ultragenyx pharmaceutical

Approval Form for Statistical Analysis Plan

Protocol Number: UX003-CL202

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

Status: v1.0

PPD

ultragenyx pharmaceutical

Approval Form for Statistical Analysis Plan

Protocol Number: UX003-CL202

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

Status: v1.0

Senior Management Review:

PPD

PPD

STATISTICAL ANALYSIS PLAN

Title	A Long-Term Open-Label Treatment and Extension Study of UX003 rhGUS Enzyme Replacement Therapy in Subjects with MPS 7
Protocol:	UX003-CL202
Investigational Product:	UX003, recombinant human beta-glucuronidase (rhGUS)
Phase:	3
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA, USA 94949
Author:	PPD Associate Director, Biostatistics
Date:	08 Mar 2016
Version Number:	1.0

Table of Contents

LIST OF TABLES

ABBREVIATIONS

2MWT	Two Minute Walk Test
3MSCT	Three Minute Stair Climb Test
6MWT	Six Minute Walk Test
ADA	anti-drug antibody
AE	adverse event
APRG	Adverse Physiology Related Group
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency
CGI	Clinicians's Global Impression
CHAQ	Childhood Health Assessment Questionnaire
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECHO	echocardiogram
ERT	Enzyme Replacement Therapy
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GAG	glycosaminoglycan
GEE	Generalized Estimating Equation
HAQ	Health Assessment Questionnaire
ICR	Individualized Clinical Response
IV	intravenous
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
MPS 7	mucopolysaccharidosis type 7, Sly Syndrome
MVV_1	maximum voluntary ventilation in one minute
PK	Pharmacokinetic
rhGUS	Recombinant Human Beta-Glucuronidase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	system organ class

TEAE	treatment emergent adverse event
uGAG	urinary glycosaminoglycan
WHODRUG	World Health Organization Drug

1 INTRODUCTION

The purpose of this statistical analysis plan is to provide details of the statistical analyses that have been outlined within the original UX003-CL202 Protocol dated 28 October 2014 through Protocol Amendment version 1.0 dated 18 December 2015. The data collected in this study will evaluate the long-term safety and efficacy of UX003 treatment in subjects with Mucopolysaccharidoses type 7 (MPS 7). This SAP does not describe any Pharmacokinetic (PK) data analyses.

2 STUDY OBJECTIVES

2.1 Primary

The primary objective is to evaluate the long-term safety of UX003 in subjects with MPS 7.

2.2 Secondary

The secondary objective is to evaluate the long-term efficacy of UX003 in reducing urinary glycosaminoglycans (uGAG) in subjects with MPS 7.

2.3 Other

Other objectives are to evaluate:

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

3 STUDY DESIGN

As background for the statistical methods presented below, this section provides an overview of the study design. This overview is a summary only. The protocol is the definitive reference for all matters discussed in what follows.

3.1 Overall Study Design and Plan

UX003-CL202 is a multi-center, multi-national, open-label treatment and extension study in subjects with MPS 7. The study will assess long-term safety and efficacy of UX003 treatment and will continue for approximately 144 weeks, or until the study drug is commercially available in the subject's local territory, or until one of the following occurs: the subject withdraws consent and discontinues from the study, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, or the study is terminated.

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

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

3.2 Study Duration

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

The schedule of events is shown in Appendix 1.

3.3 Determination of Sample Size

Up to 20 subjects with a confirmed diagnosis of MPS 7, who were previously treated with UX003 in either an Ultragenyx-sponsored study (rollover subjects) or a non-Ultragenyx sponsored study (IST subjects) as well as UX003 treatment-naïve subjects will be enrolled into this study. Hence, there is not a formal sample size calculation and justification.

3.4 Interim Analysis

After the first 8 rollover subjects from 301 complete the Week 12 assessment, an analysis will be conducted to support filing.

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

3.5 Data Monitoring Committee

Safety in this open-label study will be monitored by Ultragenyx. An independent data monitoring committee will not be used.

3.6 Randomization and Blinding

All subjects received UX003 on an open-label basis. Randomization, blinding and stratification factors are not needed for this study design.

4 STUDY CLINICAL OUTCOMES

4.1 Safety Assessments

Safety will be evaluated by the incidence, frequency and severity of AEs and serious adverse events (SAEs), including clinically significant changes from study baseline to scheduled time points in vital signs, weight, physical examination, clinical laboratory evaluations, and concomitant medications.

