Clinical Study Protocol

NCT Number : NCT01506141

Title: An Open-Label Extension of Study HGT-HIT-045 Evaluating Long-Term Safety and Clinical Outcomes of Intrathecal Idursulfase-IT Administered in Conjunction with Intravenous Elaprase® in Pediatric Patients with Hunter Syndrome and Cognitive Impairment

Study Number: HGT-HIT-046

Document Version and Date: Amendment 13, 17 August 2021

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

Clinical Trial Protocol: HGT-HIT-046

Study Title:	An Open-Label Extension of Study HGT-HIT-045 Evaluating Long-Term Safety and Clinical Outcomes of Intrathecal Idursulfase-IT Administered in Conjunction with Intravenous Elaprase® in Pediatric Patients with Hunter Syndrome and Cognitive Impairment
Study Number:	HGT-HIT-046
Study Phase:	I/II
Product Name:	Idursulfase for Intrathecal Administration (idursulfase-IT [HGT-2310])
Device(s) Name(s):	SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire PORT-A-CATH® II Low Profile™ *Intrathecal Implantable Access System*
IND Number:	100,610
EudraCT Number:	2011-000212-25
Indication:	Hunter syndrome with cognitive impairment
Sponsor:	Shire Human Genetic Therapies (HGT), Inc.
Sponsor Contact:	300 Shire Way Lexington, MA 02421
Medical Monitor:	[redacted], DO

	Date
Original Protocol:	29 April 2009
Amendment 1	03 May 2010
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Amendment 8	16 July 2015
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Amendment 10	17 January 2018
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Amendment 12	29 May 2018
Amendment 13	17 August 2021

PROTOCOL SIGNATURE PAGE

I have read Protocol HGT-HIT-046 Amendment 13, "An Open-Label Extension of Study HGT-HIT-045 Evaluating Long-Term Safety and Clinical Outcomes of Intrathecal Idursulfase-IT Administered in Conjunction with Intravenous Elaprase® in Pediatric Patients with Hunter Syndrome and Cognitive Impairment," and the current edition of the idursulfase-IT investigator's brochure.

I agree to conduct the study as outlined herein.

Signatory

Investigator

Signature	**Date**
Print Name	**Institution**

I have read and approved this protocol amendment.

Signatory

Shire Medical Monitor

[redacted]

Date

[redacted], DO, [redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

Term	Definition
ABR	auditory brainstem response
AE	adverse event
AUC	area under the curve
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency, Second Edition
BSID-III	Bayley Scales of Infant Development, Third Edition
BRIEF	Behavior Rating Inventory of Executive Function
BRIEF-P	Behavior Rating Inventory of Executive Function-Preschool
BW	body weight
CBC	complete blood count
CFR	Code of (United States) Federal Regulations
CI	confidence interval
CL	clearance
Cmax	maximum concentration
CNS	central nervous system
COVID-19	2019 novel coronavirus disease
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSF	cerebrospinal fluid
DAS-II	Differential Ability Scales, Second Edition
DS	dermatan sulfate
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
ERT	enzyme replacement therapy
EU	European Union
FDA	(United States) Food and Drug Administration
GAG	glycosaminoglycan
GCA	General Conceptual Ability
GCP	Good Clinical Practices
HGT	Human Genetic Therapies
HS	heparan sulfate
IC	intracranial
ICH	International Conference on Harmonisation
ICP	intracranial pressure
ICV	intracerebroventricular
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IRB	Institutional Review Board
Ig	immunoglobulin
IKO	idursulfase knockout

Term	Definition
IND	Investigational New Drug Application
IT	intrathecal
IV	intravenous
kg	kilogram(s)
LC-MS/MS	liquid chromatography tandem mass spectrometry
M6P	mannose-6-phosphate
MDR	Medical Device Report
MedDRA	Medical Dictionary for Regulatory Activities
MPS II	Mucopolysaccharidosis II
MRI	magnetic resonance imaging
MRT	mean residence time
N	normal
NCI CTC	National Cancer Institute Common Terminology Criteria
NCS	not clinically significant
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PDMS-2	Peabody Developmental Motor Scales-2
PET	positron emission tomography
PK	pharmacokinetic(s)
PORT-A-CATH	PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System
PT	prothrombin time
PTT	partial thromboplastin time
QTc	corrected QT interval
REB	Research Ethics Board
SAE	serious adverse event
SAP	Statistical Analysis Plan
SIB-R	Scale of Independent Behavior-revised
SNC	Special Nonverbal Composite
SOC	system organ class
SOPH-A-PORT Mini S	SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire
T4	thyroxine
$t_{1/2}$	terminal elimination half-life
T_{max}	time to maximum concentration
UADE	Unanticipated Adverse Device Effect
US	United States
Vss	apparent volume of distribution at steady state
WBC	white blood cell (count)

1 PROTOCOL SYNOPSIS

Protocol Title:

An Open-Label Extension of Study HGT-HIT-045 Evaluating Long-Term Safety and Clinical Outcomes of Intrathecal Idursulfase-IT Administered in Conjunction with Intravenous Elaprase® in Pediatric Patients with Hunter Syndrome and Cognitive Impairment

Protocol Number: HGT-HIT-046 Amendment 13

Phase of Development: I/II

Investigational Product:

idursulfase for intrathecal administration (idursulfase-IT, HGT-2310)

Name(s) of Intrathecal Drug Delivery Device(s):
SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire (SOPH-A-PORT Mini S)

PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System (PORT-A-CATH)

Study Objectives:

The primary objective of this study is:

- To collect long-term safety data in pediatric patients with Hunter syndrome and cognitive impairment who are receiving intrathecal idursulfase-IT and intravenous (IV) Elaprase® enzyme replacement therapy (ERT)

The secondary objectives of this study are:

- To determine the serum pharmacokinetic (PK) profile of idursulfase when administered as intrathecal idursulfase-IT and in conjunction with Elaprase
- To determine the effect of intrathecal idursulfase-IT, given in conjunction with Elaprase, on cerebrospinal fluid (CSF) biomarkers (eg, total glycosaminoglycan [GAG] including heparan sulfate [HS]/dermatan sulfate [DS])
- To determine the effects of intrathecal idursulfase-IT, given in conjunction with Elaprase, on urinary GAG

The exploratory objectives of this study are:

- To evaluate the long-term effects of intrathecal idursulfase-IT, given in conjunction with Elaprase, on clinical parameters (eg, physiological assessments, neurocognitive assessments, neurologic function, and brain structure volumes)
- To evaluate the long-term effects of intrathecal idursulfase-IT, given in conjunction with Elaprase, on functional activities of daily living, as determined by the Scales of Independent Behavior-Revised (SIB-R)
- To explore potential relationships between biomarkers and central nervous system (CNS) symptomatology
- To determine whether monthly idursulfase-IT administrations results in accumulation of idursulfase within the CSF compartment by measuring idursulfase levels in CSF immediately prior to idursulfase-IT administration
- To determine the safety and performance of the SOPH-A-PORT Mini S

Study Endpoints:

The primary endpoints of this study are:

- Safety of intrathecal idursulfase-IT administration. Safety will be measured by adverse events (AEs, by type and severity), changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, urinalysis), 12-lead electrocardiogram (ECG), CSF chemistries (contingent on sample availability; cell counts, glucose, and protein), anti-idursulfase antibodies and antibodies having enzyme neutralizing activity in CSF and serum

The secondary endpoints include:

- Serum idursulfase concentration-time profiles and serum PK parameters of idursulfase, administered as intrathecal idursulfase-IT and in conjunction with Elaprase
- Change from baseline in CSF biomarkers (eg, GAG [HS/DS])
- Change from baseline in urinary GAG

The exploratory endpoints for this study include:

- Change from Baseline in additional clinical parameters (eg, physiological assessments, standardized neurocognitive assessments, neurologic function, brain magnetic resonance imaging [MRI])
- Change from Baseline in functional activities of daily living parameters
- Levels of idursulfase in CSF immediately prior to idursulfase-IT administration

Number of Patients Planned and Duration of Patient Participation:

Patients who participated in Study HGT-HIT-045 and completed the HGT-HIT-045 end-of-study (EOS) evaluations, and meet all criteria for inclusion in this extension study will be eligible for enrollment. Up to 15 patients are expected.

Patients will continue treatment in this extension study, unless they discontinue the study or Shire discontinues the study, for a maximum duration of 14 years of treatment across Studies HGT-HIT-045 and/or HGT-HIT-046.

The study will conclude after the last patient has completed his last visit.

Treatments Administered and Treatment Schedule:

In the original study design it was planned that idursulfase-IT would be administered once monthly (ie, every 28 days) via an intrathecal drug delivery device (IDDD) at doses of 1, 10, or 30 mg. Because the 1 mg dose was assessed as suboptimal, all patients in the study are currently receiving doses of either 10 or 30 mg. In addition, to extend flexibility to patients the idursulfase-IT dosing visit window has been extended so that monthly administration may occur every 28 (±7) days.

Device(s), Intended Use(s)

The PORT-A-CATH system is intended for long-term, continuous access to the intraspinal space for the delivery of drugs approved for intraspinal delivery.

Due to recurrent issues with the PORT-A-CATH IDDD in the intended patient population, Shire has qualified a new IDDD for use in this study, the SOPH-A-PORT Mini S®. 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.

It is intended that use of the PORT-A-CATH will be phased out in favor of use of the SOPH-A-PORT Mini S device. An implanted PORT-A-CATH IDDD will be allowed to remain in situ for as long as it is functional, but when a PORT-A-CATH IDDD becomes nonfunctional and needs to be replaced, it will be replaced by a SOPH-A-PORT Mini S IDDD.

Study Methodology:

This is an open-label extension of Study HGT-HIT-045. This study is designed to evaluate the long-term safety and clinical outcomes of monthly (ie, every 28 [±7] days) intrathecal (IT) injections of idursulfase-IT (HGT-2310) in conjunction with weekly IV infusions of Elaprase in patients with Hunter syndrome and cognitive impairment. Elaprase will be prescribed by the patient's physician and will be administered in accordance with local prescribing information.

There are 2 patient groups in Study HGT-HIT-046: those that were previously treated in the antecedent study (HGT-HIT-045) and continue to receive treatment in Part B (defined as Months 7-54) of this extension study, and those that were not previously treated in the antecedent study and receive treatment in Parts A (defined as Months 0-6) and B (defined as Months 7-54) of this extension study. Once patients in Study HGT-HIT-046 have completed Part B, they may continue to receive treatment with idursulfase-IT in Part C (defined as Months 55-168) while

undergoing a reduced, and less burdensome, schedule of study assessments.

Initial Treatment Phase (previously untreated patients only, Part A): Patients who did not receive treatment with intrathecal idursulfase-IT in Study HGT-HIT-045 will, during the Initial Treatment Phase of this study (ie, the first 6 months), undergo treatment and assessments corresponding in schedule and content to those performed for patients who were treated in Study HGT-HIT-045. After completion of the Initial Treatment Phase and if there are no safety concerns, patients may continue receiving monthly (ie, every 28 [±7] days) intrathecal idursulfase-IT in the Extended Treatment Phase of this study.

Extended Treatment Phase (all patients, Parts B and C): Patients who received 6 months of treatment with intrathecal idursulfase-IT in Study HGT-HIT-045 will be eligible for enrollment after completing the EOS evaluations in HGT-HIT-045. If there are no safety concerns, previously treated patients may continue receiving monthly (ie, every 28 [±7] days) intrathecal idursulfase-IT in this extension study. Patients will receive their monthly doses of intrathecal idursulfase-IT at the main study site or at a local site. Patients will undergo pretreatment and safety assessments on Day 1 and will receive an IT injection of idursulfase-IT on Day 2 of each IT Dosing Week. Standardized neurodevelopmental assessments will be performed every 6 months during Part B of the Extended Treatment Phase and annually during Part C of the Extended Treatment Phase. MRI of the spine and brain and any other procedures deemed necessary, such as auditory brainstem response (ABR), that require anesthesia will be performed annually.

When a patient has received and tolerated a total of 9 monthly doses of intrathecal idursulfase-IT across Studies HGT-HIT-045 and HGT-HIT-046, the sponsor and principal investigator will consider the feasibility of transitioning the patient's monthly IT dosing to local sites to reduce the burden imposed by monthly travel. The local sites will be selected and approved by the sponsor, and the patient must have no safety or medical issues that would preclude transitioning to a local site (Note: the main site may serve as a local site as needed; and in this case, the main site will follow the assessment schedule for a local site). The first 3 IT injections of idursulfase-IT (Months 7-9) in this extension study will be administered at the main study site. Patients will be discharged a minimum of 24 hours after IT dosing and when deemed clinically stable by the investigator. Thereafter, IT injections of idursulfase-IT may be performed at either the main study site or at a local site and, through Month 54, patients may be discharged a minimum of 4 hours after dosing and when deemed clinically stable by the investigator (ie, a 24-hour inpatient stay is no longer required). Exceptions include the IT injections of idursulfase-IT at Months 19, 31, and 43 when PK assessments are scheduled; these will take place at the main site. Due to PK sample collection at these visits, discharge at Months 19, 31, and 43 will be upon discretion of the investigator. Patients may undergo a streamlined schedule

of evaluation and assessment after completing at least 54 months of treatment in Study HGT-HIT-045 and/or HGT-HIT-046. Additionally, from Month 55 onward, patients may be discharged a minimum of 1 hour after IT dosing and if deemed clinically stable in the investigator's judgment.

All patients will receive their weekly IV infusions of Elaprase throughout the study. Elaprase infusions may be administered at the main study site, at a local site, or at the patient's home depending upon the standard location as determined for each patient. Patients must provide a separate written informed consent/assent to participate in study procedures to be conducted at the local site prior to the conduct of any procedures.

All patients in the study will undergo EOS procedures 30 (±7) days following their last administration of intrathecal idursulfase-IT.

Surgical IDDD implantation and revision will be performed at the main study center only. Explantation of the IDDD will be performed at the main study center or at the patient's local site, as necessary.

It is intended that the IDDD will be used to deliver all IT injections of study drug and to obtain CSF samples. No other medication will be administered through the device. However, if the IDDD appears to be nonfunctional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD manual(s), which provides details on the investigation and management of any IDDD-related issues. This may include partial revision or complete replacement of the IDDD as indicated.

If there are medical contra-indications to the re-implantation of a new device, repeat monthly lumbar punctures may be considered as an alternative way of delivering the study drug and obtaining CSF samples under limited circumstances. As long as no safety risks are identified by the investigator, consecutive lumbar punctures may be performed across Studies HGT-HIT-045 and HGT-HIT-046.

Continued treatment via repeat lumbar puncture should only be considered in individual cases of patients where this treatment is very well tolerated and the investigator has not identified any safety concerns associated with repeat lumbar puncture and repeat sedation/anesthesia.

General anesthesia may be required for injections of study drug and some evaluations, and can be used at the discretion of the investigator as indicated in the study manuals. It is anticipated that study procedures such as lumbar puncture, MRI, and audiometry will have to be performed with sedation/anesthesiology support.

Patients should have the IDDD removed when they discontinue from the study, unless they are continuing to receive treatment through another mechanism (eg, supplemental study, expanded access program, etc) or the investigator determines that it should not be removed based upon safety assessments. The device can remain in the patient (partial [catheter only] or full [port, catheter, and suture wings]) if the patient is doing clinically well and there are no known risk factors such as infection (eg, meningitis). The device may be partially or fully removed as medically required and determined by the neurosurgeon at a future date.

If patients in the study require revision and/or replacement of the PORT-A-CATH IDDD, it will be removed and replaced with the SOPH-A-PORT Mini S device at a time judged appropriate by the investigator. A nonfunctional PORT-A-CATH IDDD cannot be replaced by a new PORT-A-CATH device.

Patients with a partial or full device still in place after completion of the study will not be followed for safety monitoring. However, the sponsor will arrange reimbursement when the device is eventually removed.

Safety Assessments:

Safety of intrathecal administration of idursulfase-IT will be measured by adverse events (AEs), changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, urinalysis), 12-lead ECG, CSF chemistries (contingent on sample availability; cell counts, glucose, and protein), anti-idursulfase antibodies and antibodies having enzyme neutralizing activity in CSF and serum.

SOPH-A-PORT Mini S 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.

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.

Pharmacodynamic and PK Assessments:

Pharmacodynamic (PD) measures will include measurement of change from baseline in CSF biomarkers (eg, GAG [HS/DS]), and change from baseline in urinary GAG.

Pharmacokinetic parameters of idursulfase, when administered as intrathecal idursulfase-IT in conjunction with Elaprase, will be measured in serum.

Statistical Methodology:

The statistical methodology will use descriptive rather than inferential approaches, given the early phase and objectives of the trial. Descriptive statistics will include the mean, standard deviation, median, minimum, and maximum. For continuous data, 95% confidence intervals (CI) for the mean change will also be presented. For categorical data, the number and percentage of patients in each category will be presented. The population for the safety analyses will consist of all eligible patients from Study HGT-HIT-045 who agreed to participate in the extension study, and had either surgical implantation of an IDDD or IT administration of study drug in the extension study. The data will be presented by dose group.

An interim clinical study report has been prepared describing the results of Parts A and B. The complete results, including Part C, will be described in the final clinical study report.

2 INTRODUCTION

2.1 Disease Background

Idursulfase-IT, recombinant human iduronate-2-sulfatase for intrathecal (IT) administration, is in development for the treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, [MPS II]) with cognitive impairment. Hunter syndrome is an inherited lysosomal storage disease caused by the missing or defective enzyme, iduronate-2-sulfatase, which acts to cleave *O*-linked sulfate moieties from two human glycosaminoglycan (GAG) molecules, dermatan sulfate and heparan sulfate.[1-3] Insufficient levels of iduronate-2-sulfatase lead to progressive accumulation of these GAGs in nearly all organs and body tissues. Many patients with Hunter syndrome develop some degree of neurodevelopmental impairment, varying from severe neurodevelopmental delays and behavioral problems to mildly impaired cognition (approximately 66 and 77%, respectively).[1-12] Other central nervous system (CNS) manifestations of Hunter syndrome include communicating hydrocephalus, increased intracranial pressure, seizures, and hearing problems.[13]

2.2 Human Enzyme Replacement Therapy Rationale

The currently approved therapy for Hunter syndrome is Elaprase®, recombinant human iduronate-2-sulfatase for IV administration.[14, 15] Enzyme replacement therapy with Elaprase in patients with Hunter syndrome has been demonstrated to be safe and efficacious in clinical studies. Elaprase is a large protein, and as such, is not expected to cross the blood-brain barrier when administered intravenously.

Idursulfase-IT is a distinct formulation of idursulfase that is suitable for direct delivery into the cerebrospinal fluid (CSF) via IT administration, and differs from the IV formulation, Elaprase. Idursulfase-IT is a highly purified recombinant form of iduronate-2-sulfatase. It is expressed in a human cell line as a single polypeptide chain of 550 amino acids and is secreted into the medium as a monomeric protein of approximately 76 kDa following cleavage of the 25 amino acid signal peptide. The enzyme contains 8 occupied N-linked glycosylation sites composed of complex, hybrid, or high mannose oligosaccharide chains. The presence of mannose-6-phosphate (M6P) residues on the high mannose oligosaccharide chains facilitates internalization of the enzyme via the M6P receptors present on the cell surface, and subsequent delivery of the enzyme to the lysosomes.

Idursulfase-IT is intended for administration to patients with Hunter syndrome who are concurrently receiving treatment with Elaprase. Long-term treatment with idursulfase is considered necessary for patients with Hunter syndrome, as GAG re-accumulates in the absence of treatment. Intravenous therapy with Elaprase is not adequate to treat the CNS manifestations

of Hunter syndrome; conversely, it is not anticipated that administration of idursulfase-IT will be sufficient to address the non-neurological aspects of the disease. Concomitant treatment with Elaprase and idursulfase-IT is proposed as a therapeutic strategy to improve both the somatic and CNS manifestations of Hunter syndrome.

Extended access of idursulfase-IT treatment to patients with Hunter syndrome and cognitive impairment who have had an intrathecal drug delivery device (IDDD) implanted specifically for participation in Study HGT-HIT-045, and inclusion of the previously untreated patients of Study HGT-HIT-045, will provide an opportunity for evaluation of long-term safety and clinical outcomes in this patient population.

There is precedent for the relative safety and potential benefit of repeated monthly IT administration (via lumbar puncture) of an ERT in populations of patients with MPS disorders. Intrathecal treatment studies have been conducted with small samples of patients with MPS I for spinal cord compression and cognitive impairment in adults, and in pediatric patients with MPS VI. Additionally, the effect of intrathecal α-L-iduronidase in patients with MPS I undergoing bone marrow transplant is being evaluated.[16-21] In these Phase I/II investigator-initiated trials, enzyme is repeatedly administered by lumbar puncture under controlled conditions.

2.3 Idursulfase Administration in the Nonclinical Setting

The nonclinical program includes studies demonstrating efficacy of IT administered idursulfase in a mouse model of disease, exposure, and distribution in non-human primates, and safety of repeated IT dosing of HGT-2310 in non-human primates via an implanted port/catheter system for IT drug delivery.

In the nonclinical pharmacodynamic assessment, IT administration of idursulfase demonstrated distribution and activity in the CNS of an idursulfase mouse model of Hunter syndrome. Based on the widespread histopathological improvement observed in a variety of regions in the brain and histological markers of disease, the nonclinical studies suggest beneficial pharmacodynamic activity following IT administration of idursulfase.

In the pivotal repeat-dose toxicity studies, idursulfase-IT was administered to monkeys using an IDDD. Pharmacokinetic results showed that following repeated IT administration idursulfase-IT is present in the CSF and in the serum in a dose-dependent manner and that idursulfase-IT is well distributed within the CNS following IT administration.

Positron emission tomography (PET) images following HGT-2310 injection (via IDDD) demonstrated appropriate distribution and showed that the presence of idursulfase-IT in the CSF

at doses ranging from 3-20 mg (approximately 30-200 mg/kg of brain weight) does not affect the intrinsic flow dynamics of the CSF in monkeys, and is unlikely to do so in humans.

Based on brain biodistribution data in non-human primates, a therapeutic intrathecally administered dose of idursulfase-IT in humans was estimated to be in a range from 5-35 mg.

Idursulfase-IT-related findings included a transient elevated white blood cell (WBC) and total protein in the CSF and slight to minimal inflammatory reactions in the meninges. In both the 3- and 6-month studies, inflammatory infiltrates were observed in all groups, but were most pronounced in the high dose groups. In the 6-month study with recovery groups, the inflammation was resolved after a 4-week washout period in the 3 mg IT group, and largely resolved in the 100 mg IT group. The transient WBC elevation was considered nonadverse and non-specific because the inflammatory reaction was considered an unavoidable reaction to injection of a protein in the intrathecal space. As exhibited in the 6-month study in monkeys, monthly idursulfase-IT administration in combination with weekly IV idursulfase (0.5 mg/kg) was generally safe up to the 100 mg dose.

The no observed adverse effect level (NOAEL) of 100 mg for idursulfase-IT in monkey corresponds to a dose level of 1000 mg/kg of brain weight. The 1 mg dose of idursulfase-IT employed in the Phase I/II clinical setting has a safety factor of 1,000-fold relative to the dose of 100 mg established in the pivotal 6-month, repeat-dose toxicity study in monkey. The 10 mg and 30 mg doses have 100-fold and a 33.3-fold safety factors, respectively.

Support for the doses of idursulfase-IT to be evaluated in the clinical setting was provided by the results of safety and distribution studies conducted in non-human primates. Collectively, these data suggest that a therapeutic IT administered dose of HGT-2310 in humans is in a range from 5-35 mg.

2.4 Previous Human Experience

In the development program to date, one patient population comprising 15 pediatric MPS II males with cognitive impairment has received treatment with idursulfase-IT, in conjunction with Elaprase therapy as standard of care, at doses of 1, 10, and 30 mg under protocols HGT-HIT-045 and its extension HGT-HIT-046.

The initial investigation of the safety and tolerability of ascending IT doses (1, 10, or 30 mg) of idursulfase-IT was conducted in study HGT-HIT-045. This first-in-human study was a randomized, open-label, no-treatment controlled study in which idursulfase-IT was administered once monthly to MPS II patients via a surgically implanted IDDD, PORT-A-CATH (Smiths Medical, US), or lumbar puncture, for 6 months in conjunction with once weekly Elaprase.

Eligible patients who completed HGT-HIT-045 are continuing to receive monthly IT injections of idursulfase-IT in conjunction with Elaprase therapy in extension study HGT-HIT-046. Across the HGT-HIT-045 and HGT-HIT-046 studies, long-term safety, PK/pharmacodynamic properties, and the effect of intrathecally administered 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. Available results of neurodevelopmental assessments 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.

Intrathecal administration of idursulfase-IT to MPS II patients in Studies HGT-HIT-045 and HGT-HIT-046 at the 10 and 30 mg dose regimens resulted in a pronounced PD reduction from baseline in the concentration of GAG in CSF, while the 1 mg dose regimen induced a less pronounced reduction in GAG concentration in CSF. 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 PD effect. This response correlates with the therapeutic dose range (5-35 mg) estimated from evaluation of HGT-2310 in non-human primates.

There have been no deaths in any studies of idursulfase-IT. The majority of SAEs in HGT-HIT-045 and HGT-HIT-046 have been associated with the use of an IDDD, and designated as serious because of the requirement for overnight hospitalization for surgical revision/removal of the IDDD. Device-related events were not entirely unexpected, given published reports of IT delivery device failures,[22, 23] and the need to rely on the device for long-term IT delivery of idursulfase-IT in HGT-HIT-045 and its extension study. As a result of the device-related concerns in Studies HGT-HIT-045 and HGT-HIT-046, additional guidelines and training materials were developed 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.

