Clinical Study Protocol

NCT Number: NCT02412787

Title: An Open Label Extension of Study HGT-HIT-094 Evaluating Long Term Safety and Clinical Outcomes of Intrathecal Idursulfase Administered in Conjunction with Elaprase® in Patients with Hunter Syndrome and Cognitive Impairment

Study Number: SHP609-302

Document Version and Date: Amendment 4, 09 October 2018

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: SHP609-302

Study Title:	An Open Label Extension of Study HGT-HIT-094 Evaluating Long Term Safety and Clinical Outcomes of Intrathecal Idursulfase Administered in Conjunction with Elaprase® in Patients with Hunter Syndrome and Cognitive Impairment
Study Number:	SHP609-302
Study Phase:	II/III
Product Name:	Idursulfase for intrathecal use (idursulfase-IT [HGT-2310])
Device Name:	SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire
IND Number:	100,610
EUDRACT Number	2014-004143-13
Indication:	Long-term treatment of Hunter syndrome in patients with cognitive impairment to slow progression of cognitive and functional impairment
Investigators:	Multicenter
Sponsor:	Shire Human Genetic Therapies, Inc. (Shire)
Sponsor Contact:	300 Shire Way Lexington, MA 02421 USA +1-617-349-0200
Medical Monitor:	[redacted], DO

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Original Protocol:	02 October 2014
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Administrative Change 3	05 May 2015
Administrative Change 4	02 November 2015
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Administrative Change 5	03 August 2016
Amendment 3	28 February 2017
Amendment 4	09 October 2018

SYNOPSIS

Sponsor:

Shire Human Genetic Therapies, Inc. (Shire)

Name of Investigational Product:

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

Name of Device:

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

Study Title:

An Open Label Extension of Study HGT-HIT-094 Evaluating Long Term Safety and Clinical Outcomes of Intrathecal Idursulfase Administered in Conjunction with Elaprase® in Patients with Hunter Syndrome and Cognitive Impairment

Study Number:

SHP609-302

Study Phase: II/III

Investigational Product, Dose, and Mode of Administration:
idursulfase-IT, 10 mg, intrathecal (IT)

Device, Intended Use

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

Comparator, Dose, and Mode of Administration:

Not applicable.

Primary Objective:

The primary objective of this study is to evaluate long-term safety in subjects with Hunter syndrome and cognitive impairment who are receiving intrathecal idursulfase-IT and intravenous (IV) Elaprase® enzyme replacement therapy (ERT).

Secondary Objectives:

The secondary objectives of this study are to evaluate long-term clinical efficacy outcomes in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT in conjunction with Elaprase therapy with respect to the following:

- Cognitive function as measured by General Conceptual Ability (GCA), the cluster areas and subtests of the Differential Abilities Scale, Second Edition (DAS-II), or domains of the Bayley Scales of Infant Development, Third Edition (BSID-III)
- Adaptive behavior as measured by the Adaptive Behavior Composite (ABC) score and standard domain scores of the Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
- Brain structure volume as measured by magnetic resonance imaging (MRI)

Pharmacokinetic and Pharmacodynamic Objectives:

- To evaluate the concentration of idursulfase and determine PK parameters in serum after IT administration in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT in conjunction with Elaprase therapy
- To evaluate the concentration of idursulfase in CSF in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT in conjunction with Elaprase therapy
- To evaluate the concentration of glycosaminoglycan (GAG) in CSF in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT in conjunction with Elaprase therapy
- To evaluate the concentration of GAG in urine in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT in conjunction with Elaprase therapy

Health Economics and Outcomes Research Objectives:

- To evaluate health status as measured by the EuroQol-5D-5L (EQ-5D-5L) instrument, in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase IT in conjunction with Elaprase therapy
- To evaluate healthcare resource utilization, as measured by the Healthcare Utilization Questionnaire (HCUQ) in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase IT in conjunction with Elaprase therapy
- To evaluate the social/emotional, physical, daily activities and financial impact on caregivers and families of subjects with Hunter syndrome and cognitive impairment as measured by Caregiver Impact Questionnaire (CIQ)
- To evaluate functional status as measured by the HS-FOCUS (Hunter Syndrome Functional Outcomes for Clinical Understanding Scale) instrument, in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT in conjunction with Elaprase therapy

SOPH-A-PORT Mini S Objective:

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

Study Endpoints:

The primary safety endpoints of this study are the following:

- Adverse events (AEs; by type, severity, and relationship to treatment [idursulfase-IT, the intrathecal drug delivery device (IDDD), device surgical procedure, or IT administration process] and IV Elaprase infusion)
- Changes in clinical laboratory testing (serum chemistry, hematology, urinalysis)
- Vital signs
- Twelve-lead ECG recordings
- CSF laboratory parameters (chemistries, cell counts)
- Anti-idursulfase antibodies in CSF and serum, including determination of anti-idursulfase antibodies having enzyme neutralizing activity

The secondary efficacy endpoints of this study are the following:

- Change from baseline in DAS-II standard scores: GCA, Special Nonverbal

Composite (SNC); and cluster scores: Verbal, Nonverbal, Spatial; and/or the age equivalents and Development Quotient (DQ) from the BSID-III domains: Cognitive and Language

- Change from baseline in standard composite scores of the VABS-II: ABC and domain standard scores: Communication, Daily Living Skills, Socialization, and Motor Skills
- Change from baseline in age equivalents, developmental quotients, and T-scores for the core subtests of the DAS-II: Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices, and Copying for the DAS-II Early Years and Recall of Designs, Word Definitions, Pattern Construction, Matrices, Verbal Similarities, and Sequential and Quantitative Reasoning for the DAS-II School Years
- Change from baseline in age equivalents, developmental quotients, and v-Scale scores of the VABS-II subdomains: Communication (Receptive, Expressive, Written), Daily Living Skills (Personal, Domestic, Community), Socialization (Interpersonal Relationships, Play and Leisure Time, Coping Skills), Motor Skills (Gross, Fine)
- Change from baseline in the v-Scale scores and observed maladaptive levels of the VABS-II Maladaptive Behavior Index and its subscales (Internalizing, Externalizing)
- Change from baseline in Brain Total Intracranial Volume, Brain Total Tissue Volume, Brain Total White Matter, Brain Total Gray Matter, and Total CSF Volume

The exploratory efficacy endpoints of this study are the following:

- Change from Visit Month 13/baseline to Visit Month 25/Week 52 in study SHP609-302 as estimated by linear regression in:
    - DAS-II GCA scores from Early Years battery
    - DAS-II Early Years core subtests T scores: Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices, and Copying
    - DAS-II Early Years battery standard cluster scores: Verbal, Nonverbal, Spatial, and SNC composite scores
    - DAS-II GCA scores including both Early Years and School Age batteries
    - VABS-II ABC scores

  Note that the interval from Visit Month 13/baseline to Visit Month 25/Week 52 in study SHP609-302 is defined as from Visit Month 13 to Visit Month 25 in SHP609-302 Extended Treatment Phase for subjects in the Early IT group, and from baseline in study SHP609-302 to Visit Week 52 in SHP609-302 Initial Treatment Phase for subjects in the Delayed IT group. The Early IT group and Delayed IT group designations are based on the treatment regimen (idursulfase-IT or No IT treatment) in the antecedent study (HGT-HIT-094).

- Ordered categorical outcome for each subject at study SHP609-302 Visit Month 25/Week 52

- Binary unreversed floor effect outcome for each subject

The health economics and outcomes research endpoints of this study are the following:

- Health status dimensions as obtained by the EQ-5D-5L questionnaire
- Health care resource utilization will be assessed using the HCUQ
- Health-related quality of life for caregivers will be assessed using the CIQ
- Functional status as obtained by the HS-FOCUS form

The pharmacokinetic and pharmacodynamic endpoints of this study are the following:

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

Study Population:

Pediatric subjects (plus potentially any pediatric subjects younger than 3 years of age in the antecedent substudy) who completed Study HGT-HIT-094, and meet the eligibility criteria may enroll in this study.

Study Design:

This is an open-label, non-randomized study for subjects who completed Study HGT-HIT-094; all subjects in this study will be treated with intrathecal idursulfase-IT in conjunction with Elaprase therapy.

Subjects who complete Visit Week 52 assessments of Study HGT-HIT-094 and who meet the eligibility criteria and for whom informed consent is provided will be enrolled in this extension study.

All subjects will receive idursulfase-IT at the same dose and frequency (10 mg once every 28 days) as selected for the HGT-HIT-094 study. Subjects who are younger than 3 years of age will continue to receive an adjusted dose.

The assessments in this study are similar to those performed in Study HGT-HIT-094 and will be performed at regular intervals; the frequency of assessments will vary depending on the treatment phase of the study (Initial Treatment Phase or Extended Treatment Phase).

Subjects who participated in the control arm (no treatment with idursulfase-IT) in Study HGT-HIT-094 will begin this study in the Initial Treatment Phase. These subjects will have the IDDD implanted following enrollment in order to begin treatment with idursulfase-IT. These subjects will, during the Initial Treatment Phase of this study (ie, the first 12 months), undergo treatment and assessments similar to those performed for subjects who were treated with idursulfase-IT in Study HGT-HIT-094. After completion of the Initial Treatment Phase and if there are no safety concerns, subjects may continue receiving monthly idursulfase-IT in the Extended Treatment Phase of this study.

Subjects who received treatment in the HGT-HIT-094 study will begin this study in the Extended Treatment Phase, which reflects a reduced frequency of assessments compared with the schedule of assessments in Study HGT-HIT-094. Standardized

neurodevelopmental assessments and health economic and outcomes research assessments will be performed every 24 weeks and CSF assessments (other than standard chemistry) and clinical laboratory tests of blood and urine will be performed every 12 weeks. Brain MRI and 12-lead ECG will be performed every 48 weeks. A pharmacokinetic assessment will be performed once during this phase of the study. All subjects in the study will undergo EOS procedures approximately 28 days following their last administration of idursulfase-IT.

It is anticipated that the IDDD will be used to obtain cerebrospinal fluid (CSF) samples and to deliver all intrathecal (IT) injections of idursulfase-IT. If the IDDD appears to be non-functional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD Manual(s), which provides details on the investigation and management of any IDDD-related issues. This includes possible partial revision or complete replacement of the IDDD as indicated. If the IT space is not accessible via the IDDD, study drug may be administered and CSF sampled by lumbar puncture (LP). General anesthesia or sedation 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. Subjects will have the IDDD removed when they discontinue from or complete the study, unless the subject is continuing to receive treatment through another mechanism (eg, extension study, expanded access program).

Study Duration:

Subjects will participate in this extension study for a duration of 10 years of treatment, unless they discontinue the study or Shire discontinues the study.

Study Inclusion and Exclusion Criteria:

Each subject must meet the following criteria to be enrolled in this study:

1. Subjects must have completed Visit Week 52 assessments in Study HGT-HIT-094.
2. The subject's parent(s) or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form after all relevant aspects of the study have been explained and discussed. Consent of the subject's parent(s) or legally authorized guardian(s) and the subject's consent/assent, as relevant, must be obtained.
3. The subject has continued to receive Elaprase on a regular basis in Study HGT-HIT-094.

Subjects who meet any of the following criteria will be excluded from the study:

1. The subject has experienced, in the opinion of the Investigator, a safety or medical issue that contraindicates treatment with idursulfase-IT, including, but not limited to, uncontrolled seizure disorder, bleeding disorder, and clinically relevant hypertension
2. The subject has a known hypersensitivity to any of the components of idursulfase-IT
3. The subject has clinically relevant intracranial hypertension
4. The subject is enrolled in another clinical study, other than HGT-HIT-094, that involves clinical investigations or use of any investigational product (drug or [intrathecal/spinal] device) within 30 days prior to study enrollment or at any time

during the study

5. The subject has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to compromised airways or other conditions.
6. The subject has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use, including:
   a. The subject has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
   b. The subject'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 subject's drug therapy requires substances known to be incompatible with the materials of construction
   d. The subject has a known or suspected local or general infection
   e. The subject is at risk of abnormal bleeding due to a medical condition or therapy
   f. The subject has 1 or more spinal abnormalities that could complicate safe implantation or fixation
   g. The subject has a functioning CSF shunt device
   h. The subject has shown an intolerance to an implanted device

Pharmacokinetic Variables:

Determination of idursulfase serum concentration-time profiles and serum pharmacokinetic parameters after IT administration.

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

Pharmacodynamic Assessments:

Determination of the concentration of GAG in CSF and urine samples.

Efficacy Assessments:

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

- The DAS-II will be used to assess all subjects of age 2 years, 6 months or older.
- Any subjects who cannot be assessed with the DAS-II due to a deteriorating condition or who are younger than 2 years, 6 months of age, will be assessed with the BSID-III. Spanish-speaking subjects will be assessed using the Spanish version of the DAS-II Early Years or DAS-II School Age.
- The VABS-II will be used to assess adaptive behavior.

Brain structure volumes will be measured by brain MRI.

SOPH-A-PORT Mini S Device Assessments:

The SOPH-A-PORT Mini S will be evaluated using assessments of device implantation, device function, device longevity, and AEs associated with the implant surgery or device. This data will be collected on the subject's eCRF from the time of initial implantation.

Safety Assessments:

Safety will be assessed by AEs (by type, severity, and relationship to treatment [idursulfase-IT, IDDD, device surgical procedure, IT administration process], IV Elaprase

infusion, IV Elaprase and/or idursulfase-IT), changes in clinical laboratory testing (serum chemistry, hematology, urinalysis), AEs determined from physical and neurological examination, vital signs, 12-lead ECG recordings, CSF laboratory parameters (chemistries, cell counts), anti-idursulfase antibodies in CSF and serum (including determination of antibodies having enzyme neutralizing activity).

Statistical Methods:

Statistical analyses will be performed by the Biostatistics and Statistical Programming Department of Shire or its designee using SAS statistical software (SAS Institute, Cary, NC, USA), unless otherwise specified. Analysis methods will be detailed in the statistical analysis plan (SAP).

Data from studies SHP609-302 and HGT-HIT-094 will be integrated for efficacy and safety analyses. Baseline for the subjects previously treated in HGT-HIT-094 will be the same as the baseline defined in HGT-HIT-094. Baseline for the previously untreated subjects (ie, No IT treatment) in HGT-HIT-094 will be the closest available assessment prior to the initial IDDD implant date, which takes place in Study SHP609-302, unless otherwise specified. This could potentially include EOS visit data from Study HGT-HIT-094. The analyses presented here will include the data measured at and after baseline.

Safety data descriptive summaries will be presented for the Early IT group, Delayed IT group, and overall. The Early IT group and Delayed IT group designations are based on the treatment regimen (idursulfase-IT or No IT treatment) in the antecedent study (HGT-HIT-094). The Early IT group is defined as subjects who were randomized to the idursulfase-IT treatment cohort in study HGT-HIT-094 and continued IT treatment in study SHP609-302. The Delayed IT group is defined as subjects who were randomized to the control cohort (No IT treatment) in study HGT-HIT-094 and began IT treatment in study SHP609-302. Subjects who participated in the HGT-HIT-094 substudy will be included in the Early IT group.

Efficacy data descriptive summaries will be presented separately for subjects who enrolled from the pivotal study or substudy of HGT HIT 094. For subjects enrolled from the pivotal study, descriptive statistics will be presented by the Early IT group, the Delayed IT group and overall. For secondary efficacy endpoints, the mean difference in the change at each time point between the 2 treatment groups (Early IT group and Delayed IT group) and the corresponding 90% confidence interval of the mean difference will be presented where appropriate. The mean values (±SD) for all efficacy endpoints will be graphed over time where appropriate.

Inferential testing is planned for some exploratory efficacy endpoints. The main exploratory efficacy analysis to examine the IT treatment effect will be rate of change (weighted) analyses of the exploratory efficacy endpoints from Visit Month 13/baseline in study SHP609-302 to Visit Month 25/Week 52 as estimated by linear regression for DAS-II Early Years GCA scores and selected neurodevelopment assessment scores.

Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of subjects in each category.

Date of Protocol Amendment: 09 Oct 2018

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABC	adaptive behavior composite
AE	adverse event
ALK	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BSID-III	Bayley Scales of Infant Development, Third Edition
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CIQ	Caregiver Impact Questionnaire
CL/f	clearance for IT-L administration
C_{max}	maximal concentration
CNS	central nervous system
CO_2	carbon dioxide
CRF	case report form (paper or electronic)
CRO	contract research organization
CS	clinically significant
CSF	cerebrospinal fluid
DAS-II	Differential Ability Scales, Second Edition
DQ	developmental quotient
DS	dermatan sulfate
DMC	Data Monitoring Committee
ECG	electrocardiogram
EOS	end of study
EQ-5D-5L	EuroQol-5D-5L instrument for use as a measure of health outcome
ERT	enzyme replacement therapy
EU	European Union
FDA	United States Food and Drug Administration
FT	full time
GAG	glycosaminoglycan
GCA	general conceptual ability
GCP	Good Clinical Practice

Abbreviation	Definition
GGT	gamma glutamyl transferase
Hct	hematocrit
HCUQ	Healthcare Utilization Questionnaire
Hgb	hemoglobin
HGT-2310	drug code name for formulation of recombinant iduronate-2-sulfatase (idursulfase) for intrathecal administration
HS	heparan sulfate
HS-FOCUS	Hunter Syndrome Functional Outcomes for Clinical Understanding Scale
ICH	International Conference on Harmonisation
IDS	iduronate-2-sulfatase
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IFU	Instructions for Use
IND	Investigational New Drug application
IRB	Institutional Review Board
IT	intrathecal
IV	intravenous(ly)
LDH	lactate dehydrogenase
LP	lumbar puncture
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	medical device report
MedDRA	Medical Dictionary for Regulatory Activities
MPS II	Mucopolysaccharidosis II (Hunter syndrome)
MRI	magnetic resonance imaging
MRT	mean residence time
N or n	number of observations
NCS	not clinically significant
NW	not working
PACU	post-anesthesia care unit
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PORT-A-CATH	PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System
PRO	patient reported outcome

Abbreviation	Definition
PT	part time
PT	prothrombin time
PTT	partial thromboplastin time
QTc	corrected QT interval
RBC	red blood cell(s)
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System©
SEM	standard error of measurement
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
Shire HGT	Shire Human Genetic Therapies, Inc. (Shire)
SmPC	Summary of Product Characteristics
SNC	special nonverbal composite
SOC	system organ class
SOPH-A-PORT Mini S	SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire
$t_{1/2}$	terminal half-life
T4	thyroxine
T_{max}	time of maximal concentration
TSH	thyroid-stimulating hormone
Tx	treatment
UK	United Kingdom
US	United States
VAS	visual analog scale
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
$V_{z/F}$	volume of distribution based on terminal phase
WBC	white blood cell(s)
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Mucopolysaccharidosis II (Hunter Syndrome)

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

The disease is caused by the absence of, or deficiency in, the activity of the lysosomal enzyme, iduronate-2-sulfatase which acts to cleave O-linked sulfate moieties from the glycosaminoglycan (GAG) molecules dermatan sulfate (DS) and heparan sulfate (HS).[4] Insufficient activity of iduronate-2-sulfatase leads to progressive accumulation of GAG in nearly all organs and body tissues.

The central underlying pathophysiological process leading to the clinical manifestations of MPS II is the chronic accumulation of dermatan sulfate and heparan sulfate inside cellular lysosomes, resulting in cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction. Accumulation of GAG affects nearly all cell types, tissues, and organs of the body including the respiratory tract, heart, liver, spleen, leptomeninges, bones, joints, oropharynx, head, neck, and central nervous system (CNS).[5] Clinical manifestations include severe airway obstruction, skeletal deformities, cardiomyopathy and, in most patients, neurological decline.[6] Death may occur in the first or second decade of life. Patients with attenuated disease may survive into adulthood, with airway obstruction and cardiac causes often contributing to death.[4]

Phenotypic expression of the disease spans a wide spectrum of clinical severity. However, two extremes at either end of the continuum of MPS II have been identified based on cognitive status.[4, 7] The first is broadly characterized as an "attenuated" or milder form in which intellectual and neurodevelopment faculties are largely intact, although somatic pathology is present. The term "severe" has been adopted to describe a second broad phenotype of MPS II patients who suffer from neurodevelopmental impairment in addition to somatic manifestations of the disease. It has been estimated that approximately three-quarters of MPS II patients will develop CNS involvement and be characterized as "severe."[7] Despite these characterizations, patients with predominantly somatic involvement may nevertheless have a life-limiting disease course.

Although there is heterogeneity with respect to disease progression, the onset of signs and symptoms typically occurs at about 2 to 4 years of age.[5-8] An earlier appearance of clinical symptoms generally, but not always, predicts a more severe clinical course.[4, 5, 9, 10] Knowledge of the genotype is of limited value in predicting a patient's clinical course with respect to CNS involvement. An exception is represented by children with complete absence of functional enzyme due to deletion/rearrangement of the iduronate-2-sulfatase (IDS) gene, who manifest severe neurodevelopmental impairment.[11, 12]

1.2 Unmet Medical Need

The currently approved therapy for Hunter syndrome is Elaprase® (idursulfase), recombinant human iduronate-2-sulfatase for intravenous (IV) administration. Elaprase has provided clinical benefit with respect to somatic pathologies in patients with Hunter syndrome, and has a well characterized safety profile. Although many of the physical symptoms of the disease can be reduced or eradicated by IV enzyme replacement,[13-15] Elaprase has not been evaluated specifically regarding its independent quantifiable impact on CNS pathology, due to the acknowledged impermeability of the blood brain barrier to macromolecules such as idursulfase. In addition, Elaprase is formulated for IV use only and it is not intended for direct injection into the CNS. Thus, no approved therapy exists for the CNS pathologies of Hunter syndrome.

Because intravenously administered idursulfase is unlikely to traverse the blood-brain barrier due to its impermeability to large macromolecules such as proteins, there is an unmet medical need in the population of MPS II patients with CNS disease to support clinical development of idursulfase-IT for intrathecal use.

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

1.3 Overview of Results of Phase I/II Studies

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

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

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

As a result of the device-related concerns in the Phase I/II program, additional guidelines and training materials were developed for implanting neurosurgeons concerning the surgical implantation of the IDDD, and repeated lumbar punctures were permitted per protocol amendment as a means of IT delivery of investigational product in the event of device malfunction. To address the frequent occurrence of device failures observed with use of the PORT-A-CATH IDDD in the Phase I/II studies, the SOPH-A-PORT Mini S is being used in the antecedent Phase II/III study (HGT-HIT-094). The SOPH-A-PORT Mini S device is intended to address the frequent occurrence of device failures observed with use of the PORT-A-CATH IDDD in the Phase I/II studies.

Intrathecal administration of idursulfase-IT to MPS II subjects in studies HGT-HIT-045 and HGT-HIT-046 at the 10 and 30 mg dose regimens resulted in a pronounced pharmacodynamic reduction from baseline in the concentration of GAG in CSF; the 1 mg dose regimen induced a slower and less pronounced reduction in GAG concentration in CSF. Available results of neurodevelopmental assessments performed across HGT-HIT-045 and HGT-HIT-046 suggest the potential of intrathecal delivery of idursulfase-IT to halt or slow the progressive decline in neurodevelopmental status in this patient population. Several subjects 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 slowing of cognitive decline.

1.3.1 Rationale for Current Phase II/III Study

The current study is an extension study to the pivotal Phase II/III study, HGT-HIT-094. Study HGT-HIT-094 is a controlled, randomized, two-arm, open-label, assessor-blinded, multicenter study to determine the effect on clinical parameters of neurodevelopmental status of monthly IT administration of idursulfase-IT for 12 months in pediatric subjects with Hunter syndrome and early cognitive impairment who have previously received and tolerated a minimum of 4 months of therapy with Elaprase. Subjects are randomized to idursulfase-IT treatment or no idursulfase-IT treatment. All subjects continue to receive Elaprase therapy.

The therapeutic strategy in the ongoing, antecedent study (HGT-HIT-094) and this extension study, consisting of idursulfase-IT administered intrathecally while the subject continues to receive Elaprase as standard of care, is intended to address both the CNS and somatic manifestations of Hunter syndrome. Idursulfase-IT is intended for long-term treatment of Hunter syndrome in subjects with cognitive impairment to slow progression of cognitive and functional impairment.

This study serves to extend the treatment, as well as safety and efficacy monitoring, for subjects who completed study HGT-HIT-094, which is designed to include the 42 pediatric subjects randomized to receive idursulfase-IT monthly, or no IT treatment, plus potentially a number of pediatric subjects younger than 3 years old in the open-label, single-arm substudy also included in HGT-HIT-094. Subjects in the substudy follow a similar schedule of study visits as subjects in the main study receiving idursulfase-IT.

The design of the antecedent study (HGT-HIT-094), including the neurodevelopmental assessment tools and endpoints, and the selection of idursulfase-IT 10 mg dose, were informed by the results of Phase I/II studies HGT-HIT-045 and HGT-HIT-046. Similar assessment tools and endpoints are employed in this study.

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

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

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

Please refer to the current edition of the investigator's brochure for additional information concerning the safety and clinical development of idursulfase-IT and for information concerning the SOPH-A-PORT Mini S delivery device.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate long-term safety in subjects with Hunter syndrome and cognitive impairment who are receiving intrathecal idursulfase-IT and IV Elaprase® enzyme replacement therapy (ERT).

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate long-term clinical efficacy outcomes in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT, in conjunction with Elaprase therapy with respect to the following:

- Cognitive function as measured by General Conceptual Ability (GCA), the cluster areas and subtests of the Differential Abilities Scale, Second Edition (DAS-II), or domains of the Bayley Scales of Infant Development, Third Edition (BSID-III)
- Adaptive behavior as measured by the Adaptive Behavior Composite (ABC) score and standard domain scores of the Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
- Brain structure volume as measured by magnetic resonance imaging (MRI)

2.3 Pharmacokinetic and Pharmacodynamic Objectives

- To evaluate the concentration of idursulfase and determine PK parameters in serum after IT administration in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT in conjunction with Elaprase therapy
- To evaluate the concentration of idursulfase in CSF in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT in conjunction with Elaprase therapy
- To evaluate the concentration of GAG in CSF in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT in conjunction with Elaprase therapy
- To evaluate the concentration of GAG in urine in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT in conjunction with Elaprase therapy

2.4 Health Economics and Outcomes Research Objectives

- To evaluate health status as measured by the EuroQol-5D-5L (EQ-5D-5L) instrument, in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT in conjunction with Elaprase therapy
- To evaluate healthcare resource utilization, as measured by the Healthcare Utilization Questionnaire (HCUQ) in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase IT in conjunction with Elaprase therapy

- To evaluate the social/emotional, physical, daily activities and financial impact on caregivers and families of subjects with Hunter syndrome and cognitive impairment as measured by Caregiver Impact Questionnaire (CIQ)
- To evaluate functional status as measured by the HS-FOCUS (Hunter Syndrome Functional Outcomes for Clinical Understanding Scale) instrument, in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT in conjunction with Elaprase therapy

2.5 SOPH-A-PORT Mini S Device Objective

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

3 STUDY ENDPOINTS

3.1 Primary Safety Endpoints

Safety will be assessed during the study by the following:

- Adverse events (AEs) (by type, severity, and relationship to treatment [idursulfase-IT, the IDDD, device surgical procedure, or IT administration process], IV Elaprase infusion, IV Elaprase and/or idursulfase-IT)
- Changes in clinical laboratory testing (serum chemistry, hematology, urinalysis)
- Vital signs
- Twelve-lead ECG recordings
- CSF laboratory parameters (chemistries, cell counts)
- Anti-idursulfase antibodies in CSF and serum, including determination of anti-idursulfase antibodies having enzyme neutralizing activity

3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are the following:

- Change from baseline in DAS-II standard scores: GCA, Special Nonverbal Composite (SNC); and standard cluster scores: Verbal, Nonverbal, Spatial; and/or the age equivalents and Development Quotient (DQ) from the BSID-III domains: Cognitive and Language
- Change from baseline in standard composite scores of the VABS-II: ABC and domain standard scores: Communication, Daily Living Skills, Socialization, and Motor Skills
- Change from baseline in age equivalents, developmental quotients, and T-scores for the core subtests of the DAS-II: Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices, and Copying for the DAS-II Early Years and Recall of Designs, Word Definitions, Pattern Construction, Matrices, Verbal Similarities, and Sequential and Quantitative Reasoning for the DAS-II School Years
- Change from baseline in age equivalents, developmental quotients, and v-Scale scores of the VABS-II subdomains: Communication (Receptive, Expressive, Written), Daily Living Skills (Personal, Domestic, Community), Socialization (Interpersonal Relationships, Play and Leisure Time, Coping Skills), Motor Skills (Gross, Fine)
- Change from baseline in the v-Scale scores and observed maladaptive levels of the VABS-II Maladaptive Behavior Index and its subscales (Internalizing, Externalizing)
- Change from baseline in Brain Total Intracranial Volume, Brain Total Tissue Volume, Brain Total White Matter, Brain Total Gray Matter, and Total CSF Volume

3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints of this study are the following:

- Change from Visit Month 13/baseline to Visit Month 25/Week 52 in study SHP609-302 as estimated by linear regression in:

- DAS-II GCA scores from Early Years battery
- DAS-II Early Years battery core subtests T scores: Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices, and Copying
- DAS-II Early Years battery standard cluster scores: Verbal, Nonverbal, Spatial, and SNC composite score
- DAS-II GCA scores including both Early Years and School Age batteries
- VABS-II ABC scores

Note that the interval from Visit Month 13/baseline to Visit Month 25/Week 52 in study SHP609-302 is defined as from Visit Month 13 to Visit Month 25 in SHP609-302 Extended Treatment Phase for subjects in the Early IT group (defined in Section 10.4.1), and from baseline in study SHP609-302 to Visit Week 52 in SHP609-302 Initial Treatment Phase for subjects in the Delayed IT group (defined in Section 10.4.1). The Early IT group and Delayed IT group designations are based on the treatment regimen (idursulfase-IT or No IT treatment) in the antecedent study (HGT-HIT-094).

- Ordered categorical outcomes for each subject at study SHP609-302 Visit Month 25/Week 52 are defined below. The definition for each response category threshold is based on the standard error of measurement (SEM) for the DAS-II. The SEM for the GCA, based on test-retest reliability of the DAS-II,[17] is approximately ±5 points. The ordered categorical outcomes will be defined for both DAS-II GCA scores from Early Years battery and GCA scores.
  - Above average cognitive development (Category 1) is defined as a subject with an observed GCA score at Visit Month 25/Week 52 which is more than 10 points (2 SEM) higher than the observed GCA score at Visit Month 13/baseline in study SHP609-302; ie,
    - GCA (Visit Month 25/Week 52) > GCA (Visit Month 13/baseline) + 10 points
  - Average cognitive development (Category 2) is defined as a subject with an observed GCA score at Visit Month 25/Week 52 which is within a range of ±10 points, inclusive (2 SEM), of the observed GCA score at Visit Month 13/baseline in study SHP609-302; ie,
    - GCA (Visit Month 13/baseline) - 10 points ≤ GCA (Visit Month 25/Week 52) ≤ GCA (Visit Month 13/baseline) + 10 points
  - Below average cognitive development (Category 3) is defined as a subject with an observed GCA score at Visit Month 25/Week 52 which is more than 10 points (2 SEM) below the observed GCA score at Visit Month 13/baseline in study SHP609-302; ie,
    - GCA (Visit Month 25/Week 52) <GCA (Visit Month 13/baseline) – 10 points

- Binary unreversed floor effect outcome for each subject

3.4 Health Economics and Outcomes Research Endpoints

The health economics and outcomes research endpoints of this study are the following:

- Health status dimensions as obtained by the EQ-5D-5L questionnaire
- Health care resource utilization will be assessed using the HCUQ
- Health-related quality of life for caregivers will be assessed using the CIQ
- Functional status as obtained by the HS-FOCUS form

3.5 Pharmacokinetic and Pharmacodynamic Endpoints

The pharmacokinetic and pharmacodynamic endpoints of this study are the following:

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

3.6 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 AEs associated with the implant surgery or device. These data will be collected on the subject's eCRF from the time of initial implantation.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is an open-label, non-randomized study for subjects who completed Study HGT-HIT-094; all subjects in this study will be treated with intrathecal idursulfase-IT in conjunction with Elaprase therapy.

Subjects who complete Visit Week 52 assessments of Study HGT-HIT-094 and who meet the eligibility criteria and for whom informed consent is provided will be enrolled in this extension study. Subjects planning to continue in this extension study will have written informed consent provided prior to completing the HGT-HIT-094 EOS assessments. The Visit Week-52 HGT-HIT-094 assessments must be completed prior to the first idursulfase-IT injection in this study.

