Statistical Analysis Plan

NCT Number: NCT01506141

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

Study Number: HGT-HIT-046

Document Version and Date: Version: 3.0, 21 February 2023

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.

STATISTICAL ANALYSIS PLAN FOR SHP609-046 Final Abbreviated CSR

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

Protocol Number: HGT-HIT-046 (Amendment 13)

Protocol Date: 17 Aug 2021

Investigation Product: idursulfase for intrathecal use (idursulfase-IT [HGT-2310]),
Device Name: SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire (SOPH-A-PORT® Mini S)
PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System

SAP Version: 3.0, an addendum to SAP for interim analysis 2.0

Date: 21 Feb 2023

Prepared by: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
CSR	clinical study report
ECG	electrocardiogram
GAG	Glycosaminoglycan(s)
IA	interim analysis
ICP	intracranial pressure
IDDD	intrathecal drug delivery device
IT	intrathecal
IV	intravenous
PD	pharmacodynamic
PK	pharmacokinetic
SAP	statistical analysis plan
SAS	Statistical Analysis System©
SQS	Statistical & Quantitative Sciences

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide specifications for the final analysis which will appear in the final abbreviated clinical study report (CSR).

Unless otherwise specified, the analyses in this SAP will apply the same methodologies as specified in the SAP for interim analysis (IA) (v2.0, dated 30 Mar 2017). Only safety and pharmacodynamic (PD) analyses will be presented in the final abbreviated CSR.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

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

The secondary and exploratory objectives are as noted in the SAP for IA in section 4.1. The final analyses will not address pharmacokinetic (PK) related or exploratory objectives.

The device objective is to evaluate the safety and performance of the SOPH-A-PORT Mini S.

2.2 Endpoints

The endpoints are defined in section 4.1 of the SAP for IA. The final analyses will focus on the safety and PD related endpoints as stated in section 4.1, 5.3 and 5.5 of the SAP for IA. The endpoints for the final abbreviated CSR are reiterated below.

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

The secondary PD endpoints include the change from baseline in CSF biomarkers; e.g., glycosaminoglycan (GAG) including heparan sulfate /dermatan sulfate) and the change from baseline in urinary GAGs.

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

3. ANALYSIS SETS

All PD and safety data analysis will be performed using the Safety Population which is defined as follows: all eligible patients from HGT-HIT-045 who have agreed to participate in the extension study and have had either surgical implantation of an intrathecal drug delivery device (IDDD) or intrathecal administration of study drug in the extension study. The definitions of each analysis population are stated in section 6.2 of the SAP for IA; however, the focus of the final analyses will be safety and PD endpoints.

4. STATISTICAL ANALYSIS

All statistical analyses will be performed by Statistics & Quantitative Sciences (SQS) Department at Takeda or its designated contract research organization (CRO) unless otherwise specified, using SAS® software version 9.4 or higher (SAS Institute, Cary, N.C., USA).

The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of the trial.

Summary tables will be tabulated as the format noted in section 6.1 of the SAP for IA. The complete results including Parts A, B & C will be described in the final abbreviated CSR.

4.1 Patient Disposition

The patient disposition (signed informed consent, patient population, and treatment status [completed, discontinued/withdrew]) will be presented in summary tables using number and percentage of subjects by treatment dose and overall, for the Safety Population. Reasons for discontinuation/withdrawal will be presented.

4.2 Protocol Deviations

Protocol deviations will be presented in a listing as noted in section 6.4 of the SAP for IA.

4.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics (as detailed in section 6.5 of the SAP for IA) will be presented in summary tables by treatment dose and overall, for the Safety Population.

4.4 Treatment Compliance and Extent of Exposure

The same methodology as in SAP for IA Section 6.6 will be used. Treatment compliance and extent of exposure will be summarized for the Safety Population.

4.5 Secondary Pharmacodynamic Analyses

The CSF GAG levels will be presented in graphs (individual patient data as well as mean observed data by visit) and descriptive statistics will be in summary tables (observed values, change from baseline and percent change from baseline) as noted in section 6.7.2.1 of the SAP for IA; however, they will not be limited to Month 55. All available scheduled visits to the end of study (including Part C) will be included in tables by treatment dose and overall.

The urine GAG levels will be presented in graphs (individual patient data as well as mean observed data by visit) and descriptive statistics will be in summary tables (observed values, change from baseline and percent change from baseline) as noted in section 6.7.2.2 of the SAP for IA; however, they will not be limited to Month 55. All available scheduled visits to the end of study (including Part C) will be included in tables by treatment dose and overall.

4.6 Analysis of Safety

Similar methodology as in the SAP for IA section 6.8 will be used for the Safety Population.

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

Adverse events will be presented as detailed in section 6.8.1 of the SAP for IA. The clinical and CSF laboratory results will be presented as detailed in section 6.8.2 of the SAP for IA; however, they will be summarized for all available scheduled study visits to the end of study. The 12-lead ECG results will be presented as detailed in section 6.8.3 of the SAP for IA; however, they will be summarized for all available scheduled study visits to the end of study. The infusion (IV) and injection (IT) vital signs and regular vital signs will be listed as detailed in section 6.8.4 of the SAP for IA; however, they will be summarized for all available scheduled visits up to the end of the study.

Similar methodology as in SAP for IA section 6.8.6 will be applied to the Safety Population for:

- Anti-idursulfase antibody formation (specifics in section 6.8.6.1)
- The idursulfase enzyme levels in CSF (specifics in section 6.8.6.2)
- Intracranial pressure (ICP) measurement (cm of H_2O) (specifics in section 6.8.6.3)
- Height (cm), weight (kg), and head circumference (cm) (specifics in section 6.8.6.4).

The details are in sections of the SAP for IA mentioned above; however, presentations will not be limited to Month 55. They will include all available scheduled study visits to the end of study.

All safety analyses will be descriptive, no statistical testing will be performed.

4.7 SOPH-A-PORT Mini S Device Performance

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

See section 6.8.6.5 of the SAP for IA for details regarding device-related terminology as well as well as device performance analyses to be presented.

4.8 Concomitant Medications

See section 6.8.7 of the SAP for IA regarding concomitant medications related presentations.

5. STATISTICAL/ANALYTIC ISSUES

See section 8 of the SAP for IA. This section has 9 subsections which give details on adjustment for covariates, handling of dropouts/missing data, IA and data monitoring, multicenter studies, multiple comparisons/multiplicity, examination of subgroups or interactions, sensitivity analyses, windowing visits, and data listings.

6. REFERENCES

1. Statistical Analysis Plan for Interim Analyses (for Protocol HGT-HIT-046, amendment 9). Version 2.0. 30 March 2017.

7. APPENDICES

See section 10 of the SAP for IA for appendix I: list of statistical outputs and appendix II: protocol violations definitions.

STATISTICAL ANALYSIS PLAN
FOR INTERIM ANALYSIS

Protocol Title:	An Open-Label Extension of Study HGT-HIT-045 Evaluating Long-Term Safety and Clinical Outcomes of Intrathecal Idursulfase-IT Administered in Conjunction with Intravenous Elaprase® in Pediatric Patients with Hunter Syndrome and Cognitive Impairment
Protocol Number:	HGT-HIT-046 (Amendment 9)
Protocol Date:	03 January 2017
Investigational Product and Device:	idursulfase for intrathecal use (idursulfase-IT [HGT-2310]), SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire (SOPH-A-PORT® Mini S)
SAP Author:	[redacted]
SAP Version:	2.0
Release Date:	30 March 2017
Shire Medical Monitor:	[redacted], DO [redacted] 300 Shire Way Lexington, MA 02421, USA Telephone: [redacted] Fax: [redacted]

Statistical Analysis Plan for Protocol HGT-HIT-046

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

The signatures below indicate approval of the Interim Statistical Analysis Plan for Protocol HGT-HIT-046 Amendment 9 dated 03 January 2017. Any changes or modifications to the Statistical Analysis Plan following approval, with the exception of minor editorial changes to table, figure or listing shells or clarification of shells for the programmers require an amendment with the corresponding approval signatures.

