

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)

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

Study Center(s): Multicenter

Lead Investigator: Joseph Muenzer, MD, PhD

Sponsor: Shire Human Genetic Therapies, Inc.

Sponsor Contact: 300 Shire Way
Lexington, MA 02421 USA
PPD [REDACTED]

Medical Monitor: PPD [REDACTED], DO

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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[®] 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[®] 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:

Investigational Product Dose:

Pivotal study - idursulfase-IT 10 mg

Substudy - Dose adjustment for patients below 3 years of age based on reference brain weight: up to 8 months of age at dosing, idursulfase-IT 5 mg; >8 months to 30 months of age at dosing, idursulfase-IT 7.5 mg; >30 months to 3 years of age at dosing, idursulfase-IT 10 mg

Mode of Administration:

intrathecal (IT) injection

Device, Intended Use:

The SOPH-A-PORT[®] 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 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 and neurological examination findings, vital signs, and electrocardiogram (ECG) results
- To evaluate the anti-idursulfase antibody response in serum and cerebrospinal fluid (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 and determine pharmacokinetic (PK) parameters in serum after IT administration
- To evaluate the concentration of idursulfase in CSF prior to each monthly administration of idursulfase-IT
- 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 EuroQol-5D (EQ-5D) instrument

Substudy Objective:

- To examine the effect of the treatment regimen on safety and efficacy measures in pediatric patients with Hunter syndrome and early cognitive impairment who are below 3 years of age

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 standard 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 standard scores of the VABS-II domains: Communication, Daily Living Skills, Socialization, and Motor Skills
- Change from baseline to Visit Weeks 16, 28, 40, and 52 in age equivalents, developmental quotients, and T-scores for the subtests 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 age equivalents, developmental quotients, and V-scale scores of the VABS-II subdomains: Communication (Receptive, Expressive, Written), Daily Living Skills (Personal, Domestic, Community), Socialization (Interpersonal Relationships, Play and Leisure Time, Coping Skills), Motor Skills (Gross, Fine)
- Change from baseline to Visit Weeks 16, 28, 40, and 52 in the V-scale scores and the observed maladaptive levels of the VABS-II Maladaptive Behavior Index and its subscales (Internalizing, Externalizing)

Study Population:

Pivotal study – approximately 48 male patients (about 32 treated, 16 untreated) are planned.

Substudy - enrollment of patients below 3 years of age into the separate substudy will be considered additional to the number of patients planned for the pivotal study, and will conclude when enrollment of patients in the pivotal study closes.

Study Design:

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 for 12 months in pediatric patients with Hunter syndrome and early cognitive impairment who have previously received and tolerated a minimum of

4 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". Approximately 48 patients will be randomized in a 2:1 ratio to IT treatment or no IT treatment arms.

The pivotal study will consist of a Screening period of up to 28 days prior to randomization (Day 0). It is planned that 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 -4 to -1 [Day -28 to Day -1])
- Randomization (Week 0 [Day 0])
- Pre-surgery, Surgery, Follow-up, and Post-operative Recovery (Week 2 [+7 days])
- 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 -4 to -1 [Day -28 to Day -1])
- Randomization (Week 0 [Day 0])
- Telephone Contact (Week 2 [+7 days])
- 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, it is planned that patients in the separate substudy will undergo surgical implantation of the SOPH-A-PORT Mini S IDDD for the purpose of IT administration of idursulfase-IT and will follow a similar schedule of treatment and assessments as idursulfase-IT-treated patients in the pivotal study.

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

- Screening (Weeks -4 to -1 [Day -28 to Day -1])
- Enrollment (Week 0 [Day 0])
- Pre-surgery, Surgery, Follow-up, and Post-operative Recovery (Week 2 [+7 days])

- Treatments and Assessments (Week 4 through Week 48 [± 7 days])
- End of Study (EOS, Week 52 [± 7 days])
- Follow-up (telephone contact) 7 (± 2) days from the Week 52 (or EOS)

Patients will complete EOS assessments at Week 52 (Visit Month 13) and will participate in a follow-up contact (by telephone) approximately 7 days after the EOS visit. (Note that for those patients who enroll in extension study SHP-609-302 within the 7 ± 2 day window of the EOS visit the follow-up contact is not required. If, however, a patient is not enrolled in the SHP-609-302 study within the 7 ± 2 day window of the EOS visit, then the follow-up contact should be completed.)

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.

It is planned that the SOPH-A-PORT Mini S IDDD will be used to obtain CSF samples and to deliver 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 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 Monitoring Committee (DMC) will oversee both idursulfase-IT and device safety. The DMC will be notified of IDDD failures and related complications on a periodic basis according to the DMC 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 and are eligible according to the inclusion/exclusion criteria for the extension study may continue, or begin, 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 meet other inclusion criteria, provided below.

2. The patient must have a documented diagnosis of MPS II. Of the three criteria below, the combinations (2a AND 2b) or (2a AND 2c) 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.

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 ≥ 3 and < 13 years of age and patients ≥ 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 ≥ 55 and ≤ 85 .

OR
- b. If the patient has a GCA score at Screening > 85 , there must be evidence of a decrease in GCA score of ≥ 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 ≥ 55 and ≤ 85

AND
 - d. There must be evidence of a decrease in GCA score of ≥ 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 4 months of therapy with Elaprase during the period immediately prior to Screening.
 5. The patient must have sufficient auditory capacity, with a hearing aid(s), if needed, in the Investigator's judgment to complete the required protocol testing and must be compliant with wearing the hearing aid(s), if needed, 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 (IRB/IEC)-approved informed consent form after all relevant aspects of the study have been explained and discussed. Consent of the patient's parent(s) or legally authorized guardian(s) and the patient's assent, 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. Of the three criteria below, the combinations (2a AND 2b) or (2a AND 2c) 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.

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 as assessed using the BSID-III and defined as a DQ ≥ 55 and ≤ 85 .
4. The patient has received and tolerated a minimum of 4 months of therapy with Elaprase during the period immediately prior to Screening.
5. The patient must have sufficient auditory capacity, with a hearing aid(s), if needed, in the Investigator's judgment, to complete the required protocol testing, and must be compliant with wearing the hearing aid(s) on scheduled testing days.
6. The patient's parent(s) or legally authorized guardian(s) must have voluntarily signed an IRB/IEC-approved informed consent form after all relevant aspects of the 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 that includes a 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 30.0 cm H₂O.
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) 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 (IFU), 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 serum concentration-time profiles and serum pharmacokinetic parameters after IT administration.

Measurement of idursulfase concentration in CSF samples obtained immediately prior to each IT administration (and at the EOS Visit) to determine the degree of accumulation of monthly idursulfase-IT administrations in the CSF.

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 who are below the age of 3 years and who have early cognitive impairment) 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. The Expanded Interview Form will be utilized.

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 laboratory parameters (chemistries, cell counts), anti-idursulfase antibodies in CSF and serum, and determination of antibodies having enzyme neutralizing activity.

SOPH-A-PORT Mini S Device Assessments:

The SOPH-A-PORT Mini S device will be evaluated using assessments of device implantation, device function, device longevity and adverse events associated with the implant surgery or device. This data will be collected on the patient's case report form (CRF) from the time of initial implantation.

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. Statistical model estimates of least squares means, p-values and 95% confidence intervals (CIs) for least squares mean treatment differences will also be

provided where relevant for efficacy endpoints. All statistical tests will be two-sided and will be performed at the 0.05 level of significance unless stated otherwise.

Safety and efficacy data from the single-arm substudy will be summarized separately or listed separately.

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 according to treatment received 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 set of patients in the Safety Population who had the device implant procedure performed.

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

All PK data analyses will be performed using the PK population. The PK population will be defined as all patients for whom the primary pharmacokinetic data are considered sufficient and interpretable.

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, baseline GCA classification factor (either ≤ 70 or > 70), and the baseline GCA score as a continuous covariate. From this model, least squares means, standard errors, treatment differences in least squares means, and 95% CIs will be estimated for each time point. Primary inference is based on the treatment comparison of least squares means at Visit Week 52 from this model, and a p-value will be presented for this time point only.

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, baseline GCA classification factor (either ≤ 70 or > 70), and the baseline ABC score as a continuous covariate. The significance test will be based on the difference in least squares means at Visit Week 52 and a p-value will be presented for this time point only.

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:

- The change from baseline to Visit Weeks 16, 28, 40, and 52 in standard scores in cluster areas of the DAS-II: Verbal, Nonverbal, Spatial, and Special Nonverbal Composite (SNC)
- The change from baseline to Visit Weeks 16, 28, 40, and 52 in the standard

domain scores of the VABS-II: Communication, Daily Living Skills, Socialization, and Motor Skills

All other secondary efficacy endpoints will be summarized descriptively by treatment group.

The family wise type-I error rate (FWER) for the statistical tests of the primary, key secondary and other selected secondary efficacy endpoints from the MMRM analyses will be controlled at 0.05. To strongly control the FWER at this level, a Gatekeeping approach will be utilized in which each family of statistical tests will be conducted in a sequential manner. The test for the primary endpoint will be conducted first at the 5% significance level and, if significant, the key secondary endpoint will be similarly tested at the 5% significance level. If these two tests are both significant, tests of the additional secondary efficacy endpoints specified below will be conducted using the Hommel closed testing procedure¹ to control the FWER.

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 severity (mild, moderate, severe) and by relationship to study drug (not related, related) for treated patients. Separate tabulations will be provided for adverse events related to study drug, IV Elaprase infusion, the IDDD, device surgical procedure, and the IT-administration process.

SOPH-A-PORT safety and performance will be summarized for implanted patients. 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 annual event rate of IDDD failures and the time to first failure will be summarized.

Laboratory values in serum and CSF components, vital signs, ECG parameters, and other safety assessments will be summarized descriptively 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 or listed, as appropriate.

Date: 21 December 2015

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
ABC	adaptive behavior composite
AE	adverse event
ALB	albumin
ALK	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AR(1)	autoregressive
BMI	body mass index
BSID-III	Bayley Scales of Infant Development, Third Edition
BUN	blood urea nitrogen
BVA	blinded variability assessment
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C _{max}	maximal concentration
CNS	central nervous system
CRF	case report form (paper or electronic)
CRO	contract research organization
CSF	cerebrospinal fluid
DAS-II	Differential Ability Scales, Second Edition
DQ	developmental quotient
DS	dermatan sulfate
DMC	Data Monitoring Committee
ECG	electrocardiogram
EOS	end of study
EQ-5D	EuroQol-5D instrument for use as a measure of health outcome
ERT	enzyme replacement therapy
EU	European Union
FDA	United States Food and Drug Administration
FWER	familywise type-I error rate
GAG	glycosaminoglycan
GCA	general conceptual ability

Term	Definition
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
Hct	hematocrit
Hgb	hemoglobin
HGT-2310	drug code name for formulation of recombinant iduronate-2-sulfatase (idursulfase) for intrathecal administration
HS	heparan sulfate
ICH	International Conference on Harmonisation
ICP	intracranial pressure
IDS	iduronate-2-sulfatase gene
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IFU	Instructions for Use
IND	Investigational New Drug application
IRB	Institutional Review Board
IT	intrathecal
ITT	intent-to-treat
IV	intravenous(ly)
IVR	interactive voice response
KM	Kaplan Meier
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	medical device report
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MPS II	Mucopolysaccharidosis II (Hunter syndrome)
MRI	magnetic resonance imaging
PACU	post-anesthesia care unit
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PORT-A-CATH	PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System
PPD	Pharmaceutical Product Development, LLC
PRO	patient reported outcome

Term	Definition
PT	prothrombin time
PTT	partial thromboplastin time
QTc	corrected QT interval
RBC	red blood cell(s)
SAE	serious adverse event
SAS	Statistical Analysis System [®]
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (ast)
SGPT	serum glutamic pyruvic transaminase (alt)
Shire HGT	Shire Human Genetic Therapies, Inc. (Shire)
SmPC	Summary of Product Characteristics
SNC	special nonverbal composite
SOC	system organ class
SOE	schedule of events
SOPH-A-PORT Mini S	SOPH-A-PORT [®] Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire
T4	thyroxine
TSH	thyroid-stimulating hormone
UADE	unanticipated adverse device effect
UK	United Kingdom
US	United States
VAS	visual analog scale
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
WBC	white blood cell(s)
WHO-DD	World Health Organization Drug Dictionary
WOCF	worst observation carried forward
WRS	Wilcoxon rank-sum test

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.²⁻³ Though typically appearing normal at birth, all MPS II patients suffer from a progressive, serious, life-limiting disease.^{4,5}

The disease is caused by the absence of, or deficiency in, the activity of the lysosomal enzyme, iduronate-2-sulfatase which acts to cleave O-linked sulfate moieties from the glycosaminoglycan (GAG) molecules dermatan sulfate (DS) and heparan sulfate (HS).⁶ Insufficient activity of iduronate-2-sulfatase 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 central nervous system (CNS).⁷ Clinical manifestations include severe airway obstruction, skeletal deformities, cardiomyopathy and, in most patients, neurological decline.⁸ Death may occur in the first or second decade of life. Patients with attenuated disease may survive into adulthood, with airway obstruction and cardiac causes often contributing to death.⁵

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.^{5,9} 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 approximately three-quarters of MPS II patients will develop CNS involvement and be characterized as “severe.”⁹ 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 2 to 4 years of age.⁷⁻¹⁰ An earlier appearance of clinical symptoms generally, but not always, predicts a more severe clinical course.^{5-7,11} 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 deletion/rearrangement of the iduronate-2-sulfatase gene (IDS), who manifest severe neurodevelopmental impairment.¹²⁻¹³

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,¹⁴⁻¹⁶ 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. 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 CSF since it is isotonic and contains excipients suitable for IT use.

