



A Long-Term, Open-Label Treatment and Extension Study of UX003 rhGUS Enzyme Replacement Therapy in Subjects with MPS 7

Protocol Number: UX003-CL202

Original Protocol: 28 Oct 2014

Amendment 1: 18 Dec 2015

Amendment 2: 04 Mar 2016

Amendment 3: 28 Jul 2016

Investigational Product: UX003, recombinant human beta-glucuronidase (rhGUS)

Indication: Mucopolysaccharidosis type 7 (MPS 7)

IND: 123,788

EudraCT Number: 2015-001875-32

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Protocol Number: UX003-CL202
Amendment 3: 28 JUL 2016



This study is to be performed in compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements.

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CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX003-CL202 Amendment 1

18 December 2015

Original Protocol UX003-CL202 (dated 28 October 2014) has been modified by Amendment 1 to remove or clarify certain procedures and update information. The introductory nonclinical and clinical background information contained within Section 5 has also been updated for completeness; additional minor edits and typographical corrections have also been made. The major protocol changes which impact study design and conduct are summarized below:

- 1. Administrative and Contact Information:** The protocol has been updated to provide the EudraCT number (2015-001875-32) for the study. The Medical Monitor has been changed to Dr. Christine Haller; contact information for the medical monitor and drug safety has been updated (Section 8.5.8).
- 2. Study Population:** Inclusion criterion #7 (Section 7.3.1) has been modified to clarify UX003 treatment naïve subjects the elevated uGAG excretion must be a minimum of 2-fold over mean normal levels for age (at baseline). Inclusion criteria # 7 and 8 have been combined; UX003 naïve participants must be at least 5 years of age at enrollment.
- 3. Study Visit Schedule:** The Early Termination Visit is now referred to as the Termination Visit. Visit qualifiers have been modified such that if a subject withdraws from the study, or if the study is terminated prior to Week 144, the termination visit should be completed within 30 days of the last dose of study drug. Assessments performed within 30 days of the termination visit will not be repeated unless clinically indicated.

Rationale: The modification clarifies procedures in case the study is terminated early by the Sponsor. The 30 day window for assessments eliminates unnecessary testing and procedures for subjects.

- 4. Study Procedures and Assessments:** Several updates have been made to clarify or remove procedures in Section 7.5 and the associated Schedule of Events (Table 2.1). Language regarding the assessments to be performed throughout this extension study has been broadened for applicability to subjects who may enroll from additional feeder trials with UX003. In general, efficacy assessments not performed during the primary (or feeder) trial will not be required for this long-term treatment and extension study; safety assessments will be conducted on all subjects as indicated in the protocol. Modifications to specific study procedures and assessments specified in the protocol text are summarized below.

Urinary and serum GAG: Serum GAG will no longer be assessed in the study. References to the specific methodologies for measurement of GAG in urine and serum have been removed from the protocol (Sections 7.5.3 and 7.5.4.2).

Rationale: Based on clinical and nonclinical evidence, uGAG is a direct pathophysiological and readily measured marker of the MPS disease process and a reasonable predictor of treatment effect and clinical benefit. Urine GAG is the primary measure of ERT efficacy in MPS disorders and will continue to be followed during this long-term extension study. Multiple assays for measuring pathologic accumulation of GAG in urine are now available; supplementary assays may be performed. Removal of serum GAG assessments reduces the number of required blood draws.

Weight for Drug Preparation: Weight for drug preparation may now be obtained up to 15 days prior to the indicated visit. Weight for drug preparation was removed from the Termination Visit procedures (Section 7.5.2.2 and Table 2.1).

Rationale: Obtaining weight up to 15 days prior to the indicated visit will provide a measure of convenience for study personnel and subjects by enabling the amount of study drug to be calculated and adjusted in advance of administration. Weight for drug preparation is not required at Termination as no study drug will be administered at the visit.

Biomarkers of Inflammation in Serum: The frequency of serum biomarker assessments has been reduced from 12-week intervals to 24-week intervals throughout the study. A qualifier has been inserted to perform if indicated based on prior studies (Section 7.5.4.2 and Table 2.1).

Rationale: The utility of assessing of biomarkers of inflammation in understanding the action of UX003 in MPS 7 has not been established. An exploratory (pilot) study is ongoing to assess biomarkers of inflammation in MPS 7 patients. The 24-week interval reduces the frequency of additional blood draws for study participants.

Physician Clinical Global Impression: The P-CGI has been removed as an assessment in the study.

Rationale: Baseline (pre-treatment) P-CGI assessments would have been conducted more than 1 year prior to UX003-CL202 enrollment for the majority of study subjects; continuing assessments are of limited utility due to likely recall inaccuracies. The open-label design of the study also limits objectivity for this assessment.

Hepatosplenomegaly: The frequency of qualitative assessments of the liver and spleen has been reduced from 12-week intervals to 48-week intervals except for naïve patients (Section 7.5.4.14); the assessment is now specified separately from physical examinations in Table 2.1.

Rationale: The frequency of hepatosplenomegaly assessments has been modified to align with the frequency of liver and spleen size assessment (hepatosplenomegaly) in other Ultragenyx-sponsored UX003 clinical studies (i.e. 48 weeks).

5. Reporting and Follow-up of Adverse Drug Events: The following modifications to Section 8.5 provide additional guidance and alignment with AE reporting requirements, primarily:

- Additional text was added to clarify that hospitalizations planned prior to study enrollment are not considered SAEs (Section 8.5.1).
- The categories for attributions of AE relatedness to study drug have been simplified (Section 8.5.3).
- A new section (Section 8.5.6) has been added to provide direction on the reporting requirements for suspected unexpected serious adverse reactions (SUSAR) to appropriate Regulatory Authorities (including Competent Authorities in all Member States concerned), IRBs/ECs, and Investigators as per local laws and regulation

**CLINICAL STUDY PROTOCOL AMENDMENT
SUMMARY OF CHANGES AND RATIONALE**

UX003-CL202 Amendment 2

04 March 2016

Protocol UX003-CL202 Amendment 1 (dated 18 October 2015) has been modified by Amendment 2 to remove or clarify certain procedures and update information. The major protocol changes that impact study design and conduct are summarized below:

- 1. Study Design and Methodology:** The protocol has been updated to remove reference to availability of commercial drug in the subject's territory as a reason for study termination. In addition "end of trial" has been defined in Section 7.5.1 as the last visit of the last subject undergoing evaluation in the study. As the planned duration of treatment in this study is up to 144 weeks, the end of trial is defined as the Week 144 visit of the last subject. In the event the study is terminated by the Sponsor prior to Week 144, all subjects should complete a termination visit and the date of the last termination visit of the last subject would define the end of the trial.

Rationale: This change and additional clarification were made in response to a request by INFARMED, the Portuguese Competent Authority and to align with current guidelines.

- 2. Study Population:** Inclusion criterion #2 (Section 7.3.1) has been updated to clarify that written informed consent by a legally authorized representative may be provided for subjects, including adult subjects, who are intellectually impaired.

Inclusion criterion #4 has been updated to specify that sexually active subjects must be willing to use a highly effective method of contraception. In addition, the list of examples of highly effective methods of contraception (Section 7.5.2.6) has been updated to remove barrier methods and include bilateral tubal occlusion.

Inclusion criterion #5 has been updated to remove tubal ligation as a reason that female subjects would be considered not of childbearing potential and to clarify the definition of those considered not of childbearing potential: Females considered not of childbearing potential include those who have not experienced menarche, are postmenopausal (defined as having no menses for at least 12 months) or are permanently sterile due to having hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

Rationale: Changes to inclusion criteria were requested by INFARMED, the Portuguese Competent Authority. As many patients with MPS 7 have intellectual impairment, the change to inclusion criterion #2 will clarify that a legally authorized representative may consent on their behalf. Changes to contraception and pregnancy testing language were made to align with the Heads of Medicines Agencies Clinical Trial Facilitation Group (CTFG) Recommendations related to contraception and pregnancy testing in clinical trials.

- 3. Pregnancy During Study.** Section 7.5.2.6 has been updated to indicate that female subjects who become pregnant during the study will be withdrawn from study drug. At

the conclusion of the pregnancy, a decision will be made if the female subject may resume study drug based on study treatment risk-benefit evaluation and willingness of the subject to comply with the contraceptive requirements. In the event of a pregnancy in the partner of a male subject, the male subject may continue with study drug and, as previously stated in the protocol, the Investigator must make every effort to follow the pregnancy of either subject or partner through resolution of the pregnancy (delivery or termination) and report the resolution to Ultragenyx or its designee.

Rationale: There are no adequate and well-controlled studies in pregnant women using UX003 and the effect of study drug on pregnancy and the fetus is unknown. Therefore, female subjects who become pregnant will be withdrawn from study drug but will continue to be followed on study. Given that MPS 7 is a chronically debilitating and life-threatening disease, the protocol allows for the potential resumption of therapy at the conclusion of pregnancy after a risk-benefit assessment is performed. Male subjects whose partners become pregnant will not be removed from study drug because seminal transmission of study drug to the fetus is considered highly unlikely.

- 4. Record Retention:** Section 8.4.3 has been updated to state that all study records must be retained for at least 25 years after the end of the clinical trial or in accordance with national law.

Rationale: This administrative change has been made to reflect upcoming changes to EU clinical trial regulations and current regulations by other health authorities.

**CLINICAL STUDY PROTOCOL AMENDMENT
SUMMARY OF CHANGES AND RATIONALE**

UX003-CL202 Amendment 3

28 July 2016

Protocol UX003-CL202 Amendment 2 (dated 04 March 2016) has been modified by Amendment 3 to clarify certain procedures and update information. The protocol changes are summarized below:

- 1. Title Page.** The title page has been updated to list Paul Harmatz, MD, as the Coordinating Investigator.

Rationale: Ultragenyx nominated Dr. Paul Harmatz, the Principal Investigator at the UCSF Benioff Children's Hospital in Oakland, California, as the Coordinating Investigator for this multicenter clinical study.

- 2. Pregnancy Testing and Contraception.** The description of highly effective methods of contraception (Section 7.5.2.6) has been updated to clarify that hormonal contraceptives should be associated with the inhibition of ovulation.

Rationale: Changes to inclusion criteria were requested by INFARMED, the Portuguese Competent Authority.

- 3. Criteria for Evaluation: Measurement of Anti-Drug Antibody (ADA) Types.** ADA testing, as one of the safety assessments (primary objective [Section 7.5.2]), has been clarified to indicate that clinically significant changes from baseline in levels of all anti-drug antibodies, not only the immunoglobulin G (IgG) isotype, will be evaluated.

Rationale: Text was updated to provide clarification that all anti-drug antibodies, not only IgG antibodies will be assessed, because it was deemed unclear in Amendment 2. This is not a change to the ADA testing.

- 4. Serum Biomarkers of Inflammation.** Blood for analysis of serum biomarkers of inflammation (Section 7.5.4.2) will not be collected after Week 48.

Rationale: Preliminary results from clinical study UX003-CL201 suggest that analysis of serum biomarkers of inflammation did not demonstrate meaningful differences upon treatment with UX003; therefore, continuation of this blood collection into the extension study was deemed unnecessary.

- 5. Bruininks-Oseretsky Test of Motor Proficiency (BOT-2).** This test of motor proficiency (Section 7.5.4.4) will not be conducted after Week 48.

Rationale: Continuing to perform the BOT-2 assessments in this open-label extension is unlikely to yield informative data. Removal of this test will reduce the burden to subjects and investigational sites participating in the study.

- 6. Childhood Health Assessment Questionnaire (CHAQ).** The person responsible for completing the CHAQ has been clarified as the subject's parent or caregiver (Section [7.5.4.12](#)).

Rationale: Text was updated to clarify the person responsible for completing the CHAQ, because the questionnaire was designed to be completed by the subject's parent or caregiver rather than the subject.

- 7. Health Assessment Questionnaire (HAQ).** The mode of administration of the HAQ and the persons permitted to complete the HAQ have been clarified (Section [7.5.4.12](#)).

Rationale: Text was updated to clarify that the HAQ may be administered to the subject via interview if the subject is deemed unable to complete a paper questionnaire. Also dependent on the ability of the subject, a parent or caregiver may complete the HAQ.

- 8. Record Retention.** Section [8.4.3](#) Record Retention was updated to clarify the responsibilities of the Investigator, Institution, and Ultragenyx with regard to record retention.

Rationale: Text was updated to clarify that it is not the explicit responsibility of Ultragenyx to assist with records retention.

2 SYNOPSIS

TITLE OF STUDY:

A Long-Term Open-Label Treatment and Extension Study of UX003 rhGUS Enzyme Replacement Therapy in Subjects with MPS 7

PROTOCOL NUMBER:

UX003-CL202

STUDY SITES:

Multi-center; multi-national; approximately 12 sites globally

PHASE OF DEVELOPMENT:

Phase 3

RATIONALE:

Mucopolysaccharidosis type 7 (MPS 7, Sly syndrome) is an ultra-rare (< 100 cases currently identified worldwide), chronically debilitating and life threatening lysosomal storage disease. It is characterized by a deficiency of the lysosomal enzyme beta-glucuronidase (GUS), required for degradation of the glycosaminoglycans (GAGs): dermatan sulfate (DS), chondroitin-6-sulfate (CS) and heparan sulfate (HS). The GUS deficiency results in lysosomal accumulation of GAGs in multiple tissues and organs throughout the body and numerous clinical signs and symptoms as a result of tissue damage and organ dysfunction. There are currently no approved treatments for MPS 7.

UX003 (recombinant human beta glucuronidase, rhGUS) is intended as a long-term enzyme replacement therapy (ERT) for the treatment of MPS 7 via intravenous (IV) administration. Ultragenyx is conducting this treatment and extension study to assess the long-term safety and efficacy of UX003 treatment in subjects with MPS 7. Subjects with MPS 7 who are UX003 treatment-naïve or have been previously enrolled and treated with UX003 in other clinical studies or programs are eligible for enrollment.

The study will continue for up to 144 weeks or until one of the following occurs: the subject withdraws consent and discontinues from the study, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, or the study is terminated.

OBJECTIVES:

The primary objective of the study is to evaluate:

- Long-term safety of UX003 in subjects with MPS 7.

The secondary objective of the study is to evaluate:

- Long-term efficacy of UX003 in reducing urinary GAG (uGAG) substrate in subjects with MPS 7.

Other objectives of the study are to evaluate:

- Measures of lysosomal storage including hepatosplenomegaly
- Measures of other clinical and functional outcomes, including pulmonary function, walking distance, shoulder flexion, fine motor function, gross motor function, climbing stairs, visual acuity, and cardiac size and function, and a composite Multi-Domain Responder Index (MDRI),

as applicable per subject status.

- Growth, as defined by impact on general health and assessed by changes in height (or length) and weight growth velocity.
- Subject-reported disability and quality of life, and fatigue, as indicated.
- Subject or parent/caregiver global assessment of change and impact on activities of daily living, as indicated.
- If an individualized clinical response (ICR) endpoint was defined for a subject from a previous UX003 study, the ICR may continue to be followed.

STUDY DESIGN AND METHODOLOGY:

This is a multi-center, multinational, open-label treatment and extension study in subjects with MPS 7. The study will assess long-term safety and efficacy of UX003 treatment and will continue for up to 144 weeks or until one of the following occurs: the subject withdraws consent and discontinues from the study, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, or the study is terminated.

Subjects with MPS 7 who are UX003 treatment-naïve or previously enrolled and treated in a prior clinical study of UX003 may have the option to enroll into this treatment and extension study provided all eligibility criteria have been met for a given subject. Subjects with MPS 7 who were enrolled in either an Ultragenyx sponsored study (e.g., UX003-CL301) or non-Ultragenyx sponsored clinical studies (e.g., Investigator sponsored trials (ISTs), expanded access/compassionate use) may be eligible for enrollment. Those subjects enrolling from a previous UX003 study should have a reasonable benefit-risk assessment from their primary study as determined by the Investigator, in order to continue with long-term therapy in this extension study. To be enrolled, subjects need to meet all inclusion/exclusion criteria.

All subjects will receive 4 mg/kg UX003 every other week (QOW) unless data from prior studies define a different dose either for that subject or the use of UX003 in general.

As has been observed with other MPS ERTs, some subjects may experience infusion-associated reactions (IARs) with the administration of UX003. Thus, prophylactic antihistamine will be administered prior to each study drug infusion. Antipyretic pretreatment may also be given at the Investigator's discretion. To minimize the potential for IARs, infusions will initially be administered on a slower rate schedule followed by an increase in rate. Infusion rate may be slowed to manage or reduce IARs.

Safety will be monitored throughout the study based on physical examinations, clinical laboratory analyses, and reporting of adverse events (AEs) and serious adverse events (SAEs).