Prior to conducting any study-related procedures, written informed consent (signed and dated) must be obtained from the subject's parent(s) or legally authorized guardian(s) (and consent/assent from the subject, if applicable). The nature, scope, and possible consequences, including risks and benefits, of the study will be explained by the investigator or designee in accordance with the guidelines described in Section 11.4. Documentation and filing of informed consent documents should be completed according to Section 11.4.

During Study SHP609-302, subjects who exceed the age of enrollment eligibility for Study HGT-HIT-094 and/or have reached the applicable legal age of consent to participate in a clinical study will be allowed to continue participation in Study SHP609-302 until the end of the study.

The HGT-HIT-094 EOS visit is intended to be the same as the first visit for subjects enrolled in this study. Subjects enrolling in this study are not required to participate in the safety follow-up visit of HGT-HIT-094. For subjects who were treated with idursulfase-IT in Study HGT-HIT-094, the visit weeks in this study are numbered continuously with visit weeks in Study HGT-HIT-094.

All subjects will receive idursulfase-IT at the same dose and frequency (10 mg once every 28 days) as selected for the HGT-HIT-094 study. Subjects who are younger than 3 years of age will continue to receive an adjusted dose as specified in Section 6.3. As in Study HGT-HIT-094, subjects will undergo pre-treatment and safety assessments on Day 1 and will receive an IT injection of idursulfase-IT on Day 2 of each IT Dosing Week, followed by a safety follow-up visit. From Week 28 onward, pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate. In addition (from Week 28 onward), and in the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

The assessments in this study are similar to those performed in Study HGT-HIT-094 and will be performed at regular intervals; the frequency of assessments will vary depending on the treatment phase of the study as described in Sections 4.1.1 and 4.1.2 for the Initial Treatment

Phase and Extended Treatment Phase, respectively. All subjects in the study will undergo EOS procedures approximately 28 days following their last administration of idursulfase-IT.

4.1.1 Initial Treatment Phase – Only Subjects Not Treated with Idursulfase-IT in Study HGT-HIT-094

Subjects who participated in the control arm (no treatment with idursulfase-IT) in Study HGT-HIT-094 will begin this study in the Initial Treatment Phase. These subjects will have the IDDD implanted following enrollment in order to begin treatment with idursulfase-IT. These subjects will, during the Initial Treatment Phase of this study (ie, the first 12 months), undergo treatment and assessments similar to those performed for subjects who were treated in Study HGT-HIT-094. After completion of the Initial Treatment Phase and if there are no safety concerns, subjects may continue receiving monthly idursulfase-IT in the Extended Treatment Phase of this study (Section 4.1.2).

The Schedule of Events for the Initial Treatment Phase is provided in Appendix 1.

4.1.2 Extended Treatment Phase – All Subjects

Subjects who received treatment with idursulfase-IT in the HGT-HIT-094 study will begin this study in the Extended Treatment Phase, which reflects a reduced frequency of assessments compared with the schedule of assessments in Study HGT-HIT-094. Standardized neurodevelopmental assessments and health economics and outcomes research assessments will be performed every 24 weeks and CSF assessments (other than standard chemistry) and clinical laboratory tests of blood and urine will be performed every 12 weeks. Brain MRI and 12-lead ECG will be performed every 48 weeks. A PK assessment will be performed once during this phase of the study.

The Study Schedule of Events for the Extended Treatment Phase is provided in Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6, Appendix 7, Appendix 8, Appendix 9, Appendix 10, Appendix 11, and Appendix 12.

4.1.3 Treatment Schedule

When a subject has received and tolerated a total of 12 monthly doses of idursulfase-IT across studies HGT-HIT-094 and SHP609-302, the sponsor and principal investigator will consider the feasibility of transitioning the subject'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 subject 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). Exceptions include study visits at which PK, MRI, and neurodevelopmental assessments are scheduled; these will take place at the main site. Subjects 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.

Subjects will receive their monthly doses of intrathecal idursulfase-IT at the main study site or at a local site. All subjects 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 a site

determined by the subject's physician or at the subject's home depending upon the standard location as determined for each subject (at the discretion of local laws and the treating physician).

4.2 Intrathecal Drug Delivery

It is anticipated that the IDDD will be used to collect CSF samples and to deliver IT injections of idursulfase-IT and preservative-free saline flushes. No other medication will be administered through the device. If the IDDD appears to be non-functional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD Manual, which provides details on the investigation and management of any IDDD-related issues. This includes possible partial revision or complete replacement of the IDDD as indicated. If the IT space is not accessible via the IDDD, investigational product may be administered by LP. Should the IDDD become clogged, undergo mechanical complications or otherwise not be accessible, the CSF sample may also be obtained by LP.

If there are medical contra-indications to the re-implantation of a new device, or if the subject so desires, repeat monthly lumbar punctures may be considered as an alternative way of delivering the study drug and obtaining CSF samples under limited circumstances. If no safety risks are identified by the investigator, up to 12 consecutive LPs may be performed across studies HGT-HIT-094 and SHP609-302. Once a subject 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 LP beyond the stipulated 12 consecutive monthly doses can be considered only in individual cases of subjects 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 or sedation may be required for injections of investigational product 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 LP and MRI will have to be performed with sedation/anesthesiology support.

A Data Monitoring Committee (DMC) will oversee both idursulfase-IT and device safety. The DMC will be notified of all IDDD failures and IDDD-related complications at times defined in the DMC charter (Section 11.8).

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

4.3 Rationale for Study Design and Comparator Group

The study design is intended to provide ongoing treatment with idursulfase-IT to subjects who received idursulfase-IT in study HGT-HIT-094 and to initiate treatment in subjects who received

no idursulfase-IT in study HGT-HIT-094. As such, all subjects will be treated during this study; there is no control group. Groups will be compared by treatment status in HGT-HIT-094.

In order to traverse the blood-brain barrier, idursulfase-IT will be administered directly to the CNS using an IDDD or, if the IDDD is non-functional, via LP. The advantage of using an IDDD is the potential to obviate the need for multiple LPs for drug delivery. Idursulfase-IT will be administered through the IDDD or, if the IDDD is non-functional, via LP.

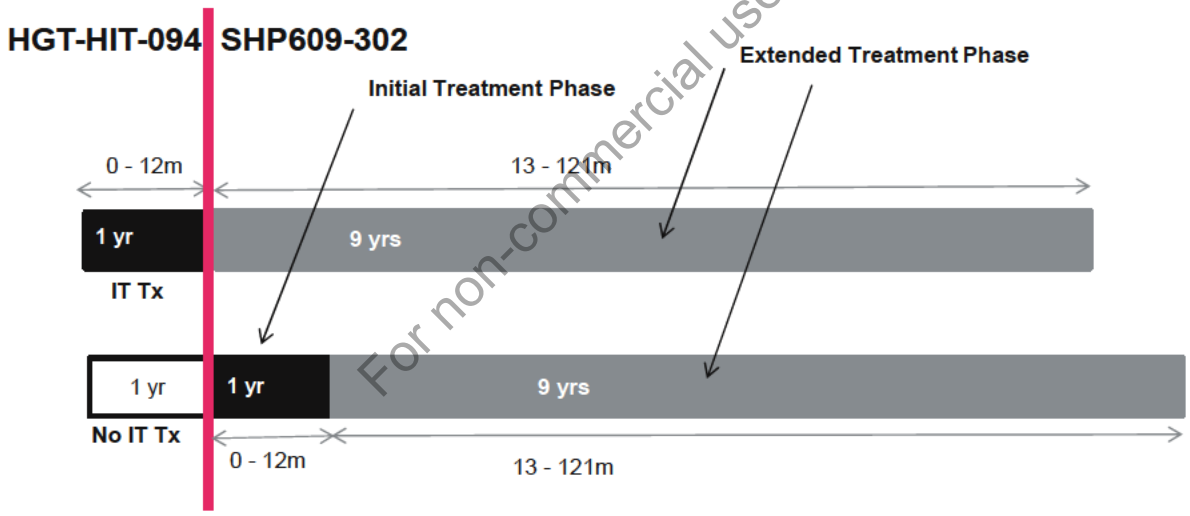
The evaluation of safety is the primary objective of the study, and the study duration has been designed to provide a reasonable time for safety follow-up.

4.4 Study Duration

Subjects will participate in this extension study for a duration of 10 years of treatment unless they discontinue the study or Shire discontinues the study.

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

Figure 1 Planned Duration of Treatment (Study HGT-HIT-094 and/or SHP609-302)



5 STUDY POPULATION SELECTION

5.1 Study Population

Pediatric subjects (plus potentially any pediatric subjects younger than 3 years of age in the antecedent substudy) who completed Study HGT-HIT-094, and meet the eligibility criteria may enroll in this study.

5.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

1. Subjects must have completed Visit Week 52 assessments in Study HGT-HIT-094
2. The subject's parent(s) or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form after all relevant aspects of the study have been explained and discussed. Consent of the subject's parent(s) or legally authorized guardian(s) and the subject's consent/assent, as relevant, must be obtained
3. The subject has continued to receive Elaprase on a regular basis in Study HGT-HIT-094

5.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. The subject has experienced, in the opinion of the investigator , a safety or medical issue that contraindicates treatment with idursulfase-IT, including, but not limited to, uncontrolled seizure disorder, bleeding disorder, and clinically relevant hypertension
2. The subject has a known hypersensitivity to any of the components of idursulfase-IT
3. The subject has clinically relevant intracranial hypertension
4. The subject is enrolled in another clinical study, other than HGT-HIT-094, that involves clinical investigations or use of any investigational product (drug or [intrathecal/spinal] device) within 30 days prior to study enrollment or at any time during the study
5. The subject has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to compromised airways or other conditions
6. The subject has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use, including:
    a. The subject has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
    b. The subject'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 subject's drug therapy requires substances known to be incompatible with the materials of construction
    d. The subject has a known or suspected local or general infection
    e. The subject is at risk of abnormal bleeding due to a medical condition or therapy
    f. The subject has 1 or more spinal abnormalities that could complicate safe implantation or fixation
    g. The subject has a functioning CSF shunt device
    h. The subject has shown an intolerance to an implanted device

6 STUDY TREATMENTS

6.1 Description of Treatments

6.1.1 Investigational Product

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

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

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

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

6.1.2 Intrathecal Drug Delivery Device

The drug product will be administered via the SOPH-A-PORT Mini S Implantable Access Port. The SOPH-A-PORT Mini S is a system intended for implantation by physicians. The SOPH-A-PORT Mini S, once implanted, allows healthcare personnel to administer drugs indicated for intrathecal delivery intermittently over a long period of time. The device is CE Marked in the European Union (EU) and 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

Further details are provided in the SOPH-A-PORT Mini S Instructions for Use.

6.1.3 Comparator Product

There is no comparator product in this study.

6.2 Treatments Administered

All subjects in this study will receive idursulfase-IT and standard-of-care therapy with Elaprase during the study. Elaprase will not be provided by the sponsor, but rather will be prescribed by the subject's physician in accordance with local prescribing information.

Subjects who did not receive treatment with idursulfase-IT in the antecedent study (HGT-HIT-094) will be scheduled to undergo surgical placement of the SOPH-A-PORT Mini S device. At least 14 days will be allowed for recovery following the placement of the IDDD before the administration of the first intrathecal idursulfase-IT dose. During this time, the subject will receive standard perioperative care.

The investigational product (idursulfase-IT) will be administered through an IDDD. Refer to Section 4.2 for further details.

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

Investigational product administration will be performed in a clinical setting by appropriately trained and skilled healthcare providers (nurses or physicians) with knowledge of the subject's drug regimen and experienced in accessing vascular or CNS ports or CNS infusion pumps. Subjects' and subjects' 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.

The investigational product may be administered on the same day (ie, the same calendar day or within a 24-hour period) as the Elaprase IV infusion. However, this can only occur for subjects participating in the Extended Treatment Phase who have already completed at least 12 months of idursulfase-IT treatment in studies HGT-HIT-094 or SHP609-302. If same-day dosing is elected, idursulfase-IT will be administered first and the Elaprase IV infusion will be administered second. Please refer to Section 7.7.1 for details.

6.3 Selection and Timing of Dose for Each Subject

The doses (1 mg, 10 mg, and 30 mg) of idursulfase-IT evaluated in the Phase I/II studies demonstrated equivalent safety profiles. The clinical PK and PD profiles of idursulfase-IT in subjects with MPS II indicated that the 10 mg dose provides a maximum pharmacologic response. The 10 mg dose of idursulfase-IT was therefore selected for the pivotal Phase II/III study, HGT-HIT-094; the dose will remain the same in this extension study.

Subjects who are younger than 3 years of age will continue to receive an adjusted dose as follows based on reference brain weight[16]:

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

All subjects will receive idursulfase-IT monthly (every 28 days) via a surgically implanted IDDD (SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire).

All subjects will also receive standard-of-care therapy with Elaprase during the study. Elaprase will not be provided by the sponsor, but rather will be prescribed by the subject's physician in accordance with local prescribing information.

6.4 Method of Assigning Subjects to Treatment Groups

All subjects will receive investigational product (idursulfase-IT).

6.5 Blinding

This is an open-label study in which all subjects receive investigational product (idursulfase-IT).

6.6 Concomitant Medications, Therapies, and Medical/Surgical Interventions

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

All subjects are to receive Elaprase therapy throughout this study. Elaprase will be prescribed by the subject's physician and will be administered in accordance with local prescribing information. Elaprase will not be provided by the study sponsor.

All medications, therapies/interventions administered to and medical/surgical procedures performed on subjects will be regarded as concomitant and recorded on the subject's eCRF as described in Section 7.14.

6.6.1 Infusion Reactions and Management

Infusions of proteins can be associated with reactions to the infusion that may or may not be immune mediated (hypersensitivity reactions). Thus, potential reactions to the infusion of an investigational product, including idursulfase-IT, are unpredictable.

It is often difficult to clinically distinguish infusion reactions from hypersensitivity reactions. Symptoms may include headache, fever, sensory paresthesias (including feeling of warmth, tingling, or pain), rash, pruritus, or autonomic symptoms, such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection over time.

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

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

Infusion-related reactions have been observed in subjects 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). Pretreatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. The safety information reported from administration of Elaprase may be relevant to management of adverse events in relation to idursulfase-IT.

Successful management of Elaprase infusion-related adverse events included slowing or interrupting the infusion at the time of the event or pre-treatment with low-dose corticosteroids and/or antihistamines. Most adverse events of this type were treated with antihistamines such as chlorpheniramine (IV administration preferred if available), oxygen, or mild glucocorticoids such as hydrocortisone and prednisolone. All were monitored closely until symptoms of the reactions had subsided. In clinical trials of Elaprase, an apparent decrease in the overall rates of adverse events, and specifically infusion-related adverse events, was observed over time, suggesting that subjects 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. As of the date of this protocol, there have been no significant concerns regarding infusion-related immune reactions following IT administration in studies HGT-HIT-045 and HGT-HIT-046. Additionally, safety assessments in the present study will evaluate the effect of same-day IV and IT regime on the incidence and/or severity of infusion-related adverse reactions, even if the subject had no prior such reactions on Elaprase alone.

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

6.7 Restrictions

6.7.1 Prior Therapy

All subjects must have received and tolerated treatment with idursulfase IV (Elaprase) therapy on a regular basis in the antecedent study and have no safety or medical issue that contraindicates treatment with idursulfase-IT.

Treatment with another investigational product (drug or [intrathecal/spinal] device) within the 30 days prior to study enrollment is prohibited according to the exclusion criteria (Section 5.3).

6.7.2 Fluid and Food Intake

Not applicable.

6.7.3 Subject Activity Restrictions

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

6.8 Treatment Compliance

Treatment with the investigational product (idursulfase-IT) will be administered via an IDDD (or LP) under the supervision of the investigator and in the controlled environment of a clinical center; therefore, full subject compliance with treatment is anticipated in this study.

6.9 Packaging and Labeling

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

6.9.1 Investigational Product

Idursulfase-IT drug product is a sterile liquid formulation of recombinant idursulfase for monthly IT administration using a medical device, and that is packaged in 2-mL type-I borosilicate glass vials that are single-use. 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. The idursulfase-IT must be used as soon as possible after it is prepared because it does not contain preservatives.

6.9.2 Intrathecal Drug Delivery Device

The SOPH-A-PORT Mini S Access Port is available in 1 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 and will be in accordance with local regulatory requirements.

6.10 Storage and Accountability

6.10.1 Investigational Product

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

- Idursulfase-IT vials should be stored at 2-8ºC (36-46°F).
- Idursulfase-IT is intended for IT use only.
- It is recommended that idursulfase-IT be filtered prior to use through a standard 0.22 µm filter.
- Perform a visual inspection of each vial. Idursulfase-IT is a clear to slightly opalescent, colorless solution. Do not use if the solution in the vials is discolored or particulate matter is present.
- DO NOT SHAKE. Idursulfase-IT should not be agitated vigorously at any time.
- Withdraw the volume of idursulfase-IT from the vial.
- Do not mix with, or administer in conjunction with other drug solutions.
- Because it does not contain preservatives, idursulfase-IT should be used as soon as possible after it is prepared.
- Idursulfase-IT is supplied in single-use vials. Only 1 dose of idursulfase-IT is to be withdrawn from a vial.

See the Pharmacy Manual for additional details.

The disposition of all investigational product delivered to a principal investigator must be recorded on a subject-by-subject basis by completing the accountability log. The date and time of administration of the investigational product and use of the device must be documented on the subject's appropriate CRF.

The principal investigator, clinical research coordinator, or designee (eg, pharmacist) must ensure that all documentation regarding investigational product receipt, storage, dispensing, loss/damaged and return of used/unused product is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the investigational product is available for the monitor to inventory and prepare for return shipment to the sponsor or designee, if required.

6.10.2 Intrathecal Drug Delivery Device

The disposition of all SOPH-A-PORT Mini S devices delivered to a principal investigator must be recorded on a subject-by-subject basis by completing the accountability log. The date and time of administration of the investigational product and use of the SOPH-A-PORT Mini S device must be documented on the subject's appropriate eCRF.

The principal investigator, clinical research coordinator, or designee (eg, pharmacist) must ensure that all documentation regarding receipt, storage, dispensing, loss/damaged SOPH-A-PORT Mini S devices and return of used/unused SOPH-A-PORT Mini S device(s) is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the SOPH-A-PORT Mini S devices are available for the monitor to inventory and prepare for product destruction or return shipment to the sponsor or designee.

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

Please refer to the IDDD Manual for device destruction or return instructions.

6.10.3 Comparator Product

Not applicable to this study.

7 STUDY PROCEDURES

Descriptions of subject procedures and evaluations required for this protocol are provided in this section. These evaluations will be performed during the days and weeks of the study as indicated in the Schedule of Events (Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6, Appendix 7, Appendix 8, Appendix 9, Appendix 10, Appendix 11, and Appendix 12).

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

During the Extended Treatment Phase only, the investigator will have the option of administering the Elaprase IV infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

Subjects who were not previously treated with idursulfase-IT in Study HGT-HIT-094 will begin participation in this study (if confirmed eligible) at the start of the Initial Treatment Phase (ie, the first 12 months) of this study, which is similar in schedule of assessments for subjects who were treated with intrathecal idursulfase-IT in Study HGT-HIT-094. At completion of these procedures and if there are no safety concerns, subjects may continue into the Extended Treatment Phase of this study.

Subjects who were previously treated with idursulfase-IT in Study HGT-HIT-094 will begin participation in this study (if confirmed eligible) at the start of the Extended Treatment Phase (ie, from Week 52 [Month 13] onward).

The Initial Treatment Phase (subjects who were not treated with idursulfase-IT in Study HGT-HIT-094) will be conducted according to the following schedule:

- Informed Consent and Review of Study Entry Criteria (Weeks -1 [Day -7 to Day -1])
- Pre-surgery, Surgery, Follow-up, and Post-operative Recovery (Week 2 [-14, +7 days])
- Treatment and Assessments (Week 4 through Week 48 [±7 days])
- If no safety concerns, subjects continue into Extended Treatment Phase.

The Extended Treatment Phase (all subjects) will be conducted according to the following schedule:

- Informed Consent and Review of Study Entry Criteria (Week 52 [±7 days], only for those subjects previously treated in HGT-HIT-094)
- Treatment and Assessments (Week 52 through Week 480 [±7 days], all subjects)
- End of Study (EOS, Week 484 [±7 days], all subjects)

Refer to Appendix 1 for the Schedule of Events for the Initial Treatment Phase (subjects who did not receive treatment with idursulfase-IT in Study HGT-HIT-094).

Refer to Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6, Appendix 7, Appendix 8, Appendix 9, Appendix 10, Appendix 11, and Appendix 12 for the Schedule of Events for the Extended Treatment Phase (continued treatment for subjects who did not receive treatment with idursulfase-IT and beginning of participation for subjects originally enrolled in the substudy in HGT-HIT-094 and subjects who received treatment with idursulfase-IT in Study HGT-HIT-094).

All data collected are to be recorded on the subject's appropriate eCRF.

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

7.1 Informed Consent

Prior to conducting any study-related procedures, written informed consent (signed and dated) must be obtained from the subject's parent(s) or legally authorized guardian(s) (and consent/assent from the subject, if applicable). The nature, scope, and possible consequences, including risks and benefits, of the study will be explained by the investigator or designee in accordance with the guidelines described in Section 11.4. Documentation and filing of informed consent documents should be completed according to Section 11.4.

During Study SHP609-302, subjects who exceed the age of enrollment eligibility for Study HGT-HIT-094 and/or have reached the applicable legal age of consent to participate in a clinical study will be allowed to continue participation in Study SHP609-302 until the end of the study.

7.2 Study Entrance Criteria

Each subject will be reviewed for eligibility against the study entrance criteria. Subjects who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the subject's ineligibility for the study will be documented. No protocol exemptions will be permitted.

7.3 Confirmation of Study Eligibility

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

7.4 Medical History

A standard medical history assessment will be performed. Medical and surgical history reflecting the period of time since the subject completed the antecedent study (HGT-HIT-094) will be recorded.

Medical history will include Hunter syndrome signs and symptoms in the following domains: head/neck, eyes, mouth, ear, nose, throat, chest/lung, cardiovascular system, abdomen, gastrointestinal system, genitourinary system, skin, skeletal system, neurological system, psychiatric disorders. Surgical history will also be recorded.

7.5 Echocardiogram

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

7.6 Device-Related Procedures

7.6.1 Intrathecal Drug Delivery Device Implantation and Revision

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

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

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

If at the time of a scheduled dosing, due to a device-related issue it is not possible to aspirate CSF prior to dose administration, administer a full medication dosage using the standard administration steps detailed in the device's IFU, 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 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 device and/or device components will be re-implanted at the earliest possible opportunity, preferably at the same time.

7.6.2 X-ray Verification of Intrathecal Drug Delivery Device Placement

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

7.6.3 Cerebrospinal Fluid Sampling Procedure

Cerebrospinal fluid will be sampled via the IDDD. If this is not possible, and if CSF sampling is necessary, either for adherence to the protocol, or to investigate clinical concerns, an LP may be performed to sample CSF, either with or without administration of drug afterwards.

7.6.4 Device Revision or Removal

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

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

Subjects will have the IDDD removed when they discontinue from or complete the study, unless the subject is continuing to receive treatment through another mechanism (eg, extension study, expanded access program, commercially available).

Details of the device removal will be recorded in the subject's CRF.

7.7 Investigational Product Administration

It is planned that idursulfase-IT will be administered every 28 days by means of the IDDD (or LP, refer to Section 4.2). 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, study drug may be administered by LP.

A 22-gauge Huber non-coring needle is to be used for access to the implanted port; standard hypodermic needles would damage the septum and may cause leakage. If no needle-free connector is present, a stopcock or 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 supplied by Sophysa in a SOPH-A-PORT Mini S (22G).

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

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

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

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

Subjects will remain under the observation of study personnel in the hospital setting (eg, may include infusion center, post-anesthesia care unit (PACU) (recovery suite), observation unit, short stay center) for 4 hours post administration of investigational product for safety assessments. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of study visit weeks at which serial blood sampling for pharmacokinetic evaluation is planned).

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

7.7.1 Same-Day Investigational Administration with Elaprase Infusion

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

During the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. If same-day dosing is elected, idursulfase-IT will be administered first and the Elaprase infusion will be administered second. Pharmacokinetic assessments are to occur at the first study visit at which same-day dosing is elected. At this visit, administration of the Elaprase infusion should start within approximately 90 minutes of completion of idursulfase-IT administration.

Note that on the occasion of the first same-day administration, the duration of IV Elaprase infusion is to be standardized to 3 hours. Thereafter, at subsequent visits on which the Elaprase infusion and idursulfase-IT are administered on the same day, the investigator may use discretion in deciding the appropriate Elaprase infusion rate based on past experience with the subject, and the subject's prior response to the same-day regime.

7.8 Pharmacokinetic Assessments

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

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

The blood and CSF sampling schedules for pharmacokinetic assessments are provided in the Schedule of Events (Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6, Appendix 7, Appendix 8, Appendix 9, Appendix 10, Appendix 11, and Appendix 12).

During the Extended Treatment Phase, blood samples for pharmacokinetic assessments will be collected on the occasion of the first same-day administration of idursulfase-IT and Elaprase. This pharmacokinetic sampling need only be scheduled once, and may occur at Month 25 or at an alternative visit during the Extended Treatment Phase (see Appendix 13 for PK sampling time points associated with same-day administration).

7.9 Pharmacodynamic/Biomarker Assessments

7.9.1 Cerebrospinal Fluid Glycosaminoglycan

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

7.9.2 Cerebrospinal Fluid and Serum Albumin

Albumin levels will be measured in samples of CSF and serum. The relative permeability of the blood-brain barrier will be monitored by the CSF/serum albumin ratio.

7.10 Efficacy Assessments

The efficacy endpoints are specified in Section 3.2.

7.10.1 Neurodevelopmental Assessment Tools

The study methodology will include standardized neurodevelopmental assessments to provide a quantifiable measure of subject neurodevelopmental status.[5] Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as follows and as summarized in Appendix 23.

7.10.1.1 Cognition

The Differential Ability Scales, Second Edition (DAS-II),[17] will be used to assess all subjects of age 2 years, 6 months or older, including Spanish-speaking subjects who will be assessed with the Spanish version of the DAS-II. The DAS-II comprises 2 overlapping batteries. The Early Years battery is designed for children ages 2 years, 6 months, through 6 years, 11 months. The Early Years battery is further divided into the Lower Level for children ages 2 years, 6 months through 3 years, 5 months and Upper Level for children ages 3 years 6 months through 6 years, 11 months. The School Age Battery is designed for children ages 7 years, 0 months through 17 years, 11 months. These batteries are fully co-normed for ages 5 years, 0 months, through 8 years, 11 months.

Any subjects who cannot be assessed with the DAS-II due to a deteriorating condition or who are younger than 2 years, 6 months, will be assessed with the BSID-III.[18]

7.10.1.2 Adaptive Behavior

The Vineland Adaptive Behavioral Scales, Second Edition (VABS-II)[19] will be used to assess all subjects. The VABS-II Expanded Interview Form will be used to measure the personal and social skills of subjects serially over time; these scales are organized within a 3-domain structure: Communication, Daily Living, and Socialization. In addition, the VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The VABS-II Expanded Interview Form assesses what a subject actually does, rather than what the subject is able to do.

Table 1 Neurodevelopmental Assessments in Study SHP609-302

Assessment	Intended Study Population	Applicable Age
DAS-II	Subjects 2 years, 6 months of age and older[a]	Early Years Battery[a, b] 2 years 6 months through 6 years 11 months (extended norms: up to 8 years, 11 months) Early Years Lower Level: 2 years 6 months through 3 years 5 months; Early Years Upper Level: 3 years 6 months through 6 years 11 months School Age Battery 7 years 0 months through 17 years 11 months
BSID-III	Subjects younger than 2 years, 6 months of age and older children who cannot perform the DAS-II	1 to 42 months
VABS-II	All subjects	Birth to 90 years

Abbreviations: BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; DAS-II=Differential Ability Scales, Second Edition; VABS-II=Vineland Adaptive Behavioral Scales, Second Edition

[a] For the DAS-II, Spanish-speaking subjects will be assessed using the Spanish versions of the DAS-II (Early Years and School Age).

[b] Extended norms may be used.

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

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

7.10.2 Brain Magnetic Resonance Imaging

Subjects will undergo MRI of the brain. Brain structure volumes will be measured. Refer to the Study Operations Manual and/or MRI Manual for specific procedures and precautions.

7.11 Health Economics and Outcomes Research Assessments

7.11.1 Health Status Assessment

The health status of subjects will be assessed using the EuroQol-5D-5L (EQ-5D-5L) questionnaire, a standardized instrument for use as a measure of health status which is applicable to a wide range of health conditions and treatments.[20, 21] The EQ-5D-5L provides a descriptive profile and index value for health status.

Applicable to a wide range of health conditions and treatments, the EQ-5D-5L provides a descriptive profile and a single index value for health status which can be used in the clinical and economic evaluation of health care, as well as in population health surveys.

The EQ-5D-5L is designed for self-completion by respondents and is suited for use in clinics and in face-to-face interviews. The questionnaire takes only a few minutes to complete. Instructions to respondents are included in the questionnaire.

7.11.2 Healthcare Resource Utilization and Impact Questionnaires

Two questionnaires assessing healthcare resource utilization and caregiver impact (the HCUQ and CIQ), developed specifically for subjects with Hunter syndrome, will be administered. These measures will focus on collecting self-reported direct and indirect costs of care for subjects with MPS II. The health economic and outcome research endpoints evaluate the key healthcare resource utilization and impact variables, such as the number of emergency room visits, caregiver employment status (full time [FT], part time [PT], and not working [NW]), and the number of hours of additional paid help needed by caregivers, over the course of the study.

7.11.3 Functional Outcomes for Clinical Understanding Scale

The functional status of subjects will be assessed using the HS-FOCUS. The parent version of HS-FOCUS will be administered.

The HS-FOCUS evaluates functional status in 5 domains (walking/standing, grip/reach, school/work, activities, and breathing) using a parent-completed form. The individual items within each function domain are scored using the following response scale:

- 0 = With NO difficulty
- 1 = With SOME difficulty
- 2 = With MUCH difficulty
- 3 = UNABLE to do

Higher scores thus correspond to a higher degree of incapacity and available items are averaged within each domain to derive the 5 domain scores. If more than half of the items within a domain are missing or marked as “Does not apply to me,” the domain score is missing.

7.12 Safety Assessments

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

7.12.1 Physical and Neurological Examination

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

Physical examinations will include a review of the subject's general appearance, neurological examination, as well as evaluation of the body systems and the device port and catheter track as listed in Table 2. Any abnormal change in findings will be recorded as an AE on the appropriate CRF.

Table 2 Assessments for Physical Examinations

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

7.12.2 Height and Weight

Height (cm) and weight (kg) will be recorded. The clinical site staff will be instructed to use a calibrated scale for weight measurement.

7.12.3 Head Circumference

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

7.12.4 Hearing Assessment

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

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

7.12.5 Vital Signs

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

7.12.6 Electrocardiography

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

7.12.7 Clinical and Other Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing. All blood samples will be collected by venipuncture or via central line. The maximum volume of blood collected is presented by study visit in Appendix 14, Appendix 15, Appendix 16, Appendix 17, Appendix 18, Appendix 19, Appendix 20, Appendix 21, and Appendix 22.

Clinical laboratory tests will include those listed in Table 3.

Table 3 List of Laboratory Tests

Hematology:

- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

Urinalysis:

- Appearance (clarity and color)
- Bilirubin
- Blood
- Glucose
- Ketones
- Leukocyte esterase
- Microscopic examination of sediment
- Nitrite
- pH
- Protein
- Specific gravity
- Urobilinogen

Coagulation:

- Prothrombin time (PT)
- Partial thromboplastin time (PTT)

Serum albumin

Serum Chemistry:

- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide (CO_2)
- Chloride (Cl)
- Creatinine
- Creatine phosphokinase
- Gamma-glutamyl transferase (GGT)
- Glucose
- Lactate dehydrogenase (LDH)
- Magnesium (Mg)
- Phosphorus (P)
- Potassium (K)
- Sodium (Na)
- Total and direct bilirubin
- Total cholesterol
- Total protein
- Total thyroxine (T4)
- Thyroid-stimulating hormone (TSH)
- Triglycerides
- Uric acid

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

7.12.8 Cerebrospinal Fluid Assessments

Cerebrospinal fluid samples will be collected via the IDDD or LP prior to idursulfase-IT administration and used to analyze standard safety laboratory parameters (chemistries, cell counts), albumin, GAG, and concentration of idursulfase enzyme. The CSF samples will also be analyzed for idursulfase-specific antibodies and antibodies with enzyme neutralizing activity (Section 7.12.9).