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1 ABBREVIATIONS AND DEFINITIONS OF TERMS

ABR	auditory brainstem response
AE	adverse event
ATC	Anatomic therapeutic class
$AUC_{0-\infty}$	Area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration
AUC_{0-t}	Area under the curve from the time of dosing to the last measureable concentration
BBB	Blood brain barrier
BLQ	Below the lower limit of quantification
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency, Second Edition
BRI	Behavioral Regulation Index
BRIEF	Behavior Rating Inventory of Executive Function
BRIEF-P	Behavior Rating Inventory of Executive Function-Preschool
BSID-III	Bayley Scales of Infant Development, Third Edition
CBC	complete blood count
CI	confidence interval
CL	Total body clearance for intravenous administration
CL/F	Total body clearance for extravascular administration divided by fraction of dose absorbed
C_{max}	Maximum serum concentration at t_{max}
CNS	central nervous system
CS	clinically significant
CSF	cerebrospinal fluid
CSR	Clinical study report
DAS-II	Differential Ability Scales, Second Edition
DQ	Developmental Quotient
DS	dermatan sulfate
eCRF	Electronic case report form
EC	Emotional Control
ECG	electrocardiogram
EMI	Emergent Metacognition Index
EOS	end of study
ERT	enzyme replacement therapy
FI	Flexibility Index
FMQ	Fine Motor Quotient
GAG	glycosaminoglycan
GCA	General Conceptual Ability
GEC	Global Executive Composite
GMQ	Gross Motor Quotient
HS	heparan sulfate
IA	interim analysis
ICP	intracranial pressure
IDDD	intrathecal drug delivery device

ILP	Inter-peak latency
ISCI	Inhibitor Self-Control Index
IT	intrathecal
IV	intravenous
KM	Kaplan-Meier
LLOQ	Lower limit of quantification
LP	Lumbar puncture
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
MI	Megacognition Index
Min	minimum
Max	maximum
MMRM	Mixed Model for Repeated Measures
MRI	magnetic resonance imaging
MRT	Mean residence time
NA	Not applicable
NCS	not clinically significant
PDMS-2	Peabody Developmental Motor Scales-2
PK	pharmacokinetic(s)
PO	Plan/Organize
PORT-A-CATH	PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System
PT	prothrombin time
PTA	Pure tone average
PTT	partial thromboplastin time
Q1	25^{th} percentile
Q3	75^{th} percentile
QTc	corrected QT interval
SAE	serious adverse event
SAP	Statistical Analysis Plan
SIB-R	Scale of Independent Behavior-revised
SNC	Special Nonverbal Composite
SOC	system organ class
SOPH-A-PORT Mini S	SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire
SD	Standard deviation
Std. Err.	Standard error
SS	Standard score
$t_{1/2}$	Terminal half-life
T4	thyroxine
t_{max}	Time to maximum serum concentration during a dosing interval
TEAE	Treatment-emergent adverse event
TMQ	Total Motor Quotient
V_{ss}	Apparent volume of distribution at steady-state
V_{ss}(%BW)	V_{ss} normalized for body weight

V_z	Volume of distribution associated with the terminal slope
V_z/F	Volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed
WHO	World Health Organization
WM	Working Memory
λ_z	First order rate constant associated with the terminal (log-linear) portion of the curve

2 INTRODUCTION

2.1 Background

Hunter syndrome is an extremely rare disease with an estimated incidence of 1 in 162,000 live births worldwide. It is expected that approximately 67%-77% of these patients will present with the severe phenotype of the disease that includes progressive cognitive impairment (communicating hydrocephalus, increased intracranial pressure, seizures and hearing problems) and serious somatic disease.

2.2 Study Rationale

The active ingredient of idursulfase-IT (for intrathecal use) drug product is idursulfase (recombinant human iduronate-2-sulfatase), which is the same active ingredient in commercially available Elaprase® (for intravenous use). Elaprase is approved in the EU, the USA, Canada, Japan, and other countries as an intravenously administered enzyme replacement therapy (ERT) for patients with Hunter syndrome. Large proteins such as Elaprase are not expected to cross the blood brain barrier (BBB) in sufficient amounts to be therapeutically beneficial. Therefore, it is not possible to treat the progressive brain disease in severe Hunter syndrome with Elaprase, and direct administration of the active enzyme to the central nervous system is required. A formulation appropriate for intrathecal administration of idursulfase (idursulfase-IT) using an intrathecal drug delivery device (IDDD) has been developed to address this unmet medical need in an extremely rare population. The advantage of using an IDDD in a chronic disease such as Hunter syndrome is the potential to obviate the need for multiple lumbar punctures for drug delivery.

Nonclinical experience with intrathecal administration of idursulfase-IT has demonstrated wide distribution of idursulfase to the central nervous system (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.

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

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

3 PURPOSE OF STATISTICAL ANALYSIS PLAN

The Study HGT-HIT-046 is an open-label extension of Study HGT-HIT-045. One interim analysis (IA) is planned for this extension study. The interim analysis of study data will be conducted at the completion of the 6 months of the antecedent study (HGT-HIT-045) or the 6 months of Initial Treatment Phase (Part A) of this extension study and the 54 months of the Extended Treatment Phase Part B of this extension study. The purpose of this statistical analysis plan (SAP) is to document technical and detailed specifications for the interim analysis of data collected for protocol HGT-HIT-046 Amendment 9. Results of the interim analysis described in this SAP will be included in the interim clinical study report (CSR). Additionally, the planned analyses identified in this SAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the interim CSR but not identified in this prospective SAP will be clearly identified in the interim CSR.

4 SUMMARY OF CLINICAL TRIAL FEATURES

4.1 General Description

Study Objectives	The primary objective of this study is: • To collect long-term safety data in pediatric patients with Hunter syndrome and cognitive impairment who are receiving intrathecal idursulfase-IT and intravenous (IV) Elaprase® enzyme replacement therapy (ERT) The secondary objectives of this study are: • To determine the serum pharmacokinetic (PK) profile of idursulfase when administered as intrathecal idursulfase-IT and in conjunction with Elaprase • To determine the effect of intrathecal idursulfase-IT, given in conjunction with Elaprase, on cerebral spinal fluid (CSF) biomarkers (eg, total glycosaminoglycan [GAG] including heparan sulfate [HS]/dermatan sulfate [DS]) • To determine the effects of intrathecal idursulfase-IT, given in conjunction with Elaprase, on urinary GAG The exploratory objectives of this study are: • To evaluate the long-term effects of intrathecal idursulfase-IT, given in conjunction with Elaprase, on clinical parameters (e.g., physiological assessments, neurocognitive assessments, neurologic function, and brain structure volumes) • To evaluate the long-term effects of intrathecal idursulfase-IT, given in conjunction with Elaprase, on functional activities of daily living, as determined by the Scales of Independent Behavior-Revised (SIB-R) • To explore potential relationships between biomarkers and CNS symptomatology • To determine whether monthly idursulfase-IT administrations results in accumulation of idursulfase within the CSF compartment by measuring idursulfase levels in CSF immediately prior to idursulfase-IT administration • To determine the safety and performance of the SOPH-A-PORT Mini S
Study Endpoints	The primary endpoints of this study are: • Safety of intrathecal idursulfase-IT administration. Safety will be measured by adverse events (AEs) (by type and severity), changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, urinalysis), 12-lead electrocardiogram (ECG), CSF chemistries (contingent on sample availability; cell counts, glucose, and protein), anti-idursulfase antibodies and antibodies having enzyme neutralizing activity in CSF and serum The secondary endpoints of this study are: • Serum idursulfase concentration-time profiles and serum PK parameters of idursulfase, administered as intrathecal idursulfase-IT and in conjunction with Elaprase • Change from baseline in CSF biomarkers (eg, GAG [HS/DS]) • Change from baseline in urinary GAGs The exploratory endpoints for this study are: • Change from baseline in additional clinical parameters (e.g., physiological assessments, standardized neurocognitive assessments, neurologic function, brain magnetic resonance imaging [MRI]) • Change from baseline in functional activities of daily living parameters • Levels of idursulfase in CSF immediately prior to idursulfase-IT administration

