Statistical Analysis Plan

NCT Number: NCT02455622

Title: A Long-Term, Open-Label, Multicenter, Phase IV Study to Assess Longitudinal Changes on Height and Weight in Patients With MPS II Who Are Receiving Elaprase and Started Treatment With Elaprase at <6 Years of Age

Study Number: SHP-ELA-401

Document Version and Date: Final 1.0, 27 Aug 2025

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STATISTICAL ANALYSIS PLAN

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Phase: *IV*

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ABBREVIATIONS

6MWT	6-minute walk text
AAOS	American Association of Orthopedic Surgeons
ABC	adaptive behavior composite
ADA	antidrug antibody
AE	adverse event
AMA	American Medical Association
ANCOVA	analysis of covariance
CHAQ	Childhood Health Assessment Questionnaire
CRIM	cross-reactive immunological material
CS	clinically significant
ERT	enzyme replacement therapy
HOS	Hunter outcome survey
HS-FOCUS	Hunter-syndrome Functional Outcome in Clinical Understanding Scale
IA	Interim analysis
I2S	iduronate-2-sulfate
IP	investigation product
IRR	infusion-related reaction
JROM	joint range of motion
LOCF	last observation carried forward
LS-mean	least squares mean
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MPS II	mucopolysaccharidosis II
MWT	minute walk test
PRO	patient-reported outcomes
PT	Preferred Term (MedDRA)
QoL	quality of life
SAE	serious adverse event
SAP	Statistical analysis plan
SAS	statistical analysis system
SOC	System Organ Class
SD	standard deviation
TEAE	treatment-emergent adverse event
uGAG	urinary glycosaminoglycans
ULN	upper limit normal
VABS-II	Vineland Adaptive Behavior Scales (second edition)
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

Note: All italicized text is taken directly from the protocol.

1.1 Objectives

1.1.1 Primary Objective

The primary objectives of this study are to assess longitudinal changes in the following parameters in patients with mucupolysaccharidosis II (MPS II) who began Elaprase treatment at <6 years of age and who were receiving treatment with Elaprase:

- *height*
- *weight*

1.1.2 Secondary Objectives

The secondary objectives of this study are to assess longitudinal changes in the following parameters in patients with MPS II who began Elaprase treatment at <6 years of age and who were receiving treatment with Elaprase:

- *Urinary glycosaminoglycans (uGAG) levels*
- *Liver and spleen volume*
- *Joint mobility, as measured by Joint Range of Motion (JROM) scores, including global, upper-limb, and lower-limb joint scores*
- *Distance walked, as measured by the 6 Minute Walk Test (6MWT)*
- *Quality of life (QoL), as measured by the Hunter-syndrome Functional Outcome in Clinical Understanding Scale (HS-FOCUS) questionnaire (shortened version)*
- *Impact of illness of ability to function in daily life, as measured by the Childhood Health Assessment Questionnaire (CHAQ)*
- *Adaptive behavior as measured by the Vineland Adaptive Behavior Scales (VABS-II)*

1.1.3 Tertiary Objectives

The tertiary objectives of the study are to evaluate the relationships between:

- *Genotype and the following parameters: residual plasma iduronate-2-sulfate (I2S) enzyme activity, cross-reactive immunologic material (CRIM) status, and antibody status*
- *Antibody status and the following parameters: height, weight, walking, joint mobility, and uGAG levels*
- *Genotype and the following parameters: height, weight, walking, joint mobility, and uGAG levels.*

- *CRIM status and the following parameters: height, weight, walking, joint mobility, uGAG levels, liver and spleen volume*
- *CRIM status and the following parameters: safety (adverse events, infusion-related adverse reactions [hypersensitivity reactions])*

1.2 Endpoints

1.2.1 Primary Endpoints

The primary endpoints of this study are:

- *Height and weight*
- *Height and weight Z-scores*
- *Safety assessments*

1.2.2 Secondary Endpoints

1.2.2.1 Secondary Endpoints

Secondary endpoints of this study are the changes in the following variables:

- Height and weight velocity
- *Urinary GAG (uGAG) levels normalized to urine creatinine*
- *Normalized uGAG divided by upper limit of normal for age (uGAG/ULN)*
- *Liver and spleen volume*
- *Joint mobility, as measured by JROM scores, including global, upper-limb, and lower-limb joint scores*
- *Distance walked, as measured by the 6MWT*
- *Quality of life, as measured by the HS-FOCUS (shortened version), including individual domain scores from the 5 functional domains: walking/standing, grip/reach, schooling/work, activities, and breathing*
- *Impact of illness on ability to function in daily life, as measured by the CHAQ Parent Report, including the Disability Index (based on 8 subscales: dressing, hygiene, arising, eating, walking, reach, grip and activities), Discomfort Index and Health Status index*
- *Adaptive behavior, as measured by the VABS-II: standardized scores for each of 4 domains: Communication; Daily Living Skills; Socialization; Motor Skills; as well as the Adaptive Behavior Composite (ABC) score*

1.2.3 Tertiary Endpoints

The tertiary endpoints of this study are the following variables:

- Residual plasma I2S enzyme activity, CRIM status, and antibody status

1.2.4 Safety Endpoints

Safety will be evaluated through the assessment of AEs, SAEs (including non-elective hospitalizations), antibody status, concomitant medications, therapies, non-elective procedures, vital signs, physical examinations, clinical laboratory testing. All summaries will be provided on the Safety Set *using all data from Study SHP-ELA-401 Baseline to study completion. All safety analyses will be descriptive; no statistical testing will be performed.*

1.2.5 Other Endpoints

Not Applicable.

1.3 Estimands

Not applicable.

2.0 STUDY DESIGN

This long-term, open-label, multicenter, Phase IV study is proposed to study longitudinal changes in height and weight in patients with MPS II who are receiving Elaprase and started treatment with Elaprase at <6 years of age. Elaprase for IV infusion will be provided to patients enrolled in this study.

The purpose of Study SHP-ELA-401 is to obtain and evaluate data for patients who initiated and continued treatment with Elaprase at <6 years of age. Patients in this study will be followed for a minimum of 5 years after initiation of Elaprase treatment, or until their 10th birthday, whichever is longer. This study will evaluate various clinical outcome measures. Genotype and enzymatic activity of I2S will be collected at Baseline.

The study will enroll at least 20 treatment-naïve patients and the length of on-study follow-up for individual patients in Study SHP-ELA-401 will range from 5 to 10 years, from Screening through the End-of-Study. Additionally, due to the scarcity of treatment-naïve patients, height and weight data from patients enrolled in the Hunter Outcome Survey (HOS) registry will be utilized for the Primary Growth Analysis.

The Primary Growth Analysis will include data on approximately 35 patients with MPS II that cover either 5 year's duration of treatment with Elaprase, or the time period from initiation of Elaprase treatment until the patient reaches his 10th birthday, whichever is longer for each individual patient. The combination of Group 1—Prospective Patient Group data (obtained from patients during their participation in the present Study SHP-ELA-401) with Group 2—Retrospective Patient Group data (obtained from patients during their participation in the HOS study) allows for sufficient data to meet the Primary Growth Analysis goals.