In order to traverse the blood-brain barrier, Shire is evaluating delivery of idursulfase-IT directly into the CNS using an intrathecal drug delivery device (IDDD), the SOPH-A-PORT[®] 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[®] II Low Profile[™] 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 receiving 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 (PK), and pharmacodynamics (PD) (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 (AEs) 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 has not been shown to 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.

It is planned that 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 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 Differential Ability Scale, Second Edition (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 Vineland Adaptive Behavior Scales, Second Edition (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 and neurological examination findings, vital signs, and electrocardiogram (ECG) results
- 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 PK and PD objectives of this study are:

- To evaluate the concentration of idursulfase and determine PK parameters in serum after IT administration
- To evaluate the concentration of idursulfase in CSF prior to each monthly administration of idursulfase-IT
- To determine the effect of the treatment regimen on the concentration of GAG in CSF

2.6 Health Status Objective

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

2.7 Substudy Objective

The objective of the substudy is:

- To examine the effect of the treatment regimen on safety and efficacy measures in pediatric patients with Hunter syndrome and early cognitive impairment who are below 3 years of age

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 standard scores in cluster areas of the DAS-II: Verbal, Nonverbal, Spatial, and SNC
- Change from baseline to Visit Weeks 16, 28, 40, and 52 in standard scores of the VABS-II domains: Communication, Daily Living Skills, Socialization, and Motor Skills
- Change from baseline to Visit Weeks 16, 28, 40, and 52 in age equivalents, developmental quotients, and T-scores for the subtests 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 age equivalents, developmental quotients, and V-scale scores of the VABS-II subdomains: Communication (Receptive, Expressive, Written), Daily Living Skills (Personal, Domestic, Community), Socialization (Interpersonal Relationships, Play and Leisure Time, Coping Skills), Motor Skills (Gross, Fine)
- Change from baseline to Visit Weeks 16, 28, 40, and 52 in the V-scale scores and observed maladaptive levels of the VABS-II Maladaptive Behavior Index and its subscales (Internalizing, Externalizing)

3.3 Pharmacokinetic and Pharmacodynamic Endpoints

The PK and PD endpoints of this study are:

- Serum concentration of idursulfase and serum PK parameters after IT administration
- CSF concentration of idursulfase prior to each monthly 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 recordings, CSF laboratory parameters (chemistries, cell counts), anti-idursulfase antibodies in CSF and serum, and determination of antibodies having enzyme neutralizing activity.

3.5 SOPH-A-PORT Mini S Device Assessments

The SOPH-A-PORT Mini S device will be evaluated using assessments of device implantation, device function, device longevity and adverse events associated with the implant surgery or device. This data will be collected on the patient's case report form (CRF) from the time of initial implantation.

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 for 12 months in pediatric patients with Hunter syndrome and early cognitive impairment who have previously received and tolerated a minimum of 4 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”. Approximately 48 patients will be randomized in a 2:1 ratio to IT treatment or no IT treatment arms.

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. Patients who are enrolled in the substudy will follow a similar schedule of study visits as idursulfase-IT-treated patients in the pivotal study.

4.1.1 Intrathecal Drug Delivery

It is planned that the study drug, idursulfase-IT (HGT-2310) will be administered to patients via the SOPH-A-PORT[®] 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 CSF samples and to deliver 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 during the treatment phase of the study.

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 Monitoring Committee (DMC) will oversee both idursulfase-IT and device safety. The DMC will be notified of IDDD failures and related complications on a periodic basis according to the DMC 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 (SOE) 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] ≥ 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 DAS-II¹⁷ GCA standard score at Screening between 85 and 55. Patients with a GCA score at Screening > 85 who are ≥ 3 to ≤ 13 years of age may still be eligible to participate if there is demonstrated evidence of a decrease in GCA score of ≥ 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 (≤ 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^{10, 18} 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 VABS-II.¹⁹ The proposed key secondary efficacy endpoint is the change from baseline in the 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 2 to 4 years.^{10, 11} 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, for instance, observed in children with a complex rearrangement/large deletion 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.^{10, 13} Such children may have measurable cognitive and functional abilities into their mid teens. MPS II patients within these two subcategories, ie, those <3 years of age and those ≥ 13 to <18 years of age, may be eligible for participation in HGT-HIT-094 and are discussed in further detail below.

Patients in whom cognitive impairment can be identified below 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 BSID-III,²⁰ 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, patients in the substudy will continue to receive the standard of care, Elaprase, under the supervision of their treating physician.

Children ≥ 13 years of age 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.^{10, 13} 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 ≥ 13 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 PK and PD data of Phase I/II studies, HGT-HIT-045 and HGT-HIT-046.

The serum PK 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 PD 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 PD profiles associated with monthly idursulfase-IT administration indicated that the 1 mg dose was suboptimal, with the 10 mg dose achieving maximal PD 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 PK and PD 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 and are eligible according to the inclusion/exclusion criteria for the extension study may continue, or begin, 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 approximately 48 patients (about 32 treated, 16 untreated) with early cognitive impairment who are ≥ 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 ≥ 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 early cognitive impairment and 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 number of 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 ≥ 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 meet other inclusion criteria, provided below.

2. The patient must have a documented diagnosis of MPS II. Of the three criteria below, the combinations (2a AND 2b) or (2a AND 2c) 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.

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 ≥ 3 and < 13 years of age and to patients ≥ 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 ≥ 55 and ≤ 85

OR

- b. If the patient has a GCA score at Screening > 85 , there must be evidence of a decrease in GCA score of ≥ 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 ≥ 55 and ≤ 85 .

AND

- d. There must be evidence of a decrease in GCA score of ≥ 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 4 months of therapy with Elaprase during the period immediately prior to Screening.
5. The patient must have sufficient auditory capacity, with a hearing aid(s), if needed, in the Investigator's judgment to complete the required protocol testing and must be compliant with wearing the hearing aid(s), if needed, 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.

5.2.2 Inclusion Criteria for the Substudy

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. Of the three criteria below, the combinations (2a AND 2b) or (2a AND 2c) 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.

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 as assessed using the BSID-III and defined as a developmental quotient (DQ) ≥ 55 and ≤ 85 .
4. The patient has received and tolerated a minimum of 4 months of therapy with Elaprase during the period immediately prior to Screening.
5. The patient must have sufficient auditory capacity, with a hearing aid(s), if needed, in the Investigator's judgment to complete the required protocol testing and must be compliant with wearing the hearing aid(s), if needed, on scheduled testing days.
6. The patient's parent(s) or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent form after all relevant aspects of the study have been explained and discussed. Consent of the patient's parent(s) or legally authorized guardian(s) 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 that includes a 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 30.0 cm H₂O.
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) 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 (IFU), 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 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 a system intended for implantation by physicians. The SOPH-A-PORT Mini S, once implanted, allows healthcare personnel to administer drugs indicated for intrathecal delivery intermittently over a long period of time. The device is CE Marked in the European Union (EU) and is considered investigational in non-EU countries.

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 IFU.

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 IT 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 administered intrathecally via IDDD (or lumbar puncture) once monthly for 12 months in addition to standard-of-care therapy with Elaprase prescribed by their physician.

6.3 Selection and Timing of Dose for Each Patient

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

It is planned that 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.

It is planned that patients who are enrolled in the separate substudy will undergo surgical implantation of the IDDD. Patients in the substudy will receive 12 monthly IT injections of idursulfase-IT, once every 28 days. The IT dose of idursulfase-IT to be administered to patients below 3 years of age will be adjusted as follows based on reference brain weight.²¹

- Up to 8 months of age at dosing, idursulfase-IT 5 mg
- >8 months to 30 months of age at dosing, idursulfase-IT 7.5 mg
- >30 months to 3 years of age at dosing, idursulfase-IT 10 mg

Please refer to the Pharmacy Manual for complete details.

For treated patients in the pivotal study and patients in the substudy, 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 eligibility 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 (≤ 70 or > 70). The randomization schedule will be generated and administered by a third-party (eg, interactive voice response [IVR] vendor) independent of the project team.

In a separate substudy, additional patients may be enrolled who are below the age of 3 years at the time of informed consent and have early cognitive impairment. 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 and each site will document the manner in which blinding will be maintained at the site.

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 assessors will not be part of the study team or participate in study team meetings.

6.6 Concomitant Medications, Therapies, and Medical/Surgical Interventions

Treatment with any other investigational therapies at any time during this study is prohibited.

All patients are to receive Elaprase therapy throughout this 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 are permitted, and will be captured during the study.

6.6.1 Infusion Reactions and Management

Infusions of proteins can be associated with reactions to the infusion that may or may not be immune mediated (hypersensitivity reactions). Thus, potential reactions to the infusion of an investigational product, including idursulfase-IT, are unpredictable. It is often difficult to clinically distinguish infusion reactions from hypersensitivity reactions. Symptoms may include headache, fever, sensory paresthesias (including feeling of warmth, tingling, or pain), rash, pruritus, or autonomic symptoms, such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection over time.

The management of infusion reactions and hypersensitivity reactions is similar. The following steps may be taken, at the discretion of the Investigator, in the event of a suspected infusion related/hypersensitivity reaction and the management of such reactions should be based on the severity of the reaction:

- Treatment with medications such as antihistamines, antipyretics, and/or corticosteroids
- Stopping and resuming treatment
- Pretreatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required

Infusion-related reactions have been observed in patients receiving IV enzyme replacement therapy (ERT) 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 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.

The ongoing clinical studies with idursulfase-IT have not revealed adverse events of the severity and frequency 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 Therapies

All patients must have received and tolerated 4 months of therapy with idursulfase IV (Elaprase) therapy prior to participation in this study.

Prior therapies that are exclusion criteria for the study include the following: treatment with another investigational product (drug or [intrathecal/spinal] device) within the 30 days prior to study enrollment (or at any time during the study, see Section 6.6), receipt of blood product transfusions within 90 days prior to Screening, receipt of a cord blood or bone marrow transplant at any time.

6.7.2 Fluid and Food Intake

Not applicable.

6.7.3 Patient Activity Restrictions

Please refer to the SOPH-A-PORT Mini S IFU for details regarding patient activity restrictions for patients to be implanted with this device. Activities that may include sudden, excessive, or repetitive bending, twisting, bouncing, or stretching can damage or dislodge IDDD components and should be avoided.

6.8 Treatment Compliance

Treatment with the investigational product will be administered via an IDDD (or lumbar puncture) 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, and have completed training with the SOPH-A-PORT Mini S. Please refer to the IFU 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 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-mL 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.