Evaluations of efficacy, including uGAG levels, 6-minute walk test (6MWT), pulmonary function testing, shoulder flexion, visual acuity, and fine and gross motor function will be performed according to the Schedule of Events (Table 2.1 and Section 7.5) if age appropriate and subject is able to perform. Additional assessments will be performed, as indicated, to assess serum biomarkers of inflammation, 3-minute stair climb test (3MSCT), hepatosplenomegaly, growth velocity, cardiac size and function, ICR endpoint (if appropriate), patient-reported outcomes, and subject/parent/caregiver global impression of change. The termination visit should be completed by all subjects who do not complete the Week 144 end of study visit. The termination visit should be completed within 30 days of the last dose of study drug. Efficacy assessments performed within 30 days will not be repeated at the termination visit. If the termination visit occurs after Week 48, blood for serum biomarkers of

inflammation will not be collected and BOT-2 assessments will not be conducted.

NUMBER OF SUBJECTS PLANNED:

Approximately 20 subjects with a confirmed diagnosis of MPS 7, who are UX003 treatment-naïve or were previously treated with UX003 in either an Ultragenyx-sponsored study or a non-Ultragenyx sponsored study (e.g., IST).

DIAGNOSIS AND CRITERIA FOR INCLUSION AND EXCLUSION:

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

1. Confirmed diagnosis of MPS 7 based on leukocyte or fibroblast glucuronidase enzyme assay or genetic testing.
2. Willing and able to provide written, signed informed consent or, in the case of subjects under the age of 18 (or 16 years, depending on the region) or subjects who are intellectually impaired, provide written assent (if required) and written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures.
3. Willing to comply with all study procedures.
4. Sexually active subjects must be willing to use a highly-effective method of contraception while participating in the study and for 30 days following the last dose.
5. Females of childbearing potential must have a negative pregnancy test at Baseline and be willing to have additional pregnancy tests during the study. Females considered not of childbearing potential include those who have not experienced menarche, are postmenopausal (defined as having no menses for at least 12 months without an alternative medical cause) or are permanently sterile due to having hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.
6. *For UX003 treatment-naïve subjects only*, apparent clinical signs of lysosomal storage disease as judged by the Investigator, including at least one of the following: enlarged liver and spleen, joint limitations, airway obstruction or pulmonary problems, limitation of mobility while still ambulatory.
7. *For UX003 treatment-naïve subjects only*, at least 5 years old at time of enrollment and with elevated uGAG excretion at a minimum of 2-fold over the mean normal levels for age (at baseline).

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. *If enrolled in a prior UX003 clinical study*, the subject experienced safety-related event(s) in the prior UX003 clinical study that, in the opinion of the Investigator and sponsor, precludes resuming UX003 treatment.
2. Undergone a successful bone marrow or stem cell transplant or has any degree of detectable chimaerism with donor cells.
3. Presence or history of any hypersensitivity to rhGUS or its excipients that, in the judgment of the Investigator, places the subject at increased risk for adverse effects.
4. Pregnant or breastfeeding at Baseline or planning to become pregnant (self or partner) at any

time during the study.

5. Other than the use of UX003, use of any investigational product (drug or device or combination) within 30 days prior to Baseline, or requirement for any investigational agent prior to completion of all scheduled study assessments.
6. Presence of a condition of such severity and acuity that, in the opinion of the Investigator, warrants immediate surgical intervention or other treatment or may not allow safe study participation.
7. Concurrent disease or condition, or laboratory abnormality that, in the view of the Investigator, places the subject at high risk of poor treatment compliance or of not completing the study, or would interfere with study participation or introduce additional safety concerns.

INVESTIGATIONAL PRODUCT(S), DOSE, AND MODE OF ADMINISTRATION:

UX003 is a sterile liquid buffered saline formulation of rhGUS that contains enzyme at a concentration of 2 mg/mL filled to allow the withdrawal of a 5.0 mL deliverable volume and supplied in a 10 mL glass vial. UX003 will be administered QOW by slow IV infusion over approximately 4 hours. Infusions will be administered on a rate schedule involving a slower infusion rate initially followed by an increase in rate to minimize the potential for IARs; the infusion rate may be slowed to manage or reduce IARs.

REFERENCE THERAPY(IES), DOSE, AND MODE OF ADMINISTRATION:

No reference therapy will be administered in this study.

DURATION OF TREATMENT:

The planned duration of treatment in this study is up to 144 weeks or until one of the following occurs: the subject withdraws consent and discontinues from the study, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, or the study is terminated.

CRITERIA FOR EVALUATION:

Primary Objective:

Safety will be evaluated in all subjects by the incidence and frequency of AEs and SAEs, including clinically significant changes from baseline to scheduled time points in:

- Physical examination findings
- Vital signs and weight
- Echocardiogram (ECHO) findings
- Clinical laboratory evaluations
- Concomitant medications
- Antibodies to rhGUS
- Complement C3, C4 and CH50 levels (as indicated)

Adverse Physiology Related Group Safety Reporting

Adverse Physiology Related Group (APRG) reporting is a novel method synthesizing safety symptoms into multi-domain physiology related groups to capture IAR information. APRG reporting will be used to detect adverse physiologies that might be expressed variably within and between subjects in a study

based on known patterns of adverse physiologies, such as anaphylactoid reactions. This reporting is related to IARs only and standard AE reporting will still be conducted in addition to the APRG.

Management of Infusion Associated Reactions (IARs)

As has been observed in other MPS enzyme therapies, some subjects may experience IARs associated with the administration of UX003. Consequently, appropriate measures have been incorporated into the study design in order to prevent, monitor and manage potential reactions. These measures include prophylactic premedication of subjects with antihistamine, and staged and controlled infusion rates to mitigate the potential for IARs.

Secondary Objective:

- Urinary GAG excretion: First morning void urine will be evaluated for uGAG concentration and normalized to urinary creatinine concentration.

Other Objectives:

For the purposes of this study, efficacy assessments listed below which were not performed during the primary or feeder study will generally not be required for this long-term treatment and extension study; safety measures will be assessed in all subjects. UX003-naïve subjects will be required to complete all of the following assessments (as appropriate).

- Biomarkers of inflammation in serum: Blood samples will be collected through Week 48 to evaluate levels of biomarkers of inflammation and response to treatment.
- Six Minute Walk Test (6MWT): The total distance walked (meters) in a six-minute period will be measured. The percent of predicted normal distance walked based on published normative data will also be determined.
- Bruininks-Oseretsky Test of Motor Proficiency (BOT-2): This test of motor proficiency will be administered through Week 48 to evaluate treatment-related changes in four domains assessing both fine and gross motor function: fine motor precision, manual dexterity, balance, running speed and agility. The test may be modified and tests omitted to accommodate the needs of the subject.
- Three Minute Stair Climb Test (3MSCT): The number of stairs climbed within a three-minute period will be assessed.
- Pulmonary function testing (spirometry): Spirometry will be administered to subjects who do not require invasive ventilatory support or have a tracheostomy. Pulmonary function variables include forced vital capacity (FVC) and maximum voluntary ventilation (MVV).
- Shoulder flexion maximum range of motion: Goniometry will be used to measure (in degrees) the maximum passive shoulder range of motion in both flexion and extension and compared to known normal standards for age.
- Growth (anthropometric): Growth will be assessed by anthropometric measurements including standing height (or recumbent length or sitting height if applicable) and weight. Growth velocity will be calculated and compared with pre-treatment growth velocity when available.
- Visual acuity will be measured using a standard eye chart and recorded for each eye independently.
- Multi-domain responder index (MDRI): consisting of the six-minute walk test (6MWT), the Bruininks-Oseretsky Test of Motor Proficiency (BOT-2; fine motor and gross motor function),

forced vital capacity (FVC), shoulder flexion, and visual acuity.

- **Individualized Clinical Response (ICR):** Will only be assessed for subjects previously enrolling from the Ultragenyx-sponsored MPS 7 Phase 3 clinical study UX003-CL301 where an outcome of interest was previously selected from the possible clinical outcome measures, the same ICR identified in the primary (or feeder) study may continue to be followed in this study.
- **Scoring of Impactful Clinical Problems:** The three most impactful clinical problems as reported by the subject/parent/caregiver during the Clinical Problem Evaluation will be scored on a Likert scale. For UX003 treatment-naïve subjects, the initial Clinical Problem Evaluation will occur at the Baseline visit. For subjects enrolling from the Ultragenyx-sponsored MPS 7 Phase 3 clinical study UX003-CL301, the Clinical Problems identified during the UX003-CL301 Randomization visit will continue to be scored throughout this study.
- **Subject-reported disability, quality of life, and fatigue:** The MPS Health Assessment Questionnaire, Childhood Health Assessment Questionnaire (CHAQ), or Health Assessment Questionnaire (HAQ) will be administered to evaluate treatment-related changes in self-care and mobility activities of daily living. The age-appropriate Pediatric Quality of Life Multidimensional Fatigue Scale (Peds QL-Multidimensional Fatigue Scale) will be administered to evaluate treatment-related changes in fatigue.
- **Subject/Parent/Caregiver Clinical Global Impression (CGI) scale:** Subjects or parents/caregivers will provide a global assessment of change using a CGI scale. In addition, subjects or parents/caregivers will provide narratives of their perception of how treatment has impacted the subject's ability to complete activities of daily living.
- **Hepatosplenomegaly:** Liver and spleen measurements will be assessed by physical exam.
- **Cardiac ventricular mass/function:** Ventricular mass will be assessed by ECHO and scored as a z-score relative to normal ventricular mass. Evaluation of valvular function and cardiac function will be made primarily for safety purposes.

STATISTICAL METHODS:

The Full Analysis Set will consist of all subjects who were received at least 1 dose of investigational product. Both safety and efficacy analysis will be based on Full Analysis Set. Continuous variables will be summarized by number of subjects and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects.

Safety Analysis

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence and frequency of AEs will be summarized by System Organ Class (SOC), Preferred Term (PT), severity, and relationship to UX003 treatment. A by-subject listing will be provided for those subjects who experience a SAE, including death, or experience an AE associated with early withdrawal from the study or study drug treatment.

Clinical laboratory data will be summarized by the type of laboratory test. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e., outside of reference ranges) and/or clinically significant abnormalities will be presented for each clinical laboratory measurement.

uGAG and Other Efficacy Analyses

Urinary GAG percent reduction from pre-treatment baseline and changes from pre-treatment baseline for other clinical efficacy endpoints will be summarized with descriptive statistics. The percentage change from pre-treatment baseline in uGAG will be tested using the GEE method. The GEE model will include baseline and time as categorical variables.

A full description of the statistical evaluations will be provided in the Statistical Analysis Plan (SAP).

Table 2.1: Schedule of Events

	Baseline ^{a,b}	Treatment / Assessment Period ^{b,c}									Termination Visit ^z
		First 48 Weeks of Treatment					Treatment Weeks 50 - 144				
		0	Every 2 Weeks	Week 12	Week 24	Week 36	Week 48	Every 2 Weeks	Every 12 Weeks ^d	Every 24 Weeks ^e	
Informed consent/assent	X										
Medical history ^g	X										
ICR identification (only for UX003-CL301 subjects) ^h	X										
Weight for drug preparation ⁱ	X		X	X	X	X		X			
Clinical Problem Evaluation ^j	X			X		X			X		X
UX003 Treatment	X	X					X				
Safety Assessments											
Physical examination ^k	X		X	X	X	X		X			X
Vital signs ^l	X	X					X				X
Clinical laboratory tests ^m	X					X				X	X
Urine pregnancy test ⁿ	X		X	X	X	X		X			X
Antibodies to rhGUS ^o	X			X		X			X		X
Complement C3, C4, CH50 (for subjects with IARs) ^p											
Concomitant medications	X	X					X				X
Adverse events ^q	X	X					X				X
Efficacy Assessments											
Urinary GAG ^r	X		X	X	X	X		X			X

	Baseline ^{a,b}	Treatment / Assessment Period ^{b,c}									
		First 48 Weeks of Treatment					Treatment Weeks 50 - 144				Termination Visit ^z
		Every 2 Weeks	Week 12	Week 24	Week 36	Week 48	Every 2 Weeks	Every 12 Weeks ^d	Every 24 Weeks ^e	Every 48 Weeks ^f	
Serum biomarkers of inflammation	X			X		X					X
6MWT, 3MSCT ^s	X			X		X			X		X
BOT-2 ^s	X			X		X					X
Spirometry ^t	X			X		X			X		X
Goniometry ^u	X			X		X			X		X
Anthropometrics ^v	X		X	X		X			X		X
Visual acuity (eye chart)	X			X		X			X		X
MPS HAQ, CHAQ/HAQ, Peds QL ^w	X			X		X			X		X
Subject/Parent/Caregiver CGI ^x	X			X		X			X		X
Liver and spleen assessment ^y	X					X				X	X
Echocardiogram	X					X				X	X

Abbreviations: CGI = clinical global impression, ICR = Individual Clinical Response, IAR = infusion-associated reaction, GAG = glycosaminoglycan, 6MWT = Six-Minute Walk Test, BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency (Second Edition), 3MSCT = Three-Minute Stair Climb Test, CHAQ = Childhood Health Assessment Questionnaire, MPS HAQ = Mucopolysaccharidosis Health Assessment Questionnaire, Peds QL = Pediatric Quality of Life Inventory™, rhGUS = recombinant human beta-glucuronidase, GAG = glycosaminoglycans

- a. For subjects enrolling from UX003-CL301, the Baseline Visit will be conducted in conjunction with the UX003-CL301 Week 48 study visit to avoid treatment disruption. Subjects enrolling from an Ultragenyx-sponsored clinical study: efficacy, ECHO and clinical laboratory assessments performed during the final or End of Treatment visit from the primary study may be used as baseline assessments if performed within 30 days of study baseline visit as indicated in Section 7.5. Assessment of antibodies to rhGUS (e.g., Week 46 rhGUS assessment in UX003-CL301) may be used as baseline assessments if performed within 30 days of study Baseline Visit. Any listed assessments not performed during the primary study final visit must be

performed before the first study drug infusion. Unless otherwise specified, Baseline assessments must be completed within 30 days prior to the first dose of study drug. For subjects who are treatment naïve or who are enrolling from a non-Ultragenyx sponsored clinical study, initial baseline safety and efficacy assessments as indicated in Section 7.5 will be performed within 30 days of the study baseline visit as indicated in Section 7.5. Refer to Study Reference Manual for additional details.

- b. For all subjects, assessments scheduled on the same day as treatment must be completed prior to the infusion.
- c. Visit windows are ± 3 days and for major assessment visits (Weeks 12, 24, 36, 48 and every 24 weeks thereafter), the window is ± 7 days.
- d. Actual study weeks for every-12-week visits = Weeks 60, 72, 84, 96, 108, 120, 132, 144.
- e. Actual study weeks for every-24-week visits = Weeks 72, 96, 120, 144.
- f. Actual study weeks for every-48-week visits = Weeks 96, 144.
- g. Medical history will be collected for all subjects who are treatment naïve or who are enrolling from a non-Ultragenyx sponsored study (e.g., Investigator sponsored trials (ISTs), expanded access/compassionate use). For subjects enrolled in UX003-CL301 or other Ultragenyx sponsored study, their previously reported medical history will carry over to this study.
- h. The ICR will only be identified for subjects enrolling from the MPS 7 Phase 3 Ultragenyx sponsored study UX003-CL301.
- i. Weight for drug preparation may be obtained up to 15 days prior to indicated visit (e.g. Weeks 10, 22, 34, and 46 visits).
- j. *For UX003 treatment-naïve subjects* the three most impactful clinical problems reported by the subject/parent/caregiver will be identified and scored at the Baseline visit. These clinical problems will continue to be scored throughout this study. *For subjects enrolling from the MPS 7 Phase 3 Ultragenyx sponsored study UX003-CL301*, the three most impactful clinical problems reported by the subject/parent/caregiver during the UX003-CL301 randomization visit will continue to be scored throughout this study.
- k. Physical examinations are to include neurologic examination and evaluation of the presence or absence of corneal clouding. If subject complains of leg weakness or fatigue, evaluate for signs of cord compression (e.g., leg reflexes and motor strength).
- l. On infusion days, vital signs will be measured at a minimum of: immediately (<30 minutes) before the infusion, at least every 30 minutes for the first hour of infusion, at least every hour for the remainder of the infusion and immediately (<30 minutes) after the infusion. Additional measurements should be obtained as appropriate.
- m. Laboratory samples (blood and urine) are to be collected prior to dosing of study drug. Clinical laboratory tests are to include hematology, chemistry, and urinalysis. Laboratory samples for safety performed within 30 days prior to Baseline may be used for the study baseline.
- n. For women of childbearing potential only. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result.
- o. Testing for any antibodies directed against rhGUS. Antibody sample must be collected before infusion.
- p. If a drug-related IAR has occurred, C3, C4 and CH50 samples should be drawn prior to and immediately after the end of infusion at the subsequent infusion.
- q. For subjects enrolling from an Ultragenyx-sponsored clinical trial, all AEs will be recorded from the time the subject signs the informed consent and completes the End of Treatment visit in the primary study until 30 days after the last dose of study drug. For subjects who are treatment naïve or who are enrolling from a non-Ultragenyx-sponsored clinical trial, all AEs will be recorded from the time the subject signs the informed consent until 30 days after the last dose of study drug.
- r. Urine samples must be collected from first morning voids.

