An Open-label Study of UX003 rhGUS Enzyme Replacement Therapy in MPS 7 Patients Less than 5 Years Old

Protocol Number: UX003-CL203

Original Protocol: 09 January 2015

Amendment 1: 05 October 2015

Amendment 2: 07 April 2016

Investigational Product:	UX003, recombinant human beta-glucuronidase (rhGUS)
Indication:	Mucopolysaccharidosis type 7 (MPS 7)
IND Number:	123788
EudraCT Number:	2015-000104-26
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA, USA 94949
Sponsor's Responsible Medical Officer:	Christine Haller, MD VP Drug Safety & Pharmacovigilance Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA USA 94949 PPD

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

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX003-CL203 Amendment 1

05 October 2015

Original Protocol UX003-CL203 (dated 09 January 2015) has been modified by Amendment 1 to expand the study size and to add or clarify certain procedures. The major protocol changes are summarized below:

1. **Overall Study Design and Plan**: In Section 7.1 and related sections, the study size has been increased from up to 7 subjects to approximately 15 subjects including approximately 5 infants with hydrops fetalis.

   Rationale: Increasing the sample size will provide a more robust assessment of safety and efficacy in this patient population.

2. **Study Procedures and Assessments**: Several updates have been made to clarify or add procedures in Section 7.5. Given the age of the study population and number of assessments, if the maximum amount of blood has been taken based on Maximum Allowable Blood Volume Guidelines for any subject on any given study visit, some assessments will not be required. A provision has been established in the study-specific Laboratory Manual for details on prioritizing blood draws. Additional modifications to study procedures and assessments specified in the protocol text are summarized below.

   Urinary and serum GAG: Reference to the NRE as the primary method for measuring urinary and serum GAG has been removed from the protocol.

   Rationale: Multiple assays for measuring pathologic accumulation of GAG are available. The specific methodology used for evaluating the primary efficacy variable will be included in the study Statistical Analysis Plan.

   Functional Development: The protocol has been updated to specify the Bayley Scales of Infant and Toddler Development® – Third Edition (Bayley-III) will not be administered if the subject has achieved the highest raw score on the instrument, or if, based on the clinical judgment of the Investigator, valid and reliable administration is not possible at the specified visit.

   Rationale: The protocol previously specified the highest level of age-equivalence on the test as a criterion for omitting the Bayley-III assessment; the change to raw score provides a more straightforward threshold. The option to withhold assessment based

on Investigator opinion provides a measure of flexibility thereby avoiding unreliable or spurious results due to mitigating factors such as language difficulties or clinical condition of the subject.

Motor Functioning: A gross motor milestone checklist has been added as an additional assessment of motor functioning as a tertiary efficacy variable.

Rationale: A gross motor milestone checklist was designed to allow for assessment of the functional status of the subject requiring limited language interaction and physical handling.

Pulmonary Function Testing: Pulmonary function assessments have been added to the Continuation Period; pulse oximetry measurements will be obtained at 12-week intervals.

Rationale: Continued monitoring of pulmonary function will provide a potential measure of maintenance of efficacy.

Biochemical Markers of Bone Turnover: Assessment of serum markers of bone formation and bone resorption including procollagen type 1 N-propeptide (P1NP), carboxy-terminal cross-linked telopeptide of type I collagen (CTX-I), bone-specific alkaline phosphatase (BALP), and vitamin D will be conducted at Weeks 0 (baseline) and 2, then approximately every 8 weeks thereafter for the remainder of the Treatment Period (i.e. Weeks 8-48), and every 24 weeks during the Continuation Period.

Rationale: Skeletal abnormalities are characteristic of MPS 7. Measurement of biochemical markers of bone turnover may allow the effects of UX003 on skeletal tissue to be evaluated.

Drug Concentration Measurements: Specific time points for collection of PK samples have been provided.

Vital Signs: Procedures for the assessment of vital signs have been clarified.

Rationale: Vital sign assessments have been clarified to be specific for young pediatric subjects.

3. **Reporting and Follow-up of Adverse Drug Events:** A new section (Section 8.5.5) 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), ECs, and Investigators as per local laws and regulations.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX003-CL203 Amendment 2

07 April 2016

Protocol Amendment 1 (dated 05 October 2015) has been modified by Amendment 2 to remove or clarify certain procedures and update information. The major protocol changes are summarized below:

1. **Overall Study Design and Plan**:

   - 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 240 weeks, the end of trial is defined as the Week 240 visit of the last subject. In the event the study is terminated by the Sponsor prior to Week 240, 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 to align with current regulatory guidelines.

   - Revised protocol to allow for Mutation Analysis at any point of the study.

     Rationale: To further characterize the disease manifestations, severity and progression of MPS 7, the sponsor aims to determine the specific genetic mutation in each patient enrolled if consent is provided for such testing.

   - Clarify the handling of spinal cord compression.

     Rationale: Patients with MPS diseases are at risk for spinal cord compression due to disease-related skeletal abnormalities including odontoid hypoplasia and vertebral subluxation. Enzyme replacement therapy may result in increased joint flexibility with possible impact on the risk of spinal cord injury. Additional text was added to the protocol to recommend appropriate monitoring and management of signs and symptoms of potential spinal cord compression.

   - Removal of serum GAG from the continuation period.

     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 continuation period. 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.

- Record Retention 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.

2. **Study Procedures and Assessments**:

   - **Vital Signs:** Procedures for the assessment of vital signs have been clarified.

     Rationale: Vital sign assessments have been clarified to be specific for young pediatric subjects.

2 SYNOPSIS

TITLE OF STUDY:

An Open-label Study of UX003 rhGUS Enzyme Replacement Therapy in MPS 7 Patients Less than 5 Years Old

PROTOCOL NUMBER:

UX003-CL203

STUDY SITES:

Multicenter; approximately 2-6 sites globally

PHASE OF DEVELOPMENT:

Phase 2

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 two glycosaminoglycans (GAGs): dermatan sulfate and heparan sulfate, the same substrates accumulated in MPS 1 (Hurler syndrome) and MPS 2 (Hunter syndrome). The GUS deficiency results in lysosomal accumulation of GAGs in multiple tissues and organs throughout the body and numerous clinical symptoms similar to those observed in MPS 1 and MPS 2. Some MPS 7 patients present at birth with severe edema or non-immune hydrops fetalis and usually die within 2-4 months.

There are currently no approved treatments for MPS 7. UX003 (recombinant human beta-glucuronidase, rhGUS) is intended as an enzyme replacement therapy (ERT) for the treatment of MPS 7. A Phase 1/2 study has shown that treatment with UX003 can reduce lysosomal storage and urinary GAG (uGAG) and is expected to provide clinical benefit; a pivotal Phase 3 study is ongoing.

Patients with MPS 7 can present as newborns, infants or young children; this Phase 2 study will evaluate treatment with UX003 in MPS 7 patients less than 5 years of age. Although young patients have the same underlying etiology, the breadth and type of clinical problems can be different, including more frequent ascites/edema, cardiac problems, and other severe manifestations. This study will assess the relative safety, pharmacokinetics (PK), and efficacy of UX003 ERT in young patients with MPS 7.

OBJECTIVES:

Primary Objective:

The primary objective is to evaluate the effect of UX003 treatment in pediatric MPS 7 subjects less than 5 years of age on:

- Safety and tolerability
- Efficacy as determined by the reduction of uGAG excretion

Secondary Objective:

The secondary objective is to evaluate the effect of UX003 on growth velocity and hepatosplenomegaly.

