

## Clinical Trial Protocol: HGT-HIT-094

**Study Title:** A Controlled, Randomized, Two-arm, Open-label, Assessor-blinded, Multicenter Study of Intrathecal Idursulfase-IT Administered in Conjunction with Elaprase® in Pediatric Patients with Hunter Syndrome and Early Cognitive Impairment

**Study Number:** HGT-HIT-094

**Study Phase:** Phase II/III

**Investigational Product and Device:** idursulfase for intrathecal use (idursulfase-IT [HGT-2310]), SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire (SOPH-A-PORT Mini S)

**IND Number:** 100,610

**Indication:** Long-term treatment of Hunter syndrome in patients with cognitive impairment to slow progression of cognitive and functional impairment

**Study Center(s):** Multicenter

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Date

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**Original Protocol:** 04 April 2013

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## SYNOPSIS

### Sponsor:

Shire Human Genetic Therapies, Inc.

### Names of Investigational Product and Device:

idursulfase for intrathecal use (idursulfase-IT [HGT-2310])

SOPH-A-PORT<sup>®</sup> Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire (SOPH-A-PORT Mini S)

### Study Title:

A Controlled, Randomized, Two-arm, Open-label, Assessor-blinded, Multicenter Study of Intrathecal Idursulfase-IT Administered in Conjunction with Elaprase<sup>®</sup> in Pediatric Patients with Hunter Syndrome and Early Cognitive Impairment

### Study Number:

HGT-HIT-094

### Study Phase:

Phase II/III

### Investigational Product Dose, Mode of Administration:

idursulfase-IT 10 mg, intrathecal (IT) injection

### Device, Intended Use:

The SOPH-A-PORT<sup>®</sup> Mini S is a system intended for implantation by physicians. The SOPH-A-PORT Mini S, once implanted, allows healthcare personnel to administer idursulfase-IT (HGT-2310) indicated for IT delivery intermittently over a long period of time.

### Comparator, Dose, and Mode of Administration:

No treatment

### Treatment Regimen:

Once monthly (ie, every 28 days) IT administration of idursulfase-IT 10 mg for 12 months via a surgically implanted intrathecal drug delivery device (IDDD), or lumbar puncture

### Primary Objective:

- To determine the effect of the treatment regimen in pediatric patients with Hunter syndrome and early cognitive impairment on the General Conceptual Ability (GCA) score as measured by the DAS-II, in conjunction with Elaprase therapy

### Key Secondary Objective:

- To determine the effect of the treatment regimen in pediatric patients with Hunter syndrome and early cognitive impairment on the Adaptive Behavior Composite (ABC) score as measured by the VABS-II, in conjunction with Elaprase therapy

### Secondary Objectives:

To determine the effect of the treatment regimen in pediatric patients with Hunter syndrome and early cognitive impairment, in conjunction with Elaprase therapy, on:

- Cognitive function as measured by the cluster areas and subtests of the DAS-II



- Adaptive behavior as measured by the domains of the VABS-II

**Safety Objectives:**

- To determine the effect of the treatment regimen on safety as assessed by adverse events, clinical laboratory testing, physical examination findings, vital signs, and electrocardiogram (ECG) recordings
- To evaluate the anti-idursulfase antibody response in serum and CSF during the treatment regimen

**SOPH-A-PORT Mini S Device Objectives:**

- To determine the safety and performance of the SOPH-A-PORT Mini S device

**Pharmacokinetic and Pharmacodynamic Objectives:**

- To evaluate the concentration of idursulfase in serum and cerebrospinal fluid (CSF) after IT administration and determine pharmacokinetic parameters
- To determine the effect of the treatment regimen on the concentration of glycosaminoglycan (GAG) in CSF

**Health Status Objective:**

- To evaluate health status as measured by the EQ-5D instrument

**Substudy Objective:**

- To examine the effect of the treatment regimen in pediatric patients with Hunter syndrome <3 years old and having a complex rearrangement genotype of the iduronate-2-sulfatase gene on safety and efficacy measures

**Study Efficacy Endpoints:**

The primary efficacy endpoint of this study is:

- Change from baseline in the GCA score after 12 months of treatment, at Visit Week 52, as obtained by DAS-II testing

The key secondary efficacy endpoint of this study is:

- Change from baseline in the ABC score after 12 months of treatment at Visit Week 52, as obtained by VABS-II testing

The secondary efficacy endpoints of this study are:

- Change from baseline to Visit Weeks 16, 28, and 40 in the GCA score as obtained by DAS-II testing
- Change from baseline to Visit Weeks 16, 28, and 40 in the ABC score as obtained by VABS-II testing
- Change from baseline to Visit Weeks 16, 28, 40, and 52 in standardized scores in cluster areas of the DAS-II: Verbal, Nonverbal, Spatial, and Special Nonverbal Composite (SNC)
- Change from baseline to Visit Weeks 16, 28, 40, and 52 in the standardized domain scores of the VABS-II: Communication, Daily Living Skills, Socialization, Motor Skills, and Maladaptive Behavior
- Change from baseline to Visit Weeks 16, 28, 40, and 52 in the age equivalents and development quotient (DQ) for the subcategories of the DAS-II (Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices and Copying for the DAS-II/Early Years, and Recall of Designs, Word

Definitions, Pattern Construction, Matrices, Verbal Similarities, and Sequential and Quantitative Reasoning for the DAS-II/School Years)

- Change from baseline to Visit Weeks 16, 28, 40, and 52 in the age equivalents and developmental quotients of the VABS-II: Communication, Daily Living Skills, Socialization, Motor Skills, and Maladaptive Behavior

**Study Population:**

42 male patients (14 untreated, 28 treated) are planned.

**Study Design:**

This is a controlled, randomized, 2-arm, open-label, assessor-blinded, multicenter study to determine the effect on clinical parameters of neurodevelopmental status of monthly IT administration of idursulfase-IT 10 mg for 12 months in pediatric patients with Hunter syndrome and cognitive impairment who have previously received and tolerated a minimum of 3 months of therapy with Elaprase.

All patients will continue to receive Elaprase therapy as standard of care throughout the study. Elaprase will not be provided by the Sponsor, but rather will be prescribed by the patient's physician in accordance with local prescribing information.

The pivotal study design is "no IT treatment-controlled" in that 28 patients are assigned randomly to receive IT treatment and 14 patients are assigned randomly to participate without receiving IT treatment.

The pivotal study will consist of a Screening period of up to 28 days prior to randomization. Those patients randomized to IT treatment will undergo surgical implantation of the SOPH-A-PORT Mini S IDDD followed by a post-operative recovery period of at least 14 days prior to the first IT administration of idursulfase-IT. Treated patients will then receive 12 monthly IT injections of 10 mg idursulfase-IT corresponding to a treatment and assessment interval of 13 (28-day) months from randomization to the end-of-study (EOS) evaluations. Likewise, patients randomized to no IT treatment will be assessed over 13 (28-day) months after randomization.

Patients in the IT treatment arm of the pivotal study will be assessed according to the following schedule:

- Screening (Weeks -1 to -4 [Day -28 to Day -1])
- Randomization (Week 0 [Day 0])
- Pre-surgery, Surgery, and Post-operative Recovery (Weeks 2 and 3)
- Treatment and Assessments(Week 4 through Week 48 [ $\pm 7$  days])
- End of study (EOS, Week 52 [ $\pm 7$  days])
- Follow-up (telephone contact) 7 ( $\pm 2$ ) days from the Week 52 (or EOS)

Patients in the no IT treatment arm of the pivotal study will be assessed according to the following schedule:

- Screening (Weeks -1 to -4 [Day -28 to Day -1])
- Randomization (Week 0 [Day 0])
- Assessments (Week 4 through Week 48 [ $\pm 7$  days])
- End of study (EOS, Week 52 [ $\pm 7$  days])
- Follow-up (telephone contact) 7 ( $\pm 2$ ) days from the Week 52 (or EOS)

The separate substudy is open-label and single arm. Patients who meet all entry criteria for participation in the substudy will be considered enrolled on Day 0. Thereafter, patients who are enrolled in the separate substudy will follow the same schedule of study visits as idursulfase-IT-treated patients in the pivotal study.

Patients in the substudy will be assessed according to the following schedule:

- Screening (Weeks -1 to -4 [Day -28 to Day -1])
- Enrollment (Week 0 [Day 0])
- Pre-surgery, Surgery, and Post-operative Recovery (Weeks 2 and 3)
- Treatments and assessments (Week 4 through Week 48 [ $\pm 7$  days])
- End of study (EOS, Week 52 [ $\pm 7$  days])
- Follow-up (telephone contact) 7 ( $\pm 2$ ) days from the Week 52 (or EOS)

Patients in both the IT treatment and no IT treatment arms of the study will complete EOS assessments at Week 52 (Visit Month 13). All patients will participate in a follow-up contact (by telephone) approximately 7 days after the EOS visit.

A patient who discontinues or is withdrawn prior to study completion will be asked to participate in an EOS visit within approximately 30 days after withdrawal or discontinuation (EOS assessments for such patients will be the same as Week 52 assessments), and also to complete a follow up contact approximately 7 days after the patient's EOS visit. There is no replacement of patients who do not complete the study.

For details see the study Schedules of Events.

The SOPH-A-PORT Mini S IDDD will be used to obtain cerebrospinal fluid (CSF) samples and to deliver all IT injections of idursulfase-IT. If the IDDD appears to be non-functional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD Manual, which provides details on the investigation and management of any IDDD-related issues. If the IT space is not accessible via the IDDD, lumbar puncture may be utilized under defined circumstances for administration of idursulfase-IT or to obtain to obtain a CSF sample.

General anesthesia/sedation may be required for injections of study drug and some evaluations, and can be used at the discretion of the Investigator.

A Data Safety Monitoring Board (DSMB) will oversee both idursulfase-IT and device safety. The DSMB will be notified of IDDD failures and related complications on a periodic basis according to the DSMB charter.

Patients will have the IDDD removed when they discontinue from the study, unless the patient is continuing to receive treatment through another mechanism (eg, extension study, expanded access program).

#### **Study Duration:**

The planned overall duration of each patient's participation in the study is approximately 14 to 15 months from Screening to the last scheduled contact.

An extension study is planned during which patients who complete HGT-HIT-094 may continue to receive IT treatment with idursulfase-IT via the SOPH-A-PORT Mini S device.

## Study Inclusion and Exclusion Criteria:

### Inclusion Criteria

Patients must meet the following criteria to be considered eligible for randomization in the pivotal study:

1. The patient is male and is **≥3 and <18 years** of age at the time of informed consent.

*Note that patients who are younger than 3 years of age may be enrolled in a separate substudy provided that they have a documented complex rearrangement genotype of the iduronate-2-sulfatase gene and meet other inclusion criteria, provided below.*

2. The patient must have a documented diagnosis of MPS II. Of the three criteria below, the combinations (1a AND 1b) or (1a AND 1c) will be accepted as diagnostic of MPS II:

- a. The patient has a deficiency in iduronate-2-sulfatase enzyme activity of  $\leq 10\%$  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 iduronate-2-sulfatase gene that leaves the FMR1 and FMR2 genes intact. In the case of a positive family history, the genotype of a brother or uncle (with appropriate informed consent, or assent if applicable) may be accepted as documentation at the discretion of the Medical Monitor.

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).

3. The patient has evidence at Screening of Hunter syndrome-related cognitive impairment, defined as follows:

*Note that separate inclusion criteria with respect to patient cognitive status at Screening apply to patients  $\geq 3$  and  $< 13$  years of age and patients  $\geq 13$  and  $< 18$  years of age.*

A patient who is **≥3 and <13 years** of age must have one of the following criteria (3a OR 3b):

- a. A GCA score  $\geq 55$  and  $\leq 85$ .

OR

- b. If the patient has a GCA score at Screening  $> 85$ , there must be evidence of a decrease in GCA score of  $\geq 10$  points over 12 months from a previously documented test result in observational study HGT-HIT-090.

A patient who is **≥13 and <18 years** of age must have both of the following criteria (3c AND 3d):

- c. A GCA score of  $\geq 55$  and  $\leq 85$   
AND
  - d. There must be evidence of a decrease in GCA score of  $\geq 10$  points over 12 months from a previously documented test result in observational study HGT-HIT-090.
4. The patient has received and tolerated a minimum of 3 months of therapy with Elaprase during the period immediately prior to Screening.
  5. The patient must have sufficient auditory capacity, with or without hearing aids in the Investigator's judgment, to complete the required protocol testing, and be compliant with wearing the aid on scheduled testing days.
  6. The patient's parent(s) or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board/Independent Ethics Committee 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, if applicable, must be obtained prior to the start of any study procedures.

Patients must meet all of the following criteria to be considered eligible for enrollment in the separate substudy:

1. The patient is male and is **<3 years** of age at the time of informed consent.
2. The patient must have a documented diagnosis of MPS II. The following two types of documentation will be accepted as diagnostic of MPS II:
  - a. The patient has a deficiency in iduronate-2-sulfatase enzyme activity of  $\leq 10\%$  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 complex chromosomal rearrangement of the iduronate-2-sulfatase gene that leaves the FMR1 and FMR2 genes intact  
In the case of a positive family history, the genotype of a brother or uncle (with appropriate informed consent, or assent if applicable) may be accepted as documentation at the discretion of the Medical Monitor.
3. The patient has received and tolerated a minimum of 3 months of therapy with Elaprase during the period immediately prior to Screening.
4. The patient must have sufficient auditory capacity, with or without hearing aids in the Investigator's judgment, to complete the required protocol testing, and be compliant with wearing the aid on scheduled testing days.
5. The patient's parent(s) or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board/Independent Ethics Committee 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 must be obtained prior to the start of any study procedures.

### Exclusion Criteria

Patients who meet any of the following criteria are not eligible to be randomized into the pivotal study or enrolled in the separate substudy:

1. The patient has clinically significant non-Hunter syndrome-related CNS involvement

- (such as Fragile-X syndrome) which is judged by the Investigator to be likely to interfere with the accurate administration and interpretation of protocol assessments.
2. The patient has a large chromosomal deletion or complex rearrangement genotype that includes an inactivation and/or deletion of the FMR1 and/or FMR2 genes.
  3. The patient has a significant medical or psychiatric comorbidity(ies) that might affect study data or confound the integrity of study results.
  4. The patient has contra-indications for performance of lumbar puncture such as musculoskeletal/spinal abnormalities or risk of abnormal bleeding.
  5. The patient has a history of complications from previous lumbar punctures or technical challenges in conducting lumbar punctures such that the potential risks would exceed possible benefits for the patient.
  6. The patient has an opening CSF pressure upon lumbar puncture that exceeds 30 cm H<sub>2</sub>O.
  7. The patient has experienced infusion-related anaphylactoid event(s) or has evidence of consistent severe adverse events related to treatment with Elaprase which, in the Investigator's opinion, may pose an unnecessary risk to the patient.
  8. The patient has received a cord blood or bone marrow transplant at any time or has received blood product transfusions within 90 days prior to Screening.
  9. The patient has a history of poorly controlled seizure disorder.
  10. The patient is unable to comply with the protocol (eg, has significant hearing or vision impairment, a clinically relevant medical condition making implementation of the protocol difficult, unstable social situation, known clinically significant psychiatric/behavioral instability, is unable to return for safety evaluations, or is otherwise unlikely to complete the study), as determined by the Investigator.
  11. The patient is enrolled in another clinical study that involves clinical investigation or use of any investigational product (drug or [intrathecal/spinal device] device) within 30 days prior to study enrollment or at any time during the study.
  12. The patient has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to compromised airways or other conditions.
  13. The patient has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use, including:
    - a. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
    - b. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the Investigator
    - c. The patient's drug therapy requires substances known to be incompatible with the materials of construction
    - d. The patient has a known or suspected local or general infection
    - e. The patient is at risk of abnormal bleeding due to a medical condition or therapy
    - f. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
    - g. The patient has a functioning CSF shunt device
    - h. The patient has shown an intolerance to an implanted device

**Pharmacokinetic Assessments:**

Determination of idursulfase concentration in serum and CSF samples.

**Pharmacodynamic Assessments:**

Determination of the concentration of GAG in CSF samples.

**Efficacy Assessments:**

Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as follows:

Cognition: the Differential Ability Scales, Second Edition (DAS-II) will be used to assess all patients randomized in the pivotal study. For patients participating in the separate substudy only (ie, patients with a complex rearrangement genotype of the iduronate-2-sulfatase gene and who are below the age of 3 years) cognition will be assessed initially using the Bayley Scales of Infant Development, Third Edition (BSID-III). When these patients reach at least 42 months of age, if considered evaluable using the DAS-II instrument, they will transition to use of the DAS-II for continued assessment of cognition.

Adaptive Behaviors: the Vineland Adaptive Behavioral Scales, Second Edition (VABS-II) will be used to assess all patients.

**Safety Assessments:**

Safety will be assessed by adverse events (by type, severity, and relationship to treatment [idursulfase-IT, IDDD, device surgical procedure, IT administration process] and IV Elaprase infusion), changes in clinical laboratory testing (serum chemistry, hematology, urinalysis), physical and neurological examination, vital signs, 12-lead ECG, CSF chemistries (including cell counts, protein, and glucose), anti-idursulfase antibodies in CSF and serum, and determination of antibodies having enzyme neutralizing activity.

**SOPH-A-PORT Mini S Device Assessments:**

SOPH-A-PORT Mini S assessments will include measures of device implantation, device function, device longevity, record of revisions, removals, and replacements of the implanted IDDD, and adverse events associated with the device. This data will be collected on the patient's electronic case report form (eCRF) from the time of implantation and continue throughout the study as long as the SOPH-A-PORT Mini S remains implanted.

**Statistical Methods:**

General Methods

Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, minimum, median, and maximum). Categorical variables will be summarized using the number and percentage of patients in each category. Data will be summarized with respect to patient disposition, demographic and baseline characteristics and concomitant medication use. The efficacy endpoints, safety assessments and other outcome results for each treatment group will be summarized descriptively unless otherwise indicated. In addition, least squares means, p-values and 95% confidence intervals for least squares mean treatment differences will also be provided where relevant for efficacy endpoints. All the hypothesis tests will be two-sided and will be performed at the 0.05 level of significance unless stated otherwise. Safety data from the single-arm

substudy will be summarized separately and efficacy data will be listed.

#### Analysis Populations

For the pivotal trial, all efficacy data analyses will be performed using the Intent-to-Treat (ITT) Population, which is defined as all randomized patients.

All safety data analyses will be performed using the Safety Population, which is defined as all randomized patients with any post-randomization safety assessments. Device related analyses will be conducted in the treated subset of the Safety Population who had the device implant procedure performed.

All PK data analyses will be performed using the PK population. The PK population will be defined as all patients who received study drug and had at least one sample collected for pharmacokinetic analysis.

For the substudy, all analyses will be performed on the Substudy Population, defined as all patients enrolled and treated with study drug in the substudy.