Cerebrospinal fluid will be obtained during the days and weeks of the study as indicated in the Schedule of Events (Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6, Appendix 7, Appendix 8, Appendix 9, Appendix 10, Appendix 11, and Appendix 12). Should the IDDD become clogged or undergo mechanical complications, the CSF sample will be obtained via LP until the subject had a functional IDDD.

7.12.9 Antibody Assessments

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

7.12.10 Device Assessments

The SOPH-A-PORT Mini S device will be evaluated using assessments of device implantation, device function, device longevity, and AEs associated with the implant surgery or device. These data will be collected on the subject's eCRF from the time of initial implantation.

7.12.11 Leachable/Extractable Assessment

As part of the assessment of the SOPH-A-PORT Mini S, the levels of leachables from the device into the CSF and blood may be determined. The subject and/or subject's parent(s) or legal representative(s) has the option to allow testing of residual CSF and serum samples to determine the levels of leachable materials related to the IDDD.

7.12.12 Pregnancy Testing

Not applicable.

7.13 Sample Collection, Storage, and Shipping

Details for study procedures, including sample collection, are provided in the Study Operations Manual and/or Laboratory Manual for this study.

A variety of biological specimens will be collected from subjects at the intervals indicated in the schedule of events. Until analyzed, these will be stored securely in a way that ensures subject confidentiality and that ensures unauthorized access is prohibited and the samples are not lost, deteriorated, or accidentally or illegally destroyed.

Testing of residual blood, urine, and CSF samples for additional scientific research is optional. The subject and/or subject's parent(s) or legal representative(s) has the option to allow this testing for additional research assessments.

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

7.14 Concomitant Medications, Therapies, and Medical/Surgical Interventions Assessments

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

Concomitant therapies such as speech therapy, ergotherapy, music therapy, and physical therapy are permitted, and will also be recorded on the subject's eCRF during the study.

Non-permitted (per the exclusion criteria) medications, therapies, or surgical interventions will lead to exclusion from the study or a possible protocol violation depending on when the non-permitted event occurs.

7.15 Adverse Events Assessments

7.15.1 Definitions of Adverse Events and Serious Adverse Events

7.15.1.1 Adverse Event

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

Adverse events include:

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

Throughout the study, the investigator must record all adverse events on the AE case report form (CRF), regardless of the severity or relationship to investigational product. The investigator should treat subjects with adverse events appropriately and observe them at suitable intervals until the events stabilize or resolve. Adverse events may be discovered through observation or examination of the subject, questioning of the subject or his parent(s)/legally authorized guardian(s), complaint by the subject or his parent(s)/legally authorized guardian(s), or by abnormal clinical laboratory values or physical findings.

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

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

7.15.1.2 Elaprase-related Adverse Event

All subjects will receive concomitant IV therapy with Elaprase throughout their participation in this study. Adverse events that are potentially related to IV Elaprase infusion will be captured. The most commonly reported adverse events that have been assessed as related to Elaprase in subjects with Hunter syndrome are listed in Section 6.6.1. Note that, during weeks of IT dose administration in the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT dosing in order to help distinguish adverse events related to IV compared to IT administration.

7.15.1.3 Elaprase and/or idursulfase-IT-related Adverse Event

During the Extended Treatment Phase, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. With same-day dosing, it may not be possible to distinguish idursulfase of IV-administered origin from that of IT-administered origin. Therefore, adverse events that are potentially related to IV Elaprase infusion and/or idursulfase-IT administration will be captured.

7.15.1.4 Intrathecal Drug Delivery Device-related Adverse Events

Examples of AEs related to use of the IDDD include, but are not limited to, the following: device failure, device malfunction, incorrect connection of IDDD components, erosion of the portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, migration of the portal/catheter, occlusion of the portal/catheter, portal site or subcutaneous tract infection. A malfunction of the device (defined in Section 7.15.2.2) should not be entered as an adverse event unless it has physiological consequences. In the event of a device failure (defined in Section 7.15.2.3), the device may need to be replaced or repaired. 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 a serious adverse event. Details of the cause of the IDDD malfunction or failure will be recorded on the device malfunction and failure eCRF, and the serious adverse event (SAE) form (where applicable). A list of the most common IDDD AEs is included in Appendix 24.

7.15.1.5 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 shortly following IDDD implant/explant, IDDD adjustment, full revision, partial revision, IDDD removal, and delayed re-implantation after previous IDDD removal (such as complications of anesthesia, excessive bleeding, wound

hematoma), and post-operative complications (such as post-operative infection). These events are related to the surgical procedure itself.

7.15.1.6 Intrathecal Administration Process Adverse Events

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

7.15.1.7 Serious Adverse Event

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

- Death
- Is life-threatening
- Requires hospitalization (Note, however, for the purpose of this study, overnight hospitalizations post intrathecal administration of idursulfase-IT that are based on practical or logistical considerations, rather than safety will not result in a serious adverse event designation [refer to Section 7.7])
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect

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

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

7.15.1.8 Unanticipated Adverse Device Effect

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 subjects (21CFR812.3[s] or other regulatory requirements, as applicable).

7.15.2 Device-associated Definitions

7.15.2.1 Device Revision (Partial and Full)

Partial device revision: surgical revision/replacement of 1 or more component(s) of the device; other component(s) of the original device remain implanted and are not affected (eg, port revision).

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

7.15.2.2 Device Malfunction

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

7.15.2.3 Device Failure

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

7.15.2.4 Device Adjustment

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

7.15.3 Classification of Adverse Events and Serious Adverse Events

The severity of AEs will be assessed by the investigator based on the definition indicated in Table 4. The severity of all AEs and SAEs should be recorded on the appropriate eCRF page to a severity of mild, moderate, or severe.

Table 4 Adverse Event Severity

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

7.15.4 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 (refer to Section 7.15.1.7). Seriousness (not severity) and causality serve as a guide for defining regulatory reporting obligations.

7.15.5 Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational product, IDDD, device surgical procedure, or IT administration process will be assessed by the investigator as follows:

- Relationship to idursulfase-IT
- Relationship to IV Elaprase infusion will be assessed by the investigator as described in Section 7.15.1.2
- Relationship to IV Elaprase infusion and/or idursulfase-IT as described in Section 7.15.1.3
- Relationship to the IDDD (examples of IDDD-related adverse events are listed in Section 7.15.1.4)
- Relationship to a device surgical procedure (surgical implantation of the IDDD, partial or full device revision as described in Section 7.15.1.5)
- Relationship to the IT administration process (examples of IT administration process-related adverse events are listed in Section 7.15.1.6)

The relationship to study treatment will be categorized based on the definitions provided in Table 5.

Table 5 Adverse Event Relatedness

Relationship	Definition
Not Related	Unrelated to investigational product, device, device surgical procedure, or IT administration process.
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, the presence of the device, device surgical procedure, or IT administration process but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, the presence of the device, device surgical procedure, or IT administration process unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely related	The event follows a reasonable temporal sequence from administration of the investigational product, the presence of the 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 subject to investigational product; however, the determination of definitely related can only be used when recurrence of event is observed.

7.15.6 Procedures for Recording and Reporting Adverse Events

7.15.6.1 Adverse Event Monitoring and Period of Observation

Adverse events will be monitored continuously throughout the study.

For the purposes of this study, the period of observation extends from the time at which the subject, the subject's parent(s), or the subject's legally authorized representative gives informed consent until the subject's final evaluation of the study. For safety purposes, the final evaluation will be defined as the follow-up (EOS) evaluation performed approximately 28 days after the last dose for subjects who complete the study.

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

7.15.6.2 Reporting Serious Adverse Events

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

The investigator must report the serious adverse event to the Shire Global Drug 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 to:

Shire Global Drug Safety Department:

International FAX: +44-1256-894715 (UK) OR United States FAX: +1-866-557-4473

Email: drugsafety@shire.com

AND

Shire Medical Monitor: [redacted], DO

Email: [redacted]

FAX: [redacted] (USA)

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 following provides contact information for the Shire medical monitor.

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

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

It is the responsibility of the sponsor to ensure that each investigator receives a copy of any CIOMS I/MDR report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected drug-related serious adverse event or unanticipated adverse device effect (submitted by the sponsor or manufacturer, respectively). The investigator must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files.

7.16 Pregnancy

Not applicable.

7.17 Abuse, Misuse, Overdose, and Medication Error

Abuse – Persistent or sporadic intentional intake of investigational product at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (eg, altering one's state of consciousness).

Misuse – Intentional or unintentional use of investigational product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note: This includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).

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

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

The investigator must report abuse, misuse, overdose, and medication error to the Shire Global Drug 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 7.15.6.2).

7.18 Removal of Subjects from the Trial or Investigational Product

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

- The subject exhibits non-compliance with the study protocol that is considered disruptive to study conduct.

- The subject was erroneously included in the study.
- The subject develops an exclusion criterion.
- The subject suffers an intolerable adverse event.
- The study is terminated by the sponsor.

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

If the subject or the subject's parent(s) or legally authorized guardian(s) acting on behalf of the subject discontinues participation in the study, or the subject is discontinued by the investigator, reasonable efforts will be made to follow the subject through the end of study assessments. The reason for refusal will be documented on the CRF. Any adverse events experienced up to the point of discontinuation must be documented on the AE CRF. If adverse events are present when the subject withdraws from the study, the subject will be re-evaluated within approximately 30 days of withdrawal. All ongoing serious adverse events at the time of withdrawal will be followed until resolution.

7.19 Other Study Procedures

7.19.1 Safety-related Study Stopping Rules

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

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

Subject safety in this study will be monitored by an independent DMC until the last subject completes his last scheduled study visit/assessment. The DMC will be an external group overseeing the safety of the study treatment, including both the investigational product and the IDDD, and will operate according to a charter determining the scope of its activities and frequency of meetings (refer to Section 11.8 for additional details).

7.20 Appropriateness of Measurements

The measures of safety to be used in the study are appropriate for a long-term follow-up interventional study in MPS II subjects. These include, but are not limited to, monitoring of adverse events and medication use, both standard parameters for the assessment of safety.

Secondary efficacy endpoints have been included for the purposes of providing additional data to support a long-term evaluation of efficacy in follow-up to the antecedent study.

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

The DAS-II has been found to be valid and reliable. Evidence from published studies and previous Shire clinical trials demonstrates that the DAS-II is able to detect both changes in a child's ability and stabilization of functioning over time following treatment. For the DAS-II, Spanish-speaking subjects will be assessed using the Spanish version of the DAS II-Early Years and the DAS-II School Year. The BSID-III will be used to assess subjects who cannot be assessed with the DAS-II.

As in the antecedent study, any subjects who cannot be assessed with the DAS-II due to a deteriorating condition or who are too young (younger than 2 years, 6 months of age) will be assessed with the BSID-III. The BSID-III measures the mental and motor development and test the behavior of infants from 1 to 42 months of age and has been used extensively worldwide. The BSID-III consists of a core battery of scales and is suitable for use in children from 1 to 42 months of age. Three scales (Motor [Fine, Gross], Language [Receptive, Expressive], and Cognitive) are administered with child interaction. The first item set of the 3 main subtests of the DAS-II (Verbal comprehension, Naming Vocabulary and Pattern Construction) will be administered initially. If the subject cannot complete these, the BSID-III will be used to assess cognition. The BSID-III scale is recommended for low-functioning and nonverbal or preverbal children, and as such, is used primarily during the study to assess the neurodevelopmental status of subjects who are unable to complete the DAS-II.

The rating of the child by the parent format of the VABS-II via the Expanded Interview Form is consistent with the Food and Drug Administration (FDA) Patient Reported Outcome (PRO) Guidance, which states that caregiver reports must be based on observable behaviors only.

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

8 STUDY ACTIVITIES

The schedule for each study activity is specified in the Schedule of Events. The Schedule of Events for the Initial Treatment Phase is in Appendix 1 and the Schedule of Events for the Extended Treatment Phase is in Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6, Appendix 7, Appendix 8, Appendix 9, Appendix 10, Appendix 11, and Appendix 12.

As described in Section 4.1.3, when a subject has received and tolerated a total of 12 monthly doses of intrathecal idursulfase-IT across studies HGT-HIT-094 and SHP609-302, the sponsor and principal investigator will consider the feasibility of transitioning the subject's monthly IT dosing to local sites to reduce the burden imposed by monthly travel. Exceptions include study visits at which PK, MRI, and neurodevelopmental assessments are scheduled; these will take place at the main site.

General anesthesia or sedation may be required for injections of investigational product 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 and MRI will have to be performed with sedation/anesthesiology support.

8.1 Initial Treatment Phase (Subjects Who Were Not Treated with Idursulfase-IT in Study HGT-HIT-094 Only)

8.1.1 Baseline (Month -1, Week -1, Days -7 to Day -1) – Initial Treatment Phase

The following procedures will be performed up to 7 days prior to enrollment (ie, Day -7 to Day -1):

- Written informed consent (assent if applicable) by subject's parent(s) or legally authorized guardian(s) prior to any study-related procedures
- Assessment of eligibility according to review of study entry criteria
- Medical history (since EOS in Study HGT-HIT-094)
- Echocardiogram (note: this assessment will not need to be performed if an echocardiogram taken within 3 months of study start is available and deemed satisfactory for evaluation of anesthesia risk.)
- HCUQ and CIQ
- HS-FOCUS
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

Any data from HGT-HIT-094 EOS assessments may be carried over to baseline in this study, as necessary for analysis.

8.1.2 Confirmation of Study Eligibility (Month 0, Week 0) – Initial Treatment Phase

Enrollment will be confirmed with a confirmation of study eligibility. An assessment of AEs and concomitant medications, therapies/interventions, and medical/surgical procedures will also be performed.

8.1.3 Intrathecal Drug Delivery Device Implantation (Week 2 [-14, +7 Days]) – Initial Treatment Phase

Subjects who did not receive treatment with idursulfase-IT in Study HGT-HIT-094 will undergo surgical implantation of the IDDD. Surgical implantation of the IDDD includes surgical implantation of the IDDD, and a post-surgical assessment. IDDD placement will require anesthesia. At least 14 days will be allowed for recovery following the placement of the IDDD before the administration of the first IT dose.

This Week 2 visit may occur as early as Week 0, as soon as the subject has been enrolled (ie, study eligibility has been confirmed).

8.1.3.1 Prior to Surgery for Intrathecal Drug Delivery Device Implantation – Initial Treatment Phase

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

8.1.3.2 Surgery to Implant Intrathecal Drug Delivery Device – Initial Treatment Phase

- Vital signs
- General anesthesia
- CSF sample collection
- IDDD implantation
- X-ray (to verify IDDD is at the mid-thoracic level in the spinal canal and correctly installed)
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

8.1.3.3 Follow-up to Surgery to Implant Intrathecal Drug Delivery Device – Initial Treatment Phase

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

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

8.1.4 Treatment and Assessments (Months 1-12, Weeks 4-48 [±7 Days]) – Initial Treatment Phase

8.1.4.1 Months 1-12 (Weeks 4-48 [±7 Days]) – Prior to Intrathecal Injection – Initial Treatment Phase

- Physical and neurological examination
- Height and weight (performed at Weeks 4, 16, 28, 40)
- Head circumference (performed at Weeks 4, 16, 28, 40)
- Hearing assessment (performed at Weeks 16, 28, 40)
- Neurodevelopmental assessments (performed at Weeks 16, 28, and 40)
  - DAS-II
  - BSID-III for subjects unable to complete the DAS-II
  - VABS-II
- Twelve-lead ECG
- Vital signs
- Clinical laboratory tests (hematology, serum chemistry, urinalysis, performed at Weeks 4, 16, 28, and 40)
- Urine GAG and creatinine (performed at Weeks 4, 16, 28, and 40)
- Anti-idursulfase antibody testing (serum and CSF, performed at Weeks 4, 16, 28, and 40)
- Serum albumin (performed at Weeks 4, 16, 28, and 40)
- CSF GAG and idursulfase (performed at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48)
- EQ-5D-5L (performed at Weeks 4, 16, 28, and 40)
- HCUQ and CIQ (performed at Weeks 4, 16, 28, and 40)
- HS-FOCUS (performed at Weeks 4, 16, 28, and 40)
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

From Week 28 onward, pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate.

8.1.4.2 Months 1-12 (Weeks 4-48 [±7 Days]) – Intrathecal Injection – Initial Treatment Phase

Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU (recovery suite), observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of Visit Weeks 4 and 48 at which serial blood sampling for PK evaluation is planned). The subject may need to be examined the following day (see follow-up, Section 8.1.4.3) by the investigator; however, there is no requirement for an overnight hospital stay. Note that, on IT Dosing Weeks, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT.

- Twelve-lead ECG (performed within 4 hours of IT injection at Weeks 4, 16, 28, 40)
- Vital signs (collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration)
- CSF sample collection (performed at each IT Dosing Week prior to idursulfase-IT injection). Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard laboratory parameters (chemistries, cell counts), GAG, albumin, concentration of idursulfase enzyme, and presence of idursulfase-specific antibodies. Analyses of CSF samples for antibodies and albumin will be performed at IT Dosing Weeks 4, 16, 28, and 40.
- Idursulfase-IT injection
- Serum sampling for PK analysis (performed at Weeks 4 and 48). Samples will be collected within 30 minutes (±5 minutes) prior to intrathecal administration of idursulfase-IT and at 30 minutes (±5 minutes), 60 minutes (±5 minutes), 120 minutes (±5 minutes), 4 hours (±5 minutes), 6 hours (±5 minutes), 8 hours (±15 minutes), 12 hours (±15 minutes), 24 hours (±15 minutes), 30 hours (±15 minutes), 36 hours (±15 minutes) after the start of intrathecal administration
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

8.1.4.3 Months 1-12 (Weeks 4-48 [±7 Days]) – Safety Follow-up for Intrathecal Injection – Initial Treatment Phase

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

- Physical and neurological examination

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

8.2 Extended Treatment Phase (All Subjects)

For subjects entering this extension study who previously received 12 months of treatment with intrathecal idursulfase-IT in Study HGT-HIT-094, results of Study HGT-HIT-094 EOS assessments may provide Month 13 values for this study, if necessary.

8.2.1 Month 13 (Week 52 [±7 Days]) – Extended Treatment Phase– All Subjects

8.2.1.1 Month 13 (Week 52 [±7 Days]) – Prior to Intrathecal Injection – Extended Treatment Phase – All Subjects

Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate.

Only Subjects Who Were Previously Treated with Idursulfase-IT in Study HGT-HIT-094

- Written informed consent (assent if applicable) by subject's parent(s) or legally authorized guardian(s) prior to any study-related procedures
- Assessment of eligibility according to review of study entry criteria
- Enrollment

Only Subjects Continuing from the Initial Treatment Phase

- Physical and neurological examination
- Height and weight
- Head circumference
- Hearing assessment
- Neurodevelopmental assessment
- Twelve-lead ECG
- Vital signs
- Clinical laboratory tests
- Urine GAG and creatinine
- Anti-idursulfase antibody testing (serum)
- General anesthesia
- Brain MRI
- Serum albumin
- EQ-5D-5L

All Subjects

- HCUQ and CIQ
- HS-FOCUS
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

8.2.1.2 Month 13 (Week 52 [±7 Days]) – Intrathecal Injection – Extended Treatment Phase – All Subjects

Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting. The subject may need to be examined the following day (see Follow-up, Section 8.1.4.3) by the investigator; however, there is no requirement for an overnight hospital stay. Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

Only Subjects Continuing from the Initial Treatment Phase

- CSF sample collection (performed prior to idursulfase-IT injection). Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze GAG, albumin, concentration of idursulfase enzyme, and presence of idursulfase-specific antibodies.

All Subjects

- Vital signs (collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration)
- CSF sample collection (performed prior to idursulfase-IT injection). Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard laboratory parameters (chemistries, cell counts)
- Idursulfase-IT injection
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

8.2.1.3 Month 13 (Week 52 [±7 Days]) – Safety Follow-up for Intrathecal Injection – Extended Treatment Phase – All Subjects

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

In the absence of any safety concerns, subjects may complete this safety follow-up visit on the same day as IT administration prior to discharge.

8.2.2 Months 14, 15, 17, 18, 20, 21, 23, 24, 26, 27, 29, 30, 32, 33, 35, 36, 38, 39, 41, 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59, 60, 62, 63, 65, 66, 68, 69, 71, 72, 74, 75, 77, 78, 80, 81, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 113, 114, 116, 117, 119, 120 (Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, 192, 200, 204, 212, 216, 224, 228, 236, 240, 248, 252, 260, 264, 272, 276, 284, 288, 296, 300, 308, 312, 320, 324, 332, 336, 344, 348, 356, 360, 368, 372, 380, 384, 392, 396, 404, 408, 416, 420, 428, 432, 440, 444, 452, 456, 464, 468, 476, 480 [±7 Days]) – Extended Treatment Phase – All Subjects

8.2.2.1 Months 14, 15, 17, 18, 20, 21, 23, 24, 26, 27, 29, 30, 32, 33, 35, 36, 38, 39, 41, 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59, 60, 62, 63, 65, 66, 68, 69, 71, 72, 74, 75, 77, 78, 80, 81, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 113, 114, 116, 117, 119, 120 (Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, 192, 200, 204, 212, 216, 224, 228, 236, 240, 248, 252, 260, 264, 272, 276, 284, 288, 296, 300, 308, 312, 320, 324, 332, 336, 344, 348, 356, 360, 368, 372, 380, 384, 392, 396, 404, 408, 416, 420, 428, 432, 440, 444, 452, 456, 464, 468, 476, 480 [±7 Days]) – Prior to Intrathecal Injection – Extended Treatment Phase – All Subjects

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

Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate.

8.2.2.2 Months 14, 15, 17, 18, 20, 21, 23, 24, 26, 27, 29, 30, 32, 33, 35, 36, 38, 39, 41, 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59, 60, 62, 63, 65, 66, 68, 69, 71, 72, 74, 75, 77, 78, 80, 81, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 113, 114, 116, 117, 119, 120 (Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, 192, 200, 204, 212, 216, 224, 228, 236, 240, 248, 252, 260, 264, 272, 276, 284, 288, 296, 300, 308, 312, 320, 324, 332, 336, 344, 348, 356, 360, 368, 372, 380, 384, 392, 396, 404, 408, 416, 420, 428, 432, 440, 444, 452, 456, 464, 468, 476, 480 [±7 Days]) – Intrathecal Injection – Extended Treatment Phase – All Subjects

Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU (recovery suite), observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Thereafter, if deemed clinically stable by the investigator,

subjects may leave the hospital setting. The subject may need to be examined the following day (see Follow-up, Section 8.1.4.3) by the investigator; however, there is no requirement for an overnight hospital stay. Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

Vital signs (collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration).

- CSF sample collection (performed prior to idursulfase-IT injection). Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard laboratory parameters (chemistries, cell counts)
- Idursulfase-IT injection
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

8.2.2.3 Months 14, 15, 17, 18, 20, 21, 23, 24, 26, 27, 29, 30, 32, 33, 35, 36, 38, 39, 41, 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59, 60, 62, 63, 65, 66, 68, 69, 71, 72, 74, 75, 77, 78, 80, 81, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 113, 114, 116, 117, 119, 120 (Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, 192, 200, 204, 212, 216, 224, 228, 236, 240, 248, 252, 260, 264, 272, 276, 284, 288, 296, 300, 308, 312, 320, 324, 332, 336, 344, 348, 356, 360, 368, 372, 380, 384, 392, 396, 404, 408, 416, 420, 428, 432, 440, 444, 452, 456, 464, 468, 476, 480 [±7 Days]) Safety Follow-up for Intrathecal Injection – Extended Treatment Phase – All Subjects

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

In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

8.2.3 Months 16, 22, 28, 34, 40, 43, 46, 52, 55, 58, 64, 70, 76, 82, 88, 94, 100, 103, 106, 112, 115, 118 (Weeks 64, 88, 112, 136, 160, 172, 184, 208, 220, 232, 256, 280, 304, 328, 352, 376, 400, 412, 424, 448, 460, 472 [±7 Days]) – Extended Treatment Phase – All Subjects

8.2.3.1 Months 16, 22, 28, 34, 40, 43, 46, 52, 55, 58, 64, 70, 76, 82, 88, 94, 100, 103, 106, 112, 115, 118 (Weeks 64, 88, 112, 136, 160, 172, 184, 208, 220, 232, 256, 280, 304, 328, 352, 376, 400, 412, 424, 448, 460, 472 [±7 Days]) – Prior to Intrathecal Injection – Extended Treatment Phase – All Subjects

- Physical and neurological examination
- Height and weight
- Vital signs
- Clinical laboratory tests (hematology, serum chemistry, urinalysis)
- Urine GAG and creatinine
- Anti-idursulfase antibody testing (serum)
- Serum albumin
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate.

8.2.3.2 Months 16, 22, 28, 34, 40, 43, 46, 52, 55, 58, 64, 70, 76, 82, 88, 94, 100, 103, 106, 112, 115, 118 (Weeks 64, 88, 112, 136, 160, 172, 184, 208, 220, 232, 256, 280, 304, 328, 352, 376, 400, 412, 424, 448, 460, 472 [±7 Days]) – Intrathecal Injection – Extended Treatment Phase – All Subjects

Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting. The subject may need to be examined the following day (see Follow-up, Section 8.1.4.3) by the investigator; however, there is no requirement for an overnight hospital stay. Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

- Vital signs (collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration)
- CSF sample collection (performed prior to idursulfase-IT injection). Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard

laboratory parameters (chemistries, cell counts), GAG, albumin, concentration of idursulfase enzyme, and presence of idursulfase-specific antibodies.
- Idursulfase-IT injection
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

8.2.3.3 Months 16, 22, 28, 34, 40, 43, 46, 52, 55, 58, 64, 70, 76, 82, 88, 94, 100, 103, 106, 112, 115, 118 (Weeks 64, 88, 112, 136, 160, 172, 184, 208, 220, 232, 256, 280, 304, 328, 352, 376, 400, 412, 424, 448, 460, 472 [±7 Days]) – Safety Follow-up for Intrathecal Injection – Extended Treatment Phase – All Subjects

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

In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

8.2.4 Months 19, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115 (Weeks 76, 100, 124, 148, 172, 196, 220, 244, 268, 292, 316, 340, 364, 388, 412, 436, 460 [±7 Days]) – Extended Treatment Phase – All Subjects

8.2.4.1 Months 19, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115 (Weeks 76, 100, 124, 148, 172, 196, 220, 244, 268, 292, 316, 340, 364, 388, 412, 436, 460 [±7 Days]) – Prior to Intrathecal Injection – Extended Treatment Phase – All Subjects

- Physical and neurological examination
- Height and weight
- Head circumference (Months 25, 37, and 49 only)
- Hearing assessment
- Neurodevelopmental assessments
  - DAS-II
  - BSID-III for subjects unable to complete the DAS-II
  - VABS-II
- Vital signs
- Clinical laboratory tests (hematology, serum chemistry, urinalysis)
- Urine GAG and creatinine
- Anti-idursulfase antibody testing (serum)
- General anesthesia
- Brain MRI (Months 25, 37, and 49 only)
- Serum albumin
- EQ-5D-5L
- HCUQ and CIQ

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

Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate.

8.2.4.2 Months 19, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115 (Weeks 76, 100, 124, 148, 172, 196, 220, 244, 268, 292, 316, 340, 364, 388, 412, 436, 460 [±7 Days]) – Intrathecal Injection – Extended Treatment Phase – All Subjects

Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU (recovery suite), observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting. The subject may need to be examined the following day (see Follow-up, Section 8.1.4.3) by the investigator; however, there is no requirement for an overnight hospital stay. Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

- Twelve-lead ECG (Months 25, 37, and 49 only)
- Vital signs (collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration)
- CSF sample collection (performed prior to idursulfase-IT injection). Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard laboratory parameters (chemistries, cell counts), GAG, albumin, concentration of idursulfase enzyme, and presence of idursulfase-specific antibodies.
- Idursulfase-IT injection
- Serum sampling for PK analysis will be collected at Month 25 only and within 30 minutes (±5 minutes) prior to intrathecal administration of idursulfase-IT and at 30 minutes (±5 minutes), 60 minutes (±5 minutes), 120 minutes (±5 minutes), 4 hours (±5 minutes), 6 hours (±5 minutes), 8 hours (±15 minutes), 12 hours (±15 minutes), 24 hours (±15 minutes), 30 hours (±15 minutes), 36 hours (±15 minutes) after the start of intrathecal administration.
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

8.2.4.3 Months 19, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115 (Weeks 76, 100, 124, 148, 172, 196, 220, 244, 268, 292, 316, 340, 364, 388, 412, 436, 460 [±7 Days]) – Safety Follow-up for Intrathecal Injection – Extended Treatment Phase – All Subjects

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

In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

8.3 End-of-study (Month 121, Week 484 [±7 Days]) – Extended Treatment Phase – All Subjects

- Physical and neurological examination
- Height and weight
- Head circumference
- Hearing assessment
- Neurodevelopmental assessments
  - DAS-II
  - BSID-III for subjects unable to complete the DAS-II
  - VABS-II
- Twelve-lead ECG
- Vital signs
- Clinical laboratory tests (hematology, serum chemistry, urinalysis)
- Urine GAG and creatinine
- Anti-idursulfase antibody testing (serum)
- General anesthesia
- Brain MRI
- X-ray
- CSF sample collection. Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard laboratory parameters (chemistries, cell counts), GAG, albumin, concentration of idursulfase enzyme, and presence of idursulfase-specific antibodies.
- Serum albumin
- EQ-5D-5L
- HCUQ and CIQ
- Concomitant medications, therapies/interventions, and medical/surgical procedures
- Adverse events

Subjects who do not continue treatment with idursulfase-IT will have the IDDD removed.

9 QUALITY CONTROL AND ASSURANCE

Training will occur at an investigator meeting or at the site initiation visit or both, and instruction manuals will be provided to aid consistency in data collection and reporting across sites.

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

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

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Global Drug Safety database.

10 STATISTICAL ANALYSES

10.1 General Methodology

Statistical analyses will be performed by the Biostatistics and Statistical Programming Department of Shire or its designee using SAS statistical software (SAS Institute, Cary, NC, USA), unless otherwise specified. Analysis methods will be detailed in the statistical analysis plan (SAP).

Data from studies SHP609-302 and HGT-HIT-094 will be integrated for efficacy and safety analyses. Baseline for the subjects previously treated in HGT-HIT-094 will be the same as the baseline defined in HGT-HIT-094. Baseline for the previously untreated subjects (ie, No IT treatment) in HGT-HIT-094 will be the closest available assessment prior to the initial IDDD implant date, which takes place in Study SHP609-302, unless otherwise specified. This could potentially include EOS visit data from Study HGT-HIT-094. The analyses presented here will include the data measured at and after baseline.

Safety data descriptive summaries will be presented for the Early IT group, Delayed IT group, and overall. The Early IT group and Delayed IT group designations are based on the treatment regimen (idursulfase-IT or No IT treatment) in the antecedent study (HGT-HIT-094). Subjects who participated in the HGT-HIT-094 substudy will be included in the Early IT group.

Efficacy data descriptive summaries will be presented separately for subjects who enrolled from the pivotal study or substudy of HGT-HIT-094. For subjects enrolled from the pivotal study, descriptive statistics will be presented by the Early IT group, the Delayed IT group, and overall. For secondary efficacy endpoints, the mean difference in the change at each time point between the 2 treatment groups (Early IT group and Delayed IT group) and the corresponding 90% confidence interval of the mean difference will be presented where appropriate. The mean values (±SD) for all efficacy endpoints will be graphed over time where appropriate.

Inferential testing is planned for some exploratory efficacy endpoints. The main exploratory efficacy analyses to examine the IT treatment effect will be rate of change (weighted) analyses of the exploratory efficacy endpoints from Visit Month 13/baseline to Visit Month 25/Week 52 as estimated by linear regression for DAS-II Early Years GCA scores and selected neurodevelopment assessment scores.

Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of subjects in each category.

Efficacy data for subjects enrolled from the HGT-HIT-094 substudy will be presented in listings.

10.2 Determination of Sample Size

This is an open-label extension trial of Study HGT-HIT-094. Only eligible subjects who participated in Study HGT-HIT-094 may enroll in SHP609-302, and therefore no sample size calculation was performed.

10.3 Method of Assigning Study Subjects to Treatment Groups

SHP609-302 is a non-randomized extension study in which all enrolled subjects receive idursulfase-IT treatment.

10.4 Population Description and Exposure

10.4.1 Data Integration Strategy

Data from studies SHP609-302 and HGT-HIT-094 will be integrated for data analyses.