- s. The 6MWT, 3MSCT and BOT-2 assessments may be conducted over a span of two days with each test performed once. The preferred order is to perform the 6MWT and 3MSCT on separate days. If performed on the same day, the 6MWT should be done before the 3MSCT. The subject's resting heart rate must return to baseline between assessments.
- t. Pulmonary function testing may be omitted for subjects with tracheostomies. If performed on the same day, pulmonary function testing should be done before the 6MWT and 3MSCT. The subject's resting heart rate must return to baseline between assessments.
- u. The highest value of three shoulder flexion and extension range of motion measurements for each side will be reported.
- v. Anthropometric measurements include standing height and weight. If standing height cannot be obtained, recumbent length or sitting height will be determined.
- w. The MPS HAQ or HAQ/CHAQ should be performed for *UX003 treatment-naïve subjects and subjects enrolling from the MPS 7 Phase 3 Ultragenyx sponsored study UX003-CL301*. The MPS HAQ will be administered to all age groups. The CHAQ should be performed for pediatric subjects only (<14 years old). The HAQ should be performed for subjects ≥ 14 years old. Subjects will consistently complete the same questionnaire (HAQ or CHAQ) administered at baseline for the duration of the study regardless of whether their age changes from 13 to 14 during the study. The age-appropriate version of the PedsQL multidimensional fatigue module will be administered throughout the study. *For subjects enrolling from previous clinical trial with UX003*, these subject-reported outcome measures will only be administered if they were previously performed in their primary (or feeder) study.
- x. As part of the subject/parent/caregiver clinical global impression assessment, subjects/parents/caregivers will be asked to provide narratives of how treatment has impacted the subject's ability to complete activities of daily living.
- y. Liver and spleen size will be assessed qualitatively by physical examination.
- z. The termination visit should be completed by all subjects who do not complete the Week 144 end of study visit. The termination visit should be completed within 30 days of the last dose of study drug. Efficacy assessments performed within 30 days will not be repeated at the termination visit. AEs ongoing at 30 days following the last dose of study drug should have a comment in the source document by the Investigator that the event has recovered, recovered with sequelae, or stabilized. If the termination visit occurs after Week 48, blood for serum biomarkers of inflammation will not be collected and BOT-2 assessments will not be conducted.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

3MSCT	Three-Minute Stair Climb Test
6MWT	Six-Minute Walk Test
AE	adverse event
ALT	alanine aminotransferase
APRG	Adverse Physiology Reporting Group
AST	aspartate aminotransferase
ATS	American Thoracic Society
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency 2 nd Edition
BUN	blood urea nitrogen
°C	degrees Celsius
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CHAQ	Childhood Health Assessment Questionnaire
CIM6PR	cation-independent mannose 6-phosphate receptor
CRF	Case Report Form
CS	chondroitin-6-sulfate
DS	dermatan sulfate
EC	Ethics Committee
ECHO	echocardiogram
EDC	electronic data capture
EMLA	eutectic mixture of local anesthetic
ERS	European Respiratory Society
ERT	enzyme replacement therapy
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FVC	forced vital capacity
GAG	glycosaminoglycan
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
GMP	Good Manufacturing Practice
GUS	beta-glucuronidase

HAQ	Health Assessment Questionnaire
HIPAA	Health Insurance Portability and Accountability Act
HS	heparan sulfate
IAR	infusion-associated reaction
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICR	Individualized Clinical Response
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IST	Investigator sponsored trial
ITT	intent-to-treat
IV	intravenous
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MDRI	Multi-domain responder index
MID	minimally important difference
MIP-1alpha	macrophage inflammatory protein 1 alpha
MPS	mucopolysaccharidosis/mucopolysaccharidoses
MPS 1	mucopolysaccharidosis type 1, Hurler Syndrome
MPS 2	mucopolysaccharidosis type 2, Hunter Syndrome
MPS 7	mucopolysaccharidosis type 7, Sly Syndrome
MPS HAQ	Mucopolysaccharidosis Health Assessment Questionnaire
MVV	maximum voluntary ventilation
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No observed adverse effect level
PedsQL	Pediatric Quality of Life Inventory™
PICC	peripherally inserted central catheter
PK	pharmacokinetic(s)
PT	Preferred Term
QOW	every other week

QW	weekly
RBC	red blood cell
rhGUS	recombinant human beta-glucuronidase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
T _{max}	time to maximum plasma concentration
TNF-alpha	tumor necrosis factor-alpha
uGAG	urinary glycosaminoglycans
US	United States
UX003	Investigational Product/study drug, recombinant human beta-glucuronidase, rhGUS
WBC	white blood cell

Definition of Terms

Investigational Product is defined as, “A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use” (from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] Harmonised Tripartite Guideline E6: Guideline for Good Clinical Practice).

The terms “Investigational Product” and “study drug” may be used interchangeably in the protocol.

Primary (or feeder) study is defined as the Ultragenyx-sponsored study a subject completed immediately prior to enrollment in this long-term treatment and extension study. The terms “primary study” and “feeder study” may be used interchangeably in the protocol.

“Study baseline” is defined as the baseline visit of this long-term treatment and extension study (UX003-CL202).

“Pre-treatment baseline” is defined as the baseline visit in the primary study (e.g., UX003-CL301) or the visit and/or assessment performed just prior to treatment with UX003.

5 INTRODUCTION

Mucopolysaccharidoses (MPS) are a group of inherited metabolic disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of glycosaminoglycans (GAGs). Although many of the characteristics are similar among the mucopolysaccharidoses, each disease is a distinct entity arising from deficiency of a specific enzyme. MPS 7 (Sly syndrome) is an ultra-rare, chronically debilitating, and life threatening lysosomal storage disease, and one of the rarest of the mucopolysaccharidoses. Varying in severity and progression rate, MPS 7 symptoms may include abnormal coarsened facies, hepatosplenomegaly, pulmonary disease, cardiovascular complications, joint stiffness, short stature, and a skeletal disease known as dysostosis multiplex. In more severely affected MPS 7 patients, there may be developmental delay as well. Most MPS 7 patients die before the second or third decade of life due to compounding medical problems.

Despite nearly two decades of animal research demonstrating effective treatment with enzyme replacement therapy (ERT) in MPS 7 models and the success of ERT in four other MPS disorders (MPS 1, MPS 2, MPS 4A, and MPS 6), MPS 7 patients do not have an approved treatment available. Development in this disease has not proceeded because the extreme rarity (less than 100 patients identified worldwide and an estimated incidence rate of less than 1 per 250,000 births) and clinical heterogeneity has made it impractical to approach with traditional clinical study designs and endpoints.

UX003 is a formulation of recombinant human beta-glucuronidase (rhGUS), intended as an ERT for MPS 7. Ultragenyx has conducted 3 clinical studies to date in support of UX003 development. A retrospective study (UX003-CL001) reviewed medical records of patients with MPS 1, 2, and 6 to evaluate the long-term impact of ERT products (Aldurazyme[®], Elaprase[®], and Naglazyme[®]) on total urinary GAG (uGAG) excretion and formally analyze the relationship of uGAG to the major clinical manifestations of MPS disorders. Prospective, interventional studies include an initial Phase 1/2 study (UX003-CL201) assessing safety, efficacy, and pharmacokinetics (PK) of UX003; a Phase 2 study (UX003-CL203) in patients under 5 years old, and a pivotal safety and efficacy Phase 3 study (UX003-CL301).

5.1 Overview of MPS 7

MPS 7 (Sly syndrome) is an extremely rare autosomal recessive lysosomal storage disorder originally described by William Sly and colleagues in 1973 ([Sly et al. 1973](#)). MPS 7 is the second rarest of the MPS disorders with fewer than 100 patients identified worldwide and also the most heterogeneous of the MPS disorders. MPS 7 is characterized by a deficiency of the lysosomal enzyme GUS, which is required for the degradation of the GAGs: dermatan sulfate (DS), chondroitin-6 sulfate (CS), and heparan sulfate (HS). This deficiency results in GAG accumulation in many tissues and organs, leading to numerous clinical symptoms similar to those observed for MPS 1 (Hurler Syndrome) and MPS 2 (Hunter Syndrome) ([Neufeld et al. 2001](#)).

MPS 7 genotypes/phenotypes have been studied for many years (reviewed in (Tomatsu et al. 2009)). A total of 49 unique mutations were identified in a total of 103 mutant alleles found in 56 patients, with 9% of the alleles unidentified. Missense mutations account for 78.6% of total alleles; the remaining were nonsense mutations, deletions, or splice site mutations, all likely leading to a null genotype and severe phenotype. This is a much higher frequency of missense mutations than is normally found in other MPS diseases. For example, in MPS 1, nearly 70% of alleles are nonsense mutations with two dominant stop mutations accounting for a large fraction of all mutations (Scott et al. 1995).

The clinical course and disease progression of MPS 7 comprise a wide spectrum of severity. The most severe form of the disease can uniquely present at birth with hydrops fetalis, a severe neonatal condition in which the child retains an enormous amount of fluid throughout the body (Vervoort et al. 1996). Infants with hydrops fetalis rarely survive beyond a few weeks to a few months of age (Neufeld et al. 2001).

Patients with severe MPS 7, who are not born with non-immune hydrops fetalis frequently present as infants or young children with clinical signs and symptoms including hepatosplenomegaly, pulmonary infections, cardiac problems, corneal clouding, hearing loss, hernias, joint stiffness and short stature (Neufeld et al. 2001). Diagnosis of MPS 7 is often made through clinical examination and urine tests for excess glycosaminoglycans excreted in the urine (Sewell et al. 1982). Due to the clinical heterogeneity of the disease, it is recommended that GUS activity in all suspected cases of lysosomal storage disease be evaluated through enzymatic analysis of leukocytes or fibroblasts (Lee et al. 1985).

Many patients experience progressive pulmonary problems as a result of airway obstruction (enlarged adenoids and tonsils, secretions, infections and tracheal abnormalities) leading to sleep apnea and pulmonary insufficiency, eventually requiring tracheostomy. Significant respiratory restriction combined with frequent recurrent and chronic nasopharyngeal and respiratory infections can lead to progressive respiratory compromise and failure (Kakkis et al. 1996b), (Neufeld et al. 2001). Heart disease is also common in patients with severe MPS 7, although it may not develop or manifest until later in life. Valvular insufficiency due to thickening and calcification of the valves, arterial lesions of the coronary arteries and obstruction of the thoracic aorta like that observed for Hurler syndrome, have been described (Kakkis et al. 1996b). In severely affected MPS 7 patients, GAG storage in the coronary vessels along with pulmonary insufficiency can lead to cardiomyopathy, cor pulmonale and/or death.

MPS 7 patients generally have a variety of the typical findings of dysostosis multiplex with significant variability. This may include odontoid dysplasia with atlantoaxial instability as in other MPS disorders. Storage within the synovium and other joint tissues can lead to significant restriction of mobility in the hip, shoulder, elbow and knee joints as in other MPS disorders. All of these disease complications can result in severe pain or the inability to walk, often resulting in the use of a wheelchair. Additional symptoms include hearing loss, cataracts, and corneal clouding among others.

Patients with an intermediate form of MPS 7 have features similar to the more severe form of the disease but may present later and have less developmental delay and less rapid disease progression. At the attenuated end of the spectrum, MPS 7 patients can present as adults with a less severe physical disease ([de Kremer et al. 1992](#)). There are also some patients that present with an attenuated form at adolescence with a wide spectrum of abnormalities, but no mental retardation or corneal clouding ([Kakkis et al. 1996b](#)), ([Neufeld et al. 2001](#)).

Life expectancy for most individuals with MPS 7 is into the teenage or young adult years; however, severe MPS 7 patients may die within the first few years of life or at birth with severe hydrops ([Vervoort et al. 1996](#)). Mortality is commonly due to cardiovascular or respiratory complications.

5.2 Enzyme Replacement Therapy for MPS Disorders

The primary treatment modalities for MPS disorders are ERT and hematopoietic stem cell transplantation. Both approaches provide active enzyme to replace the deficiency and confer substantial benefit, but are not curative. ERT is now commercially available for MPS 1 (Aldurazyme[®], laronidase), MPS 2 (Elaprase[®], idursulfase), MPS 4A (Vimizim[™] (elosulfase alfa), and MPS 6 (Naglazyme[®], galsulfase). At present, there are no approved treatments for MPS 7. Multiple clinical trials have been conducted to establish safety and efficacy of ERT in MPS diseases (reviewed in ([Valayannopoulos et al. 2011](#))). The treatment regimen for ERT involves weekly (QW) or every other week (QOW) intravenous (IV) infusions of the recombinant human enzyme. Many patients treated with ERT experience infusion-associated reactions (IARs). Observed clinical benefits include improved walking ability, joint range of motion, improved lung function, decreased liver volume, and decreased (but not normalized) uGAG levels. Most MPS patients develop antibodies to the recombinant enzyme; in some severely affected MPS 1 patients, antibody titer was inversely related to the reduction in uGAG levels ([Clarke et al. 2009](#)).

Clinical study data in the Phase 3 studies of laronidase, galsulfase and idursulfase have demonstrated significant predictive value of uGAG levels. The uGAG levels are significantly reduced during the first 4-6 weeks of ERT treatment, then reach a plateau ([Wraith et al. 2004](#)), ([Kakkis 2002](#)), ([Harmatz et al. 2006](#)); the clinical effect evolves over the next 6-12 months. This pattern of uGAG reduction preceding clinical effect is expected considering the additional time needed for inflammation and injury to heal and recover following the resolution of lysosomal storage, and is consistent with uGAG's potential as a predictor of tissue response. In the clinical studies, changes in uGAG were able to differentiate between effective and less effective dose regimens, with reductions of >50% associated with substantial efficacy based on clinical measures ([Table 5.2.1](#)). In all cases, uGAG reduction $\geq 50\%$ was associated with significant clinical benefit. For idursulfase, the QOW regimen showed less than 50% reduction and less efficacy; this difference was detected and predicted by the uGAG levels early in the study ([Muenzer et al. 2006](#)). For this reason, a measure of uGAG should be predictive of changes in lysosomal storage conducive to clinical improvement in MPS patients.

Table 5.2.1: Urinary GAG Reduction of > 50% is Likely to Predict Clinical Benefit

Study	Design	Dose (mg/kg)	uGAG (% Reduction)	Walk Test (m)	FVC (% predicted)	Liver Volume (% decrease)
Laronidase for MPS 1						
Phase 3 (Wraith et al. 2004)	RDBPC N=45	0.58 QW 26 weeks	- 54.1%	38.1 p=0.037	5.6 p=0.009	-18.9 p=0.009
Idursulfase for MPS 2						
Phase 3 (Muenzer et al. 2006)	RDBPC N=96	0.5 QOW 53 weeks	- 44.7%	30.3 p=.0732	0.004 p=0.95	-24.0 p<0.0001
		0.5 QW 53 weeks	- 52.5%	44.3 p=0.00131	3.45 p=0.065	-25.3 p<0.0001
Galsulfase for MPS 6						
Phase 3 (Harmatz et al. 2006)	RDBPC N=39	1.0 QW 24 weeks	- 75% p<0.001	92* p=0.025	No improvement	Not done

*12MWT

5.3 Brief Overview of UX003 Development

UX003 is intended as an IV ERT for the treatment of MPS 7. A brief overview of existing information on UX003 is provided below; a comprehensive review of available data is contained in the Investigator’s Brochure (IB) provided by Ultragenyx Pharmaceutical Inc. (Ultragenyx), which should be reviewed prior to initiating the study.

5.3.1 Brief Description of UX003

The active pharmaceutical ingredient in UX003, rhGUS, is produced in a genetically engineered Chinese hamster ovary cell line that expresses the normal full length human GUS protein. The rhGUS protein is synthesized as an 80 kDa monomer with 651 amino acids remaining after removal of the 22 amino acid signal peptide (Oshima et al. 1987). After glycosylation at four N-linked glycosylation sites at asparagines 173, 272, 420 and 631, the apparent molecular weight is 82 kDa for each monomer. Although usually intact at the C-terminus after production, once delivered to the lysosome, proteolysis removes 18 amino acids from the C-terminal end to form a 78 kDa monomer (Islam et al. 1993). Biologically, purified rhGUS exists as a ~332 kDa homotetramer with two active sites per tetramer.