Currently, there are 2 types of IDDD in use in the intrathecal programs. The original IDDD, the PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System (PORT-A-CATH), was implanted from 2009-2013. The events related to the use of the PORT-A-CATH IDDD included surgical removal and replacement of the device because of mechanical failures, such as connector pin breaks and catheter slippage, overnight admissions to the hospital for a suspected

device infection, and device removal because of wound issues. In response to the occurrence of failures of the PORT-A-CATH device in the MPS II patient population, Shire introduced a different IDDD, the SOPH-A-PORT Implantable Access Port, Spinal, Mini Unattached, with Guidewire (Sophysa SA, France; hereafter referred to as SOPH-A-PORT Mini S), in the idursulfase-IT development program.

In HGT-HIT-046 some patients are still receiving idursulfase-IT via a functioning PORT-A-CATH device, which will be left in situ until a device failure occurs, at which point they will be replaced by a SOPH-A-PORT Mini S device.

Please see the current edition of the investigator's brochure for a detailed summary of safety information for idursulfase-IT. Further information concerning the SOPH-A-PORT Mini S device is provided as an addendum to the investigator's brochure.

Intravenous infusion of Elaprase has been well tolerated in patients with Hunter syndrome across the clinical development program and in the post-marketing setting. The most common adverse reactions are infusion-related, and include cutaneous reactions (rash, pruritus, urticaria), pyrexia, headache, hypertension, and flushing.[14, 15]

2.5 Use of Repeat Lumbar Puncture to Administer Enzyme Replacement Therapy

In this study, it is intended that the IDDD be used to deliver all IT injections of study drug and to obtain CSF samples. However, should the IDDD become nonfunctional or if its use is otherwise precluded causing the IT space to be inaccessible via the device; repeat monthly lumbar punctures may be considered, under limited circumstances, as an alternative way of delivering the study drug and obtaining CSF samples. Guidance concerning the performance of lumbar puncture for study drug administration and CSF sample collection is provided in Section 7.8.

The use of IV ERT is a well-established treatment modality in the MPS patient community, and as several of the MPS disorders are associated with cognitive impairment and/or spinal compression, the concept of administering ERT directly into the intrathecal space has been investigated. There are case histories of patients with MPS being treated with recombinant enzyme via repeat lumbar puncture, as well as trials investigating this therapeutic option in patients with non-malignant neurological diseases and CNS malignancies.[24-29] These reports provide evidence that IT administration of medication by repeat lumbar puncture is a viable alternative to the implantation of IDDD.

2.6 Study Rationale

Concomitant treatment with idursulfase-IT and Elaprase is intended to address the CNS and somatic manifestations of Hunter syndrome. 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 Elaprase therapy, IV enzyme replacement is not sufficient for treatment of CNS symptoms 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. The idursulfase-IT formulation was developed specifically to access CNS tissues via IT administration and to overcome macromolecular distribution limits imposed by the blood-brain barrier.

Monthly IT administration of idursulfase-IT in conjunction with weekly IV infusion of Elaprase was well tolerated in HGT-HIT-045, a completed Phase I/II safety and ascending dose ranging study in pediatric patients with Hunter syndrome and cognitive impairment. Extension study HGT-HIT-046 is intended to continue evaluation of the effects of IT administration of idursulfase-IT on long-term safety and clinical outcomes for patients who enrolled in HGT-HIT-045. This study will also provide an opportunity for patients who participated, but did not receive treatment, in HGT-HIT-045 to receive IT treatment with idursulfase-IT.

2.7 Benefit/Risk Assessment

In patients with Hunter syndrome, the deficiency of iduronate-2-sulfatase causes accumulation of GAG in nearly all body organs and tissues. Systemic IV ERT with Elaprase improves somatic manifestations of Hunter syndrome and is associated with reduced levels of GAG in urine. Accumulation of GAG molecules in the CNS is associated with impairment of cognitive function and other CNS pathologies. No specific therapy exists for the CNS pathologies of Hunter syndrome. Treatment of the CNS manifestations of the disease remains an unmet medical need.

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

Repeat dosing by lumbar puncture requires repeat general anesthesia. Because of musculoskeletal abnormalities and potential airway obstruction, patients with MPS II represent a higher-than-average anesthesia risk. By using an easy-to-access IDDD, the need for multiple general anesthesias is reduced, compared to repeat access by lumbar puncture.

Clinical experience in studies of idursulfase-IT to date in pediatric patients with MPS II indicates no safety concerns for idursulfase-IT. The major safety signals in clinical studies were related to the use and functionality of the IDDD.

In consideration of the occurrence of device failures observed with the PORT-A-CATH IDDD in Studies HGT-HIT-045 and HGT-HIT-046, the SOPH-A-PORT Mini S IDDD was made available to patients in HGT-HIT-046. The SOPH-A-PORT Mini S has a patented screw-lock mechanism to secure the catheter to the port pin and suture wings to anchor the catheter to the lumbar fascia near the insertion into the intrathecal space.

In conclusion, assessment of the benefit/risk of intrathecally administered idursulfase-IT based on the clinical data collected to date indicates a positive benefit/risk balance. It is the sponsor's view that IT administration of idursulfase-IT, concurrent with Elaprase therapy, represents a novel treatment that may provide clinical benefit to Hunter syndrome patients with cognitive impairment.

2.8 Global Health Emergencies and Clinical Trial Continuity

Global health emergencies, such as the 2019 novel coronavirus disease (COVID-19) pandemic, present significant logistical challenges for many clinical sites around the world, with variable restrictions being placed on site resources and operations, and on an individual patient's ability to attend clinic visits. In some places, medical visits are occurring, and in others, research clinics are operating with only emergency staff.

Based on these challenges, it may be necessary to adopt additional measures and procedures to protect patient safety, and to ensure that there are no gaps in the conduct of the study for patients enrolled in this clinical trial.

This protocol includes the measures which are approved for implementation within this clinical trial to protect patient safety and to ensure the integrity of the trial as a result of COVID-19 only. These measures may be implemented in accordance with any requirements and expectations set out by local Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and National Competent Authorities, as necessary.

These specific measures do not apply for patient management issues that are unrelated to a documented impact from a public health emergency, such as the COVID-19 pandemic.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is:

- To collect long-term safety data in pediatric patients with Hunter syndrome and cognitive impairment who are receiving intrathecal idursulfase-IT and IV Elaprase® ERT

3.2 Secondary Objectives

The secondary objectives of this study are:

- To determine the serum PK profile of idursulfase when administered as intrathecal idursulfase-IT and in conjunction with Elaprase
- To determine the effect of intrathecal idursulfase-IT, given in conjunction with Elaprase, on CSF biomarkers (eg, total GAG including HS/DS)
- To determine the effects of intrathecal idursulfase-IT, given in conjunction with Elaprase, on urinary GAG

3.3 Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate the long-term effects of intrathecal idursulfase-IT, given in conjunction with Elaprase, on clinical parameters (eg, physiological assessments, neurocognitive assessments, neurologic function, and brain structure volumes)
- To evaluate the long-term effects of intrathecal idursulfase-IT, given in conjunction with Elaprase, on functional activities of daily living, as determined by the Scales of Independent Behavior-Revised (SIB-R)
- To explore potential relationships between biomarkers and CNS symptomatology
- To determine whether monthly idursulfase-IT administrations results in accumulation of idursulfase within the CSF compartment by measuring idursulfase levels in CSF immediately prior to idursulfase-IT administration
- To determine the safety and performance of the SOPH-A-PORT Mini S

4 STUDY ENDPOINTS

4.1 Primary Endpoint

The primary endpoints of this study are:

- Safety of intrathecal idursulfase-IT administration. Safety will be measured by AEs (by type and severity), changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, urinalysis), 12-lead ECG, CSF chemistries (contingent on sample availability; cell counts, glucose, and protein), anti-idursulfase antibodies and antibodies having enzyme neutralizing activity in CSF and serum

4.2 Secondary Endpoints

The secondary endpoints of this study are:

- Serum idursulfase concentration-time profiles and serum PK parameters of idursulfase, administered as intrathecal idursulfase-IT and in conjunction with Elaprase
- Change from baseline in CSF biomarkers (eg, GAG [HS/DS])
- Change from baseline in urinary GAG

4.3 Exploratory Endpoints

The exploratory endpoints for this study are:

- Change from Baseline in additional clinical parameters (eg, physiological assessments, standardized neurocognitive assessments, neurologic function, brain MRI)
- Change from Baseline in functional activities of daily living parameters
- Levels of idursulfase in CSF immediately prior to idursulfase-IT administration

4.4 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 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.

5 OVERALL STUDY DESIGN AND PLAN

5.1 Study Design

This is an open-label extension of Study HGT-HIT-045. This study is designed to evaluate the long-term safety and clinical outcomes of monthly (ie, every 28 [±7] days) IT injection of idursulfase-IT (HGT-2310) in conjunction with weekly IV infusion of Elaprase in patients with Hunter syndrome and cognitive impairment.

Shire is evaluating administration of idursulfase-IT directly to the CNS using an IDDD in order to traverse the blood-brain barrier. The advantage of using an IDDD is the potential to obviate the need for multiple lumbar punctures for drug delivery. Idursulfase-IT will be administered through this port or, if the IDDD is nonfunctional, via lumbar puncture.

Elaprase will be prescribed by the patient's physician and will be administered in accordance with local prescribing information.

Patients who participated in Study HGT-HIT-045 and completed the HGT-HIT-045 end-of-study (EOS) evaluations, and meet all criteria for inclusion in this extension study will be eligible for enrollment. Patients in Study HGT-HIT-046 who exceed the age of enrollment eligibility for Study HGT-HIT-045 during this study will be allowed to continue participation in Study HGT-HIT-046 until the end of the study. Patients will be re-consented once they have reached the applicable legal age of consent to participate in a clinical study. If the patient has been deemed by the investigator, in accordance with applicable law, as lacking mental capacity to provide informed consent, the patient's parent(s) or legally authorized representative(s) will be asked to provide informed consent on behalf of the patient. Patients will be screened for entry into the study based on their known medical histories and participation in Study HGT-HIT-045. Once eligibility is determined, the investigator will fully inform, as appropriate, the patient and/or the patient's parent(s) or legally authorized representative(s) of the nature and scope of the study, potential risks and benefits of participation, and the study procedures involved, and will answer all questions prior to the signing of the informed consent form. The date of study enrollment is defined as the date the patient's parent(s) or the patient's legally authorized representative(s) signs the informed consent form. The informed consent (and patient assent as relevant) must be obtained prior to performing any extension study-related procedures.

There are 2 patient groups in Study HGT-HIT-046 (refer to Figure 5-1): those (Group 1) that were previously treated in the antecedent study (HGT-HIT-045) and continue to receive treatment in Part B (defined as Months 7 to 54) of this extension study, and those (Group 2) that were not previously treated in the antecedent study and receive treatment in Parts A (defined as Months 0-6) and B (defined as Months 7-54) of this extension study. Once patients in Study

HGT-HIT-046 have completed Part B, they may continue to receive treatment with idursulfase-IT in Part C (defined as Months 55-168) while undergoing a reduced, and less burdensome, schedule of study assessments.

Initial Treatment Phase (previously untreated patients only, Part A): Patients who did not receive treatment with intrathecal idursulfase-IT in Study HGT-HIT-045 will, during the Initial Treatment Phase of this study (ie, the first 6 months), undergo treatment and assessments corresponding in schedule and content to those performed for patients who were treated in Study HGT-HIT-045. After completion of the Initial Treatment Phase and if there are no safety concerns, patients may continue receiving monthly (ie, every 28 [±7] days) intrathecal idursulfase-IT in the Extended Treatment Phase of this study. The dose of idursulfase-IT to be administered to a patient in the initial treatment phase was planned to correspond to the dose (1, 10, or 30 mg) received by other patients in the same cohort of Study HGT-HIT-045 within which the patient was randomized.

Extended Treatment Phase (all patients, Parts B and C): Patients who received 6 months of treatment with intrathecal idursulfase-IT in HGT-HIT-045 will be eligible for enrollment after completing the EOS evaluations in Study HGT-HIT-045. If there are no safety concerns, previously treated patients may continue receiving monthly (ie, every 28 [±7] days) intrathecal idursulfase-IT in this extension study. The dose of idursulfase-IT to be administered to a patient in the extended treatment phase was planned to correspond to the dose (1, 10, or 30 mg) received by the patient in Study HGT-HIT-045.

In the original study design, it was planned that idursulfase-IT would be administered intrathecally once monthly (ie, every 28 [±7] days) via an IDDD at doses of 1, 10, or 30 mg. Because the 1 mg dose was assessed as suboptimal, all patients in the study are currently receiving doses of either 10 or 30 mg (see Section 5.2).

It is intended that the IDDD be used to deliver IT injections of study drug and to obtain CSF samples. No other medication will be administered through the device. Should the IDDD become nonfunctional during the study, causing the IT space to be inaccessible via the device, or its use is otherwise precluded on a scheduled day of dosing; lumbar puncture may be performed under prescribed circumstances (see Section 7.8) for the purposes of study drug administration and CSF sample collection. Site personnel will refer to the IDDD manual, which provides details on the investigation and management of any IDDD-related issues.

General anesthesia may be required for injections of study drug and some evaluations, and can be used at the discretion of the investigator as indicated in the study manuals. It is anticipated that study procedures such as lumbar puncture, MRI, and audiometry will have to be performed with sedation/anesthesiology support.

Due to recurrent issues with the PORT-A-CATH IDDD, Shire has qualified a new IDDD for use in this study, the SOPH-A-PORT Mini S. It is intended that use of the PORT-A-CATH will be phased out in favor of use of the SOPH-A-PORT Mini S device. An implanted PORT-A-CATH IDDD will be allowed to remain in situ for as long as it is functional, but when a PORT-A-CATH IDDD becomes nonfunctional and needs to be replaced, it will be replaced by a SOPH-A-PORT Mini S IDDD.

If patients in the study require revision and/or replacement of the PORT-A-CATH IDDD, it will be removed and replaced with the SOPH-A-PORT Mini S device at a time judged appropriate by the investigator. A nonfunctional PORT-A-CATH IDDD cannot be replaced by a new PORT-A-CATH device.

Surgical IDDD implantation and revision will be performed at the main study center only. Explantation of the IDDD will be performed at the main study center or at the patient's local site, as necessary.

Patients should have the IDDD removed when they discontinue participation in the study, unless they are continuing to receive treatment through another mechanism (eg, supplemental study, expanded access program, etc) or the investigator determines that it should not be removed based upon safety assessments. The device can remain in the patient (partial [catheter only] or full [port, catheter, and suture wings]) if the patient is doing clinically well and there are no known risk factors such as infection (eg, meningitis). The device may be partially or fully removed as medically required and determined by the neurosurgeon at a future date.

Patients who do not have the IDDD removed (partial or full device) when they discontinue from the study or the study ends will not be followed for safety monitoring. However, the sponsor will arrange reimbursement when the device is eventually removed.

5.2 Rationale for Study Design, Device Use, and Comparator Group

The PD profiles associated with monthly idursulfase-IT administration in Study HGT-HIT-045 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 PD effect. The 3 doses evaluated in Study HGT-HIT-045 demonstrated equivalent safety profiles, and evaluation of effects on neurodevelopmental health showed evidence of stabilization or improvement of cognitive function at the 10 mg or 30 mg doses. Therefore, all patients in HGT-HIT-046 are currently receiving doses of either 10 or 30 mg idursulfase-IT. The patients assigned previously to the 1 mg dose have been switched to 10 mg dose; whereas, patients assigned previously to the 10 mg and 30 mg doses have continued to receive those assigned doses.

5.2.1 Initial Treatment Phase (Part A)

After completion of EOS assessments in Study HGT-HIT-045 and enrollment in Study HGT-HIT-046, patients will undergo surgical insertion of the IDDD at the main study site. Approximately 2 weeks after surgery, Week 3 assessments will be conducted and the patient will begin receiving monthly (ie, every 28 [±7] days) administration of intrathecal idursulfase-IT at the main study site. Patients who receive and tolerate 6 monthly doses of intrathecal idursulfase-IT and complete the Month 7 (Week 27) evaluations will then follow the assessment schedule for the Extended Treatment Phase of this study (see Section 5.2.2).

During their first 6 months in this study, patients who were previously untreated in Study HGT-HIT-045 will undergo study procedures corresponding in schedule and content to those performed for treated patients in Study HGT-HIT-045. These will include:

- Surgical implantation of the IDDD: Surgical Week 1, Days 1-7. Includes pre-surgical assessments (Day 1 Pre-Surgery), surgical implantation of the IDDD (Day 2), and follow-up assessments at Days 3-6 and Day 7.
- Post-operative recovery: Week 2 (Days 8-14). Approximately 14 days are expected for full recovery from surgery after implantation of the IDDD.
- Initial Treatment Phase Week 3: Assessments for safety, biochemical, and neurological baseline measures will occur on Pre-Treatment Day 1 before the first IT injection of idursulfase-IT. CSF sample assessment will be obtained from these patients on Day 2 immediately prior to the first IT injection. Note: “Week 3” will occur during the week of the first idursulfase-IT dose, irrespective of whether the period between IDDD implantation and the first dose of idursulfase-IT is 14 days or more than 14 days.
- Initial Treatment Phase Week 3 through Week 23: Pre-treatment assessments will occur on Day 1, IT injection of idursulfase-IT on Day 2, and follow-up assessments on Days 3-7 of each IT Dosing Week (Weeks 3, 7, 11, 15, 19, and 23). Assessments for safety, biochemical, and neurological measures will be completed before IT administration on Pre-Treatment Day 1 of each dosing week. A CSF sample will be obtained from these patients immediately prior to administration of idursulfase-IT on IT Injection Day 2 of each dosing week. Note: All study weeks are measured from the first dose of idursulfase-IT, which is considered “Week 3” regardless of whether the period between IDDD implantation and the first dose of idursulfase-IT is 14 days or more than 14 days.
- Safety Assessments and Evaluations: Month 7 (Week 27), 30 (±7) days after the last IT administration of idursulfase-IT.

During the Initial Treatment Phase only, patients who did not previously receive idursulfase-IT injections as part of Study HGT-HIT-045 will undergo a mid-cycle neurological examination during the time interval following each IT Dosing Week (ie, at Weeks 5, 9, 13, 17, 21, and 25). This mid-cycle neurological examination may be performed by the local site physician, by a physician at the patient's home, or by an investigator at the main study site.

If there are no safety concerns after administration of the Week 23 intrathecal idursulfase-IT dose, patients may continue to receive monthly administration of intrathecal idursulfase-IT in the Extended Treatment Phase of this study (see Section 5.2.2 below).

5.2.2 Extended Treatment Phase (Parts B and C)

Patients who received 6 months of intrathecal idursulfase-IT in Study HGT-HIT-045 will be eligible for enrollment after completing the EOS evaluations in HGT-HIT-045. If there are no safety concerns identified by the investigator, previously treated patients may continue receiving monthly (ie, every 28 [±7] days) IT injections of idursulfase-IT in this extension study.

Patients will receive their monthly (ie, every 28 [±7] days) IT doses of intrathecal idursulfase-IT at the main study site or at a local site, depending on the visit. Patients treated previously at the idursulfase-IT 10 mg and 30 mg dose levels will continue receiving treatment at the same dose of study drug as in Study HGT-HIT-045, or in the Initial Treatment Phase (see Section 5.2.1) of this study. Based on the results of Study HGT-HIT-045, it was determined that patients assigned to the suboptimal idursulfase-IT 1 mg dose level should be switched to the 10 mg dose.

For their first 3 months on study (ie, Months 7-9), patients will undergo pretreatment and safety assessments on Day 1 and will receive an IT injection of idursulfase-IT on Day 2 of each IT Dosing Week. Standardized neurodevelopmental assessments will be performed every 6 months during Part B of the Extended Treatment Phase and annually during Part C of the Extended Treatment Phase. MRI of the spine and brain and any other procedures deemed necessary, such as ABR, that require anesthesia will be performed annually.

When a patient has received and tolerated a total of 9 monthly doses of intrathecal idursulfase-IT across Studies HGT-HIT-045 and HGT-HIT-046, the sponsor and principal investigator will consider the feasibility of transitioning the patient's monthly IT dosing to local sites to reduce the burden imposed by monthly travel. The local sites will be selected and approved by the sponsor, and the patient must have no safety or medical issues that would preclude transitioning to a local site (Note: the main site may serve as a local site as needed; and in this case, the main site will follow the assessment schedule for a local site). The first 3 IT injections of idursulfase-IT (Months 7-9) in this extension study will be administered at the main study site. Patients will be discharged a minimum of 24 hours after IT dosing and when deemed clinically

stable by the investigator. Thereafter, IT injections of idursulfase-IT may be performed at either the main study site or at a local site and, through Month 54, patients may be discharged a minimum of 4 hours after dosing and when deemed clinically stable by the investigator (ie, a 24-hour inpatient stay is no longer required). Exceptions include the IT injections of idursulfase-IT at Months 19, 31, and 43 when PK assessments are scheduled; these will take place at the main site. Due to PK sample collection at these visits, discharge at Months 19, 31, and 43 will be upon discretion of the investigator. Additionally, from Month 55 onward, patients may be discharged a minimum of 1 hour after IT dosing and if deemed clinically stable in the investigator's judgment.

All patients will receive their weekly IV infusions of Elaprase throughout the study. Elaprase infusions may be administered at the main study site, at a local site, or at the patient's home depending on the standard treatment location for each patient. Patients must provide a separate written informed consent/assent to participate in study procedures to be conducted at the local site prior to the conduct of these procedures.

Patients may undergo a streamlined schedule of assessments (Part C) after completing at least 54 months of treatment in Study HGT-HIT-045 and/or HGT-HIT-046. As noted, there are 2 patient groups in Study HGT-HIT-046: those that were previously treated in the antecedent study (HGT-HIT-045) and continue to receive treatment in Part B (Months 7-54) of this extension study, and those that were not previously treated in the antecedent study and receive treatment in Parts A (Months 0-6) and B (Months 7-54) of this extension study. Once patients in Study HGT-HIT-046 have completed Part B, they may continue to receive treatment with idursulfase-IT in Part C (Months 55-168) while undergoing a reduced, and less burdensome, schedule of study assessments.

All patients will undergo EOS procedures at 30 (±7) days after the last IT injection of idursulfase-IT.

The EOS procedures will include standard clinical laboratory tests (serum chemistry, hematology, and urinalysis), MRI of the lumbar spine and brain, 12-lead ECG, vision and hearing assessments, ABR evaluation, CSF sample collection, intracranial pressure (ICP) measurement, protocol-specific laboratory testing, and standardized developmental and cognitive tests.

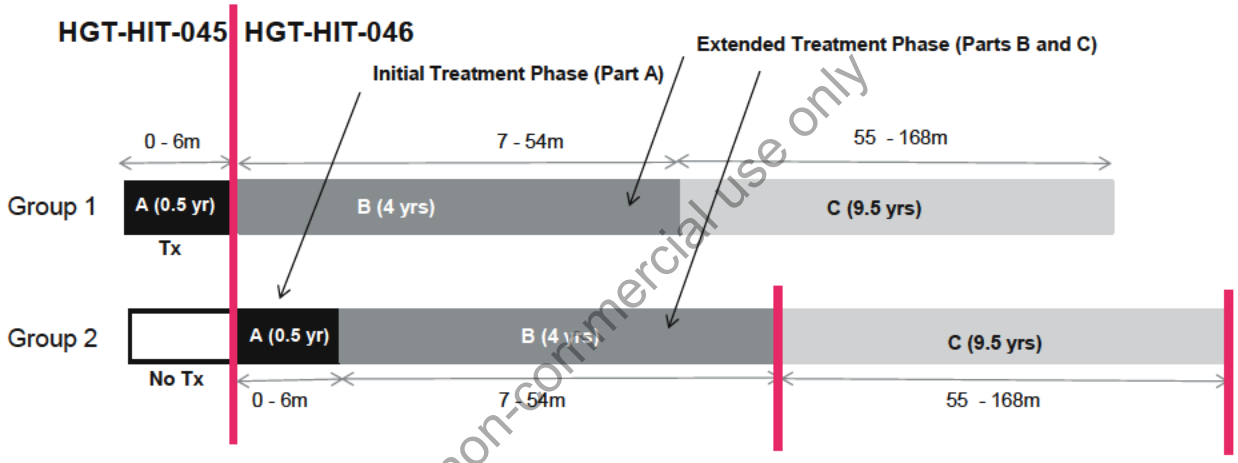
See Section 14 for the Schedules of Study Procedures for the Initial Treatment Phase (Part A: Table 14-1) and Extended Treatment Phase (Part B: Table 14-2) and (Part C: Table 14-3) of this study.

5.3 Study Duration

Patients will continue treatment in this extension study, unless they discontinue the study or Shire discontinues the study, or an alternative mechanism for recombinant human iduronate-2-sulfatase access becomes available, for a maximum duration of 14 years of treatment across Studies HGT-HIT-045 and/or HGT-HIT-046. Specifically, patients in Group 1 of Study HGT-HIT-046 will receive treatment for at least 4 years in Part B and patients in Group 2 of study HGT-HIT-046 will receive treatment for at least 4.5 years in Parts A and B of the protocol. Patients will receive treatment in Part C for up to 9.5 years.

The planned duration of treatment (Tx) is depicted in Figure 5-1.

Figure 5-1 Planned Duration of Treatment (Study HGT-HIT-045 and/or HGT-HIT-046)



The study will conclude after the last patient has completed his last visit. Patients with a partial or full device still in place after completion of the study will not be followed for safety monitoring. However, the sponsor will arrange reimbursement when the device is eventually removed.

6 SELECTION OF STUDY POPULATION

Patients who participated in Study HGT-HIT-045 and completed the HGT-HIT-045 EOS evaluations, and meet all criteria for inclusion in this extension study will be eligible for enrollment. Up to 15 patients are expected.

