA patients.

Urinary protein levels may be tested as per SOC and data collected at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.23.3 Immunogenicity Testing

The formation of antibodies is common in people receiving intravenous (IV) protein products, and, in the clinical studies for Vimizim, all treated patients developed anti-drug antibodies. The primary objective of antibody monitoring is to better understand the immune response to Vimizim within the MPS IVA patient population and the potential impact on safety and effectiveness. For more information, please refer to the Vimizim Summary of Product Characteristics. Results from these tests are for informational purposes only and must not be used for patient assessment, diagnosis and/or treatment.

Immunogenicity testing should be completed for patients receiving Vimizim (if allowed per current SOC) as described within this section and at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1) and should only be taken for patients receiving Vimizim. Additional details, including further sample collection and shipping guidelines, are provided in the SRM.

Routine Immunogenicity Sample Collection

- At Registry entry, serum samples may be collected for antibody testing for:
- Total anti-drug antibodies (TAbs)
- Neutralising antibodies (NAbs)
- Drug-specific immunoglobulin E (IgE)
- Total IgE

Total IgE samples obtained at study entry should be collected and tested as per the Institution's protocol for future analysis of total IgE, serum tryptase, and complement consumption (C4) by the treatment centre's local laboratory. The drug-specific IgE sample collected at study entry will be stored at BioMarin's designated laboratory for

future comparison in the event of a severe hypersensitivity reaction, a serious reaction temporally related to a Vimizim infusion, or anaphylaxis.

Serum samples for TAb and Nab testing may be collected according to the Data Elements of Interest, international guidelines, and the discretion of the investigator. If the serum sample tests positive for TAb, NAb testing will also be performed. If the sample tests negative for TAb, NAb testing will not be performed.

Additional TAb and NAb samples may be collected in the event of a suspected loss of treatment effect. Investigators are asked to contact the BioMarin Medical Monitor regarding patients who experience an unexplained or persistent change in clinical outcome measurements or a persistent increase in urine KS levels of at least 50% compared to values within the last 6 months (indicating a possible change in pharmacodynamic activity) at any time during Registry participation.

Hypersensitivity Adverse Event Sample Collection

If a patient experiences a severe hypersensitivity reaction temporally associated with a Vimizim infusion, Investigators are asked to collect additional serum samples for testing of:

- Drug-specific IgE
- Total IgE
- Serum tryptase
- C4

A serum sample for detecting total IgE, serum tryptase, and C4 should be collected while the patient is experiencing the reaction. A serum sample for drug-specific IgE should be collected no sooner than 6 to 8 hours post infusion.

11.24 Occurrence of Pregnancy and Menarche

Female patients may be asked about their pregnancy and menarche status as outlined in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

If a patient receiving Vimizim treatment becomes pregnant while enrolled in MARS, the patient may participate in the Pregnancy Substudy. Please refer to Section 13 for further details regarding the Pregnancy Substudy.

In addition, all pregnancies in patients receiving Vimizim treatment will need to be reported to BioMarin Pharmacovigilance (BPV) regardless of enrolment in Pregnancy Substudy. Please refer to the AE reporting, Section 22, for further reporting instructions.

11.25 Occurrence of Hematopoietic Stem Cell Transplant/Bone Marrow Transplant

If a patient has received a HSCT or BMT prior to enrolment into the Registry, Investigators may report this by entering data into the Registry database. If the transplantation occurs during the patient's participation in the Registry, this would be considered a reportable serious adverse event (SAE) if the patient is receiving Vimizim (Section 22) and should be reported to BPV in addition to entry into the Registry database.

Information on occurrence of HSCT/BMT may be collected at timepoints indicated in the Data Elements of Interest (Table 8.1.1.1). Additional details are provided in the SRM.

11.26 Prior and Concomitant Medications

Medications (i.e., prescription, over-the-counter [OTC], and herbal) and nutritional supplements taken at Registry entry should be entered into the Registry database. At each subsequent visit, changes since the previous visit should be recorded. Additional details are provided in the SRM.

12 MOR-005 AND MOR-007 SUBSTUDIES

In order to further characterise the spectrum of clinical signs and symptoms of MPS IVA disease, and to further characterise the clinical outcomes and safety profile of Vimizim in patients who have completed the MOR-005 and MOR-007 clinical trials, this Registry will collect additional data on patients who have completed enrolment in the MOR-005 and MOR-007 clinical trials through 2 Substudies of this Registry. The MOR-005 and MOR-007 patients will be enrolled into the appropriate Substudy for a minimum of 5 years from the time of enrolment in the MOR-005 clinical study or MOR-007 clinical study. After the 5-year period, these patients are encouraged to remain in the MARS Registry until the Registry is complete. Participants of the MOR-005 and MOR-007 Substudies must provide written authorisation (ICF/PIAF) or, if under 18 years, provide written assent (if required) and written authorisation (ICF/PIAF) by a parent or legal guardian.

Patients enrolled in the MOR-005 or MOR-007 Substudies should complete assessments as outlined in the MARS Registry Data Elements of Interest (Table 8.1.1.1). Data from additional assessments may also be collected for these Substudy patients such as the MPS Health Assessment Questionnaire, DXA scans, and the PedsQL Measurement Model for Pediatric Quality of Life Inventory at the timepoints suggested in the applicable Substudy Data Elements of Interest (Table 8.1.1.1). The MPS Health Assessment Questionnaire will be completed by a parent or guardian for patients who are under 14 years of age.

In addition to completing the assessments for the overall MARS Registry, patients enrolled in the MOR-007 Registry Substudy will be asked to complete the PedsQL Generic Core Scales (Section 11.22.3). Patients who become older than age 7 during the Registry Substudy will no longer be assessed using this tool. The age-appropriate PedsQL should be completed at the timepoints indicated in the Data Elements of Interest (Table 8.1.1.1).

Imaging studies will also be read centrally for patients in the MOR-005/007 Substudies.

Data collected for patients enrolled in the Substudies will be used for the long-term analysis of safety and effectiveness of Vimizim as per the original MOR-005 and MOR-007 studies. Additional details are provided in the SRM.

13 PREGNANCY SUBSTUDY

This section provides an overview of the assessments for pregnant patients.

Vimizim should be used during pregnancy only if the benefits outweigh the risks as assessed by the treating physician. In addition, all pregnancies in patients receiving Vimizim must be reported to BPV regardless of enrolment in the Pregnancy Substudy. Please refer to Section 22 for AE reporting requirements.

Patients who become pregnant while receiving Vimizim will be encouraged to enroll in the Pregnancy Substudy. To be eligible to participate in the Pregnancy Substudy, patients must have received at least 1 infusion of Vimizim while pregnant. Patients who want to enroll in the Pregnancy Substudy must also provide written authorisation (ICF/PIAF) or, if under 18 years, provide written assent (if required) and written authorisation (ICF/PIAF) by a parent or legal guardian. The ICF/PIAF will detail maternal and infant outcome assessment data to be collected (including the patient's pregnancy-specific history and current pregnancy, neonatal, and infant information) from the patient and, if possible, from the patient's obstetrician and the infant's paediatrician.

Pregnancy-specific history information to be collected will, if possible, include (with sources [e.g., obstetrician, mother] of information provided): known maternal risk factors for adverse pregnancy outcomes including environmental or occupational exposures, and obstetrical history (number of pregnancies and outcome of each [live birth, spontaneous abortion, elective termination, ectopic pregnancy, molar pregnancy], previous maternal pregnancy complications, previous foetal/neonatal abnormalities and type.
This information will be collected at enrolment into the Pregnancy Substudy at the timepoints specified in the Data Elements of Interest (Table 8.2.1).

Current pregnancy information to be collected will, if possible, include (with sources [e.g., obstetrician, mother] of information provided): date of last menstrual period; number of foetuses; MPA IVA-specific disease course during pregnancy and any complications; intercurrent illnesses and complications during pregnancy (including any adverse drug reactions) and dates; exposures to medications (prescription drugs, OTC products, and dietary supplements), including name, dosage, route, date of first use, duration of use, and indication for each; recreational drug use (e.g., tobacco, alcohol, illicit) and amount; and labour and delivery complications. This information will be collected at enrolment into the Pregnancy Substudy at the timepoints specified in the Data Elements of Interest (Table 8.2.1.).

Upon delivery of the infant or termination of the pregnancy, neonatal information to be collected will, if possible, include (with sources [e.g., paediatrician, mother] of information provided): the neonate's gestational age at birth or termination of pregnancy; gestational outcome (live born, foetal death/stillborn, elective/spontaneous abortion); sex;

condition at birth using Apgar scores at 1 and 5 minutes (minimum) plus additional data when available including additional Apgar scores, abnormalities in umbilical cord vessels, blood gases, need for resuscitation, admission to intensive care nursery; weight, length, and head circumference at birth, indicating whether small, appropriate, or large for gestational age; results of neonatal physical examination, including anomalies diagnosed at birth, termination, or in the neonatal period; and neonatal illnesses, hospitalisations, and drug therapies. This information will be collected at enrolment into the Pregnancy Substudy at the timepoints specified in the Data Elements of Interest (Table 8.2.1.).

Please refer to local labelling for recommendations on the use of Vimizim during breastfeeding.

Infant information to be collected will through 12 months of age, if possible, include (with sources [e.g., paediatrician, mother] of information provided): anomalies diagnosed since initial report; infant weight gain and growth, including percentiles; and infant illnesses, hospitalisations, drug therapies, and developmental delays.

Additional details are provided in the SRM.

14 SHIPPING OF URINARY KERATAN SULFATE AND IMMUNE RESPONSE SAMPLES

Urine samples collected to monitor uKS may be assayed at the participating Registry site as per the institutions' laboratory guidelines and procedures and/or at BioMarin's designated laboratory. Serum samples to monitor immune response will be assayed by BioMarin's designated laboratory.