For safety and efficacy descriptive summary analyses using integrated data, the 2 treatment groups are the Early IT group and Delayed IT group based on HGT-HIT-094 treatment regimen (idursulfase-IT or No IT Treatment), defined as follows:

- The Early IT group is defined as subjects who were randomized to the idursulfase-IT treatment cohort in study HGT-HIT-094 and continued IT treatment in study SHP609-302. HGT-HIT-094 substudy will be included in the Early IT group.

- The Delayed IT group is defined as subjects who were randomized to the control cohort (No IT treatment) in study HGT-HIT-094 and began IT treatment in study SHP609-302.

For exploratory efficacy analyses, only data collected in study SHP609-302 will be used; the 2 treatment groups are the Early IT group and Delayed IT group.

Visit Month 13 of the SHP609-302 Extended Treatment Phase corresponds to the scheduled visit at which subjects in the Early IT group have completed 12 months of IT treatment in antecedent study HGT-HIT-094. The treatment regimen in HGT-HIT-094 comprised 1 month for surgical IDDD implantation at the beginning of the study followed by 12 months of IT treatment during HGT-HIT-094.

Likewise, Visit Month 25 of the SHP609-302 Extended Treatment Phase corresponds to the scheduled visit at which subjects in the Early IT group have completed two 12-month periods of IT treatment, and comprises 1 month for surgical IDDD implantation at the beginning of HGT-HIT-094, 12 months of IT treatment during HGT-HIT-094, and a continued 12 months of IT treatment in the Extended Treatment Phase of SHP609-302.

Visit Week 52 of the SHP609-302 Initial Treatment Phase is the scheduled visit at which subjects in the Delayed IT group have completed 12 months of IT treatment in study SHP609-302, and comprises 12 months of No IT treatment during HGT-HIT-094, 1 month for surgical IDDD implantation at the beginning of SHP609-302, and 12 months of IT treatment in the Initial Treatment Phase of SHP609-302.

It is noted that Visit Month 25 and Visit Week 52 of SHP609-302 are 4 weeks apart for the Early IT and Delayed IT groups. This difference is accounted for by the need for subjects in the Delayed IT group, who enrolled into the Initial Treatment Phase of SHP609-302 from the HGT-HIT-094 No IT treatment group, to undergo surgical implantation of the device at the beginning of study SHP609-302. Therefore, the first dose of SHP609 was administered 4 weeks

later to these subjects compared with subjects in the Early IT group who were randomized to IT treatment and underwent IDDD implantation in HGT-HIT-094 prior to enrolling in the Extended Treatment Phase of SHP609-302. For evaluation of the long-term efficacy of IT treatment in SHP609-302, this 4-week difference is considered to have minimal impact on neurodevelopmental assessment scores.

10.4.2 Analysis Populations

All descriptive summary analyses of safety and efficacy data will be based on the Safety Population, which is defined as all subjects in study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial).

The following nomenclature will be used to identify "A", "B", "C", and "D" in Figure 2.

- Observation Groups A and C identify the period of observation during study HGT-HIT-094, for subjects randomized to IT treatment and No IT treatment, respectively.
- Observation Groups B and D identify the period of observation during study SHP609-302 up to completion of 1 year, for subjects who were randomized in HGT-HIT-094 to receive IT treatment and No IT treatment, respectively, noting that all subjects in SHP609-302 received IT treatment.

The subjects in "B" are the same subjects as in "A" with periods of observation from studies SHP609-302 and HGT-HIT-094, respectively, as we can view "B" as a continuation of "A". The subjects in "D" are the same subjects as in "C" with periods of observation from studies SHP609-302 and HGT-HIT-094, respectively, as we can view "D" as a continuation of "C".

"D" subjects are therefore similar to "A" subjects since these subjects all transitioned from receiving weekly IV infusion of Elaprase, to also receive monthly IT idursulfase. More generally, because study SHP609-302 did not have baseline GCA inclusion criteria, such as that employed for study HGT-HIT-094, "B" and "D" subjects could differ with regard to their baseline GCA score at the beginning of the observation period. Therefore, for consideration of "B" and "D", only subjects meeting the key inclusion criteria to HGT-HIT-094 will be included in inferential efficacy analyses, ie, with GCA scores between 55 and 85 inclusive at the enrollment of SHP609-302.

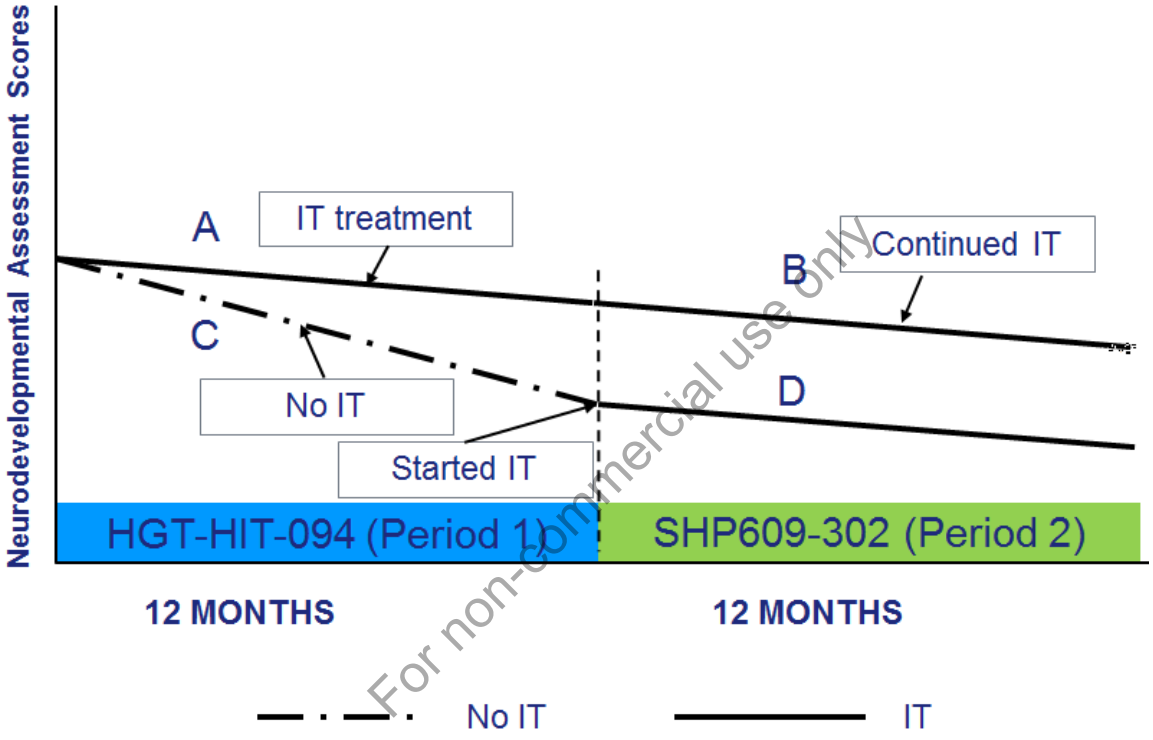
The exploratory efficacy analyses will be conducted on "HGT-HIT-094 Comparable Set," "HGT-HIT-094 Comparable Set 1", and "HGT-HIT-094 Comparable Set 2". The primary analysis population is HGT-HIT-094 Comparable Subset 1, which may be the subject population with the most potential to benefit from the idursulfase-IT treatment.

- HGT-HIT-094 Comparable Set: subjects in the Safety Population who met the key HGT-HIT-094 inclusion criterion (baseline GCA scores between 55 and 85 inclusive) at enrollment in SHP609-302 (Visit Month 13/baseline), ie, Safety Population subjects with GCA scores between 55 and 85 inclusive at enrollment in SHP609-302
- HGT-HIT-094 Comparable Subset 1 (primary analysis population): subjects in the HGT-HIT-094 Comparable Set with age <6 years at enrollment in SHP609-302 (Visit

Month 13/baseline), ie, Safety Population subjects with GCA scores between 55 and 85 inclusive and age <6 years at enrollment in SHP609-302

- HGT-HIT-094 Comparable Subset 2: subjects in the HGT-HIT-094 Comparable Set with age <55 months at the enrollment of SHP609-302 (Visit Month 13/baseline), ie, Safety Population subjects with GCA scores between 55 and 85 inclusive and age <55 months at enrollment in SHP609-302

Figure 2 Conceptual Plot of Treatment Periods in Early IT and Delayed IT Groups in Studies HGT-HIT-094 and SHP609-302



Device-related analyses will be conducted in the subset of subjects in the Safety Population who had the device implanted.

All pharmacokinetic data analyses will be performed using the PK population. The PK population will be defined as all subjects who received study drug and had sufficient serum samples collected to derive pharmacokinetic parameters.

10.4.3 Subject Disposition

The number of subjects screened, included in the Safety Population, completed the study, and discontinued prematurely will be presented in a summary table by the Early IT group, the Delayed IT group, and overall; reasons for discontinuation/withdrawal will also be summarized.

10.4.4 Protocol Deviations

Reported protocol deviations and subject data will be examined prior to database lock to determine if conditions set forth in the study protocol have been violated. The complete list of protocol deviations will not be summarized; however, if applicable, protocol violations identified will be listed for the Safety Population.

10.4.5 Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be summarized by the Early IT group, the Delayed IT group, and overall for the Safety Population.

Medical history will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 or higher and will be similarly summarized.

10.4.6 Treatment Compliance

Treatment compliance will be summarized by the Early IT group, the Delayed IT group, and overall for the Safety Population. Treatment compliance is defined as: [(Number of Complete IT administrations) ÷ (Expected Number of IT administrations)] * 100.

10.4.7 Extent of Exposure

The total number of doses of study drug, the number of doses received via IDDD, the number of doses received via LP and the average duration of IT administration will be summarized by the Early IT group, the Delayed IT group, and overall for the Safety Population. The duration of IT administration is calculated by subtracting the IT administration start time from the IT administration end time.

10.5 Analysis of Efficacy

10.5.1 Primary Efficacy Analysis

Not applicable.

10.5.2 Key Secondary Efficacy Analysis

Not applicable.

10.5.3 Other Secondary Efficacy Analysis

For all other efficacy endpoints described in Section 3.2, the observed values and change from baseline will be summarized descriptively for each assessment time point by the Early IT group, the Delayed IT group, and overall. Any HGT-HIT-094 substudy subjects will be included in the Early IT group for analysis. The mean difference in the change at each time point between the two HGT-HIT-094 treatment groups and the corresponding 90% confidence interval of the mean difference will be presented. The BSID-III endpoints will be listed only. Graphical plots of the mean value for each endpoint over time will be presented. A spaghetti plot of the age equivalent scores for individual subjects will be plotted against chronological age.

10.5.4 Subgroup Analyses

Subgroup descriptive summary analyses of the secondary efficacy endpoints, change from baseline in GCA and ABC scores will be performed for baseline GCA groups (either ≤70 or >70) and baseline age groups (either <6 years or ≥6 years; <55 months or ≥55 months). Descriptive summaries within these subgroups and plots of mean values (±SD) over time will be presented. The baseline is defined in Section 10.1.

Subgroup analyses are planned for the rate of change (weighted) analyses in GCA scores from the Early Years battery, GCA scores and ABC scores for GCA classification groups at Visit Month 13/baseline (either ≤70 or >70), age groups at Visit Month 13/baseline (either <6 years or ≥6 years), and age groups at Visit Month 13/baseline (either <55 months or ≥55 months).

10.5.5 Exploratory Analyses

The main exploratory efficacy analyses to examine the IT treatment effect will be rate of change (weighted) analyses of the exploratory efficacy endpoints from Visit Month 13/baseline to Visit Month 25/Week 52 in study SHP609-302 as estimated by linear regression for the following neurodevelopmental assessment scores:

- DAS-II GCA scores from Early Years battery
- DAS-II Early Years core subtests T scores: Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices, and Copying
- DAS-II Early Years battery standard cluster scores: Verbal, Nonverbal, Spatial, and SNC composite scores
- DAS-II GCA scores including both Early Years and School Age batteries
- VABS-II ABC scores

Complete details of the rate of change (weighted) analysis, including examination of premises of the rate of change (weighted) analysis, model diagnostics, and estimation and comparison of the treatment effects during observation periods “B” and “D” will be described in the SAP.

The descriptive summary of ordered categorical outcomes will be presented at Month 25/Week 52 by the Early IT group, the Delayed IT group, and overall using the SHP609-302 data “B” and “D”. The definitions of ordered categorical outcomes for each subject are described in Section 3.3.

For each of the neurodevelopmental assessments, there may be a “floor effect”, ie, the lower limitation of the assessment tool, below which the assessment may not be reliable or meaningful. Refer to the SAP for complete details.

Other exploratory analyses may include assessment of the correlation between PD and efficacy endpoints; and between composite scores and their components (ie, correlations between the GCA and ABC scores and their respective cluster/domain scores). Scatter plots may be presented to explore the relationships among variables.

10.5.6 Health Economics and Outcomes Research Endpoint Analyses

The EQ-5D-5L measures 5 dimensions of health status: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each dimension, there are 5 levels of response. The number and percent of subjects with each response will be presented by dimension at each visit. The visual analog scale (VAS) records the subject's parent/caregiver-rated health on a 0 (worst health) to 100 (best health) scale. The VAS score, as well as the change from baseline will be summarized as each time point.

HCUQ variables include the number of emergency room visits, caregiver employment status (full time [FT], part time [PT], and not working [NW]), and the number of hours of additional paid help needed by caregivers, over the course of the study. The CIQ question items measure social, emotional, physical, and financial impacts on the caregiver. Descriptive statistics, including n, mean, median, and range (for continuous variables), and n and proportions (for categorical variables), for these key HCUQ and CIQ variables will be presented.

The HS-FOCUS shortened form will be used to assess subjects. Domain scores from the 5 functional domains (walking/standing, grip/reach, schooling/work, activities, and breathing) will be summarized.

Additional pharmacoeconomic analyses may be performed by the sponsor staff in the Health Economics and Outcomes Research group or designee and reported separately in a pharmacoeconomic report to be appended to the clinical study report. Accordingly, any planned pharmacoeconomic analyses related to this data may be described in a separate document.

10.6 Analysis of Pharmacokinetic and Pharmacodynamic Data

10.6.1 Pharmacokinetic Measurement and Parameters

The PK population will be used to perform the analysis of pharmacokinetic data. Idursulfase concentrations in all collected serum samples will be measured and reported. Individual subject idursulfase serum concentration-time profiles will be presented. Individual PK parameters will be derived by a noncompartmental analysis and reported. The actual PK blood sample collection times will be used to determine the individual subject idursulfase serum concentration-time profiles. Pharmacokinetic parameters will be calculated if sufficient idursulfase concentration-time points exist to derive values. Individual subject CSF idursulfase concentrations at each collection time point will be reported.

Pharmacokinetic parameters calculated will include:

- Maximum observed serum concentration (C_{max})
- Time of C_{max} (T_{max})
- Area under the serum concentration-time curve from time zero to the last sampling time at which serum concentrations were measurable ($AUC_{0\text{-}last}$)
- Area under the serum concentration-time curve extrapolated to infinity ($AUC_{0\text{-}\infty}$)
- Apparent terminal rate constant (λ_z) derived from the slope of the log-linear regression of the log-linear terminal portion of the serum concentration-time curve.

- Terminal half-life ($t_{1/2}$) calculated as $0.693/ \lambda_z$
- Mean residence time ($MRT_{0-\infty}$), calculated as $AUMC_{0-\infty}/AUC_{0-\infty}$
- Clearance for IT-L administration ($CL/_F$)
- Volume of distribution based on the terminal phase for IT-L administration ($V_z/_F$)

The analysis of PK parameter data will be performed by the Shire Clinical Pharmacology and Pharmacokinetics department or its designee.

10.6.2 Pharmacodynamic Analyses

The levels of GAG in CSF and urine are PD endpoints. Analyses of PD endpoints will be performed in the Safety Population. The observed values and changes from baseline in CSF GAG levels will be summarized for each assessment time by the Early IT group, Delayed IT group, and overall. A graphical plot of mean CSF GAG levels across time will be presented. The urine GAG levels will be analyzed in a manner similar to that described for CSF data.

10.7 Analysis of Safety

All analyses of safety data will be descriptive and presented by the Early IT group, Delayed IT group, and overall. The analysis of safety will be based on the Safety Population.

10.7.1 Adverse Events

Adverse events will be recorded throughout the study. Adverse events will be coded using the MedDRA dictionary, version 16.0 or higher.

Treatment-emergent AEs, defined as all AEs from the time of initial intervention (first surgery for IDDD implantation, including failed surgeries, or first dose if before first IDDD implantation surgery) to the EOS visit, will be summarized by the Early IT group, Delayed IT group, and overall.

The number and percentage of subjects having an AE and the number of events, by system organ class (SOC) and preferred term will be presented. Treatment-emergent AEs will also be summarized by severity and degree of relationship to study drug. An adverse event will be considered related if indicated to be "possibly," "probably," or "definitely" related. In the case of multiple occurrences of the same AE (at the preferred term level) in an individual subject, the AE that is classified as the most severe (ie, maximum severity) will be identified for the analysis by severity and the AE that has the closest relationship to study drug/procedure will be identified for the analysis by relationship. In general, an AE will be considered a treatment-emergent AE if it cannot be definitively categorized otherwise by documentation that its onset preceded either IDDD surgery or first dose.

Serious adverse events will be similarly tabulated according to SOC and preferred term and presented in a separate listing.

10.7.1.1 Investigational Product

Treatment-emergent AEs deemed by the investigator to be related to idursulfase-IT study drug will be summarized by presenting the number and percentage of subjects having an AE and the number of events, by SOC and preferred term. Separate tabulations of IV Elaprase infusion-related adverse events and IV Elaprase infusion and/or idursulfase-IT-related AEs will also be presented.

10.7.1.2 Intrathecal Drug Delivery Device and Surgical Procedure-related AEs

IDDD and procedure-related AEs will be summarized within MedDRA system organ class by preferred term. Separate tabulations will be provided for adverse events related to the IDDD, device surgical procedure and IT administration process.

An overall summary of adverse events related to the IT treatment regimen (ie, related to 1 or more of the following: study drug, IDDD, device surgical procedure, and IT-administration process) will also be presented. IDDD and procedure-related events will be analyzed in the set of treated subjects in the Safety Population with the IDDD implanted.

10.7.2 Clinical Laboratory Evaluation

Observed values and changes from baseline for continuous laboratory test results will be summarized for each assessment time by the Early IT group, Delayed IT group, and overall. Each laboratory result will be categorized as a subject having had (1) an abnormal and clinically significant (CS) value at any time post-baseline, (2) no CS values at any time post-baseline, but had at least 1 Abnormal and not CS (NCS) value, and (3) no CS or NCS values at any time post-baseline; the number and percentage in each category will be presented. For any subject who experiences a CS laboratory result at any time post-baseline that was not CS at baseline (or the most recent non-missing value prior to the start of the treatment), their entire profile for that particular laboratory parameter will be presented in a listing.

10.7.3 Electrocardiogram Evaluation

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

10.7.4 Vital Signs

The observed values and changes from baseline for IT-administration vital sign parameters will be summarized. The IT vital signs will be graphed as box plots over the time from the start of the IT injection for each IT injection.

Height (cm), weight (kg), and head circumference (cm) and the change from baseline will be summarized for each assessment time point.

10.7.5 Physical Findings

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

10.7.6 Other Observations Related to Safety

10.7.6.1 Intrathecal Drug Delivery Device Performance

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

The proportion of subjects with at least 1 device failure and/or malfunction, as well as the number of and reasons for device failures/malfunctions will be summarized. The rate of device failures/malfunctions and 90% confidence interval will also be estimated. The time from initial implant surgery to first device failure and/or malfunction will be summarized. Subjects without a device failure/malfunction will be censored at their last study drug injection date. A by-subject listing of the device failure/malfunction data will be displayed.

The rate of successful IDDD injections will be calculated for each subject 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 90% confidence interval for the mean rate will be estimated, where appropriate. Injections that are not administered for subject-related reasons (eg, subject uncooperative, competing medical issue, etc.) will not be included in the determination of the injection success rate.

10.7.6.2 Immunogenicity

Anti-idursulfase antibody formation will be monitored throughout the study for both serum and CSF. The number and percentage of subjects testing anti idursulfase antibody positive and negative at each scheduled time point from baseline will be summarized by the Early IT group, Delayed IT group, and overall. Titer values will be summarized as box plots over time in subjects with positive antibodies at or prior to each scheduled visit by treatment group. Similar summaries will be presented for subjects who developed positive neutralizing antibodies.

10.7.7 Hearing Assessment

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

10.7.8 Concomitant Medications

Concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD). The concomitant medications that occur from the time of the surgery for IDDD implantation to the last subject visit in the study, will be summarized by therapeutic class and preferred term. Concomitant therapies will be mapped using the MedDRA Version 16.0 or higher and will be similarly summarized by the SOC and preferred term.

10.8 Statistical/Analytical Issues

10.8.1 Adjustment for Covariates

The rate of change (weighted) analysis will adjust for GCA classification (either ≤70 or >70) at enrollment of SHP609-302 in the weighted generalized linear model.

10.8.2 Handling of Dropouts or Missing Data

In general, no imputation will be performed and analyses will be based on available data. Missing or partial AE dates will not be imputed. However, a conservative approach will be adopted in such cases so that the AE will be deemed to be treatment emergent if it cannot be definitively categorized to have occurred prior to surgery for IDDD implantation. Similar logic will be applied to deal with missing and partial date for concomitant medications.

10.8.3 Interim Analyses and Data Monitoring

Interim analyses may be conducted before trial completion for safety monitoring, regulatory reporting or general planning purposes. Analyses will be descriptive in nature, with no formal comparisons planned and no hypotheses tested formally. An independent DMC will be established to provide an ongoing, independent review and assessment of subject safety data (refer to Section 11.8). An analysis of the data for DMC review will occur at specific times during the study as specified in the DMC charter.

10.8.4 Multicenter Studies

It is planned that the data from all centers that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis. Because of the potential for a relatively large number of centers, and small numbers of subjects at some centers, no subset analyses by center are planned.

10.8.5 Multiple Comparisons/Multiplicity

No multiple comparison procedure or multiplicity adjustment will be performed.

10.8.6 Sensitivity Analyses

Given the design and objectives of the study, no sensitivity analyses are planned.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

Before initiation of the study, the investigator must provide the sponsor with a completed Form FDA 1572, Investigator Agreement, or other applicable regulatory documentation. Investigational product may be administered only under the supervision of the investigator(s) listed on these forms.

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. Curriculum vitae must be provided for the investigators and sub-investigators listed on Form FDA 1572 or other regulatory documentation, as applicable.

11.2 Institutional Review Board or Independent Ethics Committee Approval

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

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

11.3 Ethical Conduct of the Study

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

11.4 Subject Information and Consent

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

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

Note: When a subject 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 and IRB/IEC guidelines, as lacking mental capacity to provide informed consent, the subject's parent(s), guardian, or legally authorized representative(s) will be asked to provide informed consent on behalf of the subject to allow for continued participation in the trial.

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

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

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

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

11.5 Subject Confidentiality

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the eCRF, and if the subject 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 subjects 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 subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

11.6 Study Monitoring

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

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

11.7 Case Report Forms and Study Records

11.7.1 Case Report Forms

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

11.7.2 Critical Documents

Before Shire initiates the trial at a clinical site (ie, obtains informed consent from the first subject), it is the responsibility of the investigator to ensure that the following documents are available to Shire or its designee:

- Applicable local regulatory documentation (eg, completed FDA Form 1572 [Statement of Investigator], signed, dated, and accurate
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed within 24 months of study initiation)
- Copy of investigator and sub-investigator(s) current medical license (indicating license number and expiration date)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed by name, number and date of approval or re approval: protocol, any amendments, Subject Information/Informed Consent Form, and any other written information to be provided regarding subject recruitment procedures

- Copy of IRB/IEC approved Subject Information/Informed Consent Form/any other written information/advertisement (with IRB approval stamp and date of approval)
- Current list of IRB/IEC Committee members/constitution (dated within 12 months prior to study initiation)
- Financial Disclosure Form signed by investigator and sub-investigator(s)
- Current laboratory reference ranges (if applicable)
- Certification/QA scheme/other documentation (if applicable)

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

11.8 Data Monitoring Committee

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

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

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

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

11.9 Device Failure Review Process

The final cause for SOPH-A-PORT Mini S device failures will be reviewed by Shire by examining the device failure information in the clinical database, safety database, and manufacturer investigation of returned SOPH-A-PORT Mini S devices.

11.10 Protocol Violations/Deviations

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

have the approval/favorable opinion of the IRB/IEC. The sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

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

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

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

11.11 Premature Closure of the Study

If the sponsor, investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable subject risk, the study may be terminated after appropriate consultation between the sponsor and the investigator(s). In addition, a decision on the part of the sponsor to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to:

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

11.12 Access to Source Documentation

Regulatory authorities, the IRB/IEC, or the sponsor (or their designee) may request access to all source documents, eCRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the eCRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

11.13 Data Generation and Analysis

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

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

11.14 Retention of Data

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

11.15 Financial Disclosure

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

11.16 Publication and Disclosure Policy

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

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

The investigator and any other clinical personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with Shire, provided Shire a copy of the draft document intended for publication, and obtained Shire's written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential.

12 LIST OF REFERENCES

1. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999;281:249-54.
2. Young ID, Harper PS. Incidence of Hunter's syndrome. Hum Genet 1982;60:391-2.
3. Beck M. Mucopolysaccharidosis type II (Hunter syndrome): clinical picture and treatment. Curr Pharm Biotechnol 2011.
4. Martin R, Beck M, Eng C, et al. Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). Pediatr 2008;121:e377-86.
5. Martin HR, Poe MD, Reinhartsen D, et al. Methods for Assessing Neurodevelopment in Lysosomal Storage Diseases and Related Disorders: a Multidisciplinary Perspective. Acta Paediatr Supp 2008;97:69-75.
6. Wraith EGR, Burton BK, Muenzer J, Clarke JT, Meirleir L De, Kroepfl T, Malm G, Beck M. Early Clinical Manifestations in Patients Diagnosed with Hunter Syndrome: Data from the Hunter Outcome Survey. Arch Dis Child 2008;93:1.
7. Young ID, Harper PS, Newcombe RG, Archer IM. A clinical and genetic study of Hunter's syndrome. 2. Differences between the mild and severe forms. J Med Genet 1982;19:408-11.
8. Holt JB, Poe MD, Escolar ML. Natural progression of neurological disease in mucopolysaccharidosis type II. Pediatr 2011;127:e1258-65.
9. Holt J, Poe MD, Escolar ML. Early clinical markers of central nervous system involvement in mucopolysaccharidosis type II. J Pediatr 2011;159:320-6.e2.
10. Neufeld E, Muenzer J. The Mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. New York: McGraw-Hill; 2001:3421-52.
11. Froissart R, Moreira da Silva I, Guffon N, Bozon D, Maire I. Mucopolysaccharidosis type II--genotype/phenotype aspects. Acta Paediatr Supp 2002;91:82-7.
12. Guffon N, Bertrand Y, Forest I, Fouilhoux A, Froissart R. Bone marrow transplantation in children with Hunter syndrome: outcome after 7 to 17 years. J Pediatr 2009;154:733-7.
13. Muenzer J, Beck M, Eng CM, et al. Multidisciplinary management of Hunter syndrome. Pediatr 2009;124:e1228-39.
14. Muenzer J, Gucsavas-Calikoglu M, McCandless SE, Schuetz TJ, Kimura A. A phase I/II clinical trial of enzyme replacement therapy in mucopolysaccharidosis II (Hunter syndrome). Mol Genet Metab 2007;90:329-37.
15. Wraith JE, Scarpa M, Beck M, et al. Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy. Eur J Pediatr 2008;167:267-77.
16. Dekaban AS. Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. Ann Neurol 1978;4:345-56.

17. Elliott, CD. Differential Ability Scales (Second Edition). San Antonio, TX: The Psychological Corporation; 2007.

18. Bayley N. Bayley Scales of Infant and Toddler Development (Third Edition). San Antonio, TX. The Psychological Corporation; 2005.

19. Sparrow S, Balla D, Cicchetti D. Vineland Adaptive Behavior Scales (Second Edition). 4201 Woodland Road Circle Pines, MN 55014-1796: American Guidance Service, Inc; 2005.

20. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Annals of medicine 2001;33:337-43.

21. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16:199-208.

13 APPENDICES

Appendix 1 Initial Treatment Phase Schedule of Events: For Subjects Who Did Not Receive Intrathecal Idursulfase-IT in Study HGT-HIT-094

Assessment	Month -1	Month 0	Months 1 to 12[i]					
	Weeks -1 Baseline	Week 0	Week 2 (-14 Days, +7 Days)[j] Pre-surgery, Surgery, Follow-up, and Post-op Recovery[k]			Weeks 4, 8, 12, 16, 20, 24, 28[m], 32, 36, 40, 44, 48 IT Dosing (±7 Days)		
	Day -7 to Day -1		Pre-surgery	Surgery	Follow-up	Pre-Tx[m]	IT Injection[m]	Follow-up[m]
	Main Site		Main Site	Main Site	Main Site	Main Site	Main Site	Main Site
Informed Consent[a]	●							
Study Entry Criteria Review	●							
Enrollment (confirmation of study eligibility)		●[h]						
Medical History (since end-of-study HGT-HIT-094)	●							
Echocardiogram[b]	●							
Physical and Neurological Examination			●		●[l]	●		●
Height and Weight			●			●[n]		
Head Circumference						●[n]		
Hearing Assessment						●[o]		
Neurodevelopmental Assessment[c]						●[o]		
12-lead ECG			●			●	●[n, p]	
Vital Signs			●	●		●	●[q]	
Clinical Laboratory Tests (Hematology, Serum Chemistry, Urinalysis)			●			●[n]		
Coagulation Tests[d]			●					
Urine GAG and creatinine						●[n]		
Anti-idursulfase Antibody Testing						●[n]		
General Anesthesia[e]				●				
CSF Sample Collection[f]				●			●[f, r]	
Serum Albumin						●[n]		

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Assessment	Month -1	Month 0	Months 1 to 12[i]					
	Weeks -1 Baseline	Week 0	Week 2 (-14 Days, +7 Days)[j] Pre-surgery, Surgery, Follow-up, and Post-op Recovery[k]			Weeks 4, 8, 12, 16, 20, 24, 28[m], 32, 36, 40, 44, 48 IT Dosing (±7 Days)		
	Day -7 to Day -1		Pre-surgery	Surgery	Follow-up	Pre-Tx[m]	IT Injection[m]	Follow-up[m]
	Main Site		Main Site	Main Site	Main Site	Main Site	Main Site	Main Site
IDDD Implantation				●				
X-ray[g]				●				
Idursulfase-IT Injection							●[s]	
Serum Sample for PK							●[t]	
EQ-5D-5L						●[n]		
HCUQ and CIQ	●					●[n]		
HS-FOCUS	●					●[n]		
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	●	●	●	●	●	●	●	●
Adverse Events	●	●	●	●	●	●	●	●

Abbreviations: CIQ=Caregiver Impact Questionnaire; CSF=cerebrospinal fluid; ECG=electrocardiogram; EOS=end-of-study; EQ-5D-5L=EuroQol-5D health status questionnaire; GAG=glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HS-FOCUS=Functional Outcomes for Clinical Understanding Scale; IDDD=intrathecal drug delivery device; IT=intrathecal; IV=intravenous; PACU=post-anesthesia care unit; PK=pharmacokinetics; Tx=treatment

[a] Informed consent (and subject consent/assent, if applicable) must be obtained from the subject's parent(s)/legally authorized guardian(s) before beginning Screening assessments. During Study SHP609-302, subjects who exceed the age of enrollment eligibility for Study HGT-HIT-094 and/or have reached the applicable legal age of consent to participate in a clinical study will be allowed to continue participation in Study SHP609-302 until the end of the study. When a subject 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 subject's parent(s) or legally authorized representative(s)will be asked to provide informed consent on behalf of the subject to allow for continued participation in the trial.

[b] This assessment will not need to be performed if an echocardiogram taken within 3 months of study start is available and deemed satisfactory for evaluation of anesthesia risk.

[c] Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as depicted in Appendix 23.

[d] Pre-surgery coagulation tests will be performed by the local laboratory.

