**Clinical Study Protocol**

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: Amendment 2, 05 Aug 2016

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

# Clinical Trial Protocol: Study SHP-ELA-401

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|---|---|
| **Study 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 |
| **Study Phase:** | Phase IV |
| **Product Name:** | Elaprase® for intravenous (IV) infusion |
| **IND Number:** | 9579 |
| **EudraCT Number:** | 2014-004804-31 |
| **Indication:** | Hunter Syndrome (Mucopolysaccharidosis II, MPS II) |
| **Investigators:** | Multicenter |
| **Sponsor:** | Shire Human Genetic Therapies, Inc. (Shire) |
| **Sponsor Contact:** | 300 Shire Way<br>Lexington, MA 02421 USA<br>+1-617-349-0200 |
| **Medical Monitor:** | [redacted], MD |



| | Date |
|---|---|
| **Original Protocol:** | 11 June 2014 |
| **Amendment 1** | 11 November 2015 |
| **Amendment 2** | 05 August 2016 |

**Confidentiality Statement**

## SYNOPSIS

**Sponsor:**

Shire Human Genetic Therapies, Inc. (Shire)

**Name of Finished Product:**

Elaprase® for intravenous (IV) infusion

**Study 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

**Study Phase:** Phase IV

**Product, Dose, and Mode of Administration:** Elaprase for IV infusion

**Comparator, Dose, and Mode of Administration:** Not applicable

**Primary Objective(s):**

The primary 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 are receiving treatment with Elaprase:

- height
- weight

**Secondary Objective(s):**

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 are receiving treatment with Elaprase:

- urinary GAG levels (uGAG)
- 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, as measured by the Hunter-syndrome Functional Outcome in Clinical Understanding Scale (HS-FOCUS) questionnaire (shortened version)
- impact of illness on 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)

**Tertiary Objective(s):**

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

- genotype and the following parameters: residual plasma 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])

**Study Outcome Measures:**

Following are the primary variables to be assessed in this study:

- height and weight
- height and weight Z-scores
- safety assessments

Changes in the following additional variables will be assessed in this study:

- urinary GAG 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 Joint Range of Motion (JROM) scores, including global, upper-limb, and lower-limb joint scores
- distance walked, as measured by the Six Minute Walk Test (6MWT)
- quality of life (QoL), as measured by the Hunter-syndrome Functional Outcome in Clinical Understanding Scale (HS-FOCUS shortened form), 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 Childhood Health Assessment Questionnaire (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 Vineland Adaptive Behavior Scales (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
- antibody status



**Study Population:**

A minimum of 20 treatment-naive patients with MPS II will be enrolled in this study. Additionally, patients enrolled in the Hunter Outcome Survey (HOS) registry will be utilized for the analyses of height and weight; approximately 35 patients are planned for inclusion in the Primary Growth Analysis. The patient groupings for the study are defined as follows:

**Group 1—Prospective Patient Group**: Treatment-naïve patients who are <6 years of age at the time of enrollment in this study. At least 20 patients will be enrolled into this patient group in this study. A patient is considered included into this patient group if informed consent is provided and the patient is treated with Elaprase in Study SHP-ELA-401.

**Group 2—Retrospective Patient Group**: Patients who are not enrolled into Study SHP-ELA-401 but are enrolled in the HOS patient registry. While not enrolled in the present Study SHP-ELA-401, their height and weight data from HOS will be utilized in the Primary Growth Analysis for this study. The data from at least 15 patients in Group 2 will be utilized in the Primary Growth Analysis for this study. A HOS patient is considered included in this patient group if he meets the eligibility requirements described below for inclusion in the analysis.

**Study Design:**

Study SHP-ELA-401 is a long-term, open-label, multicenter, Phase IV study designed to assess longitudinal changes in height and weight in patients with MPS II who are receiving Elaprase and started Elaprase treatment at <6 years of age. Elaprase for IV infusion will be provided to patients enrolled in this study.

The study will enroll at least 20 treatment-naïve patients (Group 1—Prospective Patient Group); additionally, height and weight data from patients enrolled in the HOS registry will be utilized for the Primary Growth Analysis due to the scarcity of treatment-naïve patients (Group 2—Retrospective Patient Group). The Primary Growth Analysis will include data on approximately 35 patients with MPS II that cover either 5 years duration of treatment with Elaprase, or the time period from initiation of Elaprase treatment until the patient reaches his 10$^{th}$ birthday, whichever is longer for each individual patient.



For enrolled patients (Group 1—Prospective Patient Group only), 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 10$^{th}$ 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 10$^{th}$ birthday, whichever is longer.

Note that the Screening Period and Baseline visits may occur on the same day (ie, 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.

A minimum number of 20 treatment-naive patients are targeted for enrollment into this study (Group 1—Prospective Patient Group). Patients may be invited for entry into the study based on their known medical histories or chart reviews. Patients who meet the initial eligibility criteria of the study and whose parent(s) and/or legally authorized representatives(s) have provided informed consent will be enrolled. Patients will have a blood sample drawn for confirmatory MPS II assay. Safety will be monitored throughout the study by the assessments of AEs, concomitant medications and surgical procedures, vital signs, physical examinations, and clinical laboratory testing (clinical chemistry, hematology and urinalysis). Testing for anti-idursulfase antibodies will take place at Baseline and every 6 months through the End-of-Study Visit.

The study will monitor height, weight, joint mobility (measured by JROM), walking distance (measured by 6MWT), uGAG levels, liver and spleen volume, QoL (measured by HS-FOCUS shortened version), impact of illness on ability to function in daily life (measured by CHAQ), adaptive function (measured by VABS-II), and antibody status. Genotype and enzymatic activity of iduronate-2-sulfatase (I2S) will be collected at Baseline. Additionally, on Day 0, a blood sample for determination of cross-reactive immunologic material (CRIM) status will be obtained from Group 1—Prospective Patient Group patients for use in the development of an assay to assess CRIM status among patients with MPS II. An additional post-treatment sample for CRIM analysis will be collected at 12 months.



**Study Duration:**

The length of on-study follow-up for individual patients in Study SHP-ELA-401 Group 1—Prospective Patient Group will range from 5 to 10 years, from Screening through the End-of-Study Visit.

**Study Patient Inclusion and Exclusion Criteria:**

Group 1—Prospective Patient Group patients will be enrolled in Study SHP-ELA-401; following are the inclusion and exclusion for admission into this study.

**Group 1: Prospective Patient Group Inclusion Criteria**

Each patient must meet all inclusion criteria to be enrolled in this study.

1. The patient is male.
2. The patient is Elaprase-naïve at study entry.
3. The patient must have a documented diagnosis of MPS II. Of the 3 criteria below, the combinations (3a AND 3b) or (3a AND 3c) will be accepted as diagnostic of MPS II:

    a. The patient has a deficiency in I2S enzyme activity of ≤10% of the lower limit of the normal range as measured in plasma, fibroblasts, or leukocytes (based on the reference laboratory's normal range).

**AND**

b. The patient has a documented mutation in the I2S gene.

**OR**

c. The patient has a normal enzyme activity level of one other sulfatase as measured in plasma, fibroblasts, or leukocytes (based on the normal range of measuring laboratory).

4. The patient will be <6 years of age at the start of Elaprase treatment.
5. The patient, patient's parent(s) or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form after all relevant aspects of the 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.

**Group 1: Prospective Patient Group Exclusion Criteria**

Patients who meet any of the following criteria are not eligible for enrollment into Study SHP-ELA-401:

1. The patient has received treatment with any investigational drug or device within the 30 days prior to study entry.
2. The patient has received or is receiving treatment with idursulfase-IT.
3. The patient has received growth hormones, a cord blood infusion, or a bone marrow transplant at any time.
4. The patient has received blood product transfusions within 90 days prior to Screening.
5. The patient is unable to comply with the protocol as determined by the Investigator.
6. The patient has a history of severe or life-threatening hypersensitivity to the active substance or to any of the excipients if hypersensitivity is not controllable.



**Retrospective Data Inclusion and Exclusion Criteria:**

Group 2—Retrospective Patient Group patients will be enrolled in HOS and not Study SHP-ELA-401; however, their growth data may be included in the analysis for Study SHP-ELA-401 if the following data inclusion and exclusion criteria are met.

**Group 2: Retrospective Patient Group Data Inclusion Criteria**

Patients from Group 2—Retrospective Patient Group must meet the following criteria for their data to be included into the Study SHP-ELA-401 Primary Growth 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 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.
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.

**Group 2: Retrospective Patient Group Exclusion Criteria**
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 intended to promote growth in the time period covered by the analysis.

**Pharmacokinetic Variables:**
Not applicable.

**Pharmacodynamic Assessments:**
Not applicable.

**Outcome Assessments:**



Height and Weight
Height and weight measurements over time will be used to evaluate growth velocity. Patient height (centimeters) and weight (kilogram) will be collected and recorded.

Joint Mobility
Joint mobility will be evaluated and recorded utilizing the JROM, including global, upper-limb, and lower-limb joint scores.

Urinary GAG Levels
Urine samples for determination of uGAG levels and urine creatinine will be collected. Urinary GAG levels will be normalized to urine creatinine and reported as µg GAG/mg creatinine. Additionally, uGAG levels divided by the ULN will also be calculated.

Liver and spleen volume
Liver and spleen volume will be assessed using abdominal ultrasonography.

Distance Walked
The 6MWT will be conducted according to the American Thoracic Society guidelines for the 6MWT in patients who are able to walk. The distance achieved in meters will be recorded.

Analysis of Quality of Life
The patient QoL will be assessed using the HS-FOCUS (shortened version) questionnaire.

Childhood Health Assessment
Impact on ability to function in daily life as measured by the CHAQ (Parent Report).

Adaptive Behavior
Adaptive behavior will be measured by the parent reported VABS-II.

**Safety Assessments:**

Physical and Neurological Examination
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, neurological examination, as well as evaluation of the body systems. Any abnormal change in findings will be recorded as an adverse event (AE).

Vital Signs
Vital sign assessments will be performed and the results will be recorded. Vital signs data will be collected with the patient at rest and in a supine position and will include pulse, temperature (using a consistent method), respiration rate, and systolic and diastolic blood pressure.

Clinical Laboratory Tests
Blood and urine samples will be collected for clinical laboratory testing and the results will be recorded. All blood samples will be collected via venipuncture. Patients will be in a seated or supine position during blood collection.



Antibody Assessments
Blood samples will be collected and analyzed for determination of anti-idursulfase antibodies every 6 months in SHP-ELA-401. Serum samples will be collected for evaluation of anti-idursulfase antibodies. Analysis of anti-idursulfase antibodies will be conducted using validated 3-tier immunoassay methods (screening, confirmatory, and titer) and the anti-idursulfase antibody positive samples will be further tested for the presence of neutralizing antibodies (NAb). All blood samples for antibody testing will be collected via venipuncture or via an indwelling IV access port. Sample collection, processing, and shipping instructions will be provided in the Study Lab Manual to be provided by the central laboratory.

**Statistical Methods:**

General Methodology
All continuous variables will be summarized using descriptive statistics, including the sample size (n), mean, standard deviation (SD), minimum, 25$^{th}$ percentile, median, and 75$^{th}$ percentile. All categorical variables will be summarized using frequency counts and percentages (%). Statistical testing is considered exploratory in this study and no adjustment for multiplicity will be performed.

Analysis Populations

The following 2 analysis populations will be defined for this study:

**Combined Population:** The Combined Population will include data from all patients in both patient groups (Group 1—Prospective Patient Group and Group 2-Retrospective Patient Group). Selected efficacy analyses will be performed using the Combined Population.

**Prospective Population:** The Prospective Population will be defined as all patients in Group 1—Prospective Patient Group. All safety analyses and selected efficacy analyses will be performed using the Prospective Population.

Analysis of Safety

Safety will be evaluated through the assessment of AEs, serious adverse events (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 Prospective Population using all data from Baseline to completion of Study SHP-ELA-401 (ie, prospective data only). All safety analyses will be descriptive; no statistical testing will be performed.



Efficacy Analyses

Descriptive summaries will generally present the data overall and by visit from Baseline (defined as Day 0) for the Prospective Population. Retrospective height and weight data from start of Elaprase ERT for Group 2—Retrospective Patient Group in the Combined Population will be used in certain statistical model analyses and figures, as described below. No retrospective data will be used in analyses of other endpoints.

Primary Outcome Measure: Height and Weight; Z-scores

Height and weight Z-scores will be calculated based on the WHO growth charts normal height/weight-for-age data. Descriptive statistics for the Prospective Population at each time point for height, weight and Z-scores and for change from baseline will be calculated overall and stratified separately by age group at start of Elaprase ERT treatment (<2 years; ≥2 years), overall antibody status, and genotype class.

Height, weight, and the corresponding Z-scores from start of ERT will be plotted against age for the Combined Population. 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 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 Prospective Population and will assess the effect of antibody status on growth.

Analysis of Covariance (ANCOVA) models for the change in uGAG, 6MWT, and JROM scores in the Prospective Population will also be used to assess the effects of age group at ERT start, antibody status and genotype class. Residual plasma I2S enzyme activity results at Baseline will be summarized overall and by antibody status and genotype class.

Interim Analyses
Two interim analyses are planned.

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

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

**Date of Amendment:** 05 August 2016

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Term | Definition |
|---|---|
| 6MWT | six minute walk test |
| AAOS | American Association of Orthopedic Surgeons |
| ABC | adaptive behavior composite |
| AE | adverse event |
| AMA | American Medical Association |
| ANCOVA | analysis of covariance |
| CBC | complete blood count |
| CFR | Code of Federal Regulations |
| CHAQ | Childhood Health Assessment Questionnaire |
| CNS | central nervous system |
| CRF | case report form |
| CRIM | cross-reactive immunologic material |
| CRO | contract research organization |
| DNA | deoxyribonucleic |
| ERT | enzyme replacement therapy |
| EU | European Union |
| FDA | United States Food and Drug Administration |
| GAG | glycosaminoglycans |
| GCP | Good Clinical Practice |
| HOS | Hunter Outcome Survey |
| HRSA | US Health Resources and Services Administration |
| HS-FOCUS | Hunter-syndrome Functional Outcome in Clinical Understanding Scale |
| I2S | iduronate-2-sulfatase |
| ICH | International Conference on Harmonization |
| *IDS* | gene encoding iduronate 2-sulfatase |
| IEC | independent ethics committee |
| IND | investigational new drug application |
| IRB | institutional review board |
| IV | intravenous(ly) |
| JROM | joint range of motion |
| LS-means | least squares means |
| M6P | mannose-6-phosphate |
| MedDRA | medical dictionary for regulatory activity |
| MPS II | Mucopolysaccharidosis II (Hunter syndrome) |

| Term | Definition |
|---|---|
| PT | preferred term |
| QoL | quality of life |
| SAE | serious adverse event |
| SAS | statistical analysis system© |
| sBLA | Supplemental Biologics License Application |
| SD | standard deviation |
| SOC | system organ class |
| TEAE | treatment-emergent adverse event |
| uGAG | urinary glycosaminoglycans |
| UK | United Kingdom |
| ULN | Upper limit of normal |
| US(A) | United States of America |
| VABS-II | Vineland Adaptive Behavior Scales, Second Edition |
| WHO-DD | World Health Organization Drug Dictionary |

# 1 INTRODUCTION

## 1.1 Disease Overview

Hunter syndrome (Mucopolysaccharidosis II, [MPS II]) is a rare, X-linked lysosomal storage disease caused by deficiency of the enzyme, iduronate-2-sulfatase (I2S), which acts to cleave *O*-linked sulfate moieties from 2 glycosaminoglycan (GAG) molecules known as dermatan sulfate and heparan sulfate.[1, 2] Insufficient levels of I2S lead to excessive accumulation of GAGs within lysosomes in nearly all organs and tissues, including the central nervous system (CNS), with progressive cellular vacuolization and cell death, urinary excretion of GAGs at high levels, and the clinical manifestations of MPS II.[2, 3] The currently approved therapy for MPS II is intravenous (IV) idursulfase (Elaprase®), a recombinant human I2S for IV administration.