15 DATA SOURCES

The Registry database maintained by BioMarin or designated vendor will collect data from all participating sites. Study site personnel at participating sites will directly enter assessments' results into the database. The validity of the data will be monitored by audit and comparing to source documents as described in Section 16.2 and Section 19. Statistical analyses will be performed as described in Section 18 and the SAP.

16 DATA MANAGEMENT

16.1 Patient Identification

All patient information is strictly confidential. Each patient will be identified by a unique patient identifier. Patients will not be identified by name for the purposes of data collection. In legal jurisdictions where the use of initials is not permitted, a substitute identifier will be used.

16.2 Case Report Forms and Source Documents

The Electronic Case Report Forms (eCRFs) must be completed using a web–based application developed and validated by BioMarin or designee. Study site personnel will be trained on the application and will enter the clinical data from source documentation. Unless explicitly allowed according to the eCRF instructions, blank data fields are not acceptable.

In the event of an entry error, or if new information becomes available, the site personnel member will correct the value by deselecting the erroneous response and then selecting or entering the factual response. In compliance with the US Code of Federal Regulations (CFR) 21 CFR §11, the system will require the site personnel member to enter a reason for changing the value. The documented audit trail will include the reason for the change, the original value, the new value, the time of the correction, and the identity of the operator.

BioMarin's policy is that study data on the eCRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and patient records. In addition, all source data should be attributable (signed and dated).
The Investigator must therefore agree to allow direct access to all source data. Patients (or their legally authorised representatives) must also allow access to their medical records, and patients will be informed of this and will confirm their agreement when giving informed consent. If an Investigator or Institution refuses to allow access to patient records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by BioMarin will compare the eCRFs with the original source documents at the study site and evaluate them for completeness and accuracy before designating them as "Source Data Verified." If an error is discovered at any time or a clarification is needed, the CRA or designee will create an electronic query on the associated field. Site personnel will then answer the query by either correcting the data or responding to the query. The CRA will then review the response and determine either to close the query or re–query the site if the response does not fully address the question. This process is repeated until all open queries have been answered and closed.

Detailed procedures for data collection and submission will be provided to participating sites in the SRM.

17 RETENTION OF RECORDS

The Investigator must retain all study records required by BioMarin and by the applicable regulations in a secure and safe facility. The Investigator must consult a BioMarin representative before disposal of any study records, and must notify BioMarin of any change in the location, disposition, or custody of the study files. The Investigator/Institution must take measures to prevent accidental or premature destruction of essential documents, i.e., documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., patient charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

The Investigator/Institution should retain patient files and other source data in accordance with the country-specific regulatory requirements for data retention. BioMarin must be notified and will assist with retention should the Investigator/Institution be unable to continue maintenance of patient files for the term required. BioMarin is responsible for informing the Investigator/Institution as to when these documents no longer need to be retained.

18 DATA ANALYSIS

18.1 Statistical and Analytical Plans

A SAP will provide full details of analyses and will be finalized prior to data analysis.

18.1.1 Study Dosage and Administration

Enrolled patients may have access to treatment of Vimizim, and such treatment information may be recorded by study personnel at the Registry sites. Based on the available data, the total number of doses received, total duration of exposure, and mean weekly dose may be presented by treatment groups using summary statistics such as n, mean, SD, median, minimum, and maximum.

18.1.2 Sample Size Determination

All MPS IVA patients will be invited to enrol in the Registry, assuming all regulatory requirements are met for sites that have agreed to participate, in countries where marketing authorisation has been granted.

The sample size of the study is not determined by statistical power consideration, as no statistical hypotheses are posed.

18.1.3 Interim Analysis

In addition to annual reporting, interim analyses will be conducted to support regulatory health authority commitments.

18.1.4 General Analysis Considerations

Descriptive summaries of continuous variables will include the mean, SD, median, range, and 95% confidence interval and/or inter-quartile range when appropriate. Descriptive summaries of categorical variables will include n and percent. When possible/applicable graphical summary statistics over time and/or summary statistics accounting for time will be utilized.

Statistical tests will be two-sided at the 0.05 level, unless otherwise specified. All confidence intervals will be two-sided 95% confidence intervals, unless otherwise specified. All statistical tests and associated p-values will be considered nominal. See Section 11.1 for definitions of timepoints.

18.1.5 Analysis Populations

18.1.5.1 Safety Population

The Safety Population will consist of all patients who receive at least 1 dose of Vimizim at or after registry entry.

18.1.5.2 Full Analysis Set Population

The Full Analysis Set will consist of all patients diagnosed with MPS IVA who provide written, signed informed consent or, in the case of patients aged <18 years, those for whom written assent (if required) and written informed consent by a legally authorised representative are provided.

18.1.5.3 Treatment Groups

ERT-naïve patients are defined as the group of patients who had never received Vimizim either prior to the Registry enrolment, or during Registry participation. ERT-treated patients are defined as the group of patients who had received at least 1 dose of Vimizim either prior to the Registry enrolment, or during Registry participation. Time on ERT treatment (defined as ERT infusion date +7 days) and not on treatment during follow-up will be identified.

Analysis of clinical outcomes, demographic and baseline characteristics will be conducted, stratified by the 2 treatment groups (ERT-naïve patients vs ERT-treated patients). Due to the observational nature of the Registry, ERT-treated patients may discontinue treatment. Treatment discontinuation will be defined based on the stop date reported in the enzyme replacement log plus 7 days (to include events potentially occurring 'on treatment' before the next anticipated infusion, if the date of last infusion was the documented stop date). Outcome analyses among the ERT-treated will generally be censored at the time of discontinuation (i.e. an 'as treated' analysis). Exceptions to this convention will be detailed in the SAP.

If there are significant numbers of patients who discontinue treatment and re-initiate, sensitivity analysis may be performed by describing outcomes during the period of re-initiation.

18.1.6 Handling of Dropouts and Missing Data

Patients who discontinued the Registry prematurely will not be replaced. The following missing data imputation rules will apply to all analyses unless otherwise specified elsewhere in the SAP. Missing dates or partially missing dates will be imputed conservatively for concomitant medications and AEs to ensure that an AE is considered treatment emergent and has the longest possible duration. Data in regards to reason for drop out or discontinuation of the Registry will be analysed.

18.1.7 Safety and Clinical Outcome Analysis

Separate data analyses of the MOR-005 and MOR-007 Substudies will be performed per the MOR-005 and MOR-007 Substudy SAPs. For the MOR-005 Substudy analyses, data from the MOR-005 substudy will be combined with data from the MOR-005 clinical study. A similar analysis will be provided for the MOR-007 Substudy data.

Analyses performed to address the objectives of this study will consider both clinical outcome variables and safety variables. The clinical outcome variables include endurance tests (6MWT and 3MSCT), anthropometric measurements, urine KS concentration (normalized to creatinine), respiratory function tests, number of respiratory infections, assisted breathing history, duration and number of times CPAP or BiPAP was used during the year, echocardiograms, surgeries, quality of life assessments (EQ-5D-5L test in all patients, MPS Health Assessment Questionnaire for MOR-005 Substudy patients only, PedsQL for MOR-007 Substudy patients only), ophthalmologic assessments, audiometric assessments, liver and spleen assessments, progression of skeletal deformities, frequency and time to orthopaedic surgeries, and Tanner Series/Scales. The safety variables include AEs, concomitant medications, occurrence of BMT/HSCT, clinical laboratory tests, vital signs, ECGs, echocardiograms, immunogenicity results, physical examinations, imaging studies, and cervical spine imaging.

Objective 1: To characterize and describe the MPS IVA population as a whole, including the heterogeneity, progression, and natural history of MPS IVA.

In order to characterise and describe the MPS IVA population as a whole, clinical outcomes variables as specified in Table 8.1.1.1 and demographics will be summarised in the 12 months prior to or 90 days after Registry Entry (for consistency with data entry at Registry Entry) stratified by ERT status at Registry Entry. The measurement closest to Registry Entry during this period will be used to describe patients. The natural history and progression of MPS IVA will be described in ERT-naïve and ERT-treated patients based on measurements while not on ERT treatment (i.e. all measurements for ERT-naïve and prior to index for ERT-treated), with progression of the disease based on measurements of clinical outcomes described over time and presented by age.

Objective 2: To evaluate the long-term effectiveness and safety of Vimizim.

The long-term effectiveness of Vimizim will be evaluated as described below using clinical outcome variables as specified in Table 8.1.1.1 based on measurements at baseline through discontinuation or end of follow-up (which ever occurs first) based on the ERT-treated patients in the Full Analysis Set population. The measurement closest to the index date during the baseline period will be used to describe patients prior to initiating therapy (i.e. ‘baseline measurement’), with the exception of uKS. For uKS, the ‘baseline measurement’ will be restricted to measurements occurring during the baseline period prior to or at index. As MPS IVA is a degenerative disease (Harmatz , 2013), a sensitivity analysis will be conducted for the outcomes of 6MWT, respiratory function, height, weight, and uKS limiting the baseline period to the 6 months before index and 30 days after index (with the same caveat for uKS as the primary analysis).

Whenever possible and/or relevant to the outcome, outcomes will be described graphically accounting for time and/or age at the assessment. When warranted by the outcome of interest, outcomes will be summarised as event rates censored at time of discontinuation or data cutoff. Change and/or percent change from baseline to follow-up outcome measurements after pre-specified amounts of exposure (e.g. after 1 or 5 years of exposure) will only be summarised for patients with a baseline measurement and a relevant follow-up measurement (near the specified time) prior to discontinuation. Additional details of analyses can be found in the SAP.