#### Analysis of Efficacy

For the pivotal trial, the primary efficacy endpoint is the change from study baseline (Screening Visit) to Visit Week 52 in the General Conceptual Ability (GCA) score as measured by the DAS-II. The primary analysis will compare the treatment groups using a linear mixed model repeated measures (MMRM) analysis. The repeated measures are the change from baseline GCA scores obtained at the scheduled Visit Weeks 16, 28, 40, and 52, respectively. The model will include fixed categorical effects for treatment, visit week, treatment by visit week interaction, and a GCA classification factor (based on baseline GCA score ( $\leq 70$  or  $> 70$ )) and the GCA classification factor by treatment interaction. The GCA classification factor by treatment interaction term will be included in the model if the interaction is significant at the 10% level; otherwise, the MMRM analysis without this interaction will be considered the final primary model. From this model, least squares means, standard errors, treatment differences in least squares means, and 95% confidence intervals and p-values will be estimated for each time point. Primary inference is based on the treatment comparison at Visit Week 52 from this model.

The key secondary efficacy endpoint is the change from study baseline (Screening Visit) to Visit Week 52 in the Adaptive Behavior Composite (ABC) score as measured by the VABS-II. This endpoint will be analyzed using an MMRM analysis with effects of treatment, visit week, treatment by visit week interaction and the baseline ABC score as a continuous covariate. The baseline ABC score by treatment interaction will be included in the model if the interaction is significant at the 10% level; otherwise, the MMRM analysis without this interaction will be considered the final model for this endpoint. The inferential test of the key secondary endpoint is based on the treatment comparison at Visit Week 52 from this model.

The overall type I error rate for tests of the primary and key secondary endpoints will be controlled at 0.05. To control an overall type I error rate at this level for the two tests, a fixed sequential testing procedure will be followed. The null hypothesis of no treatment difference for the primary endpoint will be tested first. The null hypothesis of no treatment difference for the key secondary endpoint then may only be rejected if the null hypothesis for the primary endpoint is first rejected.



The following secondary efficacy endpoints will be analyzed using an MMRM analysis in the same manner as described above for the key secondary endpoint with the continuous covariate corresponding to the baseline score for each measure:

- (1) The change from baseline to Visit Weeks 16, 28, 40, and 52 in standardized scores in cluster areas of the DAS-II: Verbal, Nonverbal, Spatial, and Special Nonverbal Composite (SNC)
- (2) The change from baseline to Visit Weeks 16, 28, 40, and 52 in the standardized domain scores of the VABS-II: Communication, Daily Living Skills, Socialization, Motor Skills, and Maladaptive Behavior.

All other secondary efficacy endpoints will be summarized descriptively by treatment group. Mean values by treatment group will be plotted over time.

#### Analysis of Safety

All safety analyses will be descriptive. Adverse events will be summarized by treatment group, both overall and within system organ class by preferred term. Adverse events will also be tabulated by highest severity (mild, moderate, severe) and by closest relationship to study drug (not related, related) for treated patients. Separate tabulations will be provided for adverse events related to IV Elaprase infusion, the IDDD, device surgical procedure, and the IT-administration process.

The proportion of patients with at least one IDDD failure and the proportion with malfunction only, as well as the number of and reasons for IDDD failures and malfunctions will be summarized. The rate of IDDD failures and malfunctions and the corresponding 95% confidence interval will also be estimated. The time from initial implant surgery to first IDDD failure and the time to first malfunction only will be analyzed using Kaplan-Meier Life Table methods.

Laboratory values in serum and CSF components, vital signs, ECG parameters and other safety assessments will be summarized by treatment group. The number and percentage of patients testing anti-idursulfase antibody positive and negative at each time point will be summarized.

All safety data from the separate substudy will be similarly summarized in a descriptive manner.

**Date of Original Protocol:** 04 April 2013

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

<b>Term</b>	<b>Definition</b>
ABC	adaptive behavior composite
AE	adverse event
ALT	alanine aminotransferase (SGPT)
AP	alkaline phosphatase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
cc	cubic centimeter(s)
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CI	confidence interval
CK	creatine kinase
C <sub>max</sub>	maximal concentration
cm	centimeter(s)
CNS	central nervous system
CO <sub>2</sub>	total carbon dioxide
CRO	contract research organization
CSF	cerebrospinal fluid
CV	coefficient of variation
DAS-II	Differential Ability Scales, Second Edition
dL	deciliter
DQ	developmental quotient
DS	dermatan sulfate
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EQ-5D	EurolQoL-5D instrument for use as a measure of health outcome
ERT	enzyme replacement therapy

<b>Term</b>	<b>Definition</b>
EU	European Union
F	Fahrenheit
FDA	United States Food and Drug Administration
g	gram(s)
g/dL	grams per deciliter
GAG	glycosaminoglycans
GCA	general conceptual ability
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practices
Hb	hemoglobin
Hct	hematocrit
Hgb	hemoglobin
HGT-2310	Drug code name for formulation of recombinant iduronate-2-sulfatase (idursulfase) for intrathecal administration
HPLC	high performance liquid chromatography
hr	hour(s)
I2S	iduronate-2-sulfatase
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICP	intracranial pressure
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IFU	Instructions for Use
Ig	immunoglobulin
IND	Investigational New Drug application
IRB	Institutional Review Board
IT	intrathecal
ITT	intent-to-treat
IV	intravenous(ly)
IVR	interactive voice response
kg	kilogram(s)
L	liter(s)
LDH	lactic dehydrogenase
m	meter(s)

<b>Term</b>	<b>Definition</b>
M6P	mannose-6-phosphate
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activity
min	minute(s)
mL	milliliter(s)
mm	millimeters
mM	millimolar
MMRM	mixed model repeated measures
MPS II	Mucopolysaccharidosis II (Hunter syndrome)
MRI	magnetic resonance imaging
MRT	mean residual time
n	number
N or n	number of observations
NCI CTC	National Cancer Institute Common Toxicity Criteria
NDA	New Drug Application
ng	nanogram(s)
PD	pharmacodynamic
PK	pharmacokinetic(s)
PRO	patient reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
QTc	corrected QT interval
RBC	red blood cell(s)
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System <sup>®</sup>
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (ast)
SGPT	serum glutamic pyruvic transaminase (alt)
SGSS	Shire Global Safety System
Shire HGT	Shire Human Genetic Therapies, Inc.
SNC	special nonverbal composite
SOC	system organ class

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<b>Term</b>	<b>Definition</b>
SOE	schedule of events
SOPH-A-PORT Mini S	SOPH-A-PORT <sup>®</sup> Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire
T4	thyroxine
U	unit(s)
UADE	unanticipated adverse device effect
ULN	upper limit of normal
US	United States
V <sub>ss</sub>	apparent volume of distribution at steady state
VAS	visual analog scale
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
WBC	white blood cell count
WHO-DD	World Health Organization Drug Dictionary

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## 1 INTRODUCTION

### 1.1 Mucopolysaccharidosis II (Hunter syndrome)

Mucopolysaccharidosis II (MPS II) is a rare, X-linked, inherited disease that affects males nearly exclusively. Its estimated incidence is 1 in approximately 162,000 live births.<sup>1,2</sup> Though typically appearing normal at birth, all MPS II patients suffer from a progressive, serious, life-limiting disease.<sup>3,4</sup>

The disease is caused by the absence of, or deficiency in, the activity of the lysosomal enzyme, iduronate-2-sulfatase (I2S) which acts to cleave O-linked sulfate moieties from the glycosaminoglycan (GAG) molecules dermatan sulfate and heparan sulfate.<sup>5</sup> Insufficient activity of I2S leads to progressive accumulation of GAG in nearly all organs and body tissues.

The central underlying pathophysiological process leading to the clinical manifestations of MPS II is the chronic accumulation of dermatan sulfate and heparan sulfate inside cellular lysosomes, resulting in cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction. Accumulation of GAG 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.<sup>6</sup> Clinical manifestations include severe airway obstruction, skeletal deformities, cardiomyopathy and, in most patients, neurological decline.<sup>7</sup> Death may occur in the first or second decade of life. Less affected patients may survive into adulthood, with airway obstruction and cardiac causes often contributing to death.<sup>4</sup>

Phenotypic expression of the disease spans a wide spectrum of clinical severity. However, two extremes at either end of the continuum of MPS II have been identified based on cognitive status.<sup>4,8</sup> The first is broadly characterized as an “attenuated” or milder form in which intellectual and neurodevelopment faculties are largely intact, although somatic pathology is present. The term “severe” has been adopted to describe a second broad phenotype of MPS II patients who suffer from neurodevelopmental impairment in addition to somatic manifestations of the disease. It has been estimated that 67 to 77% of MPS II patients will develop CNS involvement and be characterized as “severe.”<sup>8</sup> Despite these characterizations, patients with predominantly somatic involvement may nevertheless have a life-limiting disease course.

Although there is heterogeneity with respect to disease progression, the onset of signs and symptoms typically occurs at about 3 years of age.<sup>6,9</sup> An earlier appearance of clinical symptoms generally, but not always, predicts a more severe clinical course.<sup>4-6,10</sup> Knowledge of the genotype is of limited value in predicting a patient’s clinical course with respect to CNS involvement. An exception is represented by children with complete absence of functional enzyme due to complex chromosomal rearrangements in the iduronate-2-sulfatase gene, who invariably develop severe neurodevelopmental impairment.<sup>11,12</sup>

### 1.2 Unmet Medical Need

The currently approved therapy for Hunter syndrome is Elaprase® (idursulfase), recombinant human iduronate-2-sulfatase for intravenous (IV) administration. Elaprase has provided clinical

benefit with respect to somatic pathologies in patients with Hunter syndrome, and has a well characterized safety profile. Although many of the physical symptoms of the disease can be reduced or eradicated by IV enzyme replacement,<sup>13-15</sup> Elaprase has not been evaluated specifically regarding its independent quantifiable impact on CNS pathology, due to the acknowledged impermeability of the blood-brain barrier to macromolecules such as idursulfase. In addition, Elaprase is formulated for IV use only and is contraindicated for direct injection into the CNS. Thus, no specific therapy exists for the CNS pathologies of Hunter syndrome.

A distinct formulation, designated idursulfase-IT (HGT-2310), was developed specifically for delivery into the cerebrospinal fluid (CSF) via intrathecal (IT) administration to access CNS tissues and overcome macromolecular distribution limits imposed by the blood-brain barrier. The active ingredient of the idursulfase-IT product [recombinant human iduronate-2-sulfatase] is the same active ingredient as in commercially available Elaprase. In contrast to Elaprase, however, idursulfase-IT is specially formulated for, and compatible with, direct introduction into the IT space, since it is isotonic and contains excipients suitable for IT use.

In order to traverse the blood-brain barrier, Shire HGT is evaluating delivery of idursulfase-IT directly into the CNS using an intrathecal drug delivery device (IDDD), the SOPH-A-PORT<sup>®</sup> Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire (SOPH-A-PORT Mini S). The advantage of using an IDDD is the potential to obviate the need for multiple lumbar punctures for drug delivery.

### 1.3 Overview of Results of Phase I/II Studies

The safety and tolerability of ascending doses (1, 10, or 30 mg) of intrathecally administered idursulfase-IT were investigated in the first-in-human study HGT-HIT-045, a randomized, open-label, no-treatment controlled Phase I/II study in which idursulfase-IT was administered once monthly to pediatric MPS II patients via a surgically implanted IDDD (PORT-A-CATH<sup>®</sup> II Low Profile<sup>™</sup> Intrathecal Implantable Access System [PORT-A-CATH]) for 6 months in conjunction with once weekly IV infusion of Elaprase. Eligible patients who completed HGT-HIT-045 are continuing to receive monthly IT injections of idursulfase-IT, in conjunction with Elaprase therapy, in extension study HGT-HIT-046. Across the HGT-HIT-045 and HGT-HIT-046 studies, long-term safety, pharmacokinetics, and pharmacodynamics (effect on GAG concentration in CSF) have been evaluated. Effects of IT administration of idursulfase-IT on neurodevelopmental health have been evaluated using standardized tests of cognitive and adaptive functions.

Based on the data available from HGT-HIT-045 and HGT-HIT-046, idursulfase-IT has been found to be well tolerated at all doses administered without safety concerns related to the study drug. There have been no deaths or discontinuations due to adverse events in either study, and no serious adverse events related to idursulfase-IT. The majority of serious adverse events in both studies have been associated with the PORT-A-CATH device, and designated as serious because of the requirement for overnight hospitalization for surgical revision/removal of the IDDD. The events related to the use of the IDDD included surgical removal and replacement of the device because of mechanical failures, primarily connector pin breaks and catheter slippage,

to overnight admissions to the clinical site for a suspected device infection, and device removal because of wound issues.

As a result of the device-related concerns in the Phase I/II program, additional guidelines and training materials were developed for implanting neurosurgeons concerning the surgical implantation of the IDDD, and repeated lumbar punctures were permitted per protocol amendment as a means of IT delivery of study drug in the event of device malfunction. To address the frequent occurrence of device failures observed with use of the PORT-A-CATH IDDD in the Phase I/II studies, the SOPH-A-PORT Mini S will be used in this Phase II/III study. The SOPH-A-PORT Mini S device is intended to address the frequent occurrence of device failures observed with use of the PORT-A-CATH IDDD in the Phase I/II studies.

Intrathecal administration of idursulfase-IT to MPS II patients in HGT-HIT-045 and HGT-HIT-046 at the 10 and 30 mg dose regimens resulted in a pronounced pharmacodynamic reduction from baseline in the concentration of GAG in CSF; the 1 mg dose regimen induced a slower and less pronounced reduction in GAG concentration in CSF. Available results of neurodevelopmental assessments performed across HGT-HIT-045 and HGT-HIT-046 suggest the potential of intrathecal delivery of idursulfase-IT to halt or slow the progressive decline in neurodevelopmental status in this patient population. Several patients at earlier stages of cognitive decline who received treatment with idursulfase-IT at the 10 mg and 30 mg doses showed evidence of stabilization or improvement of cognitive and adaptive functions.

### 1.3.1 Rationale for Current Phase II/III Study

Because intravenously administered idursulfase cannot traverse the blood-brain barrier due to its impermeability to large macromolecules such as proteins, there is an unmet medical need in the population of MPS II patients with CNS disease to support clinical development of idursulfase-IT for intrathecal use.

The SOPH-A PORT Mini S delivery device will be used for IT administration of idursulfase-IT to MPS II patients in this study. In contrast to IT administration via lumbar puncture, the use of an IDDD does not always require full anesthesia; in many cases, sedation may be appropriate. Multiple drug administrations, therefore, may require only a single episode of general anesthesia (for device implantation), in contrast to the multiple episodes of general anesthesia that would be required for repeated lumbar punctures in this patient population.

Nonclinical experience with IT administration of idursulfase-IT has demonstrated wide distribution of idursulfase to the CNS tissues. Idursulfase-IT has been shown to be well tolerated in several species and to be active in a murine disease model of idursulfase deficiency.

In Phase I/II clinical studies in MPS II patients, idursulfase-IT has been generally well tolerated. Stabilization or improvement in cognitive and adaptive functions has been noted in some of the children enrolled in the trials. The available data support the Sponsor's hypothesis that a therapeutic benefit may be expected in MPS II children with cognitive impairment.

The therapeutic strategy consisting of idursulfase-IT administered intrathecally via the SOPH-A-PORT Mini S device and concomitant IV Elaprase therapy is intended to address both



the CNS and somatic manifestations of Hunter syndrome. Idursulfase-IT is intended for long-term treatment of Hunter syndrome in patients with cognitive impairment to slow progression of cognitive and functional impairment.

The design of the proposed study, including the neurodevelopmental assessment tools and endpoints, and the selection of idursulfase-IT 10 mg dose, have been informed by the results of Phase I/II studies HGT-HIT-045 and HGT-HIT-046 (See Section 1.3). Please refer to the current edition of the Investigator's Brochure for additional information concerning the safety and clinical development of idursulfase-IT and for information concerning the SOPH-A-PORT Mini S delivery device.

## 2 STUDY OBJECTIVES

The treatment regimen is defined as once monthly (ie, every 28 days) intrathecal administration of idursulfase-IT 10 mg for 12 months via a surgically implanted IDDD or lumbar puncture.

### 2.1 Primary Objective

The primary objective of this study is:

- To determine the effect of the treatment regimen in pediatric patients with Hunter syndrome and early cognitive impairment on the General Conceptual Ability (GCA) score as measured by the DAS-II, in conjunction with Elaprase therapy

### 2.2 Secondary Objectives

The key secondary objective of this study is:

- To determine the effect of the treatment regimen in pediatric patients with Hunter syndrome and early cognitive impairment on the Adaptive Behavior Composite (ABC) score as measured by the VABS-II, in conjunction with Elaprase therapy

The secondary objectives of this study are:

- To determine the effect of the treatment regimen in pediatric patients with Hunter syndrome and early cognitive impairment, in conjunction with Elaprase therapy, on:
  - Cognitive function as measured by the cluster areas and subtests of the DAS-II
  - Adaptive behavior as measured by the domains of the VABS-II

### 2.3 Safety Objectives

- To determine the effect of the treatment regimen on safety as assessed by adverse events, clinical laboratory testing, physical examination findings, vital signs, and electrocardiogram (ECG) recordings
- To evaluate the anti-idursulfase antibody response in serum and CSF during the treatment regimen

### 2.4 SOPH-A-PORT Mini S Device Objectives:

- To determine the safety and performance of the SOPH-A-PORT Mini S device

## 2.5 Pharmacokinetic and Pharmacodynamic Objectives

The pharmacokinetic (PK) and pharmacodynamic (PD) objectives of this study are:

- To evaluate the concentration of idursulfase in serum and cerebrospinal fluid (CSF) after IT administration and determine pharmacokinetic parameters
- To determine the effect of the treatment regimen on the concentration of glycosaminoglycan (GAG) in CSF

## 2.6 Health Status Objective

- To evaluate health status as measured by the EQ-5D instrument

## 2.7 Substudy Objective

The objective of the substudy is:

- To examine the effect of the treatment regimen in pediatric patients with Hunter syndrome <3 years old and having a complex rearrangement genotype of the iduronate-2-sulfatase gene on safety and efficacy measures

### 3 STUDY ENDPOINTS

#### 3.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is:

- Change from baseline in the GCA score after 12 months of treatment, at Visit Week 52, as obtained by DAS-II testing

#### 3.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoint of this study is:

- Change from baseline in the ABC score after 12 months of treatment at Visit Week 52, as obtained by VABS-II testing

The secondary efficacy endpoints of this study are:

- Change from baseline to Visit Weeks 16, 28, and 40 in the GCA score as obtained by DAS-II testing
- Change from baseline to Visit Weeks 16, 28, and 40 in the ABC score as obtained by VABS-II testing
- Change from baseline to Visit Weeks 16, 28, 40, and 52 in standardized scores in cluster areas of the DAS-II: Verbal, Nonverbal, Spatial, and Special Nonverbal Composite (SNC)
- Change from baseline to Visit Weeks 16, 28, 40, and 52 in the standardized domain scores of the VABS-II: Communication, Daily Living Skills, Socialization, Motor Skills, and Maladaptive Behavior
- Change from baseline to Visit Weeks 16, 28, 40, and 52 in the age equivalents and development quotient (DQ) for the subcategories of the DAS-II (Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices, and Copying for the DAS-II/Early Years, and Recall of Designs, Word Definitions, Pattern Construction, Matrices, Verbal Similarities, and Sequential and Quantitative Reasoning for the DAS-II/School Years)
- Change from baseline to Visit Weeks 16, 28, 40, and 52 in the age equivalents and developmental quotients of the VABS-II: Communication, Daily Living Skills, Socialization, Motor Skills, and Maladaptive Behavior

#### 3.3 Pharmacokinetic and Pharmacodynamic Endpoints

The PK and PD endpoints of this study are:

- Serum and CSF concentration of idursulfase and serum pharmacokinetic parameters after IT administration
- Change from baseline in the concentration of GAG in CSF

### **3.4 Safety Assessments**

Safety will be assessed during the study by collection of adverse events (by type, severity, and relationship to treatment [idursulfase-IT, the IDDD, device surgical procedure, or IT administration process] and IV Elaprase infusion), changes in clinical laboratory testing (serum chemistry, hematology, urinalysis), physical and neurological examination, vital signs, 12-lead ECG, CSF chemistries (including cell counts, protein, and glucose), anti-idursulfase antibodies in CSF and serum, and determination of antibodies having enzyme neutralizing activity.

