Clinical Trial Protocol: HGT-MLD-070

Study Title:	A Phase I/II Multicenter Open-label Dose Escalation Study of HGT-1110 Administered Intrathecally in Children with Metachromatic Leukodystrophy
Study Number:	HGT-MLD-070
Study Phase:	I/II
Product Name:	HGT-1110 (recombinant human arylsulfatase A, rhASA)
IND Number:	Not Applicable
EudraCT Number:	2011-002044-28
Indication:	Metachromatic Leukodystrophy
Investigators:	Multicenter
Sponsor:	Shire Human Genetic Therapies, Inc. (Shire) 300 Shire Way Lexington, MA 02421, USA
Medical Monitor:	PPD PPD, MD

	Date
Original Protocol:	24 January 2011
Amendment 1	03 June 2011
Amendment 2	17 August 2011
Amendment 3	20 October 2011
Amendment 4	08 December 2011
Amendment 5	05 April 2012
Amendment 6	24 June 2013
Amendment 7	31 July 2013
Amendment 8	10 February 2015
Amendment 9	26 August 2015

Confidentiality Statement

SYNOPSIS

Sponsor:

Shire Human Genetic Therapies, Inc. (Shire)

Name of Finished Product:

HGT-1110 (recombinant human arylsulfatase A, rhASA)

Name of Active Ingredient:

Recombinant human arylsulfatase A (rhASA)

Name of Devices:

- SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire (SOPH-A-PORT Mini S)
- PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System (PORT-A-CATH)

Study Title:

A Phase I/II Multicenter Open-label Dose Escalation Study of HGT-1110 Administered Intrathecally in Children with Metachromatic Leukodystrophy

Study Number:

HGT-MLD-070

Study Phase: I/II

Investigational Drug Product, Dose, and Mode of Administration:

Patients in Cohorts 1-3 received intrathecal (IT) injections at 1 of 3 dose levels (10, 30, or 100 mg) of HGT-1110 every other week (EOW) (±3 days). Patients in Cohorts 4 will receive 100 mg of HGT-1110 EOW (±3 days).

Device, Intended Use:

The SOPH-A-PORT Mini S is a system intended for implantation by physicians. The SOPH-A-PORT Mini S, once implanted, allows healthcare personnel to administer HGT-1110 indicated for IT delivery intermittently over a long period of time.

Primary Objective:

- Cohorts 1-3: The primary objective is to determine the safety of ascending doses of HGT-1110 administered by IT injection for 38 weeks in children with metachromatic leukodystrophy (MLD).
- Cohort 4: The primary objective is to determine the safety of HGT-1110 produced with a revised drug substance manufacturing process administered by IT injection for 38 weeks in children with MLD.

Secondary Objectives:

- To evaluate the effects of IT administration of HGT-1110 on gross motor function
- To evaluate the effects of IT administration of HGT-1110 on the ability to swallow

- To evaluate the effects of IT administration of HGT-1110 on nerve conduction capabilities
- To evaluate the effects of IT administration of HGT-1110 on adaptive behavior
- To evaluate the effects of IT administration of HGT-1110 on health status and the ability to carry out activities of daily life
- To assess single and repeated-dose pharmacokinetics (PK) of HGT-1110 in serum
- To assess concentrations of HGT-1110 in cerebrospinal fluid (CSF)

Study Endpoints:

Safety will be measured by the following endpoints:

- Reporting of treatment-emergent adverse events (TEAE)
- Change from baseline in clinical laboratory testing (serum chemistry including liver function tests, hematology, and urinalysis)
- Change from baseline in 12-lead electrocardiograms (ECGs), vital signs, physical examinations, and CSF chemistry (including cell counts, glucose, and protein)
- Determination of the presence of anti-HGT-1110 antibodies in CSF and/or serum

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 HGT-1110 in serum
- Concentrations of HGT-1110 in CSF at selected time points after single and repeated investigational drug product administration

Study Population:

Approximately 24 male or female patients with a confirmed diagnosis of MLD are planned.

Study Design:

This is a multicenter open-label dose-escalation study designed to evaluate the safety of HGT-1110 in 4 cohorts. In Cohorts 1-3, three dose levels (10, 30, or 100 mg) of HGT-1110 were administered. In Cohort 4, patients will be administered 100 mg of HGT-1110. HGT-1110 is administered via an intrathecal drug delivery device (IDDD) every other week (EOW) for a total of 38 weeks (20 IT injections, Weeks 0 to 38) to children with MLD. The study also includes the assessment of HGT-1110 drug product produced with a revised drug substance manufacturing process (referred to as Process B) in a fourth cohort (Cohort 4).

For Cohorts 1-3, 18 patients were enrolled, 6 in each of the 3 dose level cohorts. The dose level cohorts were sequentially enrolled starting with the 10 mg dose as follows:

- Cohort 1: HGT-1110 by IT injection 10 mg EOW for a total of 38 weeks (6 patients)
- Cohort 2: HGT-1110 by IT injection 30 mg EOW for a total of 38 weeks (6 patients)
- Cohort 3: HGT-1110 by IT injection 100 mg EOW for a total of 38 weeks (6 patients)

Cohorts 1-3 received HGT-1110 drug product manufactured using Process A.

Patient enrollment was staggered in this study to facilitate adequate safety evaluation per cohort.

Dose escalation of HGT-1110 for Cohorts 2 and 3 was contingent on review of safety data by the Data Safety Monitoring Board (DSMB). Following enrollment of Cohort 1, the decision to escalate to the next higher dose level (Cohort 2) was based on a review of the safety data obtained in Cohort 1 (after all treated patients in the cohort have each received a minimum of 2 IT doses) by an independent DSMB and representatives from the Sponsor. The decision to escalate to the next higher dose level (Cohort 3) followed the same safety review process as that used for Cohort 2. A DSMB meeting will be held after completion of Cohorts 1-3.

Cohort 4 will be enrolled following Cohort 3, after DSMB review of Cohorts 1-3 and drug product manufactured with Process B becomes available. Approximately 6 patients who undergo device implant surgery or receive at least 1 dose of study drug will be included in Cohort 4, which will receive 100 mg HGT-1110 EOW for a total of 38 weeks. .

During the course of their participation in the study, a patient may request a transfer to a different qualified site, if agreed by both the sites and the Sponsor.

This study will have the following 5 phases:

Cohorts 1-3: Phases 1-3

Phase 1: Screening: Day -40 through Day -11

Upon obtaining informed consent, the procedures and assessments required for the determination of the patient's eligibility will be completed at the clinical site within 40 days of the baseline visit (Week 0). Sample collection for diagnostic testing should take place between Day -40 and Day -29 to ensure diagnostic results are received prior

to IDDD implantation in Phase 2 of the study.

Sites will be allowed one opportunity to re-screen any patient who fails initial screening or withdraws consent prior to device implantation. If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study.

Phase 2: Surgical Implantation of the IDDD: Day -10 to Day -1

Patients will undergo surgical implantation of an IDDD and a post-surgical assessment.

Phase 3: Baseline and Treatment Week 0 to Week 38 (±3 days for injection of HGT-1110)

Upon confirmation of study eligibility, baseline assessments (ie, those scheduled for Week 0) may be performed at any time prior to dosing, including the Phase 2 period of the study, but baseline assessments should be performed as close to dosing as possible. Patients will undergo pre-dose baseline assessments at Week 0, which will include a standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis), serum assessments of anti-HGT-1110 antibodies and CSF assessments (cell counts, protein, glucose, albumin, anti-HGT-1110 antibodies, and HGT-1110 levels) as well as safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures assessments).

Baseline efficacy outcome assessments including the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS will be performed as well as sample collection for CSF, serum, and urine biomarker assessments.

Patients will receive their first dose (Week 0) and begin the HGT-1110 EOW dosing period (through Week 38). At Week 0, blood will also be drawn for a PK assessment at the time points specified in the Schedule of Events.

During the EOW treatment period (Weeks 2 through 38), all assessments will be performed prior to IT injection of HGT-1110 unless otherwise indicated. Safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures assessments) will be performed. Patients 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. Additionally, anti-HGT-1110 antibody sampling, the standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis) and sample collection for analysis of CSF concentration of HGT-1110, and CSF, serum, and urine biomarkers will be performed every 4 weeks.

In addition to the scheduled assessments performed Weeks 2 through 38, Weeks 16 and 28 will also include the efficacy outcome assessments of the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS. For Weeks 16 and 28, the window for assessments will be -5 days. In

addition, at Week 38 blood will be drawn for a PK assessment at the time points specified in the Schedule of Events.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all 20 IT injections of HGT-1110. If the IT space is not accessible via the IDDD, investigational drug product may be administered by LP. Should the IDDD become clogged, undergo mechanical complications or otherwise not be accessible, the CSF sample may also be obtained by LP. Anesthesia may be required for injections of investigational drug product and some evaluations, and can be used at the discretion of the Investigator. The IDDD Manual provides details on the investigation and management of any IDDD-related issues.

Cohort 4: Phases 1-3

Note: Enrollment may occur prior to IDDD implantation or the first dose (baseline); however, implantation of the device should occur within 28 days of the first dose.

Phase 1: Screening: Day-40 through Day -1

Upon obtaining informed consent, the procedures and assessments required for the determination of the patient's eligibility, including GMFM-88, will be completed at the clinical site within 40 days prior to the baseline visit (Week 0). Sample collection for central diagnostic testing should take place at the screening visit to ensure diagnostic results are received promptly. Local laboratory results confirming the MLD diagnosis (analysis of urine sulfatide, ASA activity in leukocytes) will be accepted to confirm the MLD diagnosis enrollment criteria while waiting for the central laboratory results so that dosing of the study medication can occur as soon as possible.

Sites will be allowed one opportunity to re-screen any patient who fails initial screening or withdraws consent prior to device implantation or dose administration (if administration to be initiated by LP prior to device implantation). If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study.

Phase 2: Surgical Implantation of the IDDD: Day -10 to Day +28

To confirm the patient meets eligibility criteria at baseline, specifically the baseline GMFM-88 assessment will be performed as close as possible to, but before device implantation or prior to first dose administration, whichever occurs first. Patients who do not continue to meet eligibility criteria will be discontinued from the study prior to device implantation and/or initial dosing. If device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment, the baseline GMFM-88 assessment will not be required. However, if more than 7 days has passed since the screening GMFM-88 assessment, the baseline GMFM-88 assessment will need to be completed prior to IDDD implantation or first dose, and prior to any other baseline assessments in order to confirm eligibility for enrollment (per inclusion criterion 3.1).

Upon confirmation of eligibility, patients will undergo surgical implantation of an IDDD and a post-surgical assessment. The patient may receive study drug by LP until

the device is implanted. Device implantation should be scheduled within 28 days of enrollment unless a delay is required due to clinical judgment for medical reasons (eg, infection).

Phase 3: Baseline and Treatment Week 0 to Week 38 (±3 days for injection of HGT-1110)

Upon confirmation of study eligibility, baseline assessments (ie, those scheduled for Week 0) may be performed at any time prior to dosing, including the Phase 2 period of the study, but baseline assessments should be performed as close to dosing as possible. Patients will undergo pre-dose baseline assessments at Week 0, which will include a standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis), serum assessments of anti-HGT-1110 antibodies and CSF assessments (cell counts, protein, glucose, albumin, anti-HGT-1110 antibodies, and HGT-1110 levels) as well as safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures assessments).

Baseline efficacy outcome assessments including the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS will be performed as well as sample collection for CSF, serum, and urine biomarker assessments. If device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment, the baseline GMFM-88 assessment will not be required.

Patients will receive their first dose (Week 0) and begin the HGT-1110 EOW dosing period (through Week 38). At Week 0, blood will also be drawn for a PK assessment at the time points specified in the Schedule of Events.

During the EOW treatment period (Weeks 2 through 38), all assessments will be performed prior to IT injection of HGT-1110 unless otherwise indicated. Safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures assessments) will be performed. Patients 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. Additionally, anti-HGT-1110 antibody sampling, the standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis) and sample collection for analysis of CSF concentration of HGT-1110, and CSF, serum, and urine biomarkers will be performed every 4 weeks.

In addition to the scheduled assessments performed Weeks 2 through 38, Weeks 16 and 28 will also include the efficacy outcome assessments of the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS. For Weeks 16 and 28, the window for assessments will be -5 days. In addition, at Week 38 blood will be drawn for a PK assessment at the time points specified in the Schedule of Events.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all 20 IT injections of HGT-1110. 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.

If the IT space is not accessible via the IDDD, investigational drug product may be administered by LP. Should the IDDD become clogged, undergo mechanical complications or otherwise not be accessible, the CSF sample may also be obtained by LP until the device is repaired or replaced. Anesthesia may be required for injections of investigational drug product and some evaluations, and can be used at the discretion of the Investigator. The IDDD Manual provides details on the investigation and management of any IDDD-related issues.

All Cohorts (1-4): Phases 4 and 5

Phase 4: End of Study: Week 40 (-5, +3 days)

The assessments scheduled at Week 40, 2 weeks after the last HGT-1110 dose, will be the same as those at Weeks 16 and 28 with the addition of a 12-lead ECG and an X-ray (to confirm that the IDDD remains positioned correctly). Patients who discontinue early will have an end-of-study (EOS) visit 2 weeks (-5, +3 days) after the last IT injection of HGT-1110. All EOS assessments should be performed. For Week 40, assessments may be performed as early as 5 days prior to the scheduled visit date.

Patients will have the IDDD removed when they discontinue from or complete the study, unless the patient is continuing to receive treatment through another mechanism (eg, a different study or commercially available).

Phase 5: Safety Follow-up: Week 42 (±3 days)

The Safety Follow-up visit will be conducted at Week 42 or 4 weeks (±3 days) after the last injection of HGT-1110 or 2 weeks after the removal of the IDDD, whichever occurs later, for patients who discontinue. The follow-up safety assessments (AEs and concomitant medications/therapies/procedures) may be performed via telephone from the clinical site.

Patients who complete all requirements in Study HGT-MLD-070 through Week 40 may be eligible to participate in an extension study. However, patients are not obligated to participate in any additional studies, and the Sponsor cannot guarantee that such studies will occur. Anesthesia may be required for injections of investigational drug product and some evaluations, and can be used at the discretion of the Investigator.

If patients in the study require revision and/or replacement of the PORT-A-CATH IDDD, it will be removed and replaced with the SOPH-A-PORT Mini S device at a time judged appropriate by the Investigator.

Study Duration:

The duration for each patient's participation in this study is approximately 47 weeks. The planned duration of HGT-1110 treatment in this study is 38 weeks (20 IT injections of HGT-1110 EOW Weeks 0 to 38).

Study Inclusion and Exclusion Criteria:

Inclusion Criteria:

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

For Cohorts 1-4:

1. Confirmed diagnosis of metachromatic leukodystrophy by both:
   - Arylsulfatase A (ASA) deficiency by assay in leukocytes

   AND

   - Elevated sulfatide in urine
2. Appearance of the first symptoms of disease at or before 30 months of age.

For Cohorts 1-3 only:

3. Ambulatory at the time of screening. The minimum level of function required to meet this criterion is defined as the ability to walk forward 10 steps with one hand held.
4. The patient is less than 12 years of age at the time of screening.

For Cohort 4 only:

3.1 Minimum motor function requirements:

a. A total GMFM-88 (percent) score ≥40 at the screening examination and a total GMFM-88 (percent) score ≥35 at the baseline examination,

AND

b. GMFM-88 Dimension E: Walking, Running & Jumping, item 68 ("walk forward 10 steps with one hand held") score of at least 1 "initiates" at the screening and baseline examinations (if applicable).

4.1 The patient is less than 8 years of age at the time of screening.

For Cohorts 1-4:

5. Neurological signs of MLD must be present at the screening examination.
6. The patient and his/her parent/representative(s) must have the ability to comply with the clinical protocol.
7. Patient's parent(s) or legally authorized representative(s) must provide written informed consent prior to performing any study-related activities. Study-related activities are any procedures that would not have been performed during normal management of the patient.

Exclusion Criteria:

Patients will be excluded from the study if there is evidence or history of any of the following criteria at screening:

For Cohorts 1-4:

1. History of hematopoietic stem cell transplantation (HSCT).
2. The patient has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to airway compromise or other conditions.

3. Any other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, would preclude participation in the trial.
4. The patient is enrolled in another clinical study that involves the use of any investigational product (drug or device) other than HGT-1110 or the IDDD used in this study within 30 days prior to study enrollment or at any time during the study.
5. The patient is pregnant or breastfeeding.
6. The patient has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use (IFU), including:
    a. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device.
    b. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the Investigator.
    c. The patient has a known or suspected local or general infection.
    d. The patient is at risk of abnormal bleeding due to a medical condition or therapy.
    e. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation.
    f. The patient has a functioning CSF shunt device.
    g. The patient has shown an intolerance to an implanted device.

Clinical Assessments:

The main efficacy outcome assessment will be the change from baseline to Week 40 in motor function, using the GMFM-88 total score (percent).

Safety Assessments:

Safety will be assessed by the reporting of AEs, measurement of vital signs, physical examination, 12-lead ECGs, anti-HGT-1110 antibodies (CSF and serum), and laboratory evaluations including serum chemistry, hematology, urinalysis, and routine CSF analysis.

Pharmacokinetic Assessments:

The concentration of HGT-1110 in the serum and CSF will be determined as the PK variable. Serum PK parameter estimates of HGT-1110 will be calculated using standard noncompartmental analysis. The effect of anti-HGT-1110 antibodies on HGT-1110 concentration-time profiles and PK parameters will be evaluated, if applicable.

Statistical Methods:

Statistical analyses of safety and efficacy outcomes will be descriptive and will be summarized by cohort. Summary statistics for continuous variables will include the number of patients, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized in a contingency table by the number and percentage of patients in each category.

Any statistical tests comparing cohorts will be 2-sided with a significance level of 0.05 and considered exploratory or hypothesis generating. The mean change, mean difference in the change between cohorts, and corresponding 95% confidence intervals, may also be presented as appropriate.

The Safety population, defined as the set of patients who underwent the device implant surgery or received at least 1 dose of study drug, will be the primary analysis population.

Intrathecal device-related analyses will be performed in the subset of the Safety population who underwent the device implant surgery.

Original Protocol: 24 January 2011

Amendment 9: 26 August 2015

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
λ_Z	apparent terminal rate constant
AE	adverse event
AMP	amplitude
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
ASA	arylsulfatase A
$AUC_{0\text{-last}}$	area under the serum concentration-time curve from time zero to the last sampling time at which serum concentrations were measurable
$AUC_{0\text{-}\infty}$	area under the serum concentration-time curve extrapolated to infinity
β-hCG	β human chorionic gonadotropin
BMI	body mass index
BMT	bone marrow transplant
CBC	complete blood count
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
$CL_{/F}$	clearance after intrathecal administration
CMAP	compound motor action potential
C_{max}	maximum observed serum concentration
CNS	central nervous system
COMFORT	Caregiver Observed MLD Functioning and Outcomes Reporting Tool
CRIM	cross-reacting immunological material
CRO	contract research organization
CS	clinically significant
CSF	cerebrospinal fluid
DL	distal latency
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECL	electrochemiluminescence

Abbreviation	Definition
eCRF	electronic case report form
ENG	electroneurography
EOS	end of study
EOW	every other week
ERT	enzyme replacement therapy
FEES	Functional Endoscopic Evaluation of Swallowing
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIMF-C	global impression of motor function-change
GIMF-S	global impression of motor function-severity
GMFM-88	Gross Motor Function Measure-88
HSCT	hematopoietic stem cell transplant
ICH	International Conference on Harmonisation
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IFU	Instructions for Use
IND	Investigational New Drug
IRB	Institutional Review Board
IT	intrathecal
IV	intravenous
LP	lumbar puncture
MedDRA	Medical Dictionary for Regulatory Activities
MDR	medical device report
MLD	metachromatic leukodystrophy
MPS	mucopolysaccharidosis
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation	Definition
NCV	nerve conduction velocity
NOAEL	no observable adverse effect level
PBMC	peripheral blood mononuclear cells
PK	pharmacokinetic(s)
PNS	peripheral nervous system
PT	prothrombin time
rhASA	recombinant human arylsulfatase A or HGT-1110
rhHNS	recombinant human heparan N-sulfatase
SAE	serious adverse event
SAP 1	saposin B-1
SAS	Statistical Analysis System
SD	standard deviation
Shire	Shire Human Genetic Therapies, Inc.
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
UADE	unanticipated adverse device effect
US	United States
USA	United States of America
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
$V_{z/F}$	volume of distribution based on the terminal phase after intrathecal administration
WHO-DD	World Health Organization – Drug Dictionary

1 INTRODUCTION

1.1 Disease Background

Metachromatic leukodystrophy (MLD) is an inherited, autosomal recessive disorder of lipid metabolism characterized by deficient activity of the lysosomal enzyme, arylsulfatase A (ASA). Deficient enzymatic activity results in progressive accumulation of galactosylceramide-3-O-sulfate (cerebroside sulfate or sulfatide), which is a major constituent of myelin. A cytotoxic metabolite of sulfatide (lysosulfatide or galactosylsphingosine-3-O-sulfate) also accumulates.[1-3] Sulfatide is normally metabolized by hydrolysis of the Cer-Gal-3-sulfate linkage to form galactocerebroside through the combined action of ASA and saposin B-1 (SAP 1), a non-catalytic protein that serves as a detergent. Progressive accumulation of sulfatide within oligodendrocytes and Schwann cells, which are the myelin forming cells of the central (CNS) and peripheral nervous system (PNS) respectively, leads to cellular injury and ultimately cell death. The consequence of these molecular and cellular events is progressive demyelination and axonal loss within the CNS and PNS, which is accompanied clinically by severe motor and cognitive dysfunction.[4] In general, the rapidity with which the disease progresses clinically correlates with the level of residual enzymatic activity within the lysosomes.

Metachromatic leukodystrophy is a rare orphan disease with an estimated overall incidence in the western world of approximately 1 in 100,000 live births.[5-8]

Human ASA gene structure has been determined, and many polymorphisms and disease-related mutations have been identified. At least 110 mutations have been described with a causal relationship to MLD.[9] The mutant alleles causing MLD can be divided into 2 groups. The first group (A) contains alleles that are associated with low amounts of residual lysosomal enzymatic activity, and the second group (B) contains alleles in which the mutation does not allow the synthesis of any functional enzyme.

Analysis of the distribution of these alleles among patients with different clinical forms of MLD reveals a general genotype-phenotype correlation. Homozygosity for group B mutations causes a severe late infantile type of disease. Having one mutation from group A and one from group B mitigates the course to an intermediate juvenile type of disease, and having 2 group A mutations usually produces a milder adult form of MLD.