Long-term safety events occurring during MARS after index or registry entry (which ever occurs later), including hypersensitivity events, will be evaluated by summarising the incidences of AEs by System Organ Class, Preferred Term, relationship to Vimizim, and severity in the Safety Population. Exposure-adjusted incidence rates and event rates while on treatment will be included as part of long-term safety evaluation. All AE summaries will include only treatment-emergent adverse events (TEAEs) and SAEs reported during the study period (AEs that occur after the first Vimizim infusion). Analyses of AEs of hypersensitivity and anaphylaxis, and AEs temporally related to a Vimizim infusion will be summarised by System Organ Class, PT, and severity All AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA).

Total and neutralizing antibody status will be summarised over the follow-up period.

Objective 3: To help the medical community with the development of recommendations for monitoring MPS IVA patients and reports on patient outcomes to optimize patient care.

In light of the recent publication of International treatment guidelines for MPS IVA, no specific analyses are planned to address this objective. Analyses conducted to address other objectives will contribute to publication(s) and inform the medical community on natural history and patient outcomes, along with describing 'real world' monitoring practices. See Section 24 describing plans for disseminating and communicating results.

Objective 4: To collect data on other treatments and evaluate the prevalences of their use and their effectiveness.

The prevalence (e.g. count and frequency) of patients using other treatments indicated for the treatment of MPS IVA will be summarised (itemised in the SAP). Data on other treatments that directly affect MPS outcomes will be collected and this data will be provided in listings as well as counts and frequencies. Effectiveness will be summarised for these other treatments consistent with Objective 2, providing that the treatment is indicated for the treatment of MPS IVA and utilised to treat >5% of the MARS population.

Concomitant medications and surgeries utilized to treat manifestations of disease will be summarised as part of Objective 2.

Objective 5: To characterize the effects and safety of Vimizim treatment up to 5 years from enrolment in the Registry for patients under 5 years of age.

Analyses consistent with those conducted to address Objective 2 will be repeated for patients with an index date occurring when the patient was <5 years of age. Analyses will be presented for safety and outcomes occurring in the 5 years after index. These analyses will include, but are not limited to, AEs, 6MWT, anthropometric evaluations, and uKS.

Objective 6: To monitor pregnancy exposure (including maternal, neonatal, and infant outcomes)

All pregnancy and neonatal data will be presented in listings regardless of enrolment in Pregnancy Substudy.

Objective 7: To monitor patients who have completed the MOR-005 and MOR-007 clinical trials.

Analyses will be repeated for the subgroup of patients in the MOR-005 Substudy and the subgroup of patients in the MOR-007 Substudy. These analyses will include but will not be limited to AEs, 6MWT, anthropometric evaluations, and uKS.

18.1.8 Changes in the Conduct of the Study or Planned Analyses

After a study has been commenced, any substantial amendments to the study protocol will be submitted, before implementation, to the Pharmacovigilance Risk Assessment Committee (PRAC) according to the provisions of Article 107 of the Directive 2001/83/EC and GVP Modules i.e. GVP Module VIII and GVP Module VIII Addendum I. Any change in study conduct considered necessary by the Investigator will be made only after consultation with BioMarin, which will then issue a formal protocol amendment to implement the change.

With the exception of minor administrative or typographical changes, the IRB/IEC/REB must review and approve all protocol amendments. Protocol amendments that have an impact on patient risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/IEC/REB prior to their implementation.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the ICF will be amended and approved by BioMarin and the IRB/IEC/REB, and all active patients must again provide informed consent.

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

19 QUALITY CONTROL

BioMarin personnel or designees will review with the site personnel information about the protocol and other regulatory document requirements, source document requirements, eCRF data entry requirements, monitoring requirements, and procedures for reporting AEs and SAEs.

At visits during and after the Registry, a BioMarin CRA or designee will monitor the sites for compliance with regulatory documentation requirements, focusing on accurate and complete recording of data from source documents on eCRFs, adherence to the protocol and protocol--specified AE/SAE reporting. Discussion of the quality of data entered as well as any gaps in data being entered into the electronic data capture (EDC) system will be addressed with each site staff during site initiation training and subsequent site visits to ensure completeness and accuracy of data. To ensure tracking of the data and patients, sites will also participate in planned remote monitoring visits by telephone with the BioMarin CRA or designee approximately twice per year specifically to discuss data entry and query resolution.

Data quality control and analysis will be performed by BioMarin or a designee, based on a predefined analysis plan.

19.1 Study Monitoring and Auditing

Qualified individuals designated by BioMarin will monitor all aspects of the Registry according to Good Clinical Practice (GCP) and standard operating procedures for compliance with applicable government regulations. The Investigator agrees to allow these monitors direct access to the Registry supplies and storage areas as well as to the Registry files, including original medical records of the study patients, and, if requested, agrees to assist the monitors. The Investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by BioMarin or its designees.

Sites will be visited by a BioMarin CRA or designate approximately 2 times per year for monitoring purposes. During this time, patient recruitment efforts, data entry requirements, and findings from source document verification (SDV) against the data entered into the EDC system will be reviewed with site staff. Discussion of the quality of data entered as well as any gaps in data will occur with site staff to ensure completeness and accuracy of data.

To ensure tracking of the data and patients, sites will be contacted approximately 2 times per year via remote monitoring teleconferences in between the on-site visits. These planned discussions will include the same items as the on-site visits with the exception of

the SDV. These calls are also an opportunity for site personnel to ask questions and receive any training that may be necessary on the protocol or EDC system.

Patient recruitment activities and the importance of entering patients into the Registry will be discussed with personnel at each participating site prior to Registry activation in an effort to ensure that all MPS IVA patients followed by the sites are contacted and informed of the Registry so that the maximum number of MPS IVA patients, both treated and untreated with Vimizim, can be enrolled. Enrolment goals, data collection, and safety reporting activities will be an ongoing discussion with sites during on-site and remote monitoring visits.

Members of BioMarin's GCP Compliance Department or designees may conduct an audit of a Registry site at any time before, during, or after completion of the study.
The Investigator will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the US FDA or other Regulatory Agencies may also conduct an inspection of the study. If informed of such an inspection, the Investigator should notify BioMarin immediately. The Investigator will ensure that the auditors and inspectors have access to the Registry supplies, study site facilities, original source documentation, and all study files.

20 LIMITATIONS OF THE RESEARCH METHODS

All assessments will be performed per participating centres' current SOC and patients' clinical management needs determined by their physicians. Thus, data for all recommended assessments may not be collected for all patients. However, Investigators are required to report AEs/ARs as described in Section 22.

20.1 Other Aspects

None.

21 PROTECTION OF HUMAN SUBJECTS

BioMarin aims to conduct its studies according to the highest ethical and scientific standards. The following sections articulate standards to which Investigators will be held accountable, as well as matters of compliance to document adherence to such standards.

21.1 Institutional Review Board, Independent Ethics Committee, and Research Ethics Board

Investigators are expected to interact with IRBs/IECs/REBs promptly, as required, during the course of the Registry. This includes, but is not limited to, providing appropriate documentation to support Registry initiation and maintaining appropriate flow of safety and other information during the course of the Registry and for Registry close-out activities. BioMarin (or designee) will assist Investigators with access to timely and accurate information and assure prompt resolution of any queries.

Prior to initiating the Registry, the Investigator will obtain written confirmation that the IRB/IEC/REB is properly constituted and compliant with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and GCP requirements, applicable laws, and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to BioMarin or its designee.

The Investigator will provide the IRB/IEC/REB with all appropriate material, including the protocol, the ICF/PIAF including compensation procedures, and any other written information provided to the patients, including. including translated ICFs/PIAFs. The Registry will not be initiated until appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol, the ICF/PIAF, and all patient recruitment materials are obtained in writing by the Investigator and copies are received at BioMarin or its designee. The approval document should refer to the Registry by protocol title and BioMarin protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. BioMarin will ensure that the appropriate reports on the progress of the Registry are made to the IRB/IEC/REB by the Investigator in accordance with applicable guidance documents and governmental regulations.

21.2 Ethical Conduct of Study

It is expected that Investigators understand and comply with the protocol and attest to this by signing the Signature Page (Section 29).

- This Registry will be conducted in accordance with the following:

- US CFR sections that address clinical research studies, and/or other national and local regulations, as applicable
- ICH Harmonised Tripartite Guideline: Guideline for GCP E6 (ICH E6 R2)
- The ethical principles established by the Declaration of Helsinki
- Regulation (EC) No 726/2004, Directive 2001/83/EC and Commission Implementing Regulation (EU) No 520/2012
- General Data Protection Regulation (GDPR) Regulation (EU) 2016/679
- Guideline on good pharmacovigilance practices (GVP) Module VIII

The Registry will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons. The benefits of the Registry are in proportion to the risks. The rights and welfare of the patients will be respected and the Investigators conducting the Registry do not find the hazards to outweigh the potential benefits. Each patient or his/her legally authorised representative will provide written, informed consent before any data from evaluations, which are part of current SOC, are collected and entered into the Registry database.

21.3 Patient Information and Informed Consent

A properly written and executed ICF/PIAF, in compliance with the Declaration of Helsinki, ICH E6 R2, US 21 CFR §50 and other applicable local regulations, will be obtained for each patient prior to entering the patient into the Registry.

BioMarin will provide the Investigator with the Registry specific ICF/PIAF templates and the Investigator will be responsible for updating these templates as required by the Institution. The templates updated by the Investigator will then need to be returned to BioMarin or designee for approval prior to submission to the IRB/IEC/REB. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF/PIAF and assent form, and if applicable, a copy of the approved patient information sheet and all ICFs translated to a language other than the native language at the Registry site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

Patients under the age of 18 years or as required by local regulations will provide written assent (if required), and his/her legally authorised representative (parent or legal guardian) will provide written informed consent for such patients. The Investigator will provide copies of the signed ICF/PIAF to each patient (or the legally authorised representative of the patient) and will maintain the original in the record file of the patient.