### **3.5 SOPH-A-PORT Mini S Device Assessments**

SOPH-A-PORT Mini S assessments will include measures of device implantation, device function, device longevity, record of revisions, removals, and replacements of the implanted IDDD, and adverse events associated with the device. This data will be collected on the patient's electronic case report form (eCRF) from the time of implantation and continue throughout the study as long as the SOPH-A-PORT Mini S remains implanted.

### **3.6 Health Status Assessment**

Health status dimensions as obtained by the EQ-5D questionnaire.

## 4 INVESTIGATIONAL PLAN

### 4.1 Overall Study Design and Plan

This is a controlled, randomized, two-arm, open-label, assessor-blinded, multicenter study to determine the effect on clinical parameters of neurodevelopmental status of monthly IT administration of idursulfase-IT 10 mg for 12 months in pediatric patients with Hunter syndrome and cognitive impairment who have previously received and tolerated a minimum of 3 months of therapy with Elaprase.

All patients will continue to receive Elaprase therapy as standard of care throughout the study.

The pivotal study design is “no IT treatment-controlled” in that 28 patients are assigned randomly to receive IT treatment and 14 patients are assigned randomly to participate without receiving IT treatment.

Those patients randomized to the IT treatment arm will undergo surgical implantation of the SOPH-A-PORT Mini S IDDD followed by a post-operative recovery period of at least 14 days prior to the first IT administration of idursulfase-IT. Treated patients will then receive 12 monthly IT injections of 10 mg idursulfase-IT corresponding to a treatment and assessment interval of 13 (28-day) months from randomization to the end-of-study (EOS) evaluations. Likewise, patients randomized to the no IT treatment arm will be assessed over 13 (28-day) months after randomization.

The separate substudy is open label and single arm.

#### 4.1.1 Intrathecal Drug Delivery

The study drug, idursulfase-IT (HGT-2310) will be administered to patients via the SOPH-A-PORT<sup>®</sup> Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire (SOPH-A-PORT Mini S), manufactured by Sophysa SA (Orsay, France) or, alternatively, via lumbar puncture in the event of device malfunction. This IDDD will be used to obtain cerebrospinal fluid (CSF) samples and to deliver all IT injections of idursulfase-IT.

If the IDDD appears to be non-functional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD Manual, which provides details on the investigation and management of any IDDD-related issues. This includes possible partial revision or complete replacement of the IDDD as indicated. If the intrathecal space is not accessible via the IDDD, study drug may be administered to a patient by lumbar puncture up to 12 times. Should the IDDD become clogged, undergo mechanical complications, or otherwise not be accessible, the CSF sample may also be obtained from a patient by lumbar puncture up to 12 times.

General anesthesia/sedation may be required for injections of study drug and some evaluations, and may be used at the discretion of the Investigator.

A Data Safety Monitoring Board (DSMB) will oversee both idursulfase-IT and device safety. The DSMB will be notified of IDDD failures and related complications on a periodic basis according to the DSMB charter (See Section 11.8).

Patients will have the IDDD removed when they discontinue from the study, unless the patient is continuing to receive treatment through another mechanism (eg, extension study, expanded access program).

See Section 13 for the Schedule of Events for the pivotal study ([Appendix 1](#) and [Appendix 2](#)) and separate substudy ([Appendix 3](#)).

## 4.2 Rationale for Study Design and Comparator Group

Hunter syndrome (MPS II) is an X-linked genetic disease that occurs predominantly in males; affected females are exceedingly rare. The primary analysis of efficacy in the pivotal study will focus on pediatric MPS II patients ([male]  $\geq 3$  and  $< 18$  years of age) with evidence of cognitive impairment. Note that for the purpose of this study, cognitive impairment is defined as a Differential Ability Scales, Second Edition [DAS-II]<sup>16</sup> General Conceptual Ability [GCA] standard score at Screening between 85 and 55. Patients with a GCA score at Screening  $> 85$  who are between 3 and 12 years of age may still be eligible to participate if there is demonstrated evidence of a decrease in GCA score of  $\geq 10$  points within a 12-month period in observational study HGT-HIT-090.

Eligible patients will be assigned randomly to either the monthly IT injection of 10 mg idursulfase-IT group or to the no treatment group in a 2:1 allocation ratio. The randomization scheme will be stratified by the baseline GCA score ( $\leq 70$  or  $> 70$ ). The duration of treatment will be 12 months, based on 12 consecutive monthly IT injections in the treated group. The treated patients will be implanted with a SOPH-A-PORT Mini S IDDD with the intent that idursulfase-IT will be administered via this IDDD. However, in case of IDDD malfunction, the drug may also be administered via lumbar puncture (refer to Section 4.1.1).

The intrathecally administered dose of idursulfase-IT (10 mg) to be used in this study and the treatment regimen were based on findings from studies HGT-HIT-045 and HGT-HIT-046 (See Section 4.2.1).

The comparator group in this study is randomized to “no IT treatment.” Surgical implantation of a device, performance of sham injections, and use of a placebo control were not considered appropriate for this group for ethical reasons.

All patients will receive standard-of-care treatment with Elaprase during the study. Elaprase will not be provided by the Sponsor, but rather will be prescribed by the patient’s physician in accordance with local prescribing information.

The endpoints will be clinical in nature, namely, changes in cognitive and adaptive functioning over time. The proposed primary efficacy endpoint is the change from baseline in the GCA score after 12 months of treatment at Visit Week 52 as obtained by DAS-II testing and a comparison of treated versus untreated patients will be performed. This primary endpoint was

chosen because of its clinical relevance. Data from the scientific literature concerning the rate of cognitive decline in children with MPS II<sup>9,17</sup> and the Sponsor's clinical trial experience with cognitively impaired MPS II patients suggest that an annual 11 to 14 point drop in GCA may be expected in the absence of an effective treatment. The change from baseline in GCA score after 12 months of treatment is a suitable endpoint for the development of idursulfase-IT in the proposed indication, and a 10 to 11 point difference compared with control in mean GCA change over that time frame represents a clinically meaningful benefit to patients. Secondary efficacy measures proposed include tests for activities of daily living using the Vineland Adaptive Behavior Scales, Second Edition [VABS-II].<sup>18</sup> The proposed key secondary efficacy endpoint is the change from baseline in the adaptive behavior composite (ABC) score after 12 months of treatment at Visit Week 52 as obtained by VABS-II testing and a comparison of treated versus untreated patients will be performed.

Given that the pivotal study will enroll only those patients with early cognitive impairment, it is expected, based on the Sponsor's Phase I/II experience, that such children will be able to complete serial neurodevelopmental assessments using the DAS-II and VABS-II assessment tools.

As discussed in Section 1.1, the age distribution of cognitive and functional impairment in MPS II indicates that cognitive deficit begins to become quantifiable at around the age of 3 years.<sup>9,10</sup> By the time a child with MPS II is 12 years old, he is typically either at the final stages of the neurodegenerative process or has largely escaped cognitive impairment. This was confirmed by the data from Phase I/II study HGT-HIT-045, where the patients with the mildest and earliest forms of cognitive impairment were in the age range of 3 to 7 years. There are two exceptions to this general pattern. In rare cases, cognitive and functional impairment may be noticeable prior to the age of 3 years. This is observed in children with a complex rearrangement of the iduronate-2-sulfatase gene who are at the severe end of the spectrum both for physical and CNS disease. Even more rarely, children may exhibit a slow progression of CNS disease.<sup>9,12</sup> Such patients may have measurable cognitive and functional abilities into their mid teens. MPS II patients within these two categories who are < 3 years of age or are ≥13 to <18 years of age may be eligible for participation in HGT-HIT-094 and are discussed in further detail below.

Children with a complex rearrangement of the iduronate-2-sulfatase gene represent a special subgroup of MPS II patients. Such cases typically arise in families where an older sibling has been diagnosed with Hunter syndrome and where a high awareness of the disease exists. These rare patients (≤20 % of all MPS II patients) invariably develop cognitive impairment, sometimes even before the age of 3 years. Such patients, if identified prior to 3 years of age, are ineligible to be part of the pivotal study and will not be randomized, but rather, will be enrolled into a separate substudy to receive IT treatment with idursulfase-IT. Because the primary assessment tool of the pivotal study, the DAS-II, is not suitable for the evaluation of these younger children, a more suitable tool, the Bayley Scales of Infant Development (BSID-III),<sup>19</sup> will be used. As these children will be identified infrequently, no enrollment target will be implemented. The analysis of substudy data will be descriptive only and will not be part of the efficacy analysis of the pivotal study. Like patients in the pivotal study, the patients in the substudy will receive concomitant therapy with Elaprase.



Children older than 12 years old with slowly progressing CNS disease were not identified in study HGT-HIT-045 or in conversations with MPS II experts, but have been described sporadically in the literature.<sup>9,12</sup> It is a reasonable hypothesis that the clinical course in these children with an attenuated disease subtype may be different from the typical course of neurodevelopmental decline. To mitigate this risk, children over 12 years of age with cognitive impairment, should they be identified during the enrollment period of this trial, will be required to have shown a decrease in GCA of at least 10 points over a 12-month period in the observational study HGT-HIT-090 and to have a DAS-II GCA standard score at Phase II/III study entry between 85 and 55. These criteria will be implemented to ensure that the clinical course of cognitive decline in these children is similar in rate to that in children, for whom the cognitive decline manifested earlier, thereby ensuring a more homogeneous target population for the trial. If these and other eligibility criteria are met, such patients will be randomized (2:1) to receive IT treatment with idursulfase-IT or no IT treatment in the pivotal study.

#### 4.2.1 Rationale for Dose Selection

Extrapolation to humans from data in non-human primates suggests that a dose from 5 to 35 mg delivered intrathecally would result in sufficient exposure to potentially elicit a clinical treatment response in MPS II patients. The selection of the 10 mg dose of idursulfase-IT to be given in this study was further informed by the pharmacokinetic and pharmacodynamic data of Phase I/II studies, HGT-HIT-045 and HGT-HIT-046.

The serum pharmacokinetic profiles of idursulfase-IT were dose proportional with respect to  $C_{max}$  between the 1 mg and 10 mg idursulfase IT dose groups. However, the 10 and 30 mg idursulfase-IT groups exhibited overlapping serum concentration-time profiles indicative of saturation of the transport processes from the CSF to the serum and CNS tissue compartments.

The pharmacodynamic properties of idursulfase IT were evaluated in HGT-HIT-045 and HGT-HIT-046 by measuring GAG concentration in CSF at 1 month after each idursulfase-IT administration. Compared with the 1 mg idursulfase-IT dose, the 10 mg and 30 mg doses produced equivalent, sustained reductions of CSF GAG concentrations. No appreciable change in CSF GAG concentration was observed in the untreated group (note that patients in this group, as well as the treated group, received weekly Elaprase infusions throughout the study). Thus, the pharmacodynamic profiles associated with monthly idursulfase-IT administration indicated that the 1 mg dose was suboptimal, with the 10 mg dose achieving maximal pharmacodynamic response and the 30 mg dose demonstrating no appreciable added benefit. This response correlates with the therapeutic dose range (5 to 35 mg) estimated from evaluation of HGT-2310 in non-human primates.

The doses (1, 10, 30 mg) of idursulfase-IT evaluated in the Phase I/II studies demonstrated equivalent safety profiles. The clinical pharmacokinetic and pharmacodynamic profiles of idursulfase-IT in MPS II patients indicated that the 10 mg dose provides a maximum pharmacologic response. Therefore, the 10 mg dose of idursulfase-IT was selected for Phase II/III investigation in this study.

### **4.3 Study Duration**

The planned overall duration of each patient's participation in the study is approximately 14 to 15 months from Screening to the last scheduled contact.

An extension study is planned during which patients who complete HGT-HIT-094 may continue to receive IT treatment with idursulfase-IT via the SOPH-A-PORT Mini S device.

## 5 STUDY POPULATION SELECTION

### 5.1 Study Population

For the pivotal study, it is planned that 42 patients (28 treated, 14 untreated) with early cognitive impairment who are  $\geq 3$  to  $< 18$  years of age at the time of informed consent and meet all study entrance criteria will be randomized. Note that, to meet study entry criteria, patients who are  $\geq 13$  to  $< 18$  years of age at the time of informed consent must have documented evidence of cognitive decline over 12 months in observational study HGT-HIT-090 in order to participate in this study.

A separate substudy will enroll patients who have a complex rearrangement genotype in the iduronate-2 sulfatase gene and who are below the age of 3 years at the time of informed consent. Such patients are ineligible for the pivotal study and will not be randomized, but may receive treatment with idursulfase-IT in the substudy. In view of the rarity of such patients, no enrollment target will be proposed. The enrollment of patients below 3 years of age into this separate substudy will be considered additional to the 42 patients planned for the pivotal study, and will conclude when enrollment of patients in the pivotal study closes.

### 5.2 Inclusion Criteria

#### 5.2.1 Inclusion Criteria for the Pivotal Study

Patients must meet all of the following criteria to be considered eligible for randomization in the pivotal study:

1. The patient is male and is  $\geq 3$  and  $< 18$  years of age at the time of informed consent.

*Note that patients who are younger than 3 years of age may be enrolled in a separate substudy provided that they have a documented complex rearrangement genotype of the iduronate-2-sulfatase gene and meet other inclusion criteria, provided below.*

2. The patient must have a documented diagnosis of MPS II. Of the three criteria below, the combinations (1a AND 1b) or (1a AND 1c) will be accepted as diagnostic of MPS II:
  - a. The patient has a deficiency in iduronate-2-sulfatase enzyme activity of  $\leq 10\%$  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 iduronate-2-sulfatase gene that leaves the FMR1 and FMR2 genes intact. In the case of a positive family history, the genotype of a brother or uncle (with appropriate informed consent, or assent if applicable) may be accepted as documentation at the discretion of the Medical Monitor.  
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).

3. The patient has evidence at Screening of Hunter syndrome-related cognitive impairment, defined as follows:

*Note that separate inclusion criteria with respect to patient cognitive status at Screening apply to patients  $\geq 3$  and  $< 13$  years of age and to patients  $\geq 13$  and  $< 18$  years of age.*

A patient who is  **$\geq 3$  and  $< 13$  years** of age must have one of the following criteria (3a OR 3b):

- a. A GCA score  $\geq 55$  and  $\leq 85$

OR

- b. If the patient has a GCA score at Screening  $> 85$ , there must be evidence of a decrease in GCA score of  $\geq 10$  points over 12 months from a previously documented test result in observational study HGT-HIT-090.

A patient who is  **$\geq 13$  and  $< 18$  years** of age must have both of the following criteria (3c AND 3d):

- c. A GCA score of  $\geq 55$  and  $\leq 85$

AND

- d. There must be evidence of a decrease in GCA score of  $\geq 10$  points over 12 months from a previously documented test result in observational study HGT-HIT-090.

4. The patient has received and tolerated a minimum of 3 months of therapy with Elaprase during the period immediately prior to Screening.
5. The patient must have sufficient auditory capacity, with or without hearing aids in the Investigator's judgment, to complete the required protocol testing, and be compliant with wearing the aid on scheduled testing days.
6. The patient's parent(s) or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board/Independent Ethics Committee 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, if applicable, must be obtained prior to the start of any study procedures.

Patients must meet all of the following criteria to be considered eligible for enrollment in the separate substudy:

1. The patient is male and is  **$< 3$  years** of age at the time of informed consent.
  2. The patient must have a documented diagnosis of MPS II. The following two types of documentation will be accepted as diagnostic of MPS II:
    - a. The patient has a deficiency in iduronate-2-sulfatase enzyme activity of  $\leq 10\%$  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 complex chromosomal rearrangement of the iduronate-2-sulfatase gene that leaves the FMR1 and FMR2 genes intact

In the case of a positive family history, the genotype of a brother or uncle (with appropriate informed consent, or assent if applicable) may be accepted as documentation at the discretion of the Medical Monitor.

3. The patient has received and tolerated a minimum of 3 months of therapy with Elaprase during the period immediately prior to Screening.
4. The patient must have sufficient auditory capacity, with or without hearing aids in the Investigator's judgment, to complete the required protocol testing, and be compliant with wearing the aid on scheduled testing days.
5. The patient's parent(s) or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board/Independent Ethics Committee 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) must be obtained prior to the start of any study procedures.

### 5.3 Exclusion Criteria

Patients who meet any of the following criteria are not eligible to be randomized into the pivotal study or enrolled in the separate substudy:

1. The patient has clinically significant non-Hunter syndrome-related CNS involvement (such as Fragile-X syndrome) which is judged by the Investigator to be likely to interfere with the accurate administration and interpretation of protocol assessments.
2. The patient has a large chromosomal deletion or complex rearrangement genotype that includes an inactivation and/or deletion of the FMR1 and/or FMR2 genes.
3. The patient has a significant medical or psychiatric comorbidity(ies) that might affect study data or confound the integrity of study results.
4. The patient has contra-indications for performance of lumbar puncture such as musculoskeletal/spinal abnormalities or risk of abnormal bleeding.
5. The patient has a history of complications from previous lumbar punctures or technical challenges in conducting lumbar punctures such that the potential risks would exceed possible benefits for the patient.
6. The patient has an opening CSF pressure upon lumbar puncture that exceeds 30 cm H<sub>2</sub>O.
7. The patient has experienced infusion-related anaphylactoid event(s) or has evidence of consistent severe adverse events related to treatment with Elaprase which, in the Investigator's opinion, may pose an unnecessary risk to the patient.
8. The patient has received a cord blood or bone marrow transplant at any time or has received blood product transfusions within 90 days prior to Screening.
9. The patient has a history of poorly controlled seizure disorder.
10. The patient is unable to comply with the protocol (eg, has significant hearing or vision impairment, a clinically relevant medical condition making implementation of the protocol difficult, unstable social situation, known clinically significant psychiatric/behavioral instability, is unable to return for safety evaluations, or is otherwise unlikely to complete the study), as determined by the Investigator.
11. The patient is enrolled in another clinical study that involves clinical investigation or use of any investigational product (drug or [intrathecal/spinal device] device) within 30 days prior to study enrollment or at any time during the study.