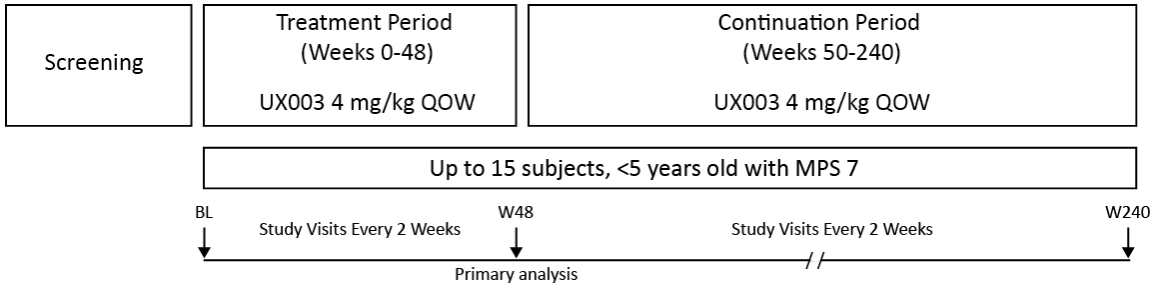
Tertiary Objectives:

Tertiary objectives are to assess PK and evaluate the effect of UX003 on measures of lysosomal storage, overall clinical change, cardiac and pulmonary function, bone turnover markers, and functional and motor development.

STUDY DESIGN AND METHODOLOGY:

UX003-CL203 is an open-label, multicenter, Phase 2 study to assess the safety and efficacy of UX003 in pediatric MPS 7 subjects. The study seeks to enroll approximately 15 subjects less than 5 years of age at the time of informed consent, and will attempt to include approximately 5 infants with hydrops fetalis if possible. Subjects with prior exposure to UX003 treatment under an emergency IND may also be enrolled at the discretion of the Sponsor. In the initial 48 weeks of treatment, subjects will receive UX003 via intravenous (IV) infusion at a dose of 4 mg/kg every other week (QOW). Subjects who complete the 48-week study may choose to continue UX003 treatment in the Continuation Period up to 240 weeks, or until the subject withdraws consent, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, or the study is terminated. Figure 2.1 provides a schematic of the overall study design.

Figure 2.1: UX003-CL203 Study Schema



NUMBER OF SUBJECTS PLANNED:

Approximately 15 subjects will be enrolled including approximately 5 subjects with hydrops fetalis. Subjects under the age of 5 years at the time of informed consent with a confirmed diagnosis of MPS 7 will be enrolled. Due to the extremely low prevalence of the disease, the sample size is not based on statistical considerations but rather the ability to find qualifying patients.

Subjects who withdraw or are removed from the study after receiving study drug may be replaced on a case-by-case basis, at the discretion of Ultragenyx.

DIAGNOSIS AND CRITERIA FOR INCLUSION AND EXCLUSION:

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

1. Confirmed diagnosis of MPS 7 based on leukocyte or fibroblast glucuronidase enzyme assay, or genetic testing
2. Under 5 years of age at the time of informed consent
3. Written informed consent of Legally Authorized Representative after the nature of the study has been explained, and prior to any research-related procedures

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

1. Undergone a successful bone marrow or stem cell transplant or has evidence of any degree of detectable chimaerism with donor cells
2. Any known hypersensitivity to rhGUS or its excipients that, in the judgment of the Investigator, places the subject at increased risk for adverse effects
3. Use of any investigational product (drug or device or combination) other than UX003 within 30 days prior to Screening, or requirement for any investigational agent prior to completion of all scheduled study assessments at any time during the study
4. Has a condition of such severity and acuity, in the opinion of the Investigator, which may not allow safe study participation. For patients with hydrops fetalis, the ongoing interventions to manage fluid balance can be continued; if the addition of ERT is considered a fluid-overload risk, the individual should be excluded.
5. Has a concurrent disease or condition 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 affect safety. Since hydropic patients have a high rate of mortality, the risk of death prior to 1 year of age should not be considered sufficient to exclude the patient from the study for compliance.

INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION:

UX003 is a sterile liquid buffered saline formulation of rhGUS at a concentration of 2 mg/mL filled to allow withdrawal of a minimal of 5.0 mL deliverable volume and supplied in a 10 mL glass vial. UX003 will be administered at a dose of 4 mg/kg 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 infusion associated reactions (IARs); the infusion rate may be slowed to manage or reduce IARs.

REFERENCE THERAPY, 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 48 weeks. Subjects successfully completing the first 48 weeks may continue treatment for up to 240 weeks (5 years) or until one of the following occurs: the patient withdraws consent, the patient is discontinued from the study at the discretion of the Investigator or Ultragenyx, or the study is terminated.

CRITERIA FOR EVALUATION:

Safety Assessments:

Safety will be evaluated by the incidence and frequency of adverse events (AEs) and serious adverse events (SAEs), including clinically significant changes from study baseline to scheduled time points in:

- Physical examination findings
- Vital signs and weight
- Clinical laboratory evaluations

- Concomitant medications
- IgG antibodies to rhGUS
- Complement C3, C4 and CH50 levels (as indicated)

Management of Infusion Associated Reactions

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 infusion reactions. The protocol also incorporates measures to minimize pain and distress, including the optional use of topical anesthetics to ease the pain of placing an IV line and the option for an in-dwelling catheter.

Primary Efficacy Variable:

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

Secondary Efficacy Variables:

- Growth will be assessed by anthropometric measurements including standing height (length or sitting height as applicable), head circumference, and weight. Growth velocity will be calculated and compared with pre-treatment growth velocity when available and published normative data for age and gender.
- Hepatosplenomegaly: The volume of the liver and spleen will be determined using ultrasound. If an ultrasound is not possible, the liver and spleen should be assessed by physical exam. The volume of liver and spleen will be compared to baseline and to normal values if available. Ascites will also be assessed.

Tertiary Efficacy Variables:

- Additional GAG measures including serum GAG and supplementary uGAG assays
- Clinical Global Impression Scale: Physicians caring for each subject will provide a global assessment of change from baseline or change from identification of a new finding using a seven point scale ranging from -3 (severe worsening) to +3 (significant improvement). The Clinical Global Impression (CGI) scale will be supported by reported changes in a list of disease-specific abnormalities projected to respond to treatment.
- Functional Development will be assessed by the Bayley Scales of Infant and Toddler Development® – Third Edition (Bayley-III).
- Motor Functioning will be assessed by a motor development milestone checklist.
- Cardiac Ventricular Mass: Ventricular mass will be assessed by echocardiogram (ECHO) and scored as a z-score relative to normal ventricular mass. Valvular and cardiac function may also be evaluated.
- Pulmonary Function: Pulse oximetry will be used to assess problems in adequate respiration; resting O_2 saturation will be measured while the subject is breathing room air.
- Biochemical Markers of Bone Turnover (BTMs): Levels of serum markers of bone formation and bone resorption will be measured including procollagen type 1 N-propeptide (P1NP), carboxy-terminal cross-linked telopeptide of type I collagen (CTX-I), bone-specific alkaline phosphatase (BALP), and vitamin D.

Pharmacokinetic Parameters derived from Population PK Analysis:

- Area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$)
- AUC from time zero to the time of last measurable concentration (AUC_{0-last})
- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (T_{max})
- Elimination half-life ($t_{1/2}$)
- Total clearance of drug after IV administration (CL)
- Apparent volume of distribution based upon the terminal phase (V_{dz})
- Apparent volume of distribution at steady-state (V_{dss})

STATISTICAL METHODS:

Descriptive statistics will be used to summarize the data. For continuous variables, the mean, the standard error, median, minimum, and maximum will be provided. For categorical variables, the frequency and percent distributions will be provided. Two-sided 95% confidence intervals will also be presented when appropriate.

Analyses may be performed at any time during the study at the discretion of the Sponsor. There is no unblinding during analysis since it is an open-label study.

Analysis Sets:

The full analysis set will consist of all enrolled subjects who receive at least 1 dose of UX003 during the study.