21.4 Compensation, Insurance and Indemnity

BioMarin will not pay for the costs of tests, procedures, or treatments described in this Registry, with the exception of costs associated with shipping and processing of uKS and immunogenicity samples sent to BioMarin's designated laboratory. BioMarin will not pay for any hospitalisations, tests, or treatments for medical problems of any sort, whether or not related to the patient's disease. Costs associated with hospitalisations, tests, and treatments should be billed and collected in the way that such costs are usually billed and collected.

The participating sites will be compensated for administrative costs for the start-up of the Registry, IRB/IEC/REB review and for entering data as outlined in the Clinical Study Agreement between BioMarin and the Institution/Investigator.

There will be no charge to patients to participate in the Registry. Patients will not be paid for being in the Registry. In addition, BioMarin will not pay for any patient travel costs.

22 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

22.1 Safety Parameters and Definitions

Investigators are requested to report the following AEs/ARs that are considered important for the evaluation of Vimizim safety and ongoing risk-benefit assessments. Report the following to the sponsor within 1 business day:

- All AEs, regardless of causality, occurring within 24 hours of Vimizim infusion (refer to the definition of a hypersensitivity reaction temporally-related to a Vimizim infusion below);
- All SAEs occurring in patients administered at least 1 dose of Vimizim, regardless of causal attribution (refer to SAE definition);
- All non-serious ARs to Vimizim (refer to AR definition);
- All occurrences of spinal cord compression in patients participating in the Registry or the Registry Substudies as SAEs, whether Vimizim was administered or not; and
- Any pregnancy that occurs in a patient administered Vimizim;
- Unusual Failure in Efficacy: a situation where Vimizim fails to produce the expected intended effect, which may result in an adverse outcome for the patient, including an exacerbation of the condition for which the product is being used.

Non-serious AEs, other than those occurring within 24 hours of Vimizim infusion, that are considered related to the underlying disease and unrelated to Vimizim administration by Investigators do not require reporting for this Registry or the Registry Substudies due to the profusion of expected AEs caused by MPS IVA. In addition, SAEs occurring in patients that have never received Vimizim do not require reporting for this Registry or the Registry Substudies, with the exception of spinal cord compression as stated above.

Stable chronic conditions that are present prior to Registry or Registry Substudy entry that do not worsen should be documented in the patient's medical record. A pre-existing condition should be assessed as an AE if the frequency, intensity, or the character of the condition worsens during participation in the Registry or Registry Substudies and meets one of the criteria above for safety reporting.

Pregnancy in a patient receiving Vimizim should be reported to the sponsor within 1 business day of the site personnel becoming aware of the pregnancy. Every effort should be made to follow the patient through the resolution of the pregnancy (delivery or termination) and to report the resolution to the sponsor. Patients who become pregnant while receiving Vimizim should be encouraged to enroll in the Pregnancy Substudy.

Adverse Event (AE): Any untoward medical occurrence in a patient administered a medicinal product, including occurrences that are not necessarily caused by or related to the product.

An AE can be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product.

Adverse Reaction (AR): Any untoward medical occurrence in a patient administered a medicinal product that is judged by the reporting Investigator (or sponsor) as having a *reasonable causal relationship* to the product.

Reasonable causal relationship means there is evidence or arguments to suggest a causal relationship.

Hypersensitivity reaction temporally-related to a Vimizim infusion: Any AEs that occur after the start of a Vimizim infusion and within 1 day following the end of the infusion. Symptoms of hypersensitivity reactions may include fever, chills/rigors, urticaria, angioedema, rash, dyspnoea, wheezing, stridor, nausea, vomiting, abdominal pain, and hypotension/hypertension.

Non-serious Adverse Event: Any AE that does not meet regulatory serious criteria.

Serious Adverse Event (SAE): Any AE or AR that:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect; or
- Is an important medical event that, based on medical judgment, may jeopardize the patient or require intervention to prevent 1 of the above consequences

23 PROCEDURES FOR COLLECTION, MANAGEMENT AND REPORTING OF AES/ARS

23.1 Adverse Event Reporting Period

The reporting period for AEs and SAEs described in Section 22 begins from the time informed consent is signed and continues throughout the patient's enrolment in the Registry.

23.2 Eliciting and Recording AEs/ARs

Investigators will seek information on reportable AEs and SAEs at each patient contact, and will promptly record solicited or patient-reported safety information on the Registry AE eCRF.

All reportable events will be entered on the AE eCRF and submitted to BPV within one business day of learning of the event to facilitate timely review by BioMarin and to meet regulatory reporting requirements. AEs and SAEs should also be recorded in the patient's medical record to facilitate source data verification.

Investigators should use correct medical terminology/concepts when recording safety parameters on the AE eCRF. Avoid colloquialisms and abbreviations. Only 1 medical concept should be recorded in the event field on the AE eCRF.

If known, a diagnosis should be recorded on the AE eCRF rather than individual signs and symptoms. However, if a constellation of signs and/or symptoms cannot be medically characterised as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the AE eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

AEs occurring secondary to other events should generally be identified by their primary cause. For example, if severe diarrhoea is known to have resulted in dehydration, it is sufficient to record diarrhoea as the event on the AE eCRF. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the AE eCRF. For example, if a severe gastrointestinal haemorrhage leads to renal failure, both events should be recorded separately on the AE eCRF.

Reportable events that occur and resolve between patient evaluation time points should be recorded again on the AE eCRF if they recur.

23.2.1 Investigator Assessments

The Investigator responsible for the care of the patient or qualified designate will assess reportable AEs/SAEs for severity, causal relationship to Vimizim, and seriousness (refer to SAE definition).

Note: Severity (as in mild, moderate or severe headache) is not equivalent to seriousness, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

23.2.1.1 Assessment of Severity

The severity of reportable AEs/SAEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0 toxicity scale and according to Table 23.2.1.1.1.1. This table is a guidance for assessing severity. For any given event, CTCAE v 4.0 should be consulted.

23.2.1.1.1 Toxicity Scale

Table 23.2.1.1.1.1: Adverse Event Grading (Severity) Scale

Severity	Description	
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[a].	
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalisation indicated; disabling; limiting self-care ADL[b].	
Grade 4	Life-threatening consequences; urgent intervention indicated.	***Note:*** *Grade 4 and 5 AEs should always be reported as* ***SAEs***
Grade 5	Death related to AE.	

[a] Instrumental ADLs refer to the following examples: preparing meals, shopping for groceries or clothes, using the telephone, managing money.

[b] Self care ADLs refer to the following examples: bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, not bedridden.

23.2.1.2 Assessment of Causality

A medically qualified physician responsible for the patients care or qualified designate will assess causality of reportable AEs/SAEs. The causal attribution guidance in Table 23.2.1.3.1 will be applied.

23.2.1.3 Causal Attribution Guidance

Table 23.2.1.3.1: Causal Attribution Guidance

Is there a reasonable possibility that the AE/SAE was caused by Vimizim based on facts (evidence) or arguments to suggest a causal relationship?

YES (Possible, probable or definite)	If there is a plausible temporal relationship between the onset of the AE/SAE and Vimizim administration and the AE/SAE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE/SAE follows a known pattern of response to Vimizim; and/or the AE/SAE abates or resolves upon discontinuation of Vimizim or dose reduction and, if applicable, reappears upon re-challenge.
NO (Not related or remote)	If data are available to identify a clear alternative cause for the AE/SAE other than Vimizim; such as the patient's clinical state, concomitant therapy, and/or other interventions. OR The AE/SAE has no plausible temporal relationship to administration of Vimizim (e.g., cancer diagnosed 2 days after first dose of Vimizim).

The Investigator's assessment of causality for individual AE reports is part of the Registry documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE/SAE reports, BioMarin will promptly evaluate all reported safety information against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities.

23.3 Adverse Event Reporting Instructions

Investigators will promptly record all solicited or patient-reported AEs and SAEs on the Registry AE eCRF.

All SAEs, non-serious ARs, hypersensitivity reactions, pregnancies in patients receiving Vimizim, and all occurrences of spinal cord compression (whether Vimizim was administered or not) will be entered on the AE eCRF and submitted to BPV within 1 business day of learning of the event.

Relevant follow-up information will be entered into the EDC system on the AE eCRF and submitted to BPV as soon as it becomes available and/or upon request.

If the EDC system is not available, all SAEs, non-serious ARs, hypersensitivity reactions, pregnancies in patients receiving Vimizim, and all occurrences of spinal cord compression should be reported to BPV by completing the Registry AE/SAE form, and faxing or emailing the completed report to BPV within 1 business day of learning of the event. Fax or email the report to:

BPV AE fax number: +1 (415) 532-3144

BPV email: drugsafety@bmrn.com

If any questions arise regarding safety reporting, please contact BPV directly at:

Phone: +1 (415) 506-6179

Investigators are encouraged to contact the Registry medical monitor if deemed necessary to discuss patient safety. Contact information for the medical monitor is as follows:

Name: Jamal Khwaja, MD
Address: 105 Digital Drive
Novato, CA 94949
US

Phone: +1 (440) 465 - 4878
Email: MARS@bmrn.com

23.4 Type and Duration of Follow-up after AEs/SAEs

The investigator should follow all reported events until resolved or stabilized, or the patient is lost to follow up. Resolution is defined as a return to baseline status or stabilization of the condition with the expectation that it will remain chronic. Resolution of AEs and SAEs (with dates) should be documented on the AE eCRF and in the patient's medical record to facilitate source data verification.

For some reported events, BPV may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to evaluate reported safety information.