6.10 Storage and Accountability

6.10.1 Investigational Product

Idursulfase-IT will be shipped by Shire or a qualified distributor to the clinical study site(s) at 2 to 8 °C (36 to 46 °F). The investigational product should be handled as follows:

- idursulfase-IT vials should be stored at 2 to 8°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 0.22 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.
- Because it does not contain preservatives, idursulfase-IT should be used as soon as possible after it is prepared.
- Idursulfase-IT is supplied in single-use vials. Only 1 dose of idursulfase-IT is to be withdrawn from a vial.

See the Pharmacy Manual for additional details.

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 CRF.

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.

6.10.2 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 CRF.

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.

6.10.3 Comparator Product

Not applicable to this study.

7 STUDY PROCEDURES

The pivotal study will consist of a Screening period of up to 28 days (during which re-testing of patients who were initially unwilling or unable to comply with all scheduled screening assessments is permitted) prior to randomization (Day 0).

It is planned that 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 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 -4 to -1 [Day -28 to Day -1])
- Randomization (Week 0 [Day 0])
- Pre-surgery, Surgery, Follow-up, and Post-operative Recovery (Week 2 [+7 days])
- Treatment and Assessments (Week 4 through Week 48 [± 7 days])
- End of Study (EOS, Week 52 [± 7 days])
- Follow-up (telephone contact) 7 (± 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 -4 to -1 [Day -28 to Day -1])
- Randomization (Week 0 [Day 0])
- Telephone Contact (Week 2 [+7 days])
- Assessments (Week 4 through Week 48 [± 7 days])
- End of Study (EOS, Week 52 [± 7 days])
- Follow-up (telephone contact) 7 (± 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, it is planned that patients in the separate substudy will undergo surgical implantation of the SOPH-A-PORT Mini S IDDD for the purpose of IT administration of idursulfase-IT and will follow a similar schedule of treatment and assessments as idursulfase-IT-treated patients in the pivotal study.

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

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

Patients will complete EOS assessments at Week 52 (Visit Month 13) and will participate in a follow-up contact (by telephone) approximately 7 days after the EOS visit. (Note that for those patients who enroll in extension study SHP-609-302 within the 7 ± 2 day window of the EOS visit the follow-up contact is not required. If, however, a patient is not enrolled in the SHP-609-302 study within the 7 ± 2 day window of the EOS visit, then the follow-up contact should be completed.)

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.

For treated patients in the pivotal study and patients in the substudy, 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 Schedules 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 CRF.

Details for study procedures including sample collection are described in the Study 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 guardian(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).

7.3.1 Genotype

Patients who have not had a previous iduronate-2-sulfatase gene (IDS) genotype analysis performed at Greenwood Genetic Center's Diagnostic Laboratory (Greenwood, South Carolina, USA), referred to here as "Greenwood Labs," will provide a blood sample for genotyping to document the diagnosis of Hunter syndrome. Even patients for whom prior genotyping was performed at Greenwood Labs may need to 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 large deletion/rearrangement mutations).

Specific instructions concerning genotyping and the timing of enrollment are provided below:

- A Greenwood Labs IDS genotype will be obtained for all patients in the study. If the patient has no Greenwood Labs IDS genotype in his file at the time of informed consent, a blood sample will be drawn at Screening. If the patient has a prior Greenwood Labs genotype in his file, and it indicates the presence of a mutation(s) that is within the IDS locus (eg, small deletion or point mutation), the test will not have to be redone. If the patient has a prior Greenwood Labs genotype in his file, and it indicates the presence of a large deletion/rearrangement mutation but does not confirm the integrity of the FMR1 and FMR2 genes, a new sample may have to be drawn.
- If the patient has no documented IDS genotype at Screening, then enrollment/randomization will have to await the arrival of the Greenwood Labs genotype results.
- If the patient has a locally determined IDS genotype indicating the presence of a small deletion or point mutation, the site may proceed and enroll/randomize him while awaiting the confirmatory results from Greenwood Labs.
- If the patient has a locally determined IDS genotype indicating the presence of a large deletion/rearrangement mutation, then enrollment/randomization will have to await the results of the Greenwood Labs genotype analysis to confirm the integrity of the FMR1 and FMR2 genes.
- If the patient has a Greenwood Labs IDS genotype indicating the presence of a small deletion or point mutation, he can be enrolled/randomized at once.
- If the patient has a Greenwood Labs IDS genotype indicating the presence of a large deletion/rearrangement mutation, he may only be enrolled/randomized if and when a Greenwood Labs genotype confirming the integrity of the FMR1 and FMR2 genes is available, either in his original genotype documentation, or by analysis of a new sample.

7.4 Echocardiogram

An echocardiogram will be performed as part of the study screening assessments. 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 IFU. 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 and may be provided; however, use of other catheter passers compatible with the SOPH-A-PORT Mini S is allowed.

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

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 CRF. 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 IFU 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 CRF. For further details, please refer to the SOPH-A-PORT Mini S IFU.

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

It is planned that idursulfase-IT will be administered every 28 days by means of the IDDD (or lumbar puncture, see Section 4.1.1). 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 CSF 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 CRF.

Intrathecal administration of investigational product will be preceded by CSF sampling for laboratory analysis, pharmacodynamic analysis (GAG concentration), and analyses of idursulfase enzyme concentration 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 the observation of study personnel in the hospital setting (eg, may include infusion center, PACU (recovery suite), observation unit, short stay center) for 4 hours post administration of investigational product for safety assessments. Thereafter, if deemed clinically stable by the Investigator, patients may leave the hospital setting (with exception of study visit weeks at which serial blood sampling for pharmacokinetic evaluation is planned). For the first 6 months of treatment with idursulfase-IT, patients must return to the clinic the day after each IT administration for a safety follow-up visit. Note that, under these circumstances, there is no requirement for an overnight hospital stay; if a decision is made to keep the patient overnight for convenience, this hospitalization should not initiate a serious adverse event report. For the latter 6 months of treatment with idursulfase-IT (ie, from Week 28 onward) and in the absence of any safety concerns, patients may complete the safety follow-up visit on the same day as IT administration prior to discharge.

7.7 Pharmacokinetic Assessments

Blood samples will be collected for determination of idursulfase serum concentration-time profiles and serum pharmacokinetic parameters after IT administration.

Idursulfase concentrations will be measured in CSF samples obtained immediately prior to each IT administration (and at the EOS Visit) to determine the degree of accumulation of monthly idursulfase-IT administrations in the CSF.

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

7.8 Pharmacodynamic/Biomarker Assessments

7.8.1 CSF Glycosaminoglycan

Cerebrospinal fluid will be collected for measurement of the concentration of GAG (refer to the SOE for the pivotal study [[Appendix 1](#) and [Appendix 2](#)] and separate substudy [[Appendix 3](#)]).

7.8.2 CSF and Serum Albumin

Albumin levels will be measured in samples of CSF (refer to the SOE for the pivotal study ([Appendix 1](#) and [Appendix 2](#)) and separate substudy ([Appendix 3](#)) to monitor the permeability of the blood-brain barrier. Measurement of albumin levels in serum is included in the panel of clinical laboratory tests ([Table 7-2](#)).

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.⁷ Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as follows.

Cognition: the Differential Ability Scales, Second Edition (DAS-II)¹⁷ will be used to assess all randomized patients. The DAS-II comprises 2 overlapping batteries. The Early Years battery is designed for children ages 2 years 6 months through 6 years 11 months. The School Age Battery is designed for children ages 7 years 0 months through 17 years 11 months. These batteries are fully co-normed for ages 5 years 0 months through 8 years 11 months.

For patients participating in the separate substudy only (ie, patients who are below the age of 3 years and who have early cognitive impairment) cognition will be assessed initially using the Bayley Scales of Infant Development, Third Edition (BSID-III).²⁰ 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)¹⁹ will be used to assess all patients. The Expanded Interview Form will be utilized.

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.

All assessments will be administered by qualified study personnel. The DAS-II will be administered by a trained practitioner.

7.10 Health Status Assessment

The health status of patients will be assessed using the EuroQol-5D (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.^{22, 23} The EQ-5D provides a descriptive profile and index value for health status.

7.11 Safety Assessments

Safety will be assessed by 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 recordings, CSF laboratory parameters (chemistries, cell counts), 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, and adverse events associated with the implant surgery or device. This data will be collected on the patient's CRF from the time of initial implantation.

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 CRF.

Table 7-1 Assessments for Physical and Neurological Examinations

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

Table 7-1 Assessments for Physical and Neurological Examinations

Assessment	Assessment
Port and catheter	

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 SOE. 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

Each patient must have sufficient auditory capacity, with a hearing aid(s), if needed, in the Investigator's judgment, to complete the required protocol testing and must be compliant with wearing the hearing aid(s), if needed, on scheduled testing days.

The Investigator will confirm that, with hearing aids in place if needed, each patient has sufficient understanding to participate in study assessments.

7.11.5 Vital Signs

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

7.11.6 Electrocardiogram

An electrocardiogram (ECG, 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, RR, QRS, and QT intervals. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the CRF.

7.11.7 Intracranial Pressure Measurement

Intracranial pressure (ICP) measurement (cm of H₂O) 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 and/or MRI 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 or via central line.

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

Table 7-2 List of Laboratory Tests

Hematology:	Serum Chemistry:
<ul style="list-style-type: none">- Hematocrit (Hct)- Hemoglobin (Hgb)- Mean corpuscular hemoglobin (MCH)- Mean corpuscular hemoglobin concentration (MCHC)- Mean corpuscular volume (MCV)- Platelet count- Red blood cell (RBC) count- White blood cell (WBC) count with differential	<ul style="list-style-type: none">- Albumin (ALB)- Alkaline phosphatase (ALK-P)- Alanine aminotransferase (ALT; SGPT)- Aspartate aminotransferase (AST; SGOT)- Blood urea nitrogen (BUN)- Calcium (Ca)- Carbon dioxide (CO₂)- Chloride (Cl)- Creatinine- Creatine phosphokinase- Gamma-glutamyl transferase (GGT)- Glucose- Lactate dehydrogenase (LDH)- Magnesium (Mg)- Phosphorus (P)- Potassium (K)- Sodium (Na)- Total and direct bilirubin- Total cholesterol- Total protein- Total thyroxine (T4)- Thyroid-stimulating hormone (TSH)- Triglycerides- Uric acid
Urinalysis:	
<ul style="list-style-type: none">- Appearance (clarity and color)- Bilirubin- Blood- Glucose- Ketones- Leukocyte esterase- Microscopic examination of sediment- Nitrite- pH- Protein- Specific gravity- Urobilinogen	
Coagulation:	
<ul style="list-style-type: none">- Prothrombin time (PT)- Partial thromboplastin time (PTT)	

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 safety laboratory parameters (chemistries, cell counts), albumin, GAG, and concentration of idursulfase enzyme. The CSF samples will also be analyzed for idursulfase-specific antibodies and antibodies with enzyme neutralizing activity (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 during the treatment phase of the study.

Patients in the no-treatment arm of the pivotal study will undergo lumbar puncture (under general anesthesia) to obtain CSF samples at the Screening and EOS Visits.

7.11.11 Antibody Assessments

Blood and CSF samples will be collected and evaluated by a Shire-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, and adverse events associated with the implant surgery or device. These data will be collected on the patient's CRF from the time of initial implantation.

As part of the assessment of the SOPH-A-PORT Mini S, it may be necessary to determine the levels of leachables from the device into the CSF and blood. Samples of stored CSF and serum may be used to determine the levels of leachable materials related to the IDDD.

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 Study Operations Manual and/or Laboratory Manual for this study.

A variety of biological specimens will be collected from patients at the intervals indicated in the SOEs. These will be stored securely until analyzed. The patients' IDs will be kept confidential.

Samples will be stored until used up or for a maximum of 10 years after the last patient visit in this trial, after which any residual material will be destroyed.

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 CRF.

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.

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
- Clinically significant abnormal laboratory values (includes shifts from baseline within the range of normal that the Investigator considers to be clinically important)
- Clinically significant abnormalities in physical and neurological examination, vital signs, ECG

Throughout the study, the Investigator must record all adverse events on the AE CRF, 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 or his parent(s)/legally authorized guardian(s), complaint by the patient or his parent(s)/legally authorized guardian(s), or by abnormal clinical laboratory values or physical findings.

