STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase I/II Multicenter Open-label Dose Escalation Study of HGT-1110 Administered Intrathecally in Children with Metachromatic Leukodystrophy
Protocol Number:	HGT-MLD-070
Protocol Date:	26 August 2015 (Amendment 9)
Investigational Product:	HGT-1110 (SHP611, recombinant human arylsulfatase, rhASA)
SAP Author(s):	PPD, PhD/PPD, PhD
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Study Sponsor:	Shire, Inc. 300 Shire Way Lexington, MA USA 02421
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HGT-MLD-070 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES:

The planned statistical analyses are appropriate for the analysis of the HGT-MLD-070 data. These analyses are in accordance with the study objectives and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

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1 ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
λ_Z	first order rate constant associated with the terminal (log-linear) portion of the curve
AE	adverse event
ALT	alanine aminotransferase
AMP	Amplitude
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
ASA	arylsulfatase A
AST	aspartate aminotransferase
AUC	area under the concentration curve
AUC_{0-24}	area under the curve over the interval from 0 to 24 hours post-dose
AUC_{0-last}	area under the curve from the time of dosing to the last measurable concentration
$AUC_{0-\infty}$	area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration
BAER	brainstem auditory evoke response
BLQ	below limit of quantification
BMI	body mass index
Bmp	beats per minute
CBC	complete blood count
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL/F	total body clearance for extravascular administration divided by the fraction of dose absorbed
CMAP	compound motor action potential
C_{max}	maximum concentration occurring at t_{max}
COMFORT	Caregiver Observed MLD Functioning and Outcomes Reporting Tool
CS	clinically significant
CSF	cerebrospinal fluid
CSR	clinical study report
DL	distal latency
DSMB	data safety monitoring board
ECG	Electrocardiogram
eCRF	electronic case report form

Abbreviation	Definition
ENG	Electroneurography
EOS	End of study
EOW	every other week
ERT	enzyme replacement therapy
FDA	Food and Drug Administration
FEES	functional endoscopic evaluation of swallowing
GGT	gamma-glutamyl transferase
GMFCS	Gross Motor Function Classification System
GMFM-88	Gross Motor Function Measure 88
GLX	Glutamine + glutamate
HSCT	hematopoietic stem cell transplantation
ICH	International Conference on Harmonisation
IDDD	intrathecal drug delivery device
IT	Intrathecal
KM	Kaplan-Meier
LDH	lactic dehydrogenase
LLOQ	lower limit of quantification
LP	lumbar puncture
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MLD	metachromatic leukodystrophy
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
Msec	Millisecond
NCV	nerve conduction velocity
NCS	not clinically significant
PK	Pharmacokinetic
PT	preferred term
rhASA	recombinant human arylsulfatase A
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SOC	system organ class
SSEP	somatosensory evoke potential

Abbreviation	Definition
TEAE	treatment-emergent adverse event
$t_{½}$	terminal half-life
t_{max}	time of maximum observed concentration sampled during a dosing interval
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
$V_{z/F}$	volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed
WHO-DD	World Health Organization Drug Dictionary

2 INTRODUCTION

Metachromatic leukodystrophy (MLD) is a rare, inherited, autosomal recessive disorder of lipid metabolism characterized by deficient activity of the lysosomal enzyme arylsulfatase A (ASA). The estimated overall incidence of MLD in the western world is approximately 1 in 100,000 live births.[1-5] Metachromatic leukodystrophy has a full range of disease severity with subjects presenting at varying ages and with a wide range and severity of signs and symptoms. Three presentations of the disease are recognized. The late infantile form of MLD is the most frequent presentation of the disorder and is usually diagnosed in the second year of life.[6] The major presenting symptom is a progressive gait disturbance that rapidly makes independent locomotion impossible. The disease is typically lethal during childhood as a result of complications arising from advanced motor system dysfunction. The juvenile type has an onset between 4 and 16 years of age with presenting signs and symptoms of gait disturbances and motor dysfunction. Typical signs and symptoms also include behavioral abnormalities, poor school performance, and language regression. The disease is progressive, and most children with a juvenile phenotype die in a quadriplegic decerebrate state 5 to 10 years after the onset of symptoms. The adult type typically begins after 16 years of age, but onset can be as late as 60+ years of age. The dominant symptoms are a gradual decline in intellectual abilities with poor school or job performance, psychiatric disturbances, and memory deficits evolving to dementia.

2.1 Background

The primary objective of Study HGT-MLD-070 is to determine the safety of ascending doses of SHP611 (formerly known as HGT-1110) administered by intrathecal (IT) injection for 38 weeks in children with MLD for Cohorts 1-3; and to determine the safety of SHP611 produced with a revised investigational product substance manufacturing process administered by IT injection for 38 weeks in children with MLD for Cohort 4.

This statistical analysis plan (SAP) describes the planned analysis for Shire protocol HGT-MLD-070, and outlines the methods to be used in the analysis of study data from Cohorts 1-4.

Populations for analyses, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

This SAP is based on protocol HGT-MLD-070, Amendment 9, dated 26 August 2015. The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study and the operational aspects of clinical assessments and timing for completing a subject in this study.

2.2 Study Rationale

There are no approved therapies for MLD. The only treatment option for MLD is bone marrow transplantation or hematopoietic stem cell transplantation (HSCT), which have shown little or no efficacy. SHP611 is a recombinant human arylsulfatase A (rhASA) that is under development as enzyme replacement therapy (ERT) for the treatment of MLD.

3 STUDY OBJECTIVES

3.1 Primary Objective

- Cohorts 1-3: The primary objective is to determine the safety of ascending doses of SHP611 administered by IT injection for 38 weeks in children with MLD.

- Cohort 4: The primary objective is to determine the safety of SHP611 produced with a revised investigational product substance manufacturing process administered by IT injection for 38 weeks in children with MLD.

3.2 Secondary Objectives

The secondary objectives of this study are to:

- To evaluate the effects of IT administration of SHP611 on gross motor function
- To evaluate the effects of IT administration of SHP611 on the ability to swallow
- To evaluate the effects of IT administration of SHP611 on nerve conduction capabilities
- To evaluate the effects of IT administration of SHP611 on adaptive behavior
- To evaluate the effects of IT administration of SHP611 on health status and the ability to carry out activities of daily life
- To assess single and repeated-dose pharmacokinetics (PK) of SHP611 in serum
- To assess concentrations of SHP611 in cerebrospinal fluid (CSF)

3.3 Exploratory Objectives

The exploratory objectives of this study are the following:

- To evaluate the effects of IT administration of SHP611 on CSF, serum, and urine biomarkers
- To evaluate the effects of IT administration of SHP611 on N-acetylaspartate metabolite levels
- To evaluate the effects of IT administration of SHP611 on the MLD severity score as measured by magnetic resonance imagining (MRI) of the brain
- To determine the safety and performance of the SOPH-A-PORT Mini S
- To evaluate the minimal clinically important change in GMFM-88 response

4 STUDY DESIGN

4.1 General Description

This is a multicenter, open-label dose escalation study designed to evaluate the safety of up to 3 dose levels (10, 30, or 100 mg) of SHP611, administered via an IT drug delivery device (IDDD) every other week (EOW) (20 IT injections of SHP611 from Weeks 0 to 38) to male or female children with a confirmed diagnosis of MLD, as well to evaluate the safety related to the IT delivery process (eg, surgery implantation, device, lumbar puncture [LP]). Subjects are expected to be less than 12 years of age at screening. Cohorts 1-3 will be enrolled sequentially. The study also includes the assessment of SHP611 manufactured with a revised investigational product substance manufacturing process (referred to as Process B) in a fourth cohort (Cohort 4).

For Cohorts 1-3, up to 18 subjects will be enrolled, up to 6 in each of the 3 dose level cohorts. Cohorts 1-3 will receive the Process A SHP611 investigational product. Cohort 4 will be enrolled following Cohort 3, after investigational product manufactured with Process B becomes available. Up to 6 subjects who undergo device implant surgery and receive at least 1 dose of investigational product will be included in Cohort 4, which will receive 100 mg SHP611 EOW for a total of 38 weeks.

When all enrolled subjects in Cohorts 1-3 complete the study, an interim analysis will be conducted. Data from Cohort 4 will not be included in the interim analysis. The exploratory objective for evaluation of minimal clinically important change in GMFM-88 response is collected for Cohort 4 only and therefore was not analyzed in the interim analysis. Because any hypothesis testing is considered exploratory, no adjustment for multiplicity will be made.

4.2 Discussion for Study Design

This is a multicenter dose escalation study in subjects with MLD designed to identify a dose that may be utilized in future IT trials of SHP611. The decision to escalate to the next dose level (Cohorts 2 and 3 only) will be based on a data safety monitoring board (DSMB) review of the safety data obtained from the previous dose cohort after all subjects in the dose cohort have each received a minimum of 2 IT doses. A fourth Cohort (Cohort 4) of up to 6 subjects who undergo device implant surgery and receive at least 1 dose of investigational product will be enrolled following Cohort 3, after Process B SHP611 becomes available. Safety of the 100 mg dose for Process A in Cohort 3 will be reviewed by the DSMB before Cohort 4 is enrolled.

Cohorts 1-3 will have the following 5 phases:

Phase 1: Screening and Enrollment (Days -40 to -11): within 40 days of the study Baseline visit (Week 0)

Phase 2: IDDD Implantation (Days -10 to -1): within 10 days of Week 0, IDDD implanted and a postsurgical assessment done

Phase 3: Baseline and Treatment (Week 0 to 38): at Week 0 Baseline assessment and first dose of treatment (±3 days) and Week 2 to 38 EOW (±3 days) treatment and required assessment

Phase 4: End of Study (EOS) Visits (Week 40): at Week 40 (-5, +3 days) EOS visit assessment. Patients who discontinue early will have an end of study (EOS) visit, 2 weeks (-5, +3 days) after the last IT injection of SHP611.

Phase 5: Safety Follow-up (Week 42): safety follow-up via telephone contact at Week 42 or 4 weeks (±3 days) after last injection of SHP611 or 2 weeks after the removal of the IDDD, whichever occurs later, for subjects who discontinue.

Cohort 4 also has 5 phases, and Phases 4 and 5 for Cohort 4 are the same as that for Cohorts 1-3:

Phase 1: Screening and Enrollment (Days -40 to -1): within 40 days of the study Baseline visit (Week 0) .

Phase 2: IDDD Implantation (Days -10 to +28): within 10 days before Week 0 and within 28 days of the first dose, IDDD implanted and a postsurgical assessment done

Phase 3: Baseline and Treatment (Week 0 to 38): at Week 0 Baseline assessment and first dose of treatment (±3 days) and Week 2 to 38 EOW (±3 days) treatment and required assessment. For subjects with IDDD implanted within 10 days before Week 0, IDDD will be used for IT injection of the first dose; for subjects with IDDD implanted within 28 days of the first dose, no more than 3 doses may be administered by lumbar puncture (LP) prior to IDDD Implantation

4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be enrolled in 1 of 3 sequential, escalating, dose cohorts:

- Cohort 1: SHP611 by IT injection 10 mg EOW
- Cohort 2: SHP611 by IT injection 30 mg EOW
- Cohort 3: SHP611 by IT injection 100 mg EOW

The decision to escalate to the next higher dose level (i.e., escalation to Cohorts 2 and 3 only) will be based on a DSMB review of the safety data obtained from the previous dose cohort after all subjects in the dose cohort have each received a minimum of 2 IT doses.

Cohort 4 will be enrolled following Cohort 3 after Process B SHP611 investigational product becomes available and after the DSMB review of Cohort 3 data. Cohort 4 will receive 100 mg SHP611 EOW by IT injection (up to 6 subjects).

4.4 Blinding

There is no blinding to investigational product as this is an open-label study.

