

STATISTICAL ANALYSIS PLAN

Title An Open-label Study of UX003 rhGUS Enzyme Replacement Therapy in MPS 7 Patients Less than 5 years old

Protocol: UX003-CL203

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

Phase: 2

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Date: 22 Dec 2015

Version Number: v1.0

Table of Contents

1	INTRODUCTION	5
2	STUDY OBJECTIVES.....	5
2.1	Primary.....	5
2.2	Secondary.....	5
2.3	Tertiary.....	5
3	STUDY DESIGN.....	5
3.1	Overall Study Design and Plan	5
3.2	Determination of Sample Size	6
3.3	Interim Analysis	6
3.4	Data Monitoring Committee	6
3.5	Randomization and Blinding Method of Assigning Subjects to Treatment Groups.....	6
4	STUDY CLINICAL OUTCOMES AND COVARIATES.....	7
4.1	Primary Efficacy Variable	7
4.2	Secondary Efficacy Variables.....	7
4.3	Tertiary Efficacy Variables.....	7
4.4	Safety Assessments	7
5	DEFINITIONS.....	8
5.1	Baseline.....	8
5.2	Fold Increase in uGAG Above Upper Normal Limit	8
5.3	Growth	8
5.4	Anti-rhGUS Antibody Titer Values	9
5.5	Duration of Exposure to UX003	9
6	ANALYSIS POPULATIONS	9
6.1	Full Analysis Set.....	9
7	DATA SCREENING AND ACCEPTANCE	9
7.1	Handling of Missing and Incomplete Data	9

7.2	Missing Date Imputation Rules.....	9
7.3	Visit Time Windows	11
7.4	Software	11
8	STATISTICAL METHODS OF ANALYSIS	12
8.1	General Principles	12
8.2	Subject Disposition	12
8.3	Demographics and Other Baseline Characteristics	12
8.4	Medical History.....	12
8.5	Prior and Concomitant Medications	12
8.6	Dosing Summary.....	12
8.7	Efficacy Analyses	13
8.7.1	Primary Efficacy Endpoint.....	13
8.7.2	Secondary Efficacy Endpoints	13
8.7.3	Other Efficacy Endpoints	13
8.8	Safety Analyses.....	14
8.8.1	Adverse Events.....	14
8.8.2	Laboratory Parameters	14
8.8.3	Other Safety Parameters	14
8.8.4	Antibodies	14
9	CHANGES TO ANALYSES SPECIFIED IN PROTOCOL	15
10	REFERENCES	16
11	APPENDICES	17

ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
Bayley-III	Bayley Scales of Infant and Toddler Development [®] – Third Edition
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
ECHO	echocardiogram
ERT	Enzyme Replacement Therapy
GAG	glycosaminoglycan
IND	Investigational New Drug (application)
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MPS 7	mucopolysaccharidosis type 7, Sly Syndrome
PK	pharmacokinetic
QOW	every other week
rhGUS	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-CL203 Protocol dated 09 January 2015 through Protocol Amendment 1 dated 03 October 2015. The data collected in this study will evaluate the safety and efficacy of UX003 treatment in pediatric MPS 7 subjects less than 5 years of age. This SAP does not describe any Pharmacokinetic (PK) data analyses.

2 STUDY OBJECTIVES

2.1 Primary

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

2.2 Secondary

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

2.3 Tertiary

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.