[e] General anesthesia or sedation may also be required for injections of investigational product 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 will have to be performed with

Appendix 1 Initial Treatment Phase Schedule of Events: For Subjects Who Did Not Receive Intrathecal Idursulfase-IT in Study HGT-HIT-094

Assessment	Month -1	Month 0	Months 1 to 12[i]					
	Weeks -1 Baseline	Week 0	Week 2 (-14 Days, +7 Days)[j] Pre-surgery, Surgery, Follow-up, and Post-op Recovery[k]			Weeks 4, 8, 12, 16, 20, 24, 28[m], 32, 36, 40, 44, 48 IT Dosing (±7 Days)		
	Day -7 to Day -1		Pre-surgery	Surgery	Follow-up	Pre-Tx[m]	IT Injection[m]	Follow-up[m]
	Main Site		Main Site	Main Site	Main Site	Main Site	Main Site	Main Site

sedation/anesthesiology support.

[f] Cerebrospinal fluid samples will be collected monthly prior to dosing via the IDDD or lumbar puncture and used to analyze standard laboratory parameters (chemistries, cell counts), GAG, and the concentration of idursulfase enzyme. Analyses of CSF samples for antibodies and albumin will be performed at IT Dosing Weeks 4, 16, 28, and 40.

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

[h] Enrollment does not need to be performed at a separate visit.

[i] If a subject discontinues any time during participation through Month 12, the subject will undergo EOS procedures, which are described in Appendix 12 (Schedule of Events from Month 58 through EOS).

[j] The Week 2 visit may occur as early as Week 0, as soon as the subject has been enrolled (ie, study eligibility has been confirmed).

[k] At least 14 days will be allowed for recovery following the placement of the IDDD before the administration of the first IT dose.

[l] The assessments indicated will be performed prior to discharge. It is expected that, for most subjects, post-surgical follow-up will occur within Week 2 (ie, within 1 to 2 days of surgery).

[m] From Week 28 onward, pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate. In addition, from Week 28 onward and in the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

[n] The assessments indicated will be performed at 3-month intervals, ie, at IT Dosing Weeks 4, 16, 28, and 40.

[o] The neurodevelopmental and hearing assessments will be performed at IT Dosing Weeks 16, 28, and 40.

[p] The 12-lead ECG is to be performed within 4 hours after IT administration of study drug at Weeks 4, 16, 28, and 40.

[q] Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of Visit Weeks 4 and 48 at which serial blood sampling for pharmacokinetic evaluation is planned). The subject may need to be examined the following day.

[r] The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.

Appendix 1 Initial Treatment Phase Schedule of Events: For Subjects Who Did Not Receive Intrathecal Idursulfase-IT in Study HGT-HIT-094

	Month -1	Month 0	Months 1 to 12[i]					
	Weeks -1 Baseline	Week 0	Week 2 (-14 Days, +7 Days)[j] Pre-surgery, Surgery, Follow-up, and Post-op Recovery[k]			Weeks 4, 8, 12, 16, 20, 24, 28[m], 32, 36, 40, 44, 48 IT Dosing (±7 Days)		
	Day -7 to Day -1		Pre-surgery	Surgery	Follow-up	Pre-Tx[m]	IT Injection[m]	Follow-up[m]
Assessment	Main Site		Main Site	Main Site	Main Site	Main Site	Main Site	Main Site

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

[t] Serum samples for PK analysis will be obtained at IT Dosing Weeks 4 and 48. Samples will be collected within 30 minutes (±5 minutes) prior to IT administration of idursulfase-IT and at 30 minutes (±5 minutes), 60 minutes (±5 minutes), 120 minutes (±5 minutes), 4 hours (±5 minutes), 6 hours (±5 minutes), 8 hours (±15 minutes), 12 hours (±15 minutes), 24 hours (±15 minutes), 30 hours (±15 minutes), 36 hours (±15 minutes) after the start of IT administration.

Appendix 2 Extended Treatment Phase Schedule of Events – Months 13-15 (Weeks 52-60)

Assessment	Month 13						Month 14			Month 15		
	Week 52 (±7 Days)						Week 56 (±7 Days)			Week 60 (±7 Days)		
	Subjects from Initial Treatment Phase			Subjects Previously Treated in Study HGT-HIT-094								
	IT Dosing Week[e] Main Site[f]			IT Dosing Week[e] Main Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]		
	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]
Informed Consent[a]				•								
Study Entry Criteria Review				•								
Enrollment (Confirmation of Study Eligibility)				•								
Physical and Neurological Examination	•						•			•		
Height and Weight	•											
Head Circumference	•											
Hearing Assessment	•											
Neurodevelopmental Assessment[b]	•											
12-lead ECG	•											
Vital Signs	•	•[h]			•[h]		•	•[h]		•	•[h]	
Blood and Urine Sample for Clinical Laboratory Tests	•											
Urine GAG and Creatinine	•											
Serum Sample for Anti-Idursulfase Antibody Testing	•											
General Anesthesia[c]	•											
Brain MRI	•											
X-ray[d]												
CSF Sample for Standard Chemistry		•[1]			•[1]			•[1]			•[1]	
CSF Sample for GAG Testing		•[1]										

Appendix 2 Extended Treatment Phase Schedule of Events – Months 13-15 (Weeks 52-60)

Assessment	Month 13						Month 14			Month 15		
	Week 52 (±7 Days)						Week 56 (±7 Days)			Week 60 (±7 Days)		
	Subjects from Initial Treatment Phase			Subjects Previously Treated in Study HGT-HIT-094								
	IT Dosing Week[e] Main Site[f]			IT Dosing Week[e] Main Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]		
	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]
CSF Sample for Anti-idursulfase Antibody Testing		●[i]										
CSF Sample for Albumin Testing		●[i]										
CSF Sample for Idursulfase Concentration		●[i]										
Serum Albumin	●											
Idursulfase-IT Injection		●[e]			●[e,j]			●[e]			●[e]	
EQ-5D-5L	●											
HCUQ and CIQ	●			●								
HS-FOCUS	●			●								
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	●	●	●	●	●	●	●	●	●	●	●	●
Adverse Events	●	●	●	●	●	●	●	●	●	●	●	●

Abbreviations: CIQ=Caregiver Impact Questionnaire; CSF=cerebrospinal fluid; ECG=electrocardiogram; EQ-5D-5L=EuroQol-5D health status questionnaire; GAG=glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HS-FOCUS=Functional Outcomes for Clinical Understanding Scale; IDDD=intrathecal drug delivery device; Inj=injection; IT=intrathecal; MRI=magnetic resonance imaging; Tx=treatment

[a] Informed consent (and subject consent/assent, if applicable) must be obtained from the subject's parent(s)/legally authorized guardian(s) before conducting any study procedures. During Study SHP609-302, subjects who exceed the age of enrollment eligibility for Study HGT-HIT-094 and/or have reached the applicable legal age of consent to participate in a clinical study will be allowed to continue participation in Study SHP609-302 until the end of the study. When a subject 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 subject's parent(s) or legally authorized representative(s)will be asked to provide informed consent on behalf of the subject to allow for continued participation in the trial.

Appendix 2 Extended Treatment Phase Schedule of Events – Months 13-15 (Weeks 52-60)

Assessment	Month 13						Month 14			Month 15		
	Week 52 (±7 Days)						Week 56 (±7 Days)			Week 60 (±7 Days)		
	Subjects from Initial Treatment Phase			Subjects Previously Treated in Study HGT-HIT-094								
	IT Dosing Week[e] Main Site[f]			IT Dosing Week[e] Main Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]		
	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]

[b] Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as depicted in Appendix 23.

[c] General anesthesia or sedation may be required for injections of investigational product 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 and MRI will have to be performed with sedation/anesthesiology support.

[d] X-rays may be performed to check placement of the device, and as needed, throughout the study. An X-ray will be performed at the end of the study to verify that the IDDD is in the correct position.

[e] Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

[f] When a subject has received and tolerated a total of 12 monthly doses of intrathecal idursulfase-IT across studies HGT-HIT-094 and SHP609-302, the sponsor and principal investigator will consider the feasibility of transitioning the subject's monthly IT dosing to local sites to reduce the burden imposed by monthly travel.

[g] Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate. In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

[h] Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of visits at which serial blood sampling for pharmacokinetic evaluation is planned). The subject may need to be examined the following day.

[i] The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.

[j] The Visit Week 52 HGT-HIT-094 assessments must be completed prior to the first idursulfase-IT injection in this study.

Appendix 3 Extended Treatment Phase Schedule of Events – Months 16-20 (Weeks 64-80)

Assessment	Month 16			Month 17			Month 18			Month 19			Month 20		
	Week 64 (±7 days)			Week 68 (±7 days)			Week 72 (±7 days)			Week 76 (±7 days)			Week 80 (±7 days)		
	IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main Site[e]			IT Dosing Week[d] Main or Local Site[e]		
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]
Physical and Neurological Examination	•			•			•			•			•		
Height and Weight	•									•					
Hearing Assessment										•					
Neurodevelopmental Assessment[a]										•					
Vital Signs	•	•[g]		•	•[g]		•	•[g]		•	•[g]		•	•[g]	
Blood and Urine Sample for Clinical Laboratory Tests	•									•					
Urine GAG and Creatinine	•									•					
Serum sample for Anti-idursulfase Antibody Testing	•									•					
General Anesthesia[b]															
X-ray[c]															
CSF Sample for Standard Chemistry		•[h]			•[h]			•[h]			•[h]			•[h]	
CSF Sample for GAG Testing		•[h]									•[h]				
CSF Sample for Anti-idursulfase Antibody Testing		•[h]									•[h]				

Appendix 3 Extended Treatment Phase Schedule of Events – Months 16-20 (Weeks 64-80)

Assessment	Month 16			Month 17			Month 18			Month 19			Month 20		
	Week 64 (±7 days)			Week 68 (±7 days)			Week 72 (±7 days)			Week 76 (±7 days)			Week 80 (±7 days)		
	IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main Site[e]			IT Dosing Week[d] Main or Local Site[e]		
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]
CSF Sample for Albumin Testing		•[h]									•[h]				
CSF Sample for Idursulfase Concentration		•[h]									•[h]				
Serum Albumin	•									•					
Idursulfase-IT Injection		•[d]			•[d]			•[d]			•[d]			•[d]	
EQ-5D-5L										•					
HCUQ and CIQ										•					
HS-FOCUS										•					
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse Events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: CIQ=Caregiver Impact Questionnaire; CSF=cerebrospinal fluid; ECG=electrocardiogram; EQ-5D-5L=EuroQol-5D health status questionnaire; GAG=glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HS-FOCUS=Functional Outcomes for Clinical Understanding Scale; IDDD=intrathecal drug delivery device; Inj=injection; IT=intrathecal; IV=intravenous; PACU=post-anesthesia care unit; Tx=treatment

[a] Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as depicted in Appendix 23.

[b] General anesthesia or sedation may be required for injections of investigational product 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 will have to be performed with sedation/anesthesiology support.

[c] X-rays may be performed to check placement of the device, and as needed, throughout the study. An X-ray will be performed at the end of the study to verify that the IDDD is in the correct position.

[d] Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT

Appendix 3 Extended Treatment Phase Schedule of Events – Months 16-20 (Weeks 64-80)

	Month 16			Month 17			Month 18			Month 19			Month 20		
	Week 64 (±7 days)			Week 68 (±7 days)			Week 72 (±7 days)			Week 76 (±7 days)			Week 80 (±7 days)		
	IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main Site[e]			IT Dosing Week[d] Main or Local Site[e]		
Assessment	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]

administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

[e] When a subject has received and tolerated a total of 12 monthly doses of intrathecal idursulfase-IT across studies HGT-HIT-094 and SHP609-302, the sponsor and principal investigator will consider the feasibility of transitioning the subject's monthly IT dosing to local sites to reduce the burden imposed by monthly travel. However, visits including neurodevelopmental assessments must be conducted at the Main Site.

[f] Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate. In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

[g] Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of visits at which serial blood sampling for pharmacokinetic evaluation is planned). The subject may need to be examined the following day.

[h] The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.

Appendix 4 Extended Treatment Phase Schedule of Events – Months 21-25 (Weeks 84-100)

Assessment	Month 21			Month 22			Month 23			Month 24			Month 25		
	Week 84 (±7 Days)			Week 88 (±7 Days)			Week 92 (±7 Days)			Week 96 (±7 Days)			Week 100 (±7 Days)		
	IT Dosing Week[f] Main or Local Site[g]			IT Dosing Week[f] Main or Local Site[g]			IT Dosing Week[f] Main or Local Site[g]			IT Dosing Week[f] Main or Local Site[g]			IT Dosing Week[f] Main Site[g]		
	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]
Physical and Neurological Examination	•			•			•			•			•		
Height and Weight				•									•		
Head Circumference													•		
Hearing Assessment													•		
Neurodevelopmental Assessment[a]													•		
12-lead ECG[b]														•[b]	
Vital Signs	•	•[i]		•	•[i]		•	•[i]		•	•[i]		•	•[i]	
Blood and Urine Sample for Clinical Laboratory Tests				•									•		
Urine GAG and Creatinine				•									•		
Serum Sample for Anti-idursulfase Antibody Testing				•									•		
General Anesthesia[c]													•		
Brain MRI													•		
X-ray[d]															
CSF Sample for Standard Chemistry		•[j]			•[j]			•[j]			•[j]			•[j]	
CSF Sample for GAG Testing					•[j]									•[j]	

Appendix 4 Extended Treatment Phase Schedule of Events – Months 21-25 (Weeks 84-100)

Assessment	Month 21			Month 22			Month 23			Month 24			Month 25		
	Week 84 (±7 Days)			Week 88 (±7 Days)			Week 92 (±7 Days)			Week 96 (±7 Days)			Week 100 (±7 Days)		
	IT Dosing Week[f] Main or Local Site[g]			IT Dosing Week[f] Main or Local Site[g]			IT Dosing Week[f] Main or Local Site[g]			IT Dosing Week[f] Main or Local Site[g]			IT Dosing Week[f] Main Site[g]		
	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]
CSF Sample for Anti-idursulfase Antibody Testing					●[j]									●[j]	
CSF Sample for Albumin Testing					●[j]									●[j]	
CSF Sample for Idursulfase Concentration					●[j]									●[j]	
Serum Albumin				●									●		
Idursulfase-IT Injection		●[f]			●[f]			●[f]			●[f]			●[f]	
Serum Sample for PK[e]														●	
EQ-5D-5L													●		
HCUQ and CIQ													●		
HS-FOCUS													●		
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Adverse Events	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

Abbreviations: CIQ=Caregiver Impact Questionnaire; CSF=cerebrospinal fluid; ECG=electrocardiogram; EQ-5D-5L=EuroQol-5D health status questionnaire; GAG=glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HS-FOCUS=Functional Outcomes for Clinical Understanding Scale; IDDD=intrathecal drug delivery device; Inj=injection; IT=intrathecal; IV=intravenous; MRI=magnetic resonance imaging; PACU=post-anesthesia care unit; Tx=treatment

[a] Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as depicted in Appendix 23.

[b] The 12-lead ECG is to be performed within 4 hours after IT administration of study drug.

Appendix 4 Extended Treatment Phase Schedule of Events – Months 21-25 (Weeks 84-100)

Assessment	Month 21			Month 22			Month 23			Month 24			Month 25		
	Week 84 (±7 Days)			Week 88 (±7 Days)			Week 92 (±7 Days)			Week 96 (±7 Days)			Week 100 (±7 Days)		
	IT Dosing Week[f] Main or Local Site[g]			IT Dosing Week[f] Main or Local Site[g]			IT Dosing Week[f] Main or Local Site[g]			IT Dosing Week[f] Main or Local Site[g]			IT Dosing Week[f] Main Site[g]		
	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]	Pre-Tx Day 1[h]	IT Inj Day 2[h]	Days 3-7[h]

[c] General anesthesia or sedation may be required for injections of investigational product 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 and MRI will have to be performed with sedation/anesthesiology support.

[d] X-rays may be performed to check placement of the device, and as needed, throughout the study. An X-ray will be performed at the end of the study to verify that the IDDD is in the correct position.

[e] Serum samples for PK analysis will be collected within 30 minutes (±5 minutes) prior to intrathecal administration of idursulfase-IT and at 30 minutes (±5 minutes), 60 minutes (±5 minutes), 120 minutes (±5 minutes), 4 hours (±5 minutes), 6 hours (±5 minutes), 8 hours (±15 minutes), 12 hours (±15 minutes), 24 hours (±15 minutes), 30 hours (±15 minutes), 36 hours (±15 minutes) after the start of intrathecal administration.

[f] Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

[g] When a subject has received and tolerated a total of 12 monthly doses of intrathecal idursulfase-IT across studies HGT-HIT-094 and SHP609-302, the sponsor and principal investigator will consider the feasibility of transitioning the subject's monthly IT dosing to local sites to reduce the burden imposed by monthly travel.

[h] Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate. In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

[i] Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of visits at which serial blood sampling for pharmacokinetic evaluation is planned). The subject may need to be examined the following day.

[j] The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.

Appendix 5 Extended Treatment Phase Schedule of Events – Months 26-30 (Weeks 104–120)

Assessment	Month 26			Month 27			Month 28			Month 29			Month 30		
	Week 104 (±7 Days)			Week 108 (±7 Days)			Week 112 (±7 Days)			Week 116 (±7 Days)			Week 120 (±7 Days)		
	IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]		
	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]
Physical and Neurological Examination	●			●			●			●			●		
Height and Weight							●								
Vital Signs	●	●[f]		●	●[f]		●	●[f]		●	●[f]		●	●[f]	
Blood and Urine Sample for Clinical Laboratory Tests							●								
Urine GAG and Creatinine							●								
Serum Sample for Anti-idursulfase Antibody Testing							●								
X-ray[a]															
General Anesthesia[b]															
CSF Sample for Standard Chemistry		●[g]			●[g]			●[g]			●[g]			●[g]	
CSF Sample for GAG Testing								●[g]							
CSF Sample for Anti-idursulfase Antibody Testing								●[g]							
CSF Sample for Albumin Testing								●[g]							
CSF Sample for Idursulfase Concentration								●[g]							
Serum Albumin							●								
Idursulfase-IT Injection		●[c]			●[c]			●[c]			●[c]			●[c]	
EQ-5D-5L															
HCUQ and CIQ															

Appendix 5 Extended Treatment Phase Schedule of Events – Months 26-30 (Weeks 104–120)

Assessment	Month 26			Month 27			Month 28			Month 29			Month 30		
	Week 104 (±7 Days)			Week 108 (±7 Days)			Week 112 (±7 Days)			Week 116 (±7 Days)			Week 120 (±7 Days)		
	IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]		
	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]
HS-FOCUS															
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse Events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: CIQ=Caregiver Impact Questionnaire; CSF=cerebrospinal fluid; EQ-5D-5L=EuroQol-5D health status questionnaire; GAG=glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HS-FOCUS=Functional Outcomes for Clinical Understanding Scale; IDDD=intrathecal drug delivery device; Inj=injection; IT=intrathecal; IV=intravenous; PACU=post-anesthesia care unit; Tx=treatment

[a] X-rays may be performed to check placement of the device, and as needed, throughout the study. An X-ray will be performed at the end of the study to verify that the IDDD is in the correct position.

[b] General anesthesia or sedation may be required for injections of investigational product 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 will have to be performed with sedation/anesthesiology support.

[c] Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

[d] When a subject has received and tolerated a total of 12 monthly doses of intrathecal idursulfase-IT across studies HGT-HIT-094 and SHP609-302, the sponsor and principal investigator will consider the feasibility of transitioning the subject's monthly IT dosing to local sites to reduce the burden imposed by monthly travel.

[e] Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate. In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

[f] Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center)

Appendix 5 Extended Treatment Phase Schedule of Events – Months 26-30 (Weeks 104–120)

Assessment	Month 26			Month 27			Month 28			Month 29			Month 30		
	Week 104 (±7 Days)			Week 108 (±7 Days)			Week 112 (±7 Days)			Week 116 (±7 Days)			Week 120 (±7 Days)		
	IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]		
	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]

for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of visits at which serial blood sampling for pharmacokinetic evaluation is planned). The subject may need to be examined the following day.

[g] The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.

Appendix 6 Extended Treatment Phase Schedule of Events – Months 31-34 (Weeks 124-136)

Assessment	Month 31			Month 32			Month 33			Month 34		
	Week 124 (±7 Days)			Week 128 (±7 Days)			Week 132 (±7 Days)			Weeks 136 (±7 Days)		
	IT Dosing Week[d] Main Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]		
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]
Physical and Neurological Examination	•			•			•			•		
Height and Weight	•									•		
Head Circumference												
Hearing Assessment	•											
Neurodevelopmental Assessment[a]	•											
Vital Signs	•	•[g]		•[g]	•[g]		•[g]	•[g]		•	•[g]	
Blood and Urine Sample for Clinical Laboratory Tests	•									•		
Urine GAG and Creatinine	•									•		
Serum Sample for Anti-Idursulfase Antibody Testing	•									•		
General Anesthesia[b]												
X-ray[c]												
CSF Sample for Standard Chemistry		•[h]			•[h]			•[h]			•[h]	
CSF Sample for GAG Testing		•[h]									•[h]	
CSF Sample for Anti-idursulfase Antibody Testing		•[h]									•[h]	
CSF Sample for Albumin Testing		•[h]									•[h]	

Appendix 6 Extended Treatment Phase Schedule of Events – Months 31-34 (Weeks 124-136)

Assessment	Month 31			Month 32			Month 33			Month 34		
	Week 124 (±7 Days)			Week 128 (±7 Days)			Week 132 (±7 Days)			Weeks 136 (±7 Days)		
	IT Dosing Week[d] Main Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]		
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]
CSF Sample for Idursulfase Concentration		●[h]									●[h]	
Serum Albumin	●									●		
Idursulfase-IT Injection		●[d]			●[d]			●[d]			●[d]	
EQ-5D-5L	●											
HCUQ and CIQ	●											
HS-FOCUS	●											
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	●	●	●	●	●	●	●	●	●	●	●	●
Adverse Events	●	●	●	●	●	●	●	●	●	●	●	●

Abbreviations: CIQ=Caregiver Impact Questionnaire; CSF=cerebrospinal fluid; ECG=electrocardiogram; EQ-5D-5L=EuroQol-5D health status questionnaire; GAG=glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HS-FOCUS=Functional Outcomes for Clinical Understanding Scale; IDDD=intrathecal drug delivery device; Inj=injection; IT=intrathecal; IV=intravenous; PACU=post-anesthesia care unit; Tx=treatment

[a] Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as depicted in Appendix 23.

[b] General anesthesia or sedation may be required for injections of investigational product 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 will have to be performed with sedation/anesthesiology support.

[c] X-rays may be performed to check placement of the device, and as needed, throughout the study. An X-ray will be performed at the end of the study to verify that the IDDD is in the correct position.

[d] Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

[e] When a subject has received and tolerated a total of 12 monthly doses of intrathecal idursulfase-IT across studies HGT-HIT-094 and SHP609-302, the sponsor and principal investigator will consider the feasibility of transitioning the subject's monthly IT dosing to local sites to reduce the burden imposed by

Appendix 6 Extended Treatment Phase Schedule of Events – Months 31-34 (Weeks 124-136)

Assessment	Month 31			Month 32			Month 33			Month 34		
	Week 124 (±7 Days)			Week 128 (±7 Days)			Week 132 (±7 Days)			Weeks 136 (±7 Days)		
	IT Dosing Week[d] Main Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]		
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]

monthly travel. However, visits including neurodevelopmental assessments must be conducted at the Main Site.

[f] Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate. In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

[g] Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of visits at which serial blood sampling for pharmacokinetic evaluation is planned). The subject may need to be examined the following day.

[h] The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.

Appendix 7 Extended Treatment Phase Schedule of Events – Months 35-37 (Weeks 140-148)

Assessment	Month 35			Month 36			Month 37		
	Week 140 (±7 Days)			Week 144 (±7 Days)			Week 148 (±7 Days)		
	IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main Site[f]		
	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]
Physical and Neurological Examination	●			●			●		
Height and Weight							●		
Head Circumference							●		
Hearing Assessment							●		
Neurodevelopmental Assessment[a]							●		
12-lead ECG[b]								●[b]	
Vital Signs	●	●[h]		●	●[h]		●	●[h]	
Blood and Urine Sample for Clinical Laboratory Tests							●		
Urine GAG and Creatinine							●		
Serum Sample for Anti-idursulfase Antibody Testing							●		
General Anesthesia[c]							●		
Brain MRI							●		
X-ray[d]									
CSF Sample for Standard Chemistry		●[i]			●[i]			●[i]	
CSF Sample for GAG Testing								●[i]	
CSF Sample for Anti-idursulfase Antibody Testing								●[i]	
CSF Sample for Albumin Testing								●[i]	
CSF Sample for Idursulfase Concentration								●[i]	
Serum Albumin								●	

Appendix 7 Extended Treatment Phase Schedule of Events – Months 35-37 (Weeks 140-148)

Assessment	Month 35			Month 36			Month 37		
	Week 140 (±7 Days)			Week 144 (±7 Days)			Week 148 (±7 Days)		
	IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main Site[f]		
	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]
Idursulfase-IT Injection		●[e]			●[e]			●[e]	
EQ-5D-5L							●		
HCUQ and CIQ							●		
HS-FOCUS							●		
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	●	●	●	●	●	●	●	●	●
Adverse Events	●	●	●	●	●	●	●	●	●

Abbreviations: CIQ=Caregiver Impact Questionnaire; CSF=cerebrospinal fluid; ECG=electrocardiogram; EOS=end of study; EQ-5D-5L=EuroQol-5D health status questionnaire; GAG=glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HS-FOCUS=Functional Outcomes for Clinical Understanding Scale; IDDD=intrathecal drug delivery device; Inj=injection; IT=intrathecal; IV=intravenous; MRI=magnetic resonance imaging; PACU=post-anesthesia care setting; Tx=treatment

[a] Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as depicted in Appendix 23.

[b] The 12-lead ECG is to be performed within 4 hours after IT administration of study drug.

[c] General anesthesia or sedation may be required for injections of investigational product 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 and MRI will have to be performed with sedation/anesthesiology support.

[d] X-rays may be performed to check placement of the device, and as needed, throughout the study. An X-ray will be performed at the end of the study to verify that the IDDD is in the correct position.

[e] Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

[f] When a subject has received and tolerated a total of 12 monthly doses of intrathecal idursulfase-IT across studies HGT-HIT-094 and SHP609-302, the sponsor and principal investigator will consider the feasibility of transitioning the subject's monthly IT dosing to local sites to reduce the burden imposed by monthly travel. However, visits including neurodevelopmental assessments must be conducted at the Main Site.

Appendix 7 Extended Treatment Phase Schedule of Events – Months 35-37 (Weeks 140-148)

Assessment	Month 35			Month 36			Month 37		
	Week 140 (±7 Days)			Week 144 (±7 Days)			Week 148 (±7 Days)		
	IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main Site[f]		
	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]

[g] Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate. In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

[h] Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of visits at which serial blood sampling for pharmacokinetic evaluation is planned). The subject may need to be examined the following day.

[i] The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.

Appendix 8 Extended Treatment Phase Schedule of Events – Months 38-42 (Weeks 152-168)

Assessment	Month 38			Month 39			Month 40			Month 41			Month 42		
	Week 152 (±7 Days)			Week 156 (±7 Days)			Week 160 (±7 Days)			Week 164 (±7 Days)			Week 168 (±7 Days)		
	IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]		
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]
Physical and Neurological Examination	•			•			•			•			•		
Height and Weight							•								
Hearing Assessment															
Neurodevelopmental Assessment[a]															
Vital Signs	•	•[g]		•	•[g]		•	•[g]		•	•[g]		•	•[g]	
Blood and Urine Sample for Clinical Laboratory Tests							•								
Urine GAG and Creatinine							•								
Serum Sample for Anti-idursulfase Antibody Testing							•								
General Anesthesia[b]															
X-ray[c]															
CSF Sample for Standard Chemistry		•[h]			•[h]			•[h]			•[h]			•[h]	
CSF Sample for GAG Testing								•[h]							
CSF Sample for Anti-idursulfase Antibody Testing								•[h]							

Appendix 8 Extended Treatment Phase Schedule of Events – Months 38-42 (Weeks 152-168)

Assessment	Month 38			Month 39			Month 40			Month 41			Month 42		
	Week 152 (±7 Days)			Week 156 (±7 Days)			Week 160 (±7 Days)			Week 164 (±7 Days)			Week 168 (±7 Days)		
	IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]		
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]
CSF Sample for Albumin Testing								•[h]							
CSF Sample for Idursulfase Concentration								•[h]							
Serum Albumin							•								
Idursulfase-IT Injection		•[d]			•[d]			•[d]			•[d]			•[d]	
EQ-5D-5L															
HCUQ and CIQ															
HS-FOCUS															
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse Events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: CIQ=Caregiver Impact Questionnaire; CSF=cerebrospinal fluid; ECG=electrocardiogram; EQ-5D-5L=EuroQol-5D health status questionnaire; GAG=glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HS-FOCUS=Functional Outcomes for Clinical Understanding Scale; IDDD=intrathecal drug delivery device; Inj=injection; IT=intrathecal; IV=intravenous; PACU=post-anesthesia care unit; Tx=treatment

[a] Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as depicted in Appendix 23.

[b] General anesthesia or sedation may be required for injections of investigational product 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 will have to be performed with sedation/anesthesiology support.

[c] X-rays may be performed to check placement of the device, and as needed, throughout the study. An X-ray will be performed at the end of the study to verify that the IDDD is in the correct position.

[d] Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after

Appendix 8 Extended Treatment Phase Schedule of Events – Months 38-42 (Weeks 152-168)

	Month 38			Month 39			Month 40			Month 41			Month 42		
	Week 152 (±7 Days)			Week 156 (±7 Days)			Week 160 (±7 Days)			Week 164 (±7 Days)			Week 168 (±7 Days)		
	IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]		
Assessment	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]

IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

[e] When a subject has received and tolerated a total of 12 monthly doses of intrathecal idursulfase-IT across studies HGT-HIT-094 and SHP609-302, the sponsor and principal investigator will consider the feasibility of transitioning the subject's monthly IT dosing to local sites to reduce the burden imposed by monthly travel. However, visits including neurodevelopmental assessments must be conducted at the Main Site.

[f] Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate. In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

[g] Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of visits at which serial blood sampling for pharmacokinetic evaluation is planned). The subject may need to be examined the following day.

[h] The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.

Appendix 9 Extended Treatment Phase Schedule of Events – Months 43-47 (Weeks 172-188)

Assessment	Month 43			Month 44			Month 45			Month 46			Month 47		
	Week 172 (±7 Days)			Week 176 (±7 Days)			Week 180 (±7 Days)			Week 184 (±7 Days)			Week 188 (±7 Days)		
	IT Dosing Week[d] Main Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]		
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]
Physical and Neurological Examination	•			•			•			•			•		
Height and Weight	•									•					
Hearing Assessment	•														
Neurodevelopmental Assessment[a]	•														
Vital Signs	•	•[g]		•	•[g]		•	•[g]		•	•[g]		•	•[g]	
Blood and Urine Sample for Clinical Laboratory Tests	•									•					
Urine GAG and Creatinine	•									•					
Serum Sample for Anti-idursulfase Antibody Testing	•									•					
General Anesthesia[b]															
X-ray[c]															
CSF Sample for Standard Chemistry		•[h]			•[h]			•[h]			•[h]			•[h]	
CSF Sample for GAG Testing		•[h]									•[h]				
CSF Sample for Anti-idursulfase Antibody Testing		•[h]									•[h]				

Appendix 9 Extended Treatment Phase Schedule of Events – Months 43-47 (Weeks 172-188)

Assessment	Month 43			Month 44			Month 45			Month 46			Month 47		
	Week 172 (±7 Days)			Week 176 (±7 Days)			Week 180 (±7 Days)			Week 184 (±7 Days)			Week 188 (±7 Days)		
	IT Dosing Week[d] Main Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]		
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]
CSF Sample for Albumin Testing		•[h]									•[h]				
CSF Sample for Idursulfase Concentration		•[h]									•[h]				
Serum Albumin	•									•					
Idursulfase-IT Injection		•[d]			•[d]			•[d]			•[d]			•[d]	
EQ-5D-5L	•														
HCUQ and CIQ	•														
HS-FOCUS	•														
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse Events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: CIQ=Caregiver Impact Questionnaire; CSF=cerebrospinal fluid; ECG=electrocardiogram; EQ-5D-5L=EuroQol-5D health status questionnaire; GAG=glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HS-FOCUS=Functional Outcomes for Clinical Understanding Scale; IDDD=intrathecal drug delivery device; Inj=injection; IT=intrathecal; IV=intravenous; PACU=post-anesthesia care unit; Tx=treatment

[a] Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as depicted in Appendix 23.

[b] General anesthesia or sedation may be required for injections of investigational product 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 will have to be performed with sedation/anesthesiology support.

[c] X-rays may be performed to check placement of the device, and as needed, throughout the study. An X-ray will be performed at the end of the study to verify that the IDDD is in the correct position.