The incidence rate of MPS II reported from several countries around the world is similar, ranging between 0.6 and 2.0 per 100,000 male births.[1, 4-9] Although the disease is heterogeneous with regard to initial presentation, MPS II is always severe, progressive, and life-limiting, despite the use of available therapies.

The central, underlying pathophysiological process leading to the clinical manifestations of MPS II is the chronic accumulation of heparan sulfate and dermatan sulfate inside cellular lysosomes, resulting in cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction. Accumulation of these GAG species affects nearly all cell types, tissues, and organs of the body including the respiratory tract, heart, liver, spleen, leptomeninges, bones, joints, oropharynx, head, neck, and CNS. Children with MPS II appear normal at birth. The clinical manifestations of MPS II vary considerably from patient to patient with pathology in 1 organ system presenting the most prominent clinical problem in some patients and impairment in other organ systems presenting the biggest challenge in others.



In the latter stages of the disease, continued accumulation of GAG leads to progressive end-organ failure and significantly shortened life span. Although the range of progressive physical abnormalities severely curtails the MPS II patient's quality of life (QoL), approximately 60% of patients with MPS II also develop global intellectual decline and severe developmental delays. Death usually occurs in the second or third decade of life, most often from respiratory and/or cardiac failure.[2, 10]

## 1.2 Elaprase

Elaprase is a formulation of idursulfase, a purified recombinant form of human I2S, a lysosomal enzyme, to be administered weekly as an IV infusion. Idursulfase is produced by recombinant deoxyribonucleic (DNA) technology in a human cell line. Idursulfase is an enzyme that hydrolyzes the 2-sulfate esters of terminal iduronate sulfate residues from the GAGs dermatan sulfate and heparan sulfate in the lysosomes of various cell types. Elaprase is a monomeric glycoprotein that is secreted as a 525 amino acid polypeptide having 8 N-linked glycosylation sites. Elaprase contains mannose-6-phosphate (M6P) residues that target the enzyme to its site of action in the lysosome. The M6P moiety binds to specific M6P receptors in the Golgi and thus directs newly synthesized I2S to pre-lysosomal compartments. Enzyme molecules that escape this routing system are secreted by the cell, and are often recaptured by cell surface M6P

receptors and return I2S to the lysosome by the endocytic pathway.[11] Enzyme replacement therapy (ERT) with Elaprase in patients with MPS II has been demonstrated to be safe and efficacious in clinical studies.

Elaprase (idursulfase) was approved in the United States (US) on 24 July 2006 and in the European Union (EU) on 10 January 2007. Since that time, Elaprase has been approved in 58 countries and is the only available ERT treatment for MPS II, except for South Korea, where Hunterase (idursulfase-beta) is approved. The recommended dose is 0.5 mg of Elaprase per kilogram of body weight (0.5 mg/kg).

Please refer to the current edition of the Investigator's Brochure for further information concerning the safety and clinical development of Elaprase.

### 1.3 Study Overview

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 years 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. See Section 4.4 for more details on this Primary Growth Analysis.

An additional purpose of Study SHP-ELA-401 is to obtain blood samples from patients to determine their cross-reactive immunologic material (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.

CRIM status has been shown to be a useful predictor of outcomes and immune response to enzyme replacement therapy in patients with Pompe disease; CRIM-negative status is associated with poorer clinical outcomes in these patients.[16] It is unknown whether this is also true for patients with MPS II and other diseases being treated with ERT.

## 1.4 Benefit/Risk Assessment

In total, 135 individual treatment-naïve male patients have been enrolled and treated with Elaprase in completed clinical studies. These patients were representative of the general MPS II population as shown by a broad spectrum of disease manifestations. A detailed summary of the safety and efficacy of Elaprase is provided in the current edition of the Investigator's Brochure.



Across all clinical studies, Elaprase was safe and generally well tolerated. As with other enzyme-replacement therapies, some patients treated with Elaprase did experience infusion-related reactions. The infusion-related reactions were generally mild, well tolerated, and treated or ameliorated by slowing the infusion rate, interrupting infusion, or by administration of medications, such as antihistamines, antipyretics, low-dose corticosteroids or beta-agonist nebulization. The most commonly reported infusion-related adverse events included cutaneous reactions (rash, pruritus, and urticaria), headache, pyrexia, hypertension, and flushing. Additionally, some patients exposed to Elaprase in clinical studies have developed anti-idursulfase antibodies. Analyses of the immunogenicity reports found no association or increased safety risk with the type or magnitude of the immune response to Elaprase, and there have been no instances of IgE-associated anaphylaxis. No clinically important changes in laboratory profiles, vital signs, or electrocardiogram (ECG) were observed in any of the clinical studies.

Elaprase efficacy is based on results of the pivotal study (TKT024) and several supportive studies (TKT008, TKT018, TKT024EXT, and HGT-ELA-038). The greatest benefit observed in the pivotal study was one of increased endurance as measured by clinically and statistically significant improvements (compared with placebo) in distance walked during the 6-Minute Walk Test, as well as clinically relevant improvements in respiratory function as measured by the percent predicted and absolute forced vital capacity. Other benefits of Elaprase treatment have been demonstrated by statistically and clinically significant reductions in liver and spleen volumes and urine glycosaminoglycan levels, as well as clinically significant improvements in cardiac function as measured by reductions in left ventricular mass. Improvements in patients' quality of life were also observed after 1 year of treatment in the pivotal study. In a post-hoc analysis of immunogenicity, pharmacodynamic and clinical effects of Elaprase treatment were observed regardless of the patient's antibody status.

Overall, the benefits obtained from Elaprase therapy outweigh the risks, which are, at this point, well characterized in clinical studies and in real-life settings. Safety risks related to infusion-related reactions are manageable. The cumulative safety data for Elaprase from post-marketing sources complements and is consistent with the experience from the clinical development program.

## 1.5 Monitoring of Burden/Risk to Study Participants

The current study (SHP-ELA-401) is designed to assess longitudinal changes in height and weight in patients with MPS II who are receiving Elaprase and who initiated therapy with Elaprase below the age of 6 years. The study will cover either 5 years duration of treatment with Elaprase, or the time period from initiation of Elaprase treatment until the patient reaches his 10th birthday, whichever is longer.

Elaprase will be administered to patients enrolled in this study by trained healthcare providers, either in a clinical setting or, if applicable, in an at-home setting. Patients will receive once weekly IV infusions of Elaprase at a dose of 0.5 mg/kg; the dose and frequency of Elaprase infusions is the same treatment regimen that patients would follow as standard of care per approved labeling. The study visits are relatively infrequent (bi-annually after completion of Screening/Baseline visits) and up to 48 hours is permitted at each study visit for completion of study activities which, in addition to height and weight measurements, include assessments of efficacy and quality of life, and standard safety parameters (refer to Appendix 1). The study assessments were selected as being minimally invasive and feasible in the patient population, and the schedule is typical of that performed in clinical practice for patients receiving Elaprase therapy. Permitting the completion of scheduled assessments over 48 hours further reduces the burden of study participation for patients. The degree of burden and risk to patients participating in this study is, therefore, considered to be low. There is no added burden or risk beyond that which patients would expect as standard of care, and no change in burden or risk to participants is expected over the duration of the study.



As noted, patients treated with Elaprase may develop infusion-related reactions. In general, such reactions are well controlled (refer to Section 7.21.1), and no patient discontinued treatment due to an infusion-related reaction during clinical studies of Elaprase. Likewise, potential risk associated with severe hypersensitivity reactions should be continually monitored; in particular, Elaprase is contraindicated in patients with severe or life-threatening hypersensitivity to the active substance or to any of the excipients if hypersensitivity is not controllable (refer to Section 5.1.2 Group 1—Prospective Patient Group Population Exclusion Criteria). Finally, any serious adverse event (SAE) experienced by a patient during the study should be monitored for and be reported by the Investigator to the Sponsor (refer to Section 7.17.3), who should apply his/her clinical judgment as to whether the reported event alters the threshold of acceptable risk beyond that which is expected with Elaprase treatment.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective(s)

The primary 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 are receiving treatment with Elaprase:

- height
- weight

## 2.2 Secondary Objective(s)

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 are receiving treatment with Elaprase:

- urinary GAG 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, as measured by the Hunter-syndrome Functional Outcome in Clinical Understanding Scale (HS-FOCUS) questionnaire (shortened version)
- impact of illness on 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)



## 2.3 Tertiary Objective(s)

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

- genotype and the following parameters: residual plasma I2S enzyme activity, 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])

# 3 STUDY OUTCOME MEASURES

Following are the primary variables to be assessed in this study:

- height and weight
- height and weight Z-scores
- safety assessments

Changes in the following additional variables will be assessed in this study:

- urinary GAG 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
- antibody status

# 4 INVESTIGATIONAL PLAN

## 4.1 Overall Study Design and Plan

Study SHP-ELA-401 is a long-term, open-label, multicenter, Phase IV study proposed to study the longitudinal changes in height and weight in patients with MPS II who are receiving treatment with Elaprase and started Elaprase treatment 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 Elaprase at <6 years of age and continued treatment with Elaprase. Patients enrolled in this study will be followed for a minimum of 5 years after initiation of Elaprase treatment, or until they reach their 10th birthday, whichever is longer. This study will evaluate various clinical outcome measures.

Study SHP-ELA-401 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 HOS registry will be utilized for the Primary Growth Analysis (see Section 4.4 for a description of HOS).

As described in Section 4.4, the Primary Growth Analysis will include data on approximately 35 patients with MPS II that cover either 5 years 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 prospective data (obtained from patients during their participation in the present Study SHP-ELA-401) with retrospective data (obtained from patients during their participation in the HOS study) allows for sufficient data to meet the Primary Growth Analysis goals.



The patient groups are defined as follows:

**Group 1—Prospective Patient Group**: Treatment-naïve patients who are <6 years of age at the time of enrollment in this study. At least 20 patients will be enrolled into this patient group in this study. A patient is considered included into this patient group if informed consent is provided and the patient is treated with Elaprase in Study SHP-ELA-401.

**Group 2—Retrospective Patient Group**: Patients who are not enrolled into Study SHP-ELA-401 but are enrolled in the HOS patient registry. While not enrolled in the present Study SHP-ELA-401, their height and weight data from HOS will be utilized in the Primary Growth Analysis for this study. A HOS patient is considered included in this patient group if he meets the eligibility requirements described below for inclusion in the analysis.

For enrolled patients (Group 1—Prospective Patient Group only), 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.

Note that the Screening Period and Baseline visits may occur on the same day (ie, Screening period activities may be completed on Day 0). For all study visits, up to 48 hours is allowed for completion of study activities.

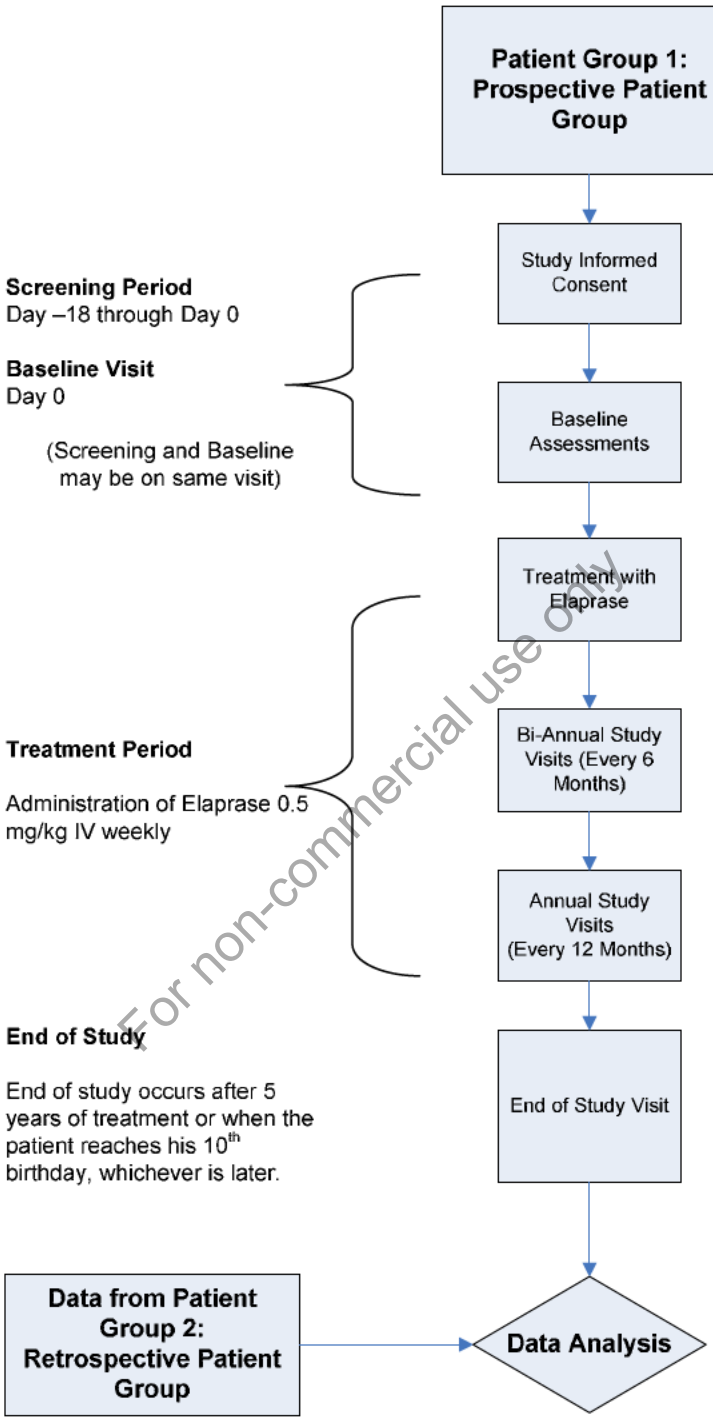
A minimum number of 20 treatment-naive patients are targeted for enrollment into this study (Group 1—Prospective Patient Group). Patients may be invited for entry into the study based on their known medical histories or chart reviews. Patients who meet the initial eligibility criteria of the study and whose parent(s) and/or legally authorized representatives(s) have provided informed consent will be enrolled. Patients will have a blood sample drawn for confirmatory MPS II assay. Safety will be monitored throughout the study by the assessments of AEs, concomitant medications and surgical procedures, vital signs, physical examinations, and clinical laboratory testing (clinical chemistry, hematology and urinalysis). Testing for anti-idursulfase antibodies will take place at Baseline and every 6 months through the End-of-Study Visit.



The study will monitor height, weight, joint mobility (measured by JROM), walking distance (measured by 6MWT), uGAG levels, liver and spleen volume, QoL (measured by HS-FOCUS shortened version), impact of illness on ability to function in daily life (measured by CHAQ), adaptive function (measured by VABS-II), and antibody status. Genotype and enzymatic activity of I2S will be collected at Baseline. Additionally, on Day 0, a blood sample for determination of cross-reactive immunologic material (CRIM) status will be obtained from Group 1—Prospective Patient Group patients only. An additional post-treatment sample for CRIM analysis will be collected at 12 months.

See Figure 4-1 for an overview of the study design and Appendix 1 for the Study Schedule of Events Table.

**Figure 4-1 Study SHP-ELA-401 Study Flow**






Note that the Screening Period and Baseline visits may occur on the same day (ie, Screening period activities may be completed on Day 0). For all study visits, up to 48 hours is allowed for completion of study activities.

Patients will return to the main site for assessments of safety and selected clinical outcomes approximately 30 days after the start of Elaprase therapy; thereafter, study assessments will occur bi-annually or annually (see Appendix 1).