4.5 Randomization

This is an open-label sequential dose escalation study with all subjects receiving treatment. There is no randomization to treatment in this study. All subjects within a dose cohort receive SHP611 at the same dose level.

4.6 Determination of Sample Size

Approximately 24 subjects are planned for 4 dose cohorts (up to 6 enrolled subjects in Cohorts 1-3 and approximately 6 subjects in Cohort 4 who undergo device implant surgery or receive at least 1 dose of investigational product). The sample size was determined outside of statistical considerations and is based on the practicalities of enrolling this number of subjects with this rare disease.

5 EFFICACY AND SAFETY VARIABLES

5.1 Schedule of Evaluations

The schedule of events can be found in Section 10.5 of this SAP; it can also be found in Appendix 1 (Cohorts 1-3) and Appendix 2 (Cohort 4) of the study protocol (Amendment 9).

5.2 Primary Endpoints

Safety will be measured by the following endpoints:

- Reporting of treatment-emergent adverse events (TEAEs)
- Change from Baseline in clinical laboratory testing (serum chemistry including liver function tests, hematology, and urinalysis)
- Change from Baseline in 12-lead electrocardiogram (ECGs), vital signs, physical examinations, and CSF chemistry (including cell counts, glucose, and protein)
- Determination of the presence of anti-SHP611 antibodies in CSF and/or serum

5.3 Secondary Endpoints

The secondary endpoints of this study are the following:

- Change from Baseline in motor function using the Gross Motor Function Measure 88 (GMFM-88) total score (percent)
- Change from Baseline in the ability to swallow as measured by the Functional Endoscopic Evaluation of Swallowing (FEES)
- Change from Baseline in nerve conduction as measured by the electroneurography (ENG) assessments of nerve conduction velocity (NCV), compound motor action potential (CMAP), amplitude (AMP), and distal latency (DL)
- Change from Baseline in the adaptive behavior composite standard score as measured by the Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
- Change from Baseline in the domain-specific Caregiver Observed MLD Functioning and Outcomes Reporting Tool (COMFORT) scores
- Single and repeated-dose PK parameter estimates for SHP611 in serum
- Concentrations of SHP611 in CSF at selected time points after single- and repeated-investigational product administration

5.4 Exploratory Endpoints

The exploratory endpoints of this study are the following:

- Change from Baseline in CSF, serum, and urine biomarkers (ie, sulfatide and lysosulfatide)
- Percent change from Baseline in ratio of N-acetylaspartate/Creatine metabolite levels in the deep white and gray matter of the brain as assessed by proton magnetic resonance spectroscopy (MRS)
- Change from Baseline in the total MLD severity score based on MRI of the brain
- Categorical assessment in the global impression of motor function-severity (GIMF-S)
- Categorical assessment in the global impression of motor function-change (GIMF-C)

5.5 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. This data will be collected on the subject's electronic case report form (eCRF) from the time of initial implantation.

6 STATISTICAL ANALYSIS

6.1 General Methodology

Statistical analyses will be performed within the Shire Biometrics Department (with the exception of the PK analysis, which will be performed by the Shire Clinical Pharmacology and Pharmacokinetics department), using SAS® software version 9.3 or higher. Data will be summarized by dose cohort and overall, if appropriate. Summary statistics for continuous variables will include the number of subjects (n), mean, standard deviation (SD), minimum (min), median, and maximum (max) values. For categorical variables, tabular summaries will consist of presenting the number and percent of subjects in each category (including a missing category, if applicable). Unless otherwise specified, percentages will be based on the number of subjects within each dose cohort or overall within the safety population. Mean within subject changes from Baseline to subsequent protocol defined time points will be calculated for each parameter of interest. Furthermore, time point Week 40/Early Termination (denote it as Week 40/EOS) will be included, whenever it is appropriate. Any statistical tests comparing dose cohorts will be 2-sided with a significance level of 0.05 and considered exploratory. The mean change, the mean difference in the change between dose cohorts, and the corresponding 95% confidence intervals (CIs), may also be presented as appropriate.

Box plots will be used as a visual representation, as appropriate, to view the center, spread, and overall range of the distribution under study; any observations more than 1.5 times the interquartile range outside the central box will be plotted as possible outliers. Other type of figures will also be used to present the data, whenever it is appropriate.

Safety summaries will be based on all post-Baseline assessments including the frequency of TEAEs and the frequency of clinically notable abnormal vital signs and clinically significant laboratory values. Adverse events reported prior to the start of treatment or IDDD implantation will be listed separately.

6.1.1 Data Derivations and Definitions

The following key derived and computed variables have been initially identified. It is expected that additional variables may be required. The SAP may not be amended for additional variables that are identified. All derived and computed variables, including additional variables later identified, will be documented in the "Define Document" and also in the SAS analysis dataset creation programs. The following are anticipated data derivations:

Age (months): Age will be calculated as the difference between date of birth (DOB) and date of informed consent (DINFC), truncated to months, using the following SAS function:

Age = floor (intck ('month', DOB, DINFC) - (day (DINFC) <day (DOB)))

For sites reporting date of birth as 01 Jan XX, if MLD diagnosis date is available, then age can be estimated as floor (intck ('month', MLD diagnosis date , DINFC) – (day (DINFC) < day (MLD diagnosis date))) + age at MLD diagnosis (months). In the case, if MLD diagnosis date is missing then the date of birth will be imputed as 01 July XX.

- Body mass index (BMI): (weight in kg)/(square of height in meters)
- Baseline: Valid data captured as the last assessment prior to the first investigational product administration, or prior to the device implant surgery, whichever is earlier. Follow this logic, if no Baseline can be identified, then Week 0 data will be used as Baseline.
- Change from Baseline for post-first dose time points: post-Baseline value – Baseline value
- Percent (%) change from Baseline: (Change from Baseline/Baseline)*100
- Percent compliance: $Percent\ Compliance = \frac{(Number\ of\ doses\ received)}{(Number\ of\ doses\ expected)} \times 100$
- Duration (minutes) of investigational product administration = Time the dose ended – Time the dose started
- Duration (weeks) of investigational product exposure = [(Date of last dose – Date of first dose + 1 day)/7 days]
- Normal ranges for clinically notable vital signs parameters are provided below.

Table 1: Normal Ranges for Vital Signs

Vital Sign Parameter/Age	Normal Range					
	1-2 years	2-4 years	4-6 years	6-8 years	8-10 years	10-12 years
Temp (Celsius)	36.0-37.9	36.0-37.9	36.0-37.9	36.0-37.9	36.0-37.9	36.0-37.9
Respiration (breaths/min)	19-53	17-40	17-34	12-34	12-30	12-30
Pulse (BPM/min)	40-190	60-150	60-140	60-140	60-140	52-140
Systolic Blood Pressure (mmHg)	70-120	70-120	75-120	75-120	80-120	80-120
Diastolic Blood Pressure (mmHg)	55-70	55-70	60-75	60-75	60-75	60-75

bpm=beats per minute; msec=millisecond

- GMFM-88 total score (percent): Calculated by averaging the percent scores programmatically for each of the 5 domains (ie, lying and rolling; sitting; crawling and kneeling; standing; and walking, running, and jumping) and rounding to the nearest whole number.[7] The percent scores for each domain are calculated as follows:
  - Lying and rolling: (Total Dimension A/51)*100
  - Sitting: (Total Dimension B/60)*100

- Crawling and kneeling: (Total Dimension C/42)*100
- Standing: (Total Dimension D/39)*100
- Walking, running, and jumping: (Total Dimension E/72)*100

- For the COMFORT questionnaire, there are 59 questions presented on a Likert scale that are organized into 8 domains. A summary score is calculated within each domain. The analysis will focus on the domain scores; there will be no total score generated.

  To standardize the scores across domains, all data will first undergo a transformation of scores to 0 to 100, with higher scores equated with greater difficulty or severity. The mean summary domain (or subdomain) score will be calculated as:

  Mean Domain-specific Summary Score = (sum of non-missing questions for the domain, after data transformation to a 100-point score)/(Number of questions in the domain for which a valid response was given, excluding questions with a response of "does not apply")

  For the domains of Personal Care; Positioning, Transfer and Mobility; and Communication (which each have 2 subdomains), an overall domain score will be calculated as the average of the subdomain scores.

  The following table displays each domain, relevant data transformations, and calculation used to create a mean summary score for each domain.

Table 2: COMFORT Domain Data Transformation

<table>
<tr><th>Domain</th><th>Domain-specific Handling of Data</th><th>Domain-specific Data Transformations</th><th>Calculation of Mean Summary Score</th></tr>
<tr><td>Personal Care – Assistance Needed: Questions 1-5</td><td>Question 5: Values=0 (does not apply) will be set to missing and the question will be excluded from calculation of the mean summary score.</td><td><table><tr><th>Original Value</th><th>Transformed Value</th></tr><tr><td>1</td><td>0</td></tr><tr><td>2</td><td>33</td></tr><tr><td>3</td><td>67</td></tr><tr><td>4</td><td>100</td></tr></table></td><td>(sum of transformed values for non-missing questions) divided by (number of non-missing questions)</td></tr>
</table>

Table 2: COMFORT Domain Data Transformation

Domain	Domain-specific Handling of Data	Domain-specific Data Transformations	Calculation of Mean Summary Score
Personal Care – Discomfort: Questions 6-13	Questions 10-12: Values=0 (does not apply) will be set to missing and the questions will be excluded from calculation of the mean summary score.	Original Value → Transformed Value: 1 → 0; 2 → 33; 3 → 67; 4 → 100	(sum of transformed values for non-missing questions) divided by (number of non-missing questions)
Positioning, Transfer, or Mobility – Assistance: Questions 14-19		Original Value → Transformed Value: 1 → 0; 2 → 33; 3 → 67; 4 → 100	(sum of transformed values for non-missing questions) divided by (number of non-missing questions)
Positioning, Transfer, or Mobility – Discomfort: Questions 20-25		Original Value → Transformed Value: 1 → 0; 2 → 33; 3 → 67; 4 → 100	(sum of transformed values for non-missing questions) divided by (number of non-missing questions)

Table 2: COMFORT Domain Data Transformation

Domain	Domain-specific Handling of Data	Domain-specific Data Transformations	Calculation of Mean Summary Score
Eating: Questions 26-33	Questions 26-33: Values=0 (does not apply) will be set to missing and the questions will be excluded from calculation of the mean summary score.	Original Value → Transformed Value 1 → 0 2 → 33 3 → 67 4 → 100	(sum of transformed values for non-missing questions) divided by (number of non-missing questions) If the subject was tube-fed only, Question 33 will be used. If the subject was not tube-fed only, Questions 26 -32 will be used.
Pain and Discomfort During the Day: Questions 34-37		Original Value → Transformed Value 1 → 0 2 → 33 3 → 67 4 → 100	(sum of transformed values for non-missing questions) divided by (number of non-missing questions)
Sleep: Questions 38-42		Original Value → Transformed Value 1 → 0 2 → 33 3 → 67 4 → 100	(sum of transformed values for non-missing questions) divided by (number of non-missing questions)
Emotions: Questions 43-45	Values for Question 43 will be reversed	Original Value after → Transformed Value	(sum of transformed values for non-