MLD has a full range of disease severity with patients presenting at varying ages and with a wide range and severity of signs and symptoms. To better understand this spectrum, there has been an attempt to divide disease presentation into types (see Table 1-1). While this grouping into types is useful clinically and for genetic counseling, MLD actually describes a continuum of clinical severity and the typing is somewhat arbitrary with an overlap of these types in many cases.

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.[10] 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. Patients are often initially diagnosed as suffering from psychosis[11] or schizophrenia.[12] Signs of peripheral neuropathy are often absent, but clumsiness of movements and incontinence are seen. A slowly progressive spastic paresis of the arms and legs develops later in the course of the disease. During the final stages of the illness, patients lose speech and vision and become bedridden and unresponsive.[13] The duration of the disease ranges from a few years to several decades.

Table 1-1 Major Features of the Late Infantile, Juvenile, and Adult Forms of MLD

Type	Age at onset (years)	Main clinical manifestations	Spinal fluid protein	Nerve conduction velocity	Urinary sulfatide excretion
Late Infantile	0.5-4	Gait disturbance, decreased tendon reflexes, mental regression, loss of speech, optic atrophy, ataxia, progressive spastic quadriparesis	Elevated	Slowed	Elevated
Juvenile	4-16	Gait and postural abnormalities, emotional and behavioral disturbances, optic atrophy, progressive spastic quadriparesis, language regression, poor school performance	Elevated	Slowed	Elevated
Adult	>16	Mental regression, psychiatric symptoms, slowly progressive spastic quadriparesis, incontinence	Normal or elevated	Normal or slowed	Elevated

Abbreviations: MLD = metachromatic leukodystrophy
Source: von Figura K et al. [13]

1.2 Study Rationale

1.2.1 Current Therapeutic Options

There are no approved therapies for MLD. The only treatment option for MLD is bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT), which have shown little or no efficacy.

Although HSCT may stabilize central demyelination in selected patients with late onset MLD (juvenile and adult forms) if performed early in the course of the disease, the procedure does not arrest progression in late infantile MLD.[14] HGT-1110 is a recombinant human arylsulfatase A (rhASA) that is under development as enzyme replacement therapy (ERT) for the treatment of MLD.

A particular challenge for lysosomal storage disorders that affect the brain is how to target ERT to the CNS.[15] In animal toxicology studies, ERT was administered intrathecally via an intrathecal (IT) drug delivery device (IDDD) and was well tolerated. Direct CNS delivery is being investigated because when ERT is administered intravenously (IV) it does not cross the blood brain barrier after the immediate postnatal period of life.[16-18] Precedent for intraspinal ERT has been published and has been shown to be both safe and effective for spinal cord compression in mucopolysaccharidosis (MPS) I.[19] In this study, a patient with MPS I received 4 intrathecal doses of enzyme (laronidase) at 1-month intervals. Safety evaluations included cerebrospinal fluid (CSF) opening pressure, serum chemistry and CSF protein, glucose, and cell count, in addition to clinical efficacy studies. No changes in safety evaluations were observed.

In a recent study, a patient with MPS VI and spinal cord compression received IT injections of enzyme (galsulfase) monthly, for 4 months. Cerebrospinal fluid analysis revealed no inflammatory reaction, nor were other types of drug-related adverse events (AEs) observed.[20]

Several patients with MPS I have been treated since 2005 with IT laronidase (recombinant α-L-iduronidase) in a clinical trial (ClinicalTrials.gov identifiers NCT00215527, NCT00786968) studying efficacy on spinal cord compression. This study has been terminated.[21] A study further investigating the effectiveness of IT ERT as a treatment for another neurological symptom in MPS I, cognitive decline, is ongoing (ClinicalTrials.gov identifier NCT00852358).[22]

The following describes the 9 Shire Human Genetic Therapies, Inc. (Shire)–sponsored IT studies other than HGT-MLD-070:

- a Phase I/II open-label extension of study HGT-MLD-070 evaluating long term safety and efficacy of IT administration of HGT-1110 in patients with MLD (HGT-MLD-071)
- a Phase I/II safety and dose escalation study of monthly idursulfase-IT intrathecal injection for cognitively impaired patients with Hunter syndrome (Study HGT-HIT-045; NCT00920647), and the open-label extension to this study (HGT-HIT-046; NCT01506141)
- a Phase II/III controlled, randomized, two-arm open-label, assessor-blinded study of idursulfase-IT administered in conjunction with Elaprase® in pediatric patients with Hunter Syndrome and early cognitive impairment (Study HGT-HIT-094; NCT02055118) and the open-label extension to this study (Study SHP-609-302; NCT02412787)
- a Phase I/II ascending dose and dose frequency study of monthly IT injection of recombinant human heparan N-sulfatase (rhHNS) in patients with Sanfilippo Syndrome Type A (Study HGT-SAN-055; NCT01155778), and the open-label extension to this study (HGT-SAN-067; NCT 01299727)

- a Phase IIb, randomized, controlled, open-label, multicenter, safety and efficacy study of HGT-1410 (recombinant heparan N-sulfatase) administration via an intrathecal drug delivery device in pediatric patients with early stage mucopolysaccharidosis Type IIIA disease (Study HGT-SAN-093; NCT02060526) and the open-label extension to this study (Study SHP-610-201 ; NCT02350816)

In light of the higher than expected complications experienced with the PORT-A-CATH IDDD, the SOPH-A-PORT Mini S device will be introduced for those patients requiring replacement or revision of their existing PORT-A-CATH IDDD or for initial implantation of their device. This new device has design features anticipated to reduce complications encountered with the PORT-A-CATH IDDD. Device assessments are included in the protocol to collect information specific to the SOPH-A-PORT Mini S device safety and function.

Cohorts 1-3 of this study were conducted to evaluate the safety of up to 3 dose levels of HGT-1110, administered via an IDDD to children with MLD to inform dose selection for future clinical studies. Since the initiation of Cohorts 1-3, changes were introduced to the original drug substance manufacturing process for HGT-1110 (referred to as Process A) to improve process robustness and efficiency in preparation for future clinical studies. Cohort 4 of this study is being conducted in order to evaluate the safety of HGT-1110 produced with the revised drug substance manufacturing process (referred to as Process B). Please refer to the current edition of the Investigator's Brochure for further information concerning the drug products produced with Process A and Process B.

1.2.2 Study Design

Nonclinical experience with IT administration of HGT-1110 has demonstrated improvement in histological markers of disease in MLD mice and biodistribution into the lysosomes of oligodendrocytes in the deep white brain matter of monkeys.

It is postulated that CNS injections of HGT-1110 in patients with MLD will restore a level of ASA enzymatic activity within both the CNS and the PNS that is sufficient to hydrolyze accumulated sulfatide and slow or prevent further substrate accumulation. Reduced accumulation of sulfatide may stabilize or slow progression of neurological dysfunction.

The key design considerations for this Phase I/II study are the target population, enzyme dose and dose administration route, and primary outcome.

The greatest opportunity to demonstrate benefits of enzyme replacement in MLD occurs early in the course of the illness prior to the onset of significant irreversible brain injury. The study is designed to be a combined Phase I/II study with a patient population selected based on disease progression. Metachromatic leukodystrophy has a full spectrum of disease severity with pediatric patients at the severe end of the spectrum and adults at the mild end. Patients who present with clinical signs and symptoms within the first few years of life have rapid progression of disease with measurable changes in symptoms over months. This same progression of disease in adults can take years to decades. The target patient population for this study, children with MLD who are ambulatory at enrollment, will be instrumental in assessing the safety and efficacy of HGT-1110 and will support the selection of appropriate dosing for a pivotal trial. This

population of children is expected to be less than 5 years of age, and no older than age 12, at enrollment. Based on published literature[23] and analysis of the LeukoNet natural history data set,[24] substantial clinical progression is anticipated over 9 months in ambulatory children with MLD. To assess clinical progression of motor function, the Gross Motor Function Measure-88 (GMFM-88) total score (percent) will serve as the main efficacy outcome measurement.

The goal of enzyme replacement is to slow or prevent accumulation of toxic quantities of sulfatide within oligodendrocytes in a setting of rapidly progressive disease. This is a first-in-human, multicenter, Phase I/II dose escalation study of HGT-1110 in children with MLD to evaluate the safety of HGT-1110. In this study, HGT-1110 will be administered directly to the CNS through an IDDD or, if the IDDD is non-functional, via lumbar puncture (LP). The advantage of using an IDDD is that it obviates the need for anesthesia and multiple LPs for drug delivery that would otherwise be required each time this procedure is performed. The data available for intrathecal administration of proteins indicate that this route of administration poses no untoward safety risks. With no treatments currently available for this progressive, ultimately fatal genetic neurological disease, a clear medical need exists for novel disease-modifying approaches that hold the potential to alter the clinical course of disease progression.

The study was initiated with the PORT-A-CATH IDDD. Following protocol Amendment 6, if patients require revision and/or replacement of the PORT-A-CATH IDDD, it will be removed and replaced with the SOPH-A-PORT Mini S device at a time judged appropriate by the Investigator. The SOPH-A-PORT Mini S device will also be implanted in any newly enrolled patients.

The initial dose level in this clinical study is based on a minimum safety factor of 10. The factors of risk for HGT-1110 administration were considered, and the no observable adverse effect level (NOAEL) was used to determine a safe starting dose.[25] In nonclinical toxicology studies, and in the proposed Phase I/II clinical trial, HGT-1110 is given as a nominal dose (mg). The nominal (mg) dose is divided by the approximate brain weight of the animal (kg) to determine the mg/kg of brain weight dose to allow scaling based on anatomical compartment size.[26]

The safety factor is then calculated as the normalized animal NOAEL (mg/kg) divided by the normalized human dose (mg/kg). For all species investigated, there is a minimum of a 10-fold safety factor for the proposed clinical starting dose (10 mg).

For the highest proposed clinical dose (100 mg), there is a 3.5-fold safety factor from the rat NOAEL, a 3.1-fold safety factor from the 6-month juvenile monkey study, and a 1.0 fold safety factor from the 3-month juvenile monkey study.

In order to estimate a minimally effective dose of HGT-1110 in humans, the levels of ASA in normal humans and MLD patients were evaluated. Patients with MLD have very low levels of ASA in the brain, generally less than 5%.[27, 28] Up to 1 to 2% of the European population has a condition known as “pseudodeficiency of ASA” in which they have low levels of ASA activity (5% to 15% of normal), but are apparently normal.[28] Based on this information, achieving a target level of 10% of normal in the CNS tissues is estimated to be a minimally effective dose. Three every-other-week (EOW) doses in administration of HGT-1110 at 1.8 mg/dose (30 mg/kg)

in juvenile cynomolgus monkeys achieved this enzyme level. This suggests that at 30 mg/kg of brain weight (30 mg/dose in the clinic for a child with an assumed brain mass of 1 kg[29]), HGT-1110 given EOW for at least one month is expected to deliver therapeutically relevant amounts of rhASA to all tissues of the brain.

Three dose-escalating cohorts will be enrolled. A staggered enrollment will be employed for this study to facilitate adequate safety monitoring per cohort. Dose selection for potential future studies will be determined by the safety profile and efficacy outcomes for each dose.

In order to minimize the degree of burden and foreseeable risk to study patients, study assessments were carefully selected to closely resemble assessments that are performed as part of current standard clinical care for patients with MLD. Some assessments, such as those including the need for anesthesia, will be coordinated with other safety assessments to minimize the number of times anesthesia is needed. The planned assessments are scheduled at the minimum possible frequency needed to fully assess the safety and establish potential efficacy for the investigational drug product with the lowest burden and risk to the patient.

The effect of IT EOW HGT-1110 on several efficacy outcome measures will be assessed. Change from baseline in motor function using the GMFM-88 total score (percent) after 38 weeks of EOW HGT-1110 IT injections will serve as the main efficacy outcome measure. The CSF sulfatide and lysosulfatide levels may be important markers for extent of brain involvement in patients with MLD. Cerebrospinal fluid, serum, and urine sulfatide and lysosulfatide levels will be monitored as surrogate measures of CNS disease burden. In addition, the integrity of neurons and axons within the central white matter will be monitored by proton magnetic resonance spectroscopy (MRS; N-acetylaspartate levels).

Please refer to the current edition of the Investigator's Brochure for further information concerning the safety and clinical development of HGT-1110.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- Cohorts 1-3: The primary objective is to determine the safety of ascending doses of HGT-1110 administered by IT injection for 38 weeks in children with MLD.
- Cohort 4: The primary objective is to determine the safety of HGT-1110 produced with a revised drug substance manufacturing process administered by IT injection for 38 weeks in children with MLD.

2.2 Secondary Objectives

- To evaluate the effects of IT administration of HGT-1110 on gross motor function
- To evaluate the effects of IT administration of HGT-1110 on the ability to swallow
- To evaluate the effects of IT administration of HGT-1110 on nerve conduction capabilities
- To evaluate the effects of IT administration of HGT-1110 on adaptive behavior
- To evaluate the effects of IT administration of HGT-1110 on health status and the ability to carry out activities of daily life
- To assess single and repeated-dose pharmacokinetics (PK) of HGT-1110 in serum
- To assess concentrations of HGT-1110 in CSF

2.3 Exploratory Objectives

The exploratory objectives of this study are the following:

- To evaluate the effects of IT administration of HGT-1110 on CSF, serum, and urine biomarkers
- To evaluate the effects of IT administration of HGT-1110 on N-acetylaspartate metabolite levels
- To evaluate the effects of IT administration of HGT-1110 on the MLD severity score as measured by magnetic resonance imaging (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

3 STUDY ENDPOINTS

3.1 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 electrocardiograms (ECGs), vital signs, physical examinations, and CSF chemistry (including cell counts, glucose, and protein)
- Determination of the presence of anti-HGT-1110 antibodies in CSF and/or serum

3.2 Secondary Endpoints

The secondary endpoints of this study are the following:

- Change from baseline in motor function using the 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 HGT-1110 in serum
- Concentrations of HGT-1110 in CSF at selected time points after single- and repeated-investigational drug product administration

3.3 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 N-acetylaspartate metabolite levels in the deep white matter of the brain as assessed by proton 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)

3.4 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 patient's electronic case report form (eCRF) from the time of initial implantation.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multicenter open-label dose-escalation study designed to evaluate the safety of HGT-1110 in 4 cohorts. In Cohorts 1-3, three dose levels (10, 30, or 100 mg) of HGT-1110 were administered. In Cohort 4, patients will be administered 100 mg of HGT-1110. HGT-1110 is administered via an IDDD EOW (20 IT injections of HGT-1110 from Weeks 0 to 38) to male or female children with a confirmed diagnosis of MLD. Patients in Cohorts 1-3 were expected to be less than 12 years of age at screening. The study also includes the assessment of HGT-1110 drug product produced with a revised drug substance manufacturing process (referred to as Process B) in a fourth cohort (Cohort 4). Patients in Cohort 4 are expected to be less than 8 years of age at screening.

For Cohorts 1-3, 18 patients were enrolled, 6 in each of the 3 dose level cohorts. The dose level cohorts will be enrolled sequentially starting with the 10 mg dose as follows.

- Cohort 1 (10 mg): HGT-1110 EOW (6 patients)
- Cohort 2 (30 mg): HGT-1110 EOW (6 patients)
- Cohort 3 (100 mg): HGT-1110 EOW (6 patients)

Cohorts 1-3 received HGT-1110 drug product manufactured using Process A.

Patient eligibility will be based on a confirmed diagnosis of MLD in patients who are ambulatory and who show neurological signs of MLD at the time of screening. Patients whose parent(s)/legal representative(s) have provided written informed consent to participate in this study will undergo screening procedures. All patients must be consented prior to any study evaluations.

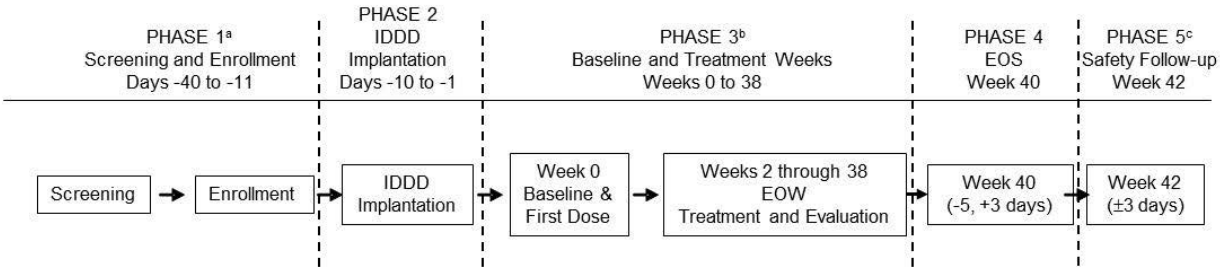
Cohort 4 will be enrolled following Cohort 3, after Data Safety Monitoring Board (DSMB) review of Cohorts 1-3 and drug product manufactured with Process B becomes available. Approximately 6 patients who undergo device implant surgery or receive at least 1 dose of study drug will be included in Cohort 4, which will receive 100 mg HGT-1110 EOW for a total of 38 weeks.

During the course of their participation in the study, a patient may request a transfer to a different qualified site, if agreed by both the sites and the Sponsor.

4.1.1 Study Design

Schematics of the overall study design are presented in Figure 4-1 for Cohorts 1-3 and in Figure 4-2 for Cohort 4.

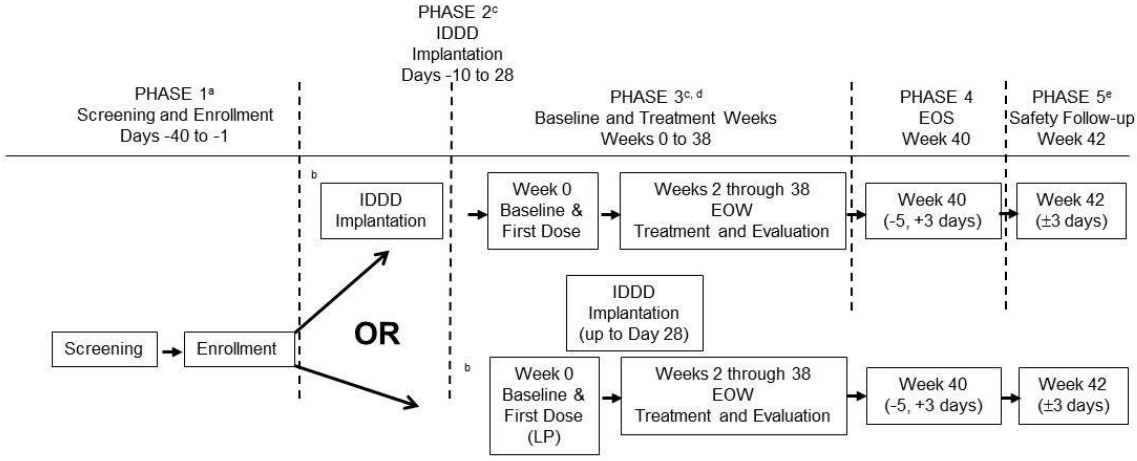
Figure 4-1 Overall Study Design: Cohorts 1-3



Note: The decision to escalate to the next higher dose level will be based on a review, by an independent Data Safety Monitoring Board (DSMB) and representatives from the Sponsor of safety data for the previous cohort after all patients in the cohort have each received a minimum of 2 IT doses.

- Sample collection for diagnostic testing will occur between Day -40 and Day -29 to ensure diagnostic results are received prior to IDDD implantation in Phase 2.
- 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 dosing 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.
- The Week 42 Safety Follow-up visit may be completed by telephone from the clinical site.

Figure 4-2 Overall Study Design: Cohort 4



a. Sample collection for central diagnostic testing should take place at the screening visit to ensure diagnostic results are received promptly. Local laboratory results confirming the MLD diagnosis will be accepted while waiting for the central laboratory results to expedite enrollment and dosing.

b. A baseline GMFM-88 assessment must be performed between Days -7 to 0, before device implantation or prior to first dose administration, whichever occurs first. The baseline GMFM-88 assessment does not need to be repeated if device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment. Upon confirmation of study eligibility, 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. Patients who do not continue to meet eligibility criteria will be discontinued from the study prior to device implantation and/or initial dosing.

c. Enrollment may occur prior to the IDDD implantation or the first dose (baseline); however, implantation of the device should occur within 28 days of the first dose. 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.

d. 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 dosing unless otherwise indicated. In addition, at Weeks 16 and 28 the window for assessments will be -5 days.

e. The Week 42 Safety Follow-up visit may be completed by telephone from the clinical site.

This study will have the following 5 phases:

Cohorts 1-3: Phases 1-3

Phase 1: Screening: Day -40 through Day -11

Upon obtaining informed consent, the procedures and assessments required for the determination of the patient's eligibility will be completed at the clinical site within 40 days of the baseline visit (Week 0). Sample collection for diagnostic testing should take place between Day -40 and Day -29 to ensure diagnostic results are received prior to IDDD implantation in Phase 2 of the study.

Sites will be allowed one opportunity to re-screen any patient who fails initial screening or withdraws consent prior to device implantation. If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study.

Phase 2: Surgical Implantation of the IDDD: Day -10 to Day -1

Patients will undergo surgical implantation of an IDDD and a post-surgical assessment.

Phase 3: Baseline and Treatment Week 0 to Week 38 (±3 days for injection of HGT-1110)

Upon confirmation of study eligibility, baseline assessments (ie, those scheduled for Week 0) may be performed at any time prior to dosing, including the Phase 2 period of the study, but baseline assessments should be performed as close to dosing as possible. Patients will undergo pre-dose baseline assessments at Week 0, which will include a standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis), serum assessments of anti-HGT-1110 antibodies and CSF assessments (cell counts, protein, glucose, albumin, anti-HGT-1110 antibodies, and HGT-1110 levels) as well as safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures assessments).

Baseline efficacy outcome assessments including the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS will be performed as well as sample collection for CSF, serum, and urine biomarker assessments.

Patients will receive their first dose (Week 0) and begin the HGT-1110 EOW dosing period (through Week 38). At Week 0, blood will also be drawn for a PK assessment at the time points specified in the Schedule of Events.

During the EOW treatment period (Weeks 2 through 38), all assessments will be performed prior to IT injection of HGT-1110 unless otherwise indicated. Safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures assessments) will be performed. Patients 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. Additionally, anti-HGT-1110 antibody sampling, the standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis) and sample collection for analysis of CSF

concentration of HGT-1110, and CSF, serum, and urine biomarkers will be performed every 4 weeks.