Safety Analysis:

The primary safety analysis will evaluate the safety of UX003 as measured by the incidence and frequency of AEs and SAEs, including clinically significant changes from baseline to scheduled time points in safety parameters. The incidence and frequency of AEs will be summarized by System Organ Class and Preferred Term, relationship to study drug, and severity. No statistical significance will be assessed.

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 after study drug administration will be presented for each clinical laboratory measurement. For each clinical laboratory measurement, descriptive statistics will be provided for baseline and all subsequent visits. Changes from baseline to the post-treatment visits will also be provided. Descriptive statistics of vital signs, imaging assessments, and concomitant medications will be provided in a similar manner.

Changes in findings from baseline physical examinations will be tabulated and listed for each subject by examination category. If there are examination findings that change in more than one subject, these will be tabulated in a separate table and expressed as the number of subjects with the change out of the total.

Anti-drug antibody data will be tabulated over the course of the study. The number of subjects converting to a positive antibody assay value defined as a titer increase of five-fold or more over baseline, and the time of onset of a positive antibody response will be determined.
Descriptive statistics on the titers achieved and the time of onset of the response will be provided (mean, standard deviation, median, range).

Efficacy Analyses:

The study is a small open-label study to obtain some clinical efficacy data from a small cohort of these ultra-rare patients. A complete hypothesis testing statistical approach is not plausible in this setting, but a reasonable approach to assessing for the biologic efficacy of UX003 will be made.

The primary efficacy analysis will evaluate the mean percent change in uGAG excretion from Week 0 (Baseline) to Week 48 using the generalized estimating equation (GEE) analysis method.
For subject(s) previously treated with UX003 under an emergency IND, percent change from initial baseline (prior to first dose of UX003) will be used, if the initial baseline data are available. The null hypothesis of no change in mean uGAG excretion will be tested. An additional analysis will also be performed on the Week 24 time point.

Secondary analysis on growth and hepatosplenomegaly will be evaluated to compare pretreatment with post treatment effects. Growth rate will be compared to historical data from medical records and also compared to published normative data for age and gender (if available). Changes in findings from baseline for other efficacy variables will be tabulated for each subject. Comparisons of certain efficacy variables with published normative data based on age and gender may also be conducted.

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

Table 2.1: Study UX003- CL203 Schedule of Events

	Screen[a]	Baseline[b]	48-Week Treatment Period[c]																							
Week	**-4 to -1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**ET[s]**
Informed consent[a]	X																										
Medical history[d]	X	X																									
Weight[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK[f]		X												X												X	
Urinary GAG[g]	X	X		X		X		X			X			X			X			X			X			X	X
Serum GAG		X						X						X						X						X	
Anthropometrics[h]		X						X						X						X						X	X
CGI		X						X						X						X						X	X
Bayley-III		X												X												X	X
Motor milestones		X												X												X	X
Echocardiogram[i]		X																								X	X
Pulse oximetry[j]		X						X						X						X						X	X
Liver & spleen Ultrasound[k]		X						X						X												X	X
Adverse events[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Con-meds, therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam[m]	X	X						X						X						X						X	X
Vital signs[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical labs[o]	X	X	X	X		X				X				X				X				X				X	X
rhGUS antibodies[p, q]		X				X				X				X				X				X				X	X
Bone markers[q]		X	X			X				X				X				X				X				X	X
Genetic Mutation Labs[t]										X																	
Complement[r, q]			As indicated for subjects with drug-related IARs																								
UX003 Treatment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 2.2: Schedule of Events Continuation Period

Assessment	Continuation Period Weeks 50-240 [c]
Urinary GAG [g]	Every 12 weeks
Anthropometrics (including weight) [h]	Every 12 weeks
CGI	Every 12 weeks
Pulse oximetry	Every 12 weeks
Bayley-III	Every 48 weeks
Motor Milestone Checklist	Every 48 weeks
Echocardiogram [i]	Every 48 weeks
Liver and spleen ultrasound [k]	Every 48 weeks
Adverse events [l]	Every 2 weeks
Concomitant medications and therapies	Every 2 weeks
Physical examination [m]	Every 12 weeks
Vital signs [n]	Every 2 weeks
Clinical laboratory tests [o]	Every 24 weeks
Antibodies to rhGUS [p]	Every 12 weeks
Bone turnover markers	Every 24 weeks
Complement C3, C4, CH50 (subjects with IARs) [q, r]	As indicated
Treatment with UX003	Every 2 weeks

Abbreviations: Bayley-III = Bayley Scales of Infant Development® – Third Edition, CGI = Clinical Global Impression scale, con-meds = concomitant medications, PK = pharmacokinetics, GAG = glycosaminoglycans, ET = early termination

a. Screening must take place within 30 days prior to Baseline Visit. Informed consent/assent must be obtained prior to any Screening procedures.

b. Baseline assessments must be completed within 7 days prior to first dose of study drug, unless otherwise specified. Physical exams and safety labs are the only Screening assessments that, if performed within 7 days of the first dose of study drug, may be used for Baseline assessment. Baseline assessments must be performed prior to the infusion if scheduled on the same day as the Week 0 visit.

c. Visit windows are ± 3 days during the Treatment Period. For major assessment visits (Weeks 12, 24, 36, and 48) and visits during the Continuation Period the window is ± 7 days. All assessments scheduled for a treatment day must be completed prior to the infusion on that day.

d. Growth history for height and weight will be collected as part of medical history. Pretreatment measurements of height and weight should be collected from the records if possible to assure a pre and post treatment growth rate can be assessed. Medical history collected at the Baseline visit record any changes in medical history since Screening.

e. Weight to determine appropriate study drug volume for the subsequent visit, and for safety; refer to Pharmacy Manual for instructions on calculating drug dosage and preparation.

f. PK samples will be collected prior to the infusion (pre-dose), 60 minutes after start of infusion, at the end of the infusion, 30-120 minutes post infusion and 4-6 hours post infusion. PK samples should not be drawn from the IV line used for administration of study drug.

g. Urinary GAG samples must be collected from first morning urine voids. Urine samples will be collected once at Screening and two times (separate days) during the Baseline Period; refer to Laboratory Manual for details.

h. Anthropometric measurements include standing height (or sitting height and recumbent length as appropriate), head circumference and weight. Anthropometric weight measurements may also be used for study drug preparation during the Continuation Period only; refer to Pharmacy Manual for calculating drug dosage and preparation.

i. ECHO performed within three months prior to Baseline visit may be used for baseline provided cardiac ventricular mass can be calculated.

j. If subject requires respiratory support, the type and duration should also be noted.

k. Ultrasound will include assessment of ascites.

l. All AE/SAEs will be recorded from the time the subject signs the consent form until 30 days after the last dose of study drug.

m. Complete physical examination. If subject has symptoms or signs of weakness, evaluate for signs of cord compression (e.g., reflexes and moor strength).

n. Vital sign time points on infusion days (at minimum; additional measurements obtained as appropriate)

Week 0 (Baseline) to Week 12: 15 minutes prior to infusion; every 15 minutes during the infusion; immediately post-infusion; 15, 30 and 60 minutes post-infusion.