APRG safety reporting is a novel method that captures symptoms and their timing, allowing the diagnostic synthesis of infusion related events into one of several multi-domain physiology related groups to capture infusion-associated reaction (IAR) information. APRG reporting has been incorporated into the study design to detect adverse physiologies that might be expressed variably within and between subjects in a study.

To assess the immune response to UX003, the development of IgG antibodies to rhGUS, and complement C3, C4, and CH50 levels only be drawn if an IAR occurs will also be evaluated as indicated. Pregnancy testing (or pregnancy of partner, if needed) will also be conducted.

4.2 Efficacy Variables

- Urinary GAG Excretion: First morning void urine will be evaluated for uGAG concentration
- Biomarkers of inflammation in serum: Blood samples will be collected to evaluate levels of biomarkers of inflammation and response to treatment.
- Six Minute Walk Test (6MWT): The total distance walked (meters) in a six minute period
- Bruininks-Oseretsky Test of Motor Proficiency (BOT-2): This test of motor proficiency will be administered to evaluate treatment-related changes in four domains assessing both fine and gross motor function: fine motor precision, manual dexterity, balance, running speed and agility. The test may be modified and tests omitted to accommodate the needs of the subject.
- Three Minute Stair Climb Test (3MSCT): The number of stairs climbed within a three minute period.
- Pulmonary function testing: Spirometry will be administered to subjects who do not require invasive ventilatory support or have a tracheostomy. Pulmonary function variables include forced vital capacity (FVC) and maximum voluntary ventilation (MVV).
- Shoulder flexion maximum range of motion: Goniometry will be used to measure (in degrees) the maximum passive shoulder range of motion in both flexion and extension.

- Growth (anthropometric): Growth will be assessed by anthropometric measurements including standing height (or recumbent length or sitting height if applicable) and weight.
- Visual acuity: will be measured using a standard eye chart and recorded for each eye independently.
- Multi-domain Responder Analysis (MDRI): The multi-domain responder analysis will consider the scoring as described in Section 5.3.
- Individualized Clinical Response (ICR): Will only be assessed for subjects previously enrolling from the Ultragenyx-sponsored MPS 7 Phase 3 clinical study UX003-CL301 where an outcome of interest was previously selected from the possible clinical outcome measures, the same ICR identified in the feeder study may continue to be followed in this study.
- Scoring of Impactful Clinical Problems: The three most impactful clinical problems as reported by the subject/parent/caregiver during the Clinical Problem Evaluation will be scored on a Likert scale. For UX003 treatment-naïve subjects, the initial Clinical Problem Evaluation will occur at the Baseline visit. For subjects enrolling from the Ultragenyx-sponsored MPS 7 Phase 3 clinical study UX003-CL301, the Clinical Problems identified during the UX003-CL301 Randomization visit will continue to be scored throughout this study.
- Subject-reported disability, health related quality of life, and fatigue: The MPS Health Assessment Questionnaire, Childhood Health Assessment Questionnaire (CHAQ), or Health Assessment Questionnaire (HAQ) will be administered to evaluate treatment-related changes in self-care and mobility activities of daily living. The age-appropriate Pediatric Quality of Life Multidimensional Fatigue Scale (Peds QL-Multidimensional Fatigue Scale) will be administered to evaluate treatment-related changes in fatigue.
- Subject/Parent/Caregiver Clinical Global Impression (CGI) scales: Subjects or parents/caregivers will provide a global assessment of change using a CGI scale. In addition, subjects or parents/caregivers will provide narratives of their perception of how treatment has impacted the subject's ability to complete activities of daily living.
- Hepatosplenomegaly: Liver and spleen measurements will be assessed by physical exam.
- Cardiac ventricular mass/function: Ventricular mass will be assessed by echocardiogram (ECHO) and scored as a z-score relative to normal ventricular mass.

5 DEFINITIONS

5.1 Baseline

Naïve subjects:

- uGAG baseline is defined as the average of all assessments prior to or on the date of the first dose of UX003 in this study. Baseline value for other endpoints is the last non-missing assessment prior to or on the date of the first dose of UX003 in this study.

IST subjects:

- uGAG baseline is the average of all assessments prior to or on the date of the initiation of the initial treatment with UX003.
- Baseline value for other endpoints is the last non-missing assessment prior to or on the date of first dose of UX003 in this study.