The data analysis is planned to consist of a final analysis performed at the end of the study, as well as 2 interim analyses (described in Section 10.9.3).

## 4.2 Rationale for Study Design

This study is designed to evaluate growth in patients with MPS II who initiate treatment with Elaprase at <6 years of age. All patients enrolled in this study will receive once-weekly IV infusions of Elaprase at a dose of 0.5 mg/kg and will be followed for a minimum of 5 years after initiation of Elaprase treatment, or until they reach their 10th birthday, whichever is longer.

As described in Section 7, this study will monitor various clinical outcome assessments, with a focus on those that assess growth. Additionally, genotype and enzymatic activity of I2S will be collected at Baseline and antibody status will be assessed every 6 months. Blood samples will be obtained from patients to determine their CRIM status and to correlate the CRIM status with outcomes data. Assessments were selected because they are minimally invasive and are feasible. No comparator group is planned.

## 4.3 Study Duration

The length of on-study follow-up for individual patients enrolled in Study SHP-ELA-401 will range from 5 to 10 years, from Screening through the End-of-Study Visit, since the intention of Study SHP-ELA-401 is to obtain and evaluate data for patients who initiated treatment with Elaprase at <6 years of age, for a duration of 5 years from initiation of Elaprase treatment or until the patient reaches their 10th birthday, whichever is longer.



## 4.4 Primary Growth Analysis

To observe longitudinal changes in as many patients as possible with this rare disease, retrospective data will be utilized from the HOS registry for the Primary Growth Analysis; these patients are referred to in this protocol as Group 2—Retrospective Patient Group.

The HOS is a long-term, voluntary, observational registry open to all patients with MPS II. This registry was developed in conjunction with leading global experts on lysosomal storage disorders in general and patients with MPS II in particular to gain a better understanding of the nature of the disease, to improve the clinical management of patients affected by MPS II, and to monitor the long-term safety and effectiveness of Elaprase in real life.

To be utilized in the Primary Growth Analysis, Group 2—Retrospective Patient Group patient data will be used from patients who started treatment with Elaprase at <6 years of age, continued treatment with Elaprase for at least 5 years, have height and weight assessments within 3 months of the time of start of Elaprase treatment, and will have had annual height and weight measurements at the time of data extraction from HOS. See Appendix 2 for a schedule of data to be included in the Primary Growth Analysis.

As described in Section 10.3, there will be 2 analysis populations in this study. The Combined Population is the only analysis population that will utilize both Group 1 and Group 2 patient data. The final clinical study report for Study SHP-ELA-401 will also evaluate the Primary Growth Analysis results in comparison to existing data about growth in patients with MPS II not treated with Elaprase. Potential sources include cross-sectional data in HOS, published literature, and any other relevant data available at the time of the development of the final clinical study report.

# 5 STUDY POPULATION SELECTION

Study SHP-ELA-401 will enroll at least 20 treatment-naïve patients with MPS II who initiate treatment with Elaprase at <6 years of age; these enrolled patients are referred to as Group 1—Prospective Patient Group.

Additionally, due to the scarcity of treatment-naïve patients, height and weight data from at least 15 patients enrolled in the HOS registry will be utilized for the primary growth analyses for Study SHP-ELA-401. Therefore, the criteria for inclusion and exclusion of the patient height and weight data into the study analyses are described below. These patients are referred to as Group-2 Retrospective Patients.

## 5.1 Study SHP-ELA-401 Population: Prospective Patients

Study SHP-ELA-401 will enroll treatment-naïve patients who are <6 years of age at the time of enrollment in this study. At least 20 patients will be enrolled into this study. Following are the inclusion and exclusion criteria for enrollment into this study.

### 5.1.1 Group 1—Prospective Patient Group Population Inclusion Criteria

Patients must meet ALL of the inclusion criteria for his group in order to enroll in the trial.



1. The patient is male.
2. The patient is Elaprase-naïve at study entry.
3. The patient must have a documented diagnosis of MPS II. Of the 3 criteria below, the combinations (3a AND 3b) or (3a AND 3c) will be accepted as diagnostic of MPS II:
    a. The patient has a deficiency in I2S enzyme activity of ≤10% of the lower limit of the normal range as measured in plasma, fibroblasts, or leukocytes (based on the reference laboratory's normal range).

    **AND**

    b. The patient has a documented mutation in the I2S gene.

    **OR**

    c. The patient has a normal enzyme activity level of one other sulfatase as measured in plasma, fibroblasts, or leukocytes (based on the normal range of measuring laboratory).
4. The patient will be <6 years of age at the start of Elaprase treatment.
5. The patient, patient's parent(s) or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form after all relevant aspects of the 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.

### 5.1.2 Group 1—Prospective Patient Group Population Exclusion Criteria

Patients who meet any of the following criteria are not eligible for enrollment into this study.

1. The patient has received treatment with any investigational drug or device within the 30 days prior to study entry.
2. The patient has received or is receiving treatment with idursulfase-IT.

3. The patient has received growth hormones, a cord blood infusion, or a bone marrow transplant at any time.
4. The patient has received blood product transfusions within 90 days prior to Screening.
5. The patient is unable to comply with the protocol as determined by the Investigator.
6. The patient has a history of severe or life-threatening hypersensitivity to the active substance or to any of the excipients if hypersensitivity is not controllable.

## 5.2 Study SHP-ELA-401 Population: Retrospective Patients

Data from at least 15 patients who are not enrolled into Study SHP-ELA-401 but are enrolled in the HOS patient registry will be utilized in the Primary Growth Analysis for Study SHP-ELA-401. For their height and weight data to be utilized in the Primary Growth Analysis for Study SHP-ELA-401, the patient data from HOS must meet the following inclusion and exclusion criteria.

### 5.2.1 Group 2—Retrospective Patient Group Inclusion Criteria

The Retrospective HOS patient data 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.
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.



### 5.2.2 Group 2— Retrospective Patient Group Exclusion Criteria

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 intended to promote growth in the time period covered by the analysis.

# 6 STUDY TREATMENT(S)

This is an open-label study. All enrolled patients will receive once-weekly IV infusions of Elaprase at a dose of 0.5 mg/kg.

Note that the entirety of Section 6 only applies to enrolled patients, Group 1—Prospective Patient Group.

## 6.1 Description of Treatment(s)

### 6.1.1 Study Product

After informed consent is signed, all patients who meet the eligibility requirements will be enrolled. Enrolled patients will receive their first infusion at Week 1. Thereafter, each enrolled patient will receive 1 infusion of Elaprase every week, until which point each individual patient completes the study. See Section 4.3 for the duration of the study for each patient.

### 6.1.2 Comparator

Not applicable.



## 6.2 Treatment(s) Administered

The dose of Elaprase administered will be calculated based on the patient's weight at each visit. Details on Elaprase storage, preparation, and administration procedures are provided in the Pharmacy Manual. Refer to country-specific prescribing information for details concerning commercially sourced drug.

## 6.3 Selection and Timing of Dose for Each Patient

All enrolled patients will receive once-weekly IV infusions of Elaprase at a dose of 0.5 mg/kg.

## 6.4 Method of Assigning Patients to Treatment Groups

Not applicable.

## 6.5 Blinding

Not applicable.

## 6.6 Concomitant Medications, Therapies, and Medical/Surgical Interventions

All non-protocol treatments that occur from the time of informed consent through follow-up are regarded as concomitant and must be documented. These include medications, therapies and/or interventions administered to, and medical/surgical procedures performed on the study patients.

## 6.7 Restrictions

### 6.7.1 Prior Therapy

Please see Section 5.1.2 Exclusion Criteria.

### 6.7.2 Fluid and Food Intake

Not applicable.

### 6.7.3 Patient Activity Restrictions

Patients are restricted from enrolling in another clinical study that involves clinical investigations or use of any investigational product (drug or device) within 30 days prior to study enrollment or at any time during the study.

## 6.8 Treatment Compliance

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.



## 6.9 Packaging and Labeling

All packaging and labeling will be in accordance with applicable regulatory requirements.

## 6.10 Storage and Accountability

### 6.10.1 Storage

See the Pharmacy Manual, or approved labeling, as applicable, for details on product storage.

### 6.10.2 Investigational Product Retention at Study Site

See the Pharmacy Manual for details on product accountability.

# 7 STUDY PROCEDURES

Detailed descriptions of evaluations for enrolled patients (Group 1 only) required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of the study (see Schedule of Events Table in Appendix 1).

All data collected are to be recorded on the appropriate case report form (CRF, paper or electronic).

Details for study procedures, including sample collection, are described in the Study Lab Manual.

Note that the entirety of Section 7 only applies to enrolled patients, Group 1-Prospective Patient Group.

## 7.1 Informed Consent

Prior to conducting any study-related procedures, written informed consent must be obtained from the patient's parent(s) or legally authorized representative(s) and assent from the patient (if applicable).

The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the patient, the patient's parent(s), or the patient's legally authorized representative(s) by the Investigator or designee in accordance with the guidelines described in Section 11.4. Documentation and filing of informed consent documents should be completed according to Section 11.4.



## 7.2 Study Entrance Criteria

At Screening, each patient will be reviewed for eligibility against the study entrance criteria. Patients who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the patient's ineligibility for the study will be documented.

## 7.3 Confirmation of Study Eligibility

Patient eligibility according to the study inclusion and exclusion criteria will be confirmed at Baseline on the basis of review of the study entrance criteria.

## 7.4 Demographics

Patient demographic information including gender, age, ethnicity, and race will be collected.

## 7.5 Medical History

Medical history will include a review of body systems, documentation of current and prior medical procedures, documentation of current concomitant medication usage, documentation of the patient's diagnosis of MPS II.

## 7.6 MPS II Diagnosis and Genotyping

Documentation of the diagnosis of MPS II will be collected and is an inclusion criterion for enrollment in this study; see Section 5.1.1 for information on acceptable documentation of diagnosis of MPS II.

The study will collect genotype information on all patients, to be analyzed by Greenwood Medical Laboratory. Patients who have a documented genotype from Greenwood Medical Laboratory do not have to have their genotype confirmed.

The Medical Monitor will review patient genotypes and adjust enrollment, if necessary, to ensure representation in the study of patients with a variety of *IDS* mutations, eg, including patients with mutations, such as complete gene deletions or early truncations/frameshifts, which abolish I2S expression.

## 7.7 Baseline Residual Plasma Residual I2S Enzyme Activity

Residual plasma I2S enzyme activity will be collected for enrolled patients prior to the first exposure to Elaprase.

## 7.8 Cross-Reactive Immunologic Material Blood Samples

Blood samples will be collected for determination of CRIM status and the results will be utilized in the analyses. Sample collection, processing, and shipping instructions will be provided in the Study Lab Manual.



## 7.9 Elaprase Administration

Idursulfase will be administered as a continuous IV infusion over a minimum of 3 hours at a dose of 0.5 mg/kg. Details on Elaprase administration procedures are provided in the Pharmacy Manual.

Refer to country-specific prescribing information for details concerning administration of commercially sourced drug.

## 7.10 Pharmacokinetic Assessments

Not Applicable.

## 7.11 Pharmacodynamic (or Biomarker) Assessments

Not Applicable.

## 7.12 Outcome Assessments

### 7.12.1 Height and Weight

Height and weight measurements over time will be collected and recorded for all patients. The following guidance should be used to obtain height and weight measurements. The procedures

are based on the training module available from the US Health Services and Resources Administration (HRSA).

#### 7.12.1.1 Height

- For patients ≥2 years of age, or for patients who can stand on their own: height should be measured using a stadiometer which is calibrated at regular intervals. Two independent height measurements should be collected and the results recorded to the nearest 0.1 centimeter. If the measurements do not agree within 0.5 centimeter, re-measure for a third time. The method of collecting height measurements should be standardized across all sites (eg, instruction to stand looking straight ahead with the chin parallel to the floor, arms by the sides of the trunk with palms facing the thighs, and back of the head, scapulae, buttocks, and heels positioned against the vertical backboards of the stadiometer; no shoes or hats are to be worn during measurements).
- For patients <2 years of age, or patients who cannot stand on their own: length should be measured using a fixed headboard. Two individuals should conduct the measurement; 1 person positioning the child and the other collecting the length measurement. Two independent length measurements should be collected and the results recorded to the nearest 0.1 centimeter. If the measurements do not agree within 1 centimeter, re-measure for a third time. The method of collecting length measurements should be standardized across all sites (eg, placement of the child supine on the measuring board, checking that the child lies straight on the board and does not change position, shoulders touching the board; spine should not be arched. The child's legs are held down with one hand, applying gentle pressure to the knees to straighten the legs without causing injury, while the footboard is moved to a position against the child's feet with the other hand. The soles of the feet should be flat against the board with toes pointing upwards).



#### 7.12.1.2 Weight

Weight measurements should be obtained from scales that have been calibrated at regular intervals.

- For patients ≥2 years of age, or who can stand on their own: weight measurements should be collected with the child standing, without assistance, on a calibrated beam balance or electronic scale. Two independent weight measurements should be collected and the results recorded to the nearest 0.1 kilogram. If the measurements do not agree within 0.3 kilogram, re-measure for a third time. The method of collecting weight measurements should be standardized across all sites (eg, weight to be collected with the child standing on the center of the scale and wearing only lightweight undergarments or a gown).
- For patients less than <2 years of age, or patients who cannot stand on their own: weight measurements should be collected using an infant scale. Two independent weight measurements should be collected and the results recorded to the nearest 0.1 kilogram. If the measurements do not agree within 0.3 kilogram, re-measure for a third time. The method of collecting weight measurements should be standardized across all sites (eg, the child is nude or wearing a clean, dry diaper and positioned in the center of the scale tray).

### 7.12.2 Urinary GAG Levels

Urine samples for determination of uGAG levels and urine creatinine will be collected.

Urinary GAG levels will be normalized to urine creatinine and reported as mg GAG/ mmol creatinine. Additionally, uGAG levels divided by the ULN will be calculated (See Section 10.8.3).

Sample collection, processing, and shipping instructions will be described in the Study Lab Manual to be provided by the central laboratory.

In the event that a baseline urine sample is unable to be collected successfully, a historical value may be used if deemed acceptable by the Sponsor.

### 7.12.3 Liver and Spleen Volume

Liver and spleen volume will be measured by abdominal ultrasonography. Ultrasound image collection, preparation, and transfer procedures will be provided to clinical sites. Patients may require sedation or anesthesia for this procedure in accordance with local clinical practice and should be recorded appropriately as concomitant medications.

Due to the timing of Protocol Amendment 2, some patients may have enrolled in the study prior to the implementation of liver and spleen volume assessments. In these cases, missed assessments will not be considered as protocol deviations. Ultrasound imaging should still be performed when indicated per protocol, despite the fact that baseline and other visit data points may be missing for some patients.



### 7.12.4 Joint Mobility

Joint mobility will be evaluated and recorded utilizing the JROM; specifically, global, upper-limb, and lower-limb joint scores.

### 7.12.5 Distance Walked

The 6MWT will be conducted according to the American Thoracic Society guidelines for the 6MWT for patients who are able to walk. The distance achieved in meters will be recorded.

### 7.12.6 Analysis of Quality of Life

Quality of life will be assessed using the HS-FOCUS (shortened version) questionnaire.

### 7.12.7 Daily Function

Determination of how illness impacts ability to function in daily life will be assessed using the CHAQ.

### 7.12.8 Adaptive Behavior

Adaptive behavior will be assessed using the VABS-II.

## 7.13 Safety Assessments

### 7.13.1 Physical and Neurological Examination

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, neurological examination, as well as evaluation of the following body systems (See Table 7-1). Any abnormal change in findings will be recorded as an adverse event (AE).