Table 2: COMFORT Domain Data Transformation

Domain	Domain-specific Handling of Data	Domain-specific Data Transformations	Calculation of Mean Summary Score
	prior to transformation such that 1 becomes "always (5)," 2 becomes "frequently (4)," 4 becomes "rarely (2)," and 5 becomes "never" (1). This is done to align the directionality of this response with that of Questions 44 and 45.	Reversals | 1 | 0 2 | 25 3 | 50 4 | 75 5 | 100	missing questions) divided by (number of non-missing questions)
Communication – Difficulties: Questions 46-49	For all questions: Values=0 (child has never done this) will be set to missing, and the question will be excluded from calculation of the mean summary score.	Original Value | Transformed Value 1 | 0 2 | 25 3 | 50 4 | 75 5 | 100	(sum of transformed values for non-missing questions) divided by (number of non-missing questions)
Communication – Frequency: Questions 50-54	For all questions: Values=0 (child has never done this) will be set to missing, and the question will be excluded from calculation of the mean summary score.	Original Value | Transformed Value 1 | 0 2 | 33 3 | 67 4 | 100	(sum of transformed values for non-missing questions) divided by (number of non-missing questions). Before transformation, reverse items 50-54 as

Table 2: COMFORT Domain Data Transformation

<table>
<tr><th>Domain</th><th>Domain-specific Handling of Data</th><th>Domain-specific Data Transformations</th><th>Calculation of Mean Summary Score</th></tr>
<tr><td></td><td></td><td></td><td>currently 1=worst and 4=best score.</td></tr>
<tr><td>Play and Leisure Activities: Questions 55-59</td><td>For all questions: Values=0 (child has never done this) will be set to missing, and the question will be excluded from calculation of the mean summary score.</td><td><table><tr><th>Original Value</th><th>Transformed Value</th></tr><tr><td>1</td><td>0</td></tr><tr><td>2</td><td>25</td></tr><tr><td>3</td><td>50</td></tr><tr><td>4</td><td>75</td></tr><tr><td>5</td><td>100</td></tr></table></td><td>(sum of transformed values for non-missing questions) divided by (number of non-missing questions)</td></tr>
</table>

- Time to first malfunction of SOPH-A-PORT® Mini S IDDD is calculated as: (Date of malfunction – Date of initial Mini S IDDD implant + 1]. If a subject has multiple malfunctions, only the first will be considered. Time to first failure of SOPH-A-PORT Mini S IDDD calculated as: [(Date of Mini S device failure) – (Date of initial Mini S IDDD implant)] + 1. If a subject has multiple IDDD failures, only the first will be considered. For reporting 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. Malfunctions that are ongoing at the end of the study will also be considered failures.

- SOPH-A-PORT Mini S IDDD malfunction: The IDDD will be declared a device malfunction if, at the time of a scheduled dosing, it is not possible to administer a full medication dosage and the SOPH-A-PORT device malfunction/failure CRF page is completed.

- SOPH-A-PORT Mini S IDDD failure: The IDDD will be declared a device failure if the device malfunction is irreversible and cannot be corrected without a device surgical intervention (ie, surgical revision/removal of IDDD), and the SOPH-A-PORT device malfunction/failure CRF page is completed. The date of the device failure is the date of the malfunction associated with the outcome of device failure (surgical procedure).

- ENG z-score: (Actual ENG Measurement – Reference Mean)/Reference SD, if the reference mean and SD both are available, and the subject's age fall into a reference age category.[8] Otherwise the z-score cannot be derived. Refer to Table A-1 in Section 11 for the reference means and SDs of the corresponding ENG parameters.

6.1.2 Handling of Outliers

For analysis purposes, an outlier is defined to be an observed value that is known to be the result of an obvious error or an observed value that is not medically plausible. No outliers will be excluded from any analyses. The analysis may be repeated, however, by excluding any potential outliers (ie, a sensitivity analysis performed).

6.1.3 Missing Dates for Adverse Events and Concomitant Medications

For partial AE and concomitant medication dates, the non-missing parts of the partial dates will be used to determine if an AE occurred or the medication was given prior to the IDDD implant or first dose date in this current study. Unless the non-missing parts are *unambiguously* before the first IDDD implant or first dose date, it will always be assumed that the AE occurred or the medication was given after the IDDD implant or first dose date in this current study.

6.2 Analysis Populations

- The Safety Population, defined as the set of subjects who received at least 1 dose of investigational product or underwent device implant surgery, will be the primary analysis population. SOPH-A-PORT Intrathecal device-related analyses will be performed in the subset of the Safety Population who underwent the SOPH-A-PORT device implant surgery. Unless otherwise specified, all analyses will be based upon the Safety Population.

- The Pharmacokinetic Population is defined as all subjects who receive at least 1 dose of investigational product and have at least one measureable serum concentration or one measurable CSF concentration of SHP611. All of the pharmacokinetic analyses will be performed using the Pharmacokinetic Population.

6.3 Subject Disposition

The number of subjects screened, included in the Safety Population, who completed the study and who discontinued prematurely will be reported. Reasons for discontinuation will be tabulated. The tabular presentation will be displayed overall and by dose cohort. Percentages will be based upon the total number of subjects in each dose cohort and overall within the Safety Population.

6.4 Protocol Deviations

For the purposes of this study, protocol deviations are defined as events that may affect subject safety and/or data integrity as determined by the medical monitor, and are classified as minor or major protocol deviations.

Subjects in the safety population having protocol deviations will be presented in a data listing along with the description of the deviation(s).

6.5 Demographics and Other Baseline Characteristics

6.5.1 Demographics

Descriptive statistics of subject demographic and Baseline characteristics will be summarized by dose cohort and overall. The continuous variables of age (months) at the time of informed consent, weight (kg), height (cm), BMI (kg/m^2), and head circumference (cm) at study entry will be summarized by descriptive statistics. The categorical variables of age category (≤48 months old; >48 months old) at the time of informed consent, race, ethnicity, gender, and country will be tabulated using frequency and percentage for each category of interest (including a missing category, if applicable).

6.5.2 Medical and Surgical History

The number and percentage of subjects with any medical and surgical history as well as medical histories in specific body systems will be tabulated by dose cohort and overall. A listing of medical and surgical histories will be provided for each subject.

6.5.3 MLD-related History

The age at MLD diagnosis (in months) and the age at onset of MLD symptoms (in months) will be summarized by dose cohort and overall using descriptive statistics. Additionally, the number and percentages of subjects having evidence of ASA deficiency in medical records including ASA level, MLD genotype result in medical records, and family history of MLD will be tabulated.

6.6 Treatment Compliance and Extent of Exposure

6.6.1 Treatment Compliance

The total number of missed doses (out of the expected number of doses) will be categorized as none, 1-2, 3-4, and ≥5 missed doses and tabulated. Additionally, treatment compliance will be tabulated as the proportion of subjects whose percent compliance was ≥80% (≥16 doses) or <80 % (<16 doses). Percent doses received will be summarized with descriptive statistics.

6.6.2 Extent of Exposure

The total number of doses received and the number of doses received via LP will be summarized. The total duration of investigational product exposure will be presented in terms of number of weeks. The duration of investigational product administrations (in minutes) will be averaged across the non-missing duration of investigational product administrations for each subject and summarized.

By-subject listings of lot numbers of SHP611 received, with date of first administration of each lot, will be presented. A listing for investigational drug product administration including duration of administration will be presented by subject.

6.7 Analysis of Efficacy

The change from Baseline in motor function using the GMFM-88 total score (percent) after EOW IT injections of SHP611 for 40 weeks (Weeks 0-40) will serve as the primary efficacy outcome measurement. Additional efficacy outcome measures include change from Baseline in ability to swallow as measured by the FEES; summary of z-scores in nerve conduction as measured by the ENG assessments of NCV, AMP, and DL; change from Baseline in the adaptive behavior composite and domain standard scores as measured by the VABS-II; and change from Baseline in the domain-specific COMFORT scores. Exploratory analyses include change from Baseline in GMFM-88 domain scores, change from Baseline in CSF, serum, and urine sulfatide and lysosulfatide levels; percent change from Baseline in N-acetylaspartate/Creatine ratio and other metabolites (Lactate/Creatine, Choline/Creatine, Myo-inositol/Creatine and glutamine + glutamate (GLX)/Creatine) in the brain as assessed by proton MRS; change from Baseline in the total MLD severity score and other MRI parameters based on MRI of the brain, and categorical assessment in the GIMF-S and in the GIMF-C (for Cohort 4 only).

Prior to Protocol Amendment 6, 2 additional endpoints, somatosensory evoke potential (SSEP) and brainstem auditory evoke response (BAER) were to be captured. Protocol Amendment 6 removed these 2 evaluations primarily to reduce subject and site burden as these were exploratory endpoints and removal was not expected to compromise the scientific validity of the study. Somatosensory evoke potential and BAER data listings will be provided as SAS datasets in Clinical Data Interchange Standards Consortium (CDISC) format.

6.7.1 Gross Motor Function Measure

The observed values at each visit as well as the change from Baseline in motor function using the GMFM-88 total score (percent), and for each domain (ie, lying and rolling; sitting; crawling and kneeling; standing; and walking, running, and jumping) will be summarized descriptively at each study visit through Week 40, and include Week 40/EOS by dose cohort and overall.

Corresponding mean and mean change from baseline plots with SE bars will be generated for GMFM-88 total scores (percent) by visit and dose cohort. These plots will also be generated for subjects with baseline GMFM-88 total score (percent) ≥35 at each visit by dose cohort and overall. Box plot for GMFM-88 total scores (percent) by visit and dose cohort will be generated as well. Data for individual subjects will also be plotted by dose cohort and visit. A listing of GMFM-88 total scores, domain scores, and Gross Motor Function Classification System (GMFCS) levels will be provided.

The dose cohorts will be compared at the end of the study visit (Week 40/EOS) using an analysis of covariance (ANCOVA) model with change from Baseline as the dependent variable including the dose cohort as a fixed effect and Baseline value of the GMFM-88 total score (percent) as the single continuous covariate. The adjusted mean (LSMean) and 95% CI for each dose cohort, as well as the difference in LSMeans between dose cohorts and the associated 95% CIs and p-values, will be estimated. This analysis will be performed for every pair of the dose cohorts 1-4 (Process A; 10, 30, and 100 mg, and 100 mg Process B), and also will compare the combined dose cohorts 3 and 4 with Process A 10 and 30 mg respectively, as well as Process A dose cohorts 10 and 30 mg combined versus dose cohorts 3 and 4 combined.

The categorical variable of GMFCS level will be tabulated for each dose cohort using frequency and percentage for each category of interest by visit (including a missing category, if applicable). The shift from Baseline to each study visit through Week 40, and include Week 40/EOS will be summarized using a shift table presented in terms of levels (I, II, III, IV, V) or missing (not done) by dose cohort.

6.7.2 Functional Endoscopic Evaluation of Swallowing

The FEES assessment will be performed to evaluate the structure and function of the upper throat during swallowing and for an assessment of aspiration risk. The within-subject shift from Baseline to each subsequent time point, as well as the shift from Baseline to Week 40 and Week 40/EOS, will be presented by dose cohort and overall for each categorical assessment, for each texture at baseline using a shift table. For all FEES assessment except texture, only post-baseline assessments with same texture as Baseline will be included; otherwise assessments will be considered missing. Assessments reported as blank are considered normal and were confirmed by the site. In particular, the within-subject shift in aspiration risk (low; moderate; high) over time will be of particular importance. For texture, some subjects reported more than one texture at all visits; therefore, all textures are presented.

A listing of all FEES categories will be presented by subject.

In particular, the following FEES categories will be analyzed as described above:

- Texture utilized for evaluation
- Palate closure (listing only)
- Airway protection screening: vocal fold motion (listing only)
- Secretions (listing only)
- Feeding assessment: laryngeal penetration
- Feeding assessment: aspiration through vocal cords
- Residue after swallow: Does residue clear with subsequent swallow?
- Aspiration risk: assessed risk of aspiration

6.7.3 Electroneurography

Evaluation of peripheral nerve function will be performed to measure the NCV, AMP, and DL. The data for assessments of interest will be analyzed separately for sensory nerves (median, sural) and motor nerves distal latency (median, peroneal, ulnar, tibial). A subject was supposed to be examined on the same side as Baseline for all post-Baseline visits. If an assessment was done on the opposite side of the side as performed at Baseline, then the assessment will be considered missing at that visit for the subject. If appropriate, the measured values for AMP will be categorized as >0, 0 or not done (ND), while for NCV and DL their measured values will be

categorized as >0, XR (conduction velocities or distal latencies were unobtainable because amplitude is 0), or ND, and a frequency table will be generated displaying data for each parameter at Baseline and at the last visit that with a post-Baseline valid assessment for each dose cohort and overall.