	• Exploration of potential relationships between biomarkers and CNS symptomatology SOPH-A-PORT Mini S assessments will include: • The SOPH-A-PORT Mini S device will be evaluated using assessments of device implantation, device function, device longevity and adverse events associated with the implant surgery or device. This data will be collected on the patient's CRF from the time of initial implantation. • As part of the assessment of the SOPH-A-PORT Mini S, it may be necessary to determine the levels of leachables from the device into the CSF and blood. Samples of stored CSF and serum may be used to determine the levels of leachable materials related to the IDDD
Study Design	This is an open-label extension of Study HGT-HIT-045. This study is designed to evaluate the long term safety and clinical outcomes of monthly IT injection of idursulfase-IT (HGT-2310) in conjunction with weekly IV infusion of Elaprase in patients with Hunter syndrome and cognitive impairment. Patients who participated in Study HGT-HIT-045 and completed the HGT-HIT-045 end-of-study (EOS) evaluations, and meet all criteria for inclusion in this extension study will be eligible for enrollment. There are 2 patient groups in Study HGT-HIT-046: those (Group 1) that were previously treated in the antecedent study (HGT-HIT-045) and continue to receive treatment in Part B (defined as Months 7 to 54) of this extension study, and those (Group 2) that were not previously treated in the antecedent study and receive treatment in Parts A (defined as Months 0 to 6) and B (defined as Months 7 to 54) of this extension study. Once patients in Study HGT-HIT-046 have completed Part B, they may continue to receive treatment with idursulfase-IT in Part C (defined as Months 55 to 108) while undergoing a reduced, and less burdensome, schedule of study assessments. The completion of 54 months of treatment is assessed at Pre-Treatment Month 55 Visit. <u>Initial Treatment Phase (previously untreated patients only, Part A)</u>: Patients who did not receive treatment with intrathecal idursulfase-IT in Study HGT-HIT-045 will, during the Initial Treatment Phase of this study (i.e., the first 6 months), undergo treatment and assessments corresponding in schedule and content to those performed for patients who were treated in Study HGT-HIT-045. After completion of the Initial Treatment Phase and if there are no safety concerns, patients may continue receiving monthly intrathecal idursulfase-IT in the Extended Treatment Phase of this study. The dose of idursulfase-IT to be administered to a patient in the initial treatment phase was planned to correspond to the dose (1, 10, or 30 mg) received by other patients in the same cohort of Study HGT-HIT-045 within which the patient was randomized. <u>Extended Treatment Phase (all patients, Parts B and C)</u>: Patients who received 6 months of treatment with intrathecal idursulfase-IT in HGT-HIT-045 will be eligible for enrollment after completing the EOS evaluations in Study HGT-HIT-045. If there are no safety concerns, previously treated patients may continue receiving monthly intrathecal idursulfase-IT in this extension study. The dose of idursulfase-IT to be administered to a patient in the extended treatment phase was planned to correspond to the dose (1, 10, or 30 mg) received by the patient in Study HGT-HIT-045. In the original study design, it was planned that idursulfase-IT would be administered intrathecally once monthly (i.e., every 28 days) via an IDDD at doses of 1, 10, or 30 mg. Because the 1 mg dose was assessed as suboptimal, all patients in the study are currently receiving doses of either 10 or 30 mg.

	It is intended that the IDDD be used to deliver IT injections of study drug and to obtain CSF samples. No other medication will be administered through the device. Should the IDDD become nonfunctional during the study, causing the IT space to be inaccessible via the device, or its use is otherwise precluded on a scheduled day of dosing, lumbar puncture may be performed under prescribed circumstances for the purposes of study drug administration and CSF sample collection. Site personnel will refer to the IDDD manual, which provides details on the investigation and management of any IDDD-related issues. General anesthesia may be required for injections of study drug and some evaluations, and can be used at the discretion of the Investigator as indicated in the study manuals. It is anticipated that study procedures such as lumbar puncture, MRI, and audiometry will have to be performed with sedation/anesthesiology support. Due to recurrent issues with the PORT-A-CATH IDDD, Shire has qualified a new IDDD for use in this study, the SOPH-A-PORT Mini S. It is intended that use of the PORT-A-CATH will be phased out in favor of use of the SOPH-A-PORT Mini S device. An implanted PORT-A-CATH IDDD will be allowed to remain in situ for as long as it is functional, but when a PORT-A-CATH IDDD becomes nonfunctional and needs to be replaced, it will be replaced by a SOPH-A-PORT Mini S IDDD. If patients in the study require revision and/or replacement of the PORT-A-CATH IDDD, it will be removed and replaced with the SOPH-A-PORT Mini S device at a time judged appropriate by the Investigator. A nonfunctional PORT-A-CATH IDDD cannot be replaced by a new PORT-A-CATH device. Surgical IDDD implantation and revision will be performed at the main study center only. Explanation of the IDDD will be performed at the main study center or at the patient's local site, as necessary. Patients will have the IDDD removed when they discontinue participation in the study, unless they are continuing to receive treatment through another mechanism (eg, supplemental study, expanded access program, etc).
Number of Patients	Patients who participated in Study HGT-HIT-045 and completed the HGT-HIT-045 EOS evaluations, and meet all criteria for inclusion in this extension study will be eligible for enrollment. Up to 15 patients are expected.
Study Product	Idursulfase for intrathecal administration (idursulfase-IT, HGT-2310) 1, 10 or 30 mg, once monthly, using either SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire (SOPH-A-PORT Mini S) or PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System (PORT-A-CATH) Commercially available Elaprase for IV infusion will be prescribed by the patient's treating physician and will be administered throughout the study as an IV infusion at a weekly dose of 0.5 mg/kg in accordance with the local prescribing information.
Treatment and Study Duration	Patients will continue treatment in this extension study, unless they discontinue the study or Shire discontinues the study, for a maximum duration of 9 years of treatment across studies HGT-HIT-045 and HGT-HIT-046. Specifically, patients in Group 1 of Study HGT-HIT-046 will receive treatment for at least 4 years in Part B and patients in Group 2 of study HGT-HIT-046 will receive treatment for at least 4.5 years in Parts A and B the protocol. The study will conclude after the last patient has completed his last visit.
Randomization and Blinding	Patients entering the Initial Treatment Phase (previously untreated patients only) received the dose of idursulfase-IT during the initial treatment dose corresponding to the dose (1,10, or 30 mg) received by other patients in the same cohort of Study HGT-HIT-045 within which the patient had originally been randomized.

4.2 Determination of Sample size/Randomization

This is an open-label extension of Study HGT-HIT-045. Patients who participated in Study HGT-HIT-045 and completed the HGT-HIT-045 EOS evaluations, and met all criteria for inclusion in this extension study were eligible for enrollment. Up to 15 patients are expected. Patients entering the Initial Treatment Phase (previously untreated patients only) received the dose of idursulfase-IT corresponding to the dose (1,10, or 30 mg) received by other patients in the same cohort of Study HGT-HIT-045 within which the patient had originally been randomized. No new randomization scheme was utilized. Because the 1 mg dose was assessed as suboptimal, all patients in the study are currently receiving doses of either 10 or 30 mg.

5 EFFICACY AND SAFETY VARIABLES

5.1 Schedule of Evaluations

This extension study has 2 phases: an Initial Treatment Phase (previously untreated patients only, Part A) and an Extended Treatment Phase (all patients, Parts B and C). The detailed schedule of evaluations is located in the HGT-HIT-046 protocol (Amendment 9).

5.2 Primary Efficacy Variable(s)

Efficacy is not a primary endpoint of this study.

5.3 Secondary Pharmacodynamic (PD) Variables

The secondary PD endpoints include:

- Change from baseline in CSF biomarkers (eg, GAG [HS/DS])
- Change from baseline in urinary GAGs

5.4 Pharmacokinetic (PK) Assessments

The PK variables of this study are:

- Serum and CSF concentrations of idursulfase
- Pharmacokinetic variables are described in Section 6.9.3

5.5 Safety Assessments

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

5.6 Exploratory Endpoints

The exploratory endpoints include:

- Change from baseline in additional clinical parameters (e.g., physiological assessments, standardized neurocognitive assessments, neurologic function, brain magnetic resonance imaging [MRI])
- Change from baseline in functional activities of daily living parameters
- Levels of idursulfase in CSF immediately prior to each idursulfase-IT administration
- Exploration of potential relationships between biomarkers and CNS symptomatology

5.7 SOPH-A-PORT Mini S Device Assessment

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

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

6 STATISTICAL ANALYSIS

6.1 General Methodology

All statistical analysis of data will be performed by the Biometrics Department at Shire (except for the PK data, which will be performed by the Clinical Pharmacology and Pharmacokinetics group at Shire) using SAS® statistical software version 9.3 or higher (SAS Institute, NC, USA).