23.5 Reporting of Pharmacovigilance Data to Competent Authorities

BioMarin will monitor the safety data generated from the Registry and Registry Substudies and consider their implications for the risk-benefit balance of Vimizim. Any new information that may affect the risk-benefit balance of Vimizim will be communicated to competent authorities in countries where Vimizim is authorised and to relevant healthcare providers. Information affecting the risk-benefit balance of Vimizim may include that arising from an analysis of ARs or of aggregated data.

Serious and non-serious ARs will be reported to competent authorities as expedited safety reports and/or in periodic safety update reports in accordance with applicable regulations.

24 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

BioMarin is required to provide reports regarding disease and patient treatment outcomes obtained from the Registry participants to the US FDA, and the European Medicines Agency on an annual basis, as well as other regulatory bodies as applicable.

BioMarin recognizes the importance of communicating medical study data and, therefore, encourages the publication of these data in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Trial Agreement between BioMarin and the Investigator/Institution. Consideration for authorship of all publications will be based on compliance with Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals of the International Committee of Medical Journal Editors (http://www.icmje.org/icmje-recommendations.pdf) and Good Publication Practice guidelines guidelines published in: (Graf, 2009), http://dx.doi.org/10.1136/bmj.b4330).

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26 ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

27 ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title:

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	☐	☐	
1.1.2 End of data collection[2]	☐	☐	☐	
1.1.3 Progress report(s)	☐	☐	☐	
1.1.4 Interim report(s)	☐	☐	☐	
1.1.5 Registration in the EU PAS Register®	☐	☐	☐	
1.1.6 Final report of study results.	☐	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☐	☐	☐	
2.1.2 The objective(s) of the study?	☐	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☐	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☐	

Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☐	☐	☐	
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☐	☐	☐	
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☐	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☐	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☐	☐	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☐	☐	☐	
4.2.2 Age and sex	☐	☐	☐	
4.2.3 Country of origin	☐	☐	☐	
4.2.4 Disease/indication	☐	☐	☐	
4.2.5 Duration of follow-up	☐	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☐	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☐	
5.3 Is exposure categorised according to time windows?	☐	☐	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☐	
6.2 Does the protocol describe how the outcomes are defined and measured?	☐	☐	☐	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☐	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☐	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☐	

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☐	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☐	
9.1.3 Covariates and other characteristics?	☐	☐	☐	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☐	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☐	
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☐	
9.3.3 Covariates and other characteristics?	☐	☐	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☐	☐	☐	
10.2 Is study size and/or statistical precision estimated?	☐	☐	☐	
10.3 Are descriptive analyses included?	☐	☐	☐	
10.4 Are stratified analyses included?	☐	☐	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☐	
10.8 Are relevant sensitivity analyses described?	☐	☐	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☐	
11.2 Are methods of quality assurance described?	☐	☐	☐	
11.3 Is there a system in place for independent review of study results?	☐	☐	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☐	
12.1.2 Information bias?	☐	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☐	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☐	
13.3 Have data protection requirements been described?	☐	☐	☐	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☐	☐	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☐	☐	

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	☐	

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year _____

Signature: _____

Note: this checklist is included as an example only and no signature is needed

28 ANNEX 3. ADDITIONAL INFORMATION

None

29 ANNEX 4. SIGNATURE PAGE

Protocol Title: MPS IVA Clinical Registry Study (MARS)

I have read the forgoing protocol and agree to conduct this study as outlined. I agree to conduct the study in compliance with all applicable regulations and guidelines, including E6 ICH, as stated in the protocol, and other information supplied to me.

Investigator Signature	Date

Printed Name

30 ANNEX 5. PROTOCOL AMENDMENT AND TEXT REVISIONS

Table 30.1 summarises the revisions made to the EU and US protocols dated 15 June 2018 and 26 July 2018, respectively, and relates the changes to the appropriate rationale (See Section 4). Text that has been added or inserted is indicated by bold font, and deleted text is indicated by strikethrough font. Minor editorial corrections incorporated for document clarity or consistency (e.g., format, grammar, and spelling) are not included in Table 30.1.

Table 30.1: Amendment 2 Revisions

Section No./Title	Revision	Rationale
Administrative changes		
Title Page	EU PASS registration number added	Update of registration
Title Page	Marketing authorisation holder address changed to Shanbally, Ringaskiddy, County Cork P43 R298, Ireland	Update of address
Title Page	Participating countries added	Update of participating countries
Title Page	Author updated to Guillermo Seratti	Update of primary author
Section 2 Responsible Parties	Responsible party contact information added	Addition of sponsor contact information
Section 3.1 Title	Deletion of contact information	Information was previously mentioned in Section 2
Throughout protocol	Changed Recommended Schedule of Events to Data Elements of Interest	Clarification that assessments are performed or data collected per current standard of care
Clarifications		
Throughout document	Standard of care SOC amended to current SOC	Clarification that assessments are performed or data collec*ted per current standar*d of care
Section 3 Abstract Section 10 Study Time Period	~~The Registry will collect medical history, clinical, and safety assessment data at least every 6 months (or as indicated in the Recommended Schedule of Events) for up to 10 years~~. **Investigators will determine the actual frequency of necessary assessments according to a patient's individualized need for medical care and routine follow-up. Data may be collected for all or some of the assessments as outlined in Table 8-1 dependent upon the patient's current standard of care (SOC).**	Clarification of frequency of assessment collection

Section No./Title	Revision	Rationale
Section 3 Abstract Section 3.2 Rationale and Background Section 8.1 Study Design	…to track the **safety and** clinical outcomes of patients with MPS IVA treated with Vimizim.	Language added for consistency with study objectives
Section 3.4 Study Design	~~The Registry~~ **Investigators** will ~~collect medical history, clinical and~~ **determine the actual frequency of necessary** assessments ~~every 6 months~~ **according to a patient's individualized need for medical care and routine follow-up. Data may be collected for all** or **some of the assessments** as ~~indicated~~ **outlined** in Table 8-1 ~~for up to 10 years~~ **dependent upon the patient's current SOC**. The Registry will enroll and collect data on patients **according to current SOC** over a period of at least 8 years from the time of the first marketing approval globally, and data on individual patients will continue to be collected for at least 2 years from the time that the last patient was enrolled or until the Registry is completed.	Clarification of frequency of assessment collection
Section 3.8 Study Size and Statistical Methods	Registry data will be analysed as per the Registry's SAP and reported periodically. Data from patients enrolled in the Registry Substudies will also be analysed as per the MOR 005 and MOR-007 ~~clinical~~ **sub**-study SAP, as applicable. Where applicable, descriptive statistics will include the number of patients, mean, median, standard deviation (SD), minimum, ~~and~~ maximum, **nominal p-values** ~~and~~ 95% confidence interval and/or inter-quartile range for continuous variables**,** ~~and~~ **as well as** count and percent for categorical variables. **For purposes of analyses, the terms Baseline and Index are defined in Section 11.1.**	Text corrected for clarity and reference to definition of baseline added
Section 4.2 Amendment 1 (US)	**Date: 26 July 2018** **The protocol was amended to include Unusual Failure in Efficacy as a reportable safety event. The purpose of this change was to align with global Good Pharmacovigilance Practices. Additionally, the name and contact information for the BioMarin Medical Monitor was updated.**	Rationale and summary of changes from previously approved US protocol added. Into this now global protocol

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Section 5 Milestones	To be provided annually **by the end of Q2**, dependent on the International Birth Date (IBD) **September 2024**	Text added to specify submission timing Date for end of data collection added
Section 6 Rationale and Background	Completed and ongoing MPS IVA clinical studies **conducted by BioMarin** are summarised in Table 6-1	Clarification that studies listed in Table 6-1 are those conducted by BioMarin
Section 6.2 Study Rationale	~~Investigators treating MPS IVA patients are encouraged to participate in the Registry by enrolling patients, following the Recommended Schedule of Events (Section 8.1 and Table 8-1), and entering all data from these assessments into the Registry database.~~	Sentence removed as it does not relate to Study Rationale
Section 12 MOR-005 and MOR 007 Substudies	… Analysis of long-term safety and ~~efficacy~~ **effectiveness** of Vimizim…	To match terminology in stated goals of the study
Section 8.1. Study Design	Patients initially enrolling into 1 of the Substudies will give their consent to participate in both the applicable Substudy and to continue participation in the MARS Registry, following the completion of the respective Substudy, by signing an IRB/IEC/REB-approved ICF/PIAF and assent, if applicable, for both the relevant Substudy and the MARS Registry. **Patients who become pregnant and are taking Vimizim may also participate in a pregnancy sub-study (see Section 13).** Investigators are encouraged to ~~follow~~ **record data in line with** the ~~Recommended Schedule of Events~~ **Data Elements of Interest**, which includes assessments that are currently used to monitor MPS IVA related clinical manifestations and to stage disease progression across the life long course of the disease.	Clarification on pregnancy sub-study and frequency of assessment collection