An additional purpose of Study SHP-ELA-401 is to obtain blood samples from patients to determine their CRIM status, and to correlate CRIM status with outcomes data, including anti-idursulfase antibody development, pharmacodynamic responses, and clinical outcomes. If a

patient's sample reacts with antibodies against I2S, it is concluded that the sample contained this enzyme, and the patient is considered CRIM-positive. If a patient's sample does not react with antibodies against I2S, the patient is considered CRIM negative.

In the context of MPS II and other lysosomal storage diseases, this means that patients who produce some endogenous enzyme, albeit in much reduced quantities or with abnormal amino acid sequence, will be CRIM-positive. From a molecular genetic standpoint, this would be expected to be the case in patients whose IDS gene mutations include missense mutations, late truncations, and late frameshifts. CRIM-negativity, on the other hand, would be expected to be seen in patients who produce no enzyme at all; specifically, in patients with complete deletions of the IDS gene or mutations resulting in early truncations and frameshifts.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

No formal hypothesis testing will be done.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Statistical testing is considered exploratory and no adjustment for multiplicity will be made. The unadjusted p-values will be interpreted descriptively as summarizing the weight of evidence for a group difference and may suggest avenues for further exploratory analyses or generate formal hypotheses to be tested in future controlled trials.

4.0 SAMPLE-SIZE DETERMINATION

The proposed sample size of at least 20 patients for Group 1— patients from SHP-ELA-401 represents a number that is feasible to enroll and was determined outside of statistical considerations. Patients who withdraw from the study prior to study completion (dropouts) will not be replaced. A total sample size of approximately 35 patients is expected for analysis from the combination of Group 1—Efficacy Set and Group 2— HOS treated patients*.*

5.0 ANALYSIS SETS

The following analysis sets *will be defined for this study:*

Combined Set*: The Combined Set will include data from all patients in Group 1—Efficacy Set and Group 2—HOS treated patients. Selected efficacy analyses will be performed using the Combined Set.*

Efficacy Set: *The Efficacy Set will be defined as all patients from study SHP-ELA-401, who have a baseline and at least 1 post-baseline efficacy assessment. Selected efficacy analyses will be performed using the Efficacy Set.*

The ***treated patients*** **(Group 2)** from HOS must meet ALL of the following criteria to be included into the Study SHP-ELA-401 analysis:

1. *The patient is male.*
2. *The patient is enrolled in HOS.*
3. *The patient was <6 years of age at the start of Elaprase treatment.*
4. *The patient received Elaprase 0.5 mg/kg IV weekly treatment for at least 5 years.*
5. *The patient had a height assessment and a weight assessment documented within 3 months before or after Elaprase treatment start* (baseline assessment).
6. *The patient has had annual height and weight assessments from start of Elaprase through age 10 years.*
7. *The patient, patient's parent(s), or legally authorized guardian(s) agree(s) to data collection.*
8. *The patient, patient's parent(s), or legally authorized guardian(s) must have voluntarily signed an IRB/IEC-approved informed consent form after all relevant aspects of the HOS study have been explained and discussed. Consent of the patient's parent(s) or legally authorized guardian(s) and the patient's assent, as relevant, must be obtained.*

HOS patients that meet the following criteria are not eligible to be included into the Study SHP-ELA-401 Primary Growth Analysis:

1. *Patient was treated with growth hormone or other medications or interventions (e.g. BMT surgery) intended to promote growth in the time period covered by the analysis.*

HOS Untreated patients **(Group 3):** Based on feedback received from the FDA (dated 20 March 2014) this analysis set will include untreated patients from HOS and will be used to compare growth data from treated patients. Elaprase untreated patients who had a BMT surgery, or who have been treated with growth hormone or other medications or interventions intended to promote growth in the time period covered by the analysis, will be excluded.

The untreated patients (Group 3) from HOS must meet ALL of the following criteria to be included in the Study SHP-ELA-401 analysis:

1. The patient is male.
2. The patient is enrolled in HOS.
3. Two or more height or weight measurements are available from when the patient was <11 years of age, with the first assessment at age <6 years, and the last >=5 years thereafter, and the patient had not received treatment with Elaprase. (This includes data collected in the HOS database prior to enrollment in HOS.)
4. The patient, patient's parent(s), or legally authorized guardian(s) agree(s) to data collection.

5. The patient, patient's parent(s), or legally authorized guardian(s) must have voluntarily signed an IRB/IEC-approved informed consent form after all relevant aspects of the HOS study have been explained and discussed. Consent of the patient's parent(s) or legally authorized guardian(s) and the patient's assent, as relevant, must be obtained.

Untreated HOS patients that meet the following criteria are not eligible to be included into the Study SHP-ELA-401 Primary Growth Analysis:

1. Patient was treated with growth hormone or other medications or interventions (e.g., BMT surgery) intended to promote growth in the time period covered by the analysis.

5.1 Safety Analysis Set

The Safety Set will consist of all patients who received any amount of investigational product (IP) in study SHP-ELA-401.

5.2 Efficacy Set (Group 1)

See Section 5.0 above.

5.3 HOS Treated Patients (Group 2)

The treated patients from HOS must meet ALL of the criteria listed in Section 5.0 above to be included in the Study SHP-ELA-401 analysis.

5.4 Combined Set (Groups 1 and 2)

The Combined Set will include data from all patients in both the Efficacy Set *and HOS* treated patients*. Selected efficacy analyses will be performed using the Combined Set.*

5.5 Untreated Set (Group 3)

The Untreated Patients from HOS must meet ALL of the criteria listed in Section 5.0 above to be included in the Study SHP-ELA-401 analysis.

5.6 Per-Protocol Analysis Set

The Per-Protocol Analysis Set will exclude all patients from Group 1 with a major/critical protocol deviation that impacts the primary endpoint on growth.

5.7 Pharmacokinetic Analysis Set

Not Applicable.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All statistical analysis will be performed using statistical analysis system (SAS) software Version 9.4 or higher (SAS Institute, Cary, NC, USA).

6.1.1 Handling of Treatment Misallocations

Missing growth data will be assumed to be missing at random (MAR) in statistical analyses and no imputation will be performed. Last observation carried forward (LOCF) will be used to impute missing data for selected efficacy outcomes (uGAGs, JROM, 6MWT). Last observation carried forward will not be done for a period beyond 1 year, e.g., if a patient has an assessment at year 2 but not year 3 and year 4, LOCF will only be done up to year 3.

6.1.2 Analysis Approach for Continuous Variables

All continuous variables will be summarized using descriptive statistics, including the sample size (n), mean, standard deviation (SD), minimum, 25th percentile, median, and 75th percentile and maximum.