12. The patient has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to compromised airways or other conditions.
13. The patient has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use, including:
  - a. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
  - b. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the Investigator
  - c. The patient's drug therapy requires substances known to be incompatible with the materials of construction
  - d. The patient has a known or suspected local or general infection
  - e. The patient is at risk of abnormal bleeding due to a medical condition or therapy
  - f. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
  - g. The patient has a functioning CSF shunt device
  - h. The patient has shown an intolerance to an implanted device

## 6 STUDY TREATMENT

### 6.1 Description of Treatments

#### 6.1.1 Investigational Product

The investigational product to be used in this study is idursulfase-IT 10 mg for intrathecal use.

The idursulfase-IT drug product is an isotonic, sterile solution intended for IT administration. It is formulated as a 10 mg/mL protein concentration in 154 mM NaCl, pH 6.0, 0.005% polysorbate 20. It does not contain any preservatives and is intended for single use.

The active ingredient of the idursulfase-IT drug product is idursulfase (recombinant human iduronate-2-sulfatase) the same active ingredient in the commercially available drug Elaprase. However, Elaprase and idursulfase-IT are specifically formulated for the IV and IT compartments respectively; they cannot be interchanged.

In contrast to Elaprase, idursulfase-IT is specially formulated for, and compatible with, direct introduction into the IT space, because it is isotonic and contains excipients suitable for IT administration.

#### 6.1.2 Intrathecal Drug Delivery Device

The investigational product will be administered via the SOPH-A-PORT Mini S Implantable Access Port. The SOPH-A-PORT Mini S is intended for long-term, intermittent access to the IT space for delivery of investigational product. The device is CE marked in the EU.

The SOPH-A-PORT Mini S device comprises the following seven components:

- One SOPH-A-PORT Mini S Access Port
- One intrathecal port closed-tip catheter
- One guidewire
- Two suture wings
- One 14-gauge Tuohy needle
- One 22-gauge non-coring Huber needle
- One Luer lock Connector.

Further details are provided in the Instructions for Use.

#### 6.1.3 Comparator

The comparator group receives no study treatment.

## 6.2 Treatments Administered

After informed consent is signed, all patients who meet the eligibility requirements for the pivotal study will be randomized on a (2:1) allocation to one of the following pivotal study arms:

- IT Treatment Arm: treatment with idursulfase-IT 10 mg administered intrathecally via the surgically implanted IDDD (or lumbar puncture) once every 28 days
- No IT Treatment Arm: no study treatment

All patients will continue to receive standard-of-care therapy with Elaprase during the study. Elaprase will not be provided by the Sponsor, but rather will be prescribed by the patient's physician in accordance with local prescribing information.

Patients who are randomized to receive treatment with idursulfase-IT will be scheduled to undergo surgical placement of the SOPH-A-PORT Mini S device. At least 14 days will be allowed for recovery following the placement of the IDDD before the administration of the first intrathecal idursulfase-IT dose. During this time, the patient will receive standard perioperative care. Thereafter, these patients will be administered idursulfase-IT 10 mg as an IT injection once monthly for 12 months.

Patients who are randomized to no treatment will not undergo surgical placement of an IDDD and will not be administered idursulfase-IT during the study.

The separate substudy is an open-label, single arm study. Patients who are enrolled in the separate substudy will undergo surgical placement of the SOPH-A-PORT Mini S device and receive treatment with idursulfase-IT 10 mg administered intrathecally via IDDD (or lumbar puncture) once every 28 days for 12 months in addition to standard-of-care Elaprase therapy.

## 6.3 Selection and Timing of Dose for Each Patient

The dosing schedule for the study is described above in Section 6.2.

Those patients randomized to treatment in the pivotal study will undergo surgical implantation of the IDDD. Treated patients will then receive 12 monthly IT injections of idursulfase-IT 10 mg, once every 28 days.

Patients who are enrolled in the separate substudy will undergo surgical implantation of the IDDD. Patients in the substudy will receive the same treatment regimen as idursulfase-IT-treated patients in the pivotal study.

Note that, on IT Dosing Weeks, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT.

## 6.4 Method of Assigning Patients to Treatment Groups

The pivotal trial is randomized and open label. Patients who have met the inclusion and exclusion criteria will be randomized (open-label, assessor-blinded) in a 2:1 randomization



scheme to either IT treatment or no IT treatment. The randomization will be stratified according to baseline (Screening Visit) GCA score ( $\leq 70$  or  $>70$ ). The randomization schedule will be generated and administered by a third-party (eg, IVR vendor) independent of the project team.

In a separate substudy, additional patients may be enrolled who have a complex rearrangement genotype in the iduronate-2 sulfatase gene and who are below the age of 3 years at the time of informed consent. Such patients are ineligible for the pivotal study and will not be randomized, but will receive idursulfase-IT treatment. The separate substudy is an open-label, single arm study. Data from patients participating in this separate substudy will be analyzed separately.

## 6.5 Blinding

Single and double blinding of patients, their families, and the Principal Investigator is not possible due to the absence of a sham device, sham injections, or placebo. The Sponsor will work with each site to clarify the process for assessor blinding.

Every effort will be made to blind the assessors of the primary and secondary endpoints obtained from the DAS-II and VABS-II. The assessors responsible for these evaluations will not be informed of patients' randomization assignments. The families will be instructed not to share this information with the assessors.

Different assessors will be responsible for administration of the DAS-II and VABS-II. The DAS-II will be administered by a qualified psychologist.

## 6.6 Infusion Reactions and Management

Infusions of proteins can be associated with reactions to the infusion that may or may not be immune mediated. Thus, potential reactions to the infusion of an investigational product are unpredictable.

Infusion-related reactions have been observed in patients receiving IV enzyme replacement therapy with Elaprase, with symptoms including cutaneous reactions (rash, pruritus, and urticaria), pyrexia, headache, hypertension, and flushing. Previous experience with Elaprase is fully described in the Elaprase US Package Insert and the European Union (EU) Summary of Product Characteristics (SmPC). Pretreatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. The safety information reported from administration of Elaprase may be relevant to management of adverse events in relation to idursulfase-IT.

Successful management of Elaprase infusion-related adverse events included slowing or interrupting the infusion at the time of the event or pre-treatment with low-dose corticosteroids and/or antihistamines. Most adverse events of this type were treated with antihistamines such as chlorpheniramine (IV administration preferred if available), oxygen, or mild glucocorticoids such as hydrocortisone and prednisolone. All were monitored closely until symptoms of the reactions had subsided. In clinical trials of Elaprase, an apparent decrease in the overall rates of adverse events, and specifically infusion-related adverse events, was observed over time, suggesting that patients may better tolerate infusions during long-term therapy.

Because idursulfase-IT is administered intrathecally, it is not expected that systemic blood levels will be high enough to cause an infusion-related reaction. Clinical studies with idursulfase-IT have not revealed adverse events consistent with infusion-related reactions sometimes observed with IV Elaprase infusion. There have been no significant concerns regarding infusion-related immune reactions following IT administration in studies HGT-HIT-045 and HGT-HIT-046.

Note that any patient with prior experience of infusion-related anaphylactoid event(s) or evidence of consistent severe adverse events related to treatment with Elaprase is excluded from participating in this study.

## **6.7 Restrictions**

### **6.7.1 Prior Therapy**

All patients are to have received and tolerated 3 months of therapy with idursulfase IV (Elaprase) therapy prior to participation in this study.

Prior therapies that are exclusion criteria for the study are: prior treatment with an investigational product (drug or [intrathecal/spinal] device) within the 30 days prior to study enrollment or anytime during the study; receipt of a cord blood or bone marrow transplant at any time; and receipt of blood product transfusions within 90 days prior to Screening.

### **6.7.2 Fluid and Food Intake**

Not applicable.

### **6.7.3 Patient Activity Restrictions**

Please refer to the SOPH-A-PORT Mini S Instructions for Use for details regarding patient activity restrictions for patients to be implanted with this device.

## **6.8 Treatment Compliance**

Treatment with the investigational product will be administered via an IDDD under the supervision of the investigator and in the controlled environment of a clinical center; therefore, full patient compliance with treatment is anticipated in this study.

The initial implantation and revision and/or explantation of the SOPH-A-PORT Mini S will be performed by pediatric or general neurosurgeons or anesthesiologists who have experience in port and catheter implant procedures and intrathecal access procedures. Please refer to the Instructions for Use for further details.

Investigational product administration will be performed in a clinical setting by appropriately trained and skilled healthcare providers (nurses or physicians) with knowledge of the patient's drug regimen and experienced in accessing vascular or central nervous system (CNS) ports or CNS infusion pumps. Patients and patients' families will not be directly using the device to

administer drugs and will have limited direct interaction with the device as there is minimal care required both during the immediate postoperative period as the implant site heals, and at times of drug administration.

## 6.9 Packaging and Labeling

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

### 6.9.1 Investigational Product

Idursulfase-IT drug product is a sterile liquid formulation for IT administration that is packaged in 2-cc Type I borosilicate glass vials. The drug product is filled to deliver a minimum dose volume of 1 mL per vial with minimal waste and for handling convenience in the clinical setting.

### 6.9.2 Intrathecal Drug Delivery Device

The SOPH-A-PORT Mini S Access Port is available in one size, individually packaged, with other SOPH-A-PORT Mini S components in double peel-off, sterile, pyrogen-free packaging, sterilized with Ethylene Oxide. Instructions for use are also included in the packaging. A guidewire is provided in separate double pouch, sterile, pyrogen-free packaging.

Labels are provided on the outer carton and on both the SOPH-A-PORT Mini S box and guidewire/cannula package inside.

### 6.9.3 Storage and Accountability

### 6.9.4 Investigational Product

Idursulfase-IT will be shipped by Shire HGT or a qualified distributor to the clinical study site(s) at 5±3 °C (36 to 46 °F). The investigational product should be handled as follows:

- idursulfase-IT vials should be stored at 5±3°C (36 to 46°F).
- idursulfase-IT is intended for IT use only.
- It is recommended that idursulfase-IT be filtered prior to use through a standard 0.2 µm filter.
- Perform a visual inspection of each vial. Idursulfase-IT is a clear to slightly opalescent, colorless solution. Do not use if the solution in the vials is discolored or particulate matter is present.
- DO NOT SHAKE. Idursulfase-IT should not be agitated vigorously at any time.
- Withdraw the volume of idursulfase-IT from the vial.
- Do not mix with, or administer in conjunction with other drug solutions.
- idursulfase-IT must be used as soon as possible after it is prepared, because it does not contain preservatives.
- Idursulfase-IT is supplied in single-use vials. Only 1 dose of idursulfase-IT is to be withdrawn from a vial.

The disposition of all investigational product delivered to a Principal Investigator must be recorded on a patient-by-patient basis by completing the Accountability Log. The date and time of administration of the investigational product and use of the device must be documented on the patient's appropriate eCRF.

The Principal Investigator, Clinical Research Coordinator, or designee (eg, Pharmacist) must ensure that all documentation regarding investigational product receipt, storage, dispensing, loss/damaged and return of used/unused product is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the investigational product is available for the monitor to inventory and prepare for return shipment to the Sponsor or designee, if required.

See the Pharmacy Manual for additional details.

### **6.9.5 Intrathecal Drug Delivery Device**

The disposition of all SOPH-A-PORT Mini S devices delivered to a Principal Investigator must be recorded on a patient-by-patient basis by completing the Accountability Log. The date and time of administration of the investigational product and use of the SOPH-A-PORT Mini S device must be documented on the patient's appropriate eCRF.

The Principal Investigator, Clinical Research Coordinator, or designee (eg, Pharmacist) must ensure that all documentation regarding receipt, storage, dispensing, loss/damaged SOPH-A-PORT Mini S devices and return of used/unused SOPH-A-PORT Mini S device(s) is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the SOPH-A-PORT Mini S devices are available for the monitor to inventory and prepare for return shipment to the Sponsor or designee, if required.

The SOPH-A-PORT Mini S and its components are sterile, single-use devices.

Please refer to the IDDD Manual for device return instructions.

### **6.9.6 Comparator Product**

Not applicable to this study.

## 7 STUDY PROCEDURES

The pivotal study will consist of a Screening period of up to 28 days prior to randomization (during which re-testing of patients who were initially unwilling or unable to comply with all scheduled screening assessments is permitted).

Those patients randomized to the IT treatment arm will undergo surgical implantation of the SOPH-A-PORT Mini S IDDD followed by a post-operative recovery period of at least 14 days prior to the first IT administration of idursulfase-IT. Treated patients will then receive 12 monthly IT injections of idursulfase-IT corresponding to a treatment and assessment interval of 13 (28-day) months from randomization to the end-of-study (EOS) evaluations. Likewise, patients randomized to the no IT treatment arm will be assessed over 13 (28-day) months after randomization.

Patients in the IT treatment arm of the pivotal study will be assessed according to the following schedule:

- Screening (Weeks -1 to -4 [Day -28 to Day -1])
- Randomization (Week 0 [Day 0])
- Pre-surgery, Surgery, and Post-operative Recovery (Weeks 2 and 3)
- Treatment and Assessments(Week 4 through Week 48 [ $\pm 7$  days])
- End of study (EOS, Week 52 [ $\pm 7$  days])
- Follow-up (telephone contact) 7 ( $\pm 2$ ) days from the Week 52 (or EOS)

Patients in the no IT treatment arm of the pivotal study will be assessed according to the following schedule:

- Screening (Weeks -1 to -4 [Day -28 to Day -1])
- Randomization (Week 0 [Day 0])
- Assessments (Week 4 through Week 48 [ $\pm 7$  days])
- End of study (EOS, Week 52 [ $\pm 7$  days])
- Follow-up (telephone contact) 7 ( $\pm 2$ ) days from the Week 52 (or EOS)

The separate substudy is open label and single arm. Patients who meet all entry criteria for participation in the substudy will be considered enrolled on Day 0. Thereafter, patients who are enrolled in the separate substudy will follow the same schedule of study visits as idursulfase-IT-treated patients in the pivotal study.

Patients in the substudy will be assessed according to the following schedule:

- Screening (Weeks -1 to -4 [Day -28 to Day -1])
- Enrollment (Week 0 [Day 0])
- Pre-surgery, Surgery, and Post-operative Recovery (Weeks 2 and 3)
- Treatments and assessments (Week 4 through Week 48 [ $\pm 7$  days])
- End of study (EOS, Week 52 [ $\pm 7$  days])
- Follow-up (telephone contact) 7 ( $\pm 2$ ) days from the Week 52 (or EOS)

Patients in both the IT treatment and no IT treatment arms of the study will complete EOS assessments at Week 52 (Visit Month 13). All patients will participate in a follow-up contact (by telephone) approximately 7 days after the EOS visit.

A patient who discontinues or is withdrawn prior to study completion will be asked to participate in an EOS visit within approximately 30 days after withdrawal or discontinuation (EOS assessments for such patients will be the same as Week 52 assessments), and also to complete a follow up contact approximately 7 days after the patient's EOS visit. There is no replacement of patients who do not complete the study.

All patients will receive weekly IV Elaprase infusions as prescribed throughout the study. Note that, on IT Dosing Weeks, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT.

See Section 13 for the Schedule of Events for the pivotal study ([Appendix 1](#) and [Appendix 2](#)) and separate substudy ([Appendix 3](#)).

All data collected are to be recorded on the appropriate electronic case report form (eCRF).

Details for study procedures including sample collection are described in the Operations Manual.

## 7.1 Informed Consent

Prior to conducting any study-related procedures, written informed consent (signed and dated) 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 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

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. No protocol exemptions will be permitted.

### 7.3 Medical History

A standard medical history of each patient will be obtained at Screening and will include age at onset of Hunter syndrome symptoms, age of Hunter syndrome diagnosis, evidence of iduronate-2-sulfatase deficiency, genotype, family history of Hunter syndrome, Hunter syndrome signs and symptoms in the following domains: head/neck, eyes, mouth, ear, nose, throat, chest/lung, cardiovascular system, abdomen, gastrointestinal system, genitourinary system, skin, skeletal system, neurological system, psychiatric disorders and surgical history.

Patients who do not have a documented diagnosis of Hunter syndrome in their medical history will provide a blood sample at Screening to assay for iduronate-2-sulfatase enzyme activity in plasma, fibroblasts, or leukocytes (patients must exhibit  $\leq 10\%$  of the reference laboratory's lower limit of the normal range to confirm diagnosis). These samples will also be assayed for normal enzyme activity level of one other sulfatase in plasma, fibroblasts, or leukocytes (based on the reference laboratory's normal range).

A blood sample for genotyping is to be collected during Screening to document the diagnosis of Hunter syndrome. Analysis of iduronate-2-sulfatase genotype will be required for all patients who have not had a previous genotyping performed at Greenwood Genetic Center's Diagnostic Laboratory (Greenwood, South Carolina, USA). Even patients for whom prior genotyping was performed at Greenwood Genetic Center's Diagnostic Laboratory may need have a repeat analysis performed if the original information was insufficient for an unambiguous classification of genotype (eg, to document the integrity of the FMR1 and FMR2 genes in patients with complex mutations/chromosomal rearrangements).

### 7.4 Echocardiogram

An echocardiogram will be performed as part of the study eligibility criteria. This procedure will not be necessary if the patient has had an echocardiogram performed within 3 months of study entry, the data are available, and deemed satisfactory for evaluation of anesthesia risk.

### 7.5 Device Related Procedures

#### 7.5.1 IDDD Implantation and Revision

The IDDD will be surgically implanted or revised at the clinical site. Procedures for implantation and revision are detailed in the device's Instructions for Use. Standard hospital procedures for surgery will be followed; the patient will be under general anesthesia for this procedure.

An additional medical device, the catheter passer, is necessary for the implantation procedure. The catheter passer is a sterile, single use device that will be used in the subcutaneous placement of the catheter. The Phoenix Neuro Disposable Catheter Passer, manufactured by Sophysa is CE marked in the EU and cleared under K853370 in the US.

Details of the implantation/revision and malfunctions/failure will be documented on the patient's eCRF.

### **7.5.2 X-ray Verification of Intrathecal Drug Delivery Device Placement**

A postoperative x-ray check of the IDDD will be performed following surgery to verify proper installation and confirmation of IDDD placement at the mid-thoracic level. The x-rays may be performed to check placement of the device, as needed, throughout the study, and will be performed at the end of the study (to verify that the IDDD is in the correct position). At a minimum, the date of the x-ray verifying correct IDDD placement will be documented on the patient's eCRF. If the device requires revision or replacement during the study, additional x-rays will be taken to document the proper positioning of the device. If the IDDD malfunctions, an x-ray will be performed to assess the potential cause of malfunction.

### **7.5.3 CSF Sampling Procedure**

Cerebrospinal fluid will be sampled via the device. If this is not possible, and if CSF sampling is necessary, either for adherence to the protocol, or to investigate clinical concerns, a lumbar puncture may be performed to sample CSF, either with or without administration of drug afterwards (See Section 4.1.1).

### **7.5.4 Device Removal**

If at the time of a scheduled dosing it is not possible to administer a full medication dosage as per the standard administration steps detailed in the device's Instructions for Use due to a device related issue, the IDDD will be declared a device malfunction. If the device malfunction is irreversible and cannot be corrected without a device surgical intervention, the IDDD will be declared a device failure, starting from the date of the initial malfunction.

The IDDD will then be surgically removed or revised and a new device and/or device components will be re-implanted at the earliest possible opportunity, preferably at the same time.

Details of the device removal will be recorded in the patient's eCRF. For further details, please refer to the SOPH-A-PORT Mini S Instructions for Use.