Week 14 to Week 240: 15 minutes prior to infusion; every 60 minutes for the remainder of the infusion; 60 minutes post-infusion.

o. 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.

p. Testing for IgG antibodies directed against rhGUS. Serum sample must be collected before infusion.

q. If maximum amount of blood has been taken based on Maximum Allowable Blood Volume Guidelines for any subject, some assessments are not required; see the Lab Manual for details on prioritizing blood draws.

r. If a drug-related IAR has occurred, blood samples for complement C3, C4, and CH50 assessment should be drawn prior to and immediately after the next infusion.

s. If a subject discontinues study treatment or withdraws from the study, every attempt should be made to complete the early termination (ET) visit within 2 weeks of the last dose of study drug. Ultrasound, Bayley-III, and motor milestone checklist will not be performed at the ET visit if the assessment was conducted within 1 month of termination.

t. Optional assessment can be performed at a different time-point if total blood volume at week 16 may exceed maximum allowable volume.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-last}	area under the plasma concentration-time curve from time zero to the time of last measurable concentration
BALP	bone-specific alkaline phosphatase
Bayley-III	Bayley Scales of Infant and Toddler Development® – Third Edition
BTM	bone turnover marker
BUN	blood urea nitrogen
°C	degrees Celsius
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CGI	Clinical Global Impression
CIM6PR	cation-independent mannose 6-phosphate receptor
CL	total clearance of drug after intravenous administration
C_{max}	maximum plasma concentration
CRF	Case Report Form
CTX-1	carboxy-terminal cross-linked telopeptide of type I collagen
EC	Ethics Committee
ECHO	echocardiogram
EDC	electronic data capture
EMLA	eutectic mixture of local anesthetic
ERS	European Respiratory Society
ERT	enzyme replacement therapy
ET	Early Termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
GAG	Glycosaminoglycan
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GGT	gamma glutamyl transpeptidase

GUS	beta-glucuronidase
HIPAA	Health Insurance Portability and Accountability Act
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
IgG	immunoglobulin G
IND	Investigational New Drug (application)
IRB	Institutional Review Board
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
MPS	mucopolysaccharidosis/mucopolysaccharidoses
MPS 7	mucopolysaccharidosis type 7, Sly Syndrome
MR	mannose receptor
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
P1NP	procollagen type 1 N propeptide
PGI-C	Physician Global Impression of Change
PICC	peripherally inserted central catheter
PK	pharmacokinetic(s)
PT	Preferred Term
QOW	every other week
QW	every week
RBC	red blood cell
rhGUS	recombinant human beta-glucuronidase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
$t_{1/2}$	half-life
T_{max}	time to maximum plasma concentration
uGAG	urinary glycosaminoglycans

US	United States
UX003	Investigational Product/study drug, recombinant human beta-glucuronidase, rhGUS
V_{dz}	apparent volume of distribution based upon the terminal phase
V_{dss}	volume of distribution at steady state
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.

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 MPS characteristics are similar, 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. Most MPS 7 patients die before the second or third decade of life due to compounding medical problems. Some MPS 7 patients present at birth with severe edema or non-immune hydrops fetalis and usually die within 2-4 months.

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), there is no approved treatment available for MPS 7. 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 multiple clinical studies to support UX003 development. Ongoing interventional studies include a Phase 1/2 study to assess safety, efficacy, and pharmacokinetics (PK) of UX003 treatment, and a confirmatory randomized placebo-controlled Phase 3 study conducted in MPS 7 patients aged 5 – 35 years. Additionally, a Phase 3 long-term extension study to assess long-term safety and efficacy for patients who complete the phase 3 study or enrolled in other UX003 studies is on-going.

This study is intended to assess the safety and efficacy of UX003 when administered to MPS 7 patients less than 5 years of age.

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 two GAGs: dermatan sulfate and heparan sulfate. 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 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 comprises 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 hydrops fetalis, present as infants or young children with typical Hurler (MPS 1)-like features (Neufeld et al. 2001). Diagnosis of MPS 7 is often made through clinical examination and urine tests for excess glycosoaminoglycans 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). Clinical features include hepatosplenomegaly, pulmonary infections, cardiac problems, corneal clouding, hearing loss, hernias, joint stiffness, short stature and dysostosis multiplex.

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 atalantoaxial 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.

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 MPS1 (Aldurazyme®, laronidase), MPS 2 (Elaprase®, idursulfase), MPS 4A (Vimizim®, elosulfase alfa), and MPS 6 (Naglazym®, 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 ((Hendriksz et al. 2014); 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, idursulfase, galsulfase 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 the potential of uGAG to predict 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 ≥ 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.

5.3.1.1 UX003 Mechanism of Action in MPS7

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 heparan sulfate and dermatan sulfate (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 distributes 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 heparan sulfate and dermatan sulfate.

5.3.3 Previous Clinical Studies

The first in-human use of UX003 was sponsored by PPD at the Steven and Alexandra Cohen Children's Medical Center of New York under an emergency IND granted by the US FDA. A PPD 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. 2014). 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).

A second emergency IND was granted to treat a PPD old MPS 7 infant born with severe hydrops fetalis (PPD, New York University School of Medicine). The patient has received infusions for 48 weeks; uGAG was reduced by approximately 70% after several infusions. No drug-related IARs have occurred in this Investigator sponsored trial.

An open-label Phase 1/2 study in 3 subjects aged 5, 9, and 25 years is ongoing to assess the safety, efficacy, and dose of UX003 in MPS 7 subjects via IV administration QOW for 36 weeks with provisions for additional treatment during the Continuation Period (UX003-CL201; NCT01856218, EudraCT 2013-001152-35). UX003 has been administered up to 4 mg/kg in this study. Results through 36 weeks of treatment suggest a reduction in uGAG excretion and decreases in liver size relative to baseline at 4 mg/kg, with no SAEs or drug-related IARs reported; the most common AEs have been infections and gastrointestinal disorders.

A Phase 3 randomized, placebo-controlled study is being conducted to confirm safety and efficacy of UX003 treatment in MPS 7 patients aged 5 – 35 years (UX003-CL301; NCT02230566).

A Phase 3 long-term open-label treatment extension study to assess long-term safety and efficacy of UX003 treatment in MPS 7 patients (UX003-CL202).

A comprehensive summary regarding previous clinical experience on the use of UX003 is provided in the UX003 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 at 4 mg/kg (5-fold safety factor). 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 heparan sulfate and dermatan sulfate 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 benefit-risk profile with UX003. Clinical trial data and experience with marketed ERT products for the treatment of related MPS disorders (MPS 1, MPS 2, MPS 4A, and MPS 6) 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 patients 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.

Studies have also been conducted in MPS 1, MPS 2, MPS 4A, and MPS 6 patients less than 5 years of age, showing benefit in reducing storage and improving some aspects of disease (Wraith et al. 2007), (Giugliani et al. 2014), (Haller et al. 2013), (Lampe et al. 2014). Early treatment with ERT can provide important benefits in improving growth, skeletal disease and overall clinical outcome (Laraway et al. 2013).

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 subjects with antihistamine, and staged and controlled infusion rates. The large fraction of MPS 7 patients with missense mutations are expected to exhibit a reduced immune response to ERT due to the presence of residual protein, consistent with observations in the tolerant mouse (Sly et al. 2001) and MPS 1 patients undergoing ERT (Yogalingam et al. 2004).

The clinical experience with UX003 in pediatric and adult patients with MPS 7 has demonstrated a sustained reduction in uGAG levels and clinical improvement. 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 treatment of pediatric MPS 7 patients less than 5 years of age.

5.5 Study Rationale

MPS 7 is an ultra-rare (< 100 cases currently identified worldwide), chronically debilitating, and life-threatening lysosomal storage disease. Some MPS 7 patients present at birth with severe edema or non-immune hydrops fetalis and usually die within 2-4 months. There are currently no approved treatments for MPS 7. UX003 is intended as an ERT for the treatment of MPS 7. A Phase 1/2 study has shown that treatment with UX003 can reduce lysosomal storage and uGAG and is expected to provide clinical benefit; a pivotal Phase 3 study is ongoing.

Patients with MPS 7 can present as newborns, infants or young children; this Phase 2 study will evaluate treatment with UX003 in MPS 7 patients less than 5 years of age. Although young patients have the same underlying etiology, the breadth and type of clinical problems can be different, including more frequent ascites/edema, cardiac problems, and other severe manifestations. This study will assess the relative safety, PK, and efficacy of UX003 ERT in young patients with MPS 7.