6.1.3 Analysis Approach for Binary Variables

Categorical variables, such as age group at start of Elaprase ERT (<2 years; ≥2 years) and genotype will be summarized using counts and percentages.

All categorical variables will be summarized using frequency counts and percentages (%). Statistical testing is considered exploratory in this observational study and no adjustment for multiplicity will be performed.

6.1.4 Analysis Approach for Time-to-Event Variables

Not Applicable.

6.2 Disposition of Subjects

The number of patients who were enrolled in Study SHP-ELA-401 and completed the study, the number of patients who discontinued the study (and the reason for discontinuation), and the number of patients in each patient group (efficacy set and Safety Set) and analysis set will be summarized for the Safety Set. A by-patient listing will also be provided, showing the reasons for discontinuation.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Patient characteristics at the start of Elaprase treatment will be summarized separately for each analysis set, i.e., Efficacy Set, Safety Set, HOS treated patients, Combined Set, and HOS untreated patients.

Demographic characteristics will also be listed for the Safety Set (with an indicator whether the patient is included in the Efficacy Set) and for the HOS treated and untreated patients, with an indicator whether the patient is treated/untreated.

6.3.2 Medical History and Concurrent Medical Conditions

Medical history will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients will be summarized by system organ class and preferred term for the Safety Set.

6.3.3 Baseline Characteristics

Similar summaries (see Section 6.3.1) will be presented for each analysis set, and by subgroups for the Safety Set and Efficacy Set (age group at start of Elaprase ERT, antibody status, CRIM status, ethnicity and genotype class).

Other baseline characteristics (liver volume, spleen volume, normalized urine GAG level) will also be summarized for the Safety Set.

6.4 Medication History and Concomitant Medications

6.4.1 Prior Medications

Prior medications will be coded using the most recent version of the World Health Organization (WHO) Drug Dictionary. Prior therapies and procedures will be coded using the most recent version of MedDRA.

Prior medication/therapies/procedures are defined as any medication/therapies/procedures with the start date prior to the date of the first dose of IP.

The prior therapies, procedures and medication usage will be summarized by the number and proportion of subjects of the safety set within each preferred term. Multiple medication usage by a subject in the same category will be counted only once.

All prior therapies, procedures, and medication will be listed for the Safety Set.

6.4.2 Concomitant Medications

Concomitant medications will be coded using the most recent version of the World Health Organization (WHO) Drug Dictionary. Concomitant therapies and procedures will be coded using the most recent version of MedDRA.

Concomitant medication/therapy is defined as any medication/therapy with a start date prior to the date of the first dose of IP and continuing after the first dose of IP or with a start date between the dates of the first and last doses of IP, inclusive. Concomitant procedure is defined as any procedure with a start date between the dates of the first and last doses of IP, inclusive. Any medication (therapy/procedure) with a start date after the date of the last dose of IP will not be considered a concomitant medication/therapy/procedure.

The concomitant therapies, procedure and medication usage will be summarized by the number and proportion of subjects in receiving each medication within each preferred term for the safety set. Multiple medication usage by a subject in the same category will be counted only once.

All concomitant therapies, procedures, and medication will be listed for the Safety Set.

6.5 Efficacy Analysis

6.5.1 Primary Endpoints Analysis

Weight and height assessments of treated patients from HOS after the age of 11 years will be excluded from the analyses. The last available assessment prior to age 11 years will serve as the end of study assessment. This will ensure that patients from HOS will have a similar age than the patients from study SHP-ELA-401.

Descriptive summaries will generally present the data overall and by visit from Study SHP-ELA-401 baseline for the Efficacy Set, as well as the Per-Protocol Analysis Set.

Height and weight data from start of Elaprase ERT for the HOS treated patients in the Combined Set will be used in certain statistical model analyses and figures for height and weight, as described below (Section 6.5.1.2).

No HOS data will be used in analyses of all other efficacy endpoints; the Efficacy Set will be utilized only.

The results from the Combined Set (descriptive analysis and comparison to Group 3) will be considered as primary growth analysis.

Growth data will also be listed in a by-patient listing.

6.5.1.1 Derivation of Endpoints

Not applicable.

6.5.1.2 Main Analytical Approach

The effect of treatment on growth at the end of study will be analyzed by comparing

a) the Combined Set (Groups 1 and 2) with the untreated patients (Group 3) and

b) the Efficacy Set (Group 1) with the untreated patients (Group 3),

using a linear mixed models with treatment (yes/no), age at time of assessment, race (Asian vs non-Asian) and baseline value of weight/height as factors – for untreated patients, the baseline value would the first available height/weight assessment. Quadratic and cubic terms for age may be added to the model if significant or necessary to better characterize the relationship between physical growth and age over time.

Height and weight Z-scores will be calculated based on the WHO-DD growth charts (for age ≤ 24 months) and the CDC growth charts (for age >24 months) normal height/weight-for-age data. Descriptive statistics for the Efficacy Set and Combined Set at each time point for height, weight and Z-scores and for change from baseline will be calculated overall and separately for each subgroup (age group at start of Elaprase ERT treatment (<2 years; ≥2 years), overall antibody status, baseline CRIM status, race (Asian vs non-Asian), , genotype class and severity of genetic variant – overall antibody status and baseline CRIM status are only applicable for the Efficacy Set).

Height, weight, and the corresponding Z-scores from start of ERT will be plotted against age for the Combined Set. Analyses using linear mixed models with random intercept and slope for age will be fit to the growth data over time from the start of ERT. Quadratic and cubic terms for age may be added to the model if significant or necessary to better characterize the relationship between physical growth and age over time. Predicted growth curves for individuals using the patient specific intercept and slope estimates from the model will be plotted. The effect of factors, such as age group at start of ERT, baseline CRIM status (only for Efficacy Set), and genotype class on growth parameters will be explored. The Least Squares means (LS-means) and standard errors at various ages estimated from the model will be summarized and plotted by factor groups. Similar analyses will be performed on the Efficacy Set and will assess the effect of baseline CRIM status and antibody status on growth.

As an additional analysis, a linear mixed model repeated measures (MMRM) will be used as a repeated measures analysis to investigate the growth over time. To account for baseline differences between groups, the model will include fixed categorical effects for visit week and baseline value of each endpoint (height and weight), race (Asian vs non-Asian) and age at baseline as continuous covariates. This will be analyzed for the Efficacy Set, the Per-Protocol Analysis Set, the Combined Set and the HOS untreated patients (Group 3).

6.5.1.3 Sensitivity Analysis

Not Applicable.

6.5.1.4 Supplementary Analyses

See subgroups specified in Section 9.2.1.