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	~~The Registry~~ **Investigators** will **determine the actual frequency of necessary** ~~collect medical histories and clinical and safety~~ assessments ~~at least every 6~~ **according to a patient's individualized need for medical care and routine follow-up. Data may be collected for all or some of the assessments as outlined in Table 8-1 dependent upon the patient's current SOC**. The Registry will enroll and collect data on patients **according to current SOC** over a period of at least 8 years from the time of the first marketing approval globally, and data on individual patients will continue to be collected for at least 2 years from the time that the last patient was enrolled or until the Registry is completed	
Table 8.1.1.1 Recommended Schedule of Events	a. ~~**All**~~ **Data on all** recommended assessments should be collected until conclusion of the Registry at intervals specified in the ~~**Recommended Schedule of Events**~~ **Data Elements of Interest if consistent with local current SOC. Data for assessments** ~~**and may be**~~ performed at additional time points and as medically indicated at the discretion of the Investigator **should also be collected. Additional details are provided in the** ~~Study Reference Manual~~ **SRM.** b. The data to be collected at entry include current as well as historic data., as available. **Index is the date of first exposure to Vimizim. Historic data prior to index will be collected with the data point closest to index in the 12 months prior to index or 30 days after index (except for measurement of uKS) is considered the baseline measurement.** q. ~~Dual emission x-ray absorptiometry (~~**If** DXA~~)~~ scans **are** ~~to be~~ performed ~~per the standard of care~~ **as part of SOC, scan results will be collected** ~~whenever possible~~	Footnotes clarified for assessments and data collection
Table 8.2.1 Pregnancy Substudy Data Elements of Interest	**a. Data on all recommended assessments should be collected until conclusion of the Registry at intervals specified in the Data Elements of Interest if consistent with local current SOC. Data for assessments performed at additional time points and as medically indicated at the discretion of the Investigator should also be collected. Additional details are provided in the SRM.**	General footnote added clarifying collection requirements

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	~~e. Pregnancy Substudy patients should continue to be tested every 6 months per Table 9.1.1.1 in addition to at the additional timepoints indicated above.~~ ~~f. If Vimizim treatment does occur during breast feeding, a breast milk sample obtained within 2 to 4 weeks after the birth of the infant and immediately following an infusion of Vimizim (administered to the mother) should be tested for the presence of Vimizim.~~ Immunogenicity tests and breast milk sample events removed from Table 8-2, with corresponding footnotes.	Removed as requested by PRAC as these events are considered to be interventional
Section 9 Genetic Testing Data	Morquio A syndrome is a rare, inherited condition with significant heterogeneity in presentation. **Morquio A syndrome is caused by mutations in the *GALNS* gene.** In MPS IVA patients currently identified, to date, more than 220 different ~~mutations of~~ **variants for the** ~~Morquio A syndrome~~**GALNS** gene have been identified. However, **not in all cases has** there ~~has~~ been ~~no~~an identifiable correlation between genotype and phenotype.	Clarification of the etiology of Morquio A syndrome.
Section 10 Study Time Period	~~The Registry will collect medical history and clinical and safety assessment data every 6 months or as indicated in~~ **Investigators will determine the actual frequency of necessary assessments according to a patient's individualized need for medical care and routine follow-up. Data may be collected for all or some of the assessments as outlined in Table 8-1** ~~for up to 10 years.~~ **dependent upon the patient's current SOC.**	To maintain consistency in collection timepoints between text and Data Elements of Interest
Section 11.1 Timepoints	**Among enzyme replacement therapy (ERT)-treated patients:** **• Registry Entry is defined as at the date of patient signed consent to participate in MARS** **• Index is defined as the date of first exposure to Vimizim (may precede or follow Registry Entry)** **• Baseline is defined as within 12 months prior to index or within 1 month after index. Historic data prior to index collected with the data point closest to index in the 12 months prior to index or 1 month after index (except for**	Analyses timepoints defined

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	measurement of urinary keratan sulfate [uKS]) is considered the baseline measurement **• Follow-up is defined as the time period after index plus 1 month (Index Date + 30 days +1) to last data point.** **Among ERT-naive patients:** **• Registry Entry is defined as at the date of patient signed consent to participate in MARS** **• Follow-up is defined as the time period from Registry Entry (exclusive) to last data point**	
Section 11.4 Medical History	Information on prior **(including ERT)** and concomitant medications will also be collected.	Clarification that information on prior ERT should be collected in medical history
Section 11.6 Vital Signs	Vital signs, including systolic and diastolic blood pressures (millimeters of mercury), heart rate (beats/minute), respiratory rate (breaths/minute), oxygen (O2) saturation, and temperature (degrees Celsius) ~~may be~~ **will be performed as per SOC and data** collected at timepoints indicated in the ~~Recommended Schedule~~ **Data Elements of** ~~Events~~ **Interest** (Table 8-1).	Clarification that these assessments are per current standard of care
Section 11.7 Physical Examination	Physical examinations ~~may~~ will be ~~completed~~ **performed as per SOC and data collected** at the timepoints indicated in the ~~Recommended Schedule~~ **Data Elements of** ~~Events~~ **Interest** (Table 8-1).	Clarification that these assessments are per current standard of care
Section 11.8 Tanner Staging	Tanner staging ~~may~~ **will** be ~~completed~~ **performed as per SOC and data collected** at the timepoints indicated in the ~~Recommended Schedule~~ **Data Elements of** ~~Events~~ **Interest** (Table 8-1).	Clarification that these assessments are per current standard of care
Section 11.9 Anthropometric Measurements	Height, sitting height, length, head circumference, and weight ~~may be~~ **will be performed as per SOC and data** collected at the timepoints indicated in the ~~Recommended Schedule~~ **Data Elements of** ~~Events~~ **Interest** (Table 8-1).	Clarification that these assessments are per current standard of care

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Section 11.10 Dental Examination	Patients may undergo a full dental examination **as per SOC and data collected** as outlined in the ~~Recommended Schedule~~ **Data Elements** of ~~Events~~ **Interest** (Table 8-1).	Clarification that these assessments are per current standard of care
Section 11.12 Audiometry	Age-appropriate audiometry assessments may be **performed as per SOC and data** collected at the timepoints indicated in the ~~Recommended Schedule~~ **Data Elements** of ~~Events~~ **Interest** (Table 8-1).	Clarification that these assessments are per current standard of care
Section 11.13 Ophthalmologic Assessments	Ophthalmologic assessments may be ~~completed~~ **performed as per SOC and data collected** at the timepoints indicated in the ~~Recommended Schedule~~ **Data Elements** of ~~Events~~ **Interest** (Table 8-1).	Clarification that these assessments are per current standard of care
Section 11.14 Respiratory Function Tests	Respiratory function tests may be ~~completed~~ **performed as per SOC and data collected** at the timepoints indicated in the ~~Recommended Schedule~~ **Data Elements** of ~~Events~~ **Interest** (Table 8-1).	Clarification that these assessments are per current standard of care
Section 11.15 Sleep Study	Sleep studies may be ~~completed~~ **performed as per SOC and data collected** at the timepoints indicated in the ~~Recommended Schedule~~ **Data Elements** of ~~Events or if clinically indicated~~ **Interest** (Table 8-1).	Clarification that these assessments are per current standard of care
Section 11.16 Liver and Spleen Assessment	Liver and Spleen Assessments ~~may be completed if these are~~ **performed per** the **current SOC should be collected** in the **Registry** ~~at the timepoints indicated in the Recommended Schedule of Events~~ (Table 8-1).	Clarification that these assessments are per current standard of care
Section 11.17 Electrocardiogram and Echocardiogram	~~A standard~~**Standard** 12-lead electrocardiogram**s** (ECG**s**) including heart rate, rhythm, intervals, axis, conduction defects ~~may~~ performed **per the current SOC** ~~and~~ **should be collected in the Registry**~~as outlined at the timepoints indicated in the Recommended Schedule of Events (Table 8-1).~~ ~~An echocardiogram may be obtained at the timepoints outlined in the Recommended Schedule of Events (Table 8-1).~~ Cardiac anatomy and function should be evaluated by a standard 2 dimensional Doppler echocardiogram, and the data recorded should include valve characterization, ventricular wall thickness, and septal wall motion. Data from an echocardiogram performed within 1 year prior to enrolment may be used. If no apparent cardiac involvement is observed after the 1-year assessment, **it is recommended that** these	Clarification that these assessments are per current standard of care

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	assessments can then be repeated every 3 years. In addition, it is recommended that these assessments be collected prior to major operative intervention.	
Section 11.20 Imaging	Imaging ~~should be completed~~ **performed** per the **current** SOC ~~or~~ **should be collected in the Registry** ~~at the timepoints indicated in the Recommended Schedule of Events (Table 8-1).~~	Clarification that these assessments are per current standard of care
Section 11.20.1 MRI and CT of Spine, Hips and Knee	MRI and CT data of spine, hips, and knees ~~should~~ **may be collected if these are performed per the current** SOC~~, or may be collected at the timepoints indicated in the Recommended Schedule of Events (Table 8-1).~~	Clarification that these assessments are per current standard of care
Section 11.20.2 Dual Emission X-Ray Absoptiometry	~~Patients in the MOR-007 Registry Substudy will also undergo~~ **Data from** DXA bone mineral density ~~scans, which~~ **will** be collected ~~as~~ **from patients in the MOR-007 Registry Substudy if these are performed** per ~~standard or at~~ the ~~timepoints indicated in the Recommended Schedule of Events (Table 8-1).~~ **current SOC**.	Clarification that these assessments are per current standard of care
Section 11.21 Upper Limb Assessment	The Upper Limb Assessment ~~may be completed at~~ **Imaging performed per** the ~~timepoints indicated~~ **current SOC should be collected** in the ~~Recommended Schedule of Events~~ **Registry** (Table 8-1)	Clarification that these assessments are per current standard of care
Section 11.23.1 Urine Keratan Sulfate and Creatinine Levels	Urine KS and urine creatinine testing may be completed **as per SOC and data collected** at the timepoints indicated in the ~~Recommended Schedule of Events~~ **Data Elements of Interest** (Table 8-1).	Clarification that these assessments are per current standard of care
Section 11.23.2 Urinary Protein	Urinary protein levels may be tested **as per SOC and data collected** at the timepoints indicated in the ~~Recommended Schedule of Events~~ **Data Elements of Interest** (Table 8-1).	Clarification that these assessments are per current standard of care
Section 11.23.3. Immunogenicity Testing	Immunogenicity testing should be completed **for patients receiving Vimizin (if allowed per current SOC)** as described within this section and at the timepoints indicated in the ~~Schedule of Events~~ **Data Elements of Interest** (Table 8-1) **and should only be taken for patients receiving Vimizim.** ~~Every 6 months, serum~~ **Serum** samples ~~should be collected to test for the presence of~~ **for TAb and Nab testing may be collected according to the Data**	Clarification of frequency of assessment collection and that these are per current standard of care