6 STUDY OBJECTIVES

Primary Objective:

The primary objective is to evaluate the effect of UX003 treatment in pediatric MPS 7 subjects less than 5 years of age on:

- Safety and tolerability
- Efficacy as determined by the reduction of uGAG excretion

Secondary Objective:

The secondary objective is to evaluate the effect of UX003 on growth velocity and hepatosplenomegaly.

Tertiary Objectives:

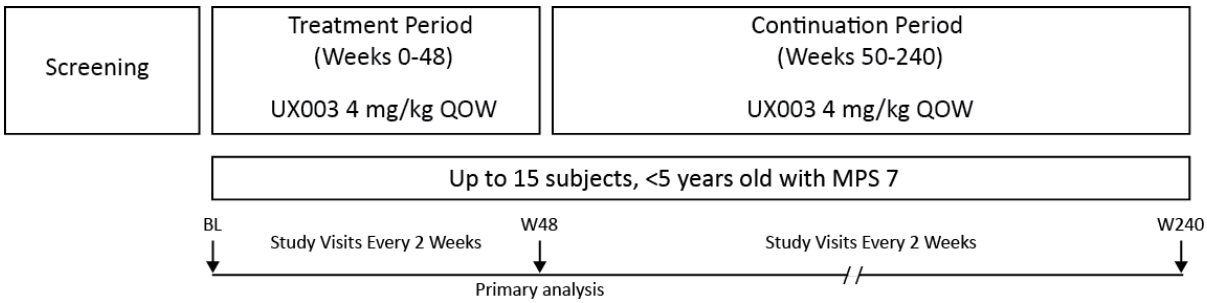
Tertiary objectives are to assess PK and evaluate the effect of UX003 on measures of lysosomal storage, overall clinical change, cardiac and pulmonary function, bone turnover markers, and functional and motor development.

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

UX003-CL203 is an open-label, multicenter, Phase 2 study to assess the safety and efficacy of UX003 in pediatric MPS 7 subjects. The study seeks to enroll approximately 15 subjects less than 5 years of age at the time of informed consent, and will attempt to include approximately 5 infants with hydrops fetalis if possible. Subjects with prior exposure to UX003 treatment under an emergency IND may also be enrolled at the discretion of the Sponsor. In the initial 48 weeks of treatment, subjects will receive UX003 via IV infusion at a dose of 4 mg/kg QOW. Subjects who complete the 48-week study may choose to continue UX003 treatment in the Continuation Period up to 240 weeks, or until the subject withdraws consent, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, or the study is terminated. Figure 7.1.1 provides a schematic of the overall study design.

Figure 7.1.1: UX003-CL203 Study Schema



7.2 Discussion of Study Design, Including Choice of Control Group

Given the history of ERT in the MPS field, this study is expected to show that UX003 (rhGUS) can reduce lysosomal storage and improve clinical function in MPS 7 patients less than 5 years of age with an acceptable benefit-risk ratio. The population of MPS 7 patients less than 5 years of age is very small and heterogeneous; therefore it is not feasible to conduct a parallel group or placebo-controlled study to assess safety and efficacy.
To demonstrate the safety and efficacy of UX003, two interventional studies are being conducted in pediatric and adult MPS 7 patients between the ages of 5 and 35 years.

This study of UX003 has incorporated several elements to make efficient and safe use of a variable and vulnerable group of subjects and leverage the extensive existing data and lessons learned from other UX003 treatment protocols and approved ERT programs.
The single-arm, open-label study design provides active treatment to all subjects with this extremely rare and serious life-threatening disease, while maintaining appropriate safety and efficacy standards in order to gain additional information about UX003 treatment in MPS 7 patients less than 5 years of age. Once a subject has demonstrated acceptable long-term safety and efficacy following the initial 48 weeks of treatment, continuation of UX003

treatment will be available. The Continuation Period enables treatment for up to a total of up to 240 weeks and has been designed with a reduced frequency of assessments to minimize inconvenience and discomfort for the subject.

7.3 Selection of Study Population

The study will be conducted in approximately 15 pediatric MPS 7 subjects. The study seeks to enroll subjects under the age of 5 years, and will attempt to include at least 5 infants with hydrops fetalis, if possible; subjects with prior exposure to UX003 treatment under an emergency IND may also be enrolled at the discretion of the Sponsor. The inclusion criteria are structured to enroll subjects with a confirmed diagnosis of MPS 7. To enroll subjects most likely to benefit from treatment and demonstrate safety and effectiveness of UX003, MPS 7 patients 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.

7.3.1 Inclusion Criteria

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

1. Confirmed diagnosis of MPS 7 based on leukocyte or fibroblast glucuronidase enzyme assay, or genetic testing
2. Under 5 years of age at the time of informed consent
3. Written informed consent of Legally Authorized Representative after the nature of the study has been explained, and prior to any research-related procedures

7.3.2 Exclusion Criteria

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

1. Undergone a successful bone marrow or stem cell transplant or has evidence of any degree of detectable chimaerism with donor cells
2. Any known hypersensitivity to rhGUS or its excipients that, in the judgment of the Investigator, places the subject at increased risk for adverse effects

3. Use of any investigational product (drug or device or combination) other than UX003 within 30 days prior to Screening, or requirement for any investigational agent prior to completion of all scheduled study assessments at any time during the study
4. Has a condition of such severity and acuity, in the opinion of the Investigator, which may not allow safe study participation. For patients with hydrops fetalis, the ongoing interventions to manage fluid balance can be continued; if the addition of ERT is considered a fluid-overload risk, the individual should be excluded.
5. Has a concurrent disease or condition 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 affect safety. Since hydropic patients have a high rate of mortality, the risk of death prior to 1 year of age should not be considered sufficient to exclude the patient from the study for compliance.

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.

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 (or legally authorized representative), 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 case report form (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.

If a subject discontinues from the study prematurely, every reasonable effort should be made to perform the Early Termination Visit procedures within 2 weeks of the last dose of study drug.

Subjects who withdraw or are removed from the study after receiving study drug may be replaced on a case-by-case basis, at the discretion of Ultragenyx.

7.3.3.1 Stopping Rules

Individual subjects who experience any unexpected and possibly, probably, or definitely drug-related 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 Institutional Review Board (IRB)/Ethics Committee (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

UX003 is a sterile liquid buffered saline formulation of rhGUS at a concentration of 2 mg/mL filled to allow withdrawal of a 5.0 mL deliverable volume and supplied in a 10 mL glass vial. UX003 will be administered at a dose of 4 mg/kg 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. Refer to the Pharmacy Manual for full details on study drug preparation and administration.

7.4.1 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 Pharmacy Manual for 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 current Good Manufacturing Practice (cGMP) regulations.

7.4.2 Reference Therapy

The protocol is designed as an open-label active treatment study, therefore no reference therapy will be administered in this study.

7.4.3 Study Drug Infusion Procedure

Study drug (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.

7.4.3.1 Pre-Dose Medication

The subject should fast for a minimum of 1 hour prior to the infusion and for the first 2 hours of infusion. If the subject is tolerating the infusion, clear liquids or oral electrolyte solutions (e.g. Pedialyte) may be instituted. This requirement may be removed if after 12 weeks of treatment, the Investigator feels that the patient is fully tolerating infusions.

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. IV antihistamine (diphenhydramine dihydrochloride) may be used for premedication if oral is not acceptable, but the doses should be one-half the usual dose when given IV due to a potential increased sensitivity to these agents in MPS patients (Dr. Kakkis, personal observations). 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 H_2 blockers, stronger anti-histamines, or glucocorticoids may be considered.

7.4.3.2 Infusion Procedure

The amount of study drug (UX003) will be determined based on the most recent 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 for a final 2-3 fold drug dilution. 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. Refer to the Pharmacy Manual for complete instructions on calculating drug dosage and preparation.

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.

A second IV site on the opposite arm from the infusion will be used for the blood samples taken for PK analysis. 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. If the second IV fails and PK samples cannot be collected from the second IV, the main IV line may be use for the post-infusion sampling after flushing the line thoroughly with saline. The samples taken through the same line as the infusion should be noted on the CRF as being drawn from the same line.