6.1 Inclusion Criteria

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

1. Patients must have completed all study requirements and EOS assessments for Study HGT-HIT-045 prior to enrolling in Study HGT-HIT-046 and must have no safety or medical issues that contraindicate participation.
2. The patient's parent(s) or legally authorized representative(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 representative(s) and the patient's assent, as relevant, must be obtained.
3. The patient has received and tolerated a minimum of 12 months of treatment with weekly IV infusions of Elaprase and has received 80% of the total planned infusions within the last 6 months.

6.2 Exclusion Criteria

Patients who meet any of the following criteria are not eligible for participation in this study:

1. The patient is enrolled in another clinical study that involves clinical investigations or use of any investigational product (drug or device) other than the PORT-A-CATH IDDD within 30 days prior to study enrollment or at any time during the study.
2. The patient is unable to comply with the protocol (eg, is unable to return for safety evaluations, or is otherwise unlikely to complete the study) as determined by the investigator.
3. The patient has experienced an adverse reaction to study drug in Study HGT-HIT-045 that contraindicates further treatment with intrathecal idursulfase-IT.
4. The patient has a known hypersensitivity to any of the components of idursulfase-IT.
5. The patient has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to airway compromise or other conditions.
6. The patient has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use, including:
    a. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
    b. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the investigator
    c. The patient's drug therapy requires substances known to be incompatible with the materials of construction
    d. The patient has a known or suspected local or general infection
    e. The patient is at risk of abnormal bleeding due to a medical condition or therapy

f. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
g. The patient has a functioning CSF shunt device
h. The patient has shown an intolerance to an implanted device

An additional exclusion criterion for patients who were previously untreated with intrathecal idursulfase-IT in Study HGT-HIT-045:

1. The patient has an opening CSF pressure upon lumbar puncture that exceeds 30.0 cm H_2O.

7 STUDY TREATMENTS

7.1 Treatment Schedule

7.1.1 Initial Treatment Phase (Part A)

Following successful surgical implantation of the IDDD at the main study site and a recovery period of at least 14 days (ie, for previously untreated patients or patients whose device was removed prior to their completion of Study HGT-HIT-045), patients will check in to the main study site approximately 24 hours prior to the first intrathecal idursulfase-IT dose (IT Dosing Week 3, Day 1) and subsequent (IT Dosing Weeks 7, 11, 15, 19, and 23) for safety and pretreatment assessments and will be required to be inpatient until approximately 24 hours after their IV Elaprase infusion (approximately 2 days after IT injection with idursulfase-IT).

Each patient will be required to check in at the main site for neurological and physical assessments on Days 3 and 7 of the first and each subsequent IT Dosing Week, then return home for regular Elaprase infusions, as well as clinical and safety assessments, from his local treating physician during the 3 weeks following the idursulfase-IT dose.

Patients will be evaluated for safety throughout the study both at a main clinical study site and by their local treating physician. Patients who have tolerated treatment with intrathecal idursulfase-IT through Week 23 may continue to receive monthly IT injection of idursulfase-IT and participate in assessments as described for the Extended Treatment Phase of this study.

7.1.2 Extended Treatment Phase (Parts B and C)

Patients will check in to the main study site on Day 1 approximately 24 hours prior to intrathecal idursulfase-IT dosing for safety and pretreatment assessments and will subsequently receive an IT injection of idursulfase-IT on Day 2 of each IT Dosing Week. The first 3 IT injections of idursulfase-IT (Months 7-9) will be administered at the main study site. Patients will be discharged a minimum of 24 hours after dosing and when deemed clinically stable by the investigator. From Month 10 onward, Day 1 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.

Thereafter, with the exceptions noted in Section 5.2.2, IT injections of idursulfase-IT may be performed at either the main study site or at a local site. Through Month 54, patients may be discharged a minimum of 4 hours after dosing at the discretion of the investigator. From Month 55 onward, patients may be discharged a minimum of 1 hour after IT dosing and when deemed clinically stable in the investigator's judgment.

7.2 Description of Study Drug

The idursulfase-IT drug product is an isotonic sterile solution for intrathecal administration, formulated as a 10 mg/mL protein concentration in 154 mM NaCl, pH 6.0, 0.005% polysorbate 20.

Note that the IT formulation differs from that of the IV idursulfase formulation, Elaprase. Compared to Elaprase, the protein concentration of idursulfase-IT has been increased based on the planned maximum dose and limited IT administration volume required for use in clinical studies. The IT formulation is suitable for direct introduction into the intrathecal space, as it is isotonic and contains excipients suitable for intrathecal administration.

The idursulfase-IT drug product is stored at 5 (±3)°C borosilicate glass vials. Each vial recovers 1 mL of idursulfase-IT.

Idursulfase-IT for IT injection will be provided by the sponsor.

Please refer to the Pharmacy Manual for further details concerning the idursulfase-IT drug product, dose preparation, and administration.

Commercially available Elaprase for IV infusion will be prescribed by the patient's treating physician and will be administered throughout the study in accordance with the local prescribing information.

7.3 Selection and Timing of Dose

This is an open-label, non-randomized study; all patients enrolled in this study will be treated with intrathecal idursulfase-IT in conjunction with Elaprase therapy. The treatment schedule for the first 6 months of this study will vary for enrolled patients dependent upon their treatment assignment in HGT-HIT-045. Patients who participated in the untreated control arm in Study HGT-HIT-045 will receive an IDDD following receipt of informed consent by the patient's parent(s)/legally authorized representative(s).

All patients enrolled in HGT-HIT-046 are currently receiving monthly (ie, every 28 [±7] days) IT doses of either 10 or 30 mg idursulfase-IT (See Section 5.2). The patients assigned previously to the 1 mg dose have been switched to 10 mg dose; whereas, patients assigned previously to the 10 mg and 30 mg doses have continued to receive those assigned doses.

7.4 Intrathecal Administration

7.4.1 IDDD Implantation

Implantation includes surgical implantation of the IDDD and a post-surgical assessment. Intrathecal drug delivery device placement will require anesthesia. An X-ray will be taken to confirm/document the position of the catheter tip in the spinal canal.

- IDDD implantation
- X-ray to verify IDDD is at the mid-thoracic level in the spinal canal and correctly installed
- Obtain vital signs
- Concomitant medications/ therapies/procedures monitoring
- Record AEs

The PORT-A-CATH system is intended for long-term, continuous access to the intraspinal space for the delivery of drugs approved for intraspinal delivery. Due to recurrent issues with the PORT-A-CATH IDDD, Shire has qualified a new IDDD for use in this study, the SOPH-A-PORT Mini S.

The SOPH-A-PORT Mini S IDDD is a system intended for implantation by physicians. The SOPH-A-PORT Mini S, once implanted, allows healthcare personnel to administer idursulfase-IT indicated for intrathecal delivery intermittently over a long period of time.

It is intended that the study drug will be administered through the IDDD. However, if the IDDD appears to be nonfunctional, or if its use is precluded on a scheduled day of dosing, consecutive monthly lumbar punctures may be considered as an alternative way of delivering the study drug and obtaining CSF samples (See Section 7.8).

7.5 Treatment Compliance

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 at the main study site 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 Instructions for Use for further details and for information regarding patient activity restrictions for patients to be implanted with this device.

Study drug 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.

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

7.6 Intrathecal Injection

The patient must not receive aspirin, non-steroidal anti-inflammatory medications, or medications that affect clotting within 1 week prior to each intrathecal idursulfase-IT injection.

Idursulfase-IT will be administered using the IDDD. After appropriate pretreatment assessments are completed, patients may receive mild sedation to alleviate anxiety and/or facilitate drug delivery. Anesthesia will be used at the discretion of the investigator. The appropriate dose of idursulfase-IT and the flush with preservative-free sterile saline will be administered via slow push/injection over 2 to 5 minutes.

If use of the IDDD is precluded, the injection of idursulfase-IT may be administered via lumbar puncture (see Section 7.8).

7.6.1 SOPH-A-PORT Mini S Intrathecal Drug Delivery Device

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 comprises the following 7 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

A visual examination of both the port and catheter track will be performed before each IT injection administered via the SOPH-A-PORT Mini S device. A 22-gauge Huber noncoring 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.

Further details are provided in the Instructions for Use, appended to the current version of the investigator's brochure.

7.6.2 PORT-A-CATH Intrathecal Drug Delivery Device

Details concerning the PORT-A-CATH IDDD system are provided in the Instructions for Use, appended to the current version of the investigator's brochure.

7.7 Cerebrospinal Fluid Collection

Cerebrospinal fluid samples will be obtained via the IDDD at every time point that the IDDD is accessed. If it is impossible to obtain a CSF sample using the IDDD, then lumbar puncture may be performed (see Section 7.8). If a lumbar puncture is to be performed, it is anticipated that the patient will be anesthetized with appropriate airway management/intubation. Once the patient is anesthetized, a lumbar puncture will be performed and a CSF sample will be obtained. A measurement of opening pressure may also be performed at that time.

7.8 Guidance Concerning Performance of Lumbar Puncture for Study Drug Administration and CSF Sample Collection

It is intended that the IDDD will be used to deliver all IT injections of study drug and to obtain CSF samples. If the IDDD appears to be nonfunctional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD manual(s), which provides details on the investigation and management of any IDDD-related issues. This may include possible partial revision or complete replacement of the IDDD as indicated. If the nonfunctional IDDD is a PORT-A-CATH device, then it will be replaced by a SOPH-A-PORT Mini S device**.**

If there are medical contra-indications to the re-implantation of a new device, repeat monthly lumbar punctures may be considered as an alternative way of delivering the study drug and obtaining CSF samples under limited circumstances. As long as no safety risks are identified by

the investigator, consecutive lumbar punctures may be performed across Studies HGT-HIT 045 and HGT-HIT-046.

Continued treatment via repeat lumbar puncture should only be considered in individual cases of patients where this treatment is very well tolerated and the investigator has not identified any safety concerns associated with repeat lumbar puncture and repeat sedation/anesthesia.

8 STUDY PROCEDURES

8.1 Study Evaluations and Procedures

In the event of a public health emergency, such as COVID-19, study activities may be disrupted due to hospital, local, state or national government restrictions, or other site related factors. In these circumstances, sites will make every effort to see patients in-person for clinical assessments; sites should use their judgment in conducting the study visits to collect as much data as possible while ensuring the protocol is being followed. Sites should reach out to their local IECs if they have questions.

If a patient misses an in-person study visit, study site personnel may speak directly with the parent(s) or legally authorized representative(s) by telephone or other medium (eg, a computer-based video communication). Assessments that cannot be completed will be considered missing data and such departures will be recorded as protocol deviations in the study records, using already established procedures. Any protocol deviations surrounding COVID-19 or any other public health emergencies will be clearly identified, described, and documented in a systematic way, and in line with regulatory authorities' recommendations. These protocol deviations will be summarized separately in the clinical study report. These data may also be handled differently in the final data analysis; all details will be documented in the Statistical Analysis Plan (SAP).

8.2 Initial and Extended Treatment Phases (All Patients)

Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of each study month (See Section 14).

Prior to conducting any study-related procedures, written informed consent for participation in Study HGT-HIT-046 must be obtained from the patient's parent(s) or legally authorized representative(s). The patient's parent(s) or legal representative(s) must provide a separate written informed consent to participate in the study procedures to be conducted at the local site, prior to the conduct of these procedures.

During the Initial Treatment Phase (ie, the first 6 months) of this study, patients who were not previously treated in Study HGT-HIT-045 will undergo assessments corresponding in schedule and content to the study procedures performed for patients who were treated with intrathecal idursulfase-IT in Study HGT-HIT-045. At completion of these procedures and if there are no safety concerns, patients may continue into the Extended Treatment Phase of this study.

During the Extended Treatment Phase (ie, from Month 7 onward), patients who were previously treated with study drug in Study HGT-HIT-045 may, if no safety concerns exist, continue receiving monthly (ie, every 28 [±7] days) IT injections of intrathecal idursulfase-IT in this extension study.

All data collected throughout the study are to be recorded on the appropriate CRF. Details concerning study procedures, including sample collection, are described in the Study Operations Manual.

All nonprotocol treatments from informed consent through the EOS visit are regarded as concomitant and will be documented on the CRF. These include medications (including Elaprase), therapies/interventions administered to patients, and medical/surgical procedures performed on the patients.

Adverse events will be monitored continuously throughout the study for all patients from the time informed consent is provided through the EOS visit. Instructions for recording and reporting AEs are provided in Section 9.

Patients may undergo a streamlined schedule of assessments (Part C, refer to Section 8.5) after completing at least 54 months of treatment in Study HGT-HIT-045 and/or HGT-HIT-046.

8.3 Initial Treatment Phase (Only for Patients Who Were Not Previously Treated with Intrathecal idursulfase-IT in Study HGT-HIT-045) (Part A)

8.3.1 Screening/Baseline Visit (Study HGT-HIT-045 EOS Visit)

Screening/Baseline assessments for the Initial Treatment Phase of the study were to have been performed during the EOS procedures in HGT-HIT-045. If fewer than 30 days have elapsed since completion of the EOS assessments for HGT-HIT-045, Screening/Baseline assessments are not required to be repeated.

However, if more than 30 days have elapsed since completion of HGT-HIT-045 EOS procedures, the following assessments are to be repeated within 30 days prior to scheduled surgical implantation of the IDDD in the Initial Treatment Phase of the Study:

- Physical examination
- Height and weight
- Head circumference
- 12-lead ECG
- Vital signs

- Hematology
- Serum chemistry
- Standard Urinalysis
- Urine GAG
- Anti-idursulfase antibody testing
- Sample collection for potential plasma proteomic marker testing
- ICP measurement
- CSF sample collection
- Neurological examination

If more than 3 months have elapsed since the completion of HGT-HIT-045 EOS procedures, the following assessments are to be repeated within 30 days prior to surgical implantation of the IDDD in the Initial Treatment Phase of the Study:

- Vision assessment
- Hearing assessment
- General Anesthesia
- ABR
- Brain and spine MRI
- Full neurodevelopmental assessment

8.3.2 Physical Examinations

During the Initial Treatment Phase, physical examinations will be performed at Screening/Baseline (if >30 days have elapsed since HGT-HIT-045 EOS procedures), Day 1 and Day 7 of Surgery Week 1, at Days 1, 3, and 7 of each IT Dosing Week, and at the Month 7 (Week 27) visit. Note: the Pre-Surgery Day 1 examination may not be necessary if performed within 7 days of the Screening/Baseline examination.

Physical examinations will include a review of the patient's general appearance as well as the evaluations listed in Table 8-1.

Table 8-1 Physical Examination

Head and neck	Genitourinary
Eyes, ears, nose, and throat	Skin
Chest and lungs	Musculoskeletal
Cardiovascular	Neurological
Abdomen	Endocrine
	Lymphatic

8.3.3 Height and Weight

During the Initial Treatment Phase, height and weight will be recorded at Screening/Baseline (if >30 days have elapsed since HGT-HIT-045 EOS procedures), Pre-Surgery Day 1 and Day 7 of Surgery Week 1, at Day 1 of each IT Dosing Week, and at the Month 7 (Week 27) visit.
Note: the Pre-Surgery Day 1 measurement may not be necessary if performed within 7 days of the Screening/Baseline measurement.

8.3.4 Head Circumference

During the Initial Treatment Phase, head circumference will be measured in a uniform manner at Screening/Baseline (if >30 days have elapsed since HGT-HIT-045 EOS procedures), on Pre-Treatment Day 1 of IT Dosing Week 3, and at the Month 7 (Week 27) visit.

8.3.5 Vision Assessment

It is intended that all patients have a vision assessment during the Initial Treatment Phase at Screening/Baseline (if >3 months have elapsed since HGT-HIT-045 EOS procedures) and at the Month 7 (Week 27) visit. However, it is recognized that the ability to conduct this assessment will depend on the patient's ability to cooperate, and that it might not be possible to complete a vision assessment for every patient. A reasonable effort should be made to perform a vision assessment for each patient; however, inability to collect these data may not be considered a protocol deviation.

8.3.6 Hearing Assessment

It is intended that all patients have a hearing assessment during the Initial Treatment Phase at Screening/Baseline (if >3 months have elapsed since HGT-HIT-045 EOS procedures), Pre-Treatment Day 1 of IT Dosing Week 3, Pre-Treatment Day 1 of IT Dosing Week 15 (before the fourth IT injection), at the Month 7 (Week 27) visit.

Hearing assessments will be performed using age-appropriate testing methods based on the patient's age at the time of testing. Instructions for age-appropriate hearing testing are described in the Study Operations Manual. However, it is recognized that the ability to conduct this

assessment will depend on the patient's ability to cooperate, and that it might not be possible to complete a hearing assessment for every patient. A reasonable effort should be made to perform a hearing assessment for each patient; however, inability to collect these data may not be considered a protocol deviation.

8.3.7 12-Lead Electrocardiogram

During the Initial Treatment Phase, a 12-lead ECG will be performed at Screening/Baseline (if >30 days have elapsed since HGT-HIT-045 EOS procedures), Pre-Surgery Day 1 of Week 1, Pre-Treatment Day 1 of IT Dosing Week 3 only, Day 2 of each IT Dosing Week after injection of the study drug, and at the Month 7 (Week 27) visit. Note: the Pre-Surgery Day 1 assessment may not be necessary if performed within 7 days of the Screening/Baseline assessment.

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

8.3.8 Vital Signs

In general, vital signs will be recorded during the Initial Treatment Phase at all main study site visits including the Screening/Baseline (if >30 days have elapsed since HGT-HIT-045 EOS procedures) and the Month 7 (Week 27) visit. In particular, vital signs will be collected for patients who will receive study drug during Surgery Week 1 at Day 1, Day 2, Days 3-6 (ie, during IV infusion of Elaprase), Day 7, and during each IT Dosing Week at Pre-Treatment Day 1, IT Injection Day 2, and Days 3-7 (ie, during IV infusion of Elaprase).

At a minimum, vital signs will be collected at the following time points on IT administration of idursulfase-IT and IV infusion of Elaprase:

IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes (±10 minutes) post end of IT administration, 60 minutes (±10 minutes) post end of IT administration, 120 minutes (±10 minutes) post end of IT administration, 4 hours (±10 minutes) post end of IT administration, 6 hours (±10 minutes) post end of IT administration, 8 hours (±10 minutes) post end of IT administration, and 12 hours (±10 minutes) post end of IT administration.

IV infusion of Elaprase: within 15 minutes prior to infusion, 30 minutes (±10 minutes) post start of infusion, 60 minutes (±10 minutes) post start of infusion, 90 minutes (±10 minutes) post start of infusion, 120 minutes (±10 minutes) post start of infusion, 150 minutes (±10 minutes) post

start of infusion, 180 minutes (±10 minutes) post start of infusion (ie, end of infusion), 30 minutes (±10 minutes) post end of infusion and 60 minutes (±10 minutes) post end of infusion.

Vital signs will include pulse, blood pressure, respiration rate, temperature, and pulse oxygen measurement.

8.3.9 Clinical Laboratory Testing

Blood and urine samples will be collected as described in Section 8.3.9.1, Section 8.3.9.2, and Section 8.3.9.3 for clinical laboratory testing. A central laboratory will be responsible for analyzing samples and reporting clinical laboratory values, except where noted below. Sample collection, processing, and shipping instructions are provided in the Study Operations Manual.

8.3.9.1 Hematology

Blood samples will be collected during the Initial Treatment Phase for hematology testing at Screening/Baseline (if >30 days have elapsed since HGT-HIT-045 EOS procedures), Pre-Surgery Day 1 of Week 1, Pre-Treatment Day 1 of each IT Dosing Week, and at the Month 7 (Week 27) visit. Note: the Pre-Surgery Day 1 assessment may not be necessary if performed within 7 days of the Screening/Baseline assessment.

The following hematology parameters will be evaluated: complete blood count (CBC) with differential, including basophils, and platelet count.

8.3.9.2 Serum Chemistry

Blood samples will be collected during the Initial Treatment Phase for serum chemistry testing at Screening/Baseline (if >30 days have elapsed since HGT-HIT-045 EOS procedures), Pre-Surgery Day 1 of Week 1, Pre-Treatment Day 1 of each IT Dosing Week, and at the Month 7 (Week 27) visit.

Note: the Pre-Surgery Day 1 assessment may not be necessary if performed within 7 days of the Screening/Baseline assessment.

The serum chemistry parameters to be evaluated are listed in Table 8-2.

Table 8-2 Serum Chemistry

Potassium	Urea nitrogen
Chloride	Total and direct bilirubin
Magnesium	Alkaline phosphatase
Phosphorous	Alanine aminotransferase
Uric acid	Aspartate aminotransferase
CO_2	Lactate dehydrogenase
Glucose	Gammaglutamyltransferase
Calcium	Creatine phosphokinase
Total protein	Triglycerides
Albumin	Cholesterol
Creatinine	
Prothrombin time (PT)[a]	Total thyroxine (T_4)
Partial thromboplastin time (PTT)[a]	Thyroid stimulating hormone
Sodium	

[a] PT and PTT will be collected at the Screening/Baseline visit only for patients previously untreated in Study HGT-HIT-045 who are to undergo surgical implantation of an IDDD in the Initial Treatment Phase of this study. An additional PT and PTT draw may be required if the Week 1 Pre-Surgery Day 1 visit is more than 2 weeks after the Screening/Baseline visit.

8.3.9.3 Standard Urinalysis

Urine samples will be collected during the Initial Treatment Phase for urinalysis at Screening/Baseline (if >30 days have elapsed since HGT-HIT-045 EOS procedures), Pre-Surgery Day 1 of Week 1, Pre-Treatment Day 1 of each IT Dosing Week, and at the Month 7 (Week 27) visit. Note: the Pre-Surgery Day 1 assessment may not be necessary if performed within 7 days of the Screening/Baseline assessment. Pretreatment urine samples may be collected up to 24 hours prior to receipt of each IT dose.

The following urinalysis parameters will be performed: pH, macroscopic evaluation, and microscopic evaluation.

8.3.9.4 Urinary GAG Levels

Urine samples for determination of urinary GAG levels and urine creatinine will be collected during the Initial Treatment Phase at Screening/Baseline (if >30 days have elapsed since HGT-HIT-045 EOS procedures), on Pre-Treatment Day 1 of each IT Dosing Week, and at the Month 7 (Week 27) visit. Pretreatment urine samples may be collected up to 24 hours prior to administration of each IT dose.

Urinary GAG levels will be analyzed and reported by a Shire-designated laboratory. Urinary GAG levels will be normalized to urine creatinine and reported as mg GAG/mmol creatinine.

Sample collection, processing, and shipping instructions are provided in the Study Operations Manual.

8.3.10 Auditory Brainstem Response

Hearing assessment via audiometry measurement will be performed during the Initial Treatment Phase at Screening/Baseline (if >3 months have elapsed since HGT-HIT-045 EOS procedures) and at the Month 7 (Week 27) visit. It is anticipated that the patient will be under general anesthesia for this procedure.

8.3.11 Brain and Spinal Magnetic Resonance Imaging

During the Initial Treatment Phase, patients will have MRI of the brain and spine at Screening/Baseline (if >3 months have elapsed since HGT-HIT-045 EOS procedures) and at the Month 7 (Week 27) visit. It is anticipated that the patient will be under general anesthesia for this procedure. Brain structure volumes will be measured and the brain and spine will be evaluated. Refer to the Study Operations Manual for specific procedures and precautions.

8.3.12 Surgical Implantation of the IDDD

During the Initial Treatment Phase, the IDDD will be surgically implanted in patients on Day 2 of Surgery Week 1. Procedures for implantation will be detailed in the device Instructions for Use Manual. The patient will be under general anesthesia for this procedure.

Standard hospital procedures for surgery will be followed and will include an X-ray to confirm device placement. A post-operative check of the wound will be performed on Day 7 following surgery. X-rays may be performed to check placement of the device, as needed, throughout the study including prior to lumbar puncture at the Month 7 (Week 27) visit (see Section 8.3.13). Sutures will be removed when deemed appropriate by the investigator, and may need to be removed by the local treating physician during Week 2.

If the device becomes nonfunctional or infected at any time during the study it will be removed and may be replaced. In the event that a patient does not receive the dose as scheduled at a study visit, the planned assessments should still be performed. If the patient discontinues from the study early, the device will be removed.

8.3.13 Intracranial Pressure Measurement

During the Initial Treatment Phase, ICP measurement (cm of H_2O) will be conducted at Screening/Baseline (if >30 days have elapsed since HGT-HIT-045 EOS procedures) and at the

Month 7 (Week 27) visit. Intracranial pressure measurement will be conducted concurrently with lumbar puncture and while the patient is under anesthesia. Patients should undergo X-ray prior to lumbar puncture at the Month 7 (Week 27) visit to verify the position of the IDDD catheter.

8.3.14 Cerebrospinal Fluid (CSF) Assessments

Cerebrospinal fluid will be obtained during the Initial Treatment Phase at Screening/Baseline (if >30 days have elapsed since HGT-HIT-045 EOS procedures) by lumbar puncture and under general anesthesia during surgical implantation of the IDDD on Day 2 of Surgery Week 1, on Day 2 of each IT Dosing Week via the IDDD immediately prior to IT injection of idursulfase-IT, and at the Month 7 (Week 27) visit. Additional CSF samples may also be collected throughout the study during any assessment or revision of the IDDD. Should the IDDD become nonfunctional or its use is otherwise precluded on a scheduled day of dosing, the CSF sample may be obtained by lumbar puncture (see Section 7.8).

Cerebrospinal fluid samples collected at scheduled or unscheduled visits will undergo the following assessments (Section 8.3.14.1 through to Section 8.3.14.4):

8.3.14.1 CSF Cell Counts

An aliquot of the CSF sample collected will be evaluated for CSF standard chemistries, glucose, protein, and cell counts.