**Table 7-1 Assessments for Physical Examinations**

| Assessment | Assessment |
|---|---|
| General appearance | Endocrine |
| Head and neck | Cardiovascular |
| Eyes | Abdomen |
| Ears | Genitourinary |
| Nose | Skin |
| Throat | Musculoskeletal |
| Chest and lungs | Neurological |



### 7.13.2 Vital Signs

Vital sign assessments will be performed and the results will be recorded. Vital signs data will be collected with the patient at rest and in a supine position and will include pulse, temperature (using a consistent method), respiration rate, and systolic and diastolic blood pressure.

### 7.13.3 Electrocardiography

Not applicable.

#### 7.13.3.1 12-Lead Electrocardiogram

Not applicable.

### 7.13.4 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing and recorded. All blood samples will be collected via venipuncture. Patients will be in a seated or supine position during blood collection. Laboratory tests will include the following (see Table 7-2):

**Table 7-2 List of Laboratory Tests**

| Hematology: | Serum Chemistry: |
|---|---|
| • Platelet count<br>• Complete blood count (CBC) count with differential | • Alanine aminotransferase<br>• Albumin<br>• Alkaline phosphatase<br>• Aspartate aminotransferase |

**Table 7-2 List of Laboratory Tests**

| | |
|---|---|
| Urinalysis:<br>• Macroscopic evaluation<br>• Microscopic evaluation<br>• pH | • Bicarbonate<br>• Chloride<br>• Cholesterol<br>• Creatine phosphokinase<br>• Creatinine<br>• Gamma-Glutamyl Transferase<br>• Glucose<br>• Lactate dehydrogenase<br>• Magnesium<br>• Phosphorous<br>• Potassium (K)<br>• Sodium<br>• Total and direct bilirubin<br>• Total calcium<br>• Total carbon dioxide<br>• Total protein<br>• Triglycerides<br>• Urea nitrogen<br>• Uric acid |



### 7.13.5 Antibody Assessments

Blood samples will be collected and analyzed for determination of anti-idursulfase antibodies.

Serum samples will be collected for evaluation of anti-idursulfase antibodies. Analysis of anti-idursulfase antibodies will be conducted using validated 3-tier immunoassay methods (screening, confirmatory, and titer) and the anti-idursulfase antibody positive samples will be further tested for the presence of neutralizing antibodies (NAb).

All blood samples for antibody testing will be collected via venipuncture or via an indwelling IV access port. Sample collection, processing, and shipping instructions will be provided in the Study Lab Manual to be provided by the central laboratory.

### 7.13.6 Pregnancy Testing

Not applicable.

## 7.14 Sample Collection, Storage, and Shipping

Sample collection, processing, and shipping instructions will be provided in the Study Lab Manual.

## 7.15 Concomitant Medications, Therapies, and Medical/Surgical Interventions Assessments

All medications, therapies/interventions administered to and medical/surgical procedures performed on the study patients from the time of informed consent through the follow-up contact are regarded as concomitant and will be recorded.

## 7.16 Confirmation of Ongoing Elaprase Treatment

Confirmation of ongoing weekly treatment with Elaprase will be recorded.

## 7.17 Adverse Events Assessments

Adverse events will be collected at weekly Elaprase infusions and at each study visit for enrolled patients (Group 1—Prospective Patient Group only). Instructions for recording and reporting AEs are provided in Section 7.17.3.

### 7.17.1 Definitions of Adverse Events and Serious Adverse Events

#### 7.17.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered product-related. This includes an exacerbation of a pre-existing condition.



Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Abnormal laboratory values (this includes significant shifts from Baseline within the range of normal that the Investigator considers to be clinically important)
- Clinically significant abnormalities in physical examination, vital signs, and weight

The Investigator must record all AEs on the AE CRF, regardless of the severity or relationship to product. The Investigator should treat patients with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. Adverse events may be discovered through observation or examination of the patient, questioning of the patient, complaint by the patient, or by abnormal clinical laboratory values.

In addition, AEs may also include laboratory values that become significantly out-of-range. In the event of an out-of-range value, the laboratory test should be repeated until it returns to normal or can be explained and the patient's safety is not at risk.

Additional illnesses present at the time when informed consent is given are regarded as concomitant illnesses and will be documented on the appropriate pages of the CRF. Illnesses first occurring or detected during the study, and worsening of a concomitant illness during the study, are to be regarded as AEs and must be documented as such in the CRF.

#### 7.17.1.2 Serious Adverse Event

An SAE is any AE that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A life-threatening AE is defined as an AE that placed the patient, in the view of the initial reporter, at immediate risk of death from the AE as it occurred (ie, it does not include an AE that, had it occurred in a more severe form, might have caused death).



#### 7.17.1.3 Infusion-Related Adverse Reaction

An infusion-related adverse reaction (hypersensitivity reaction) will be defined as an AE that 1) occurs on the day of the infusion, ie, within 24 hours following the infusion, 2) begins either during or after the infusion, and 3) is judged as possibly or probably related to idursulfase infusion.

### 7.17.2 Classification of Adverse Events and Serious Adverse Events

The severity of AEs will be assessed by the Investigator based on the definitions shown in Table 7-3. The severity of all AEs/SAEs should be recorded on the appropriate CRF page as mild, moderate, or severe.

**Table 7-3 Adverse Event Severity**

| Severity | Definition |
|---|---|
| Mild | No limitation of usual activities. |
| Moderate | Some limitation of usual activities. |
| Severe | Inability to carry out usual activities. |

Relationship of an adverse event or serious adverse event to the Elaprase is to be determined by the Investigator based on the following definitions:

**Table 7-4 Adverse Event Relatedness**

| Relationship to Product(s) | Definition |
|---|---|
| Not Related | Unrelated to investigational product. |
| Possibly Related | A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, but which could also be explained by concurrent disease or other drugs or chemicals. |
| Probably Related | A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds. |
| Definitely related | The event follows a reasonable temporal sequence from administration of the investigational product, follows a known or suspected response pattern to the investigational product, is confirmed by improvement upon stopping the investigational product (de-challenge), and reappears upon repeated exposure (re-challenge). Note that this is not to be construed as requiring re-exposure of the patient to investigational product; however, the determination of definitely related can only be used when recurrence of event is observed. |



#### 7.17.2.1 Clarification between Serious and Severe

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); however, the event itself may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) and causality serve as a guide for defining regulatory reporting obligations.

### 7.17.3 Procedures for Recording and Reporting Adverse Events

#### 7.17.3.1 Adverse Event Monitoring and Period of Observation

Adverse events will be monitored at weekly Elaprase infusions and at each study visit under the oversight of the Investigator.

For the purposes of this study, the period of observation extends from the time at which the patient, the patient's parent(s), or the patient's legally authorized representative(s) gives informed consent until the patient's final evaluation of the study. For safety purposes, the final evaluation will be defined as the End-of-Study Visit.

If the Investigator considers it necessary to report an AE in a study patient after the end of the safety observation period, he or she should contact the Sponsor to determine how the AE should be documented and reported.

#### 7.17.3.2 Reporting Serious Adverse Events

Any SAE that occurs in a patient after informed consent should be recorded by the clinical site on an SAE form. The SAE must be completely described on the patient's CRF. The Investigator

will promptly supply all information identified and requested by the Sponsor (or contract research organization [CRO]) regarding the SAE.

The Investigator must report the SAE to the Shire Pharmacovigilance and Risk Management Department AND to the Shire Medical Monitor on an SAE form. This form must be completed and FAXED or EMAILED within 24 hours of the Investigator's learning of the event to:

**Shire Pharmacovigilance and Risk Management Department:**
**International FAX: +44-1256-894715 (UK)**
**OR**
**United States FAX: +1-866-557-4473**
**Email: globalpharmacovigilance@shire.com**
**AND**
**Shire Medical Monitor: [redacted], MD**
**Email: [redacted]**
**FAX: [redacted]**

Any follow-up information must also be completed on an SAE form and faxed or emailed to the same numbers or emails listed above.

In the event of a severe and unexpected, fatal, or life-threatening SAE, the clinical site must contact the Shire Medical Monitor by telephone, in addition to completing and transmitting the SAE form as stated above. Following is contact information for the Shire Medical Monitor.

| **If an SAE is assessed as severe and unexpected, fatal, or life-threatening, contact:** |
|---|
| **[redacted], MD**<br>**Shire**<br>**300 Shire Way**<br>**Lexington, MA 02421 USA**<br>**Telephone: [redacted]**<br>**Mobile: [redacted] (24 hour access)**<br>**Email: [redacted]**<br>**Fax: [redacted]** |



The Investigator must promptly report all required information to the IRB/IEC. It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any CIOMS I/ MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The Investigator or Sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files.

### 7.18 Pregnancy

Not applicable.

## 7.19 Abuse, Overdose, and Medication Error

- **Abuse** – Persistent or sporadic intentional intake of investigational medicinal product at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (eg, altering one's state of consciousness)
- **Misuse** – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note: This includes a situation where the test article is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of investigational medicinal product higher than the approved dose.
- **Medication Error** – A mistake made in prescribing, dispensing, administration and/or use of the investigational medicinal product.

All investigational medicinal product provided to pediatrics should be supervised by the parent/legally-authorized representative/caregiver.

## 7.20 Removal of Patients from the Trial

A patient's participation in the study may be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a patient from the study:

- Non-compliance, including failure to appear at 1 or more study visits
- The patient was erroneously included in the study
- The patient develops an exclusion criterion
- The patient suffers an intolerable AE
- The study is terminated by the Sponsor



The patient, the patient's parent(s), or the patient's legally authorized representative(s) acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment.

If a patient, the patient's parent(s), or the patient's legally authorized representative(s) acting on behalf of the patient, discontinues participation in the study, or the patient is discontinued by the Investigator, reasonable efforts will be made to follow the patient through the end-of-study assessments. The reason for refusal will be documented. Any AEs experienced up to the point of discontinuation must be recorded. If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

## 7.21 Other Study Procedures

### 7.21.1 Management of Infusion-Related Adverse Events

If a patient develops an infusion-related AE during the infusion, the investigator should decide, based on his or her clinical judgment, whether the infusion should be discontinued or not. If the

nature and severity of the event requires termination of the infusion, clinical assessment should be focused on the determination of whether or not the reaction may be an IgE-mediated process. If the event is clearly anaphylaxis, then subcutaneous epinephrine should be used.

An initial study drug infusion causing a severe infusion-related AE should not be restarted.

Patients experiencing a mild infusion-related AE may be premedicated with an anti-pyretic and/or an antihistamine (eg, with diphenhydramine) for subsequent infusions. Patients experiencing a moderate or severe infusion-related AE may be premedicated with both an antihistamine and corticosteroid (eg, with diphenhydramine and hydrocortisone) in addition to acetaminophen for subsequent infusions. Premedication with ranitidine (in conjunction with hydrocortisone as a protective agent for the intestinal mucosa) may also be considered. If subsequent infusions continue without incident, then tapering of medications may also be considered.

An anaphylactoid or hypersensitivity reaction may have occurred when any two of the following criteria are observed after exposure to idursulfase:

- Involvement of the skin-mucosal tissue (eg, generalized hives, rash, pruritus, flushing, erythema, urticaria, facial edema, swollen lips-tongue-uvula)
- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia [defined as $O_2$ saturation below 88% during the infusion AND with corresponding $O_2$ saturation at least above 91% prior to infusion], respiratory, failure, or insufficiency, respiratory distress, cyanosis)
- Reduced blood pressure (systolic blood pressure less than 80 recorded during an infusion AND at least 20 points lower than the systolic blood pressure recorded prior to infusion) or associated symptoms (eg, hypotonia [collapse], syncope).



For suspected, severe or recurrent hypersensitivity reactions, an anti-idursulfase antibody sample should be drawn no sooner than 12 hours after completion of the infusion and no later than 24 hours after the end of the infusion. A second anti-idursulfase antibody specimen should be obtained 1 week (±24 hours) after the hypersensitivity reaction and PRIOR to the next weekly idursulfase infusion.

### 7.21.2 Safety-Related Study Stopping Rules

This study will be stopped and safety data reviewed if any patient experiences a life-threatening SAE or a death occurs, if either is considered possibly or probably related to the product.

Following the review of safety data, the study will be either:

- Resumed unchanged
- Resumed with modifications to the protocol
- Terminated

Patient safety will be monitored on a continuous basis during this study until the last patient completes his or her last scheduled study visit/assessment.

## 7.22 Appropriateness of Measurements

The measurements utilized in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant to the study purpose of studying the longitudinal changes in height and weight in patients with MPS II who are receiving treatment with Elaprase and started Elaprase treatment at <6 years of age. Patient CRIM status will be determined using a validated I2S CRIM assay.[17]

# 8 STUDY ACTIVITIES

Following are all activities to occur for all enrolled patients (Group 1—Prospective Patient Group only) within the present study. Please see Appendix 1 for the Schedule of Events and Figure 4-1 for the Study Flowchart.

Note that the entirety of Section 8 only applies to enrolled patients, Group 1—Prospective Patient Group.

## 8.1 Screening Period (Days -18 to Day 0)

The following procedures and observations* will be performed up to 18 days prior to enrollment:

- Study informed consent
- Confirmation of eligibility
- Demographic information
- Medical history
- Physical and neurological examination
- Concomitant medications, therapies, and procedures
- Adverse events

*The Screening and Baseline visits may be combined in a single visit.



## 8.2 Baseline Visit (Day 0)

The following procedures and observations* will be performed on Day 0:

- Blood sample for CRIM assay**
- Blood sample for MPS II confirmatory assay
  - Blood sample for genotype (Patients who have a documented genotype from Greenwood Medical Laboratory do not have to have their genotype confirmed.)
  - Blood sample for residual plasma I2S enzyme activity
- Blood sample for clinical laboratory tests
- Blood sample for anti-idursulfase antibody testing
- Height
- Weight
- Vital signs
- Collection of urine sample for GAG levels***
- Ultrasonography of liver****
- Ultrasonography of spleen****
- Quality of life (HS-FOCUS shortened version)
- Joint mobility (JROM upper and lower limbs)
- Distance walked (6MWT)
- Childhood health assessment (CHAQ)

- Adaptive behavior (VABS-II)
- Concomitant medications, therapies, and procedures
- Adverse events
- Elaprase administration: First dose of Elaprase to be administered within 1 week of baseline assessments and only after all previous assessments have been completed.

*The Screening and Baseline visits may be combined in a single visit. Baseline may last up to 48 hours (Day 0, Day 1).

## 8.3 Treatment Period (Day 1 [or Day 2] to End-of-Study Visit)

Elaprase will be administered weekly throughout the study. Details on administration procedures are provided in the Pharmacy Manual; refer to country-specific prescribing information for details concerning administration of commercially sourced drug.

Elaprase treatment will be administered under the oversight of the Investigator 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.