[d] Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after

Appendix 9 Extended Treatment Phase Schedule of Events – Months 43-47 (Weeks 172-188)

Assessment	Month 43			Month 44			Month 45			Month 46			Month 47		
	Week 172 (±7 Days)			Week 176 (±7 Days)			Week 180 (±7 Days)			Week 184 (±7 Days)			Week 188 (±7 Days)		
	IT Dosing Week[d] Main Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]		
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]

IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

[e] When a subject has received and tolerated a total of 12 monthly doses of intrathecal idursulfase-IT across studies HGT-HIT-094 and SHP609-302, the sponsor and principal investigator will consider the feasibility of transitioning the subject's monthly IT dosing to local sites to reduce the burden imposed by monthly travel. However, visits including neurodevelopmental assessments must be conducted at the Main Site.

[f] Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate. In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

[g] Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of visits at which serial blood sampling for pharmacokinetic evaluation is planned). The subject may need to be examined the following day.

[h] The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.

Appendix 10 Extended Treatment Phase Schedule of Events – Months 48-112 (Weeks 192-448)

Assessment	Month 48			Month 49, 61, 73, 85, 97, 109			Month 50, 62, 74, 86, 98, 110			Month 51, 63, 75, 87, 99, 111			Month 52, 64, 76, 88, 100, 112		
	Week 192 (±7 Days)			Week 196, 244, 292, 340, 388, 436 (±7 Days)			Week 200, 248, 296, 344, 392, 440 (±7 Days)			Week 204, 252, 300, 348, 396, 444 (±7 Days)			Week 208, 256, 304, 352, 400, 448 (±7 Days)		
	IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]		
	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]
Physical and Neurological Examination	•			•			•			•			•		
Height and Weight				•									•		
Head Circumference				•											
Hearing Assessment				•											
Neurodevelopmental Assessment[a]				•											
12-lead ECG[b]					•[b]										
Vital Signs	•	•[h]		•	•[h]		•	•[h]		•	•[h]		•	•[h]	
Blood and Urine Sample for Clinical Laboratory Tests				•									•		
Urine GAG and Creatinine				•									•		
Serum Sample for Anti-idursulfase Antibody Testing				•									•		
General Anesthesia[c]				•											
Brain MRI				•											
X-ray[d]															
CSF Sample for Standard Chemistry		•[i]			•[i]			•[i]			•[i]			•[i]	
CSF Sample for GAG					•[i]									•[i]	

Appendix 10 Extended Treatment Phase Schedule of Events – Months 48-112 (Weeks 192-448)

Assessment	Month 48			Month 49, 61, 73, 85, 97, 109			Month 50, 62, 74, 86, 98, 110			Month 51, 63, 75, 87, 99, 111			Month 52, 64, 76, 88, 100, 112		
	Week 192 (±7 Days)			Week 196, 244, 292, 340, 388, 436 (±7 Days)			Week 200, 248, 296, 344, 392, 440 (±7 Days)			Week 204, 252, 300, 348, 396, 444 (±7 Days)			Week 208, 256, 304, 352, 400, 448 (±7 Days)		
	IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]		
	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]
Testing															
CSF Sample for Anti-idursulfase Antibody Testing					•[i]									•[i]	
CSF Sample for Albumin Testing					•[i]									•[i]	
CSF Sample for Idursulfase Concentration					•[i]									•[i]	
Serum Albumin				•									•		
Idursulfase-IT Injection		•[e]			•[e]			•[e]			•[e]			•[e]	
EQ-5D-5L				•											
HCUQ and CIQ				•											
HS-FOCUS				•											
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse Events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: CSF=cerebrospinal fluid; ECG=electrocardiogram; EQ-5D-5L=EuroQol-5D health status questionnaire; GAG=glycosaminoglycan; HS-FOCUS=Functional Outcomes for Clinical Understanding Scale; IDDD=intrathecal drug delivery device; Inj=injection; IT=intrathecal; IV=intravenous; MRI=magnetic resonance imaging; PACU=post-anesthesia care unit; Tx=treatment

[a] Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as depicted in Appendix 23.

Appendix 10 Extended Treatment Phase Schedule of Events – Months 48-112 (Weeks 192-448)

Assessment	Month 48			Month 49, 61, 73, 85, 97, 109			Month 50, 62, 74, 86, 98, 110			Month 51, 63, 75, 87, 99, 111			Month 52, 64, 76, 88, 100, 112		
	Week 192 (±7 Days)			Week 196, 244, 292, 340, 388, 436 (±7 Days)			Week 200, 248, 296, 344, 392, 440 (±7 Days)			Week 204, 252, 300, 348, 396, 444 (±7 Days)			Week 208, 256, 304, 352, 400, 448 (±7 Days)		
	IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]		
	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]	Pre-Tx Day 1[g]	IT Inj Day 2[g]	Days 3-7[g]

[b] The 12-lead ECG is to be performed within 4 hours after IT administration of study drug.

[c] General anesthesia or sedation may be required for injections of investigational product 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 and MRI will have to be performed with sedation/anesthesiology support.

[d] X-rays may be performed to check placement of the device, and as needed, throughout the study. An X-ray will be performed at the end of the study to verify that the IDDD is in the correct position.

[e] Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

[f] When a subject has received and tolerated a total of 12 monthly doses of intrathecal idursulfase-IT across studies HGT-HIT-094 and SHP609-302, the sponsor and principal investigator will consider the feasibility of transitioning the subject's monthly IT dosing to local sites to reduce the burden imposed by monthly travel.

[g] Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate. In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

[h] Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of visits at which serial blood sampling for pharmacokinetic evaluation is planned). The subject may need to be examined the following day.

[i] The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.

Appendix 11 Extended Treatment Phase Schedule of Events – Months 53-117 (Weeks 212-468)

Assessment	Month 53, 65, 77, 89, 101, 113			Month 54, 66, 78, 90, 102, 114			Month 55, 67, 79, 91, 103, 115			Month 56, 68, 80, 92, 104, 116			Month 57, 69, 81, 93, 105, 117		
	Week 212, 260, 308, 356, 404, 452 (±7 Days)			Week 216, 264, 312, 360, 408, 456 (±7 Days)			Week 220, 268, 316, 364, 412, 460 (±7 Days)			Week 224, 272, 320, 368, 416, 464 (±7 Days)			Week 228, 276, 324, 372, 420, 468 (±7 Days)		
	IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]		
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]
Physical and Neurological Examination	•			•			•			•			•		
Height and Weight							•								
Hearing Assessment							•								
Neurodevelopmental Assessment[a]							•								
Vital Signs	•	•[g]		•	•[g]		•	•[g]		•	•[g]		•	•[g]	
Blood and Urine Sample for Clinical Laboratory Tests							•								
Urine GAG and Creatinine							•								
Serum Sample for Anti-idursulfase Antibody Testing							•								
General Anesthesia[b]															
X-ray[c]															
CSF Sample for Standard Chemistry		•[h]			•[h]			•[h]			•[h]			•[h]	
CSF Sample for GAG Testing								•[h]							
CSF Sample for Anti-idursulfase								•[h]							

Appendix 11 Extended Treatment Phase Schedule of Events – Months 53-117 (Weeks 212-468)

Assessment	Month 53, 65, 77, 89, 101, 113			Month 54, 66, 78, 90, 102, 114			Month 55, 67, 79, 91, 103, 115			Month 56, 68, 80, 92, 104, 116			Month 57, 69, 81, 93, 105, 117		
	Week 212, 260, 308, 356, 404, 452 (±7 Days)			Week 216, 264, 312, 360, 408, 456 (±7 Days)			Week 220, 268, 316, 364, 412, 460 (±7 Days)			Week 224, 272, 320, 368, 416, 464 (±7 Days)			Week 228, 276, 324, 372, 420, 468 (±7 Days)		
	IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]		
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]
Antibody Testing															
CSF Sample for Albumin Testing								•[h]							
CSF Sample for Idursulfase Concentration								•[h]							
Serum Albumin							•								
Idursulfase-IT Injection		•[d]			•[d]			•[d]			•[d]			•[d]	
EQ-5D-5L							•								
HCUQ and CIQ							•								
HS-FOCUS							•								
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse Events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: CIQ=Caregiver Impact Questionnaire; CSF=cerebrospinal fluid; ECG=electrocardiogram; EQ-5D-5L=EuroQol-5D health status questionnaire; GAG=glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HS-FOCUS=Functional Outcomes for Clinical Understanding Scale; IDDD=intrathecal drug delivery device; Inj=injection; IT=intrathecal; IV=intravenous; PACU=post-anesthesia care unit; Tx=treatment

[a] Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as depicted in Appendix 23.

[b] General anesthesia or sedation may be required for injections of investigational product 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 will have to be performed with

Appendix 11 Extended Treatment Phase Schedule of Events – Months 53-117 (Weeks 212-468)

Assessment	Month 53, 65, 77, 89, 101, 113			Month 54, 66, 78, 90, 102, 114			Month 55, 67, 79, 91, 103, 115			Month 56, 68, 80, 92, 104, 116			Month 57, 69, 81, 93, 105, 117		
	Week 212, 260, 308, 356, 404, 452 (±7 Days)			Week 216, 264, 312, 360, 408, 456 (±7 Days)			Week 220, 268, 316, 364, 412, 460 (±7 Days)			Week 224, 272, 320, 368, 416, 464 (±7 Days)			Week 228, 276, 324, 372, 420, 468 (±7 Days)		
	IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main Site[e]			IT Dosing Week[d] Main or Local Site[e]			IT Dosing Week[d] Main or Local Site[e]		
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]

sedation/anesthesiology support.

[c] X-rays may be performed to check placement of the device, and as needed, throughout the study. An X-ray will be performed at the end of the study to verify that the IDDD is in the correct position.

[d] Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

[e] When a subject has received and tolerated a total of 12 monthly doses of intrathecal idursulfase-IT across studies HGT-HIT-094 and SHP609-302, the sponsor and principal investigator will consider the feasibility of transitioning the subject's monthly IT dosing to local sites to reduce the burden imposed by monthly travel. However, visits including neurodevelopmental assessments must be conducted at the Main Site.

[f] Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate. In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

[g] Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of visits at which serial blood sampling for pharmacokinetic evaluation is planned). The subject may need to be examined the following day.

[h] The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.

Appendix 12 Extended Treatment Phase Schedule of Events – Month 58 (Week 232) – End-of-study (Month 121, Week 484)

Assessment	Month 58, 70, 82, 94, 106, 118			Month 59, 71, 83, 95, 107, 119			Month 60, 72, 84, 96, 108, 120			EOS Month 121
	Week 232, 280, 328, 376, 424, 472 (±7 Days)			Week 236, 284, 332, 380, 428, 476 (±7 Days)			Week 240, 288, 336, 384, 432, 480 (±7 Days)			Week 484 (±7 Days) (Main Site)
	IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]			
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Day 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	
Physical and Neurological Examination	•			•			•			•
Height and Weight	•									•
Head Circumference										•
Hearing Assessment										•
Neurodevelopmental Assessment[a]										•
12-lead ECG[b]										•[b]
Vital Signs	•	•[h]		•	•[h]		•	•[h]		•
Blood and Urine Sample for Clinical Laboratory Tests	•									•
Urine GAG and Creatinine	•									•
Serum Sample for Anti-idursulfase Antibody Testing	•									•
General Anesthesia[c]										
Brain MRI										•
X-ray[d]										•
CSF Sample for Standard Chemistry		•[i]			•[i]			•[i]		•
CSF Sample for GAG Testing		•[i]								•
CSF Sample for Anti-idursulfase Antibody Testing		•[i]								•
CSF Sample for Albumin Testing		•[i]								•
CSF Sample for Idursulfase Concentration		•[i]								•

Appendix 12 Extended Treatment Phase Schedule of Events – Month 58 (Week 232) – End-of-study (Month 121, Week 484)

Assessment	Month 58, 70, 82, 94, 106, 118			Month 59, 71, 83, 95, 107, 119			Month 60, 72, 84, 96, 108, 120			EOS Month 121
	Week 232, 280, 328, 376, 424, 472 (±7 Days)			Week 236, 284, 332, 380, 428, 476 (±7 Days)			Week 240, 288, 336, 384, 432, 480 (±7 Days)			Week 484 (±7 Days) (Main Site)
	IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]			
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Day 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	
Serum Albumin	•									•
Idursulfase-IT Injection		•[e]			•[e]			•[e]		
EQ-5D-5L										•
HCUQ and CIQ										•
HS-FOCUS										•
Concomitant Medications, Therapies/Interventions, Medical/Surgical Procedures	•	•	•	•	•	•	•	•	•	•
Adverse Events	•	•	•	•	•	•	•	•	•	•

Abbreviations: CIQ=Caregiver Impact Questionnaire; CSF=cerebrospinal fluid; ECG=electrocardiogram; EOS=end of study; EQ-5D-5L=EuroQol-5D health status questionnaire; GAG=glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HS-FOCUS=Functional Outcomes for Clinical Understanding Scale; IDDD=intrathecal drug delivery device; Inj=injection; IT=intrathecal; IV=intravenous; MRI=magnetic resonance imaging; PACU=post-anesthesia care unit; Tx=treatment

[a] Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as depicted in Appendix 23.

[b] The 12-lead ECG is to be performed within 4 hours after IT administration of study drug.

[c] General anesthesia or sedation may be required for injections of investigational product 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 and MRI will have to be performed with sedation/anesthesiology support.

[d] X-rays may be performed to check placement of the device, and as needed, throughout the study. An X-ray will be performed at the end of the study to verify that the IDDD is in the correct position.

[e] Note that, on IT Dosing Weeks during the Initial Treatment Phase, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.

[f] When a subject has received and tolerated a total of 12 monthly doses of intrathecal idursulfase-IT across studies HGT-HIT-094 and SHP609-302, the

Appendix 12 Extended Treatment Phase Schedule of Events – Month 58 (Week 232) – End-of-study (Month 121, Week 484)

Assessment	Month 58, 70, 82, 94, 106, 118			Month 59, 71, 83, 95, 107, 119			Month 60, 72, 84, 96, 108, 120			EOS Month 121
	Week 232, 280, 328, 376, 424, 472 (±7 Days)			Week 236, 284, 332, 380, 428, 476 (±7 Days)			Week 240, 288, 336, 384, 432, 480 (±7 Days)			Week 484 (±7 Days) (Main Site)
	IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]			IT Dosing Week[e] Main or Local Site[f]			
	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Day 3-7[f]	Pre-Tx Day 1[f]	IT Inj Day 2[f]	Days 3-7[f]	

sponsor and principal investigator will consider the feasibility of transitioning the subject's monthly IT dosing to local sites to reduce the burden imposed by monthly travel. However, visits including neurodevelopmental assessments must be conducted at the Main Site.

[g] Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the subject can arrive at the study site early in the day and if the investigator deems this clinically appropriate. In the absence of any safety concerns, subjects may complete the safety follow-up visit on the same day as IT administration prior to discharge.

[h] Subjects will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the investigator, subjects may leave the hospital setting (with exception of visits at which serial blood sampling for pharmacokinetic evaluation is planned). The subject may need to be examined the following day.

[i] The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.

Appendix 13 Pharmacokinetic Sample Collection for Same-Day Investigational Product Administration with Elaprase Infusion

Assessment	Monthly Visits 13-120[a]		
	IT Dosing Week: Main Site only		
	Pre-Tx Day 1	IT Inj Day	Days 3-7
Serum Sample for PK[b,c]		•	
Same-day Elaprase IV infusion and idursulfase-IT administration[c]		•	

Abbreviations: Inj=injection; IT=intrathecal; IV=intravenous; PK=pharmacokinetic; Tx=treatment

[a] Same-day administration of the IV Elaprase infusion and idursulfase-IT can only occur during the Extended Treatment Phase, ie Months 13-120.

[b] Samples for PK assessments are to be collected on the occasion of the first same-day administration. This pharmacokinetic sampling need only be scheduled once, and may occur at Month 25 or at an alternative visit during the Extended Treatment Phase.

[c] Serum samples for PK analysis will be collected within 30 minutes (±5 minutes) prior to intrathecal administration of idursulfase-IT, within 30 minutes prior to the start of Elaprase infusion, and at 30 minutes (±5 minutes), 60 minutes (±5 minutes), 120 minutes (±5 minutes), 3 hours (±5 minutes; ie, the end of Elaprase infusion), 4 hours (±5 minutes), 6 hours (±5 minutes), 8 hours (±15 minutes), 12 hours (±15 minutes), 24 hours (±15 minutes), 30 hours (±15 minutes), 36 hours (±15 minutes) after the start of Elaprase Infusion.

Appendix 14 Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Initial Treatment Phase (Subjects Who Did Not Receive Intrathecal Idursulfase-IT in Study HGT-HIT-094)

Procedure	Baseline		IDDD Implantation Period			Initial Treatment Phase											TOTAL
	Months																
	-1	0	1	1	1	2	3	4	5	6	7	8	9	10	11	12	
	Weeks																
	-1	0	2 - Pre-surgery	2- Surgery	2 - Post-op	4	8	12	16	20	24	28	32	36	40	48	
BLOOD (mL)																	
Hematology			1.2			1.2			1.2			1.2			1.2		**102.3**
Serum Chemistry			2.5			2.5			2.5			2.5			2.5		
Anti-idursulfase Antibody Testing						4			4			4			4		
Serum Sample for PK						33										33	
Coagulation			1.8														
Total Blood Volume	**0**	**0**	**5.5**	**0**	**0**	**40.7**	**0**	**0**	**7.7**	**0**	**0**	**7.7**	**0**	**0**	**7.7**	**33**	

Abbreviations: IDDD=intrathecal drug delivery device; mL=milliliter; PK=pharmacokinetics

Appendix 15 Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Extended Treatment Phase (Months 13-27 - Weeks 52-108)

Procedure	Extended Treatment Phase																TOTAL
	Months																
	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	13-120[a]	
	Weeks																
	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	52-480[a]	
BLOOD (mL)																	
Hematology	1.2			1.2			1.2			1.2			1.2				**108.5**
Serum Chemistry	2.5			2.5			2.5			2.5			2.5				
Anti-idursulfase Antibody Testing	4			4			4			4			4				
Serum Sample for PK													33			37	
Coagulation																	
Total Blood Volume	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**40.7**	**0.0**	**0**	**37**	

Abbreviations: IDDD=intrathecal drug delivery device; mL=milliliter; PK=pharmacokinetics

- To be collected only once at any study visit during Months 13-120 (Weeks 52-480).

Appendix 16 Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Extended Treatment Phase (Months 28-42 - Weeks 112-168)

Procedure	Extended Treatment Phase															TOTAL
	Months															
	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	
	Weeks															
	112	116	120	124	128	132	136	140	144	148	152	156	160	164	168	
BLOOD (mL)																
Hematology	1.2			1.2			1.2			1.2			1.2			**38.5**
Serum Chemistry	2.5			2.5			2.5			2.5			2.5			
Anti-idursulfase Antibody Testing	4			4			4			4			4			
Serum Sample for PK																
Coagulation																
Total Blood Volume	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0.0**	**0**	

Abbreviations: IDDD=intrathecal drug delivery device; mL=milliliter; PK=pharmacokinetics

Appendix 17 Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Extended Treatment Phase (Months 43-60 - Weeks 172-240

Procedure	Extended Treatment Phase																		TOTAL
	Months																		
	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	
	Weeks																		
	172	176	180	184	188	192	196	200	204	208	212	216	220	224	228	232	236	240	
BLOOD (mL)																			
Hematology	1.2			1.2			1.2			1.2			1.2			1.2			**46.2**
Serum Chemistry	2.5			2.5			2.5			2.5			2.5			2.5			
Anti-idursulfase Antibody Testing	4			4			4			4			4			4			
Serum Sample for PK																			
Coagulation																			
Total Blood Volume	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0.0**	**0.0**	**7.7**	**0.0**	**0.0**	

Abbreviations: EOS=End of Study; IDDD=intrathecal drug delivery device; mL=milliliter; PK=pharmacokinetics

Appendix 18 Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Extended Treatment Phase (Months 61-72 - Weeks 244-288

Procedure	Extended Treatment Phase												TOTAL
	Months												
	61	62	63	64	65	66	67	68	69	70	71	72	
	244	248	252	256	260	264	268	272	276	280	284	288	
BLOOD (mL)													
Hematology	1.2			1.2			1.2			1.2			30.8
Serum Chemistry	2.5			2.5			2.5			2.5			
Anti-idursulfase Antibody Testing	4			4			4			4			
Serum Sample for PK													
Coagulation													
Total Blood Volume	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	

Abbreviations: IDDD=intrathecal drug delivery device; mL=milliliter; PK=pharmacokinetics

Appendix 19 Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Extended Treatment Phase (Months 73-87 - Weeks 292-348

Procedure	Extended Treatment Phase															TOTAL
	Months															
	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	
	Weeks															
	292	296	300	304	308	312	316	320	324	328	332	336	340	344	348	
BLOOD (mL)																
Hematology	1.2			1.2			1.2			1.2			1.2			**38.5**
Serum Chemistry	2.5			2.5			2.5			2.5			2.5			
Anti-idursulfase Antibody Testing	4			4			4			4			4			
Serum Sample for PK																
Coagulation																
Total Blood Volume	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0.0**	**0**	

Abbreviations: IDDD=intrathecal drug delivery device; mL=milliliter; PK=pharmacokinetics

Appendix 20 Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Extended Treatment Phase (Months 88-102 - Weeks 352-408

Procedure	Extended Treatment Phase															TOTAL
	Months															
	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	
	Weeks															
	352	356	360	364	368	372	376	380	384	388	392	396	400	404	408	
BLOOD (mL)																
Hematology	1.2			1.2			1.2			1.2			1.2			**38.5**
Serum Chemistry	2.5			2.5			2.5			2.5			2.5			
Anti-idursulfase Antibody Testing	4			4			4			4			4			
Serum Sample for PK																
Coagulation																
Total Blood Volume	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0.0**	**0**	

Abbreviations: IDDD=intrathecal drug delivery device; mL=milliliter; PK=pharmacokinetics

Appendix 21 Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Extended Treatment Phase (Months 103-121 - Weeks 412-484

Procedure	Extended Treatment Phase																		EOS	TOTAL
	Months																			
	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120		
	Weeks																			
	412	416	420	424	428	432	436	440	444	448	452	456	460	464	468	472	476	480		
BLOOD (mL)																				
Hematology	1.2			1.2			1.2			1.2			1.2			1.2			1.2	
Serum Chemistry	2.5			2.5			2.5			2.5			2.5			2.5			2.5	
Anti-idursulfase Antibody Testing	4			4			4			4			4			4			4	
Serum Sample for PK																				**53.9**
Coagulation																				
Total Blood Volume	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0.0**	**0.0**	**7.7**	**0.0**	**0.0**	**7.7**	

Abbreviations: EOS=End of Study; IDDD=intrathecal drug delivery device; mL=milliliter; PK=pharmacokinetics

Appendix 22 Cumulative Maximum Blood Volume Collection for Subjects in the Initial Treatment and Extended Treatment Phases (Months -1-121) and Subjects Only in the Extended Treatment Phase (Months 13-121)

Months	Initial and Extended Treatment Phase	Extended Treatment Phase
	Blood Volume (mL)	
1-12	102.3	0
13-27	108.5	108.5
28-42	38.5	38.5
43-60	46.2	46.2
61-72	30.8	30.8
73-87	38.5	38.5
88-102	38.5	38.5
103-121	53.9	53.9
Total	457.2	354.9

Appendix 23 Neurodevelopmental Assessments in Study SHP609-302

Assessment	Intended Study Population	Applicable Age
DAS-II	Subjects 2 years, 6 months of age and older[a]	Early Years Battery[a, b] 2 years 6 months through 6 years 11 months (extended norms: up to 8 years, 11 months); Early Years Lower Level: 2 years 6 months through 3 years 5 months; Early Years Upper Level: 3 years 6 months through 6 years 11 months School Age Battery 7 years 0 months through 17 years 11 months
BSID-III	Subjects younger than 2 years, 6 months of age and older children who cannot perform the DAS-II	1 to 42 months
VABS-II	All subjects	Birth to 90 years

Abbreviations: BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; DAS-II=Differential Ability Scales, Second Edition; VABS-II=Vineland Adaptive Behavioral Scales, Second Edition

[a] For the DAS-II, Spanish-speaking subjects will be assessed using the Spanish version of the DAS-II Early Years and the DAS-II School Years.

[b] Extended norms may be used.

Appendix 24 Expected SOPH-A-PORT Mini S Adverse Device Effects

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

Procedure-related Complications

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

System-related Complications

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

Appendix 25 Protocol Amendment Summary of Changes

Amendment Summary and Rationale

Amendment 4 (applicable to all countries):

On 05 Mar 2018, Shire met with members of the FDA Division of Gastroenterology and Inborn Errors Products (DGIEP). Shire proposed to amend the study SHP609-302 protocol to include statistical testing of efficacy data to provide a self-contained data set from 12-24 months collected as part of the SHP609-302 study. The Agency recommended Shire to submit a formal Meeting Request and to submit the draft SHP609-302 protocol amendment, draft SHP609-302 SAP and draft ISE SAP as briefing documentation for written FDA feedback. Based on this feedback, clinical protocol SHP609-302 was amended from the previous version to add the following:

- Exploratory efficacy endpoints to evaluate change from Visit Month 13/baseline to Visit Month 25/Week 52 as estimated by linear regression for DAS-II Early Years GCA and selected neurodevelopmental assessment scores
- Other exploratory efficacy endpoints to evaluate change from Visit Month 13/baseline to Visit Month 25/Week 52 as estimated by ordered categorical outcomes
- Clarification regarding statistical methods and addition of inferential testing for the exploratory efficacy endpoints
- Strategy for data integration
- Language regarding planned subgroup analyses
- Description of lower and upper levels of the Early Years battery for DAS-II
- Extension of the duration of treatment from a maximum of 5 years to a maximum of 10 years
- Clarifications to language regarding operational aspects of the study

Detailed Summary of Changes for the Amendment 4:

This is a section that has been updated to describe significant changes from the previous protocol version (Amendment 3). Noteworthy changes and additions to the protocol text are captured below. Bold text indicates new text. Strikethrough text indicates deleted text.

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

Change: Update of “patient” to “subject”
Rationale: To align with Shire submission standards for clinical trials
Section impacted by this change: Entire protocol except for study title and Section 1, Introduction

Change: Clarification of health economics and outcomes research objectives
Rationale: To enable statistical analysis of outcomes
Section impacted by this change: Section 2.4, Health Economics and Outcomes Research Objectives
Revised Text: • **To evaluate healthcare resource utilization, as measured by the Healthcare Utilization Questionnaire (HCUQ) in subjects with Hunter syndrome and cognitive impairment who are treated with idursulfase IT in conjunction with Elaprase therapy** • **To evaluate the social/emotional, physical, daily activities and financial impact on caregivers and families of subjects with Hunter syndrome and cognitive impairment as measured by Caregiver Impact Questionnaire (CIQ)** • ~~To evaluate healthcare resource utilization, as measured by 2 questionnaires consisting of the Healthcare Utilization Questionnaire (HCUQ) and Caregiver Impact Questionnaire (CIQ), in patients with Hunter syndrome and cognitive impairment who are treated with idursulfase IT in conjunction with Elaprase therapy~~
Other sections impacted by this change: Synopsis, Section 3 Study Endpoints

Change: Clarification of secondary efficacy endpoints
Rationale: To enable statistical analysis of efficacy
Section impacted by this change: Section 3.2, Secondary Efficacy Endpoints
Revised Text: The secondary efficacy endpoints of this study are the following: • Change from baseline in **DAS-II** standard scores ~~in cluster areas of the DAS-II~~: **GCA**~~, Verbal, Nonverbal, Spatial, and~~ Special Nonverbal Composite (SNC)~~,~~**; and standard cluster scores: Verbal, Nonverbal, Spatial; and/**or the age equivalents and Development Quotient (DQ) from the BSID-III domains: Cognitive and Language • Change from baseline in standard **composite** scores of the VABS-II ~~domains~~: ABC~~,~~ **and domain standard scores:** Communication, Daily Living Skills, Socialization, and Motor Skills • Change from baseline in age equivalents, developmental quotients, and T-scores for the **core** subtests of the DAS-II: Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices, and Copying for the DAS-II Early Years and Recall of Designs, Word Definitions, Pattern Construction, Matrices, Verbal Similarities, and Sequential and Quantitative Reasoning for the DAS-II School Years
Other sections impacted by this change: Synopsis, Study Endpoints

Change: Addition of exploratory efficacy endpoints to evaluate change from Visit Month 13/baseline to Visit Month 25/Week 52, ordered categorical outcomes and binary outcomes for each subject
Rationale: To enable statistical analysis of efficacy
Section impacted by this change: Section 3.3, Exploratory Efficacy Endpoints

New Text:
The exploratory efficacy endpoints of this study are the following:
• **Change from Visit Month 13/baseline to Visit Month 25/Week 52 in study SHP609-302 as estimated by linear regression in:**
  • **DAS-II GCA scores from Early Years battery**
  • **DAS-II Early Years core subtests T scores: Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices, and Copying**
  • **DAS-II Early Years battery standard cluster scores: Verbal, Nonverbal, Spatial, and SNC composite scores**

- **DAS-II GCA scores including both Early Years and School Age batteries**
- **VABS-II ABC scores**

Note that the interval from Visit Month 13/baseline to Visit Month 25/Week 52 in study SHP609-302 is defined as from Visit Month 13 to Visit Month 25 in SHP609-302 Extended Treatment Phase for subjects in the Early IT group (defined in Section 10.4.1), and from baseline in study SHP609-302 to Visit Week 52 in SHP609-302 Initial Treatment Phase for subjects in the Delayed IT group (defined in Section 10.4.1). The Early IT group and Delayed IT group designations are based on the treatment regimen (idursulfase-IT or No IT treatment) in the antecedent study (HGT-HIT-094).

- **Ordered categorical outcomes for each subject at study SHP609-302 Visit Month 25/Week 52 are defined below. The definition for each response category threshold is based on the standard error of measurement (SEM) for the DAS-II. The SEM for the GCA, based on test-retest reliability of the DAS-II,[17] is approximately ±5 points. The ordered categorical outcomes will be defined for both DAS-II GCA scores from Early Years battery and GCA scores.**
  - **Above average cognitive development (Category 1) is defined as a subject with an observed GCA score at Visit Month 25/Week 52 which is more than 10 points (2 SEM) higher than the observed GCA score at Visit Month 13/baseline in study SHP609-302; ie,**
    - **GCA (Visit Month 25/Week 52) > GCA (Visit Month 13/baseline) + 10 points**
  - **Average cognitive development (Category 2) is defined as a subject with an observed GCA score at Visit Month 25/Week 52 which is within a range of ±10 points, inclusive (2 SEM), of the observed GCA score at Visit Month 13/baseline in study SHP609-302; ie,**
    - **GCA (Visit Month 13/baseline) – 10 points ≤ GCA (Visit Month 25/Week 52) ≤ GCA (Visit Month 13/baseline) + 10 points**
  - **Below average cognitive development (Category 3) is defined as a subject with an observed GCA score at Visit Month 25/Week 52 which is more than 10 points (2 SEM) below the observed GCA score at Visit Month 13/baseline in study SHP609-302; ie,**
    - **GCA (Visit Month 25/Week 52) < GCA (Visit Month 13/baseline) – 10 points**
- **Binary unreversed floor effect outcome for each subject**

Other sections impacted by this change: Synopsis, Study Endpoints

Change: Clarification that the health-related quality of life for caregivers will be assessed using the CIQ

Rationale: Clarification of an operational aspect of the study

Section impacted by this change: Section 3.4, Health Economics and Outcomes Research Endpoints

Revised Text:

- Health care resource utilization will be assessed using the HCUQ ~~and CIQ~~
- **Health-related quality of life for caregivers will be assessed using the CIQ**

Other sections impacted by this change: Synopsis, Study Endpoints

Change: Addition of language clarifying that consent may be obtained from a subject, such as when they reach the legal age of consent

Rationale: Clarification of an operational aspect of the study

Section impacted by this change: Section 4.1, Overall Study Design and Plan

New Text:

Prior to conducting any study-related procedures, written informed consent (signed and dated) must be obtained from the subject's parent(s) or legally authorized guardian(s) (and consent/assent from the subject,

if applicable). The nature, scope, and possible consequences, including risks and benefits, of the study will be explained by the investigator or designee in accordance with the guidelines described in Section 11.4. Documentation and filing of informed consent documents should be completed according to Section 11.4.

During Study SHP609-302, subjects who exceed the age of enrollment eligibility for Study HGT-HIT-094 and/or have reached the applicable legal age of consent to participate in a clinical study will be allowed to continue participation in Study SHP609-302 until the end of the study.