Rollover subjects:

- The baseline (efficacy and safety) defined in feeder study will be used for this study.

5.2 Fold increase in uGAG above upper normal limit

The fold increase in uGAG above upper limit of normal is the ratio of the uGAG value over the uGAG upper limit of normal. If the ratio is less than 1, then it is set 1.

5.3 Multidomain responder index

The multidomain responder score will be calculated as the total score across the following six domains (6MWT, $FVC_{\%pred}$, Shoulder flexion, Visual acuity, and BOT-2 fine motor and BOT-2 gross motor) (Table 5.3.1).

Table 5.3.1: Definition of the Minimal Important Difference for multi-domain responder analysis

Domain	Minimal important difference (MID)	References
6MWT	23 meter AND 10% change from baseline	(Redelmeier et al. 1997), (Puhan et al. 2008), (du Bois et al. 2011), (Mathai et al. 2012), (Wraith et al. 2004), (Clarke et al. 2009), (Muenzer et al. 2006), (Harmatz et al. 2006), (BioMarin 2013)
$FVC_{\%pred}$	5% absolute change or 10% relative change from baseline in $FVC_{\%pred}$	(Wraith et al. 2004), (Muenzer et al. 2006), (BioMarin 2013)
Shoulder flexion	20 degree change of passive shoulder range of motion	(Wraith et al. 2004), (Harmatz et al. 2006), (Clarke et al. 2009), (Okuyama et al. 2010)

Domain	Minimal important difference (MID)	References
Visual acuity	3 lines (corrected, both eyes)	(Arch-Ophthalmol 1999); (Ferris et al. 1982), (Reeves et al. 1993)
BOT-2 fine motor	Fine Motor Precision: change of 0.72 Manual Dexterity: change of 1.47	(Wuang et al. 2009)
BOT-2 gross motor	Balance: 0.57 Running speed and agility:0.59	(Wuang et al. 2009)

To compute the multi-domain responder index, changes over time in each domain variable will be scored and classified as follows. In general, if the change is equal or greater than one minimal clinically important difference (MID), the score of +1 is provided. If changed negatively by one MID or greater, the score is -1. If there is no clinically significant change (>-1.0 to <1.0 MID), the score is 0. Furthermore:

- For 6MWT distance, the score +1 will be assigned when there is an increase of 23 meters or more AND a greater than 10% increase from baseline are observed, while the score -1 will be assigned when there is a decrease of 23 meters or more and a decrease of 10% or more from baseline are observed. Otherwise the score for this domain is 0.
- For $FVC_{\%pred}$, the score +1 will be assigned when a 5% absolute increase or 10% relative increase from baseline, while the score -1 will be assigned when a 5% absolute decrease or 10% relative decrease from baseline. Otherwise the score for this domain is 0.
- For visual acuity, the score +1 will be assigned when both eyes, corrected, have 3 lines or more improvement in visual acuity scales, while the score -1 will be assigned when both eyes, corrected, declined 3 lines or more in visual acuity scales. Otherwise the score for this domain is 0. One line of improvement is defined as -0.10 of change in LogMAR scale.
- For shoulder flexion domain where there are two tests to evaluate MID: the score +1 will be assigned when at least one side (left or right) range of motion improves at least one MID or more where the other side does not decline for more than one MID. The score -1 will be assigned when both shoulder range of motion decline for more than one MID. Otherwise the score will be set as 0.
- For BOT-2 fine motor and gross motor domains where there are two tests to evaluate MID: the score +1 will be assigned when at least one test improves at least one MID or more where the other test does not decline for more than one MID. The score -1 will be assigned when both tests decline for more than one MID. Otherwise the score will be set as 0. The scaled score from BOT-2 is used to evaluate MID.

The integration of benefit will occur by summing the responses, positive, negative or zero, across all domain variables to derive the subject-specific multi-domain responder index.

If a subject is unable to reliably or safely perform a particular assessment at a visit, that domain will be scored as 0 for that visit.

5.4 Fatigue MID score

The MID score +1 will be assigned if ≥10 points increase from baseline in fatigue total score. The MID score -1 will be assigned if ≥10 points reduction from baseline in fatigue total score. Otherwise the MID score is 0.

5.5 Growth Velocity

Growth will be assessed by anthropometric measurements of height. Z-scores and percentiles will be calculated using CDC growth chart (Kuczmarski, 2000), and for both historical (up to 2 years) and on study anthropometric measurements for males ≤18 years and females ≤15 at informed consent of this study.