In addition to the scheduled assessments performed Weeks 2 through 38, Weeks 16 and 28 will also include the efficacy outcome assessments of the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS. For Weeks 16 and 28, the window for assessments will be -5 days. In addition, at Week 38 blood will be drawn for a PK assessment at the time points specified in the Schedule of Events.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all 20 IT injections of HGT-1110. If the IT space is not accessible via the IDDD, investigational drug product may be administered by LP. Should the IDDD become clogged, undergo mechanical complications or otherwise not be accessible, the CSF sample may also be obtained by LP. Anesthesia may be required for injections of investigational drug product and some evaluations, and can be used at the discretion of the Investigator. The IDDD Manual provides details on the investigation and management of any IDDD-related issues.

Cohort 4: Phases 1-3

Note: Enrollment may occur prior to IDDD implantation or the first dose (baseline); however, implantation of the device should occur within 28 days of the first dose.

Phase 1: Screening: Day-40 through Day -1

Upon obtaining informed consent, the procedures and assessments required for the determination of the patient's eligibility, including GMFM-88, will be completed at the clinical site within 40 days prior to the baseline visit (Week 0). Sample collection for central diagnostic testing should take place at the screening visit to ensure diagnostic results are received promptly. Local laboratory results confirming the MLD diagnosis (analysis of urine sulfatide, ASA activity in leukocytes) will be accepted to confirm the MLD diagnosis enrollment criteria while waiting for the central laboratory results so that dosing of the study medication can occur as soon as possible.

Sites will be allowed one opportunity to re-screen any patient who fails initial screening or withdraws consent prior to device implantation or dose administration (if administration to be initiated by LP prior to device implantation). If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study.

Phase 2: Surgical Implantation of the IDDD: Day -10 to Day +28

To confirm the patient meets eligibility criteria at baseline, specifically the baseline GMFM-88 assessment will be performed as close as possible to, but before device implantation or prior to first dose administration, whichever occurs first. Patients who do not continue to meet eligibility criteria will be discontinued from the study prior to device implantation and/or initial dosing. If device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment, the baseline GMFM-88 assessment will not be required. However, if more than 7 days has passed since the screening GMFM-88 assessment, the baseline GMFM-88 assessment will need to be completed prior to IDDD implantation or first

dose, and prior to any other baseline assessments in order to confirm eligibility for enrollment (per inclusion criterion 3.1 in Section 5.2).

Upon confirmation of eligibility, patients will undergo surgical implantation of an IDDD and a post-surgical assessment. The patients may receive study drug by LP until the device is implanted. Device implantation should be scheduled within 28 days of enrollment unless a delay is required due to clinical judgment for medical reasons (eg, infection).

Phase 3: Baseline and Treatment Week 0 to Week 38 (±3 days for injection of HGT-1110)

Upon confirmation of study eligibility, baseline assessments (ie, those scheduled for Week 0) may be performed at any time prior to dosing, including the Phase 2 period of the study, but baseline assessments should be performed as close to dosing as possible. Patients will undergo pre-dose baseline assessments at Week 0, which will include a standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis), serum assessments of anti-HGT-1110 antibodies and CSF assessments (cell counts, protein, glucose, albumin, anti-HGT-1110 antibodies, and HGT-1110 levels) as well as safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures assessments).

Baseline efficacy outcome assessments including the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS will be performed as well as sample collection for CSF, serum, and urine biomarker assessments. If device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment, the baseline GMFM-88 assessment will not be required.

Patients will receive their first dose (Week 0) and begin the HGT-1110 EOW dosing period (through Week 38). At Week 0, blood will also be drawn for a PK assessment at the time points specified in the Schedule of Events.

During the EOW treatment period (Weeks 2 through 38), all assessments will be performed prior to IT injection of HGT-1110 unless otherwise indicated. Safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures assessments) will be performed. Patients 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. Additionally, anti-HGT-1110 antibody sampling, the standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis) and sample collection for analysis of CSF concentration of HGT-1110, and CSF, serum, and urine biomarkers will be performed every 4 weeks.

In addition to the scheduled assessments performed Weeks 2 through 38, Weeks 16 and 28 will also include the efficacy outcome assessments of the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS. For Weeks 16 and 28, the window for assessments will be -5 days. In addition, at Week 38 blood will be drawn for a PK assessment at the time points specified in the Schedule of Events.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all 20 IT injections of HGT-1110. 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.

If the IT space is not accessible via the IDDD, investigational drug product may be administered by LP. Should the IDDD become clogged, undergo mechanical complications or otherwise not be accessible, the CSF sample may also be obtained by LP until the device is repaired or replaced. Anesthesia may be required for injections of investigational drug product and some evaluations, and can be used at the discretion of the Investigator. The IDDD Manual provides details on the investigation and management of any IDDD-related issues.

All Cohorts (1-4): Phases 4 and 5

Phase 4: End of Study: Week 40 (-5, +3 days)

The assessments scheduled at Week 40, 2 weeks after the last HGT-1110 dose, will be the same as those at Weeks 16 and 28 with the addition of a 12-lead ECG and an X-ray (to confirm that the IDDD remains positioned correctly). Patients who discontinue early will have an end-of-study (EOS) visit 2 weeks (-5, +3 days) after the last IT injection of HGT-1110. All EOS assessments should be performed. Patients will have the IDDD removed when they discontinue from or complete the study, unless the patient is continuing to receive treatment through another mechanism (eg, a different study or commercially available).

Phase 5: Safety Follow-up: Week 42 (±3 days)

The Safety Follow-up visit will be conducted at Week 42 or 4 weeks (±3 days) after the last injection of HGT-1110 or 2 weeks after the removal of the IDDD, whichever occurs later, for patients who discontinue. The follow-up safety assessments (AEs and concomitant medications/therapies/procedures) may be performed via telephone from the clinical site.

Patients who complete all requirements in Study HGT-MLD-070 through Week 40 may be eligible to participate in an extension study. However, patients are not obligated to participate in any additional studies, and the Sponsor cannot guarantee that such studies will occur.

4.2 Investigational Drug Product Dose Escalation Guidelines

Study eligibility will be confirmed, followed by surgical implantation of an IDDD and administration of IT treatment with HGT-1110 by means of an IDDD EOW at fixed doses based on the assigned IT dose (Cohort 1: 10 mg, Cohort 2: 30 mg, or Cohorts 3 and 4: 100 mg). The decision to escalate to the next higher dose level (ie, escalation to Cohorts 2 and 3 only) was based on a DSMB review of the safety data obtained for the previous cohort after all patients in the cohort have each received a minimum of 2 IT doses. Dose escalation guidelines are provided in Section 6.5 and apply only to Cohorts 1-3.

4.3 Study Duration

The duration for each patient's participation in this study is approximately 47 weeks. The planned duration of HGT-1110 treatment in this study is 38 weeks (20 IT injections of HGT-1110 EOW Weeks 0 to 38).

5 STUDY POPULATION SELECTION

5.1 Study Population

Approximately 24 patients are planned who are less than 12 years of age with a confirmed diagnosis of MLD, approximately 6 per cohort. Patients must be ambulatory at the time of screening and untreated with investigational drug products for MLD.

5.2 Inclusion Criteria

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

For Cohorts 1-4:

1. Confirmed diagnosis of metachromatic leukodystrophy by both:
   - Arylsulfatase A (ASA) deficiency by assay in leukocytes

   AND

   - Elevated sulfatide in urine
2. Appearance of the first symptoms of disease at or before 30 months of age.

For Cohorts 1-3 only:

3. Ambulatory at the time of screening. The minimum level of function required to meet this criterion is defined as the ability to walk forward 10 steps with one hand held.
4. The patient is less than 12 years of age at the time of screening.

For Cohorts 4 only:

3.1 Minimum motor function requirements:

   a. A total GMFM-88 (percent) score ≥40 at the screening examination and a total GMFM-88 (percent) score ≥35 at the baseline examination,

AND

   b. GMFM-88 Dimension E: Walking, Running & Jumping, item 68 ("walk forward 10 steps with one hand held") score of at least 1 "initiates" at the screening and baseline examinations (if applicable).

4.1 The patient is less than 8 years of age at the time of screening.

For Cohorts 1-4:

5. Neurological signs of MLD must be present at the screening examination.
6. The patient and his/her parent/representative(s) must have the ability to comply with the clinical protocol.
7. Patient's parent(s) or legally authorized representative(s) must provide written informed consent prior to performing any study-related activities. Study-related activities are any procedures that would not have been performed during normal management of the patient.

5.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence or history of any of the following criteria at screening:

For Cohorts 1-4:

1. History of hematopoietic stem cell transplantation (HSCT).
2. The patient has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to airway compromise or other conditions.
3. Any other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, would preclude participation in the trial.
4. The patient is enrolled in another clinical study that involves the use of any investigational product (drug or device) other than HGT-1110 or the IDDD used in this study within 30 days prior to study enrollment or at any time during the study.
5. The patient is pregnant or breastfeeding.
6. The patient has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use (IFU), including:
    a. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device.
    b. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the Investigator.
    c. The patient has a known or suspected local or general infection.
    d. The patient is at risk of abnormal bleeding due to a medical condition or therapy.
    e. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation.
    f. The patient has a functioning CSF shunt device.
    g. The patient has shown an intolerance to an implanted device.

6 STUDY TREATMENTS

6.1 Description of Treatments

6.1.1 Investigational Drug Product

The following description applies to both the drug product manufactured with Process A and Process B.

Recombinant human arylsulfatase A (rhASA, HGT-1110) is a multimeric glycoprotein produced using a genetically engineered human cell line (HT-1080) to secrete the human lysosomal enzyme, arylsulfatase A. The mature form of the enzyme consists of 489 amino acids. The drug product is a sterile solution for IT administration. It is formulated at 30 mg/mL rhASA in an aqueous isotonic solution containing 154 mM sodium chloride, 0.005% polysorbate 20 at pH 6.0. The drug product is packaged in single use vials and is stored at 2 to 8°C.

Please refer to the current edition of the Investigator's Brochure for further information concerning the drug products produced with Process A and Process B.

6.1.2 Intrathecal Drug Delivery Device

The use of the IDDD will be restricted to study-related activities only and should not be accessed for any other purpose. The PORT-A-CATH IDDD will continue to be used for the administration of drug product for each patient until such time as an IDDD replacement may be required. Following protocol Amendment 6, any replacements will be performed using the SOPH-A-PORT Mini S and any newly enrolled patients will receive the SOPH-A-PORT Mini S.

After IDDD replacement the drug product will be administered via the SOPH-A-PORT Mini S Implantable Access Port. The SOPH-A-PORT Mini S device is intended for long-term, intermittent access to the IT space for the delivery of investigational drug.

The SOPH-A-PORT Mini S is comprised of the following 7 components:

- One SOPH-A-PORT Mini S Access Port
- One intrathecal port closed-tip catheter
- One guidewire
- Two suture wings
- One 14-gauge Tuohy needle
- One 22-gauge non-coring Huber needle
- One Luer lock connector

Further details are provided in the IFU.

6.2 Treatment Administered

For Cohort 4 only, if eligibility has been confirmed, and IDDD implantation cannot be scheduled to occur within the Phase 2 window (see Section 8.2), 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.

Following successful surgical implantation of the IDDD and assessment of baseline procedures with no safety concerns, patients will receive their first IT injection of HGT-1110. Patients may receive anesthesia at the discretion of the Investigator.

If use of the IDDD is precluded on a scheduled day of dosing, the investigational drug product may be administered by means of an LP.

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

Drug administration will be performed in a clinical setting by appropriately trained and skilled healthcare providers (nurses or physicians) with knowledge of the patient's drug regimen and experienced in accessing vascular or CNS ports or CNS infusion pumps. Patients and patients' families will not be directly using the device to administer drugs and will have limited direct interaction with the device as there is minimal care required both during the immediate postoperative period as the implant site heals and also at times of drug administration.

Patients will receive their appropriate dose of HGT-1110 via slow push/injection over 2 to 5 minutes in a hospital setting supervised by a healthcare provider. Patients 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. An attempt will be made to replace the total volume of CSF fluid removed with drug solution and sterile normal saline (as needed). Vital signs will be obtained 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. See the Manual of Operations for complete details.

If there is any evidence of infection involving the CNS, IDDD, or area involved with port access at the time of planned dosing, then the dose should not be administered. Doses may also be delayed or missed if the Investigator believes that the patient is not well enough for dose administration due to an illness. Once the patient is well enough for dose administration, delayed doses can be administered per the instructions in Section 6.3.

6.3 Selection and Timing of Dose for Each Patient

6.3.1 Dose Selection

This is a multicenter open-label dose-escalation study designed to evaluate the safety of up to 3 dose levels (10, 30, and 100 mg) of HGT-1110 administered via an IDDD EOW for a total of 38 weeks (20 injections, Weeks 0 to 38) to children with MLD.

The DSMB agreed to open enrollment of the final dose-escalation cohort (Cohort 3), which has an assigned dose level of 100 mg (Process A). As the highest dose level being administered to patients, the 100 mg dose level was selected as the dose level for Cohort 4. Safety data in Cohorts 1-3 will be reviewed by the DSMB.

6.3.2 Dose Timing

In all cohorts, if a patient 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 patient's first dose. If a patient has a delay in 2 consecutive scheduled doses, the patient can receive doses as frequently as every 7 days until the site is able to resume 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.

6.4 Method of Assigning Patients to Treatment Cohorts

After study eligibility was confirmed, patients were enrolled in 1 of 3 sequential, escalating, dose cohorts:

- Cohort 1: HGT-1110 by IT injection 10 mg EOW
- Cohort 2: HGT-1110 by IT injection 30 mg EOW
- Cohort 3: HGT-1110 by IT injection 100 mg EOW

Cohort 4 will be enrolled following Cohort 3, after DSMB review of Cohorts 1-3 and drug product manufactured with Process B becomes available. Cohort 4 will receive 100 mg HGT-1110 EOW by IT injection.

6.5 Staggered Enrollment/Dose Escalation

A staggered enrollment was utilized for this study to facilitate adequate safety monitoring per cohort. Within each cohort, administration of HGT-1110 was contingent on normal results for the relevant safety laboratory tests and measures (eg, CSF and serum).

The decision to escalate to the next higher dose level (Cohort 2) was based on review of the safety data obtained for patients in dose Cohort 1 (included a minimum of 2 HGT-1110 doses

received by all patients in the cohort) by an independent DSMB and representatives from the Sponsor. As all relevant clinical and laboratory tests indicated a satisfactory safety profile and there were no safety concerns, enrollment and dosing in Cohort 2 (30 mg EOW IT dose level) started. The decision to escalate to the next higher dose level (Cohort 3 at 100 mg EOW IT) followed the same safety review process as that used for Cohort 2. A DSMB meeting will be held after completion of Cohorts 1-3.

No further dose escalation was to take place if either 50% of the patients in a cohort suffer clinically significant (moderate or severe) AEs or if 1 patient experienced an unacceptable severe AE that was determined to be related to investigational drug product.

6.6 Concomitant Medications, Therapies, and Medical/Surgical Interventions

All non-protocol treatments and procedures that occur from the time of informed consent (or assent, if applicable) through the Safety Follow-up visit are regarded as concomitant and will be documented on the appropriate pages of the eCRF. Concomitant therapy includes medications, therapies/interventions administered to patients, and medical/surgical procedures performed on the patients.

Changes in medications are acceptable if necessary according to clinical judgment. All changes will be recorded on the appropriate eCRF. Concomitant medications will be coded using World Health Organization – Drug Dictionary (WHO-DD).

6.6.1 Infusion/Hypersensitivity Reactions and Management

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

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

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

6.7 Restrictions

6.7.1 Therapy

The use of any investigational drug product other than HGT-1110 is restricted within 30 days prior to study enrollment and during the study.

6.7.2 Pregnancy

Pregnancy testing will be performed for females of child-bearing potential who are sexually active or who become sexually active during the study. If the patient has a positive pregnancy test result, the procedures described in Section 7.15 are to be followed.

6.7.3 Patient Activity Restrictions

For patients implanted with the SOPH-A-PORT Mini S please refer to the SOPH-A-PORT Mini S IFU for details regarding patient activity restrictions for patients to be implanted with this device.

6.8 Treatment Compliance

Investigational drug product HGT-1110 will be administered in accordance with the protocol, under the direction of the Investigator or sub-Investigator as listed on the Form Food and Drug Administration (FDA) 1572 and recorded on the eCRF.

6.9 Packaging and Labeling

6.9.1 Investigational Drug Product

The following description applies to both the drug product manufactured with Process A and Process B.

Investigational drug product will be supplied in a clear, colorless glass (Type I) vial. The closure is a 13 mm stopper composed of butyl rubber with a fluoro resin lamination. The overseal is an aluminum seal with a flip-off, plastic, tamper evident cap.

Investigational drug product will be clearly labeled according to country specifications. This will include, but is not limited to: manufacturer's name, protocol number, lot number, storage conditions, and expiration date.

See the Pharmacy Manual for additional details.

6.9.2 SOPH-A-PORT Mini S Access Port

The SOPH-A-PORT Mini S Access Port is available in one size, individually packaged, with other SOPH-A-PORT Mini S components in double peel-off, sterile, pyrogen-free packaging, sterilized with ethylene oxide. Instructions for Use are also included in the packaging. A guidewire is provided in separate double pouch, sterile, pyrogen-free packaging.

Labels are provided on the outer carton, and on both the SOPH-A-PORT Mini S box and guidewire/cannula package inside.

6.10 Storage and Accountability

6.10.1 Investigational Drug Product

The following information should be considered when storing and using the investigational drug product.

Investigational drug product should be stored refrigerated (2 to 8°C). Do not shake. Avoid exposure to intense direct sun light. Investigational drug product may not be stored beyond the expiration date on the vial.

The disposition of all investigational drug product delivered to a Principal Investigator must be recorded on a patient-by-patient basis by completing the accountability log. The date and time of administration of the investigational drug product must be documented on the appropriate eCRF.

The Principal Investigator, Clinical Research Coordinator, or designee (eg, Pharmacist) must ensure that all documentation regarding investigational drug product receipt, storage, dispensing, loss/damaged and return of used/unused product is complete, accurate, and ready for review at each monitoring visit or audit. The sites must ensure that the investigational drug product is available for the monitor to inventory and prepare for return shipment to the Sponsor or designee, if required.

6.10.2 Investigational Drug Delivery Device

6.10.2.1 PORT-A-CATH Intrathecal Drug Delivery Device

Please refer to the relevant IDDD Manual for return instructions.

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

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

The Principal Investigator, Clinical Research Coordinator, or designee (eg, Pharmacist) must ensure that all documentation regarding receipt, storage, dispensing, loss/damaged SOPH-A-PORT Mini S intrathecal drug delivery devices and return of used/unused intrathecal drug delivery devices) is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the SOPH-A-PORT Mini S devices are available for the monitor to inventory and prepare for return shipment to the Sponsor or designee, if required.

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

Please refer to the relevant IDDD Manual for device return instructions.

6.11 Investigational Drug Product Retention at Study Site

The process for return and destruction of investigational drug product must be determined and documented during the study start-up phase. If the sites do not have an Investigational Drug Product Returns or Destruction Process/Policy, the Sponsor or designee must provide guidelines to the sites. Sites must retain copies of these documents within the Site Regulatory Binder.

If the investigational drug product is to be destroyed by the sites, sites must follow their own process/policy that describes such activities. Sites must retain copies of these documents within the Site Regulatory Binder. Sites must ensure that the accountability and destruction log is complete, accurate, and ready for review or audit at each monitoring visit.

All manifests documenting shipments of investigational drug product must be retained as well as copies of any investigational drug product return forms.

See the Pharmacy Manual for additional details.

7 STUDY PROCEDURES

Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated times, days, and weeks of the study described in Section 8 and the Schedule of Events tables in Appendix 1 (Cohorts 1-3) and Appendix 2 (Cohort 4).

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

Additional details for study procedures, including sample collection, are described in the Manual of Operations or Laboratory Manual as appropriate for this study.

7.1 Informed Consent

Prior to conducting any study-related procedures, written informed consent must be obtained from the patient's parent(s) or legally authorized representative(s) and assent from the patient (if applicable). At a minimum, the date of the initial consent will be captured on the eCRF.

The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the patient, the patient's parent(s), or the patient's legally authorized representative by the Investigator or designee in accordance with the guidelines described in Section 11.4. Documentation of the consent process and filing of informed consent documents should be completed according to Section 11.4.

7.2 Inclusion/Exclusion Criteria

At Screening, each patient will be reviewed for eligibility against the study entrance criteria. Patients who do not continue to meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the patient's ineligibility for the study will be documented. Refer to the eCRF Completion Manual for additional instructions for patient screen failures.

7.3 Confirmation of Study Eligibility and MLD Diagnosis and Genotype

Cohorts 1-3:

Patient eligibility according to the study inclusion and exclusion criteria will be assessed during the Screening period. Sites will be allowed one opportunity to re-screen any patient who fails initial screening or withdraws consent prior to device implantation). If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study.

Assays for leukocyte arylsulfatase A enzyme activity, urine sulfatide, and genotype determination will be performed by specialty laboratory(ies) designated by Shire to confirm the diagnosis of MLD.[5, 30] Biochemical confirmation of MLD diagnosis is required for study eligibility, but genotype results are not.

Local leukocyte arylsulfatase A enzyme activity and urine sulfatide will be allowed to confirm the diagnosis of MLD, if available and deemed sufficient by the Principal Investigator and

Medical Monitor. Sample collection for diagnostic testing will still be performed if local results are used to confirm the diagnosis of MLD.

Cohort 4:

Patient eligibility according to the study inclusion and exclusion criteria will be assessed during the Screening period. Sites will be allowed one opportunity to re-screen any patient who fails initial screening or withdraws consent prior to device implantation or dose administration (if administration to be initiated by LP prior to device implantation. If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study.

Assays for leukocyte arylsulfatase A enzyme activity, urine sulfatide, and genotype determination will be performed by specialty laboratory(ies) designated by Shire to confirm the diagnosis of MLD.[5, 30] Biochemical confirmation of MLD diagnosis is required for study eligibility, but genotype results are not.

Local laboratory results for leukocyte arylsulfatase A enzyme activity and urine sulfatide will be allowed to confirm the diagnosis of MLD, 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 used to confirm the diagnosis of MLD. If local laboratory results are not in agreement with central laboratory results and the patient has already been dosed with study medication and/or has received device implantation, then the central laboratory tests will be repeated. If repeat central laboratory results confirm a positive local laboratory result then the patient will continue in the study. However, if the repeat central laboratory results are in discordance with the local laboratory results then the Investigator must contact the Shire Medical Monitor to evaluate what action should be taken regarding this patient. Dosing will be stopped if the Investigator and Medical Monitor determine that the patient does not have a diagnosis of MLD; however, such a patient would still be followed for safety.