The active drug substance is purified using standard chromatography methods and formulated for IV administration. UX003, the drug product in this clinical trial, is a sterile liquid buffered saline formulation of rhGUS that contains enzyme at a concentration of 2 mg/mL in a 10 mL glass vial filled to allow the withdrawal of a 5.0 mL deliverable volume.

5.3.1.1 UX003 Mechanism of Action in MPS 7

UX003 belongs to a class of ERTs that includes approved products for MPS 1, MPS 2, MPS 4A and MPS 6. The active pharmaceutical ingredient in UX003, rhGUS, is a member of the lysosomal hydrolase family of enzymes that catalyze breakdown of complex carbohydrates. Human GUS catalyzes the hydrolysis of β D-glucuronic acid residues from the non-reducing end of glycosaminoglycans: DS, CS, and HS (Vervoort et al. 1996). In vitro and in vivo, rhGUS is taken up by cells and tissues by the cation independent mannose 6-phosphate receptor (CIM6PR) via the mannose 6-phosphate recognition residues located on the enzyme's N-linked oligosaccharides. Uptake by the CIM6PR occurs in a large number of tissues and is important for the maximal effectiveness of the enzyme. The enzyme can also be taken up by the mannose receptor (MR) due to some terminal mannose residues located on high mannose N-linked oligosaccharides. Clearance by the MR occurs mainly by the cells in the reticuloendothelial system: the spleen, Kupffer cells in the liver, and circulating macrophages in the plasma. Together, these recognition signals are responsible for the rapid clearance and tissue distribution of infused lysosomal enzymes such as rhGUS from the circulation. Both types of delivery can have therapeutic benefit as tissues with the MR also manifest substantial GAG storage in the MPS disorders, although the mannose 6-phosphate system is sufficient for uptake into all cell types.

5.3.2 Nonclinical Studies

Ultragenyx has conducted a comprehensive nonclinical program to support the chronic QOW IV administration of UX003. In addition, the nonclinical pharmacology of recombinant GUS has been evaluated in a large number of published studies in vitro and in murine models of MPS 7. Studies of potential clinical significance and relevance to this protocol are summarized below. Additional details are provided in the IB.

Nonclinical studies have been completed in MPS 7 mice (including newborns). The nonclinical toxicology program includes five studies, including an 8-week biodistribution study in tolerant MPS 7 mice, a GLP acute toxicity study in Sprague Dawley rats, a 26-week chronic toxicity study in juvenile cynomolgus monkeys, and dose range-finding developmental toxicity studies in rabbits and Sprague Dawley rats. At dose levels up to 20 mg/kg QOW, no toxicologically-significant findings were related to the administration of UX003. These studies support a 5-fold safety factor relative to the 4 mg/kg dose planned in this clinical study. The no observed adverse-effect level (NOAEL) for single IV dose administration in these studies was 20 mg/kg.

A large number of studies in MPS 7 mouse models have shown that recombinant GUS enzyme replacement is distributed to many tissues and significantly reduces or prevents lysosomal storage during treatment (O'Connor et al. 1998), (Sands et al. 1994), (Sands et al. 1997), (Sands et al. 2001), (Vogler et al. 1996), (Vogler et al. 2005). Biodistribution of rhGUS has been seen in many tissues affected by MPS 7 including the brain, liver, spleen, heart, kidney, bone and lung (Vogler et al. 2005), (Grubb et al. 2008), (Sly et al. 2006).

The reduced lysosomal storage following ERT correlates with significant pathologic improvement and clinical benefit, with prolonged effects including dramatic improvements in bone development, growth, cognitive ability, hearing, immune function, and survival (Sands et al. 1997), (Sands et al. 2001), (Vogler et al. 1996). Additionally, treatment of MPS 7 mice with high doses of rhGUS resulted in widespread delivery of enzyme as well as delivery across the blood-brain barrier with corresponding reductions in lysosomal storage in nearly all tissues, including the brain. The increased enzyme levels and accompanying reduction in lysosomal storage correlated with both dose and duration of treatment (Vogler et al. 2005). Histopathologic evaluation of tissues from MPS 7 mice showed no pathologic effects related to the enzyme-mediated increased clearance of HS and DS.

5.3.3 Clinical Studies

The first in-human use of UX003 was sponsored by Dr. Joyce Fox and Steven and Alexandra Cohen Children's Medical Center of New York under an emergency IND granted by the FDA. A 12-year-old patient with advanced multi-system MPS 7 including respiratory insufficiency was treated with 2 mg/kg rhGUS QOW; the case study and results following initial treatment were recently reported (Fox et al. 2015). Through 24 weeks of treatment, a decline in uGAG excretion (~ 65%) and a sustained reduction in the size of the enlarged liver and spleen have been observed. The data through 52 weeks also show improved pulmonary function, oral feeding, and increased activity level. No drug-related serious adverse events (SAEs) or IARs have been reported (Fox et al. 2015). The patient elected to continue UX003 treatment.

A second emergency IND was granted to treat a 4-month old MPS 7 infant born with severe non-immune hydrops fetalis (Dr. Heather Lau, New York University School of Medicine). The patient has received infusions for approximately 1 year; uGAG was reduced by at least 70% after several infusions. No drug-related IARs have occurred in this Investigator-sponsored trial (IST). The patient was subsequently enrolled in the Phase 2 study (UX003-CL203) described below.

The clinical development program for UX003 rhGUS ERT consists primarily of the following studies, in addition to Study UX003-CL202:

- An open-label Phase 1/2 study to assess the safety, efficacy, and dose of UX003 in pediatric and adult MPS 7 patients via IV administration QOW for 36 weeks with up to an additional 36 weeks treatment during the Continuation Period (UX003-CL201; NCT01856218 followed by ongoing long-term treatment at 4 mg/kg QOW)
- A randomized, placebo-controlled, blind-start, single-crossover Phase 3 study to assess the efficacy and safety of UX003 in pediatric and adult MPS 7 patients via IV administration QOW for 48 weeks (UX003-CL301; NCT02230566)

- An open-label Phase 2 study of UX003 in MPS 7 patients less than 5 years old (UX003-CL203; NCT02418455)

Available efficacy and safety data in humans is provided in the IB.

5.4 Summary of Overall Risks and Potential Benefits

An initial Phase 1/2 study has shown that UX003 can reduce lysosomal storage and uGAG and is expected to provide clinical benefit. Data from nonclinical toxicology and safety pharmacology studies, along with published data from MPS 7 mouse model studies, provide guidance on potential benefits and risks of UX003 treatment. The nonclinical data support the safe use of UX003 when dosed up to 4 mg/kg as an IV infusion and support a 5-fold safety factor relative to the 4 mg/kg dose. The risk for off-target effects is reduced by the extreme specificity of the enzyme and the fact that the mechanism of action for GUS is restricted to the lysosome. The enzymatic activity of GUS has a pH optimum between 3.5 and 4.5 (data on file). At pH 7 near the pH of plasma, enzymatic activity is drastically reduced. Hence, the ability of GUS to degrade GAGs outside of the lysosome is limited.

In addition, an understanding of the benefits and risks associated with ERT for other closely related MPS disorders makes it possible to anticipate the benefit-risk profile with UX003. Clinical trial data and experience with marketed ERT products for the treatment of related MPS disorders supports the safety and efficacy of MPS ERT as a class. These therapies have been approved and distributed to more than 40 countries worldwide, with hundreds of subjects treated for several years. Laronidase has now been marketed for more than 10 years without a significant change in the benefit-risk profile. In each of these programs, the reduction in lysosomal storage was demonstrated by reductions in liver and spleen size and uGAG excretion. The reduction was associated with clinically important changes in mobility, pulmonary function, joint stiffness, and other reported findings.

The most common adverse effects of ERT relate to increased antibody titers and IARs. There have been no other consistent adverse effects across the different MPS disorders. Though IARs represent the most serious safety concern with ERTs, appropriate measures have been incorporated into the design of the current study to prevent, monitor and manage potential reactions. These measures include prophylactic premedication of patients with antihistamine, and staged and controlled infusion rates. The large fraction of MPS 7 patients with missense mutations may result in a reduced immune response to ERT since residual protein in the tolerant mouse (Sly et al. 2001) and also in MPS 1 humans undergoing ERT is associated with reduced immune responses (Yogalingam et al. 2004).

With no treatments currently available for this progressive, ultimately-fatal genetic ultra-rare disease, a clear medical need exists for a novel disease-modifying approach that holds the potential for altering the clinical course of disease progression. Overall, the safety and efficacy data from clinical and nonclinical studies in combination with an understanding of

the risks associated with ERTs for other MPS disorders indicate the benefit-risk ratio of UX003 is sufficient to support clinical development for the treatment of MPS 7.

5.5 Study Rationale

Mucopolysaccharidosis type 7 (MPS 7, Sly syndrome) is an ultra-rare (< 100 cases currently identified worldwide), chronically debilitating and life threatening lysosomal storage disease. It is characterized by a deficiency of the lysosomal enzyme GUS, required for degradation of the GAGs: DS, CS and HS. The GUS deficiency results in lysosomal accumulation of GAGs in multiple tissues and organs throughout the body and numerous clinical signs and symptoms as a result of tissue damage and organ dysfunction. There are currently no approved treatments for MPS 7.

UX003 (recombinant human beta glucuronidase, rhGUS) is intended as a long-term ERT for the treatment of MPS 7 via IV administration. Ultragenyx is conducting this treatment and extension study to assess the long-term safety and efficacy of UX003 treatment in subjects with MPS 7. Subjects with MPS 7 who are UX003 treatment-naïve or have been previously enrolled and treated with UX003 in other clinical studies or programs are eligible for enrollment.

The study will continue for up to 144 weeks or until one of the following occurs: the subject withdraws consent and discontinues from the study, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, or the study is terminated.

6 STUDY OBJECTIVES

The primary objective of the study is to evaluate:

- Long-term safety of UX003 in subjects with MPS 7

The secondary objective of the study is to evaluate:

- Long-term efficacy of UX003 in reducing uGAG substrate in subjects with MPS 7

Other objectives of the study are to evaluate:

- Measures of lysosomal storage including hepatosplenomegaly
- Measures of other clinical and functional outcomes, including pulmonary function, walking distance, shoulder flexion, fine motor function, gross motor function, climbing stairs, visual acuity, and cardiac size and function, and a composite Multi-Domain Responder Index (MDRI), as applicable per subject status
- Growth, as defined by impact on general health and assessed by changes in height (or recumbent length) and weight growth velocity
- Subject-reported disability and quality of life, and fatigue, as indicated
- Subject or parent/caregiver global assessment of change and impact on activities of daily living, as indicated
- If an individualized clinical response (ICR) endpoint was defined for a subject from a previous UX003 study, the ICR may continue to be followed

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

This is a multi-center, multinational, open-label treatment and extension study in subjects with MPS 7. The study will assess long-term safety and efficacy of UX003 treatment and will continue for approximately 144 weeks or until one of the following occurs: the subject withdraws consent and discontinues from the study, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, or the study is terminated.

Subjects with MPS 7 who are UX003 treatment-naïve or previously enrolled and treated in a prior clinical study of UX003 may have the option to enroll into this treatment and extension study provided all eligibility criteria have been met for a given subject. Subjects with MPS 7 who were enrolled in either an Ultragenyx sponsored study (e.g., UX003-CL301) or non-Ultragenyx sponsored clinical studies (e.g., ISTs, expanded access/compassionate use) may be eligible for enrollment. Those subjects enrolling from a previous UX003 study should have a reasonable benefit-risk assessment from their primary study as determined by the Investigator, in order to continue with long-term therapy in this extension study. To be enrolled, subjects need to meet all inclusion/exclusion criteria.

All subjects will receive 4 mg/kg UX003 QOW unless data from prior studies define a different dose either for that subject or the use of UX003 in general.

As has been observed with other MPS ERTs, some subjects may experience infusion-associated reactions (IARs) with the administration of UX003. Thus, prophylactic antihistamine will be administered prior to each study drug infusion. Antipyretic pretreatment may also be given at the Investigator's discretion. To minimize the potential for IARs, infusions will initially be administered on a slower rate schedule followed by an increase in rate. Infusion rate may be slowed to manage or reduce IARs.

Safety will be monitored throughout the study based on physical examinations, clinical laboratory analyses, and reporting of adverse events (AEs) and SAEs.

Evaluations of efficacy, including uGAG levels, 6-minute walk test (6MWT), pulmonary function testing, shoulder flexion, visual acuity, and fine and gross motor function will be performed according to the Schedule of Events (Table 2.1 and Section 7.5) if age appropriate and subject is able to perform. Additional assessments will be performed, as indicated, to assess serum biomarkers, 3-minute stair climb test (3MSCT), hepatosplenomegaly, growth velocity, cardiac size and function, ICR endpoint (if appropriate), patient-reported outcomes, and subject/parent/caregiver global impression of change.

The termination visit should be completed by all subjects who do not complete the Week 144 end of study visit. The termination visit should be completed within 30 days of the last dose of study drug. Efficacy assessments performed within 30 days will not be repeated at the

termination visit. If the termination visit occurs after Week 48, blood for serum biomarkers of inflammation will not be collected and BOT-2 assessments will not be conducted.

7.2 Discussion of Study Design

This open-label treatment and extension study in subjects with MPS 7 will further establish the long-term safety and efficacy profile of QOW infusions of UX003 (rhGUS) at a dose of 4 mg/kg.

7.2.1 Adverse Physiology Related Group Safety Reporting

In this study, in addition to standard AE collection and laboratory evaluations, safety assessments will also include Adverse Physiology Related Group (APRG) reporting, a novel method synthesizing safety symptoms into multi-domain physiology related groups. APRG reporting provides the opportunity to detect variable adverse physiologies that might be expressed variably within and between subjects in a study. For example, anaphylactoid reactions are common IARs in ERT programs, and have a set pattern of specific symptoms and timing of reactions. During treatment, soon after the acceleration of the infusion, fever/chills, tachycardia/lower blood pressure, respiratory distress or desaturation, and abdominal pain/nausea/spontaneous smooth muscle contraction may occur. This is one example of a set of symptoms associated with a complement-mediated IAR. Symptoms may occur to varying degrees or be reported differently depending on the observer. Pre-set associated symptoms for adverse physiologies like anaphylactoid/complement mediated IARs, will help drive the assessment of the IARs in a more precise way, and assure the IAR is reported accurately. IAR findings will be recorded and tracked within the case report form (CRF) for likely APRGs, to enhance the detection of the common pattern of IARs.

7.2.2 Urinary GAG Excretion

The extensive research conducted on MPS disorders provides significant relevant scientific data that allows for the qualification of uGAG as a biomarker that is reasonably likely to predict clinical benefit. The disease process and mechanism of action for UX003 in MPS 7 are well understood and data from other MPS disorders with comparable ERTs have established that uGAG is a direct pathophysiological marker of the disease process and uGAG is a reasonable predictor of treatment effect and clinical benefit in MPS disorders (Section 5.2). Considering the evidence on qualification of uGAG as a relevant biomarker for MPS disorders, the similarity of MPS 7 to other MPS disorders, and the critical nature of this disease, which is too rare to be easily studied in traditional study designs with clinical endpoints, uGAG is reasonable for use as an important endpoint in a pivotal study of ERT in MPS 7.

7.2.3 Multi-domain Responder Index

In traditional clinical study design, efficacy is typically established based on one limited measure in one dimension of a complex multi-system clinical disease. For the subject, the total impact of therapy is an integration of the effects on all important clinical domains. Particularly in rare disease studies with heterogeneous populations, single clinical endpoints may not adequately cover the breadth of disease or capture enough data. Novel approaches to combine independent multi-domain analyses assure that the broader basis for efficacy can be assessed without the complexity of trying to construct qualified composite endpoints. Proof of concept for this approach in MPS programs was demonstrated using a meta-analysis of data from three MPS ERT Phase 3 clinical programs ([Signorovitch 2011](#)). The results demonstrated a combination analysis of three clinical endpoints predicted subject-reported treatment benefit better than each endpoint alone.

A multi-domain responder index (MDRI) has been incorporated into the study design to provide an assessment of UX003 efficacy across a broad spectrum of clinical characteristics commonly observed in MPS 7 subjects. The minimal important difference (MID) for each variable will be defined and each subject scored for response to each variable.