8.3.14.2 Immunoassay for Idursulfase-specific Antibodies

An aliquot of the CSF sample collected will be quick frozen for subsequent analysis of idursulfase-specific antibodies. Note that it is not required to perform antibody testing on CSF samples collected at scheduled visits.

8.3.14.3 CSF Biomarker Analysis

An aliquot of the CSF sample collected will be quick frozen for subsequent analysis of levels of biomarkers (eg, GAG [HS/DS]).

8.3.14.4 CSF Analysis of Idursulfase Enzyme Levels

An aliquot of the CSF sample collected will be quick frozen for subsequent idursulfase enzyme analysis.

Cerebrospinal fluid sample collection, processing, and shipping instructions are provided in the Study Operations Manual.

8.3.15 Intrathecal Idursulfase-IT Injection

During the Initial Treatment Phase, Idursulfase-IT will be injected intrathecally via the IDDD on Day 2 of Weeks 3, 7, 11, 15, 19, and 23. The patient may be mildly sedated for this procedure. Idursulfase-IT will be administered over 2 to 5 minutes. If the IT space is not accessible via the IDDD, idursulfase-IT may be administered by lumbar puncture (see Section 7.8).

8.3.16 Elaprase Infusion

Elaprase will be administered during the Initial Treatment Phase as an IV infusion at a weekly dose of 0.5 mg/kg in accordance with local prescribing information.

Patients will receive their weekly Elaprase infusion on every IT Dosing Week at the main study site approximately 2 days after receiving their IT injection of idursulfase-IT (note that the Elaprase infusion should be administered even in instances in which the IT dose is not). At other times during the study, IV infusion of Elaprase may be administered at the patient's local infusion location (site or home).

8.3.17 Neurological Examination

A neurological examination to monitor CNS status and any changes during the Initial Treatment Phase will be conducted at the main study site at Screening/Baseline (if >30 days have elapsed since HGT-HIT-045 EOS procedures), Pre-Surgery Day 1 of Week 1, post surgery at Day 4, on Days 1, 3, and 7 of each IT Dosing Week, and at the Month 7 (Week 27) visit. Note: the Pre-Surgery Day 1 examination may not be necessary if performed within 7 days of the Screening/Baseline examination.

Neurological examinations will also be performed once during the time interval between each IT Dosing Week (at Weeks 5, 9, 13, 17, 21, and 25). This mid-cycle neurological examination may be performed by the local site physician, by a physician at the patient's home, or by an investigator at the main study site.

8.3.18 Serum Anti-Idursulfase Antibody and Plasma Proteomic Biomarker Determination

During the Initial Treatment Phase, patients will have blood samples collected at Screening/Baseline (if >30 days have elapsed since HGT-HIT-045 EOS procedures), on Pre-Treatment Day 1 of each IT Dosing Week, and at the Month 7 (Week 27) visit. A 10-mL blood sample will be collected from each patient for the first sample; a 5-mL sample will be collected for all subsequent blood collections. Blood samples collected will be evaluated for determination of anti-idursulfase antibodies, antibodies that have enzyme neutralizing activity, and potential exploratory plasma proteomic biomarkers of disease progression. Blood sample collection, processing, and shipping instructions are provided in the Study Operations Manual.

8.3.19 Neurodevelopmental Assessments

An extensive set of neurodevelopmental assessments are available to measure a wide range of cognitive, motor, and adaptive functions in children with Hunter syndrome. Patients in this study will undergo neurodevelopmental assessments using appropriate standardized tests to provide a surrogate and quantifiable measure of global CNS neurodevelopmental status. It is intended that full neurodevelopmental assessments of cognitive, motor, and adaptive functions be conducted for all patients; however, it is recognized that the feasibility of conducting these assessments is dependent on the patient's ability to cooperate and/or level of cognitive impairment, and that it may not be possible to complete full neurodevelopmental evaluation of every patient. A reasonable effort should be made to perform neurodevelopmental assessments for each patient; however, inability to collect these data may not be considered a protocol deviation.

8.3.19.1 Full Neurodevelopmental Assessment

A full neurodevelopmental assessment will be conducted during the Initial Treatment Phase at Screening/Baseline (if >3 months have elapsed since HGT-HIT-045 EOS procedures), Pre-Treatment Day 1 of IT Dosing Week 3, and at the Month 7 (Week 27) visit.

For this study, outcome measures will be computed for each patient enrolled at each assessment. The instruments are summarized in Table 8-3. For cognitive testing the first item set of the 6 main subtests of the Differential Ability Scales, Second Edition (DAS-II) will be administered. If the patient cannot complete these, the Bayley Scales of Infant Development, Third Edition (BSID-III) will be used to assess cognition.

Table 8-3 Full Neurodevelopmental Assessment Tests

Cognitive domain	Patient age and representative cognitive test or scale
Cognitive[a]	Differential Ability Scales, Second Edition (DAS-II) (provides general conceptual ability through the 6 main subtests) OR Bayley Scales of Infant Development, Third Edition (BSID-III) (provides mental development index based on cognitive development, behavioral development, motor development)
Adaptive	Scale of Independent Behavior-Revised (SIB-R)
Motor	<6 years: Peabody Developmental Motor Scales-2 (PDMS-2) ≥6 years: Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2)
Measures of Executive Function	<6 years: Behavior Rating Inventory of Executive Function-Preschool version (BRIEF-P) ≥6 years: Behavior Rating Inventory of Executive Function-Parent Form (BRIEF)

[a] For cognitive testing the first item set of the 6 main subtests of the DAS-II will be administered. If the patient cannot complete these, the BSID-III will be used to assess cognition.

8.3.19.2 Brief Neurodevelopmental Assessment

A brief neurodevelopmental assessment will be conducted during the Initial Treatment Phase on Pre-Treatment Day 1 of IT Dosing Week 15 (before the fourth IT injection) and will consist of the SIB-R and DAS-II or BSID-III tests.

8.3.20 Pharmacokinetic Evaluations

During the Initial Treatment Phase, serum samples for PK evaluation of idursulfase will be collected at IT Dosing Weeks 3 and 23 and will be drawn at the following times:

- Within 15 minutes prior to intrathecal idursulfase-IT injection (pre-injection baseline); then at 1, 2, 3, 4, 6, 8, 12, 24, 30, and 36 hours after intrathecal idursulfase-IT administration
- Within 15 minutes prior to the Elaprase IV infusion (pre-infusion baseline); then at 0.5, 1, 1.5, 2, 2.5, and 3 hours during the infusion; and at 3.5, 4, 5, 6, 7, 9, 11, and 24 hours after the infusion

The PK sampling schedule for the study is also located in Section 14 (Table 14-4). Sample collection, processing, and shipping instructions are provided in the Study Operations Manual.

Note that when vital sign collection and collection of a sample for PK analysis are scheduled to occur at the same time, vital sign collection should occur first and the blood draw for PK sampling should be performed as soon as possible after vital collection. The actual time of collection of the PK sample should be recorded.

8.4 Extended Treatment Phase (All Patients, Month 7 through Month 54) (Part B)

8.4.1 Study HGT-HIT-045 EOS Visit

If fewer than 30 days have elapsed since the completion of Study HGT-HIT-045 EOS procedures, pretreatment assessments are not required to be repeated. However, if more than 30 days have elapsed since these procedures, the following pretreatment assessments are to be repeated within 30 days prior to the first scheduled intrathecal idursulfase-IT dose in the Extended Treatment Phase of the study:

- Physical examination
- Height and weight
- Head circumference
- 12-lead ECG
- Vital signs
- Hematology
- Serum chemistry
- Standard Urinalysis
- Urine GAG
- Anti-idursulfase antibody testing
- Sample for potential plasma proteomic marker testing
- Intracranial pressure (ICP) measurement
- X-ray
- Neurological examination

If more than 3 months have elapsed since the completion of HGT-HIT-045 EOS, the following pretreatment assessments are to be repeated within 30 days prior to the first scheduled intrathecal idursulfase-IT dose in the Extended Treatment Phase of the study:

- Vision assessment
- Hearing assessment
- General Anesthesia
- ABR
- Brain and spine MRI
- Full neurodevelopmental assessment

Patients who have received 6 months of intrathecal idursulfase-IT during the Initial Treatment Phase of this study may, if no safety concerns exist, move immediately on to the next IT administration in the Extended Treatment Phase; ie, they will not need to repeat pretreatment assessments that may be redundant with Month 7 (Week 27) assessments.

Note that during the Extended Treatment Phase from Month 10 onward, Day 1 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.

8.4.2 Physical Examinations

Physical examinations will be performed at a minimum on Pre-Treatment Day 1 of Month 7 (only if >30 days have elapsed since HGT-HIT-045 EOS procedures), and the Pre-Treatment Day of each monthly IT Dosing Week. Physical examinations will include a review of the patient's general appearance, device port and catheter track, and evaluations listed in Table 8-1.

8.4.3 Height and Weight

Height and weight will be recorded on Pre-Treatment Day 1 of Month 7 (only if >30 days have elapsed since HGT-HIT-045 EOS procedures), on the Pre-Treatment Day of each Monthly IT Dosing Week.

8.4.4 Head Circumference

Head circumference will be measured in a uniform manner on Pre-Treatment Day 1 of Month 7 (only if >30 days have elapsed since HGT-HIT-045 EOS procedures), on the Pre-Treatment Day of the 12-Month visits (ie, at Months 19, 31, and 43).

8.4.5 Vision Assessment

A vision assessment will be performed as described in Section 8.3.5 on Pre-Treatment Day 1 of Month 7 (only if >3 months have elapsed since HGT-HIT-045 EOS procedures), on the Pre-Treatment Day of the 6-Month and 12-Month visits (ie, at Months 13, 19, 25, 31, 37, 43, and 49).

8.4.6 Hearing Assessment

A hearing assessment will be performed as described in Section 8.3.6 at Month 7 on Pre-Treatment Day 1 (only if >3 months have elapsed since HGT-HIT-045 EOS procedures), on the Pre-Treatment Day of the 6-Month and 12-Month visits (ie, at Months 13, 19, 25, 31, 37, 43, and 49).

8.4.7 12-Lead Electrocardiogram

A 12-lead ECG will be performed (at minimum) on Pre-Treatment Day 1 of Month 7 (only if >30 days have elapsed since HGT-HIT-045 EOS procedures), after injection of study drug on Monthly IT Dosing Weeks at Months 7 to 9, 19, 31, and 43. Each 12-lead ECG will include the assessments described in Section 8.3.7.

8.4.8 Vital Signs

Vital signs will be collected on Pre-Treatment Day 1 and on the IT Injection Day of each monthly IT Dosing Week.

At a minimum, vital signs will be collected at the following time points on IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes (±10 minutes) post end of IT administration, 60 minutes (±10 minutes) post end of IT administration, 120 minutes (±10 minutes) post end of IT administration, and 4 hours (±10 minutes) post end of IT administration.

8.4.9 Clinical Laboratory Testing

Blood and urine samples will be collected for clinical laboratory testing as described in Section 8.4.9.1, Section 8.4.9.2, and Section 8.4.9.3. Sample collection, processing, and shipping instructions are provided in the Study Operations Manual.

8.4.9.1 Hematology

Blood samples will be collected for hematology testing (at minimum) on Pre-Treatment Day 1 of Month 7 (only if >30 days have elapsed since HGT-HIT-045 EOS procedures), and at 3-month intervals on the Pre-Treatment Day of Monthly IT Dosing Weeks (ie, at Months 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, and 52). The hematology parameters to be evaluated are described in Section 8.3.9.1.

8.4.9.2 Serum Chemistry

Blood samples will be collected for serum chemistry testing (at minimum) on Pre-Treatment Day 1 of Month 7 (only if >30 days have elapsed since HGT-HIT-045 EOS procedures), and at 3-month intervals on the Pre-Treatment Day of Monthly IT Dosing Weeks (ie, at Months 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, and 52). The serum chemistry parameters to be evaluated are described in Section 8.3.9.2 and listed in Table 8-2.

8.4.9.3 Standard Urinalysis

Urine samples will be collected for urinalysis (at minimum) on Pre-Treatment Day 1 of Month 7 (only if >30 days have elapsed since HGT-HIT-045 EOS procedures), and at 3-month intervals on the Pre-Treatment Day of Monthly IT Dosing Weeks (ie, at Months 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, and 52). Pre-treatment urine samples may be collected up to 24 hours prior to receipt of each IT dose. The urinalysis parameters to be evaluated are described in Section 8.3.9.3.

8.4.9.4 Urinary GAG Levels

Urine samples for determination of urinary GAG levels and urine creatinine will be collected (at minimum) on Pre-Treatment Day 1 of Month 7 (only if >30 days have elapsed since HGT-HIT-045 EOS procedures), and at 3-month intervals on the Pre-Treatment Day of monthly IT Dosing Weeks (ie, at Months 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, and 52).

Pre-treatment urine samples may be collected up to 24 hours prior to administration of each IT dose. Urinary GAG levels will be analyzed and reported as described in Section 8.3.9.4.

8.4.10 Auditory Brainstem Response

Hearing assessment via audiometry measurement will be performed when deemed necessary as described in Section 8.3.10 on Pre-Treatment Day 1 of Month 7 (only if >3 months have elapsed since HGT-HIT-045 EOS procedures), and on the Pre-Treatment Day of the 12-Month visits (ie, at Months 19, 31, and 43). It is anticipated that the patient will be under general anesthesia for this procedure.

8.4.11 Brain and Spinal Magnetic Resonance Imaging

Patients will have MRI of the brain and spine on Pre-Treatment Day 1 of Month 7 (only if >3 months have elapsed since HGT-HIT-045 EOS procedures), on the Pre-Treatment Day of the 12-Month visits (ie, at Months 19, 31, and 43). It is anticipated that the patient will be under general anesthesia for this procedure. Brain structure volumes will be measured and the brain and spine will be evaluated. Refer to the Study Operations Manual for specific procedures and precautions.

8.4.12 Intracranial Pressure Measurement

ICP measurement (cm of H_2O) will be performed at Month 7 on Pre-Treatment Day 1 (only if >30 days have elapsed since HGT-HIT-045 EOS), on the Pre-Treatment Day of the 12-Month visits (ie, at Months 19, 31, and 43). The ICP measurement will be conducted concurrently with the lumbar puncture (see Section 8.3.13) and while the patient is under anesthesia. Patients should undergo X-ray prior to the lumbar puncture to verify the position of the IDDD catheter.

8.4.13 Cerebrospinal Fluid (CSF) Assessments

CSF will be obtained via the IDDD immediately prior to IT injection of idursulfase-IT on IT Injection Day 2 of Month 7, on the IT Injection Day of each monthly IT Dosing Week.

Note: CSF standard chemistries, glucose, protein, and cell count assessments will be conducted at the local laboratory, however review of these results by the treating investigator is not required prior to each intrathecal idursulfase-IT dose. If a CSF sample cannot be obtained for 6 consecutive months, then a lumbar puncture will be performed. Additional CSF samples may also be collected throughout the study during any assessment or revision of the IDDD.

CSF samples collected at scheduled or unscheduled visits will undergo the following assessments (Section 8.4.13.1 through to Section 8.4.13.4). CSF sample collection, processing, and shipping instructions are provided in the Study Operations Manual.

8.4.13.1 CSF Cell Counts

An aliquot of the CSF sample collected will be evaluated for CSF standard chemistries, glucose, protein, and cell counts.

8.4.13.2 Immunoassay for Idursulfase-specific Antibodies

An aliquot of the CSF sample collected will be quick frozen for subsequent analysis of idursulfase-specific antibodies. Note that it is not required to perform antibody testing on CSF samples collected at unscheduled visits.

8.4.13.3 CSF Biomarker Analysis

An aliquot of the CSF sample collected will be quick frozen for subsequent analysis of levels of biomarkers (eg, GAG [HS/DS]).

8.4.13.4 CSF Analysis of Idursulfase Enzyme Levels

An aliquot of the CSF sample collected will be quick frozen for subsequent idursulfase enzyme analysis.

8.4.14 SOPH-A-PORT Mini S Device Assessments

SOPH-A-PORT Mini S device assessments will include measures of device implantation, device function, device longevity, and AEs associated with the device. These data will be collected on the patient's CRF from the time of implantation and continue throughout the study as long as the SOPH-A-PORT Mini S remains implanted. Please refer to the IDDD manual for further information.

8.4.15 Intrathecal Idursulfase-IT Injection

Idursulfase-IT will be injected intrathecally via the IDDD at each monthly (ie, every 28 [±7] days) IT Dosing Week. The patient may be mildly sedated for this procedure. Idursulfase-IT will be administered over 2 to 5 minutes. A visual examination of both the port and catheter track will be performed before each IT injection.

If the IT space is not accessible via the IDDD, idursulfase-IT may be administered by lumbar puncture (see Section 7.8).

8.4.16 Elaprase Infusion

Elaprase will be administered as an IV infusion at a weekly dose of 0.5 mg/kg in accordance with local prescribing information.

Patients will receive their weekly Elaprase infusion on every IT Dosing Week approximately 2 days after receiving their IT injection of idursulfase-IT (note that the Elaprase infusion should be administered even in instances in which the IT dose is not). Elaprase infusion may be administered at the main site or at the patient's local infusion location (site or home).

8.4.17 Neurological Examination

Neurological examination to monitor CNS status and any changes will be performed at minimum on Pre-Treatment Day 1 of Month 7 (only if >30 days have elapsed since HGT-HIT-045 EOS procedures), on the Pre-Treatment Day of each monthly IT Dosing Week.

8.4.18 Serum Anti-idursulfase Antibody and Plasma Proteomic Biomarker Determination

Patients will have blood samples collected at minimum on Pre-Treatment Day 1 of Month 7 (only if >30 days have elapsed since HGT-HIT-045 EOS procedures), and at 3-month intervals on the Pre-Treatment Day of Monthly IT Dosing Weeks (ie, at Months 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, and 52).

A 10-mL blood sample will be collected from each patient for the first sample; a 5-mL sample will be collected for all subsequent blood collections. Blood samples collected will be evaluated

for determination of anti-idursulfase antibodies, antibodies that have enzyme neutralizing activity, and potential exploratory plasma proteomic biomarkers of disease progression. Blood sample collection, processing, and shipping instructions are provided in the Study Operations Manual.

8.4.19 Neurodevelopmental Assessments

Patients will undergo neurodevelopmental assessments using appropriate standardized tests to provide a surrogate and quantifiable measure of global CNS neurodevelopmental status as described in Section 8.3.19. It is intended that full neurodevelopmental assessments of cognitive, motor, and adaptive functions be conducted for all patients; however, it is recognized that the feasibility of conducting these assessments is dependent on the patient's ability to cooperate and/or level of cognitive impairment, and that it may not be possible to complete full neurodevelopmental evaluation of every patient. A reasonable effort should be made to perform neurodevelopmental assessments for each patient; however, inability to collect these data may not be considered a protocol deviation.

8.4.19.1 Full Neurodevelopmental Assessment

A full neurodevelopmental assessment will be conducted on Pre-Treatment Day 1 of Month 7 (only if >3 months have elapsed since HGT-HIT-045 EOS procedures), and prior to treatment at the 6-Month and 12-Month IT Dosing Week visits (ie, at Months 13, 19, 25, 31, 37, 43, and 49).

Full neurodevelopment assessment tests are summarized in Table 8-3. For cognitive testing the first item set of the 6 main subtests of the DAS-II will be administered. If the patient cannot complete these, the BSID-III will be used to assess cognition.

8.4.20 Pharmacokinetic Evaluations

Serum samples for PK evaluation of idursulfase will be collected on IT Injection Day 2 of the 12-Month visits (ie, at Months 19, 31, and 43) and will be drawn at the following times:

- Within 15 minutes prior to IT injection, then at 1, 2, 3, 4, 6, 8, 12, 24, 30 and 36 hours following IT injection

The PK sampling schedule for the study is also located in Section 14 (Table 14-4). Sample collection, processing, and shipping instructions are provided in the Study Operations Manual.

Note that when vital sign collection and collection of a sample for PK analysis are scheduled to occur at the same time, vital sign collection should occur first and the blood draw for PK sampling should be performed as soon as possible after vital sign collection. The actual time of collection of the PK sample should be recorded.

8.5 Extended Treatment Phase (All Patients, from Month 55 to EOS) (Part C)

8.5.1 Physical Examinations

Physical examinations on Pre-Treatment Day 1 of the Month 55 visit will include a review of the patient's general appearance, device port and catheter track, and evaluations listed in Table 8-1. Thereafter, symptom-directed physical examinations may be performed at the investigator's discretion on the Pre-Treatment Day of each monthly IT Dosing Week, and at the EOS visit.

8.5.2 Height and Weight

Height and weight will be recorded on Pre-Treatment Day 1 of the Month 55 visit, at the 6-Month and 12-Month visits (ie, at Months 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151, 157, and 163), and at the EOS visit.

8.5.3 Head Circumference

Head circumference will be measured in a uniform manner on Pre-Treatment Day 1 of the Month 55 visit, and 12-Month visits (ie, at Months 67, 79, 91, 103, 115, 127, 139, 151, and 163), and at the EOS visit.

8.5.4 Vision Assessment

A vision assessment will be performed as described in Section 8.3.5 on Pre-Treatment Day 1 of the Month 55 visit, and at the EOS visit.

8.5.5 Hearing Assessment

A hearing assessment will be performed as described in Section 8.3.6 on Pre-Treatment Day 1 of the Month 55 visit, at the 12-Month visits (ie, at Months 67, 79, 91, 103, 115, 127, 139, 151, and 163), and at the EOS visit.

8.5.6 12-Lead Electrocardiogram

A 12-lead ECG will be performed after injection of study drug on Monthly IT Dosing Weeks at Months 55, 67, 79, 91, 103, 115, 127, 139, 151, and 163, and at the EOS visit. Each 12-lead ECG will include the assessments described in Section 8.3.7.

8.5.7 Vital Signs

Vital signs will be collected on Pre-Treatment Day 1 and on the IT Injection Day of each Monthly IT Dosing Week, and at the EOS visit.

At a minimum, vital signs will be collected at the following time points on IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes (±10 minutes) post end of IT administration, and upon discharge.

8.5.8 Clinical Laboratory Testing

Blood and urine samples will be collected for clinical laboratory testing as described in Section 8.4.9.1, Section 8.4.9.2, and Section 8.4.9.3. Sample collection, processing, and shipping instructions are provided in the Study Operations Manual.

8.5.8.1 Hematology

Blood samples will be collected for hematology testing (at minimum) at 6-month intervals on Pre-Treatment Day 1 of Monthly IT Dosing Weeks (ie, at Months 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151, 157, and 163), and at the EOS visit. The hematology parameters to be evaluated are described in Section 8.3.9.1.

8.5.8.2 Serum Chemistry

Blood samples will be collected for serum chemistry testing (at minimum) at 6-month intervals on Pre-Treatment Day 1 of Monthly IT Dosing Weeks (ie, at Months 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151, 157, and 163), and at the EOS visit. The serum chemistry parameters to be evaluated are described in Section 8.3.9.2 and listed in Table 8-2.

8.5.8.3 Standard Urinalysis

Urine samples will be collected for urinalysis (at minimum) at 6-month intervals on Pre-Treatment Day 1 of Monthly IT Dosing Weeks (ie, at Months 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151, 157, and 163), and at the EOS visit. Pre-treatment urine samples may be collected up to 24 hours prior to receipt of each IT dose. The urinalysis parameters to be evaluated are described in Section 8.3.9.3.

8.5.8.4 Urinary GAG Levels

Urine samples for determination of GAG levels and urine creatinine will be collected (at minimum) at 6-month intervals on Pre-Treatment Day 1 of Monthly IT Dosing Weeks (ie, at Months 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151, 157, and 163), and at the EOS visit.

Pretreatment urine samples may be collected up to 24 hours prior to administration of each IT dose. Urinary GAG levels will be analyzed and reported as described in Section 8.3.9.4.

8.5.9 Auditory Brainstem Response

Hearing assessment via audiometry measurement will be performed when deemed necessary as described in Section 8.3.10 on Pre-Treatment Day 1 of the Month 55 visit, at the 12-Month visits (ie, at Months 67, 79, 91, 103, 115, 127, 139, 151, and 163), and at the EOS visit. It is anticipated that patients will be under general anesthesia for this procedure.

8.5.10 Brain and Spinal Magnetic Resonance Imaging

Patients will have MRI of the brain and spine on Pre-Treatment Day 1 of the Month 55 visit, at the 12-Month visits (ie, at Months 67, 79, 91, 103, 115, 127, 139, 151, and 163), and at the EOS visit. It is anticipated that patients will be under general anesthesia for this procedure. Brain structure volumes will be measured and the brain and spine will be evaluated. Refer to the Study Operations Manual for specific procedures and precautions.

8.5.11 Intracranial Pressure Measurement

ICP measurement (cm of H_2O) will be performed on Pre-Treatment Day 1 of the Month 55 visit and at the EOS visit. The ICP measurement will be conducted concurrently with the lumbar puncture (see Section 8.3.13) and while the patient is under anesthesia. Patients should undergo X-ray prior to the lumbar puncture to verify the position of the IDDD catheter.

8.5.12 Cerebrospinal Fluid Assessments

Cerebrospinal fluid will be obtained via the IDDD immediately prior to IT injection of idursulfase-IT on IT Injection Day 2 of Month 55 and on the IT Injection Day of each monthly IT Dosing Week.

Note: CSF standard chemistries, glucose, protein, and cell count assessments will be conducted at the local laboratory, however review of these results by the treating investigator is not required prior to each intrathecal idursulfase-IT dose. If a CSF sample cannot be obtained for 6 consecutive months, then a lumbar puncture will be performed. Additional CSF samples may also be collected throughout the study during any assessment or revision of the IDDD.

Cerebrospinal fluid samples collected at scheduled or unscheduled visits will undergo the analyses described in Section 8.4.13.1 through to Section 8.4.13.4. Measurements of GAG, idursulfase enzyme, and anti- idursulfase antibody levels in CSF samples will be analyzed (at minimum) at 6-month intervals at Months 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151, 157, and 163), and at the EOS visit.