Growth velocity will be assessed by a model-based approach. A linear regression model for each subject will be built for selected pre-treatment data and post-treatment data:

$$Y_t = \beta_0 + \beta_1 X_t + \varepsilon_i$$

Where Y_t is the standing height (cm) or Z score based on the standing height measured at Time t; X_t is the time when standing height is measured; β_0 is the intercept, $\beta_1$is the slope of the regression model; ε_i is random error term.

5.6 Percent predicted Six-Minute Walk Tests

To calculate the percent predicted 6MWT value, the following formulas will be applied (Geiger et al. 2007) for subjects aged <20 years old at informed consent of this study

$$For\ Males: X_i = \frac{X_{0i}}{196.72 + (39.81 * Age) - (1.36 * Age^2) + (132.28 * Height)} * 100$$

$$For\ Females: X_i = \frac{X_{0i}}{188.61 + (51.50 * Age) - (1.86 * Age^2) + (86.10 * Height)} * 100$$

Where:
X_i = The percent predicted 6MWT result at time i for subject X
X_{0i} = The 6MWT (m) result at time i for subject X

To calculate the percent predicted 6MWT value, the following formulas will be applied (Gibbons et al. 2001) for subjects aged ≥ 20 years old 15 at informed consent of this study:

$$X_i = \frac{X_{0i}}{868.8 - (2.99 * Age) + (74.7 * Women)} * 100$$

Where:
X_i = The percent predicted 6MWT result at time i for subject X
X_{0i} = The 6MWT (m) result at time i for subject X
The age and height measured at corresponding visit will be used to calculate percent predicted 6MWT value.

5.7 Anti-rhGUS Antibody Titer Values

Subject sera will be tested using a bridging anti-drug antibody (ADA) ELISA to screen for antibodies to rhGUS. Samples which are positive in the confirmation assay will then be tested in the titer assay giving a titer value, and also be tested with the neutralizing antibody assay (NAb).

5.8 Duration of exposure to UX003

Duration of exposure to UX003 in days in this is defined as: last date of UX003 infusion – first date of UX003 infusion in this study + 14 days.

6 ANALYSIS POPULATIONS

Full Analysis Set: consists of all enrolled subjects who receive at least one dose of investigational product in this study.

7 DATA SCREENING AND ACCEPTANCE

7.1 Handling of Missing and Incomplete Data

Missing clinical outcome data can occur for multiple reasons, including missed subject visits and scales or measures with missing item scores. Missing and incomplete data will be identified by Data Management through a review of tables and listings for this study and investigated for possible resolution prior to the study database lock.

In general, missing data will be treated as missing, unless otherwise specified. When a change from baseline is assessed, only subjects with a baseline and at least one post-baseline measurement will be included in the analysis.

Assessments performed on unscheduled/end of treatment visits can be mapped to scheduled visits (based on target days of the scheduled visits), if the scheduled visits are missing

7.2 Missing Date Imputation Rules

For scheduled visit, the visit number will be used for analyses and the missing date will not be imputed.

Missing Date of the Last Dose of Investigational Product

When the date of the last dose of investigational product is missing for a subject, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last visit date will be used as the last dose date.

Missing Medical History Related Dates (eg, diagnosis date) or Birth Date

- If only the day is missing, impute the day to first day of the month.
- If day and month are missing, impute to January
- If year is missing, then no imputation will be done, the date will be missing.

If the imputed medical history related date is earlier than birth date, then birth date will be used.

Missing Date Information for Adverse Events and Concomitant Medications

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications. Note that the imputed values outlined here may not always provide the most conservative date.

Missing Start Dates

- If the day is unknown, then:

    - If the month and year match the first dose of investigational product start date month and year in this study, then impute the day of the first dose date.
    - Otherwise, assign the first day of the month.
- If the month is unknown, then:
    - If the year matches the year of the first dose of investigational product date in this study, then impute the month and day of the first dose date in this study.
    - Otherwise, assign 'January'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value.

If the imputed start date is earlier than birth date, then birth date will be used.

Missing Stop Dates

- If the day is unknown, then assign the last day of the month.
- If the month is unknown, then assign 'December.'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the resulting end date is after the date of study completion / discontinuation, set the imputed end date as the date of study completion / discontinuation.