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

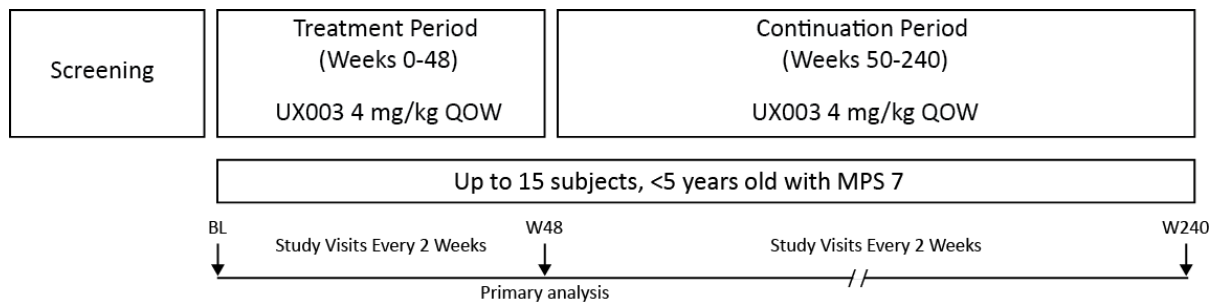
UX003-CL203 is an open-label, multicenter, Phase 2 study to assess the safety and efficacy of UX003 in pediatric MPS 7 subjects less than 5 years of age. UX003 is a formulation of recombinant human rhGUS, a human enzyme produced by recombinant DNA methods that is intended as an enzyme replacement therapy (ERT) for MPS 7. The study seeks to enroll up to 15 subjects less than 5 years of age at the time of signing informed consent, and will attempt to include approximately 5 infants with hydrops fetalis if possible. Subjects less than 5 years of age with prior exposure to UX003 treatment under an emergency IND may also be enrolled at the discretion of the Ultragenyx. 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. 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.

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, the study is terminated, or UX003 becomes commercially available.

Figure 3.1 provides a schematic of the study design.

Figure 3.1. Study Schema



3.2 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 eligible subjects.

3.3 Interim Analysis

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.

3.4 Data Monitoring Committee

Safety will be monitored by Ultragenyx on a continual basis. An independent data monitoring committee will not be used.

3.5 Randomization and Blinding Method of Assigning Subjects to Treatment Groups

Not applicable. This is an open label study without randomization of treatment assignment.

4 STUDY CLINICAL OUTCOMES AND COVARIATES

All data are collected according to the schedule of assessments included in the protocol.

4.1 Primary Efficacy Variable

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

4.2 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. Ascites will also be assessed.

4.3 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 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 gross motor development milestone checklist.
- Cardiac Ventricular Mass: Ventricular mass will be assessed by echocardiogram (ECHO). Valvular and cardiac function may also be evaluated.
- Pulmonary Function: Pulse oximetry will be used to assess respiratory difficulties; resting O₂ 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.

4.4 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:

- Vital signs and weight
- Physical examination findings
- Clinical laboratory evaluations
- Concomitant medications
- Antibodies to rhGUS
- Complement C3, C4 and CH50 levels (if indicated to characterize the immune response following a drug related IAR)

5 DEFINITIONS

5.1 Baseline

- uGAG baseline is defined as the average of all study assessments prior to or on the date of initiation of treatment with UX003 in this study. For subject(s) previously treated with UX003 under an emergency IND, initial baseline will be derived as the average of all assessments prior to or on the date of initiation of the initial treatment with UX003.
- Baseline for growth measurement is defined as the last non-missing study assessment prior to the first dose of UX003. For subject(s) previously treated with UX003 under an emergency IND, the last assessment prior to the initial UX003 treatment may also be used.
- The baseline for echocardiogram: ECHO performed within three months prior to baseline visit may be used as baseline provided cardiac ventricular mass can be calculated.
- Baseline value for other endpoints is the last non-missing study assessment prior to the first dose of UX003 in this study unless otherwise specified.

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 as 1.

5.3 Growth

Growth will be assessed by anthropometric measurements. Z-scores and percentiles will be calculated using CDC growth chart ([Kuczmarski, 2000](#)).

Growth velocity of standing height (cm or Z score) may be assessed by a model-based approach. A linear regression model for each subject will be built for selected pre-treatment (eg., within 2 years prior to Baseline) 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, β_1 is the slope of the regression model; ε_t is random error term.

5.4 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).

5.5 Duration of Exposure to UX003

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

6 ANALYSIS POPULATIONS

6.1 Full Analysis Set

The full analysis set is defined as all enrolled subjects who received at least 1 dose of UX003 during the 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 measures with missing item scores. Missing and incomplete data will be identified through a review of tables and listings for this study. Missing and incomplete data will be identified for investigation, and possible resolution, by Data Management 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.