### 8.3.1 One Month Visit (Day 30, ±7 days)

The following procedures and observations will be performed at 1 month, calculated from Day 0:

- Collection of urine sample for GAG levels***
- Ultrasonography of liver****
- Ultrasonography of spleen****
- Concomitant medications, therapies, and procedures
- Confirmation of Elaprase administration compliance between visits
- Adverse events

### 8.3.2 Bi-Annual Visits (Every 6 months, ±14 days)

The following procedures and observations will be performed every 6 months, calculated from Day 0:

- Height
- Weight
- Blood sample collection for anti-idursulfase antibody testing
- Collection of urine sample for GAG levels***
- Ultrasonography of liver****
- Ultrasonography of spleen****
- Concomitant medications, therapies, and procedures
- Confirmation of Elaprase administration compliance between visits
- Adverse events

### 8.3.3 Annual Visits (Every 12 months, ±14 days)

The following procedures and observations will be performed every 12 months, calculated from Day 0:

- Physical and neurological examination
- Height
- Weight
- Vital signs
- Blood sample collection for clinical laboratory tests
- Blood sample for CRIM assay**
- Collection of urine sample for GAG levels***
- Ultrasonography of liver****
- Ultrasonography of spleen****
- Blood samples collection for anti-idursulfase antibody testing
- Quality of life (HS-FOCUS shortened version)
- Joint mobility (JROM upper and lower limbs)
- Distance walked (6MWT)
- Childhood health assessment (CHAQ)
- Adaptive behavior (VABS-II)
- Concomitant medications, therapies, and procedures
- Confirmation of Elaprase administration compliance between visits
- Adverse events



## 8.4 End-of-Study Visit (±14 days)

The following procedures and observations will be performed at the End-of-Study Visit:

- Physical and neurological examination
- Height
- Weight
- Vital signs
- Blood sample collection for clinical laboratory tests
- Collection of urine sample for GAG levels***
- Ultrasonography of liver****
- Ultrasonography of spleen****
- Blood sample collection for anti-idursulfase antibody testing
- Quality of life (HS-FOCUS shortened version)
- Joint mobility (JROM upper and lower limbs)
- Distance walked (6MWT)
- Childhood health assessment (CHAQ)
- Adaptive behavior (VABS-II)
- Concomitant medications, therapies, and procedures

- Confirmation of Elaprase administration compliance between visits
- Adverse events

Notes

*The Screening Period and Baseline visits may occur on the same day (ie, Screening period activities may be completed on Day 0). For all study visits, up to 48 hours is allowed for completion of study activities.

**Blood sample collection for the CRIM assay is planned at Baseline and at the 12-Month Study Visit.

***The uGAG assessment is planned at the Baseline, 1-Month, 6-Month, and 12-Month Study Visits, and annually thereafter until the End-of-Study Visit. In the event that a baseline urine sample is unable to be collected successfully, a historical value may be used if deemed acceptable by the Sponsor.

****Liver and spleen ultrasound assessments are planned at the Baseline, 1-Month, 6-Month, 12-Month, and 24-Month Study Visits, and at the End-of-Study Visit. Due to the timing of Protocol Amendment 2, some patients may have enrolled in the study prior to the implementation of liver and spleen volume assessments. In these cases, missed assessments will not be considered as protocol deviations. Ultrasound imaging should still be performed when indicated per protocol, despite the fact that baseline and other visit data points may be missing for some patients.

# 9 QUALITY CONTROL AND ASSURANCE

For all study activities that occur within Study SHP-ELA-401 (and not pertaining to HOS data collection), training will occur at an Investigator meeting or at the site initiation visit or both, and instruction manuals will be provided to aid consistency in data collection and reporting across sites.

Clinical sites will be monitored by Shire or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role(s) in the study, through a password-protected environment.

Data entered in the system will be reviewed manually for validity and completeness against the source documents by a clinical monitor from the Sponsor or its designee. If necessary, the study site will be contacted for corrections or clarifications; all missing data will be accounted for.

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance and Risk Management database.

Note that this section only applies to enrolled patients, Group 1—Prospective Patient Group.

# 10 STATISTICAL ANALYSIS

## 10.1 General Methodology

All statistical analysis will be performed by Shire Biometrics Department using statistical analysis system (SAS) software Version 9.3 or higher (SAS Institute, Cary, NC, USA). All continuous variables will be summarized using descriptive statistics, including the sample size (n), mean, standard deviation (SD), minimum, 25$^{th}$ percentile, median, and 75$^{th}$ percentile. 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.

## 10.2 Determination of Sample Size

The proposed sample size of at least 20 patients for Group 1—Prospective Patient Group 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—Prospective Patient Group and Group 2—Retrospective Patient Group.



## 10.3 Analysis Populations

The following 2 analysis populations will be defined for this study:

**Combined Population:** The Combined Population will include data from all patients in both patient groups (Group 1—Prospective Patient Group and Group 2—Retrospective Patient Group). Selected efficacy analyses will be performed using the Combined Population.

**Prospective Population:** The Prospective Population will be defined as all patients in Group 1—Prospective Patient Group. All safety analyses and selected efficacy analyses will be performed using the Prospective Population.

## 10.4 Patient Disposition

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 and analysis population will be summarized.

## 10.5 Demographics and Baseline Characteristics

Patient characteristics at the start of Elaprase treatment will be summarized for the Combined Population, overall, and by patient group. Continuous variables such as age, weight, and height will be summarized using descriptive statistics. Categorical variables, such as age group at start of Elaprase ERT (<2 years; ≥2 years) and genotype will be summarized using counts and percentages.

## 10.6 Elaprase ERT Exposure

The total duration of Elaprase ERT exposure for all patients will be summarized for the Combined Population, overall and by patient group.

## 10.7 Analysis of Safety

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 Prospective Population using all data from Study SHP-ELA-401 Baseline to study completion. All safety analyses will be descriptive; no statistical testing will be performed.

### 10.7.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.0 or higher. 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.

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.



### 10.7.2 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 PAb+, NAb+ and PNAb+ responses. Additionally, immunoglobulin G (IgG) antibody titer at each visit will be summarized by baseline CRIM status.

### 10.7.3 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.

### 10.7.4 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.

### 10.7.5 Physical Findings

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

### 10.7.6 Antibody Assessments

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

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.

### 10.7.7 Concomitant Medications/Therapies

Concomitant medications are defined as all medications taken on or after Study SHP-ELA-401 Baseline. Concomitant medications will be mapped using the World Health Organization Drug Dictionary (WHO-DD) and summarized by the therapeutic class and preferred term. Concomitant therapies will be mapped using MedDRA Version 16.0 or higher and summarized by class and preferred term.

## 10.8 Pharmacodynamic and Efficacy Analyses

Descriptive summaries will generally present the data overall and by visit from Study SHP-ELA-401 baseline for the Prospective Population.

Retrospective height and weight data from start of Elaprase ERT for Group 2—Retrospective Patient Group in the Combined Population will be used in certain statistical model analyses and figures for height and weight, as described below.

No retrospective data will be used in analyses of all other efficacy endpoints (with exception of instances in which historical data may provide missing baseline values); the Prospective Population will be utilized only.

### 10.8.1 Growth Parameters: Height and Weight

Height and weight Z-scores will be calculated based on the WHO-DD growth charts normal height/weight-for-age data. Descriptive statistics for the Prospective Population at each time point for height, weight and Z-scores and for change from baseline will be calculated overall and stratified separately by age group at start of Elaprase ERT treatment (<2 years; ≥2 years), overall antibody status, baseline CRIM status, and genotype class.



Height, weight, and the corresponding Z-scores from start of ERT will be plotted against age for the Combined Population. 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, 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 Prospective Population and will assess the effect of baseline CRIM status and antibody status on growth.

### 10.8.2 Joint Range of Motion (JROM)

See Table 10-1 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.[12] and rely on norms produced by the American Medical Association (AMA)[13] and the American Association of Orthopedic Surgeons (AAOS).[14] 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.[15] 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 Table 10-1 . The experience with MPS II patients in HOS has indicated that these are the predominantly affected joint movements[12]
- Full Score: This score will be the average of the percent scores from all the joint motions.

**Table 10-1 Study SHP-ELA-401 Overview of Joints/Motions with Normal Values and Clinically Meaningful Changes**

| 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 |
| | Extension | 70 | ≥10 |

[a] Link et al.[12]

[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 stratified separately by 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.

### 10.8.3 Urinary GAG Levels

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 below in Table 10-2.

**Table 10-2 Upper Limit of Normal for uGAG by Age Ranges**

| Age | uGAG ULN |
|---|---|
| 0-4 months | <=53.0 mg/mmol creatinine (468.6 ug/mg) |
| 5-18 months | <=31.0 mg/mmol creatinine (274.1 ug/mg) |
| 19 months-2 years | <=24.0 mg/mmol creatinine (212.2 ug/mg) |
| 3-5 years | <=16.0 mg/mmol creatinine (141.5 ug/mg) |
| 6-10 years | <=12.0 mg/mmol creatinine (106.1 ug/mg) |
| 11-14 years | <=10.0 mg/mmol creatinine (88.4 ug/mg) |
| >14 years | <=6.5 mg/mmol creatinine (57.5 ug/mg) |



Descriptive summaries for the observed values, the change from baseline and the % change from baseline in normalized uGAG will be presented for each time point overall and stratified separately by 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.

### 10.8.4 Liver Volume

Abdominal ultrasound examinations will be used to assess the liver volume. The liver volume will be calculated using the following formula:[18]

$$Liver\ Volume = 0.2618 * (AAL2 + MCL2 + STL2)$$

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 % change from baseline in liver volume will be presented for each time point overall and stratified separately by 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.

### 10.8.5 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:[18]

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

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 % change from baseline in spleen volume will be presented for each time point overall and stratified separately by 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.



### 10.8.6 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 stratified separately by 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.

### 10.8.7 Analysis of Quality of Life

The analysis of QoL will be performed from study baseline for the Prospective Population utilizing the HS-FOCUS (shortened version).

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:

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

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.



### 10.8.8 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 Prospective Population utilizing the CHAQ.

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

### 10.8.9 Analysis of Adaptive Behavior

The analysis of adaptive behavior will be performed from study baseline for the Prospective Population 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.

### 10.8.10 Analyses of the Relationship between Genotype Class, Residual Plasma I2S Enzyme Activity, and Antibody Status

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

## 10.9 Statistical/Analytical Issues

### 10.9.1 Adjustment for Covariates

Analyses utilizing ANCOVA models as described above will adjust for the baseline value of the corresponding outcome of interest as a continuous covariate in the model.

### 10.9.2 Handling of Drop-outs or Missing Data

Missing growth data will be assumed to be missing at random in statistical analyses and no imputation will be performed. Last observation carried forward may be used to impute missing data for other efficacy outcomes.



### 10.9.3 Interim Analyses

Two interim analyses are planned.

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

Interim Analysis 2 will 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 will be conducted after the last patient in the Prospective Patient Group completes 2-year assessments.

### 10.9.4 Multiple Comparisons/Multiplicity

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.

### 10.9.5 Sensitivity Analyses

The CRIM status determination at Baseline will be compared to the CRIM status determination at the 12-Month Visit to ascertain whether the established in vitro wash-out procedure is sufficient to assay I2S CRIM status in patients receiving treatment with Elaprase.

No additional sensitivity analyses are planned.

# 11 ADMINISTRATIVE CONSIDERATIONS

## 11.1 Investigators and Study Administrative Structure

Before initiation of the study, the Investigators must provide the Sponsor with a completed Form FDA 1572. Curriculum vitae must be provided for the Investigators and sub-investigators listed on Form FDA 1572.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study related duties and functions. The Investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study related duties.

## 11.2 Institutional Review Board or Independent Ethics Committee Approval

Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/IEC approval of the protocol and the informed consent form. This approval must refer to the informed consent form and to the study title, study number, and version and date of issue of the study protocol, as given by the Sponsor on the cover page of the protocol.

Status reports must be submitted to the IRB/IEC at least once per year. The IRB/IEC must be notified of completion of the study. Within 3 months of study completion or termination, a final report must be provided to the IRB/IEC. A copy of these reports will be sent to the study clinical monitor. The Investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. Unexpected, related SAEs which are reported to the US FDA (Investigational New Drug [IND] safety reports) or other regulatory agencies must be submitted promptly to the IRB/IEC.



## 11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 54, 56, and 312 and the International Conference on Harmonisation (ICH) GCP Guidelines Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

## 11.4 Patient Information and Consent

Before enrolling in the clinical study, the patient's parent(s) or legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her.

An informed consent form (assent form if applicable) that includes information about the study will be prepared and given to the patient or the patient's parent(s) or legally authorized representative(s). This document will contain all FDA and ICH-required elements. The informed consent (or assent) form must be in a language understandable to the patient or the patient's

parent(s) or legally authorized representative(s) and must specify who informed the patient, the patient's parent(s), or the patient's legally authorized representative(s).

After reading the informed consent document, the patient or the patient's parent(s) or legally authorized representative(s) must give consent in writing. Consent must be confirmed at the time of consent by the personally dated signature of the patient, the patient's parent(s) or the patient's legally authorized representative(s) and by the personally dated signature of the person conducting the informed consent discussions.

If the patient or the patient's parent(s) or legally authorized representative(s) is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the patient or by a local legally recognized alternative (eg, the patient's thumbprint or mark) or by the personally dated signature of the patient's parent(s) or the patient's legally authorized representative(s). The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent was given.

A copy of the signed and dated consent document(s) must be given to the patient or the patient's parent(s) or legally authorized representative(s). The original signed and dated consent document will be retained by the Investigator.

The Investigator will not undertake any measures specifically required solely for the clinical study until valid consent has been obtained.

A model of the informed consent form to be used in this study will be provided to the sites separately from this protocol.



## 11.5 Patient Confidentiality

Patient names will not be supplied to the Sponsor. Only the patient number and patient initials will be recorded, and if the patient name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be told that representatives of the Sponsor, a designated CRO, the IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The Investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

## 11.6 Study Monitoring

Monitoring procedures that comply with current GCP guidelines will be followed. Review of the CRF's for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor) who will review the CRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

## 11.7 Case Report Forms and Study Records

Case report forms (paper or electronic) are provided for each patient. All forms must be filled out by authorized study personnel. All corrections to the original CRF entry must indicate the reason for change. The Investigator is required to sign the CRF after all data have been captured for each patient. If corrections are made after review and signature by the Investigator, he or she must be made aware of the changes, and his or her awareness documented by resigning the CRF.

### 11.7.1 Critical Documents

Before Shire initiates the trial (ie, obtains informed consent from the first patient), it is the responsibility of the Investigator to ensure that the following documents are available to Shire or their designee:



- Completed FDA Form 1572 (Statement of Investigator), where applicable, signed, dated, and accurate
- Curricula vitae of Investigator and sub-investigator(s) (current, dated, and signed within 24 months of study initiation)
- Copy of Investigator and sub-investigator(s) current medical license (indicating license number and expiration date)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed by name, number and date of approval or re approval: protocol, any amendments, Patient Information/Informed Consent Form, and any other written information to be provided regarding patient recruitment procedures
- Copy of IRB/IEC approved Patient Information/Informed Consent Form/any other written information/advertisement (with IRB approval stamp and date of approval)
- Current list of IRB/IEC Committee members/constitution (dated within 12 months prior to study initiation)
- Financial Disclosure Form signed by Investigator and sub-investigator(s)
- Current laboratory reference ranges (if applicable)
- Laboratory certification/QA scheme/other documentation (if applicable)

Regulatory approval and notification as required must also be available; these are the responsibility of Shire.

## 11.8 Data Monitoring Committee

Not applicable.

## 11.9 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

A record of patients screened, but not entered into the study, is also to be maintained. No protocol exemption will be granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC.

Protocol modifications will only be initiated by the Sponsor and must be approved by the IRB/IEC and submitted to the FDA or other applicable international regulatory authority before initiation.



## 11.10 Premature Closure of the Study

If the Sponsor, Investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation between the Sponsor and the Investigator(s). Conditions that may warrant termination of the study or site include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure of the Investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities
- Insufficient adherence by the Investigator to protocol requirements

## 11.11 Access to Source Documentation

Regulatory authorities, the IRB/IEC, or the Sponsor may request access to all source documents, CRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines

will be followed. On-site review of the CRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

### 11.12 Data Generation and Analysis

The clinical database will be developed and maintained by a contract research organization or an electronic data capture technology provider as designated by Shire. Shire or its designee will be responsible for performing study data management activities.

Adverse events will be coded using MedDRA. Concomitant medication will be coded using WHO-DD. Centralized laboratories will be employed as described in the Study Lab Manual to aid in consistent measurement of efficacy and safety parameters.

### 11.13 Retention of Data

Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. The Sponsor will notify the Investigator if these documents must be retained for a longer period of time. It is the responsibility of the Sponsor to inform the Investigator or institution as to when these documents no longer need to be retained.