For a given age group, when both reference mean and SD are available for a specific parameter, a z-score for the parameter at each visit will be derived programmatically for each measurement of a subject (refer to Section 6.1.1 for derivation method). Otherwise, if the reference mean and SD are not available for a specific parameter of an age group, the z-score cannot be generated. The z-scores at each visit will be summarized descriptively. Additionally, individual subject z-scores will be plotted (trellis) over time by assessment visit for each dose cohort and overall within each motor and sensory nerve conduction. By-subject listing including observed values and z-scores along with the reference mean and SD or range of the reference mean will be provided.

The following motor nerve conduction studies are performed and relevant assessments will be reported as described above:

- Median motor thenar
    - Elbow to wrist conduction velocity (m/s)
    - Wrist amplitude Baseline to peak (mv)
    - Wrist-abductor pollicis brevis muscle distal latency (ms)
    - F-wave latency (ms)
- Peroneal motor
    - Ankle to fibular head conduction velocity (m/s)
    - Ankle amplitude baseline to peak (mv)
    - Fibular head amplitude baseline to peak (mv)
    - Ankle-extensor digitorum brevis distal latency (ms)
    - F-wave latency (ms)
- Ulnar motor (if available)
    - Elbow to wrist conduction velocity (peak; m/s)
    - Wrist amplitude baseline to peak (mv)
    - Elbow amplitude baseline to peak (mv)

- Wrist-abductor digiti minimi distal latency (ms)
- F-wave latency (ms)

- Tibial motor (if available)
  - Ankle to knee conduction velocity (m/s)
  - Ankle amplitude baseline to peak (mv)
  - Knee amplitude baseline to peak (mv)
  - Ankle-abductor hallucis distal latency (ms)
  - F-wave latency (ms)

The following sensory nerve conduction studies will be performed and relevant assessments will be reported as described above:

- Median sensory
  - Wrist amplitude peak to peak (mv)
  - Wrist to digit distal latency (peak; ms)
- Sural sensory
  - B-point amplitude peak to peak (mv)
  - B-point distal latency peak (ms)

6.7.4 Vineland Adaptive Behavior Scales, Second Edition

The observed values at each visit, as well as the change from Baseline in the domain standard scores within each of the 4 domains, communication (receptive; expressive; written), daily living skills (personal; domestic; community), socialization (interpersonal relationships; play and leisure time; coping skills), motor skills (gross; fine), and the adaptive behavior composite standard score across all 4 domains will be summarized descriptively by dose cohort and overall.

If there are at least 2 subjects per dose cohort, corresponding subject plots for each dose cohort will be generated for standard scores for the VABS-II domains at each visit. By subject listing of VABS-II domain scores will be provided.

6.7.5 COMFORT Questionnaire

All of the statistical analyses will be performed within a domain: Personal Care in the Past 7 Days; Positioning, Transfer, or Mobility; Eating; Pain and Discomfort During the Day; Sleep; Emotions; Communication; and Play and Leisure Activities. The observed values and change

from Baseline at each visit in the domain-specific summary scores will be summarized by dose cohort and overall.

Corresponding subject plots for each dose cohort will be generated for observed COMFORT domain values over time at each visit. By-subject listing of COMFORT questionnaire will be generated.

6.7.6 Exploratory Analyses

6.7.6.1 Biomarker Analyses

Observed values for sulfatide and lysosulfatide will be summarized at Baseline and at Weeks 16, 28, 40 and 40/EOS by dose cohort and overall. The change from Baseline and percent change from Baseline to Weeks 16, 28, 40 and 40/EOS will also be summarized by dose cohort and overall. These summaries will be presented for sulfatide and lysosulfatide obtained from CSF, serum. Furthermore, corresponding mean plots with SE bars for each dose cohort will be plotted at each appropriate visit, and data for individual subjects will also be plotted by dose cohort and visit for all biomarker parameters above.

The dose cohorts will be compared at the end of the study visit (Week 40/EOS) using an ANCOVA model with change from Baseline as the dependent variable including the dose cohort as a fixed effect and Baseline value of the applicable biomarker as the single continuous covariate. The analysis will be conducted if we have sufficient quantifiable observations. The adjusted mean (LSMean) and 95% CI for each dose cohort and the difference in LSMeans between dose cohorts and the associated 95% CIs and p-values will be estimated. This analysis will be performed for every pair of the dose cohorts 1-4 (Process A; 10, 30, and 100 mg; and 100 mg Process B), and also will compare the combined dose cohorts 3 and 4 with Process A 10 and 30 mg respectively, as well as Process A dose cohorts 1 and 2 (10 and 30 mg) combined versus dose cohorts 3 and 4 combined (100 mg dose cohorts combined).

Correlations and 95% CIs of sulfatide and lysosulfatide levels obtained in CSF, serum, and urine, with the GMFM-88 total scores (percepts) will be examined at Baseline, Week 40/EOS, and change from Baseline to Week 40/EOS for Process A Cohort 3 and Process B Cohort 4, respectively. A measure of the linear association between variables at Baseline and Week 40/EOS will be obtained using Spearman correlation. Scatterplots of biomarkers (sulfatide and lysosulfatide) and GMFM-88 total scores (percent) will be plotted by dose cohort across all visits. Furthermore, scatterplot of serum sulfatide in CSF and GMFM-88 total sore change from Baseline at Week 40/EOS for 100 mg dose cohorts (process A and B separately) will be produced.

A by-subject listing of biomarkers, GMFM total scores (percent), and MLD severity scores and NAA/Creatine will be generated. Listings of genotype, neutralizing antibody and other variables of interest may be presented by subject for the assessment of the association with GMFM-88 scores.

6.7.6.2 Magnetic Resonance Spectroscopy

For N-acetylaspartate/Creatine, Choline/Creatine, Lactate /Creatine, Myo-inositol/Creatine and GLX/Creatine metabolite levels in the brain as assessed by proton MRS in regions of interest (eg, the frontal and parieto-occipital white matter, corpus callosum, centrum semiovale, and occipital cortex), the observed values at each visit and both the change and percent change from Baseline to Weeks 16, 28, 40 and 40/EOS will be summarized by dose cohort.

The dose cohorts will be compared at the end of the study visit (Week 40/EOS) using an ANCOVA model of the N-acetylaspartate/Creatine, Lactate /Creatine, Myo-inositol/Creatine and GLX/Creatine metabolite levels in deep white matter with change from Baseline as the dependent variable including the dose cohort as a fixed effect and Baseline value of the each MRS measurement as the single continuous covariate. The adjusted mean (LSMean) and 95% CI for each MRS variable and each dose cohort and the difference in LSMeans between dose cohorts and the associated 95% CIs and p-values will be estimated. This analysis will be performed for the dose cohorts 1-4 (Process A; 10, 30, and 100 mg, and 100 mg Process B) and also for the combined dose cohorts 3 and 4 (Process A 10 and 30 mg cohorts versus 100 mg dose cohorts combined).

Correlations and 95% CIs of N-acetylaspartate/Creatine, Lactate /Creatine, Myo-inositol/Creatine and GLX/Creatine metabolite levels with the CSF, serum, and urine sulfatide and lysosulfatide levels will be examined at Baseline, Week 40/EOS, and change from Baseline to Week 40/EOS for Process A Cohort 3 (100 mg) and Process B Cohort 4 (100 mg) only. A measure of the linear association between variables at the time point will be obtained using Spearmancorrelation. Additional correlations of N-acetylaspartate with the GMFM-88 total score (percent) also will be estimated.

Subject plots by dose cohort of the observed values of N-acetylaspartate/Creatine, Choline/Creatine, Lactate /Creatine, Myo-inositol/Creatine and GLX/Creatine metabolite levels for each area of the brain region (i.e. midline occipital gray; right frontal white; right frontal-parietal white; right parieto-occipital white) at each visit will be generated by dose cohort.

Scatterplots of N-acetylaspartate/Creatine with biomarkers (sulfatide and lysosulfatide) and also GMFM-88 total scores (percent) will be generated by dose cohort across all visits.

6.7.6.3 Magnetic Resonance Imaging

Each subject will have a serially measured MRI of the brain. Based on a visual scoring method of the MRI, a total MLD severity score (range: 0-34) will be calculated for each subject at each time point where higher scores indicate more severe brain involvement. The observed values at each visit as well as the change from Baseline to Weeks 16, 28, 40 and 40/EOS in the total MLD severity score will be summarized by dose cohort and overall.

The dose cohorts will be compared at the end of the study visit (Week 40/EOS) using an ANCOVA model with change from Baseline in severity score as the dependent variable including the dose cohort as a fixed effect and Baseline value of the total MLD severity score as the single continuous covariate. The adjusted mean (LSMean) and 95% CI for each dose cohort

and the difference in LSMeans between dose cohorts and the associated 95% CIs and p-values will be estimated.

Mean plots with SE error bars for observed total MLD severity score at each visit for each dose cohort will be generated.

The raw values of the MLD severity will be listed by subject.

6.7.6.4 Global Impression of Motor Function Change and Severity

The GIMF-C and GIMF-S will only be performed for subjects in Cohort 4. The items of the GIMF-C and GIMF-S will be summarized by the number and percentage of subjects by study visit

6.8 Analysis of Safety

The primary objective of this study for Cohorts 1-3 is to determine the safety of ascending doses of SHP611 administered EOW by IT injection for 38 weeks in children with MLD. The primary objective for Cohort 4 is to determine the safety of SHP611 produced with a revised investigational product substance manufacturing process administered by IT injection for 38 weeks in children with MLD. The safety analysis will be based on the following:

Type and frequency of pre-treatment AEs (from informed consent to surgical implantation of the IDDD or first dose date [whichever occurs first]), treatment-emergent AEs, and serious adverse events (SAEs) (by relationship to investigational product, device, procedure and severity)

- Laboratory testing (serum chemistry including liver function test, hematology, and urinalysis)
- Twelve-lead electrocardiograms, vital signs, and CSF chemistry (including cell counts, glucose, and protein)
- Determination of the presence of anti-SHP611 antibodies in CSF and/or serum
- Safety of SOPH-A-PORT Mini S IDDD

No statistical tests are planned for the safety parameters.

6.8.1 Adverse Events

Pre-treatment AEs are defined as AEs that occur after the date the informed consent form was signed but before the first dose of the investigational product and IDDD implant date.

Treatment-emergent AEs are defined as all AEs that occurred at or after the first dose of the investigational product or device implant surgery (whichever occurs earlier) and through the last follow-up date in the study HGT-MLD-070, with this follow-up evaluation occurring 4 weeks after the last injection of SHP611 or 2 weeks after the removal of the last IDDD, whichever occurred later; for subjects who did not enroll in the extension study, HGT-MLD-071, and this

follow-up evaluation occurring at the end-of-study (Week 40) for subjects who did enroll in HGT-MLD-071.

If the AE occurs on the day of first dose of the investigational product or IDDD implant and the AE onset time is missing, the AE will be classified as treatment-emergent. One of the criteria to determine an AE related to which device is that if the preferred term (PT) of the AE is "Device Failure", it will only be considered as related to SOPH-A-PORT IDDD if the AE start date is strictly after the initial SOPH-A-PORT implant date. Otherwise it will be assumed to be related to the PORT-A-CATH IDDD. SOPH-A-PORT IDDD-specific analyses will be based on the subset of the Safety Population with the SOPH-A-PORT IDDD implanted.