Missing Causal Relationship to Investigational Product for Adverse Events

If the causal relationship to the investigational product is missing for an AE that started on or after the date of the first dose of double-blind investigational product, a causality of yes will be assigned. The imputed values for causal relationship to investigational product will be used for the incidence summary; the values will be shown as missing in the data listings.

7.3 Visit Time Windows

Table 7.3.1 presents the visit window assigned for scheduled efficacy and safety assessments scheduled for every 12 weeks and the corresponding range of treatment days (window) during which an actual visit may occur.

Table 7.3.1: Visit Time Windows

Period	Visit	*Scheduled Visit Day*	*Window*
First 48-Week Treatment Period	Baseline	Day 1	Days ≤ 1
	Week 12	Day 85	Days [2, 127]
	Week 24	Day 169	Days [128, 211]
	Week 36	Day 253	Days [212, 295]
	Week 48	Day 337	For subjects entered into continuation period Days [296, start of continuation period-1] For subjects did not enter into continuation period Days ≥ 296
Treatment Weeks 50-240	Week 60	Day 421	Days [start of continuation period, 463]
	Every 12 Weeks	Day 84x[a]+421	[380+84x,463+84x]
	Week 144	Day 1009	Days ≥ 968

a x=1,2…6

Termination visit for subjects who didn't complete the study, and unscheduled visits will be mapped to the closest post baseline scheduled visits if the scheduled visits are missing. If there are more than one unscheduled/end of study visits mapped to the same window, the one closer to the target day will be used. If more than one visit has the equal distance to the target day then the later one will be used, if more than one visits on the same day, use the time or the sequence number to select the later record. For listings and shift tables, all data points will be included.

7.4 Software

SAS® software version 9.4 or higher will be used to perform most or all statistical analyses.

8 STATISTICAL METHODS OF ANALYSIS

8.1 General Principles

All analysis will be performed based on full analysis set, and summaries will be presented overall and for naïve, IST and rollover subjects separately. The statistical analyses will be reported using summary tables, figures, and data listings. Statistical tests will be 2-sided at the alpha =0.05 significance level. All p-values will be presented as nominal p-values. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentages of subjects in corresponding categories. All raw data obtained from the CRFs as well as any derived data will be included in data listings.

8.2 Subject Disposition

The subjects in the full analysis set will be summarized. The reasons for study discontinuation will be summarized.

8.3 Demographics and Other Baseline Characteristics

For rollover subjects, demographic parameters (e.g., age, sex, race and ethnicity) and other baseline characteristics (i.e., initial diagnosis, height and weight) measured at baseline of the feeder study will be used. For naïve subjects or IST subjects, demographic and other baseline characteristics measured at the baseline of this study will be used.

8.4 Medical History

Medical and MPS treatment history will be summarized. Medical and MPS treatment history for rollover subjects are recorded in the feeder study.

8.5 Prior and Concomitant Medications

The latest World Health Organization Drug (WHODRUG) dictionary will be used to classify prior and concomitant medications.

For rollover subjects, prior medication will be defined as any medication taken before the first dose in the feeder study. For naïve and IST subjects, prior medication will be defined as any medication taken prior to the first dose of the investigational product in this study.

Concomitant medication is defined as any medication taken during the study between the day of the first dose of the investigational product and the day of the last dose of the investigational product in this study.

The number and proportion of subjects receiving each reported prior and concomitant medication will be summarized by Anatomical Therapeutic Chemical (ATC) code and preferred term. Multiple uses by a subject of the same drug will be counted only once in the summary tables.

8.6 Dosing Summary

The number of infusions and cumulative dose and duration of exposure to UX003 per subject in this study will be summarized. Treatment compliance will be displayed.

8.7 Efficacy Analyses

Because the primary objective of this study is to evaluate the long-term safety, the efficacy parameters will not be grouped into primary or secondary categories.

The percent change in uGAG excretion will be analyzed using the generalized estimating equation (GEE) method. Model will include baseline a covariate and visit (in this study) as a factor. The covariance structure within subjects will be assumed to be exchangeable.

Descriptive statistics will be presented by assessment time point for observed and change from baseline for the following other efficacy parameters.