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

<i>Period</i>	<i>Visit</i>	<i>Scheduled Visit Day</i>	<i>Window</i>
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
Continuation Period 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 240	Day 1681	Days ≥ 1640

a $x=1,2,\dots,14$

End of Treatment visit for subjects who didn't complete either the 48-week treatment period or the continuation period, 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 visits have 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

Due to the small sample size, all raw data obtained from the Case Report Forms (CRFs) as well as any derived data will be included in data listings or graphs. Descriptive statistics will be used to summarize the data. For continuous variables, means, standard deviations, medians, minimums, and maximums will be provided. For categorical variables, the counts and percentages of subjects in corresponding categories will be provided. All analysis will be based on full analysis set. Statistical tests will be 2-sided at the $\alpha = 0.05$ significance level. All p-values will be presented as nominal p-values. Summary statistics will be provided separately for subjects treated with UX003 under an emergency IND or not. Combined summaries will only be provided for uGAG and safety analyses, as prior data to initial treatment will be available for uGAG.

8.2 Subject Disposition

The subjects in the full analysis set will be listed. Date of informed consent, the reason for treatment discontinuation and study discontinuation will be displayed.

8.3 Demographics and Other Baseline Characteristics

Demographic parameters (e.g., age, sex, race and ethnicity) and other baseline characteristics (i.e., initial diagnosis, height and weight) assessed at baseline will be summarized and listed.

8.4 Medical History

Medical history and MPS treatment history will be summarized.

8.5 Prior and Concomitant Medications

The World Health Organization Drug (WHODRUG) dictionary will be used to classify prior and concomitant medications. Prior medication is 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. Any medications started after the date of the last dose of the investigational products will not be considered concomitant medications. The number and proportion of subjects receiving each reported concomitant medication will be summarized by Anatomical Therapeutic Chemical (ATC) code and preferred term. Multiple drug usage by a subject in the same category will be counted only once in the summary tables.

8.6 Dosing Summary

The number of infusions and cumulative dose per subject administered and duration of exposure to UX003 on this study will be summarized. Treatment compliance calculated as received dose divided by expected dose over specified period will also be displayed.

8.7 Efficacy Analyses

8.7.1 Primary Efficacy Endpoint

The primary efficacy analysis will evaluate the mean percent change in uGAG excretion from baseline at week 48 using the generalized estimating equation (GEE) analysis method. The model will include baseline and visit (up to week 48) as a categorical variable. The covariance structure within subjects will be assumed to be exchangeable. For subject(s) previously treated with UX003 under an emergency IND, percent change from initial baseline will be calculated.

In addition, the change and percentage change from baseline, fold increase in uGAG excretion and number of uGAG responders (defined as $\geq 50\%$ decrease in uGAG excretion from baseline) will be presented by visit.

8.7.2 Secondary Efficacy Endpoints

Change from baseline in anthropometric measurements will be summarized by visit, and for all subjects (including subject(s) previously treated with UX003 under an emergency IND), the last non-missing study assessment prior to the first dose in this study will be used as baseline.

All anthropometric measurements with z scores and percentiles will be listed. Growth velocity will be presented for pre-treatment and post-treatment periods, and for the subject(s) previously treated with UX003 under an emergency IND the growth velocity will be calculated for pre initial UX003 treatment and post initial UX003 treatment.

The change from baseline in liver and spleen size will be summarized by visit.

8.7.3 Other Efficacy Endpoints

The change from baseline for the following parameters will be summarized by visit.

- Serum GAG measures
- Functional development: Bayley-III scores: cognitive, language and motor development, and social emotions and adaptive behavior
- Cardiac ventricular mass
- Pulmonary function: pulse oximetry
- Biochemical markers of bone turnover
- Motor functioning

For serum GAG excretion, the percentage change from baseline will also be displayed

The value of CGI will be summarized by visit

8.8 Safety Analyses

8.8.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs to a system organ class (SOC) and a 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 and was not present prior to the first dose in this study, or it was present at the first dose but increased in severity during this 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 of study drug or discontinuation of study, and death will also be generated. The severity will be based on Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. 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.