Other sections impacted by this change: Synopsis, Study Inclusion and Exclusion Criteria; Section 5.2, Section 7.1 Informed Consent; Appendix 1, Initial Treatment Phase Schedule of Events: For Subjects Who Did Not Receive Intrathecal Idursulfase IT in Study HGT-HIT-094; Appendix 2, Extended Treatment Phase Schedule of Events – Months 13-15 (Weeks 52-60)

Change: Addition of a figure describing the planned treatment duration

Rationale: Clarification of an operational aspect of the study

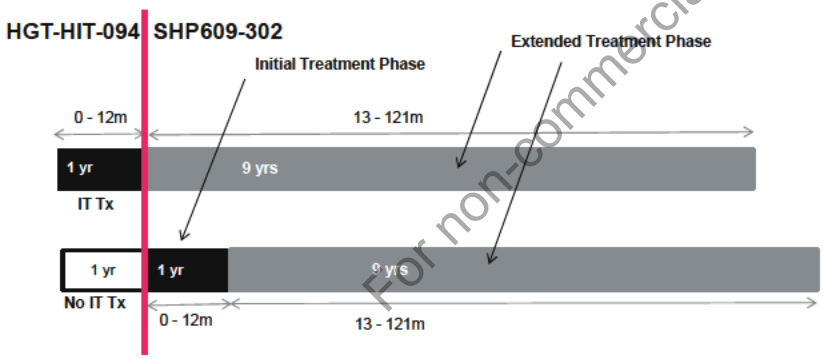
Section impacted by this change: Section 4.4, Study Duration

New Text:

Subjects will participate in this extension study for a duration of ~~5~~ **10** years of treatment unless they discontinue the study or Shire discontinues the study.

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

Figure 1 Planned Duration of Treatment (Study HGT-HIT-094 and/or SHP609-302)



Other sections impacted by this change: Appendix 10; Appendix 11; Appendix 12; Appendix 13; Appendix 15; Appendix 18; Appendix 19; Appendix 20; Appendix 21; Appendix 22

Change: Addition of language regarding the lower and upper levels for the Early Years battery for DAS-II

Rationale: Clarification of an operational aspect of the study

Section impacted by this change: Section 7.10.1.1, Cognition

New Text:

The Early Years battery is further divided into the Lower Level for children ages 2 years, 6 months through 3 years, 5 months and Upper Level for children ages 3 years 6 months through 6 years, 11 months.

Other sections impacted by this change: Table 1 and Appendix 19, Neurodevelopmental Assessments in Study SHP609-302

Change: Change Pharmacovigilance and Risk Management department name to Global Drug Safety, with update to e-mail address
Rationale: Clarification of an operational aspect of the study
Section impacted by this change: Section 7.15.6.2, Reporting Serious Adverse Events
Updated Text: The investigator must report the serious adverse event to the Shire ~~Pharmacovigilance and Risk Management~~**Global Drug 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 to: **Shire Global Drug Safety ~~Pharmacovigilance and Risk Management~~ Department:** **International FAX: +44-1256-894715 (UK) OR United States FAX: +1-866-557-4473** **Email: drugsafety~~globalpharmacovigilance~~@shire.com**
Other sections impacted by this change: Section 7.17, Abuse, Misuse, Overdose, and Medication Error; Section 9, Quality Control and Assurance

Change: Addition of language clarifying that the subject is free to withdraw consent and discontinue participation in the study
Rationale: Clarification of an operational aspect of the study
Section impacted by this change: Section 7.18, Removal of Subjects from the Trial or Investigational Product
Revised Text: The **subject or the** subject's parent(s) or legally authorized guardian(s) acting on behalf of the subject is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. If the **subject or the** subject's parent(s) or legally authorized guardian(s) acting on behalf of the subject discontinues participation in the study, or the subject is discontinued by the investigator , reasonable efforts will be made to follow the subject through the end of study assessments.
Other sections impacted by this change: Not applicable

Change: Addition of months and weeks extending the study to a duration of 10 years
Rationale: Clarification of an operational aspect of the study
Sections impacted by this change: Sections 8.2.2, 8.2.3, and 8.2.4
Revised Text: 8.2.2 Months 14, 15, 17, 18, 20, 21, 23, 24, 26, 27, 29, 30, 32, 33, 35, 36, 38, 39, 41, 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59, 60, **62, 63, 65, 66, 68, 69, 71, 72, 74, 75, 77, 78, 80, 81, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 113, 114, 116, 117, 119, 120** (Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, 192, 200, 204, 212, 216, 224, 228, 236, 240, **248, 252, 260, 264, 272, 276, 284, 288, 296, 300, 308, 312, 320, 324, 332, 336, 344, 348, 356, 360, 368, 372, 380, 384, 392, 396, 404, 408, 416, 420, 428, 432, 440, 444, 452, 456, 464, 468, 476, 480** [±7 Days]) – Extended Treatment Phase – All Subjects 8.2.3 Months 16, 22, 28, 34, 40, 43, 46, 52, 55, 58, **64, 70, 76, 82, 88, 94, 100, 103, 106, 112, 115, 118** (Weeks 64, 88, 112, 136, 160, 172, 184, 208, 220, 232, **256, 280, 304, 328, 352, 376, 400, 412, 424, 448, 460, 472** [±7 Days]) – Extended Treatment Phase – All Subjects 8.2.4 Months 19, 25, 31, 37, 43, 49, 55, **61, 67, 73, 79, 85, 91, 97, 103, 109, 115** (Weeks 76, 100, 124, 148, 172, 196, 220**, 244, 268, 292, 316, 340, 364, 388, 412, 436, 460** [±7 Days]) – Extended Treatment Phase – All Subject
Other sections impacted by this change: Appendix 10; Appendix 11; Appendix 12; Appendix 13; Appendix 15; Appendix 18; Appendix 19; Appendix 20; Appendix 21; Appendix 22

Change: Clarification regarding statistical methods for efficacy and safety combined analyses for SHP609-302 and HGT-HIT-094 studies, including descriptive summaries presentation (Early IT group, Delayed IT group and overall) and the addition of inferential testing for the primary efficacy endpoints and one of the secondary endpoints.
Rationale: To enable statistical analysis of efficacy
Section impacted by this change: Section 10.1, General Methodology
Revised Text: Statistical analyses will be performed by the ~~Biometrics~~**Biostatistics and Statistical Programming** Department of Shire **or its designee** using SAS statistical software (SAS Institute, Cary, NC, USA), unless otherwise specified. Analysis methods will be detailed in the **statistical analysis plan (**SAP**).** **Data from studies** SHP609-302 ~~data~~ **and HGT-HIT-094 will be** ~~combined with that of Study HGT-HIT-094~~ **integrated for efficacy and safety analyses**. Baseline for the **subjects** previously treated in HGT-HIT-094 will be the same as the baseline defined in HGT-HIT-094. Baseline for the **previously** untreated **subjects (ie, No IT treatment) in HGT-HIT-094** ~~is~~ **will be** the closest available assessment prior to the initial IDDD implant date, which takes place in Study SHP609-302, **unless otherwise specified**. This could potentially include EOS visit data from Study HGT-HIT-094. The analyses presented here will include the data measured at and after baseline. Safety ~~and efficacy~~ data **descriptive** summaries will be presented ~~by the antecedent study, HGT-HIT-094, treatment regimen (idursulfase-IT or No Treatment) and overall.~~ **for the Early IT group, Delayed IT group, and overall. The Early IT group and Delayed IT group designations are based on the treatment regimen (idursulfase-IT or No IT treatment) in the antecedent study (HGT-HIT-094).**~~Any former HGT-HIT-094 Substudy patients will be included in the idursulfase-IT treated group.~~ **Subjects who participated in the HGT-HIT-094 substudy will be included in the Early IT group.** **Efficacy data descriptive summaries will be presented separately for subjects who enrolled from the pivotal study or substudy of HGT-HIT-094. For subjects enrolled from the pivotal study, descriptive statistics will be presented by the Early IT group, the Delayed IT group, and overall. For secondary efficacy endpoints, the mean difference in the change at each time point between the 2 treatment groups (Early IT group and Delayed IT group) and the corresponding 90% confidence interval of the mean difference will be presented where appropriate. The mean values (±SD) for all efficacy endpoints will be graphed over time where appropriate.**

Inferential testing is planned for some exploratory efficacy endpoints. The main exploratory efficacy analyses to examine the IT treatment effect will be rate of change (weighted) analyses of the exploratory efficacy endpoints from Visit Month 13/baseline to Visit Month 25/Week 52 as estimated by linear regression for DAS-II Early Years GCA scores and selected neurodevelopment assessment scores.

Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of subjects in each category.

~~The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the design and objectives of this trial.~~ Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of ~~patients~~**subjects** in each category.

~~All safety and efficacy data will be summarized descriptively at scheduled visits. For efficacy endpoints, the mean difference in the change at each time point between the 2 HGT-HIT-094 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented where appropriate. The mean values for all efficacy endpoints will be graphed over time where appropriate.~~
Efficacy data for subjects enrolled from the HGT-HIT-094 substudy will be presented in listings.

Other sections impacted by this change: Synopsis, Statistical Methods; Section 10.4.3, Subject Disposition; Section 10.4.5, Demographics and Baseline Characteristics; Section 10.4.6, Treatment Compliance; Section 10.4.7, Extent of Exposure; Section 10.6.2, Pharmacodynamic Analyses; Section 10.7, Analysis of Safety; Section 10.7.1, Adverse Events; Section 10.7.2, Clinical Laboratory Evaluation; Section 10.7.6.2, Immunogenicity

Change: Addition of strategy regarding data integration

Rationale: To enable statistical analysis of integrated safety and efficacy data

Section impacted by this change: Section 10.4.1, Data Integration Strategy

New Text:

Data from studies SHP609-302 and HGT-HIT-094 will be integrated for data analyses.

For safety and efficacy descriptive summary analyses using integrated data, the 2 treatment groups are the Early IT group and Delayed IT group based on HGT-HIT-094 treatment regimen (idursulfase-IT or No IT Treatment), defined as follows:

- **The Early IT group is defined as subjects who were randomized to the idursulfase-IT treatment cohort in study HGT-HIT-094 and continued IT treatment in study SHP609-302. HGT-HIT-094 substudy will be included in the Early IT group.**
- **The Delayed IT group is defined as subjects who were randomized to the control cohort (No IT treatment) in study HGT-HIT-094 and began IT treatment in study SHP609-302.**

For exploratory efficacy analyses, only data collected in study SHP609-302 will be used; the 2 treatment groups are the Early IT group and Delayed IT group.

Visit Month 13 of the SHP609-302 Extended Treatment Phase corresponds to the scheduled visit at which subjects in the Early IT group have completed 12 months of IT treatment in antecedent study HGT-HIT-094. The treatment regimen in HGT-HIT-094 comprised 1 month for surgical IDDD implantation at the beginning of the study followed by 12 months of IT treatment during HGT-HIT-094.

Likewise, Visit Month 25 of the SHP609-302 Extended Treatment Phase corresponds to the scheduled visit at which subjects in the Early IT group have completed two 12-month periods of IT treatment, and comprises 1 month for surgical IDDD implantation at the beginning of HGT-HIT-094, 12 months of IT treatment during

HGT-HIT-094, and a continued 12 months of IT treatment in the Extended Treatment Phase of SHP609-302.

Visit Week 52 of the SHP609-302 Initial Treatment Phase is the scheduled visit at which subjects in the Delayed IT group have completed 12 months of IT treatment in study SHP609-302, and comprises 12 months of No IT treatment during HGT-HIT-094, 1 month for surgical IDDD implantation at the beginning of SHP609-302, and 12 months of IT treatment in the Initial Treatment Phase of SHP609-302.

It is noted that Visit Month 25 and Visit Week 52 of SHP609-302 are 4 weeks apart for the Early IT and Delayed IT groups. This difference is accounted for by the need for subjects in the Delayed IT group, who enrolled into the Initial Treatment Phase of SHP609-302 from the HGT-HIT-094 No IT treatment group, to undergo surgical implantation of the device at the beginning of study SHP609-302. Therefore, the first dose of SHP609 was administered 4 weeks later to these subjects compared with subjects in the Early IT group who were randomized to IT treatment and underwent IDDD implantation in HGT-HIT-094 prior to enrolling in the Extended Treatment Phase of SHP609-302. For evaluation of the long-term efficacy of IT treatment in SHP609-302, this 4-week difference is considered to have minimal impact on neurodevelopmental assessment scores.

Other sections impacted by this change: Not applicable

Change: Text and figure added to describe the conceptual plot of treatment periods in Early IT and Delayed IT Groups in Studies HGT-HIT-094 and SHP609-302

Rationale: To enable statistical analysis of efficacy

Section impacted by this change: Section 10.4.2, Analysis Populations

Revised Text:

All ~~data~~ **descriptive summary** analyses **of safety and efficacy data** will be based on the Safety Population, which is defined as all ~~patients~~**subjects** in Study SHP609-302 who underwent IDDD implantation or received at least 1 dose of study drug (full or partial).

The following nomenclature will be used to identify "A", "B", "C", and "D" in Figure 2.

- **Observation Groups A and C identify the period of observation during study HGT-HIT-094, for subjects randomized to IT treatment and No IT treatment, respectively.**
- **Observation Groups B and D identify the period of observation during study SHP609-302 up to completion of 1 year, for subjects who were randomized in HGT-HIT-094 to receive IT treatment and No IT treatment respectively, noting that all subjects in SHP609-302 received IT treatment.**

The subjects in "B" are the same subjects as in "A" with periods of observation from studies SHP609-302 and HGT-HIT-094, respectively as we can view "B" as a continuation of "A". The subjects in "D" are the same subjects as in "C" with periods of observation from studies SHP609-302 and HGT-HIT-094, respectively as we can view "D" as a continuation of "C".

"D" subjects are therefore similar to "A" subjects since these subjects all transitioned from receiving weekly IV infusion of Elaprase, to also receive monthly IT idursulfase. More generally, because study SHP609-302 did not have baseline GCA inclusion criteria, such as that employed for Study HGT-HIT-094, "B" and "D" subjects could differ with regard to their baseline GCA score at the beginning of the observation period. Therefore, for consideration of "B" and "D", only subjects meeting the key inclusion criteria to HGT-HIT-094 will be included in inferential efficacy analyses, ie, with GCA scores between 55 and 85 inclusive at the enrollment of SHP609-302.

The exploratory efficacy analyses will be conducted on "HGT-HIT-094 Comparable Set", "HGT-HIT-094 Comparable Subset 1", and "HGT-HIT-094 Comparable Subset 2". The primary analysis population is HGT-HIT-094 Comparable Subset 1, which may be the subject population with the most potential to benefit from the idursulfase-IT treatment.

- **HGT-HIT-094 Comparable Set: subjects in the Safety Population who met the key HGT-HIT-094 inclusion criterion (baseline GCA scores between 55 and 85 inclusive) at enrollment in SHP609-302 (Visit Month 13/baseline), ie, Safety Population subjects with GCA scores between 55 and 85 inclusive at enrollment in SHP609-302**

• **HGT-HIT-094 Comparable Subset 1 (primary analysis population): subjects in the HGT-HIT-094 Comparable Set with age <6 years at enrollment in SHP609-302 (Visit Month 13/baseline), ie, Safety Population subjects with GCA scores between 55 and 85 inclusive and age <6 years at enrollment in SHP609-302** • **HGT-HIT-094 Comparable Subset 2: subjects in the HGT-HIT-094 Comparable Set with age <55 months at the enrollment of SHP609-302 (Visit Month 13/baseline), ie, Safety Population subjects with GCA scores between 55 and 85 inclusive and age <55 months at enrollment in SHP609-302**
Other sections impacted by this change: Figure 2, Conceptual Plot of Treatment Periods in Early IT and Delayed IT Groups in Studies HGT-HIT-094 and SHP609-302

Change: Clarification regarding other efficacy endpoints (analysis groups and confidence interval)
Rationale: To clarify statistical analysis of efficacy
Section impacted by this change: Section 10.5.3, Other Secondary Efficacy Analysis
Revised Text: For ~~each~~**all other** efficacy endpoint**s** described in Section 3.2, the observed values and change from baseline will be summarized descriptively for each assessment time point by **the Early IT group, the Delayed IT group** ~~the HGT-HIT-094 treatment regimen (idursulfase-IT or No Treatment)~~ and overall. Any HGT-HIT-094 Substudy ~~patients~~ **subjects** will be included in the ~~idursulfase-IT treated group~~ **Early IT group** for analysis. The mean difference in the change at each time point between the two HGT-HIT-094 treatment groups and the corresponding 9~~5~~**0**% confidence interval of the mean difference will be presented. The BSID-III endpoints will be listed only. Graphical plots of the mean value for each endpoint over time will be presented. A spaghetti plot of the age equivalent scores for individual ~~patients~~**subjects** will be plotted against chronological age.
Other sections impacted by this change: Not applicable

Change: Addition of language regarding planned subgroup analyses
Rationale: To enable statistical analysis of efficacy for the subgroups
Section impacted by this change: Section 10.5.4, Subgroup Analyses
Revised Text: Section 10.5.4, Sub~~set~~**group** Analyses Subgroup **descriptive summary** analyses of the **secondary efficacy endpoints**, change from baseline in GCA and ABC scores will be performed for baseline GCA groups (either ≤70 or >70) and baseline age groups (either ≤~~<~~6 years or ≥~~>~~6 years; **<55 months or ≥55 months**). Descriptive summaries within these subgroups and plots of mean values **(±SD)** over time will be presented. **The baseline is defined in Section 10.1.** **Subgroup analyses are planned for the rate of change (weighted) analyses in GCA scores from Early Years battery, GCA scores and ABC scores for GCA classification groups at Visit Month 13/baseline (either ≤70 or >70), age groups at Visit Month 13/baseline (either <6 years or ≥6 years), and age groups at Visit Month 13/baseline (either <55 months or ≥ 55 months).**
Other sections impacted by this change: Not applicable

Change: Addition of language regarding exploratory analyses, including text regarding the possible floor effector for neurodevelopmental assessments
Rationale: To enable statistical analysis of efficacy
Section impacted by this change: Section 10.5.5, Exploratory Analyses
New Text: **The main exploratory efficacy analyses to examine the IT treatment effect will be rate of change (weighted)**

analyses of the exploratory efficacy endpoints from Visit Month 13/baseline to Visit Month 25/Week 52 in study SHP609-302 as estimated by linear regression for the following neurodevelopmental assessment scores:

- **DAS-II GCA scores from Early Years battery**
- **DAS-II Early Years core subtests T scores: Verbal Comprehension, Picture Similarities, Naming Vocabulary, Pattern Construction, Matrices, and Copying**
- **DAS-II Early Years battery standard cluster scores: Verbal, Nonverbal, Spatial, and SNC composite scores**
- **DAS-II GCA scores including both Early Years and School Age batteries**
- **VABS-II ABC scores**

Complete details of the rate of change (weighted) analysis, including examination of premises of the rate of change (weighted) analysis, model diagnostics for the 2 analysis stages, and estimation and comparison of the treatment effects during observation periods "B" and "D" will be described in the SAP.

The descriptive summary of ordered categorical outcomes will be presented at Month 25/Week 52 by the Early IT group, the Delayed IT group, and overall using the SHP609-302 data "B" and "D". The definitions of ordered categorical outcomes for each subject are described in Section 3.3.

For each of the neurodevelopmental assessments, there may be a "floor effect", ie, the lower limitation of the assessment tool, below which the assessment may not be reliable or meaningful. Refer to the SAP for complete details.

Other e~~E~~xploratory analyses may include assessment of the correlation between PD and efficacy endpoints; and between composite scores and their components (ie, correlations between the GCA and ABC scores and their respective **cluster/**domain scores). Scatter plots may be presented to explore the relationships among variables.

Other sections impacted by this change: Not applicable

Change: Language added regarding the CIQ question items for clarification

Rationale: Clarification of an operational aspect of the study

Section impacted by this change: Section 10.5.6, Health Economics and Outcomes Research Endpoint Analyses

New Text:

HCUQ ~~and CIQ~~ variables include the number of emergency room visits, caregiver employment status (full time [FT], part time [PT], and not working [NW]), and the number of hours of additional paid help needed by caregivers, over the course of the study. **The CIQ question items measure social, emotional, physical and financial impacts on the caregiver.** Descriptive statistics, including n, mean, median, and range (for continuous variables), and n and proportions (for categorical variables), for these key HCUQ and CIQ variables will be presented.

Other sections impacted by this change: Study Endpoints

Change: Clarification that 90% rather than 95% confidence interval will be estimated.

Rationale: Clarification of statistical analysis of IDDD performance

Section impacted by this change: Section 10.7.6.1, IDDD Performance

New Text:

The proportion of subjects with at least ~~one~~**1** device failure and/or malfunction, as well as the number of and reasons for device failures/malfunctions will be summarized. The rate of device failures/malfunctions and 9~~5~~**0**% confidence interval will also be estimated. The time from initial implant surgery to first device failure and/or malfunction will be summarized. Subjects without a device failure/malfunction will be censored at their last study drug injection date. A by-subject listing of the device failure/malfunction data will be displayed.

The rate of successful IDDD injections will be calculated for each subject 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 9~~5~~**0**% confidence interval for the mean rate will be estimated, where appropriate. Injections that are not administered for subject-related reasons (eg, subject uncooperative, competing medical issue, etc.) will not be included in the determination of the injection success rate.
Other sections impacted by this change: Not applicable

Change: Addition of new language for adjustment for covariates
Section impacted by this change: Section 10.8.1, Adjustment for Covariates
Revised Text: ~~Given the design of this study, no statistical modeling or covariate adjustment is planned.~~ **The rate of change (weighted) analysis will adjust for GCA classification (either ≤70 or >70) at enrollment of SHP609-302 in the weighted generalized linear model.**
Other sections impacted by this change: Not applicable

Change: Addition of new language indicating no multiple comparisons or multiplicity adjustments to be made
Section impacted by this change: Section 10.8.5, Multiple Comparisons/Multiplicity
Revised Text: ~~Statistical analyses are descriptive and no adjustment for~~ **No multiple comparison procedure or** multiplicity **adjustment** will be performed.
Other sections impacted by this change: Not applicable

Change: Clarification that when a subject is the legal age of majority but lacking mental capacity to provide informed consent, the subject's parent or legally authorized representative will provide informed consent
Rationale: Clarification of an operational aspect of the study
Section impacted by this change: Section 11.4, Subject Information and Consent
New Text: **When a subject 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 subject's parent(s) or legally authorized representative(s) will be asked to provide informed consent on behalf of the subject to allow for continued participation in the trial.**
Other sections impacted by this change: Appendix 1, Initial Treatment Phase Schedule of Events: For Subjects Who Did Not Receive Intrathecal Idursulfase IT in Study HGT-HIT-094; Appendix 2, Extended Treatment Phase Schedule of Events – Months 13-15 (Weeks 52-60)

Change: Clarifications to List of References
Rationale: Clarification to literature cited
Section impacted by this change: Section 12, List of References
New Text: 17. Elliott, CD ~~2007~~. Differential Ability Scales (~~2nd ed~~ **Second Edition**). San Antonio, TX: ~~Harcourt Assessment~~ **The Psychological Corporation; 2007**. 18. Bayley N. Bayley Scales of Infant and Toddler Development. ~~3 ed~~ **(Third Edition)**. San Antonio, TX. The Psychological Corporation; 2005.
Other sections impacted by this change: Not Applicable

Appendix 1 Protocol Signature Page

Study Title: An Open Label Extension of Study HGT-HIT-094 Evaluating Long Term Safety and Clinical Outcomes of Intrathecal Idursulfase Administered in Conjunction with Elaprase® in Patients with Hunter Syndrome and Cognitive Impairment

Study Number: SHP609-302

Amendment 4

Final Date: 09 Oct 2018

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

Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.

Signatory:

Shire Medical Monitor [redacted] _____ [redacted]
Date

[redacted], DO, [redacted]
Printed Name

Appendix 21 Protocol Amendment Summary of Changes

Amendment Summary and Rationale

Amendment 3 (applicable to all countries):

Clinical protocol SHP-609-302 was amended from the previous version to introduce the option of same-day administration of IV Elaprase and idursulfase-IT for patients who have already completed at least 12 months of idursulfase-IT treatment in studies HGT-HIT-094 or SHP-609-302, ie, those patients participating in the Extended Treatment Phase of the present study. Same-day administration may be elected at the investigator's discretion and is intended to offer convenience to patients participating in the Extended Treatment Phase, who otherwise would be required to schedule an extra clinic visit in order to receive Elaprase at least 48 hours after their monthly IT dose.

If same-day dosing is elected, idursulfase-IT is to be administered first and the IV Elaprase infusion will be administered second. Per this protocol amendment, additional pharmacokinetic assessments will be implemented to measure any increase in total systemic exposure to idursulfase under the same-day administration regime. While, with same-day dosing, it will not be possible to distinguish idursulfase of IV-administered origin from that of IT-administered origin, pharmacokinetic and safety assessments will evaluate the effect of the same-day IV and IT regime on total idursulfase exposure and on safety parameters such as the incidence and/or severity of infusion-related reactions, even if the patient had no prior such reactions on Elaprase alone. The clinical safety profile of Elaprase is well understood. Based on the known pharmacokinetic properties and safety profile of idursulfase-IT in pediatric MPS II patients also receiving Elaprase therapy, the contribution to total systemic exposure of IT-administered idursulfase in the setting of same-day IV Elaprase infusion is not expected to detrimentally impact patient safety. With this amendment, a new category of adverse event relatedness, related to IV Elaprase and/or idursulfase-IT, will be incorporated into the protocol to facilitate the collection and analysis of adverse events observed with same-day administration.

Note that, on the occasion of the first same-day administration, the duration of IV Elaprase infusion is to be standardized to 3 hours, corresponding to the recommended infusion rate for new Elaprase patients per product labeling. This cautious approach is in the interest of patient safety, as well as to promote the homogeneity in data collection needed for the interpretation of pharmacokinetic data. Thereafter, at subsequent monthly visits at which same-day administration of IV Elaprase infusion and idursulfase-IT are elected, the investigator may use discretion in deciding the appropriate Elaprase infusion rate based on past experience with the patient, and the patient's prior response to the same-day administration regime.

Detailed Summary of Changes for the Amendment 3

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

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

Change: Addition of adverse event relationship category
Section impacted by this change: 3.1 Primary Endpoints
Revised Text: Safety will be assessed during the study by the following: • Adverse events (AEs) (by type, severity, and relationship to treatment [idursulfase-IT, the IDDD, device surgical procedure, or IT administration process], IV Elaprase infusion, **IV Elaprase and/or idursulfase-IT**)
Other sections impacted by this change: Synopsis; 6.6.1 Infusion Reactions and Management; 7.15.1.3 Elaprase and/or idursulfase-IT-related Adverse Event; 7.15.5 Relatedness of Adverse Events and Serious Adverse Events; 10.7.1.1 Investigational Product

Change: Introduction of same-day dosing regime
Section impacted by this change: 6.2 Treatments Administered
Revised Text: **The investigational product may be administered on the same day (ie, the same calendar day or within a 24-hour period) as the Elaprase IV infusion. However, this can only occur for patients participating in the Extended Treatment Phase who have already completed at least 12 months of idursulfase-IT treatment in studies HGT-HIT-094 or SHP-609-302. If same-day dosing is elected, idursulfase-IT will be administered first and the Elaprase IV infusion will be administered second Please refer to Section 7.7.1 for details.**
Other sections impacted by this change: 7 Study Procedures

Change: Clarification of safety assessment with same-day dosing
Section impacted by this change: 6.6.1 Infusion Reactions and Management
Revised Text: 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. As of the date of this protocol, there have been no significant concerns regarding infusion-related immune reactions following IT administration in studies HGT-HIT-045 and HGT-HIT-046. **Additionally, safety assessments in the present study will evaluate the effect of same-day IV and IT regime on the incidence and/or severity of infusion-related adverse reactions, even if the patient had no prior such reactions on Elaprase alone.**
Other sections impacted by this change: 7.15.1.3 Elaprase and/or idursulfase-IT-related Adverse Event; 7.15.5 Relatedness of Adverse Events and Serious Adverse Events; 10.7.1.1 Investigational Product

Change: Introduction of same-day dosing regime
Section impacted by this change: 7 Study Procedures
Revised Text: All patients will receive weekly IV Elaprase infusions as prescribed throughout the study. **During the Initial Treatment Phase,** on IT Dosing Weeks the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT.