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

The study data will be combined with that of studies HGT-HIT-045 and HGT-HIT-050 for analysis as appropriate. The efficacy and safety analyses will be based on the idursulfase-IT treatment baseline (abbreviated as treatment baseline), which is prior to the date of first IDDD implant surgery or first dose (whichever is earlier). This treatment baseline for the treated patients in HGT-HIT-045 is the closest available Screening/Baseline assessment (including the HGT-HIT-050 screening data) on or before the randomization date in Study HGT-HIT-045, unless specified otherwise. The treatment baseline for the untreated patients in HGT-HIT-045 is the closest available Screening/Baseline assessment prior to the date of first IDDD implant surgery or first dose (whichever is earlier) during the Initial Treatment Phase in HGT-HIT-046, unless specified otherwise. The Screening/Baseline assessments for the untreated patients in HGT-HIT-045 will be performed during the EOS procedures in HGT-HIT-045. If fewer than 30 days had elapsed since completion of the EOS assessments for HGT-HIT-045, Screening/Baseline assessments were not required to be repeated.

Summary tables will tabulate the number, mean, standard deviation (SD) and/or standard error (Std. Err.), median, minimum (min), and maximum (max) values for continuous variables, and the number and percentage of patients for categorical variables; a missing category may be added as needed. For changes from baseline variables the 95% confidence intervals (CI) will also be provided. As appropriate, data plots will be provided.

Data will be summarized by treatment dose (1 mg, 1 or 10 mg and 30 mg) and overall. The treatment dose group 1 or 10 mg includes patients who were initially treated with 10 mg and patients who were initially treated with 1 mg during the Initial Treatment Phase and then switched to 10 mg during the Extended Treatment Phase.

Listing will be provided as per Shire's standard recommended listings. Additional listings may be produced as deemed appropriate.

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

The interim analysis data cutoff date was 12 Jan 2017, which was the date by which all patients completed at least 54 months of treatment in Study HGT-HIT-045 and / or HGT-HIT-046, and also completed Pre-treatment assessment at the Month 55 Visit.

6.2 Analysis Populations

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

All efficacy, pharmacodynamic (PD), safety data analysis will be performed using the Safety Population. All pharmacokinetic (PK) data analyses will be performed using the Pharmacokinetic Population. Device-related analyses will be conducted separately for the SOPH-A-PORT and PORT-A-CATH devices, as well as devices combined, in the set of patients in the Safety Population who had the corresponding device implant procedure performed.

Population	Criteria for Inclusion
Safety	All eligible patients from HGT-HIT-045 who have agreed to participate in the extension study and have had either surgical implantation of an IDDD or intrathecal administration of study drug in the extension study.
Pharmacokinetic	All patients who receive study drug and participate in the scheduled pharmacokinetic studies, and for whom at least 1 post-dose PK blood sample was collected.

6.3 Patient Disposition

Patient disposition (signed informed consent, patient population [Safety and PK Population], treatment status [completed, discontinued/withdrew]) will be presented in summary tables using number and percentage of patients by treatment dose and overall. Reasons for discontinuation/withdrawal will be presented.

6.4 Protocol Deviations

An incident involving noncompliance with the protocol, but one which typically does not have significant effects on the patient's rights, safety, or welfare, or the integrity of the resultant data will be considered a protocol deviation.

Protocol violations will be defined as any major protocol deviation that affects study evaluations. Patients will be examined on a case-by-case basis prior to final 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, a list of protocol deviation will be presented.

6.5 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics (eg, age [years], race, ethnicity, weight [kg], height [cm], and baseline disease status) will be reported in summary tables for the Safety Population by treatment dose and overall.

For patients previously receiving active treatment in study HGT-HIT-045, age (in years) = (randomization date from study HGT-HIT-045 – birth date + 1)/365.25. For patients previously receiving no treatment in study HGT-HIT-045, age (in years) = (date of informed consent for the Initial Treatment Phase of study HGT-HIT-046 – birth date + 1)/365.25. When age is presented in the table, it will be rounded down to the first decimal point. Since height and weight may be measured for multiple times during a visit, the average, if any, of these measurements for the same visit will be used as the value for that visit.

6.6 Treatment Compliance and Extent of Exposure

The number of IT injections received, the number of patients who received IT injections via lumbar puncture (LP), actual average dose, the actual average duration of administrations, the duration of idursulfase-IT treatment, and the percent doses received will be summarized for the Safety Population.

The duration of idursulfase-IT treatment, summarized in months, is defined as the time from the first IT administration to the last administration.

The duration for each idursulfase-IT administrations (in minutes) is calculated by subtracting the administration start time from the administration end time. The actual average duration of idursulfase-IT administration (in minutes) will be calculated as an average value of the idursulfase-IT administrations across all available administrations for the same patient.

Treatment compliance will be summarized in terms of the percent of scheduled doses received. The percent of scheduled doses received for each patient is defined as: [(Number of Complete IT injections Received) ÷ (Expected Number of IT injections at date cut)] * 100.

6.7 Analysis of Efficacy

6.7.1 Primary Efficacy Analysis

Not applicable since there is no primary efficacy endpoint.

6.7.2 Secondary Pharmacodynamics Analyses

6.7.2.1 CSF GAG levels

Individual patient data as well as mean observed data by visit will be graphed for CSF GAG levels. In addition, the observed CSF GAG values, change from baseline, and the percent change from baseline in these values will be summarized descriptively by treatment dose and overall at scheduled study visits. Other CSF biomarkers may be analyzed if deemed necessary.

- During the HGT-HIT-045/Initial Treatment Phase, descriptive statistics at observed values, changes from baseline, and the percent change from baseline will be summarized at Screening/Baseline, on Day 2 of each IT Dosing Week via IDDD immediately prior to IT injection of idursulfase-IT, and at the Month 7 (Week 27) visit.
- During the Extended Treatment Phase Part B, descriptive statistics at observed values, changes from baseline, and the percent change from baseline will be summarized on IT

Injection Day 2 of Month 7 via IDDD immediately prior to IT injection of idursulfase-IT and at 6-month intervals on the IT Injection Day of Monthly IT Dosing Weeks (ie, at Months 13, 19, 25, 31, 37, 43, 49 and 55).

6.7.2.2 Urine GAG levels

Individual patient data as well as mean observed data by visit will be graphed for urine GAG levels. In addition, the observed urine GAG values, change from baseline, and the percent change from baseline in these values will be summarized descriptively by treatment dose and overall at scheduled study visits. Baseline is defined as the Pre-Treatment Day 1 of Week 3 measurement.

- During the HGT-HIT-045/Initial Treatment Phase, descriptive statistics at observed values, changes from baseline, and the percent change from baseline will be summarized at Screening/Baseline, on Pre-Treatment Day 1 of each IT Dosing Week, and at the Month 7 (Week 27) visit.
- During the Extended Treatment Phase Part B, descriptive statistics at observed values, changes from baseline, and the percent change from baseline will be summarized on Pre-Treatment of Day 1 of Month 7 and at 6-month intervals on the Pre Treatment Day of Monthly IT Dosing Weeks (ie, at Months 13, 19, 25, 31, 37, 43, 49 and 55).

6.7.3 Subset Analyses

Due to small sample size, no subset analyses are planned.

6.7.4 Exploratory Analyses

For the parameters listed in each subsection below except as noted, the following analyses will be done:

- The observed values and change from baseline will be summarized at the scheduled study visits, unless specified otherwise.
  - During the HGT-HIT-045/Initial Treatment Phase, descriptive statistics at observed values and changes from baseline will be summarized at Screening/Baseline, on Pre-Treatment Day 1 of IT Dosing Week 3, and at the Month 7 (Week 27) visit.
  - During the Extended Treatment Phase Part B, descriptive statistics at observed values and changes from baseline will be summarized on Pre-Treatment of IT Day 1 of Month 7 and at 6-month intervals on the Pre Treatment Day of Monthly IT Dosing Weeks (ie, at Months 13, 19, 25, 31, 37, 43, 49 and 55).
- Individual patient data of the parameters by time since first IT dose will be also graphed.

Chronological age, when presented, is the age of the patient at the time of the test. It will be calculated by (test date – birth date + 1)/365.25 and 2 decimals will be kept in the dataset.