- Biomarkers of inflammation in serum
- 6MWT and the percent predicted 6MWT value
- BOT-2
- 3MSCT
- Pulmonary function testing (eg., FVC, FEV and MVV1)
- Shoulder range of motion (goniometry) in extension and flexion by shoulder and the average of the right and left shoulders.
- Visual acuity
- Fatigue
- MPS HAQ
- CHAQ
- HAQ
- Scoring of impactful clinical problems
- Cardiac ventricular mass

Descriptive statistics will be presented by assessment time point for the following other efficacy parameters.

- MDRI
- Fatigue MID
- Subject/Parent/Caregiver CGI scales
- Hepatosplenomegaly

For growth, anthropometric measurements with z scores and percentiles will be summarized by historical time point and on study visit. For naïve subjects, the slopes of growth velocities will be summarized for pre (historical up to 2 years and baseline data) and post (baseline and post treatment data) treatment periods. For IST subjects, the growth velocities will be calculated for pre-initial UX003 treatment (up to 2 years) and post-initial UX003 treatment. For rollover subjects, the growth velocities will be calculated for pre first treatment in the feeder study (up to 2 years) and post first treatment in the feeder study.

For ICR, whether a positive change, according to the MID criteria, has occurred in the pre-specified ICR will be assessed. The percentage of subjects achieving an ICR MID will be calculated for the rollover subjects and presented by assessment time point.

8.8 Safety Analyses

8.8.1 Adverse Events

The latest Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs to a system organ class (SOC) and preferred term.

An AE (classified by preferred term) will be considered a treatment emergent adverse event (TEAE) if it occurred on or after the first dose in this study, and was not present prior to the first dose in this study, or it was present at the first dose in this study but increased in severity during the study.

Subject incidence of TEAEs will be tabulated by SOC and preferred term. Serious adverse events (SAEs), treatment-related TEAEs and treatment-related SAEs will also be summarized.

Detailed listings for all AEs, SAEs, treatment related TEAEs, treatment related SAEs, AEs leading to the discontinuation, and death will also be generated. The severity will be based on Common Terminology Criteria for Adverse Events (CTCAE). If an AE cannot be graded based on CTCAE, the investigator will assign a severity based on 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = Death related to AE.

Patterns of Infusion Associated Reactions (IARs) will be specifically evaluated throughout the study. IARs will be characterized into 4 distinct types based on timing of onset relative to the infusion and specific clinical manifestations: anaphylactoid, anaphylaxis, urticarial (with or without angioedema), and immune complex. Safety reporting of individual AEs will be recorded in parallel. Detailed listings of IARs will be provided.

8.8.2 Laboratory Parameters

Clinical laboratory values (in SI units) and changes from baseline at each assessment time point will be summarized for laboratory parameters in hematology, chemistry and urinalysis. 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 by laboratory measurement.

8.8.3 Other Safety Parameters

Other data such as vital signs, physical examination findings, IgG antibodies to rhGUS and Complement C3, C4 and CH50 levels with IAR will be summarized as appropriate.

8.8.4 Antibodies

Listing of ADA titer levels and neutralizing antibody will be provided by subject and visit

9 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

There are no major changes to the analyses specified in the Protocol Amendment 1 (dated 18 December 2015)

10 REFERENCES

Arch-Ophthalmol. 1999. "Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials--TAP report. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group." *Arch Ophthalmol* 117 (10):1329-45.

BioMarin. 2013. "Vimizim (elosulfase alfa) for the treatment of Mucopolysaccharidosis Type IVA (Morquio A Syndrome)." *Briefing Document for the Endocrinologic and Metabolic Drugs Advisory Committee (19 November 2013)*.

Clarke, LA, Wraith, JE, Beck, M, Kolodny, EH, Pastores, GM, Muenzer, J, Rapoport, DM, Berger, KI, Sidman, M, Kakkis, ED, and Cox, GF. 2009. "Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I." *Pediatrics* 123 (1):229-40.

du Bois, RM, Weycker, D, Albera, C, Bradford, WZ, Costabel, U, Kartashov, A, Lancaster, L, Noble, PW, Sahn, SA, Szwarcberg, J, Thomeer, M, Valeyre, D, and King, TE, Jr. 2011. "Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference." *Am J Respir Crit Care Med* 183 (9):1231-7.

Ferris, FL, 3rd, Kassoff, A, Bresnick, GH, and Bailey, I. 1982. "New visual acuity charts for clinical research." *Am J Ophthalmol* 94 (1):91-6.