Cerebrospinal fluid sample collection, processing, and shipping instructions are provided in the Study Operations Manual.

8.5.13 SOPH-A-PORT Mini S Device Assessments

SOPH-A-PORT Mini S device assessments will be performed as described in Section 8.4.14.

8.5.14 Intrathecal Idursulfase-IT Injection

Idursulfase-IT will be injected intrathecally via the IDDD at each monthly (ie, every 28 [±7] days) IT Dosing Week. The patient may be mildly sedated for this procedure.

Idursulfase-IT will be administered over 2 to 5 minutes. A visual examination of both the port and catheter track will be performed before each IT injection.

If the IT space is not accessible via the IDDD, idursulfase-IT may be administered by lumbar puncture (see Section 7.8).

8.5.15 Elaprase Infusion

Elaprase will be administered as an IV infusion at a weekly dose of 0.5 mg/kg in accordance with local prescribing information.

Patients will receive their weekly Elaprase infusion on every IT Dosing Week approximately 2 days after receiving their IT injection of idursulfase-IT (note that the Elaprase infusion should be administered even in instances in which the IT dose is not). Elaprase infusion may be administered at the main site or at the patient's local infusion location (site or home).

8.5.16 Neurological Examination

Neurological examination to monitor CNS status and any changes will be performed on Pre-Treatment Day 1 of the Month 55 visit. Thereafter, symptom-directed neurological examinations will be performed at the investigator's discretion on Pre-Treatment Day 1 of each monthly IT Dosing Week, and at the EOS visit.

8.5.17 Serum Anti-idursulfase Antibody

Patients will have blood samples collected (at minimum) at 6-month intervals on Pre-Treatment Day 1 of Monthly IT Dosing Weeks (ie, at Months 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151, 157, and 163), and at the EOS visit for determination of anti-idursulfase antibodies.

A 10-mL blood sample will be collected from each patient for the first sample; a 5-mL sample will be collected for all subsequent blood collections. Blood samples collected will be evaluated for determination of anti-idursulfase antibodies and antibodies that have enzyme neutralizing activity. Blood sample collection, processing, and shipping instructions are provided in the Study Operations Manual.

8.5.18 Neurodevelopmental Assessments

A full neurodevelopmental assessment will be conducted on the Pre-Treatment Day 1 of the Month 55 visit. Full neurodevelopment assessment tests are summarized in Table 8-3.

Thereafter, a limited neurodevelopmental assessment, focused on neurocognitive function, will be performed. The SIBR, BRIEF/BRIEF-P, PDMS, BOT-2 will no longer be administered. For

cognitive testing the first item set of the 6 main subtests of the DAS-II will be administered. If the patient cannot complete these, the BSID-III will be used to assess cognition.

The limited neurodevelopmental assessment will be conducted on the Pre-Treatment Day 1 of the 12-Month visits (ie, at Months 67, 79, 91, 103, 115, 127, 139, 151, and 163), and at the EOS visit. Subjects exceeding 17 years 11 months of age will no longer undergo neurodevelopmental assessment using the DAS-II.

8.6 Device-related Study Procedures

8.6.1 IDDD Implantation or Revision Procedures

The IDDD will be surgically implanted or revised at the main clinical site. Procedures for implantation and revision are detailed in the device's Instructions for Use.

Standard hospital procedures for surgery will be followed; the patient will be under general anesthesia for this procedure.

An additional medical device, the catheter passer, is necessary for the implantation procedure. The catheter passer is a sterile, single use device that will be used in the subcutaneous placement of the catheter. The Phoenix Neuro Disposable Catheter Passer, manufactured by Sophysa is CE marked in the EU and cleared under K853370 in the US and may be provided; however, use of other catheter passers compatible with the SOPH-A-PORT Mini S is allowed. Compatible catheter passers must be able to support a catheter with an outer diameter of 1.6 mm.

8.6.2 Device Removal

It is planned that device explantation will occur at the main site unless urgent device removal is medically required to be performed at a local site.

For the SOPH-A-PORT Mini S, if at the time of a scheduled dosing it is not possible due to a device-related issue to aspirate CSF prior to dose administration, administer a full medication dosage as per the standard administration steps detailed in the SOPH-A-PORT Mini S Instructions for Use, or flush the system following dose administration, the IDDD will be declared a device malfunction. If the device malfunction is irreversible and cannot be corrected without a device surgical intervention (ie, partial or full device revision or removal), 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 SOPH-A-PORT Mini S device and/or device components will be re-implanted at the earliest possible opportunity, preferably at the same time. Details of the device removal will be recorded in the patient's eCRF. Refer to the device's Instructions for Use for further details.

Patients who have a PORT-A-CATH IDDD device failure may have this device replaced by a SOPH-A-PORT Mini S; the nonfunctional PORT-A-CATH IDDD will be removed and replaced with the SOPH-A-PORT Mini S device at a time judged appropriate by the investigator. A nonfunctional PORT-A-CATH IDDD cannot be replaced by a new PORT-A-CATH device.

Patients should have the IDDD removed when they discontinue from the study, unless they are continuing to receive treatment through another mechanism (eg, supplemental study, expanded access program, etc) or the investigator determines that it should not be removed based upon safety assessments. The device can remain in the patient (partial [catheter only] or full [port, catheter, and suture wings]) if the patient is doing clinically well and there are no known risk factors such as infection (eg, meningitis). The device may be partially or fully removed as medically required and determined by the neurosurgeon at a future date.

9 ADVERSE EVENTS

9.1 Definitions of Adverse Events and Serious Adverse Events

9.1.1 Adverse Events

An adverse event (AE) is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, and/or laboratory changes occurring in any phase of a clinical trial, and whether or not considered study drug-related. This includes an exacerbation of a pre-existing condition. Once the patient signs the informed consent/assent, any AE prior to the start of study drug must be reported. Adverse events will be collected until the EOS visit, and/or until the event has been resolved/stabilized or an outcome is reached, whichever comes first.

AEs include:

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

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

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

9.1.2 Serious Adverse Event Definition

An (SAE) is any AE occurring at any dose that results in any of the following outcomes:

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A life-threatening AE is defined as an AE that placed the patient, in the view of the initial reporter, at immediate risk of death from the AE as it occurred (ie, it does not include an AE that, had it occurred in a more severe form, might have caused death). Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s). Furthermore, this does not apply to device failures resulting in scheduled surgical revisions, which should be reported as SAEs.

9.1.3 Unanticipated Adverse Device Effect Definition

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).

9.1.4 SOPH-A-PORT Mini S Device-associated Definitions

9.1.4.1 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.

9.1.4.2 Device Malfunction

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

9.1.4.3 Device Failure

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

9.1.4.4 Device Adjustment

Device adjustment is defined as surgery of the device which does not result in partial or complete device revision or removal (eg, surgical exploration only or placement of additional sutures, tissue glue, and/or fascial repair).

9.1.5 Classification of Adverse Events and Serious Adverse Events

The National Cancer Institute Common Terminology Criteria (NCI CTC) Version 4.0 grading scale should be referenced when assessing the severity of an AE (provided in the Study Operations Manual).

If an AE is not described in the NCI CTC, the severity should be recorded based on the scale below (Table 9-1). The severity of AEs/SAEs should be recorded on the appropriate CRF page as Grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or fatal.

Table 9-1 Classification of AE/SAE Severity

Severity	Definition
Grade 1 (Mild)	No limitation of usual activities
Grade 2 (Moderate)	Some limitation of usual activities
Grade 3 (Severe)	Inability to carry out usual activities
Grade 4 (Life-threatening)	Immediate risk of death
Grade 5 (Fatal)	Death

The relationship of an AE or SAE to the study treatment (ie, study drug [idursulfase-IT], device [PORT-A-CATH or SOPH-A-PORT IDDD], device surgical procedure, or IT administration process) will be determined by the investigator and classified based on the relatedness definitions provided in Table 9-2.

Table 9-2 Classification of AE/SAE Relatedness

Relationship	Definition
Not Related	Unrelated to study drug, device, device surgical procedure, or IT administration process.
Possibly Related	A clinical event/laboratory abnormality with a reasonable time sequence to administration of study drug, device, device surgical procedure, or IT administration process but which could also be explained by concurrent disease or other drugs/chemicals.
Probably Related	A clinical event/laboratory abnormality with a reasonable time sequence to administration of study drug, 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/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 study drug, 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.

In addition, the relationship of an AE or SAE to IV Elaprase infusion will be assessed by the investigator as not related, possibly related, probably related, or definitely related.

9.1.5.1 Categories of Adverse Events

Adverse events collected throughout this study will be categorized as follows:

Device Surgical Procedure-related Adverse Events

Examples of AEs 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 postoperative complications (such as post-operative infection).

Device-related Adverse Events

Examples of IDDD-related AEs include, but are not limited to, the physiologic consequences (noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes) of 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 9.1.4.2) should not be entered as an AE unless it has physiopathological consequences such as those listed above. In the event of a device failure (defined in Section 9.1.4.3), the device will need a partial or complete revision or removal. If overnight hospitalization is required for such a procedure (or the device failure meets any other serious criteria, eg, medically important), the "device failure" will be reported as an SAE. Details of the cause of SOPH-A-PORT Mini S IDDD malfunction or failure will be recorded on the device malfunction and failure CRF and the SAE form (where applicable).

A list of the most common AEs related to the SOPH-A-PORT Mini S is reproduced from the device Instructions for Use in Appendix 4.

A list of the most common AEs related to the PORT-A-CATH is reproduced from the device Instructions for Use in Appendix 5.

Intrathecal Administration Process Adverse Events

Examples of AEs related to the IT administration process include, but are not limited to, the following: AEs caused by anesthesia during drug administration or other drug administration issues (eg, extravasation during infusion or hematoma due to the Huber needle), or complications of lumbar puncture.

Idursulfase-IT-related Adverse Events

It is not possible to predict study drug-related AEs in humans based on data from animals where intrathecally administered idursulfase was observed to be well tolerated.

The most common (reported in at least 2 patients) events with a potential causal relationship to idursulfase-IT in Studies HGT-HIT-045 and HGT-HIT-046 have included agitation, vomiting, pyrexia, changes in heart rate, blood pressure, oxygen saturation, body temperature, CSF protein, and cell count. All of these events were nonserious. Please see the current edition of the investigator's brochure for details.

Because idursulfase-IT is administered intrathecally in this study, it is not expected that systemic blood levels will be high enough to cause an infusion-related reaction. However, systemic exposure resulting from diffusion from the CSF into the peripheral circulation has the potential to cause events that have been seen in patients receiving Elaprase and other ERTs known as infusion-related reactions.

IV Elaprase infusion-related Adverse Events

Infusion-related reactions have been observed in patients receiving IV ERT with Elaprase, with symptoms including cutaneous reactions (rash, pruritus, and urticaria), pyrexia, headache, hypertension, and flushing. An Elaprase-associated infusion-related reaction will be defined as an AE that begins either during or within 24 hours after the start of IV infusion, and is judged as at least possibly related to the infusion.

9.1.5.2 Clarification between Serious and Severe

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

9.2 Adverse Event Monitoring and Period of Observation

For the purposes of this study, the period of observation extends from the time the patient's parent(s) or the patient's legally authorized representative(s) gives informed consent until the EOS visit, and/or until the event has been resolved/stabilized or an outcome is reached, whichever comes first.

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

9.3 Procedures for Recording and Reporting Adverse Events

9.3.1 Serious Adverse Event Reporting

Any SAE, regardless of the relationship to the study drug, device, device surgical procedure, IT administration process, or IV infusion of Elaprase which occurs in a patient after informed consent, should be recorded by the clinical site on an SAE form. The SAE must be completely described on the patient's CRF, including the judgment of the investigator as to the relationship

of the SAE to the study drug, device, device surgical procedure, IT drug administration process, or IV infusion of Elaprase.

The investigator will promptly supply all information identified and requested by the sponsor (and/or contract research organization [CRO]) regarding the SAE. The investigator must report the SAE to the sponsor's safety department AND to the Shire medical monitor on an SAE form. This form must be completed and FAXED OR EMAILED within 24 hours of the investigator learning of the event to:

Sponsor's Safety Department:

International FAX: +1 484 595 8155 (Global)

drugsafety@shire.com

AND

Shire Medical Monitor:

[redacted], DO

[redacted]

[redacted]

Shire

MOBILE: [redacted] **(24-hour access)**

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

In the event of a severe and unexpected, fatal, or life-threatening SAE, the clinical site must contact the Shire medical monitor by telephone; this is in addition to completing and transmitting the SAE form as stated above. The contact information for the Shire medical monitor is provided above.

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.

The investigator must promptly report all SAEs and any unanticipated problems involving risk to human patients in a timely manner to his/her IRB/IEC. It is the responsibility of the sponsor to

ensure that each investigator receives a copy of any MedWatch/CIOMS I/MDR report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected drug-related SAE or UADE. The investigator or sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files. The investigator or sponsor must also ensure that the IRB/IEC receives copies of UADE reports that have been submitted by the device manufacturer (or designated agent) to the relevant regulatory agencies.

9.3.2 Eliciting Adverse Events

Patients should be asked non-leading questions, eg, "How do you feel?" and further questions should be posed if there is indication of an AE. The questioning should be conducted with due regard for objectivity and, in particular, the questioner should gather information regarding AEs from questioning the patient, the patient's parent/legally authorized representative, spontaneous report by the patient or parent/legally authorized representative, laboratory reports, and any health care provider's observations.

The onset date, resolution date, treatment administered, and outcome of each AE must be recorded on the appropriate CRF. In addition, the relationship of each AE to study drug must be recorded.

9.3.3 Protocol Deviations for Medical Emergency or Adverse Event

During and following a patient's participation in the study, the investigator should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory test results. The investigator should inform the patient, the patient's parent(s), or the patient's legally authorized representative(s) when medical care is needed for intercurrent illness(es) of which the investigator becomes aware. In an emergency situation, the investigator should contact the Shire medical monitor (see Section 9.3.1).

Only when an emergency occurs that requires an immediate deviation from the protocol for the safety of a patient, will there be such a deviation and this will be only for that patient. The investigator or other physician in attendance in such an emergency must contact the Shire medical monitor as soon as possible. The investigator, along with the Shire medical monitor, will make a decision as to whether or not the patient should continue in the study. The departure from the protocol and the grounds for it should be stated in the CRF.

9.4 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose or medication error must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 9.3.1.

- **Abuse** – Persistent or sporadic intentional intake of investigational medicinal product at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (eg, altering one's state of consciousness)
- **Misuse** – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note that this includes a situation where the test article is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of the investigational medicinal product, with the exception of the protocol-specified dose and dose frequency, or a dose 2-times higher than the protocol-specified dose.
- **Medication Error** – A mistake made in prescribing, dispensing, administration and/or use of the investigational medicinal product.

The investigator must report abuse, misuse, overdose, and medication errors to the sponsor's safety 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 9.3.1).

9.5 Safety-related Study Stopping Rules

If at least 1 patient experiences a life-threatening (Grade 4) AE or death (Grade 5) which is considered either possibly, probably, or definitely related to the study treatment (study drug, device, device surgical procedure, or the IT administration process) or if 2 or more patients experience a Grade 3 or higher AE during the trial, which is considered possibly, probably, or definitely related to the study treatment (study drug, device, device surgical procedure, or the IT administration process), then all sites will be instructed to halt further intrathecal idursulfase-IT administration to all patients. All available data relating to the safety of idursulfase-IT will be reviewed. 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 will be monitored on a continuous basis during this study until the last patient completes his last scheduled study visit/assessment.

9.6 Concomitant Medications, Therapies, and Medical/Surgical Procedures

All non-protocol treatments from informed consent and through the EOS visit are regarded as concomitant and will be documented on the appropriate pages of the CRF.

These include medications (eg, Elaprase), therapies/interventions administered to patients, and medical/surgical procedures performed on the patients.

All patients are to receive Elaprase during the study. Elaprase will be prescribed by the patient's physician and will be administered in accordance with local prescribing information.

9.6.1 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
- Pre-treatment 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 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). Pre-treatment 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 pretreatment 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.

9.7 Removal of Patients from the Trial

The patient or the patient's parent(s) or legally authorized representative(s) acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. For this protocol, withdrawn patients will not be replaced.

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

- Non-compliance, including failure to appear at one or more study visits
- The patient was erroneously included in the study
- The patient suffers an intolerable AE
- The study is terminated by the sponsor

If the patient or the patient's parent(s) or legally authorized representative(s), acting on behalf of the patient, discontinues participation in the study, or the patient is discontinued by the investigator, the Patient Completion/Discontinuation CRF describing the reason for discontinuation must be completed. Any AEs experienced up to the point of discontinuation must be documented on the AE CRF.

If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal should be followed until resolution.

10 STATISTICAL METHODS

10.1 General Statistical Methodology

This is an open-label extension of study HGT-HIT-045 to evaluate the long-term safety and clinical outcomes of intrathecal idursulfase-IT, administered in conjunction with Elaprase, in pediatric patients with Hunter syndrome and cognitive impairment. The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of the trial.

The study data will be combined with that of studies HGT-HIT-045 and HGT-HIT-050 for analysis as appropriate. The efficacy and safety analyses will be based on the idursulfase-IT treatment baseline (abbreviated as treatment baseline), which is prior to the initial IDDD implant date. This treatment baseline for the treated patients in HGT-HIT-045 is the closest available screening assessment (including the HGT-HIT-050 screening data) on or before the randomization date in HGT-HIT-045. The treatment baseline for the untreated patients in HGT-HIT-045 is the closest available assessment (including HGT-HIT-045 and HGT-HIT-050 data if necessary) prior to the IDDD implantation date in HGT-HIT-046.

No formal statistical testing is planned. Descriptive analyses of the data before trial completion may be performed for safety monitoring, regulatory reporting, or general planning purposes.

An interim clinical study report is planned describing the results of Parts A and B. The complete results, including Part C, will be described in the final clinical study report.

10.2 Patient Disposition and Demographics

Patient disposition (signed informed consent, treatment status, completed, discontinued/withdrew) will be presented in summary tables using number and percentage of patients per dose. Reasons for discontinuation/withdrawal will be presented.

Demographic and baseline characteristics (eg, age, race, ethnicity, and baseline disease status) will be reported in summary tables.

10.3 Efficacy, Safety, and Pharmacokinetic Evaluations

10.3.1 Populations for Analyses

The following 2 classifications of patients based on their treatment status will determine how their data will be pooled for statistical analysis.

Population	Criteria for Inclusion
Safety	All eligible patients from HGT-HIT-045 who have agreed to participate in the extension study and have had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study.
Pharmacokinetic	All patients who receive study drug and participate in the scheduled PK studies, and have at least 1 reported serum or CSF concentration of idursulfase.

Abbreviations: CSF = cerebrospinal fluid; IDDD = intrathecal drug delivery device; PK = pharmacokinetic

Device-related analyses will be conducted separately for the PORT-A-CATH and SOPH-A-PORT devices, as well as devices combined, in the set of patients in the safety population who had the corresponding device implant procedure performed.

10.3.2 Primary Analyses

10.3.2.1 Safety and Tolerability Assessments

The assessment of safety will be performed in the safety population, primarily on the frequency of treatment-emergent AEs, and on the frequency of clinically notable abnormal laboratory values.

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 or later.

Treatment-emergent AEs, defined as all AEs occurring on or after the first IDDD surgery date or first dose (whichever is earlier) for the patient (whether it is in this extension study or in HGT-HIT-045) and before the EOS visit (+30 days), will be summarized by dose group and overall. The number and percentage of patients having AEs will be presented by system organ class (SOC) and preferred term, and by severity and relationship to study drug and IV Elaprase infusion. In addition, any event which resulted in death or was otherwise classified as serious will be presented in a separate listing.

Intrathecal drug delivery device and procedure-related AEs will also be summarized by SOC and preferred term. For the PORT-A-CATH and SOPH-A-PORT devices, separate tabulations will be provided for AEs related to the IDDD, device surgical procedure, and IT administration process.

The infusion (IV) and injection (IT) vital sign measurements will be shown in individual patient line graphs over time by visit.

10.3.2.2 Laboratory Evaluations

Clinical laboratory results (hematology, serum chemistry, urinalysis) and the results of analysis of CSF parameters will be summarized and, for selected parameters, presented as the number and percentage of patients with post-baseline values categorized as follows:

- Clinically significant (CS): The patient had at least one clinically significant value at any time during the study post baseline;
- Not clinically significant (NCS): The patient had no clinically significant value at any time during the study post baseline, but had at least one abnormal value,
- Normal (N): The patient had no abnormal or clinically significant value at any time during the study post baseline.

10.3.2.3 Anti-Idursulfase Antibody Formation

Anti-idursulfase antibody formation and enzyme neutralizing activity in serum and CSF will be monitored throughout the study. Results will be summarized and presented graphically by visit, dose, and overall.

Antibody and neutralizing antibody status will be presented as shift tables by visit, dose, and overall. The titer will be presented graphically by visit for each patient with a positive result. The percent inhibition will be graphed by visit for each patient with a positive neutralizing antibody result.

10.3.3 Secondary Analyses

10.3.3.1 Pharmacodynamic Analyses

The observed CSF and urine GAG values, the change from baseline, and the percent change from baseline in these values will be summarized descriptively by dose and overall.

10.3.3.2 Pharmacokinetic Analyses

The PK analysis will be conducted by the Clinical Pharmacology and PK Department of Shire Pharmaceuticals or its designee using Phoenix WinNonlin version 6.2 or higher (Pharsight Corporation, Mountain View, California, USA).

Idursulfase concentrations in serum and CSF will be determined using a validated enzyme-linked immunosorbent assay (ELISA) method. The idursulfase concentrations in serum will also be determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method for the serum samples collected at Week 3 and Week 23 only. The LC-MS/MS method is expected to be less susceptible to interference by anti-idursulfase antibodies.

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 assay method (ELISA or LC-MS/MS), route of administration (IV and IT administration), dose (0.5mg/kg for IV administration; 10mg and 30mg for IT administration), and visit (Week 3 and Week 23 for the initial treatment phase [previously untreated patients in HGT-HIT-045], and Months 19, 31, and 43 for the Extended Treatment Phase).

For the IT treatment, the PK parameters will include, but not be limited to, the following:

- $AUC_{0-\infty}$ - 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
- C_{max} - Maximum concentration occurring at t_{max}
- t_{max} - Time of maximum observed concentration sampled during a dosing interval
- Cl/F - Total body clearance for extravascular administration divided by the fraction of dose absorbed. This parameter will be presented with and without normalization for body weight.
- V_z/F - Volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed. This parameter will be presented with and without normalization for body weight.
- λ_z - First order rate constant associated with the terminal (log-linear) portion of the curve
- $t_{½}$ - Terminal half-life

For the IV treatment, the PK parameters will include, but not be limited to the following:

- $AUC_{0-\infty}$ - 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
- C_{max} - Maximum concentration occurring at t_{max}
- t_{max} - Time of maximum observed concentration sampled during a dosing interval

- Cl - Total body clearance got IV administration. This will be presented with and without normalization for body weight.
- V_z - Volume of distribution associated with the terminal slope. This parameter will be presented with and without normalization for body weight
- V_{ss} - Observed steady-state volume of distribution. This parameter will be presented with and without normalization for body weight.
- MRT - Mean residence time
- $t_{½}$ - Terminal half-life

Summary statistics (number of observations, mean, SD, coefficient of variation, median, maximum, minimum, and geometric mean) will be determined for all PK parameters and presented by assay method (ELISA or LC-MS/MS), route of administration, dose, and visit. Serum concentrations of idursulfase at each nominal sampling time will also be summarized by assay method, route of administration, dose, and visit using descriptive statistics.

10.3.3.3 SOPH-A-PORT Mini S IDDD Safety and Performance

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

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

The rate of successful IDDD injections will be calculated for each patient and summarized descriptively. The 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.

10.3.3.4 Exploratory Endpoints

Descriptive statistics for the observed value and change from baseline of the neurodevelopment parameters will be summarized by visit, dose group, and overall. Individual patient values will be listed. Observed value and mean change from baseline line plots of neurodevelopment parameters by study visit (month) and patient will be presented for DAS-II and SIB-R parameters. Scatter plots and correlations between the following parameters will be presented:

- Standard score for General Conceptual Ability (GCA) and Verbal, Nonverbal, Spatial and Special Nonverbal Composite (SNC) scores in DAS-II
- Standard score for GCA in DAS-II and standard scores for SIB-R
- Standard score for GCA and average CSF GAG level

The planned analyses and presentations including any exploratory group comparisons will be defined in the SAP.

10.3.3.5 Protocol Violations

Protocol violations will be defined as any major protocol deviation that affects study evaluations. A list of protocol violations will be presented.

11 ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

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 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 current version of the Declaration of Helsinki.

11.2 Investigators and Administrative Information

Before initiation of the study, the investigators must provide the sponsor with a completed Form Food and Drug Administration (FDA) 1572 or Investigator Agreement. Study drug may be administered only under the supervision of the investigators listed on these forms. Curriculum vitae must be provided for the investigators and sub-investigators listed on Form FDA 1572. As the study involves use of an investigational device and 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).

11.3 Delegation of Responsibilities

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

11.4 Investigator 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.

11.5 Institutional Review Board/ Independent Ethics Committee/Research Ethics Board

Before initiation of the study, the investigator must provide the sponsor with a copy of the written IRB/IEC/research ethics board (REB) 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 study protocol, as given by the sponsor on the cover page of the protocol.