### 11.14 Financial Disclosure

The Investigator should disclose any financial interests in the Sponsor as described in 21 CFR Part 54 prior to beginning this study. The appropriate form will be provided to the Investigator by the Sponsor, which will be signed and dated by the Investigator, prior to the start of the study. The investigator should promptly update this information if any relevant changes occur in the course of the investigation or for 1 year following completion of the study.

### 11.15 Publication and Disclosure Policy

All information concerning the study material, such as patent applications, manufacturing processes, basic scientific data, and formulation information supplied by the Sponsor and not previously published are considered confidential and will remain the sole property of the Sponsor. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes.

It is understood by the Investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

The Investigator and any other clinical personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with Shire, provided Shire a copy of the draft document intended for publication, and obtained Shire's

written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential.

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# Appendix 1 Group 1—Prospective Patient Group Study Schedule of Events

| | Screening[a] Day -18 to Day 0 | Baseline[a] Day 0 | One Month (±7 Days) | Bi-Annual[a]—Every 6 Months (±14 Days) | Annual[a]—Every 12 Months (±14 Days) | End of Study[a,b] (±14 Days) |
|---|---|---|---|---|---|---|
| | Main Site | Main Site | Main Site | Main Site | Main Site | Main Site |
| Study SHP-ELA-401 Informed Consent[c] | ● | | | | | |
| Confirmation of Eligibility | ● | | | | | |
| Demographic Information | ● | | | | | |
| Medical History | ● | | | | | |
| Blood Sample for Confirmation of MPS II[d] | | ● | | | | |
| Blood Sample for CRIM Assay[i] | | ● | | | ● | |
| Blood Sample for Genotype[e] | | ● | | | | |
| Sample for Residual Plasma I2S Enzyme Activity | | ● | | | | |
| Physical and Neurological Examination | ● | | | | ● | ● |
| Height[f] | | ● | | ● | ● | ● |
| Weight[f] | | ● | | ● | ● | ● |
| Vital Signs | | ● | | | ● | ● |
| Clinical Laboratory Tests | | ● | | | ● | ● |
| Urine GAG Levels[j] | | ● | ● | ● | ● | ● |
| Anti-Idursulfase Antibody Testing | | ● | | ● | ● | ● |
| HS-FOCUS (shortened version) | | ● | | | ● | ● |
| JROM | | ● | | | ● | ● |
| 6MWT | | ● | | | ● | ● |
| CHAQ | | ● | | | ● | ● |
| VABS-II | | ● | | | ● | ● |
| Liver ultrasound[k] | | ● | ● | ● | ● | ● |
| Spleen ultrasound[k] | | ● | ● | ● | ● | ● |
| Concomitant Medications, Therapies, and Procedures | ● | ● | ● | ● | ● | ● |
| Elaprase administration[g] | | ● | | | | |

| | Screening[a] Day -18 to Day 0 | Baseline[a] Day 0 | One Month (±7 Days) | Bi-Annual[a]— Every 6 Months (±14 Days) | Annual[a]— Every 12 Months (±14 Days) | End of Study[a,b] (±14 Days) |
|---|---|---|---|---|---|---|
| | Main Site | Main Site | Main Site | Main Site | Main Site | Main Site |
| Confirmation of Elaprase administration compliance between visits | | | ● | ● | ● | ● |
| Adverse Events[h] | ● | ● | ● | ● | ● | ● |

Abbreviations: 6MWT= 6 minute walk test, CRIM= cross-reactive immunologic material, GAG= glycosaminoglycans, HS-FOCUS=Hunter syndrome Functional Outcome in Clinical Standing Scale, I2S= iduronate-2-sulfatase, JROM= joint range of motion, MPS II= mucopolysaccharidosis II

[a] The Screening Period and Baseline visits may occur on the same day (ie, Screening period activities may be completed on Day 0). For all study visits, up to 48 hours is allowed for completion of study activities.

[b] End of Study Visit is not needed if one of the annual visits took place less than 6 months previously.

[c] Informed consent must be obtained from the patient's parent(s)/legally authorized representative(s) before beginning Screening procedures.

[d] A blood sample will be drawn for confirmatory MPS II assay.

[e] Patients who have a documented genotype result from Greenwood Medical Laboratory need not have this repeated.

[f] Height and weight assessments must be performed per standardized methodology, described in the protocol (refer to Section 7.12.1).

[g] The first dose of Elaprase must be administered after all assessments are completed for Baseline at Day 0 and within 1 week after the completion of the baseline assessments. Thereafter, Elaprase will be administered weekly throughout the study. Details on administration procedures are provided in the Pharmacy Manual; refer to country-specific prescribing information for details concerning administration of commercially sourced drug. Elaprase treatment will be administered under the oversight of the Investigator 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.

[h] Adverse events will be collected at weekly Elaprase infusions and at each study visit.

[i] Blood sample collection for the CRIM assay is planned at Baseline and at the 12-Month Study Visit.

[j] The uGAG assessment is planned at the Baseline, 1-Month, 6-Month, and 12-Month Study Visits, and annually thereafter until the End-of-Study Visit. In the event that a baseline urine sample is unable to be collected successfully, a historical value may be used if deemed acceptable by the Sponsor.

[k] Liver and spleen ultrasound assessments are planned at the Baseline, 1-Month, 6-Month, 12-Month, and 24-Month Study Visits, and at the End-of-Study Visit. Due to the timing of Protocol Amendment 2, some patients may have enrolled in the study prior to the implementation of liver and spleen volume assessments. In these cases, missed assessments will not be considered as protocol deviations. Ultrasound imaging should still be performed when indicated per protocol, despite the fact that baseline and other visit data points may be missing for some patients.

## Appendix 2 Group 2—Retrospective Patient Group Data to be Utilized in Study SHP-ELA-401 Final Analysis

| | Data Used in Study SHP-ELA-401 Analysis |
|---|---|
| Confirmation of HOS informed consent[a] | ● |
| Demographic Information | ● |
| Genotype, if available | ● |
| Date of first dose of Elaprase | ● |
| Annual height assessments[b] | ● |
| Annual weight assessments[b] | ● |

MPS II= mucopolysaccharidosis II

[a] HOS Study informed consent must be confirmed for data to be utilized in the SHP-ELA-401 analysis.

[b] First height and weight assessments must be within 3 months of the first dose of Elaprase.

# Appendix 3 Protocol Amendment Summary of Changes

## AMENDMENT SUMMARY AND RATIONALE

Clinical protocol SHP-ELA-401 has been amended from the previous version to allow the Sponsor to meet postmarketing requirement (PMR) 2792-3 required under 505(o) for sBLA 125151/184.

The following major changes will be implemented in this protocol version; a detailed list of changes to the text is provided below:

- Five additional patients will be enrolled into the Prospective Patient Cohort of Study SHP-ELA-401, for a total of at least 20 prospectively enrolled patients. It is anticipated that this patient population will comprise an appropriate mix of genotype and CRIM status to allow for evaluation of the impact of CRIM status on clinical outcomes.
- Ultrasonographic measurements of liver and spleen volume will be added to the schedule of study assessments at baseline and post-treatment at the 1-Month, 6-Month, 12-Month, and 24-Month Study Visits, and at the End-of-Study Visit. CRIM status will be correlated to changes in liver and spleen volume. While changes in spleen and/or liver volume are not clinical endpoints per se, they are pharmacodynamic biomarkers which may be sensitive to change and may aid in correlating changes in outcomes with CRIM status.
- Two interim analyses are planned to satisfy PMR 2792-3. The first will examine CRIM assay results with respect to patient genotype and I2S enzyme status and will be conducted once the last patient enrolls in the study and completes baseline assessments. The second will examine the correlation of CRIM status to prospectively collected data on the antibody response, uGAG levels, liver and spleen volume, and clinical outcomes. Additionally, CRIM status will be correlated with changes in height and weight, parameters which are already being assessed in study SHP-ELA-401.



## DETAILED SUMMARY OF CHANGES FOR THE AMENDMENT

This is a section that has been updated to list changes from the previous protocol version. Noteworthy changes and additions to the protocol text are captured below. **Bold** text indicates new text. ~~Strikethrough~~ text indicates deleted text.

Changes in grammar, spelling, punctuation, format, minor editorial changes (including changes for consistency and clarity), and refinements to the introductory text, list of abbreviations and cross references are not reflected in this change summary.

| Change: Change to planned enrollment and Primary Growth Analysis |
|---|
| Section impacted by this change: 1.3 Study Overview |
| Revised Text:<br>The study will enroll at least ~~15~~ **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.<br><br>The Primary Growth Analysis will include data on ~~at least 30~~ **approximately 35** patients with MPS II that |

| |
|---|
| cover either 5 years 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. See Section 4.4 for more details on this Primary Growth Analysis. |
| Other sections impacted by this change: Synopsis; 4.1 Overall Study Design and Plan; 5 Study Population Selection; 5.1 Study SHP-ELA-401 Population: Prospective Patients; 10.2 Determination of Sample Size |

| |
|---|
| Change: Addition of CRIM status evaluation and interpretation |
| Section impacted by this change: 1.3 Study Overview |
| Revised Text:<br>**An additional purpose of Study SHP-ELA-401 is to obtain blood samples from patients to determine their cross-reactive immunologic material (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.**<br><br>**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.**<br><br>**CRIM status has been shown to be a useful predictor of outcomes and immune response to enzyme replacement therapy in patients with Pompe disease; CRIM-negative status is associated with poorer clinical outcomes in these patients.[16] It is unknown whether this is also true for patients with MPS II and other diseases being treated with ERT.** |
| Other sections impacted by this change: 12 List of References |



| |
|---|
| Change: Change to study objectives |
| Section impacted by this change: 2.2 Secondary Objective(s) and 2.3Tertiary Objective(s) |
| Revised Text:<br>**2.2 Secondary Objective(s)**<br>• **liver and spleen volume**<br>**2.3 Tertiary Objective(s)**<br>• genotype and the following parameters: residual plasma I2S enzyme activity, **CRIM status,** and antibody status<br>• **CRIM status and the following parameters: height, weight, walking, joint mobility, uGAG levels, liver and spleen volume**<br>• **CRIM status and the following parameters: safety (adverse events, infusion-related adverse reactions [hypersensitivity reactions])** |
| Other sections impacted by this change: Synopsis |

| Change: Change to study outcome measures |
|---|
| Section impacted by this change: 3 Study Outcome Measures |
| Revised Text:<br>Changes in the following additional variables will be assessed in this study:<br>• **liver and spleen volume** |
| Other sections impacted by this change: Synopsis |

| Change: Addition of visit to the study schedule of events |
|---|
| Section impacted by this change: 4.1 Overall Study Design and Plan |
| Revised Text:<br>For enrolled patients (Group 1—Prospective Patient Group only), the study will flow as follows:<br>• **Screening Period:** Day -18 through Day 0<br>• **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)<br>• **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.<br>• **One Month Study Visit: Day 30**<br>• **Bi-Annual Study Visit:** Every 6 months<br>• **Annual Study Visit:** Every 12 months<br>• **End-of-Study Visit:** After 5 years of treatment observation data are collected or until the patient reaches his 10th birthday, whichever is longer. |
| Other sections impacted by this change: Synopsis; Figure 4-1 Study SHP-ELA-401 Study Flow; 8.3.1 One Month Visit (Day 30, ±7 days); Appendix 1 Group 1—Prospective Patient Group Study Schedule of Events |



| Change: Clarifications of changes to study plan |
|---|
| Section impacted by this change: 4.1 Overall Study Design and Plan |
| Revised Text:<br>A minimum number of ~~15~~ **20** treatment-naive patients are targeted for enrollment into this study (Group 1—Prospective Patient Group). Patients may be invited for entry into the study based on their known medical histories or chart reviews. Patients who meet the initial eligibility criteria of the study and whose parent(s) and/or legally authorized representatives(s) have provided informed consent will be enrolled. ~~Patients without a documented biochemical or genetic diagnosis of MPS II will have blood drawn for confirming genetic diagnosis~~. **Patients will have a blood sample drawn for confirmatory MPS II assay**. Safety will be monitored throughout the study by the assessments of AEs, concomitant medications and surgical procedures, vital signs, physical examinations, and clinical laboratory testing (clinical chemistry, hematology and urinalysis). Testing for anti-idursulfase antibodies will take place at Baseline and every 6 months **through the End-of-Study Visit.**<br><br>The study will monitor height, weight, joint mobility (measured by JROM), walking distance (measured by 6MWT), uGAG levels, **liver and spleen volume,** QoL (measured by HS-FOCUS shortened version), impact of illness on ability to function in daily life (measured by CHAQ), adaptive function (measured by VABS-II), and antibody status. Genotype and enzymatic activity of I2S will be collected at Baseline. Additionally, on Day 0, a blood sample for determination of cross-reactive immunologic material (CRIM) status will be obtained from Group 1—Prospective Patient Group patients only. **An additional post-treatment sample for CRIM analysis will be collected at 12 months.** |
| Other sections impacted by this change: Synopsis; 8 Study Activities; Appendix 1 Group 1—Prospective Patient Group Study Schedule of Events |

| Change: Expansion of study purpose |
|---|
| Section impacted by this change: 4.2 Rationale for Study Design |
| Revised Text:<br>As described in Section 7, this study will monitor various clinical outcome assessments, with a focus on those that assess growth. Additionally, genotype and enzymatic activity of I2S will be collected at Baseline and antibody status will be assessed every 6 months. **Blood samples will be obtained from patients to determine their CRIM status and to correlate the CRIM status with outcomes data.** Assessments were selected because they are minimally invasive and are feasible. No comparator group is planned. |
| Other sections impacted by this change: Synopsis; 1.3 Study Overview; 2.2 Secondary Objective(s) and 2.3 Tertiary Objective(s); 4.1 Overall Study Design and Plan |

| Change: Description of plan to monitor enrollment |
|---|
| Section impacted by this change: 7.6 MPS II Diagnosis and Genotyping |
| Revised Text:<br>**The Medical Monitor will review patient genotypes and adjust enrollment, if necessary, to ensure representation in the study of patients with a variety of *IDS* mutations, eg, including patients with mutations, such as complete gene deletions or early truncations/frameshifts, which abolish I2S expression.** |
| Other sections impacted by this change: None |

| Change: Addition of blood sample collections for CRIM status determination |
|---|
| Section impacted by this change: 7.8 Cross-Reactive Immunologic Material Blood Samples |
| Revised Text:<br>~~A blood sample for determination of CRIM status will be obtained for assay development and potentially for exploratory analyses~~. **Blood samples will be collected for determination of CRIM status and the results will be utilized in the analyses. Sample collection, processing, and shipping instructions will be provided in the Study Lab Manual.** |
| Other sections impacted by this change: 8 Study Activities; Appendix 1 Group 1—Prospective Patient Group Study Schedule of Events |



| Change: Clarification to uGAG collection |
|---|
| Section impacted by this change: 7.12.2 Urinary GAG Levels |
| Revised Text:<br>Urine samples for determination of uGAG levels and urine creatinine will be collected.<br><br>Urinary GAG levels will be normalized to urine creatinine and reported as ~~µg~~ **mg** GAG/~~mg~~ **mmol** creatinine. Additionally, uGAG levels divided by the ULN will be calculated **(See Section** 10.8.3**)**.<br><br>Sample collection, processing, and shipping instructions will be **described** ~~provided~~ in the Study Lab Manual to be provided by the central laboratory.<br><br>I**n the event that a baseline urine sample is unable to be collected successfully, a historical value may be used if deemed acceptable by the Sponsor.** |
| Other sections impacted by this change: 8 Study Activities; Appendix 1 Group 1—Prospective Patient Group Study Schedule of Events (footnote j) |

| Change: Addition of liver and spleen volume assessments |
|---|
| Section impacted by this change: 7.12.3 Liver and Spleen Volume |
| Revised Text:<br>**Liver and spleen volume will be measured by abdominal ultrasonography. Ultrasound image collection, preparation, and transfer procedures will be provided to clinical sites. Patients may require sedation or anesthesia for this procedure in accordance with local clinical practice and should be recorded appropriately as concomitant medications.**<br>**Due to the timing of Protocol Amendment 2, some patients may have enrolled in the study prior to the implementation of liver and spleen volume assessments. In these cases, missed assessments will not be considered as protocol deviations. Ultrasound imaging should still be performed when indicated per protocol, despite the fact that baseline and other visit data points may be missing for some patients.** |
| Other sections impacted by this change: 8 Study Activities; Appendix 1 Group 1—Prospective Patient Group Study Schedule of Events (footnote k) |

| Change: Reference to CRIM assay |
|---|
| Section impacted by this change: 7.22 Appropriateness of Measurements |
| Revised Text:<br>~~All~~ **The** measurements utilized in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant to the study purpose of studying the longitudinal changes in height and weight in patients with MPS II who are receiving treatment with Elaprase and started Elaprase treatment at <6 years of age. **Patient CRIM status will be determined using a validated I2S CRIM assay.**[17] |
| Other sections impacted by this change: 12 List of References |

| Change: Change to planned assessments |
|---|
| Section impacted by this change: 8 Study Activities |
| Revised Text:<br>**8.2 Baseline Visit (Day 0)**<br>The following procedures and observations* will be performed on Day 0:<br>• Blood sample for CRIM assay**<br>• Blood sample for MPS II confirmatory assay ~~(only for patients without a biochemical diagnosis of MPS II)~~<br>  • Blood sample for genotype **(Patients who have a documented genotype from Greenwood Medical Laboratory do not have to have their genotype confirmed.)**<br>  • Blood sample for residual plasma I2S enzyme activity<br>• Collection of urine sample for GAG levels***<br>• **Ultrasonography of liver******<br>• **Ultrasonography of spleen******<br><br>**8.3.1 One Month Visit (Day 30, ±7 days)**<br>**The following procedures and observations will be performed at 1 month, calculated from Day 0:**<br>• **Collection of urine sample for GAG levels*****<br>• **Ultrasonography of liver******<br>• **Ultrasonography of spleen******<br>• **Concomitant medications, therapies, and procedures** |