Physical examinations will be performed during the study EOW. All the clinically significant changes after screening will be reported as an AE.

Adverse event tabular summaries presented according to dose cohort and overall will be based on all TEAEs and coded using the Medical Dictionary for Regulatory Activities coding dictionary (MedDRA) version 15.0 or higher. An overall safety summary of TEAEs will be presented according to dose cohort and overall. This summary table will display the numbers of subjects and associated percentage in each of the following categories:

- Subjects who experienced no TEAEs
- Subjects who experienced at least 1 TEAE
- Subjects who experienced at least 1 SHP611-related TEAE
- Subjects who experienced at least 1 surgical device implantation-related TEAE
- Subjects who experienced at least 1 IDDD-related TEAE (PORT-A-CATH or SOPH-A-PORT)
- Subjects who experienced at least 1 SOPH-A-PORT IDDD-related TEAE
- Subjects who experienced at least 1 IT administration process-related TEAE
- Subjects who experienced at least 1 general anesthesia-related TEAE
- Subjects who experienced at least 1 severe TEAE
- Subjects who experienced at least 1 life-threatening or fatal TEAE
- Subjects who experienced at least 1 serious TEAE
- Subject discontinuation due to an TEAE(s)
- Subject deaths

Treatment-emergent AEs will also be summarized by system organ class (SOC) and PT. The number and proportion of subjects experiencing an AE will be tabulated, along with the number of events; at the subject level, recurrent AEs observed within a subject will be counted once. A similar analysis will be presented for SAEs.

Treatment-emergent AEs closest relationship to SHP611 (ie, the highest relationship [possibly<probably<definitely] observed for a TEAE during the study, HGT-1110-related TEAEs, IDDD-related TEAEs, SOPH-A-PORT IDDD-related TEAEs, device surgical procedure-related TEAEs, IT administration process-related TEAEs, general anesthesia-related TEAEs, LP-related TEAEs, and FEES evaluation-related TEAEs will be summarized by SOC and PT, with the number and proportion of subjects experiencing such events being tabulated, along with the number of events. At the beginning of the study, the CRF was designed to allow for collection of only one out of the following categories for related AEs: surgical implantation of IDDD, IDDD, IT administration process, general anesthesia, LP, and FEES. During the study, the CRF was changed to allow for collection of relationship for each of these separately. Hence for the AEs reported before this change, if AE was considered related to more than one category, it would have not been captured.

Adverse events by SOC and PT will also be tabulated at the subject level by maximum severity. In the case of the same AEs occurring on multiple days or times in an individual subject (separately at the SOC and PT levels), only the AE that is classified as the most severe (ie, maximum severity, [mild<moderate<severe]) will be presented. Total number of AEs occurring for each PT will be presented, whenever it is applicable.

Listings of all TEAEs, severe and life-threatening AEs, pre-treatment AEs, SAEs, permanent discontinuation due to AEs, and TEAEs leading to subject deaths, presented in chronological order within each SOC and PT for each subject, will be presented.

6.8.2 Clinical Laboratory Evaluation

Laboratory results for hematology, chemistry and urinalysis are collected at screening, Week 0, and every 4 weeks through Week 40/EOS. The following parameters will be collected:

- Hematology: complete blood count (CBC) with differential and platelet count, Prothrombin time and activated partial thromboplastin time (aPTT) at screening visit

- Serum chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, alkaline phosphatase, amylase, total bilirubin, calcium, creatinine, creatine kinase, gamma-glutamyl transferase (GGT), iron, potassium, lactate dehydrogenase (LDH), sodium, inorganic phosphate, magnesium

- Urinalysis: pH, macroscopic evaluations, microscopic evaluations

Laboratory results will be categorized as a subject having had (1) an Abnormal and Clinically Significant (CS) value at any time post-Baseline, (2) one or more abnormal values, but no CS values at any time post-Baseline, and (3) no abnormal values at any time post-Baseline; (4) missing; the number and percentage in each category will be presented. For any subject who

experiences a CS laboratory result at any time that was not CS at Baseline, his/her entire profile for that particular laboratory parameter will be presented as a listing. Clinical significance is assessed for values outside the normal range and is based on the investigator's assessment and captured on the eCRF. In addition, the shift from Baseline to the last available measurement will be summarized using a shift table presented in terms of Normal, Out of Normal Range and Not Clinically Significant (NCS), Out of Normal Range and CS, or Missing not done). These shift tables from Baseline to the last available measurement will be used to supplement the high-level analyses presented immediately above should any safety signals be observed there. For the purpose of analysis, laboratory values designated as "<X" will be assigned a value of X/2.

All laboratory data from both scheduled and unscheduled (ie, unexpected) study visits will be captured and recorded and included for the above analyses.

For all relevant laboratory chemistry and hematology parameters, the observed values and the change from Baseline will be summarized descriptively at each study visit by dose cohort and overall.

6.8.3 Cerebrospinal Fluid Assessments

Cerebrospinal fluid will be obtained via the IDDD or LP in aliquots prior to each IT injection at Week 0 and every 2 weeks through Week 38, as well as at Week 40/EOS. The same analyses outlined above for clinical laboratory evaluations will be implemented here for the CSF chemistries (total cell count, glucose, protein, and albumin). For CSF chemistry any values reported as blank will be considered normal.

For red blood cells and differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), the CRF design does not distinguish between normal and abnormal. Hence, the above categorization for laboratory analysis cannot be used. The shift from Baseline to the last available measurement will be summarized using a shift table presented in terms of CS, NCS or Missing/ND. The status for both absolute values and percentages will be considered for the CSF differential shift tables.

For any subject who experiences a CS laboratory result at any time that was not CS at Baseline, his/her entire profile for that particular laboratory parameter will be presented as a listing.

6.8.4 Immunogenicity

Serum and CSF samples for the determination of anti-SHP611 antibodies will be taken at Week 0 and every 4 weeks through Week 40/EOS (as discussed in Section 6.8.3 above). The number and percentage of subjects who became anti-SHP611 antibody-positive and neutralizing antibody-positive in serum during the study will be presented by dose cohort. For this presentation, subjects with at least 1 positive result during the study will be classified overall as positive. The number of subjects classified as positive will be tabulated at each time point by dose cohort. The same analyses will be repeated for the development of anti-SHP611 antibodies in CSF.

For time to first positive anti-SHP611 antibody result in either serum or CSF, this information will be summarized and a cumulative incidence curve will be presented by dose cohort and

overall. The time (date blood taken – date of first injection) to develop a positive result will be determined by Kaplan-Meier (KM; product-limit) analysis. Subjects who do not experience a positive anti-SHP611 antibody result will be censored at the time of the last known evaluation for that subject.

A by-subject listing of antibody results, including GMFM-88 total score (percent), will be presented. The listing will be sorted by subjects who were positive at least once and then subjects who were negative always, then dose cohort, and within subject sort by visit.

All subjects from the three dose cohorts will be classified into two subgroups for CSF and serum SHP611 antibody and neutralizing antibody:

1. Positive at any visit- Subjects who have been positive at least once in the study

2. Negative at all visits-Subjects who were always negative in the study

A listing of an anti-SHP611 antibody results for subjects with positive titer values with serum and CSF anti-SHP611 antibody values will be generated.

GMFM-88 total score (percent), N-acetylaspartate/Creatine and biomarker data will be summarized by visit and antibody subgroups. Scatterplots of GMFM-88 total score (percent), N-acetylaspartate/Creatine and biomarker with antibody titer values (serum and CSF) will be plotted. Also, individual plots for GMFM-88 by visits for subjects who were ever positive may be plotted. These individual plots will include antibody status by visits.

6.8.5 Electrocardiogram Evaluations

Subjects will undergo a 12-lead ECG at screening and at Week 40/EOS. The following 12-lead ECG parameters will be assessed: heart rate (beats per minute [bpm]), PR interval (milliseconds [msec]), QRS interval (msec), and the corrected QTc (msec) interval as recorded on the CRF. The clinically relevant QTc interval will be reported rather than the QT interval. For all ECG parameters, the observed values will be summarized descriptively at each study visit by dose cohort and overall.

Twelve-lead ECG will also assess if subjects experience abnormal sinus rhythm (yes; no), atrial or ventricular hypertrophy (yes; no), or other abnormalities (yes; no). Each of these 12-lead ECG results will be categorized as a subject having reported *yes* at any time during the study post-screening; the number and percentage in each category will be presented by dose cohort and overall. If any abnormal findings were clinically significant, a listing of all abnormal ECG findings will be generated.

6.8.6 Vital Signs

There are 2 types of vital signs assessment: those taken at the time of IT injection and those taken at times when there is no IT injection. The non-IT injection vital signs observed values will be summarized descriptively at screening, on surgery day (IDDD implantation), and at Week 40/EOS.

Intrathecal injection vital signs will be recorded at every visit where an injection is given. Vital sign assessments will include pulse (bpm), blood pressure (systolic mmHg/diastolic mmHg), respiration rate (per minute), and temperature (ºC) and will be recorded prior to IT administration and at multiple post-IT administrations. Vital signs observed values and change from pre-dose will be summarized descriptively by dose cohort and overall.

Any abnormal vial sign which is above the normal range, below the normal range, and all clinically notable abnormal vital signs above or below the normal range will be tabulated by frequency and percentage by dose cohort and overall. This will be presented by time intervals for each visit. The time intervals of interest are pre-dose (measurement prior to IT administration), up to 4 hours (includes the scheduled time points measured at 30 minutes, 60 minutes and 4 hours post IT administration), 4-36 hours (includes scheduled time points measured at 8 hours, 16 hours, 24 hours and 36 hours post IT administration) and overall (across all these time points for that visit).

Individual subject values for each IT injection vital sign parameter will be plotted as a trellis (multi-panel) graph over time by assessment visit.

6.8.7 Concomitant Medications, Therapies, and Medical Surgical/Interventions

All non-protocol treatments, including medications and over-the-counter medications, therapies/interventions administered to subjects, and medical/surgical procedures performed on the subjects that started on or post Baseline through the Safety Follow-up visit (Week 42) in the study, are regarded as concomitant. Any medications/surgical procedures which ended before the baseline date will be excluded; however, a medication/surgical procedure that started before Baseline and ended on or after the baseline will be included.

The number and percentage of subjects who reported use of at least 1 concomitant medication will be summarized by Therapeutic Class, ATC level4, and PT (concomitant medications will be mapped using the World Health Organization Drug Dictionary (WHO-DD) version 1 June 2012 or later). Listings of all subjects who required concomitant therapies and those with a medical or surgical procedure will also be generated. Concomitant medications will be sorted in alphabetical order by ATC level 4 and within ATC level 4 by PT sorted in descending frequency based on the total number of subjects.

Concomitant medications will be listed by subject and include the reported term, PT, ATC level 4, indication, medication start date/time, medication end date/time, route and frequency.

6.9 SOPH-A-PORT Intrathecal Drug Delivery Device Analysis

6.9.1 Device Performance

6.9.1.1 Device-related Terminology

- Initial device implant: The first IDDD implant that a subject 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 surgical intervention. 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 either ongoing or device failure (surgical procedure). The date of the device failure is the date of the initial malfunction.

6.9.2 Device-related Adverse Events

Intrathecal drug delivery device- and procedure-related AEs will be tabulated within SOC by PT (refer to Section 6.8.1). Separate tabulations will be provided for AEs related to the IDDD, device surgical procedure, and IT administration process. In addition, by-subject listings of IDDD malfunction/failures will be provided for the PORT-A-CATH and for the SOPH-A-PORT IDDDs.

6.9.3 Device Performance Analyses

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

- With the initial device implant only (ie, no additional surgeries)
- Who had any post-initial implantation device surgeries
- Who had difficulties associated with the implant procedure (eg, difficulty accessing spinal canal, etc.)