Patients will have the IDDD removed when they discontinue from the study, unless the patient is continuing to receive treatment through another mechanism (eg, extension study, expanded access program).

## **7.6 Investigational Product Administration**

Idursulfase-IT will be administered every 28 days by means of the IDDD. A visual examination of both the port and catheter track will be performed before each IT injection.

A 22-gauge Huber non-coring needle is to be used for access to the implanted port; standard hypodermic needles would damage the septum and may cause leakage. If no needle free connector is present, either a stopcock of the Huber needle infusion set's clamp is to be used to prevent CSR backflow and to mitigate the risk of air entering the system. It is possible to use other brands of Huber non-coring needles, provided that their specifications are identical to that of the Huber needle (22G) supplied by Sophysa in a SOPH-A-PORT Mini S.



If the intrathecal space is not accessible via the IDDD, idursulfase-IT may be administered by lumbar puncture (See Section 4.1.1).

The injection date, injection start/stop time, planned dose, injection volume, and flush volume will be recorded on the patient's eCRF.

Intrathecal administration of investigational product will be preceded by CSF sampling for safety laboratory analysis (cell count, protein, glucose), pharmacodynamic analysis (GAG concentration), and analyses of idursulfase enzyme and anti-idursulfase antibodies. The total volume of investigational product and flush administered is targeted towards replenishing the volume of CSF withdrawn. Therefore, while the total volume of idursulfase-IT administered will be less than the total volume of CSF withdrawn, additional saline will be administered to ensure a balance between the amount administered and the amount withdrawn.

Specifically, the investigational product will be administered in a volume of 1 mL (1 mL of a 10 mg/mL solution) (See Section 6.1.1). The minimal proposed flush volume is 2 mL, so the minimal volume administered will be 3 mL. Additional volume of preservative-free saline will be administered to add up to a total volume that is equal to that which was withdrawn.

This design was intended to mitigate any risk of overfilling or underfilling the IT compartment as well as the risk of inducing acute intracranial hypertension or brain herniation.

Patients will remain under observation in the hospital setting (may include lounge, infusion center, or waiting room) for at least 4 hours post administration of investigational product and will be discharged when deemed clinically stable by the Investigator. The patient will need to be examined the following day by the Investigator; however, there is no requirement for an overnight hospital stay. If a decision is made to keep the patient overnight for convenience, this should not initiate a serious adverse event report.

## 7.7 Pharmacokinetic Assessments

Blood samples will be collected for measurement of serum concentrations of idursulfase and determination pharmacokinetic parameters after intrathecal administration. CSF samples will also be collected immediately prior to IT dosing for measurement of CSF concentrations of idursulfase. The results of these assessments will be addressed in a separate pharmacokinetic report.

The blood and CSF sampling for pharmacokinetic assessments is provided in the Schedule of Events for patients in the treated arm of the pivotal study ([Appendix 1](#)) and in the separate substudy ([Appendix 3](#)).

## 7.8 Pharmacodynamic Assessments

Cerebrospinal fluid and urine samples will be collected for measurement of the concentration of GAG.

## 7.9 Efficacy Assessments

The efficacy endpoints are specified in Section 3.

### 7.9.1 Neurodevelopmental Assessment Tools

The study methodology will include standardized neurodevelopmental assessments to provide a quantifiable measure of patient neurodevelopmental status.<sup>6</sup> Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as follows.

**Cognition:** the Differential Ability Scales, Second Edition (DAS-II)<sup>16</sup> will be used to assess all randomized patients. For patients participating in the separate substudy only (ie, patients with a complex rearrangement genotype of the iduronate-2-sulfatase gene and who are below the age of 3 years) cognition will be assessed initially using the Bayley Scales of Infant Development, Third Edition (BSID-III).<sup>19</sup> When these patients reach at least 42 months of age, if considered evaluable using the DAS-II instrument, they will transition to use of the DAS-II for continued assessment of cognition.

**Adaptive Behaviors:** the Vineland Adaptive Behavioral Scales, Second Edition (VABS-II)<sup>18</sup> will be used to assess all patients.

It is intended that full neurodevelopmental assessments be conducted for all patients; however, it is recognized that the feasibility of conducting these assessments may be dependent on the patient's ability to cooperate and/or level of cognitive impairment.

### 7.10 Health Status Assessment

The health status of patients will be assessed using the EQ-5D questionnaire, a standardized instrument for use as a measure of health status which is applicable to a wide range of health conditions and treatments.<sup>20,21</sup> The EQ-5D provides a descriptive profile and index value for health status.

### 7.11 Safety Assessments

Safety will be assessed by adverse events (adverse events, by type, severity, and relationship to treatment [idursulfase-IT, the IDDD, device surgical procedure, or IT administration process] and IV Elaprase infusion), changes in clinical laboratory testing (serum chemistry, hematology, urinalysis), physical and neurological examination, vital signs, 12-lead ECG, CSF chemistries (including cell counts, protein, and glucose), anti-idursulfase antibodies in CSF and serum, and determination of antibodies having enzyme neutralizing activity.

SOPH-A-PORT Mini S assessments will include measures of device implantation, device function, device longevity, record of revisions, removals, and replacements of the implanted IDDD, and adverse events associated with the device. This data will be collected on the patient's electronic case report form (eCRF) from the time of implantation and continue throughout the study as long as the SOPH-A-PORT Mini S remains implanted.

### 7.11.1 Physical and Neurological Examination

A physical examination will be performed with a thorough review of body systems on specified study days.

Physical examinations will include a review of the patient's general appearance, neurological examination, as well as evaluation of the body systems listed in [Table 7-1](#) and the device port and catheter track. Any abnormal change in findings will be recorded as an adverse event on the appropriate eCRF.

**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
Port and catheter track	

### 7.11.2 Height and Weight

Height (cm) and weight (kg) will be recorded for all patients at Screening and during the study at time points specified in the Schedule of Events. The clinical site staff will be instructed to use a calibrated scale for weight measurement.

### 7.11.3 Head Circumference

Head circumference (cm) will be measured in a uniform manner for all patients.

### 7.11.4 Hearing Assessment

Hearing assessments will be performed using age-appropriate testing methods based on the patient's age at the time of testing. It is recognized that the ability to conduct this assessment will depend on the patient's ability to cooperate and that it might not be possible to complete a hearing assessment for every patient. A reasonable effort should be made to perform a hearing assessment for each patient; however, inability to collect these data may not be considered a protocol deviation.

### 7.11.5 Vital Signs

Vital signs are to be recorded for all patients and will include pulse, blood pressure, respiration rate, and temperature.

### 7.11.6 Electrocardiogram

An electrocardiogram (12-lead) will be performed in accordance with the clinical site's standard practice(s). Electrocardiogram recordings will be read locally at the clinical site by a qualified cardiologist. The ECG will include assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, and assessment of PR, QRS, QT, and corrected QT (QTc) intervals. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the eCRF.

### 7.11.7 Intracranial Pressure Measurement

Intracranial pressure (ICP) measurement (cm of H<sub>2</sub>O) will be assessed for all patients. The ICP measurement will be conducted by lumbar puncture and while the patient is under anesthesia.

Patients with a surgically implanted IDDD should undergo X-ray prior to lumbar puncture to verify the position of the catheter.

### 7.11.8 Brain Magnetic Resonance Imaging

Patients will undergo magnetic resonance imaging (MRI) of the brain. Brain structure volumes will be measured. Refer to the Study Operations Manual for specific procedures and precautions.

### 7.11.9 Clinical and Other Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing. All blood samples will be collected by venipuncture. Patients will be in a seated or supine position during blood collection.

Clinical laboratory tests will include the following (See [Table 7-2](#)):

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

Hematology:	Serum Chemistry:
- Hematocrit (Hct)	- Albumin (ALB)
- Hemoglobin (Hgb)	- Alkaline phosphatase (ALK-P)
- Mean corpuscular hemoglobin (MCH)	- Alanine aminotransferase (ALT; SGPT)
- Mean corpuscular hemoglobin concentration (MCHC)	- Aspartate aminotransferase (AST; SGOT)
- Mean corpuscular volume (MCV)	- Blood urea nitrogen (BUN)
- Platelet count	- Calcium (Ca)
- Red blood cell (RBC) count	- Carbon dioxide (CO <sub>2</sub> )
- White blood cell (WBC) count with differential	- Chloride (Cl)
	- Creatinine
Urinalysis:	- Creatine phosphokinase
- Appearance (clarity and color)	- Gamma-glutamyl transferase (GGT)
- Bilirubin	- Globulin

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

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- Blood	- Glucose
- Glucose	- Lactate dehydrogenase (LDH)
- Ketones	- Magnesium (Mg)
- Leukocyte esterase	- Phosphorus (P)
- Microscopic examination of sediment	- Potassium (K)
- Nitrite	- Sodium (Na)
- pH	- Total and direct bilirubin
- Protein	- Total cholesterol
- Specific gravity	- Total protein
- Urobilinogen	- Total thyroxine (T4)
	- Thyroid-stimulating hormone (TSH)
Coagulation:	- Triglycerides
- Prothrombin time (PT)	- Uric acid
- Partial thromboplastin time (PTT)	

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Urine samples will be collected for determination of GAG concentration. Urine GAG will be analyzed and reported by a Sponsor-designated laboratory. Urine creatinine will be analyzed in the collected samples. Urine GAG concentration will be normalized to urine creatinine and reported as mg GAG/mmol creatinine.

#### **7.11.10 Cerebrospinal Fluid Assessments**

Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard laboratory parameters (cell count, protein, glucose), and concentrations of GAG and idursulfase enzyme. The CSF samples will also be analyzed for idursulfase-specific antibodies (See Section 7.11.11).

Cerebrospinal fluid will be obtained from patients in the treated arm of the pivotal study and in the substudy at Screening (by lumbar puncture and under general anesthesia), during surgical implantation of the IDDD, prior to each intrathecal injection of investigational product, and at the EOS visit. Should the IDDD become clogged, undergo mechanical complications or otherwise not be accessible, the CSF sample may be obtained by lumbar puncture up to 12 times.

Patients in the no treatment arm of the pivotal study will undergo lumbar puncture (under general anesthesia) to obtain CSF samples.

#### **7.11.11 Antibody Assessments**

Blood and CSF samples will be collected and evaluated by a Shire-HGT designated laboratory for the presence of anti-idursulfase antibodies and antibodies with enzyme neutralizing activity.

### **7.11.12 Device Assessments**

SOPH-A-PORT Mini S assessments will include measures of device implantation, device function, device longevity, record of revisions, removals, and replacements of the implanted IDDD, and adverse events associated with the device. These data will be collected on the patient's eCRF from the time of implantation and continue throughout the study as long as the SOPH-A-PORT Mini S remains implanted.

### **7.11.13 Pregnancy Testing**

Not applicable.

## **7.12 Sample Collection, Storage, and Shipping**

Details for study procedures, including sample collection, are provided in the Operations Manual for this study.

## **7.13 Concomitant Medications, Therapies/Interventions, and Medical/Surgical Procedures Assessments**

All medications, therapies/interventions administered to and medical/surgical procedures performed on patients from the time of informed consent through the follow-up contact are regarded as concomitant and will be documented on the eCRF. Non-permitted (per the exclusion criteria) medications, therapies, or surgical interventions will lead to exclusion from the study or a possible protocol violation depending on when the non-permitted event occurs.

All patients are to receive Elaprase during the study. Elaprase will be prescribed by the patient's physician and will be administered in accordance with local prescribing information. Elaprase will not be provided by the study Sponsor.

Concomitant therapies such as speech therapy, ergotherapy, music therapy, and physical therapy, will be captured at baseline and throughout the study.

## **7.14 Adverse Events Assessments**

### **7.14.1 Definitions of Adverse Events and Serious Adverse Events**

#### **7.14.1.1 Adverse Events**

An adverse event 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 investigational 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

Throughout the study, the Investigator must record all adverse events on the AE electronic case report form (eCRF), regardless of the severity or relationship to investigational product. The Investigator should treat patients with adverse events 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, adverse events 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 eCRF. Illnesses first occurring or detected during the study, and worsening of a concomitant illness during the study, are to be regarded as adverse events and must be documented as such in the eCRF.

#### **7.14.1.2 Elaprase Infusion-related Adverse Events**

All patients will receive concomitant IV therapy with Elaprase throughout their participation in this study. Adverse events that are potentially related to IV Elaprase infusion will be captured. An Elaprase-associated infusion-related reaction will be defined as an adverse event that begins either during or within 24 hours after the start of the infusion, and is judged as at least possibly related to the infusion. Adverse events that are considered infusion-related reactions will be noted as such in the appropriate field on the eCRF. The most common infusion-related adverse events that have been reported in patients with Hunter syndrome during Elaprase infusions are listed in Section 6.6. Note that, during weeks of IT dose administration, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT dosing.

#### **7.14.1.3 IDDD-related Adverse Events**

Examples of adverse events related to use of the IDDD include, but are not limited to, the following: device failure, device malfunction, incorrect connection of IDDD components, erosion of the portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, migration of the portal/catheter, occlusion of the portal/catheter, portal site or subcutaneous tract infection. The device may also need to be replaced or repaired as needed. A list of adverse effects expected with use of the SOPH-A-PORT Mini S is provided in [Appendix 4](#).

#### 7.14.1.4 Device Surgical Procedure-related Adverse Events

Examples of adverse events related to surgical procedures include, but are not limited to, the following: IDDD implant/explant, IDDD adjustment, full revision, partial revision, IDDD removal, and delayed re-implantation after previous IDDD removal, and post operative infection.

#### 7.14.1.5 Intrathecal Administration Process Adverse Events

Intrathecal administration process adverse events may include those caused by anesthesia during drug administration and other drug administration issues (eg, extravasation during infusion or hematoma due to the Huber needle), or complications of lumbar puncture.

#### 7.14.1.6 Serious Adverse Event

A serious adverse event (SAE) is any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires hospitalization. Note, however, for the purpose of this study, overnight hospitalizations post intrathecal administration of idursulfase-IT that are based on practical or logistical considerations, rather than safety will not be deemed serious adverse events (See Section 7.6).
- 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 a serious adverse event 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 adverse event is defined as an adverse event that placed the patient, in the view of the initial reporter, at immediate risk of death from the adverse event as it occurred (ie, this definition does not include an adverse event that, had it occurred in a more severe form, might have caused death).

#### 7.14.1.7 Unexpected Adverse Device Event

An unexpected adverse device event (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients (21CFR812.3[s] or other regulatory requirements, as applicable).



## 7.14.2 Device-associated Definitions

### 7.14.2.1 Device Revision (Partial and Full)

Partial device revision: surgical revision/replacement of one or more component(s) of the device; other component(s) of the original device remain implanted and are not affected (eg, port revision).

Full device revision: the device is removed (explanted) in its entirety and a completely new device is implanted.

### 7.14.2.2 Device Malfunction

The device does not perform as intended, based on the description in the device's Instructions for Use, but does not require either a partial or full device revision.

### 7.14.2.3 Device Failure

The device irreversibly fails to perform as intended and requires either a partial or full device revision or removal.

## 7.14.3 Classification of Adverse Events and Serious Adverse Events

The severity of adverse events will be assessed by the Investigator using the National Cancer Institute Common Toxicity Criteria (NCI CTC) grading scale (provided in the Study Operations Manual). If an adverse event is not described in the NCI CTC, the severity should be recorded based on the scale in [Table 7-3](#). The severity of all adverse events and serious adverse events should be recorded on the appropriate eCRF 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.

### 7.14.3.1 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); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on 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.

#### 7.14.4 Relatedness of Adverse Events and Serious Adverse Events

The relationship of an adverse event or serious adverse event to study treatment (study drug, the IDDD, device surgical procedure, or IT administration process) will be assessed by the investigator as follows. The relationship to treatment will be categorized based on the definitions provided in [Table 7-4](#).

- Relationship to idursulfase-IT
- Relationship to the IDDD (examples of IDDD-related adverse events are listed in Section [7.14.1.3](#))
- Relationship to a device surgical procedure (surgical implantation of the IDDD, partial or full device revision as described in Section [7.14.1.4](#))
- Relationship to the IT administration process (examples of IT administration process-related adverse events are listed in Section [7.14.1.5](#))

**Table 7-4 Adverse Event Relatedness**

<b>Relationship to Treatment</b>	<b>Definition</b>
Not Related	Unrelated to investigational product, device, device surgical procedure, or IT administration process.
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, device, device surgical procedure, or IT administration process, 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, device, device surgical procedure, or IT administration process 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, device, device surgical procedure, or IT administration process 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.

The relationship of an adverse event or serious adverse event to IV Elaprase infusion will be assessed by the investigator as described in Section [7.14.1.2](#).

## 7.14.5 Procedures for Recording and Reporting Adverse Events

### 7.14.5.1 Adverse Event Monitoring and Period of Observation

Adverse events will be monitored continuously throughout the study.

For the purposes of this study, the period of observation extends from the time at which informed consent is obtained until the patient's final evaluation of the study. For safety purposes, the final evaluation for patients who complete this study will be defined as the follow-up evaluation performed 7 ( $\pm$ 2) days after the EOS visit.

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

### 7.14.5.2 Reporting Serious Adverse Events

Any serious adverse event, regardless of relationship to investigational product, device, device surgical procedure, IT administration process, or IV Elaprase infusion, which occurs in a patient after informed consent will be recorded by the clinical site on the SAE form. The serious adverse event must be completely described on the patient's eCRF, including the judgment of the Investigator as to the relationship of the serious adverse event to the investigational product and/or device. The Investigator will promptly supply all information identified and requested by the Sponsor (or contract research organization [CRO]) regarding the serious adverse event.

The Investigator must report the serious adverse event to the Shire Pharmacovigilance and Risk Management Department AND to the Shire HGT Medical Monitor on the 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:** PPD [REDACTED] (UK) **OR United States FAX:** PPD [REDACTED]

**Email:** PPD [REDACTED]

**AND**

**Shire HGT Medical Monitor:** PPD [REDACTED], MD, PhD

**Email:** PPD [REDACTED]

**FAX:** PPD [REDACTED] (USA)

Any follow-up information must also be completed on the 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 serious adverse event, the clinical site must contact the Shire HGT Medical Monitor by telephone; this is in addition to completing and transmitting the SAE form as stated above. The following provides contact information for the Shire HGT Medical Monitor.

<b>If an SAE is assessed as severe and unexpected, or life-threatening, contact:</b>
<p>PPD [REDACTED] MD, PhD PPD [REDACTED] Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA Telephone: PPD [REDACTED] Mobile: PPD [REDACTED] (24-hour access) Email: PPD [REDACTED] Fax: PPD [REDACTED] (USA)</p>

The Investigator must promptly report all required information to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any CIOMS I/MDR report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected drug-related serious adverse event or unexpected adverse device event. 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. The Investigator or Sponsor must also ensure that the IRB/IEC receives copies of UADE reports that have been submitted by Sophysa (or its designated agent) to the relevant regulatory agencies.

### 7.15 Pregnancy

Not applicable.

### 7.16 Abuse, Overdose, and Medication Error

**Abuse** – Persistent or sporadic intentional intake of investigational 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 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 investigational product is not used as directed at the dose prescribed by the protocol).