To confirm the patient meets eligibility criteria at baseline, the baseline GMFM-88 assessment will be performed as close as possible to, but before device implantation or prior to first dose administration, whichever occurs first. Patients who do not continue to meet eligibility criteria will be discontinued from the study prior to device implantation and/or initial dosing. If device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment, the baseline GMFM-88 assessment will not be required. However, if more than 7 days has passed since the screening GMFM-88 assessment, the baseline GMFM-88 assessment will need to be completed prior to IDDD implantation or first dose, and prior to any other baseline assessments in order to confirm eligibility for enrollment (per inclusion criterion 3.1 in Section 5.2).

7.4 Study Enrollment

After all screening procedures are completed, diagnosis of MLD is confirmed, the patient has met all eligibility criteria, including confirmation of eligibility at baseline, and the patient has undergone device implant surgery or received at least 1 dose of study drug, the patient will be enrolled in the study.

7.5 Cross-reacting Immunologic Material

A blood sample will be obtained from each patient at Screening and the leukocytes from it will be tested for the presence of ASA cross-reacting immunological material (CRIM).

The peripheral blood mononuclear cells (PBMC) will be isolated and the tests will be performed at Shire or its designee.

7.6 Medical History and Demographics

Demographic information will be recorded for each patient and will include the following information: gender, age, and ethnic origin. MLD-related history will be recorded and will include age at onset of first MLD symptoms, age at MLD diagnosis, evidence of ASA deficiency, genotype, and family history of MLD.

Medical and surgical history will include the following systems: head, neck, eyes, mouth, ears, nose, throat, chest, lungs, cardiovascular, abdomen, gastrointestinal, genito-urinary, skin, musculoskeletal, neurological, and psychiatric system.

7.7 Height, Weight, and Head Circumference

Height and weight will be recorded for all patients.

Height or length (cm) measured with the patient in a supine position on a standard measuring board and weight (kg) will be recorded and used to calculate growth velocity. The clinical site staff will be instructed to use calibrated scales for weight measurement. It is recommended that the same scale be used at the clinical site for all patients at each specified time point during the study.

Body weight and height measurements will be used to calculate the body mass index (BMI).

Head circumference will be measured in a uniform manner for all patients.

7.8 Anesthesia

Anesthesia may be required for certain procedures (at the discretion of the Investigator). Any anesthesia used will be recorded as Concomitant Medications (see Section 6.6).

Administration of anesthesia may be given prior to obtaining CSF, if the use of the IDDD is precluded.

Anesthesia may also be administered prior to performing the following:

- Brain MRI and MRS
- ENG studies (motor and sensory conduction)
- Implantation of the IDDD
- Injection of HGT-1110

The physical examination and GMFM-88, FEES, and VABS-II assessments must be performed prior to the administration of anesthesia or after the patient has fully recovered from anesthesia.

7.9 Device-related Study Procedures

7.9.1 Intrathecal Drug Delivery Device Implantation, Replacement, or Revision

The IDDD will be surgically implanted at the clinical site. Procedures for implantation are detailed in the device's IFU Manual. Standard hospital procedures for surgery will be followed; the patient may be under general anesthesia for this procedure. It is planned that device explantation will occur at the main site unless urgent device removal is medically required to be performed locally or patient travel to the main site is medically inadvisable.

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

At a minimum, the date of the implantation and spinal placement will be documented on the eCRF. If the device becomes nonfunctional at any time during the study, it will be removed and may be replaced or revised as appropriate.

7.9.2 X-ray Verification of Intrathecal Drug Delivery Device Placement

A post-operative X-ray check of the IDDD will be performed following surgery to verify proper installation and confirmation of IDDD placement at the mid-thoracic level. X-rays may be performed to check placement of the device, as needed, throughout the study. An X-ray will be performed at the end of the study (to verify that the IDDD is in the correct position).

At a minimum, the date of the X-ray verifying correct IDDD placement and the date that the X-ray is read will be documented on the eCRF. If the device requires revision or replacement during the study, additional X-rays will be taken to document proper positioning of the device. Fluoroscopy should be used during device implantation procedures.

7.9.3 Cerebrospinal Fluid Sampling Procedure

Cerebrospinal fluid will be obtained from patients via an IDDD in aliquots appropriate for the specified analyses prior to each IT injection. If on a scheduled day of dosing, the use of the IDDD is precluded, the CSF samples may be obtained by LP, under anesthesia (if deemed necessary by the Investigator). Instructions for CSF withdrawal are included in the Manual of Operations.

7.9.4 Intrathecal Drug Delivery Device Removal

If at the time of a scheduled dosing, due to a device-related issue it is not possible to aspirate CSF prior to dose administration, administer a full medication dosage using the standard administration steps detailed in the device's IFU, or flush the system following dose administration, the IDDD will be declared a device malfunction. If the device malfunction is irreversible and cannot be corrected without a partial or full device revision or removal, the IDDD will be declared a device failure, starting from the date of the initial malfunction. The IDDD will then be surgically removed or revised and a new device and/or device components will be re-implanted at the earliest possible opportunity, preferably at the same time.

Patients who have a PORT-A-CATH IDDD failure will have this device replaced by a SOPH-A-PORT Mini S.

Details of the device removal will be recorded in the patient's eCRF. Refer to the relevant IFU for further details.

If the IT space is not accessible via the IDDD, investigational drug product may be administered by LP and CSF may be collected by LP.

Patients will have the IDDD removed when they discontinue from or complete the study, unless the patient is continuing to receive treatment through another mechanism (eg, a different study or commercially available).

7.10 Investigational Drug Product Administration

HGT-1110 will be administered EOW by means of an IDDD. A visual examination of both the port and catheter track will be performed before each IT injection. Patients 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. Please refer to Sections 6.2 and 6.3 for details. If the IT space is not accessible via the IDDD, investigational drug product may be administered by LP.

A 22-gauge Huber non-coring needle is to be used for access to the implanted port; standard hypodermic needles would damage the septum and may cause leakage. If no needle-free connector is present, either a stopcock of the Huber needle infusion set's clamp is to be used to prevent CSF backflow and to mitigate the risk of air entering the system. It is possible to use other brands of Huber non-coring needles, provided that their specifications are identical to that of the Huber needle supplied by Sophysa in a SOPH-A-PORT Mini S (22-gauge). Please refer to the Manual of Operations and the Pharmacy Manual for more details regarding investigational drug product administration.

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

7.11 Pharmacokinetic Assessments

Blood and CSF samples for determination of HGT-1110 concentration will be collected from patients for PK evaluations.

Blood samples will be obtained at Week 0 and Week 38, and will be drawn at the following nominal times: within 1 hour prior to IT injection of HGT-1110 and then 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of the IT injection.

The concentration of HGT-1110 in CSF will be assessed at Weeks 0 (Baseline), 4, 8, 12, 16, 20, 24, 28, 32, 36, and 40 (EOS). The CSF samples will be drawn prior to IT injection of HGT-1110. The concentration of HGT-1110 in CSF will also be assessed when any delayed doses are administered (see Section 6.3). Should the IDDD become clogged, undergo mechanical complications, or otherwise not be accessible, the CSF sample may also be obtained by LP until the device is repaired or replaced.

7.12 Efficacy Outcome Assessments

The change from baseline in motor function using the GMFM-88 total score (percent) after EOW IT injections of HGT-1110 for 38 weeks (Weeks 0 to 38) will serve as the main efficacy outcome measurement. Additional efficacy outcome measures include changes from baseline in FEES, ENG studies, VABS-II, COMFORT questionnaire, CSF, serum, and urine sulfatide and lysosulfatide levels, brain MRI and MRS, and GIMF-C and GIMF-S.

7.12.1 Gross Motor Function Measure

The GMFM-88[31] will be used to measure motor function. The GMFM-88 will be performed by a trained physiotherapist. It will be administered in the morning when the child is well rested and the assessments will be video-recorded. The video recordings may be used for an independent assessment. Patients will be evaluated in a one-on-one format.

The test requires approximately 60 minutes of exercise. This measurement is validated for cerebral palsy; however, as the GMFM-88 records motor skills that are typical of normal development, it is useful for assessments in children with other neurological diagnoses. The original validation sample included children 5 months to 16 years old. The GMFM-88 is appropriate for children whose motor skills are at or below those of a 5-year-old child without any motor disability.[31]

The GMFM-88 item scores can be used to calculate domain-specific percent score for each of the 5 GMFM-88 dimensions (lying and rolling; sitting; crawling and kneeling; standing; walking, running, and jumping).

7.12.2 Global Impression of Motor Function Change and Severity

The GIMF-C and GIMF-S will be used to evaluate the minimal clinically important change in GMFM-88 response to IT administration of HGT-1110. Each questionnaire contains 6 items addressing the clinician's global impression of change or severity in the 5 GMFM-88 dimensions

and overall. These assessments are to be administered after each GMFM-88 assessment and will only be performed for patients in Cohort 4.

7.12.3 Functional Endoscopic Evaluation of Swallowing

A Functional Endoscopic Evaluation of Swallowing (FEES) will be performed to fully evaluate the structure and function of the upper throat during swallowing and for an assessment of aspiration risk. Each patient will have this assessment performed at the clinical site using transnasal flexible laryngoscopy. The examination will be video recorded.

7.12.4 Electroneurography

Evaluation of peripheral nerve function via ENG studies may be performed under anesthesia by a neurophysiologist by measurement of NCV, CMAP, AMP, and DL.

7.12.4.1 Motor Nerve Conduction Studies

For motor nerves, NCV, CMAP, and DL will be measured in the median and peroneal nerves of each patient (may be performed under anesthesia). In the event that no relevant signal can be generated at baseline in either of these nerves, the ulnar nerve, the tibial nerve, or both will be evaluated as well. One nerve in the arm and one in the leg will be selected on the basis of available responses for repeated evaluations.

7.12.4.2 Sensory Nerve Conduction Studies

For sensory nerves, NCV, AMP, and DL will be measured in the median and sural nerves at baseline for each patient (this may be performed under anesthesia). One median and one sural nerve will be selected for repeated evaluations.

7.12.5 Vineland Adaptive Behavior Scales, Second Edition

The VABS-II Survey Interview Form will be used to measure the personal and social skills of patients serially over time; these scales are organized within a 3-domain structure: Communication, Daily Living, and Socialization. In addition, the VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The VABS-II Survey Interview Form assesses what a patient actually does, rather than what he or she is able to do. The VABS-II Survey Interview Form will be administered to the patient's parent(s) or legally authorized representative(s) by a trained medical professional. It will be conducted in available, validated languages.

7.12.6 Caregiver Observed MLD Functioning and Outcomes Reporting Tool

The Caregiver Observed MLD Functioning and Outcomes Reporting Tool (COMFORT) is a questionnaire that will be used to assess health status and the impact of disease on the ability of patients with MLD to carry out activities of daily life. The questionnaire is organized by 8 domains (ie, Personal Care, Positioning, Transfer or Mobility, Eating, Pain and Discomfort During the Day, Sleep, Emotions, Communication, Play and Leisure Activities) and will be

completed by the patient's parent(s) or legally authorized representative(s). It will be conducted in available, validated languages.

7.12.7 Assessments Using Stored Biological Samples

7.12.7.1 Biomarker Assessments

Samples of blood, urine, and CSF will be collected from patients participating in this study according to the Schedule of Events and stored for biomarker studies that may elucidate the pathogenesis of MLD and help to better characterize the response to the experimental treatment.

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

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

The identification of biomarkers that reflect the disease process and/or treatment response represent a potentially important exploratory aspect to this study that may contribute to patient and/or dose selection for future trials. Given our incomplete understanding of the pathogenesis of MLD, the range of biomarkers that might be informative is extensive. The CSF, blood, and urine samples will be examined for accumulation of sulfatide and lysosulfatide, which are known to reflect the primary biochemical lesion in MLD.

Additional testing of residual sample volumes may include biomarkers that reflect the known pathological processes in MLD – demyelination, neuroaxonal degeneration and neuroinflammation, as well as markers of lysosomal dysregulation (lysosomal proteins, enzymes, and their substrates).

Urine and blood-derived serum and/or plasma will be examined in parallel with CSF samples to:

- Assess CSF/blood quotients for biomarkers of interest to provide insight into their CNS versus peripheral provenance
- Identify potential peripheral urinary and/or blood biomarkers that might reflect CNS disease and/or treatment response

7.12.7.2 SOPH-A-PORT Mini S Assessments in Cerebrospinal Fluid and Serum

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

7.12.8 Magnetic Resonance Imaging and Brain Magnetic Resonance Spectroscopy

Each patient will have an MRI and MRS of the brain (may be performed under anesthesia), using methods specified in the Imaging Protocol contained in the Imaging Manual. Review of the images will focus on MLD-related abnormalities with measurement of metabolite levels (N-acetylaspartate, choline, and creatine) in regions of interest, for example, the frontal and parieto-occipital white matter, corpus callosum, centrum semiovale, and occipital cortex. Other metabolites and regions of interest may be explored.

7.13 Safety Assessments

7.13.1 Physical Examination

A complete physical examination will be performed, which will include an evaluation of the port and catheter track.

If results of the physical examination show clinically significant worsening from baseline or the previous visit, the change will be documented as an AE/serious AE (SAE) in the eCRF and will be followed as an AE consistent with the procedure outlined in Section 7.18. Clinical significance is defined as any variation in physical findings that has medical relevance resulting in an alteration in medical care. The Investigator will continue to monitor the patient until the parameter returns to baseline levels or until the Investigator determines that follow-up is no longer medically necessary.

7.13.2 Vital Signs

For all patients, vital signs (blood pressure, heart rate, respiratory rate, and body temperature measured when the child is not irritable or crying) will be obtained at each visit and recorded on the eCRF. Vital signs measured on IT dosing days will be obtained at times detailed in Section 8.3 and the Schedule of Events (see Appendix 1 and Appendix 2). Vital signs do not need to be measured if the patient is asleep.

7.13.3 Electrocardiography

Twelve-lead ECGs will be performed in accordance with the clinical site's standard practice(s). Identification of any clinically significant findings and conduction abnormalities will be recorded as AEs on the eCRF.

7.13.4 Clinical Laboratory Tests

Blood, urine, and CSF samples will be collected as described in the Laboratory Manual in the section for clinical laboratory testing. A central laboratory, a local laboratory, laboratories at Shire, or specialty laboratories will be used for analyzing samples and for reporting clinical laboratory values.

The Screening and Baseline visit required approximately 24 and 20 mL of blood for all patients in Cohorts 1-3, respectively, and will require 28 and 20 mL of blood, respectively, for patients in Cohort 4. The remaining visits will require approximately 11 mL of blood for the required

assessments (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 38, and 40). Approximately 7 mL of CSF will be drawn to approximate the volume of investigational drug product and flush to be injected. The CSF will be used for required and optional assessments at each treatment visit and the EOS visit.

7.13.4.1 Whole Blood Assessments

All blood samples will be collected via venipuncture. Patients will be in a seated or supine position during blood collection.

HEMATOLOGY

The following hematology parameters will be evaluated:

- Complete blood count (CBC) with differential and platelet count
- Prothrombin time (PT) and activated partial thromboplastin time (aPTT) (Screening visit only)

ASSESSMENT OF POTENTIAL ASSAYS FOR NEWBORN SCREENING

Blood samples will be collected for the potential future development of newborn screening assays for the diagnosis of MLD.

7.13.4.2 Serum Assessments

SERUM CHEMISTRY

Blood samples will be collected for serum chemistry testing that will include the assessments listed in Table 7-1.

Table 7-1 Routine Serum Chemistry Assessments

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

SERUM SULFATIDES (BIOMARKER ASSESSMENT)

Blood samples will be collected for biomarker assessments to determine serum sulfatide and lysosulfatide levels. Additional biomarker testing and additional testing related to the

SOPH-A-PORT Mini S may be performed with any residual volume of samples (see Section 7.12.7), which will determine serum levels of other analytes.

SERUM IMMUNOASSAY FOR ANTI-HGT-1110 ANTIBODIES

Blood samples will be collected for the determination of anti-HGT-1110 antibodies and, as appropriate, for neutralizing activity as well. Anti-HGT-1110 antibodies in blood samples are tested following a tiered approach per regulatory guidance and industry best practices. Samples are first screened using an electrochemiluminescence (ECL) bridging assay. Samples screened positive are then confirmed by competition with HGT-1110. The titers of confirmed positive samples are determined, and all confirmed positive samples are also further characterized using an enzyme activity based neutralization assay.

7.13.4.3 Urinalysis

STANDARD URINALYSIS

Urine samples will be collected for routine urinalysis.

Urinalysis will include the following:

- pH
- Macroscopic evaluations
- Microscopic evaluations

URINE SULFATIDES (CONFIRMATION OF DIAGNOSIS AND BIOMARKER ASSESSMENT)

A urine sample will be collected for the analysis of urinary sulfatide levels for confirmation of diagnosis. The assay will be performed at a reference laboratory.

Urine samples will be collected for the quantitative analysis of urinary sulfatides (sulfatide and lysosulfatide). The assay will be performed at a specialty laboratory. Additional testing may be performed with any residual volume of sample (see Section 7.12.7), which will determine urine levels of other analytes.

Refer to the Laboratory Manual for more information.

7.13.4.4 Cerebrospinal Fluid Assessments

Each CSF sample collected will be analyzed for cell count, protein, glucose, albumin, HGT-1110 levels, anti-HGT-1110 antibodies, and sulfatide and lysosulfatide levels. A summary of CSF analyses is presented in Table 7-2.

Additional biomarker testing and additional testing related to the SOPH-A-PORT Mini S may be performed with any residual volume of sample (see Section 7.12.7), which will determine the CSF levels of other analytes.

Table 7-2 Summary of Cerebrospinal Fluid Assessments

CSF Analysis Type	Purpose of Analysis	Lab at Which Analysis Will be Performed
Routine Analyses	CSF will be collected for the evaluation of glucose, protein, albumin, and cell count.	Local site
Biomarkers	CSF will be collected as described in the study Laboratory Manual for analysis of sulfatide and lysosulfatide (optional consent required for other biomarkers).	Shire or designee
Anti-HGT-1110 Antibodies	CSF will be collected for determination of anti-HGT-1110 antibodies.[a]	Shire or designee
HGT-1110 Levels/Concentration	CSF will be collected for the determination of HGT-1110 concentration.	Shire or designee

Abbreviations: CSF=cerebrospinal fluid

[a] Anti-HGT-1110 antibodies in CSF samples are tested following a tiered approach per regulatory guidance and industry best practices. Samples are first screened using an electrochemiluminescence (ECL) bridging assay. Samples screened positive are then confirmed by competition with HGT-1110. The titers of confirmed positive samples are determined and all confirmed positive samples are also further characterized using an enzyme activity based neutralization assay.

7.14 Device Data

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 patient's eCRF from the time of initial implantation.

7.15 Pregnancy Testing

Female patients of child-bearing potential who are sexually active or who become sexually active during the study will have a pregnancy test at each study visit.

Pregnancy testing will be performed with a urine test. If the urine test is positive, a blood sample will be collected for serum β-human chorionic gonadotropin (β-hCG) testing. The clinical site's local laboratory will analyze and report all pregnancy testing results. If a urine pregnancy test result is positive at any time during the study, the patient will not receive the planned injection(s) of investigational drug product until the result of the serum test is available. If the β-hCG result is also positive, no additional doses of investigational drug product are to be administered and the Investigator must contact the Shire Medical Monitor (see Section 7.19).

7.16 Sample Collection, Storage, and Shipping

Biological material will be stored and secured, in a way that ensures patient confidentiality and that ensures unauthorized access is prohibited and the samples are not lost, deteriorated, or accidentally or illegally destroyed.

The blood and CSF samples will be analyzed at central, local, or specialty laboratories or at Shire. Biorepositories will be maintained where samples will be archived in order to facilitate specimen management, batch testing, and storage.

Detailed instructions for laboratory sample collection, processing, and shipping instructions will be provided in the Laboratory Manual and will include country-specific requirements, as appropriate.

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

All medications, therapies/interventions administered to and medical/surgical procedures performed on the study patients from the time of informed consent through the Safety Follow-up visit (Week 42) are regarded as concomitant and will be documented on the eCRF.

7.18 Adverse Events Assessments

7.18.1 Definitions of Adverse Events and Serious Adverse Events

7.18.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered investigational drug product-related. This includes an exacerbation of a pre-existing condition. Once the patient's parents/legal representative(s) signs the informed consent, all AEs must be reported. Adverse events will be collected until 4 weeks (±3 days) after the last dose of investigational drug product or 2 weeks after the removal of the IDDD, whichever occurs later. Adverse events will be followed until the event has been resolved/stabilized or an outcome is reached, whichever comes first.

Adverse events include the following:

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

Throughout the study, the Investigator must record all AEs on the AE case report form (eCRF), regardless of the severity or relationship to investigational drug product, IDDD, device surgical procedure, or IT administration process. The Investigator should treat patients with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. Adverse events may be discovered through observation or examination of the patient, questioning of the patient, complaint by the patient, or by abnormal clinical laboratory values.

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

All AEs should be recorded with causality assessment as described in Section 7.18.3.

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

7.18.1.2 Serious Adverse Event

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

- Death
- Is life-threatening
- Requires hospitalization
- Requires prolongation of existing hospitalization
- For the purposes of this study, overnight hospitalizations post intrathecal administration of HGT-1110 that are based on practical or logistical considerations rather than safety (see Section 7.10) will not result in an SAE designation.
- A persistent or significant disability or incapacity

- A congenital anomaly or birth defect

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

Hospitalization that is the result of elective or previously scheduled surgery for a pre-existing condition, which has not worsened after initiation of treatment, should not result in an SAE designation. This does not apply to device failures resulting in scheduled surgical revisions, which should be reported as SAEs.

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients (21 Code of Federal Regulations [CFR] 812.3[s] or other regulatory requirements, as applicable).

7.18.2 Device-associated Definitions

7.18.2.1 Device Revision (Partial and Full)

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

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

7.18.2.2 Device Malfunction

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

7.18.2.3 Device Failure

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

7.18.2.4 Device Adjustment

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

7.18.3 Classification of Adverse Events and Serious Adverse Events

The severity of AEs will be assessed by the Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 grading scale (provided in the Study Operations Manual). If an AE is not described in the NCI CTCAE, the severity should be recorded based on the scale below (Table 7-3). The severity of all AEs/SAEs should be recorded on the appropriate eCRF page as Grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or fatal.