Intrathecal drug delivery device-related surgical procedure details for initial implants, delayed implantation, and full system revisions across all IDDD implantations for all subjects 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, suture wing configuration, distance between the suture wings (cm), 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 subjects 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 subjects and IDDDs with 1 or more total malfunctions (including malfunctions leading to failure and resolved malfunctions), malfunctions leading to failure, and resolved malfunctions, as well as the corresponding number of event, will be presented. The types of total malfunctions and the reasons for IDDD failures reported by the site will be summarized at the subject, IDDD, and event level.

The annual event rate of IDDD failures and malfunctions will be calculated for each subject, 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 subjects 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 at the end of the study, from initial implantation, delayed implantation, or revision for all IDDDs.

Additionally, for the time from implantation of a SOPH-A-PORT Mini S IDDD until first device failure in weeks for each subject, a cumulative incidence will be calculated. The time until first failure will be determined by KM analysis. Subjects who do not have failure will be censored at the time of the last IT injection for that subject. This analysis will be repeated for time until first malfunction.

The IDDD longevity (time to failure in weeks) and time to first malfunction, for all implanted IDDDs, will be estimated using the KM method. A new port identifies a new IDDD, starting

from the date of device implantation (either an initial implantation, a partial or full revision, or a delayed device implant after previous removal). The time to IDDD failure (weeks) will be obtained by subtracting the date of the IDDD implantation from the date of IDDD failure (ie, the initial malfunction date that persists leading to surgical intervention) plus 1, and divided by 7; 1 decimal will be kept. A similar analysis will be performed for total malfunctions. Intrathecal drug delivery devices that did not fail or malfunction will be censored at the last investigational product injection date for each IDDD. 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 number of doses received via IDDD will be summarized.

The rate of successful IDDD injections (attempted and expected) will be calculated for each subject and summarized descriptively. The IDDD success rate will be calculated as the number of IDDD injections given as a percentage of IDDD injections given plus any malfunctions reported for inability to dose. The corresponding 95% confidence interval for the mean rate will be estimated, where appropriate. Injections that are not administered for subject-related reasons (e.g. subject 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 (ie, 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.

6.10 Analysis of Pharmacokinetic Data

6.10.1 Pharmacokinetics Population

See Section 6.2.

6.10.2 Pharmacokinetic Methods

All summaries and analyses of the pharmacokinetic data will be performed for the Pharmacokinetic population.

6.10.2.1 Drug Concentration

SHP611 concentrations in serum and CSF will be measured using an enzyme linked immunosorbent assay (ELISA), and the antibodies in serum and CSF will be determined using an electrochemiluminescence (ECL) immunoassay.

6.10.3 Handling BLQ Values

The following procedures will be used for serum and CSF concentrations below the lower limit of quantification (LLOQ) (reported as not quantifiable (NQ)):

- Samples that are BLQ are reported as zero on the data listings.

- Samples that are BLQ are treated as zero in the calculation of summary statistics (eg, mean, SD, etc.) for the serum and CSF 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 and CSF concentration versus time plots.

- For calculation of area under the concentration curve (AUC), BLQ values are set equal to zero in the dataset loaded into WinNonlin for pharmacokinetic 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 the AUC calculation for all later time points.

6.10.4 Pharmacokinetic Parameters

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

Pharmacokinetic parameters will be determined from the serum concentration-time data for SHP611 by non-compartmental analysis. The PK parameters will include but not be limited to the following:

C_{max}	Maximum concentration occurring at t_{max}
t_{max}	Time of maximum observed concentration sampled during a dosing interval
$AUC_{0-\infty}$	Area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration
AUC_{0-last}	Area under the curve from the time of dosing to the last measurable concentration
AUC_{0-24}	Area under the curve over the interval from 0 to 24 hours post-dose
λ_z	First order rate constant associated with the terminal (log-linear) portion of the curve
$t_{½}$	Terminal half-life
CL/F	Total body clearance for extravascular administration divided by the fraction of dose absorbed
V_z/F	Volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed

CL/F and V_z/F will also be corrected for body weight.

6.10.5 Statistical Analysis of Pharmacokinetic Data

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

The association of the presence of anti-SHP611 antibodies and SHP611 concentration-time profiles and pharmacokinetic parameters will be evaluated, if applicable.

6.10.6 Drug-drug and Drug-disease Interactions

There will be no analysis of drug-drug or drug-disease interactions.

7 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any changes in the conduct of the study after approval of this analysis plan, which may impact analyses performed, may require a revision of this analysis plan prior to database lock.

The following analyses, which were not specified in protocol, have been added to the SAP:

- The ANCOVA discussed above for GMFM-88 Total Score (Percent) will be repeated for biomarker analyses and MRS analyses.
- The calculation of MRT was removed from the planned PK analysis.
- Changes in IDDD analysis text for clarity.
- Added ENG z-scores analysis for measurements that with reference values.

The Pharmacokinetic Population is clarified as: All subjects who receive at least 1 dose of investigational product and have at least one measureable serum concentration or one measurable CSF concentration of SHP611.

8 STATISTICAL/ANALYTIC ISSUES

8.1 Adjustment for Covariates

Analyses of dose cohorts for the change from Baseline in GMFM-88 total score (percent) include an ANCOVA model. For this model, Baseline values of the GMFM-88 total score (percent) will be included as a covariate. Similar analyses are planned for exploratory endpoints.

8.2 Handling of Dropouts or Missing Data

Subjects who discontinue or are withdrawn from the study will not be replaced.

Missing values will not be imputed.

8.3 Interim Analyses and Data Monitoring

Safety data in this study will be monitored by an independent DSMB until the last subject completes his or her last scheduled study visit/assessment.

An interim analysis of all data will be performed after all enrolled subjects in Cohorts 1-3 completed the study. All data from Cohorts 1-3 will be entered into the database and reviewed and discrepancies resolved for this analysis. Because any hypothesis testing is considered exploratory in this early phase trial, no adjustment for multiplicity will be made. The analysis methods are detailed in an interim SAP, and an interim study report based on these data will be completed. Other descriptive analyses of the data before trial completion may be performed for additional safety monitoring, regulatory reporting, or general planning.

The DSMB is 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. To support the safety review by the DSMB and to facilitate their decision making, a separate SAP was developed. Planned DSMB meetings occur prior to each dose escalation and prior to the start of Cohort 4. In addition, an ad hoc DSMB meeting will be convened if the safety related study stopping rules are met. At the end of the trial there may be an additional meeting to allow the DMC to discuss the final data with the principal trial investigators/sponsor and give advice about data interpretation.

One or more data review meetings will be held prior to database lock to facilitate clinical data review prior to completion of final analyses. Descriptive analyses of the data before trial completion may be performed for internal safety monitoring, regulatory reporting, or general planning purposes. All final planned analyses per the protocol and this final SAP will be performed only after the last subject has completed the study and the database has been locked.

8.4 Multicenter Studies

Due to anticipated small sample sizes within each site, statistical analyses will not be adjusted for site, and the summaries of the results will not be presented by site.

8.5 Multiple Comparisons and Multiplicity

All statistical testing is considered exploratory in this study, and no adjustment for multiplicity will be made.

8.6 Examination of Subgroups and Interactions

Given the small number of subjects within each dose cohort, there are no planned subgroup analyses or tests of interactions.

8.7 Sensitivity Analyses

No sensitivity analyses are planned. However, if outliers are present in the primary efficacy analyses, those analyses may be repeated by excluding any potential outliers.

8.8 Data Listings

All data will be presented as SAS datasets in CDISC format. This includes data on SSEP and BAER.

9 REFERENCES

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10 DATA PRESENTATIONS

The following tables, listings, and figures will be presented for the Safety Population.

10.1 List of Tables

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14.1.1	Subject Disposition by Cohort and Overall (All Subjects)
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14.2.1.2.8	GMFCS Level: Shift from Baseline Over Time by Dose Cohort and Overall (Safety Population)
14.2.1.2.9	GMFM-88 Subgroup (Baseline GMFM-88 >40 or <=40) analysis: Observed Value and Change from Baseline by Visit, Cohort, and Overall (Safety Population)
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Figure Number	Figure Title
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Listing Number	Listing Title
	Population)
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10.3 List of Statistical Outputs

Appendix Number	Statistical Output Title
10.11.1	Analysis of the GMFM-88 Total Scores (Percent): Change from Baseline by Dose Cohort (Table 14.2.1.1)
10.11.2	Analysis of the Biomarkers: Change from Baseline by Dose Cohort (Table 14.2.6.1)
10.11.3	Analysis of N-acetylaspartate/ Creatine Metabolite Levels in Deep White Matter of the Brain as Assessed by Proton MRS: Change from Baseline by Dose Cohort (Table 14.2.7.1)
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10.4 Definitions and Programming Conventions

10.4.1 General Reporting Conventions

- All tables and data listings will be presented in landscape orientation, unless presented as part of the text in a CSR.

- Figures will be presented in landscape orientation, unless portrait orientation suggests that the information presented is easier to interpret.

- Legends will be used for all figures with more than 1 variable or item displayed.

- All titles will be centered on a page. The first line contains the report numeration. The second line shows the description of the report. Subsequent lines are to be added, if necessary, to

clarify the report content. The ICH numeration convention is to be used for all tables, listings, and graphics.

- All footnotes will be left-justified at the bottom of the report page. They are to be used sparingly and must add value to the report.

- Missing values for both numeric and character variables will be presented as blanks in a table or data listing.

- All date values will be presented as ddMMMyyyy (eg, 29AUG2009) format. A 4-digit year is preferred for all dates.

- All observed time values will be presented using a 24-hour clock HH:MM format (eg, 01:35 or 15:26).

- Time durations will be reported in days:hours:mins format, as appropriate. If a single-valued duration is presented, a unit must accompany it.

- All tables and figures will have the program name and a date/time stamp on the bottom of each output.

- All analysis programs developed for a table or figure must be written to facilitate transfer and execution over multiple computing environments, if requested by a regulatory agency.

10.4.2 Population Summary Conventions

- Subpopulation(s) or special population(s) descriptions may be added to ensure understanding of the population used in a table or figure (eg, Age < 65 years).

- Population sizes are presented for each treatment group or dosing category as totals in the column header as (N=xxx).

- Sample sizes illustrated in summary statistics represent the number of subjects (n) with non-missing values.

- All population summaries for categorical variables will include categories selected for response. Percentage corresponding to null categories will be suppressed.

- All population summaries for continuous variables will include: n, mean, SD, median, minimum, maximum, and 95% CI as appropriate.

- All percentages are rounded and reported to a single decimal point (x.x%). If percentages are reported as integers, percentages greater than 0% but <1% will be reported as <1%, whereas percentages greater than 99% but <100% will be reported as >99%. A percentage of 100% will be reported as 100%. No value of 0% should be reported. Any computation of percent that results in 0% is to be reported as a blank.

- Population summaries that include p-values will report the p-value to four decimal places with a leading zero (0.0001). All p-values reported on default output from statistical software (ie, SAS®) may be reported at the default level of precision. p-values <0.0001 should be reported as <0.0001 and not 0.0000.