Geiger, R, Strasak, A, Treml, B, Gasser, K, Kleinsasser, A, Fischer, V, Geiger, H, Loeckinger, A, and Stein, JI. 2007. "Six-minute walk test in children and adolescents." *J Pediatr* 150 (4):395-9, 399.

Gibbons, WJ, Fruchter, N, Sloan, S, and Levy, RD. 2001. "Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years." *J Cardiopulm.Rehabil.* 21 (2):87-93.

Harmatz, P, Giugliani, R, Schwartz, I, Guffon, N, Teles, EL, Miranda, MC, Wraith, JE, Beck, M, Arash, L, Scarpa, M, Yu, ZF, Wittes, J, Berger, KI, Newman, MS, Lowe, AM, Kakkis, E, and Swiedler, SJ. 2006. "Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study." *J.Pediatr.* 148 (4):533-539.

Kuczmarski RJ, Ogden C, Grummer-Strawn L, et al. CDC Growth Charts: United States. Advance Data Report No. 314. NCHS. 2000.

Mathai, SC, Puhan, MA, Lam, D, and Wise, RA. 2012. "The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension." *Am J Respir Crit Care Med* 186 (5):428-33.

Muenzer, J, Wraith, JE, Beck, M, Giugliani, R, Harmatz, P, Eng, CM, Vellodi, A, Martin, R, Ramaswami, U, Gucsavas-Calikoglu, M, Vijayaraghavan, S, Wendt, S, Puga, AC, Ulbrich, B, Shinawi, M, Cleary, M, Piper, D, Conway, AM, and Kimura, A. 2006. "A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome)." *Genet.Med* 8 (8):465-473.

Okuyama, T, Tanaka, A, Suzuki, Y, Ida, H, Tanaka, T, Cox, GF, Eto, Y, and Orii, T. 2010. "Japan Elaprase Treatment (JET) study: idursulfase enzyme replacement therapy in adult patients with attenuated Hunter syndrome (Mucopolysaccharidosis II, MPS II)." *Mol Genet Metab* 99 (1):18-25.

Puhan, MA, Mador, MJ, Held, U, Goldstein, R, Guyatt, GH, and Schunemann, HJ. 2008. "Interpretation of treatment changes in 6-minute walk distance in patients with COPD." *Eur Respir J* 32 (3):637-43.

Redelmeier, DA, Bayoumi, AM, Goldstein, RS, and Guyatt, GH. 1997. "Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients." *Am J Respir Crit Care Med* 155 (4):1278-82.

Reeves, BC, Wood, JM, and Hill, AR. 1993. "Reliability of high- and low-contrast letter charts." *Ophthalmic Physiol Opt* 13 (1):17-26.

Wraith, JE, Clarke, LA, Beck, M, Kolodny, EH, Pastores, GM, Muenzer, J, Rapoport, DM, Berger, KI, Swiedler, SJ, Kakkis, ED, Braakman, T, Chadbourne, E, Walton-Bowen, K, and Cox, GF. 2004. "Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase)." *J Pediatr* 144 (5):581-8.

Wuang, YP, and Su, CY. 2009. "Reliability and responsiveness of the Bruininks-Oseretsky Test of Motor Proficiency-Second Edition in children with intellectual disability." *Res Dev Disabil* 30 (5):847-55.