Status reports must be submitted to the IRB/IEC at least once per year. The IRB/IEC must be notified of completion of the study. Within 3 months of study completion or termination (or as required), a final report must be provided to the IRB/IEC. A copy of these reports shall be sent to the study clinical monitor. The investigator 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 AEs which are reported to the US FDA (IND Safety Reports) or other regulatory agencies, and UADEs reported to regulatory agencies must be submitted promptly to the IRB/IEC/REB. Unanticipated adverse device effects will be reported to regulatory agencies by the device manufacturer consistent with applicable regulations. Copies of UADE reports will be submitted to the IRB/IEC/REB in a timely fashion.

11.6 Data and Safety Monitoring Board

Not applicable to this study.

11.7 Patient Information and Informed Consent

Before enrolling in the clinical study, each patient, the patient's parent(s), or the patient's legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him/her. An informed consent form that includes information about the study will be prepared and given to the patient, the patient's parent(s), or the patient's legally authorized representative(s). This document will contain all required elements per ICH and meet all applicable regulatory requirements. The informed consent form must be in a language understandable to the patient, the patient's parent(s), or the patient's legally authorized representative(s) and must specify who informed the patient, the patient's parent(s), or the patient's legally authorized representative(s). Note: When a patient has reached the legal age of consent to participate in a clinical study, but has been deemed by the investigator, in accordance with applicable law, as lacking mental capacity to provide informed consent, the patient's parent(s) or legally authorized representative(s) will be asked to provide informed consent on behalf of the patient to allow for continued participation in the trial.

After reading the informed consent document, the patient, the patient's parent(s), or the patient's legally authorized representative(s) must give consent in writing. The patient's assent (as relevant) 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, the patient's parent(s), or the patient's legally authorized representative(s) is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to the patient must take place in the presence of an impartial witness.

Consent must be confirmed at the time of consent orally and by the personally dated signature of the patient, or by a local legally recognized alternative (eg, the patient's thumbprint or mark) or by the personally dated signature of the patient's parent(s) or the patient's legally authorized representative(s). The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent was given.

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

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

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

11.8 Patient Confidentiality

Patient names will not be supplied to the sponsor. Only the patient number and 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.

11.9 Protocol Compliance

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 authority(ies) 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 authority(ies) 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 authority(ies) in accordance with the governing regulations.

A record of patients screened, but not entered into the study, is also to be maintained. There will be no protocol exemptions 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 on the appropriate page of the CRF.

11.10 Protocol Amendments

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 Case Report Form Completion

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 re-signing the CRF.

11.12 Study Monitoring

Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed whenever possible; however, remote data review and verification may also be conducted during unavoidable circumstances (such as the COVID-19 pandemic) to ensure data quality and integrity and maintain patient safety.

The study will be monitored by the sponsor or its designee.

Whenever possible, monitoring will be done by personal visits from a representative of the sponsor (Clinical Study Monitor) who will review the CRFs and source documents to ensure data quality and integrity and maintain patient safety. Remote monitoring and data review may also be conducted to mitigate significant business disruption during unavoidable circumstances, such

as the COVID-19 pandemic. The 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).

Regulatory authorities, the IEC/IRB, and/or the sponsor may request access to all source documents, CRFs, and other study documentation for audit or inspection. Access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11.13 Packaging and Labeling

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

11.13.1 Study Drug

Idursulfase-IT drug product is a sterile liquid formulation for IT administration that is packaged in 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.

11.13.2 Intrathecal Drug Delivery Device(s)

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.

11.14 Storage and Accountability

11.14.1 Study Drug

The idursulfase-IT drug product is stored at 5 (±3)°C.

The fate of all idursulfase-IT study drug delivered to an investigator must be recorded on a patient-by-patient basis. The date and time of administration of the study drug will be documented on the appropriate CRF.

All unused study drug and other study materials are to be returned to the sponsor or its designee or disposed after sponsor approval per site policy after accountability has been performed.

11.14.2 Intrathecal Drug Delivery Device(s)

The SOPH-A-PORT and PORT-A-CATH IDDDs are both sterile, single-use devices. The disposition of all 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 study drug and use of the device must be documented on the patient's appropriate eCRF.

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

Please refer to the IDDD manuals for device return instructions.

11.15 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.

11.16 Premature Closure of the Study

11.16.1 Study Termination

If the sponsor or an investigator discovers 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 Shire and the investigator. In addition, a decision on the part of Shire to suspend or discontinue development of the study drug may be made at any time.

11.16.2 Site Termination

A specific site may be terminated separate from the general study for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site.
- Failure of the investigator to enter patients at an acceptable rate.
- 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.

11.16.3 Record Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there is 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/institution as to when these documents no longer need to be retained.

12 PUBLICATION OF STUDY FINDINGS

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 investigators agree 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, ethics committees, REBs, 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.

Shire may perform analyses of interim study data for the purpose of publication.

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14 APPENDIX 1: SCHEDULE OF STUDY PROCEDURES

Table 14-1 Study Procedures for the Initial Treatment Phase: For Patients Who Were Not Treated Previously in Study HGT-HIT-045 with Intrathecal Idursulfase-IT (Part A)

	Screening/Baseline	Surgery Week 1				Post-op Week 2	IT Dosing Weeks 3, 7, 11, 15, 19, 23			Interim Tx Weeks	
Assessment	EOS HGT-HIT-045 (or Day -30 to Day 1 Pre-Surgery)	Day 1 Pre-Surgery	Day 2 Surgery	Days 3-6	Day 7	Days 8-14	Pre-Tx[b] Day 1	IT Injection Day 2	Days 3-7	Weeks 4-6, 8-10, 12-14, 16-18, 20-22; 24-26	Month 7 (Week 27)[g]
Location	Main Site	Main Site	Main Site	Main Site	Main Site	Local	Main Site	Main Site	Main Site	Local	Main Site
Informed Consent[a]	●					●					
Physical Examination	●[q]	●[c]			●		●		●[n]		●
Height and Weight	●[q]	●[c]			●		●				●
Head Circumference	●[q]						●[d]				●
Vision Assessment	●[r]										●
Hearing Assessment	●[r]						●[d, k]				●
12-lead ECG	●[q]	●[c]					●[d]	●[h]			●
Vital Signs	●[q]	●	●	●[s]	●		●	●[s]	●[s]		●
Hematology	●[q]	●[c]					●				●
Serum Chemistry	●[q]	●[c]					●				●
Standard Urinalysis	●[q]	●[c]					●				●
Urine GAG	●[q]						●				●
Anti-idursulfase Antibody Testing	●[q]						●				●
Plasma Proteomic Marker Testing	●[q]						●				●
General Anesthesia	●[r]		●								●
Auditory Brainstem Response	●[r]										●
Brain and Spine MRI	●[r]										●
IDDD Implantation			●								
X-ray[m]			●								●[p]
Post-op Check of Wound					●						
ICP Measurement	●[q]										●

Table 14-1 Study Procedures for the Initial Treatment Phase: For Patients Who Were Not Treated Previously in Study HGT-HIT-045 with Intrathecal Idursulfase-IT (Part A)

	Screening/Baseline	Surgery Week 1				Post-op Week 2	IT Dosing Weeks 3, 7, 11, 15, 19, 23			Interim Tx Weeks	
Assessment	EOS HGT-HIT-045 (or Day -30 to Day 1 Pre-Surgery)	Day 1 Pre-Surgery	Day 2 Surgery	Days 3-6	Day 7	Days 8-14	Pre-Tx[b] Day 1	IT Injection Day 2	Days 3-7	Weeks 4-6, 8-10, 12-14, 16-18, 20-22; 24-26	Month 7 (Week 27)[g]
Location	Main Site	Main Site	Main Site	Main Site	Main Site	Local	Main Site	Main Site	Main Site	Local	Main Site
CSF Sample Collection	●[q]		●					●[e]			●
Idursulfase-IT Injection[l]								●			
Elaprase Infusion				●		●			●[f]	●	
Blood Sample for PK								●[j]	●[j]		
Neurological Examination	●[q]	●[c]		●[o]			●		●[o]	●[i]	●
Brief Neurodevelopmental Assessment							●[k]				
Full Neurodevelopmental Assessment[l]	●[r]						●[d]				●
Concomitant Medications, Therapies, and Procedures	●	●	●	●	●	●	●	●	●	●	●
Adverse Event Monitoring	●	●	●	●	●	●	●	●	●	●	●

Abbreviations: CSF = cerebrospinal fluid; ECG = electrocardiogram; GAG = glycosaminoglycan; Local = patient local Elaprase infusion site; ICP = intracranial pressure; IDDD = intrathecal drug delivery device; MRI = magnetic resonance imaging; PK = pharmacokinetics; Tx = treatment; LP = lumbar puncture; IT = intrathecal.

[a] Informed consent must be obtained from the patient's parent(s)/legally authorized representative(s) before beginning Screening/Baseline procedures. During Study HGT-HIT-046, patients who exceed the age of enrollment eligibility for the Study HGT-HIT-045 will be allowed to continue participation in Study HGT-HIT-046 until the end of the study. Patients will be re-consented once they have reached the applicable legal age of consent to participate in the clinical study. If the patient has been deemed by the investigator, in accordance with applicable law, as lacking mental capacity to provide informed consent, the patient's parent(s) or legally authorized representative(s) will be asked to provide informed consent on behalf of the patient.

[b] Assessments performed on the first day of the first IT Dosing Week (Pre-Tx Day 1 of Week 3) will include a full neurodevelopmental assessment. Subsequent dosing weeks (Weeks 7, 11, 15, 19, 23) will not include a full neurodevelopmental assessment.

[c] The assessments indicated will not be necessary if performed previously at Screening/Baseline within 7 days prior to Pre-Surgery Day 1.

[d] The assessments indicated will be performed on Pre-Tx Day 1 of IT Dosing Week 3 (ie, prior to the first dose of idursulfase-IT).

Table 14-1 Study Procedures for the Initial Treatment Phase: For Patients Who Were Not Treated Previously in Study HGT-HIT-045 with Intrathecal Idursulfase-IT (Part A)

	Screening/Baseline	Surgery Week 1				Post-op Week 2	IT Dosing Weeks 3, 7, 11, 15, 19, 23			Interim Tx Weeks	
Assessment	EOS HGT-HIT-045 (or Day -30 to Day 1 Pre-Surgery)	Day 1 Pre-Surgery	Day 2 Surgery	Days 3-6	Day 7	Days 8-14	Pre-Tx[b] Day 1	IT Injection Day 2	Days 3-7	Weeks 4-6, 8-10, 12-14, 16-18, 20-22; 24-26	Month 7 (Week 27)[g]
Location	Main Site	Main Site	Main Site	Main Site	Main Site	Local	Main Site	Main Site	Main Site	Local	Main Site

[e] A CSF sample will be obtained prior to injection of idursulfase-IT.

[f] Elaprase infusion will be administered approximately 2 days after the idursulfase-IT injection. Patients will be discharged from the study unit a minimum of 24 hours after the Elaprase infusion or when deemed clinically stable by the investigator.

[g] All patients will have Month 7 (Week 27) assessments performed 30 (±7) days after their last dose of study drug in the Initial Treatment Phase of the study and prior to their first scheduled dose (Month 7) in the Extended Treatment Phase of the study.

[h] The 12-lead ECG will be performed on IT Injection Day 2 after IT administration of study drug.

[i] A neurological exam will be performed by the local physician on Interim Tx Weeks 5, 9, 13, 17, 21, and 25.

[j] PK samples will be obtained at Weeks 3 and 23 only; see Table 14-4 for the PK assessment schedule.

[k] The assessment will be performed on Pre-Tx Day 1 of IT Dosing Week 15.

[l] Age- and cognitive status-appropriate assessments will be administered as feasible.

[m] X-rays may be performed to check placement of the device, and as needed, throughout the study.

[n] Physical exams will be performed at Days 3-7 of each IT Dosing Week on Day 3 and on Day 7.

[o] Neurological exams will be performed at Days 3-6 of Surgery Week 1 on Day 4, and at Days 3-7 of each IT Dosing Week on Day 3 and on Day 7.

[p] Patients with an IDDD will undergo X-ray prior to lumbar puncture at the Month 7 (Week 27) visit to verify the position of the catheter.

[q] If >30 days have elapsed since completion of HGT-HIT-045 EOS procedures, these assessments are to be repeated within 30 days prior to surgery.

[r] If >3 months have elapsed since completion of HGT-HIT-045 EOS procedures, these assessments are to be repeated within 30 days prior to surgery.

[s] At a minimum, vital signs will be collected at the following time points on days of IT administration of idursulfase-IT and IV infusion of Elaprase:

IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes (±10 minutes) post end of IT administration, 60 minutes (±10 minutes) post end of IT administration, 120 minutes (±10 minutes) post end of IT administration, 4 hours (±10 minutes) post end of IT administration, 6 hours (±10 minutes) post end of IT administration, 8 hours (±10 minutes) post end of IT administration, and 12 hours (±10 minutes) post end of IT administration.

IV infusion of Elaprase: within 15 minutes prior to infusion, and 30 minutes (±10 minutes) post start of infusion, 60 minutes (±10 minutes) post start of

Table 14-1 Study Procedures for the Initial Treatment Phase: For Patients Who Were Not Treated Previously in Study HGT-HIT-045 with Intrathecal Idursulfase-IT (Part A)

	Screening/Baseline	Surgery Week 1				Post-op Week 2	IT Dosing Weeks 3, 7, 11, 15, 19, 23			Interim Tx Weeks	
Assessment	EOS HGT-HIT-045 (or Day -30 to Day 1 Pre-Surgery)	Day 1 Pre-Surgery	Day 2 Surgery	Days 3-6	Day 7	Days 8-14	Pre-Tx[b] Day 1	IT Injection Day 2	Days 3-7	Weeks 4-6, 8-10, 12-14, 16-18, 20-22; 24-26	Month 7 (Week 27)[g]
Location	Main Site	Main Site	Main Site	Main Site	Main Site	Local	Main Site	Main Site	Main Site	Local	Main Site

infusion, 90 minutes (±10 minutes) post start of infusion, 120 minutes (±10 minutes) post start of infusion, 150 minutes (±10 minutes) post start of infusion, 180 minutes (±10 minutes) post start of infusion (ie, end of infusion), 30 minutes (±10 minutes) post end of infusion, and 60 minutes (±10 minutes) post end of infusion.

[t] The monthly idursulfase-IT injection may be administered every 28 (±7) days to extend flexibility to patients.

Table 14-2 Study Procedures for the Extended Treatment Phase: For All Patients Who Have Received 6 Months of Treatment with Intrathecal Idursulfase-IT in Study HGT-HIT-045 or Study HGT-HIT-046 (Part B)

	Monthly Visits 7-12, 14-18, 20-24, 26-30, 32-36, 38-42, 44-48, 50-54			6-Month Visits[h]			12-Month Visits[i]			Interim Tx Weeks of Each Month
				Months 13, 25, 37, 49			Months 19, 31, 43			
	IT Dosing Week[o]			IT Dosing Week[o]			IT Dosing Week[o]			
Assessment[a,b]	Pre-Tx Day 1	IT Injection Day 2[f]	Days 3-7	Pre-Tx Day 1	IT Injection Day 2[f]	Days 3-7	Pre-Tx Day 1	IT Injection Day 2[f]	Days 3-7	
Location	Main or Local Site	Main or Local Site	Main Site or Local	Main or Local Site	Main or Local Site	Main Site or Local	Main Site	Main Site	Main Site or Local	Local
Informed Consent	●									
Physical Examination	●[j]			●			●			
Height and Weight	●[j]			●			●			
Head Circumference	●[j]						●			
Vision Assessment	●[k]			●			●			
Hearing Assessment	●[k]			●			●			
12-lead ECG	●[j]	●[d]						●[d]		
Vital Signs	●[j]	●[m]		●	●[m]		●	●[m]		
Hematology	●[j,n]			●[n]			●[n]			
Serum Chemistry	●[j,n]			●[n]			●[n]			
Standard Urinalysis	●[j,n]			●[n]			●[n]			
Urine GAG	●[j,c]			●[c]			●[c]			
Anti-idursulfase Antibody Testing	●[j,c]			●[c]			●[c]			
Plasma Proteomic Marker Testing	●[j,c]			●[c]			●[c]			
General Anesthesia	●[k]						●			
Auditory Brainstem Response	●[k]						●[r]			
Brain and Spine MRI	●[k]						●			
X-ray[l]	●[j]						●			
ICP Measurement	●[j]						●			
CSF Sample Collection		●[e]			●[e]			●[e]		
Idursulfase-IT Injection[q]		●			●			●		
Elaprase Infusion			●			●			●	●

Table 14-2 Study Procedures for the Extended Treatment Phase: For All Patients Who Have Received 6 Months of Treatment with Intrathecal Idursulfase-IT in Study HGT-HIT-045 or Study HGT-HIT-046 (Part B)

	Monthly Visits 7-12, 14-18, 20-24, 26-30, 32-36, 38-42, 44-48, 50-54			6-Month Visits[h]			12-Month Visits[i]			Interim Tx Weeks of Each Month
				Months 13, 25, 37, 49			Months 19, 31, 43			
	IT Dosing Week[o]			IT Dosing Week[o]			IT Dosing Week[o]			
Assessment[a,b]	Pre-Tx Day 1	IT Injection Day 2[f]	Days 3-7	Pre-Tx Day 1	IT Injection Day 2[f]	Days 3-7	Pre-Tx Day 1	IT Injection Day 2[f]	Days 3-7	
Location	Main or Local Site	Main or Local Site	Main Site or Local	Main or Local Site	Main or Local Site	Main Site or Local	Main Site	Main Site	Main Site or Local	Local
Blood Sample for PK								●[g]		
Neurological Examination	●[j]			●			●			
Full Neurodevelopmental Assessment	●[k]			●[p]			●[p]			
Concomitant Medications, Therapies, and Procedures	●	●	●	●	●	●	●	●	●	●
Adverse Event Monitoring	●	●	●	●	●	●	●	●	●	●

Abbreviations: CSF = cerebrospinal fluid; ECG = electrocardiogram; GAG = glycosaminoglycan; Local = patient local Elaprase infusion site; ICP = intracranial pressure; IDDD = intrathecal drug delivery device; MRI = magnetic resonance imaging; PK = pharmacokinetics; Tx = treatment; LP = lumbar puncture.

[a] For patients entering this extension study who previously received 6 months of treatment with intrathecal idursulfase-IT in Study HGT-HIT-045, results of Study HGT-HIT-045 EOS assessments may provide Screening/Baseline values for this study if they occurred within specified time limits (see footnotes j and k) and may not need to be repeated.

[b] Patients who previously received 6 months of treatment with intrathecal idursulfase-IT during the Initial Treatment Phase of this study may move immediately on to their next IT injection in the Extended Treatment Phase, ie, they will not need to repeat informed consent or pretreatment assessments that may be redundant with Month 7 (Week 27) assessments.

[c] These assessments will be performed (at minimum) at 3-month intervals on Pre-Treatment Day 1 of Monthly IT Dosing Weeks according to the same schedule as the clinical laboratory assessments.

[d] The 12-lead ECG is to be performed after administration of study drug at Months 7 to 9, 19, 31, and 43.

[e] A CSF sample will be collected via the IDDD immediately prior to administration of intrathecal idursulfase-IT. If a CSF sample cannot be obtained for 6 consecutive months, then a lumbar puncture will be performed.

[f] The first 3 IT injections of idursulfase-IT (Months 7-9) will be administered at the main study site. Patients will be discharged a minimum of 24 hours after dosing and when deemed clinically stable by the investigator. Thereafter, IT injections of idursulfase-IT may be performed at either the main study site or at a local site, and patients may be discharged a minimum of 4 hours after dosing and when deemed clinically stable by the investigator, with exception of the visits at Months 19, 31, and 43 at which PK assessments are performed. Due to PK sample collection, discharge at Months 19, 31, and 43 will be upon

Table 14-2 Study Procedures for the Extended Treatment Phase: For All Patients Who Have Received 6 Months of Treatment with Intrathecal Idursulfase-IT in Study HGT-HIT-045 or Study HGT-HIT-046 (Part B)

	Monthly Visits 7-12, 14-18, 20-24, 26-30, 32-36, 38-42, 44-48, 50-54			6-Month Visits[h] Months 13, 25, 37, 49			12-Month Visits[i] Months 19, 31, 43			Interim Tx Weeks of Each Month
	IT Dosing Week[o]			IT Dosing Week[o]			IT Dosing Week[o]			
Assessment[a,b]	Pre-Tx Day 1	IT Injection Day 2[f]	Days 3-7	Pre-Tx Day 1	IT Injection Day 2[f]	Days 3-7	Pre-Tx Day 1	IT Injection Day 2[f]	Days 3-7	
Location	Main or Local Site	Main or Local Site	Main Site or Local	Main or Local Site	Main or Local Site	Main Site or Local	Main Site	Main Site	Main Site or Local	Local

discretion of the investigator.

g PK samples will be obtained at Months 19, 31, and 43. See Table 14-4 for the PK assessment schedule.

h These visits may take place at the main study site or local site.

i The visits will take place at the main study site.

j At Month 7 only, and only if >30 days have elapsed since completion of HGT-HIT-045 EOS procedures, these assessments are to be repeated within 30 days prior to the scheduled intrathecal idursulfase-IT dose.

k At Month 7 only, and only if >3 months have elapsed since completion of HGT-HIT-045 EOS procedures, these assessments are to be repeated within 30 days prior to the scheduled intrathecal idursulfase-IT dose.

l X-rays may be performed to check placement of the device, and as needed, throughout the study. In particular, patients with an IDDD will undergo X-ray prior to lumbar puncture to verify the position of the catheter.

m At a minimum, vital signs will be collected at the following time points on IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes (±10 minutes) post end of IT administration, 60 minutes (±10 minutes) post end of IT administration, 120 minutes (±10 minutes) post end of IT administration, and 4 hours (±10 minutes) post end of IT administration.

n Clinical laboratory assessments (serum chemistry, hematology, urinalysis) will be performed at 3-month intervals prior to dosing on Monthly IT Dosing Weeks (ie, at Months 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, and 52).

o From Month 10 onward, Day 1 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.

p The full neurodevelopmental assessment will be performed at the main study site on Pre-Treatment Day 1 or within 7 days of IT administration of idursulfase-IT.

q The monthly idursulfase-IT injection may be administered every 28 (±7) days to extend flexibility to patients.

r Auditory brainstem response assessments will be performed at the 12-month visits when deemed necessary by the investigator.

Table 14-3 Study Procedures for the Extended Treatment Phase: For All Patients Who Have Received 54 Months of Treatment with Intrathecal Idursulfase-IT in Study HGT-HIT-045 or Study HGT-HIT-046 (Part C)

	Monthly Visits 56-60, 62-66, 68-72, 74-78, 80-84, 86-90, 92-96, 98-102, 104-108, 110-114, 116-120, 122-126, 128-132, 134-138, 140-144, 146-150, 152-156, 158-162, 164-168			6-Month Visits			12-Month Visits[f]			Interim Tx Weeks of Each Month	End of Study (EOS)[e]
				Months 61, 73, 85, 97, 109, 121, 133, 145, 157			Months 55, 67, 79, 91, 103, 115, 127, 139, 151, 163				
	IT Dosing Week[k]			IT Dosing Week[k]			IT Dosing Week[k]				
Assessment	Pre-Tx Day 1	IT Injection Day 2[d]	Days 3-7	Pre-Tx Day 1	IT Injection Day 2[d]	Days 3-7	Pre-Tx Day 1	IT Injection Day 2[d]	Days 3-7		
Location	Main or Local Site	Main or Local Site	Main Site or Local	Main or Local Site	Main or Local Site	Main Site or Local	Main Site	Main Site	Main Site or Local	Local	Main Site
Physical Examination[n]	●			●			●				●
Height and Weight				●			●				●
Head Circumference							●				●
Vision Assessment							●[m]				●
Hearing Assessment							●				●
12-lead ECG								●[b]			●
Vital Signs		●[i]		●	●[i]		●	●[i]			●
Hematology				●[j]			●[j]				●
Serum Chemistry				●[j]			●[j]				●
Standard Urinalysis				●[j]			●[j]				●
Urine GAG				●[a]			●[a]				●
Anti-idursulfase Antibody Testing				●[a]			●[a]				●
General Anesthesia[g]				●			●				●
Auditory Brainstem Response							●[p]				●
Brain and Spine MRI							●				●
X-ray[h]							●[m]				●
ICP Measurement							●[m]				●
CSF Sample Collection		●[c]			●[c]			●[c]			●[c]
Idursulfase-IT Injection[o]		●			●			●			

Table 14-3 Study Procedures for the Extended Treatment Phase: For All Patients Who Have Received 54 Months of Treatment with Intrathecal Idursulfase-IT in Study HGT-HIT-045 or Study HGT-HIT-046 (Part C)

	Monthly Visits 56-60, 62-66, 68-72, 74-78, 80-84, 86-90, 92-96, 98-102, 104-108, 110-114, 116-120, 122-126, 128-132, 134-138, 140-144, 146-150, 152-156, 158-162, 164-168			6-Month Visits Months 61, 73, 85, 97, 109, 121, 133, 145, 157			12-Month Visits[f] Months 55, 67, 79, 91, 103, 115, 127, 139, 151, 163			Interim Tx Weeks of Each Month	End of Study (EOS)[e]
	IT Dosing Week[k]			IT Dosing Week[k]			IT Dosing Week[k]				
Assessment	Pre-Tx Day 1	IT Injection Day 2[d]	Days 3-7	Pre-Tx Day 1	IT Injection Day 2[d]	Days 3-7	Pre-Tx Day 1	IT Injection Day 2[d]	Days 3-7		
Location	Main or Local Site	Main or Local Site	Main Site or Local	Main or Local Site	Main or Local Site	Main Site or Local	Main Site	Main Site	Main Site or Local	Local	Main Site
Elaprase Infusion			●			●			●	●	
Neurological Examination[a]	●			●			●				●
Neurodevelopmental Assessment							●[l]				●
Concomitant Medications, Therapies, and Procedures	●	●	●	●	●	●	●	●	●	●	●
Adverse Event Monitoring	●	●	●	●	●	●	●	●	●	●	●

Abbreviations: CSF = cerebrospinal fluid; ECG = electrocardiogram; GAG = glycosaminoglycan; Local = patient local Elaprase infusion site; ICP = intracranial pressure; IDDD = intrathecal drug delivery device; MRI = magnetic resonance imaging; PK = pharmacokinetics; Tx = treatment; LP = lumbar puncture.