10.5 Study Schedule of Events

Table 3: Study Schedule of Events: Cohorts 1, 2, and 3

Cohorts 1, 2, and 3																								
PHASE[a,b]	1	2	3[b]																				4	5
VISIT NUMBER	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
STUDY WEEK	SCRN	SURG	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	EOS 40[p]	Follow-up 42[q]
DAYS[b]	-40 to -11[d]	-10 to -1	0	14	28	42	56	70	84	98	112	126	140	154	168	182	196	210	224	238	252	266	280	294
Informed consent[c]	•																							
Inclusion/exclusion criteria	•																							
MLD diagnosis, genotype[d]	•																							
Enrollment[e]		•	•																					
CRIM	•																							
Newborn screening	•																							
Medical history and demographics	•																							
Anesthesia[f]		•	•								•						•						•	
IDDD placement[f]		•																						
IDDD X-ray[g]		•																					•	
IDDD removal[h]																							•	
Physical exam[i]	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
12-lead ECG	•																						•	
Vital signs[j]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Height and weight	•										•						•						•	
Head circumference	•										•						•						•	
Injection of HGT-1110[f,k]			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		

Table 3: Study Schedule of Events: Cohorts 1, 2, and 3

Cohorts 1, 2, and 3																								
PHASE[a,b]	1	2	3[b]																				4	5
VISIT NUMBER	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
STUDY WEEK	SCRN	SURG	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	EOS 40[p]	Follow-up 42[q]
DAYS[b]	-40 to -11[d]	-10 to -1	0	14	28	42	56	70	84	98	112	126	140	154	168	182	196	210	224	238	252	266	280	294
Serum PK sampling[l]			•																			•		
GMFM-88[i]			•								•						•						•	
GIMF-C[i]			•								•						•						•	
GIMF-S[i]			•								•						•						•	
FEES[i]			•								•						•						•	
ENG studies[f]			•								•						•						•	
VABS-II[i]			•								•						•						•	
COMFORT			•								•						•						•	
Serum biomarkers			•		•		•		•		•		•		•		•		•		•		•	
CSF biomarkers[f]			•		•		•		•		•		•		•		•		•		•		•	
Urine biomarkers			•		•		•		•		•		•		•		•		•		•		•	
Serum and CSF anti-HGT-1110 antibodies[f]			•		•		•		•		•		•		•		•		•		•		•	
Brain MRI/MRS[f]			•								•						•						•	
Serum chemistry (including albumin) Hematology[m]	•		•		•		•		•		•		•		•		•		•		•		•	
CSF routine analysis, including albumin[f]			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CSF concentration			•		•		•		•		•		•		•		•		•		•		•	

Table 3: Study Schedule of Events: Cohorts 1, 2, and 3

Cohorts 1, 2, and 3																								
PHASE[a,b]	1	2	3[b]																				4	5
VISIT NUMBER	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
STUDY WEEK	SCRN	SURG	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	EOS 40[p]	Follow-up 42[q]
DAYS[b]	-40 to -11[d]	-10 to -1	0	14	28	42	56	70	84	98	112	126	140	154	168	182	196	210	224	238	252	266	280	294
of HGT-1110[f]																								
Urinalysis	•		•		•		•		•		•		•		•		•		•		•		•	
Pregnancy testing[n]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Concomitant Medications/ Therapies/ Procedures[o]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse events[o]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: aPTT = activated partial thromboplastin time; ASA = arylsulfatase A; CRIM = cross-reacting immunological material; COMFORT = Caregiver Observed MLD Functioning and Outcomes Reporting Tool; CSF = cerebrospinal fluid; ECG = electrocardiogram; ENG = electroneurography; EOS = end-of-study; FEES = functional endoscopic evaluation of swallowing; GMFM-88 = Gross Motor Function Measure-88; IDDD = intrathecal drug delivery device; IT = intrathecal; MLD = metachromatic leukodystrophy; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; PK = pharmacokinetic; PT = prothrombin time; SCRN = screening; SURG = surgery; VABS-II = Vineland Adaptive Behavior Scales, Second Edition

[a] Phase 1 = Screening; Phase 2= IDDD implantation and Post-surgical assessment; Phase 3= Baseline (Week 0) and treatment weeks (Weeks 2-38); Phase 4= EOS; Phase 5 = Safety follow-up

[b] In Phase 3 of the study, the visit window will be ±3 days for the IT injection of HGT-1110. All assessments will be performed prior to IT injection of HGT-1110 unless otherwise indicated. Upon confirmation of study eligibility, Week-0 assessments may be performed at any time prior to dosing, including the Phase 2 period of the study, but should be performed as close to dosing as possible. In addition, at Weeks 16 and 28 the window for assessments will be -5 days.

[c] Written informed consent must be provided by the subject's parent(s) or legal representative(s) prior to conducting any study procedures.

[d] Blood and urine samples will be collected for ASA activity in leukocytes and urinary sulfatide to confirm a MLD diagnosis and determine MLD genotype between Day -40 and Day -29. Local leukocyte arylsulfatase A enzyme activity and urine sulfatide information will be allowed for use in confirming MLD diagnosis if available and deemed sufficient by the Principal Investigator and Medical Monitor. Sample collection for diagnostic testing will still be

Table 3: Study Schedule of Events: Cohorts 1, 2, and 3

Cohorts 1, 2, and 3																								
PHASE[a,b]	**1**	**2**	**3[b]**																				**4**	**5**
VISIT NUMBER	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
STUDY WEEK	**SCRN**	**SURG**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**EOS 40[p]**	**Follow-up 42[q]**
DAYS[b]	**-40 to -11[d]**	**-10 to -1**	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**

performed if local results are used to confirm the diagnosis of MLD.

[e] A patient will be considered enrolled in the study once they have undergone device implant surgery or received at least 1 dose of investigational product.

[f] Anesthesia may be required (as determined by Investigator) for the following procedures: IDDD implantation, injection of HGT-1110, CSF sampling, ENG studies, and brain MRI and MRS assessments.

[g] An X-ray will be performed to confirm the placement of the IDDD. X-rays may be performed as needed throughout the study to check placement of the device.

[h] 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, a different study or commercially available)

[i] The physical examination, GMFM-88, GIMF-C, GIMF-S, FEES, and VABS-II assessments must be performed prior to the administration of anesthesia or after the subject has fully recovered from anesthesia. The GIMIF-C and GIMF-S assessments are to be administered after each GMFM-88 assessment and will only be performed for subjects in Cohort 4

[j] Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature measurements (to be measured when the subject is not irritable or crying). Vital signs will be measured within 30 minutes prior to IT administration and 30 (±10) minutes, 60 (±10) minutes, 4 hours (±30 minutes), 8 hours (±30 minutes), 16 hours (±30 minutes), 24 hours(±30 minutes), and 36 hours (±30 minutes), post IT administration. Vital signs do not need to be measured if the subject is asleep.

[k] Subjects will undergo safety assessments, and if no safety concerns exist, will subsequently receive the EOW IT injection of HGT-1110. Subjects will remain under observation in the hospital setting for at least 36 hours following dosing and will be discharged when deemed clinically stable by the Investigator. In the 10 and 30 mg cohorts, if a subject does not receive a scheduled dose within the planned visit window, the site should administer the dose as soon as possible. After the dose is administered, the next scheduled dose may be administered as soon as 7 days later. Administration of subsequent doses will return to the original schedule, which is based on the date of the subject's first dose. If a subject has a delay in 2 consecutive scheduled doses, the subject can receive doses as frequently as every 7 days until the subject has returned to the original dosing schedule set by the first dose. If more than 2 consecutive doses are delayed, the third and any subsequent consecutive dose will be considered missed due to lack of nonclinical toxicology data to support weekly dosing beyond 4 weeks. If a subject in the 100 mg cohort does not receive a scheduled dose within the planned visit window, this dose will be

Table 3: Study Schedule of Events: Cohorts 1, 2, and 3

Cohorts 1, 2, and 3																								
PHASE[a,b]	**1**	**2**	**3[b]**																				**4**	**5**
VISIT NUMBER	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
STUDY WEEK	**SCRN**	**SURG**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**EOS 40[p]**	**Follow-up 42[q]**
DAYS[b]	**-40 to -11[d]**	**-10 to -1**	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**

considered missed due to lack of nonclinical toxicology data to support dosing more frequently than EOW. After a missed dose, subjects in the 100 mg cohort will receive their next dose according to the original schedule for dosing set by the first dose.

[l] Serum PK will be assessed on Week 0 and Week 38. Blood will be drawn for PK assessments within 1 hour prior to IT injection and then drawn at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection.

[m] PT and aPTT will be performed at the Screening visit only (Phase 1).

[n] Urine pregnancy tests will be performed for females of child-bearing potential who are sexually active or who become sexually active during the study. If the urine test is positive, results will be confirmed with a serum pregnancy test.

[o] Adverse events and concomitant medications/therapies/procedures will be collected from the time of informed consent.

[p] If a subject discontinues early, the EOS visit will occur 2 weeks (-5, +3 days) after the last IT injection of HGT-1110.

[q] Follow-up safety assessments may be performed via telephone from the clinical site. If a subject terminates early, the Safety Follow-up visit will occur 4 weeks (±3 days) after the last IT injection of HGT-1110 or 2 weeks after the removal of the IDDD, whichever occurs later. Patients may be allowed to enroll in an HGT-1110 extension study, if eligible, after completing all requirements of HGT-MLD-070. Any patient enrolled in such an extension study will not participate in the Safety Follow-up visit, unless there is a delay in enrollment in the extension study.

Table 4: Study Schedule of Events: Cohort 4

Cohort 4																									
PHASE[a,b]	1	1	2	3[b]																				4	5
VISIT NUMBER	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
STUDY WEEK	SCRN	Baseline GMFM[m]	SURG	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	EOS 40[q]	Follow-up 42[r]
DAYS[b]	-40 to -1[d]	-40 to -1	-10 to +28	0	14	28	42	56	70	84	98	112	126	140	154	168	182	196	210	224	238	252	266	280	294
Informed consent[c]	•																								
Inclusion/exclusion criteria	•																								
MLD diagnosis, genotype[d]	•																								
Enrollment[e]	•																								
CRIM	•																								
Newborn screening	•																								
Medical history and demographics	•																								
Anesthesia[f]			•	•								•						•						•	
IDDD placement[f]			•																						
IDDD X-ray[g]			•																					•	
IDDD removal[h]																								•	
Physical exam[i]	•			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
12-lead ECG	•																							•	
Vital signs[j]	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Height and weight	•											•						•						•	
Head circumference	•											•						•						•	
Injection of HGT-1110[f,k]				•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		

Table 4: Study Schedule of Events: Cohort 4

Cohort 4																									
PHASE[a,b]	1	1	2	3[b]																				4	5
VISIT NUMBER	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
STUDY WEEK	SCRN	Baseline GMFM[m]	SURG	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	EOS 40[q]	Follow-up 42[r]
DAYS[b]	-40 to -1[d]	-40 to -1	-10 to +28	0	14	28	42	56	70	84	98	112	126	140	154	168	182	196	210	224	238	252	266	280	294
Serum PK sampling[l]				•																			•		
GMFM-88[i,m]	•	•	•	•								•						•						•	
GIMF-C[i,m]	•	•	•	•								•						•						•	
GIMF-S[i,m]	•	•	•	•								•						•						•	
FEES[i]				•								•						•						•	
ENG studies[f]				•								•						•						•	
VABS-II[i]				•								•						•						•	
COMFORT				•								•						•						•	
Serum biomarkers				•		•		•		•		•		•		•		•		•		•		•	
CSF biomarkers[f]				•		•		•		•		•		•		•		•		•		•		•	
Urine biomarkers				•		•		•		•		•		•		•		•		•		•		•	
Serum and CSF anti-HGT-1110 antibodies[f]				•		•		•		•		•		•		•		•		•		•		•	
Brain MRI/MRS[f]				•								•						•						•	
Serum chemistry (including albumin) Hematology[n]	•			•		•		•		•		•		•		•		•		•		•		•	
CSF routine analysis, including albumin[f]				•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CSF concentration				•		•		•		•		•		•		•		•		•		•		•	

Table 4: Study Schedule of Events: Cohort 4

Cohort 4																									
PHASE[a,b]	1	1	2	3[b]																				4	5
VISIT NUMBER	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
STUDY WEEK	SCRN	Baseline GMFM[m]	SURG	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	EOS 40[q]	Follow-up 42[r]
DAYS[b]	-40 to -1[d]	-40 to -1	-10 to +28	0	14	28	42	56	70	84	98	112	126	140	154	168	182	196	210	224	238	252	266	280	294
of HGT-1110[f]																									
Urinalysis	•			•		•		•		•		•		•		•		•		•		•		•	
Pregnancy testing[o]	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Concomitant Medications/ Therapies/ Procedures[p]	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse events[p]	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: aPTT = activated partial thromboplastin time; ASA = arylsulfatase A; CRIM = cross-reacting immunological material; COMFORT = Caregiver Observed MLD Functioning and Outcomes Reporting Tool; CSF = cerebrospinal fluid; ECG = electrocardiogram; ENG = electroneurography; EOS = end-of-study; FEES = functional endoscopic evaluation of swallowing; GMFM-88 = Gross Motor Function Measure-88; IDDD = intrathecal drug delivery device; IT = intrathecal; MLD = metachromatic leukodystrophy; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; PK = pharmacokinetic; PT = prothrombin time; SCRN = screening; SURG = surgery; VABS-II = Vineland Adaptive Behavior Scales, Second Edition

[r] Phase 1 = Screening; Phase 2= IDDD implantation and Post-surgical assessment; Phase 3= Baseline (Week 0) and treatment weeks (Weeks 2-38); Phase 4= EOS; Phase 5 = Safety follow-up. If eligibility has been confirmed, and IDDD implantation cannot be scheduled to occur within the Phase 2 window, or it is desired to shorten the screening period to promptly initiate first dose administration, investigational drug product may be administered by means of an LP. No more than 3 doses may be administered by LP prior to IDDD implantation.