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 CRF. 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 CRF.

7.14.1.2 Elaprase-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. The most commonly reported adverse events that have been assessed as related to Elaprase in patients with Hunter syndrome are listed in Section 6.6.1. 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 in order to help distinguish adverse events related to IV compared to IT administration.

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 (such as may occur with migration of the portal/catheter, occlusion of the portal/catheter, incorrect connection of IDDD components, fibrin sheath formation around the catheter tip), erosion of the portal/catheter through the skin, hematoma, implant rejection, or subcutaneous tract infection. A malfunction of the device (defined in Section 7.14.2.2) should not be entered as an adverse event unless this has physiopathological consequences such as those listed above. In the event of device failure (defined in Section 7.14.2.3), the device may need to be replaced or repaired as needed. Hospitalization for such a procedure will be reported as a serious adverse event. Details of the cause of IDDD malfunction or failure will be recorded on the device Malfunction/Failure CRF. A list of the most common IDDD adverse events is included in [Appendix 4](#).

7.14.1.4 Device Surgical Procedure-related Adverse Events

Examples of adverse events related to device surgical procedures include, but are not limited to, the following: events that occur during or following IDDD implant/explant, IDDD adjustment, full revision, partial revision, IDDD removal, and delayed re-implantation after previous IDDD removal (such as complications of anesthesia, excessive bleeding, wound hematoma), and post-operative complications (such as 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 Events

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 result in a serious adverse event designation [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).

Hospitalization, which is the result of elective or previously scheduled surgery for pre-existing condition that has not worsened after initiation of treatment, should not result in a serious adverse event designation. For example, an admission for a previously scheduled ventral hernia repair would not be classified as a serious adverse event; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as serious adverse event(s). Furthermore, this does not apply to device failures resulting in scheduled surgical revisions, which should be reported as serious adverse events.

7.14.1.7 Unanticipated Adverse Device Effect

An unanticipated adverse device effect (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 (21 Code of Federal Regulations [CFR] 812.3[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 IFU, 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 based on the definitions shown in [Table 7-3](#). The severity of all adverse events and serious adverse events should be recorded on the appropriate CRF page as mild, moderate, or severe.

Table 7-3 Adverse Event Severity

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

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 may pose a threat to life or functioning (see Section 7.14.1.6). 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 study 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

Relationship to Treatment	Definition
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 CRF, 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 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 Medical Monitor: PPD [REDACTED], DO

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 SAE, the clinical site must contact the Shire 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 Medical Monitor.

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

The device manufacturer will submit mandatory medical device reports (MDRs) (ie, UADEs) to the relevant regulatory agencies consistent with applicable regulations and Shire will submit MDRs to the Investigational New Drug Application (IND). Shire will report expedited drug related events (serious, unexpected/unlisted, causally related) to the relevant regulatory agencies consistent with applicable regulations.

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 unanticipated adverse device effect (submitted by the Sponsor or manufacturer, respectively). The Investigator must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files.

7.15 Pregnancy

Not applicable.

7.16 Abuse, Misuse, 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.

The Investigator must report abuse, misuse, overdose, and medication error to the Shire Pharmacovigilance and Risk Management Department AND to the Shire 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 (refer to the contact information for reporting of SAEs provided in Section 7.14.5.2).

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 guardian(s) acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment.

If the patient's parent(s) or legally authorized guardian(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 CRF. Any adverse events experienced up to the point of discontinuation must be documented on the AE CRF. 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 the 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 DMC until the last patient completes his last scheduled study visit/assessment. The DMC 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 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 via the Expanded Interview Form is consistent with the Food and Drug Administration (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-II. 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 standard 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
Primary Endpoint		
Cognitive Function	General Conceptual Ability (GCA)	DAS II
Key Secondary Endpoint		
Adaptive Behavior	Adaptive Behavior Composite (ABC)	VABS-II
Secondary Endpoints		
Cognitive Function	Standard score in DAS-II cluster areas: Verbal, Nonverbal, Spatial, GCA, and Special Nonverbal Composite (SNC)	
	Developmental quotient for the following:	
	Group 1 ^a { Verbal Comprehension Picture Similarities Naming Vocabulary Pattern Construction Matrices Copying	DAS-II - Early Years
	or:	
	Group 2 ^a { Recall of Designs Word Definition Pattern Construction Matrices Verbal Similarities Sequential Reasoning Quantitative Reasoning	DAS-II - School Age
Adaptive Behavior	Standard scores and developmental quotients (based on age equivalents) in VABS-II domains: Communication Daily Living Skills Socialization Motor Skills Maladaptive Behavior	VABS-II

Abbreviations: ABC = adaptive behavior composite; DAS-II = Differential Ability Scales, Second Edition; GCA = general conceptual ability; VABS-II = Vineland Adaptive Behavior Scales, Second Edition

^a 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 Schedule of Events (SOE). See Section 13 for the SOE 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 (blood sample collection for testing of iduronate-2-sulfatase activity and genotyping, as appropriate based on the patient's medical history). Note that analysis of 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 large deletion/rearrangement mutations). Please refer to Section 7.3.1 for specific instructions.
- 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)
 - Bayley Scales of Infant Development, Third Edition (BSID-III) for patients in the substudy only who are too young (<3 years of age) or unable to complete the DAS-II
 - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
- 12-lead ECG
- Vital signs
- Clinical laboratory tests (hematology, serum chemistry, urinalysis)
- Urine GAG and creatinine
- Anti-idursulfase antibody testing (serum and CSF)
- General anesthesia
- Brain MRI

- ICP measurement (by lumbar puncture)
- CSF sample collection (by lumbar puncture). CSF samples will be used to analyze standard laboratory parameters (chemistries, cell counts), as well as GAG, concentration of idursulfase enzyme, albumin, and presence of idursulfase-specific antibodies.
- Health status assessment (EQ-5D questionnaire)
- 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
- Concomitant medications, therapies/interventions, and medical/surgical procedures *
- Adverse events *

*These assessments may occur by telephone.

8.2.2 All Patients in the Substudy

- Documentation of entry criteria for enrollment
- Concomitant medications, therapies/interventions, and medical/surgical procedures *
- Adverse events *

*These assessments may occur by telephone.

8.3 Treatment Period (Months 1 to 12)

During this period, several phases of activity will occur. These are designated in the SOE as: Pre-surgery, Surgery, Follow-up, and Post-op Recovery at Week 2 (+7 days) and IT Dosing at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 [± 7 days] (Pre-treatment, IT Injection, Follow-up).

8.3.1 Patients in the IT Treatment Group of the Pivotal Study and All Patients in the Substudy: Pre-surgery, Surgery, Follow-up, and Post-op Recovery (Week 2 [+7 days])

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

Note: Patients in the USA who were randomized in the pivotal study prior to FDA authorization of investigational use of the SOPH-A-PORT Mini S IDDD and treated with idursulfase-IT via lumbar puncture will have the assessments originally planned at Week 2 [+7 days] performed at the time of the delayed device implantation surgery.

8.3.1.1 Pre-surgery

- Physical and neurological examination*
- Height and weight*
- 12-lead ECG*
- Vital signs*
- Clinical laboratory tests (hematology, serum chemistry, urinalysis)*
- Coagulation tests ([PT, PTT] to be performed by the local laboratory)
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

*The assessments indicated do not need to be repeated if completed as part of Screening assessments within 7 days prior to surgery.

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

The following assessments will be performed after surgery and prior to discharge. It is expected that, for most patients, post-surgical follow-up will occur within Week 2 (ie, within 1 to 2 days of surgery).

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

8.3.1.4 Post-op Recovery

Surgical implantation of the IDDD will be followed by a post-operative recovery period of at least 14 days prior to the first IT administration of idursulfase-IT.

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
- Height and weight (performed at Weeks 4, 16, 28, 40)
- Head circumference (performed at Weeks 4, 16, 28, 40)
- Hearing assessment (performed at Weeks 16, 28, 40)
- Neurodevelopmental assessments (performed at Weeks 16, 28, and 40)
- Differential Ability Scales, Second Edition (DAS-II)
- Bayley Scales of Infant Development, Third Edition (BSID-III) for patients in the substudy only who are too young (<3 years of age) or unable to complete the DAS-II
- Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
- 12-lead ECG
- Vital signs
- Clinical laboratory tests (hematology, serum chemistry, urinalysis, performed at Weeks 4, 16, 28 and 40)
- Urine GAG and creatinine (performed at Weeks 4, 16, 28, 40)
- Anti-idursulfase antibody testing (serum [and CSF, see Section 8.3.2.2], performed at Weeks 4, 16, 28, and 40)
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

From Week 28 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.

8.3.2.2 IT Injection

Patients will remain under observation in the hospital setting (eg, may include infusion center, post-anesthesia care unit [PACU; recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Thereafter, if deemed clinically stable by the Investigator, patients may leave the hospital setting (with exception of Visit Weeks 4, 24, and 48 at which serial blood sampling for PK evaluation is planned). The patient may 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.

- 12-lead ECG (performed within 4 hours of IT injection at Weeks 4, 16, 28, 40)
- Vital signs (collected at the following time points (± 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, and 4 hours post end of IT administration)
- CSF sample collection (performed at each IT Dosing Week prior to idursulfase-IT injection). Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard laboratory parameters (chemistries, cell counts), as well as GAG, concentration of idursulfase enzyme, albumin, and presence of idursulfase-specific antibodies. Analyses of CSF samples for antibodies and albumin will be performed at IT Dosing Weeks 4, 16, 28, and 40.
- idursulfase-IT injection
- Serum sampling for PK analysis (performed at Weeks 4, 24, and 48). Samples will be collected within 15 minutes (± 5 minutes) prior to intrathecal administration of idursulfase-IT and at 30 minutes (± 5 minutes), 60 minutes (± 5 minutes), 120 minutes (± 5 minutes), 4 hours (± 5 minutes), 6 hours (± 5 minutes), 8 hours (± 15 minutes), 12 hours (± 15 minutes), 24 hours (± 15 minutes), 30 hours (± 15 minutes), 36 hours (± 15 minutes) after the start of intrathecal administration.
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

8.3.2.3 Follow-up (Post IT Injection)

For the first 6 months of treatment with idursulfase-IT (ie, Weeks 4, 8, 12, 16, 20, 24), patients must return to the clinic the day after each IT administration for a safety follow-up visit. Note that, under these circumstances, there is no requirement for an overnight hospital stay; if a decision is made to keep the patient overnight for convenience, this hospitalization should not initiate a serious adverse event report. For the latter 6 months of treatment with idursulfase-IT (ie, from Week 28 onward) and in the absence of any safety concerns, patients may complete the safety follow-up visit on the same day as IT administration prior to discharge.

- 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 Week 2 (+7 days)

The following will be assessed by telephone contact:

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

Note: Week 2 [+7 days] assessments are not applicable to patients in the USA who are randomized in the pivotal study prior to FDA authorization of use of the SOPH-A-PORT Mini S IDDD.

8.3.3.2 Weeks 4, 16, 28, 40 (\pm 7 days)

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

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

The following will be assessed by telephone contact:

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

8.4 End of Study: Month 13 (Week 52[\pm 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)
- Bayley Scales of Infant Development, Third Edition (BSID-III) for patients in the substudy only who are too young (<3 years of age) or unable to complete the DAS-II
- Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
- 12-lead ECG
- Vital signs
- Clinical laboratory tests (hematology, serum chemistry, urinalysis)

- Urine GAG and creatinine
- Anti-idursulfase antibody testing (serum and CSF)
- General anesthesia
- Brain MRI
- ICP measurement (by lumbar puncture)
- CSF sample collection. CSF samples will be used to analyze standard laboratory parameters (chemistries, cell counts), as well as GAG, concentration of idursulfase enzyme, albumin, and presence of idursulfase-specific antibodies.
- X-ray
- Health status assessment (EQ-5D questionnaire)
- 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 (hematology, serum chemistry, urinalysis)
- Urine GAG and creatinine
- Anti-idursulfase antibody testing (serum and CSF)
- General anesthesia
- Brain MRI
- ICP Measurement (by lumbar puncture)
- CSF sample collection (by lumbar puncture). CSF samples will be used to analyze standard laboratory parameters (chemistries, cell counts), as well as GAG, concentration of idursulfase enzyme, albumin, and presence of idursulfase-specific antibodies.
- Health status assessment (EQ-5D questionnaire)
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

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

8.5.1 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

(Note that for those patients who enroll in extension study SHP-609-302 within the 7 \pm 2 day window of the EOS visit the follow-up contact is not required. If, however, a patient is not enrolled in the SHP-609-302 study within the 7 \pm 2 day window of the EOS visit, then the follow-up contact should be completed.)