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

7.4.4 Selection of Doses and Study Duration

The planned UX003 dose of 4 mg/kg is based on data from clinical studies in pediatric and adult MPS 7 patients, 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, providing a 5-fold safety factor.

The therapeutic ERT doses in prior successful programs for other MPS disorders (0.58, 0.5, 2 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 ~10-207 nM in the circulation. These enzyme levels are approximately 10- to 30-fold the uptake constants (1-7 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).

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.

Study Duration

The planned duration of treatment in this study is 48 weeks. Subjects successfully completing the first 48 weeks may continue for up to 240 weeks (5 years), or until one of the following occurs: the subject withdraws consent, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, or the study is terminated.

7.4.5 Method of Assigning Subjects to Treatment Groups

Eligible subjects will be enrolled in the study and sequentially assigned an identification number. All subjects will receive active treatment (UX003); there is only one treatment group in the study.

7.4.6 Blinding

The study drug will be administered open-label; no study participants will be blinded to study treatment.

7.4.7 Prior and Concomitant Therapy

7.4.7.1 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 Screening, 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.

7.4.7.2 Permitted Medications

Subjects may receive concomitant medications as required. Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to Screening will be reviewed and recorded at the Screening visit. At the Baseline visit, current medications will be 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.

7.4.8 Treatment Compliance

Study drug is not to be dispensed to subjects. Study drug 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

Informed consent must be obtained prior to any Screening procedures. The Baseline (Week 0) visit must take place within 30 days of the Screening visit. Screening assessments (physical exam and safety labs) performed within 7 days prior to the first dose of study drug may be used for Baseline assessments. Subjects will be treated only after all inclusion/exclusion criteria have been confirmed. Baseline assessments must be completed within 7 days prior to first dose of study drug, unless otherwise specified. Assessments scheduled on the same day as treatment must be performed prior to the infusion.

Subjects will return to the clinic at 2-week intervals (± 3 days) throughout the 48-week Treatment Period for study drug infusion and basic safety measures. Major assessment visits (Weeks 12, 24, 36, and 48) are scheduled at 12-week intervals (± 7 days).
All assessments scheduled for a treatment day must be completed prior to the infusion on that day. For subjects who discontinue prior to completing the study, every reasonable effort should be made to perform the Early Termination visit procedures within 2 weeks of administration of last dose of study drug.

Following completion of the 48-week Treatment Period, subjects may participate in the Continuation Period for up to 240 weeks. Subjects will return to the clinic for UX003 administration every 2 weeks; additional assessments will be conducted at 12, 24 or 48-week intervals (± 7 days).

7.5.1 Schedule of Events

The parameters to be assessed in Study UX003-CL203, along with timing of assessments, are provided in the Schedule of Events (Table 2.1 and Table 2.2). Refer to the Study Reference Manual for additional details on specific assessments. For any given study visit, if the maximum amount of blood has been taken based on Maximum Allowable Blood Volume Guidelines for any subject, some assessments are not required; see the Lab Manual for details on prioritizing blood draws.

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 240 weeks, the end of trial is defined as the Week 240 visit of the last subject. In the event the study is terminated by the Sponsor prior to Week 240, 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.

7.5.2 Efficacy Measures

The primary efficacy variable in this study, uGAG excretion, will provide a biochemical measure of the biological action of UX003. The primary efficacy measure will be supported by multiple secondary and tertiary variables to provide an assessment of UX003 efficacy in MPS 7 patients less than 5 years of age.

7.5.2.1 Primary Efficacy Measure: Urinary GAG Excretion

Clinical evidence for the use of uGAG as a relevant primary endpoint is based on nonclinical research work over 20 years, clinical disease survey studies, and Phase 3 controlled studies in MPS 1, 2 and 6 patients using other ERTs. The results 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. The overall summary of 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 the time points listed in the schedule of events (Table 2.1). Urine samples will be collected once during Screening Period and on two separate days during the Baseline Period (Week 0). Urine samples must be collected from first morning voids to assure the urine is adequately concentrated. Samples will be evaluated for uGAG concentration and normalized to urinary creatinine concentration. Refer to the Laboratory Manual for details on sample collection and processing requirements.

7.5.2.2 Secondary Efficacy Measures

7.5.2.2.1 Growth

Growth will be assessed as a secondary efficacy measure to assess changes in growth velocity and comparisons to normative data matched for age and gender. Anthropometric measurements include standing height (recumbent length or sitting height as appropriate), head circumference, and weight, and will be obtained at twelve-week intervals beginning at the Baseline visit (Week 0). Every effort should be made to collect standing height. If unable to collect standing height, sitting height or length should be collected for that subject.

Growth velocity will be calculated and compared with pre-treatment growth velocity when available. Anthropometric measurements may also be compared to normative reference data matched for age and gender. Refer to the Study Reference Manual for additional details on anthropometric measurements.

7.5.2.2.2 Hepatosplenomegaly

The volume of the liver and spleen will be determined using ultrasound and compared with normal values for age and gender if available; ascites will also be assessed. Ultrasounds will be conducted at the Baseline (Week 0) and Week 12, 24, and 48 (or Early Termination) study visits. During the Continuation Period, an ultrasound of the liver and spleen will be performed annually (every 48 weeks). If an ultrasound cannot be performed, liver and spleen size may be assessed qualitatively by physical exam. Ultrasound will not be performed at the ET visit if the assessment was conducted within 1 month of termination.

7.5.2.3 Tertiary Efficacy Measures

The following tertiary efficacy variables will also be evaluated in the study. Refer to the Study Reference Manual for additional details.

7.5.2.3.1 Serum and Supplementary Urinary GAG Measures

Abnormal (pathologic) GAG in the serum will be assessed. One serum sample should be collected prior to dosing at the Baseline, Weeks 12, 24, 36, and 48 visits during the Treatment Period. . Supplementary assays for uGAG may be performed; samples will be collected as described in Section 7.5.2.1.

7.5.2.3.2 Clinical Global Impression Scale

The Clinical Global Impression (CGI) scale was developed for use in National Institute of Mental Health-sponsored clinical trials to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication (Guy 1976). The CGI provides an overall clinician-determined summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. The Sponsor has developed an MPS disease-specific and age-appropriate version of the CGI (also referred to as the Physician Global Impression of Change [PGI-C] in some studies) to be used in this study.

Physicians caring for each subject will provide a global assessment of change using a seven point scale ranging from -3 (severe worsening) to +3 (significant improvement). The CGI score will be supported by reported changes relative to baseline or identification of a new finding based on a list of disease-specific abnormalities projected to respond to treatment. The CGI will be evaluated at the Baseline (Week 0) visit and at 12-week intervals throughout the Treatment Period and Continuation Period.

7.5.2.3.3 Functional Development

Functional Development will be assessed by the Bayley Scales of Infant and Toddler Development – Third Edition (Bayley-III). The instrument will be administered at Baseline (Week 0), and at the Week 24 and 48 (or Early Termination) study visits. During the

Continuation Period, the Bayley-III will be completed at 48-week intervals. Bayley-III will not be performed at the ET visit if the assessment was conducted within 1 month of termination.

The Bayley-III (Bayley 2006) is a standard series of measurements developed to assess the motor (fine and gross), language (receptive and expressive), and cognitive development of infants and toddlers, aged 1 month - 42 months. This measure consists of a series of developmental play tasks and takes between 45 - 60 minutes to administer. The total raw score will be converted into a scaled score and a composite score with percentile rank to compare performance to healthy same-age peers. Unless a child has achieved the highest raw score on the test, the Bayley-III assessments will continue throughout the study to monitor the progress of a child. Additionally, if valid and reliable administration of the instrument is not possible based on the clinical judgment of the Investigator, e.g. language difficulties or clinical condition of the subject, testing may be omitted at that visit.