6.5.2 Secondary Endpoints Analysis

The following endpoints are considered to be secondary endpoints:

- Height and weight velocity (using the Efficacy Set, the Combined Set and untreated patients)
- The remaining secondary endpoints below will be analyzed using the Efficacy Set only: *Urinary GAG (uGAG) levels normalized to urine creatinine*
- *Normalized uGAG divided by upper limit of normal for age (uGAG/ULN)*
- *Liver and spleen volume*
- *Joint mobility, as measured by JROM scores, including global, upper-limb, and lower-limb joint scores*
- *Distance walked, as measured by the 6MWT*
- *Quality of life, as measured by the HS-FOCUS (shortened version), including individual domain scores from the 5 functional domains: walking/standing, grip/reach, schooling/work, activities, and breathing*

- *Impact of illness on ability to function in daily life, as measured by the CHAQ Parent Report, including the Disability Index (based on 8 subscales: dressing, hygiene, arising, eating, walking, reach, grip and activities), Discomfort Index and Health Status index*
- *Adaptive behavior, as measured by the VABS-II: standardized scores for each of 4 domains: Communication; Daily Living Skills; Socialization; Motor Skills; as well as the Adaptive Behavior Composite (ABC) score*

6.5.2.1 Secondary Endpoint Analysis

Height and Weight velocity, and cross-sectional analysis of height and weight data

Height and weight velocity will be analyzed descriptively, in a similar way as absolute height and weight Z-scores, for the Efficacy Set, the Combined Set and untreated patients, i.e., summarized at each time point, and calculating change from baseline.

To obtain meaningful data for the calculation of height/weight velocity from the height/weight measurements available from the HOS treated patients (recorded at unequal intervals during routine clinical practice), only consecutive values having a minimum of 3 months' and a maximum of 2 years' difference will be included in this part of the analysis. Height/weight velocity will be calculated as the difference in height/weight, divided by the difference in age between consecutive study visits. Mid-age will be calculated at the midpoint between the ages at these consecutive study visits, and the annualized height/weight will be assigned to that mid-age. Outlying values, defined as height velocity >20 cm/year, or weight velocity >15 kg/year, will be excluded. Calculated velocities that are < 0 will be imputed to 0 cm/year or 0 kg/year.

Untreated patients (Group 3) who had at least 2 height/weight assessments, at least 1 year apart, while untreated before the age of 11 years will be included in the longitudinal analysis.

All patients (Efficacy Set, HOS treated patients and HOS untreated patients) who had height/weight assessments at age 10 years will be included in a cross-sectional analysis. The height/weight and height/weight z-scores at age 10 years (one value per patient who had an assessment at age 10 years) will be summarized descriptively for the 3 analysis sets. If multiple height/weight assessments are available at age 10 years, the value closest to turning 10 years will be used. Any age ≥ 9.9 to < 11 years will be considered as age 10.

In addition to the primary analysis, exploratory analysis may also examine the effect of genetic mutation (severe vs non-severe, for participants with available data) on growth.

Urinary GAG (uGAG) levels normalized to urine creatinine

Urinary GAG levels will be normalized to urine creatinine (normalized uGAG) and normalized uGAG divided by the upper limit of normal for age (uGAG/ULN) will be calculated, where the ULN for uGAG was obtained from Mayo Clinic as shown in the table below:

Age	***uGAG ULN***
0 – 4 months	*≤53.0 mg/mmol creatinine (468.6 µg/mg)*
5 – 18 months	*≤31.0 mg/mmol creatinine (274.1 µg/mg)*
19 months – 2 years	*≤24 mg/mmol creatinine (212.2 µg/mg)*
3 – 5 years	*≤16 mg/mmol creatinine (141.5 µg/mg)*
6 – 10 years	*≤12.0 mg/mmol creatinine (106.1 µg/mg)*
11 – 14 years	*≤10.0 mg/mmol creatinine (88.4 µg/mg)*
>14 years	*≤6.5 mg/mmol creatinine (57.5 µg/mg)*

Descriptive summaries for the observed values, the change from baseline and the percent change from baseline in normalized uGAG will be presented for each time point overall and separately for each subgroup (age group at ERT start, baseline CRIM status, antibody status, and genotype class). Similar tables will be presented for the normalized uGAG/ULN.

Analysis of covariance will be used to compare the antibody status, genotype, and age at ERT start groups with respect to the change from baseline at each time point in uGAG and uGAG/ULN. The group indicator (baseline CRIM status, antibody status, genotype, or age group) and the corresponding baseline value will be included in the model as fixed effects.

The uGAG analysis will be done using the Efficacy Set. Furthermore, by-patient data will also be presented in a listing.

Liver Volume

Abdominal ultrasound examinations will be used to assess the liver volume. The liver volume will be calculated using the following formula:

$$Liver\ Volume = 0.2618 * (AAL^2 + MCL^2 + STL^2).$$

The calculation of the upper limit of normal (ULN) for the liver volume will be as follows:

$$0.53 \times height\ (cm) + 13.$$

Liver volume divided by ULN (liver volume/ULN) will be calculated for each liver volume measurement.

Descriptive summaries for the observed values, the change from baseline and the percent change from baseline in liver volume will be presented for each time point overall and separately for each subgroup (age group at ERT start, baseline CRIM status, antibody status, and genotype class).

Analysis of covariance will be used to compare the baseline CRIM status, antibody status, genotype, and age at ERT start groups with respect to the change from baseline at each time point for liver volume. The group indicator (baseline CRIM status, antibody status, genotype, or age group at ERT start) and the corresponding baseline value will be included in the model as fixed effects.

The liver volume analysis will be done using the Efficacy Set. Furthermore, by-patient data will also be presented in a listing.

Spleen Volume

Abdominal ultrasound examinations will be conducted to assess spleen volume. The spleen volumes will be calculated using the following formula for an ellipsoid:

$$Spleen\ Volume = 0.523 * L * B * (DL + DB)/2.$$

The calculation of the ULN for spleen volume will be as follows:

$$0.7 + (4.6 \times weight\ [kg]) + 150.$$

Spleen volume divided by ULN (spleen volume/ULN) will be calculated for each spleen volume measurement.

Descriptive summaries for the observed values, the change from baseline and the percent change from baseline in spleen volume will be presented for each time point overall and separately for each subgroup (age group at ERT start, baseline CRIM status, antibody status, and genotype class).

Analysis of covariance will be used to compare the baseline CRIM status, antibody status, genotype, and age at ERT start groups with respect to the change from baseline at each time point in spleen volume. The group indicator (baseline CRIM status, antibody status, genotype, or age group at ERT start) and the corresponding baseline value will be included in the model as fixed effects.

The spleen volume analysis will be done using the Efficacy Set. Furthermore, by-patient data will also be presented in a listing.

Joint Mobility

See the table below for a list of the joints/movements that will be assessed in Study SHP-ELA-401, as well as normal values and clinically meaningful changes from Baseline. The normal values are taken from the paper by Link et al.[1] and rely on norms produced by the American Medical

Association (AMA)[2] and the American Association of Orthopedic Surgeons (AAOS)[3]. The clinically meaningful changes (in degrees of joint range) are identical to those used in the Study TKT024 Clinical Study Report, the original pivotal study of Elaprase.