11 APPENDICES

Appendix 1 Schedule of Events

Table 11.1.1: Schedule of Events

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

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

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

a. For subjects enrolling from UX003-CL301, the Baseline Visit will be conducted in conjunction with the UX003-CL301 Week 48 study visit to avoid treatment disruption. Subjects enrolling from an Ultragenyx-sponsored clinical study: efficacy, ECHO and clinical laboratory assessments performed during the final or End of Treatment visit from the feeder study may be used as baseline assessments if performed within 30 days of study baseline visit as indicated in Section 7.5. Any listed assessments not performed during the feeder study final visit must be performed before the first study drug infusion. Unless otherwise specified, Baseline assessments must be completed within 30 days prior to the first dose of study drug. For subjects who are treatment naïve or who are enrolling from a non-Ultragenyx sponsored clinical study, initial baseline safety and efficacy assessments as indicated in Section 7.5 will be performed within 30 days of the study baseline visit as indicated in Section 7.5. Refer to Study Reference Manual for additional details.
b. For all subjects, assessments scheduled on the same day as treatment must be completed prior to the infusion.
c. Visit windows are ± 3 days and for major assessment visits (Weeks 12, 24, 36, 48 and every 24 weeks thereafter), the window is ± 7 days.
d. Actual study weeks for every-12-week visits = Weeks 60, 72, 84, 96, 108, 120, 132, 144.
e. Actual study weeks for every-24-week visits = Weeks 72, 96, 120, 144.
f. Actual study weeks for every-48-week visits = Weeks 96, 144.
g. Medical history will be collected for all subjects who are treatment naïve or who are enrolling from a non-Ultragenyx sponsored study (e.g., Investigator sponsored trials (ISTs), expanded access/compassionate use). For subjects enrolled in UX003-CL301 or other Ultragenyx sponsored study, their previously reported medical history will carry over to this study.
h. The ICR will only be identified for subjects enrolling from the MPS 7 Phase 3 Ultragenyx sponsored study UX003-CL301.
i. Weight for drug preparation may be obtained up to 15 days prior to indicated visit (e.g. Weeks 10, 22, 34, and 46 visits).
j. For UX003 treatment-naïve subjects the three most impactful clinical problems reported by the subject/parent/caregiver will be identified and scored at the Baseline visit. These clinical problems will continue to be scored throughout this study. For subjects enrolling from the MPS 7 Phase 3 Ultragenyx sponsored study UX003-CL301, the three most impactful clinical problems reported by the subject/parent/caregiver during the UX003-CL301 randomization visit will continue to be scored throughout this study.
k. Physical examinations are to include neurologic examination and evaluation of the presence or absence of corneal clouding. If subject complains of leg weakness or fatigue, evaluate for signs of cord compression (e.g., leg reflexes and motor strength).
l. On infusion days, vital signs will be measured at a minimum of: immediately (<30 minutes) before the infusion, at least every 30 minutes for the first hour of infusion, at least every hour for the remainder of the infusion and immediately (<30 minutes) after the infusion. Additional measurements should be obtained as appropriate.
m. Laboratory samples (blood and urine) are to be collected prior to dosing of study drug. Clinical laboratory tests are to include hematology, chemistry, and urinalysis. Laboratory samples for safety performed within 30 days prior to Baseline may be used for the study baseline.
n. For women of childbearing potential only. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result.
o. Testing for IgG antibodies directed against rhGUS. Antibody sample must be collected before infusion.
p. If a drug-related IAR has occurred, C3, C4 and CH50 samples should be drawn prior to and immediately after the next infusion.

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

r. Urine samples must be collected from first morning voids.

s. The 6MWT, 3MSCT and BOT-2 assessments may be conducted over a span of two days with each test performed once. The preferred order is to perform the 6MWT and 3MSCT on separate days. If performed on the same day, the 6MWT should be done before the 3MSCT. The subject's resting heart rate must return to baseline between assessments.

t. Pulmonary function testing may be omitted for subjects with tracheostomies. If performed on the same day, pulmonary function testing should be done before the 6MWT and 3MSCT. The subject's resting heart rate must return to baseline between assessments.

u. The highest value of three shoulder flexion and extension range of motion measurements for each side will be reported.

v. Anthropometric measurements include standing height and weight. If standing height cannot be obtained, recumbent length or sitting height will be determined.

w. The MPS HAQ or HAQ/CHAQ should be performed for UX003 treatment-naïve subjects and subjects enrolling from the MPS 7 Phase 3 Ultragenyx sponsored study UX003-CL301. The MPS HAQ will be administered to all age groups. The CHAQ should be performed for pediatric subjects only (<14 years old). The HAQ should be performed for subjects ≥14 years old. Subjects will consistently complete the same questionnaire (HAQ or CHAQ) administered at baseline for the duration of the study regardless of whether their age changes from 13 to 14 during the study. The age-appropriate version of the PedsQL multidimensional fatigue module will be administered throughout the study. For subjects enrolling from previous clinical trial with UX003, these subject-reported outcome measures will only be administered if they were previously performed in their feeder study.

x. As part of the subject/parent/caregiver clinical global impression assessment, subjects/parents/caregivers will be asked to provide narratives of how treatment has impacted the subject's ability to complete activities of daily living.

y. Liver and spleen size will be assessed qualitatively by physical examination.

z. If a subject withdraws from the study, or if the study terminated prior to Week 144, the termination visit should be completed within 30 days of the last dose of study drug. Assessments performed within 30 days of the termination visit will not be repeated unless clinically indicated.