[a] These assessments will be performed (at minimum) at 6-month intervals on Pre-Treatment Day 1 of Monthly IT Dosing Weeks according to the same schedule as the clinical laboratory assessments.

[b] The 12-lead ECG is to be performed after administration of study drug at Months 55, 67, 79, 91, 103, 115, 127, 139, 151, and 163.

[c] A CSF sample will be collected via the IDDD immediately prior to administration of intrathecal idursulfase-IT. If a CSF sample cannot be obtained for 6 consecutive months, then a lumbar puncture will be performed. Measurements of GAG, idursulfase enzyme, and anti- idursulfase antibody levels in CSF samples will be performed (at minimum) at 6-month intervals at Months 55, 61, 67, 73, 79, 85, 91, 97, 103, 115, 127, 139, 151, and 163), and at the EOS visit.

[d] Injections of idursulfase-IT may be performed at either the main study site or at a local site, and patients may be discharged a minimum of 1 hour after dosing and when deemed clinically stable by the investigator.

[e] All patients will have EOS assessments performed at the main study site 30 (±7) days after their last dose of study drug.

[f] These visits will take place at the main study site.

Table 14-3 Study Procedures for the Extended Treatment Phase: For All Patients Who Have Received 54 Months of Treatment with Intrathecal Idursulfase-IT in Study HGT-HIT-045 or Study HGT-HIT-046 (Part C)

	Monthly Visits 56-60, 62-66, 68-72, 74-78, 80-84, 86-90, 92-96, 98-102, 104-108, 110-114, 116-120, 122-126, 128-132, 134-138, 140-144, 146-150, 152-156, 158-162, 164-168			6-Month Visits			12-Month Visits[f]			Interim Tx Weeks of Each Month	End of Study (EOS)[e]
				Months 61, 73, 85, 97, 109, 121, 133, 145, 157			Months 55, 67, 79, 91, 103, 115, 127, 139, 151, 163				
	IT Dosing Week[k]			IT Dosing Week[k]			IT Dosing Week[k]				
Assessment	Pre-Tx Day 1	IT Injection Day 2[d]	Days 3-7	Pre-Tx Day 1	IT Injection Day 2[d]	Days 3-7	Pre-Tx Day 1	IT Injection Day 2[d]	Days 3-7		
Location	Main or Local Site	Main or Local Site	Main Site or Local	Main or Local Site	Main or Local Site	Main Site or Local	Main Site	Main Site	Main Site or Local	Local	Main Site

[g] General anesthesia may be used as needed during the study.

[h] X-rays may be performed to check placement of the device, and as needed, throughout the study.

[i] At a minimum, vital signs will be collected at the following time points on IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes (±10 minutes) post end of IT administration, and upon discharge.

[j] Clinical laboratory assessments (serum chemistry, hematology, urinalysis) will be performed at 6-month intervals prior to dosing on Monthly IT Dosing Weeks (ie, at Months 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151, 157, and 163).

[k] Day 1 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.

[l] A limited neurodevelopmental assessment consisting of the DAS-II will be performed at the main study site on Pre-Treatment Day 1 or within 7 days of IT administration of idursulfase-IT. Subjects exceeding 17 years 11 months of age will no longer undergo neurodevelopmental assessment using the DAS-II.

[m] The assessment will be performed at the 12-Month Visit scheduled at Month 55.

[n] After Month 55, these exams may be symptom-directed and performed at the investigator's discretion.

[o] The monthly idursulfase-IT injection may be administered every 28 (±7) days to extend flexibility to patients.

[p] Auditory brainstem response assessments will be performed at the 12-month visits when deemed necessary by the investigator.

Table 14-4 Pharmacokinetic Sampling Schedule (Parts A and B)

Patients/Study Phase	Drug Administration	PK Sampling Times
Previously untreated patients in HGT-HIT-045, during the Initial Treatment Phase only	Intrathecal idursulfase-IT	Within 15 minutes prior to IT injection, then at 1, 2, 3, 4, 6, 8, 12, 24, 30, and 36 hours following IT injection, at Weeks 3 and 23 only
	Elaprase	Within 15 minutes prior to IV infusion; then at 0.5, 1, 1.5, 2, 2.5, and 3 hours during the infusion; and at 3.5, 4, 5, 6, 7, 9, 11, and 24 hours following IV infusion, at Weeks 3 and 23 only
All patients, during the Extended Treatment Phase	Intrathecal idursulfase-IT	Within 15 minutes prior to IT injection, then at 1, 2, 3, 4, 6, 8, 12, 24, 30, and 36 hours following IT injection at Months 19, 31, and 43

Note that when vital sign collection and collection of a blood sample for PK analysis are scheduled to occur at the same time, vital sign collection should occur first and the blood draw for PK sampling should be performed as soon as possible after vital sign collection. The actual time of PK sample collection should be recorded.

15 APPENDIX 2: NEURODEVELOPMENTAL ASSESSMENTS

Table 15-1 details the specific psychometric instruments that will be used to provide measures of each of the relevant neurobehavioral or developmental domain to be assessed. The table also summarizes the rules used to select a test for a patient, the clusters/subtests included in each instrument and the subscales generated by the test battery.

Table 15-1 Summary of Neurodevelopmental Outcome Measures

Neurobehavioral domain to be assessed	Inclusion criteria for test	Test battery	Clusters/subtests for the test battery	Overall outcome measure generated from the test battery
Cognition	No criteria	Differential Ability Scale, 2nd edition (DAS II) OR Bayley Infant Scales of Development, 3rd edition (BSID-III)	Verbal, Nonverbal, Spatial Cognitive development Language development Motor development	General Conceptual Ability (GCA) Special Nonverbal Composite (SNC) Mental Development Index
Adaptive	No criteria	Scale of independent behavior – revised (SIB-R)		Broad Independence
Gross Motor	<6 years	Peabody Developmental Motor Scales	Object manipulation Stationary Locomotion	
	≥6 years	Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition	Fine Manual Control Manual Coordination Body Coordination Strength and Agility	
Measures of Executive Function	<6 years	Behavior Rating Inventory of Executive Function Preschool version (BRIEF-P)	Behavioral Regulation Metacognition	Global Executive Composite Score
	≥6 years	Behavior Rating Inventory of Executive Function – Parent Form (BRIEF)	Behavioral Regulation Metacognition	Global Executive Composite Score

Neurodevelopmental Assessment: Clinical Trial Considerations

The term "neurodevelopmental" refers to the process by which the neurological system matures and changes over time. Assessing these changes in a population of children whose neurological system is progressively more affected can be very challenging. Typically, neurodevelopmental progress is reflected by the child's abilities to perform certain skills (sitting, walking, and talking). However, a child with a neurological disorder may be able to perform age appropriate skills but with atypical patterns. For example, the child may be able to walk but his gait is not normal. Most assessments will therefore measure the skills, but are not designed to capture the abnormalities in pattern or quality of the skill.[30]

These qualitative differences will be evident to the skilled test administrator/clinician who is familiar with the disorder. However, only longitudinal tracking and repeated measures will reveal the significance of these abnormalities in overall function to the less experienced clinician.[30]

The rate at which different skills develop or regress over time will give insight into the disease process. The next step is to determine how the learned skills are used for daily functional activities so that as the children grow up they become independent from caregivers. These functional skills can be tracked to reflect quality of life issues for both parents and children.[30]

Neurodevelopmental assessments described below will be scheduled for administration in the morning and estimated to last between 2 and 6 hours. Patients in this study will be evaluated in a one-on-one format.

The list of assessments is:

Cognition

- Differential Ability Scales, Second Edition (DAS-II)[31]
- Bayley Infant Scales of Development, Third Edition (BSID-III)[32]

Note: For cognitive testing, the first item set of the 6 main subtests of the DAS-II will be administered. If the patient cannot complete these, the BSID-III will be used to assess cognition.

Adaptive

- Scales of Independent Behavior-Revised (SIB-R)[33]

Hearing and Visual Abilities

- Hearing assessment
- Visual function: clinical assessment

Motor Skills and Voluntary Movement

- Peabody Developmental Motor Scales, Second Edition (PDMS-2)[34, 35]
- Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2)[36]

Executive Function

- Behavior Rating Inventory of Executive Function-preschool (BRIEF-P)[37]
- Behavior Rating Inventory of Executive Function-parent (BRIEF)[38]

Domain: Cognitive Measures

Rationale for Choice of Cognitive Assessments

To achieve the goals of this assessment, the instrument chosen will be either DAS-II or the BSID-III. It is intended that the first item set of the 6 main subtests of the DAS-II be administered to the patient. If the patient cannot complete these, the BSID-III will be used to assess cognition.

Differential Ability Scales, Second Edition (DAS-II)[31]

Purpose: To assess cognitive abilities in children 2.6 years of age and older.

Description: The DAS-II is a battery of cognitive and achievement tests for children and adolescents aged 2 years, 6 months through 17 years, 11 months. As such, it has a wider age range than any one of the Wechsler Scales, and it had standard deviations similar to other measures. The DAS-II cognitive clusters permit evaluation of strengths and weaknesses. It yields a composite standard score focused on reasoning and conceptual abilities called the General Conceptual Ability (GCA) score; lower level composite scores for Nonverbal and Verbal skills (at the preschool level) and for Nonverbal Reasoning, Verbal, and Spatial skills (at the school-age level); and diverse specific ability measures, including the core subsets, which compose the GCA, and diagnostic subtests.

Bayley Scales of Infant Development, Third Edition (BSID-III)[32]

Purpose: To assess cognitive abilities in children 1-42 months years of age.

Description: The BSID-III assesses 5 key developmental domains in children (ages 1-42 months): language, social-emotional, motor and adaptive behavior. It consists of a core battery of 5 scales. Three scales are administered with child interaction; cognitive, motor, language. Two scales are conducted with parent questionnaires; social-emotional, adaptive behavior. The Bayley scale is recommended for low-functioning and nonverbal or preverbal children.

Domain: Adaptive Behavior Assessment

Purpose: To determine the patient's ability to function independently at home and in a community setting via the Adaptive Behavior Assessments listed below.

Assessment: Scales of Independent Behavior-Revised (SIB-R)[33]

This scale measures adaptive functioning from infancy to adulthood. It is widely used scale with acceptable validity and reliability. It is designed as a questionnaire that can be easily completed by parents during the visit.

Domain: Audiological Assessment

The appropriate audiological test battery will be chosen, administered, and interpreted by trained clinicians at the test facility.

Because study patients are at risk for permanent (sensorineural) hearing loss, and some are also at increased risk for chronic or recurrent middle ear disease, the assessment of the patient level of functioning is crucial for appropriate interpretation of these results with the assessment of speech and cognitive function.

Domain: Motor Assessments

The topics typically addressed by motor assessments include: a) engaging the environment through sensory-motor exploration, b) postural control, c) equilibrium/righting reactions, d) protective responses, muscle strength and tone, e) voluntary (automatic and conscious)/reflexive movements, balance, and ambulation.

Assessment: Peabody Developmental Motor Scales, Second Edition (PDMS-2)[34, 35]

The PDMS-2 captures both quantitative and qualitative abilities on some items increasing the sensitivity to changing motor patterns as the children's disease progresses or during recovery. There are 3 domains measured using T-scores: stationary, locomotion, and object manipulation.

Assessment: Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2)[36]

The Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2) is an individually administered test that uses engaging, goal-directed activities to measure a wide array of motor skills in individuals aged 4-21. It is designed to provide practitioners such as occupational therapists, physical therapists, developmental adaptive physical education teachers, and researchers, among others, with a reliable and efficient measure of fine and gross motor control skills.

Assessment: Executive Function: Behavior Rating Inventory of Executive Function[37-39]

The Behavior Rating Inventory of Executive Function (BRIEF) consists of 2 rating forms: a parent questionnaire and a teacher questionnaire designed to assess executive functioning in the home and school environments. The BRIEF is useful in evaluating children with a wide spectrum of developmental and acquired neurological conditions. Each questionnaire contains 86 items in 8 nonoverlapping clinical scales and 2 validity scales. These theoretically and statistically derived scales form 2 broader indexes: Behavioral Regulation (3 scales) and Metacognition (5 scales), as well as a Global Executive Composite score.

The observations of parents and teachers provide a wealth of information about a child's behavior that is directly relevant to an understanding of that child's executive functioning. The assessment of executive function in preschool-aged children is often difficult because of the variable nature of behavior in this age range (ages 2.0-5.11 years); the limitations in motor and verbal proficiency at this age; and the many neuropsychological, psychological, developmental, and other medical conditions that begin to manifest during the preschool years. The BRIEF-P is the first standardized rating scale designed to specifically measure the range of behavioral manifestations of executive function in preschool-aged children—thus facilitating intervention at earlier stages of development.

The BRIEF-P consists of a single rating form used by parents, teachers, and day care providers to rate a child's executive functions within the context of his/her everyday environments - home and preschool. The original BRIEF was the basis for the development of the BRIEF-P. Consequently, the BRIEF-P is a valid and efficient toll for screening, assessing, and monitoring a young child's executive functioning and development.

The hand-scorable BRIEF-P rating form consists of 63 items that measure various aspects of executive functioning: Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. The clinical scales form 3 broad indexes (Inhibitory Self-Control, Flexibility, and Emergent Metacognition) and one composite score (Global Executive Composite).

For this clinical study, only the parent form will be utilized.

16 APPENDIX 3: SAMPLE NEUROLOGICAL EXAM

Performed as an outpatient exam	Normal	Abnormal
Appearance		
Awareness		
Position and spontaneous movements of body		
Responsiveness to touch and handling		
Activity		
Orientation		
Behavior changes (parent's report)		
Verbal responses		
Gait		
Eyes		
Visual changes		
Photophobia		
Pupillary reaction to light		
Spontaneous eye movements		
Vision fields		
Fundus (papilledema, papillitis)		
Strength		
Neck stiffness		
Muscle tone		
Hypertonia		
Hypotonia		
Asymmetry		
Other		
Cerebellar function		
Rapid alternating movements		
Finger to nose		
Romberg		
Involuntary movements		
Tics, fasciculations, chorea, athetosis, dystonia, tremor		
Cranial nerves		
Deep tendon reflexes		

17 APPENDIX 4: ADVERSE DEVICE EFFECTS EXPECTED WITH THE SOPH-A-PORT IDDD

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

Note: These are potential complications noted in the Sophysa Instructions for Use for the SOPH-A-PORT® Mini S IDDD (Sophysa is the manufacturer of this IDDD). Date of Issue: April 2013.

18 APPENDIX 5: DEVICE RELATED ADVERSE REACTIONS ASSOCIATED WITH THE PORT-A-CATH IDDD

Risks associated with insertion or use of IDDD

- Catheter disconnection or fracture
- Erosion of portal/catheter through the skin
- Fibrin sheath formation around catheter tip
- Hematoma
- Implant rejection
- Malposition of catheter
- Migration of portal/catheter
- Occlusion of portal/catheter
- Portal site or subcutaneous tract infection
- Sepsis

Risks associated with intraspinal access

- Cerebrospinal fluid leaks
- Dura mater or epidural vein perforation
- Epidural or intrathecal space infection, which could result in meningitis
- Meningoencephalitis, which could result in brain injury (eg, seizures, loss of motor control or cognitive function)
- Inadvertent epidural placement
- Pain on injection
- Spinal cord or nerve injury
- Spinal cord pressure, which could lead to paralysis
- Spinal headache

Note: These are potential complications noted in the Smiths Medical Instructions for Use for the PORT-A-CATH® IDDD (Smiths Medical is the manufacturer of this IDDD). Date of Issue: September 2008.

19 APPENDIX 6: SUMMARY OF CHANGES FOR AMENDMENT 13

Summary of Changes and the Rationale for the Amendment

Clinical protocol HGT-HIT-046 has been revised from the previous version as follows:

- To add language to allow a dosing window of ±7 days to the monthly idursulfase-IT injections (ie, every 28 [±7] days), as communicated to the study team on 11 Feb 2019
- To remove out-of-date data from Study HGT-HIT-046 and reference the idursulfase-IT investigator's brochure
- To add language with regards to global health emergencies and clinical trial continuity
- To clarify that neurodevelopmental assessments will be performed annually from Month 55 (ie, during Part C of the Extended Treatment Phase)
- To clarify that ABR assessments will be performed annually during the Extended Treatment Phase (Parts B and C) when deemed necessary
- To clarify that patients may discontinue treatment if an alternative mechanism for recombinant human iduronate-2-sulfatase access is developed
- To clarify that patients with a partial or full device still in place after completion of the study will not be followed for safety monitoring
- To clarify that consecutive lumbar punctures may be performed when there are no safety concerns associated with repeat lumbar puncture and repeat sedation/anesthesia
- To clarify that for cognitive testing, the first item set of the 6 main subtests of the DAS-II will be administered, as communicated to the study team on 02 May 2019
- To clarify and update the SAE reporting information
- To add language to allow remote source data review and verification when on-site monitoring is not possible
- To correct an error and clarify that brain and spine MRIs will be performed annually (rather than every 6 months) from Month 55 (ie, during Part C of the Extended Treatment Phase), as communicated to the study team on 02 May 2019

Noteworthy changes and additions to the protocol text are captured below. **Bold** text indicates new or revised text. ~~Strikethrough~~ text indicates deleted text.

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

New or Deleted Text

Change: Language added to allow monthly idursulfase-IT injections to be administered every 28 (±7) days
Rationale: Clarification of an operational aspect of the study
Section impacted by this change: Section 1, Protocol Synopsis
Revised Text In the original study design it was planned that idursulfase-IT would be administered once monthly (ie, every 28 days) via an intrathecal drug delivery device (IDDD) at doses of 1, 10, or 30 mg. Because the 1 mg dose was assessed as suboptimal, all patients in the study are currently receiving doses of either 10 or 30 mg. **In addition, to extend flexibility to patients the idursulfase-IT dosing visit window has been extended so that monthly administration may occur every 28 (±7) days.** … This is an open-label extension of Study HGT-HIT-045. This study is designed to evaluate the long term safety and clinical outcomes of monthly (ie, every 28 **[±7]** days) intrathecal (IT) injections of idursulfase-IT (HGT-2310) in conjunction with weekly ~~intravenous (~~IV~~)~~ infusions of Elaprase in patients with Hunter syndrome and cognitive impairment.
Other sections impacted by this change: Section 5.1, Study Design; Section 5.2.1, Initial Treatment Phase (Part A); Section 5.2.2, Extended Treatment Phase (Parts B and C); Section 7.3, Selection and Timing of Dose; Section 8.2, Initial and Extended Treatment Phases (All Patients); Section 8.4.15, Intrathecal Idursulfase-IT Injection; Section 8.5.14, Intrathecal Idursulfase-IT Injection; Section 14, Appendix 1: Schedule of Study Procedures, Table 14-1, Study Procedures for the Initial Treatment Phase: For Patients Who Were Not Treated Previously in Study HGT-HIT-045 with Intrathecal Idursulfase-IT (Part A) footnote t; Section 14, Appendix 1: Schedule of Study Procedures, Table 14-2, Study Procedures for the Extended Treatment Phase: For All Patients Who Have Received 6 Months of Treatment with Intrathecal Idursulfase-IT in Study HGT-HIT-045 or Study HGT-HIT-046 (Part B) footnote q; Section 14, Appendix 1: Schedule of Study Procedures, Table 14-3, Study Procedures for the Extended Treatment Phase: For All Patients Who Have Received 54 Months of Treatment with Intrathecal Idursulfase-IT in Study HGT-HIT-045 or Study HGT-HIT-046 (Part C) footnote o

Change: Removal of out-of-date data from Study HGT-HIT-046 and reference to the idursulfase-IT investigator's brochure
Rationale: A detailed summary of the latest idursulfase-IT safety information is included in the current edition of the investigator's brochure
Section impacted by this change: Section 2.4, Previous Human Experience
Revised Text There have been no deaths in any studies of idursulfase-IT. ~~There have been 2 discontinuations from Study HGT-HIT-046 through 12 January 2017. One patient was discontinued by the investigator for behavioral issues unrelated to the study. A second patient discontinued due to AEs of IDDD failure, vomiting, and coagulase-negative staphylococcal CSF infection (which resolved without sequelae). As of 12 January 2017, there have been 14 SAEs reported that were related to idursulfase-IT.~~ … Please see the current edition of the investigator's brochure for a detailed summary of safety information for idursulfase-IT. Further information concerning the SOPH-A-PORT Mini S device is provided as an addendum to the investigator's brochure.
Other sections impacted by this change: Section 2.5, Use of Repeat Lumbar Puncture to Administer Enzyme Replacement Therapy; Section 2.7, Benefit/Risk Assessment

Change: Language added with regards to global health emergencies and clinical trial continuity
Rationale: Clarification of an operational aspect of the study
Section impacted by this change: Section 2.8, Global Health Emergencies and Clinical Trial Continuity
Revised Text **Global health emergencies, such as the COVID-19 pandemic, present significant logistical challenges for many clinical sites around the world, with variable restrictions being placed on site resources and operations, and on an individual patient's ability to attend clinic visits. In some places, medical visits are occurring, and in others, research clinics are operating with only emergency staff.** **Based on these challenges, it may be necessary to adopt additional measures and procedures to protect patient safety, and to ensure that there are no gaps in the conduct of the study for patients enrolled in this clinical trial.** **This protocol includes the measures which are approved for implementation within this clinical trial to protect patient safety and to ensure the integrity of the trial as a result of COVID-19 only. These measures may be implemented in accordance with any requirements and expectations set out by local Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and National Competent Authorities, as necessary.** **These specific measures do not apply for patient management issues that are unrelated to a documented impact from a public health emergency, such as the COVID-19 pandemic.**
Other sections impacted by this change: Section 8.1, Study Evaluations and Procedures

Change: Clarification that neurodevelopmental assessments will be performed annually from Month 55 (ie, during Part C of the Extended Treatment Phase)
Rationale: Clarification of an operational aspect of the study
Section impacted by this change: Section 5.2.2, Extended Treatment Phase (Parts B and C)
Revised Text For their first 3 months on study (ie, Months 7-9), patients will undergo pretreatment and safety assessments on Day 1 and will receive an IT injection of idursulfase-IT on Day 2 of each IT Dosing Week. Standardized neurodevelopmental assessments will be performed every 6 months **during Part B of the Extended Treatment Phase and annually** during **Part C of** the Extended Treatment Phase.
Other sections impacted by this change: Section 1, Protocol Synopsis; Section 8.5.18, Neurodevelopmental Assessments; Section 14, Appendix 1: Schedule of Study Procedures, Table 14-3, Study Procedures for the Extended Treatment Phase: For All Patients Who Have Received 54 Months of Treatment with Intrathecal Idursulfase-IT in Study HGT-HIT-045 or Study HGT-HIT-046 (Part C)

Change: Clarification that ABR assessments will be performed annually during the Extended Treatment Phase (Parts B and C) when deemed necessary
Rationale: Clarification of an operational aspect of the study
Section impacted by this change: Section 5.2.2, Extended Treatment Phase (Parts B and C)
Revised Text ~~Auditory brainstem response (ABR),~~ MRI of the spine and brain~~,~~ and any other procedures **deemed necessary, such as ABR, that** require~~ing~~ anesthesia will be performed annually.
Other sections impacted by this change: Section 1, Protocol Synopsis; Section 8.4.10, Auditory Brainstem Response; Section 8.5.9, Auditory Brainstem Response; Section 14, Appendix 1: Schedule of Study Procedures, Table 14-2, Study Procedures for the Extended Treatment Phase: For All Patients Who Have Received 6 Months of Treatment with Intrathecal Idursulfase-IT in Study HGT-HIT-045 or Study HGT-HIT-046 (Part B) footnote r; Section 14, Appendix 1: Schedule of Study Procedures, Table 14-3, Study Procedures for the Extended Treatment Phase: For All Patients Who Have Received 54 Months of Treatment with Intrathecal Idursulfase-IT in Study HGT-HIT-045 or Study HGT-HIT-046 (Part C) footnote p

Change: Clarification that patients may discontinue treatment if an alternative mechanism for recombinant human iduronate-2-sulfatase access is developed
Rationale: Clarification of an operational aspect of the study
Section impacted by this change: Section 5.3, Study Duration
Revised Text Patients will continue treatment in this extension study, unless they discontinue the study or Shire discontinues the study, **or an alternative mechanism for recombinant human iduronate-2-sulfatase access is developed,** for a maximum duration of 14 years of treatment across Studies HGT-HIT-045 and/or HGT-HIT-046. Specifically, patients in Group 1 of Study HGT-HIT-046 will receive treatment for at least 4 years in Part B and patients in Group 2 of study HGT-HIT 046 will receive treatment for at least 4.5 years in Parts A and B the protocol. Patients will receive treatment in Part C for up to 9.5 years.
Other sections impacted by this change: Not applicable

Change: Clarification that patients with a partial or full device still in place after completion of the study will not be followed for safety monitoring
Rationale: Clarification of an operational aspect of the study
Section impacted by this change: Section 5.3, Study Duration
Revised Text The study will conclude after the last patient has completed his last visit. Patients with a partial or full device still in place after completion of the study ~~may~~ **will not** be followed for safety **monitoring** ~~up to an additional 3 years or until the device is removed in the last patient~~. **However, the sponsor will arrange reimbursement when the device is eventually removed.**
Other sections impacted by this change: Section 1, Protocol Synopsis; Section 5.1, Study Design; Section 8.2, Initial and Extended Treatment Phases (All Patients); Section 8.4.2, Physical Examinations; Section 8.4.9, Clinical Laboratory Testing; Section 8.5.1, Physical Examinations; Section 8.5.8, Clinical Laboratory Testing

Change: Clarification that consecutive lumbar punctures may be performed when there are no safety concerns associated with repeat lumbar puncture and repeat sedation/anesthesia
Rationale: Clarification of an operational aspect of the study
Section impacted by this change: Section 7.8, Guidance Concerning Performance of Lumbar Puncture for Study Drug Administration and CSF Sample Collection
Revised Text If there are medical contra-indications to the re-implantation of a new device, repeat monthly lumbar punctures may be considered as an alternative way of delivering the study drug and obtaining CSF samples under limited circumstances. ~~If~~ **As long as** no safety risks are identified by the investigator, ~~up to 12~~ consecutive lumbar punctures may be performed across Studies HGT-HIT-045 and HGT-HIT-046. ~~Once a patient has reached the maximum of 12 consecutive lumbar punctures, a new IDDD may be re implanted for subsequent dosing, unless, in the opinion of the investigator and medical monitor, assessment of risk/benefit favors continued dosing via lumbar puncture.~~ Continued treatment via repeat lumbar puncture ~~beyond the stipulated 12 consecutive monthly doses can~~**should only** be considered ~~only~~ in individual cases of patients where this treatment is very well tolerated and the investigator has not identified any safety concerns associated with repeat lumbar puncture and repeat sedation/anesthesia.
Other sections impacted by this change: Section 1, Protocol Synopsis; Section 2.5, Use of Repeat Lumbar Puncture to Administer Enzyme Replacement Therapy

Change: Clarification that the first item set of the 6 main subtests of the DAS-II will be administered

Rationale: Clarification regarding neurodevelopmental assessment tests

Section impacted by this change: Section 8.3.19.1, Full Neurodevelopmental Assessment

Revised Text

For this study, outcome measures will be computed for each patient enrolled at each assessment. The instruments are summarized in Table 8-3. For cognitive testing the first item set of the ~~3-~~**6** main ~~clusters~~ **subtests** of the Differential Ability Scales, Second Edition (DAS-II)~~, Verbal Comprehension, and Naming Vocabulary and Pattern Construction~~ will be administered. If the patient cannot complete these, the Bayley Scales of Infant Development, Third Edition (BSID-III) will be used to assess cognition.