Table 7-3 Adverse Event Severity

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

7.18.4 Clarification Between Serious and Severe

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

7.18.5 Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational drug product, device, device surgical procedure, or IT administration process is to be determined by the Investigator based on the definitions in Table 7-4.

Table 7-4 Adverse Event Relatedness

Relationship to Product(s)	Definition
Not Related	Unrelated to investigational drug product, device, device surgical procedure, or IT administration process.
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational drug product, device, device surgical procedure, or IT administration process, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational drug product, device, device surgical procedure, or IT administration process unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely Related	The event follows a reasonable temporal sequence from administration of the investigational drug product, device, device surgical procedure, or IT administration process, and follows a known or suspected response pattern to the investigational drug product, device, device surgical procedure, or IT administration process, is confirmed by improvement upon stopping the investigational drug product, device, device surgical procedure, or IT administration process (de-challenge), and reappears upon repeated exposure (re-challenge). Note that this is not to be construed as requiring re-exposure of the patient to investigational drug product, device, device surgical procedure, or IT administration process; however, the determination of definitely related can only be used when recurrence of event is observed.

7.18.5.1 Adverse Events with Respect to Investigational Drug Product, Investigational Drug Product Administration, Device, and Associated Procedures

Adverse events of special interest will be recorded in this first-in-human study of HGT-1110. Please refer to the current Investigator's Brochure, Section 6.1.3, Adverse Reactions, for additional safety information. Adverse events of special interest in this study include the following:

DEVICE SURGICAL PROCEDURE-RELATED ADVERSE EVENTS

Examples of AEs related to device surgical procedures include, but are not limited to, the physiologic consequences of the following: events that occur during or shortly following IDDD implant/explant, IDDD adjustment, full revision, partial revision, IDDD removal, and delayed re-implantation after previous IDDD removal (such as complications of anesthesia, excessive

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

INTRATHECAL DRUG DELIVERY DEVICE-RELATED ADVERSE EVENTS

Examples of AEs related to use of the IDDD include, but are not limited to, the physiologic consequences (noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes) of the following: device failure, device malfunction, incorrect connection of IDDD components, erosion of the portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, migration of the portal/catheter, and occlusion of the portal/catheter, portal site, or subcutaneous tract infection. A malfunction of the device (defined in Section 7.18.2.2) should not be entered as an AE unless it has physiological consequences. In the event of a device failure (defined in Section 7.18.2.3), the device will need to be replaced or repaired by removal and replacement of a component or removed in its entirety. "Device failure" will be reported as the SAE term. Details of the cause of the IDDD malfunction or failure will be recorded on the device malfunction and failure eCRF and the SAE form (where applicable).

A list of the most common IDDD AEs is included in the list of complications in Appendix 3.

INTRATHECAL ADMINISTRATION PROCESS ADVERSE EVENTS

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

HGT-1110 - RELATED ADVERSE EVENTS

To support a proposed Phase I/II clinical study, a comprehensive nonclinical program has been conducted to investigate HGT-1110 administered intrathecally to rats and juvenile monkeys to mimic human exposure at different age groups. Nonclinical studies were performed to compare Process A and B HGT-1110 drug product. Pharmacodynamic and pharmacokinetics were comparable for Process A and B HGT-1110, and no new safety findings were identified for Process B HGT-1110. In a first-in-human study of intrathecally administered HGT-1110, it is not possible to predict study IT drug-related AEs in humans. However, examples of AEs observed in published clinical trials with other intrathecally administered peptides or proteins include, but are not limited to the following: headache, fever, feeling of warmth, sensory paresthesias (including feelings of warmth, tingling, or pain), and autonomic symptoms such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection, over time.

Although in this study HGT-1110 is only administered via the IT route, some proportion of the drug is likely to diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that have been seen in patients receiving other enzyme replacement therapies known as infusion-related or hypersensitivity reactions, as well as possible development of antibodies to HGT-1110.

RISKS ASSOCIATED WITH ANESTHESIA REQUIRED FOR STUDY ASSESSMENTS

The use of an IDDD has been chosen to minimize the risks inherent in utilizing novel delivery systems and to alleviate the need for multiple administrations of anesthesia required for drug injection via repeated LP. The general risks include respiratory depression, aspiration, cardiac events, hypoxia, hypotension and hypertension, difficult intubations and extubations, stroke, rapid changes in body temperature, laryngospasm or laryngeal edema, and allergic reaction.

Risks from anesthesia include death from complications such as changes in heartbeat, blood pressure, body temperature, or breathing. Patients will be closely monitored for changes in vital signs and related events.

RISKS ASSOCIATED WITH LUMBAR PUNCTURE

Risks associated with LP include pain at the injection site, infection, meningitis, encephalitis, cerebritis, failed procedure, bleeding, dural tears, spinal headache, spinal fluid leakage, nerve damage, and focal and non-focal neurological injury (including paralysis). Patients may require anesthesia prior to an LP. Risks from anesthesia are discussed separately in this section (Section 7.18.5.1).

RISKS ASSOCIATED WITH FUNCTIONAL ENDOSCOPIC EVALUATION OF SWALLOWING

Risks associated with FEES include discomfort, gagging, vomiting, fainting, nose bleeds, and laryngospasm.

7.18.6 Procedures for Recording and Reporting Adverse Events

7.18.6.1 Adverse Event Monitoring and Period of Observation

Adverse events will be monitored continuously throughout the study.

For the purposes of this study, the period of observation extends from the time at which the patient's parent(s) or the patient's legally authorized representative(s) gives informed consent until the patient's final evaluation of the study. For safety purposes, the final evaluation will be defined as the follow-up evaluation performed approximately 4 weeks after the last dose 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. The final evaluation for any patient enrolled in such an extension study will be defined as the patient's last visit in Study HGT-MLD-070.

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

7.18.6.2 Reporting Serious Adverse Events

Any SAE, regardless of relationship to investigational drug product, device, device surgical procedure, or IT administration process, which occurs in a patient after informed consent, should be recorded by the clinical site on an SAE form.

The SAE must be completely described on the patient's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the investigational drug product. The Investigator will promptly supply all information identified and requested by the Sponsor (or contract research organization [CRO]) regarding the SAE.

The Investigator must report the SAE to the Shire Pharmacovigilance and Risk Management Department AND to the Shire Medical Monitor on an SAE form. This form must be completed and FAXED or EMAILED within 24 hours of the Investigator's learning of the event to the following:

Shire Pharmacovigilance and Risk Management Department:

International FAX: PPD **(UK)**

OR

United States FAX: PPD

Email: PPD

AND

Shire Medical Monitor: PPD **, MD**

Email: PPD

FAX: PPD **(USA)**

Any follow-up information must also be completed on an SAE form and faxed to the same numbers listed above.

In the event of a severe and unexpected, fatal, or life-threatening SAE, the clinical site must contact the Shire Medical Monitor by telephone in addition to completing and transmitting the SAE form as stated above. The following provides contact information for the Shire Medical Monitor.

If an SAE is assessed as severe and unexpected, or life-threatening, contact:
PPD , MD PPD Shire 300 Shire Way Lexington, MA 02421, USA Telephone: PPD Mobile: PPD Email: PPD

The Investigator must promptly report all required information to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

It is the responsibility of the Sponsor to report suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening within a maximum of 7 days and to report all other SUSARs to the competent authorities concerned and to the Ethics Committee concerned within a maximum of 15 days of first knowledge by the Sponsor as per the European Directive 2001/20/EC.

Mandatory medical device reports (MDRs), ie, UADEs, will be submitted to relevant regulatory agencies consistent with applicable regulations by the device manufacturer or Shire according to the region. Expedited drug-related events (serious, unexpected/unlisted, causally related) will be reported by Shire, as applicable.

It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any Council for International Organizations of Medical Sciences (CIOMS) I/MedWatch/MDR report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The Investigator or Sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files.

7.19 Pregnancy

The Sponsor must be notified in the event of a pregnancy occurring during the course of the study and through 30 days after the patient's last dose of investigational drug product. Pregnancy is not to be reported as an AE; the pregnancy reporting form should be used to report the pregnancy. The pregnancy will be followed up through delivery or final outcome.

7.20 Abuse, Overdose, and Medication Error

- **Abuse** – Persistent or sporadic intentional intake of investigational drug product at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (eg, altering one's state of consciousness)
- **Misuse** – Intentional or unintentional use of investigational drug product other than as directed or indicated at any dose, which is at or below the dose defined for overdose.

(Note: This includes a situation where the test article is not used as directed at the dose prescribed by the protocol.)

- **Overdose** – Intentional or unintentional intake of a dose of investigational drug product higher than that prescribed for the patient in this study
- **Medication Error** – A mistake made in prescribing, dispensing, administration or use of the investigational drug product

All investigational drug product provided to pediatric patients should be supervised by the parent/legally authorized representative. The required process for reporting abuse, overdose, and medication errors is provided in the Manual of Operations.

7.21 Removal of Patients from the Trial or Investigational Drug Product

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

- Non-compliance, including failure to appear at 1 or more study visits
- The patient was erroneously included in the study.
- The patient develops an exclusion criterion.
- The patient undergoes HSCT at any time during the study.
- The patient suffers an intolerable AE.
- The study is terminated by the Sponsor.
- The patient experiences an adverse event NCI CTCAE Grade 3 or higher that is possibly, probably, or definitely related to treatment.

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

If a patient's parent(s) or the patient's legally authorized representative(s), acting on behalf of the patient, discontinues patient participation in the study or the patient is discontinued by the Investigator, the Patient Completion/Discontinuation eCRF describing the reason for discontinuation must be completed.

Any AEs experienced up to the point of discontinuation must be documented on the AE CRF. If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

7.22 Safety-related Study Stopping Rules

If at least 1 patient experiences a life-threatening (Grade 4) AE or death (Grade 5) that is considered either possibly, probably, or definitely related to treatment with investigational drug product or the IDDD (ie, a UADE), or if 2 or more patients experience at least one Grade 3 or higher AE during the study that is considered possibly, probably, or definitely related to treatment with HGT-1110, then dose escalation may not occur (see Section 6.5) and all sites will be instructed to halt further administration of HGT-1110 to all patients. An ad hoc DSMB meeting will be convened and all available data relating to the safety of HGT-1110 will be reviewed. Following the review of safety data and consultation with Regulatory Authorities as necessary, the study will be either:

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

Patient safety will be monitored on a continuous basis during this study until the last patient completes his or her last scheduled study visit/assessment.

7.23 Appropriateness of Measurements

The safety, clinical effect, and PK parameters selected for this study were chosen based upon knowledge of the disease process and experience with intrathecal ERT in other lysosomal storage disorders.

The main efficacy outcome variable, change from baseline in motor function as assessed with the GMFM-88 total score (percent), provides a clinically meaningful measurement of neurological function in children with progressive degenerative brain disease accompanied by rapid loss of motor function. Portions of the GMFM-88 that focus on timed motor activities, such as the ability to sit without support, will provide valuable supplemental information on disease progression as it related to motor function deficit.[32] The GMFM-88 item scores can be used to calculate a domain-specific percent score for each of the 5 GMFM-88 dimensions, which are the following:

- Lying and rolling
- Sitting
- Crawling and kneeling
- Standing
- Walking, running, and jumping

The domain-specific percent scores are averaged to obtain the total score (percent). The GMFM-88 tool is validated for children with cerebral palsy[33] and Down syndrome.[34] The original validation sample included children with cerebral palsy who ranged in age from

5 months to 15 years of age.[31] It is appropriate for children whose motor skills are at or below those of a 5-year-old child without any motor disability. Because the GMFM-88 measures motor skills that are typical of normal development, it is appropriate for use in MLD and other neurological diagnoses.[35]

Quantitative assessment of the ability to swallow (FEES), ENG measurements, CSF sulfatide and lysosulfatide, and white matter spectroscopic measure of N-acetylaspartate levels will provide supplemental information on CNS disease burden.

Children with MLD often present with impairments in adaptive behavior, which is a composite of various dimensions. The scales of the VABS-II[36] are organized within a 3-domain structure: Communication, Daily Living, and Socialization. This structure corresponds to the following 3 broad domains of adaptive functioning defined by the American Association of Intellectual and Developmental Disabilities: Conceptual, Practical, and Social. In addition, VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The scores are interpreted by means of score equivalents for the raw scores in each domain, percentile ranks, age equivalents, adaptive levels, and maladaptive levels. Children with MLD often present with behavioral and intellectual impairments that would be detected with the VABS-II Survey Interview Form. The VABS-II Survey Interview Form measures adaptive behaviors, including the ability to cope with environmental changes, to learn new everyday skills and to demonstrate independence. It is an instrument that supports the diagnosis of intellectual and developmental disabilities, which are also often reflected in the presentation of MLD symptoms in children. It is an appropriate test for the age range of the patient population (<12 years of age), encompassing ages from birth to 90 years.

An assessment of the ability of children with MLD to carry out activities of daily life is an important measure because of the severity of the disease and its rapid progression, which impact cognitive function and the motor system. The COMFORT questionnaire was developed specifically for patients with MLD to evaluate key clinical domains affected by MLD. The questionnaire has a total of 59 questions spanning the following 8 domains:

- Personal Care
- Positioning, Transfer, or Mobility
- Eating
- Pain and Discomfort During the Day
- Sleep
- Emotions
- Communication
- Play and Leisure Activities

The COMFORT questionnaire will be used to evaluate the effect of HGT-1110 beyond efficacy outcome measures such as the GMFM-88 and FEES. Effective treatment would be expected to stabilize or improve a patient's COMFORT result.

Evaluation of all chosen parameters will document the safety and impact of HGT-1110 on clinical manifestations of MLD and on the ability to carry out activities in daily life and will provide evidence on the risk-benefit profile of the product.

8 STUDY ACTIVITIES

Patients in Cohorts 1, 2, 3, and 4 will undergo the schedule of procedures as presented at all visits listed in this section.

8.1 Phase 1: Screening (Days -40 to -11 for Cohorts 1-3; Days -40 to Day -1 for Cohort 4)

Written informed consent must be obtained from the patient's parent(s) or legal representative(s) before any study related procedures are performed. Upon obtaining informed consent, the following procedures and assessments required for the determination of the patient's eligibility must be completed at least 11 days prior to the baseline visit (Week 0), with exceptions noted below.

Screening visit procedures will include the following:

- Assess inclusion/exclusion criteria, including GMFM-88 (Cohort 4 only) (see note below)
- Confirmation of MLD diagnosis (analysis of urine sulfatide, ASA activity in leukocytes, and genotype, as noted below). Samples for MLD diagnosis should be collected between Day -40 and Day -29 (for Cohorts 1-3) or Day -40 to Day -1 (for Cohort 4).
- Medical history and demographic information
- Physical examination
- Vital signs
- Height and weight
- Head circumference
- Perform a 12-lead ECG
- Urine sample collection for:
  - Routine urinalysis and sulfatide level (between Day -40 and Day -29)
- Blood sample collection for:
  - Serum chemistry (including albumin) and hematology, including PT and aPTT
  - Arylsulfatase A activity in leukocytes (between Day -40 and Day -29 for Cohorts 1-3 or Day -40 to Day -1 for Cohort 4)
  - Presence of arylsulfatase A cross-reacting immunological material (CRIM) in leukocytes
  - Genotyping (between Day -40 and Day -29)
  - Development of newborn screening tests
- Urine pregnancy test (if applicable)
- Begin AE reporting

- Begin monitoring concomitant medications/therapies/procedures

NOTE: If a patient does not meet inclusion/exclusion criteria, no further procedures will occur at that time. Sites will be allowed one opportunity to re-screen any patient who fails initial screening or withdraws consent prior to 1) device implantation or 2) dose administration (if administration to be initiated by LP prior to device implantation for Cohort 4 only). If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study.

8.2 Phase 2: IDDD Implantation (Day -10 to Day -1 for Cohorts 1-3; Day -10 to Day +28 for Cohort 4)

For Cohort 4 only: To confirm the patient meets eligibility criteria at baseline, specifically the baseline GMFM-88 assessment will be performed as close as possible to, but before device implantation or prior to first dose administration, whichever occurs first. Patients who do not continue to meet eligibility criteria will be discontinued from the study prior to device implantation and/or initial dosing. If device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment, the baseline GMFM-88 assessment will not be required. However, if more than 7 days has passed since the screening GMFM-88 assessment, the baseline GMFM-88 assessment will need to be completed prior to IDDD implantation or first dose, and prior to any other baseline assessments in order to confirm eligibility for enrollment (per inclusion criterion 3.1 in Section 5.2).

Upon confirmation of eligibility, patients will have an IDDD surgically implanted. Surgical implantation of the IDDD includes surgical implantation of the IDDD and a post-surgical assessment. The IDDD placement may require anesthesia. The patient may receive study drug by LP until the device is implanted. Device implantation should be scheduled within 28 days of enrollment unless a delay is required due to clinical judgment for medical reasons (eg, infection).

- IDDD implantation and post-surgical assessment
- X-ray to verify IDDD was placed at the mid-thoracic level in the spinal canal and correctly installed
- Vital signs
- Urine pregnancy test (if applicable)
- Enrollment (A patient will be considered enrolled in the study once they have undergone device implant surgery or received at least 1 dose of study drug.)
- Concomitant medications/therapies/procedures monitoring
- AE reporting

8.3 Phase 3: Baseline and Treatment (Weeks 0 to 38)

8.3.1 Baseline: Week 0 (±3 days for IT injection of HGT-1110)

For Cohort 4 only: To confirm the patient meets eligibility criteria at baseline, the baseline GMFM-88 will be performed as close as possible to, but before device implantation or prior to

first dose administration, whichever occurs first. Upon confirmation of study eligibility, all other baseline assessments may be performed at any time prior to dosing, including the Phase 2 period of the study (Section 8.2), but should be performed as close to dosing as possible. For Cohort 4, patients who do not continue to meet eligibility criteria will be discontinued from the study prior to device implantation and/or initial dosing. If device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment, the baseline GMFM-88 assessment will not be required.

The following Week 0 assessments will be performed at the clinical site:

- Physical examination
- GMFM-88 (as applicable, for Cohort 4: if device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment, the baseline GMFM-88 assessment will not be required.)
- GIMF-C and GIMF-S questionnaires
- FEES
- The following assessments may be performed under anesthesia:
  - Motor and sensory nerve conduction studies (ENG studies)
  - Brain MRI and MRS
- VABS-II
- COMFORT questionnaire
- Blood sample collection for:
  - Serum chemistry (including albumin) and hematology
  - Serum biomarkers (sulfatide and lysosulfatide levels)
  - Serum anti-HGT-1110 antibodies
- Urine sample collection for:
  - Urinalysis
  - Biomarkers (sulfatide and lysosulfatide levels)
- CSF sample collection for:
  - Routine analysis, including albumin
  - Anti-HGT-1110 antibodies
  - Concentration of HGT-1110
  - Biomarkers (sulfatide and lysosulfatide levels)
- Concomitant medications/therapies/procedures monitoring
- Urine pregnancy test (if applicable)
- AE reporting

- Blood sample collection for PK: within 1 hour prior to IT injection and then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection.
- Administer HGT-1110 by IT injection. Patients 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. **The first day of dosing will be defined as Day 0. (All subsequent doses will be administered at 14 (±3) days (ie, 2-week) intervals based on the timing of the initial dose.)**
- Vital signs 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.
- Enrollment – (A patient will be considered enrolled in the study once they have undergone device implant surgery or received at least 1 dose of study drug.)

8.3.2 Treatment Weeks (Weeks 2 through 38, excluding Weeks 16 and 28)

The following assessments will be performed at Weeks 2, 4, 6, 8, 10, 12, 14, 18, 20, 22, 24, 26, 30, 32, 34, 36, and 38 (each visit window will be ±3 days) and prior to IT injection of HGT-1110 unless otherwise indicated:

- Physical examination
- CSF sample collection for routine analysis, including albumin
- Administer HGT-1110 by IT injection. Patients 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.
- Vital signs 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.
- Urine pregnancy test (if applicable)
- Concomitant medications/therapies/procedures monitoring
- AE reporting

The following assessments will be performed at Weeks 4, 8, 12, 20, 24, 32, and 36 (each visit window will be ±3 days) in **addition** to those listed immediately above, and prior to IT injection of HGT-1110 unless otherwise indicated:

- CSF sample collection for analysis for:
  - Anti-HGT-1110 antibodies
  - Concentration of HGT-1110

- Biomarkers (sulfatide and lysosulfatide levels)

- Blood sample collection for:
- Serum chemistry (including albumin) and hematology
- Serum anti-HGT-1110 antibodies
- Serum for biomarkers (sulfatide and lysosulfatide levels)

- Urine sample collection for:
- Urinalysis
- Urine biomarkers (sulfatide and lysosulfatide levels)

On Week 38 **only,** the following PK sampling will be performed:

- Blood sample collection for PK: within 1 hour prior to IT injection and then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection.

See Section 8.3.3 for the list of assessments to be performed at Weeks 16 and 28.