7.5.2.3.4 Motor Functioning

A gross motor milestone checklist, developed for use in this trial, will assess gross motor functioning and development. The checklist was designed to allow for assessment of the functional status of the subject requiring limited language interaction and physical handling. See Study Reference Manual for details.

The checklist will be assessed at Baseline (Week 0), and at the Week 24 and 48 (or Early Termination) study visits. During the Continuation Period, the gross motor milestone checklist will be completed at 48-week intervals. The checklist will not be completed at the ET visit if conducted within 1 month of termination.

7.5.2.3.5 Cardiac Ventricular Mass

Ventricular mass will be assessed by echocardiogram (ECHO) and scored as a z-score relative to normal ventricular mass. Valvular and cardiac function may also be evaluated. An ECHO performed within three months prior to the Baseline visit may be used for the study baseline ECHO provided cardiac ventricular mass can be calculated. ECHO will be performed at the Baseline (Week 0) and Week 48 (or Early Termination) study visits. During the Continuation Period, ECHO will be assessed annually (every 48 weeks).

7.5.2.3.6 Pulmonary Function Testing

In young patients, traditional pulmonary function testing (i.e. spirometry) is difficult to perform, but measuring pulse oximetry can help assess basic problems in adequate respiration in the youngest patients Resting O_2 saturation will be assessed as a measure of pulmonary function while the subject is breathing room air during the Baseline (Week 0) and Weeks 12, 24, 36, and 48 (or Early Termination) visits. If the subject requires respiratory support, the type and duration should also be noted on the CRF. Pulse oximetry will be assessed every 12 weeks during the Continuation Period.

7.5.2.3.7 Biochemical Markers of Bone Turnover

Biochemical markers of bone turnover (BTMs) will be evaluated as an indicator of changes in bone metabolism in response to UX003 treatment. BTMs in serum include procollagen type 1 N-propeptide (P1NP), carboxy-terminal cross-linked telopeptide of type I collagen (CTX-I), bone specific alkaline phosphatase (BALP) and vitamin D. Serum samples will be collected at the Baseline (Week 0) and Week 2, 8, 16, 24, 32, 40 and 48 visits (or Early Termination). Bone turnover markers will be assessed at 24-week intervals during the Continuation Period.

7.5.3 Drug Concentration Measurements

The concentration of rhGUS in the blood will be measured to characterize the PK of UX003 following a single dose and multiple doses. Blood samples for PK analysis will be obtained at Weeks 0 (Baseline), 24, and 48. PK samples will be collected prior to the infusion (pre-dose), 60 minutes after start of infusion, at the end of the infusion, 30-120 minutes post infusion and 4-6 hours post infusion.

Samples may be obtained by separate venipunctures, indwelling catheters, peripherally inserted central catheter (PICC) line or by combinations of these or other suitable methods. The indwelling or PICC line should be managed as prescribed by the clinic procedures. Collection and processing instructions can be found in Laboratory Manual. The same IV line post-infusion end, may be used if the primary line fails, but extensive saline flushing of the line should occur before drawing PK.

7.5.4 Safety Measures & General Assessments

General assessments include medical history, demographics and weight for study drug preparation (Section 7.4.3.2). 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. To assess the immune response to UX003, the development of IgG antibodies to rhGUS will be evaluated as indicated in the Schedule of Events. Complement C3, C4, and CH50 levels will also be evaluated if a drug-related hypersensitivity reaction is suspected. Refer to the Study Reference Manual for additional details.

To further characterize the disease manifestations, severity and progression of MPS 7, the sponsor aims to determine the specific genetic mutation in each patient enrolled if consent is provided for such testing. This optional assessment can be performed at week 16 or at different time-point if total blood volume at week 16 may exceed maximum allowable volume.

7.5.4.1 Medical History

A complete medical history will be obtained at the Screening visit. At the Baseline visit, any changes in medical history since Screening will be recorded. 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 and weight will be collected. Pretreatment measurements of height and weight should be collected from the records if possible to assure a pre and post treatment growth rate can be assessed. MPS7 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.

7.5.4.2 Weight

During the initial 48-week Treatment Period, weight will be obtained at each visit to determine appropriate study drug volume for the subsequent visit, and for safety (refer to Pharmacy Manual for instructions on calculating drug dosage). During the Continuation Period, weight will be obtained at 12-week intervals (in conjunction with anthropometric measurements). Weight will be measured in kilograms using a scale.

7.5.4.3 Physical Examination

Complete physical examinations will be performed at the Screening, Baseline, Week 12, 24, 36, and 48 study visits (or Early Termination Visit). During the Continuation Period, physical examinations will be conducted at 12-week intervals. Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, neurological, and musculoskeletal systems. If the subject exhibits signs or symptoms of weakness or other new neurological findings, evaluate for cord compression (e.g. reflexes and motor strength).

7.5.4.4 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 is administered, vital signs will be measured as outlined below.

Week 0 (Baseline) to Week 12, vital signs will be obtained:

- 15 minutes prior to infusion
- Every 15 minutes during the infusion
- Immediately post-infusion

- 15, 30, and 60 minutes post-infusion

Additional measurements should be obtained as appropriate.

Week 14 to Week 240, vital signs will be obtained:

- 15 minutes prior to infusion
- Every 60 minutes for the remainder of the infusion
- Immediately post-infusion
- 60 minutes post infusion

Additional measurements should be obtained as appropriate.

7.5.4.5 Clinical Laboratory Tests for Safety

The clinical laboratory evaluations to be performed in this study are listed in Table 7.5.4.5.1. Clinical laboratory testing for serum chemistry, hematology, and urinalysis will be performed at the Screening, Baseline (Week 0), Week 2, 4, and 8 visits. After Week 8, clinical laboratory evaluations will be performed every 8 weeks until Week 48 (or Early Termination visit). During the Continuation Period, clinical laboratory testing will be performed at 24-week intervals as indicated in the Schedule of Events (Table 2.1). Blood and urine samples will be collected prior to administration of study drug; fasting is not required. See Section 7.4.3.1 for infusion related fasting and refer to the Laboratory Manual for additional details.

Table 7.5.4.5.1: Clinical Laboratory Assessments for Safety

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.

7.5.4.6 Antibodies to rhGUS

Prior Phase 3 studies in ERT for MPS have shown that anti-IgG 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 IgG antibodies directed against rhGUS will take place at Baseline (Week 0) and the Week 8, 16, 24, 32, 40, and 48 (or Early Termination) visits. During the Continuation Period, anti-drug antibody screening will occur at 12-week intervals. Serum samples for antibodies must be collected before infusion of study drug. 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 if warranted.

7.5.4.7 Concomitant Medications

Concomitant medications will be reviewed and recorded in the subject's CRF at each study visit, beginning at the Screening visit. Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to Screening will be reviewed and recorded. At each subsequent visit, change in medications since the previous visit will be recorded. A discussion of prohibited and permitted medications is provided in Section 7.4.7.

7.5.4.8 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.

7.5.4.9 Adverse Events

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, weight, vital signs, and clinical laboratory parameters, will be recorded as AEs or SAEs, if appropriate.

7.5.5 Appropriateness of Measures

The primary efficacy variable in this study, uGAG, is a measure of the underlying biochemical defect in MPS 7 patients. 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. In a multinational study of Laronidase in MPS I patients younger than 5 years, clinical responses in liver size and left ventricular hypertrophy were observed (Wraith et al. 2007). Pulse oximetry will be conducted to assess respiratory compromise, an important component of disease progression and mortality in MPS 7 subjects. ECHO, ultrasound, 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 Bayley-III is useful for assessing the compounded impact of multisystem clinical manifestations on the cognitive, motor, and adaptive behavioral development of infants and toddlers. In MPS 7, development in these domains is likely to be affected by the co-morbidities present in these subjects (McDonald et al. 2010). The Bayley-III may not be reliably administered.to all subjects, therefore a motor milestone checklist is also included as an assessment of gross motor functioning and development. The checklist developed for this trial requires limited language interaction or physical handling and allows for a gross motor assessment across all subjects.