7.3 Selection of Study Population

The study will be conducted in approximately 20 MPS 7 subjects who are UX003 treatment-naïve or were previously treated with UX003 in either an Ultragenyx-sponsored clinical study or a non-Ultragenyx sponsored clinical study. The inclusion criteria are structured to enroll UX003 treatment-naïve subjects with a confirmed diagnosis of MPS 7, presenting with clinical characteristics of lysosomal storage disease, and subjects previously treated with UX003 that have had a reasonable benefit-risk assessment from their primary study as determined by the Investigator, in order to continue with long-term therapy in this treatment and extension study. To enroll subjects most likely to benefit from long-term treatment and demonstrate safety and efficacy of UX003, MPS 7 subjects who have undergone successful bone marrow or stem cell transplantation will be excluded from the study.

The Sponsor has taken reasonable measures to ensure the protection and safety of this population. Appropriate pediatric expertise will be available at all trial sites, and site personnel will be focused on minimizing risk, fear, pain and distress during conduct of the study. The protocol incorporates measures to minimize pain and distress including use of topical anesthetic to ease the pain of placing an IV line and the option for an in-dwelling catheter. Prophylactic premedication of subjects with antihistamine and staged and controlled infusion rates mitigate the potential for IARs.

Subjects with MPS 7 who are UX003 treatment naïve or have been enrolled and treated in a previous UX003 clinical study are eligible for this long-term treatment and extension study. Subjects who were reported to have safety-related events in a previous UX003 clinical study

that, in the opinion of the Investigator and sponsor, preclude resuming UX003 treatment will also be excluded.

7.3.1 Inclusion Criteria

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

1. Confirmed diagnosis of MPS 7 based on leukocyte or fibroblast glucuronidase enzyme assay or genetic testing.
2. Willing and able to provide written, signed informed consent, or in the case of subjects under the age of 18 (or 16 years, depending on the region) or subjects who are intellectually impaired, provide written assent (if required) and written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures.
3. Willing to comply with all study procedures.
4. Sexually active subjects must be willing to use a highly effective method of contraception while participating in the study and for 30 days following the last dose.
5. Females of childbearing potential must have a negative pregnancy test at Baseline and be willing to have additional pregnancy tests during the study. Females considered not of childbearing potential include those who have not experienced menarche, are postmenopausal (defined as having no menses for at least 12 months without an alternative medical cause) or are permanently sterile due to having hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.
6. *For UX003 treatment-naïve subjects only*, apparent clinical signs of lysosomal storage disease as judged by the Investigator, including at least one of the following: enlarged liver and spleen, joint limitations, airway obstruction or pulmonary problems, limitation of mobility while still ambulatory.
7. *For UX003 treatment-naïve subjects only*, aged 5 years and older and elevated uGAG excretion at a minimum of 2-fold over mean normal levels for age (at baseline).

7.3.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. *If enrolled in a prior UX003 clinical study*, the subject experienced a safety-related event in a prior UX003 clinical study that, in the opinion of the Investigator and sponsor, precludes resuming UX003 treatment.
2. Undergone a successful bone marrow or stem cell transplant or has any degree of detectable chimaerism with donor cells.

3. Presence or history of any hypersensitivity to rhGUS or its excipients that, in the judgment of the Investigator, places the subject at increased risk for adverse effects.
4. Pregnant or breastfeeding at Baseline or planning to become pregnant (self or partner) at any time during the study.
5. Use of any investigational product (drug or device or combination) other than UX003 within 30 days prior to Baseline, or requirement for any investigational agent prior to completion of all scheduled study assessments.
6. Presence of a condition of such severity and acuity that, in the opinion of the Investigator, warrants immediate surgical intervention or other treatment or may not allow safe study participation.
7. Concurrent disease or condition, or laboratory abnormality that, in the view of the Investigator, places the subject at high risk of poor treatment compliance or of not completing the study, or would interfere with study participation or introduce additional safety concerns.

7.3.3 Removal of Subjects from Therapy or Assessment

In accordance with the Declaration of Helsinki, subjects have the right to withdraw from the study at any time for any reason. The Investigator and Ultragenyx also have the right to remove subjects from the study. Ultragenyx must be notified of all subject withdrawals as soon as possible. Ultragenyx also reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation of an individual subject or Investigator due to poor enrollment or noncompliance, as applicable. Female subjects who become pregnant will be withdrawn from study drug (refer to Section 7.5.2.6).

Subjects may be removed from the study for the following reasons:

- Occurrence of an unacceptable AE
- An illness that, in the judgment of the Investigator or Ultragenyx, might place the subject at risk or invalidate the study
- At the request of the subject, Investigator, or Ultragenyx, for administrative or other reasons
- Protocol deviation or unreliable behavior

If the reason for removal of a subject from the study is an AE, the AE and any related test or procedure results will be recorded in the source documents and transcribed onto the CRF. Each clinically significant abnormal laboratory value or other clinically meaningful abnormality should be followed until the abnormality resolves or until a decision is made that it is not likely to resolve. If such abnormalities do not return to normal within 30 days after

the last dose given, their etiology should be identified and Ultragenyx should be notified. All unscheduled tests must be reported to Ultragenyx immediately.

The termination visit should be completed by all subjects who do not complete the Week 144 end of study visit. The termination visit should be completed within 30 days of the last dose of study drug. Efficacy assessments performed within 30 days will not be repeated at the termination visit. If the termination visit occurs after Week 48, blood for serum biomarkers of inflammation will not be collected and BOT-2 assessments will not be conducted.

7.3.3.1 Stopping Rules

Individual subjects who experience any unexpected and possibly, probably, or definitely drug-related serious adverse events (SAEs; Section 8.5.3) that represent a change in the nature or an increase in frequency of the serious event from their prior medical history or known MPS 7-related medical issues will be assessed as to whether the subject will continue on the study.

The IRB/EC will be informed should unexpected and possibly, probably, or definitely study drug-related SAEs occur. A full evaluation of the event will be performed in order to make a decision regarding what actions to take, including whether to recommend stopping the study.

7.4 Treatments

Approximately 20 subjects may be dosed QOW for up to 144 weeks. All subjects will receive 4 mg/kg UX003 QOW unless data from prior studies define a different dose either for that subject or the use of UX003 in general.

7.4.1 Identity of Investigational Product

UX003 (recombinant human beta-glucuronidase, rhGUS) is a multimeric glycoprotein produced using a genetically engineered Chinese hamster ovary cell line to secrete the human lysosomal enzyme, beta-glucuronidase. The mature form of the enzyme consists of 651 amino acids. The drug product is formulated at 2 mg/mL rhGUS in UX003 formulation buffer. Refer to the Investigational Brochure or Pharmacy Manual for details about buffer excipients. UX003 is supplied as a sterile solution for IV administration packaged in single use 10 mL glass vials and is stored at 2 to 8°C.

The study drug is manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) regulations.

7.4.2 Study Drug Infusion Procedure

UX003 will be administered QOW by slow IV infusion over a period of approximately 4 hours. Subjects will be pre-medicated prior to infusions and study drug will be administered on a rate-schedule that minimizes the potential for IARs. The infusion will

begin at a low rate that will be gradually increased, as tolerated by the subject, until the planned maximum rate is reached.

Refer to the Study Reference Manual for additional details on study drug infusion procedures.

7.4.2.1 Pre-Dose Medication

Approximately 30 – 60 minutes prior to each infusion of study drug and after performing pre-infusion efficacy assessments, all subjects will be pretreated with an appropriate dose of antihistamine medication. Non-sedating antihistamines, such as cetirizine or loratadine, are preferred. For subjects who have a history of IARs or other risk factors (e.g. history of allergies), a sedating antihistamine (e.g. diphenhydramine or chlorpheniramine) may be administered. Antipyretic medications such as ibuprofen or acetaminophen may be administered at the discretion of the Investigator. For subjects with IARs, slowing the infusion rate is important but additional premedication with agents such as H₂ blockers, or steroids may be considered.

7.4.2.2 Infusion Procedure

The amount of UX003 will be determined based on subject weight (in kg). The volume of study drug calculated to deliver the correct dose will be withdrawn from the vial and aseptically transferred to an infusion bag of normal saline. Undiluted UX003 must never be infused.

PLEASE NOTE FOR PREPARATION OF INFUSION SOLUTIONS: UX003 (rhGUS) is a recombinant protein and is therefore sensitive to bubbles and aggressive mixing that can lead to denaturation and loss of enzyme activity. When preparing diluted infusion solutions, the product should be withdrawn VERY SLOWLY through a sufficiently large needle (18 gauge) to minimize shear and turbulence. When adding study drug solution to an infusion bag, this must be done slowly, with liquid to liquid contact and without generating bubbles or turbulence; the bags should be rocked gently for mixing. Shaking of vials or infusion bags or “volutrols” devices in which aggressive mixing and bubbles can occur are not acceptable.

Study drug will be administered by slow IV infusion over approximately 4 hours. Infusions will be administered on a rate-schedule involving a slower infusion rate initially followed by an increase in rate that minimizes the potential for infusion reactions and may be slowed to manage or reduce IARs. Refer to the Pharmacy Manual for additional details on the infusion rate schedule. Topical eutectic mixture of local anesthetic (EMLA) cream or equivalent may be applied to the IV site prior to the infusion to ease the pain of placing an IV line.

At the discretion of the Investigator, an in-dwelling IV catheter (such as a Port-a-Cath[®] or other brand) may be inserted if there are difficulties in achieving IV access for the QOW infusions.

Equipment necessary for resuscitation must be available during study drug infusion.

7.4.3 Selection of Doses in the Study

The planned UX003 dose of 4 mg/kg is based on doses examined in an ongoing Phase 2 clinical study in MPS 7 subjects, and further supported by nonclinical studies in the MPS 7 mouse model and relevant species. The nonclinical data support chronic QOW administration of UX003 at dose levels up to 4 mg/kg, with a relative 5-fold safety factor. The pharmacologic studies in the MPS 7 mouse showed that both 2 mg/kg and 4 mg/kg were effective doses with only a few tissues or cell types such as osteocytes responding better at 4 mg/kg versus 2 mg/kg. Safety was the same at all doses.

The Phase 1/2 study (UX003-CL201) in MPS 7 subjects evaluated UX003 administered at doses of 1, 2, and 4 mg/kg QOW. Preliminary results suggest the percent reduction in urinary GAG excretion is greatest with the 4 mg/kg dose with mean reductions of approximately 60% observed, while the reductions at 2 mg/kg were in the 40-50% range. Additionally, during the forced dose titration process, the reductions in uGAG observed at 4 mg/kg lessened when subjects returned to the 2 mg/kg dose, suggesting a decrease in efficacy. These changes in uGAG exceeded an absolute difference of 10% and were of sufficient magnitude to consider the 4 mg/kg dose a more appropriate dose. In the clinical studies of ERT for other MPS disorders, changes in uGAG were able to differentiate between effective and less effective dose regimens, with reductions of >50% associated with substantial efficacy based on clinical measures. Infusions at 4 mg/kg in 3 subjects in the UX003-CL201 study for 8 weeks showed no safety issues, and there have been no drug-related IARs at any dose to date. Therefore, the 4 mg/kg dose appears to be well tolerated at this time.

The therapeutic ERT doses in prior successful programs for other MPS disorders (0.58, 0.5 and 1 mg/kg weekly for MPS 1, 2, 4A, and 6, respectively) were based on comparable doses that exhibited efficacy in their respective animal models. PK data in MPS 1, MPS 2, MPS 4A, and MPS 6 subjects demonstrate that doses of 0.2 to 2 mg/kg are adequate to achieve enzyme concentrations of ~10-27 nM in the circulation. These enzyme levels are approximately 10- to 30-fold the uptake constants (1-2.7 nM) for the mannose 6 phosphate receptor and are believed to saturate delivery of enzyme to the tissues (Kakkis et al. 1994), (Kakkis et al. 1996a), (Kakkis et al. 2001), (Dvorak-Ewell et al. 2010). Similar uptake constants (1.2-2.6 nM) were obtained in studies with human MPS 7 fibroblast cells in vitro (Ultragenyx data). Studies with rhGUS in MPS 7 mice at doses of 4 mg/kg show that serum GUS concentrations of >10-fold the uptake constant were readily achieved and demonstrated that enzyme was delivered to a variety of important tissues, implying that the efficacious dose should be within this range (Grubb et al. 2008).

A higher dose is needed to provide the same rhGUS molar concentration as other MPS enzymes, since rhGUS enzyme has two active sites per tetramer and the molecular weight (332 kDa tetramer) is approximately 4-fold higher compared to the other MPS enzymes. The equivalent number of moles of enzyme active sites would require about two

times the efficacious dose for other MPS enzymes on a mass or milligram basis. Therefore, approximately 1-4 mg/kg UX003 is estimated to achieve the same molar concentration of active enzyme.

The QOW dosing regimen is supported by the long in vitro half-life and increased stability of rhGUS compared with other MPS enzymes. Data from the earliest MPS ERT studies showed that when human enzymes for MPS 1 or 2 were applied to deficient human fibroblasts, the half-life of the enzyme in the lysosome was on the order of 2-5 days (Kakkis et al. 1994), (Elaprase 2006) leading to weekly dosing frequency as the optimal choice. For rhGUS, this experiment showed a half-life of about 40 days, which is a substantial increase over MPS 1 or MPS 2 enzymes, which are dosed weekly. The rhGUS enzyme is also a more stable enzyme than the other MPS enzymes at neutral pH, as it might be exposed to the circulation before uptake by lysosomes. Both the increased half-life and stability of rhGUS indicate QOW dosing should be adequate in humans.

All subjects may receive up to 144 weeks of UX003 treatment. The treatment duration is sufficient to assess long-term safety and provide sufficient insight on sustained clinical effects and improvements in pediatric, adolescent, and adult efficacy of UX003 treatment in MPS 7 subjects.

7.4.4 Prior and Concomitant Therapy

7.4.4.1 Prohibited Medications

Subjects may not be enrolled if they have used any investigational product (other than UX003) or investigational medical device within 30 days prior to Baseline, or if they require any investigational agent prior to completion of all scheduled study assessments.

The use of genistein is specifically prohibited during study participation.

7.4.4.2 Permitted Medications

Subjects may receive concomitant medications as required.

For subjects enrolling from an Ultragenyx-sponsored clinical trial, medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements reported as ongoing at the primary study's End of Treatment visit and any new medications taken prior to Baseline will be reviewed and recorded at the Baseline visit. Any enrolling subject who had an early termination in the primary study will have their baseline concomitant medications collected in the same manner as a subject who is treatment naïve or enrolling from a non-Ultragenyx sponsored study (see following paragraph).

For subjects who are treatment naïve or who are enrolling from a non-Ultragenyx sponsored clinical trial, medications (investigational, prescription, over-the-counter, and herbal) and

nutritional supplements taken during the 30 days prior to Baseline will be reviewed and recorded.

At each visit, any concomitant medications added or discontinued during the study should be recorded on the CRF. The site personnel should record the following in the CRF: date and time the medication was taken, the dose and name of the medication, and the reason the medication was taken.

Medications administered prior to each infusion of study drug and any non-study therapies provided by the Investigator during study participation will be similarly recorded in the CRF.

7.4.5 Treatment Compliance

UX003 is not to be dispensed to subjects. UX003 will be administered by IV infusion by a qualified health care professional at the clinical site. The date, time, and volume of each dose of study drug administered to each subject must be recorded in the dispensing log for the study, as well as on the appropriate CRF.

7.5 Study Procedures and Assessments

7.5.1 Schedule of Events

Informed consent must be obtained prior to any study procedures. Subjects will be enrolled only after inclusion/exclusion criteria have been confirmed.

For subjects previously enrolled in the Ultragenyx-sponsored MPS 7 Phase 3 clinical study UX003-CL301, the Baseline Visit will be conducted in conjunction with the UX003-CL301 Week 48 study visit to avoid treatment disruption. Data collected at the UX003-CL301 Week 48 visit may serve as the Baseline data for this study. All additional Baseline assessments (not included in the UX003-CL301 Week 48 assessments), other than UX003 treatment, must also be completed prior to determination of eligibility. Following confirmation of eligibility, subjects will receive their first study drug infusion in this study and will return for assessments according to the Schedule of Events ([Table 2.1](#)).

For subjects enrolling from other Ultragenyx sponsored clinical studies, clinical outcome assessments including efficacy, echocardiogram (ECHO) and clinical laboratory tests performed during the final, or End of Treatment, visit from the primary (or feeder) study may be used as baseline assessments for this study if performed within 30 days of the Baseline visit as specified below.

Subjects enrolling from an Ultragenyx sponsored clinical study who had an early termination in their primary (or feeder) study will have their baseline assessments collected in the same manner as a subject who is treatment naïve or enrolling from a non-Ultragenyx sponsored study (see following paragraph).

For subjects who are treatment naïve or who are enrolling from a non-Ultragenyx sponsored clinical study, initial baseline safety and efficacy assessments will be performed within 30 days of the Baseline visit. All assessments scheduled on the same day as UX003 treatment must be performed prior to the first study drug infusion for this treatment and extension study.