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	Elements of Interest and international guidelines, and at the discretion of the investigator.	
Section 11.24 Occurrence of Pregnancy and Menarche Section 13 Pregnancy Substudy	In addition, all pregnancies in patients receiving Vimizim treatment will need to be reported to BioMarin Pharmacovigilance (BPV) **regardless of enrolment in Pregnancy Substudy**.	Clarification of required pregnancy reporting
Section 12 MOR-005 and MOR-007 Substudies	After the 5-year period, these patients ~~should will~~ **are encouraged to** remain in the MARS Registry until the Registry is complete. Patients enrolled in the MOR-005 or MOR-007 Substudies **should** ~~will~~ complete assessments as outlined in the MARS Registry ~~Recommended Schedule of Events~~ **Data Elements of Interest** (Table 8-1). **Data from** ~~A~~**a**dditional assessments may also be collected for these Substudy patients such as the MPS Health Assessment Questionnaire, DXA scans, and the PedsQL Measurement Model for Pediatric Quality of ~~Live~~ **Life** Inventory at the timepoints ~~specified~~ **suggested** in the applicable Substudy ~~Recommended Schedule of Events~~ **Data Elements of Interest** (Table 8-1). The age-appropriate PedsQL **should** ~~will~~ be completed at the timepoints indicated in the ~~Recommended Schedule of Events~~ **Data Elements of Interest** (Table 8-1). ~~In addition to completing the assessments for the overall MARS Registry, patients enrolled in the MOR-005 Registry Substudy will be asked to complete the MPS Health Assessment Questionnaire (Section 11.22.3).~~ ~~Patients in the MOR-007 Registry Substudy will also undergo DXA scans per the SOC or annually whenever possible.~~	Desire to continue follow-up on these patients Clarification of required assessments
Section 13 Pregnancy Substudy	To be eligible to participate in the Pregnancy Substudy, patients must ~~be receiving~~ have received at least 1 infusion of Vimizim while pregnant. ~~Pregnancy Substudy patients should continue to be tested every 6 months for the formation or continued presence of anti-drug antibodies. Additional samples for TAb and NAb testing should be collected from the mother at Pregnancy Substudy enrollment, pregnancy Month 6, and 2 months post-partum (Section 12.22.3).~~	Clarification of language for consistency Removal of antibody testing and breast milk collection as requested by PRAC as

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	~~A breast milk sample should be collected at the end of a Vimizim infusion **within 2 to 4 weeks postpartum,** at 2 months postpartum and assessed for the presence of Vimizim.~~	these assessments are considered interventions
Section 12 MOR-005 and MOR-007 Substudies Section 18.1.5.3 Treatment Groups Section 18.1.7 Safety and Clinical Outcome Analysis	"Efficacy" measurements changes to "Outcome" measurements throughout document	Text corrected for clarity
Section 18.1.8 Changes in the Conduct of the Study or Planned Analyses	**After a study has been commenced, any substantial amendments to the study protocol will be submitted, before implementation, to the Pharmacovigilance Risk Assessment Committee (PRAC) according to the provisions of Article 107 of the Directive 2001/83/EC and GVP Modules i.e. GVP Module VIII and GVP Module VIII Addendum I** ~~Only BioMarin may modify the protocol.~~	Text updated based on PRAC request
Section 21.2 Ethical Conduct of Study	It is expected that Investigators understand and comply with the protocol and attest to this by signing the Signature Page (Section 29). • This Registry will be conducted in accordance with the following: • US CFR sections that address clinical research studies, and/or other national and local regulations, as applicable • ICH Harmonised Tripartite Guideline: Guideline for GCP E6 (ICH E6 **R2**) • The ethical principles established by the Declaration of Helsinki • **Regulation (EC) No 726/2004, Directive 2001/83/EC and Commission Implementing Regulation (EU) No 520/2012**	Regulations updated
Section 22.1 Safety Parameters and Definitions	Non-serious AEs, other than those occurring within 24 hours of Vimizim infusion, that are considered **related to the underlying disease** and unrelated to Vimizim administration by Investigators do not require reporting for this Registry or the Registry Substudies **due to the profusion of expected AEs caused by MPS IVA**. In addition, SAEs occurring in patients ~~not receiving~~that have never	Text corrected for clarity

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	received Vimizim do not require reporting for this Registry or the Registry Substudies, with the exception of spinal cord compression as stated above.	
Section 27 ANNEX 2. ENCEPP Checklist for Study Protocols	Check list updated to current template	Template updated
Section 23.3 Adverse Event Reporting Instructions	Medical Monitor updated to Jamal Khwaja	Update of Medical Monitor
Section 29 Signature Page	Signature page updated to current template	Template updated
Updates based upon SAP		
Table 8.1.1.1 Data Elements of Interest Section 11.1 Timepoints	**Index is defined as the date of first exposure to Vimizim (may precede or follow Registry Entry).** **Baseline is defined as within 12 months prior to index or within 1 month after index. Historic data prior to index collected with the data point closest to index in the 12 months prior to infex or 1 month after index (except for measurement of urinary keratan sulfate [uKS]) is considered the baseline measurement**	Text added to reflect updates made to the SAP
Section 11.1 Time18.1.7points	**Among enzyme replacement therapy (ERT)-treated patients:** **• Registry Entry is defined as at the date of patient signed consent to participate in MARS** **• Index is defined as the date of first exposure to Vimizim (may precede or follow MARS Registry Entry)** **• Baseline is defined as within 12 months prior to index or within 1 month after index. Historic data prior to index collected with the data point closest to index in the 12 months prior to index or 1 month after index (except for measurement of urine keratan sulfate [uKS]) is considered the baseline measurement** **• Follow-up is defined as the time period after index plus 1 month (Index Date + 30 days + 1) to last data point**	Text modified to reflect updates made to the SAP

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	Among ERT-naive patients: **• Registry Entry is defined as at the date of patient signed consent to participate in MARS** **• Follow-up is defined as the time period from Registry Entry (exclusive) to last data point**	
Section 18.1.4 General Analysis Considerations	Descriptive summaries of continuous variables will include the mean, SD, median, range, and 95% confidence interval and/or inter-quartile range when appropriate. Descriptive summaries of categorical variables will include n and percent. **When possible/applicable graphical summary statistics over time and/or summary statistics accounting for time will be utilized.** ~~For Vimizim treated patients, the baseline value of an assessment is defined as the last available measurement within 6 months prior to, or up to 30 days after first administration of Vimizim after the Registry enrollment, unless otherwise specified. For Vimizim treated patients, the baseline value of urinary KS is defined as the last available measurement within 6 months prior to, or up to 1 day after first administration of Vimizim. For Vimizim treatment naïve patients, all baseline values are the first data available, either at enrollment or historical data.~~ Statistical tests will be two-sided at the 0.05 level, unless otherwise specified. All confidence intervals will be two-sided 95% confidence intervals, unless otherwise specified. **All statistical tests and associated p-values will be considered nominal. See Section 11.1 for definitions of timepoints.**	Text added to reflect updates made to the SAP
Section 18.1.5.2 Full Analysis Set Population	**The Full Analysis Set will consist of all patients diagnosed with MPS IVA who provide written, signed informed consent or, in the case of patients aged <18 years, those for whom written assent (if required) and written informed consent by a legally authorised representative are provided.**	Text added to reflect updates made to the SAP
Section 18.1.5.3 Treatment Groups	ERT-naïve patients are defined as the group of patients who had never received Vimizim **either prior to the Registry enrolment, or during Registry participation. Time on ERT treatment (defined as ERT infusion date +7 days) and not on treatment during follow-up will be identified.**	Text modified to reflect updates made to the SAP

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	~~Separate data analyses of the MOR-005 and MOR-007 Substudies will be performed per the MOR-005 and MOR-007 clinical study SAP, which will enable results to be reported separately to facilitate interim and final reporting commitments for MOR-005 and MOR-007. Additionally, data from the MARS Registry and the MOR-005 and MOR-007 Substudies will be collected and analyzed in the Registry combined to maximize interpretability.~~ Analysis of ~~Efficacy, Safety, Demographic and Baseline~~**clinical outcomes, demographic and baseline** characteristics will be conducted, **stratified** by ~~comparing~~ the 2 ~~main~~ treatment groups (ERT-naïve patients vs ERT-treated patients). Due to the observational nature of the Registry, ERT-treated patients may ~~have a~~**discontinue** treatment ~~gap~~. **Treatment discontinuation will be defined based on the stop date reported in the enzyme replacement log plus 7 days (to include events potentially occurring 'on treatment' before the next anticipated infusion, if the date of last infusion was the documented stop date). Outcome analyses among the ERT-treated will generally be censored at the time of discontinuation (i.e. an 'as treated' analysis). Exceptions to this convention will be detailed in the SAP.** If there are significant numbers of patients who ~~have such~~**discontinue** treatment ~~gap~~**and re-initiate**, sensitivity analysis may be performed by ~~excluding patients with treatment gap.~~**describing outcomes during the period of re-initiation.**	
Section 18.1.7 Safety and Clinical Outcome Analysis	**Separate data analyses of the MOR-005 and MOR-007 Substudies will be performed per the MOR-005 and MOR-007 clinical Substudy SAPs. For the MOR-005 Substudy analyses, data from the MOR-005 substudy will be combined with data from the MOR-005 clinical study. A similar analysis will be provided for the MOR-007 Substudy data.** **Analyses performed to address the objectives of** ~~MARS.All efficacy~~**this study will consider both clinical outcome** variables ~~will be summarized descriptively for baseline and post-baseline timepoints; these~~**and safety variables. The clinical outcome** variables include endurance tests (6MWT, and 3MSCT)**,** ~~wheel chair and walking aid use,~~ anthropometric measurements, urine KS concentration	Text modified to reflect updates made to the SAP