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

All statistical analysis will be performed by Shire Biometrics Department using Statistical Analysis System (SAS) software version 9.3 or higher (SAS Institute, Cary, NC, USA) unless otherwise specified.

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. Statistical model estimates of least squares means, treatment differences, p-values and 95% confidence intervals (CIs) 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/or other diagnostic plots as appropriate. All statistical 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. The safety and efficacy data from the substudy will be summarized descriptively or listed, as appropriate, in a manner similar to that of the pivotal study.

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, which is considered a clinically meaningful treatment difference.

Using a 2:1 allocation ratio, a sample size of approximately 48 randomized patients (about 32 IT treated patients, 16 no IT control patients) will yield 80% power to detect a clinically meaningful mean treatment difference of 11 points in the primary endpoint, GCA change from baseline to Visit Week 52. This calculation further assumes a common standard deviation for the change from baseline of 11.6 points, a type-I error rate of 0.05 for a two-sided two-sample t-test, with approximately up to 10% missing an assessment at Visit Week 52. Given this sample size, and conditional on rejection of the null hypothesis for the primary endpoint, the power would be 80% to detect a mean difference of 10 points in the key secondary endpoint, assuming a common standard deviation for the change from baseline of 10.5 points for a two-sided two-sample t-test with a significance level of 5% and 10% missing an assessment at Visit Week 52. The variance

estimate for this sample size was determined based on a blinded variability assessment (BVA) performed as specified in the prior protocol version (Amendment 3); refer to [Appendix 5](#) for details. Given that uncertainty around this variability estimate remains, a second BVA using the same approach as specified in [Appendix 5](#) is planned to confirm the estimate after approximately 27 patients complete the Week 52 primary endpoint assessment. Based on this second blinded assessment, the sample size may be increased to a maximum of 54 patients while maintaining the 2:1 allocation ratio.

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 pivotal 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: less than or equal to 70 versus greater than 70. The randomization schedule will be generated and administered centrally by Pharmaceutical Product Development, LLC (PPD), independent of the Sponsor's project team. There is no replacement of patients who do not complete the study.

In a separate substudy, additional patients with cognitive impairment may be enrolled who are below the age of 3 years at the time of informed consent. Such patients are ineligible for the pivotal trial and will not be randomized, but will receive idursulfase-IT treatment monthly.

10.4 Population Description and Exposure

10.4.1 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 according to treatment received 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 set of patients in the Safety Population who had the device implant procedure performed.

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

All pharmacokinetic data analyses will be performed using the Pharmacokinetic Population. The Pharmacokinetic Population is defined as all patients for whom the primary pharmacokinetic data are considered sufficient and interpretable.

The planned analyses described below pertain to the pivotal study data. Similar descriptive summaries or listings as appropriate will be provided for the substudy data.

10.4.2 Patient Disposition

The total number of patients screened (ie, signed informed consent) will be presented. The number and percentage of patients screened (ie, signed informed consent), randomized, completed, and discontinued prematurely by reason for withdrawal will be summarized by treatment group. The number of patients included in the ITT and Safety populations will be summarized.

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, age [years], race, ethnicity, genotype, weight [kg], height [cm], body mass index [BMI, kg/m²], country, age at onset of Hunter syndrome symptoms, age of Hunter syndrome diagnosis, family history of Hunter syndrome) will be summarized by treatment group and overall in the pivotal study.

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 efficacy analyses described below refer to the pivotal trial; all efficacy data from patients treated in the separate substudy will be listed, including any measurements from the BSID-III and VABS-II.

10.5.1 Primary Efficacy Endpoint Analysis

For the pivotal trial, the primary efficacy endpoint is the change from study baseline (screening visit) to Visit Week 52 in the 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.^{24, 25} 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, baseline GCA classification factor (either ≤ 70 or > 70), and the baseline GCA score as a continuous covariate. 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. The assumptions of the model, including normality, will be evaluated using residual and other diagnostic plots of model fit.

From this model, least squares means, standard errors, treatment differences in least squares means, and 95% CIs will be estimated for each time point. Primary inference is based on the treatment comparison of least squares means at Visit Week 52 from this model, and a p-value will be presented for this time point only. 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 μ_{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%. Estimated least squares means (\pm SE) 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 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, baseline GCA classification factor (either ≤ 70 or > 70) and the baseline ABC score as a continuous covariate. SAS Proc Mixed with REML and an unstructured within-patient covariance structure will be used. If this model fails to converge, a

first order 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. The assumptions of the model, including normality, will be evaluated using residual and other diagnostic plots of model fit. From this model, least squares means, standard errors, treatment differences in least squares means, and 95% CIs will be estimated for each time point. The significance test will be based on the difference in least squares means at Visit Week 52 and a p-value will be presented for this time point only. Estimated least squares means (\pm SE) by treatment group will be plotted over time.

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:

- The change from baseline to Visit Weeks 16, 28, 40, and 52 in standard scores in cluster areas of the DAS-II: Verbal, Nonverbal, Spatial, and SNC
- The change from baseline to Visit Weeks 16, 28, 40, and 52 in standard scores of the VABS-II domains: Communication, Daily Living Skills, Socialization, and Motor Skills

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:

- The change from baseline to Visit Weeks 16, 28, 40, and 52 in the age equivalents, developmental quotients, and T-scores for the subtests 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
- The change from baseline to Visit Weeks 16, 28, 40, and 52 in the age equivalents, developmental quotients, and V-scale scores of the VABS-II subdomains: Communication (Receptive, Expressive, Written), Daily Living Skills (Personal, Domestic, Community), Socialization (Interpersonal Relationships, Play and Leisure Time, Coping Skills), Motor Skills (Gross, Fine)
- The change from baseline to Visit Weeks 16, 28, 40, and 52 in V-scale scores and observed maladaptive levels of the VABS-II Maladaptive Behavior Index and its subscales (Internalizing, Externalizing)

10.5.4 Exploratory Analyses

As exploratory analyses, the primary and key secondary MMRM models will be refit including the continuous baseline covariate by treatment interaction term in the model. Estimated least square means and 95% CIs for each treatment adjusting at the 25th, 50th, and 75th percentiles of the pooled baseline covariate distribution will be evaluated.

Additional subgroup analyses are planned for exploratory purposes for the change from baseline in GCA and ABC scores. An MMRM model will be used to test for subgroup interactions at the 10% significance level. In general, the model will include effects for treatment, visit week, treatment by visit week interaction, subgroup, treatment by subgroup interaction, subgroup by visit interaction and the 3-way interaction between treatment, visit and subgroup. The p-values from interaction tests will be presented, as well as the least square means and 95% CIs by treatment and visit within each subgroup. Descriptive statistics of observed values and change from baseline will also be presented by treatment and visit week within each subgroup.

A subgroup analysis will be performed for baseline GCA groups. For this analysis, patients with a baseline GCA score of greater than 70 will be classified as having “Moderate” cognitive impairment, while 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. Similar exploratory subgroup analyses may be performed for age group (either ≤ 6 years or > 6 years), language, geographic region or other baseline factors using MMRM.

A linear random coefficients model (ie, random slope and intercept for continuous time) will be fit for the primary and key secondary endpoints if appropriate. The average of the subject-specific slope estimates from the model will be compared between treatment groups using the two-sample t-test. To explore the relationship between composite scores and their components, correlations between the GCA and ABC scores (absolute value and change from baseline) and their respective domain scores will be estimated. Scatter plots will also be presented.

10.6 Pharmacokinetic, Pharmacodynamic and Health Status Outcomes

10.6.1 Pharmacokinetic Measurements and Parameters

All pharmacokinetic analyses will be performed using the Pharmacokinetic Analysis Population.

Blood samples will be collected for determination of idursulfase serum concentration-time profiles and serum pharmacokinetic parameters after IT administration. Serum samples will be assayed for idursulfase using validated analytical methods.

Pharmacokinetic parameters will be determined from serum concentration-time data using noncompartmental methods and all calculations will be based on actual sampling times. Serum concentration vs. time will be plotted for each patient. Mean serum concentration vs. time curves will also be presented by dose (5 mg, 7.5 mg, and 10 mg) and visit (Week 4, Week 24, and Week 48).

The pharmacokinetic parameters to be determined will include, but not be limited to, the following:

C_{\max}	Maximum concentration occurring at t_{\max}
t_{\max}	Time of maximum observed concentration sampled during a dosing interval
$t_{1/2}$	Terminal half-life

$AUC_{0-\infty}$	Area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration
AUC_{0-t}	Area under the curve from the time of dosing to the last measurable concentration
CL/F	Total body clearance for extravascular administration divided by the fraction of dose absorbed
V_z/F	Volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed
λ_z	First order rate constant associated with the terminal (log-linear) portion of the curve

Summary statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, minimum, and geometric mean) will be determined for all pharmacokinetic parameters and presented by dose and visit. Serum concentrations of idursulfase at each nominal sampling time will also be summarized by dose and visit using descriptive statistics.

Additionally, idursulfase concentrations in CSF will be listed by patient and summarized by study visit.

10.6.2 Pharmacodynamic Outcome

Glycosaminoglycan levels in CSF and urine and the change from baseline (Screening Visit) will be summarized by visit and treatment group. Mean (\pm SE) values will be plotted over time. A Wilcoxon Rank Sum test will be used to compare treatment groups on the CSF GAG change and percent change from baseline to the Week 52/EOS visit. Analysis of both total GAG and heparan sulfate, if available, will be performed.

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 5 levels of response. The number and percent of patients with each response will be presented by dimension at each visit. The visual analog 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 or designee 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 pivotal trial; safety data from the separate substudy will be similarly summarized or listed as relevant.

10.7.1 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 16.0 or later. Adverse events occurring on or after randomization and on or before the follow-up visit (scheduled 7 days after EOS Visit) will be summarized by treatment group, both overall and within system organ class (SOC) by preferred term. A summary of adverse events related to study drug will be presented. An adverse event will be considered related if indicated to be “possibly,” “probably,” or “definitely” related. A separate tabulation of IV Elaprase infusion-related adverse events will also be presented by treatment group. Adverse events will be tabulated by severity (mild, moderate, severe) and treatment group. In addition, those events which resulted in death or were otherwise classified as serious will be summarized and presented in a separate listing.

10.7.2 IDDD and Procedure Related Adverse Events

IDDD and procedure related adverse events will be summarized within SOC by preferred term. Separate tabulations will be provided for adverse events related to the IDDD, device surgical procedure, and IT-administration process. An overall summary of adverse events related to the IT treatment regimen (ie, related to one or more of the following: study drug, IDDD, device surgical procedure, and IT-administration process) will also be presented. IDDD and procedure related events will be analyzed in the set of treated patients in the Safety Population with the device implanted.

10.7.3 Clinical Laboratory Evaluations

Laboratory values (eg, chemistries, hematology, etc) including CSF components 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 any clinically significant post-baseline laboratory result will be presented by treatment group.

10.7.4 Electrocardiogram Evaluations

The 12-lead ECG parameters (heart rate [bpm], PR interval [msec], RR interval [msec], QRS interval [msec], QT interval [msec] and QTc [msec] interval) will be summarized in terms of absolute value and change from baseline. The corrected QT interval (QTc) will be calculated using Bazett's formula as QT divided by the square root of RR interval. The number and percentage of patients with ECG abnormalities by treatment group will be presented.

10.7.5 Vital Signs and Physical Measurements

Vital signs (temperature [C], pulse [bpm], blood pressure [systolic and diastolic, mmHg], respiration [per min], and oxygen saturation [%]) 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. Intracranial pressure measurements (cm of H₂O) and brain MRI volumes will be similarly summarized.