For all subjects, Baseline study visits should be conducted at a primary site from an Ultragenyx sponsored clinical study. Following the Baseline visit, subjects may return to their primary, or Baseline, study site for all safety assessments, efficacy assessments, and infusions every 24 weeks through the end of study. Alternatively, the 24-week visits may be performed at the subject's local site if feasible. All other clinic visits, including assessments and infusions, may be performed at the subject's local site as appropriate.

Subjects will return to the clinic at 2-week intervals (± 3 days) for study drug infusion and basic safety measures. Subjects will have assessment of uGAG levels and physical exams at 12-week intervals. Major assessment visits are scheduled at 24-week intervals (± 7 days) through the end of study.

The end of trial is defined as the last visit of the last subject undergoing evaluation in the study. As the planned duration of treatment in this study is up to 144 weeks, the end of trial is defined as the Week 144 visit of the last subject. In the event the study is terminated by the Sponsor prior to Week 144, all subjects should complete a termination visit and the date of the last termination visit of the last subject would define the end of the trial. The termination visit should be completed within 30 days of the last dose of study drug. Efficacy assessments performed within 30 days will not be repeated at the termination visit. If the termination visit occurs after Week 48, blood for serum biomarkers of inflammation will not be collected and BOT-2 assessments will not be conducted.

The parameters to be assessed in Study UX003-CL202, along with timing of assessments, are provided in the Schedule of Events ([Table 2.1](#)). All assessments scheduled on the same day as a UX003 treatment day must be completed prior to the infusion on that day. Where caregiver assessments are required, the same individual should complete the assessment for consistency of reporting, when possible. Refer to the Study Reference Manual for additional details on specific assessments.

7.5.2 Safety Assessments (Primary Objective)

For the purposes of this study, all safety assessments will be performed on all subjects entering from a prior study with UX003, unless otherwise specified. UX003-naïve subjects will be required to complete all applicable (age- and ability-appropriate) study assessments as indicated in [Table 2.1](#).

Safety will be evaluated by the incidence, frequency and severity of AEs and SAEs, including clinically significant changes from study baseline to scheduled time points in vital

signs, weight, physical examination, clinical laboratory evaluations, and concomitant medications. Evaluation of valvular function and cardiac function by ECHO will be made primarily for safety purposes.

APRG reporting is a novel method synthesizing safety symptoms into multi-domain physiology related groups. APRG reporting has been incorporated into the study design to detect adverse physiologies that might be expressed variably within and between subjects in a study.

To assess the immune response to UX003, the development of any antibodies to rhGUS, and complement C3, C4, and CH50 levels will also be evaluated if a drug-related hypersensitivity reaction is suspected. Pregnancy testing (or pregnancy of partner, if needed) will also be conducted.

7.5.2.1 Medical History

For subjects continuing treatment from a previous Ultragenyx sponsored study, general medical history information obtained during the primary (or feeder) study (e.g., UX003-CL301) will carry over to this study. The general medical history includes subject demographics (date of birth, ethnicity, and sex) and a history of major medical illnesses, diagnoses, surgeries and confirmation of MPS 7 diagnosis. To ensure all medical histories are complete and current, any enrolling subject who had an early termination in the primary study will have any changes or new information since their discontinuation in the primary study recorded.

For subjects who are treatment naïve or who enroll from a non-Ultragenyx sponsored study, a complete medical history is to be completed prior to the Baseline visit, or at the Baseline visit prior to first study treatment, to ensure subject meets all eligibility criteria. General medical information includes subject demographics (date of birth, ethnicity, and sex) and a history of major medical illnesses, diagnoses, and surgeries. Growth history for height (or recumbent length) and weight will be collected. MPS 7 treatment history and relevant concomitant medications will be recorded (start date, stop date, dose, dose regimen). Medications include prescription, over-the-counter, herbal and nutritional supplements. Any relevant concomitant therapy, including physical/occupational therapy will be recorded.

7.5.2.2 Weight

Weight will be obtained at Baseline, and at every 12 weeks as needed to determine appropriate study drug volume. Weight for drug preparation may be obtained up to 15 days prior to the indicated visit (e.g. Weeks 10, 22, 34, and 46 visits). Weight will be measured in kilograms using a scale.

7.5.2.3 Physical Examination

Complete physical examinations will be performed at Baseline then every 12 weeks until the end of study visit (or termination visit). A physical examination performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline.

Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, and musculoskeletal systems. Physical examinations are to include neurologic examination and evaluation of the presence or absence of corneal clouding. If subject complains of leg weakness or fatigue, evaluate for signs of cord compression (e.g. leg reflexes and motor strength).

7.5.2.4 Vital Signs

Vital signs will include seated systolic blood pressure and diastolic blood pressure measured in millimeters of mercury (mm Hg), heart rate in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius (°C). Vital signs measurements will be performed at every visit before any additional assessments are completed. On days when study drug will be administered, vital signs will be measured within 30 minutes before the infusion, at least every 30 minutes for the first hour of infusion, at least every hour for the remainder of the infusion, and within 30 minutes after the infusion. Additional measurements should be obtained as appropriate. Refer to the Study Reference Manual for additional details on vital sign assessments.

7.5.2.5 Clinical Laboratory Tests for Safety

The clinical laboratory evaluations to be performed in this study are listed in [Table 7.5.2.5.1](#).

Clinical laboratory testing will be performed at the Baseline visit and at 48-week intervals as indicated in the Schedule of Events ([Table 2.1](#)). Clinical laboratory tests performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline. Blood and urine samples will be collected prior to administration of study drug; fasting is not required. Refer to the Laboratory Manual for additional details.

Table 7.5.2.5.1: Clinical Laboratory Assessments

Chemistry	Hematology	Urinalysis
Alanine aminotransferase (ALT)	Hematocrit	Appearance
Alkaline phosphatase	Hemoglobin	Color
Amylase	Mean corpuscular hemoglobin (MCH)	pH
Aspartate aminotransferase (AST))	MCH concentration (MCHC)	Specific gravity
Bilirubin (direct and total)	Mean corpuscular volume (MCV)	Ketones
Blood urea nitrogen (BUN)	Platelet count	Protein
Calcium	Red blood cell (RBC) count	Glucose
Chloride	Reticulocyte count	Bilirubin
Creatinine	Neutrophil count (absolute and %)	Nitrite
Gamma-glutamyl transpeptidase (GGT)	Lymphocyte count (absolute and %)	Urobilinogen
Glucose	Monocyte count (absolute and %)	Hemoglobin
Lactate dehydrogenase (LDH)	Eosinophil count (absolute and %)	Creatinine
Phosphorus	Basophil count (absolute and %)	
Potassium	White blood cell (WBC) count	
Protein (albumin and total)	WBC differential	
Sodium		

Subjects who experience a SAE possibly or probably related to study drug or other AE of concern may, at the discretion of the Investigator (and/or medical monitor), have additional blood samples taken for safety laboratory tests.

7.5.2.6 Pregnancy Testing

Female subjects of childbearing potential will have urine pregnancy tests at the Baseline visit and every 12 weeks throughout the study (and at the Termination visit). Female subjects with a positive pregnancy test at Baseline will not be enrolled in the study. Females who have not experienced menarche will not undergo pregnancy testing. Should a female subject experience menarche during the course of the study, the subject will be considered a female subject of childbearing potential and undergo urine pregnancy testing per the Schedule of Events ([Table 2.1](#)).

Additional pregnancy tests will be performed at any visit in which pregnancy status is in question. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result, or can be performed if pregnancy test by urine is not feasible. Pregnancy in subject or partner must be reported ([Section 7.5.2.6.1](#)); pregnant subjects will be withdrawn from study drug. At the conclusion of the pregnancy, a decision will be made if the female subject may resume study drug based on study treatment risk-benefit evaluation and willingness of the subject to comply with the contraceptive requirements. In the event of a pregnancy in the partner of a male subject, the male subject may continue with study drug.

Experience with UX003 in pregnant women is limited. The study drug may involve risks to a pregnant female or unborn baby that are currently unknown. Sexually active male and female subjects of childbearing potential or with partners of child-bearing potential must consent to use a highly effective method of contraception during and for 30 days following the last dose of study drug. Examples of highly effective methods include:

- Established use of hormonal contraceptives, such as the birth control pill, injection or implant, associated with inhibition of ovulation
- Intrauterine device (IUD) or intrauterine system (IUS), a small device with hormones that goes inside the uterus
- Bilateral tubal occlusion
- Male sterilization, also called vasectomy
- True abstinence which means not having sex because subject chooses not to

7.5.2.6.1 Pregnancy in Subject or Partner

Pregnancies in subjects or partners must be reported within 24 hours of knowledge of the event to Ultragenyx or its designee. The Investigator must make every effort to follow the pregnancy of either subject or partner through resolution of the pregnancy (delivery or termination) and report the resolution to Ultragenyx or its designee. In the event of a pregnancy in the partner of a subject, the Investigator should make every effort to obtain the female partner's consent for release of protected health information. Refer to the Study Reference Manual for details on the reporting procedures to follow in the event of pregnancy.

7.5.2.7 Antibodies to rhGUS

Prior Phase 3 studies in ERT for MPS have shown that antibodies to the recombinant protein do not have a precise relationship to IARs, but the presence of antibodies may impact on enzyme distribution and efficacy (Dickson et al. 2008). To determine the immunogenicity profile of UX003, testing for antibodies directed against rhGUS will take place at the Baseline visit, and every 24 weeks through the end of trial (or termination) visit. Testing for rhGUS antibodies performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline. Serum samples for antibodies must be collected before infusion of study drug. Refer to the Laboratory Manual for additional details on sample processing. For subjects with a positive antibody and/or IAR response, further laboratory evaluation of the immune response to UX003 (i.e. antibodies and complement) may be conducted as indicated.

7.5.2.8 Complement Levels

Complement components will be assessed to characterize the immune response following a drug-related IAR. For subjects who experience an IAR that is potentially a complement-mediated (anaphylactoid) hypersensitivity reaction, blood samples will be drawn pre- and immediately post-infusion during the subsequent infusion for measurement of the change in C3, C4 and CH50 levels during an infusion. Refer to the Laboratory Manual for additional details on sample processing.

7.5.2.9 Concomitant Medications

Concomitant medications will be reviewed and recorded in the subject's CRF at each study visit, beginning at the Baseline visit.

For subjects enrolling from an Ultragenyx-sponsored clinical trial, medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements reported as ongoing at primary study's End of Treatment visit and any new medications taken prior to Baseline will be reviewed and recorded at Baseline visit. Any enrolling subject who had an early termination in the primary study will have their baseline concomitant medications collected in the same manner as a subject who is treatment naïve or enrolling from a non-Ultragenyx sponsored study (see following paragraph).

For subjects who are treatment naïve or who are enrolling from a non-Ultragenyx sponsored clinical trial, medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to Baseline will be reviewed and recorded.

At each subsequent visit, change in medications since the previous visit will be recorded. A discussion of prior and concomitant medications is provided in Section 7.4.4.

7.5.2.10 Adverse Events

For subjects enrolling from an Ultragenyx-sponsored clinical trial, all AEs will be recorded from the time the subject signs the informed consent for this extension study and completion of the End of Treatment visit in the primary study until 30 days after the last dose of study drug. Adverse events reported as ongoing at the primary study's End of Treatment visit and any new AEs prior to Baseline will be reviewed and recorded at Baseline visit. Any enrolling subject who had an early termination in the primary study will have their baseline AE information collected in the same manner as a subject who is treatment naïve or enrolling from a non-Ultragenyx sponsored study (see following paragraph).

For subjects who are treatment naïve or who are enrolling from a non-Ultragenyx sponsored clinical trial, all AEs will be recorded from the time the subject signs the informed consent until 30 days after the last dose of study drug.

The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 8.5. At each visit subjects will be asked about any new or ongoing AEs since the previous visit. Assessments of AEs will occur at each study visit.

Clinically significant changes from study baseline in physical examination findings, vital signs, and clinical laboratory parameters, will be recorded as AEs or SAEs, if appropriate.

7.5.2.11 Adverse Physiology Related Group Reporting

APRG is an approach to safety reporting for common expected AEs that have a set of symptoms all related to an adverse physiologic pathway. Patterns of IARs will be specifically evaluated throughout the study. IARs will be characterized into 4 distinct types based on timing of onset relative to the infusion and specific clinical manifestations: anaphylactoid, anaphylaxis, urticarial (with or without angioedema), and immune complex. Safety reporting of individual AEs will be recorded in parallel.

Refer to the Study Reference Manual for additional details on APRG reporting.

7.5.3 Urinary GAG Excretion (Secondary Objective)

Results of prior non-clinical and clinical work demonstrate a direct relationship between disease severity and clinical outcomes with uGAG levels. The studies also demonstrate the sensitivity of uGAG to differences in clinical effect within the therapeutic range of doses and verified the sustained long-term effects of the ERT. These data show that uGAG reductions above a threshold of >50% are associated with clinically meaningful changes in clinical parameters in all three MPS ERT programs.

First morning void urine will be evaluated for uGAG at Baseline then every 12 weeks throughout the study (or termination visit). A uGAG assessment performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline. Urine samples must be collected from first morning voids to assure the urine is adequately concentrated. Refer to the Laboratory Manual for details on sample collection and processing requirements. Supplementary assays for uGAG may be performed.

Urinary GAG excretion will provide a biochemical measure of the biological action of UX003. These assessments will be supported by other efficacy measures, including a multi-domain responder index to provide an assessment of UX003 efficacy in MPS 7 subjects.

7.5.4 Other Efficacy Measures

Other efficacy assessments, including a multi-domain clinical responder index, will be used to assess clinical changes following UX003 treatment. In general, other efficacy assessments will be performed only if they were performed in the primary (or feeder) study. Efficacy assessments not performed during the primary (or feeder study) will not be required

for this long-term treatment and extension study, unless otherwise specified. UX003-naïve subjects will be required to complete all applicable (age- and ability-appropriate) study assessments as indicated in [Table 2.1](#).

7.5.4.1 Multi-domain Responder Index

Single clinical endpoints may not adequately cover the breadth of disease. Novel approaches to combine independent multi-domain analyses assure that the broader basis for efficacy can be assessed. The MDRI consisting of 6MWT, FVC, shoulder flexion, visual acuity, and BOT-2 (fine motor and gross motor), provides an assessment of UX003 efficacy across a broad spectrum of clinical characteristics commonly observed in MPS 7 subjects. The MID for each variable will be defined and each subject scored for each variable.

For subjects enrolling from prior clinical studies with UX003, the MDRI will only be evaluated if the clinical outcomes described above were previously assessed in their primary (or feeder) study.

7.5.4.2 Serum Biomarkers of Inflammation

Blood samples will be collected at the Baseline, Week 24, and Week 48 visits for assessment of biomarkers of inflammation in serum using established quantitative methods, if indicated based on prior work. If the termination visit occurs after Week 48, blood for serum biomarkers of inflammation will not be collected. An inflammation biomarker assessment performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline. The inflammatory biomarkers may include, but not be limited to, the following: tumor necrosis factor-alpha (TNF-alpha) and macrophage inflammatory protein 1 alpha (MIP-1alpha).

7.5.4.3 Six Minute Walk Test

Subjects who cannot walk may omit the 6MWT. Some subjects may be too young and/or physically impaired to reliably perform the test, the test performance at the Baseline visit will be used to determine feasibility for naïve subjects. The 6MWT may not be performed at subsequent study visits if the subject is unable to reliably or safely perform the test at Baseline. Subjects enrolling from an Ultragenyx sponsored study (e.g., UX003-CL301) will continue to perform the 6MWT if evaluated during the primary/feeder study. The 6MWT will be administered to appropriate subjects once per test day to appropriate subjects during the Baseline visit, then every 24 weeks thereafter (or at termination visit). A 6MWT performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline assessment.

For subjects enrolling from prior clinical studies with UX003, the 6MWT will only be administered if previously performed in their primary (or feeder) study. A 6MWT performed within 30 days prior to Baseline may be used for the study baseline assessment.

The 6MWT will be conducted based on American Thoracic Society guidelines ([ATS 2002](#)). Subjects will be instructed to walk the length of a pre-measured course for 6 consecutive minutes. If applicable, the use of any walking aids in the performance of the 6MWT will be noted. Refer to the Study Reference Manual for detailed instructions on conducting the 6MWT.

The 6MWT and 3MSCT should be performed on separate days, if possible. If performed on the same day, the 6MWT should be done before the 3MSCT; the subject's resting heart rate must return to baseline between assessments.