[s] In Phase 3 of the study, the visit window will be ±3 days for the IT injection of HGT-1110. All assessments will be performed prior to IT injection of HGT-1110 unless otherwise indicated. In addition, at Weeks 16 and 28 the window for assessments will be -5 days.

[t] Written informed consent must be provided by the subject's parent(s) or legal representative(s) prior to conducting any study procedures.

[u] Blood and urine samples will be collected for ASA activity in leukocytes and urinary sulfatide to confirm a MLD diagnosis and determine MLD genotype between Day -40 and Day -29. Local laboratory results for leukocyte arylsulfatase A enzyme activity and urine sulfatide will be allowed for use in confirming MLD diagnosis if available and deemed sufficient by the Principal Investigator and Medical Monitor, while waiting for the central laboratory results so that dosing of the study medication could occur as soon as possible. Sample collection for diagnostic testing will still be performed at Screening if local results are

Table 4: Study Schedule of Events: Cohort 4

Cohort 4																									
PHASE[a,b]	1	1	2	3[b]																				4	5
VISIT NUMBER	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
STUDY WEEK	SCRN	Baseline GMFM[m]	SURG	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	EOS 40[q]	Follow-up 42[r]
DAYS[b]	-40 to -1[d]	-40 to -1	-10 to +28	0	14	28	42	56	70	84	98	112	126	140	154	168	182	196	210	224	238	252	266	280	294

used to confirm the diagnosis of MLD.

[v] A patient will be considered enrolled in the study once they have undergone device implant surgery or received at least 1 dose of investigational product. Enrollment may occur prior to the IDDD implantation or the first dose (baseline); however, implantation of the device must occur within 28 days of the first dose.

[w] Anesthesia may be required (as determined by Investigator) for the following procedures: IDDD implantation, injection of HGT-1110, CSF sampling, ENG studies, and brain MRI and MRS assessments.

[x] An X-ray will be performed to confirm the placement of the IDDD. X-rays may be performed as needed throughout the study to check placement of the device.

[y] 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, a different study or commercially available)

[z] The physical examination, GMFM-88, GIMF-C, GIMF-S, FEES, and VABS-II assessments must be performed prior to the administration of anesthesia or after the subject has fully recovered from anesthesia. The GIMIF-C and GIMF-S assessments are to be administered after each GMFM-88 assessment and will only be performed for subjects in Cohort 4

[aa] Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature measurements (to be measured when the subject is not irritable or crying). Vital signs will be measured within 30 minutes prior to IT administration and 30 (±10) minutes, 60 (±10) minutes, 4 hours (±30 minutes), 8 hours (±30 minutes), 16 hours (±30 minutes), 24 hours(±30 minutes), and 36 hours (±30 minutes), post IT administration. Vital signs do not need to be measured if the subject is asleep.

[bb] Patients will undergo safety assessments, and if no safety concerns exist, will subsequently receive the EOW IT injection of HGT-1110. Subjects will remain under observation in the hospital setting for at least 36 hours following dosing and will be discharged when deemed clinically stable by the Investigator. In the 10 and 30 mg cohorts, if a subject does not receive a scheduled dose within the planned visit window, the site should administer the dose as soon as possible. After the dose is administered, the next scheduled dose may be administered as soon as 7 days later. Administration of subsequent doses will return to the original schedule, which is based on the date of the subject's first dose. If a subject has a delay in 2 consecutive scheduled doses, the subject can receive doses as frequently as every 7 days until the subject has returned to the original dosing schedule set by the first dose. If more than 2 consecutive doses are delayed, the third and any subsequent consecutive dose will be considered missed due to lack of nonclinical toxicology data to support weekly dosing beyond 4 weeks. If a

Table 4: Study Schedule of Events: Cohort 4

Cohort 4																									
PHASE[a,b]	**1**	**1**	**2**	**3[b]**																				**4**	**5**
VISIT NUMBER	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
STUDY WEEK	**SCRN**	**Baseline GMFM[m]**	**SURG**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**EOS 40[q]**	**Follow-up 42[r]**
DAYS[b]	**-40 to -1[d]**	**-40 to -1**	**-10 to +28**	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**

subject in the 100 mg cohort does not receive a scheduled dose within the planned visit window, this dose will be considered missed due to lack of nonclinical toxicology data to support dosing more frequently than EOW. After a missed dose, subjects in the 100 mg cohort will receive their next dose according to the original schedule for dosing set by the first dose.

[cc] Serum PK will be assessed on Week 0 and Week 38. Blood will be drawn for PK assessments within 1 hour prior to IT injection and then drawn at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection.

[dd] A baseline GMFM-88 assessment will be performed before device implantation or prior to first dose administration, whichever occurs first. The baseline GMFM-88 assessment will not be required if device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment. Upon confirmation of study eligibility (including GMFM-88 baseline assessment), all other Week 0 assessments may be performed at any time prior to first dose, including prior to IDDD implantation, but should be performed after enrollment and as close to the first dose as possible. Subjects who do not continue to meet eligibility criteria will be discontinued from the study prior to device implantation and/or initial dosing.

[ee] PT and aPTT will be performed at the Screening visit only (Phase 1).

[ff] Urine pregnancy tests will be performed for females of child-bearing potential who are sexually active or who become sexually active during the study. If the urine test is positive, results will be confirmed with a serum pregnancy test.

[gg] Adverse events and concomitant medications/therapies/procedures will be collected from the time of informed consent.

[hh] If a subject discontinues early, the EOS visit will occur 2 weeks (-5, +3 days) after the last IT injection of HGT-1110.

[ii] Follow-up safety assessments may be performed via telephone from the clinical site. If a subject terminates early, the Safety Follow-up visit will occur 4 weeks (±3 days) after the last IT injection of HGT-1110 or 2 weeks after the removal of the IDDD, whichever occurs later. Subjects may be allowed to enroll in an HGT-1110 extension study, if eligible, after completing all requirements of HGT-MLD-070. Any subject enrolled in such an extension study will not participate in the Safety Follow-up visit, unless there is a delay in enrollment in the extension study.

11 APPENDIX

Table A-1: MLD Electroneurography Reference Values by Age[8]

Variables from CRF		Variable from Pediatric Clinical ENG	Data range	Age: mean (SD)
Median Motor Thenar	Variable code			
Elbow to Wrist Conduction Velocity Fixed Unit: m/s	M1	Table 1 (b) Parano; MNCV (m/s)	7-63 , 1 XR, 1 blank	2-4y: 53.59 (5.29) 4-6y: 56.26 (4.61) 6-14y: 57.32 (3.35)
Wrist Amplitude Baseline to Peak Fixed Unit: mv	M2	Table 1 (b) Parano; (mV)	0-9.9, no XR, 7 blank	2-4y: 9.55 (4.34) 4-6y: 10.37 (3.66) 6-14y: 12.37 (4.79)
Elbow Amplitude Baseline to Peak Fixed Unit: mv	M3			
F-wave Latency Fixed Unit: ms	M4	Table 2 (c) Parano; (ms)	0-90 , 40 XR/ND/blank	2-4y: 17.91 (1.11) 4-6y: 19.44 (1.51) 6-14y: 23.23 (2.57)
Wrist-APB Distal Latency Fixed Unit: ms	M5	Table 1 (b) Parano; (ms)	2-16, 1 XR, 1 ND, 1 blank	2-4y: 2.18 (0.43) 4-6y: 2.27 (0.45) 6-14y: 2.73 (0.44)
Ulnar Motor				
Wrist amplitude		Table 4b (miller and kuntz)		13-24 mo: 2.6-9.7
Elbow amplitude				
Elbow to wrist conduction velocity		Table 4b (miller and kuntz) Table 4c (baer and Johnson)		13-24mo: 41.3-63.5 4-16y: 58.2 (9.7)
Wrist-ADM distal latency		Table 4b (miller and kuntz)		13-24 mo: 1.1-2.2
Ulnar F-wave latency		Table 5b (Kwast)		3-5y: 15.9 (0.8) 5-7y: 17.6 (0.9) 7-12y: 19.1 (1.0)
Peroneal Motor				
Ankle amplitude		Table 7b (Parano)		2-4y: 6.10 (2.99) 4-6y: 7.10 (4.76) 6-14y: 8.15 (4.19)
Fibular head amplitude				
Ankle to fib head conduction velocity		Table 7b (Parano)		2-4y: 55.73 (4.45) 4-6y: 56.14 (4.96) 6-14y: 57.05 (4.54)
Ankle-EDB distal latency		Table 7b (Parano)		2-4y: 2.62 (0.75) 4-6y: 3.01 (0.43) 6-14y: 3.25 (0.51)
Peroneal motor f-		Table 8b (Parano)		2-4y: 29.52 (2.15)

Table A-1: MLD Electroneurography Reference Values by Age[8]

Variables from CRF		Variable from Pediatric Clinical ENG	Data range	Age: mean (SD)
wave				4-6y: 29.98 (2.68) 6-14y: 34.27 (4.29)
Tibial Motor				
Ankle amplitude		Table 9a (Cruz Martinez et al)		6-11y: 12 (5-20)
Knee amplitude				
Ankle to knee conduction velocity		Table 9a (Cruz Martinez et al)		2-4y: 49.8 (5.79) 4-6y: 50.0 (4.26) 6-11y: 52.4 (4.19)
Ankle to AH distal latency		Table 9a (Cruz Martinez et al)		2-4y: 2.81 (0.47) 4-6y: 3.20 (0.56) 6-11y: 3.60 (0.67)
Tibial f-wave latency		Table 10 (Miller and Kuntz)		13-24mo: 22-26
Median Sensory				
Wrist to digit distal latency		Table 12a (miller and kuntz)		13-24mo: 1.7-3.0
Wrist amplitude		Table 12b (parano)		2-4y: 24.28 (5.49) 4-6y: 25.12 (5.22) 6-14y: 26.72 (9.43)
Sural Sensory				
B point latency		Table 14a (miller and kuntz)		13-24mo: 1.4-2.8
B point amplitude		Table 14b (parano)		2-4y: 23.27 (6.84) 4-6y: 22.66 (5.42) 6-14y: 26.75 (6.59)