Table 8-3 Full Neurodevelopmental Assessment Tests

Cognitive domain	**Patient age and representative cognitive test or scale**
Cognitive[a]	Differential Ability Scales, Second Edition (DAS-II) (provides general conceptual ability ~~consisting of 3 clusters; verbal, non-verbal, and spatial~~**through the 6 main subtests**)
…	

a For cognitive testing the first item set of the ~~3-~~**6** main ~~clusters~~ **subtests** of the DAS-II ~~(Verbal Comprehension, Naming Vocabulary, and Pattern Construction)~~ will be administered. If the patient cannot complete these, the BSID-III will be used to assess cognition.

Other sections impacted by this change: Section 8.4.19.1, Full Neurodevelopmental Assessment; Section 8.5.18, Neurodevelopmental Assessments

Change: Clarification of the SAE reporting information

Rationale: Clarification of an operational aspect of the study

Section impacted by this change: Section 9.3.1, Serious Adverse Event Reporting

Revised Text

The investigator will promptly supply all information identified and requested by the sponsor (and/or contract research organization [CRO]) regarding the SAE. The investigator must report the SAE to the ~~Shire Global Drug Safety~~**sponsor's safety** department AND to the Shire medical monitor on an SAE form. This form must be completed and FAXED **OR EMAILED** within 24 hours of the investigator learning of the event to:

~~Shire Global Drug Safety~~**Sponsor's Safety** Department:
International FAX: +1 484 595 8155 (Global)
drugsafety@shire.com
AND
Shire Medical Monitor:
~~FAX:~~ [redacted]
[redacted], DO
[redacted]
Shire
~~TELEPHONE:~~ [redacted]
MOBILE: [redacted] (24-hour access)

Any follow-up information must also be completed on an SAE form and FAXED **OR EMAILED** to the same numbers **or emails** listed above.

Other sections impacted by this change: Section 9.4, Abuse, Misuse, Overdose, and Medication Error

Change: Language added to allow remote data review and verification when on-site monitoring is not possible

Rationale: Clarification of an operational aspect of the study

Section impacted by this change: Section 11.12, Study Monitoring

Revised Text

Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed **whenever possible; however, remote data review and verification may also be conducted during unavoidable circumstances (such as the COVID-19 pandemic) to ensure data quality and integrity and maintain patient safety.**

The study will be monitored by the sponsor or its designee.

Whenever possible, ~~M~~monitoring will be done by personal visits from a representative of the sponsor (Clinical Study Monitor) who will review the CRFs and source documents **to ensure data quality and integrity and maintain patient safety. Remote monitoring and data review may also be conducted to mitigate significant business disruption during unavoidable circumstances, such as the COVID-19 pandemic.** 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).

Regulatory authorities, the IEC/IRB, and/or the sponsor may request access to all source documents, CRFs, and other study documentation for ~~on-site~~ audit or inspection. ~~Direct a~~**A**ccess to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

Other sections impacted by this change: Not applicable

Change: Clarification that brain and spine MRIs will be performed annually from Month 55 (ie, during Part C of the Extended Treatment Phase)

Rationale: Clarification of an operational aspect of the study

Section impacted by this change: Section 14, Appendix 1: Schedule of Study Procedures, Table 14-3, Study Procedures for the Extended Treatment Phase: For All Patients Who Have Received 54 Months of Treatment with Intrathecal Idursulfase-IT in Study HGT-HIT-045 or Study HGT-HIT-046 (Part C)

Revised Text

	Monthly Visits 56-60, 62-66, 68-72, 74-78, 80-84, 86-90, 92-96, 98-102, 104-108, 110-114, 116-120, 122-126, 128-132, 134-138, 140-144, 146-150, 152-156, 158-162, 164-168			**6-Month Visits**			**12-Month Visits[f]**			**Interim Tx Weeks of Each Month**	**End of Study (EOS)[e]**
				Months 61, 73, 85, 97, 109, 121, 133, 145, 157			**Months 55, 67, 79, 91, 103, 115, 127, 139, 151, 163**				
	IT Dosing Week[k]			**IT Dosing Week[k]**			**IT Dosing Week[k]**				
Assessment	**Pre-Tx Day 1**	**IT Injection Day 2[d]**	**Days 3-7**	**Pre-Tx Day 1**	**IT Injection Day 2[d]**	**Days 3-7**	**Pre-Tx Day 1**	**IT Injection Day 2[d]**	**Days 3-7**		
Location	**Main or Local Site**	**Main or Local Site**	**Main Site or Local**	**Main or Local Site**	**Main or Local Site**	**Main Site or Local**	**Main Site**	**Main Site**	**Main Site or Local**	**Local**	**Main Site**
…											
Brain and Spine MRI				•			•				•
…											

Other sections impacted by this change: Not applicable

19 APPENDIX 6: SUMMARY OF CHANGES FOR AMENDMENT 12

SUMMARY OF CHANGES AND THE RATIONALE FOR THE AMENDMENT

Clinical protocol HGT-HIT-046 has been revised from the previous version as follows:

- To add language to clarify those patients who exceed the age of enrollment eligibility for Study HGT-HIT-045 will be allowed to continue in Study HGT-HIT-046 until the end of the study. Patients will be re-consented once reaching the applicable legal age of consent.

- To indicate that if a patient is deemed as lacking mental capacity to provide informed consent and in accordance with applicable law, either the patient's parent(s) or their legally authorized representative(s) will be asked to sign an informed consent form

19 APPENDIX 6: SUMMARY OF CHANGES FOR AMENDMENT 11

SUMMARY OF CHANGES AND THE RATIONALE FOR THE AMENDMENT

Clinical protocol HGT-HIT-046 has been revised from the previous version as follows:

- To extend the duration of the study by 5 years.
- To allow for patients to retain a full or partial IDDD in situ after they discontinue the study, at the discretion of the investigator based upon safety assessment, with safety follow-up.

19 APPENDIX 6: SUMMARY OF CHANGES FOR AMENDMENT 10

SUMMARY OF CHANGES AND THE RATIONALE FOR THE AMENDMENT

Clinical protocol HGT-HIT-046 has been revised from the previous version as follows:

- To clarify that patients enrolled in Study HGT-HIT-046 who reach their 18th birthday while participating are allowed to remain in the study and continue to receive treatment with idursulfase-IT according to the protocol.

19 APPENDIX 6: SUMMARY OF CHANGES FOR AMENDMENT 9

SUMMARY OF CHANGES AND THE RATIONALE FOR THE AMENDMENT

Clinical protocol HGT-HIT-046 has been revised from the previous version as follows:

A new Schedule of Study Procedures (Part C, Table 14-3) has been created for patients who have completed 54 months of treatment with idursulfase-IT in study HGT-HIT-046 or across studies HGT-HIT-045 and HGT-HIT 046. It is intended that these patients undergo a streamlined schedule of evaluation and assessment to reduce the burden of continued study participation. For example, in study Part C pharmacokinetic sampling will no longer be performed, and several other assessments have been eliminated or scheduled at a reduced frequency.

The changes to the protocol in Part C (Month 55 to EOS) include the following:

- Elimination of blood sample collection for PK and exploratory proteomic biomarker testing, and reduced frequency of sample collection for clinical laboratory and other (anti-idursulfase antibody, GAG) tests
- Limited neurodevelopmental assessment focused on cognitive (DAS-II or BSID-III) testing; other tests (SIBR, BRIEF/BRIEF-P, PDMS, and BOT-2) no longer administered after pre-treatment at the Month 55 visit.
- Monthly symptom-directed physical and neurological exams performed at the Investigator's discretion
- After Month 55, ICP assessment not repeated until the EOS visit; no lumbar punctures are expected to be performed as long as patient has a functioning IDDD for the purpose of intrathecal dose administration.
- Reduced frequency of height, weight, head circumference measurements; after Month 55, vision assessment not repeated until the EOS visit.
- Reduced interval of inpatient stay after IT dosing and reduced frequency of vital signs collection after idursulfase-IT injection
- Provision of additional guidance regarding management of infusion reactions

An interim clinical study report is planned describing the results of Parts A and B. The complete results, including Part C, will be described in the final clinical study report.

19 APPENDIX 6: SUMMARY OF CHANGES FOR AMENDMENT 8

SUMMARY OF CHANGES AND THE RATIONALE FOR THE AMENDMENT

Clinical protocol HGT-HIT-046 has been revised from the previous version as follows:

- The duration of the study will be extended by 3 years. Patients will continue treatment in the extension study, unless they discontinue the study or Shire discontinues the study, for a maximum duration of 9 years of treatment with idursulfase-IT across studies HGT-HIT-045 and/or HGT-HIT-046.
- Updates were made to text pertaining to use of the SOPH-A-PORT Mini S IDDD and analysis of device-related data
- The Shire Medical Monitor for the study has changed and the text updated accordingly.

19 APPENDIX 6: SUMMARY OF CHANGES FOR AMENDMENT 7

- Summary of Changes and the Rationale for the Amendment
- Clinical protocol HGT-HIT-046 has been revised from the previous version to:
- Provide information concerning a new 10 mg/mL concentration of the idursulfase-IT drug product to be used in the study;
- Clarify that in the event of failure of an implanted intrathecal drug delivery device, a nonfunctional PORT-A-CATH device cannot be replaced by a new PORT-A-CATH device;
- Allow for the assessment of device leachables from residual CSF;
- Clarify the definitions of categories of adverse events collected during the study, ie, events related to idursulfase-IT, device [PORT-A-CATH or SOPH-A-PORT IDDD], device surgical procedure, IT administration process, or IV Elaprase infusion;
- Provide guidance concerning the reporting procedure for abuse, misuse, overdose, or medication error.
- Listing of Changes for the Amendment

21 APPENDIX 6: SUMMARY OF CHANGES FOR AMENDMENT 6

1. Summary of Changes and the Rationale for the Amendment

Clinical protocol HGT-HIT-046 has been revised from the previous version (Amendment 5) to provide guidance concerning the introduction of a new delivery device for intrathecal administration of idursulfase-IT, the SOPH-A-PORT Mini S, to study participants. Additionally, the study procedures sections and schedule of events for the Extended Treatment Phase of the study have been updated to extend the maximum duration of the extension component of the protocol. An itemized listing of significant changes or additions to the protocol pertaining to introduction of the SOPH-A-PORT Mini S device, study objectives/endpoints, dose selection, study procedures, and the planned statistical analysis is provided below. Other noteworthy changes to the protocol text include the following:

Introductory text in sections 3.2 Human Enzyme Replacement Therapy Rationale, 3.3 Idursulfase Administration in the Nonclinical Setting, and 3.6 Study Rationale was revised for completeness and clarity. Section 3.4 Previous Human Experience was updated to provide a summary of clinical experience with idursulfase-IT in studies HGT-HIT-045 and HGT-HIT-046 through 19 January 2013. A new section, 3.7 Benefit/Risk Assessment, was provided; its conclusion is that assessment of the benefit/risk of intrathecally administered idursulfase-IT based on the clinical data collected through 19 January 2013 indicates a positive benefit/risk balance. Finally, two new appendices were added to the protocol to provide summaries of adverse device effects expected with the SOPH-A-PORT Mini S (19 Appendix 4) and PORT-A-CATH (20 Appendix 5).

18 APPENDIX 4: SUMMARY OF CHANGES FOR AMENDMENT 5

1. Summary of Changes and the Rationale for the Amendment

Clinical protocol HGT-HIT-046 has been revised from the previous version (Amendment 4) to provide guidance concerning the performance of lumbar punctures during the study for the purposes of drug administration and CSF collection, and to align operational aspects of the study with recent changes to the protocol of study HGT-HIT-045, which have included the removal of the 100 mg dose cohort (HGT-HIT-045 Amendment 13) and the addition of a 1 mg dose cohort (HGT-HIT-045 Amendment 11).

Additionally, information concerning the safety of idursulfase-IT and the intrathecal drug delivery device in ongoing studies HGT-HIT-045 and HGT-HIT-046 has been updated based on a review of safety data available through May 2012 and with data summarized in the current edition of the idursulfase-IT Investigator's Brochure. Re-assessment of the benefit/risk ratio of intrathecal treatment with idursulfase-IT based on the safety data collected through May 2012 showed that the previous assessment was maintained, ie, the benefit/risk ratio is considered to be positive. Lastly, several refinements were made to the planned statistical analysis.

18 APPENDIX 4: SUMMARY OF CHANGES FOR AMENDMENT 4

1. Summary of Changes and the Rationale for the Amendment

Clinical protocol HGT-HIT-046 has been revised from the previous version (Amendment 3) to clarify operational aspects of the trial related to the duration of on-site observation after IT administration. Clarifications to the timing of collection of certain study assessments (vital signs, ECGs, physical and neurological examinations, clinical laboratory and PK sampling) have also been made. To reduce the burden of travel on study participants, the option of combining Day 1 and Day 2 assessments has been allowed, if the patient can arrive at the study site early in the day and if the investigator deems this clinically appropriate, during the Extended Treatment Phase of the study from Month 10 onward. Additionally, updated information about the safety of idursulfase-IT and the intrathecal drug delivery device (IDDD) in the ongoing studies has been added, and refinements have been made to the planned statistical analysis. Finally, the cover page of the protocol was modified to reflect a change in the Sponsor's address.

18 APPENDIX 4: SUMMARY OF CHANGES FOR AMENDMENT 3

1. Summary of Changes and the Rationale for the Amendment

Clinical protocol HGT-HIT-046 has been revised from the previous version (Amendment 2, 20 September 2010) to clarify that the maximum study duration will be 3 years.

18 APPENDIX 4: SUMMARY OF CHANGES FOR AMENDMENT 2

1. Summary of Changes and the Rationale for the Amendment

Clinical protocol HGT-HIT-046 has been amended to incorporate changes to the age range of eligible patients and to the neurodevelopmental assessments to be performed. The study will now include pediatric patients from 3 to <18 years of age with Hunter syndrome who have cognitive impairment (ie, not only patients with early signs and symptoms of cognitive impairment, but also patients who may have more advanced impairment and very low cognitive status). These modifications to the protocol are intended to align patient eligibility criteria and assessments in this screening study with those of the ongoing safety study (HGT-HIT-045) which is evaluating ascending doses of the investigational agent, idursulfase-IT, administered intrathecally in conjunction with intravenous idursulfase (Elaprase®) in pediatric patients from 3 to <18 years of age with Hunter syndrome and cognitive impairment. The Bayley Scales of Infant Development (BSID-III) now in use in the HGT-HIT-045 study will also be added to this amended protocol as an alternative to the Differential Ability Scales (DAS-II). In addition, like the HGT-HIT-045 protocol, a new section will be added to this protocol text describing the classification of adverse events with respect to study drug, study drug administration device, and associated procedures. With these and other changes to improve protocol clarity and consistency with protocol HGT-HIT-045, the schedule of study treatments and assessments for the Initial Treatment Phase (ie, first 6 months) of the study will be brought into close alignment with the schedule of study treatments and assessments for Study HGT-HIT-045; and the schedule of study treatments and assessments for the Extended Treatment Phase of this study will be organized and represented in the amended protocol in a manner that is more similar to the presentations in Study HGT-HIT-045 and in the Initial Treatment Phase of this study. Introductory text will be updated in the amended protocol with currently available information concerning the safety profiles of idursulfase-IT and Elaprase including updated information from ongoing clinical trials. All such introductory text is derived from the current edition of the idursulfase-IT Investigator's Brochure. Finally, minor edits and/or corrections will be made to the protocol text as needed to describe aspects of the study with greater clarity and to more closely align in-text descriptions of study procedures with tabulations and footnotes in the Schedules of Study Procedures.

Appendix 4 Summary of Changes and Justification for Amendment

Clinical Trial Protocol HGT-HIT-046 has been revised from the previous version (29 April 2009). HGT-HIT-046 is the extension study to Study HGT-HIT-045. Changes incorporated in this protocol amendment are made consistent with revisions incorporated in HGT-HIT-045 Protocol Amendment 7, dated 23 March 2010.

The primary purposes of this amendment were to:

- allow for more than one main clinical site.
- revise safety objectives of the study to clarify that the study's primary objective and respective endpoint is the investigation of the safety and tolerability of the investigational drug, idursulfase-IT, consistent with revision included in HGT-HIT-045 Amendment 7.
- revise the "naming" of study visits, for patients who were previously untreated with intrathecal idursulfase-IT n Study HGT-HIT-045. The visit previously described as Baseline/Week 3, initiating the Treatment Period of the protocol, is now defined as Week 1, and subsequent visits are re-numbered accordingly. The post-surgical follow-up visit previously described as occurring at Day 3 6 and the post intrathecal idursulfase-IT visit previously described as occurring at Day 3-7 have each been revised to Day 4, consistent with the timing detailed in HGT-HIT-045 Amendment 7.
- For patients who were previously untreated with intrathecal idursulfase-IT in Study the Safety Follow Up Visit which was previously described at Week 31 has been deleted. After the completion of the first 6 months of intrathecal idursulfase-IT treatment, these patients will continue to be treated and monitored in Study HGT-HIT-046 in the Extended Treatment Phase of the study, following the same treatment and assessment schedule as that detailed for patients who were previously treated in Study HGT-HIT-045. Therefore, a Safety Follow Up at Week 31 would be redundant with the assessments being completed as part of the Extended Treatment Phase.
- Clarification added to Section 4.3, Study Duration and Dates, to define the maximum duration of treatment in the study as 3 years for each enrolled patient.
- Clarification of different requirements for CSF sample assessment prior to administration of intrathecal idursulfase-IT, for patients participating in the Initial Treatment Phase of the study vs the Extended Treatment Phase. During the Initial Treatment Phase of this study (for patients who were not previously treated with intrathecal idursulfase-IT in Study HGT-HIT-045), the results of the CSF chemistry and cell count assessment must be reviewed by the treating Investigator prior to each IT dose.
- Revision to planned assessments included in the Full Neurodevelopmental Assessment, consistent with changes previously described in Study HGT-HIT-045 Amendments 5 and 6.
- Revision to Section 10, Planned Statistical Methods, specifically Section 10.1 and 10.2. Addition of detail, to clarify that the data will be summarized by Study HGT-HIT-045 treatment group assignment (10 mg, 30 mg, 100 mg and no treatment with intrathecal idursulfase-IT.) Extraneous language related to exploratory analyses deleted. Language revised consistent with revised safety objectives, to clarify that the study's primary objective and respective endpoint is the investigation of the safety and tolerability of the

investigational drug, idursulfase-IT (consistent with revision included in HGT-HIT-045 Amendment 7.)

Additional clarifications or changes incorporated in this amendment include:

- Section 1.3, Idursulfase-IT (Introduction). Sentence added to reflect initiation of Study HGT-HIT-045 in June 2009. No clinical information available to date.
- deletion of the Exploratory Endpoint describing the exploration of potential relationships between biomarkers and CNS symptomatology. Although this is defined as one of the Exploratory Objectives of Study HGT-HIT-046, defining exploration of a relationship between assessments as an endpoint is not appropriate.
- minor revision to exclusion criterion #5 (applicable only to patients previously untreated with intrathecal idursulfase-IT in Study HGT-HIT-045, to clarify that measurement of opening CSF pressure upon lumbar puncture may not exceed 30.0 cm H2O (previously defined as 30 cm H2O), consistent with revision included in HGT-HIT-045 Amendment 7
- • addition of a statement (and addition to Schedule of Events) to clarify that a separate written informed consent/assent will be required to approve the patient's participation in the study procedures to be conducted at the local site, consistent with revision included in HGT-HIT-045 Amendment 7.
- requirement for additional PT and PTT blood draw (for patients previously untreated with idursulfase-IT, participating in the Initial Treatment Phase) if the Pre-Surgery visit is more than 2 weeks following the EOS visit for Study HGT-HIT-045 (or Screening Visit, if applicable), consistent with revision included in HGT-HIT-045 Amendment 7
- Section (previously 6.4) Concomitant Therapy separated into 2 Sections, now Section 6.5, Concomitant Therapy and Section 6.5 Restrictions, per Shire's standard protocol template. Changes in standard text; no affect on study design.
- minor corrections to Section 7, Study Procedures to ensure consistency with study plan (and consistent with study procedures for Study HGT-HIT-045, Amendment 7, 23 Mar 2010) as outlined in Schedule of Events and throughout protocol.
- addition of Section 7.2, Echocardiogram, to the Study Procedures section of the protocol. This assessment was previously described in the Schedule of Events but was missing from this section.
- addition of Section 7.9.7, Surgical Implantation of the IDDD to the Study Procedures section of the protocol to describe the procedures associated with IDDD implantation, for patients who were not previously treated with intrathecal idursulfase-IT in Study HGT-HIT-045. Procedures are consistent with those described in Study HGT-HIT-045, Amendment 7. This section was inadvertently missing from the original protocol.
- addition of Section 7.9.8, Intracranial Pressure Measurement, to the Study Procedures section of the protocol to describe the measurement of intracranial pressure. This is not a new addition to the protocol and was previously described in the Schedule of Events (Appendix 1 and Appendix 2), but was previously missing from this section.
- addition of Section 7.12, Elaprase Infusion, to the Study Procedures section of the protocol. This section was inadvertently missing from the original protocol,

- addition of Section 7.13.1, Brief Neurodevelopmental Assessments to the Study Procedures section of the protocol. This section was inadvertently missing from the original protocol. A brief neurodevelopmental assessment will be conducted during the Initial Treatment Phase, in patients who were previously untreated in Study HGT-HIT-045, on Week 9 Day 1 (before the 3rd IT injection) and will consist of the SIB-R and DAS II tests.
  This is also added to the Schedule of Events for the Initial Treatment Phase, consistent with the study design for HGT-HIT-045.
- clarification that, in the event of early discontinuation, the IDDD will be removed from the patient (Section 7.9.7 and Synopsis), consistent with HGT-HIT-045 Amendment 7
- minor clarifications/corrections to the Schedule of Events (Appendix 1 and Appendix 2) and corresponding text in protocol
- Section 7.12.1.2 in the original Protocol, Infusion-Related Reactions Definition has been deleted, consistent with a revision described in Study HGT-HIT-045 Amendment 5 (08 July 2009). Upon review by Shire Pharmacovigilance and Risk Management, this section has been deemed appropriate for deletion as it contains information that is specific to Elaprase and that can be found in the Elaprase package insert.
- addition of Shire's Global Pharmacovigilance e-mail contact information for purposes of SAE reporting
- addition of Section 7.14.3, specifying the period of observation for adverse event monitoring in Study HGT-HIT-046 (from time of informed consent until 28 (+7) days after the patient's EOS visit.

In addition, several language changes have been made throughout the protocol, including:

- references to idursulfase-IT administration throughout protocol were revised to read "intrathecal idursulfase-IT" to clarify both the route of administration and formulation, and references to idursulfase-IT infusion were revised to "injection", to be more accurate
- adoption of the terms "Initial Treatment Phase" to describe the study schedule during the first 6 months of the extension study, for patients who were previously untreated with intrathecal idursulfase-IT in Study HGT-HIT-045, and "Extended Treatment Phase" to describe the study schedule for patients who were previously treated with intrathecal idursulfase-IT in Study HGT-HIT-045, and for patients continuing in this extension study after completion of the Initial Treatment Phase.
- references to CNS involvement were revised to "early cognitive impairment", providing a more accurate description of the patient population being studied, consistent with revision included in HGT-HIT-045 Amendment 7

The changes summarized above and detailed below in this document have been made in Protocol Amendment 1 (03 May 2010). The more substantial changes are summarized below by section number; new or additional text is indicated in bold and deleted text is indicated as strikethrough below. Editorial changes have been made throughout for consistency and grammar. Other sections affected by the same change are listed below each change.