8.3.3 Treatment and Evaluation: Weeks 16 and 28 (±3 days for IT injection of HGT-1110, -5 days for assessments)

At Weeks 16 and 28, the window for IT injection of HGT-1110 will be ±3 days and the window for assessments will be -5 days. All assessments will be performed prior to dosing unless otherwise indicated in the list that follows. The following assessments will be performed at Weeks 16 and Week 28:

- Physical examination
- Vital signs 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.
- Height and weight
- Head circumference
- GMFM-88
- GIMF-C and GIMF-S questionnaires
- FEES
- The following assessments may be performed under anesthesia:
  - Motor and sensory nerve conduction studies (ENG studies)
  - Brain MRI and MRS
- VABS-II

- COMFORT questionnaire
- Urine sample collection for:
  - Urinalysis
  - Urine biomarkers (sulfatide and lysosulfatide levels)
- Blood sample collection for:
  - Serum chemistry (including albumin) and hematology
  - Serum anti-HGT-1110 antibodies
  - Serum biomarkers (sulfatide and lysosulfatide levels)
- CSF sample collection for:
  - Routine analysis, including albumin
  - Anti-HGT-1110 antibodies
  - Concentration of HGT-1110
  - Biomarkers (sulfatide and lysosulfatide levels)
- Urine pregnancy test (if applicable)
- Concomitant medications/therapies/procedures monitoring
- Administer HGT-1110 by IT injection. Patients 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.
- AE reporting

8.4 Phase 4: End of Study: Week 40 (-5, +3 days)

The EOS visit will occur at Week 40. Patients who discontinue early will have an EOS visit 2 weeks (-5, +3 days) after the last IT injection of HGT-1110. The following procedures will be performed at the EOS visit:

- Physical examination
- 12-lead ECG
- Vital signs
- Height and weight
- Head circumference
- GMFM-88
- GIMF-C and GIMF-S questionnaires
- The following assessments may be performed under anesthesia:
  - Motor and sensory nerve conduction studies (ENG studies)

  - Brain MRI and MRS
- FEES
- VABS-II
- COMFORT questionnaire
- Urine sample collection for:
  - Urinalysis
  - Biomarkers (sulfatide and lysosulfatide levels)
- Blood sample collection for:
  - Serum chemistry (including albumin) and hematology
  - Serum anti-HGT-1110 antibodies
  - Serum biomarkers (sulfatide and lysosulfatide levels)
- CSF sample collection for:
  - Routine analysis, including albumin
  - Anti-HGT-1110 antibodies
  - Concentration of HGT-1110
  - Biomarkers (sulfatide and lysosulfatide)
- X-ray confirmation of IDDD placement
- IDDD removal unless the patient is continuing to receive treatment through another mechanism (eg, a different study or commercially available)
- Urine pregnancy test (if applicable)
- AE reporting
- Concomitant medications/therapies/procedures monitoring

8.5 Phase 5: Safety Follow-up Visit: Week 42 (±3 days)

The Safety Follow-up visit will occur at Week 42 or at 4 weeks (±3 days) after the last dose of HGT-1110 or removal of the IDDD, whichever occurs later (for patients who discontinue early from the study). Patients may be allowed to enroll in an HGT-1110 extension study, if eligible, after completing all requirements in Study HGT-MLD-070 through Week 40. 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. The following procedures will be performed at the Safety Follow-up visit and may be performed by telephone from the clinical site:

- AE reporting
- Concomitant medications/therapies/procedures monitoring

9 QUALITY CONTROL AND ASSURANCE

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

Clinical sites will be monitored by the Sponsor or its designee to ensure the accuracy of data against source documents.

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

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

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance database.

10 STATISTICAL ANALYSIS

10.1 General Methodology

All statistical analyses will be performed by the Shire Biometrics department (with the exception of the PK analysis, which will be performed by the Shire Clinical Pharmacology and Pharmacokinetics department). Statistical analyses will be performed using SAS® software Version 9.3 or higher. Data will be summarized by cohort and overall, if appropriate. Summary statistics for continuous variables will include the number of patients, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized in a contingency table by the number and percentage of patients in each category (including a missing category, if applicable). Any statistical tests comparing cohorts will be 2-sided with a significance level of 0.05 and considered exploratory or hypothesis generating. The mean change, mean difference in the change between cohorts, and the corresponding 95% confidence intervals (CIs), may also be presented as appropriate.

Safety data summaries will be descriptive, and based on all post-baseline assessments including the frequency of TEAEs and the frequency of clinically notable abnormal vital signs and laboratory values.

10.2 Determination of Sample Size

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

10.3 Method of Assigning Patients to Treatment Cohorts

This is a multicenter open-label dose-escalation study to evaluate the safety of HGT-1110. Each of the first 3 cohorts of patients was assigned in an ascending order of the dose level sequentially. The Cohort 1 patients were assigned to the lowest dose level of HGT-1110 (10 mg), Cohort 2 patients were assigned to the middle dose level (30 mg), and Cohort 3 patients were assigned to the highest dose level (100 mg) EOW treatment. Cohort 4 will be assigned to the 100 mg dose level administered EOW.

10.4 Analysis Populations

The Safety population, defined as the set of patients who underwent the device implant surgery or received at least 1 dose of study drug, will be the primary analysis population. Intrathecal device-related analyses will be performed in the subset of the Safety population who underwent the device implant surgery.

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

10.5 Patient Disposition

The number of patients who had baseline assessments, who were dosed, and completed the study, as well as the number who discontinued, will be reported in summary tables using number and percentage of patients per category by cohort; reasons for discontinuation/withdrawal will be presented.

10.6 Demographics and Baseline Characteristics

Descriptive statistics of patient demographic and baseline characteristics data will be summarized by cohort and overall using the Safety population. The continuous variables (eg, age, weight, and height) will be summarized by descriptive statistics using n, mean, median, SD, minimum, and maximum. The categorical variable (eg, sex and race) will be tabulated using frequency and percentage for each category of interest (including a missing category, if applicable).

10.7 Primary Endpoints

Safety will be measured by the following endpoints:

- Reporting of TEAEs
- Change from baseline in clinical laboratory testing (serum chemistry including liver function tests, hematology, and urinalysis)
- Change from baseline in 12-lead ECGs, vital signs, physical examinations, and CSF chemistry (including cell counts, glucose, and protein)
- Determination of the presence of anti-HGT-1110 antibodies in CSF and/or serum

10.8 Secondary Endpoints

The secondary endpoints of this study are the following:

- Change from baseline in motor function using the GMFM-88 total score
- Change from baseline in the ability to swallow as measured by the FEES
- Change from baseline in nerve conduction as measured by the ENG assessments of NCV, CMAP, AMP, and DL
- Change from baseline in the adaptive behavior composite standard score as measured by the VABS-II
- Change from baseline in the domain-specific COMFORT scores
- Single and repeated-dose PK parameter estimates for HGT-1110 in serum
- Concentrations of HGT-1110 in CSF at selected time points after single and repeated investigational drug product administration

10.9 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 N-acetylaspartate metabolite levels in the deep white matter of the brain as assessed by proton MRS
- Change from baseline in the total MLD severity score based on MRI of the brain
- Categorical assessment in the GIMF-S
- Categorical assessment in the GIMF-C

10.10 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 patient's eCRF from the time of initial implantation.

10.11 Pharmacokinetic Analysis

The concentrations of HGT-1110 in the serum and CSF samples will be determined. Individual serum HGT-1110 concentration-time profiles will be reported. Individual PK parameters will be calculated if sufficient HGT-1110 concentration time points exist to derive values. The PK parameters will be derived using noncompartmental analysis, and the actual blood collection times relative to the start of the IT administration will be used in the analysis. Individual CSF HGT-1110 concentration at each time point will be reported. The association of the presence of anti-HGT-1110 antibodies and HGT-1110 concentration-time profiles and PK parameters will be evaluated, if applicable.

Pharmacokinetic parameters calculated will include the following:

- Maximum observed serum concentration (C_{max})
- Time of Cmax (T_{max})
- Area under the serum concentration-time curve from time zero to the last sampling time at which serum concentrations were measurable ($AUC_{0\text{-}last}$)
- Area under the serum concentration-time curve extrapolated to infinity ($AUC_{0\text{-}\infty}$)
- Apparent terminal rate constant (λZ) derived from the slope of the log-linear regression of the log-linear terminal portion of the serum concentration-time curve.
- Terminal half-life ($t_{1/2}$) calculated as 0.693/apparent terminal rate constant (λZ)
- Clearance after IT administration (CL/F)
- Volume of distribution based on the terminal phase after IT administration (Vz/F)

Summary statistics (number of observations, mean, SD, coefficient of variation, median, maximum, minimum, and geometric mean) will be determined for all PK parameters and presented by cohort, visit, and drug product (Process A and Process B). Serum concentrations of HGT-1110 at each nominal sampling time will also be summarized by treatment and visit using descriptive statistics.

10.12 Primary Analyses

The analysis of safety data will be performed using the Safety population, primarily on the total number of patients and frequency of TEAEs and on the frequency of clinically significant (CS) laboratory values and clinically notable abnormal vital signs, change in vital signs, and abnormal 12-lead ECG parameters. The proportion of patients with TEAEs and CS abnormal laboratory values during the study will be presented by cohort and overall.

Adverse events will be collected throughout the study and at early termination if a patient prematurely withdraws from the study. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent AEs, defined as all AEs occurring at or after the first dose of study drug or device implant surgery (whichever occurs first) and through the last follow-up date in HGT-MLD-070, will be summarized by system organ class and preferred term for the Safety population and by cohort. In addition, the severity and relationship to investigational drug product of the TEAE will be summarized overall and by cohort. Those events that resulted in death or were otherwise classified as serious will be presented in a by-patient data listing. For each of the clinical laboratory parameters (serum chemistry including liver function tests, hematology, and urinalysis), both the observed results and changes from baseline at each post-baseline visit will be summarized overall and by cohort.

Anti-HGT-1110 antibody formation will be monitored throughout the study. Antibody assay results will be summarized by cohort including, number and percentage of positive and negative values by cohort and study visits, for both serum and CSF. These results may also be presented in the by-patient data listings.

Anti-HGT-1110 antibodies will be evaluated for enzyme neutralizing activity using an in vitro assay. Results will be presented in summary tables by assay methodology used to identify antibodies and enzyme-neutralizing activity.

All safety data may also be presented in data listings.

10.13 Secondary Analyses

The change from baseline in motor function using the GMFM-88 total score (percent) will be summarized descriptively at each study visit. The cohorts will be compared at the end of study visit using an analysis of covariance (ANCOVA) model with change from baseline as the dependent variable including the cohort as a fixed effect and baseline values of the GMFM-88 total score (percent) as the single continuous covariate. The adjusted mean for each cohort and the difference in means between cohorts and the associated 95% confidence intervals and

p-values will be estimated. If the parametric assumptions are not justified, then the ANCOVA model will be analyzed using the rank data. The total score (percent) is calculated by averaging the percent scores 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.[31]

Pharmacokinetic analysis of HGT-1110 in serum will be performed using individual concentration-time data and the PK parameters will be derived. Summary tabulations of PK parameters will be presented by cohort, visit, and drug process (Process A and Process B). Continuous data will be summarized with descriptive statistics: number of observations, mean, SD, geometric mean, co-efficient of variation, median, minimum, and maximum values. Individual HGT-1110 concentrations in CSF at each time point will be reported.

Unless otherwise indicated, all below secondary analyses will be performed by cohort.

The FEES assessment will be performed to fully evaluate the structure and function of the upper throat during swallowing, and for an assessment of aspiration risk. Data will be presented by individual patient; summary statistics or shift tables will be prepared, as appropriate. In particular, the within-patient shift in aspiration risk (low; moderate; high) over time will be of particular importance.

The observed values and change from baseline will be summarized for sensory and motor nerves by left and right side, if appropriate, for NCV, CMAP, AMP, and DL as measured by ENG. This data will be summarized descriptively by cohort and overall. Data may be presented graphically over time.

The VABS-II Survey Interview Form will be used to measure the personal and social skills of patients serially over time. These scales assess what a patient actually does, rather than what he or she is able to do and those activities will be assessed by a trained medical professional. The observed value and change from baseline in the standard score (standardized to other people of the same age) within each of 4 domains (communication; daily living skills; socialization; motor skills), as well as the adaptive behavior composite standard score across all 4 domains will be presented. Data may be presented graphically over time.

To understand the effect that HGT-1110 has on patients' ability to carry out activities in daily life, the COMFORT questionnaire will be implemented throughout the study. The questions, presented on a Likert scale, ask about some activities a patient with MLD has to do on most days. There are several domains and a summary score is calculated within each domain. All of the statistical analyses will be performed within a domain. The observed data and change from baseline in the domain-specific summary scores will be presented. Data may be presented graphically over time.

All secondary endpoint data may be presented in data listings.

10.14 Exploratory Analyses

The exploratory endpoints listed in Section 10.9 will be summarized descriptively at each study visit.

In addition, correlations of efficacy outcome measures with the CSF, serum, and urine sulfatide and lysosulfatide levels and with spectroscopic data (N-acetylaspartate) will be examined for exploratory purposes at baseline, Week 40, and change from baseline to Week 40. A measure of the linear association between variables at each time point will be obtained using Pearson correlation or the Spearman rank correlation as appropriate.

Additionally, the correlations will be estimated of the GMFM-88 total score (percent) versus the following variables: N-acetylaspartate, CSF, serum, and urine sulfatide and lysosulfatide.

Each patient 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 patient at each time point where higher scores indicate more severe brain involvement. The pairwise comparison between cohorts will be conducted at the EOS visit using an ANCOVA model with change from baseline as the dependent variable including the cohort as a fixed effect and baseline values of the total MLD severity score as the single continuous covariate.

In addition, change from baseline in GMFM-88 domain scores will be summarized descriptively at each study visit.

The items of the GIMF-C and GIMF-S will be summarized by the number and percentage of patients by study visit for each dose cohort.

All exploratory endpoint data may be presented in data listings.

10.15 Intrathecal Drug Delivery Device Analyses

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

Intrathecal drug delivery device and procedure-related AEs will be summarized within system organ class by preferred term. Adverse events will be tabulated by severity (mild, moderate, severe) and degree of relatedness. Separate tabulations will be provided for AEs related to the IDDD, device surgical procedure and IT administration process.

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

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

10.16 Interim Analysis

An interim analysis of all data will be performed after all enrolled patients in Cohorts 1-3 have completed the study. All data from Cohorts 1-3 will be entered into the database, reviewed, and discrepancies resolved for this analysis. Because any hypothesis testing is considered exploratory, no adjustment for multiplicity will be made. The analysis methods will be detailed in an interim statistical analysis plan, 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 (Section 11.8).

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

Before initiation of the study, the Investigators must provide the Sponsor with a completed Form FDA 1572. Investigational drug product may be administered only under the supervision of the Investigators listed on this form. Curriculum vitae must be provided for the Investigators and sub-investigators listed on Form FDA 1572 or Investigator Agreement.

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

A coordinating Investigator will be selected based on overall contribution to the study and development program.

11.2 Institutional Review Board or Independent Ethics Committee Approval

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

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

11.3 Ethical Conduct of the Study

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

11.4 Patient Information and Consent/Assent

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

An informed consent form (assent form if applicable) that includes information about the study will be prepared and given to the patient or the patient's parent(s) or legally authorized representative(s). This document will contain all FDA and ICH-required elements.

The informed consent (or assent) form must be in a language understandable to the patient or the patient's parent (s) or legally authorized representative(s) and must specify who informed the patient, the patient's parent(s), or the patient's legally authorized representative(s). Patient assent will be obtained, as applicable.

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

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

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

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

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

11.5 Patient Confidentiality

Patient names will not be supplied to the Sponsor. Only the patient number and date of birth, as applicable per country regulations, will be recorded in the eCRF, and if the patient name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be told that representatives of the Sponsor, a designated CRO, the IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The Investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

11.6 Study Monitoring

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

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

11.7 Case Report Forms and Study Records

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

11.7.1 Critical Documents

Before Shire initiates the study (ie, obtains informed consent from the first patient), it is the responsibility of the Investigator to ensure that the following documents are available to Shire or their designee:

- Completed FDA Form 1572 (Statement of Investigator), signed, dated, and accurate
- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed within 24 months of study initiation)
- Current copy of Investigator and sub-investigator(s) medical license (indicating license number and expiration date)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed by name, number and date of approval or reapproval: protocol, any amendments, Subject Information/Informed Consent Form, and any other written information to be provided regarding subjects' recruitment procedures
- Copy of IRB/IEC approved Subject Information/Informed Consent Form/any other written information/advertisement (with IRB approval stamp and date of approval)
- Current list of IRB/IEC Committee members/constitution (dated within 12 months prior to study initiation)
- Financial Disclosure Form signed by Investigator and sub-investigator(s)
- Current laboratory reference ranges (if applicable)

- Certification/Quality Assurance scheme/other documentation (if applicable)

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

11.8 Data Safety Monitoring Board

An independent DSMB will be established to provide an ongoing, independent review and assessment of safety data, to safeguard the interests and safety of the patients participating in the study, and to make recommendations with respect to dose escalation and the start of Cohort 4. The DSMB will consist of 3 clinical experts.

The DSMB will adhere to a prospectively determined charter, which will be written by Shire and approved by the DSMB. The charter will define the responsibilities of the DSMB and Shire, describe the conduct and frequency of the meetings and define the data sets to be reviewed.

Planned DSMB meetings will occur prior to each dose escalation (see Section 6.5). A DSMB meeting will be held after completion of Cohorts 1-3. In addition, an ad hoc DSMB meeting will be convened if the safety-related study stopping rules are met (see Section 7.22).

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

11.9 Device Failure Review Process

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

11.10 Protocol Violations/Deviations

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

A record of patients screened, but not entered into the study, is also to be maintained. No protocol exemptions are to be allowed.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented

as a protocol deviation. Protocol deviations will need to be reviewed by the Medical Monitor and may also be required to be submitted to the IRB/IEC.

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

11.11 Premature Closure of the Study

If the Sponsor, Investigator, or regulatory authorities discover conditions arising during the study that indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation between the Sponsor and the Investigator(s).

In addition, a decision on the part of the Sponsor to suspend or discontinue development of the investigational drug product may be made at any time. It will be the responsibility of the Investigator(s) to promptly inform the study patients of any change in study status. Conditions that may warrant termination of the study or site include, but are not limited to the following:

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

11.12 Access to Source Documentation

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

11.13 Data Generation and Analysis

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

Adverse events will be coded using MedDRA. Concomitant medication will be coded using WHO-DD. Centralized laboratories will be employed as described in the study manual to aid in consistent measurement of efficacy outcome and safety parameters.

11.14 Retention of Data

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

11.15 Financial Disclosure

The Investigator should disclose any financial interests in the Sponsor as described in 21 CFR Part 54 prior to beginning this study. The appropriate form will be provided to the Investigator by the Sponsor, which will be signed and dated by the Investigator, prior to the start of the study.

11.16 Publication and Disclosure Policy

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

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

The Investigator and any other clinical personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with Shire and have provided Shire a copy of the draft document intended for publication. Shire's written consent for such publication is required to ensure that publication standards are met (eg, removal of any Shire confidential information (excluding study results), request for publication delay for to allow for patent filing). All information obtained during the conduct of this study will be regarded as confidential. Shire will use the information for registration purposes and for the general development of the drug.

12 LIST OF REFERENCES

1. Hans M, Pusch A, Dai L, et al. Lysosulfatide regulates the motility of a neural precursor cell line via calcium-mediated process collapse. Neurochem Res 2009;34:508-17.
2. Sugiyama E, Uemura K, Hara A, Taketomi T. Effects of various lysosphingolipids on cell growth, morphology and lipid composition in three neuroblastoma cell lines. Biochemical and biophysical research communications 1990;169:673-9.
3. Toda K, Kobayashi T, Goto I, et al. Lysosulfatide (sulfogalactosylsphingosine) accumulation in tissues from patients with metachromatic leukodystrophy. J Neurochem 1990;55:1585-91.
4. Liu HM. Ultrastructure of central nervous system lesions in metachromatic leukodystrophy with special reference to morphogenesis. J Neuropathol Exp Neurol 1968;27:624-44.
5. Berger J, Loschl B, Bernheimer H, et al. Occurrence, distribution, and phenotype of arylsulfatase A mutations in patients with metachromatic leukodystrophy. Am J Med Genet 1997;69:335-40.
6. Draghia R, Letourneur F, Drugan C, et al. Metachromatic leukodystrophy: identification of the first deletion in exon 1 and of nine novel point mutations in the arylsulfatase A gene. Human mutation 1997;9:234-42.
7. Gustavson KH, Hagberg B. The incidence and genetics of metachromatic leucodystrophy in northern Sweden. Acta Paediatr Scand 1971;60:585-90.
8. Heinisch U, Zlotogora J, Kafert S, Gieselmann V. Multiple mutations are responsible for the high frequency of metachromatic leukodystrophy in a small geographic area. Am J Hum Genet 1995;56:51-7.
9. Gieselmann V, Matzner U, Hess B, et al. Metachromatic leukodystrophy: molecular genetics and an animal model. Journal of inherited metabolic disease 1998;21:564-74.
10. Kolodny EH, Fluharty AL. Metachromatic leukodystrophy and multiple sulfatase deficiency: sulfatide lipidosis. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic basis of inherited disease. 7 ed. New York: McGraw-Hill; 1995:2693-739.
11. Hyde TM, Ziegler JC, Weinberger DR. Psychiatric disturbances in metachromatic leukodystrophy. Insights into the neurobiology of psychosis. Arch Neurol 1992;49:401-6.
12. Estrov Y, Scaglia F, Bodamer OA. Psychiatric symptoms of inherited metabolic disease. Journal of inherited metabolic disease 2000;23:2-6.
13. von Figura K, Gieselmann V, Jaeken J. Metachromatic Leukodystrophy. In: Charles Scriver AB, William Sly, David Valle, Barton Childs, Kenneth Kinzler, Bert Vogelstein, ed. The Metabolic and Molecular Basis of Inherited Disease. 8 ed: McGraw-Hill Professional; 2000:3695-723.
14. Sevin C, Aubourg P, Cartier N. Enzyme, cell and gene-based therapies for metachromatic leukodystrophy. Journal of inherited metabolic disease 2007;30:175-83.
15. Vellodi A. Lysosomal storage disorders. Br J Haematol 2005;128:413-31.

16. Hemsley KM, Beard H, King BM, Hopwood JJ. Effect of high dose, repeated intra-CSF injection of sulphamidase on neuropathology in MPS IIIA mice. Genes, Brain, and Behavior 2008:740-53.

17. Hemsley KM, Hopwood JJ. Delivery of recombinant proteins via the cerebrospinal fluid as a therapy option for neurodegenerative lysosomal storage diseases. Int J Clin Pharmacol Ther 2009;47 Suppl 1:S118-23.

18. Urayama A, Grubb JH, Sly WS, Banks WA. Mannose 6-phosphate receptor-mediated transport of sulfamidase across the blood-brain barrier in the newborn mouse. Molecular therapy : the journal of the American Society of Gene Therapy 2008;16:1261-6.

19. Munoz M, Horovitz D, Vieira T, et. a. Intrathecal enzyme replacement therapy in a child with mucopolysaccharidosis VI and symptomatic spinal cord compression. Ameri Soc of Hum Genet. San Diego, CA2007.

20. Muñoz-Rojas M, Dain D, Horovitz G, et al. Intrathecal administration of recombinant human N-acetylgalactosamine 4-sulfatase to a MPS VI patient with pachymeningitis cervicalis. Molecular Genetics and Metabolism 2010;99:346-50.

21. Dickson PI, Kaitila I, Harmatz P, et al. Safety of laronidase delivered into the spinal canal for treatment of cervical stenosis in mucopolysaccharidosis I. Mol Genet Metab 2015.

22. Chen A, Dickson P, Shapiro E, Lyons B, Kan S, Guillaume D. A study of intrathecal enzyme replacement for cognitivedecline in mucopolysaccharidosis. Mol Genet Metab 2010;99:S13-S4.

23. MacFaul R, Cavanagh N, Lake BD, Stephens R, Whitfield AE. Metachromatic leucodystrophy: review of 38 cases. Archives of disease in childhood 1982;57:168-75.