**Overdose** – Intentional or unintentional intake of a dose of investigational product higher than the protocol-mandated dose. No clinical information on overdose is available. Idursulfase-IT has been well tolerated at the highest once monthly dose (30 mg) administered intrathecally to pediatric patients in clinical trials.

**Medication Error** – A mistake made in prescribing, dispensing, administration and/or use of the investigational product.

## 7.17 Removal of Patients from the Trial or Investigational Product

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

- The patient exhibits non-compliance with the study protocol that is considered disruptive to study conduct.
- The patient was erroneously included in the study.
- The patient develops an exclusion criterion.
- The patient suffers an intolerable adverse event.
- The study is terminated by the Sponsor.

The patient's parent(s) or legally authorized representative 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 the patient's parent(s) or 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 on the eCRF. Any adverse events experienced up to the point of discontinuation must be documented on the AE eCRF. If adverse events are present when the patient withdraws from the study, the patient will be re-evaluated within approximately 30 days of withdrawal. All ongoing serious adverse events at the time of withdrawal will be followed until resolution.

## 7.18 Other Study Procedures

### 7.18.1 Safety-related Study Stopping Rules

This study will be stopped and safety data reviewed if any patient experiences a life-threatening serious adverse event or a death occurs, if either is considered possibly or probably related to the study treatment (investigational product, the IDDD, device surgical procedure, or the IT administration process). After review of the safety data, the status of the study will be one of the following:

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

Patient safety in this study will be monitored by an independent DSMB until the last patient completes his last scheduled study visit/assessment. The DSMB will be an external group overseeing the safety of the study treatment, including both the investigational product and the

IDDD, and will operate according to a charter determining the scope of its activities and frequency of meetings (See Section 11.8 for additional details).

## 7.19 Appropriateness of Measurements

The measures of safety to be used in the study are appropriate for an interventional study in MPS II patients. These include monitoring of adverse events and medication use, both standard parameters for the assessment of safety, as well as measurement of ICP and imaging.

Cognitive impairment is a key symptom of MPS II; however, clinical research in this area has been broadly lacking, instead focusing on the biological and physical aspects of the disease, and remains an unmet medical need. This highlights the need for a treatment that targets the cognitive involvement of MPS II, and an endpoint strategy that specifically targets the cognitive and behavioral symptoms associated with MPS II. The neurodevelopment measures planned for this study will assess cognitive and adaptive functions in children with MPS II. These assessment tools (DAS-II, VABS-II) will provide a quantifiable measure of CNS neurodevelopment status and are appropriate for use in the target population.

The DAS-II has been found to be valid and reliable. Evidence from published studies and previous Shire HGT clinical trials demonstrates that the DAS-II is able to detect both changes in a child's ability and stabilization of functioning over time following treatment. The rating of the child by the parent format of the VABS-II is consistent with the FDA Patient-reported Outcome (PRO) Guidance, which states that caregiver reports must be based on observable behaviors only.

The concepts measured by the DAS-II were mapped onto an MPS II conceptual model. The concept mapping exercise indicated adequate concept coverage across the three assessment tools, collectively. Following feedback from experts in the field of neurodevelopmental functioning, the concept mapping exercise was repeated for the VABS-II. The VABS-II was found to have strong concept coverage when combined with the DAS. Based on this evidence, the DAS-II and VABS-II will be utilized as the primary and secondary assessment tools for efficacy.

A model illustrating the efficacy endpoints in this study is presented in Table 7-5. The endpoints have been classified as primary, key secondary, and secondary based on their clinical importance. Secondary efficacy endpoints have been included for the purposes of providing additional data to support both the primary and key secondary endpoints. The change from baseline in GCA, as assessed by the DAS-II, will be the primary endpoint. The DAS-II will be used to measure secondary endpoints, including standardized scores in cluster areas and developmental quotients. Key secondary and other secondary endpoints are derived from the VABS-II to assess adaptive behaviors.

**Table 7-5. Endpoint Model**

Concept	Subconcept	Assessment Tool		
<b>Primary Endpoint</b>				
Cognitive Function	General Conceptual Ability (GCA)	DAS II		
<b>Key Secondary Endpoint</b>				
Adaptive Behavior	Adaptive Behavior Composite (ABC)	VABS-II		
<b>Secondary Endpoints</b>				
Cognitive Function	Standardized score in DAS-II cluster areas: Verbal, Nonverbal, Spatial, GCA, and Special Nonverbal Composite (SNC)			
	Developmental quotient for the following:			
	Group 1 <sup>a</sup>	Verbal Comprehension	DAS II - Early Years	
		Picture Similarities		
		Naming Vocabulary		
		Pattern Construction		
	or:	Matrices		
		Copying		
		Group 2 <sup>a</sup>	Recall of Designs	DAS-II - School Age
			Word Definition	
Pattern Construction				
Matrices				
Verbal Similarities				
	Sequential Reasoning			
	Quantitative Reasoning			
Adaptive Behavior	Standardized scores and developmental quotients (based on age equivalents) in VABS-II domains:			
	Communication	VABS-II		
	Daily Living Skills			
	Socialization			
	Motor Skills			
	Maladaptive Behavior			

<sup>a</sup> The concepts assessed will be dependent on the chronological age of the child. The child will be given the relevant version of the DAS-II (Early Years or School Age) per their age and ability.

## 8 STUDY ACTIVITIES

Each activity will be performed as specified in the Schedules of Events. See Section 13 for the Schedule of Events for the pivotal study ([Appendix 1](#) and [Appendix 2](#)) and separate substudy ([Appendix 3](#)).

### 8.1 Screening (Month -1, Week -4 to -1)

#### 8.1.1 All Patients in the Pivotal Study and Substudy

The following procedures will be performed up to 28 days prior to randomization/enrollment (ie, Day -28 to Day -1):

- Written informed consent (assent if applicable) by patient's parent(s) or legally authorized guardian(s) prior to any study-related procedures
- Assessment of eligibility according to review of study entry criteria
- Medical history
- Hunter syndrome diagnosis and genotyping. Analysis of iduronate-2-sulfatase genotype will be required for all patients who have not had a previous genotyping performed at Greenwood Genetic Center's Diagnostic Laboratory (Greenwood, South Carolina, USA). Even patients for whom prior genotyping was performed at Greenwood Genetic Center's Diagnostic Laboratory may need have a repeat analysis performed if the original information was insufficient for an unambiguous classification of genotype (eg, to document the integrity of the FMR1 and FMR2 genes in patients with complex mutations/chromosomal rearrangements).
- Echocardiogram (note: this assessment will not need to be performed if an echocardiogram taken within 3 months of study start is available and deemed satisfactory for evaluation of anesthesia risk.)
- Physical and neurological examination
- Height and weight
- Head circumference
- Hearing assessment
- Neurodevelopmental assessments:
  - Differential Ability Scales, Second Edition (DAS-II)
  - For patients in the substudy only, who are too young (<3 years of age) or unable to complete the DAS-II, the Bayley Scales of Infant Development, Third Edition (BSID-III)
  - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
- 12-lead ECG
- Vital signs
- Clinical laboratory tests
- Urinary GAG
- Anti-idursulfase antibody testing
- General anesthesia
- Brain MRI



- ICP measurement
- CSF sample collection (by lumbar puncture)
- Health status assessment (EQ-5D)
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

## **8.2 Randomization/Enrollment: Clinic Admission (Month 0, Week 0, Day 0)**

### **8.2.1 All Patients (IT Treatment and No IT Treatment Groups) in the Pivotal Study**

- Randomization

### **8.2.2 All Patients in the Substudy**

- Documentation of entry criteria for enrollment

## **8.3 Treatment Period (Months 1 to 12)**

During this period, several phases of activity will occur. These are designated in the Schedules of Events as: Pre-surgery, Surgery, Follow up at Weeks 2 and 3 (Pre-surgery, Surgery, and Post-op Recovery) and Pre-treatment, IT Injection, Follow up at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 (IT Dosing).

### **8.3.1 Patients in the IT Treatment Group of the Pivotal Study and All Patients in the Substudy: Surgery and Post-op Recovery (Weeks 2 and 3)**

IDDD placement will require surgical implantation under general anesthesia and post-surgical assessment.

#### **8.3.1.1 Pre-surgery**

- Physical and neurological examination
- Height and weight
- 12-lead ECG
- Vital signs
- Clinical laboratory tests
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

#### **8.3.1.2 Surgery**

- Vital signs
- General anesthesia
- CSF sample collection
- IDDD implantation

- X-ray (to verify IDDD is at the mid-thoracic level in the spinal canal and correctly installed)
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

#### **8.3.1.3 Follow up**

- Physical and neurological examination
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

### **8.3.2 Patients in the IT Treatment Group of the Pivotal Study and All Patients in the Substudy: IT Dosing (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 [ $\pm$ 7 days])**

#### **8.3.2.1 Pre-treatment**

- Physical and neurological examination (performed only at Weeks 4, 16, 28, 40)
- Height and weight
- Head circumference
- Hearing assessment
- Neurodevelopmental assessments (performed only at Weeks 16, 28, and 40)
  - Differential Ability Scales, Second Edition (DAS-II)
  - For patients in the substudy only, who are too young (<3 years of age) or unable to complete the DAS-II, the Bayley Scales of Infant Development, Third Edition (BSID-III)
  - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
- 12-lead ECG
- Vital signs
- Clinical laboratory tests (performed only at Weeks 4, 16, 28 and 40)
- Urinary GAG (performed only at Weeks 4, 16, 28, 40)
- Anti-idursulfase antibody testing
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

#### **8.3.2.2 IT Injection**

- 12-lead ECG (performed only at Weeks 4, 16, 28, 40)
- Vital signs
- CSF sample collection (performed at each IT Dosing Week prior to idursulfase-IT injection)
- idursulfase-IT injection. Patients will remain under observation in the hospital setting (may include lounge, infusion center, or waiting room) for at least 4 hours post IT injection and will be discharged when deemed clinically stable by the Investigator. The patient will need to be examined the following day (See Follow Up, Section 8.3.2.3) by the Investigator; however, there is no requirement for an overnight hospital stay. Note

that, on IT Dosing Weeks, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT.

- Serum sampling for pharmacokinetic analysis (performed only at Weeks 4, 24, and 48). Samples will be collected within 15 minutes ( $\pm 5$  minutes) prior to intrathecal administration of idursulfase-IT and at 30 minutes ( $\pm 5$  minutes), 60 minutes ( $\pm 5$  minutes), 120 minutes ( $\pm 5$  minutes), 4 hours ( $\pm 5$  minutes), 6 hours ( $\pm 5$  minutes), 8 hours ( $\pm 15$  minutes), 12 hours ( $\pm 15$  minutes), 24 hours ( $\pm 15$  minutes), 30 hours ( $\pm 15$  minutes), 36 hours ( $\pm 15$  minutes) after the start of intrathecal administration.
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

### 8.3.2.3 Follow Up

- Physical and neurological examination
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

### 8.3.3 Patients in the No IT Treatment Group of the Pivotal Study (Months 1 to 12)

#### 8.3.3.1 Weeks 4, 16, 28, 40 ( $\pm 7$ days)

- Physical and neurological examination
- Height and weight
- Head circumference
- Hearing assessment
- 12-lead ECG
- Vital signs
- Clinical laboratory tests
- Urinary GAG
- Anti-idursulfase antibody testing
- Neurodevelopmental assessments (performed only at Weeks 16, 28, and 40)
  - Differential Ability Scales, Second Edition (DAS-II)
  - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

#### 8.3.3.2 Weeks 8, 12, 20, 24, 32, 36, 44, 48 ( $\pm 7$ days)

- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

## 8.4 End of Study: Month 13 (Week 52[± 7 days])

### 8.4.1 Patients in the IT Treatment Group of the Pivotal Study and All Patients in the Substudy

- Physical and neurological examination
- Height and weight
- Head circumference
- Hearing assessment
- Neurodevelopmental assessments
  - Differential Ability Scales, Second Edition (DAS-II)
  - For patients in the substudy only, who are too young (<3 years of age) or unable to complete the DAS-II, the Bayley Scales of Infant Development, Third Edition (BSID-III)
  - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
- 12-lead ECG
- Vital signs
- Clinical laboratory tests
- Urinary GAG
- Anti-idursulfase antibody testing
- General anesthesia
- Brain MRI
- ICP measurement
- CSF sample collection
- X-ray
- Health status assessment (EQ-5D)
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

### 8.4.2 Patients in the No IT Treatment Group of the Pivotal Study

- Physical and neurological examination
- Height and weight
- Head circumference
- Hearing assessment
- Neurodevelopmental assessments:
  - Differential Ability Scales, Second Edition (DAS-II)
  - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
- 12-lead ECG
- Vital signs
- Clinical laboratory tests
- Urinary GAG
- Anti-idursulfase antibody testing
- General anesthesia

- Brain MRI
- ICP Measurement
- CSF sample collection
- Health status assessment (EQ-5D)
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

## **8.5 Follow-up Visit (Day 7 [ $\pm$ 2 Days] Post EOS)**

### **8.5.1 All Patients in the Pivotal Study and Substudy**

The following will be assessed by telephone contact:

- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

## 9 QUALITY CONTROL AND ASSURANCE

Training on the study protocol, device usage, and investigational product administration will occur at an Investigator meeting, at the site initiation visit, or both. Instructions will be provided to aid consistency in data collection and reporting across sites.

Clinical sites will be monitored by the Sponsor 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 FDA 21 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.

## 10 STATISTICAL ANALYSIS

### 10.1 General Methodology

Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, minimum, median, and maximum). Categorical variables will be summarized using the number and percentage of patients in each category. Data will be summarized with respect to patient disposition, demographic and baseline characteristics and concomitant medication use. The efficacy endpoints, safety assessments and other outcome results for each treatment group will be summarized descriptively unless otherwise indicated. In addition, least squares means, treatment differences, p-values and 95% confidence intervals for least squares mean treatment differences will also be provided where relevant for efficacy endpoints. The fit of linear models will be assessed using residual plots and other diagnostic plots. All the hypothesis tests will be 2-sided and will be performed at the 0.05 level of significance unless stated otherwise.

The separate substudy is an open-label, single arm study. Data from patients participating in this separate substudy will be analyzed separately. Safety data from the single-arm substudy will be summarized and efficacy data will be listed.

There are no formal hypotheses associated with the evaluation of the safety and performance of the IDDD device (SOPH-A-PORT Mini S). All analyses of device safety and performance will be descriptive and no statistical testing will be performed. Device related analyses will be based on patients for whom the device implant procedure was performed and are described below.

### 10.2 Determination of Sample Size

Based on study HGT-HIT-050/045 Phase I/II data, the observed decline in mean GCA score in untreated patients was estimated to be 13.7 points with a standard deviation of 9.4 after 12 months. For the sample size calculation, we conservatively assumed an approximately 1 point per month rate of decline in the untreated control arm, so that the theoretical decline would be 13 points from baseline (screening) to Visit Week 52. As up to 2 months may elapse between the screening assessment and the start of idursulfase-IT treatment, a mean decline of 2 points at end of study would be expected if idursulfase was effective in stabilizing the decline. Therefore, in such a case, the mean projected treatment difference at Visit Week 52 would be 11 points (ie, 13 minus 2), which is considered a clinically meaningful treatment difference.

Using a 2:1 randomization, a sample size of 42 randomized patients (28 IT patients, 14 control patients) will yield 80% power to detect a clinically meaningful mean treatment difference in the primary endpoint, GCA change from baseline to Visit Week 52 of 11 points. This calculation further assumes a common standard deviation for the change from baseline of 10 points, a type-I error rate of 0.05 for a two-sided two-sample t-test, with approximately up to 20% missing an assessment at Visit Week 52.

After approximately one-half of the planned number of patients (ie, 21 patients) has completed the Week 52 visit, and prior to enrollment closure, a blinded assessment of overall variability for the primary endpoint will be made by estimating the pooled standard deviation. The variability

assessment will be performed by an independent statistician who is not involved in the final analysis of this study. If it does not appear that the variability is consistent with the assumptions used in the sample size calculation, the sponsor may consider increasing the sample size by amending the protocol.

For the separate substudy, there is no target sample size. All patients meeting eligibility criteria for the substudy will be enrolled until enrollment for the randomized trial is completed.

### **10.3 Method of Assigning Study Patients to Treatment Groups**

Patients will be randomized (open-label, assessor-blinded) in a 2:1 allocation ratio between the active (idursulfase-IT treatment regimen) and control groups. Although this is a multi-center study, the randomization will not be stratified by center. The baseline GCA score (at Screening Visit) is expected to be a key prognostic factor. Therefore, the randomization will be stratified according to baseline GCA score: greater than 70 versus less than or equal to 70. The randomization schedule will be generated and administered centrally by a third-party (eg, IVR vendor) independent of the project team. There is no replacement of patients who do not complete the study.

In a separate substudy, additional patients may be enrolled who have a complex rearrangement genotype in the iduronate-2 sulfatase gene and who are below the age of 3 years at the time of informed consent. Such patients are ineligible for the randomized trial and will not be randomized, but will receive idursulfase-IT treatment monthly at a dose of 10 mg.

### **10.4 Population Description and Exposure**

#### **10.4.1 Analysis Populations**

For the randomized trial, all efficacy data analyses will be performed using the Intent-to-Treat (ITT) Population, which is defined as all randomized patients.

All safety data analyses will be performed using the Safety Population, which is defined as all randomized patients with any post-randomization safety assessments. IDDD and procedure related analyses will be conducted in the treated set of the Safety Population who had the device implant procedure performed.

All pharmacokinetic data analyses will be performed using the PK population. The PK population will be defined as all patients who received study drug and had at least one sample collected for pharmacokinetic analysis.

For the substudy, all analyses will be performed on the Substudy Population, defined as all patients enrolled and treated with study drug in the substudy.

#### **10.4.2 Patient Disposition**

The number and percentage of patients screened, randomized, completing each visit of the study, and discontinued prematurely by reason for withdrawal will be summarized by treatment group



for the ITT and Safety populations in the randomized trial. A similar summary will be provided for the separate substudy.

### 10.4.3 Protocol Deviations

An incident involving noncompliance with the protocol, but one which typically does not have significant effects on the patient's rights, safety, or welfare, or the integrity of the resultant data will be considered a protocol deviation. An incident involving noncompliance with the protocol which may affect the patient's rights, safety, or welfare, or the integrity of the resultant data will be known as a protocol violation. In particular, any serious deviation that affects the collection of data for the primary endpoint will be considered a protocol violation.

Examples of potential protocol violations may include violation of important admission (inclusion/exclusion) criteria, occurrence of a treatment dispensing error, treatment noncompliance or substantial use of a prohibited medication during the study. Reported protocol deviations and patient data will be examined prior to database lock to determine if conditions set forth in the study protocol have been violated and a more comprehensive list will be constructed at that time. The list of protocol deviations will not be presented; however, identified protocol violations will be summarized.

### 10.4.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics (eg, genotype, age [years], race, ethnicity, weight [kg], height [cm], BMI [kg/m<sup>2</sup>], country, medical history) will be summarized by treatment group in the randomized trial. A similar summary will be provided for the separate substudy.