6.7.4.1 Differential Ability Scale, second edition (DAS-II) and Bayley Scales of Infant Development (BSID-III) Analyses

DAS-II

Descriptive statistics at observed values and changes from baseline will be summarized for the following:

- Standard scores in patients who had taken DAS-II test (either version) for each cluster:
  - Verbal
  - Nonverbal
  - Spatial
  - General Conceptual Ability (GCA)
  - Special Nonverbal Composite (SNC)
- T scores in patients who had taken a DAS-II test for Early Years for each core subtest:
  - Verbal Comprehension (Vcom)
  - Picture Similarities (Psim)
  - Naming Vocabulary (Nvoc)
  - Pattern Construction (Pcon)
  - Matrices (Mat)
  - Coping (Copy)
- T scores in patients who had a DAS-II test for School Age for each core subtest:
  - Recall of Designs (RDes)
  - Word Definitions (WDef)
  - Pattern Construction
  - Matrices (Mat)
  - Verbal Similarities (VSim)
  - Sequential & Quantitative Reasoning (SQR)

Listings will be presented for the above parameters as well as the parameters below:

- Standard Scores / percentiles in each patient who had taken a DAS-II test for each cluster:
  - Verbal
  - Nonverbal
  - Spatial
  - GCA
  - SNC
- T-scores, percentiles of the T-scores and age equivalents (directly from eCRF) versus chronological age as well as Developmental Quotient (DQ) in each patient who had taken a

DAS-II test for Early Years for each core subtest, where DQ=Age equivalent*100/Chronological age:

- Verbal Comprehension
- Picture Similarities
- Naming Vocabulary
- Pattern Construction
- Matrices
- Copying

- T-scores, percentiles of the T-scores and age equivalents versus chronological age as well as DQ in each patient who had taken a DAS-II test for School Age for each core subtest:
  - Recall of Designs (RDes)
  - Word Definitions (WDef)
  - Pattern Construction (Pcon)
  - Matrices
  - Verbal Similarities (VSim)
  - Sequential & Quantitative Reasoning (SQR)

Individual patient data of DAS-II standard scores, core subtests for DAS-II for early years, and core subtests for DAS-II for school age by time on treatment will be graphed.

BSID-III

Listings will be presented for:

- Composite scores, age equivalents versus chronological age as well as DQ and percentiles in each patients who had taken BSID-III test for each domain
  - Cognitive
  - Language
  - Social-emotional
  - Adaptive behavior

6.7.4.2 Scale of Independent Behavior- revised (SIB-R) Analyses

Listings will be presented for:

- Standard scores and percentiles for each category
  - Motor skills
  - Social interaction/communication skills
  - Personal living skills
  - Community living skills

- Broad Independence

6.7.4.3 Behavior Rating Inventory of Executive Function (BRIEF) Analysis – Regular Version and Preschool Version (BRIEF-P)

Listings will be presented for:

- The common scales and indexes that exist in both versions of BRIEF tests and for each patient for whom either version of BRIEF test has been performed. Note: for school version (5-18 years old) of BRIEF, GEC= Behavioral Regulation Index (BRI) + Metacognition Index (MI); for preschool version BRIEF test, GEC= Inhibit + Shift + EC + WM+PO.
  - The common scales:
    - Inhibit
    - Shift
    - Emotional Control (EC)
    - Working Memory (WM)
    - Plan/Organize (PO)
  - The common index:
    - Global Executive Composite (GEC)
  - Each index that is unique to the BRIEF-P test:
    - Inhibitor Self-Control Index (ISCI) = Inhibit+EC
    - Flexibility Index (FI) = Shift+EC
    - Emergent Metacognition Index (EMI) = WM+PO
  - Each scale and index that are unique to the BRIEF test:
    - Scales:
      - Initiate
      - Organization of Material
      - Monitor
    - Indexes:
      - Behavior Regulation Index (BRI) = Inhibit + Shift + Emotional Control
      - Megacognition Index (MI) = Initiate + WM + PO + Organization of Materials + Monitor

6.7.4.4 Peabody Developmental Motor Scales-2 (PDMS-2) and Bruininks-Oseretsky Test of Motor Proficiency 2nd edition (BOT-2) Analyses

PDMS-2

Listings will be presented for:

- Standard Scores and DQ=Age equivalent*100/Chronological age of the PDMS-2 subtests:

- Reflexes
- Stationary
- Locomotion
- Object Manipulation
- Grasping
- Visual-Motor Integration:
  - Gross Motor Quotient (GMQ)
  - Fine Motor Quotient (FMQ)
  - Total Motor Quotient (TMQ)

BOT-2

Listings will be presented for:

- Composite Standard Scores and percentiles of Total Motor and the each subtest:
  - Fine Manual Control
  - Manual Coordination
  - Body Coordination
  - Strength and Agility

6.7.4.5 Correlation Analyses

Correlation coefficients between the following parameters will be calculated using a Mixed Model for Repeated Measures (MMRM):

- Standard scores for GCA and SNC in DAS-II
- Standard scores for GCA in DAS-II and standard scores for SIB-R, including the following:
  - Motor skills
  - Social interaction/communication skills
  - Personal living skills
  - Community living skills
  - Broad Independence
- Standard scores for GCA and CSF GAG level

Scatter plots of the above paired variables and their correlation coefficients will be presented in graphs.

6.7.4.6 Brain MRI

The Brain MRI measurements will be summarized descriptively for the following parameters:

- Brain Total Intracranial Volume (cm^3)
- Brain Total Tissue Volume (cm^3)
- Brain Total White Matter (cm^3)
- Brain Total Gray Matter (cm^3)
- Total CSF Volume (cm^3)

Descriptive statistics of observed values and changes from baseline will be summarized by treatment dose and overall at scheduled study visits.

- During the HGT-HIT-045/Initial Treatment Phase, descriptive statistics at observed values and changes from baseline will be summarized at Screening/Baseline and at Month 7 (Week 27) visit.
- During the Extended Treatment Phase Part B, descriptive statistics at observed values and changes from baseline will be summarized on Pre-Treatment of IT Day 1 of Month 7 and at 12-month intervals on the Pre Treatment Day of Monthly IT Dosing Weeks (ie, at Months 19, 31, 43 and 55).

6.7.4.7 Auditory Brain Stem Response (ABR)

Hearing assessment via audiometric measurement will be performed on all patients. The following parameters will be calculated:

- Inter-peak latency (IPL) for each ear
  - IPL I-III = Wave III latency minus Wave I latency (unit in ms)
  - IPL III-V= Wave V latency minus Wave III latency (unit in ms)
- Inter-aural latency = Wave V latency of the right ear minus that of left ear
- Mean air conduction (dBnHL) and Bone conduction Threshold (dBnHL) at 0.25 KHz, 0.5 KHz, 1 KHz, 2 KHz and 4 KHz for each ear

The observed values of IPL 1-V (unit in ms), the absolute latencies [Wave I, III and V (unit in ms)], the above calculated parameters, and the estimated pure tone average (PTA) for each ear (directly from eCRF) and change from baseline for those variables will be summarized by treatment dose and overall at scheduled study visits for each ear.

- During the HGT-HIT-045/Initial Treatment Phase, descriptive statistics at observed values and changes from baseline will be summarized at Screening/Baseline and at Month 7 (Week 27) visit.
- During the Extended Treatment Phase Part B, descriptive statistics at observed values and changes from baseline will be summarized on Pre-Treatment Day 1 of Month 7, on the Pre-

Treatment Day of the 12- Month Visits (ie, at Months 19, 31, 43 and 55).

6.7.4.8 Hearing Assessment

It is intended that patients who receive study drug will have hearing assessments performed at scheduled study visits. The number and percentage of patients in the hearing assessment categories (hearing aid, right ear test results, left ear test results, right ear level of hearing loss and left ear level of hearing loss) will be summarized by treatment dose and overall at scheduled study visits.

- During the HGT-HIT-045/Initial Treatment Phase, descriptive statistics will be summarized at Screening/Baseline, Pre-Treatment Day 1 of IT Dosing Week 3, Pre-Treatment Day 1 of IT Dosing Week 15 (before the fourth IT injection), and at Month 7 (Week 27) visit.
- During the Extended Treatment Phase Part B, descriptive statistics will be summarized on Pre-Treatment of IT Day 1 of Month 7 and at 6-month intervals on the Pre Treatment Day of Monthly IT Dosing Weeks (ie, at Months 13, 19, 25, 31, 37, 43, 49 and 55).

6.7.4.9 Vision Assessment

It is intended that all patients have a vision assessment performed at scheduled study visits. The number and percentage of patients of the vision assessment results (normal, abnormal or missing) will be summarized by treatment dose and overall at scheduled study visits.

- During the HGT-HIT-045/Initial Treatment Phase, descriptive statistics will be summarized at Screening/Baseline, and at Month 7 (Week 27) visit.
- During the Extended Treatment Phase Part B, descriptive statistics will be summarized on Pre-Treatment of IT Day 1 of Month 7 and at 6-month intervals on the Pre Treatment Day of Monthly IT Dosing Weeks (ie, at Months 13, 19, 25, 31, 37, 43, 49 and 55).