- **Confirmation of Elaprase administration compliance between visits**
- **Adverse events**

**8.3.2 Bi-Annual Visits (Every 6 months, ±14 days)**

The following procedures and observations will be performed every 6 months, calculated from Day 0:

- **Collection of urine sample for GAG levels**[***]
- **Ultrasonography of liver**[****]
- **Ultrasonography of spleen**[****]

**8.3.3 Annual Visits (Every 12 months, ±14 days)**

The following procedures and observations will be performed every 12 months, calculated from Day 0:

- **Blood sample for CRIM assay**[**]
- Collection of urine sample for GAG levels[***]
- **Ultrasonography of liver**[****]
- **Ultrasonography of spleen**[****]

**8.4 End-of-Study Visit (±14 days)**

The following procedures and observations will be performed at the End-of-Study Visit:

- Collection of urine sample for GAG levels[***]
- **Ultrasonography of liver**[****]
- **Ultrasonography of spleen**[****]

**Notes**

[*]The Screening Period and Baseline visits may occur on the same day (ie, Screening period activities may be completed on Day 0). For all study visits, up to 48 hours is allowed for completion of study activities.

[**]**Blood sample collection for the CRIM assay is planned at Baseline and at the 12-Month Study Visit.**

[***]**The uGAG assessment is planned at the Baseline, 1-Month, 6-Month, and 12-Month Study Visits, and annually thereafter until the End-of-Study Visit. In the event that a baseline urine sample is unable to be collected successfully, a historical value may be used if deemed acceptable by the Sponsor.**

[****]**Liver and spleen ultrasound assessments are planned at the Baseline, 1-Month, 6-Month, 12-Month, and 24-Month Study Visits, and at the End-of-Study Visit. Due to the timing of Protocol Amendment 2, some patients may have enrolled in the study prior to the implementation of liver and spleen volume assessments. In these cases, missed assessments will not be considered as protocol deviations. Ultrasound imaging should still be performed when indicated per protocol, despite the fact that baseline and other visit data points may be missing for some patients.**

Other sections impacted by this change: 8 Study Activities; Appendix 1 Group 1—Prospective Patient Group Study Schedule of Events (footnotes d, i, j, k)

Change: Changes to planned statistical analysis

Section impacted by this change: 10 Statistical Analysis

Revised Text:

**10.7.1 Adverse Events**

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) **Version 16.0 or**

**higher.** 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.

**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.**

**10.7.2 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 PAb+, NAb+ and PNAb+ responses. Additionally, immunoglobulin G (IgG) antibody titer at each visit will be summarized by baseline CRIM status.**

**10.7.6 Antibody Assessments**

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.

**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.**

**10.8 Pharmacodynamic and Efficacy Analyses**

No retrospective data will be used in analyses of all other efficacy endpoints **(with exception of instances in which historical data may provide missing baseline values);** the Prospective Population will be utilized only.

Other sections impacted by this change: None

Change: Changes to planned statistical analysis relating to CRIM status correlations

Section impacted by this change: 10 Statistical Analysis

Revised Text:

**10.8.1 Growth Parameters: Height and Weight**

Height and weight Z-scores will be calculated based on the WHO-DD growth charts normal height/weight-for-age data. Descriptive statistics for the Prospective Population at each time point for height, weight and Z-scores and for change from baseline will be calculated overall and stratified separately by age group at start of Elaprase ERT treatment (<2 years; ≥2 years), overall antibody status, **baseline CRIM status,** and genotype class.

Height, weight, and the corresponding Z-scores from start of ERT will be plotted against age for the Combined Population. 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, 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 Prospective Population and will assess the effect of **baseline CRIM status** and antibody status on growth.

Other sections impacted by this change: 10.8.2 Joint Range of Motion (JROM); 10.8.3 Urinary GAG Levels; 10.8.6 Distance Walked via Six Minute Walk Test (6MWT); 10.8.7 Analysis of Quality of Life; 10.8.8 Analysis of Daily Function; 10.8.9 Analysis of Adaptive Behavior; 10.8.10 Analyses of the Relationship between Genotype Class, Residual Plasma I2S Enzyme Activity, and Antibody Status

Change: Addition of analyses of liver and spleen volumes

Section impacted by this change: 10 Statistical Analysis

Revised Text:

**10.8.4 Liver Volume**

**Abdominal ultrasound examinations will be used to assess the liver volume. The liver volume will be calculated using the following formula:[18]**

***Liver Volume = 0.2618 * (AAL2 + MCL2 + STL2)***

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

***0.53 x 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 % change from baseline in liver volume will be presented for each time point overall and stratified separately by 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.**

**10.8.5 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:[18]**

***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 x 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 % change from baseline in spleen volume will be presented for each time point overall and stratified separately by 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.**

Other sections impacted by this change: 12 List of References

| |
|---|
| Change: Addition of interim analyses to support completion of PMR 2792-3 |
| Section impacted by this change: 10.9.3 Interim Analyses |
| Revised Text:<br>~~No interim analysis is planned during the course of the study.~~<br><br>**Two interim analyses are planned.**<br><br>**Interim Analysis 1 will examine CRIM assay results with respect to patient genotype and I2S enzyme status. This analysis is intended to evaluate suitability of blood samples for CRIM testing by confirming that the CRIM status determination is consistent with patient genotype. Patients with severe disease presentations, eg, as a result of complete deletion or early truncation of I2S enzyme-coding sequence, would be expected to test CRIM-negative. Interim Analysis 1 will be conducted once the last patient in the Prospective Patient Group enrolls in the study and completes baseline assessments.**<br><br>**Interim Analysis 2 will 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 will be conducted after the last patient in the Prospective Patient Group completes 2-year assessments.**<br><br>~~Following the completion of the study and collection and verification of all final data, the database will be locked and the results of the planned statistical analysis will be described in a final study report.~~ |
| Other sections impacted by this change: Synopsis |

| |
|---|
| Change: Addition of sensitivity analysis comparing CRIM assay results at baseline and post treatment |
| Section impacted by this change: 10.9.5 Sensitivity Analysis |
| Revised Text:<br>**The CRIM status determination at Baseline will be compared to the CRIM status determination at the 12-Month Visit to ascertain whether the established in vitro wash-out procedure is sufficient to assay I2S CRIM status in patients receiving treatment with Elaprase.**<br>No **additional** sensitivity analyses are planned. |
| Other sections impacted by this change: None |

## Appendix 4 Protocol Signature Page

**Study 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

**Final Date:** 05 August 2016

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

**Signatory:**

**Investigator**

_____
**Signature** **Date**

_____
**Printed Name**



I have read and approve the protocol described above.

**Signatory:**

**Shire Medical Monitor** [redacted]

[redacted], MD
**Printed Name**

# Appendix 3 Protocol Amendment Summary of Changes

## AMENDMENT SUMMARY AND RATIONALE

Clinical protocol SHP-ELA-401 has been amended from the previous version as follows. The changes are intended to incorporate feedback obtained from participating clinical sites and to implement regulatory authority recommendations.

- Clarification to the instructions for obtaining height and weight measurements.
- Permitting a visit window of 48 hours for sites to complete scheduled procedures.
- With Sponsor approval, allowing home infusion of Elaprase by a trained healthcare provider.
- Per BfArM (Germany), addition of an assessment of the risk and burden of study participation to patients; addition of contraindications to the study exclusion criteria per Elaprase labeling.
- Notification of a change in Medical Monitor contact information
- Clarification to instructions for AE collection and the AE severity scale; inclusion of definitions for AE relatedness terms and infusion-related adverse reactions; addition of instructions for management of infusion-related adverse events.

## DETAILED SUMMARY OF CHANGES FOR THE AMENDMENT 1

This is a section that has been updated to describe significant changes from the original protocol version. Noteworthy changes and additions to the protocol text are captured below. **Bold** text indicates new text. ~~Strikethrough~~ text indicates deleted text.

Changes in grammar, spelling, punctuation, format, minor editorial changes (including changes for consistency and clarity), and refinements to the introductory text, list of abbreviations and cross references are not reflected in this change summary.



| Change: Addition of section regarding benefit/risk assessment of patients treated with Elaprase in completed clinical studies |
|---|
| Section impacted by this change: Section 1, Introduction |
| Revised Text:<br>**Section 1.4 Benefit/Risk Assessment**<br>**In total, 135 individual treatment-naïve male patients have been enrolled and treated with Elaprase in completed clinical studies. These patients were representative of the general MPS II population as shown by a broad spectrum of disease manifestations. A detailed summary of the safety and efficacy of Elaprase is provided in the current edition of the Investigator's Brochure.**<br><br>**Across all clinical studies, Elaprase was safe and generally well tolerated. As with other enzyme-replacement therapies, some patients treated with Elaprase did experience infusion-related reactions. The infusion-related reactions were generally mild, well tolerated, and treated or ameliorated by slowing the infusion rate, interrupting infusion, or by administration of medications, such as antihistamines, antipyretics, low-dose corticosteroids or beta-agonist nebulization. The most commonly reported infusion-related adverse events included cutaneous reactions (rash, pruritus, and urticaria), headache, pyrexia, hypertension, and flushing. Additionally, some patients exposed to Elaprase in clinical studies have developed anti-idursulfase antibodies. Analyses of the immunogenicity reports found no association or increased safety risk with the type or magnitude of the immune response to Elaprase, and there have been no instances of IgE-associated anaphylaxis. No clinically important changes in laboratory profiles, vital signs, or ECG were observed in any of the** |

**clinical studies.**

**Elaprase efficacy is based on results of the pivotal study (TKT024) and several supportive studies (TKT008, TKT018, TKT024EXT, and HGT-ELA-038). The greatest benefit observed in the pivotal study was one of increased endurance as measured by clinically and statistically significant improvements (compared with placebo) in distance walked during the 6-Minute Walk Test, as well as clinically relevant improvements in respiratory function as measured by the percent predicted and absolute forced vital capacity. Other benefits of Elaprase treatment have been demonstrated by statistically and clinically significant reductions in liver and spleen volumes and urine glycosaminoglycan levels, as well as clinically significant improvements in cardiac function as measured by reductions in left ventricular mass. Improvements in patients' quality of life were also observed after 1 year of treatment in the pivotal study. In a post-hoc analysis of immunogenicity, pharmacodynamic and clinical effects of Elaprase treatment were observed regardless of the patient's antibody status.**

**Overall, the benefits obtained from Elaprase therapy outweigh the risks, which are, at this point, well characterized in clinical studies and in real-life settings. Safety risks related to infusion-related reactions are manageable. The cumulative safety data for Elaprase from post-marketing sources complements and is consistent with the experience from the clinical development program.**

Other sections impacted by this change: Not applicable

Change: Addition of a section regarding monitoring of burden/risk to participants in this study (SHP-ELA-401)

Section impacted by this change: Section 1, Introduction

Revised Text:

**Section 1.5 Monitoring of Burden/Risk to Study Participants**

**The current study (SHP-ELA-401) is designed to assess longitudinal changes in height and weight in patients with MPS II who are receiving Elaprase and who initiated therapy with Elaprase below the age of 6 years. The study will cover either 5 years duration of treatment with Elaprase, or the time period from initiation of Elaprase treatment until the patient reaches his 10th birthday, whichever is longer.**

**Elaprase will be administered to patients enrolled in this study by trained healthcare providers, either in a clinical setting or, if applicable, in an at-home setting. Patients will receive once weekly IV infusions of Elaprase at a dose of 0.5 mg/kg; the dose and frequency of Elaprase infusions is the same treatment regimen that patients would follow as standard of care per approved labeling. The study visits are relatively infrequent (bi-annually after completion of Screening/Baseline visits) and up to 48 hours is permitted at each study visit for completion of study activities which, in addition to height and weight measurements, include assessments of efficacy and quality of life, and standard safety parameters (refer to Appendix 1). The study assessments were selected as being minimally invasive and feasible in the patient population, and the schedule is typical of that performed in clinical practice for patients receiving Elaprase therapy. Permitting the completion of scheduled assessments over 48 hours further reduces the burden of study participation for patients. The degree of burden and risk to patients participating in this study is, therefore, considered to be low. There is no added burden or risk beyond that which patients would expect as standard of care, and no change in burden or risk to participants is expected over the duration of the study.**

**As noted, patients treated with Elaprase may develop infusion-related reactions. In general, such reactions are well controlled (refer to Section 7.21.1), and no patient discontinued treatment due to an infusion-related reaction during clinical studies of Elaprase. Likewise, potential risk associated with severe hypersensitivity reactions should be continually monitored; in particular, Elaprase is contraindicated in patients with severe or life-threatening hypersensitivity to the active substance or to any of the excipients if hypersensitivity is not controllable (refer to Section 5.1.2 Group 1—**

| |
|---|
| **Prospective Patient Group Population Exclusion Criteria). Finally, any serious adverse event (SAE) experienced by a patient during the study should be monitored for and be reported by the Investigator to the Sponsor (refer to Section 7.17.3), who should apply his/her clinical judgment as to whether the reported event alters the threshold of acceptable risk beyond that which is expected with Elaprase treatment.** |
| Other sections impacted by this change: Not applicable |

| |
|---|
| Change: Baseline Visit (Day 0) may also extend to Day 1; however all assessments must be performed and eligibility confirmed prior to first dose of Elaprase |
| Section impacted by this change: Section 4.1, Overall Study Design and Plan |
| Revised Text:<br>• **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)** |
| Other sections impacted by this change: Synopsis, Study Design; Section 8.2, Baseline Visit; Section 10, Statistical Analysis |