The total distance walked (meters) following the six minute period will be recorded; an interim measurement will also be obtained following the first two minutes of the 6MWT. The total time spent walking during the test will be recorded. The percent of predicted normal distance walked will also be determined based on published normative data ([Geiger et al. 2007](#)), ([Gibbons et al. 2001](#)).

7.5.4.4 Bruininks-Oseretsky Test of Motor Proficiency

The Bruininks-Oseretsky Test of Motor Proficiency – 2nd Edition (BOT-2) is a standardized, norm-referenced test of fine and gross motor skills for children (≥ 4 years of age) and young adults ([Bruininks et al. 2005](#)). Four subtests of the BOT-2 will be administered to evaluate treatment-related changes in fine motor proficiency and gross motor function: fine motor precision, manual dexterity, balance, running speed and agility. The test may be modified and tests omitted to accommodate the needs of the subject. The BOT-2 will be assessed at the Baseline, Week 24, and Week 48 visits. If the termination visit occurs after Week 48, BOT-2 assessments will not be conducted. A BOT-2 assessment performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline assessment.

For subjects enrolling from previous clinical studies with UX003, the BOT-2 will only be administered if previously performed in their primary (or feeder) study. A BOT-2 performed within 30 days prior to Baseline may be used for the study baseline assessment.

7.5.4.5 Three Minute Stair Climb Test

The 3MSCT ([Zech et al. 2011](#)) will be used to assess functional power via stair climbing capacity. Subjects who cannot climb stairs may omit this test. Some subjects may be too young and/or physically impaired to reliably perform the test, the test performance at the Baseline visit will be used to determine feasibility for naïve subjects. The 3MSCT may not be performed at subsequent study visits if the subject is unable to reliably or safely perform the test at Baseline. Subjects enrolling from an Ultragenyx sponsored study (e.g., UX003-CL301) will continue to perform the 3MSCT if evaluated during the primary/feeder study. The 3MSCT will be administered to appropriate subjects during the Baseline visit, then every 24 weeks thereafter (or at termination visit). A 3MSCT assessment

performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline assessment.

For subjects enrolling from previous clinical studies with UX003, the 3MSCT will only be administered if previously performed in their primary (or feeder) study. A 3MSCT performed within 30 days prior to Baseline may be used for the study baseline assessment.

The 3MSCT will be administered once per indicated visit by a licensed physical therapist. Oxygen saturation will be measured before and after the test using a pulse oximeter. The subject will be asked to stand at the foot and center of the stairs and climb the stairs upon command. Use of any available stair railing will be allowed if preferred by the subject. The number of stairs climbed within a three minute period will be recorded.

The 6MWT (Section 7.5.4.3) and 3MSCT should be performed on separate days, if possible. If performed on the same day, the 6MWT should be done before the 3MSCT. The subject's resting heart rate must return to baseline between assessments.

7.5.4.6 Pulmonary Function Testing

Spirometry will not be conducted on subjects who require invasive ventilatory support or have a tracheostomy. Invasive ventilation is defined as any form of ventilatory support applied with the use of an endotracheal tube. Spirometry will be administered in accordance with ATS/ERS guidelines ([ATS/ERS 2002](#)) to appropriate subjects during the Baseline visit, then every 24 weeks thereafter (or at termination visit). Spirometry performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline. If performed on the same day, spirometry should be done before the 6MWT and 3MSCT. The subject's resting heart rate must return to baseline between assessments.

For subjects enrolling from prior clinical studies with UX003, Spirometry will only be administered if previously performed in their primary (or feeder) study. Spirometry performed within 30 days prior to Baseline may be used for the study baseline assessment.

Pulmonary function variables include forced vital capacity (FVC) and maximum voluntary ventilation (MVV). The percent predicted values will be calculated after testing using published normative data ([Wang et al. 1993](#)), ([Eigen et al. 2001](#)), ([Hankinson et al. 1999](#)). If standing height cannot be obtained, an estimate of standing height may be used to derive the height measurement required to calculate percent predicted values.

7.5.4.7 Goniometry

The maximum passive shoulder range of motion in both flexion and extension will be measured in degrees using a goniometer. Shoulder flexion will be the evaluable measure. The highest value of three shoulder flexion and extension range of motion measurements for each side will be reported and compared to known normal standards for age. Goniometry will be performed during the Baseline visit, then every 24 weeks thereafter (or at termination visit). A shoulder flexion, or goniometry, assessment performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline.

For subjects enrolling from previous clinical studies with UX003, goniometry will only be administered if they were previously performed in their primary (or feeder) study. Goniometry performed within 30 days prior to Baseline may be used for the study baseline assessment.

7.5.4.8 Anthropometrics

Growth will be assessed from anthropometric measurements (standing height [or recumbent length, if applicable] and weight) at 12-week intervals beginning at the Baseline visit to Week 24, then every 24 weeks thereafter (or at termination visit). Every effort should be made to collect standing height when appropriate. If unable to collect standing height, sitting height should be collected for that subject. Growth velocity will be calculated and compared with pre-treatment growth velocity when available.

7.5.4.9 Visual Acuity

Visual acuity will be measured (corrected and uncorrected) using a standard eye chart and recorded for each eye independently. For this study, visual acuity will be assessed at the Baseline visit, then every 24 weeks thereafter (or at termination visit). A visual acuity assessment performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline.

For subjects enrolling from previous clinical studies with UX003, visual acuity assessments will only be administered if they were previously performed in their primary (or feeder) study. A visual acuity assessment performed within 30 days prior to Baseline may be used for the study baseline assessment.

7.5.4.10 Individual Clinical Response

The ICR may provide a specific assessment of the ability of UX003 to impact the most important clinical manifestation of MPS 7 for a given subject.

For subjects who were previously treated in the Ultragenyx-sponsored MPS 7 Phase 3 clinical study UX003-CL301 and had an ICR assigned, that same ICR may be followed in this long-term treatment and extension study. If applicable, the ICR will be identified during the Baseline visit and then assessed every 24 weeks thereafter (or at termination visit).

During the previous Ultragenyx sponsored MPS 7 Phase 3 clinical study UX003-CL301, the physician will have queried the subject or parent/caregiver about signs and symptoms of MPS 7 that interfere most with the subject's daily life (Clinical Problem Evaluation). Answers will have been mapped to an appropriate clinical outcome measure. For example, difficulty walking could map to the 6MWT; breathing problems to FVC; trouble manipulating small objects to BOT-2 fine motor function; difficulty with balance or agility to BOT-2 gross motor function; reduced joint mobility to shoulder flexion maximum range of motion; and tiredness/fatigue to the PedsQL-multidimensional fatigue scale.

The determination of the ICR in Ultragenyx study UX003-CL301 will have been based on, but not limited to: 1) the specific concerns that the subject/parent/caregiver has reported; 2) the ability of the subject to reliably complete the assessment; and 3) the extent of impairment measured in the outcome of interest and will take into consideration developmental, cognitive, and behavioral factors observed at both the Screening and Randomization (Week 0) visits. The clinical outcome ranked with the highest impact on daily life that can be reliably completed by the subject and meets a threshold level of impairment will be selected as the ICR for that subject. The Investigator will be responsible for defining the ICR for each subject in consultation with an independent clinical consultant during previous study, UX003-CL301.

For subjects that have not participated in the UX003-CL301 study, the ICR endpoint will not be defined in this study.

7.5.4.11 Scoring of Impactful Clinical Problems

The three most impactful clinical problems as reported by the subject or parent/caregiver during the Clinical Problem Evaluation may be identified and scored on a Likert scale. The Likert scale will be administered during the Baseline visit, then every 24 weeks thereafter (or at termination visit).

For UX003 treatment-naïve subjects, the initial Clinical Problem Evaluation will occur at the Baseline visit. For subjects previously enrolled in the Ultragenyx-sponsored MPS 7 Phase 3 clinical study UX003-CL301, the Clinical Problems identified during the UX003-CL301 Randomization visit will continued to be scored throughout this study. For these subjects the

Clinical Problem scores rated at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline.

This assessment will not be evaluated for subjects enrolling from previous clinical studies, other than UX003-CL301 noted above (e.g. ISTs, expanded access/compassionate use).

Refer to the Study Reference Manual for more details of the scoring.

7.5.4.12 Subject-Reported Disability, Quality of Life, and Fatigue

For UX003 treatment-naïve subjects and subjects enrolling from the MPS 7 Phase 3 Ultragenyx sponsored study (i.e., UX003-CL301), subject-reported disability and pain will be assessed by the MPS Health Assessment Questionnaire (MPS HAQ), and either Childhood Health Assessment Questionnaire (CHAQ) or Health Assessment Questionnaire (HAQ) (as appropriate for subject age). These subject-reported outcome measures will be administered to evaluate treatment-related changes in self-care and mobility activities of daily living including feeding, dressing, bathing, grooming, tooth brushing, toileting, mobility, walking and stair climbing.

For subjects enrolling from previous clinical studies with UX003, these subject-reported outcome measures will only be administered if they were previously performed in their primary (or feeder) study. Subject-reported outcome measures performed within 30 days prior to Baseline may be used for the study baseline assessment.

Age-appropriate questionnaires will be completed at the Baseline visit, then every 24 weeks thereafter (or at termination visit). *For subjects enrolling from the MPS 7 Phase 3 Ultragenyx sponsored study (i.e., UX003-CL301),* subject-reported outcome assessments performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline.

The MPS HAQ will be administered to all age groups. Subjects will consistently complete the same questionnaire (HAQ or CHAQ) administered at baseline for the duration of the study regardless of whether their age changes from 13 to 14 during the study. The age-appropriate version of the PedsQL multidimensional fatigue module will be administered throughout the study.

MPS Health Assessment Questionnaire: The MPS HAQ was developed to assess the self-care and mobility skills of subjects with MPS 1. As MPS 7 shares many similar features with MPS 1, use of the MPS HAQ in this study should provide important information on the functional independence of MPS 7 subjects. 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 mode of administration will be based on subject ability. If possible, the subject should complete the questionnaire, or this may be done via interview. If not feasible for the subject to provide this information, it may be completed by a parent or caregiver. The same person should complete the questionnaire throughout the course of the study.

Childhood Health Assessment Questionnaire: The CHAQ was initially developed to assess health status in children with juvenile rheumatoid arthritis (Singh et al. 1994). The instrument consists of 30 items in the Disability Index comprising 8 subscales: dressing, grooming, arising, eating, walking, reach, grip, and activities; pain is indicated on a sliding scale. Higher scores reflect greater disability. The CHAQ should be administered for pediatric subjects only (<14 years old). The subject's parent or caregiver should complete the CHAQ, and the same person should complete the questionnaire throughout the course of the study.

Health Assessment Questionnaire: The full HAQ is among the first PRO instruments initially designed to represent a model of subject-oriented outcome assessment (Bruce et al. 2005). The HAQ disability and pain scales (Fries et al. 1982) have been extensively validated and employed in a variety of diseases and conditions. There are 20 items in 8 categories that represent a comprehensive set of functional activities – dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The HAQ should be administered for subjects ≥14 years old. The mode of administration will be based on subject ability. If possible, the subject should complete the questionnaire, or this may be done via interview. If not feasible for the subject to provide this information, it may be completed by a parent or caregiver. The same person should complete the questionnaire throughout the course of the study.

Fatigue: Subject-reported fatigue will be assessed by the Pediatric Quality of Life Inventory™ (PedsQL)-Multidimensional Fatigue Scale. The PedsQL multidimensional fatigue scale is a specific module of the PedsQL™ designed to measure fatigue in subjects aged 2 and above (Varni et al. 1999), (Varni et al. 2001). The 18-item scale is comprised of three subscales: general fatigue (6 items), sleep/rest fatigue (6 items) and cognitive fatigue (6 items). The age-appropriate version of the PedsQL will be completed by the subject or caregiver.

7.5.4.13 Clinical Global Impression

The CGI provides an overall measure that takes into account the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function.

Subjects or parents/caregivers will provide a global assessment of change using a seven point scale ranging from -3 (severe worsening) to +3 (significant improvement). This global assessment will be accompanied by narratives from the subjects or parents/caregivers on their perception of how treatment has impacted the subjects' ability to perform activities of daily living.

For UX003 treatment-naïve subjects and subjects enrolling from the MPS 7 Phase 3 Ultragenyx sponsored study UX003-CL301, the Subject/Parent/Caregiver CGI will be evaluated at the Baseline visit, then every 24 weeks thereafter (or at termination visit).

For subjects enrolling from the MPS 7 Phase 3 Ultragenyx sponsored study UX003-CL301, CGIs performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to Baseline may be used for the study baseline assessment.

For subjects enrolling from clinical studies with UX003 other than UX003-CL301, the Subject/Parent/Caregiver CGI will only be administered if previously performed in their primary (or feeder) study. CGIs performed within 30 days prior to Baseline may be used for the study baseline assessment.

7.5.4.14 Hepatosplenomegaly

Liver and spleen size will be assessed qualitatively by physical examination at 48-week intervals (or at Termination Visit).

Refer to the Study Reference Manual for more detail.

7.5.4.15 Cardiac Ventricular Mass

Ventricular mass will be assessed by ECHO and scored as a z-score relative to normal ventricular mass. Evaluation of valvular function and cardiac function will be made primarily for safety purposes. ECHO will be performed at the Baseline visit, then every 48 weeks thereafter (or at termination visit).

An ECHO performed at the primary (or feeder) study End of Treatment visit or within 30 days prior to the Baseline visit may be used for the Baseline assessment provided cardiac ventricular mass can be calculated.

7.5.5 Appropriateness of Measurements

The safety parameters to be evaluated in this study include standard assessments such as recording of medical history, AEs and SAEs, physical examination, vital signs, serum chemistry and hematology, urinalysis, concomitant medications, and other routine clinical and laboratory procedures. In addition, anti-rhGUS antibody levels and complement C3, C4 and CH50 levels will be determined (as indicated) as a measure of the immune response to UX003 treatment.

Urinary GAG is a measure of the underlying biochemical defect in MPS 7 subjects. Accumulated GAGs and uGAGs are a direct result of the genetic enzyme deficiency state. Based on clinical and nonclinical evidence, uGAG is a direct pathophysiological and readily measured marker of the MPS disease process and a reasonable predictor of treatment effect

and clinical benefit. Therefore, if the UX003 restores the underlying biochemical block, a reduction of uGAG is expected.

The additional variables assessed in the program are intended to replicate the clinical assessments used in other MPS ERT programs. The clinical assessments in the study employ standard measures used in other diseases and conditions that impact the respiratory, cardiac, gastrointestinal, skeletal, and central nervous systems. Spirometry, goniometry, ECHO, visual acuity, and anthropometrics are routine, non-invasive procedures inflicting minimal pain/distress for the subject, while providing relevant indicators of clinical disease phenotype and progression.

The 6MWT, BOT-2, and 3MSCT are useful for assessing the compounded impact of multisystem clinical manifestations on the performance of activities of daily living. In MPS 7, performance on these tests is likely to be affected by the pulmonary, cardiovascular, and musculoskeletal morbidity present in these subjects (McDonald et al. 2010). Spirometry will be conducted to assess respiratory compromise, an important component of disease progression and mortality in MPS 7 subjects. Where possible, additional subject-reported outcomes were included to assess functional disability and activities of daily living (e.g., MPS HAQ, CHAQ/HAQ, PedsQL, and CGI). Other efficacy assessments, including a multi-domain clinical responder index enable a composite analysis of clinical changes.

The ICR is a measure of each subject's response to treatment that is selected based on the relevance of the outcome measure to concerns that the subject/parent/caregiver has reported, the subject's ability to complete clinical outcome assessment reliably, and the extent of impairment for that individual. The ICR enables evaluation of the clinical benefit of UX003 by assessing change in a pre-specified individualized clinical outcome that is deemed most relevant for each subject and then determining an overall response rate for the study population. For subjects who were previously treated in an Ultragenyx sponsored study (i.e., UX003-CL301) and had an ICR assigned, that same ICR may be followed in this long-term treatment and extension study.

7.6 Statistical Methods and Determination of Sample Size

7.6.1 Sample Size

Approximately 20 subjects with a confirmed diagnosis of MPS 7, who were previously treated with UX003 in either an Ultragenyx-sponsored study or a non-Ultragenyx sponsored study, or UX003 treatment-naïve subjects at least 5 years old at the time of informed consent with a confirmed diagnosis of MPS 7 will be enrolled into this study. Hence, there is not a formal sample size calculation and justification.

7.6.2 Analysis Populations

Full Analysis Set: The full analysis set will consist of all subjects who receive at least 1 dose of investigational product.

7.6.3 Statistical Principles

Continuous variables will be summarized by number of subjects and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects. Statistical tests will use 2-sided $\alpha = 0.05$ significance level. Two-sided 95% confidence intervals will also be presented. Safety and Efficacy analysis will all be based on Full Analysis Set using observed data. Missing values will not be imputed, unless otherwise specified.