6.8 Analysis of Safety

As specified in Section 5.4, the primary assessments of this study are the safety of idursulfase-IT administration. Safety will be measured by AEs (by type and severity), changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, urinalysis), 12-lead ECG, CSF chemistries (contingent on sample availability; cell counts, glucose, and protein), anti-idursulfase antibodies and antibodies having enzyme neutralizing activity in CSF and serum.

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

All safety analyses will be descriptive, no statistical testing will be performed.

6.8.1 Adverse Events

AEs will be recorded throughout the study and at early termination. AEs and medical conditions will be coded using the MedDRA version 16.0 or higher.

For IA analysis, treatment-emergent AEs (TEAE) are defined as all AEs occurring on or after the date of the first IDDD implant surgery or first dose (whichever is earlier) and on or before the EOS visit (+30 days) or 2 weeks after the removal of the last IDDD if early termination (whichever is later). In general, an AE will be deemed TEAE if it cannot be definitively categorized by the available components (day, month, year) of the AE onset date with respect to the date of intervention (the date of the first IDDD implant surgery or first dose [whichever is earlier]). Summaries for the following TEAE categories will be presented:

1. Patients who experienced no AEs,
2. Patients who experienced at least one AE
3. Patients who discontinued due to an AE(s)
4. Patients who died
5. Patients who experienced at least one serious adverse event (SAE),
6. Patients who experienced at least one severe/life-threatening AE,
7. Patients who experienced at least one IV Elaprase infusion-related adverse event
8. Patients who experienced at least one idursulfase-IT-related adverse event
9. Patients who experienced at least one IT Treatment Regimen-related adverse event (i.e., related to one or more of the following: study drug, IDDD, device surgical procedure, lumbar puncture, and IT-administration process)
10. Patients who experienced at least one IDDD surgical procedure-related adverse event
11. Patients who experienced at least one IDDD-related adverse event
12. Patients who experienced at least one IT Administration Process-related adverse event

The AE categories 1-7 will be presented by each treatment dose and overall, while the AE categories 8-12 will be presented for patients in the Safety Population who received idursulfase-IT. IT administration process-related AEs will be summarized by IT administration method (LP or IDDD) as well. The AE categories 10-11 will be presented for patients in the Safety Population with the device implanted.

The number and percentage of patients, and the number of corresponding AEs will be summarized in the overall summary tables. In addition, the number and percentage of patients having any treatment-emergent AE within the AE categories 2, 5, 7-12 and the number of corresponding AEs will be displayed by MedDRA System Organ Class (SOC), Preferred Term (PT) and treatment dose group. The most common treatment-emergent AEs which happened in >20% patients in any treatment dose group will also be summarized by SOC and PT.

The number and percentage of patients having any treatment-emergent AE, and the number of corresponding AEs will be summarized by severity; at the patient level, a patient is counted only once by any event, SOC, or PT under the most severe category.

The number and percentage of patients having any treatment-emergent AE, and the number of corresponding AEs will be summarized by relationship to IV Elaprase, idursulfase-IT, and at least one IT treatment regimen, and displayed by MedDRA SOC, PT and treatment dose; at the patient level, a patient is counted only once by any event, SOC, or PT under the most related category.

Furthermore, listings of all the AEs of categories 3-6 will be provided if applicable.

6.8.2 Clinical and CSF Laboratory Evaluations

Chemistry and hematology serum laboratory and CSF (standard chemistries, glucose, protein, and cell counts) values will be summarized in terms of the absolute value and change from baseline by treatment dose at scheduled study visits.

- During the HGT-HIT-045/Initial Treatment Phase, descriptive statistics at observed values and changes from baseline will be summarized at Screening/Baseline, Pre-Surgery Day 1 of Week 1, Pre-Treatment Day 1 of each IT Dosing Week, and at the Month 7 (Week 27) visit.
- During the Extended Treatment Phase Part B, descriptive statistics at observed values and changes from baseline will be summarized on Pre-Treatment of IT Day 1 of Month 7 and at 6-month intervals on the Pre-Treatment Day of Monthly IT Dosing Weeks (ie, at Months 13, 19, 25, 31, 37, 43, 49 and 55).

Box plots for total protein, glucose, and total nucleated cells by treatment dose will be presented at each scheduled study visit.

All the laboratory (chemistry, hematology, urinalysis and CSF) values will be categorized as a patient having had: (1) an Abnormal and Clinically Significant (CS) value at any time during the study post baseline, (2) no CS values at any time during the study post baseline but had at least one Abnormal value, and (3) Normal values at all time during the study post baseline. The number and percentage of patients in each category will be presented by treatment dose and overall. Patients with a Normal or non-CS value for a particular laboratory parameter at baseline who experience a change to CS for that laboratory parameter post-baseline will be identified and listed separately along with the corresponding laboratory values over time. The baseline is defined as the Screening/Baseline measurement. If it is not available, the Pre-Surgery Day 1 of Week 1 measurement will be used as baseline.

If a particular laboratory measurement has been either repeated or retested, then the repeated or retested measurement for that laboratory parameter, with respect to date/time, will be used in the statistical analysis unless this value is invalid/missing. The handling of repeated or retested laboratory measurements should only consider the specific laboratory measurement that was repeated or retested.

6.8.3 12-Lead ECG Evaluations

The 12-lead ECG parameters (heart rate [bpm], PR interval [msec], QRS interval [msec], QT interval [msec] and the corrected QT interval (QTc) [msec]) will be summarized in terms of absolute value and change from baseline by treatment dose at scheduled study visits. The QTc

interval will be calculated using Bazett's formula as QT divided by the square root of RR interval. The number and percentage of patients with ECG abnormalities post baseline will be presented by treatment dose and overall at scheduled study visits.

- During the HGT-HIT-045/Initial Treatment Phase, descriptive statistics at observed values and changes from baseline will be summarized at Screening/Baseline, Pre-Surgery Day 1 of Week 1, Pre-Treatment Day 1 of IT Dosing Week 3 only, Day 2 of each IT Dosing Week after injection of the study drug, and at Month 7 (Week 27) visit.
- During the Extended Treatment Phase Part B, descriptive statistics of observed values and changes from baseline will be summarized on Pre-Treatment of IT Day 1 of Month 7, after injection of study drug on Monthly IT Dosing Weeks at Months 7, 8, and 9, and at 12-month intervals of after injection of study drug on Monthly IT Dosing Weeks (ie, at Months 19, 31, 43 and 55).

Additionally, the 12-Lead ECG will assess if patients experience normal or abnormal sinus rhythm, and atrial or ventricular hypertrophy (normal or abnormal, where normal means that atrial or ventricular hypertrophy was absent and abnormal means that atrial or ventricular hypertrophy was present). Both of these 12-Lead ECG results will be categorized as abnormal post baseline for the patient as long as at least one abnormal finding is reported at any time during the study post baseline; the number and percentage in each category will be presented. The baseline is defined as the Screening/Baseline measurement. If it is not available, the Pre-Surgery Day 1 of Week 1 measurement will be used as baseline.

A list of Clinical Significant ECG findings will be presented. Additionally, individual patients' plots of ECG parameters at each visit will be graphed.

6.8.4 Vital Signs

The infusion (IV), injection (IT) vital signs and regular vital signs (temperature [C], pulse [bpm], blood pressure [systolic and diastolic, mmHg], oxygen saturation, and respiration rate [per min] will be listed.

- During the HGT-HIT-045/Initial Treatment Phase, vital signs will be collected at Screening/Baseline, during Surgery Week 1 at Day 1, Day 2, Days 3-6 (ie, during IV infusion of Elaprase), Pre-Treatment Day 1 of each IT Dosing Week, Day 2 and Days 3-7 (ie, during IV infusion of Elaprase) of each IT Dosing Week after injection of the study drug, and at Month 7 (Week 27) visit.

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

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

    - IV infusion of Elaprase: within 15 minutes prior to infusion, 30 minutes (±10 minutes) post start of infusion, 60 minutes (±10 minutes) post start of infusion, 90 minutes (±10 minutes) post start of infusion, 120 minutes (±10 minutes) post start of infusion, 150 minutes (±10 minutes) post start of infusion, 180 minutes (±10 minutes) post start of infusion (ie, end of infusion), 30 minutes (±10 minutes) post end of infusion and 60 minutes (±10 minutes) post end of infusion.
- During the Extended Treatment Phase Part B, vital signs will be collected on Pre-Treatment Day 1 and on the IT Injection Day of Month 7 and 6-month intervals of Pre-Treatment Day 1 and on the IT Injection Day on Monthly IT Dosing Weeks (ie, at Months 13, 19, 25, 31, 37, 43, 49 and 55).
    - At a minimum, vital signs will be collected at the following time points on IT administration of idursulfase-IT: within 15 minutes prior to IT administration, 30 minutes (±10 minutes) post end of IT administration, 60 minutes (±10 minutes) post end of IT administration, 120 minutes (±10 minutes) post end of IT administration, and 4 hours (±10 minutes) post end of IT administration.