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| Change: Visit window of 48 hours for completion of study activities for all visits |
| Section impacted by this change: Section 4.1, Overall Study Design and Plan |
| Revised Text:<br><br>Note that the Screening Period and Baseline visits may occur on the same day **(ie, Screening period activities may be completed on Day 0). For all study visits, up to 48 hours is allowed for completion of study activities.**<br><br>**Footnote to Figure 4-1, Study SHP-ELA-401 Study Flow added:**<br><br>**Note that the Screening Period and Baseline visits may occur on the same day (ie, Screening period activities may be completed on Day 0). For all study visits, up to 48 hours is allowed for completion of study activities.** |
| Other sections impacted by this change: Synopsis, Study Design; Section 8, Study Activities; Section 8.2, Baseline Visit; Appendix 1, Group 1—Prospective Patient Group Study Schedule of Events |



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| Change: Exclusion criterion regarding hypersensitivity to active substance or excipients added for Group 1: Prospective Patient Group |
| Section impacted by this change: Section 5.1.2, Group 1—Prospective Patient Group Population Exclusion Criteria |
| Revised Text:<br>**6. The patient has a history of severe or life-threatening hypersensitivity to the active substance or to any of the excipients if hypersensitivity is not controllable.** |
| Other sections impacted by this change: Synopsis, Study Patient Inclusion and Exclusion Criteria |

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| Change: Clarification concerning treatment |
| Section impacted by this change: Section 6.2, Treatment(s) Administered |
| Revised Text:<br>The dose of Elaprase administered will be calculated based on the patient's weight at each visit. Details on Elaprase storage, preparation, and administration procedures are **provided** ~~outlined~~ in the **Pharmacy** ~~Study~~ |

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| ~~Operations~~ Manual. **Refer to country-specific prescribing information for details concerning commercially sourced drug**. |
| Other sections impacted by this change: Not applicable |

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| Change: Clarification concerning restrictions |
| Section impacted by this change: Section 6.7.2, Fluid and Food Intake |
| Revised Text:<br>**Not applicable.** ~~Patients are to follow Elaprase current country-specific prescribing information throughout the course of this study.~~ |
| Other sections impacted by this change: Not applicable |

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| Change: Home infusion of Elaprase by a trained healthcare provider allowed, with Sponsor approval |
| Section impacted by this change: Section 6.8, Treatment Compliance |
| Revised Text:<br>**All enrolled patients will receive once weekly treatment with Elaprase under the oversight of the Investigator.** ~~Treatment with~~ 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 ~~and in the controlled environment of a clinical center~~; 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.** |
| Other sections impacted by this change: Section 8.3, Treatment Period (Day 1 [or Day 2] to End of Study Visit); Appendix 1, Group 1—Prospective Patient Group Study Schedule of Events |



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| Change: Clarification concerning storage and accountability |
| Section impacted by this change: Section 6.10, Storage and Accountability |
| Revised Text:<br>**6.10 Storage and Accountability**<br><br>See the **Pharmacy** ~~Study Operations~~ Manual, **or approved labeling, as applicable**, for details on **product** storage ~~and accountability~~.<br><br>**6.10.2 Investigational Product Retention at Study Site**<br><br>See the **Pharmacy** ~~Study Operations~~ Manual for details on **product** ~~storage and~~ accountability. |
| Other sections impacted by this change: Not applicable |

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| Change: Clarification to product administration |
| Section impacted by this change: Section 7.9, Elaprase Administration |
| Revised Text:<br>~~Not applicable~~. **Idursulfase will be administered as a continuous IV infusion over a minimum of 3 hours at a dose of 0.5 mg/kg. Details on Elaprase administration procedures are provided in the Pharmacy Manual.**<br><br>**Refer to country-specific prescribing information for details concerning administration of** |

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| **commercially sourced drug.** |
| Other sections impacted by this change: Appendix 1, Group 1—Prospective Patient Group Study Schedule of Events |

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| Change: Clarification to the instructions for obtaining height measurements |
| Section impacted by this change: Section 7.12.1, Height and Weight |
| Revised Text:<br>**7.12.1 Height and Weight**<br><br>Height and weight measurements over time will be collected and recorded for all patients. **The** following ~~specific~~ **guidance** should be **used** to ~~for~~ obtain~~ing~~ height **and weight** measurements. **The procedures are based on the training module available from the US Health Services and Resources Administration (HRSA).**<br><br>**7.12.1.1 Height**<br><br>• For patients ≥2 years of age, **or for patients who can stand on their own**: height ~~measurements~~ should be ~~collected~~ measured using a ~~calibrated~~ stadiometer **which is calibrated at regular intervals. Two independent height measurements should be collected and the results recorded** to the nearest 0.1 centimeter. **If the measurements do not agree within 0.5 centimeter, re-measure for a third time.** The method of collecting height measurements should be standardized across all sites (eg, instruction to stand looking straight ahead with the chin parallel to the floor, arms by the sides of the trunk with palms facing the thighs, and back of the head, scapulae, buttocks, and heels **positioned** against the vertical backboards of the stadiometer; no ~~socks~~ shoes or hats are to be worn during measurements~~; collection of 3 reproducible measurements; same calibration frequency~~).<br>• For patients ~~less than~~ <2 years of age, **or patients who cannot stand on their own**: length should ~~have their lengths~~ **be** measured using a fixed headboard. **Two individuals should conduct the measurement; 1 person positioning the child and the other collecting the length measurement. Two independent length measurements should be collected and the results recorded to the nearest 0.1 centimeter. If the measurements do not agree within 1 centimeter, re-measure for a third time. The method of collecting length measurements should be standardized across all sites (eg, placement of the child supine on the measuring board, checking that the child lies straight on the board and does not change position, shoulders touching the board; spine should not be arched. The child's legs are held down with 1 hand, applying gentle pressure to the knees to straighten the legs without causing injury, while the footboard is moved to a position against the child's feet with the other hand. The soles of the feet should be flat against the board with toes pointing upwards).**<br><br>**7.12.1.2 Weight**<br><br>Weight measurements should be obtained from scales that have been calibrated at regular intervals.<br><br>• **For patients ≥2 years of age, or who can stand on their own: weight measurements should be collected with the child standing, without assistance, on a calibrated beam balance or electronic scale. Two independent weight measurements should be collected and the results recorded to the nearest 0.1 kilogram. If the measurements do not agree within 0.3 kilogram, re-measure for a third time. The method of collecting weight measurements should be standardized across all sites (eg, weight to be collected with the child standing on the center of the scale and wearing only lightweight undergarments or a gown).**<br>• For patients less than <2 years of age, **or patients who cannot stand on their own: weight measurements should be collected using an infant scale. Two independent weight measurements should be collected and the results recorded to the nearest 0.1 kilogram. If the measurements do not agree within 0.3 kilogram, re-measure for a third time. The method of collecting weight** |

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| **measurements should be standardized across all sites (eg, the child is nude or wearing a clean, dry diaper and positioned in the center of the scale tray).** |
| Other sections impacted by this change: Not applicable |

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| Change: Clarification that the 6MWT will be conducted in patients able to walk |
| Section impacted by this change: Section 7.12.4, Distance Walked |
| Revised Text:<br>Distance Walked<br>The 6MWT will be conducted according to the American Thoracic Society guidelines for the 6MWT for patients who are able to ~~comply with this assessment~~ **walk**. |
| Other sections impacted by this change: Synopsis, Outcome Assessments |

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| Change: Clarification to adverse events assessments |
| Section impacted by this change: Section 7.17 Adverse Events Assessments |
| Revised Text:<br>Adverse events will be collected **at weekly Elaprase infusions and** at each study visit for enrolled patients (Group 1—Prospective Patient Group only). Instructions for recording and reporting AEs are provided in Section 7.17.3. |
| Other sections impacted by this change: Section 7.17.3.1, Adverse Event Monitoring and Period of Observation; Appendix 1, Group 1—Prospective Patient Group Study Schedule of Events |



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| Change: Addition of section to define infusion-related adverse reactions |
| Section impacted by this change: Section 7.17.1, Definitions of Adverse Events and Serious Adverse Events |
| Revised Text:<br>**Section 7.17.1.3 Infusion-Related Adverse Reaction**<br>**An infusion-related adverse reaction will be defined as an AE that 1) occurs on the day of the infusion, ie, within 24 hours following the infusion, 2) begins either during or after the infusion, and 3) is judged as possibly or probably related to idursulfase infusion.** |
| Other sections impacted by this change: Not applicable |

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| Change: Clarification to the AE severity scale and inclusion of definitions for AE relatedness terms |
| Section impacted by this change: Section 7.17.2, Classification of Adverse Events and Serious Adverse Events |
| Revised Text:<br>The severity of AEs will be assessed by the Investigator **based on the definitions shown in** ~~using the National Cancer Institute Common Toxicity Criteria (NCI CTC) grading scale (provided in the Study Operations Manual). If an AE is not described in the NCI CTC, the severity should be recorded based on the scale in~~ Table 7-3. The severity of all AEs/SAEs should be recorded on the appropriate CRF page as ~~Grade 1, 2, or 3 corresponding, respectively, to a severity of~~ mild, moderate, or severe. |

**Table 7-3 Adverse Event Severity**

| Severity | Definition |
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| ~~Grade 1 (Mild)~~ **Mild** | No limitation of usual activities. |

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| ~~Grade 2 (Moderate)~~ **Moderate** | Some limitation of usual activities. |
| ~~Grade 3 (Severe)~~ **Severe** | Inability to carry out usual activities. |

**Relationship of an adverse event or serious adverse event to the Elaprase is to be determined by the Investigator based on the following definitions:**

**Table 7-4 Adverse Event Relatedness**

| Relationship to Product(s) | Definition |
|---|---|
| **Not Related** | **Unrelated to investigational product.** |
| **Possibly Related** | **A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, but which could also be explained by concurrent disease or other drugs or chemicals.** |
| **Probably Related** | **A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on dechallenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.** |
| **Definitely related** | **The event follows a reasonable temporal sequence from administration of the investigational product, follows a known or suspected response pattern to the investigational product, is confirmed by improvement upon stopping the investigational product (de-challenge), and reappears upon repeated exposure (re-challenge). Note that this is not to be construed as requiring re-exposure of the patient to investigational product; however, the determination of definitely related can only be used when recurrence of event is observed.** |

Other sections impacted by this change: Not applicable

Change: Clarification to adverse events monitoring and oversight

Section impacted by this change: Section 7.17.3.1, Adverse Event Monitoring and Period of Observation

Revised Text:
Adverse events will be monitored **at weekly Elaprase infusions and** at each study visit **under the oversight of the Investigator**.

Other sections impacted by this change: Section 7.17, Adverse Events Assessments; Appendix 1, Group 1—Prospective Patient Group Study Schedule of Events

Change: Change in Shire Medical Monitor

Section impacted by this change: Section 7.17.3.2, Reporting Serious Adverse Events

Revised Text:

Shire Pharmacovigilance and Risk Management Department:
International FAX: +44-1256-894715 (UK)
OR
United States FAX: +1-866-557-4473
Email: globalpharmacovigilance@shire.com
AND
Shire Medical Monitor: [redacted] ~~, MD, PhD~~ [redacted], **MD**
Email: [redacted]

FAX: [redacted]

…

If an SAE is assessed as severe and unexpected, fatal, or life-threatening, contact:

[redacted], MD~~, PhD~~
Shire, Inc.
300 Shire Way
Lexington, MA 02421 USA
Telephone: [redacted]
Mobile: [redacted]
Email: [redacted]
Fax: [redacted]

Other sections impacted by this change: Title Page; Protocol Signature Page

Change: Management of infusion-related adverse events

Section impacted by this change: Section 7.21.1, Management of Infusion-Related Adverse Events

Revised Text:

**If a patient develops an infusion-related AE during the infusion, the investigator should decide, based on his or her clinical judgment, whether the infusion should be discontinued or not. If the nature and severity of the event requires termination of the infusion, clinical assessment should be focused on the determination of whether or not the reaction may be an IgE-mediated process. If the event is clearly anaphylaxis, then subcutaneous epinephrine should be used.**

**An initial study drug infusion causing a severe infusion-related AE should not be restarted. Patients experiencing a mild infusion-related AE may be premedicated with an anti-pyretic and/or an antihistamine (eg, with diphenhydramine) for subsequent infusions. Patients experiencing a moderate or severe infusion-related AE may be premedicated with both an antihistamine and corticosteroid (eg, with diphenhydramine and hydrocortisone) in addition to acetaminophen for subsequent infusions. Premedication with ranitidine (in conjunction with hydrocortisone as a protective agent for the intestinal mucosa) may also be considered. If subsequent infusions continue without incident, then tapering of medications may also be considered.**

**An anaphylactoid or hypersensitivity reaction may have occurred when any two of the following criteria are observed after exposure to idursulfase:**

- **Involvement of the skin-mucosal tissue (eg, generalized hives, rash, pruritus, flushing, erythema, urticaria, facial edema, swollen lips-tongue-uvula)**
- **Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia [defined as $O_2$ saturation below 88% during the infusion AND with corresponding $O_2$ saturation at least above 91% prior to infusion], respiratory, failure, or insufficiency, respiratory distress, cyanosis)**
- **Reduced blood pressure (systolic blood pressure less than 80 recorded during an infusion AND at least 20 points lower than the systolic blood pressure recorded prior to infusion) or associated symptoms (eg, hypotonia [collapse], syncope).**

**For suspected, severe or recurrent hypersensitivity reactions, an anti-idursulfase antibody sample should be drawn no sooner than 12 hours after completion of the infusion and no later than 24 hours after the end of the infusion. A second anti-idursulfase antibody specimen should be obtained 1 week (±24 hours) after the hypersensitivity reaction and PRIOR to the next weekly idursulfase infusion.**

Other sections impacted by this change: Not applicable

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| Change: Clarification that Baseline is not defined strictly as Day 0 |
| Section impacted by this change: Section 10.8, Efficacy Analyses |
| Revised Text:<br>Descriptive summaries will generally present the data overall and by visit from Study SHP-ELA-401 Baseline ~~(defined as Day 0)~~ for the Prospective Population. |
| Other sections impacted by this change: Section 4.1, Overall Study Design and Plan; Section 10.7, Analysis of Safety |

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| Change: Removal of footnote pertaining to first height and weight measurements within 3 months of first dose of Elaprase |
| Section impacted by this change: Appendix 1, Group 1—Prospective Patient Group Study Schedule of Events |
| Revised Text:<br>Footnote f modified:<br>[f] ~~First height and weight assessments must be within 3 months of the first dose of Elaprase~~. Height and weight assessments must be performed per standardized methodology, described in the protocol (refer to Section 7.12.1). |
| Other sections impacted by this change: Not applicable |

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| Change: Clarification to footnote concerning Elaprase administration |
| Section impacted by this change: Appendix 1, Group 1—Prospective Patient Group Study Schedule of Events |
| Revised Text:<br>Footnote g modified:<br>[g] The first dose of Elaprase must be administered after all assessments are completed for Baseline at Day 0 and within 1 week after the completion of the baseline assessments. Thereafter, Elaprase will be administered weekly throughout the study. **Details on administration procedures are provided in the Pharmacy Manual; refer to country-specific prescribing information for details concerning administration of commercially sourced drug. Elaprase treatment will be administered under the oversight of the Investigator 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 ~~and in the controlled environment of a clinical center~~. |
| Other sections impacted by this change: Section 6.8, Treatment Compliance, Section 7.9 Elaprase Administration; Section 8.3 Treatment Period (Day 1 [or Day 2] to End of Study Visit) |

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| Change: addition of footnote clarifying AE collection |
| Section impacted by this change: Appendix 1, Group 1—Prospective Patient Group Study Schedule of Events |
| Revised Text:<br>Footnote h added:<br>[h] **Adverse events will be collected at weekly Elaprase infusions and at each study visit.** |
| Other sections impacted by this change: Section 7.17, Adverse Events Assessments; Section 7.17.3.1, Adverse Event Monitoring and Period of Observation |