The scoring method for the JROM will use a similar approach as that described in Epps et al.[4] The measurement (in degrees) of a given joint motion will be averaged across the right and left side, then divided by the normal value and multiplied by 100 to obtain a percent score. The percent scores of every motion in a given joint will be averaged to obtain an overall joint score.

For example, for the knee, the 2 percent scores (representing flexion and extension, respectively) will be averaged to produce an overall knee joint score. The Upper Limb score will be the average of the 3 joint scores in the upper limb (shoulder-elbow-wrist) and the Lower Limb Score will be the average of the 3 joint scores in the lower limb (hip-knee-ankle).

Two global scores will also be calculated:

- *Key Elements Score: This score will be the average of the percent scores from the joint motions bolded in the table below. The experience with MPS II patients in HOS has indicated that these are the predominantly affected joint movements[1].*
- *Full Score: This score will be the average of the percent scores from all the joint motions.*

Joint	***Motion Tested***	***Normal Value[a]***	***Clinically Meaningful Change[b]***
Lower Limb			
Hip	***Flexion, Knee Bent***	*120*	*≥10*
	Extension	*30*	*≥10*
	Abduction	*40*	*≥5*
	Adduction	*20*	*Not given*
	External Rotation	*50*	*≥5*
	Internal Rotation	*45*	*≥5*
Knee	*Flexion*	*150*	*≥10*
	Extension	*10*	*≥5*
Ankle	*Dorsal Extension*	*20*	*≥5*
	Plantar Flexion	*50*	*Not given*
Upper Limb			
Shoulder	***Flexion***	*180*	*≥10*
	Abduction	*180*	*≥10*
	Internal Rotation	*90*	*≥10*
	External Rotation	*90*	*≥10*
	Extension	*60*	*≥10*
Elbow	*Flexion*	*150*	*≥10*
	Extension	*10*	*≥10*
Wrist	*Flexion*	*80*	*≥10*

Joint	*Motion Tested*	*Normal Value*[a]	*Clinically Meaningful Change*[b]
	Extension	*70*	*≥10*

[a] *Link et al.*[1]

[b] *As described in the TKT024 CSR*

Scores and changes from baseline in individual joint movements (in degrees) as well as joint, upper, lower, and global scores will be summarized descriptively at each time point, overall and separately for each subgroup (age group at ERT start, baseline CRIM status, antibody status, and genotype class). The proportion of patients with clinically meaningful changes in each joint movement will be similarly summarized.

Analysis of covariance (ANCOVA) will be used to compare the antibody status, baseline CRIM status, genotype, and age at ERT start groups with respect to the change from baseline at each time point in upper, lower, key elements and full JROM scores. The group indicator (antibody status or genotype or age group) and the corresponding baseline JROM score will be included in the model as fixed effects.

The joint mobility analysis will be done using the Efficacy Set. Furthermore, by-patient data will also be presented in a listing.

Distance Walked via Six Minute Walk Test (6MWT)

Descriptive summaries for the observed values and the change from baseline in distance walked as measured by 6MWT will be presented for each time point overall and separately for each subgroup (age group at ERT start, baseline CRIM status, antibody status, and genotype class). Analysis of covariance will be used to compare the antibody status, baseline CRIM status, genotype, and age at ERT start groups with respect to the change from baseline at each time point in distance walked. The group indicator (baseline CRIM status, antibody status, genotype, or age group at ERT start) and the baseline value will be included in the model as fixed effects.

The 6MWT analysis will be done using the Efficacy Set. Furthermore, by-patient data will also be presented in a listing.

Quality of Life as measured by HS-FOCUS

The analysis of QoL will be performed from study baseline for the Efficacy Set utilizing the HS-FOCUS (shortened version). Results will be presented in tabular format, as well as in a by-patient listing.

The HS-FOCUS (shortened version) questionnaire has 5 function domains (walking/standing, grip/reach, schooling/work, activities, and breathing). The scale of the 5 function domains ranges from 0 to 3, with a 3-score denoting highest disability:

0: With NO difficulty

1: With SOME difficulty

2: With MUCH difficulty

3: Unable to do

Missing: Does not apply

The response option "Does not apply" is treated as "missing" with no score, the same as if the item had not been completed in the questionnaire.

For each of the 5 functional domains, the respective domain scores will be calculated as:

$$Domain\ Score = \frac{\sum item\ scores\ within\ domain}{\#\ items\ completed\ within\ domain}$$

For both the parent and the child-reported questionnaires, the domain scores and the changes from baseline in each of the domains will be summarized descriptively by baseline CRIM status, antibody status, genotype, and age at ERT start.

For HS-FOCUS, listings for each question within each domain will be presented as follows:

- Walking/Standing (lower body tasks)
  - Able to walk on flat feet for 20 meters
  - Able to walk without getting tired for 15-20 minutes
  - Able to stand without getting tired for 10 minutes
  - Able to step on a stool
  - Able to walk up a flight of stairs
- Grip/Reach (upper body tasks)
  - Able to touch the top of his head
  - Able to place his palm and fingers flat on a table
  - Able to pour a fizzy drink or juice from a can or carton into a cup
  - Able to put on shoes while sitting in a chair
  - Able to button a shirt
  - Able to reach all parts of his body, to keep neat and clean
  - Able to throw and catch a medium-sized ball
  - Able to turn pages in a book
- School/Work
  - Able to attend l day of school or work
  - Able to finish all classroom assignments or work tasks

- Activities
    - Able to take part in physical activities or play with others for 1 hour
    - Able to go out with friends and/or family such as going shopping or to dinner
- Breathing
    - Able to breathe without making noise at rest
    - Able to carry our daily activities without becoming short of breath
    - Able to talk with someone else without becoming short of breath
    - Able to sleep without snoring

Box plots of domain scores and changes from baseline for each of the domains will be plotted over time by overall and stratified separately by CRIM status, antibody status, genotype, and age at ERT start. A trellis plot of these same scores within each patient will be presented.

Analysis of Daily Function

The analysis of impact of illness on ability to function in daily life will be performed from study baseline for the Efficacy Set utilizing the CHAQ. Results will be presented in tabular format, as well as in a by-patient listing.

The CHAQ includes 30 items measured on a scale of 0 to 3:

0=Without any difficulty

1=With some difficulty

2=With much difficulty

3=Unable to do

Missing: Does not apply

The highest scoring item in each category determines the score for that category. The mean score for the 8 subscales is the Disability Index (dressing, hygiene, arising, eating, walking, reach, grip and activities). The Discomfort Index and Health Status Index are measured on separate 15 cm scales. The distance from the left end of the scale to the respondent's mark is measured and multiplied by 0.2 to calculate the score.

The 4 AIDS and DEVICES questions, which do not have the 0 – 3 score will only be listed.

The index scores and the changes from baseline will be summarized descriptively by baseline CRIM status, antibody status, genotype, and age at ERT start.