6.8.5 Physical and Neurological Findings

Clinically significant physical and neurological examination findings will be recorded and summarized either as part of the medical history or adverse event data. No additional summary or listing will be provided.

6.8.6 Other Observations Related to Safety

6.8.6.1 Anti-Idursulfase Antibody Formation

Anti-idursulfase antibody formation will be monitored throughout the study for both serum and CSF. The number and percentage of patients testing anti-idursulfase antibody will be summarized by treatment dose at baseline, any time post-baseline and scheduled study visits. Baseline is defined as the Pre-Treatment Day 1 of Week 3 measurement for the serum antibodies. Baseline is defined as the Screening/Baseline measurement for the CSF antibodies.

- During the HGT-HIT-045/Initial Treatment Phase, descriptive statistics at observed values will be summarized at Screening/Baseline, on Pre-Treatment Day 1 of each IT Dosing Week, and at the Month 7 (Week 27) visit.
- During the Extended Treatment Phase Part B, descriptive statistics at observed values will be summarized on Pre-Treatment of IT Day 1 of Month 7, and at 6-month intervals on the Pre-Treatment Day of Monthly IT Dosing Weeks (ie, at Months 13, 19, 25, 31, 37, 43, 49 and 55).

Titer values will be summarized as box plots over time in patients with positive antibodies at the scheduled visit. A similar plot for patients who developed positive neutralizing antibodies at the scheduled visit will be presented by treatment dose.

6.8.6.2 CSF Enzyme Level

The Idursulfase enzyme levels in CSF will be plotted for individual patient. If a measurement is less than the lower level of quantification (LLOQ), then it will be replaced by zero.

6.8.6.3 Intracranial Pressure

Intracranial pressure (ICP) measurement (cm of H_2O) for those patients undergoing lumbar puncture will be summarized at scheduled study visits. Additionally, the change from baseline to each applicable post-baseline assessment will also be summarized.

- During the HGT-HIT-045/Initial Treatment Phase, descriptive statistics at observed values and changes from baseline will be summarized at Screening/Baseline, and at the Month 7 (Week 27) visit.
- During the Extended Treatment Phase Part B, descriptive statistics at observed values and changes from baseline will be summarized on Pre-Treatment of IT Day 1 of Month 7 and at 12-month intervals on the Pre Treatment Day of Monthly IT Dosing Weeks (ie, at Months 19, 31, 43 and 55).

6.8.6.4 Height, Weight, and Head Circumference

Height (cm), weight (kg), and head circumference (cm) observed values, and the change from baseline will be summarized by treatment dose at scheduled study visits. If multiple measurements were taken for the same visit, their mean will be the measurement for that visit.

For height and weight,

- During the HGT-HIT-045/Initial Treatment Phase, descriptive statistics at observed values and changes from baseline will be summarized at Screening/Baseline, Pre-Surgery Day 1 and Day 7 of Surgery Week 1, at Day 1 of each IT Dosing Week, and at the Month 7 (Week 27) visit.
- During the Extended Treatment Phase Part B, descriptive statistics at observed values and changes from baseline will be summarized on Pre-Treatment Day 1 of Month 7 and at 6-month intervals on the Pre Treatment Day of Monthly IT Dosing Weeks (ie, at Months 13, 19, 25, 31, 37, 43, 49 and 55).

For head circumference,

- During the Initial Treatment Phase, descriptive statistics at observed values and changes from baseline will be summarized at Screening/Baseline, on Pre-Treatment Day 1 of IT Dosing Week 3, and at the Month 7 (Week 27) visit.
- During the Extended Treatment Phase Part B, descriptive statistics at observed values and changes from baseline will be summarized at on Pre-Treatment Day 1 of Month 7, and at 12-month intervals on the Pre Treatment Day of Monthly IT Dosing Weeks (ie, at Months 19, 31, 43 and 55).

6.8.6.5 SOPH-A-PORT Mini S Device Performance

Device-related Terminology

- Initial device implant: The first IDDD implant that a patient ever receives
- 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 (e.g., port revision).
- Full device revision: The device is removed (explanted) in its entirety, and a completely new device is implanted.
- Complete device removal without immediate replacement: All parts of the device (both port and catheter) are removed, and there is no new device implant.
- Device adjustment: A surgical procedure where the device is adjusted but all existing components remain implanted
- Delayed device implant after previous removal: Implant of a new device after a previous device had been completely removed without immediate replacement on a separate and earlier occasion
- Device malfunction: The device does not perform as intended, based on the description in the device's Instructions for Use, but does not require either a partial or full device revision. If at the time of a scheduled dosing it is not possible to administer a full medication dosage as per the standard administration steps detailed in the device's Instructions for Use due to a device-related issue, the IDDD will be declared a device malfunction.
- Resolved device malfunction: A temporary device malfunction that resolves without the need for a full or partial device revision. Programmatically, it is when the malfunction date is present and outcome of malfunction is resolved.
- Device failure: When the device irreversibly fails to perform as intended and cannot be corrected without a device surgical intervention (either a partial or full device revision or removal). The IDDD will be declared a device failure, starting from the date of the initial malfunction that persisted and lead to the surgical intervention. Intrathecal drug delivery devices that are considered to be malfunctioning at the end of the study will be categorized as failures. For programming purposes, a device failure is when the malfunction date is present and outcome of malfunction is device failure. The date of the device failure is the date of the initial malfunction.
- IDDD Longevity: Total number of IDDD failures and explant divided by the total time at risk across all subjects in years (sum of time to IDDD failure or the last injection if not failed at the end of the data cut or explant date, from initial implantation, delayed implantation, or revision for all IDDDs).

Device Performance Analyses

SOPH-A-PORT safety and performance will be summarized for IDDD-implanted patients in the Safety population. The number and proportion of patients of the following categories and the corresponding event count and event percentage will be summarized:

- With the initial device implant only (i.e., no additional surgeries)
- Who had any post-initial implantation device surgeries and type of surgery
- Who had difficulties associated with the implant procedure (e.g., difficulty accessing spinal canal, etc.)

IDDD-related surgical procedure details for initial implants, delayed implantation, and full system revisions across all IDDD implantations for all patients will be summarized by failed or not failed IDDDs and overall, including incision region (paramedian vs. other), identification of the catheter passer used (Phoenix Neuro vs. other), number of suture wings implanted, interspace for catheter insertion into lumbar spine (L1-2, L2-3, L3-4, L4-5, L5-S1), spinal vertebral level of catheter tip (cervical, thoracic, lumbar, and sacral), and clinical site.

The number and proportion of patients who had at least 1 abnormal IDDD radiological assessment finding and the number of abnormal findings from the IDDD radiological assessments will be also summarized by types of the abnormality.

The number and proportion of patients and IDDDs with 1 or more total malfunctions (including malfunctions leading to failure, resolved malfunctions, and malfunctions that are ongoing), malfunctions leading to failure, resolved or ongoing malfunctions, as well as the corresponding number of events, will be presented. The types of total malfunctions and the reasons for IDDD failures reported by the site will be summarized at the patient, IDDD, and event level.

The annual event rate of IDDD failures and malfunctions will be calculated for each patient, and the descriptive statistics will be summarized. The overall IDDD failure rate and the corresponding 95% CI will be presented. The overall IDDD failure rate is calculated as the total number of IDDD failures for all patients divided by the total IDDD time at risk, which is defined as the total time to IDDD failure or the last injection if IDDD is not failed, from initial implantation, delayed implantation, or revision for all IDDDs.

The time from initial implant surgery to first IDDD failure and the time to first malfunction will be analyzed using the Kaplan Meier (KM) method for each patient who is in the Safety Population and had at least one IDDD implanted. The time to first IDDD failure or malfunction (weeks) will be obtained by subtracting the date of the first IDDD implantation for the patient from the date of first failure or malfunction plus 1, divided by 7, and one decimal will be kept. Patients without an IDDD failure or malfunction will be censored at their last study drug injection date. For the interim analysis, patients without an IDDD failure or malfunction will be censored at the data cutoff date, which is January 12, 2017. The number of IDDDs at risk, the cumulative number of IDDDs failed and censored, and the cumulative probability of failure with the corresponding standard error will be summarized in a table at each event time. The 25th percentile (Q1), median and 75th percentile (Q3) of the time to first failure or malfunction

distribution and the 95% confidence interval (CI) will be presented together with the KM plots. A by-patient listing of the device failure and malfunction data will be displayed.