24. Kehrer C, Blumenstock G, Gieselmann V, Krageloh-Mann I. The natural course of gross motor deterioration in metachromatic leukodystrophy. Dev Med Child Neurol 2011;53:850-5.

25. Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products. Ref.EMEA/CHMP/SWP/28367/07 European Medicines Agency (EMA), 2007. (Accessed October 18, 2011, at http://www.emea.europa.eu/pdfs/human/swp/2836707enfin.pdf)

26. Estimating the Maximum Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers. United States Food and Drug Administration, Center for Drug Evaluation and Research (CDER): July; 2005.

27. Austin J, McAfee D, Armstrong D, O'Rourke M, Shearer L, Bachhawat B. Abnormal sulphatase activities in two human diseases (metachromatic leucodystrophy and gargoylism). The Biochemical journal 1964;93:15C-7C.

28. Neufeld E, Muenzer J. The Mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. New York: McGraw-Hill; 2001:3421-52.

29. Dekaban AS. Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. Annals of neurology 1978;4:345-56.

30. Farrell DF. Heterozygote detection in MLD. allelic mutations at the ARA locus. Hum Genet 1981;59:129-34.

31. Russell D, Rosenbaum P, Avery L, Lane M. The Gross Motor Function Measure (GMFM-66 and GMFM-88) User's Manual. London, UK: MacKeith Press; 2002.

32. Lundkvist Josenby A, Jarnlo GB, Gummesson C, Nordmark E. Longitudinal construct validity of the GMFM-88 total score and goal total score and the GMFM-66 score in a 5-year follow-up study. Phys Ther 2009;89:342-50.

33. Russell DJ, Rosenbaum PL, Cadman DT, Gowland C, Hardy S, Jarvis S. The gross motor function measure: a means to evaluate the effects of physical therapy. Developmental medicine and child neurology 1989;31:341-52.

34. Russell D, Palisano R, Walter S, et al. Evaluating motor function in children with Down syndrome: validity of the GMFM. Dev Med Child Neurol 1998;40:693-701.

35. Tieman BL, Palisano RJ, Sutlive AC. Assessment of motor development and function in preschool children. Ment Retard Dev Disabil Res Rev 2005;11:189-96.

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

Appendix 1 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]			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Serum PK sampling[l]			•																			•		
GMFM-88[i]			•								•						•						•	

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
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 of HGT-1110[f]			•		•		•		•		•		•		•		•		•		•		•	
Urinalysis	•		•		•		•		•		•		•		•		•		•		•		•	
Pregnancy testing[n]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Concomitant Medications/ Therapies/	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

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
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 patient'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 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 study drug.

[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] Patients will have the IDDD removed when they discontinue from or complete the study, unless the patient 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

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**

after the patient 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 patients in Cohort 4

j Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature measurements (to be measured when the patient 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 patient is asleep.

k Patients will undergo safety assessments, and if no safety concerns exist, will subsequently receive the EOW IT injection of HGT-1110. Patients 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 patient 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 patient's first dose. If a patient has a delay in 2 consecutive scheduled doses, the patient can receive doses as frequently as every 7 days until the patient 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 patient 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, patients 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 patient 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 patient 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

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

not participate in the Safety Follow-up visit, unless there is a delay in enrollment in the extension study.

Appendix 2 Study Schedule of Events: Cohort 4

Cohort 4																									
PHASE[a,b]	1	2/3	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	Eligibility 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]	-7 to 0	-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]				•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Serum PK sampling[l]				•																			•		
GMFM-88[i,m]	•	•	•	•								•						•						•	

Cohort 4																									
PHASE[a,b]	1	2/3	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	Eligibility 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]	-7 to 0	-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
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 of HGT-1110[f]				•		•		•		•		•		•		•		•		•		•		•	
Urinalysis	•			•		•		•		•		•		•		•		•		•		•		•	
Pregnancy testing[o]	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Concomitant Medications/ Therapies/	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Cohort 4																									
PHASE[a,b]	1	2/3	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	Eligibility 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]	-7 to 0	-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
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

[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. 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.

[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. In addition, at Weeks 16 and 28 the window for assessments will be -5 days.

[c] Written informed consent must be provided by the patient'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 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 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 study drug. Enrollment may occur prior to the IDDD implantation or the first dose (baseline); however, implantation of the device should occur within 28 days of the first dose.

[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] Patients will have the IDDD removed when they discontinue from or complete the study, unless the patient 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

Cohort 4																									
PHASE[a,b]	1	2/3	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	Eligibility 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]	-7 to 0	-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

the patient 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 patients in Cohort 4

j Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature measurements (to be measured when the patient 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 patient is asleep.

k Patients will undergo safety assessments, and if no safety concerns exist, will subsequently receive the EOW IT injection of HGT-1110. Patients 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 patient 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 patient's first dose. If a patient has a delay in 2 consecutive scheduled doses, the patient can receive doses as frequently as every 7 days until the patient 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 patient 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, patients 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 Upon confirmation of study eligibility (including the GMFM-88 assessment requiring a total GMFM-88 percent score ≥35 at baseline), 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. The baseline GMFM-88 assessment will be performed before device implantation or prior to first dose administration, whichever occurs first. If device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment, the baseline GMFM-88 assessment will not be required. However, if more than 7 days has passed since the screening GMFM-88 assessment, the baseline GMFM-88 assessment will need to be completed prior to IDDD implantation or first dose, and prior to any other baseline assessments in order to confirm eligibility for enrollment. Patients who do not continue to meet eligibility criteria will be discontinued from the study prior to device implantation and/or initial dosing.

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

o 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

Cohort 4																									
PHASE[a,b]	1	2/3	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	Eligibility 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]	-7 to 0	-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

urine test is positive, results will be confirmed with a serum pregnancy test.

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

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

[r] Follow-up safety assessments may be performed via telephone from the clinical site. If a patient 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.

Appendix 3 Expected Adverse Device Effects

The information in this appendix was taken from the SOPH-A-PORT Mini S intrathecal drug delivery device Instructions for Use.

Procedure-Related Complications

- Components handled improperly before, during, or after implantation
- Access port implanted incorrectly
- Catheter positioned improperly
- Injection through septum performed incorrectly
- Injection of incorrect medication through access port
- Injection outside the access port into pocket or subcutaneous tissue or extravasation
- Pocket seroma, hematoma, erosion, or infection

Intrathecal Access Complications

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

System-Related Complications

- Improperly positioned access port
- Erosion of the skin because of the underlying access port or the catheter
- Wound dehiscence

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

Appendix 4 Protocol Signature Page

Study Title: A Phase I/II, Multicenter Open-label Dose Escalation Study of HGT-1110 Administered Intrathecally in Children with Metachromatic Leukodystrophy

Study Number: HGT-MLD-070

Amendment: 9

Final Date: 26 August 2015

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.

Signatory:

Shire Medical Monitor

PPD _____ PPD
Signature **Date**

PPD , MD
Printed Name

Appendix 5 Summary of Changes for Amendment 9

Justification for the Amendment and Summary of Changes

The HGT-MLD-070 protocol is primarily being amended to update the study design prior to enrollment start for Cohort 4, which will evaluate the HGT-1110 investigational drug product produced with the revised drug substance manufacturing process (referred to as Process B). A DSMB meeting will be held after completion of Cohorts 1-3.

Approximately 24 patients, including approximately 6 patients in Cohort 4, will be enrolled in the study. The revised study design for Cohort 4 will change the age inclusion criterion (from <12 years of age to <8 years of age); enroll patients with GMFM-88 total score (percent) ≥40 at screening with eligibility confirmed at baseline with a GMFM-88 score ≥35 and an additional inclusion criteria based on the walking dimension of the GMFM-88; permit patients to initiate treatment via lumbar puncture, if IDDD implantation is delayed; and allow use of local laboratories to confirm MLD diagnosis and eligibility with central laboratory confirmation.

Other changes in this amendment include, but are not limited to, the addition of information regarding the new Medical Monitor; an increase in blood volume collected at Screening for Cohort 4, updates to information regarding studies with IT treatment, including the list of Shire-sponsored studies in other intrathecal programs, and clarification regarding statistical methodology language.

Changes in grammar, spelling, punctuation, format, minor editorial changes (including changes for consistency and clarity), and updates to the list of abbreviations and cross-references are not reflected in the list above or in the Detailed Summary of Changes, which follows.

Detailed Summary of Changes from Amendment 9

The changes from the previous protocol version are detailed below and include changes and additions to the protocol text. **Bold** text indicates new text. ~~Strikethrough~~ text indicates deleted text. Only those changes that are associated with each purpose are indicated with bold and strikethrough text.

Purpose: To update the medical monitor information.	
Primary Section Impacted By This Change: Title Page	
Formerly read	… Medical Monitor: PPD, MD …
Now reads	… Medical Monitor: PPD, MD …
Other Sections Impacted By This Change: • Section 7.18.6, Procedures for Recording and Reporting Adverse Events • Appendix 4, Protocol Signature Page	

Purpose: To update information regarding studies with IT treatment, including the list of Shire-sponsored studies in other intrathecal programs	
Primary Section Impacted By This Change: Section 1.2.1, Current Therapeutic Options	
Formerly read	… Several patients with MPS I have been treated since 2005 with IT laronidase (recombinant α-L-iduronidase) in a clinical trial (ClinicalTrials.gov identifiers NCT00215527, NCT00786968) studying efficacy on spinal cord compression. ~~No results of this trial have yet been published.~~ ~~However, in June 2009~~ a study further investigating the effectiveness of IT ERT as a treatment for another neurological symptom in MPS I, cognitive decline, ~~was initiated~~ (ClinicalTrials.gov identifier NCT00852358). ~~This study is a 24-month, open-label, prospective, randomized trial in 16 patients with MPS I, 6 years of age or older, who have documented evidence of cognitive decline. The clinical safety of the regimen will be assessed by AE monitoring, CSF laboratory assessments, and clinical evaluations.~~[21] The following describes the ~~7~~ Shire Human Genetic Therapies, Inc. (Shire)–sponsored IT studies other than HGT-MLD-070: • a Phase I/II open-label extension of study HGT-MLD-070 evaluating long term safety and efficacy of IT administration of HGT-1110 in patients with MLD (HGT-MLD-071)

Purpose: To update information regarding studies with IT treatment, including the list of Shire-sponsored studies in other intrathecal programs	
	• a Phase I/II safety and dose escalation study of monthly idursulfase-IT intrathecal injection for cognitively impaired patients with Hunter syndrome (Study HGT-HIT-045; NCT00920647), and the open-label extension to this study (HGT-HIT-046; NCT01506141) • a Phase II/III controlled, randomized, two-arm open-label, assessor-blinded study of idursulfase-IT administered in conjunction with Elaprase® in pediatric patients with Hunter Syndrome and early cognitive impairment (Study HGT-HIT-094) • a Phase I/II ascending dose and dose frequency study of monthly IT injection of recombinant human heparan N-sulfatase (rhHNS) in patients with Sanfilippo Syndrome Type A (Study HGT-SAN-055; NCT01155778), and the open-label extension to this study (HGT-SAN-067; NCT 01299727) • a Phase IIb, randomized, controlled, open-label, multicenter, safety and efficacy study of HGT-1410 (recombinant heparan N-sulfatase) administration via an intrathecal drug delivery device in pediatric patients with early stage mucopolysaccharidosis Type IIIA disease (Study HGT-SAN-093) …
Now reads	… Several patients with MPS I have been treated since 2005 with IT laronidase (recombinant α-L-iduronidase) in a clinical trial (ClinicalTrials.gov identifiers NCT00215527, NCT00786968) studying efficacy on spinal cord compression. **This study has been terminated**.[21] **A** study further investigating the effectiveness of IT ERT as a treatment for another neurological symptom in MPS I, cognitive decline, **is ongoing** (ClinicalTrials.gov identifier NCT00852358).[22] The following describes the **9** Shire Human Genetic Therapies, Inc. (Shire)–sponsored IT studies other than HGT-MLD-070: • a Phase I/II open-label extension of study HGT-MLD-070 evaluating long term safety and efficacy of IT administration of HGT-1110 in patients with MLD (HGT-MLD-071) • a Phase I/II safety and dose escalation study of monthly idursulfase-IT intrathecal injection for cognitively impaired patients with Hunter syndrome (Study HGT-HIT-045;

Purpose: To update information regarding studies with IT treatment, including the list of Shire-sponsored studies in other intrathecal programs	
	NCT00920647), and the open-label extension to this study (HGT-HIT-046; NCT01506141) • a Phase II/III controlled, randomized, two-arm open-label, assessor-blinded study of idursulfase-IT administered in conjunction with Elaprase® in pediatric patients with Hunter Syndrome and early cognitive impairment (Study HGT-HIT-094**; NCT02055118) and the open-label extension to this study (Study SHP-609-302; NCT02412787**) • a Phase I/II ascending dose and dose frequency study of monthly IT injection of recombinant human heparan N-sulfatase (rhHNS) in patients with Sanfilippo Syndrome Type A (Study HGT-SAN-055; NCT01155778), and the open-label extension to this study (HGT-SAN-067; NCT 01299727) • a Phase IIb, randomized, controlled, open-label, multicenter, safety and efficacy study of HGT-1410 (recombinant heparan N-sulfatase) administration via an intrathecal drug delivery device in pediatric patients with early stage mucopolysaccharidosis Type IIIA disease (Study HGT-SAN-093**; NCT02060526) and the open-label extension to this study (Study SHP-610-201; NCT02350816**) …
Other Sections Impacted By This Change: N/A	

Purpose: To update the study design to require GMFM-88 evaluation at screening and baseline and to allow for dosing with study medication as soon as possible by allowing use of LP and the use of local laboratory results to confirm MLD diagnosis prior to receipt of central laboratory results	
Primary Section Impacted By This Change: Section 4.1, Overall Study Design and Plan	
Formerly read	… This study will have the following 5 phases: **Phase 1: Screening: Day -40 through Day -11** Upon obtaining informed consent, the procedures and assessments required for the determination of the patient's eligibility will be completed at the clinical site within 40 days of the baseline visit (Week 0). Sample collection for diagnostic testing should take place between Day -40 and Day -29 to ensure diagnostic results are

Purpose: To update the study design to require GMFM-88 evaluation at screening and baseline and to allow for dosing with study medication as soon as possible by allowing use of LP and the use of local laboratory results to confirm MLD diagnosis prior to receipt of central laboratory results	
	received prior to IDDD implantation in Phase 2 of the study. Sites will be allowed one opportunity to re-screen any patient who fails initial screening or withdraws consent prior to device implantation. If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study. **Phase 2: Surgical Implantation of the IDDD: Day -10 to Day -1** Patients will undergo surgical implantation of an IDDD and a post-surgical assessment. **Phase 3: Baseline and Treatment Week 0 to Week 38 (±3 days for injection of HGT-1110)** Upon confirmation of study eligibility, baseline assessments (ie, those scheduled for Week 0) may be performed at any time prior to dosing, including the Phase 2 period of the study, but baseline assessments should be performed as close to dosing as possible. Patients will undergo pre-dose baseline assessments at Week 0, which will include a standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis), serum assessments of anti-HGT-1110 antibodies and CSF assessments (cell counts, protein, glucose, albumin, anti-HGT-1110 antibodies, and HGT-1110 levels) as well as safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures assessments). Baseline efficacy outcome assessments including the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS will be performed as well as sample collection for CSF, serum, and urine biomarker assessments. Patients will receive their first dose (Week 0) and begin the HGT-1110 EOW dosing period (through Week 38). At Week 0, blood will also be drawn for a PK assessment at the time points specified in the Schedule of Events. During the EOW treatment period (Weeks 2 through 38), all assessments will be performed prior to IT injection of HGT-1110 unless otherwise indicated. Safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures

Purpose: To update the study design to require GMFM-88 evaluation at screening and baseline and to allow for dosing with study medication as soon as possible by allowing use of LP and the use of local laboratory results to confirm MLD diagnosis prior to receipt of central laboratory results	
	assessments) will be performed. Patients 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. Additionally, anti-HGT-1110 antibody sampling, the standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis) and sample collection for analysis of CSF concentration of HGT-1110, and CSF, serum, and urine biomarkers will be performed every 4 weeks. In addition to the scheduled assessments performed Weeks 2 through 38, Weeks 16 and 28 will also include the efficacy outcome assessments of the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS. For Weeks 16 and 28, the window for assessments will be -5 days. In addition, at Week 38 blood will be drawn for a PK assessment at the time points specified in the Schedule of Events. It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all 20 IT injections of HGT-1110. If the IT space is not accessible via the IDDD, investigational drug product may be administered by LP. Should the IDDD become clogged, undergo mechanical complications or otherwise not be accessible, the CSF sample may also be obtained by LP. Anesthesia may be required for injections of investigational drug product and some evaluations, and can be used at the discretion of the Investigator. The IDDD Manual provides details on the investigation and management of any IDDD-related issues. …
Now reads	… This study will have the following 5 phases: **<u>Cohorts 1-3: Phases 1-3</u>** **Phase 1: Screening: Day -40 through Day -11** Upon obtaining informed consent, the procedures and assessments required for the determination of the patient's eligibility will be completed at the clinical site within 40 days of the baseline visit (Week 0). Sample collection for diagnostic testing should take place between Day -40 and Day -29 to ensure diagnostic results are

Purpose: To update the study design to require GMFM-88 evaluation at screening and baseline and to allow for dosing with study medication as soon as possible by allowing use of LP and the use of local laboratory results to confirm MLD diagnosis prior to receipt of central laboratory results	
	received prior to IDDD implantation in Phase 2 of the study. Sites will be allowed one opportunity to re-screen any patient who fails initial screening or withdraws consent prior to device implantation. If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study. **Phase 2: Surgical Implantation of the IDDD: Day -10 to Day -1** Patients will undergo surgical implantation of an IDDD and a post-surgical assessment. **Phase 3: Baseline and Treatment Week 0 to Week 38 (±3 days for injection of HGT-1110)** Upon confirmation of study eligibility, baseline assessments (ie, those scheduled for Week 0) may be performed at any time prior to dosing, including the Phase 2 period of the study, but baseline assessments should be performed as close to dosing as possible. Patients will undergo pre-dose baseline assessments at Week 0, which will include a standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis), serum assessments of anti-HGT-1110 antibodies and CSF assessments (cell counts, protein, glucose, albumin, anti-HGT-1110 antibodies, and HGT-1110 levels) as well as safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures assessments). Baseline efficacy outcome assessments including the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS will be performed as well as sample collection for CSF, serum, and urine biomarker assessments. Patients will receive their first dose (Week 0) and begin the HGT-1110 EOW dosing period (through Week 38). At Week 0, blood will also be drawn for a PK assessment at the time points specified in the Schedule of Events. During the EOW treatment period (Weeks 2 through 38), all assessments will be performed prior to IT injection of HGT-1110 unless otherwise indicated. Safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures

Purpose: To update the study design to require GMFM-88 evaluation at screening and baseline and to allow for dosing with study medication as soon as possible by allowing use of LP and the use of local laboratory results to confirm MLD diagnosis prior to receipt of central laboratory results	
	assessments) will be performed. Patients 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. Additionally, anti-HGT-1110 antibody sampling, the standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis) and sample collection for analysis of CSF concentration of HGT-1110, and CSF, serum, and urine biomarkers will be performed every 4 weeks. In addition to the scheduled assessments performed Weeks 2 through 38, Weeks 16 and 28 will also include the efficacy outcome assessments of the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS. For Weeks 16 and 28, the window for assessments will be -5 days. In addition, at Week 38 blood will be drawn for a PK assessment at the time points specified in the Schedule of Events. It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all 20 IT injections of HGT-1110. If the IT space is not accessible via the IDDD, investigational drug product may be administered by LP. Should the IDDD become clogged, undergo mechanical complications or otherwise not be accessible, the CSF sample may also be obtained by LP. Anesthesia may be required for injections of investigational drug product and some evaluations, and can be used at the discretion of the Investigator. The IDDD Manual provides details on the investigation and management of any IDDD-related issues. **<u>Cohort 4: Phases 1-3</u>** **Note: Enrollment may occur prior to IDDD implantation <u>or</u> the first dose (baseline); however, implantation of the device should occur within 28 days of the first dose.** **Phase 1: Screening: Day-40 through Day -1** **Upon obtaining informed consent, the procedures and assessments required for the determination of the patient's eligibility, including GMFM-88, will be completed at the clinical site within 40 days prior to the baseline visit (Week 0). Sample collection for central diagnostic testing should take place at the screening visit to ensure diagnostic results are received promptly. Local laboratory results confirming the MLD**

Purpose: To update the study design to require GMFM-88 evaluation at screening and baseline and to allow for dosing with study medication as soon as possible by allowing use of LP and the use of local laboratory results to confirm MLD diagnosis prior to receipt of central laboratory results	
	diagnosis (analysis of urine sulfatide, ASA activity in leukocytes) will be accepted to confirm the MLD diagnosis enrollment criteria while waiting for the central laboratory results so that dosing of the study medication can occur as soon as possible. **Sites will be allowed one opportunity to re-screen any patient who fails initial screening or withdraws consent prior to device implantation or dose administration (if administration to be initiated by LP prior to device implantation). If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study.** **Phase 2: Surgical Implantation of the IDDD: Day -10 to Day +28** **To confirm the patient meets eligibility criteria at baseline, specifically the baseline GMFM-88 assessment will be performed as close as possible to, but before device implantation or prior to first dose administration, whichever occurs first. Patients who do not continue to meet eligibility criteria will be discontinued from the study prior to device implantation and/or initial dosing. If device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment, the baseline GMFM-88 assessment will not be required. However, if more than 7 days has passed since the screening GMFM-88 assessment, the baseline GMFM-88 assessment will need to be completed prior to IDDD implantation or first dose, and prior to any other baseline assessments in order to confirm eligibility for enrollment (per inclusion criterion 3.1 in Section 5.2).** **Upon confirmation of eligibility, patients will undergo surgical implantation of an IDDD and a post-surgical assessment. The patient may receive study drug by LP until the device is implanted. Device implantation should be scheduled within 28 days of enrollment unless a delay is required due to clinical judgment for medical reasons (eg, infection).** **Phase 3: Baseline and Treatment Week 0 to Week 38 (±3 days for injection of HGT-1110)** **Upon confirmation of study eligibility, baseline assessments (ie, those scheduled for Week 0) may be performed at any time prior to dosing, including the Phase 2 period of the study, but baseline assessments should be performed as close to dosing as**