Analysis of Adaptive Behavior

The analysis of adaptive behavior will be performed from study baseline for the Efficacy Set utilizing the VABS-II. The observed value and change from baseline in the standardized scores for each of the 4 domains (communication; daily living skills; socialization; motor skills), as

well as the adaptive behavior composite score, will be summarized descriptively by baseline CRIM status, antibody status, genotype, and age at ERT start.

Results will be presented in tabular format, as well as in a by-patient listing.

6.5.2.2 Derivation of Endpoints

See Section 6.5.2.1 above.

6.5.2.3 Main Analytical Approach

See Section 6.5.2.1 above.

6.5.2.4 Sensitivity Analysis

Not Applicable.

6.5.2.5 Supplementary Analyses

Not Applicable.

6.5.3 Tertiary Endpoints Analysis

Residual plasma I2S enzyme activity results at baseline will be summarized overall and by baseline CRIM status, antibody status, and genotype class for the Efficacy Set. No hypothesis testing will be conducted.

Data will also be listed in a by-patient listing.

6.5.4 Subgroup Analyses (if applicable)

See Section 9.2.1.

6.6 Safety Analysis

Safety will be evaluated through the assessment of AEs, SAEs (including non-elective hospitalizations), antibody status, concomitant medications, therapies, non-elective procedures, vital signs, physical examinations, clinical laboratory testing. All summaries will be provided on the safety set using all data from Study SHP-ELA-401 Baseline to study completion. All safety analyses will be descriptive; no statistical testing will be performed.

6.6.1 Adverse Events

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events and SAEs will be summarized according to the Medical Dictionary for Regulatory Activities System Organ Class (SOC) and Preferred Term (PT). The number and percentage of patients reporting each PT and SOC will be tabulated globally and by genotype, baseline CRIM status, and antibody status. A patient experiencing the same AE multiple times will only be counted once for the corresponding PT. Similarly, if a patient experiences

multiple AEs within the same SOC, that patient will be counted only once for that SOC. Adverse events will be presented in alphabetical order by SOC.

AEs occurring on or after the first infusion to the end of study (EOS) visit are defined as treatment-emergent AEs (TEAEs). In general, an AE will be considered a treatment-emergent AE (TEAE) if it cannot be definitively categorized as otherwise by documentation that its onset preceded the time of informed consent. The analyses described in this section will be based on TEAEs. Summaries for the following AE categories will be presented:

1. Patients who experienced no TEAEs,
2. Patients who experienced at least one TEAE
3. Patients who discontinued due to an TEAE(s)
4. Patients who experienced at least one serious treatment-emergent adverse event (SAE)
5. Patients who experienced at least one severe or life-threatening TEAE
6. Patients who experienced at least one Elaprase-related TEAE
7. Patients who experienced at least one serious Elaprase-related TEAE
8. Patients who died

The number and proportion of patients and the corresponding number of TEAEs within TEAE categories 2 and 5 will be summarized by SOC and PT. The most common TEAEs which happened in >10% patients will also be summarized by SOC and PT.

Listings of all the TEAEs of categories 3-6 will be provided if applicable.

The number and percentage of patients, as well as number of events will be summarized by severity; at the patient level, a patient is counted once by any event, SOC, or PT under the most severe category.

The number and percentage of patients having any TEAE, and the number of corresponding TEAEs will be summarized by relationship to Elaprase and displayed by MedDRA SOC and PT; at the patient level, a patient is counted only once by any event, SOC, or PT under the most related category.

Hypersensitivity reactions, treatment-emergent adverse events (TEAEs), and SAEs will each be analyzed by baseline CRIM status for both time to first event and number and percentage of patients experiencing AEs by SOC and PT. Kaplan-Meier plots of time to first event will be graphed by baseline CRIM status and the groups will be compared using the log-rank test. A time-varying proportional hazards (Cox) model will also be used to assess the relationship between baseline CRIM status and AEs.

6.6.2 Adverse Events of Special Interest (if applicable)

Infusion-related reactions (IRRs) and hypersensitivity reactions will be summarized in a similar way as overall TEAEs, using the Safety Set.

An IRR is defined as any TEAE related to elaprase treatment (definitely related, possibly related probably related), that began either during or within 24 hours after the start of the infusion.

IRRs and hypersensitivity reactions will also be listed for each patient experiencing an IRR.

6.6.3 Other Safety Analysis

Immunogenicity

The number and percentage of patients who became antibody positive (Ab+) overall (at any time during the study) will be tabulated, and the proportion of patients ever developing a positive result during the study will be compared between the CRIM-positive and CRIM-negative patients using a two-sided Fisher's Exact test. Additionally, Kaplan-Meier plots for time to becoming Ab+ will be provided by baseline CRIM status. The time to first event by CRIM status groups will be tested using a log-rank test. A similar analysis may be conducted for persistent Ab+, NAb+ and persistent NAb+ responses (see definition for persistent positive below). Additionally, immunoglobulin G (IgG) antibody titer at each visit will be summarized by baseline CRIM status.

The following additional analyses will also be performed:

- Correlation of genotyping by DNA sequence and RNA sequence

Immunogenicity data will be summarized for the Safety Set. A by-patient listing will also be provided.

Clinical Laboratory Evaluations

Laboratory values (eg, chemistries, hematology, etc) will be summarized in terms of the absolute value and change from baseline at each time point. The number and percentage of patients with any clinically significant post-Baseline laboratory result will be presented.

Box plots for Total protein and Glucose will be presented at each scheduled study visit.

All the laboratory values will be categorized as a patient having had:

(1) an Abnormal and Clinically Significant (CS) value at any time during the study post baseline,

(2) no CS values at any time during the study post baseline but had at least one Abnormal and not CS (NCS) value, and

(3) Normal values (no CS or NCS values) at all time during the study post baseline.

The number and percentage of patients in each category will be presented. Patients with non-CS at baseline to CS post-baseline shifts will be identified and listed separately along with their entire profile for that particular laboratory parameter.

If a particular laboratory measurement has been either repeated or retested, then the repeated or retested measurement for that laboratory parameter, with respect to date/time, will be used in the statistical analysis unless this value is invalid/missing. The handling of repeated or retested laboratory measurements should only consider the specific laboratory measurement that was repeated or retested.

Clinical laboratory data will be summarized and listed for the Safety Set.

Vital Signs

Vital signs (temperature [˚C], pulse [bpm], blood pressure [systolic and diastolic, mmHg], respiration [per minute], and oxygen saturation [%]) will be summarized by study time point.

Additionally, vital signs will be summarized by reporting the number and proportion of patients experiencing at least one above normal (and at least one below normal) change in each vital sign parameter. Patients who satisfy the conditions for the 2 categories will be included in both categories. The values considered above normal will be defined as those above the upper limit of the normal ranges in the table below.

Vital Signs Parameter	Normal Range
Temperature (˚C)	36.5 to 37.2
Respiration (/min)	12-24
Pulse (bpm)	40-100
Systolic blood pressure (mmHg)	90-180
Diastolic blood pressure (mmHg)	50-110

Vital signs will also be presented in a trellis layout so that the vital signs data within a patient will be presented on a single page.