10.7.6 Physical Findings

Clinically significant physical and neurological examination findings will be recorded and summarized as part of the medical history or adverse event data.

10.7.7 Other Observations Related to Safety

10.7.7.1 Hearing Assessments

Any hearing assessment data will be summarized by treatment group or listed as appropriate.

10.7.7.2 Immunogenicity

Anti-idursulfase antibody formation will be monitored throughout the study for both serum and CSF. The number and percentage of patients testing anti-idursulfase antibody positive and negative at each time point will be summarized by treatment group. Titer values will be summarized using box plots over time in patients with positive antibodies at or prior to each scheduled visit. The percent inhibition and titer will be plotted similarly for patients who developed positive neutralizing antibodies at or prior to each scheduled visit.

10.7.7.3 Device Performance

SOPH-A-PORT safety and performance will be summarized for implanted patients. 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 annual event rate of IDDD failures and malfunctions will be calculated for each patient and summarized descriptively. The time from initial implant surgery to first IDDD failure and the time to first malfunction will be analyzed using the Kaplan Meier (KM) method. Patients without an IDDD failure or malfunction will be censored at their last study drug injection date. The IDDD longevity (time to failure in weeks) and time to first malfunction for all implanted IDDDs will also be plotted using the KM method. A by-patient listing of the device failure and malfunction data will be displayed.

The rate of successful IDDD injections will be calculated for each patient and summarized descriptively. The IDDD success rate will be calculated as the number of IDDD injections given as a percentage of IDDD injections given plus any malfunctions reported for inability to dose. The corresponding 95% confidence interval for the mean rate will be estimated, where appropriate. Injections that are not administered for patient-related reasons (eg, patient uncooperative, competing medical issue, etc) will not be included in the determination of the injection success rate.

10.7.8 Concomitant Medications/Therapies

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 (scheduled 7 days after EOS Visit). Concomitant medications will be mapped using the World Health Organization Drug Dictionary (WHO-DD) and summarized by the therapeutic class and preferred term for each treatment group. Concomitant therapies will be mapped using the MedDRA Version 16.0 or higher and summarized by the SOC and preferred term for each treatment group.

10.8 Statistical/Analytical Issues

10.8.1 Handling of Drop-outs and Missing Data

For randomized patients who discontinue early from the study, 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. In general, no further imputation will be used for descriptive analyses, or for primary and secondary efficacy analyses utilizing MMRM methodology. However, in the unlikely event that a patient has no post-baseline efficacy assessments, the first post-baseline assessment (Visit Week 16) will be imputed so that all randomized patients are included in MMRM analyses. The median value estimated from the pooled data at Week 16 across all randomized patients with available data will be used for this purpose. Imputation of missing primary and key secondary endpoint values at the Visit Week 52 time point will be performed in sensitivity analyses only. The planned imputation methods for sensitivity analyses are described below in Section 10.8.6.

10.8.2 Adjustment for Covariates

Analyses of the change from baseline in efficacy endpoints utilizing MMRM methodology will adjust for the baseline score of the parameter of interest as a continuous covariate in the model. As the randomization of the study is stratified by the baseline GCA classification factor (either ≤ 70 or >70), MMRM analyses will also take into account the GCA strata as a classification factor.

10.8.3 Interim Analysis

No interim analysis for treatment comparison is planned during the course of the study. The DMC will monitor safety data periodically. 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. The randomization is not stratified by center. 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 familywise type-I error rate (FWER) for the statistical tests of the primary, key secondary and other selected secondary efficacy endpoints from the MMRM analyses specified above will be controlled at 0.05. To strongly control the FWER at this level, a Gatekeeping approach will be utilized in which each family of statistical tests will be conducted in a sequential manner. The test for the primary endpoint will be conducted first at the 5% significance level and, if significant, the key secondary endpoint will be similarly tested at the 5% significance level. If these two tests are both significant, tests of the additional secondary efficacy endpoints specified below will be conducted using the Hommel closed testing procedure¹ to control the FWER.

The hypotheses for the primary, key secondary and other selected secondary efficacy endpoints will therefore be grouped into 3 ordered Gatekeeper families defined as follows:

- Family 1 (F1): Hypothesis test for primary endpoint
- Family 2 (F2): Hypothesis test for key secondary endpoint
- Family 3 (F3): Hypothesis tests for the change from baseline to Visit Week 52 for the following 6 endpoints:
 - Verbal, Nonverbal, and Spatial standard scores in cluster areas of the DAS-II
 - Communication, Daily Living Skills, and Socialization standard domain scores of the VABS-II.

The 3 sets of hypotheses in F1, F2 and F3 will be tested sequentially, with F1 and F2 serving as serial gatekeepers. The null hypothesis of no treatment difference for the primary endpoint will be tested first in F1. The statistical test for the key secondary endpoint in F2 may only be declared statistically significant if a significant result is also achieved for the primary efficacy endpoint. Since F1 and F2 each contain a single null hypothesis to be tested, each of the two tests will be conducted at the 5% significance level.

Further, only if the null hypotheses for both the primary and key secondary endpoints are rejected in F1 and F2, can any of the tests for the endpoints specified in F3 be declared statistically significant. If statistical significance is obtained for F1 and F2, the Hommel closed testing procedure¹ will be used to control the FWER within F3, with each hypothesis test in F3 equally weighted. In this case, SAS Proc MULTTEST will be used to calculate and report adjusted p-values for each endpoint in F3.

All other endpoints not included in F1, F2 or F3 above are considered supportive and any statistical tests comparing treatments will be made without adjustment for multiplicity. The resulting unadjusted 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

Sensitivity analyses for the primary and key secondary endpoints will be conducted to assess missing data assumptions in the MMRM analyses. The sensitivity analyses below will use worst-observation-carried forward (WOCF) to impute missing data at the Visit Week 52 time point. Within a given patient, the worst (lowest) observed score prior to Visit Week 52 (including the baseline value) will be used for the imputation of their missing Visit Week 52 value.

The first sensitivity analysis will compare the treatment groups at the Visit Week 52 time point using an analysis of covariance model with WOCF (ANCOVA-WOCF). The ANCOVA-WOCF model will include fixed categorical effects for treatment and baseline GCA classification factor (either ≤ 70 or > 70), and the corresponding baseline score as a continuous covariate. The treatment difference in least squares means, 95% CI and p-value from this model will be compared to the corresponding inferential statistics at Visit Week 52 from the primary or key secondary MMRM model. As a second sensitivity analysis, the Wilcoxon Rank-Sum test with WOCF (WRS-WOCF) will be used to compare treatment groups at Visit Week 52. This test is based on the ranked changes from baseline after imputation of the Visit Week 52 value using WOCF.

If the model for the primary or key secondary endpoint fails to converge using an unstructured covariance matrix, an AR(1) covariance structure will be used. In this case, additional covariance structures will be tried as sensitivity analyses to assess the robustness of the results, including compound symmetric and Toeplitz structures.

Additional sensitivity analyses and imputation methods will be specified in the statistical analysis plan.

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 Lead 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. Unanticipated adverse device effects will be reported to regulatory agencies by the device manufacturer 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 guardian(s)/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(s). The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent (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 legally authorized representative(s). The original signed and dated consent document will be retained by the Investigator.

The Investigator will not undertake any measures specifically required solely for the clinical study until valid consent (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. The patient number (and in some regions, patient initials) will be recorded in the CRF, 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 CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

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

11.7 Case Report Forms and Study Records

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

11.7.1 Critical Documents

Before the Sponsor initiates the trial (ie, obtains informed consent [and assent, if applicable] from the first patient's parent[s] and/or legally authorized guardian(s), it is the responsibility of the Investigator to ensure that the following documents are available to the Sponsor or its 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 to subjects regarding 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, if applicable)
- 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 Monitoring Committee

An independent, external DMC 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 DMC will be notified of all IDDD failures and IDDD-related complications at times defined in the DMC charter.

The DMC will consist of a biostatistician and two clinical experts. The DMC will adhere to a prospectively determined charter, which will be written by Shire or its designee and approved by the DMC. The charter will define the responsibilities of the DMC and Shire, 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 DMC periodically for review.

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

11.9 Device Failure Review Process

The final cause for SOPH-A-PORT Mini S device failures will be reviewed by Shire by examining the device failure information in the clinical database, safety database, and manufacturer investigation of returned SOPH-A-PORT Mini S 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, DMC, 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. 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, CRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the CRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

11.13 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 the Sponsor. Shire or its designee will be responsible for performing study data management activities.

Adverse events will be coded using MedDRA. Concomitant medication will be coded using the 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, provided Shire a copy of the draft document intended for publication, and obtained Shire's written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential.

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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	Week 2 (+7 days) ^u Pre-surgery, Surgery, Follow-up, and Post-op Recovery ^o			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 ¹	IT Injection	Follow- Up ^r	Telephone	
Informed Consent ^a	●									
Review of Study Entry Criteria	●									
Medical History	●									
Hunter Syndrome Diagnosis and Genotype	● ^t									
Echocardiogram ^k	●									
Physical and Neurological Examination	●		● ^s		● ¹	●		●	●	
Height and Weight	●		● ^s			● ^d			●	
Head Circumference	●					● ^d			●	
Hearing Assessment	●					● ⁿ			●	
Neurodevelopmental Assessment	●					● ⁿ			●	
12-lead ECG	●		● ^s			●	● ^{d,f}		●	
Vital Signs	●		● ^s	●		●	● ^h		●	
Clinical Laboratory Tests (Hematology, Serum Chemistry, Urinalysis)	●		● ^s			● ^d			●	
Coagulation Tests ^q			●							
Urine GAG and creatinine	●					● ^d			●	
Anti-Idursulfase Antibody Testing	●					● ^d			●	
General Anesthesia	●			●					●	
Brain MRI	●								●	
ICP Measurement (by lumbar	●								●	

	Month -1	Month 0	Months 1 to 12						Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Randomization	Week 2 (+7 days) ^u Pre-surgery, Surgery, Follow-up, and Post-op Recovery ^o			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 ^l	IT Injection	Follow- Up ^r		Telephone
puncture)										
CSF Sample Collection ^m	• ^j			•			• ^{e,m}		•	
Randomization		• ^b								
IDDD Implantation				•						
X-ray (Additional imaging may be required) ^c				•					•	
idursulfase-IT Injection							• ^p			
Serum Sample for PK							• ^g			
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.

- ^a Informed consent (and patient assent, if applicable) must be obtained from the patient's parent(s)/legally authorized guardian(s) before beginning Screening assessments.
- ^b Patients will be randomized after they have completed Screening assessments and met all eligibility criteria. The day of randomization is Day 0.
- ^c X-rays may be performed to check placement of the device, and as needed, throughout the study.
- ^d The assessments indicated will be performed at 3-month intervals, ie, at IT Dosing Weeks 4, 16, 28, and 40.
- ^e The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.
- ^f The 12-lead ECG is to be performed within 4 hours after IT administration of study drug at Weeks 4, 16, 28, and 40.
- ^g Serum samples for PK analysis will be obtained at IT Dosing Weeks 4, 24, and 48. Samples will be collected within 15 minutes (± 5 minutes) prior to intrathecal administration of idursulfase-IT and at 30 minutes (± 5 minutes), 60 minutes (± 5 minutes), 120 minutes (± 5 minutes), 4 hours (± 5 minutes), 6 hours (± 5 minutes), 8 hours (± 15 minutes), 12 hours (± 15 minutes), 24 hours (± 15 minutes), 30 hours (± 15 minutes), 36 hours (± 15 minutes) after the start of intrathecal administration.
- ^h Patients will remain under observation in the hospital setting (eg, may include infusion center, PACU (recovery suite), observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (± 10 minutes) in

	Month -1	Month 0	Months 1 to 12						Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Randomization	Week 2 (+7 days) ^u Pre-surgery, Surgery, Follow-up, and Post-op Recovery ^o			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 ^l	IT Injection	Follow-Up ^r	Telephone	

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, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the Investigator, patients may leave the hospital setting (with exception of Visit Weeks 4, 24, and 48 at which serial blood sampling for pharmacokinetic evaluation is planned). The patient may need to be examined the following day (See Follow-up, Section 8.3.2.3)

- ⁱ From Week 28 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.
- ^j The CSF sample will be obtained via lumbar puncture and while the patient is under general anesthesia.
- ^k 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.
- ^l The assessments indicated will be performed prior to discharge. It is expected that, for most patients, post-surgical follow-up will occur within Week 2 (ie, within 1 to 2 days of surgery).
- ^m Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard laboratory parameters (chemistries, cell counts), as well as concentration of idursulfase enzyme, GAG, albumin, and presence of idursulfase-specific antibodies. Analyses of CSF samples for antibodies and albumin will be performed at Screening, IT Dosing Weeks 4, 16, 28, and 40, and at Week 52 (EOS).
- ⁿ These neurodevelopmental and hearing assessments will be performed at IT Dosing Weeks 16, 28, 40 (±7 days).
- ^o At least 14 days will be allowed for recovery following the placement of the IDDD before the administration of the first IT dose.
- ^p 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.
- ^q Pre-surgery coagulation tests will be performed by the local laboratory.
- ^r The follow-up visit is to occur on the day after IT administration during the first 6 months of IT treatment (ie, at Weeks 4, 8, 12, 16, 20, 24). For the latter 6 months of treatment with idursulfase-IT (ie, from Week 28 onward) and in the absence of any safety concerns, patients may complete the safety follow-up visit on the same day as IT administration prior to discharge.
- ^s The assessments indicated do not need to be repeated if completed as part of Screening assessments within 7 days prior to surgery.
- ^t The results of patients' genotype analyses must be known prior to randomization (see Section 7.3.1).
- ^u Patients in the USA who were randomized in the pivotal study prior to FDA authorization of investigational use of the SOPH-A-PORT Mini S IDDD and treated with idursulfase-IT via lumbar puncture will have the assessments originally planned at Week 2 [+7 days] performed at the time of the delayed device implantation surgery.