Patterns of Infusion Associated Reactions (IARs) will be specifically evaluated throughout the study (see details in [Appendix](#)). 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 clinical laboratory parameters in hematology, chemistry, urinalysis and thyroids panels. Abnormal values will be flagged. 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 clinical 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 05 October 2015)

10 REFERENCES

- Kakkis, ED, Muenzer, J, Tiller, GE, Waber, L, Belmont, J, Passage, M, Izykowski, B, Phillips, J, Doroshow, R, Walot, I, Hoft, R, and Neufeld, EF. 2001. "Enzyme-replacement therapy in mucopolysaccharidosis I." *N Engl J Med* 344 (3):182-8.
- Kuczmarski RJ, Ogden C, Grummer-Strawn L, et al. CDC Growth Charts: United States. Advance Data Report No. 314. NCHS. 2000.

11 APPENDICES

Identification and Timing of IARs

Hypersensitivity reactions including anaphylaxis, the most severe form, and less severe allergic reactions are identified risks from ERT, including potentially ERT with UX003.

IMPORTANT: All adverse events occurring from the onset of the study treatment infusion, and within four hours following the end of the infusion, regardless of the investigator's assessment of whether or not the event was related to study drug administration will be considered an IAR.

It is expected that the IARs of greatest clinical importance will fall into the category of hypersensitivity reactions. Managing severe infusion related reactions requires early signs and symptoms to be recognized and well trained clinicians in the management of acute events.

Infusion associated reactions (IARs) may or may not occur in a recognized pattern of immune-mediated responses. The following table lists patterns of IARs that have been observed:

Patterns of IARs

Type	Time of onset	Cardiovascular Hypotension Tachycardia	Pulmonary Respiratory distress Hypoxemia	Skin Urticaria Raised, red, itchy rash	Mucosa Tongue Throat Angioedema	Abdomen Cramping/pain Episodic/ Bowel/bladder	Joint Pain/swelling	Fever/Chills?	Labs
Anaphylactoid	Early in infusion*	+	++ (Drop O2 saturation)	+/-	+/-	++	-	++	↓ C3, ↓ C4, ↓ CH50 +IgG
Anaphylaxis	Early in infusion*	+++	++	-	-	-	-	-	+IgE +Skin test
Urticarial with or without angioedema	Early to later in infusion	-	+/-	+++ (Rash starts in body creases/folds, starts central to peripheral)	+++/-	-	-	-	+ IgE or +IgG +Skin test
Immune Complex	Day of infusion, 2-3 days after infusion	-	-	+/- (Rash)	-	++	++	-	+Blood/protein in the urine +IgG

* Tend to see after initial increase in infusion rate

KEY:	
+	Sign often present
++, +++	Sign present and likely significant
+/-	Sign may or may not be present
-	Sign not typically present

Anaphylactoid reactions are the most important severe type of IAR and are caused by synchronous complement activation due to IgG1 antibodies to the enzyme and most commonly begins during the first hour after the infusion rate is increased. In MPS 7 mice, these types of reactions were observed approximately 4-6 weeks after infusions were started. The slow rate of infusion for one hour followed by the increased rate of infusion is expected to reduce clinical complement-mediated hypersensitivity responses, based on studies with laronidase in MPS 1 ([Kakkis et al. 2001](#)).

True anaphylaxis due to an IgE mediated response has not been observed as frequently, but still can occur at any time, though it would be expected to be early during the infusion. The premedication with an anti-histamine is primarily to minimize IgE mediated histamine release and to help mitigate a reaction if one were to occur.

Urticarial skin reactions with or without angioedema (tongue and throat swelling) is a common type of reaction observed often after several months of therapy. This can be associated with substantial pruritis and discomfort. Increased premedication and slower infusion rates can help. With time, these type of reactions will tend to subside over a period

of weeks to months with continued therapy. Airway obstruction is potentially serious in patients with MPS who have enlarged tongues, tonsils and adenoids and floppy tracheal cartilage, so the appearance of angioedema requires particular care and caution in management.

Immune complex disease can be observed with ERT but is more difficult to discern and diagnose primarily because of the delay in onset and variable symptoms. Abdominal pain, joint pain/swelling, proteinuria/hematuria, and skin rashes within the 1-5 days after an infusion may indicate that the antigen-antibody ratio is close to 1:1 leading to polymerization of antigen- antibody complexes, which may precipitate and locally activate complement and result in tissue injury.

IARs may present as described above, or may present with variable signs and symptoms alone or in combination. This guide is intended to help investigators evaluate and treat subjects who experience an IAR with UX003 ERT.