Vital signs will be summarized and listed for the Safety Set.

Physical Findings

Abnormal physical examination findings will be recorded and summarized as part of the medical history or AE data.

A full physical examination will be performed with a thorough review of body systems.

Physical examinations will include a review of the patient's general appearance, as well as evaluation of the following body systems.

Physical examination results will be summarized and listed for the Safety Set.

Antibody Assessment

Anti-idursulfase antibody formation will be monitored at Study SHP-ELA 401 Baseline and throughout the study. The number and percentage of patients testing anti-idursulfase antibody positive and negative at each time point will be summarized overall, by baseline CRIM status, and by genotype. Titer values will be summarized using box plots over time in patients with positive antibodies at or prior to each scheduled visit. The titer values will be plotted similarly for patients who developed positive neutralizing antibodies at or prior to each scheduled visit.

Overall antibody status groups will be summarized and are defined as follows:

- *Ab-: Patients who never had a positive antibody sample*

- *Ab+: Patients who had at least 1 positive antibody sample*
- *NAb-: Patients who never had neutralizing antibodies*
    - *NAb+: Patients who had at least 1 neutralizing antibody sample*

All assessments starting from Baseline in this study will be considered for this determination. If sample size permits, the overall Ab+ group will be further divided into:

- *O-Ab+: Occasional Ab+ patients: patients who had antibodies in 25% or less of their blood samples*
- *I-Ab+: Intermittent Ab+ patients: patients who had antibodies in between 25 and 50% of their blood samples*
- *C-Ab+: Consistently Ab+ patients: patients who had antibodies in 50% or more of their blood samples*

In addition, the status of ADA or NAb will be classified and summarized at baseline and throughout the study as below:

- Baseline Positive

  Subject is positive for ADA or NAb prior Elaprase ERT treatment.

- Baseline Negative

  Subject is negative for ADA or NAb prior Elaprase ERT treatment.

- Treatment-induced Positive

  Subject who is negative for ADA or NAb at baseline is positive for ADA or NAb at a post baseline visit.

- Treatment-boosted Positive

  Subject's ADA or NAb titer is boosted to a higher titer (greater than or equal to the baseline titer by fourfolds or more) at a post baseline visit for a subject who is ADA or NAb positive at baseline.

- Transient Positive

  Subject tested positive for ADA or NAb once during treatment period (excluding last test), or positive for ADA or NAb two times or more where the first and last time points for ADA or NAb positive are separated by a period less than 16 weeks and the subject's last test is negative.

- Persistent Positive

  Subject tested ADA or NAb positive two times or more (more than 16 weeks apart) during study period.

The proportion of patients ever developing a positive result during the study will be compared between by baseline CRIM status using a two-sided Fisher's exact test. Additionally, Kaplan-

Meier plots for time to becoming Ab+ will be provided by baseline CRIM status. The time to first event by baseline CRIM status groups will be tested using a log-rank test.

Titer values will be summarized using box plots over time in patients with positive antibodies at or prior to each scheduled visit. The titer values will be plotted similarly for patients who developed positive neutralizing antibodies at or prior to each scheduled visit.

Antibody data will be summarized and listed for the Safety Set.

6.6.4 Extent of Exposure and Compliance

The total duration of Elaprase ERT exposure for all patients will be summarized for the safety set and the retrospective group. Number of doses will be summarized for the Safety Set only.

The actual average dose is defined as the total doses divided by the number of infusions.

All enrolled patients will receive once weekly treatment with Elaprase under the oversight of the Investigator. Elaprase treatment will be administered in a clinical setting or may be administered in the patient's home (with Sponsor approval) after the patient has completed at least 6 months of treatment in a hospital setting by appropriately trained and skilled healthcare providers (nurses or physicians) with knowledge of the patient's drug regimen; therefore, full patient compliance with treatment is anticipated in this study. The home healthcare provider will record details of infusions administered at the patient's home to ensure treatment compliance and document any AEs.

Compliance will be calculated (for the Safety Set) as follows:

$$\text{compliance (\%)} = \frac{actual\ number\ of\ doses\ received}{planned\ number\ of\ doses}\ X\ 100.$$

For HOS treated patients, if dose frequency is marked as "Other", it will be excluded from dose calculations.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

Not Applicable.

6.7.2 Pharmacodynamic Analysis

Not Applicable.

6.7.3 Biomarker Analysis

Not Applicable.

6.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

6.8.1 PRO Analysis

See Section 6.5.2.1 above.

6.8.2 Health Care Utilization Analysis

Not Applicable.

6.9 Other Analyses

Not Applicable.

6.10 Interim Analyses

Two interim analyses were pre-planned and conducted. The statistical analysis plans of these interim analyses were approved prior to the specific interim analysis, and are separate from this final statistical analysis plan.

Interim Analysis 1 was to examine CRIM assay results with respect to patient genotype and I2S enzyme status. This analysis was intended to evaluate suitability of blood samples for CRIM testing by confirming that the CRIM status determination was consistent with patient genotype. Patients with severe disease presentations, e.g., as a result of complete deletion or early truncation of I2S enzyme-coding sequence, would be expected to test CRIM-negative. Interim Analysis 1 was conducted once the last patient in the Prospective Patient Group enrolls in the study and completed baseline assessments.

Interim Analysis 2 was to examine the correlation of CRIM status to prospectively collected data on the antibody response, uGAG levels, liver and spleen volumes, and clinical outcomes. This second analysis was conducted after the last patient in the Prospective Patient Group completed 2-year assessments.

6.11 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not Applicable.

7.0 REFERENCES

1. *Link B, de Camargo Pinto LL, Giugliani R, et al. Orthopedic manifestations in patients with mucopolysaccharidosis type II (Hunter syndrome) enrolled in the Hunter Outcome Survey. Orthopedic reviews 2010;2:e16.*
2. *Anon. Guides to the Evaluation of Permanent Impairment. 3rd ed: American Medical Association; 1990.*
3. *Bigliani. Joint Motion: Method of Measuring and Recording: American Academy of Orthopaedic Surgeons; 1965.*
4. *Epps H, Hurley M, Utley M. Development and evaluation of a single value score to assess global range of motion in juvenile idiopathic arthritis. Arthritis Rheum 2002;47:398-402.*

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not Applicable.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

All statistical analysis of data will be performed using SAS® statistical software version 9.4 or higher (SAS Institute, NC, USA) on a suitably qualified environment.

It is planned that the data from all centers that participate in this protocol will be combined so that an adequate number of patients will be available for analysis.

All continuous variables will be summarized using descriptive statistics, including the sample size (n), mean, standard deviation (SD), minimum (min), 25th percentile (Q1), median, 75th percentile (Q3), and maximum (max).