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,	Week 2 (+7 days)	Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 (± 7 days)	Weeks 8, 12, 20, 24, 32, 36, 44, 48	Week 52 End of Study (EOS) (±7 days)	
Assessment	Day -28 to Day -1	Day 0	Telephone		Telephone		Telephone	
Informed Consent ^a	•							
Review of Study Entry Criteria	•							
Medical History	•							
Hunter Syndrome Diagnosis and Genotype	• ^f							
Echocardiogram ^d	•							
Physical and Neurological Examination	•			•		•		
Height and Weight	•			•		•		
Head Circumference	•			•		•		
Hearing Assessment	•			• ^e		•		
Neurodevelopmental Assessment	•			• ^e		•		
12-lead ECG	•			•		•		
Vital Signs	•			•		•		
Clinical Laboratory Tests (Hematology, Serum Chemistry, Urinalysis)	•			•		•		
General Anesthesia	•					•		
Urine GAG and creatinine	•			•		•		
Anti-idursulfase Antibody Testing (serum)	•			•		•		
Anti-idursulfase Antibody Testing	•					•		
Brain MRI	•					•		
ICP measurement (by lumbar puncture)	•					•		
CSF Sample Collection ^c	•					•		
Randomization		• ^b						
Health status Questionnaire	•					•		
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	•	•	•	•	•	•	•	

	Month -1	Month 0	Months 1 to 12			Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Randomization,	Week 2 (+7 days)	Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 (± 7 days)	Weeks 8, 12, 20, 24, 32, 36, 44, 48	Week 52 End of Study (EOS) (±7 days)	7 (±2) Days Post EOS
Assessment	Day -28 to Day -1	Day 0	Telephone		Telephone		Telephone
Adverse Events	•	•	•	•	•	•	•
<p>Abbreviations: CSF = cerebrospinal fluid; ECG = electrocardiogram; GAG = glycosaminoglycan; ICP = intracranial pressure; MRI = magnetic resonance imaging.</p> <p>^a Informed consent (and patient assent, if applicable) must be obtained from the patient's parent(s)/legally authorized guardian(s) before beginning Screening procedures.</p> <p>^b Patients will be randomized after they have completed Screening assessments and met all eligibility criteria. The day of randomization is Day 0.</p> <p>^c 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), as well as concentration of idursulfase enzyme, GAG, albumin, and presence of idursulfase-specific antibodies.</p> <p>^d 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.</p> <p>^e These neurodevelopmental and hearing assessments will be performed at Weeks 16, 28, 40 (±7 days).</p> <p>^f The results of patients' genotype analyses must be known prior to randomization (see Section 7.3.1).</p>							

Appendix 3 Schedule of Events for Patients Enrolled in the Substudy

Assessment	Month -1	Month 0	Months 1 to 12						Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Enrollment	Week 2 (+7 days) Pre-surgery, Surgery, Follow-up, and Post-op Recovery ^o			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
	Day -28 to Day -1	Day 0	Pre- Surgery	Surgery	Follow- Up	Pre-Tx ^l	IT Injection	Follow- Up ^r		Telephone
Informed Consent ^a	•									
Review of Study Entry Criteria	•									
Medical History	•									
Hunter Syndrome Diagnosis and Genotype	• ^t									
Echocardiogram ^k	•									
Physical and Neurological Examination	•		• ^s		• ^l	•		•	•	
Height and Weight	•		• ^s			• ^d			•	
Head Circumference	•					• ^d			•	
Hearing Assessment	•					• ⁿ			•	
Neurodevelopmental Assessment	•					• ⁿ			•	
12-lead ECG	•		• ^s			•	• ^{d,f}		•	
Vital Signs	•		• ^s	•		•	• ^h		•	
Clinical Laboratory Tests (Hematology, Serum Chemistry, Urinalysis)	•		• ^s			• ^d			•	
Coagulation Tests ^q			•							
Urine GAG and creatinine	•					• ^d			•	
Anti-Idursulfase Antibody Testing	•					• ^d			•	
General Anesthesia	•			•					•	
Brain MRI	•								•	
ICP Measurement (by lumbar puncture)	•								•	
CSF Sample Collection ^m	• ^j			•			• ^{e,m}		•	
Documentation of Entry		• ^b								

	Month -1	Month 0	Months 1 to 12					Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Enrollment	Week 2 (+7 days) Pre-surgery, Surgery, Follow-up, and Post-op Recovery ^o			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 ¹	IT Injection	Follow- Up ^r	Telephone
Criteria									
IDDD Implantation				•					
X-ray (Additional imaging may be required) ^c				•				•	
idursulfase-IT Injection							• ^p		
Serum Sample for PK							• ^g		
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.

- ^a Informed consent must be obtained from the patient's parent(s)/legally authorized guardian(s) before beginning Screening assessments.
- ^b Patients will be enrolled into the substudy only after they have completed Screening assessments and met all eligibility criteria. For these patients, the day of enrollment is considered Day 0. Note that once a patient is enrolled in the substudy, he cannot later be randomized into the pivotal study.
- ^c X-rays may be performed to check placement of the device, and as needed, throughout the study.
- ^d The assessments indicated will be performed at 3-month intervals, ie, at IT Dosing Weeks 4, 16, 28, and 40.
- ^e The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.
- ^f The 12-lead ECG is to be performed within 4 hours after IT administration of study drug at Weeks 4, 16, 28, and 40.
- ^g Serum samples for PK analysis will be obtained at IT Dosing Weeks 4, 24, and 48. Samples will be collected within 15 minutes (± 5 minutes) prior to intrathecal administration of idursulfase-IT and at 30 minutes (± 5 minutes), 60 minutes (± 5 minutes), 120 minutes (± 5 minutes), 4 hours (± 5 minutes), 6 hours (± 5 minutes), 8 hours (± 15 minutes), 12 hours (± 15 minutes), 24 hours (± 15 minutes), 30 hours (± 15 minutes), 36 hours (± 15 minutes) after the start of intrathecal administration.
- ^h Patients will remain under observation in the hospital setting (eg, may include infusion center, PACU (recovery suite), observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (± 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, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable

	Month -1	Month 0	Months 1 to 12						Month 13	Follow-up
	Weeks -4 to -1 Screening Day -28 to -1	Week 0 Enrollment	Week 2 (+7 days) Pre-surgery, Surgery, Follow-up, and Post-op Recovery ^o			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 ⁱ	IT Injection	Follow-Up ^r	Telephone	

by the Investigator, patients may leave the hospital setting (with exception of Visit Weeks 4, 24, and 48 at which serial blood sampling for pharmacokinetic evaluation is planned). The patient may need to be examined the following day (See Follow-up, Section 8.3.2.3)

- ⁱ From Week 28 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.
- ^j The CSF sample will be obtained via lumbar puncture and while the patient is under general anesthesia.
- ^k 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.
- ^l The assessments indicated will be performed prior to discharge. It is expected that, for most patients, post-surgical follow-up will occur within Week 2 (ie, within 1 to 2 days of surgery).
- ^m Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard laboratory parameters (chemistries, cell counts), as well as concentration of idursulfase enzyme, GAG, albumin, and presence of idursulfase-specific antibodies. Analyses of CSF samples for antibodies and albumin will be performed at Screening, IT Dosing Weeks 4, 16, 28, and 40, and Week 52 (EOS).
- ⁿ The neurodevelopmental and hearing assessments will be performed at IT Dosing Weeks 16, 28, 40 (± 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.
- ^o At least 14 days will be allowed for recovery following the placement of the IDDD before the administration of the first IT dose.
- ^p 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.
- ^q Pre-surgery coagulation tests will be performed by the local laboratory.
- ^r The follow-up visit is to occur on the day after IT administration during the first 6 months of IT treatment (ie, at Weeks 4, 8, 12, 16, 20, 24). For the latter 6 months of treatment with idursulfase-IT (ie, from Week 28 onward) and in the absence of any safety concerns, patients may complete the safety follow-up visit on the same day as IT administration prior to discharge.
- ^s The assessments indicated do not need to be repeated if completed as part of Screening assessments within 7 days prior to surgery.
- ^t The results of patients' genotype analyses must be known prior to enrollment (see Section 7.3.1).

Appendix 4 Expected Adverse Device Effects

A list of the adverse effects expected with the SOPH-A-PORT Mini S is reproduced below from the device's IFU.

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 Amendment Summary of Changes

AMENDMENT SUMMARY AND RATIONALE

Clinical protocol HGT-HIT-094 has been amended from the previous version as follows:

- To allow for the enrollment of approximately 48 patients based on a blinded variability assessment (BVA). In accordance with the study protocol, after 35 patients were randomized, and prior to enrollment closure, a blinded assessment of overall variability for the primary and key secondary endpoints was made by estimating the pooled standard deviation (SD) for each endpoint. The BVA was performed by an external, independent statistician who is not involved in the final analysis of this study. Based on this assessment, it did not appear that the variability was consistent with the original assumption used in the sample size calculation; therefore, the sample size was increased from 42 to approximately 48 patients. The sample size re-calculation was identical to the original calculation except that the estimate of the common standard deviation used for the primary and/or key secondary endpoint was revised upward based on the pooled SD assessment. As there was no treatment comparison involved, no inflation of the type-I error from this procedure was expected, and no adjustment to the significance levels for the final analysis was necessary. The results of the BVA support the increase in sample size being implemented by this amendment. However, given that uncertainty around the variance estimate remains, a second BVA using the same approach as specified above is planned to confirm it after approximately 27 patients complete the Week 52 primary endpoint assessment. Based on this second blinded assessment, the sample size may be increased to a maximum of 54 patients while maintaining the 2:1 allocation ratio.
- To remove the portion of inclusion criterion #1 requiring that Spanish-speaking patients who are to be assessed using the Spanish version of the DAS-II be <7 years 8 months of age at the time of informed consent. Because a Spanish version of the DAS-II School Age Years instrument has become available for use in the study, this restriction is no longer necessary.
- To align the protocol text with changes (clarification concerning conduct of the follow-up contact by telephone and change to medical monitor contact information) which were implemented previously by administrative memo.
- To modify the planned statistical analysis to allow for the exploratory subgroup analyses of efficacy by language and geographic region requested by the FDA.
- To update text pertaining to the SOPH-A-PORT Mini S IDDD for consistency with other Shire protocols utilizing this device for intrathecal drug delivery.
- To clarify aspects of the study schedule pertaining to analysis of CSF and serum samples
- To clarify text concerning the management of infusion-related reactions.
- To include the EudraCT number on the protocol cover page.