### 10.4.5 Treatment Compliance

Treatment compliance will be summarized in terms of the percent of scheduled doses received in the idursulfase-IT arm. Percent compliance is defined as:

$$[(\text{No. of Complete IT injections Received}) \div (\text{Expected No. of IT injections at EOS})] * 100.$$

### 10.4.6 Extent of Exposure

The number of IT injections received overall and by lumbar puncture, average dose, the duration of idursulfase-IT treatment and IT administration duration will be summarized descriptively in the idursulfase-IT arm. The duration of idursulfase-IT treatment, summarized in months, is defined as the time from first to last IT administration during the study. The duration for each idursulfase-IT administration (in minutes) is calculated by subtracting the administration start time from the administration end time.

## 10.5 Analysis of Efficacy

All analyses described below refer to the randomized trial; all efficacy data from patients treated in the separate substudy will be listed only, including composite scores, age equivalents and development quotients as measured by the BSID-III.

### 10.5.1 Primary Efficacy Endpoint Analysis

For the randomized trial, the primary efficacy endpoint is the change from study baseline (screening visit) to Visit Week 52 in the General Conceptual Ability (GCA) score as measured by the DAS-II. The primary analysis will compare the treatment groups using a linear mixed model repeated measures (MMRM) analysis.<sup>22</sup> The repeated measures are the change from baseline GCA scores obtained at the scheduled Visit Weeks 16, 28, 40, and 52, respectively. The model will include fixed categorical effects for treatment, visit week, treatment by visit week interaction, and a GCA classification factor (based on baseline GCA score ( $\leq 70$  or  $> 70$ )) and the GCA classification factor by treatment interaction. The GCA classification factor by treatment interaction term will be included in the model if the interaction is significant at the 10% level; otherwise, the MMRM analysis without this interaction will be considered the final primary model. SAS Proc Mixed with restricted maximum likelihood estimation (REML) and an unstructured within-patient covariance structure will be used. If this model fails to converge, a first order autoregressive (AR(1)) covariance structure will be used for the primary analysis. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for tests of fixed effects.

From this model, least squares means, standard errors, treatment differences in least squares means, and 95% confidence intervals and p-values will be estimated for each time point. Significance tests will be based on the difference in least squares means. Primary inference is based on the treatment comparison at Visit Week 52 from this model. The null hypothesis is that the mean difference in the primary endpoint between the two treatment groups is zero, versus the alternative hypothesis that this difference is not zero. The hypotheses can be expressed as follows:

$$H_0: \mu_{IT} - \mu_{control} = 0 \text{ versus } H_1: \mu_{IT} - \mu_{control} \neq 0$$

Where  $\mu_{IT}$  refers to the mean change from baseline to Visit Week 52 in GCA score in the idursulfase-IT treated group and  $\mu_{control}$  refers to the mean change from baseline to Visit Week 52 in GCA score in the untreated control group. The test will be performed using the final, MMRM model-based t-test with a two-sided significance level of 5%. Similar secondary treatment comparisons from this model at Visit Weeks 16, 28, and 40 will also be presented. Estimated least squares means by treatment group will be plotted over time.

### 10.5.2 Key Secondary Efficacy Endpoint Analysis

The key secondary efficacy endpoint is the change from study baseline (Screening Visit) to Visit Week 52 in the Adaptive Behavior Composite (ABC) score as measured by the VABS-II. The key secondary analysis will compare the treatment groups using a linear mixed model repeated measures (MMRM) analysis. The repeated measures are the change from baseline ABC scores obtained at the scheduled Visit Weeks 16, 28, 40, and 52, respectively. The model will include effects of treatment, visit week, treatment by visit week interaction and the baseline ABC score as a continuous covariate. The baseline ABC score by treatment interaction will be included in the model if the interaction is significant at the 10% level; otherwise, the MMRM analysis without this interaction will be considered the final model for this endpoint. SAS Proc Mixed

with restricted maximum likelihood estimation (REML) and an unstructured within-patient covariance structure will be used. If this model fails to converge, a first order autoregressive (AR(1)) covariance structure will be used instead. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for tests of fixed effects. From this model, least squares means, standard errors, treatment differences in least squares means, and 95% confidence intervals and p-values will be estimated for each time point. The inferential test of the key secondary endpoint is based on the treatment comparison at Visit Week 52 from this model.

### 10.5.3 Other Secondary Efficacy Endpoints Analyses

The following secondary efficacy endpoints will be analyzed using an MMRM analysis in the same manner as described above for the key secondary endpoint with the continuous covariate corresponding to the baseline score for each measure:

- (1) The change from baseline to Visit Weeks 16, 28, 40, and 52 in standardized scores in cluster areas of the DAS-II: Verbal, Nonverbal, Spatial, and Special Nonverbal Composite (SNC)
- (2) The change from baseline to Visit Weeks 16, 28, 40, and 52 in the standardized domain scores of the VABS-II: Communication, Daily Living Skills, Socialization, Motor Skills, and Maladaptive Behavior.

All other secondary efficacy endpoints will be summarized descriptively by treatment group. Mean values by treatment group will be plotted over time. This includes the following endpoints:

- (1) The change from baseline to Visit Weeks 16, 28, 40, and 52 in the age equivalents and development quotients for the subcategories of the DAS-II: Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices and Copying for the DAS-II/Early Years; and Recall of Designs, Word Definitions, Pattern Construction, Matrices, Verbal Similarities and Sequential and Quantitative Reasoning for the DAS-II/School Years
- (2) The change from baseline to Visit Weeks 16, 28, 40, and 52 in the age equivalents and developmental quotients in domains of the VABS-II: Communication, Daily Living Skills, Socialization, Motor Skills, and Maladaptive Behavior.

### 10.5.4 Exploratory Subset Analyses

Subgroup analyses are planned for exploratory purposes. Patients with a baseline GCA score of greater than 70 will be classified as having “Moderate” cognitive impairment, whilst patients with a baseline GCA score equal to or below 70 will be classified as having “Severe” cognitive impairment. The randomization is stratified by this classification variable to ensure treatment group balance within these subgroups. The primary endpoint model (MMRM) also includes baseline GCA score ( $\leq 70$  or  $> 70$ ) as a factor. The treatment by baseline GCA factor interaction will be tested using this model at the 10% significance level. Descriptive statistics for the primary endpoint will be presented by treatment within each GCA subgroup (Moderate versus Severe cognitive impairment, as described above). The baseline GCA factor by Visit interaction

and the three-way interaction of treatment, baseline GCA factor and Visit will likewise be investigated for this model. Similar exploratory subset analyses of the primary endpoint may be performed for age ( $\leq 6$  years versus  $> 6$  years), country, native language (Spanish versus English speaking region) or other baseline factors using MMRM.

## **10.6 Pharmacokinetic, Pharmacodynamic and Health Status Outcomes**

### **10.6.1 Pharmacokinetic Measurements and Parameters**

The pharmacokinetic concentrations and derived pharmacokinetic parameters will be analyzed by the sponsor staff in the Clinical Pharmacology and Pharmacokinetics group and reported separately in a pharmacokinetic report to be appended to the Clinical Study Report. Accordingly, the planned analyses related to those data are described elsewhere.

### **10.6.2 Pharmacodynamic Outcome**

Urine and CSF GAG levels, and the change from baseline (Screening Visit) will be summarized by visit and treatment group. Mean values will be plotted over time. A Wilcoxon Rank Sum test will be used to compare treatment groups on the CSF GAG change from baseline to the Week 52/EOS visit.

### **10.6.3 Health Status Outcome**

The EQ-5D measures 5 dimensions of health status: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each dimension, there are 3 levels of response:

- no problems
- some problems
- severe problems.

The number and percent of patients with each response will be presented by dimension at each visit. The visual analogue scale (VAS) records the patient's parent/caregiver-rated health on a 0 (worst health) to 100 (best health) scale. The VAS score, as well as the change from baseline (screening visit to Week 52/EOS) will be summarized. A Wilcoxon Rank Sum test will be used to compare treatment groups on the change from baseline to Week 52/EOS visit in VAS score. Pharmacoeconomic analyses may be performed by the sponsor staff in the Health Economics and Outcomes Research group and reported separately in a pharmacoeconomic report to be appended to the Clinical Study Report. Accordingly, any planned pharmacoeconomic analyses related to this data may be described elsewhere.

## **10.7 Safety Assessments**

All safety analyses will be descriptive, no statistical testing will be performed. All analyses described below refer to the randomized trial; safety data from the separate substudy will be similarly summarized where relevant.

## 10.7.1 Adverse Events

### 10.7.1.1 Adverse Events

Adverse events will be recorded throughout the study and at early termination. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 12.1 or later. Adverse events occurring on or after randomization and on or before the follow-up visit (7 days after EOS) will be summarized by treatment group, both overall and within system organ class by preferred term. Adverse events will also be tabulated by highest severity (mild, moderate, severe) and by closest relationship to study drug (not related, related) for treated patients. A separate tabulation of IV Elaprase infusion-related adverse events will also be presented. In addition, those events which resulted in death or were otherwise classified as serious will be summarized and presented in a separate listing.

### 10.7.1.2 IDDD and Procedure Related Adverse Events

IDDD and procedure related adverse events will be summarized within system organ class by preferred term. Adverse events will be tabulated by severity (mild, moderate, severe) and degree of relatedness. Separate tabulations will be provided for adverse events related to the IDDD, device surgical procedure and IT-administration process. IDDD and procedure related events will be analyzed in the set of treated patients in the Safety Population with device implanted.

## 10.7.2 Clinical Laboratory Evaluations

Laboratory values (chemistries, hematology, and urinalysis), including CSF components (standard chemistries, glucose, protein, and cell counts) will be summarized in terms of the absolute value and change from baseline at each time point by treatment group. The number and percentage of patients with clinically significant post-baseline laboratory results will be presented by treatment group.

### 10.7.3 ECG Evaluations

The 12-lead ECG parameters (sinus rhythm, atrial or ventricular hypertrophy, heart rate [bpm], pulse rate interval [msec], QRS interval [msec], QT interval [msec] and the corrected QTc [msec] interval) will be summarized in terms of absolute value and change from baseline. The number and percentage of patients with clinically significant post-baseline ECG results will be presented by treatment group.

### 10.7.4 Vital Signs and Physical Measurements

Vital signs (temperature [C], pulse [bpm], blood pressure [systolic and diastolic, mmHg], and respiration [per min]), and the change from baseline (Screening Visit) will be summarized graphically by study time point and treatment group.

Height (cm), weight (kg), and head circumference (cm) and the change from baseline (Screening Visit) will be summarized by study time point and treatment group. ICP measurement (cm of H<sub>2</sub>O) and brain MRI volumes will be similarly summarized.

### 10.7.5 Physical Findings

Physical and neurological examination findings will be listed for all patients.

### 10.7.6 Other Observations Related to Safety

#### 10.7.6.1 Hearing Assessments

The number and percentage of patients in the hearing assessment categories (hearing aid, right ear test results, left ear test results, right ear level of hearing loss and left ear level of hearing loss) will be summarized by treatment group, and visit. The number and percentage of patients with abnormal hearing assessments will be summarized by study time point and treatment group.

#### 10.7.6.2 Immunogenicity

Anti-idursulfase antibody formation will be monitored throughout the study for both serum and CSF in the Idursulfase-IT treatment group. The number and percentage of patients testing anti-idursulfase antibody positive and negative at each time point will be summarized. Titer values will be summarized and means plotted over time.

#### 10.7.6.3 Device Performance

SOPH-A-PORT safety and performance will be summarized for implanted patients. Difficulties associated with the implant procedure (eg, excessive bleeding, CSF leakage, etc) will be summarized. A summary of abnormal findings from the IDDD radiological assessments will also be presented.

The proportion of patients with at least one IDDD failure and the proportion with malfunction only, as well as the number of and reasons for IDDD failures and malfunctions and actions taken will be summarized. The rate of IDDD failures and malfunctions and the corresponding 95% confidence interval will also be estimated. The time from initial implant surgery to first IDDD failure and the time to malfunction only will be analyzed using Kaplan-Meier Life Table methods. Patients without an IDDD failure or malfunction will be censored at their last study drug injection date. A by-patient listing of the device failure and malfunction data will be displayed.

The proportion of patients for whom a successful first injection of study drug occurred will be summarized among those for whom a first injection was attempted (ie, those who had an apparently successful implantation and did not suffer a device removal or revision prior to first scheduled injection). The proportion of patients who had no failed injection attempts during the study will also be summarized. The corresponding 95% confidence intervals of the proportion of interest will be estimated, where appropriate. Injections not given for patient reasons (eg, patient uncooperative, competing medical issue, etc) will not be included in the determination of these estimates. The frequency and reasons for unsuccessful injection attempts will be reported.

### **10.7.7 Concomitant Medications**

Concomitant medications are defined as all medications taken on or after the time of the randomization and on or before the last follow up date (EOS Visit date plus 7 days). Concomitant medications will be mapped using the WHO drug dictionary and summarized by the therapeutic class and preferred term for each treatment group.

## **10.8 Statistical/Analytical Issues**

### **10.8.1 Handling of Drop-outs and Missing Data**

In general, no imputation will be used for descriptive analyses, or for primary and secondary efficacy analyses utilizing MMRM methodology. A possible exception is for randomized patients who discontinue early from the study. For these patients, their early EOS efficacy evaluations will be used for the next scheduled time point only if the EOS evaluation is performed within 45 days of the next scheduled visit. For sensitivity analyses using the Wilcoxon Rank-Sum test at the Week 52 Visit, the most conservative or lowest score will be imputed for missing data as a sensitivity analysis for the primary and key secondary endpoints. Imputation methods will be described in the prospective statistical analysis plan.

### **10.8.2 Adjustment for Covariates**

As the randomization of the study is stratified by the baseline GCA classification factor ( $\leq 70$  or  $> 70$ ), the primary MMRM analysis of the change from study baseline to Visit Week 52 in GCA score will take into account the GCA score as a classification factor. In addition, for a supportive analysis, a similar MMRM analysis will be performed adjusting for the baseline GCA score as a continuous covariate. Key secondary and secondary analyses of the change from baseline in efficacy scores utilizing MMRM methodology will adjust for the baseline score of the parameter of interest as a continuous covariate in the model. Exploratory MMRM analyses to evaluate treatment interactions or other interactions and to identify potential predictors of efficacy outcome may also utilize covariate adjustment.

### **10.8.3 Interim Analysis**

No formal interim analysis or interim statistical testing is planned. The DSMB will monitor safety data periodically during the trial. A pooled, blinded assessment of the overall variability of the primary endpoint will be conducted during the study in order to assess the appropriateness of the variability assumption used in the sample size calculation. 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.

### **10.8.4 Multicenter Studies**

This is a multicenter study utilizing a central randomization. It is planned that the data from all centers that participate in this protocol will be combined so that an adequate number of patients will be available for analysis. Because of the potential for a relatively large number of centers,

and small numbers of patients at some centers, no subset analyses by center are planned. No adjustment for center effect will be utilized in the statistical analyses.

### **10.8.5 Multiple Comparisons/Multiplicity**

The overall type I error rate for tests of the primary and key secondary endpoints will be controlled at 0.05. To control an overall type I error rate at this level for the two tests, a fixed sequential testing procedure will be followed. The null hypothesis of no treatment difference for the primary endpoint will be tested first. The null hypothesis of no treatment difference for the key secondary endpoint then may only be rejected if the null hypothesis for the primary endpoint is first rejected.

All other secondary endpoints and time points are considered supportive and treatment comparisons will be made without adjustment for multiplicity. The resulting p-values from these supportive analyses will be interpreted descriptively as summarizing the weight of evidence for a treatment difference and may suggest avenues for further exploratory analyses or generate formal hypotheses to be tested in future trials.

### **10.8.6 Sensitivity Analyses**

As a sensitivity analysis of the primary endpoint, the Wilcoxon Rank-Sum test will be used to compare treatment groups at Visit Week 52. This test is based on the ranked changes from baseline. Patients who terminate the study early or who have a Week 52 visit, but are not able to complete the GCA assessment for any reason, including either low cognitive ability or behavioral problems during the assessment, will have the rank of their change from baseline imputed to the lowest possible value, to represent the worst possible outcome. This imputation method was chosen because a missing score may be indicative of low cognitive function and/or behavioral issues. The same sensitivity analysis using the Wilcoxon Rank-Sum test as described above for the primary endpoint will also be performed for the key secondary endpoint.



## 11 ADMINISTRATIVE CONSIDERATIONS

### 11.1 Investigators and Study Administrative Structure

Before initiation of the study, the Investigator must provide the Sponsor with a completed Form FDA 1572 or Investigator Agreement. Investigational product may be administered only under the supervision of the Investigators and Sub-investigators listed on these forms. Curriculum vitae must be provided for the Investigators and Sub-investigators listed on Form FDA 1572 or the Investigator Agreement. If the study involves use of an investigational device and the study is being conducted in compliance with 21 CFR 812, the Sponsor will obtain a signed agreement from each participating investigator per the requirements of 21 CFR 812.43 (c).

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.

The Principal Investigator for this study is Joseph Muenzer, MD, PhD, Professor at the Departments of Pediatrics and Genetics, School of Medicine, University of North Carolina at Chapel Hill (North Carolina, USA).

### 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; a final status report must be provided to the IRB/IEC within 3 months of study completion or termination (or as required). Copies of the status 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. Drug-related adverse events which are reported to the US FDA or other regulatory agencies (IND Safety Reports) and UADEs reported to regulatory agencies must be submitted promptly to the IRB/IEC. Unexpected adverse device events will be reported to regulatory agencies by Sophysa consistent with relevant regulations. Copies of UADE reports will be submitted to the IRB/IEC in a timely fashion.

### 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, 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 or the patient's parent(s) or legally authorized representative(s), as appropriate, 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, if applicable) 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 (or assent, if applicable) 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 (or assent, if applicable) 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. 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 (or assent, if applicable) 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 legal 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 (or assent, if applicable) 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 in some regions, patient initials) will be recorded in the eCRF, 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 eCRF'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 eCRFs 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 eCRF entry must indicate the reason for change. The Investigator is required to sign the eCRF 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 eCRF.

### 11.7.1 Critical Documents

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

- Applicable local regulatory documentation (eg, FDA 1572 Form); 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, Subject Information/Informed Consent Form, and any other written information to be provided regarding subjects recruitment procedures

- Copy of IRB/IEC approved Subject 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)
- Certification/QA scheme/other documentation (if applicable)

Regulatory approval and notification as required must also be available. The protocol will not be initiated until regulatory approval and notification are obtained; these are the responsibility of the Sponsor.

### **11.8 Data Safety Monitoring Board**

An independent, external DSMB will be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study.

The DSMB will be notified of all IDDD failures and IDDD-related complications at times defined in the DSMB charter.

The DSMB will consist of a biostatistician and two clinical experts. The DSMB will adhere to a prospectively determined charter, which will be written by Shire HGT and approved by the DSMB. The charter will define the responsibilities of the DSMB and Shire HGT, describe the conduct of the meetings, and define the data sets to be reviewed. Serious adverse events and other data will be distributed to the members of the DSMB periodically for review.

The first meeting of the DSMB will be an orientation meeting and will be held prior to the start of the study. Thereafter, it is anticipated that the DSMB will meet at least annually. The DSMB will keep detailed minutes of their discussions during the meetings, which will be kept in strict confidence.

### **11.9 Device Failure Adjudication Process**

The final cause for device failures will be adjudicated by a Shire team by examining the clinical database, safety database, and manufacturer investigation of returned devices.