The number of doses received via IDDD will be summarized. 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 (e.g. patient uncooperative, competing medical issue, etc.) will not be included in the determination of the injection success rate.

Whether any device component was implanted will be summarized for all IDDD kits which were opened. For the implanted IDDDs, their status (i.e., removed or not) at the end of the study will be reported. If an IDDD was removed, whether the catheter was removed along with the port will also be summarized.

By-patient listings of SOPH-A-PORT malfunctions and failures, and IDDD exposure will be provided.

6.8.7 Concomitant Medications

For IA analysis, concomitant medications are defined as all medications taken on or after the date of the first IDDD surgery or first dose (whichever is earlier) and on or before the EOS visit (+30 days) or 2 weeks after the removal of the last IDDD if early termination (whichever is later). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version 16.0 or higher. Concomitant medication use will be summarized by Therapeutic Class and Preferred Term for each treatment dose group and overall for the Safety Population.

6.9 Analysis of Pharmacokinetic Data

All pharmacokinetic analyses will be performed using the PK Population.

6.9.1 Concentration Data

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

6.9.2 Handling BLQ Values

The following procedures will be used for serum concentrations below the lower limit of quantification (LLOQ) (reported as BLQ):

Samples that are BLQ are treated as zero in the calculation of summary statistics (e.g., mean, SD, etc.) for the serum concentrations at individual time points.

Mean concentrations are reported as zero if all values are BLQ, and no descriptive statistics are reported. If the calculated mean (± SD) concentration is less than the LLOQ, the value will be reported as calculated. The mean values derived using these conventions will be used to create the mean serum concentration versus time plots.

For calculation of area under the serum concentration curve (AUC), BLQ values are set equal to zero in the dataset loaded into WinNonlin for pharmacokientic analysis. WinNonlin uses the zero values that occur before the first time point with a concentration greater than LLOQ, but WinNonlin excludes the zero values from AUC calculation for all later time points.

Serum samples that are BLQ are reported as zero on the data listings.

6.9.3 Pharmacokinetic Parameters

The pharmacokinetic analysis will be conducted by the Clinical Pharmacology and Pharmacokinetics Department of Shire Pharmaceuticals using Phoenix WinNonlin version 6.3 or higher (Pharsight Corporation, Mountain View, California, USA).

Pharmacokinetic parameters will be determined from serum concentration-time data using noncompartmental methods and all calculations will be based on actual sampling times. Serum concentration vs. time will be plotted for each patient. Mean serum concentration vs. time curves will also be presented by route of administration (IV and IT administration), treatment dose (0.5mg/kg for IV administration, and 1mg, 10mg, and 30mg for IT administration) at scheduled study visits.

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

- $AUC_{0-\infty}$ - Area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration
- AUC_{0-t} - Area under the curve from the time of dosing to the last measureable concentration
- C_{max} - Maximum concentration occurring at t_{max}
- t_{max} - Time of maximum observed concentration sampled during a dosing interval
- CL/F – Total body clearance for extravascular administration divided by the fraction of dose absorbed. This parameter will be presented with and without normalization for body weight.
- V_z/F – Volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed. This parameter will be presented with and without normalization for body weight.
- λ_z – First order rate constant associated with the terminal (log-linear) portion of the curve
- t½ - Terminal half-life

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

- $AUC_{0-\infty}$ - Area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration
- AUC_{0-t} - Area under the curve from the time of dosing to the last measureable concentration
- C_{max} - Maximum concentration occurring at t_{max}
- t_{max} - Time of maximum observed concentration sampled during a dosing interval
- CL – Total body clearance for intravenous administration. This will be presented with and without normalization for body weight.
- V_z – Volume of distribution associated with the terminal slope. This parameter will be presented with and without normalization for body weight
- V_{ss} – Observed steady-state volume of distribution. This parameter will be presented with and without normalization for body weight.
- MRT - Mean residence time
- t½ - Terminal half-life

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

6.10 Drug-Drug and Drug-Disease Interactions

This study was not designed to evaluate drug-drug or drug-disease interactions and therefore the interactions will not be assessed in the study.

7 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

7.1 Changes in the Conduct of the Study

Please see the amendment summaries in the HGT-HIT-046 protocol Amendment 9.

7.2 Changes from the Analyses Planned in the Protocol

There were no changes proposed from those planned in the protocol.

8 STATISTICAL/ANALYTIC ISSUES

8.1 Adjustment for Covariates

All analyses will be descriptive in nature, therefore there will be no adjustment for covariates.

8.2 Handling of Dropouts or Missing Data

No data imputation will be performed.

8.3 Interim Analyses and Data Monitoring

One interim analysis and an interim clinical study report are planned describing the results of Parts A and B. Descriptive analyses of the data before trial completion may be performed for safety monitoring, regulatory reporting or general planning purposes. Because no formal hypothesis testing is planned, multiplicity concerns regarding repeated analyses in the final are not an issue.

8.4 Multicenter Studies

There are two centers planned for this study. No subset analyses of center effect will be conducted. No adjustment due to multi-centers will be utilized in the analyses.

8.5 Multiple Comparisons/Multiplicity

Analyses are descriptive in nature. No multiple comparison procedure or multiplicity adjustment will be performed.

8.6 Examination of Subgroups and Interactions

No subgroup analyses are planned. In addition, interaction effects will not be examined for the outcome measurements due to the small sample size.

8.7 Sensitivity Analyses

Not applicable

8.8 Windowing Visits

Although there is a visit window of +/- 7 days around the expected visit date, nominal visits will be used for the per-visit analyses. Therefore, no windowing of visits by actual study day will be done for data obtained at the scheduled visits. For subjects who withdraw from the study pre-maturely, if the early termination visit falls into the window of a scheduled visit as defined in the protocol, the early termination visit is also summarized for that scheduled visit, unless the scheduled visit already took place.

8.9 Data Listings

All data will be presented as SAS datasets in CDISC format. Unless specifically stated in above sections, no other by-patient data listings will be provided.

9 REFERENCES

1. Elliot CD. The Differential Abilities Scales (DAS) San Antonio, TX The Psychological Corporation; 1995.
2. Bayley N. Bayley Scales of Infant and Toddler Development: Third Edition. San Antonio, TX The Psychological Corporation; 2005.
3. Bruininks RH, Woodcock RW, Weatherman RF, Hill BK. Scales of Independent Behavior – Revised. Itasca, IL: Riverside Publishing; 1996.
4. Folio M, Fewell R. Peabody Developmental Motor Scales, Second Examiner's Manual. Austin, TX: Pro-ed; 2002.
5. Folio MR, Fewell R. Peabody Developmental Motor Scales: Examiner's Manual. 2nd ed. Austin TX; 2000.
6. Bruininks RH, Bruininks BD. Bruininks-Oseretsky Test of Motor Proficiency. In: Pearson Assessment 2nd ed. Minneapolis; 2005.
7. Elliot CD. The Differential Abilities Scales (DAS) San Antonio, TX The Psychological Corporation; 1995.
8. Bayley N. Bayley Scales of Infant and Toddler Development: Third Edition. San Antonio, TX The Psychological Corporation; 2005.
9. Bruininks RH, Woodcock RW, Weatherman RF, Hill BK. Scales of Independent Behavior – Revised. Itasca, IL: Riverside Publishing; 1996.
10. Folio M, Fewell R. Peabody Developmental Motor Scales, Second Examiner's Manual. Austin, TX: Pro-ed; 2002.
11. Folio MR, Fewell R. Peabody Developmental Motor Scales: Examiner's Manual. 2nd ed. Austin TX; 2000.
12. Bruininks RH, Bruininks BD. Bruininks-Oseretsky Test of Motor Proficiency. In: Pearson Assessment 2nd ed. Minneapolis; 2005.

10 APPENDICES

10.1 Appendix I List of Statistical Outputs

These are attached as a separate document called "Table Shells" including Tables, Figures and Listings.

10.2 Appendix II Protocol Violations Definitions

A list of possible protocol violations is given below. A more comprehensive list will be constructed once the review of patient data has been completed, immediately prior to locking the database.

Violations

- Violation of admission (inclusion/exclusion) criteria (i.e., eligibility violation) for which no exemption was obtained
- Occurrence of a treatment dispensing error