DETAILED SUMMARY OF CHANGES FOR THE AMENDMENT 4

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

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

Change: addition of EudraCT number
Section impacted by this change: Cover page
Revised Text: EudraCT Number: 2013-002885-38
Other sections impacted by this change: None

Change: change to medical monitor contact
Section impacted by this change: Cover page
Revised Text: Medical Monitor: PPD [REDACTED], MD, PhD PPD [REDACTED], DO
Other sections impacted by this change: 7.14.5.2 Reporting Serious Adverse Events

Change: clarification concerning study population
Section impacted by this change: Synopsis
Revised Text: Pivotal study – approximately 48 42 male patients (about 28 32 treated, 14 16 untreated) are planned. Substudy - enrollment of patients below 3 years of age into the separate substudy will be considered additional to the 42 number of patients planned for the pivotal study, and will conclude when enrollment of patients in the pivotal study closes.
Other sections impacted by this change: 5.1 Study Population

Change: clarification to study design
Section impacted by this change: Synopsis
Revised Text: The pivotal study design is “no IT treatment-controlled”. Approximately 48 patients will be randomized in a 2:1 ratio to IT treatment or no IT treatment arms. in that 28 patients are assigned randomly to receive IT treatment and 14 patients are assigned randomly to participate without receiving IT treatment.
Other sections impacted by this change: 4.1 Overall Study Design and Plan

Change: clarification concerning performance of follow-up telephone contact
Section impacted by this change: Synopsis
Revised Text: All Patients will complete EOS assessments at Week 52 (Visit Month 13) and will participate in a follow-up contact (by telephone) approximately 7 days after the EOS visit. (Note that for those patients who enroll in extension study SHP-609-302 within the 7 ±2 day window of the EOS visit the follow-up contact is not required. If, however, a patient is not enrolled in the SHP-609-302 study within the 7 ±2 day window of the EOS visit, then the follow-up contact should be completed.)
Other sections impacted by this change: 7 Study Procedures , 8.5.1 Patients in the Pivotal Study and

Substudy

Change: Elimination of age restriction for inclusion of Spanish-speaking patients

Section impacted by this change: [Synopsis](#)

Revised Text:

1. The patient is male and is ≥ 3 and < 18 years of age at the time of informed consent. ~~Spanish-speaking patients who are to be assessed using the Spanish version of the DAS-II Early Years must be < 7 years 8 months of age at the time of informed consent.~~

Other sections impacted by this change: [5.2.1](#) Inclusion Criteria for the Pivotal Study

Change: Change in cognitive testing of Spanish-speaking patients

Section impacted by this change: [Synopsis](#)

Revised Text:

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. ~~Only the DAS-II Early Years (Spanish version) will be used for assessment of eligible Spanish-speaking patients.~~

Other sections impacted by this change: [7.9.1](#) Neurodevelopmental assessment Tools

Change: Clarification concerning the IDDD

Section impacted by this change: [6.1.2](#) Intrathecal Drug Delivery Device

Revised Text:

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 European Union (EU). The SOPH-A-PORT Mini S is a system intended for implantation by physicians. The SOPH-A-PORT Mini S, once implanted, allows healthcare personnel to administer drugs indicated for intrathecal delivery intermittently over a long period of time. The device is CE Marked in the European Union (EU) and is considered investigational in non-EU countries.~~

Other sections impacted by this change: None

Change: Clarification concerning infusion-related reactions

Section impacted by this change: [6.6.1](#) Infusion Reactions and Management

Revised Text:

Infusions of proteins can be associated with reactions to the infusion that may or may not be immune mediated (**hypersensitivity reactions**). Thus, potential reactions to the infusion of an investigational product, **including idursulfase-IT**, are unpredictable. **It is often difficult to clinically distinguish infusion reactions from hypersensitivity reactions. Symptoms may include headache, fever, sensory paresthesias (including feeling of warmth, tingling, or pain), rash, pruritus, or autonomic symptoms, such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental status or level of consciousness that are not caused by pre-medication may either occur acutely**

or develop post-injection over time.

The management of infusion reactions and hypersensitivity reactions is similar. The following steps may be taken, at the discretion of the Investigator, in the event of a suspected infusion related/hypersensitivity reaction and the management of such reactions should be based on the severity of the reaction:

- **Treatment with medications such as antihistamines, antipyretics, and/or corticosteroids**
- **Stopping and resuming treatment**
- **Pretreatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required**

Infusion-related reactions have been observed in patients receiving IV enzyme replacement therapy (ERT) 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 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.~~ **The ongoing** clinical studies with idursulfase-IT have not revealed **adverse events of the severity and frequency** 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.

Other sections impacted by this change: None

Change: Clarification to activity restrictions for patients with an implanted IDDD

Section impacted by this change: [6.7.3 Patient Activity Restrictions](#)

Revised Text:

Please refer to the SOPH-A-PORT Mini S IFU for details regarding patient activity restrictions for patients to be implanted with this device. **Activities that may include sudden, excessive, or repetitive bending, twisting, bouncing, or stretching can damage or dislodge IDDD components and should be avoided.**

Other sections impacted by this change: None

Change: Clarification concerning treatment compliance

Section impacted by this change: [6.8 Treatment Compliance](#)

Revised Text:
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, **and have completed training with the SOPH-A-PORT Mini S**. Please refer to the IFU for further details.

Other sections impacted by this change: None

Change: Clarification concerning serum albumin assessment

Section impacted by this change: 7.8.2 CSF and Serum Albumin

Revised Text:
Albumin levels will be measured in samples of CSF ~~and serum~~ (refer to the SOE for the pivotal study (Appendix 1 and Appendix 2) and separate substudy (Appendix 3) to monitor the permeability of the blood-brain barrier. **Measurement of albumin levels in serum is included in the panel of clinical laboratory tests** (Table 7-2).

Other sections impacted by this change: Appendix 1 Schedule of Events for Patients Randomized to Treatment in the Pivotal Study, Appendix 2 Schedule of Events for Patients Randomized to No Treatment in the Pivotal Study, Appendix 3 Schedule of Events for Patients Enrolled in the Substudy

Change: Clarification to CSF assessment

Section impacted by this change: 7.11.10 Cerebrospinal Fluid Assessments

Revised Text:
Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard safety laboratory parameters (chemistries [~~including protein, glucose~~], cell counts), albumin, GAG, and concentration of idursulfase enzyme.

Other sections impacted by this change: None

Change: Clarification to study activities

Section impacted by this change: 8.1.1 All Patients in the Pivotal Study and Substudy

Revised Text:

- CSF sample collection (by lumbar puncture). **CSF samples will be used to analyze standard laboratory parameters (chemistries, cell counts), as well as GAG, concentration of idursulfase enzyme, albumin, and presence of idursulfase-specific antibodies.**
- ~~Albumin (serum and CSF)~~

Other sections impacted by this change: 8.3.2.1 Pre-treatment 8.4.1 Patients in the IT Treatment Group of the Pivotal Study and All Patients in the Substudy, 8.4.2 Patients in the No IT Treatment Group of the Pivotal Study

Change: Change on sample size based on results of a planned blinded variability assessment

Section impacted by this change: 10.2 Determination of Sample Size

Revised Text:
Using a 2:1 allocation ratio, a sample size of ~~42~~ **approximately 48** randomized patients (**about 28 32** IT treated patients, ~~44 16~~ no IT control patients) will yield 80% power to detect a clinically meaningful mean treatment difference of 11 points in the primary endpoint, GCA change from baseline to Visit Week 52. This calculation further assumes a common standard deviation for the change from baseline of ~~10~~ **11.6** points, a

type-I error rate of 0.05 for a two-sided two-sample t-test, with approximately up to ~~20~~ **10%** missing an assessment at Visit Week 52. Given this sample size, and conditional on rejection of the null hypothesis for the primary endpoint, the power would be 80% to detect a ~~clinically meaningful~~ mean difference of ~~14.5~~ **10** points in the key secondary endpoint, assuming a common standard deviation for the change from baseline of ~~13.5~~ **10.5** points for a two-sided two-sample t-test with a significance level of 5% and ~~20~~ **10%** missing an assessment at Visit Week 52. The variance estimate for this sample size was determined based on a blinded variability assessment (BVA) performed as specified in the prior protocol version (Amendment 3); refer to [Appendix 5](#) for details. Given that uncertainty around this variability estimate remains, a second BVA using the same approach as specified in [Appendix 5](#) is planned to confirm the estimate after approximately 27 patients complete the Week 52 primary endpoint assessment. Based on this second blinded assessment, the sample size may be increased to a maximum of 54 patients while maintaining the 2:1 allocation ratio.

~~After approximately 36 patients have been randomized, and prior to enrollment closure, a blinded assessment of overall variability for the primary and key secondary endpoints will be made by estimating the pooled standard deviation (SD) for each endpoint. The blinded variability assessment will be performed by an external, 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. The sample size re-calculation in this case would be identical to the original calculation except that the estimate of the common standard deviation used for the primary and/or key secondary endpoint would be revised upward based on the pooled SD assessment. As there is no treatment comparison involved, no inflation of the type I error from this procedure is expected, and no adjustment to the significance levels for the final analysis is necessary.~~

Other sections impacted by this change: None

Change: Clarifications to exploratory analyses

Section impacted by this change: [10.5.4 Exploratory Analyses](#)

Revised Text:

A subgroup analysis will be performed for baseline GCA groups. For this analysis, patients with a baseline GCA score of greater than 70 will be classified as having “Moderate” cognitive impairment, while 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. Similar exploratory subgroup analyses may be performed for age group (either ≤6 years or >6 years), native language, **geographic region** (~~Spanish versus English speaking region~~) or other baseline factors using MMRM.

A linear random coefficients model (ie, random slope and intercept for continuous time) will be fit for the primary and key secondary endpoints if appropriate. The average of the subject-specific slope estimates from the model will be compared between treatment groups using the two-sample t-test. To explore the relationship between composite scores and their components, correlations between the GCA and ABC scores (absolute value and change from baseline) and their respective domain scores will be estimated. Scatter plots will also be presented.

Other sections impacted by this change: None

Change: Clarification to analysis of IDDD performance

Section impacted by this change: [10.7.7.3 Device Performance](#)

Revised Text:

~~The number and 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 number and proportion of patients who had no failed injection attempts during the study and the total number of successful injections will also be summarized. Injections not given for patient reasons (eg, patient uncooperative, competing medical issue, etc) will not be included in the determination of these estimates.

The rate of successful IDDD injections will be calculated for each patient and summarized descriptively. The IDDD success rate will be calculated as the number of IDDD injections given as a percentage of IDDD injections given plus any malfunctions reported for inability to dose. The corresponding 95% confidence interval for the mean rate will be estimated, where appropriate. Injections that are not administered for patient-related reasons (eg, patient uncooperative, competing medical issue, etc) will not be included in the determination of the injection success rate.

Other sections impacted by this change: None

Change: Clarification concerning serum albumin assessment

Section impacted by this change: [Appendix 1](#) Schedule of Events for Patients Randomized to Treatment in the Pivotal Study

Revised Text:

Serum albumin

Other sections impacted by this change: [Appendix 2](#) Schedule of Events for Patients Randomized to No Treatment in the Pivotal Study, [Appendix 3](#) Schedule of Events for Patients Enrolled in the Substudy

Change: Change to footnote

Section impacted by this change: [Appendix 1](#) Schedule of Events for Patients Randomized to Treatment in the Pivotal Study

Revised Text:

Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard laboratory parameters (chemistries, cell counts), **as well as albumin, GAG**, concentration of idursulfase enzyme, **GAG, albumin**, and presence of idursulfase-specific antibodies. Analyses of CSF samples for antibodies and albumin will be performed at **Screening**, IT Dosing Weeks 4, 16, 28, and 40, **and at Week 52 (EOS)**.

Other sections impacted by this change: [Appendix 3](#) Schedule of Events for Patients Enrolled in the Substudy

Appendix 6 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

Amendment 4

Final Date: 21 December 2015

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 Medical Monitor

PPD _____ PPD _____
Signature **Date**

PPD _____, DO, PPD _____
Printed Name, Title