The analyses planned in this protocol will be expanded in the UX003-CL202 SAP. The SAP will be approved prior to the database lock. Any deviations from the analyses described in the protocol and SAP will be noted in the final clinical study report (CSR).

The statistical analyses will be reported using summary tables, figures, and data listings. All analyses and tabulations will be performed using SAS[®]. All raw data obtained from the CRFs as well as any derived data will be included in data listings.

7.6.4 Demography, Baseline Characteristics, and Disposition

Demographics (age, sex, and race) and other baseline disease characteristics will be summarized using descriptive statistics.

The number of subjects enrolled, treated, and completed will be summarized. Subject discontinuation from the study, and from treatment, will each be summarized including reason for discontinuation.

7.6.5 Efficacy endpoints

The percentage change from pre-treatment baseline in uGAG and changes from pre-treatment baseline for other efficacy endpoints will be described across subjects in terms of the mean and standard deviation. The percentage change from pre-treatment baseline in uGAG will be tested using the GEE method. The GEE model will include baseline and time as categorical variables.

7.6.6 Safety Analyses

The following safety measures in this study will be summarized:

- Incidence and frequency of AEs, treatment related AEs, and SAEs

- Clinically significant changes from baseline in vital signs, weight, physical examination findings, ECHO and clinical laboratory tests
- Concomitant medications
- UX003 antibodies
- Complement C3, C4 and CH50 levels (as indicated)

7.6.6.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence and frequency of AEs will be summarized by System Organ Class, Preferred Term (PT), relationship to study drug, and severity. All reported AEs with onset during the treatment (i.e. treatment-emergent AEs) will be included in the analysis. Special attention will be given to those subjects who died, discontinued treatment due to an AE, or experienced a SAE (e.g., summaries, listings, and narrative preparation may be provided, as appropriate).

7.6.6.2 Clinical Laboratory Evaluations

Clinical laboratory data will be summarized by the type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e., outside of reference ranges) and/or clinically significant abnormalities will be presented for each clinical laboratory measurement. A listing of subjects with any markedly abnormal laboratory results will be provided.

7.6.6.3 Vital Signs

Vital signs will be summarized and listed by individual subject. Summaries of vital signs data over time and changes from Baseline over time will be provided.

7.6.6.4 Exposure

Exposure to UX003 will be summarized using the number of doses and total amount of drug administered to each subject during the study.

7.6.7 Interim Analyses

No interim analyses are planned for this study.

7.6.8 Data Monitoring Committee

There will not be a Data Monitoring Committee used in this study.

8 STUDY CONDUCT

8.1 Ethics

8.1.1 Institutional Review Board (IRB) or Ethics Committee (EC)

The IRB/EC must be a properly constituted board or committee operating in accordance with 21 CFR Part 56, "Institutional Review Boards." This protocol, any protocol amendments, the associated informed consent forms (ICFs), and the informed consent procedures must be submitted to the IRB/EC for review and must be approved before the enrollment of any subject into the study. Investigational Product may not be shipped to the Investigator until Ultragenyx or its designee has received a copy of the letter or certificate of approval from the IRB/EC for the protocol and any protocol amendments, as applicable.

All subject recruitment and/or advertising information must be submitted to the IRB/EC and Ultragenyx or its designee for review and approval prior to implementation. IRB/EC approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to protect subject safety. In such cases, the chair of the IRB/EC should be notified immediately and the amendment forwarded to the IRB/EC for review and approval.

8.1.2 Ethical Conduct of Study

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The Investigator will make every effort that the study described in this protocol is conducted in full conformance with those principles, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, and local ethical and regulatory requirements. Should a conflict arise, the Investigator will follow whichever law or guideline affords the greater protection to the individual subject. The Investigator will also make sure he or she is thoroughly familiar with the appropriate administration and potential risks of administration of the Investigational Product, as described in this protocol and the Investigator's Brochure, prior to the initiation of the study.

8.1.3 Subject Information and Consent

Appropriate forms for documenting written informed consent will be provided by the Investigator and reviewed and approved by Ultragenyx or its designee before submission to the IRB/EC. Ultragenyx or its designee must receive a copy of the IRB/EC's approval of the ICF before the shipment of Investigational Product to the study site.

It is the Investigator's responsibility to obtain signed written informed consent from each potential study subject prior to the conduct of any study procedures. This written informed consent will be obtained after the methods, objectives, requirements, and potential risks of

the study have been fully explained to each potential subject. The Investigator must explain to each subject that the subject is completely free to refuse to enter the study or to withdraw from it at any time. Subjects under the age of 18 years (or 16 years, depending on the region) will provide written assent (if possible), and his/her legally authorized representative (parent or legal guardian) will provide written informed consent for such subjects.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Subjects," the Health Insurance Portability and Accountability Act (HIPAA) regulations, and all other applicable regulatory requirements. Subjects will be given a copy of the signed ICF and will be provided any new information during the course of the study that might affect their continued participation in the study. The Investigator or a qualified designee will be available to answer each subject's questions throughout the study, and all of the subject's questions must be answered to the subject's satisfaction. If the protocol is amended and the ICF is revised, each subject will be required to provide written informed consent again using the revised ICF.

Receipt of written informed consent will be documented in each potential subject's CRF. The signed ICF will remain in each subject's study file and must be available to the study monitor(s) at all times.

8.2 Investigators and Study Administrative Structure

Each Investigator must provide Ultragenyx and/or its designee a completed and signed Form FDA 1572 and a Financial Disclosure Form. All Sub-Investigators must be listed on Form FDA 1572 and Financial Disclosure Forms must be completed for all Sub-Investigators listed on Form FDA 1572.

Ultragenyx and/or its designee will be responsible for managing and monitoring the clinical trial to ensure compliance with FDA and ICH GCP guidelines. Ultragenyx's trained designated representative (the monitor) will conduct regular visits to the clinical site, to perform Source Document Verification (SDV). The monitor will verify the Investigator's ongoing qualifications, to inspect clinical site facilities, and to inspect study records, including proof of EC/IRB review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements.

A Coordinating Investigator will be identified for multicenter trials. The Coordinating Investigator will be selected on the basis of active participation in the trial, thorough knowledge of the therapeutic area being studied, and the ability to interpret data. The Coordinating Investigator will read and sign the Clinical Study Report (CSR).

8.3 Investigational Product Accountability

While at the clinical site, Investigational Product must be stored in a secure limited access location at controlled temperature as described in the Investigator's Brochure and according to product packaging. The storage facility must be available for inspection by the study monitor at any time during the study.

A drug accountability record must be maintained for all Investigational Product received, dispensed, returned, and/or lost during the study. This record must be kept current and made available to the study monitor for inspection. Following the close-out of the study, all unused Investigational Product must be returned to Ultragenyx and/or its designee unless other instructions have been provided for final disposition of the Investigational Product.

8.4 Data Handling and Record Keeping

8.4.1 Case Report Forms and Source Documents

The Investigator is required to initiate and maintain, for each subject, an adequate and accurate case history that records all observations and other data related to the study for that subject. A validated Electronic Data Capture (EDC) system will be used for entry of the data into electronic CRFs. Data must be recorded on CRFs approved by Ultragenyx or its designee. All information recorded on CRFs for this study must be consistent with the subject's source documentation.

Initial data entry and any changes to the data will be made only by Ultragenyx-authorized users, and data entries and changes will be captured in an electronic audit trail.

An explanation of any data change should be recorded in the CRF. All data entered in to the CRF must be verifiable; therefore, CRFs will be routinely checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records by Ultragenyx or its designee. The Investigator must allow direct access to all source documents.

8.4.2 Data Quality Assurance

Monitoring and auditing procedures developed by Ultragenyx and/or its designee will be implemented to ensure compliance with FDA and ICH GCP guidelines. Ultragenyx's designated representative (the monitor) will contact the Investigator and conduct regular visits to the study site. The monitor will be expected and allowed to verify the Investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of IRB/EC review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements. The monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. CRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents,

including laboratory test reports and other subject records. Instances of missing or uninterrupted data will be resolved in coordination with the Investigator.

The monitor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications with the study site by e-mail, telephone, facsimile, and/or mail. The Investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve any and all questions raised and any and all issues identified by the monitor.

The Investigator understands that regulatory authorities, the IRB/EC, and/or Ultragenyx or its designees have the right to access all CRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. The Investigator is required to guaranty access to these documents and to cooperate with and support such audits and inspections.

8.4.3 Record Retention

All study records must be retained for at least 25 years after the end of the clinical trial or in accordance with national law. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 25 years. Ultragenyx must be notified should the Investigator/institution be unable to continue maintenance of subject files for the full 25 years. All study records must be stored in a secure and safe facility.

8.5 Reporting and Follow-up of Adverse Events

8.5.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) products.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that, in the view of either the Investigator or Ultragenyx, places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An SAE or serious suspected adverse reaction is an AE or suspected adverse reaction that at any dose, in the view of either the Investigator or Ultragenyx, results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Note that hospitalizations planned prior to study enrollment (e.g. for elective surgeries) are not considered SAEs. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

8.5.2 Severity of Adverse Events

Wherever possible, the severity of all AEs will be graded using the NCI CTCAE (version 4.0). The majority of AEs can be graded using this system.

If an AE cannot be graded using the CTCAE criteria, it should be graded as mild, moderate, severe, life-threatening, or death using the following definitions.

- Mild (Grade 1): Awareness of signs or symptoms, but easily tolerated and of a minor irritant type, causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- Moderate (Grade 2): Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- Severe (Grade 3): Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

- Life-threatening (Grade 4): Events that place the participant at immediate risk of death or are disabling.
- Death (Grade 5): Events that result in death.

To make sure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious" which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.5.3 Relationship of Adverse Events to Study Drug

The Investigator will assess the potential relationship of the AE to study drug using the following descriptions.

Categories of attributions for “Unrelated” events:

- **Unrelated:** This category applies to an AE that *is clearly not related* to the investigational agent/procedure, beyond a reasonable doubt.
- **Unlikely Related:** This category applied to an AE that *is doubtfully related* to the investigational agent/procedure.

Categories of attributions for “Related” events:

- **Possibly Related:** This category applies to an AE that *may be related* to the investigational agent/procedure.
- **Probably Related:** This category applies to an AE that *is likely related* to the investigational agent/procedure.
- **Definitely Related:** This category applies to an AE that *is clearly related* to the investigational agent/procedure.

For the purposes of reporting to regulatory agencies, AEs deemed as Definitely, Probably or Possibly Related will be considered Related and those deemed Unrelated or Unlikely Related will be considered Unrelated.

8.5.4 Adverse Event Reporting to Ultragenyx

8.5.4.1 General

All AEs (i.e. any new or worsening in severity or frequency of a pre-existing condition) with an onset after the subject signs consent for study participation must be promptly documented on the AE eCRF via the EDC system. The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and ensuring documentation of the event is adequate. Details of the AE must include severity, relationship to study drug, duration, and outcome.

For subjects enrolling from an Ultragenyx-sponsored clinical trial, all AEs will be recorded from the time the subject signs the informed consent for this extension study and completion of the End of treatment visit in the primary study until 30 days after the last dose of study drug. Adverse events reported as ongoing at primary study's End of treatment visit and any new AEs prior to Baseline will be reviewed and recorded at Baseline visit. Any enrolling subject who had an early termination in the primary study will have their baseline AE information collected in the same manner as a subject who is treatment naïve or enrolling from a non-Ultragenyx sponsored study (see following paragraph).

For subjects who are treatment naïve or who are enrolling from a non-Ultragenyx sponsored clinical trial, all AEs will be recorded from the time the subject signs the informed consent until 30 days after the last dose of study drug.

In addition, the Investigator should report any AE that occurs after this time period that is believed to have a reasonable possibility of being associated with study drug.

AEs ongoing at 30 days following the last dose of study drug should have a comment in the source document by the Investigator that the event has recovered, recovered with sequelae, or stabilized.

8.5.5 Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting

Any SAE that occurs from the time of signing the ICF through 30 days following the last dose of study drug, including a clinically significantly abnormal laboratory test result that is considered serious, must be reported within 24 hours of knowledge of the event to Ultragenyx or its designee. These requirements apply equally to all subjects, regardless of the study phase or the at-risk subject's treatment assignment or dosage. All initial SAE reports must be followed by detailed descriptions. These should include copies of hospital case records and other documents when requested. SAEs will be reported by completing and submitting SAE report forms to Ultragenyx or designee.

Follow-up SAE information must be submitted in a timely manner as additional information becomes available. All SAEs regardless of relationship to study drug must be followed to resolution or stabilization if improvement is not expected.

All deaths, regardless of causality, from the time of consent through 30 days after last dose of study drug must be reported as an SAE to Ultragenyx or its designee within 24 hours of knowledge.

The Investigator also must notify the IRB/EC of the occurrence of the SAE, in writing, as soon as is practicable and in accordance with local law. A copy of this notification must be provided to Ultragenyx or its designee.

8.5.5.1 Pregnancy Reports

Reported pregnancy of a subject or a subject's partner, while participating in this study, will be monitored for the full duration and/or followed until the outcome of the pregnancy is known. Pregnancy associated SAEs will be processed and submitted, as required, as per the SAE reporting process.

8.5.6 Adverse Drug Reaction Reporting

Ultragenyx or its designee will submit suspected unexpected serious adverse reactions (SUSAR) to appropriate Regulatory Authorities (including Competent Authorities in all Member States concerned), IRBs/ECs, and Investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7-calendar days of first knowledge of the event and follow-up information submitted within an additional eight (8) days, or as otherwise required per local laws and regulations. All other SUSARs will be submitted within 15-calendar days of first knowledge of the event.

Principal Investigators are required to report any urgent safety matters to Ultragenyx or its designee within 24 hours. Ultragenyx or its designee will inform Regulatory Authorities, IRBs/ECs, and Investigators of any events (e.g. change to the safety profile of UX003, major safety findings) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may affect the safety of subjects participating in the clinical trials, as required, in accordance with applicable laws and regulations. The reporting period for urgent safety issues is the period from signing the ICF through 30 days following the last dose of study drug.

The Principal Investigator will notify the IRBs/ECs of SAEs and urgent safety matters, in accordance with IRB/EC requirements and local laws and regulations. A copy of this notification must be provided to Ultragenyx or its designee.

Non-SUSARs will be maintained in the Ultragenyx safety database and provided in annual and/or periodic reports as per local laws and regulations. Ultragenyx or its designee will

prepare and submit annual safety reports and/or other aggregate periodic summary reports to Regulatory authorities and IRBs/ECs, as per local laws and regulations.

8.5.7 Urgent Safety Measures

The regulations governing clinical studies state that the Sponsor and Investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subjects, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union (EU) Clinical Trial Directive 2001/20/EC, "...in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the Sponsor and the Investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The Sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the Ethics Committee (EC) is notified at the same time." The reporting period for urgent safety measures is the period from the signing of the ICF through 30 days following the last administration of study drug. Investigators are required to report any urgent safety measures to Ultragenyx within 24 hours.

8.5.8 Safety Contact Information

Drug Safety	Medical Monitor
PrimeVigilance Fax: PPD [REDACTED] e-mail: PPD [REDACTED]	Christine Haller, MD Telephone: PPD [REDACTED] Mobile: PPD [REDACTED] e-mail: PPD [REDACTED]

8.6 Financing and Insurance

Financing and insurance for this clinical trial will be addressed in clinical trial agreements with the study sites.

8.7 Publication Policy

Any publication or presentation by the Investigator and/or the Institution based on data or results resulting from the Ultragenyx study shall only be done in strict accordance with the Publication section in the Clinical Trial Agreement executed between Ultragenyx and the Institution and/or the Investigator.

9 REFERENCES

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Protocol Number: UX003-CL202
Amendment 3: 28 JUL 2016



10 SIGNATURE PAGE

Protocol Title: A Long Term Open-Label Treatment and Extension Study of UX003 rhGUS Enzyme Replacement Therapy in Subjects with MPS 7

Protocol Number: UX003-CL202 Amendment 3

I have read Protocol UX003-CL202. I agree to conduct the study as detailed in this protocol and in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP) and all applicable regulatory requirements and guidelines.

Investigator Signature _____ Date _____

Printed Name: _____

Accepted for the Sponsor:

As the Sponsor representative, I confirm that Ultragenyx will comply with all Sponsor obligations as detailed in all applicable regulations and guidelines. I will ensure that the Investigator is informed of all relevant information that becomes available during the conduct of this study.

PPD
[Redacted Signature]

PPD
[Redacted Date]

Christine Haller, MD
VP Drug Safety & Pharmacovigilance
Ultragenyx Pharmaceutical Inc.

Date