Purpose: To update the study design to require GMFM-88 evaluation at screening and baseline and to allow for dosing with study medication as soon as possible by allowing use of LP and the use of local laboratory results to confirm MLD diagnosis prior to receipt of central laboratory results	
	possible. Patients will undergo pre-dose baseline assessments at Week 0, which will include a standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis), serum assessments of anti-HGT-1110 antibodies and CSF assessments (cell counts, protein, glucose, albumin, anti-HGT-1110 antibodies, and HGT-1110 levels) as well as safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures assessments). **Baseline efficacy outcome assessments including the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS will be performed as well as sample collection for CSF, serum, and urine biomarker assessments. If device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment, the baseline GMFM-88 assessment will not be required.** **Patients will receive their first dose (Week 0) and begin the HGT-1110 EOW dosing period (through Week 38). At Week 0, blood will also be drawn for a PK assessment at the time points specified in the Schedule of Events.** **During the EOW treatment period (Weeks 2 through 38), all assessments will be performed prior to IT injection of HGT-1110 unless otherwise indicated. Safety assessments (ie, vital signs, physical examination, routine CSF analysis, pregnancy testing [if applicable], AEs, and concomitant medication/therapies/procedures assessments) will be performed. Patients 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. Additionally, anti-HGT-1110 antibody sampling, the standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis) and sample collection for analysis of CSF concentration of HGT-1110, and CSF, serum, and urine biomarkers will be performed every 4 weeks.** **In addition to the scheduled assessments performed Weeks 2 through 38, Weeks 16 and 28 will also include the efficacy outcome assessments of the GMFM-88, FEES, ENG studies, VABS-II, COMFORT questionnaire, and brain MRI and MRS. For Weeks 16 and 28, the window for assessments will be -5**

Purpose: To update the study design to require GMFM-88 evaluation at screening and baseline and to allow for dosing with study medication as soon as possible by allowing use of LP and the use of local laboratory results to confirm MLD diagnosis prior to receipt of central laboratory results	
	days. In addition, at Week 38 blood will be drawn for a PK assessment at the time points specified in the Schedule of Events. **It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all 20 IT injections of HGT-1110. 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.** **If the IT space is not accessible via the IDDD, investigational drug product may be administered by LP. Should the IDDD become clogged, undergo mechanical complications or otherwise not be accessible, the CSF sample may also be obtained by LP until the device is repaired or replaced. Anesthesia may be required for injections of investigational drug product and some evaluations, and can be used at the discretion of the Investigator. The IDDD Manual provides details on the investigation and management of any IDDD-related issues.** **<u>All Cohorts (1-4): Phases 4 and 5</u>** …

Purpose: To update the study design to require GMFM-88 evaluation at screening and baseline and to allow for dosing with study medication as soon as possible by allowing use of LP and the use of local laboratory results to confirm MLD diagnosis prior to receipt of central laboratory results
Other Sections Impacted By This Change: • Synopsis • Section 6.2, Treatment Administered • Section 7.9.4, Intrathecal Drug Delivery Device Removal • Section 7.10, Investigational Drug Product Administration • Section 7.11, Pharmacokinetic Assessments • Section 7.13.2, Vital Signs • Section 8, Study Activities • Section 8.1, Phase 1: Screening (Days -40 to -11 for Cohorts 1-3; Days -40 to Day -1 for Cohort 4) • Section 8.2, Phase 2: IDDD Implantation (Day -10 to Day -1 for Cohorts 1-3; Days -10 to Day +28 for Cohort 4) • Section 8.3.1, Baseline: Week 0 (±3 days for IT injection of HGT-1110) • Appendix 1, Study Schedule of Events: Cohorts 1, 2, and 3 • Appendix 2, Study Schedule of Events: Cohort 4

Purpose: To clarify that approximately 24 patients are planned for this study, based on the number of patients enrolled in Study HGT-MLD-070	
Primary Section Impacted By This Change: Section 5.1, Study Population	
Formerly read	~~Up to~~ 24 patients are planned who are less than 12 years of age with a confirmed diagnosis of MLD, 6 per cohort. Patients must be ambulatory at the time of screening and untreated with investigational drug products for MLD.
Now reads	**Approximately** 24 patients are planned who are less than 12 years of age with a confirmed diagnosis of MLD, **approximately** 6 per cohort. Patients must be ambulatory at the time of screening and untreated with investigational drug products for MLD.
Other Sections Impacted By This Change: • Synopsis • Section 10.2, Determination of Sample Size	

<table>
<tr><td colspan="2">Purpose: To revise the inclusion criteria to require that patients are less than 8 years of age and to revise the GMFM-88 requirements at screening and baseline</td></tr>
<tr><td colspan="2">Primary Section Impacted By This Change: Section 5.2, Inclusion Criteria</td></tr>
<tr><td>Formerly read</td><td>Patients must meet all of the following criteria to be considered eligible for enrollment:

1. Confirmed diagnosis of metachromatic leukodystrophy by both:
• Arylsulfatase A (ASA) deficiency by assay in leukocytes
AND
• Elevated sulfatide in urine
2. Appearance of the first symptoms of disease at or before 30 months of age.
3. Ambulatory at the time of screening. The minimum level of function required to meet this criterion is defined as the ability to walk forward 10 steps with one hand held.
4. The patient is less than 12 years of age at the time of screening.
5. Neurological signs of MLD must be present at the screening
…</td></tr>
<tr><td>Now reads</td><td>Patients must meet all of the following criteria to be considered eligible for enrollment:

For Cohorts 1-4:

1. Confirmed diagnosis of metachromatic leukodystrophy by both:
• Arylsulfatase A (ASA) deficiency by assay in leukocytes
AND
• Elevated sulfatide in urine
2. Appearance of the first symptoms of disease at or before 30 months of age.
For Cohorts 1-3 only:
3. Ambulatory at the time of screening. The minimum level of function required to meet this criterion is defined as the ability to walk forward 10 steps with one hand held.
4. The patient is less than 12 years of age at the time of screening.
For Cohort 4 only:
3.1 Minimum motor function requirements:
a. A total GMFM-88 (percent) score ≥40 at the screening examination and a total GMFM-88 (percent) score ≥35 at the baseline examination,</td></tr>
</table>

Purpose: To revise the inclusion criteria to require that patients are less than 8 years of age and to revise the GMFM-88 requirements at screening and baseline	
	AND b. **GMFM-88 Dimension E: Walking, Running & Jumping, item 68 ("walk forward 10 steps with one hand held") score of at least 1 "initiates" at the screening and baseline examinations (if applicable).** **4.1. The patient is less than 8 years of age at the time of screening.** **For Cohorts 1-4:** 5. Neurological signs of MLD must be present at the screening …
Other Sections Impacted By This Change: • Synopsis • Section 4.1, Overall Study Design and Plan • Section 7.4, Study Enrollment	

Purpose: To indicate that no restrictions are made regarding the patient's symptomatic MLD treatment	
Primary Section Impacted By This Change: Section 6.6, Concomitant Medications, Therapies, and Medical/Surgical Interventions	
Removed text:	… ~~Every effort should be made to keep the patient's symptomatic MLD treatment constant throughout the study. However,~~ **C**hanges in medications are acceptable if necessary according to clinical judgment. All changes will be recorded on the appropriate eCRF. Concomitant medications will be coded using World Health Organization – Drug Dictionary (WHO-DD).
Other Sections Impacted By This Change: • NA	

<table>
<tr><td colspan="2">Purpose: To allow for dosing with study drug based on central laboratory results and provide clarification regarding what action should be taken if the central and local laboratory results are not aligned.</td></tr>
<tr><td colspan="2">Primary Section Impacted By This Change: Section 7.3, Confirmation of Study Eligibility and MLD Diagnosis and Genotype</td></tr>
<tr><td>Formerly read</td><td>Patient eligibility according to the study inclusion and exclusion criteria will be assessed during the Screening period. Sites will be allowed one opportunity to re-screen any patient who fails initial screening or withdraws consent prior to device implantation. If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study.

Assays for leukocyte arylsulfatase A enzyme activity, urine sulfatide, and genotype determination will be performed by specialty laboratory(ies) designated by Shire to confirm the diagnosis of MLD.[5,30] Biochemical confirmation of MLD diagnosis is required for study eligibility, but genotype results are not.

Local leukocyte arylsulfatase A enzyme activity and urine sulfatide information will be allowed to confirm the diagnosis of MLD, if available and deemed sufficient by the Principal Investigator and Medical Monitor. Sample collection for diagnostic testing will still be performed if local results are used to confirm the diagnosis of MLD.</td></tr>
<tr><td>Now reads</td><td><u>Cohorts 1-3:</u>

Patient eligibility according to the study inclusion and exclusion criteria will be assessed during the Screening period. Sites will be allowed one opportunity to re-screen any patient who fails initial screening or withdraws consent prior to device implantation). If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study.

Assays for leukocyte arylsulfatase A enzyme activity, urine sulfatide, and genotype determination will be performed by specialty laboratory(ies) designated by Shire to confirm the diagnosis of MLD.[5,30] Biochemical confirmation of MLD diagnosis is required for study eligibility, but genotype results are not.

Local leukocyte arylsulfatase A enzyme activity and urine sulfatide will be allowed to confirm the diagnosis of MLD, if available and deemed sufficient by the Principal Investigator and Medical Monitor. Sample collection for diagnostic testing will still be performed if local results are used to confirm the diagnosis of MLD.

<u>Cohort 4:</u></td></tr>
</table>

	Patient eligibility according to the study inclusion and exclusion criteria will be assessed during the Screening period. Sites will be allowed one opportunity to re-screen any patient who fails initial screening or withdraws consent prior to device implantation or dose administration (if administration to be initiated by LP prior to device implantation. If the patient subsequently screen fails, the patient will no longer be considered for inclusion in the study. **Assays for leukocyte arylsulfatase A enzyme activity, urine sulfatide, and genotype determination will be performed by specialty laboratory(ies) designated by Shire to confirm the diagnosis of MLD.[5,30] Biochemical confirmation of MLD diagnosis is required for study eligibility, but genotype results are not.** **Local laboratory results for leukocyte arylsulfatase A enzyme activity and urine sulfatide will be allowed to confirm the diagnosis of MLD, 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 used to confirm the diagnosis of MLD. If local laboratory results are not in agreement with central laboratory results and the patient has already been dosed with study medication and/or has received device implantation, then the central laboratory tests will be repeated. If repeat central laboratory results confirm a positive local laboratory result then the patient will continue in the study. However, if the repeat central laboratory results are in discordance with the local laboratory results then the Investigator must contact the Shire Medical Monitor to evaluate what action should be taken regarding this patient. Dosing will be stopped if the Investigator and Medical Monitor determine that the patient does not have a diagnosis of MLD; however, such a patient would still be followed for safety.** **To confirm the patient meets eligibility criteria at baseline, the baseline GMFM-88 assessment will be performed as close as possible to, but before device implantation or prior to first dose administration, whichever occurs first. Patients who do not continue to meet eligibility criteria will be discontinued from the study prior to device implantation and/or initial dosing. If device implantation and/or initial dosing occur within 7 days of the screening GMFM-88 assessment, the baseline GMFM-88 assessment will not be required.**

Other Sections Impacted By This Change: • Synopsis • Appendix 2, Study Schedule of Events: Cohort 4

Purpose: To specify that device explantation occur at the main site unless urgent device removal requires otherwise	
Primary Section Impacted By This Change: Section 7.9.1, Intrathecal Drug Delivery Device Implantation, Replacement, or Revision	
Added text:	The IDDD will be surgically implanted at the clinical site. Procedures for implantation will be detailed in the device's IFU Manual. Standard hospital procedures for surgery will be followed; the patient may be under general anesthesia for this procedure. **It is planned that device explantation will occur at the main site unless urgent device removal is medically required to be performed locally or patient travel to the main site is medically inadvisable.** …
Other Sections Impacted By This Change: • NA	

Purpose: To clarify the intrathecal drug delivery device removal process	
Primary Section Impacted By This Change: Section7.9.4, Intrathecal Drug Delivery Device Removal	
Formerly read:	If at the time of a scheduled dosing it is not possible to administer a full medication dosage ~~as per~~ the standard administration steps detailed in the device's IFU~~ due to a device-related issue~~, the IDDD will be declared a device malfunction. If the device malfunction is irreversible and cannot be corrected without a device ~~surgical intervention~~, the IDDD will be declared a device failure, starting from the date of the initial malfunction. **…**
Now reads	If at the time of a scheduled dosing**, due to a device-related issue** it is not possible to **aspirate CSF prior to dose administration,** administer a full medication dosage **using** the standard administration steps detailed in the device's IFU, **or flush the system following dose administration,** the IDDD will be declared a device malfunction. If the device malfunction is irreversible and cannot be corrected without a **partial or full** device **revision or removal**, the IDDD will be declared a

Purpose: To clarify the intrathecal drug delivery device removal process	
	device failure, starting from the date of the initial malfunction. …
Other Sections Impacted By This Change: • NA	

Purpose: Blood collection volume at Screening was increased for patients in Cohort 4 due to a change in the ASA sample collection and handling process	
Primary Section Impacted By This Change: Section 7.13.4, Clinical Laboratory Tests	
Formerly read:	… The Screening and Baseline visit will require approximately 24 and 20 mL of blood for all patients, respectively. The remaining visits will require approximately 11 mL of blood for the required assessments (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 38, and 40). Approximately 7 mL of CSF will be drawn to approximate the volume of investigational drug product and flush to be injected. The CSF will be used for required and optional assessments at each treatment visit and the EOS visit.
Now reads	… The Screening and Baseline visit will require approximately 24 and 20 mL of blood for all patients **in Cohorts 1-3**, respectively**, and 28 and 20 mL of blood, respectively, for patients in Cohort 4**. The remaining visits will require approximately 11 mL of blood for the required assessments (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 38, and 40). Approximately 7 mL of CSF will be drawn to approximate the volume of investigational drug product and flush to be injected. The CSF will be used for required and optional assessments at each treatment visit and the EOS visit.
Other Sections Impacted By This Change: • NA	

Purpose: To define device adjustment	
Primary Section Impacted By This Change: Section 7.18.2.4, Device Adjustment	
Added section:	**Surgery of the device which does not result in partial or complete device revision or removal (eg, surgical exploration only or placement of additional sutures, tissue glue, and/or fascial repair).**
Other Sections Impacted By This Change: • NA	

Purpose: Clarification of device-related adverse events	
Primary Section Impacted By This Change: Section 7.18.5.1, Adverse Events with Respect to Investigational Drug Product, Investigational Drug Product Administration, Device, and Associated Procedures	
Formerly read:	**DEVICE SURGICAL PROCEDURE–RELATED ADVERSE EVENTS** Examples of AEs related to device surgical procedures include, but are not limited to, the following: events that occur during or shortly following IDDD implant/explant, IDDD adjustment, full revision, partial revision, IDDD removal, and delayed re-implantation after previous IDDD removal (such as complications of anesthesia, excessive bleeding, wound hematoma), and post-operative complications (such as post-operative infection). These events are related to the surgical procedure itself. **INTRATHECAL DRUG DELIVERY DEVICE–RELATED ADVERSE EVENTS** Examples of AEs related to use of the IDDD include, but are not limited to, the following: device failure, device malfunction, incorrect connection of IDDD components, erosion of the portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, migration of the portal/catheter, and occlusion of the portal/catheter, portal site or subcutaneous tract infection. A malfunction of the device (defined in Section 7.18.2.2) should not be entered as an AE unless it has physiological consequences. In the event of a device failure (defined in Section 7.18.2.3), the device ~~may~~ need to be replaced or repaired. ~~If overnight hospitalization is required for such a procedure (or the device failure meets any other serious criteria, eg, medically important), the device failure will be reported as an SAE.~~ Details of the cause of the IDDD malfunction or failure will be recorded on the device malfunction and failure eCRF, and the SAE form (where applicable). A list of the most common IDDD AEs is included in Appendix ~~2~~.

Purpose: Clarification of device-related adverse events	
	…
Now reads	**DEVICE SURGICAL PROCEDURE–RELATED ADVERSE EVENTS** Examples of AEs related to device surgical procedures include, but are not limited to, the **physiologic consequences of the** following: events that occur during or shortly following IDDD implant/explant, IDDD adjustment, full revision, partial revision, IDDD removal, and delayed re-implantation after previous IDDD removal (such as complications of anesthesia, excessive bleeding, wound hematoma), and post-operative complications (such as post-operative infection). These events are related to the surgical procedure itself. **INTRATHECAL DRUG DELIVERY DEVICE–RELATED ADVERSE EVENTS** Examples of AEs related to use of the IDDD include, but are not limited to, **the physiologic consequences (noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes) of** the following: device failure, device malfunction, incorrect connection of IDDD components, erosion of the portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, migration of the portal/catheter, and occlusion of the portal/catheter, portal site or subcutaneous tract infection. A malfunction of the device (defined in Section 7.18.2.2) should not be entered as an AE unless it has physiological consequences. In the event of a device failure (defined in Section 7.18.2.3), the device **will** need to be replaced or repaired **by removal and replacement of a component or removed in its entirety. "Device failure" will be reported as the SAE term**. Details of the cause of the IDDD malfunction or failure will be recorded on the device malfunction and failure eCRF, and the SAE form (where applicable). A list of the most common IDDD AEs is included in **the list of complications in** Appendix **3** **…**
Other Sections Impacted By This Change: • NA	

Purpose: To clarify the statistical methodology language	
Primary Section Impacted By This Change: Section 10.1, General Methodology	
Formerly read	All statistical analyses will be performed by the Shire Biometrics department (with the exception of the PK analysis, which will be performed by the Shire Clinical Pharmacology and Pharmacokinetics department). **S**tatistical analyses will be performed using SAS® software Version 9.3 or higher. Data will be summarized by cohort and overall, if appropriate. Summary statistics for continuous variables will include the number of patients, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized in a contingency table by the number and percentage of patients in each category (including a missing category, if applicable). Any statistical tests comparing cohorts will be 2-sided with a significance level of 0.05 and considered hypothesis generating. The mean change, mean difference in the change between cohorts, and the corresponding 95% confidence intervals, may also be presented as 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 laboratory values. Any analyses of safety and PK summarizing Cohort 3 and Cohort 4 (Process A and Process B) will be descriptive.
Now reads	All statistical analyses will be performed by the Shire Biometrics department (with the exception of the PK analysis, which will be performed by the Shire Clinical Pharmacology and Pharmacokinetics department). **S**tatistical analyses will be performed using SAS® software Version 9.3 or higher. Data will be summarized by cohort and overall, if appropriate. Summary statistics for continuous variables will include the number of patients, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized in a contingency table by the number and percentage of patients in each category (including a missing category, if applicable). Any statistical tests comparing cohorts will be 2-sided with a significance level of 0.05 and considered **exploratory or** hypothesis generating. The mean change, mean difference in the change between cohorts, and the corresponding 95% confidence intervals, may also be presented as 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 laboratory values. Any analyses of safety and PK summarizing Cohort 3 and Cohort 4 (Process A and Process B) will be descriptive.

Other Sections Impacted By This Change: • Synopsis • Section 10.13, Secondary Analyses

Purpose: To remove detailed statistical methodology language, which will be added to the Statistical Analysis Plan	
Primary Section Impacted By This Change: Section 10.14, Exploratory Analyses	
Formerly read	The exploratory endpoints listed in Section 10.9 will be summarized descriptively at each study visit. ~~For each endpoint of the change, the analysis will be performed using the same methodology used in the secondary analysis.~~ ….
Now reads	The exploratory endpoints listed in Section 10.9 will be summarized descriptively at each study visit. **…**
Other Sections Impacted By This Change: • NA	

Purpose: To clarify the statistical methodology language	
Primary Section Impacted By This Change: Section 10.15, Intrathecal Drug Delivery Device Analyses	
Formerly read	… ~~The proportion of patients for whom a successful first injection of investigational drug product occurred will be reported among those for whom a first injection was attempted (ie, those who had an apparently successful implantation and did not suffer a device removal or revision prior to first scheduled injection). The proportion of patients who had no failed injection attempts during the study will also be summarized. The corresponding 95% CIs of the proportion of interest will be estimated, where appropriate. Injections that are not administered for patient related reasons (eg, patient uncooperative or competing medical issue) will not be included in the determination of the success of injection rate.~~ …
Now reads	**…** **The rate of successful IDDD injections will be calculated for each patient and summarized descriptively. The success rate will be calculated as the number of IDDD injections given as a percentage of IDDD injections given plus any malfunctions reported for**

	inability to dose. The corresponding 95% confidence interval for the mean rate will be estimated, where appropriate. Injections that are not administered for patient-related reasons (e.g. patient uncooperative, competing medical issue, etc) will not be included in the determination of the injection success rate. **…**
Other Sections Impacted By This Change: • NA	

Purpose: To clarify the statistical methodology language	
Primary Section Impacted By This Change: Section 10.16, Interim Analysis	
Formerly read	An interim analysis of all data will be performed after all enrolled patients in Cohorts 1-3 have completed the study. All data from Cohorts 1-3 will be entered into the database, reviewed, and discrepancies resolved for this analysis. Because any hypothesis testing is considered exploratory, no adjustment for multiplicity will be made. The analysis methods will be detailed in an interim statistical analysis plan, and a ~~full~~ 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 (Section 11.8).
Now reads	An interim analysis of all data will be performed after all enrolled patients in Cohorts 1-3 have completed the study. All data from Cohorts 1-3 will be entered into the database, reviewed, and discrepancies resolved for this analysis. Because any hypothesis testing is considered exploratory, no adjustment for multiplicity will be made. The analysis methods will be detailed in an interim statistical analysis plan, and a**n** 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 (Section 11.8).
Other Sections Impacted By This Change: • Synopsis	

<table>
<tr><td colspan="2">Purpose: To clarify that a DSMB meeting will be held after completion of Cohorts 1-3</td></tr>
<tr><td colspan="2">Primary Section Impacted By This Change: Section 11.8, Data Safety Monitoring Board</td></tr>
<tr><td>Formerly read</td><td>…

Planned DSMB meetings will occur prior to each dose escalation (see Section 6.5) <s>and prior to the start of Cohort 4</s>. In addition, an ad hoc DSMB meeting will be convened if the safety-related study stopping rules are met (see Section 7.22).

…</td></tr>
<tr><td>Now reads</td><td>…

Planned DSMB meetings will occur prior to each dose escalation (see Section 6.5). A DSMB meeting will be held after completion of Cohorts 1-3. In addition, an ad hoc DSMB meeting will be convened if the safety-related study stopping rules are met (see Section 7.22).

…</td></tr>
<tr><td colspan="2">Other Sections Impacted By This Change:
Synopsis
Section 4.1, Overall Study Design and Plan
Section 6.3.1, Dose Selection
Section 6.5, Staggered Enrollment/Dose Escalation</td></tr>
</table>