During the Extended Treatment Phase only, the investigator will have the option of administering the Elaprase IV infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.
Other sections impacted by this change: 7.7.1 Same Day Investigational Administration with Elaprase Infusion

Change: Description of same-day dosing regime
Section impacted by this change: 7.7.1 Same-Day Investigational Administration with Elaprase Infusion
Revised Text: **During the Initial Treatment Phase,** on IT Dosing Weeks the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. **During the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. If same-day dosing is elected, idursulfase-IT will be administered first and the Elaprase infusion will be administered second. Pharmacokinetic assessments are to occur at the first study visit at which same-day dosing is elected. At this visit, administration of the Elaprase infusion should start within approximately 90 minutes of completion of idursulfase-IT administration.** **Note that on the occasion of the first same-day administration, the duration of IV Elaprase infusion is to be standardized to 3 hours. Thereafter, at subsequent visits on which the Elaprase infusion and idursulfase-IT are administered on the same day, the investigator may use discretion in deciding the appropriate Elaprase infusion rate based on past experience with the patient, and the patient's prior response to the same-day regime.**
Other sections impacted by this change: 7.8 Pharmacokinetic Assessments

Change: Timing of CSF sample collection and PK sampling
Section impacted by this change: 7.8 Pharmacokinetic Assessments
Revised Text: Blood samples will be collected for determination of idursulfase serum concentration-time profiles and serum pharmacokinetic parameters after IT administration**.** Idursulfase concentrations will be measured in CSF samples obtained immediately prior to ~~each~~ IT administration (and at the EOS Visit) to determine the degree of accumulation of monthly idursulfase-IT administrations in the CSF. The blood and CSF sampling schedules for pharmacokinetic assessments are provided in the Schedule of Events (Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6, Appendix 7, Appendix 8, Appendix 9, Appendix 10, Appendix 11, and Appendix 12). **During the Extended Treatment Phase, blood samples for pharmacokinetic assessments will be collected on the occasion of the first same-day administration of idursulfase-IT and Elaprase. This pharmacokinetic sampling need only be scheduled once, and may occur at Month 25 or at an alternative visit during the Extended Treatment Phase (see Appendix 13 for PK sampling time points associated with same-day administration).**
Other sections impacted by this change: Appendix 13 Pharmacokinetic Sample Collection for Same-Day Investigational Product Administration with Elaprase Infusion

Change: Addition of adverse event relationship category
Section impacted by this change: 7.15.1.3 Elaprase and/or idursulfase-IT-related Adverse Event

Revised Text: **During the Extended Treatment Phase, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. With same-day dosing, it may not be possible to distinguish idursulfase of IV-administered origin from that of IT-administered origin. Therefore, adverse events that are potentially related to IV Elaprase infusion and/or idursulfase-IT administration will be captured.**
Other sections impacted by this change: 7.15.5 Relatedness of Adverse Events and Serious Adverse Events; 10.7.1.1 Investigational Product

Change: Addition of adverse event relationship category
Section impacted by this change: 7.15.5 Relatedness of Adverse Events and Serious Adverse Events
Revised Text: Relationship of an AE or SAE to investigational product, IDDD, device surgical procedure, or IT administration process will be assessed by the Investigator as follows: • Relationship to idursulfase-IT • Relationship to IV Elaprase infusion will be assessed by the Investigator as described in Section 7.15.1.2 • **Relationship to IV Elaprase infusion and/or idursulfase-IT as described in Section** 7.15.1.3 • Relationship to the IDDD (examples of IDDD-related adverse events are listed in Section 7.15.1.4) • Relationship to a device surgical procedure (surgical implantation of the IDDD, partial or full device revision as described in Section 7.15.1.5) • Relationship to the IT administration process (examples of IT administration process-related adverse events are listed in Section 7.15.1.6)
Other sections impacted by this change: Synopsis; 3.1 Primary Endpoints

Change: Clarification to timing of CSF sample collection
Section impacted by this change: 8.1.4.1 Prior to Intrathecal Injection (Months 1-12, Weeks 4-48 [±7 Days]) - Initial Treatment Phase
Revised Text: • **CSF GAG and idursulfase (performed at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48)**
Other sections impacted by this change: Appendix 1 Initial Treatment Phase Schedule of Events: For Patients Who Did Not Receive Intrathecal Idursulfase IT in Study HGT HIT 094

Change: Clarification to timing of PK sample collection
Section impacted by this change: 8.1.4.2 Intrathecal Injection (Months 1-12, Weeks 4-48 [±7 Days]) – Initial Treatment Phase
Revised Text: • Serum sampling for PK analysis (performed at Weeks 4 and 48). Samples will be collected within ~~15~~ **30** minutes (±5 minutes) prior to intrathecal administration of idursulfase-IT and at 30 minutes (±5 minutes), 60 minutes (±5 minutes), 120 minutes (±5 minutes), 4 hours (±5 minutes), 6 hours (±5 minutes), 8 hours (±15 minutes), 12 hours (±15 minutes), 24 hours (±15 minutes), 30 hours (±15 minutes), 36 hours (±15 minutes) after the start of intrathecal administration
Other sections impacted by this change: 8.2.4.2 Months 19, 25, 31, 37, and 49 (Weeks 76, 100, 124, 148,

and 196 [±7 Days]) – Intrathecal Injection – Extended Treatment Phase – All Patients; Appendix 1 Initial Treatment Phase Schedule of Events: For Patients Who Did Not Receive Intrathecal Idursulfase IT in Study HGT-HIT-094; Appendix 4 Extended Treatment Phase Schedule of Events – Months 21-25 (Weeks 84-100)

Change: Introduction of same-day dosing regime
Section impacted by this change: 8.2.1.2 Month 13 (Week 52 [±7 Days]) – Intrathecal Injection – Extended Treatment Phase – All Patients
Revised Text: Patients will remain under observation in the hospital setting (eg, may include infusion center, PACU [recovery suite], observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Thereafter, if deemed clinically stable by the Investigator, patients may leave the hospital setting. The patient may need to be examined the following day (see Follow-up, Section 8.1.4.3) by the Investigator; however, there is no requirement for an overnight hospital stay. Note that, on IT Dosing Weeks **during the Initial Treatment Phase**, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. **However, during the Extended Treatment Phase only, the investigator will have the option of administering the IV Elaprase infusion and idursulfase-IT on the same day. Please refer to Section 7.7.1 for details.**
Other sections impacted by this change: 8.2.2.2 Months 14, 15, 17, 18, 20, 21, 23, 24, 26, 27, 29, 30, 32, 33, 35, 36, 38, 39, 41, 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59, and 60 (Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, 192, 200, 204, 212, 216, 224, 228, 236, and 240 [±7 Days]) – Intrathecal Injection – Extended Treatment Phase – All Patients; 8.2.3.2 Months 16, 22, 28, 34, 40, 43, 46, 52, 55, and 58 (Weeks 64, 88, 112, 136, 160, 172, 184, 208, 220, and 232 [±7 Days]) – Intrathecal Injection – Extended Treatment Phase – All Patients; 8.2.4.2 Months 19, 25, 31, 37, and 49 (Weeks 76, 100, 124, 148, and 196 [±7 Days]) – Intrathecal Injection – Extended Treatment Phase – All Patients; Appendix 2 Extended Treatment Phase Schedule of Events – Months 13-15 (Weeks 52-60); Appendix 3 Extended Treatment Phase Schedule of Events – Months 16-20 (Weeks 64-80); Appendix 4 Extended Treatment Phase Schedule of Events – Months 21-25 (Weeks 84-100); Appendix 5 Extended Treatment Phase Schedule of Events – Months 26-30 (Weeks 104–120); Appendix 6 Extended Treatment Phase Schedule of Events – Months 31-34 (Weeks 124-136); Appendix 7 Extended Treatment Phase Schedule of Events – Months 35-37 (Weeks 140-148); Appendix 8 Extended Treatment Phase Schedule of Events – Months 38-42 (Weeks 152-168); Appendix 9 Extended Treatment Phase Schedule of Events – Months 43-47 (Weeks 172-188); Appendix 10 Extended Treatment Phase Schedule of Events – Months 48-52 (Weeks 192-208); Appendix 11 Extended Treatment Phase Schedule of Events – Months 53-57 (Weeks 212-228); Appendix 12 Extended Treatment Phase Schedule of Events – Month 58 (Week 232) – End of study (Month 61, Week 244);

Change: Clarification to PK analysis
Section impacted by this change: 10.6.1 Pharmacokinetic Measurement and Parameters
Revised Text: The analysis of PK parameter data will be performed by the Shire Clinical Pharmacology and Pharmacokinetics department **or its designee**.
Other sections impacted by this change: None

Change: Clarification to TEAE definition
Section impacted by this change: 10.7.1 Adverse Events
Revised Text: Treatment-emergent AEs, defined as all AEs from the time of initial intervention (first surgery for IDDD implantation, including failed surgeries, or first dose if before first IDDD implantation surgery) to the **EOS visit** ~~last patient visit in the study~~, will be summarized by the HGT-HIT-094 treatment regimen (idursulfase-

IT or No Treatment) and overall.

Other sections impacted by this change: 7.15.6.1 Adverse Event Monitoring and Period of Observation

Change: Addition of adverse event relationship category

Section impacted by this change: 10.7.1.1 Investigational Product

Revised Text:

Treatment-emergent AEs deemed by the investigator to be related to idursulfase-IT study drug will be summarized by presenting the number and percentage of patients having an AE and the number of events, by SOC and preferred term. ~~A~~ Separate tabulation**s** of IV Elaprase infusion-related adverse events **and IV Elaprase infusion and/or idursulfase-IT-related adverse events** will also be presented.

Other sections impacted by this change: Synopsis; 3.1 Primary Endpoints

Change: Clarification concerning interim analyses

Section impacted by this change: 10.8.3 Interim Analyses and Data Monitoring

Revised Text:

~~No formal interim analysis or statistical testing is planned. Descriptive analyses of the data~~ **Interim analyses may be conducted** before trial completion ~~may be performed~~ for safety monitoring, regulatory reporting or general planning purposes. **Analyses will be descriptive in nature, with no formal comparisons planned and no hypotheses tested formally**.

Other sections impacted by this change: None

Change: Addition of PK sampling with same-day IT-IV dosing

Section impacted by this change: **Appendix 13 Pharmacokinetic Sample Collection for Same-Day Investigational Product Administration with Elaprase Infusion**

Revised Text:

Assessment	Monthly Visits 13-60[a]		
	IT Dosing Week: Main Site only		
	Pre-Tx Day 1	IT Inj Day	Days 3-7
Serum Sample for PK[b,c]		•	
Same-day Elaprase IV infusion and idursulfase-IT administration[c]		•	

Abbreviations: Inj=injection; IT=intrathecal; IV=intravenous; PK=pharmacokinetic; Tx=treatment

[a] Same-day administration of the IV Elaprase infusion and idursulfase-IT can only occur during the Extended Treatment Phase, ie, Months 13-60.

[b] Samples for PK assessments are to be collected on the occasion of the first same-day administration. This pharmacokinetic sampling need only be scheduled once, and may occur at Month 25 or at an alternative visit during the Extended Treatment Phase.

[c] Serum samples for PK analysis will be collected within 30 minutes (±5 minutes) prior to intrathecal administration of idursulfase-IT, within 30 minutes prior to the start of Elaprase infusion, and at 30 minutes (±5 minutes), 60 minutes (±5 minutes), 120 minutes (±5 minutes), 3 hours (±5 minutes; ie, the end of Elaprase infusion), 4 hours (±5 minutes), 6 hours (±5 minutes), 8 hours (±15 minutes), 12 hours (±15 minutes), 24 hours (±15 minutes), 30 hours (±15 minutes), 36 hours (±15 minutes) after the start

of Elaprase Infusion.

Other sections impacted by this change: 7.8 Pharmacokinetic Assessments

Change: Change to blood sample collection volumes

Section impacted by this change: Appendix 14 Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Initial Treatment Phase (Patients Who Did Not Receive Intrathecal Idursulfase-IT in Study HGT HIT-094)

Revised Text:

BLOOD (mL)																	**TOTAL**
Hematology	~~1.2~~		1.2			1.2			1.2			1.2			1.2		**102.3 ~~110~~**
Serum Chemistry	~~2.5~~		2.5			2.5			2.5			2.5			2.5		
Anti-idursulfase Antibody Testing	0					4			4			4			4		
Serum Sample for PK						33										33	
Coagulation			1.8														
Total Blood Volume	**~~7.7~~ 0**	**0**	**5.5**	**0**	**0**	**40.7**	**0**	**0**	**7.7**	**0**	**0**	**7.7**	**0**	**0**	**7.7**	**33**	

Other sections impacted by this change: None

Change: Change to blood sample collection volumes

Section impacted by this change: Appendix 15 Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Extended Treatment Phase (Months 13-27 - Weeks 52-108)

Revised Text:

Procedure	**Extended Treatment Phase**																**TOTAL**
	Months																
	13	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**13-60[a]**	
	Weeks																
	52	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**52-240[a]**	
BLOOD (mL)																	
Hematology	1.2			1.2			1.2			1.2			1.2				**~~71.5~~ 108.5**
Serum Chemistry	2.5			2.5			2.5			2.5			2.5				
Anti-idursulfase Antibody Testing	4			4			4			4			4				
Serum Sample for PK													33			**37**	
Coagulation																	
Total Blood Volume	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**7.7**	**0**	**0.0**	**40.7**	**0.0**	**0**	**37**	

Abbreviations: IDDD=intrathecal drug delivery device; mL=milliliter; PK=pharmacokinetics

[a] To be collected only once at any study visit during Months 13-60 (Weeks 52-240).

Other sections impacted by this change: None

Change: Change to blood sample collection volumes

Section impacted by this change: Appendix 18 Cumulative Maximum Blood Volume Collection for Patients in the Initial Treatment and Extended Treatment Phases (Months -1-61) and Patients Only in the Extended Treatment Phase (Months 13-61)

Revised Text:

Months	**Initial and Extended Treatment Phase**	**Extended Treatment Phase**
	Blood Volume (mL)	
1-12	~~110~~ **102.3**	0
13-27	~~71.5~~ **108.5**	~~71.5~~ **108.5**
28-42	38.5	38.5
43-61	53.9	53.9
Total	~~273.9~~ **303.5**	~~163.9~~ **200.9**

Other sections impacted by this change: None

Appendix 16 Protocol Amendment Summary of Changes

AMENDMENT SUMMARY AND RATIONALE

Amendment 1 (applicable only to UK): Clinical protocol SHP-609-302 was amended from the original version as follows:

- The original protocol specified a duration of treatment of 3 years, but left open the possibility that patients could transition to receiving commercial drug once the product became available. At the request of the health authority in the United Kingdom (MHRA), the protocol was amended in Amendment 1 to specify a firm commitment on the part of the Sponsor to a duration of treatment of 3 years in this study.
- This amendment also incorporated clarifications to the text which were implemented previously under Administrative Change Memo #1 (25 November 2014) and Administrative Change Memo #2 (13 January 2015) and the further clarification that a treatment and assessment window of ±7 days applies to both the initial and extended treatment phases of the study as specified in Section 8 Study Activities and in the Schedules of Events provided as appendices.

Amendment 2 (applicable to all countries): Clinical protocol SHP-609-302 was amended from the previous version as follows:

- To implement Amendment 1 in all countries (this was only implemented in UK initially)
- To provide clarification concerning study population
- To extend the treatment duration in the study to 5 years
- To specify the maximum volume of blood to be collected from a patient by study visit.
- To remove language requiring Spanish-speaking patients older than 8 years, 11 months, to use the BAS-II for cognitive testing, as a Spanish version of the DAS-II School Age Years instrument has become available for use in the study
- To update text pertaining to the SOPH-A-PORT Mini S IDDD for consistency with other Shire protocols utilizing this device for intrathecal drug delivery
- To clarify text concerning the management of infusion-related reactions
- To clarify that there are 2 questionnaires, the HCUQ and CIQ, to evaluate health resource utilization and impact
- To clarify that the Month 13 (Week 52) infusion must be performed at the main study site

DETAILED SUMMARY OF CHANGES FOR THE AMENDMENT 1

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

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

Change: Change to planned study duration
Section impacted by this change: 4.4 Study Duration
Revised Text: Patients will participate in this extension study **for a duration of 3 years of treatment** unless they discontinue the study **or** Shire discontinues the study~~, or until they are transitioned onto commercially available treatment, for a maximum duration of 3 years of treatment in this study (SHP-609-302)~~.
Other sections impacted by this change: Synopsis

Change: Removal of duplicated text
Section impacted by this change: 7.15.6.2 Reporting Serious Adverse Events
Revised Text: ~~The following provides contact information for the Shire Medical Monitor.~~
Other sections impacted by this change: None

Change: Clarification to study procedure
Section impacted by this change: 8.2.4.1 Months 19, 25, and 31 (Weeks 76, 100, and 124 [±7 days]) – Prior to Intrathecal Injection – Extended Treatment Phase - All Patients
Revised Text: • Head circumference **(**~~Week~~ **Month** 25 only**)** • Brain MRI (~~Week~~ **Month** 25 only)
Other sections impacted by this change: None

Change: Clarification to study procedure
Section impacted by this change: 8.2.4.2 Months 19, 25, and 31 (Weeks 76, 100, and 124 [±7 days]) – Intrathecal Injection – Extended Treatment Phase - All Patients
Revised Text: • 12-lead ECG **(**~~Week~~ **Month** 25 only**)** • Serum sampling for PK analysis will be collected at ~~Week~~ **Month** 25 only …
Other sections impacted by this change: None

Change: Clarification to study procedure
Section impacted by this change: 8.1.4Treatment and Assessments (Months 1 – 12, Weeks 4 – 48 [±7 days]) – Initial Treatment Phase
Revised Text: Treatment and Assessments (Months 1 – 12, Weeks 4 – 48 **[±7 days]**) – Initial Treatment Phase
Other sections impacted by this change: 7 Study Procedures, 8.2.1 Month 13 (Week 52 [±7 days]) – Extended Treatment Phase – All Patients, 8.2.2 Months 14, 15, 17, 18, 20, 21, 23, 24, 26, 27, 29, 30, 32, 33, 35, and 36 (Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, and 144 [±7 days]) – Extended Treatment Phase - All Patients, 8.2.3 Months 16, 22, 28, and 34 (Weeks 64, 88, 112, and 136 [±7 days]) –Extended Treatment Phase - All Patients, 8.2.4 Months 19, 25, and 31 (Weeks 76, 100, and 124 [±7 days]) – Extended Treatment Phase - All Patients, 8.3 End-of-Study (Month 37, Week 148 [±7 days]) – Extended Treatment Phase - All Patients, Schedules of Events in Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6 and Appendix 7

Change: Clarification to recording of information
Section impacted by this change: 11.5 Patient Confidentiality
Revised Text: Only the patient number ~~and patient initials~~ will be recorded in the eCRF, and if the patient name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor.
Other sections impacted by this change: None

Change: Clarification to footnote lettering
Section impacted by this change: Appendix 4 Extended Treatment Phase Schedule of Events - Months 21 - 25 (Weeks 84 - 100)
Revised Text: *[Due to duplication of footnote a in the list of footnotes shown below the schedule of assessments in Appendix 4, the sequential lettering of the listed footnotes should be readjusted to appear as follows:]* [a] Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as depicted in Appendix 8. [b] The 12-lead ECG is to be performed within 4 hours after IT administration of study drug. [c] General anesthesia or sedation may be required for injections of investigational product 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 and MRI will have to be performed with sedation/anesthesiology support. [d] X-rays may be performed to check placement of the device, and as needed, throughout the study. An X-ray will be performed at the end of the study to verify that the IDDD is in the correct position. [e] Serum samples for PK analysis will be collected within 15 minutes (±5 minutes) prior to intrathecal administration of idursulfase-IT and at 30 minutes (±5 minutes), 60 minutes (±5 minutes), 120 minutes (±5 minutes), 4 hours (±5 minutes), 6 hours (±5 minutes), 8 hours (±15 minutes), 12 hours (±15 minutes), 24 hours (±15 minutes), 30 hours (±15 minutes), 36 hours (±15 minutes) after the start of intrathecal administration. [f] Note that, on IT Dosing Weeks, the IV infusion of Elaprase should be scheduled to occur a minimum of 48 hours after IT administration of idursulfase-IT. [g] When a patient has received and tolerated a total of 12 monthly doses of intrathecal idursulfase-IT across studies HGT-HIT-094 and SHP-609-302, 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. [h] Pre-treatment assessments may be performed on the same day as IT administration of idursulfase-IT, if the patient can arrive at the study site early in the day and if the Investigator deems this clinically appropriate. In the absence of any safety concerns, patients may complete the safety follow-up visit on the same day as IT administration prior to discharge. [i] Patients will remain under observation in the hospital setting (eg, may include infusion center, PACU (recovery suite), observation unit, short stay center) for 4 hours post IT injection for vital signs and other safety assessments. Vital signs will be collected at the following time points (±10 minutes) in association with IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes post end of IT administration, 60 minutes post end of IT administration, 120 minutes post end of IT administration, and 4 hours post end of IT administration. Thereafter, if deemed clinically stable by the Investigator, patients may leave the hospital setting (with exception of Visits at which serial blood sampling for pharmacokinetic evaluation is planned). The patient may need to be examined the following day.

[j] The CSF sample is to be obtained at each IT Dosing Week prior to the injection of idursulfase-IT.
Other sections impacted by this change: None

Change: Correction to superscripted reference to footnote in Study Schedule of Events
Section impacted by this change: Appendix 5 Extended Treatment Phase Schedule of Events - Months 26 - 30 (Weeks 104 - 120)
Revised Text: *[A typographical error in the idursulfase-IT injection entries for Week 104 and Week 108 of the schedule of assessments in Appendix 5 (Extended Treatment Schedule of Events – Months 26-30 [Weeks 104-120]), should be corrected such that the superscript references footnote c, not footnote e (see below).]*

	Month 26			Month 27			Month 28			Month 29			Month	
	Week 104			Week 108			Week 112			Week 116			Week 1	
	IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]			IT Dosing Week[c] Main or Local Site[d]			IT Dosing Main or L Site[d]	
Assessment	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]	Days 3-7[e]	Pre-Tx Day 1[e]	IT Inj Day 2[e]
idursulfase-IT Injection		●[e c]			●[e c]			●[c]			●[c]			●[c]

Other sections impacted by this change: None

DETAILED SUMMARY OF CHANGES FOR THE AMENDMENT 2

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

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

Change: change to medical monitor contact
Section impacted by this change: Cover page
Revised Text: **Medical Monitor:** [redacted]**, DO**
Other sections impacted by this change: 7.15.6.2 Reporting Serious Adverse Events

Change: Clarification that 2 questionnaires are used to evaluate healthcare resource utilization
Section impacted by this change: 2.4 Health Economics and Outcomes Research Objectives
Revised Text: • To evaluate healthcare resource utilization, as measured by **2 questionnaires consisting of the~~a~~** Healthcare ~~Resource~~ Utilization **Questionnaire (HCUQ)** and **Caregiver** Impact Questionnaire **(CIQ)**, in patients with Hunter syndrome and cognitive impairment who are treated with idursulfase-IT in conjunction with Elaprase therapy
Other sections impacted by this change: Synopsis; 3.3 Health Economics and Outcomes Research Endpoints; 7.11.2 Healthcare Resource Utilization and Impact Questionnaires; 8.1.1 Baseline (Month 1, Week 1, Days -7 to Day -1) – Initial Treatment Phase; 8.1.4.1 Prior to Intrathecal Injection (Months 1-12, Weeks 4-48 [±7 Days]) – Initial Treatment Phase; 8.2.1.1 Month 13 (Week 52 [±7 Days]) – Prior to Intrathecal Injection – Extended Treatment Phase – All Patients; 8.2.4.1 Months 19, 25, 31, 37, 49, and 61 (Weeks 76, 100, 124, 148, 196, and 244 [±7 Days]) – Prior to Intrathecal Injection – Extended Treatment Phase – All Patients; 8.3 End of Study (Month 61, Week 244 [±7 Days]) – Extended Treatment Phase – All Patients; 10.5.6 Health Economics and Outcomes Research Endpoint Analyses; Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6, and Appendix 7

Change: Clarification regarding treatment at home
Section impacted by this change: 4.1.3 Treatment Schedule
Revised Text: Patients will receive their monthly doses of intrathecal idursulfase-IT at the main study site or at a local site. 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 a site determined by the patient's physician, or** at the patient's home depending upon the standard location as determined for each patient **(at the discretion of local laws and the treating physician)**.
Other sections impacted by this change: Appendix 2

Change: Change to planned study duration, extended treatment phase increased to 5 years
Section impacted by this change: 4.4 Study Duration
Revised Text: Patients will participate in this extension study for a duration of ~~3~~**5** years of treatment unless they discontinue the study **or** Shire discontinues the study.
Other sections impacted by this change: Synopsis; 4.1.2 Extended Treatment Phase – All Patients; Appendix 1, Appendix 7, Appendix 8, Appendix 9, Appendix 10, Appendix 11, and Appendix 12; 7 Study Procedures; 7.8 Pharmacokinetic Assessments; 7.12.8 Cerebrospinal Fluid Assessments; 8 Study Activities; 8.2.2 Months 14, 15, 17, 18, 20, 21, 23, 24, 26, 27, 29, 30, 32, 33, 35, 36, 38, 39, 41, 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59, and 60 (Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, 192, 200, 204, 212, 216, 224, 228, 236, and 240 [±7 Days]) – Extended Treatment Phase – All Patients; 8.2.3 Months 16, 22, 28, 34, 40, 43, 46, 52, 55, and 58 (Weeks 64, 88, 112, 136, 160, 172, 184, 208, 220, and 232 [±7 Days]) – Extended Treatment Phase – All Patients; 8.2.4 Months 19, 25, 31, 37, 43, 49, 55, and 61 (Weeks 76, 100, 124, 148, 196, and 244 [±7 Days]) – Extended Treatment Phase – All Patients; 8.3 End of Study (Month 61, Week 244 [±7 Days]) – Extended Treatment Phase – All Patients

Change: Clarification concerning study population
Section impacted by this change: 5.1 Study Population
Revised Text: ~~Up to42 p~~**P**ediatric patients (plus potentially any pediatric patients younger than 3 years of age in the antecedent substudy) who completed Study HGT-HIT-094, and meet the eligibility criteria may enroll in this study.
Other sections impacted by this change: Synopsis; 1.3.1 Rationale for Current Phase II/III Study

Change: Clarification concerning the IDDD
Section impacted by this change: 6.1.2 Intrathecal Drug Delivery Device
Revised Text: The drug product will be administered via the SOPH-A-PORT Mini S Implantable Access Port. The SOPH-A-PORT Mini S **is a system intended for implantation by physicians. The SOPH-A-PORT Mini S, once implanted, allows healthcare personnel to administer drugs indicated for intrathecal delivery intermittently over a long period of time**~~device is intended for long-term, intermittent access to the IT space for the delivery of investigational drug~~. The device is CE Marked in the European Union (EU) and considered investigational in non-EU countries.
Other sections impacted by this change: None

Change: Clarification concerning infusion-related reactions
Section impacted by this change: 6.6.1 Infusion Reactions and Management
Revised Text: Infusions of proteins can be associated with reactions to the infusion that may or may not be immune mediated **(hypersensitivity reactions)**. Thus, potential reactions to the infusion of an investigational product**, including idursulfase-IT,** are unpredictable. **It is often difficult to clinically distinguish infusion reactions from hypersensitivity reactions. Symptoms may include headache, fever, sensory paresthesias (including feeling of warmth, tingling, or pain), rash, pruritus, or autonomic symptoms, such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection over time.** **The management of infusion reactions and hypersensitivity reactions is similar. The following steps may be taken, at the discretion of the Investigator, in the event of a suspected infusion related/hypersensitivity reaction and the management of such reactions should be based on the severity of the reaction:** • Treatment with medications such as antihistamines, antipyretics, and/or corticosteroids • Stopping and resuming treatment • Pretreatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required Infusion-related reactions have been observed in patients receiving IV ERT with Elaprase, with symptoms including cutaneous reactions (rash, pruritus, and urticaria), pyrexia, headache, hypertension, and flushing. Previous experience with Elaprase is fully described in the Elaprase US Package Insert and the EU Summary of Product Characteristics (SmPC). Pretreatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. The safety information reported from administration of Elaprase may be relevant to management of adverse events in relation to idursulfase-IT.

Successful management of Elaprase infusion-related adverse events included slowing or interrupting the infusion at the time of the event or pre-treatment with low-dose corticosteroids and/or antihistamines. Most adverse events of this type were treated with antihistamines such as chlorpheniramine (IV administration preferred if available), oxygen, or mild glucocorticoids such as hydrocortisone and prednisolone. All were monitored closely until symptoms of the reactions had subsided. In clinical trials of Elaprase, an apparent decrease in the overall rates of adverse events, and specifically infusion-related adverse events, was observed over time, suggesting that patients may better tolerate infusions during long-term therapy. ~~Because idursulfase-IT is administered intrathecally, it is not expected that systemic blood levels will be high enough to cause an infusion-related reaction. C~~**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. As of the date of this protocol, there have been no significant concerns regarding infusion-related immune reactions following IT administration in studies HGT-HIT-045 and HGT-HIT-046.
Other sections impacted by this change: None

Change: Guidance concerning IDDD malfunction
Section impacted by this change: 7.6.1 IDDD Implantation and Revision
Revised Text: **If at the time of a scheduled dosing, due to a device-related issue it is not possible to aspirate CSF prior to dose administration, administer a full medication dosage using the standard administration steps detailed in the device's IFU, 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 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 device and/or device components will be re-implanted at the earliest possible opportunity, preferably at the same time.**
Other sections impacted by this change: None

Change: Clarification concerning serum albumin assessment
Section impacted by this change: 7.9.2 Cerebrospinal Fluid and Serum Albumin
Revised Text: Albumin levels will be measured in samples of CSF and serum ~~to monitor the permeability of the blood-brain barrier~~. **The relative permeability of the blood-brain barrier will be monitored by the CSF/serum albumin ratio.**
Other sections impacted by this change: 7.12.7 Clinical and Other Laboratory Tests

Change: Change in cognitive testing of Spanish-speaking patients
Section impacted by this change: 7.10.1 Neurodevelopmental Assessment Tools
Revised Text: **COGNITION** The Differential Ability Scales, Second Edition (DAS-II),[17] will be used to assess all patients of age 2 years, 6 months or older**, including Spanish-speaking patients who will be assessed with the Spanish version of the DAS-II**. The DAS-II comprises 2 overlapping batteries. The Early Years battery is designed for children ages 2 years 6 months through 6 years 11 months. The School Age Battery is designed for children ages 7 years 0

months through 17 years 11 months. These batteries are fully co-normed for ages 5 years 0 months through 8 years 11 months.

Any patients who cannot be assessed with the DAS-II due to a deteriorating condition or who are younger than 2 years, 6 months of age, will be assessed with the BSID-III.[18] ~~Spanish-speaking patients will be assessed using the Spanish version of the DAS-II Early Years only for patients of age 8 years, 11 months or younger. Spanish-speaking patients older than 8 years, 11 months will be assessed with the Spanish version of the BAS-II.~~

Table 7-1 Neurodevelopmental Assessments in Study SHP-609-302

Assessment	Intended Study Population	Applicable Age
DAS-II	Patients 2 years, 6 months of age and older[a]	Early Years Battery[a, b] 2 years, 6 months through 6 years, 11 months (extended norms: up to 8 years, 11 months) School Age Battery 7 years, 0 months through 17 years, 11 months
BSID-III	Patients younger than 2 years, 6 months of age and older children who cannot perform the DAS-II ~~or BAS-II~~	1 to 42 months
~~BAS-II~~[a]	~~Spanish-speaking patients older than 8 years, 11 months~~	~~School Age Scale~~ ~~6 years 0 months to 17 years 11 months~~
VABS-II	All patients	Birth to 90 years

Abbreviations: ~~BAS-II=British Abilities Scale, Second Edition;~~ BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; DAS-II=Differential Ability Scales, Second Edition; VABS-II=Vineland Adaptive Behavioral Scales, Second Edition

[a] For the DAS-II, Spanish-speaking patients will be assessed using the Spanish version**s** of the DAS-II **(**Early Years **and School Age)** ~~only~~. ~~The BAS-II will be used instead of the DAS-II to assess any Spanish-speaking patients older than 8 years, 11 months of age~~

[b] Extended norms may be used.

Other sections impacted by this change: Synopsis; 2.2 Secondary Objectives; 3.2 Secondary Efficacy Endpoints; 7.20 Appropriateness of Measurements; 8.1.4.1 Prior to Intrathecal Injection (Months 1-12, Weeks 4-48 [±7 Days]) – Initial Treatment Phase; 8.2.4 Months 19, 25, 31, 37, 43, 49, 55, and 61 (Weeks 76, 100, 124, 148, 196, and 244 [±7 Days]) – Extended Treatment Phase – All Patients; 8.3 End of Study (Month 61, Week 244 [±7 Days]) – Extended Treatment Phase – All Patients; 10.1 General Methodology

Change: Clarification to CSF assessment

Section impacted by this change: 7.12.8 Cerebrospinal Fluid Assessments

Revised Text:

Cerebrospinal fluid samples will be collected via the IDDD or lumbar puncture and used to analyze standard safety laboratory parameters (chemistries ~~[including protein, glucose]~~, cell counts), albumin, GAG, and concentration of idursulfase enzyme. The CSF samples will also be analyzed for idursulfase-specific antibodies and antibodies with enzyme neutralizing activity (Section 7.12.9).

Cerebrospinal fluid will be obtained during the days and weeks of the study as indicated in the Schedule of Events (Appendix 1Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6, ~~and~~ Appendix 7, **Appendix 8, Appendix 9, Appendix 10, Appendix 11, and Appendix 12**). Should the IDDD become

clogged or undergo mechanical complications, the CSF sample will be obtained via LP **until the subject had a functional IDDD**.
Other sections impacted by this change: None

Change: Clarification regarding device adjustment
Section impacted by this change: 7.15.2.4 Device Adjustment
New section: **7.15.2.4 Device Adjustment** **Surgery of the device which does not result in partial or complete revision or removal (eg, surgical exploration only or placement of additional sutures, tissue glue, and/or fascial repair.**
Other sections impacted by this change: None

Change: Clarification regarding statistical methods, details to be included in Statistical Analysis Plan
Section impacted by this change: 10.1 General Methodology
New section: All safety and efficacy data will be summarized descriptively at scheduled visits. For efficacy endpoints, the mean difference in the change at each time point between the 2 HGT-HIT-094 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented **where appropriate**. ~~If the parametric assumption for the distribution cannot be justified, a non-parametric approach will be utilized to estimate the treatment difference and the corresponding 95% confidence interval (ie, median difference or Hodges–Lehmann estimator and the corresponding confidence intervals).~~ The mean values for all efficacy endpoints will be graphed over time where appropriate.
Other sections impacted by this change: Synopsis

Change: Modification of TEAE definition for statistical analysis
Section impacted by this change: 10.7.1 Adverse Events
Revised Text: Treatment-emergent AEs, defined as all AEs from the time of initial **intervention (first surgery for** IDDD implantation ~~(~~**including failed surgeries,** or first dose if ~~no~~ **before first** IDDD implant**ation surgery),** to the last patient visit in the study, will be summarized by the HGT-HIT-094 treatment regimen (idursulfase-IT or No Treatment) and overall.
Other sections impacted by this change: None

Change: Clarification to analysis of IDDD performance
Section impacted by this change: 10.7.6.1 IDDD Performance
Revised Text: ~~The proportion of patients for whom a successful first injection of study drug occurred will be reported among those for whom a first injection was attempted (i.e. those who had an apparently successful implantation and did not suffer a device removal or revision prior to first scheduled injection). The proportion of patients who had no failed injection attempts during the study will also be summarized. The corresponding 95% confidence intervals of the proportion of interest will be estimated, where appropriate. Injections that are not administered for patient-related reasons (e.g. patient uncooperative, competing medical issue, etc) will not be included in the determination of the success of injection rate.~~

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.
Other sections impacted by this change: None

Change: Addition of tables summarizing maximum blood volume collection by study visit
Section impacted by this change: Appendix 13 Maximum Blood Volume Collected by Study Visit
Revised Text: See 4 new tables, as follows: **Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Initial Treatment Phase (Patients Who Did Not Receive Intrathecal Idursulfase-IT in Study HGT-HIT-094)** **Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Extended Treatment Phase (Months 13-27 – Weeks 52-108)** **Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Extended Treatment Phase (Months 28-42 – Weeks 112-168)** **Maximum Blood Volume Collection by Study Visit (Months/Weeks) for the Extended Treatment Phase (Months 43-60 – Weeks 172-240)**
Other sections impacted by this change: 7.12.7 Clinical and Other Laboratory Tests