All categorical variables will be summarized using frequency counts and percentages (%). 95% confidence intervals (CI) will be presented where appropriate. Statistical testing is considered exploratory in this observational study and no adjustment for multiplicity will be performed.

For efficacy and safety analyses, baseline will be defined as the last observation prior to the patient's first dose of Elaprase for the Efficacy Set and the Safety Set; baseline height and weight assessments will be defined as the first height and weight assessments within 3 months of the first dose of Elaprase for the HOS treated patients, and first available assessment for the untreated patients.

The following subgroups for analyses will be defined:

Age group at start of Elaprase enzyme replacement therapy (ERT) treatment:

- <2 years
- ≥2 years

Race

- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or Other Pacific Islander
- White
- Other

Pooled Race group

- Asian
- Non-Asian

Overall antibody status:

- Ab- : Patients who never had a positive antibody sample
- Ab+: Patients who had at least 1 positive antibody sample
- NAb- : Patients who never had neutralizing antibodies
- NAb+: Patients who had at least 1 neutralizing antibody sample

If sample size permits, the overall Ab+ group will be further divided into:

- O-Ab+: Occasional Ab+ patients: patients who had antibodies in 25% or less of their blood samples
- I-Ab+: Intermittent Ab+ patients: patients who had antibodies in between 25 and 50% of their blood samples
- C-Ab+: Consistently Ab+ patients: patients who had antibodies in 50% or more of their blood samples

CRIM status

- Positive
- Negative

Genotype class

- Complete Deletion/Large Rearrangement

- Inversion
- Missense
- Indel
- Deletion
- Nonsense
- Splicing
- Frameshift
- Intronic Mutation

Severity of genetic variant

- Severe
- Non-severe

9.2.2 Definition of Baseline

For efficacy and safety analyses, baseline will be defined as the last observation prior to the patient's first dose of Elaprase for the Efficacy Set and the Safety Set; baseline height and weight assessments will be defined as the first height and weight assessments within 3 months of the first dose of Elaprase for the HOS treated patients, and first available assessment for the untreated patients.

9.2.3 Definition of Visit Windows

For enrolled patients (all SHP-ELA-401 patients), the study will flow as follows:

- ***Screening Period**: Day -18 through Day 0*
- ***Baseline Visit**: Day 0 (may extend to Day 1; however, all Baseline assessments must be completed, and eligibility confirmed prior to the patient's first dose of Elaprase)*
- ***Treatment Period**: As of the first Elaprase infusion in this study until adequate data are obtained; specifically, until the patient reaches his 10th birthday or until the patient has been in the study for 5 years, whichever is longer.*
- ***One Month Study Visit**: Day 30*
- ***Bi-Annual Study Visit**: Every 6 months*
- ***Annual Study Visit**: Every 12 months*
- ***End-of-Study Visit**: After 5 years of treatment observation data are collected or until the patient reaches his 10th birthday, whichever is longer.*

The Screening Period and Baseline Visit may occur on the same day (i.e., Screening period activities may be completed on Day 0). For all study visits, up to 48 hours is allowed for completion of study activities. The study ends with the last End-of-Study Visit for the last patient.

The following visit windows will be applied for the HOS treated and untreated patients:

HOS Visit Windows (for ADVSHOS only):							
Observation	**Month**	**Year**	**Target Day**	**Window min**	**Window max**	**AVISIT**	**AVISITN**
0	0	0	1	-365	90	Baseline	0
1	6	0.5	183	123	243	6 Months	6
2	12	1	365	305	425	12 Months	12
3	18	1.5	548	488	608	18 Months	18
4	24	2	731	671	791	24 Months	24
5	30	2.5	913	853	973	30 Months	30
6	36	3	1096	1036	1156	36 Months	36
7	42	3.5	1278	1218	1338	42 Months	42
8	48	4	1461	1401	1521	48 Months	48
9	54	4.5	1644	1584	1704	54 Months	54
10	60	5	1826	1766	1886	60 Months	60
11	66	5.5	2009	1949	2069	66 Months	66
12	72	6	2192	2132	2252	72 Months	72
13	78	6.5	2374	2314	2434	78 Months	78
14	84	7	2557	2497	2617	84 Months	84
15	90	7.5	2739	2679	2799	90 Months	90
16	96	8	2922	2862	2982	96 Months	96
17	102	8.5	3105	3045	3165	102 Months	102
18	108	9	3287	3227	3347	108 Months	108
19	114	9.5	3470	3410	3530	114 Months	114
20	120	10	3653	3593	3713	120 Months	120
21	126	10.5	3835	3775	3895	126 Months	126
22	132	11	4018	3958	4078	132 Months	132
23	138	11.5	4200	4140	4260	138 Months	138
24	144	12	4383	4323	4443	144 Months	144
25	150	12.5	4566	4506	4626	150 Months	150
26	156	13	4748	4688	4808	156 Months	156
27	162	13.5	4931	4871	4991	162 Months	162
28	168	14	5114	5054	5174	168 Months	168
29	174	14.5	5296	5236	5356	174 Months	174
30	180	15	5479	5419	5539	180 Months	180
31	186	15.5	5661	5601	5721	186 Months	186

HOS Visit Windows (for ADVSHOS only):							
Observation	**Month**	**Year**	**Target Day**	**Window min**	**Window max**	**AVISIT**	**AVISIT N**
32	192	16	5844	5784	5904	192 Months	192
33	198	16.5	6027	5967	6087	198 Months	198
34	204	17	6209	6149	6269	204 Months	204

9.2.4 Imputation of missing dates

Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of treatment duration.

Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant medications (and/or therapies/procedures), including rescue medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

- Incomplete Start Date

  The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

- Missing Day and Month
  - If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
  - If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields
  - If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.
- Missing Month Only
  - The day will be treated as missing and both month and day will be replaced according to the above procedure.
- Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

- Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

- Missing Day and Month
  - If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
  - If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
  - If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.
- Missing Month Only
  - The day will be treated as missing and both month and day will be replaced according to the above procedure.
- Missing Day Only
  - If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
  - If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day

- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

- Missing Date Information for Adverse Events

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, e.g. AE start year and month are the same as the year and month of the first dose of investigational product, then the AE will be classified as treatment-emergent.

To facilitate categorization of AEs as treatment emergent, imputation of dates can be used. For AEs, the default is to only impute incomplete (i.e., partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

- Incomplete Start Date
  - Follow the same rules as above for missing dates of concomitant medications.
- Incomplete Stop Date
  - Follow the same rules as above for missing dates of concomitant medications.
- Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while both the actual and the imputed values will be used in data listings.

- Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to double-blind investigational product will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

The following imputations on treatment start and stop dates will be done for HOS treated patients:

1. If only day is missing
   - If partial start date – impute day to the first of month
   - If partial end date – impute day to the end of month
2. If Only year is present

- For start date impute to Jan 01
- For end date impute to Dec 31

Ensure that start date is on or before end date when end date is complete.

9.3 Analysis Software

SAS version 9.4 or higher.

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