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	(normalized to creatinine), respiratory function tests, number of respiratory infections, assisted breathing history, duration and number of times CPAP or BiPAP was used during the year, echocardiograms, surgeries, quality of life assessments (EQ-5D-5L test **in** all patients, MPS Health Assessment **Questionnaire** for MOR -005 Substudy patients only, PedsQL for MOR-007 Substudy patients only), ophthalmologic assessments, audiometric assessments, liver and spleen assessments, ~~Visual Analog Scale~~, progression of skeletal deformities, frequency and time to orthopaedic surgeries, and Tanner Series/Scales. ~~18.1.8 Annual Efficacy Analysis~~ ~~When applicable for the specific efficacy variable, the change from the baseline to post baseline (post baseline at annual or semi annual, depending on the specific efficacy variable), and/or its percent change will be summarized descriptively. The change and/or percent change from baseline will be analyzed for clinical parameters, by using recommended clinical criteria for each efficacy variable. The significance of the change and/or percent change will be tested.~~ ~~Change and/or percent change in efficacy parameters will be compared, between ERT treated patients and ERT naïve patients.~~ ~~In addition, statistical models using matching or covariate adjustment may be used to account for the influences of the baseline characteristics to reduce confounding.~~ ~~Efficacy analysis will also evaluate time to wheelchair dependence, time to respiratory support, time to (invaliding) corneal clouding, and time to deafness.~~ ~~18.1.9 Long Term Efficacy Analysis~~ ~~To utilize the longitudinal data collected over time, the change/percent change from the baseline to post baseline throughout the Registry will be compared between ERT treated patients and ERT naïve patients.~~ ~~18.1.10 Historical Baseline~~ ~~Due to the observational nature of the Registry, there may be a limited number of patients with assessments prior to the first Vimizim dose available. All available patients' measurements prior to the first dose of Vimzim, may be used to produce~~	

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	~~a historical baseline for a specific efficacy measurement. In such cases, ERT-treated patients will be compared with the historical baseline to evaluate long term treatment efficacy.~~ ~~18.1.11 Safety Analysis~~ ~~The analyses of~~ The safety ~~will~~**variables** include ~~all patients in the Safety Population. Adverse events will be coded in accordance with the most current version of Medical Dictionary for Regulatory Activities (MedDRA). The incidences of~~ AEs ~~will be summarized by System Organ Class (SOC), Preferred Term (PT), relationship to Vimizim, and severity. Incidence rate will be included as part of long-term safety evaluation. Patient listings will be provided for SAEs, deaths, and AEs leading to Vimizim discontinuation, or study withdrawals. All AE summaries will include only treatment-emergent adverse events (TEAEs) and SAEs reported during the study period (AEs that occur after the first Vimizim infusion). Analyses of AEs of hypersensitivity and anaphylaxis and AEs temporally related to a Vimizim infusion will be summarized by SOC, PT, and severity. Patients will be followed for 30 days after completion or study discontinuation for the occurrence of any SAE or reported pregnancy exposure. Serious Adverse Events and AEs temporally related to a Vimizim infusion will be reported to the appropriate regulatory bodies on the annual basis, or other required frequency, following the methods below (Section 24).~~ ~~The following safety measures will be also summarized descriptively~~ AEs, concomitant medications, occurrence of BMT/HSCT, clinical laboratory tests, vital signs, ECGs, echocardiograms, immunogenicity results, physical examinations, imaging studies, and cervical spine imaging. ~~Safety analysis will be reported annually and long-term safety will be analyzed over the course of the Registry. When applicable, safety analysis will be repeated for patients who are younger than 5 years of age at enrollment.~~ ~~1.1.1 Natural History of MPS IVA Population~~ ~~The natural history (the clinical progression of the disease over time) of MPS IVA patients (ERT-treated patients vs ERT-naïve patients) will be based on the Efficacy Population.~~	

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	~~MOR-001 was a study to analyze the natural history of ERT-naïve MPS IVA patients. The objectives of that study were to quantify endurance and respiratory function in patients with MPS IVA and to better characterize the spectrum of symptoms and biochemical abnormalities in MPS IVA disease over time.~~ ~~Patients from the MOR-001 study as well as all other MPS IVA clinical studies will be invited to participate in the Registry. The Registry may be combined with the MOR-001 data to better evaluate the natural history of MPS IVA patients. When applicable, other clinical study data may be included in the integrated analysis of natural history for certain protocol assessments.~~ ~~When assessing the natural history, descriptive summary statistics will be provided for related protocol assessments.~~ **Objective 1: To characterize and describe the MPS IVA population as a whole, including the heterogeneity, progression, and natural history of MPS IVA.** **In order to characterise and describe the MPS IVA population as a whole, clinical outcomes variables as specified in Table 8-1 and demographics will be summarised in the 12 months prior to or 90 days after Registry Entry (for consistency with data entry at Registry Entry) stratified by ERT status at Registry Entry. The measurement closest to Registry Entry during this period will be used to describe patients. The natural history and progression of MPS IVA will be described in ERT-naïve and ERT treated patients based on measurements while not on ERT treatment (i.e. all measurements for ERT-naïve and prior to index for ERT-treated), with progression of the disease based on measurements of clinical outcomes described over time and presented by age.** **Objective 2: To evaluate the long-term effectiveness and safety of Vimizim.** **The long-term effectiveness of Vimizim will be evaluated as described below using clinical outcome variables as specified in Table 8-1 based on measurements at baseline through discontinuation or end of follow-up (which ever occurs first) based on the ERT-treated patients in the Full**	

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	Analysis Set population. The measurement closest to the index date during the baseline period will be used to describe patients prior to initiating therapy (i.e. 'baseline measurement'), with the exception of uKS. For uKS, the 'baseline measurement' will be restricted to measurements occurring during the baseline period prior to or at index. As MPS IVA is a degenerative disease (Harmatz , 2013), a sensitivity analysis will be conducted for the outcomes of 6MWT, respiratory function, height, weight, and uKS limiting the baseline period to the 6 months before index and 30 days after index (with the same caveat for uKS as the primary analysis). **Whenever possible and/or relevant to the outcome, outcomes will be described graphically accounting for time and/or age at the assessment. When warranted by the outcome of interest, outcomes will be summarised as event rates censored at time of discontinuation or data cutoff. Change and/or percent change from baseline to follow-up outcome measurements after pre-specified amounts of exposure (e.g. after 1 or 5 years of exposure) will only be summarised for patients with a baseline measurement and a relevant follow-up measurement (near the specified time) prior to discontinuation. Additional details of analyses can be found in the SAP.** **Long-term safety events occurring during MARS after index or registry entry (which ever occurs later), including hypersensitivity events, will be evaluated by summarising the incidences of AEs by System Organ Class, Preferred Term, relationship to Vimizim, and severity in the Safety Population. Exposure-adjusted incidence rates and event rates while on treatment will be included as part of long-term safety evaluation. All AE summaries will include only treatment-emergent adverse events (TEAEs) and SAEs reported during the study period (AEs that occur after the first Vimizim infusion). Analyses of AEs of hypersensitivity and anaphylaxis, and AEs temporally related to a Vimizim infusion will be summarised by System Organ Class, PT, and severity All AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA).**	

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	Total and neutralizing antibody status will be summarised over the follow-up period. **Objective 3: To help the medical community with the development of recommendations for monitoring MPS IVA patients and reports on patient outcomes to optimize patient care.** **In light of the recent publication of International treatment guidelines for MPS IVA, no specific analyses are planned to address this objective. Analyses conducted to address other objectives will contribute to publication(s) and inform the medical community on natural history and patient outcomes, along with describing 'real world' monitoring practices. See Section 24 describing plans for disseminating and communicating results.** **Objective 4: To collect data on other treatments and evaluate the prevalences of their use and their effectiveness.** **The prevalence (e.g. count and frequency) of patients using other treatments indicated for the treatment of MPS IVA will be summarised (itemised in the SAP). Data on other treatments that directly affect MPS outcomes will be collected and this data will be provided in listings as well as counts and frequencies. Effectiveness will be summarised for these other treatments consistent with Objective 2, providing that the treatment is indicated for the treatment of MPS IVA and utilised to treat >5% of the MARS population. Concomitant medications and surgeries utilized to treat manifestations of disease will be summarised as part of Objective 2.** **Objective 5: To characterize the effects and safety of Vimizim treatment up to 5 years from enrolment in the Registry for patients under 5 years of age.** **Analyses consistent with those conducted to address Objective 2 will be repeated for patients with an index date occurring when the patient was <5 years of age. Analyses will be presented for safety and outcomes occurring in**	

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	the 5 years after index. These analyses will include, but are not limited to, AEs, 6MWT, anthropometric evaluations, and uKS. **Objective 6: To monitor pregnancy exposure (including maternal, neonatal, and infant outcomes)** **All pregnancy and neonatal data will be presented in listings regardless of enrolment in Pregnancy Substudy.** **Objective 7: To monitor patients who have completed the MOR-005 and MOR-007 clinical trials.** **Analyses will be repeated for the subgroup of patients in the MOR-005 Substudy and the subgroup of patients in the MOR-007 Substudy. These analyses will include but will not be limited to AEs, 6MWT, anthropometric evaluations, and uKS.**	