Assessments of serum markers of bone formation and bone resorption were included to measure the biochemical markers of bone turnover, which may enable evaluation of the effects of UX003 on skeletal tissue.

Measurements of UX003 drug concentration in blood samples will provide information on relevant PK parameters following a single-dose and at steady-state. Where possible, timing of assessments has been coordinated with standard safety laboratory tests to minimize risk and discomfort and avoid unnecessary sampling.

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 IgG antibody levels and complement C3, C4 and CH50 levels (as indicated) will be determined as a measure of UX003 immunogenicity. Since the study population is comprised of pediatric subjects, age-appropriate safety and efficacy measures have been incorporated into the study design.

7.6 Statistical Methods and Determination of Sample Size

The completeness of the data affects the integrity and accuracy of the final study analysis. Therefore, every effort will be made to ensure complete, accurate and timely data collection, and to avoid missing data. Detailed procedures for handling missing, unused, or spurious data, along with the detailed method for analyses will be presented in the Statistical Analysis Plan (SAP); the information below is intended as a guide to planned analyses.

The statistical analyses will be reported using summary tables, figures, and data listings. All raw data obtained from the CRFs as well as any derived data will be included in data listings. All analyses and tabulations will be performed using SAS®. Descriptive statistics will be used to summarize the data. For continuous variables, the mean, standard error, median, minimum, and maximum will be provided. For categorical variables, the frequency and percent distributions will be provided. Statistical tests will be two-sided at the alpha =0.05 significance level. Two-sided 95% confidence intervals will also be presented when appropriate. The statistical method employed for the analysis of each assessment will be defined in more detail in the SAP.

7.6.1 Determination of Sample Size

Approximately 15 subjects will be enrolled including approximately 5 subjects with hydrops fetalis. Subjects under the age of 5 years at the time of informed consent with a confirmed diagnosis of MPS 7 will be enrolled. Additional subjects previously treated with UX003 under an emergency IND or similar process may also be enrolled at the discretion of the Sponsor. Due to the extremely low prevalence of the disease, the sample size is primarily based on the ability to find qualifying patients.

7.6.2 Subject Information

Subject disposition summaries will include the number of subjects, the number of subjects receiving study medication, the number of subjects completing the study, and the reasons for discontinuation. Demographic variables include age, sex, and race.

7.6.3 Populations Analyzed

The full analysis set will consist of all enrolled subjects who receive at least 1 dose of UX003 during the study.

7.6.4 Primary Efficacy Endpoint

The study is a small open label study to obtain some clinical efficacy data from a small cohort of these ultra-rare patients. A complete hypothesis testing statistical approach is not plausible in this setting, but a reasonable approach to assessing for the biologic efficacy of UX003 will be made.

The primary efficacy analysis will evaluate the mean percent change in uGAG excretion from Week 0 (Baseline) to Week 48 using the generalized estimating equation (GEE) analysis method. For subject(s) previously treated with UX003 under an emergency IND, percent change from initial baseline (prior to first dose of UX003) will be used, if the initial baseline data are available. The null hypothesis of no change in mean uGAG excretion will be tested. An additional analysis will also be performed on the Week 24 time point.

7.6.5 Secondary and Tertiary Endpoints and Analyses

Secondary analysis on growth and hepatosplenomegaly will be evaluated to compare pretreatment with post treatment effects. Growth rate will be compared to historical data obtained from medical history and records (if available), and also compared to published normative data for age and gender. Changes in findings from Baseline for other efficacy variables will be tabulated for each subject. Comparisons of certain efficacy variables with published normative data based on age and gender may also be conducted.

7.6.6 Pharmacokinetic Analyses

The following PK parameters will be calculated from the plasma concentrations of rhGUS measured in these blood samples:

- Area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$)
- AUC from time zero to the time of last measurable concentration ($AUC_{0\text{-last}}$)
- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (T_{max})
- Elimination half-life ($t_{1/2}$)
- Total clearance of drug after IV administration (CL)
- Apparent volume of distribution based upon the terminal phase (Vd_z)
- Apparent volume of distribution at steady-state (Vd_{ss})

7.6.7 Safety Analyses

The primary safety analysis will evaluate the safety of UX003 as measured by the incidence, frequency and severity of AEs and SAEs, including clinically significant changes from study baseline to scheduled time points in:

- Vital signs and weight
- Physical examination findings
- Clinical laboratory evaluations

- Concomitant medications
- IgG antibodies to rhGUS
- Complement C3, C4 and CH50 levels (as indicated)

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), relationship to study drug, and severity. No statistical significance will be assessed. 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 after study drug administration will be presented for each clinical laboratory measurement. For each clinical laboratory measurement, descriptive statistics will be provided for study baseline and all subsequent visits. Changes from study baseline to the post-treatment visits will also be provided. Descriptive statistics of vital signs, imaging assessments for safety, and concomitant medications will be provided in a similar manner.

Changes in findings from study baseline physical examinations will be tabulated and listed for each subject by examination category. If there are examination findings that change in more than one subject, these will be tabulated in a separate table and expressed as the number of subjects with the change out of the total.

Anti-drug antibody data will be tabulated over the course of the study. The number of subjects converting to a positive antibody assay value by increasing titer by five-fold over study baseline or more and the time of onset of a positive antibody response will be determined. Descriptive statistics on the titers achieved and the time of onset of the response will be provided (mean, standard deviation, median, range). 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.

7.6.8 Analyses

Analyses may be performed at any time during the study at the discretion of the Sponsor. There is no unblinding during these analyses since it is an open-label study.

8 STUDY CONDUCT

8.1 Ethics

8.1.1 Institutional Review Board or Ethics Committee

The IRB/EC must be a properly constituted board or committee operating in accordance with 21 CFR Part 56, "Institutional Review Boards", International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) requirements, and applicable laws and local regulations. This protocol, any protocol amendments, and the associated informed consent forms (ICFs) must be submitted to the IRB/EC for review and must be approved before screening of any subject into the study. Study drug 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 Association General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The Investigator will make every effort to assure 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 study drug, as described in this protocol and the IB, 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 study drug 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.

The date 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. The monitor will verify the Investigator's ongoing qualifications, inspect clinical site facilities, and 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.

8.3 Investigational Product Accountability

While at the clinical site, study drug must be stored in a secure limited access location at controlled temperature as described in the IB 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 study drug 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 study drug

must be returned to Ultragenyx and/or its designee unless other instructions have been provided for final disposition of the study drug.

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/EMA 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 progress notes, laboratory test reports and other subject records. Instances of missing or uninterruptable 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 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 two years after the last approval of a marketing application or for at least two 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 and will assist with retention should the Investigator/institution be unable to continue maintenance of subject files for the full 25 years. 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 and will assist with retention 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 AE
- 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 patient 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 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 to Ultragenyx or its designee within 24 hours of knowledge.

8.5.5 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), 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. 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 designee within 24 hours. Ultragenyx or its designee will inform Regulatory Authorities, 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 ECs, as per local laws and regulations.

8.5.6 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.

8.5.7 Safety Contact Information

Drug Safety	Medical Monitor
PPD	Christine Haller, M.D. Telephone: PPD Mobile: PPD e-mail: PPD

8.6 Financing and Insurance

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

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.

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10 SIGNATURE PAGE

Protocol Title: An Open-label Study of UX003 rhGUS Enzyme Replacement Therapy in MPS 7 Patients Less than 5 Years Old

Protocol Number: UX003-CL203

I have read Protocol UX003-CL203. 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 the Investigator is informed of all relevant information that becomes available during the conduct of this study.

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