### **11.10 Protocol Violations/Deviations**

Any violation of the protocol as described can be considered a protocol violation including not meeting inclusion/exclusion criteria during the study, not adhering to the study treatment and other issues of noncompliance.

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.

### **11.11 Premature Closure of the Study**

If the Sponsor, Investigator, DSMB, 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). In addition, a decision on the part of the Sponsor to suspend or discontinue development of the investigational product may be made at any time. 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

### **11.12 Access to Source Documentation**

Regulatory authorities, the IRB/IEC, and the Sponsor (or its representatives) may request access to all source documents, eCRFs, 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 eCRFs for completeness and

clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

### **11.13 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 HGT. Shire HGT or its designee will be responsible for performing study data management activities.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded using WHO Drug Dictionary (WHO-DD). Centralized laboratories will be employed as described in the study manual to aid in consistent measurement of efficacy and safety parameters.

### **11.14 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 investigational 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.

### **11.15 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. Changes in status concerning financial interests during the study and after its completion will be disclosed by the Investigator in accordance 21 CFR Part 54.

### **11.16 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 HGT,

provided Shire HGT a copy of the draft document intended for publication, and obtained Shire HGT's written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential.

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### 13 APPENDICES

#### Appendix 1 Schedule of Events for Patients Randomized to Treatment in the Pivotal Study

	Month -1	Month 0	Months 1 to 12						Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Randomization	Weeks 2 and 3 Pre-surgery, Surgery, and Post-op Recovery <sup>o</sup>			Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 IT Dosing (± 7 days)			Week 52 End of Study (EOS) (± 7 days)	7 (±2) Days Post EOS
Assessment	Day -28 to Day -1	Day 0	Pre- Surgery	Surgery	Follow Up	Pre-Tx <sup>1</sup>	IT Injection	Follow Up		Telephone
Informed Consent <sup>a</sup>	•									
Review of Study Entry Criteria	•									
Medical History	•									
Hunter Syndrome Diagnosis and Genotype	•									
Echocardiogram <sup>k</sup>	•									
Physical and Neurological Examination	•		•		• <sup>l</sup>	•		•	•	
Height and Weight	•		•			• <sup>d</sup>			•	
Head Circumference	•					• <sup>d</sup>			•	
Hearing Assessment	•					• <sup>d</sup>			•	
Neurodevelopmental Assessment	•					• <sup>n</sup>			• <sup>n</sup>	
12-lead ECG	•		•			•	• <sup>d,f</sup>		•	
Vital Signs	•		•	•		•	• <sup>h</sup>		•	
Clinical Laboratory Tests	•		•			• <sup>d</sup>			•	
Urine GAG	•					• <sup>d</sup>			•	
Anti-Idursulfase Antibody Testing	•					•			•	
General Anesthesia	•			•					•	
Brain MRI	•								•	
ICP Measurement	•								•	
CSF Sample Collection <sup>m</sup>	• <sup>j</sup>			•			• <sup>e</sup>		•	
Randomization		• <sup>b</sup>								
IDDD Implantation				•						

	Month -1	Month 0	Months 1 to 12						Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Randomization	Weeks 2 and 3 Pre-surgery, Surgery, and Post-op Recovery <sup>o</sup>			Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 IT Dosing ( $\pm$ 7 days)			Week 52 End of Study (EOS) ( $\pm$ 7 days)	7 ( $\pm$ 2) Days Post EOS
Assessment	Day -28 to Day -1	Day 0	Pre- Surgery	Surgery	Follow Up	Pre-Tx <sup>1</sup>	IT Injection	Follow Up		Telephone
X-ray (Additional imaging may be required) <sup>c</sup>				•					•	
idursulfase-IT Injection							• <sup>p</sup>			
Serum Sample for PK							• <sup>g</sup>			
Health status questionnaire	•								•	
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	•		•	•	•	•	•	•	•	•
Adverse Events	•		•	•	•	•	•	•	•	•

**Abbreviations:**

CSF = cerebrospinal fluid; ECG = electrocardiogram; GAG = glycosaminoglycan; ICP = intracranial pressure; IDDD = intrathecal drug delivery device; MRI = magnetic resonance imaging; PK = pharmacokinetics; Tx = treatment.

**Footnotes:**

- <sup>a</sup> Informed consent must be obtained from the patient's parent(s)/legal guardian(s) before beginning Screening assessments.
- <sup>b</sup> Patients will be randomized after completion of Screening assessments. The day of randomization is Day 0.
- <sup>c</sup> X-rays may be performed to check placement of the device, and as needed, throughout the study.
- <sup>d</sup> The assessments indicated will be performed at 3-month intervals, ie, at IT Dosing Weeks 4, 16, 28, and 40 only.
- <sup>e</sup> The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.
- <sup>f</sup> The 12-lead ECG is to be performed within 4 hours after IT administration of study drug.
- <sup>g</sup> Blood samples for PK analysis will be obtained at IT Dosing Weeks 4, 24, and 48 only. Samples will be collected within 15 minutes ( $\pm$ 5 minutes) prior to intrathecal administration of idursulfase-IT and at 30 minutes ( $\pm$ 5 minutes), 60 minutes ( $\pm$ 5 minutes), 120 minutes ( $\pm$ 5 minutes), 4 hours ( $\pm$ 5 minutes), 6 hours ( $\pm$ 5 minutes), 8 hours ( $\pm$ 15 minutes), 12 hours ( $\pm$ 15 minutes), 24 hours ( $\pm$ 15 minutes), 30 hours ( $\pm$ 15 minutes), 36 hours ( $\pm$ 15 minutes) after the start of intrathecal administration.
- <sup>h</sup> Vital signs will be collected at the following time points ( $\pm$ 10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, 4 hours post end of IT administration, 6 hours post end of IT administration, 8 hours post end of IT administration, and 12 hours post end of IT administration.
- <sup>i</sup> From Week 20 onward, pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the patient can arrive at the study site early in the day and if the Investigator deems this clinically appropriate.

	Month -1	Month 0	Months 1 to 12						Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Randomization	Weeks 2 and 3 Pre-surgery, Surgery, and Post-op Recovery <sup>o</sup>			Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 IT Dosing ( $\pm$ 7 days)			Week 52 End of Study (EOS) ( $\pm$ 7 days)	7 ( $\pm$ 2) Days Post EOS
Assessment	Day -28 to Day -1	Day 0	Pre- Surgery	Surgery	Follow Up	Pre-Tx <sup>j</sup>	IT Injection	Follow Up	Telephone	

<sup>j</sup> The CSF sample will be obtained via lumbar puncture and while the patient is under general anesthesia.

<sup>k</sup> This assessment will not need to be performed if an echocardiogram taken within 3 months of study start is available and deemed satisfactory for evaluation of anesthesia risk.

<sup>l</sup> The assessments indicated will be performed prior to discharge.

<sup>m</sup> Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard laboratory parameters (chemistries, cell counts), concentrations of GAG and idursulfase enzyme, and presence of idursulfase-specific antibodies.

<sup>n</sup> The neurodevelopmental assessments will be performed at IT Dosing Weeks 16, 28, 40 ( $\pm$ 7 days) and at EOS Week 52 ( $\pm$ 7 days).

<sup>o</sup> At least 14 days will be allowed for recovery following the placement of the IDDD before the administration of the first IT dose.

<sup>p</sup> Note that, on IT Dosing Weeks, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT.

## Appendix 2 Schedule of Events for Patients Randomized to No Treatment in the Pivotal Study

	Month -1	Month 0	Months 1 to 12			Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Randomization,	Weeks 2 and 3	Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 (± 7 days)	Week 52 End of Study (EOS) (± 7 days)	7 (±2) Days Post EOS	
Assessment	Day -28 to Day -1	Day 0	No assessments		Telephone	Telephone	
Informed Consent <sup>a</sup>	•						
Review of Study Entry Criteria	•						
Medical History	•						
Hunter Syndrome Diagnosis and Genotype	•						
Echocardiogram <sup>d</sup>	•						
Physical and Neurological Examination	•			•	•		
Height and Weight	•			•	•		
Head Circumference	•			•	•		
Hearing Assessment	•			•	•		
12-lead ECG	•			•	•		
Vital Signs	•			•	•		
Clinical Laboratory Tests	•			•	•		
General Anesthesia	•				•		
Urine GAG	•			•	•		
Anti-idursulfase Antibody Testing	•			•	•		
Brain MRI	•				•		
ICP measurement	•				•		
CSF Sample Collection <sup>c</sup>	•				•		
Randomization		• <sup>b</sup>					
Neurodevelopmental Assessment	•			• <sup>e</sup>	• <sup>e</sup>		
Health status Questionnaire	•				•		
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	•			•	•	•	
Adverse Events	•		•	•	•	•	

**Abbreviations:**

CSF = cerebrospinal fluid; ECG = electrocardiogram; GAG = glycosaminoglycan; ICP = intracranial pressure; MRI = magnetic resonance imaging.

<sup>a</sup> Informed consent must be obtained from the patient's parent(s)/legal guardian(s) before beginning Screening

	Month -1	Month 0	Months 1 to 12		Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Randomization,	Weeks 2 and 3	Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 (± 7 days)	Week 52 End of Study (EOS) (± 7 days)	7 (±2) Days Post EOS
Assessment	Day -28 to Day -1	Day 0	No assessments	Telephone		Telephone

procedures.

- <sup>b</sup> Patients will be randomized after completion of Screening assessments. The day of randomization is Day 0.
- <sup>c</sup> The CSF sample will be obtained via lumbar puncture and while the patient is under general anesthesia. The samples will be used to analyze standard laboratory parameters (chemistries, cell counts), concentrations of GAG and idursulfase enzyme, and presence of idursulfase-specific antibodies.
- <sup>d</sup> This assessment will not need to be performed if an echocardiogram taken within 3 months of study start is available and deemed satisfactory for evaluation of anesthesia risk.
- <sup>e</sup> The neurodevelopmental assessments will be performed at Weeks 16, 28, 40 (±7 days) and at EOS Week 52 (±7 days).

**Appendix 3 Schedule of Events for Patients Enrolled in the Substudy**

	Month -1	Month 0	Months 1 to 12						Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Enrollment	Weeks 2 and 3 Pre-surgery, Surgery, and Post-op Recovery <sup>o</sup>			Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 IT Dosing (± 7 days)			Week 52 End of Study (EOS) (± 7 days)	7 (±2) Days Post EOS
Assessment	Day -28 to Day -1	Day 0	Pre- Surgery	Surgery	Follow Up	Pre-Tx <sup>l</sup>	IT Injection	Follow Up	Telephone	
Informed Consent <sup>a</sup>	•									
Review of Study Entry Criteria	•									
Medical History	•									
Hunter Syndrome Diagnosis and Genotype	•									
Echocardiogram <sup>k</sup>	•									
Physical and Neurological Examination	•		•		• <sup>l</sup>	•		•	•	
Height and Weight	•		•			• <sup>d</sup>			•	
Head Circumference	•					• <sup>d</sup>			•	
Hearing Assessment	•					• <sup>d</sup>			•	
Neurodevelopmental Assessment	•					• <sup>n</sup>			• <sup>n</sup>	
12-lead ECG	•		•			•	• <sup>d,f</sup>		•	
Vital Signs	•		•	•		•	• <sup>h</sup>		•	
Clinical Laboratory Tests	•		•			• <sup>d</sup>			•	
Urine GAG	•					• <sup>d</sup>			•	
Anti-Idursulfase Antibody Testing	•					•			•	
General Anesthesia	•			•					•	
Brain MRI	•								•	
ICP Measurement	•								•	
CSF Sample Collection <sup>m</sup>	• <sup>j</sup>			•			• <sup>e</sup>		•	
Documentation of Entry Criteria		• <sup>b</sup>								
IDDD Implantation				•						
X-ray (Additional imaging may				•					•	

	Month -1	Month 0	Months 1 to 12						Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Enrollment	Weeks 2 and 3 Pre-surgery, Surgery, and Post-op Recovery <sup>o</sup>			Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 IT Dosing ( $\pm$ 7 days)			Week 52 End of Study (EOS) ( $\pm$ 7 days)	7 ( $\pm$ 2) Days Post EOS
Assessment	Day -28 to Day -1	Day 0	Pre- Surgery	Surgery	Follow Up	Pre-Tx <sup>1</sup>	IT Injection	Follow Up		Telephone
be required) <sup>c</sup>										
idursulfase-IT Injection							• <sup>p</sup>			
Serum Sample for PK							• <sup>g</sup>			
Health status questionnaire	•								•	
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	•		•	•	•	•	•	•	•	•
Adverse Events	•		•	•	•	•	•	•	•	•

**Abbreviations:**

CSF = cerebrospinal fluid; ECG = electrocardiogram; GAG = glycosaminoglycan; ICP = intracranial pressure; IDDD = intrathecal drug delivery device; MRI = magnetic resonance imaging; PK = pharmacokinetics; Tx = treatment.

**Footnotes:**

- <sup>a</sup> Informed consent must be obtained from the patient's parent(s)/legal guardian(s) before beginning Screening assessments.
- <sup>b</sup> Patients will be enrolled into the substudy only after they have completed Screening assessments and have been documented to meet all criteria for inclusion. For these patients, the day of enrollment is considered Day 0. Note that once a patient is enrolled in the substudy, they cannot later be randomized into the pivotal study.
- <sup>c</sup> X-rays may be performed to check placement of the device, and as needed, throughout the study.
- <sup>d</sup> The assessments indicated will be performed at 3-month intervals, ie, at IT Dosing Weeks 4, 16, 28, and 40 only.
- <sup>e</sup> The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.
- <sup>f</sup> The 12-lead ECG is to be performed within 4 hours after IT administration of study drug.
- <sup>g</sup> Serum samples for PK analysis will be obtained at IT Dosing Weeks 4, 24, and 48 only. Samples will be collected within 15 minutes ( $\pm$ 5 minutes) prior to intrathecal administration of idursulfase-IT and at 30 minutes ( $\pm$ 5 minutes), 60 minutes ( $\pm$ 5 minutes), 120 minutes ( $\pm$ 5 minutes), 4 hours ( $\pm$ 5 minutes), 6 hours ( $\pm$ 5 minutes), 8 hours ( $\pm$ 15 minutes), 12 hours ( $\pm$ 15 minutes), 24 hours ( $\pm$ 15 minutes), 30 hours ( $\pm$ 15 minutes), 36 hours ( $\pm$ 15 minutes) after the start of intrathecal administration.
- <sup>h</sup> Vital signs will be collected at the following time points ( $\pm$ 10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, 4 hours post end of IT administration, 6 hours post end of IT administration, 8 hours post end of IT administration, and 12 hours post end of IT administration.
- <sup>i</sup> From Week 20 onward, pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the patient can arrive at the



	Month -1	Month 0	Months 1 to 12						Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Enrollment	Weeks 2 and 3 Pre-surgery, Surgery, and Post-op Recovery <sup>o</sup>			Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 IT Dosing ( $\pm$ 7 days)			Week 52 End of Study (EOS) ( $\pm$ 7 days)	7 ( $\pm$ 2) Days Post EOS
Assessment	Day -28 to Day -1	Day 0	Pre- Surgery	Surgery	Follow Up	Pre-Tx <sup>1</sup>	IT Injection	Follow Up	Telephone	

study site early in the day and if the Investigator deems this clinically appropriate.

- <sup>j</sup> The CSF sample will be obtained via lumbar puncture and while the patient is under general anesthesia.
- <sup>k</sup> This assessment will not need to be performed if an echocardiogram taken within 3 months of study start is available and deemed satisfactory for evaluation of anesthesia risk.
- <sup>l</sup> The assessments indicated will be performed prior to discharge.
- <sup>m</sup> Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard laboratory parameters (chemistries, cell counts), concentrations of GAG and idursulfase enzyme, and presence of idursulfase-specific antibodies.
- <sup>n</sup> The neurodevelopmental assessments will be performed at IT Dosing Weeks 16, 28, 40 ( $\pm$ 7 days) and at EOS Week 52 ( $\pm$ 7 days). Note that, unlike patients in the pivotal study, the cognitive status of patients in the substudy will be assessed initially using the BSID-III. When these patients reach 42 months of age, if considered evaluable using the DAS-II instrument, they will transition to use of the DAS-II for continued assessments of cognition.
- <sup>o</sup> At least 14 days will be allowed for recovery following the placement of the IDDD before the administration of the first IT dose.
- <sup>p</sup> Note that, on IT Dosing Weeks, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT..

## Appendix 4 Expected Adverse Device Effects

A list of the adverse effects expected with the SOPH-A-PORT Mini S is provided in this appendix.

### Procedure-Related Complications

- Components handled improperly before, during, or after implantation
- Access port implanted incorrectly
- Catheter positioned improperly
- Injection through septum performed incorrectly
- Injection of incorrect medication through access port
- Injection outside the access port into pocket or subcutaneous tissue or extravasation
- Pocket seroma, hematoma, erosion, or infection

### Intrathecal Access Complications

- Surgical complications such as hemorrhage or hematoma
- Infection of the implant site or catheter track
- Radiculitis or arachnoiditis
- Intrathecal space infection resulting in meningitis or encephalitis
- Bleeding
- Spinal cord damage or trauma to the spinal cord or nerve roots
- Post-lumbar puncture, cerebrospinal fluid (CSF) leak, leading to headache, or subcutaneous CSF collection
- Epidural instead of intrathecal placement of catheter
- Inflammatory mass resulting in neurological impairment, including paralysis
- Pain on injection
- Complications of anesthesia
- Pseudomeningocele

### System-Related Complications

- Improperly positioned access port
- Erosion of the skin because of the underlying access port or the catheter
- Wound dehiscence
- Access port migration, fracture, breakage or occlusion
- Catheter damage, dislodgement, migration, disconnection, kinking or occlusion, fibrosis, or hygroma, resulting in tissue damage or a loss of or change in therapy, or other potentially serious adverse health consequences
- Catheter breakage and migration of residual catheter fragments, potentially resulting in serious adverse health consequences and the need for surgical removal
- Local immunological or fibrous reaction to the presence of a foreign body (the device)
- End of device service life or component failure, requiring surgical replacement
- Component failure, resulting in loss of therapy
- Access port inversion (“flipping”), rotation, or extrusion

- Access port or catheter rejection
- Fibrin sheath formation around catheter tip

**Appendix 5 Protocol Signature Page**

**Study Title:** A Controlled, Randomized, Two-arm, Open-label, Assessor-blinded, Multicenter Study of Intrathecal Idursulfase-IT Administered in Conjunction with Elaprase® in Pediatric Patients with Hunter Syndrome and Early Cognitive Impairment  
**Study Number:** HGT-HIT-094  
**Final Date:** 04 April 2013

I have read Protocol HGT-HIT-094, “A Controlled, Randomized, Two-arm, Open-label, Assessor-blinded, Multicenter Study of Intrathecal Idursulfase-IT Administered in Conjunction with Elaprase® in Pediatric Patients with Hunter Syndrome and Early Cognitive Impairment”, and the idursulfase-IT Investigator's Brochure.

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 HGT  
Medical  
Monitor**

PPD \_\_\_\_\_ PPD \_\_\_\_\_  
**Signature** **Date**

PPD \_\_\_\_\_ MD, PhD  
**Printed Name**